Study of Total Synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin and 3-*O*-Feruloylcassine by Copper-mediated Nucleophilic Substitution and Gold-catalyzed Cycloisomerization

Dissertation

For the achievement of the academic degree of the

Doctors in Natural Sciences

(Dr. rer. nat.)

Submitted to

The Faculty of Chemistry and Chemical Biology

TU Dortmund University

By

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From Hubei, China

Dortmund 2019

The work described in this Dissertation was performed from October 2015 to March 2019 at the department of Organic Chemistry of the Technical University of Dortmund under the guidance of Prof. Dr. Norbert Krause.

Erster Gutachter: Prof. Dr. Norbert Krause

Zweiter Gutachter: Prof. Dr. Ralf Weberskirch

Eingereicht am:

Datum der mündlichen Prüfung:

Although the road is endless and faraway, I still want to find and pursue the truth in the world.

Yuan Qu (339 *B.C.*~278 *B.C.*)

A poet of the State of Chu, China

Dedicated to my parents and my wife during my PhD study

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Abstract

In this dissertation, the main work is the synthesis of 6-membered heterocyclic natural products by using the synthetic methods developed in our group, *i.e.* the copper-mediated nucleophilic substitution for synthesizing functionalized allenes, as well as, the gold-catalyzed cycloisomerization of functionalized allenes for synthesizing heterocycles.

Chapter 2 demonstrates the journey of the first total synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin including the racemic synthesis route and enantioselective synthesis route. In the racemic synthesis route, starting from the commercially available but-2-yn-1-ol, through the key steps of the copper-mediated S_N2'-substitution of propargyl acetates and the gold-catalyzed cycloisomerization of β-hydroxyallenes, the core ring system of agerafastin was obtained. Subsequently, a sequence of epoxidation/esterification/oxidation/olefination was performed to afford the final racemic natural product. Based on the racemic synthesis, changing the starting material to the allyl alcohol, the three chiral centers of agerafastin were obtained by the *Sharpless* dihydroxylation, asymmetric epoxidation and selective opening of epoxide to provide enantiomerically pure core ring system. Finally, the last step of modified *Julia* olefination affords the natural product with high stereoselectivity as well as good *E*/*Z* ratio.

Chapter 3 studies the total synthesis of (+)-3-*O*-Feruloylcassine based on our previous work. Starting from the propargyl alcohol, through a sequence of *HWE* reaction/ reduction/*Mitsunobu* reaction/*Sharpless* dihydroxylation, the important intermediate propargyl dicarbonate was obtained. Then, the NHC-ligand for the key step of CuH-catalyzed S_N2'-reduction was synthesized. After that, the CuH-catalyzed S_N2'-reduction of propargyl dicarbonates was optimized to give desired β-aminoallene. The other key step, gold-catalyzed cycloisomerization of β-aminoallenes, will be further optimized by using more active gold catalysts until the desired core ring system of natural product (+)-3-*O*-Feruloylcassine is formed with good results and the total synthesis will be continued.

Kurzfassung

Diese Dissertation befasst sich mit der Synthese von 6-gliedrigen heterocyclischen Naturstoffen unter Verwendung zweier in unserer Gruppe entwickelten Synthesemethoden, der Kupfer-vermittelten nucleophilen Substitution zur Synthese funktionalisierter Allene, sowie deren Gold-katalysierter Cycloisomerisierung zur Synthese von Heterocyclen.

Kapitel 2 beschreibt die erste Totalsynthese von racemischem und enantiomerenreinem 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin. Bei der Synthese des racemischen Naturstoffs, ausgehend vom kommerziell erhältlichen But-2-in-1-ol, wurde durch die Schlüsselschritte, der Kupfer-vermittelten S_N2'-Substitution von Propargylacetaten und der Gold-katalysierten Cycloisomerisierung von β-Hydroxyallenen, das Ringsystem des Agerafastins erhalten. Anschließend wurde der Naturstoff durch Epoxidierung, Epoxidöffnung, Veresterung, Oxidation und Olefinierung erhalten. Für den enantioselektiven Syntheseweg wurde zunächst das Ausgangsmaterial modifiziert, und die drei Chiralitätszentren des Agerafastins konnten durch *Sharpless*-Dihydroxylierung, diastereoselektive Epoxidierung und anschließende regio- und stereoselektive Öffnung des Epoxids erhalten werden. Schließlich lieferte der letzte Schritt, eine modifizierte *Julia*-Olefinierung, den Naturstoff mit hoher Stereoselektivität. Durch die erste enantioselektive Synthese konnte auch die absolute Konfiguration des natürlich vorkommenden 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastins bestimmt werden.

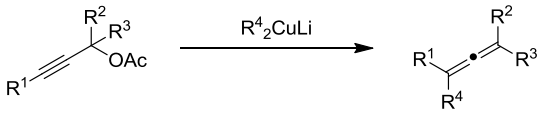
In Kapitel 3 werden die Schlüsselschritte der Totalsynthese von (+)-3-*O*-Feruloylcassin auf der Grundlage früherer Arbeiten untersucht. Ausgehend von Propargylalkohol konnte durch *HWE*-Reaktion, Reduktion, *Mitsunobu*-Reaktion und *Sharpless*-Dihydroxylierung das benötigte Propargyldicarbonat erhalten werden. Die Kupferhydrid-katalysierte S_N2'-Reduktion des Propargyldicarbonats zum β-Aminoallen wurde optimiert. Der abschließende Syntheseschritt, die Gold-katalysierte Cycloisomerisierung des β-Aminoallens zum Ringbaustein des Naturstoffs, bedarf weiterer Verbesserung unter Verwendung von hochreaktiven Goldkatalysatoren.

Chapter 1. Introduction

1.1 Copper-catalyzed nucleophilic substitution for synthesizing functionalized allenes

The use of organometallic reagents for the synthesis of allenes is highly developed [1] and several fundamentally different methods, including substitution reactions, [2] addition reactions, [3] elimination reactions[4] and isomerization reactions,[5] are well established. In these transformations, organocopper compounds are favored in the metal-mediated synthesis of allenes, although other metals such as aluminum, titanium, samarium and indium have also shown their good capacities to synthesize allenes. Furthermore, the copper-mediated S_N2'-substitution is one of the most useful methods for synthesizing allenes because this kind of reaction with organocopper reagents has broad substrate scope and high isolated yield as well as high *anti*-stereoselectivity. [1]

The first examples of allene synthesis by means of copper-mediated S_N2'-substitution was reported by *Rona* and *Crabbé* in 1968. The reaction of propargylic acetates **1.1** with lithium dialkylcuprates led to the formation of allenes **1.2** with moderate to good yields (Scheme 1.1).[6]



1.1 **1.2**

Scheme 1.1: Copper-mediated S_N2'-substitution for synthesizing allene **1.2**.

The propargylic acetates are very classic substrates of the copper-mediated S_N2'-substitution for synthesizing allenes. The reaction of functionalized pyridyl-substituted propargylic

[1] (a) Modern Allene Chemistry, Eds.: N. Krause, A. S. K. Hashmi, Wiley-VCH: Weinheim, **2004**; (b) N. Krause, A. Hoffmann-Röder, *Tetrahedron* **2004**, *60*, 11671-11694.

[2] (a) The Chemistry of the Allenes, Ed.: S. R. Landor, Academic Press: London, **1982**; (b): Allenes in Organic Synthesis, Eds.: H. F. Schuster, G. M. Coppola, Wiley: New York, **1984**.

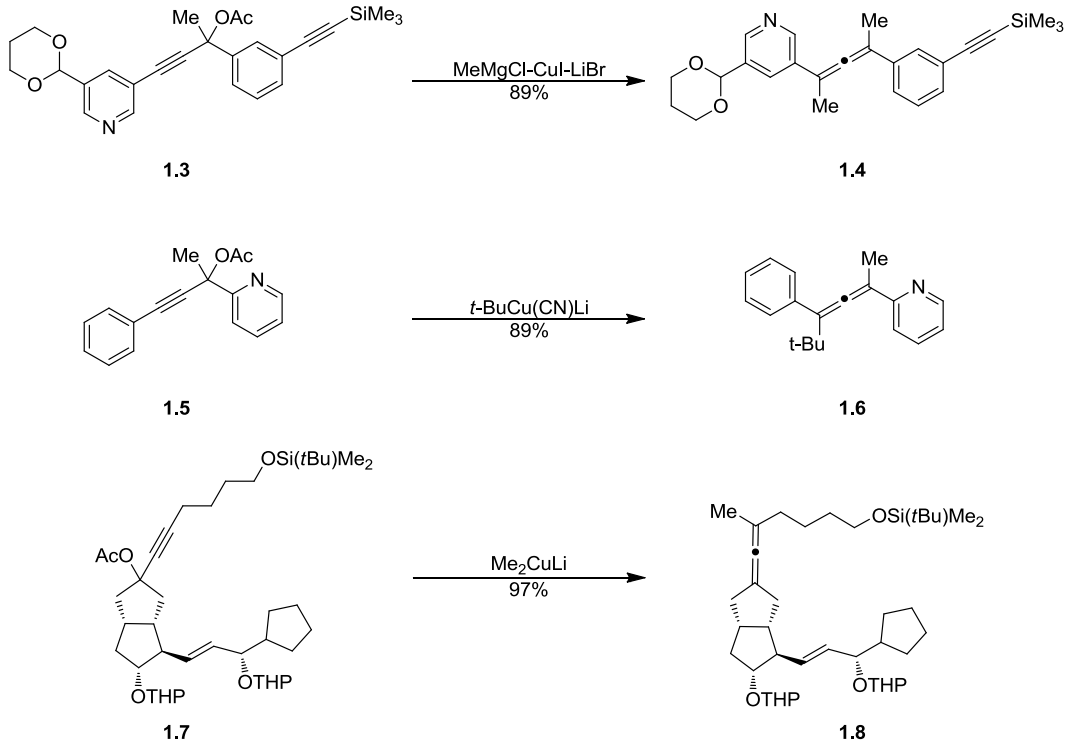
[3] (a) T. Kusumoto, T. Hiyama, *Chem. Lett.* **1985**, 1405-1408; (b) T. Kusumoto, K. Ando, T. Hiyama, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1280-1290.

[4] M. Suginome, A. Matsumoto, Y. Ito, *J. Org. Chem.* **1996**, *61*, 4884-4885.

[5] (a) The Chemistry of Ketenes, Allenes and Related Compounds, Part 2, Ed.: S. Patai, Wiley: Chichester, **1980**; (b) S. Dai, R. S. Pappas, G.-F. Chen, Q.-X. Guo, J. T. Wang, F. Williams, *J. Am. Chem. Soc.* **1989**, *111*, 8759-8761.

[6] (a) P. Rona, P. Crabbé, *J. Am. Chem. Soc.* **1968**, *90*, 4733-4734; (b) P. Rona, P. Crabbé, *J. Am. Chem. Soc.* **1969**, *91*, 3289-3292.

acetate **1.3** with the magnesium cuprate MeMgCl-CuI-LiBr was performed efficiently to afford functionalized pyridylallene **1.4** [7] with high yield of 89%. The allene **1.6**[8] and allene **1.8**[9] were also efficiently formed by copper-mediated S_N2'-substitution of the corresponding propargylic acetates **1.5** and **1.7** (Scheme 1.2).



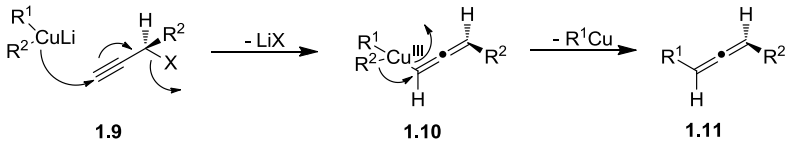
Scheme 1.2: Copper-mediated S_N2'-substitution of propargylic acetate.

The mechanism of this copper-mediated S_N2'-substitution of propargylic electrophiles was proposed to involve an interaction of a copper-centered d-orbital with the σ and π* orbitals of the substrate **1.9**. This leads to the formation of a σ-copper(III) species **1.10**, which finally undergoes a reductive elimination of an alkylcopper compound to furnish the *anti*-substitution product **1.11** (Scheme 1.3).[1]

[7] A. Jansen, N. Krause, *Synthesis* **2002**, *14*, 1987-1992.

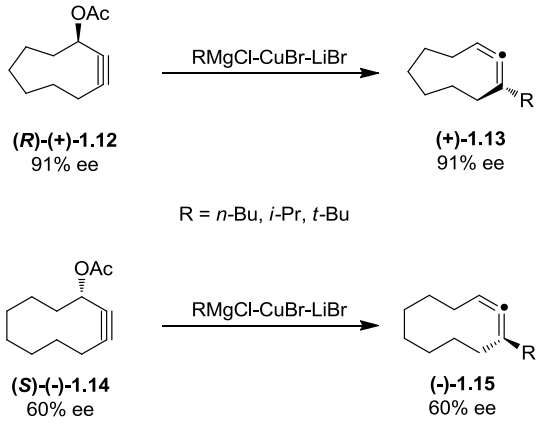
[8] A. Jansen, N. Krause, *Inorg. Chim. Acta* **2006**, *359*, 1761-1766.

[9] S. W. Djuric, M. Miyano, M. Clare, R. M. Rydzewski, *Tetrahedron Lett.* **1987**, *28*, 299-302.



Scheme 1.3: Proposed mechanism of *anti*-stereoselective S_N2'-substitution of propargylic electrophiles.

Owing to the reliability and excellent center-to-axis chirality transfer of the S_N2'-substitution, enantiomerically enriched allenes were synthesized. The *anti*-selective S_N2'-substitution of the chiral propargylic acetates **(*R*)-(+)-1.12** and **(*S*)-(+)-1.14**, achieved through lipase-catalyzed kinetic resolution (KR), with magnesium cuprates obtained from Grignard reagents, copper(I) bromide and lithium bromide gave chiral allenes **(+)-1.13** (91% ee) and **(-)-1.15** (60% ee) with the same enantiomeric excess as substrates, which proved a complete center-to-axis chirality transfer in the S_N2'-substitution (Scheme 1.4). [10]

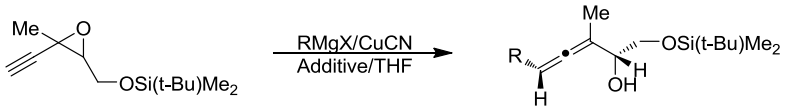


Scheme 1.4: Synthesis of cyclic allenes **(+)-1.13** and **(-)-1.15** by copper-mediated S_N2'-substitution.

Propargyl oxiranes are also very interesting substrates for the copper-mediated S_N2'-substitution for synthesizing functionalized allenes. The S_N2'-substitution of propargyl epoxide of **1.16** with cuprates formed from 2 equivalents of Grignard reagent and 1 equivalent of CuCN in the presence of 1 equivalent of tri-*n*-butylphosphine or triethyl phosphite, which improve the chemo- and stereoselectivity of the S_N2'-substitution of propargyl epoxides, consistently afforded the desired functionalized allenes **1.17** with good yields and high *anti*-diastereoselectivity (Scheme 1.4). [11]

[10] C. Zelder, N. Krause, *Eur. J. Org. Chem.* **2004**, 3968-3971.

[11] (a) N. Krause, A. Hoffmann-Röder, J. Canisius, *Synthesis* **2002**, 1759-1774; (b) A. Hoffmann-Röder, PhD Thesis, TU Dortmund, **2003**.



1.16 **1.17**

MeMgBr/*n*-Bu_3P:	71% (ds = 94 : 6)
t-BuMgCl/$(EtO)_3P$:	82% (ds > 95 : 5)
n-HexMgBr/$(EtO)_3P$:	95% (ds > 95 : 5)
i-PrMgCl/$(EtO)_3P$:	76% (ds > 95 : 5)
PhMgBr/*n*-Bu_3P:	84% (ds = 95 : 5)

Scheme 1.5: Copper-mediated S_N2'-substitution of propargyl oxirane **1.16** with magnesium cuprates.

In addition to propargyl acetates and oxiranes, various propargyl derivatives (benzoates and carbonates,[12-13] propargylic sulfonates,[14] ethers and acetals,[15] halides[16] and aziridines[17]) have been utilized as substrates of copper-mediated S_N2'-substitution successfully.

Interestingly, when the nucleophile is a "hydride" in the reaction, the S_N2'-substitution is also called S_N2'-reduction. The CuH-catalyzed S_N2'-reduction for synthesizing allenes was only reported by *Stryker et al.* and by *Brummond* and *Lu*, who treated terminal propargyl acetates with the hexameric copper hydride complex $[(Ph_3P)CuH]_6$ (*Stryker*'s reagent) (Scheme 1.6). [18]

[12] (a) A. Alexakis, P. Mangeney, A. Ghribi, I. Marek, R. Sedrani, C. Guir, J. F. Normant, *Pure Appl. Chem.* **1988**, *60*, 49-56; (b) A. Alexakis, *Pure Appl. Chem.* **1992**, *64*, 387-392; (c) E. Erdik, *Tetrahedron Lett.* **1992**, *48*, 9577-9648.

[13] (a) K.-M. Wu, M. M. Midland, W. H. Okamura, *J. Org. Chem.* **1990**, *55*, 4381-4392; (b) S.-K. Kang, S.-G. Kim, D.-G. Cho, *Tetrahedron: Asymmetry* **1992**, *3*, 1509-1510; (c) C. Spino, C. Thibault, S. Gingras, *J. Org. Chem.* **1998**, *63*, 5283-5287.

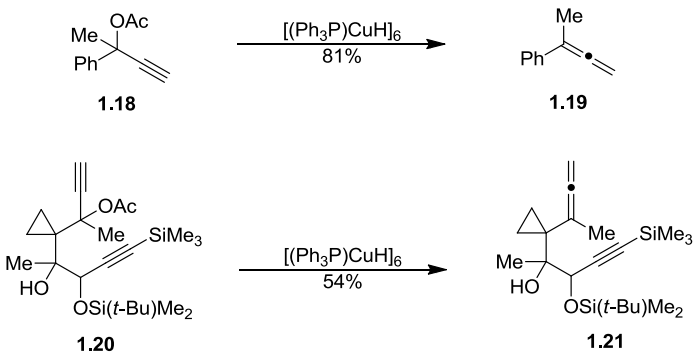
[14] (a) I. Gridnev, G. Kanai, N. Miyaura, A. Suzuki, *J. Organomet. Chem.* **1994**, *481*, C4-C7; (b) C. Agami, F. Couty, G. Evano, H. Mathieu, *Tetrahedron* **2000**, *56*, 367-376; (c) H. Ohno, M. Anzai, A. Toda, S. Ohishi, N. Fujii, T. Tanaka, Y. Takemoto, T. Ibuka, *J. Org. Chem.* **2001**, *66*, 4904-4914.

[15] (a) I. Marek, P. Mangeney, A. Alexakis, J. F. Normant, *Tetrahedron Lett.* **1986**, *27*, 5499-5502; (b) A. Alexakis, I. Marek, P. Mangeney, J. F. Normant, *J. Am. Chem. Soc.* **1990**, *112*, 8042-8047; (c) I. Marek, A. Alexakis, P. Mangeney, J. F. Normant, *Bull. Soc. Chim. Fr.* **1992**, *129*, 171-190.

[16] (a) D. J. Burton, G. A. Hartgraves, J. Hsu, *Tetrahedron Lett.* **1990**, *31*, 3699-3702; (b) M. H. Hung, *Tetrahedron Lett.* **1990**, *31*, 3703-3706; (c) M. Yus, J. Gomis, *Eur. J. Org. Chem.* **2003**, 2043-2048.

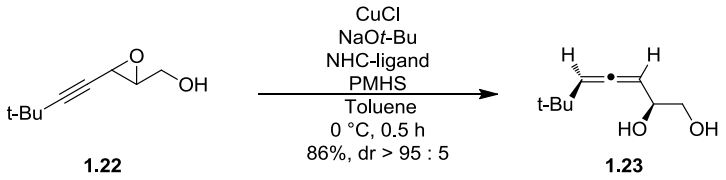
[17] (a) H. Ohno, A. Toda, Y. Miwa, T. Taga, N. Fujii, T. Ibuka, *Tetrahedron Lett.* **1999**, *40*, 349-352; (b) H. Ohno, A. Toda, N. Fujii, Y. Takemoto, T. Tanaka, T. Ibuka, *Tetrahedron* **2000**, *56*, 2811-2820.

[18] (a) J. F. Daeuble, C. McGettigan, J. M. Stryker, *Tetrahedron Lett.* **1990**, *31*, 2397-2400; (b) K. M. Brummond, J. Lu, *J. Am. Chem. Soc.* **1999**, *121*, 5087-5088.



Scheme 1.6: CuH-catalyzed S_N2'-reduction of propargyl acetates to terminal allenes with Stryker's reagent.

In 2007, the CuH-catalyzed S_N2'-reduction of propargyl oxiranes with N-heterocyclic carbene (NHC) ligands has been developed by *Deutsch* and *Krause*.[19] The S_N2'-reduction of propargyl oxiranes **1.22** with (NHC)CuH formed from 3 mol% of CuCl, 3 mol% of NHC ligand and 0.1 equivalent of sodium *tert*-butoxide in the presence of 2 equivalents of polymethylhydridosiloxane (PMHS) as the stoichiometric hydride source gave α-hydroxyallene **1.23** with excellent center-to-axis chirality transfer and excellent *anti*-stereoselectivity (Scheme 1.7).

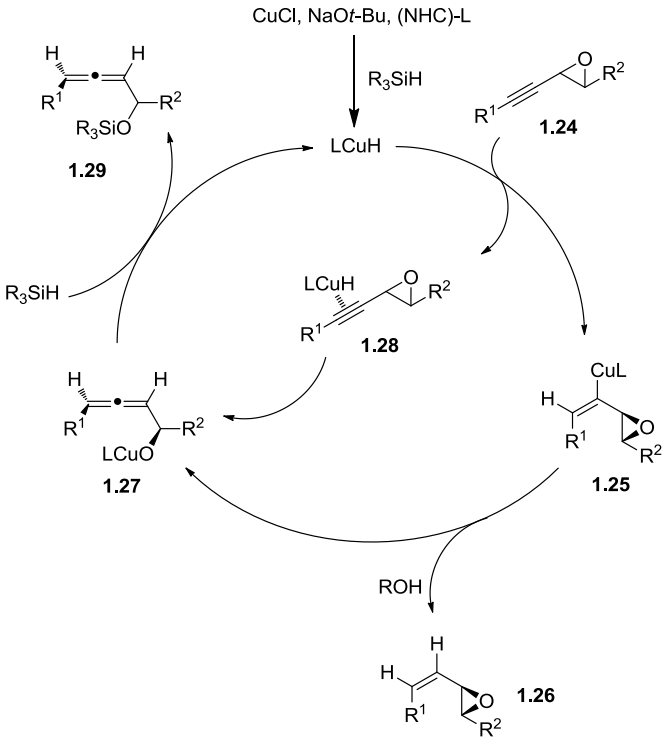


Scheme 1.7: (NHC)CuH-catalyzed S_N2'-reduction of propargyl oxirane **1.22** to give α-hydroxyallene **1.23**.

Additionally, a mechanism of the (NHC) CuH-catalyzed S_N2'-reduction of propargyl oxiranes was also proposed by *Deutsch* and *Krause*.[19] The vinylcopper intermediate **1.25** is first formed by *syn* addition of the copper hydride to the triple bond of propargyl oxirane **1.24** and the α-alkoxyallene **1.27** is obtained by an *anti*-selective β-elimination. Then, transmetalation of **1.27** with the stoichiometric hydride source PHMS provides the silyl ether **1.29** and releases the catalyst LCuH. Fluoride-mediated hydrolytic workup of **1.29** affords the final α-hydroxyallene. If an alcohol is present in the reaction system, the vinyloxirane **1.26** can be isolated by a hydrocupration-protodemetalation. An alternative way is that the α-alkoxyallene **1.27** can be obtained from the π-complex **1.28** by reductive elimination. The isolation of **1.26**

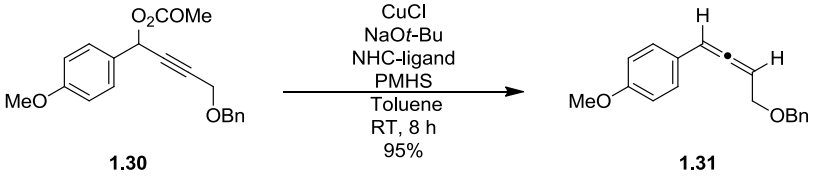
[19] C. Deutsch, B. H. Lipshutz, N. Krause, *Angew. Chem. Int. Ed.* **2007**, *46*, 1650 -1653.

makes the first path plausible, while the second approach better explains the observed high *anti*-selectivity and cannot be ruled out (Scheme 1.8).



Scheme 1.8: Proposed mechanism of copper-catalyzed S_N2'-reduction of propargyl oxiranes.

Two years later, the (NHC)CuH-catalyzed S_N2'-reduction of propargyl carbonates was also reported by *Deutsch* and *Krause*,[20] which shows that this method is an efficient route to functionalized allenes with high reactivity and stereoselectivity (Scheme 1.9).

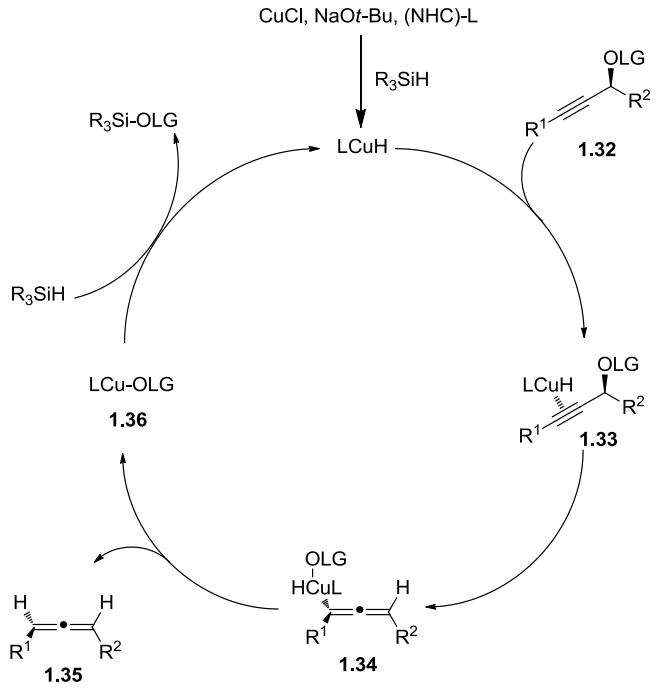


Scheme 1.9: (NHC)CuH-catalyzed S_N2'-reduction of propargylic carbonate **1.30**.

The following mechanism was proposed for the (NHC)CuH-catalyzed S_N2'-reduction of propargyl carbonates.[20] The π-complex **1.33** is first formed from the catalyst LCuH and propargyl carbonate **1.32**. Then **1.33** is converted into σ-copper(III) species **1.34** which can be transformed to the product allene **1.35** and copper salt **1.36** by reductive elimination.

[20] C. Deutsch, B. H. Lipshutz, N. Krause, *Org. Lett.* **2009**, *11*, 5010-5012.

Transmetalation of **1.36** with PMHS regenerates the catalyst LCuH and the rate of this transmetalation step depends on the basicity of the copper salt (Scheme 1.10).



Scheme 1.10: Proposed mechanism of copper-catalyzed S_N2'-reduction of propargyl carbonates.

1.2 Gold-catalyzed cycloisomerization of functionalized allenes and their application in total synthesis of natural products

Allenes play a highly important role in synthetic organic chemistry because of their characteristics for undergoing various transformations. [1,21] After activation of the cumulated double bonds by a Brønsted or Lewis acid, it allows a nucleophilic attack, which provides a new C-C or C-heteroatom bond in an inter- or intramolecular reaction. Furthermore, functionalized allenes can be utilized for asymmetric synthesis because their axial chirality can be transferred to the product.

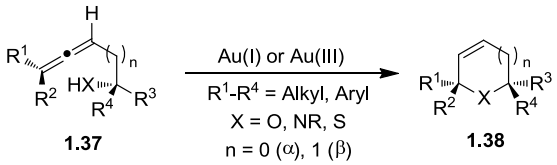
Gold catalysis is one of the fast growing sectors of modern chemistry.[22] Homogenous gold catalysed transformations are often effective with excellent atom economy, great functional

[21] (a) S. Ma, *Chem. Rev.* **2005**, *105*, 2829-2871. (b) Cumulenes and Allenes, Science of Synthesis, Ed.: N. Krause, Thieme: Stuttgart, **2007**. (c) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994-2009.

[22] (a) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem. Int. Ed.* **2006**, *45*, 7896-7936; (b) D. J. Gorin, F. D. Toste, *Nature*, **2007**, *446*, 395-403; (*c*) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180-3211; (d) Z. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239-3265; (e) A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657-1712; (f) D. Pflästerer, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 1331-1367.

group tolerance and sometimes tremendously increased molecular complexity.[23] Because of the unique ability of gold catalysts to act as soft carbophilic Lewis acids towards C-C double and triple bonds, they are quite suitable for the selective activation of functionalized allenes. [21c,24]

Recently, the *Krause* group has developed the gold-catalyzed cycloisomerization of functionalized allenes bearing a hydroxy,[11a,25] amino,[25c,26] or thiol group[27] in α-/β-position to the corresponding 5- and 6-membered heterocycles with high reactivity and excellent axis-to-center chirality transfer (Scheme 1.11).



Scheme 1.11: Gold-catalyzed cycloisomerization of α- or β-hetero-substituted allenes to 5- and 6-membered heterocycles.

The mechanism of the gold-catalyzed cycloisomerization of functionalized allenes has not yet been clearly elucidated. According to *Hoffmann-Röder* and *Krause*,[1a,11b,21c,28] the mechanism is proposed as follows (Scheme 1.12). The carbophilic gold catalyst is coordinated to the distal double bond of the allene **1.37** to form the π-complex **1.39**, which undergoes a cyclization to afford zwitterionic σ-gold species **1.40**. After protodeauration of **1.40**, the heterocyclic compound **1.38** is formed and the catalyst is regenerated.

[23] (a) A. S. K. Hashmi, *Acc. Chem. Res.* **2014**, *47*, 864-876; (b) D.-H. Zhang, X.-Y. Tang, M. Shi, *Acc. Chem. Res.* **2014**, *47*, 913-924; (c) B. Alcaide, P. Almendros, *Acc. Chem. Res.* **2014**, *47*, 939-952; (d) L. Fensterbank, M. Malacria, *Acc. Chem. Res.* **2014**, *47*, 953-965.

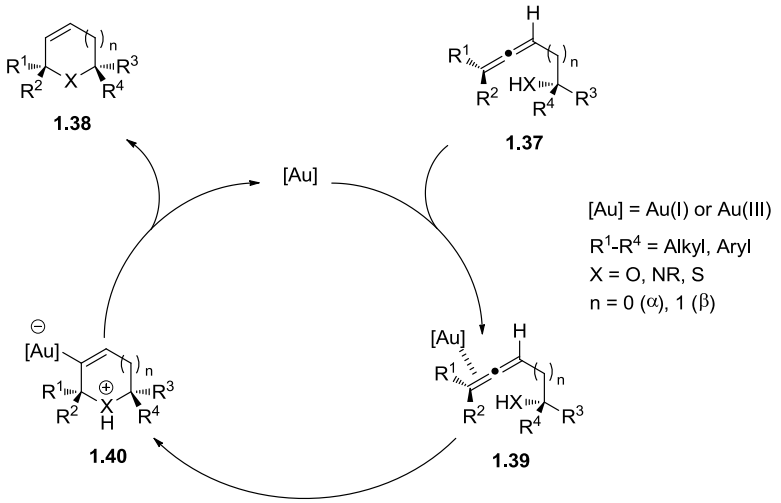
[24] (a) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885-3903; (b) P. Belmont, E. Parker, *Eur. J. Org. Chem.* **2009**, 6075-6.89; (c) N. Krause, V. Belting, C. Deutsch, J. Erdsack, H.-T. Fan, B. Gockel, A. Hoffmann-Röder, N. Morita, F. Volz, *Pure Appl. Chem.* **2008**, *80*, 1063-1069; (d) N. Krause, Ö. Aksin-Artok, V. Breker, C. Deutsch, B. Gockel, M. Poonoth, Y. Sawama, Y. Sawama, T. Sun, C. Winter, *Pure Appl. Chem.* **2010**, *82*, 1529-1536.

[25] (*a*) A. Hoffmann-Röder, N. Krause, *Org. Lett.* **2001**, *3*, 2537-2538; (b) C. Deutsch, B. Gockel, A. Hoffmann-Röder, N. Krause, *Synlett* **2007**, *11*, 1790-1794; (c) B. Gockel, N. Krause, *Org. Lett.* **2006**, *8*, 4485-4488.

[26] (*a*) N. Morita, N. Krause, *Org. Lett.*, **2004**, *6*, 4121-4123; (*b*) N. Morita, N. Krause, *Eur. J. Org. Chem.* **2006**, 4634-4641.

[27] N. Morita, N. Krause, *Angew. Chem. Int. Ed.* **2006**, *45*, 1897-1899.

[28] W. Yang, A. S. K. Hashmi, *chem. Soc. Rev.* **2014**, *43*, 2941-2955.



Scheme 1.12: Proposed mechanism of gold-catalyzed cycloisomerization of functionalized allenes.

Owing to the reliability, the gold-catalyzed cycloisomerization of functionalized allenes is successfully applied to the synthesis of natural products, natural product derivatives and interesting ring systems. As shown in Figure 1.1, there are nine examples with dihydro- or tetrahydrofuran ring **1.41-1.49** [11a,29-35] which are synthesized by the gold-catalyzed cycloisomerization of α-hydroxyallenes. The first and only application of the gold-catalyzed cycloisomerization of β-hydroxyallenes is to afford (*R*,*R*,*R*)-Bejarol **1.50.** [36]

[29] J. A. Marshall, K. G. Pinney, *J. Org. Chem.* **1993**, *58*, 7180-7184.

[30] F. Volz, N. Krause, *Org. Biomol. Chem.* **2007**, *5*, 1519-1521.

[31] T. Sun, C. Deutsch, N. Krause, *Org. Biomol. Chem.* **2012**, *10*, 5965-5970.

[32] J. Erdsack, N. Krause, Synthesis **2007**, *23*, 3741-3750.

[33] F. Volz, S. H. Wadman, A. Hoffmann-Röder, N. Krause, *Tetrahedron* **2009**, *65*, 1902-1910.

[34] V. M. Schmiedel, S. Stefani, H.-U. Reissig, *Beilstein J. Org. Chem.* **2013,** *9*, 2564-2569.

[35] (a) B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978-15979; (b) O. F. Jeker, E. M. Carreira, *Angew. Chem. Int. Ed.* **2012**, *51*, 3474-3477.

[36] Y. Sawama, Y. Sawama, N. Krause, *Org. Biomol. Chem.* **2008**, *6*, 3573-3579.

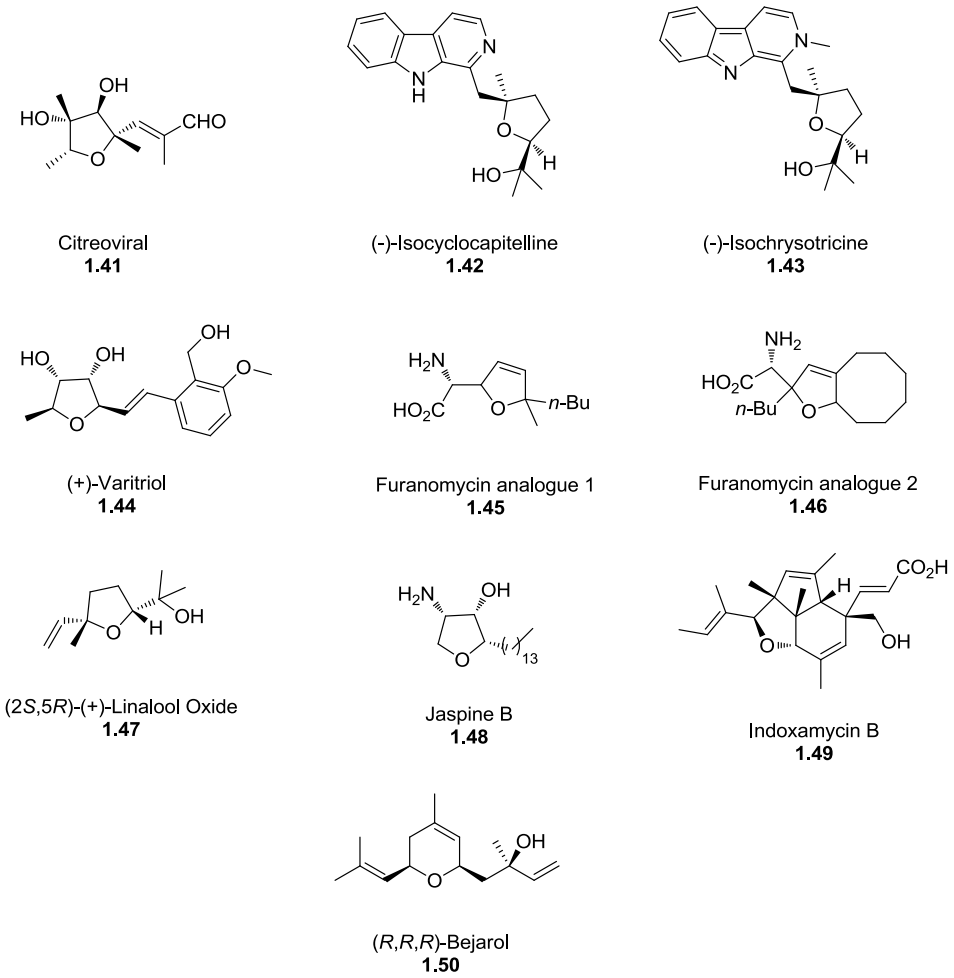


Figure 1.1: Synthesis of natural products and their analogues with *O*-heterocyclic rings by gold-catalyzed cycloisomerization of functionalized allenes.

As shown in Figure 1.2, swainsonine **1.51**[37] was obtained through a gold-catalyzed 6-*exo*-cycloisomerization to provide the piperidine. Azafuranomycin analogues **1.52** and **1.53** were synthesized by the means of the gold-catalyzed *endo*-cycloisomerization of α-aminoallenes.[38] The first example of the gold-catalyzed *endo*-cycloisomerization of a β-aminoallene to prepare a tetrahydropyridine derivative **1.54** was reported by *Gockel* and *Krause* in 2006[25c] and several further tetrahydropyridine derivatives **1.55** were prepared by them later. [39]

[37] (a) R. W. Bates, M. R. Dewey, *Org. Lett.* **2009**, *11*, 3706-3708; (b) C. W. G. Au, S. G. Pyne, *J. Org. Chem.* **2006**, *71*, 7097-7099.

[38] J. Erdsack, N. Krause, *Beilstein J. Org. Chem.* **2013,** *9*, 1936-1942.

[39] B. Gockel, PhD Thesis, TU Dortmund, **2009**.

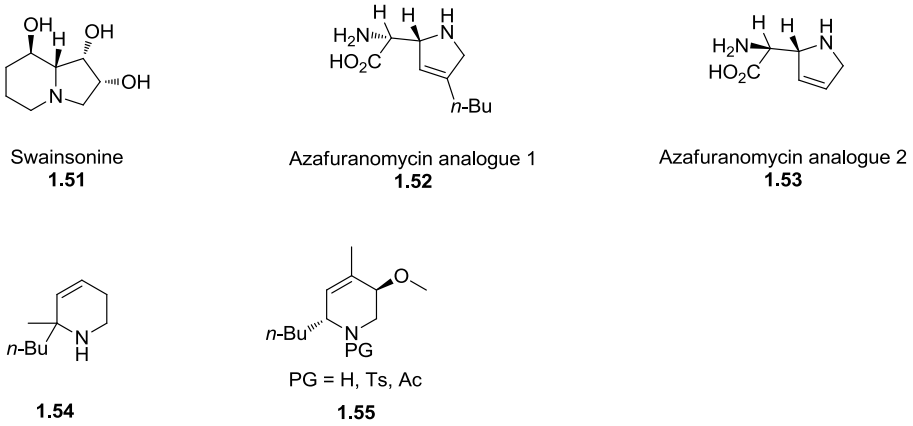


Figure 1.2: Synthesis of natural products and their analogues and interesting ring systems with *N*-heterocyclic rings by gold-catalyzed cycloisomerization of functionalized allenes.

1.3 Objectives

Owing to the interesting ability of allenes, which can be obtained successfully by copper-catalyzed nucleophilic substitution, to undergo gold-catalyzed cycloisomerization, it is interesting to obtain different heterocyclic rings and use them for the synthesis of natural products, natural product derivatives and interesting ring systems. However, both the *O*-heterocyclic 6-membered rings and *N*-heterocyclic 6-membered rings were rarely synthesized by these methods so far, which makes this a very interesting and challenging goal.

The aim of the first project is the total synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin **1.56** by using the copper-mediated S_N2'-substitution and the gold-catalyzed cycloisomerization as key steps to build the core ring system (Figure 1.3).

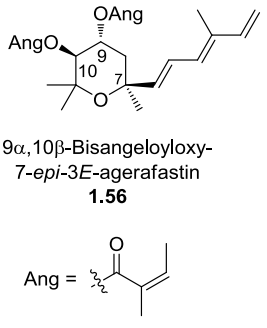
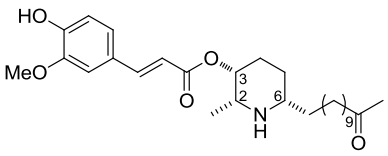


Figure 1.3

The aim of the second project is the total synthesis of 3-*O*-Feruloylcassine **1.57** by using the CuH-catalyzed S_N2'-reduction and the gold-catalyzed cycloisomerization as key steps to build the core ring system (Figure 1.4).



(+)-3-*O*-Feruloylcassine
1.57

Figure 1.4

Not only the total synthesis is not reported so far, but also the absolute configuration of these two natural products is unknown. Therefore, the enantioselective synthesis of the target molecules is an important objective of this work.

Chapter 2. The total synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin

2.1 Introduction

The 9α,10β-Bisangeloyloxy agerafastins (**2.1-2.3**)[40] were first isolated by *Robinson et al*. from *Brickellia vernicosa* in 1985 and its structure was deduced from ^{1}H NMR spectroscopy, IR spectroscopy, UV spectroscopy and mass spectrometry (Figure 2.1).

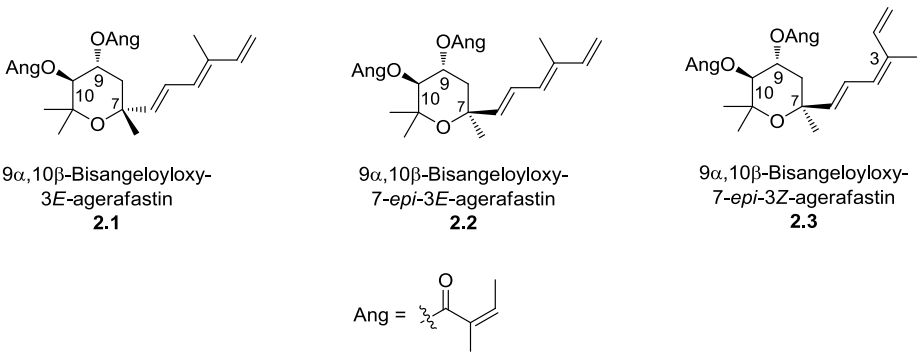


Figure 2.1: 9α,10β-Bisangeloyloxy-agerafastin **2.1-2.3**.

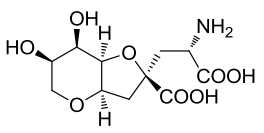
The core structure of agerafastin is substituted tetrahydropyran which is one of the important classes of heterocycles because this special structure is a common element in a variety of natural products and pharmaceuticals (Figure 2.2). The (-)-neodysiherbaine A **2.4**,[41] a potent convulsant and a highly selective agonist for kainate (KA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) glutamate receptors, was isolated from the marine sponge *Dysidea herbacea* by *Sakai et al*. The caespitol **2.5**[42] could be isolated from both *Laurencia caespitosa* and the sea hare *Aplysia dactylomela*. Biological studies have shown that **2.5** has activity in the brine shrimp lethality assay and exhibits nematicidal effects toward *Caenorrhabditis elegans* as well as shows weak cytotoxic activity against HeLa cells (cervical cancer). The thailanstatin A **2.6**[43] is potent pre-mRNA splicing inhibitor and antiproliferative agent from *Burkholderia thailandensis* MSMB43.

[40] R. N. Baruah, C. Zdero, F. Bohlmann, R. M. King, H. Robinson, *Phytochemistry* **1985**, *24*, 2641-2644.

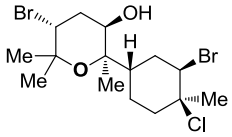
[41] (a) R. Sakai, T. Koike, M. Sasaki, K. Shimamoto, C. Oiwa, A. Yano, K. Suzuki, K. Tachibana, H. Kamiya, *Org. Lett.* **2001**, *3*, 1479-1482; (b) T. J. Donohoe, P. C. M. Winship, M. R. Tatton, Peter Szeto, *Angew. Chem. Int. Ed.* **2011**, *50*, 7604-7606.

[42] (a) J. J. Sims, G. H. Y. Lin, R. M. Wing, *Tetrahedron Lett.* **1974**, *39*, 3487-3490; (b) M. Wessels, G. M. König, A. D. Wright, *J. Nat. Prod.* **2000**, *63*, 920-928; (c) I. Brito, T. Dias, A. R. Díaz-Marrero, J. Darias, M. Cueto, *Tetrahedron* **2006**, *62*, 9655-9660.

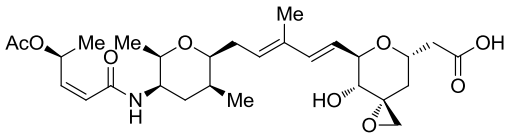
[43] (a) X. Liu, S. Biswas, M. G. Berg, C. M. Antapli, F. Xie, Q. Wang, M.-C. Tang, G.-L. Tang, L. Zhang, G. Dreyfuss, Y.-Q. Cheng, *J. Nat. Prod.* **2013**, *76*, 685-693; (b) K. C. Nicolaou, D. Rhoades, S. M. Kumar, *J. Am. Chem. Soc.* **2018**, *140*, 8303-8320.



(-)-Neodysiherbaine A
2.4



Caespitol
2.5



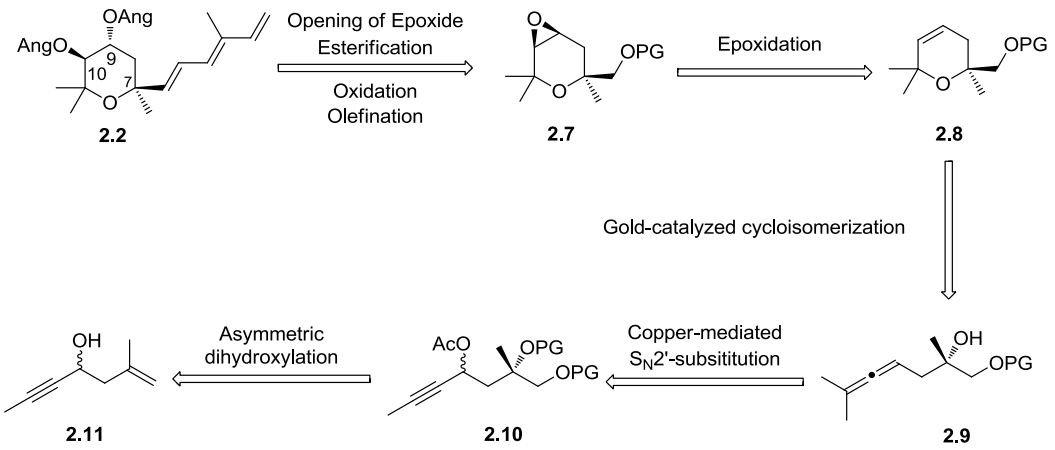
Thailanstatin A
2.6

Figure 2.2

To the best of our knowledge, the total synthesis and absolute configuration of agerafastin derivatives **2.1-2.3** have not been reported. Based on our group's previous works,[39] the gold-catalyzed cycloisomerization of β-hydroxyallenes obtained by copper-mediated S_N2'-substitution is an effective and efficient method to synthesize dihydropyrans which can be easily changed to tetrahydropyrans. This method should be highly suitable for the synthesis of one of the displayed agerafastin derivatives **2.1-2.3** and to elucidate the absolute configuration during the total synthesis.

2.2 Retrosynthetic analysis I

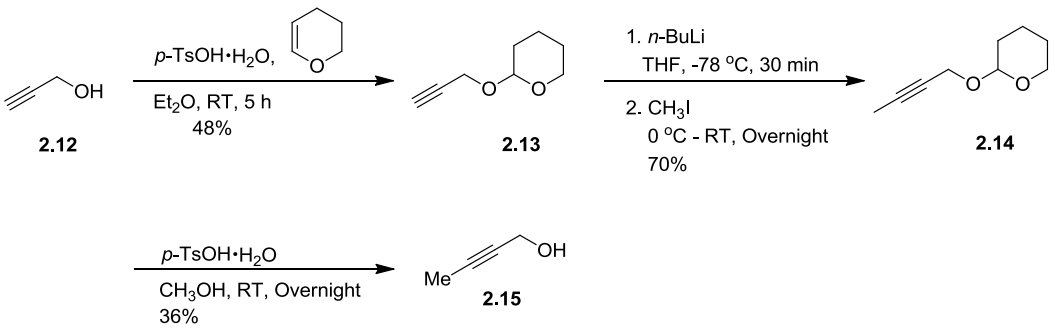
We have chosen 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin **2.2** as the target for our total synthesis. According to the retrosynthetic analysis shown in Scheme 2.1, **2.2** could be obtained from tetrahydropyran **2.7** through a sequence of opening of epoxide/esterification/ oxidation/olefination. The key intermediate dihydropyran **2.8**, which could be synthesized from **2.9** by gold-catalyzed cycloisomerization, could be transferred to **2.7** by means of epoxidation. The copper-mediated S_N2'-substitution of **2.10** should provide the β-hydroxyallene **2.9**. **2.10** could be accessible from the propargyl alcohol **2.11** through asymmetric dihydroxylation.



Scheme 2.1: Retrosynthesis I of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin **2.2**.

2.3 Synthesis of 2-methylhept-1-en-5-yn-4-ol 2.11

According to the retrosynthetic analysis I, we need to obtain ***rac*-2.11** at the beginning. Firstly, as shown in Scheme 2.2, the synthesis of **2.15** was achieved from propargyl alcohol **2.12**. The protected propargyl alcohol **2.13** was reacted with *n*-butyllithium and methyl iodide to provide **2.14** which can be converted into **2.15** [44] through deprotection with moderate yield of 36%. Taking the time and cost into consideration, we finally decided to buy the but-2-yn-1-ol **2.15** directly.



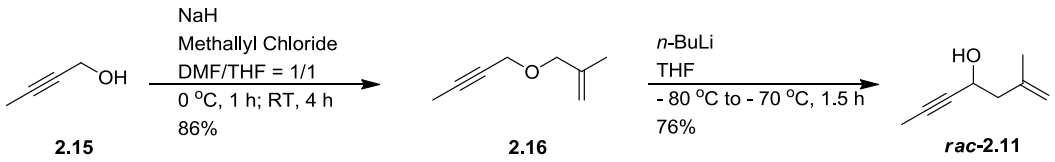
Scheme 2.2: Synthesis of but-2-yn-1-ol **2.15**.

Then, the propargyl alcohol ***rac*-2.11** should be accessible by a [2,3]-*Wittig* rearrangement[45] of **2.16** which can be obtained from commercially available alcohol **2.15** (Scheme 2.3). After deprotonation of the alcohol **2.15** with sodium hydride in a mixed solvent THF/DMF (1:1), methallyl chloride was added to provide the desired ether **2.16** with a good yield of 86%. The

[44] J. Rehbein, S. Leick, M. Hiersemann, *J. Org. Chem.* **2009**, *74*, 1531-1540.

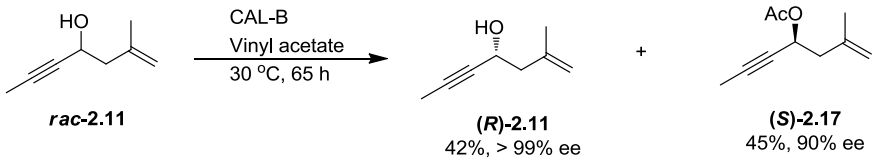
[45] (a) T. Nakai, K. Mikami, *Chem. Rev.* **1986**, *86*, 885-902; (b) K. Mikami, T. Nakai, *Synthesis* **1991**, 594-604.

subsequent [2,3]-*Wittig* rearrangement of **2.16** by using *n*-butyllithium as a base was carried out at -80 ℃ to -70 ℃ for 1.5 h and the homoallylic alcohol ***rac*-2.11** was obtained in 76% yield.



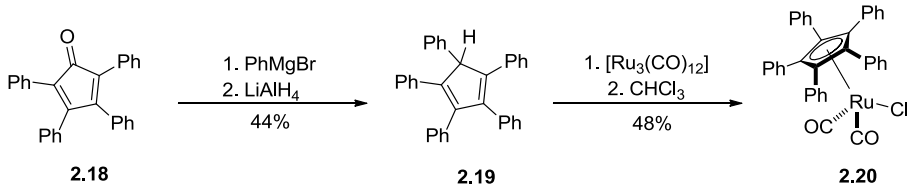
Scheme 2.3: Synthesis of alcohol ***rac*-2.11**.

With the desired starting materials ***rac*-2.11** in hand, we tried to get the enantiomerically pure (***R*)-2.11** by kinetic resolution (KR)[36,46] catalyzed by Lipase B from *Candida antarctica* (CAL-B) (Scheme 2.4). (***R*)-2.11** was efficiently obtained with 42% yield and up to 99% ee and the acetate **(*S*)-2.17** with high selectivity (45% yield, 90% ee).



Scheme 2.4: The kinetic resolution of ***rac*-2.11**

Both **(*R*)-2.11** and **(*S*)-2.17** can be used in the following steps as substrates for a *Sharpless* dihydroxylation for obtaining diol intermediates with different selectivity. For obtaining enantiomerically pure **(*S*)-2.17**, a dynamic kinetic resolution (DKR)[47] of ***rac*-2.11** was examined, too. Firstly, the racemization catalyst ruthenium complex **2.20**[48] was synthesized from 2,3,4,5-tetraphenylcyclopentadienone **2.18** in two steps and the total yield was 21%.



Scheme 2.5: The synthesis of racemization catalyst **2.20**

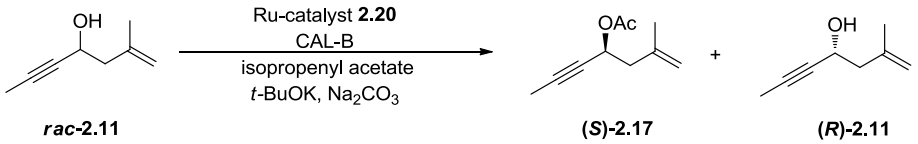
[46] (a) V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *J. Am. Chem. Soc.* **1981**, *103*, 6237-6240; (*b*) Z.-M. Wang, W.-S. Zhou, *Tetrahedron*, **1987**, *13*, 2935-2944.

[47] (a) O. Pàmies, J.-E. Bäckvall, *Chem. Rev.* **2003,** *103*, 3247-3261; (*b*) O. Verho J.-E. Bäckvall, *J. Am. Chem. Soc.* **2015**, *137*, 3996-4009.

[48] B. Martín-Matute, M. Edin, K. Bogár,† F. B. Kaynak, J.-E. Bäckvall, *J. Am. Chem. Soc.* **2005**, *127*, 8817-8825.

Then, the DKR of ***rac*-2.11** was optimized. As shown in Table 1, the best ee of **(*S*)-2.17** was 94%, however, the yield was only 12% (Table 1, entry 8). When the reaction mixture was stirred at room temperature for 45 h without solvent, the highest yield was obtained with 36% yield and 92% ee (Table 1, entry 4). Through eight different reaction conditions were tested, unfortunately, the results of DKR were not better than KR. The DKR needs to be further optimized with different ruthenium catalysts, different acyl donors, different reaction temperatures and so on.

Table 1: The dynamic kinetic resolution (DKR) of ***rac*-2.11**.



Entry	**2.20**/mol%	T/℃	t/h	Toluene/mL	Acyl donor equiv.	**(*S*)-2.17** Yield%[a]	Ee/%[b]	**(*R*)-2.11** Yield/%[c]	Ee/%[d]
1	8	50	68	1	1.5	13	91	87	24
2	8	RT	68	1	1.5	26	91	74	66
3	16	50	45	0	36	36	86	64	22
4	16	RT	45	0	36	36	92	64	14
5	16	50	45	1	20	17	91	83	18
6	16	RT	45	1	20	24	93	76	9
7	16	RT	45	1	1.5	19	92	81	51
8	16	RT	64	1	1.5	12	94	88	8

[a] Isolated yield of **(*S*)-2.17**.

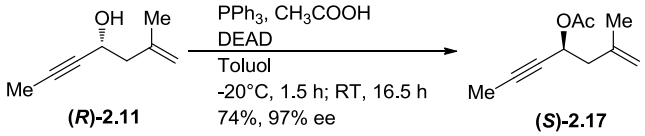
[b] Ee of **(*S*)-2.17** was determined by chiral GC.

[c] Recovered isolated yield of **(*R*)-2.11**.

[d] Ee of **(*R*)-2.11** was determined by chiral GC.

[49] (a) T. Y. S. But, P. H. Toy, *Chem. Asian J.* **2007**, *2*, 1340-1355; (b) K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551-2651; (c) D. Hirose, T. Taniguchi, H. Ishibashi, *Angew. Chem. Int. Ed.* **2013**, *52*, 4613-4617.

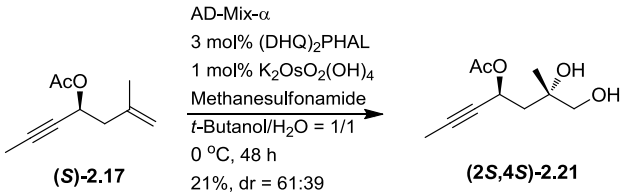
At the same time, we also tried the *Mitsunobu* reaction[49] to obtain **(*S*)-2.17** with higher selectivity by using enantiomerically pure **(*R*)-2.11** as a substrate. After optimization, the best result was 74% yield with 97 % ee (Scheme 2.6).



Scheme 2.6: The *Mitsunobu* reaction of **(*R*)-2.11**.

2.4 Sharpless dihydroxylation of homoallylic alcohol derivatives

Based on our group's previous works,[39] a protective group of alcohol **2.11** was necessary to perform the *Sharpless* dihydroxylation.[50] Otherwise, the yield of the *Sharpless* dihydroxylation was low because of the presence of the free hydroxyl group in β-position. First, **(*S*)-2.17** was chosen as substrate for the *Sharpless* dihydroxylation. The dihydroxylation with AD-mix-α, additional ligand $(DHQ)_2PHAL$[51] and additional catalyst $K_2OsO_2(OH)_4$ was disappointing with only 21% of **(2*S*,4*S*)-2.21** isolated which means this substrate is unsuitable (Scheme 2.7).



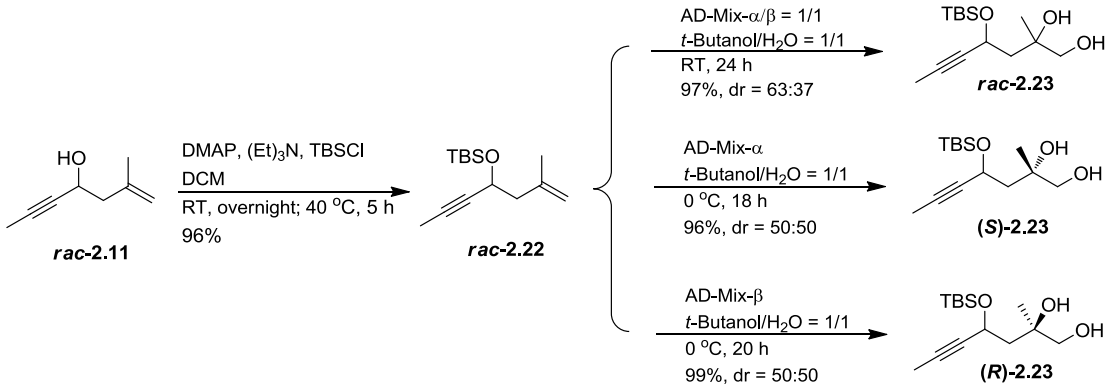
Scheme 2.7: *Sharpless* dihydroxylation of **(*S*)-2.17**.

Then other protecting groups were tried. Firstly, The TBS-protected alcohol ***rac*-2.22** could be obtained with a very good yield of 96% from propargyl alcohol ***rac*-2.11**. Subsequent *Sharpless* dihydroxylation proceeded with a mixture of AD-mix-α and AD-mix-β (1:1), AD-mix-α or AD-mix-β easily with excellent yields of 97%, 96% and 99% respectively (Scheme 2.8). The reason for using the mixture of AD-mix-α and AD-mix-β (1:1) is to obtain the racemate which will be utilized to determine the enantiomeric excess (ee) later. Both (*S*)- and

[50] (a) H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483-2547; (b) A. B. Zaitsev, H. Adolfsson, *Synthesis* **2006**, 1725-1756; (c) J. K. Cha, N.-S. Kim, *Chem. Rev.* **1995**, *95*, 1761-1795; (d) C. Bolm, A. Gerlach, *Eur. J. Org. Chem.* **1998**, 21-27.

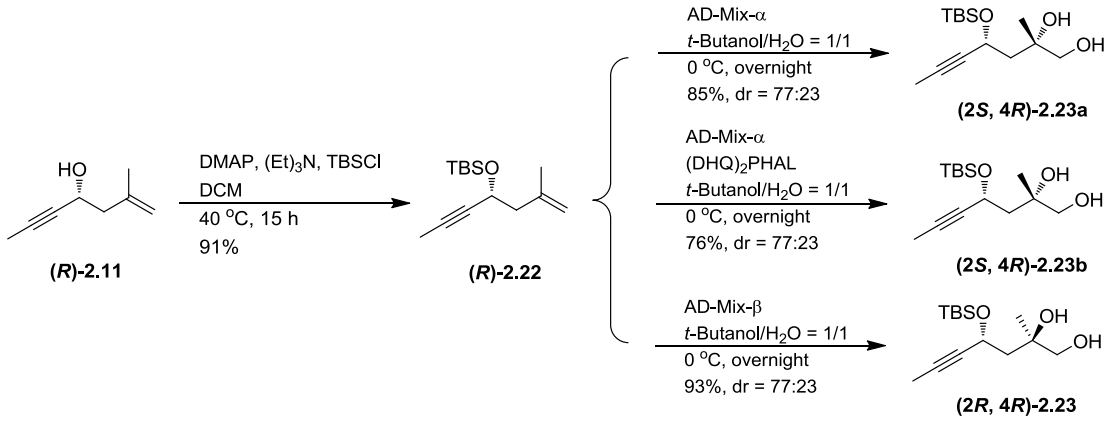
[51] D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem. Int. Ed.* **1995**, *34*, 1059-1070.

(*R*)-configured diol **2.23** are corresponding to the natural products 9α,10β-Bisangeloyloxy-agerafastin **2.1-2.3** (see Figure 2.1).



Scheme 2.8: *Sharpless* dihydroxylation of TBS-protected propargyl alcohol ***rac*-2.22**.

Secondly, started from enantiomerically pure propargyl alcohol **(*R*)-2.11, (*R*)-2.22** was obtained with very high yield of 91%. Subsequent dihydroxylation was performed by using AD-mix-α or AD-mix-β (Scheme 2.9). Additionally, AD-mix-α and 2 mol% additional ligand $(DHQ)_2PHAL$ were utilized to optimize the reaction condition for getting higher stereoselectivity. However, unfortunately, the yield was lower with the same selectivity.

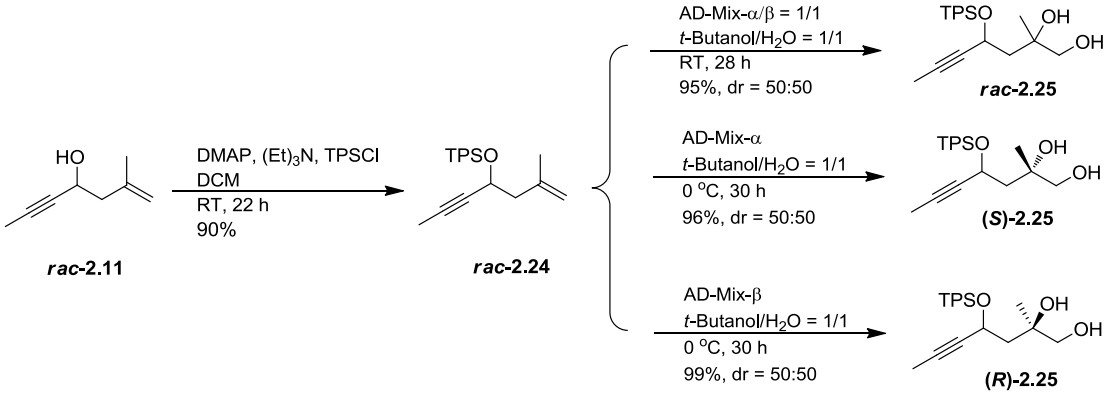


Scheme 2.9: *Sharpless* dihydroxylation of TBS-protected propargyl alcohol **(*R*)-2.22**.

Thirdly, *tert*-butyl(chloro)diphenylsilane (TPSCl)[52] was chosen as the protecting reagent for the free hydroxyl group of ***rac*-2.11** because the TPS group is much larger than a TBS group which may lead to a higher stereoselectivity of *Sharpless* dihydroxylation. As shown in Scheme 2.10, The TPS-protected alcohol ***rac*-2.24** was obtained with excellent yield (90%)

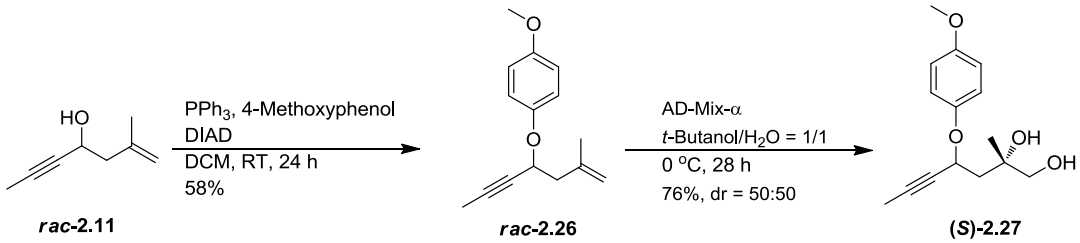
[52] H. Jullien, D. Brissy, P. Retailleau, A. Marinetti, *Eur. J. Inorg. Chem.* **2011**, 5083-5086.

from ***rac*-2.11**. The subsequent dihydroxylation proceeded with a mixture of AD-mix-α and AD-mix-β (1:1), AD-mix-α or AD-mix-β easily with excellent yields of 95%, 96% and 99%, respectively.



Scheme 2.10: *Sharpless* dihydroxylation of TBS-protected propargyl alcohol ***rac*-2.24**.

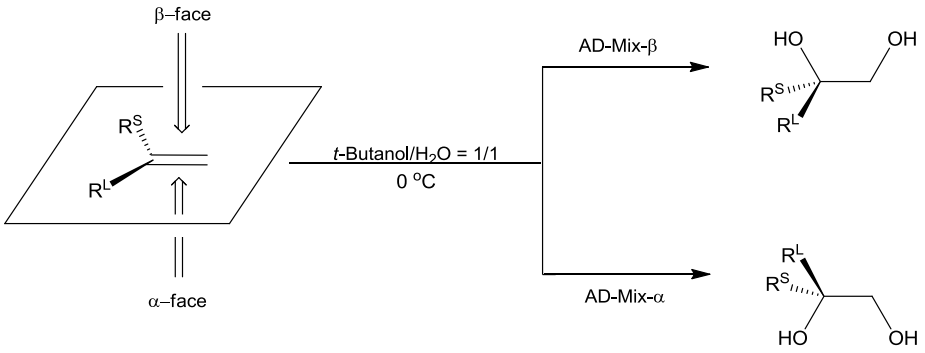
Finally, 4-methoxyphenol[53] was also chosen as protecting reagent because of a large steric hindrance and the product ***rac*-2.26** is similar to known substrates of *Sharpless* dihydroxylation which generally give excellent ee. The product ***rac*-2.26** was obtained with moderate yield of 58% by means of *Mitsunobu* reaction (Scheme 2.11). The dihydroxylation proceeded at 0 °C for 28 h to give a good yield of 76% by using AD-mix-α (Scheme 2.11).



Scheme 2.11: *Sharpless* dihydroxylation of TBS-protected propargyl alcohol ***rac*-2.26**.

The absolute configuration of the diols can be predicted by means of the mnemonic device. Taking the double bond in a plane with the smallest group R^S to the left behind and the largest group R^L to the left front, as shown in Scheme 2.12, the dihydroxylation is performed with AD-mix-β preferably from above and with AD-mix-α preferably from underneath.

[53] (a) E. J. Corey, A. Guzman-Perez, M. C. Noe, *J. Am. Chem. Soc.* **1995**, *117*, 10805-10816; (b) L. F. Tietze, J. Görlitzer, Synthesis, 1998, 873-878.

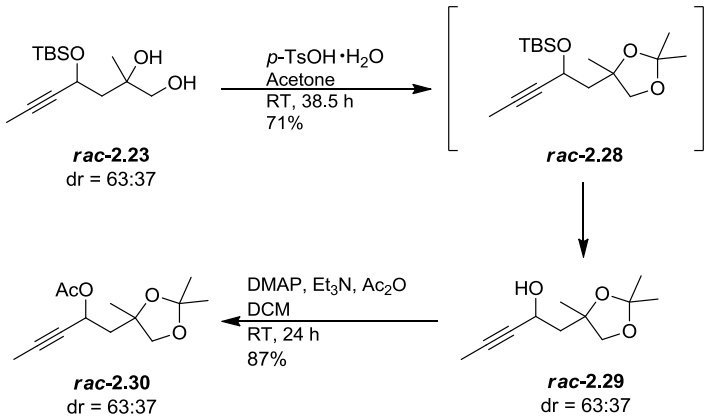


Scheme 2.12: Preferred absolute configuration of *Sharpless* dihydroxylation.

With the racemate in hand, the determination of the ee of diols **(2*S*, 4*S*)-2.21, (2*S*, 4*R*)-2.23, (2*R*, 4*R*)-2.23, (*S*)-2.23, (*R*)-2.23, (*S*)-2.25, (*R*)-2.25** and **(*S*)-2.27** was examined. However, it is impossible to separate the four diastereomers and enantiomers by Chiral GC and HPLC. Therefore, the ee analysis had to be done at a later stage.

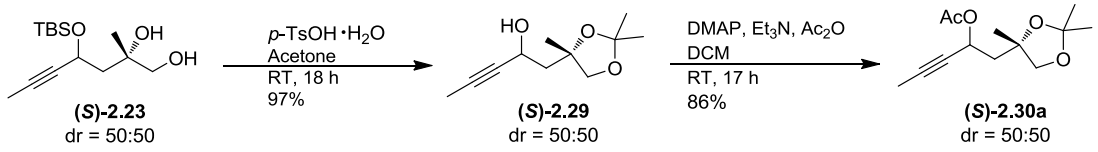
2.5 Copper-mediated S_N2'-substitution for synthesis of β-hydroxyallenes

The intermediate ***rac*-2.23** was selected to examine the following steps. The diol was reacted with acetone and *p*-toluenesulfonic acid hydrate, achieving two steps (protection of the diol and deprotection of the TBS ether), and the total yield over two steps was 71%. After esterification, the desired propargyl acetate ***rac*-2.30** was obtained with a very good yield. This could be used for the copper-mediated S_N2'-substitution to afford of β-hydroxyallenes (Scheme 2.13). However, neither ***rac*-2.29** nor ***rac*-2.30** could be analyzed by chiral GC and HPLC. Therefore, the ee analysis had to be tried at the next step.



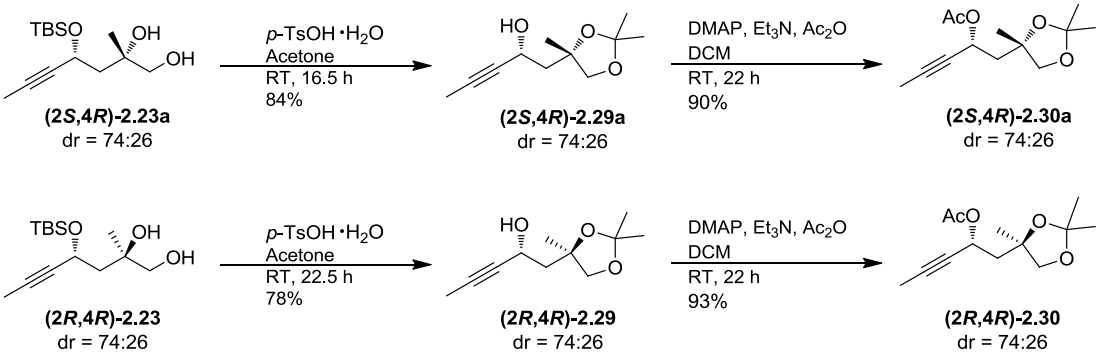
Scheme 2.13: Synthesis of propargyl acetate ***rac*-2.30**.

Furthermore, starting from **(*S*)-2.23**, the **(*S*)-2.30a** was synthesized efficiently in the same route (Scheme 2.14). And the enantiomer **(*R*)-2.30a** was also synthesized in this way in the total yield of 57%.



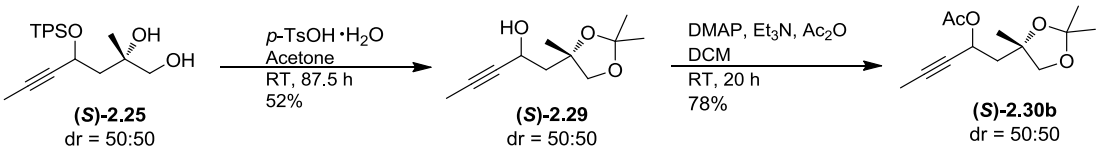
Scheme 2.14: Synthesis of propargyl acetates **(*S*)-2.30a**.

As shown in Scheme 2.15, **(2*S*,4*R*)-2.30a** and **(2*R*,4*R*)-2.30** were provided with total yield of 76% and 73%, respectively and with the same diastereomeric ratio (dr = 74:26). **(2*S*,4*R*)-2.30b** was also provided from **(2*S*,4*R*)-2.23b** in this way.



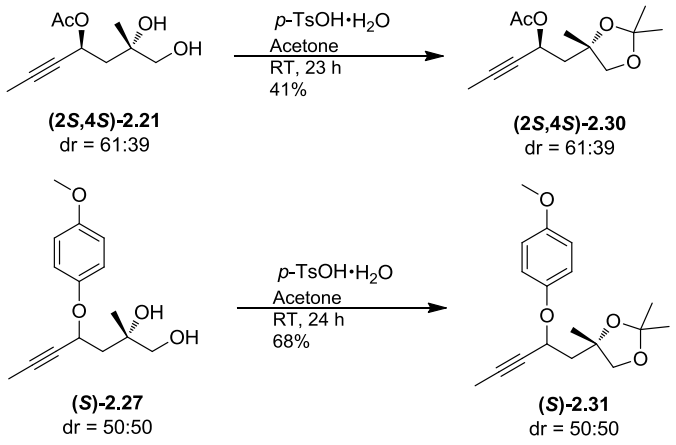
Scheme 2.15: Synthesis of propargyl acetates **(2*S*,4*R*)-2.30a** and **(2*R*,4*R*)-2.30**.

Then, through the sequence of protection/deprotection/protection, **(*S*)-2.30b** was obtained from **(*S*)-2.25**, the diol with bigger protecting group (Scheme 2.16). And the enantiomer **(*R*)-2.30b** was also synthesized in this way.



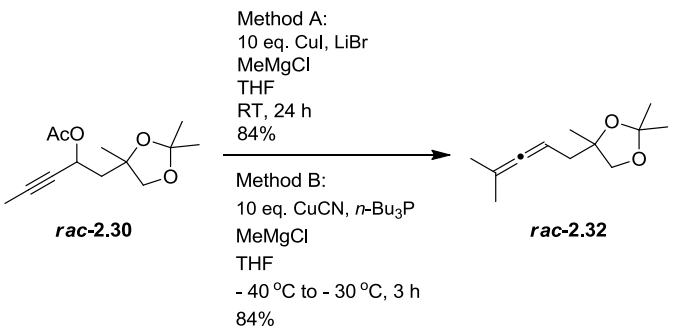
Scheme 2.16: Synthesis of propargyl acetate **(*S*)-2.30b**.

At the last, as shown in Scheme 2.17, the starting material **(2*S*,4*S*)-2.21** was reacted with acetone to get **(2*S*,4*S*)-2.30** with a moderate yield of 41%. **(*S*)-2.27** was also reacted with acetone to get **(*S*)-2.31** with a yield of 68%. Both of these two products could be used for the next step directly.



Scheme 2.17: Synthesis of propargyl acetate **(2*S*,4*S*)-2.30** and protected diol **(*S*)-2.31**.

There are two ways to perform the copper-mediated S_N2'-substitution (Scheme 2.18). In method A,[36] the β-hydroxyallene ***rac*-2.32** was obtained by S_N2'-substitution of propargyl acetate ***rac*-2.30** with the magnesium cuprate MeMgCl CuI LiBr. After being reacted for 24 h at room temperature, a very good yield 84% was obtained. In method B,[30] the magnesium cuprate was formed from MeMgCl and CuCN in the presence of tri-*n*-butylphosphine. The yield was also 84% in 3 h at -40 ℃. Both methods were strongly influenced by the reaction conditions, especially the temperature.

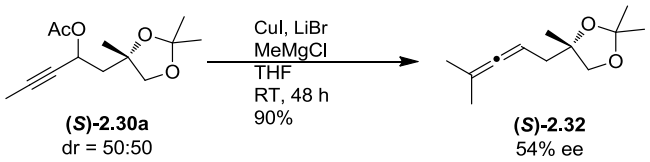


Scheme 2.18: The copper-mediated S_N2'-substitution for synthesis of β-hydroxyallene ***rac*-2.32**.

Fortunately, the enantiomers of the allene ***rac*-2.32** could be separated by both chiral GC and HPLC, which offered the opportunity to analyze the enantiomeric excess at this stage. The chirality center of the β-hydroxyallene derivatives was formed in the *Sharpless* dihydroxylation. So, according to the results of chiral GC and HPLC analysis of ***rac*-2.32**, we can conclude the optimal reaction condition for the asymmetric dihydroxylation.

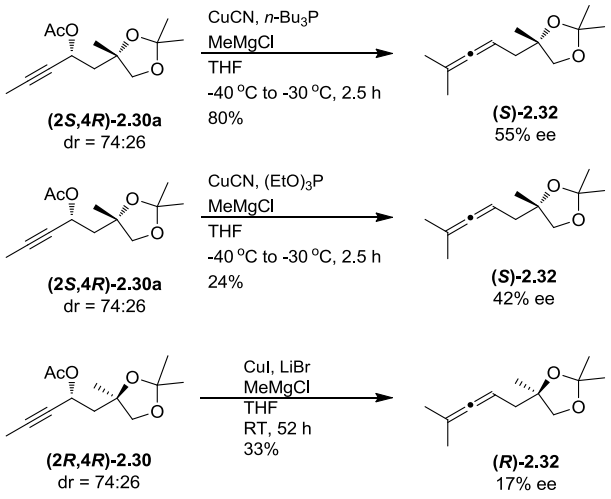
Then, the copper-mediated S_N2'-substitution of propargyl acetates **2.30** was examined with method A or method B. Firstly, for the (*S*)-configuration, the **(*S*)-2.30a** was reacted with

method A in 48 h at room temperature to afford the desired allene **(*S*)-2.32** with high yield of 90% and moderate ee of 54% (Scheme 2.19). For the (*R*)-configuration, the allene **(*R*)-2.32** (85%, 63% ee) was synthesized from **(*R*)-2.30a** by method A, too.



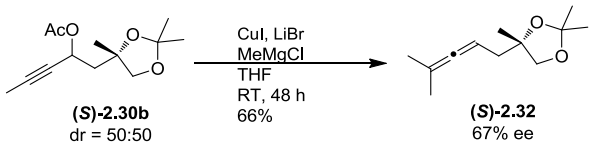
Scheme 2.19: The copper-mediated S_N2'-substitution for synthesis of β-hydroxyallene **(*S*)-2.32**.

Secondly, for the (*S*)-configuration, the method B was optimized by using different ligands (Scheme 2.20). Obviously, the tri-*n*-butylphosphine is much better than triethyl phosphite. However, the ee value was not good enough and the *Sharpless* dihydroxylation step needs to be further optimized. For the (*R*)-configuration, the method A was used to provide **(*R*)-2.32** with 33% yield and 17% ee which means **(2*R*,4*R*)-2.30** was not suitable for this copper-mediated S_N2'-substitution.



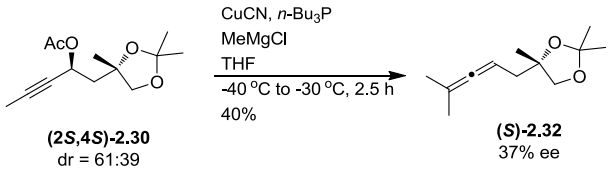
Scheme 2.20: The copper-mediated S_N2'-substitution for synthesis of β-hydroxyallenes.

After that, the S_N2'-substitution of the propargyl acetate **(*S*)-2.30b** was carried out with method A to give **(*S*)-2.32** with 66% yield and with higher ee of 67% (Scheme 2.21). The **(*R*)-2.32** was also obtained higher ee of 58%. Therefore, the bigger protecting group for the homoallylic alcohol **2.11** is better but not good enough.



Scheme 2.21: The copper-mediated S_N2'-substitution for synthesis of β-hydroxyallene **(*S*)-2.32**.

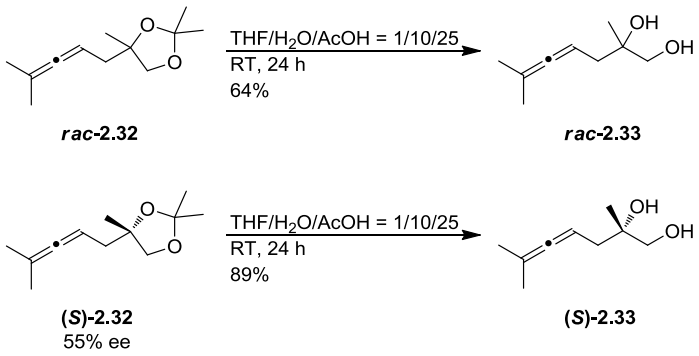
Finally, the reaction of **(2*S*,4*S*)-2.30** was performed with method B to give **(*S*)-2.32** with 40% yield and 37% ee (Scheme 2.22).



Scheme 2.22: The copper-mediated S_N2'-substitution for synthesis of β-hydroxyallene **(*S*)-2.32**.

All in all, the stereoselectivity was not improved by using protected propargyl alcohols, and the method B for copper-mediated S_N2'-substitution is more suitable and reliable. All of these ee values were not good enough and the *Sharpless* dihydroxylation needs to be further optimized.

With allenes ***rac*-2.32** and **(*S*)-2.32** the next step in the total synthesis of agerafastin was studied. Deprotection with a mixture of water, THF and acetic acid gave the β,γ-dihydroxyallene ***rac*-2.33** with a good yield 64% and the β,γ-dihydroxyallene **(*S*)-2.33** with a very good yield of 89% (Scheme 2.23).

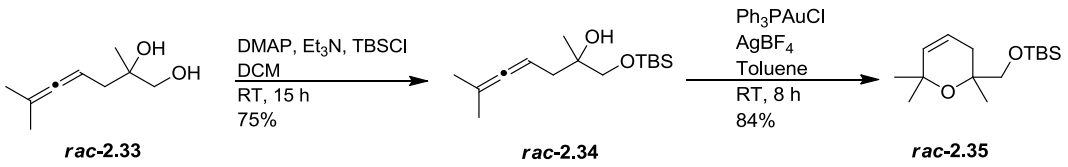


Scheme 2.23: Synthesis of β,γ-dihydroxyallene **2.33**.

2.6 Gold-catalyzed cycloisomerization

Based on our group's previous works,[39] the gold-catalyzed cycloisomerization of unprotected β,γ-dihydroxyallenes affords tetrahydrofurans instead of the desired dihydropyrans because the γ-hydroxy group attacks the activated allene at the C-4.[54]

To prevent this undesired reaction, the primary alcohol needed to be protected. The TBS group is a very good protecting group for primary alcohols in the presence of a secondary alcohol and can easily be removed. Successfully, the β-hydroxyallene ***rac*-2.34** was produced with good yield 75% (Scheme 2.24).

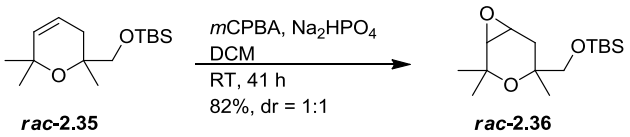


Scheme 2.24: Synthesis of dihydropyran ***rac*-2.35**.

Fortunately, the key step, gold-catalyzed cycloisomerization of β-hydroxyallene ***rac*-2.34**, was performed with 2.5 mol% of Ph_3PAuBF_4 in toluene after just eight hours with a very good yield of 84% to get the desired dihydropyran ***rac*-2.35** in gram scale efficiently (Scheme 2.24).

2.7 Epoxidation of dihydropyran for synthesis of tetrahydropyran

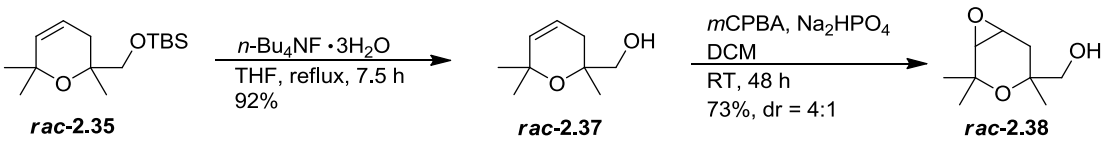
The epoxidation of dihydropyran ***rac*-2.35** was performed with 2 equivalents of *m*CPBA and Na_2HPO_4 for 41 hours at room temperature to give the product tetrahydropyran ***rac*-2.36** in good yield of 82%. However, the diastereomeric ratio (dr) was only 1:1 (analyzed by NMR spectroscopy) (Scheme 2.25).



Scheme 2.25: Synthesis of tetrahydropyran ***rac*-2.36**.

[54] (a) Z. Zhang, C. Liu, R. E. Kinder, X. Han, H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2006**, *128*, 9066-9073; (b) Z. Zhang, R. A. Widenhoefer, *Angew. Chem. Int. Ed.* **2007**, *46*, 283-285; c) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496-499.

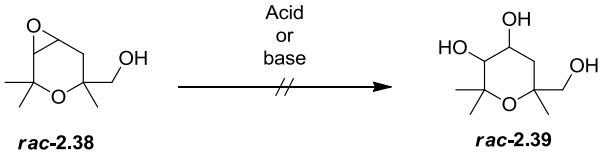
The free hydroxyl group should have a positive effect in the epoxidation selectivity because of hydroxyl group directivity.[55] Therefore, the TBS protecting group was removed by using tetrabutylammonium fluoride trihydrate to afford ***rac*-2.37** with excellent yield of 92%. By epoxidation, the tetrahydropyran ***rac*-2.38** was formed with good yield of 73% and good dr (4:1) (Scheme 2.26). The amount of *m*CPBA and temperature were optimized as well as the additive Na_2HPO_4. In the end, 2 equivalents of *m*CPBA and Na_2HPO_4 were the best. The epoxidation with $VO(acac)_2$ and TBHP[56] was also tried but was very slow.



Scheme 2.26: Synthesis of tetrahydropyran ***rac*-2.38**.

2.8 Ring opening of epoxide

With the tetrahydropyran ***rac*-2.38** in hand, opening the epoxide ring was studied. At the beginning, different acids and bases[57-61] in water were tested to synthesize ***rac*-2.39**. Unfortunately, all attempts were failed (Scheme 2.27). It is possible that the epoxide bearing the free hydroxyl group forms a hydrogen bond which makes the molecule very stable.



Scheme 2.27: Synthesis of triol ***rac*-2.39**.

[55] W. Adam, T. Wirth, *Acc. Chem. Res.* **1999**, *32*, 703-710.

[56] G. Torres, W. Torres, J. A. Prieto, *Tetrahedron* **2004**, *60*, 10245-10251.

[57] G. Mehta, S. Sen, S. S. Ramesh, *Eur. J. Org. Chem.* **2007**, 423-436.

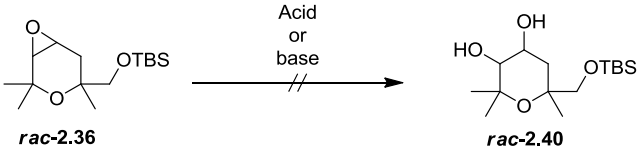
[58] A. Guaragna, D. D'Alonzo, C. Paolella, C. Napolitano, G. Palumbo, *J. Org. Chem.* **2010**, *75*, 3558-3568.

[59] C. J. Bartlett, D. P. Day, Y. Chan, S. M. Allin, M. J. McKenzie, A. M. Z. Slawin, P. C. B. Page, *J. Org. Chem.* **2012**, *77*, 772-774.

[60] B. Schmidt, *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 2627-2637.

[61] P. C. B. Page, L. F. Appleby, D. Day, Y. Chan, B. R. Buckley, S. M. Allin, M. J. McKenzie, *Org. Lett.* **2009**, *9*, 1991-1993.

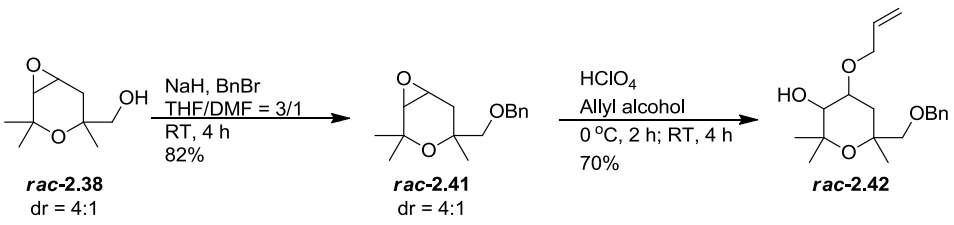
Next, epoxide ***rac*-2.36** with a TBS protecting group was treated with different acids and bases. The starting material ***rac*-2.36** was decomposed without formation of the desired product ***rac*-2.40** (Scheme 2.28). Using acids or bases to open the epoxide ring is impossible because the epoxide ring is very stable. Therefore, much harsher reaction conditions were tested.



***rac*-2.36** ***rac*-2.40**

Scheme 2.28: Synthesis of diol ***rac*-2.40**.

After optimization, a protection of the free hydroxy group of the tetrahydropyran ***rac*-2.38** was performed with NaH and BnBr in THF/DMF (3:1)[62-65] at room temperature for 4 hours to give ***rac*-2.41** in good yield of 82%. Next, a S_N2-substitution was carried out with allyl alcohol and 5 equivalents of $HClO_4$[66] to give ***rac*-2.42** with good yield of 70% (Scheme 2.29). Interestingly, the allyl alcohol only reacted with the major diastereomer so that it is possible to obtain diastero- and enantiomerically pure tetrahydropyran **2.42** later. Only one regioisomer was obtained, probably by S_N2-substitution at the sterically less hinded position of epoxide ***rac*-2.41**.



***rac*-2.38** dr = 4:1 ***rac*-2.41** dr = 4:1 ***rac*-2.42**

Scheme 2.29: Synthesis of the tetrahydropyran ***rac*-2.42**.

With such a positive result in hand, the deprotection of the allyl and benzyl ether could be done in a stepwise way. First, the cleavage of the allyl ether with $PdCl_2$ in $MeOH/CH_2Cl_2$ (3:2) was performed at room temperature for 40 minutes without further purification and the

[62] B. M. Trost,.D. B. Horne, M. J. Woltering, *Angew. Chem. Int. Ed.* **2003**, *42*, 5987-5990.

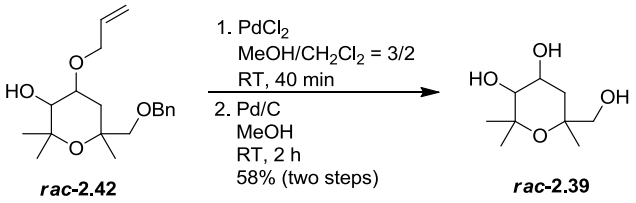
[63] N. Berezina, V. Alphand, R. Furstoss, *Tetrahedron: Asymmetry* **2002**, *13*, 1953-1955.

[64] H. Onoue, T. Baba, K. Konoki, K. Torikai, M. Ebine, T. Oishi, *Chem. Lett.* **2014**, *43*, 1904-1906.

[65] M. Hirama, T. Oishi, H. Uehara, M. Inoue, M. Maruyama, H. Oguri, M. Satake, *Science* **2001**, *294*, 1904-1907.

[66] C. M. Ko1nig, K. Harms, U. Koert, *Org. Lett.* **2007**, *23*, 4777-4779.

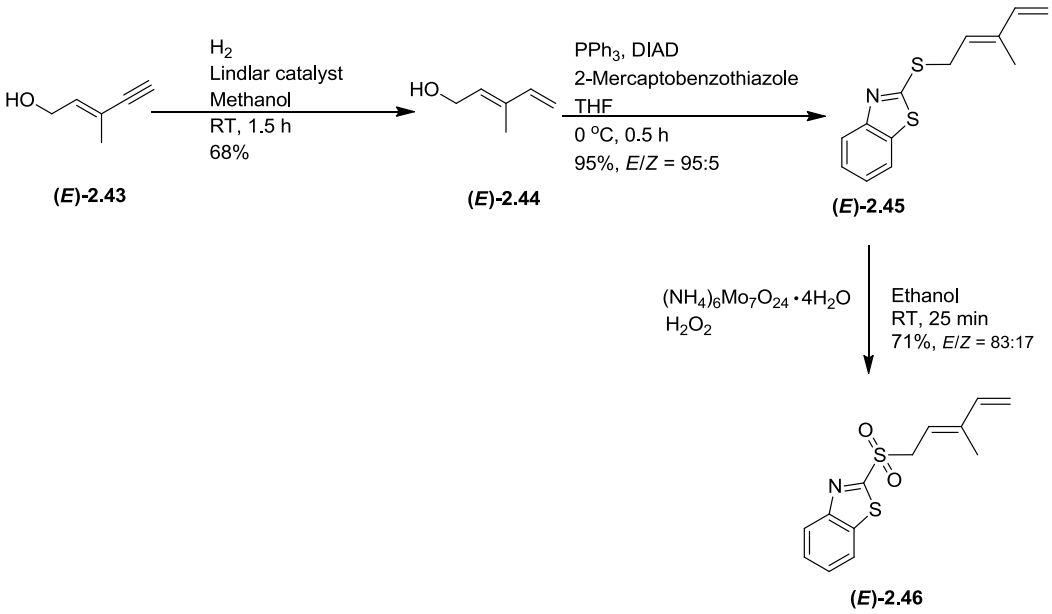
product was used directly in the next step. Second, hydrogenolysis of the benzyl ether gave the target molecule ***rac*-2.39** in 58% yield over two steps[66] (Scheme 2.30).



Scheme 2.30: Synthesis of the triol ***rac*-2.42**.

2.9 Synthesis of the side chain

After opening the epoxide ring successfully, the total synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin **2.2** was nearly reached the final stage. Next, sulfone **(*E*)-2.46** was synthesized to introduce the side chain of the target molecule through modified *Julia* olefination.



Scheme 2.31: Synthesis of the sulfone **(*E*)-2.46**.

The dienol **(*E*)-2.44** was obtained by partial hydrogenation of the enynol **(*E*)-2.43** with molecular hydrogen and *Lindlar* catalyst ($Pd/CaCO_3$, $Pd(OCOCH_3)_2$)[67] with a good yield of 68%. To prevent over-reduction, the reaction was monitored by gas chromatography. After

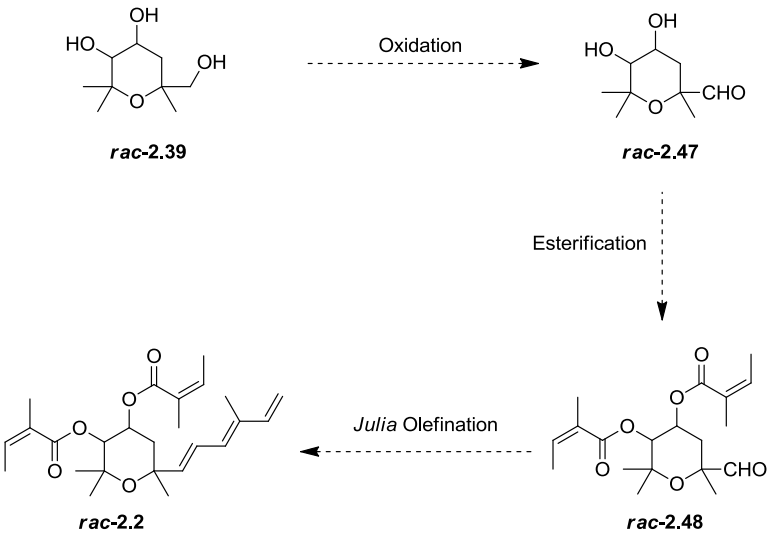
[67] K. A. Parker, I. A. Katsoulis, *Org. Lett.* **2004**, *9*, 1413-1416.

complete reduction of the triple bond, the reaction was terminated by removing the catalyst through filtration. Subsequent *Mitsunobu* reaction produced **(*E*)-2.45** with excellent yield of 95% and an *E*/*Z*-ratio of 95:5. The desired sulfone **(*E*)-2.45** was oxidized with ammoniummolybdate and hydrogen peroxide as co-oxidant to provide **(*E*)-2.46** with a good yield of 71% (Scheme 2.31). Interestingly, the product was obtained with *E*/*Z*-ratio of 83:17, which indicates a partial *E*/*Z*-isomerization during the oxidation.

2.10 Synthesis of racemic 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin

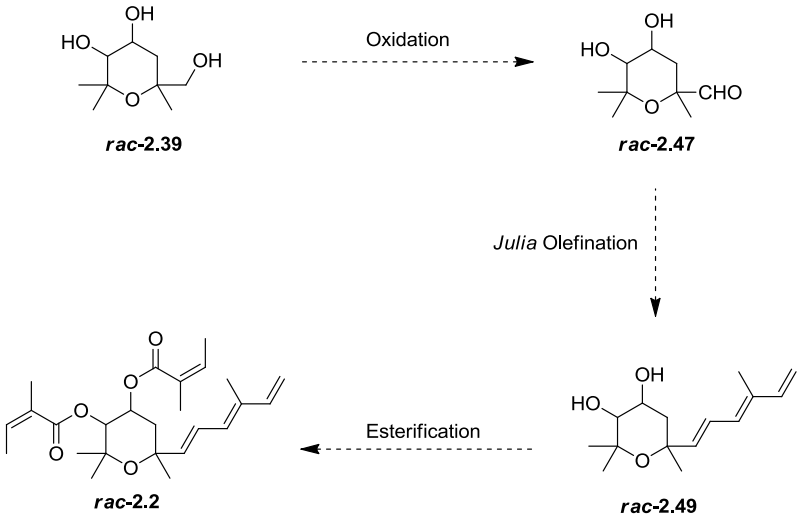
With the positive results obtained through the journey, there were different ways to reach the racemic target molecules. If starting from ***rac*-2.39**, there would be two possible routes for the synthesis of ***rac*-2.2**.

In route 1, the strategy is first to perform a selective oxidation of primary alcohol to provide ***rac*-2.47** with esterification and *Julia* olefination following to achieve the final molecule ***rac*-2.2** (Scheme 2.32). However, the first problem is the selective oxidation of the primary alcohol to provide ***rac*-2.47**, which is not easy to realize because it may be necessary to protect the secondary hydroxy groups first. Then, the second problem for this route was the esterification. Possibly, the aldehyde group has to be protected to prevent it from interfering the esterification. Then, the protecting group needs to be removed later. The route appears to be very time-consuming.



Scheme 2.32: Route 1 for snthesis of ***rac*-2.2**.

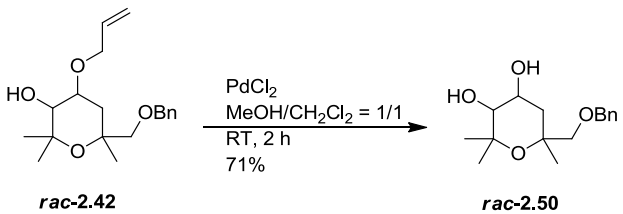
In route 2, the first step was the same to the route 1, the selective oxidation of the primary alcohol to provide ***rac*-2.47**. Then the *Julia* olefination could be performed with **(*E*)-2.46** to provide ***rac*-2.49** with esterification following to afford ***rac*-2.2**. However, besides the same problem like in the route 1 for the oxidation, the another problem could be the final esterification because of a strong steric hindrance of the side chain (Scheme 2.33).



Scheme 2.33: Route 2 for snthesis of ***rac*-2.2**.

Overall, triol ***rac*-2.39** appears to be unsuitable for an efficient synthesis of the natural product.

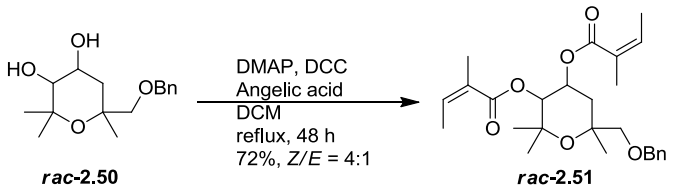
Consequently, ***rac*-2.42** was chosen as a starting material for the next stage. The allyl group of ***rac*-2.42** was removed while keeping the benzyl ether intact. After optimization, the best reaction conditions for the cleavage of the allyl ether was using 0.1 equivalents of $PdCl_2$ in $MeOH/CH_2Cl_2$ (1:1) to give the diol ***rac*-2.50** in a good yield of 71% after two hours at room temperature (Scheme 2.34).



Scheme 2.34: Synthesis of the diol ***rac*-2.50**.

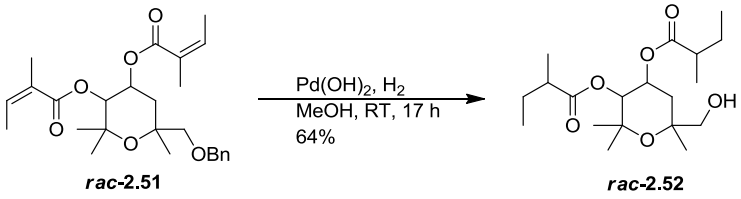
[68] (a) K. S. Feldman, M. D. Lawlor, *J. Am. Chem. Soc.* **2000**, *122*, 7396-7397; (b) T. Wakabayashi, K. Mori, S. Kobayashi, *J. Am. Chem. Soc.* **2001,** *123*, 1372-1375.

After that, the ester ***rac*-2.51** was formed by *Steglich* esterification[68] with 4 equivalents of angelic acid and DCC as well as 2 equivalents of DMAP at reflux for 48 hours with good yield of 72% and good *Z/E* ratio (4:1). Since the *Z*-configured angelic acid can isomerize to the *E*-configured tiglic acid easily during the reaction, it is hard to obtain pure *Z*-configured ester ***rac*-2.51**. It may be possible to make the reaction time shorter for getting higher *Z*/*E* ratio (Scheme 2.35).



Scheme 2.35: Synthesis of the ester ***rac*-2.51**.

Next, the benzyl ether needed to be removed for the final stage of the total synthesis of ***rac*-2.2**. Firstly, the hydrogenolysis of the benzyl ether ***rac*-2.51** was examined with $Pd(OH)_2$ under hydrogen atmosphere. Instead of the desired product, the over-reduced[69] product ***rac*-2.52** was obtained with moderate yield of 64% (Scheme 2.36).



Scheme 2.36: Hydrogenolysis of the benzyl ether ***rac*-2.51**.

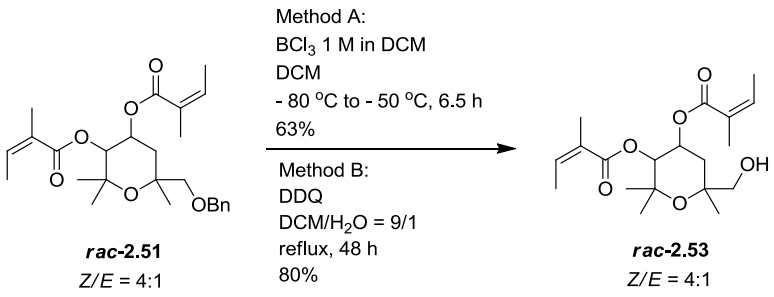
Secondly, for the deprotection of the benzyl group, boron trichloride (BCl_3)[70] (1 M in CH_2Cl_2) was utilized to provide the desired product ***rac*-2.53** with moderate yield of 63% (Scheme 2.37). However, this method was not easy to handle because the BCl_3 is very moisture sensitive and active so that the reaction can easily fail. At the same time, DDQ[71] was selected to try this reaction, too. With the optimized reaction condition, DDQ in the mixed solvent DCM/H_2O (9:1) gave ***rac*-2.53** with a better yield of 80% and a good *Z/E* ratio

[69] A. Fürstner, F. Jeanjean, P. Razon, *Angew. Chem. Int. Ed.* **2002**, *41*, 2097-2101.

[70] D. L. Sloman, J. W. Bacon, J. A. Porco, *J. Am. Chem. Soc.* **2011**, *133*, 9952-9955.

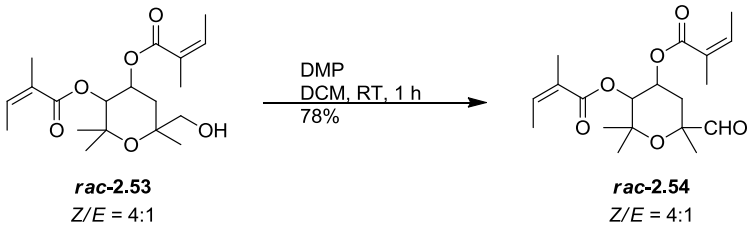
[71] (a) S. Baek, H. Jo, H. Kim, H. Kim, S. Kim, D. Kim, *Org. Lett.* **2005**, *1*, 75-77; (b) D. Crich, O. Vinogradova, *J. Org. Chem.* **2007**, *72*, 3581-3584.

(4:1) (Scheme 2.37). The *E*/*Z*-isomers could be separated by column chromatography. However, for the racemic synthesis of 9α,10β-Bisangeloyloxy-7-epi-3*E*-agerafastin, the mixture was used for the next step directly. They would be separated for the enantioselective synthesis of 9α,10β-Bisangeloyloxy-7-epi-3*E*-agerafastin later.



Scheme 2.37: Synthesis of the alcohol ***rac*-2.53**.

After synthesizing ***rac*-2.53** successfully, the oxidation proceeded efficiently by using Dess-Martin periodinane (DMP)[72] in DCM for one hour at room temperature to give the desired aldehyde ***rac*-2.54** with a good yield of 78% (Scheme 2.38).



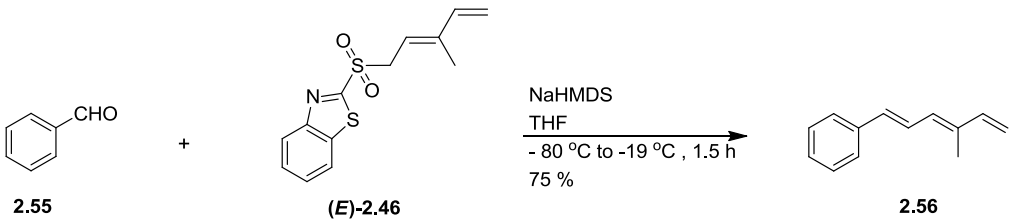
Scheme 2.38: Synthesis of the aldehyde ***rac*-2.54**.

Finally, the last step of the racemic synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin, the *Julia* olefination, was reached. Although the modified *Julia* olefination[73] is very promising for the implementation of the reaction of conjugated diene **(*E*)-2.46** with the natural product precursor ***rac*-2.54**, a test reaction was carried out with the sulfone **(*E*)-2.46** and benzaldehyde **2.55**. The procedure was as follows. At first, the sulfone **(*E*)-2.46** and benzaldehyde **2.55** were mixed together. Then, sodium bis(trimethylsilyl)amide (NaHMDS) was added to deprotonate the sulfone **(*E*)-2.46** at -80 ℃ (Scheme 2.39). After warming up to

[72] K. C. Nicolaou, C. J. N. Mathison, *Angew. Chem. Int. Ed.* **2005**, *44*, 5992-5997.

[73] (a) A. B. Charette, H. Lebel, *J. Am. Chem. Soc.* **1996**, *118*, 10327-10328; (b) S. Das, D. Paul, R. K. Goswami, *Org. Lett.* **2016**, *18*, 1908-1911.

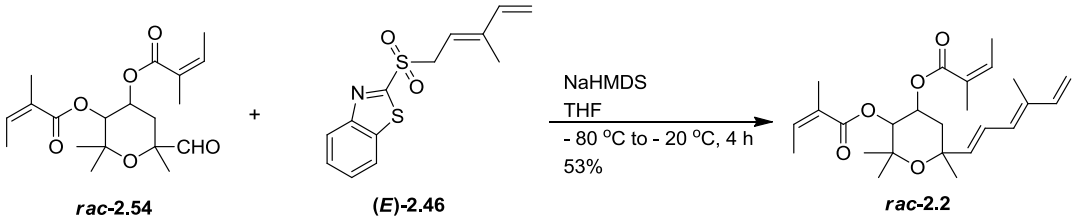
-19 ℃ for 1.5 hours, the desired triene **2.56** was isolated (75%). However, the analysis of *E*/*Z*-isomer ratio by ^{1}H-NMR spectroscopy could not be achieved.



2.55 **(*E*)-2.46** **2.56**

Scheme 2.39: The test of *Julia* olefination.

Since the reaction was successful, an analogous reaction with the aldehyde ***rac*-2.54** was performed. After using the similar procedure like the test reaction, only 21% of the desired product was obtained, so the reaction needs further optimization. A new procedure was that the sulfone **(*E*)-2.46** was deprotonated with NaHMDS at -80 ℃ for 30 minutes before the aldehyde ***rac*-2.54** was added (Scheme 2.40). After warming to -20 °C for 4 hours, the desired product ***rac*-2.2** was obtained with a much higher yield of 53%. However the *E*/*Z*-isomer ratio could not be determined because the aldehyde ***rac*-2.54** was used as 4:1-mixture of diasteroisomers and the sulfone **(*E*)-2.46** as *E*/*Z*-mixture (83:17).



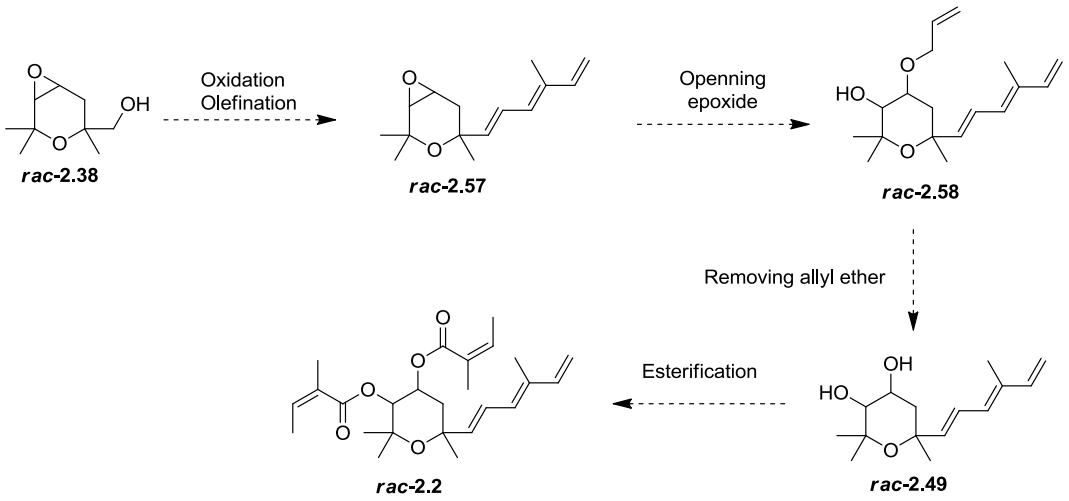
***rac*-2.54** **(*E*)-2.46** ***rac*-2.2**

Scheme 2.40: The *Julia* olefination for synthesis of ***rac*-2.2**.

With the racemic target ***rac*-2.2** in hand, the synthesis route starting from **2.15** proved to be suitable. However, the longest linear route is 19 steps which is very long journey.

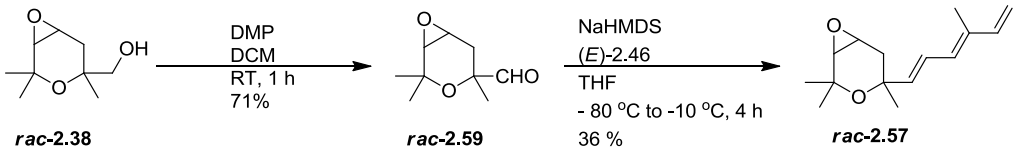
Based on previous works,[39] triene ***rac*-2.57** could be synthesized from the tetrahydropyran ***rac*-2.38** through oxidation and *Julia* olefination. However, it was impossible to open the epoxide ring of the triene ***rac*-2.57** by using a variety of acids and bases to produce diol ***rac*-2.49**. Rather, an efficient method for the stereo- and regioselective epoxide opening with allyl alcohol was applied to open the epoxide ***rac*-2.41**. If this method could be also used for ***rac*-2.57** to obtain ***rac*-2.58**, a shorter synthesis route would be possible. As shown in Scheme 2.41, after synthesizing ***rac*-2.58**, the diol ***rac*-2.49** should be available by removing the allyl group. With the esterification following, the final target ***rac*-2.2** could be obtained. And the

longest linear route is 17 steps in this synthesis route which is two steps shorter than the previous successful synthetic route.



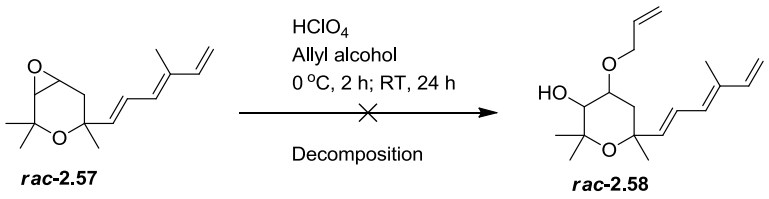
Scheme 2.41: Route 3 for snthesis of ***rac*-2.2**.

Therefore, this synthesis route was tested. Starting from epoxide ***rac*-2.38**, the oxidation proceeded with DMP to give aldehyde ***rac*-2.59 (**71%). By adding ***rac*-2.59** and **(*E*)-2.46** with NaHMDS, the desired product triens ***rac*-2.57** was obtained with moderate yield (36%) (Scheme 2.42).



Scheme 2.42: Snthesis of triens ***rac*-2.57**.

After synthesizing ***rac*-2.57** successfully, the stereo- and regioselective epoxide opening with allyl alcohol was tried (Scheme 2.43). The S_N2-substitution was carried out with allyl alcohol and 2 equivalents of $HClO_4$. Unfortunately, this time a low conversion was observed and the starting material was completely decomposed in one day. As a result, this synthesis route was not working so that the 19 linear steps synthesis route is the best way to obtain racemic 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin.



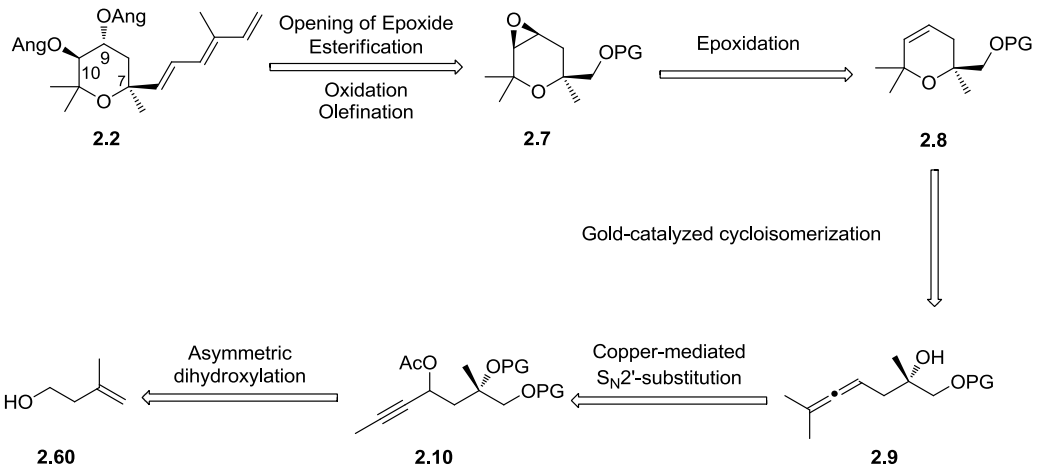
Scheme 2.43: Snthesis of the tetrahydropyran ***rac*-2.58**.

2.11 Retrosynthetic analysis II

There are three chiral carbon centers in the natural product 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin. Chirality centers at C-9 and C-10 were fixed in the diastereoselective epoxidation which is controlled by the free side hydroxy group. The third chirality center at C-7 was controlled by the *Sharpless* dihydroxylation.

If a similar synthetic route to the racemic version were chosen for the enantioselective synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin **2.2**, the epoxidation would proceed with a good yield 73% and good dr (4:1). For the *Sharpless* dihydroxylation, different protecting groups and reaction conditions were optimized. Unfortunately, the best ee value of **(*S*)-2.32-5** obtained from the dihydroxylation was only 67% ((*S*)-configuration). Therefore, a new substrate needs to be selected to perform the *Sharpless* dihydroxylation.

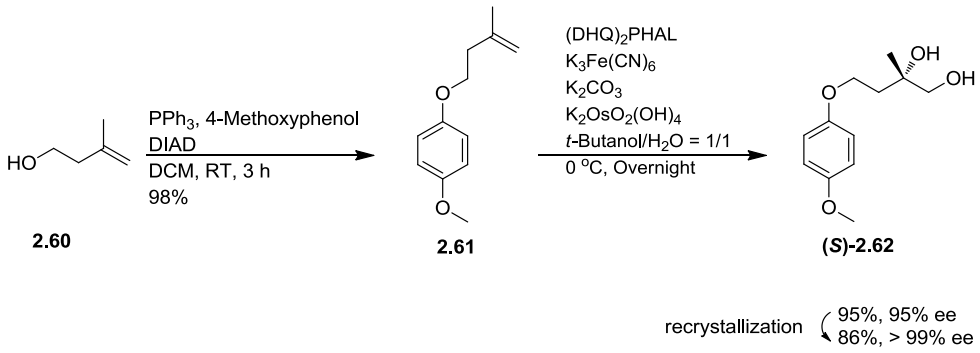
As shown in scheme 2.44, a new retrosynthesis was designed. Again, 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin **2.2** was selected as the target for our total synthesis. The key steps were similar to retrosynthesis **I**, such as opening of epoxide, esterification, olefination, gold-catalyzed cycloisomerization and copper-mediated S_N2'-substitution. The different part is the synthesis of propargyl acetate **2.10** by *Sharpless* dihydroxylation starting from homoallyl alcohol **2.60**.



Scheme 2.44: Retrosynthesis II of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin **2.2**.

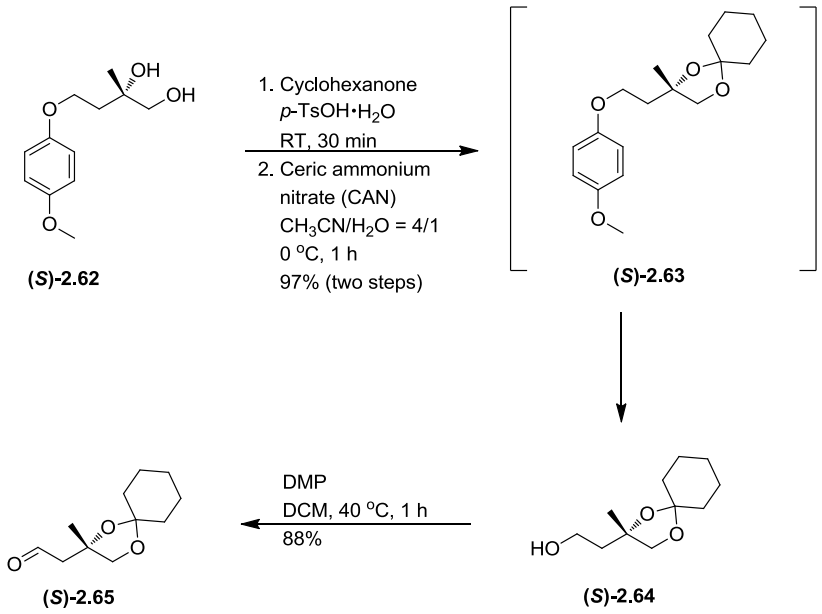
2.12 Enantioselective synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin

Our approach to enantiomerically pure 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin **2.2** started with the formation of the protected homoallylic alcohol **2.61**[53] by *Mitsunobu* reaction of the homoallyl alcohol **2.60** with 4-methoxyphenol, triphenylphosphine and DIAD, which afforded **2.61** with excellent yield of 98% in ten-gram scale. Next, the *Sharpless* dihydroxylation was performed with respective addition of reagents from AD-mix-α to provide diol **(*S*)-2.62** with excellent yield 95% and 95% ee (***rac*-2.62**: 89%). After a single recrystallization, enantiomerically pure diol **(*S*)-2.62** was obtained with high yield (Scheme 2.45).



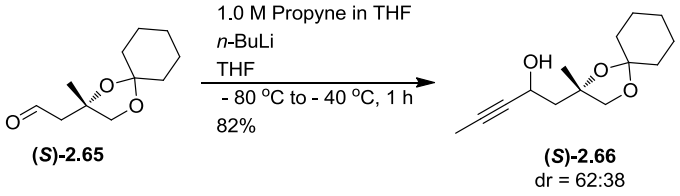
Scheme 2.45: Snthesis of the diol **(*S*)-2.62**.

The enantiomerically pure diol **(*S*)-2.62** was converted into alcohol **(*S*)-2.64** by ketalization with cyclohexanone and oxidative cleavage of the protecting group with very high yield of 97% in two steps[36,74] (***rac*-2.64**: 79%) (Scheme 2.46). Oxidation of **(*S*)-2.64** with *Dess-Martin* periodinane (DMP) produced the aldehyde **(*S*)-2.65** in high yield of 88% in one hour (***rac*-2.65:** 73%) (Scheme 2.46).



Scheme 2.46: Snthesis of the aldehyde **(*S*)-2.65**.

The significant step for preparing the propargyl alcohol **(*S*)-2.66**, an important intermediate for this synthesis plan, followed. Propyne (1.0 M in THF) was deprotonated with *n*-BuLi at -80 °C under argon for 30 min before the aldehyde **(*S*)-2.65** was added to give the propargyl alcohol **(*S*)-2.66** in 82% yield[75] (***rac*-2.66**: 64%) (Scheme 2.47).



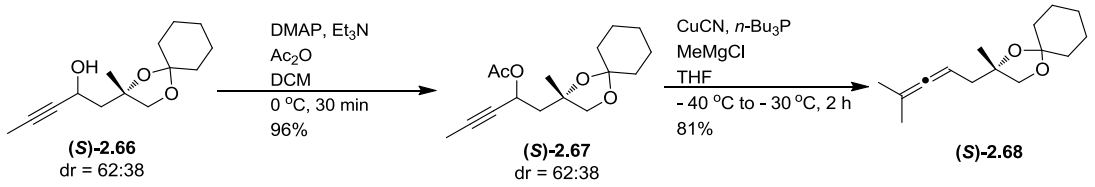
Scheme 2.47: Snthesis of the propargyl alcohol **(*S*)-2.66**.

The propargyl alcohol **(*S*)-2.66** was converted in excellent yield (96%) into the propargyl acetate **(*S*)-2.67** by acetylation with Ac_2O (***rac*-2.67**: 82%). Then, the allene **(*S*)-2.68** was

[74] M. Shimizu, M. Kimura, T. Watanabe, Y. Tamaru, *Org. Lett.* **2005**, *4*, 637-640.

[75] D. E. Frantz, R. F ässler, C. S. Tomooka, E. M. Carreira, *Acc. Chem. Res.* **2000**, *33*, 373-381.

synthesized by means of the copper-mediated S_N2'-substitution of propargyl acetate **(*S*)-2.67** with a magnesium cuprate formed from MeMgCl and CuCN in the presence of tri-*n*-butylphosphine to afford a good yield of 81% (***rac*-2.68**: 97%) (Scheme 2.48). The racemic allene **2.68** could not be separated by chiral GC or HPLC.



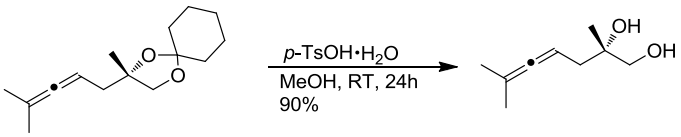
(*S*)-2.66
dr = 62:38

(*S*)-2.67
dr = 62:38

(*S*)-2.68

Scheme 2.48: The copper-mediated S_N2'-substitution for synthesis of allene **(*S*)-2.68**.

Instead of a mixture of water, THF and acetic acid, *p*-toluenesulfonic acid hydrate was used in methanol for the acetal cleavage to give diol **(*S*)-2.33** with high yield of 90% (***rac*-2.33**: 76%) (Scheme 2.49).

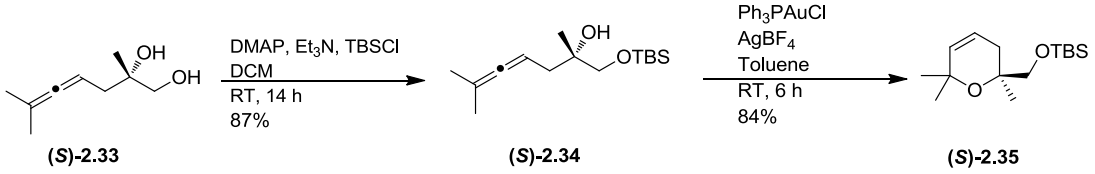


(*S*)-2.68

(*S*)-2.33

Scheme 2.49: Synthesis of the β,γ-dihydroxyallene **(*S*)-2.33**.

It was necessary to protect the primary alcohol of **(*S*)-2.33** before synthesizing the desired dihydropyran **(*S*)-2.35** because otherwise undesired the tetrahydrofuran would be produced. The β-hydroxyallene **(*S*)-2.34** was obtained by using TBS as protecting group with high yield of 87%. Subsequent gold-catalyzed cycloisomerization of β-hydroxyallene **(*S*)-2.34** was performed with 2.5 mol% Ph_3PAuBF_4 in toluene to give the desired dihydropyran **(*S*)-2.35** in good yield of 84% in grams scale (Scheme 2.50). Fortunately, ***rac*-2.35** could be separated by chiral GC so that the ee value of **(*S*)-2.35** was measured. This was over 99% so that there was no loss of enantiomeric excess through the steps from **(*S*)-2.62**.



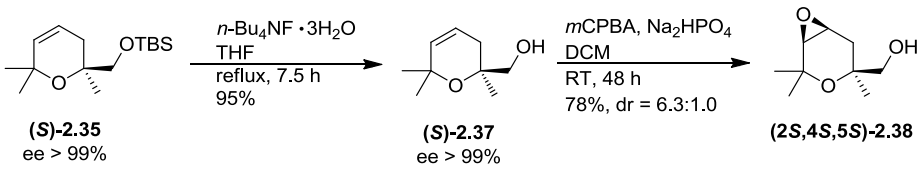
(*S*)-2.33

(*S*)-2.34

(*S*)-2.35
ee > 99%

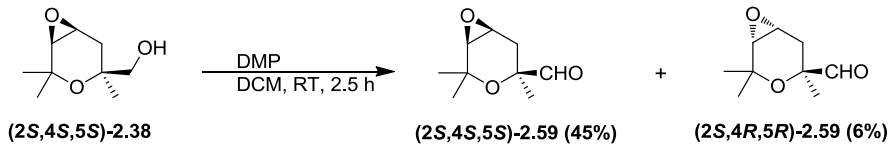
Scheme 2.50: Synthesis of the dihydropyran **(*S*)-2.35**.

The TBS protecting group was removed by using tetrabutylammonium fluoride trihydrate so that the free hydroxyl group would direct the epoxidation. The following deprotection provided enantiomerically pure **(*S*)-2.37** with excellent yield of 95%. With the epoxidation the tetrahydropyran **(*S*,*S*,*S*)-2.38** was obtained with good yield of 78% and good selectivity (dr = 6.3:1.0) (Scheme 2.51). However, the two isomers could not be separated by column chromatography, and the relative configuration of the major isomer could not be assigned at this stage.



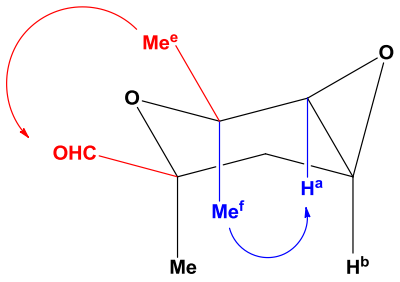
Scheme 2.51: Synthesis of the tetrahydropyran **(*S*,*S*,*S*)-2.38**.

Next, **(2*S*,4*S*,5*S*)-2.38** was oxidized with *Dess-Martin* periodinane to give **(2*S*,4*S*,5*S*)-2.59** in an isolated yield of 45% and **(2*S*,4*R*,5*R*)-2.59** in an isolated yield of 6% (Scheme 2.52).



Scheme 2.52: Synthesis of the tetrahydropyran **(2*S*,4*S*,5*S*)-2.59**.

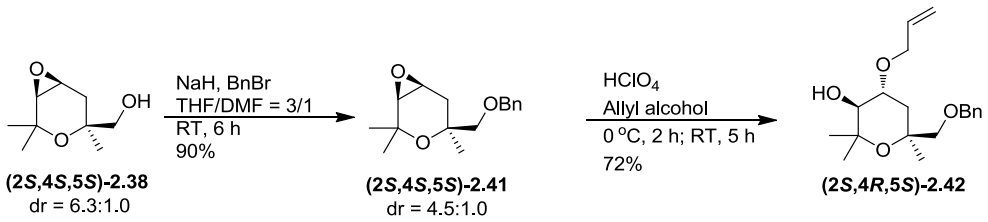
Since the two diastereoisomers of **2.59** could be separated by column chromatography, the relative configuration could be determined by NOESY (Figure 2.3). In the NOESY spectrum of the main diastereoisomer **(2*S*,4*S*,5*S*)-2.59**, the aldehyde proton signal (δ = 9.60) correlated with the Me^e protons signal (δ = 1.43), and the Me^f protons signal (δ = 1.34) correlated with the H^a signal (δ = 2.99), respectively. This proves that the carbonyl group and the epoxide are on the same side of the six-membered ring and also proved that the free hydroxy group of the main diastereoisomer of **(2*S*,4*S*,5*S*)-2.38** was also on the same side with the epoxide.



(2*S*,4*S*,5*S*)-2.59

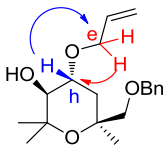
Figure 2.3: Key NOESY correlations of **(2*S*,4*S*,5*S*)-2.59**.

Combining this information with the configuration predicted by the *Sharpless* dihydroxylation, the absolute configuration of the intermediate **2.38** was determined to be (2*S*,4*S*,5*S*). Then, protected tetrahydropyran **(2*S*,4*S*,5*S*)-2.41** was synthesized with excellent yield of 90% and a good diastereoisomer ratio of 4.5:1.0. Subsequent ring opening of epoxide **(2*S*,4*S*,5*S*)-2.41** proceeded by using allyl alcohol and 5 equivalents of $HClO_4$ to afford enantiomerically and diastereomerically pure tetrahydropyran **(2*S*,4*R*,5*S*)-2.42** with good yield because the allyl alcohol only reacted with the major isomer of **(2*S*,4*S*,5*S*)-2.41** (Scheme 2.53).



Scheme 2.53: Synthesis of the tetrahydropyran **(2*S*,4*R*,5*S*)-2.42**.

The nucleophile allyl alcohol should preferably attack the less hindered carbon (C-4), so that the relative configuration of the tetrahydropyran **(2*S*,4*R*,5*S*)-2.42** accorded with the natural product **2.2**. The 2D NMR spectrum of the enantiomerically pure tetrahydropyran **(2*S*,4*R*,5*S*)-2.42** was measured. In the HMBC spectrum of **(2*S*,4*R*,5*S*)-2.42** (Figure 2.4), both protons **e** signals (δ = 3.92 and δ = 4.10) correlated with the carbon **h** signal (δ = 75.7), while proton **h** signal (δ = 3.52) correlated with carbon **e** signal (δ = 69.9). This illustrates that the allyl alcohol attacked the C-4 position and the desired **(2*S*,4*R*,5*S*)-2.42** was obtained. This result suggests that the absolute configuration can be expected to be (2*S*,4*R*,5*S*) as shown in Figure 2.4.

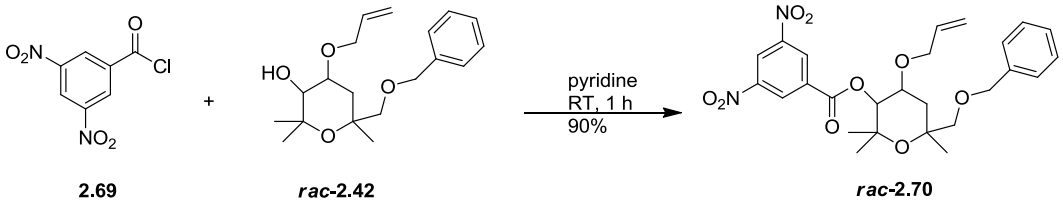


(2*S*,4*R*,5*S*)-2.42

Figure 2.4: Key HMBC correlations of **(2*S*,4*R*,5*S*)-2.42**.

To confirm the absolute configuration of the tetrahydropyran **(2*S*,4*R*,5*S*)-2.42**, X-ray analysis of the single crystal should be the first choice. Since the **(2*S*,4*R*,5*S*)-2.42** was an oil, solid derivatives were needed to be prepared by coupling the free hydroxy group of **(2*S*,4*R*,5*S*)-2.42** with various groups, and those derivatives could be used to prepare single crystal as follows.

As shown in Scheme 2.54, ***rac*-2.42** was used as the starting material to prepare the solid product at the beginning. At first, 3,5-dinitrobenzoyl chloride **2.69** was selected as the coupling reagent. Fortunately, the white solid product ***rac*-2.70** was obtained in high yield of 90%.

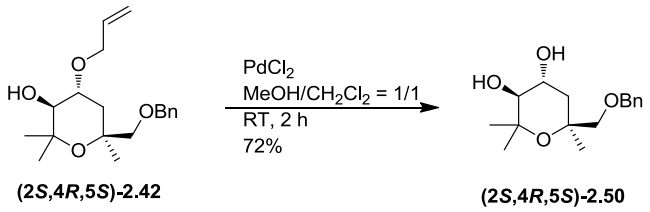


2.69 ***rac*-2.42** ***rac*-2.70**

Scheme 2.54: Synthesis of ***rac*-2.70**.

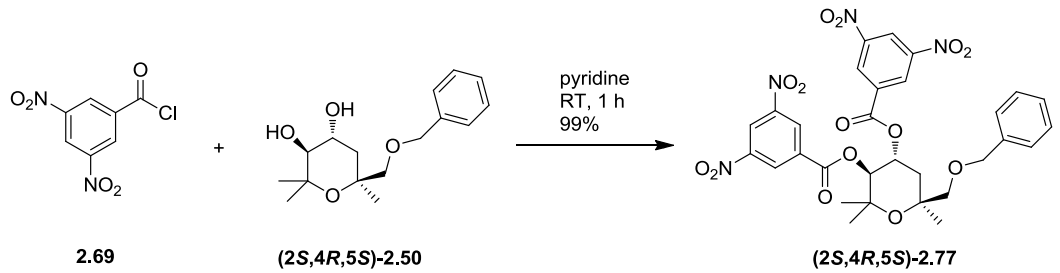
It is better to introduce heavy atoms to the molecule so that the absolute configuration could be determined more clearly. Thus, the 4-bromobenzoyl chloride **2.71**, 4-iodobenzoyl chloride **2.73** and ferrocenecarboxylic acid **2.75** were reacted with ***rac*-2.42**, but no solid products were produced. Finally the enantiomerically pure tetrahydropyran **(2*S*,4*R*,5*S*)-2.42** was reacted with 3,5-dinitrobenzoyl chloride **2.69** in pyridine to afford the white solid product **(2*S*,4*R*,5*S*)-2.70** with an excellent yield of 99%. However, this solid product did not afford any single crystals.

Next, the deprotection of the allyl group of **(2*S*,4*R*,5*S*)-2.42** was performed with 0.1 equivalent of $PdCl_2$ in the mixed solvent of $MeOH/CH_2Cl_2$ (1:1) to afford the diol **(2*S*,4*R*,5*S*)-2.50** with good yield of 72% as a singer diastereomer (Scheme 2.55).



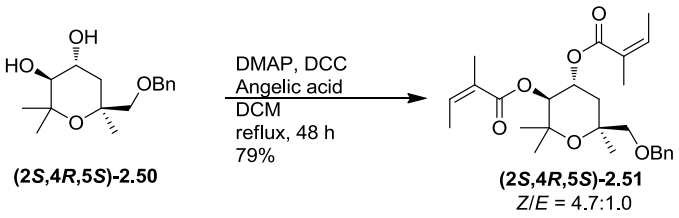
Scheme 2.55: Synthesis of the diol **(2*S*,4*R*,5*S*)-2.50**.

To couple the free hydroxy groups in **(2*S*,4*R*,5*S*)-2.50**, 3,5-dinitrobenzoyl chloride **2.69** was also used in pyridine to provide product **(2*S*,4*R*,5*S*)-2.77** with an excellent yield of 99% (Scheme 2.56). Unfortunately, the product **(2*S*,4*R*,5*S*)-2.77** was oil, and it was impossible to produce single crystals.



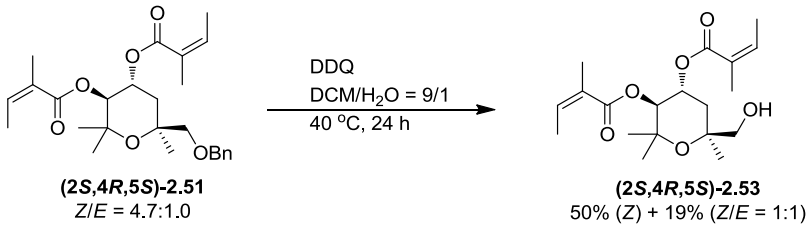
Scheme 2.56: Synthesis of the tetrahydropyran **(2*S*,4*R*,5*S*)-2.77**.

After that, the ester **(2*S*,4*R*,5*S*)-2.51** was synthesized by the *Steglich* esterification with 4 equivalents of angelic acid and DCC as well as 2 equivalents of DMAP under reflux for 48 hours in good yield of 80% with good *Z/E* ratio (4.7:1.0) (Scheme 2.57).



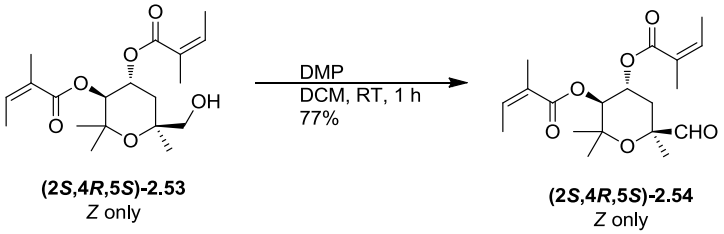
Scheme 2.57: Synthesis of the ester **(2*S*,4*R*,5*S*)-2.51**.

Deprotection of benzyl group of **(2*S*,4*R*,5*S*)-2.51** with DDQ in the mixed solvent DCM/H_2O (9:1) was performed at 40 ℃ at a shorter reaction time 24 hours to obtain a larger amount of major *Z*-isomer (Scheme 2.58). Separated by column chromatography, the pure *Z*-isomer of **(2*S*,4*R*,5*S*)-2.53** was achieved in a moderate yield of 50% and a 1:1-mixture of *Z*-isomer and *E*-isomer of **(2*S*,4*R*,5*S*)-2.53** was afforded in 19% yield.



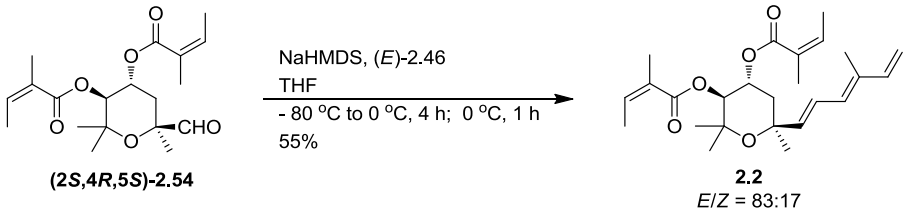
Scheme 2.58: Synthesis of the ester **(2*S*,4*R*,5*S*)-2.53**.

The pure *Z*-isomer of **(2*S*,4*R*,5*S*)-2.53** was utilized for the next step. The oxidation was performed with DMP to provide the pure *Z*-isomer of aldehyde **(2*S*,4*R*,5*S*)-2.54** in good yield of 77% in one hour at room temperature (Scheme 2.59).



Scheme 2.59: Synthesis of the aldehyde **(2*S*,4*R*,5*S*)-2.54**.

With the enantiomerically pure aldehyde **(2*S*,4*R*,5*S*)-2.54** in hand, the final step, the modified *Julia* olefination was carried out with the sulfone **(*E*)-2.46** and NaHMDS to give the desired product **2.2** in a moderate yield of 55% with a good *E*/*Z* ratio of 83:17 (Scheme 2.60). Unfortunately, it was impossible to separate these two *E*/*Z* isomers. However, the product was the mixture of the natural products of **2.2** and **2.3** in a ratio of 83:17.



Scheme 2.60: Synthesis of the natural product **2.2**.

The specific rotation of the synthesized product is $[\alpha]_D^{20}$ = -20.1 (*c* = 0.50, $CHCl_3$). The reported specific rotation for the isolated natural product is $[\alpha]_D^{20}$ = +103 (*c* = 0.10, $CHCl_3$). This indicates that the absolute configuration of the natural product is (7*R*,9*S*,10*R*).

2.13 Summary

In this chapter, both of racemic and enantiomerically pure synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastins **2.2** were successfully completed.

In the synthesis route to the racemic product, the longest linear route included 19 steps. The first key step was the copper-mediated S_N2'-substitution of propargyl acetate ***rac*-2.30** to provide the desired β-hydroxyallene ***rac*-2.32**. Then, the gold-catalyzed cycloisomerization of ***rac*-2.32** followed to afford the dihydropyran ***rac*-2.35** efficiently which provided the structural core of the agerafastin. After epoxidation of ***rac*-2.35**, the regio- and stereoselective opening of the epoxide by allyl alcohol and $HClO_4$ was another key step to give ***rac*-2.42** with a good yield of 70%. Subsequently, after combining the *Steglich* esterification and selective deprotection of the benzyl group to give alcohol ***rac*-2.53**, the final product ***rac*-2.2** was obtained by oxidation and *Julia* olefination.

In the enantioselective synthesis route, *Sharpless* dihydroxylation of homoallylic alcohol **2.11** was optimized many times with unsatisfactory results at the beginning. Then, the synthesis strategy was changed to use the homoallyl alcohol **2.60** as a starting material. The enantiomerically pure diol **(*S*)-2.62** was obtained with high yield by *Sharpless* dihydroxylation. Based on the racemic synthesis, the key steps, the copper-mediated S_N2'-substitution of propargyl acetate **(*S*)-2.67** and the gold-catalyzed cycloisomerization of β-hydroxyallene **(*S*)-2.34**, were performed to afford the desired dihydropyran **(*S*)-2.35** with good yield of 84% in gram scale. Then, the following steps were similar to the racemic synthesis. After the 19 steps, the natural product of **2.2** was obtained as a mixture with **2.3**.

In conclusion, the first enantioselective total synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin was achieved by using methods developed by our group, *i.e.* the gold-catalyzed cycloisomerization of β-hydroxyallenes, as well as the copper-mediated S_N2'-substitution, as key steps.

2.14 Experimental Part

2.14.1 General Information

Solvents and reagents:

All reactions with air- or moisture-sensitive chemicals were carried out under an inert atmosphere of argon. All glassware for reactions were baked under reduced pressure and cooled under argon before use carefully. The reagents were added either in an argon countercurrent or by injection through a septum. Tetrahydrofuran (THF), dichloromethane (DCM), diethyl ether (Et_2O), toluene and dimethylformamide (DMF) were dried before use with the solvent cleaning system MB-SPS 800 from *M. Braun*. Acetone was dried with magnesium sulfate. Commercial reagents were purchased from *ABCR*, *Acros Organics*, *Sigma Aldrich*, *Fluorochem*, *Fisher scientific* and *TCI* and used without purification, unless otherwise noted.

The content determinations of the *n*-butyllithium and methylmagnesium chloride solution used were carried out by titration in each case against salicylaldehyde phenylhydrazone.[76]

Chromatography:

Flash column chromatography was carried out using silica gel 60 M (0.040-0.063) from *Macherey-Nagel*. Thin layer chromatography (TLC) was performed on TLC plates ALUGRAM Xtra SIL G UV254 from *Macherey-Nagel*.

Nuclear magnetic resonance (NMR) spectra:

^{1}H-NMR and ^{13}C-NMR were recorded on a *Bruker DRX400* (400 MHz), *Bruker DRX500* (500 MHz), *INOVA500* (500 MHz) and *Bruker DRX700* using CD_2Cl_2, $CDCl_3$, benzene-d_6 or methanol-d_4 as solvent. Data are reported in the following order: chemical shift (δ) values are reported in ppm with the solvent resonance as internal standard (CD_2Cl_2: δ = 5.32 for ^{1}H, δ = 54.00 for ^{13}C; $CDCl_3$: δ = 7.26 for ^{1}H, δ = 77.16 for ^{13}C; benzene-d_6: δ = 7.16 for ^{1}H, δ = 128.06 for ^{13}C; methanol-d_4: δ = 4.87 for ^{1}H, δ = 49.00 for ^{13}C); coupling constants (*J*) are given in Hertz (Hz). Observed multiplicities are described by the following abbreviations:

[76] B.E. Love, E. G. Jones, *J. Org. Chem.* **1999,** *64*, 3755-3756.

s (singlet) d (doublet) t (triplet)

q (quartet) qi (quintet) sx (sextet)

m (multiplet) dd (doublet of doublet) td (triplet of doublet)

dt (doublet of triplet) br (broad) p (pseudo)

Mass spectrocopy:

Mass spectra were recorded using the following spectrometers:

LC-ESI-LRMS: Thermo TSQ

HPLC-ESI-HRMS: Thermo LTQ Orbitrap with enclosed Hypersil gold column (50 mm × 1 mm ID, grain size 1.9 μm)

Analytical GC and HPLC:

Gas chromatography (GC) analyses were carried out on a gas chromatograph GC 8000 TOP from *CE Instruments* using helium as carrier gas (80 kPa) and the capillary column CP-SIL-5CB (30 m, 0.32 mm ID, DF 0.25 μm). Chiral measurements were carried out on a gas chromatograph GC 8000 TOP from *CE Instruments* with hydrogen as the carrier gas (60 kPa) and the capillary column hydrodex-beta-3P (25 m, 0.25 mm ID, DF 0.25 μm).

High performance liquid chromatography (HPLC) analyses were carried out on an HPLC system from *Agilent Technologies* and columns from *Chiral Technologies Europe* (precolumn: Chiralpak® IA 1 cm × 0.4 cm ID, main column: Chiralpak® IA 25 cm × 0.46 cm ID).

Infrared Spectroscopy:

The IR spectroscopy was measured by FT-IR spectrometer TENSOR 27 from *Bruker* using the thin-film technique. The signal intensities have been characterized by the following abbreviations: s = strong, m = medium, w = weak, br = broad signal.

Polarimeter:

The rotation of optically active compounds was measured with an automatic Polarimeter P8000-T from *A. Krüss Optronic* and is given as specific rotation $[\alpha]_D^{20}$.

2.14.2 General procedures

AAV 1: General procedure for dynamic kinetic resolution (DKR) of a propargyl alcohol[47]

To a 10 mL Schlenk flask, 0.1 eq. of *t*-BuOK, CAL-B (40 mg/mmol), 0.1 eq. of Na_2CO_3 and 8 %mol Ru-catalyst were quickly added. The Schlenk flask was evacuated and filled with argon. Dry toluene (2 mL/mmol) was added, and the mixture was stirred for 6 min. Then 1.0 eq. of the substrate was added. After stirring for 4 min, 1.5 eq. of isopropenyl acetate was added. After being stirred for 24 h at room temperature, the reaction mixture was filtered and concentrated. The crude product is purified by flash column chromatography on silica gel.

AAV 2: General procedure for *Mitsunobu* reaction of an alcohol[49]

To a solution of 1 eq. of alcohol in dry toluene (8 mL/mmol) was added 1.2 eq. of acetic acid, 1.2 eq. of triphenylphosphine at room temperature. After being stirred for 5 minutes at room temperature and then cooled to 0 ℃ , 1.2 eq. of DEAD or DIAD was added dropwise and the solution was stirred for 3 h at room temperature. The reaction mixture was quenched with water and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The crude product is purified by flash column chromatography on silica gel.

AAV3: General procedure for silylation of primary alcohols with *tert*-butyldimethylsilyl chloride (TBSCl)

To a solution of 1 eq. of the alcohol in dry DCM (1 ml/mmol), 0.1 eq. of N, N-dimethylaminopyridine (DMAP), 5 eq. of Triethylamine and 1.5 eq. of *tert*-butyldimethylsilyl chloride (TBSCl) were added and the solution was stirred overnight at room temperature. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The crude product is purified by flash column chromatography on silica gel.

AAV 4: General Procedure for the *Sharpless* dihydroxylation[50]

Method A: To a suspension of AD-mix-α/β (1.4 g/mmol) in *n*-butanol/H_2O (1 : 1, 10 mL/mmol), 1 eq. of the substrate was added at 0 °C. After being stirred overnight at 0 °C, Na_2SO_3 sodium sulfite (1.5 g/mmol) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The crude product is purified by flash column chromatography on silica gel.

Method B: To a suspension of 1 mol% $(DHQ)_2PHAL$, 3 eq. of $K_3Fe(CN)_6$, 3 eq. of K_2CO_3 and 0.4 mol% $K_2OsO_2(OH)_4$ in *n*-butanol/H_2O (1 : 1, 10 mL/mmol) was added 1 eq. of the substrate at 0 °C. After being stirred 17 hours at this temperature, Na_2SO_3 sodium sulfite (1.5 g/mmol) was added and then warmed to room temperature and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The crude product is purified by flash column chromatography on silica gel.

AAV 5: General procedure for the esterification of secondary alcohols with acetic anhydride

To a solution of 1 eq. of the alcohol in DCM (15 mL/mmol) was added 2 eq. of Ac_2O, 2 eq. of Et_3N and 0.2 eq. of DMAP at 0 °C. After being stirred for 30 min at this temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The crude product is purified by flash column chromatography on silica gel.

AAV 6: General procedure for the copper-mediated S_N2'-substitution of propargyl acetates[30,36]

Method A: To a flask 10 eq. of LiBr were added and heated under vacuum at about 300 °C for 5 minutes and cooled under argon to room temperature. Then, 10 eq. of copper (I) iodide and dry THF (20 mL/mmol) was added at room temperature and cooled at ice bath. 10 eq. of Methylmagnesium chloride (3 M in THF) was slowly added dropwise at 0 °C. It was stirred at this temperature for 30 minutes. To the yellow suspension, a solution of 1 eq. of the substrate in dry THF (4 mL/mmol) was added dropwise. After being stirred for 24 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed

and stirred for another 15 minutes. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, the crude product is purified by flash column chromatography on silica gel.

Method B: To a suspension of 10 eq. of CuCN in dry THF (20 mL/mmol) was added dropwise 10 eq. of *n*-Bu_3P. The mixture was stirred at room temperature until the solution was homogeneous and then cooled to -40 °C. 10 eq. of MeMgCl (3 M in THF) was added dropwise, the mixture was stirred for a further 30 min during -40 °C to -30 °C. A solution of 1 eq. of the substrate in dry THF (4 mL/mmol) was added dropwise and the reaction mixture was stirred at this temperature for 2.5 h. sat. aq. NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes while warming to room temperature. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, the crude product is purified by flash column chromatography on silica gel.

AAV 7: General procedure for the gold-catalyzed cycloisomerization of β-hydroxyallenes

To a solution of 1 eq. of β-hydroxyallenes in dry toluene (16 mL/mmol) was added 2.5 mol% Triphenylphosphingold (I) chloride, 2.5 mol% silver tetrafluoroborate at room temperature under argon. After being stirred for 6 h, the reaction mixture was filtrated through Celite and the filtrate was concentrated under vacuum. The crude product is purified by flash column chromatography on silica gel.

AAV 8: General procedure for the epoxidation of dihydropyrans with *m*CPBA

To a solution of 1 eq. of dihydropyrans in dry DCM (10 ml/mmol) was added 2 eq. of disodium hydrogen phosphate (677 mg, 4.77 mmol) and 2 eq. of *m*CPBA (70%-75% in water) at 0 ℃. After being stirred for 48 h at room temperature, the reaction mixture was quenched with sat. aq. Na_2CO_3 (10 mL/mmol) and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The crude product is purified by flash column chromatography on silica gel.

AAV 9: General procedure for the oxidation of primary alcohols[72]

To a solution of 1 eq. of the substrate in DCM (10 ml/mmol) was added 1.2 eq. of Dess-Martin periodinane at room temperature. After being stirred for 1 h at room temperature, the

reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The crude product is purified by flash column chromatography on silica gel.

AAV 10: General procedure for the benzylation of primary alcohols[62-65]

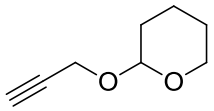
To a solution of 1 eq. of the substrate in the mixture of THF/DMF (3 : 1, 10 ml/mmol) was added 2.2 eq. of NaH was added and stirred for 30 min at 0 ^{o}C. 2.1 eq. of BnBr was added dropwise to the solution. After being stirred for 6 h at room temperature, the reaction mixture was quenched with water carefully and the aqueous phase was extracted five times with ethyl acetate. The organic layers were dried with $MgSO_4$, the solvent was removed. Toluene (3 x 20 mL/mmol) was added and removed in vacuum to remove traces of DMF. The crude product is purified by flash column chromatography on silica gel.

2.14.3 The total synthesis of 9*α*,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin

2-(Prop-2-yn-1-yloxy)tetrahydro-2*H*-pyran (2.13)[44]

V2.1

(ZY-65)



To a solution of propargyl alcohol (1.0 g, 17.9 mmol) in 40 mL Et_2O 3, 4-dihydro-2*H*-pyran (6.0 g, 71.6 mmol) and *p*-toluenesulfonic acid hydrate (26.6 mg, 0.14 mmol) were added. After being stirred for 5 h, the mixture was hydrolyzed with water and extracted three times with diethyl ether. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (20 : 1) to give **2.13** (1.2 g, 8.6 mmol, 48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.81 (t, *J* = 3.3 Hz, 1H), 4.30-4.20 (m, 2H), 3.85-3.80 (m, 1H), 3.54-3.51 (m, 1H), 2.40 (t, *J* = 2.4 Hz, 1H), 1.86-1.77 (m, 1H), 1.76-1.69 (m, 1H), 1.65-1.50 (m, 4H).

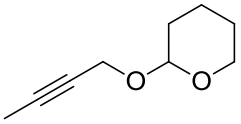
^{13}C NMR (100 MHz, $CDCl_3$): δ = 96.9, 79.9, 74.1, 62.1, 54.1, 30.3, 25.4, 19.1.

The NMR data are consistent with the literature data.[44]

2-(But-2-yn-1-yloxy)tetrahydro-2*H*-pyran (2.14)[44]

V2.2

(ZY-68)



To a solution of **2.13** (600 mg, 4.28 mmol) in 15 ml dry THF was added *n*-butyllithium (1.8 mL, 4.5 mmol, 2.5 M in hexane) was added dropwise at -80 ^{o}C. After being stirred 30 minutes at this temperature, methyl iodide (0.53 mL, 8.56 mmol) was added dropwise and the reaction was stirred overnight at room temperature. The mixture was hydrolyzed with water and extracted three times with diethyl ether. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (20:1) to give **2.14** (461 mg, 2.99 mmol, 70%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.79 (t, J = 3.3 Hz, 1H), 4.28-4.13 (m, 2H), 3.85-3.80 (m, 1H), 3.53-3.50 (m, 1H), 1.85-1.80 (m, 4H), 1.75-1.69 (m, 1H), 1.64-1.50 (m, 4H).

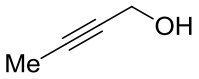
^{13}C NMR (100 MHz, $CDCl_3$): δ = 96.9, 82.3, 75.1, 62.1, 54.8, 30.4, 25.5, 19.2, 3.8.

The NMR data are consistent with the literature data.[44]

But-2-yn-1-ol (2.15)[44]

V2.3

(ZY-76)



To a solution of **2.14** (1.0 g, 6.5 mmol) in 10 mL methanol *p*-toluenesulfonic acid hydrate (124 mg, 0.65 mmol) was added at room temperature. After being stirred overnight, K_2CO_3 (90 mg, 0.65 mmol) was added and the reaction solution was filtered through Celite. The solvent was concentrated under vacuum and the residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give **2.15** (510 mg, 32% in Et_2O, 2.3 mmol, 36%) as light yellow oil.

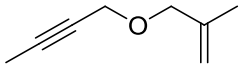
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.23 (q, J = 2.3 Hz, 2H), 1.86 (t, J = 2.4 Hz, 3H), 1.67 (bs, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.2, 77.6, 51.5, 3.7.

The NMR data are consistent with the literature data.[44]

1-((2-Methylallyl)oxy)but-2-yne (2.16)

V2.4



(ZY-528)

To a suspension of sodium hydride (60% in mineral oil, 1.26 g, 31.4 mmol) in dry DMF (29 mL) was added **2.15** (2.0 g, 28.6 mmol) in dry THF (29 mL) dropwise at 0 ^{o}C. After being stirred for 1 h at this temperature, methallyl chloride (3.09 mL, 31.4 mmol) was added and stirred for an additional four hours at room temperature. Then, the reaction mixture was quenched with water and extracted three times with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **2.16** (3.58 g, 85% in Et_2O, 24.5 mmol, 86%) as light yellow oil.

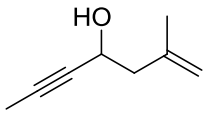
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.98 (s, 1H), 4.91 (s, 1H), 4.08-1.07 (m, 2H), 3.94 (s, 2H), 1.86-1.85 (m, 3H), 1.74 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.8, 112.8, 82.4, 75.3, 73.6, 57.7, 19.7, 3.7.

The NMR data are consistent with the literature data.[39]

2-Methylhept-1-en-5-yn-4-ol (*rac*-2.11)

V2.5



(ZY-529)

To a solution of **2.16** (3.0 g, 24.17 mmol) in dry THF (120 mL) was added *n*-BuLi (2.5 M in hexane, 14.5 mL, 36.26 mmol) was added dropwise at -80 ^{o}C. After being stirred for 1.5 h from -80 ^{o}C to -70 ^{o}C, the reaction mixture was quenched with sat. aq. NaCl, warmed up to room temperature and the aqueous phase extracted three times with diethyl ether. The organic

layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give ***rac*-2.11** (2.85 g, 80% in Et_2O, 18.37 mmol, 76%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.90 (s, 1H), 4.83 (s, 1H), 4.48-4.44 (m, 1H), 2.40 (d, *J* = 6.6 Hz, 2H), 1.90 (bs, 1H), 1.84 (d, *J* = 2.1 Hz, 3H), 1.78 (s, 3H).

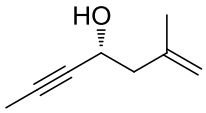
^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.4, 114.2, 81.2, 80.1, 60.6, 46.6, 22.7, 3.7.

The NMR data are consistent with the literature data.[39]

(*R*)-2-Methylhept-1-en-5-yn-4-ol ((*R*)-2.11)[36,46]

V2.6

(ZY-532)



To a solution of ***rac*-2.11** (2.0 g, 16.12 mmol) in vinyl acetate (18 mL) was added CAL-B (1.0 g) at room temperature under air. After being stirred for 65 h, the reaction mixture was filtered. The residue was concentrated under vacuum and purified by column chromatography using pentane-Et_2O (4:1) to give **(*R*)-2.11** (990 mg, 85% in Et_2O, 6.78 mmol, 42%) as light yellow oil.

The ee was determined by chiral GC: start temperature, 40 ^{o}C; flow rate, 0.5 ^{o}C min^{-1} to 80 ^{o}C; retention time, (*R*)-**6** 64.4 min, (*S*)-**6** 68.6 min.

ee = >99%.

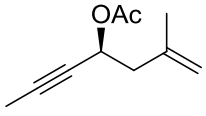
$[\alpha]_D^{20}$ = -28.8 (*c* = 1.28, $CHCl_3$).

Spectroscopic data of the alcohol **(*R*)-2.11**: see experiment **V 2.5**.

(*S*)-2-Methylhept-1-en-5-yn-4-yl acetate ((*S*)-2.17)

V2.7

(ZY-532)



To a solution of *rac*-2.11 (2.0 g, 16.12 mmol) in vinyl acetate (18 mL) was added CAL-B (1.0 g) at room temperature under air. After being stirred for 65 h, the reaction mixture was filtered. The residue was concentrated under vacuum and purified by column chromatography using pentane-Et_2O (4:1) to give **(*S*)-2.17** (1.2 g, 7.22 mmol, 45%) as light yellow oil.

The ee was determined by chiral GC: start temperature, 40 ^oC; flow rate, 0.5 $^oC\ min^{-1}$ to 80 ^oC; retention time, (*S*)-**2.17** 54.3 min, (*R*)-**2.17** 55.5 min.

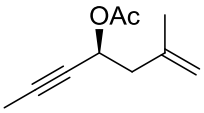
^1H NMR (400 MHz, $CDCl_3$): δ = 5.51-5.46 (m, 1H), 4.84 (s, 1H), 4.79 (s, 1H), 2.51-2.39 (m, 2H), 2.06 (s, 3H), 1.84 (d, J = 2.1 Hz, 3H), 1.76 (s, 3H).

ee = 90%.

The NMR data are consistent with the literature data.[39]

V2.8

(ZY-697)

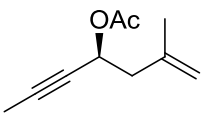


Based on AAV 1, to a 10 mL Schlenk flask, *t*-BuOK (5.6 mg, 50 umol), CAL-B (20 mg), Na_2CO_3 (53 mg, 0.5 mmol) and Ru-catalyst **2.20** (25 mg, 40 umol) were quickly added. The Schlenk flask was evacuated and filled with argon. Toluene (1 mL) was added, and the mixture was stirred for 6 min. Then ***rac*-2.11** (62 mg, 0.5 mmol) was added, and after 4 min, isopropenyl acetate (83 μL, 0.75 mmol) was added. After being stirred for 68 h at 50 ^oC, the reaction mixture was filtered and concentrated. Purification by column chromatography pentane-diethyl ether (4:1) afforded **(*S*)-2.17** (11 mg, 13%, 91% ee) and **(*R*)-2.11** (54 mg, 87%, 24% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**; Spectroscopic data of the alcohol **(*R*)-2.11**: see experiment **V 2.5**.

V2.9

(ZY-698)

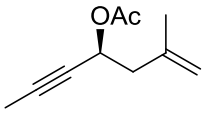


Based on AAV 1, to a 10 mL Schlenk flask, *t*-BuOK (5.6 mg, 50 umol), CAL-B (20 mg), Na_2CO_3 (53 mg, 0.5 mmol) and Ru-catalyst **2.20** (25 mg, 40 umol) were quickly added. The Schlenk flask was evacuated and filled with argon. Toluene (1 mL) was added, and the mixture was stirred for 6 min. Then ***rac*-2.11** (62 mg, 0.5 mmol) was added, and after 4 min, isopropenyl acetate (83 μL, 0.75 mmol) was added. After being stirred for 68 h at room temperature, the reaction mixture was filtered and concentrated. Purification by column chromatography pentane-diethyl ether (4:1) afforded **(*S*)-2.17** (22 mg, 26%, 91% ee) and **(*R*)-2.11** (46 mg, 74%, 66% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**; Spectroscopic data of the alcohol **(*R*)-2.11**: see experiment **V 2.5**.

V2.10

(ZY-670)

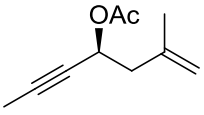


Based on AAV 1, to a 10 mL Schlenk flask, *t*-BuOK (5.6 mg, 50 umol), CAL-B (20 mg), Na_2CO_3 (53 mg, 0.5 mmol) and Ru-catalyst **2.20** (25 mg, 40 umol) were quickly added. The Schlenk flask was evacuated and filled with argon. Then ***rac*-2.11** (31 mg, 0.25 mmol) and isopropenyl acetate (1 mL, 9.0 mmol) was added. After being stirred for 45 h at 50 ^oC, the reaction mixture was filtered and concentrated. Purification by column chromatography pentane-diethyl ether (4:1) afforded **(*S*)-2.17** (15 mg, 36%, 86% ee) and **(*R*)-2.11** (19.8 mg, 64%, 22% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**; Spectroscopic data of the alcohol **(*R*)-2.11**: see experiment **V 2.5**.

V2.11

(ZY-671)



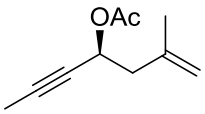
Based on AAV 1, to a 10 mL Schlenk flask, 0.1 eq. *t*-BuOK (5.6 mg, 50 umol), CAL-B (20 mg), Na_2CO_3 (53 mg, 0.5 mmol) and Ru-catalyst **2.20** (25 mg, 40 umol) were quickly added. The Schlenk flask was evacuated and filled with argon. Then ***rac*-2.11** (31 mg, 0.25 mmol) and isopropenyl acetate (1 mL, 9.0 mmol) was added. After being stirred for 45 h at room

temperature, the reaction mixture was filtered and concentrated. Purification by column chromatography pentane-diethyl ether (4:1) afforded **(*S*)-2.17** (15 mg, 36%, 92% ee) and **(*R*)-2.11** (19.8 mg, 64%, 14% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**; Spectroscopic data of the alcohol **(*R*)-2.11**: see experiment **V 2.5**.

V2.12

(ZY-674)

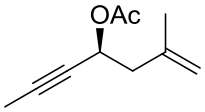


Based on AAV 1, to a 10 mL Schlenk flask, *t*-BuOK (5.6 mg, 50 umol), CAL-B (20 mg), Na_2CO_3 (53 mg, 0.5 mmol) and Ru-catalyst **2.20** (25 mg, 40 umol) were quickly added. The Schlenk flask was evacuated and filled with argon. Toluene (1 mL) was added, and the mixture was stirred for 6 min. Then ***rac*-2.11** (31 mg, 0.25 mmol) was added, and after 4 min, isopropenyl acetate (553 μL, 5.0 mmol) was added. After being stirred for 45 h at 50 ^{o}C, the reaction mixture was filtered and concentrated. Purification by column chromatography pentane-diethyl ether (4:1) afforded **(*S*)-2.17** (7 mg, 17%, 91% ee) and **(*R*)-2.11** (25.7 mg, 83%, 18% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**; Spectroscopic data of the alcohol **(*R*)-2.11**: see experiment **V 2.5**.

V2.13

(ZY-675)

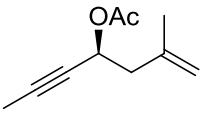


Based on AAV 1, to a 10 mL Schlenk flask, *t*-BuOK (5.6 mg, 50 umol), CAL-B (20 mg), Na_2CO_3 (53 mg, 0.5 mmol) and Ru-catalyst **2.20** (25 mg, 40 umol) were quickly added. The Schlenk flask was evacuated and filled with argon. Toluene (1 mL) was added, and the mixture was stirred for 6 min. Then ***rac*-2.11** (31 mg, 0.25 mmol) was added, and after 4 min, isopropenyl acetate (553 μL, 5.0 mmol) was added. After being stirred for 45 h at room temperature, the reaction mixture was filtered and concentrated. Purification by column chromatography pentane-diethyl ether (4:1) afforded **(*S*)-2.17** (10 mg, 24%, 93% ee) and **(*R*)-2.11** (23.6 mg, 76%, 9% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**; Spectroscopic data of the alcohol **(*R*)-2.11**: see experiment **V 2.5**.

V2.14

(ZY-676)

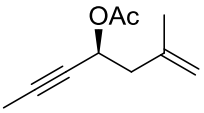


Based on AAV 1, to a 10 mL Schlenk flask, *t*-BuOK (5.6 mg, 50 umol), CAL-B (20 mg), Na_2CO_3 (53 mg, 0.5 mmol) and Ru-catalyst **2.20** (25 mg, 40 umol) were quickly added. The Schlenk flask was evacuated and filled with argon. Toluene (1 mL) was added, and the mixture was stirred for 6 min. Then ***rac*-2.11** (31 mg, 0.25 mmol) was added, and after 4 min, isopropenyl acetate (42 μL, 0.38 mmol) was added. After being stirred for 45 h at room temperature, the reaction mixture was filtered and concentrated. Purification by column chromatography pentane-diethyl ether (4:1) afforded **(*S*)-2.17** (8 mg, 19%, 92% ee) and **(*R*)-2.11** (25.1 mg, 81%, 51% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**; Spectroscopic data of the alcohol **(*R*)-2.11**: see experiment **V 2.5**.

V2.15

(ZY-677)

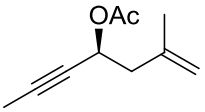


Based on AAV 1, to a 10 mL Schlenk flask, *t*-BuOK (5.6 mg, 50 umol), CAL-B (20 mg), Na_2CO_3 (53 mg, 0.5 mmol) and Ru-catalyst **2.20** (25 mg, 40 umol) were quickly added. The Schlenk flask was evacuated and filled with argon. Toluene (1 mL) was added, and the mixture was stirred for 6 min. Then ***rac*-2.11** (31 mg, 0.25 mmol) was added, and after 4 min, isopropenyl acetate (42 μL, 0.38 mmol) was added. After being stirred for 64 h at room temperature, the reaction mixture was filtered and concentrated. Purification by column chromatography pentane-diethyl ether (4:1) afforded **(*S*)-2.17** (5 mg, 12%, 94% ee) and **(*R*)-2.11** (27.3 mg, 88%, 8% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**; Spectroscopic data of the alcohol **(*R*)-2.11**: see experiment **V 2.5**.

V2.16

(ZY-699)

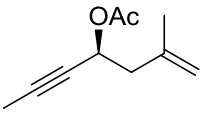


Based on AAV2, to a solution of **(*R*)-2.11** (32 mg, 0.26 mmol) in toluene (2 mL) was added acetic acid (18 uL, 0.31 mmol), triphenylphosphine (81 mg, 0.31 mmol) at room temperature. After being stirred for 5 minutes at room temperature and then cooled to -20 ℃, DEAD (0.14 mL, 0.31 mmol) was added dropwise and the solution was stirred at this temperature for 1.5 h and another 16.5 h at room temperature. The reaction mixture was quenched with water and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give **(*S*)-2.17** (32 mg, 74%, 97% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**.

V2.17

(ZY-673)

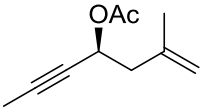


Based on AAV2, to a solution of **(*R*)-2.11** (32 mg, 0.26 mmol) in toluene (2 mL) was added acetic acid (18 uL, 0.31 mmol), triphenylphosphine (81 mg, 0.31 mmol) at room temperature. After being stirred for 5 minutes at room temperature and then cooled to -20 ℃, DEAD (0.14 mL, 0.31 mmol) was added dropwise and the solution was stirred at this temperature for 6 h and another 10 h at room temperature. The reaction mixture was quenched with water and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give **(*S*)-2.17** (27 mg, 63%, 98% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**.

V2.18

(ZY-678)

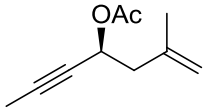


Based on AAV2, to a solution of **(*R*)-2.11** (32 mg, 0.26 mmol) in toluene (2 mL) was added acetic acid (18 uL, 0.31 mmol), triphenylphosphine (81 mg, 0.31 mmol) at room temperature. After being stirred for 5 minutes at room temperature and then cooled to 0 ℃, DIAD (65 uL, 0.31 mmol) was added dropwise and the solution was stirred at this temperature for 1 h and another 23 h at room temperature. The reaction mixture was quenched with water and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give **(*S*)-2.17** (20 mg, 46%, 98% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**.

V2.19

(ZY-679)



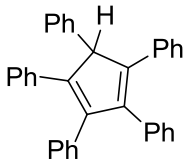
Based on AAV2, to a solution of **(*R*)-2.11** (32 mg, 0.26 mmol) in THF (2 mL) was added acetic acid (18 uL, 0.31 mmol), triphenylphosphine (81 mg, 0.31 mmol) at room temperature. After being stirred for 5 minutes at room temperature and then cooled to 0 ℃, DIAD (65 uL, 0.31 mmol) was added dropwise and the solution was stirred at this temperature for 1 h and another 23 h at room temperature. The reaction mixture was quenched with water and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give **(*S*)-2.17** (19 mg, 44%, 98% ee) as light yellow oil.

Spectroscopic data of the alcohol **(*S*)-2.17**: see experiment **V 2.7**.

Cyclopenta-1, 3-diene-1, 2, 3, 4, 5-pentaylpentabenzene (2.19)[48]

V2.20

(ZY-241)



To a suspension of Mg turnings (100 mg, 4 mmol) in THF (1 mL) a solution of PhBr (736 mg, 4.7 mmol) in dry THF (4 mL) was added dropwise at room temperature. After being stirred 1

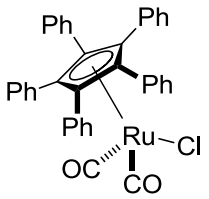
h, 2, 3, 4, 5-tetraphenylcyclopentadienone (1 g, 2.6 mmol) was added with 4 mL dry THF. After being stirred 2 h, $LiAlH_4$ (250 mg, 6.5 mmol) was added in portions. The mixture was quenched after 2 h with an aqueous saturated solution of NH4Cl and extracted with hot DCM, and dried over $MgSO_4$. After evaporation, the product was obtained as a white solid (515 mg, 1.15 mmol, 44%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22-6.94 (m, 25H), 5.08 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 144.1, 138.2, 136.3, 135.9, 130.2, 129.1, 128.7, 128.6, 128.0, 127.8, 126.8, 126.7, 126.5, 62.8.

The NMR data are consistent with the literature data.[48]

Ruthenium complexes (η^5-Ph_5Cp)$Ru(CO)_2Cl$ (2.20)[48]



V2.21

(ZY-254)

To a suspension of 2.19 (400 mg, 0.88 mmol) and [$Ru_3(CO)_{12}$] (188 mg, 0.29 mmol) in decane (4 mL) and toluene (2 mL) was heated at 160 ^{o}C in a 20 mL sealed tube for 64 h. After cooling the mixture to room temperature, $CHCl_3$ (0.5 mL) was added and the mixture was heated at 160 ^{o}C for 1 h. After cooling down to room temperature, pentane was added and the resulting yellow powder was filtered off. After purification by column chromatography pentane-DCM (3:1) to give complex **2.20** (270 mg, 0.42 mmol, 48%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 7.3 Hz, 5H), 7.10 (t, *J* = 7.7 Hz, 10H), 7.04-7.02 (m, 10H).

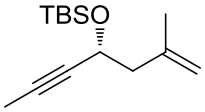
^{13}C NMR (101 MHz, $CDCl_3$): δ = 197.0, 132.3, 129.7, 128.5, 128.0, 106.6.

The NMR data are consistent with the literature data.[48]

(*R*)-*tert*-Butyldimethyl((2-methylhept-1-en-5-yn-4-yl)oxy)silane ((*R*)-2.22)

V2.22

(ZY-550)



Based on AAV3, to a solution of **(*R*)-2.11** (1.6 g, 12.9 mmol) in dry DCM (13 mL) was added N,N-dimethylaminopyridine (DMAP) (156 mg, 1.29 mmol), triethylamine (8.8 mL, 64.5 mmol) and *t*-butyldimethylsilyl chloride (TBSCl) (2912 mg, 19.4 mmol) at room temperature. After being stirred for 15 h at 40 ^{o}C, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **(*R*)-2.22** (2.8 g, 11.75 mmol, 91%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.82-4.81 (m, 1H), 4.77-4.76 (m, 1H), 4.44-4.41 (m, 1H), 2.39-2.31 (m, 2H), 1.82 (d, J = 2.1 Hz, 3H), 1.76 (s, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H).

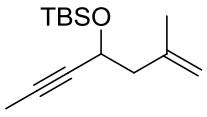
^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 113.4, 81.0, 80.4, 62.4, 47.4, 26.0, 23.1, 18.4, 3.7, -4.4, -4.9.

The NMR data are consistent with the literature data.[39]

***tert*-Butyldimethyl((2-methylhept-1-en-5-yn-4-yl)oxy)silane (*rac*-2.22)**

V2.23

(ZY-109)



Based on AAV3, to a solution of ***rac*-2.11** (800 mg, 6.44 mmol) in dry DCM (6.4 mL) was added N,N-dimethylaminopyridine (DMAP) (78 mg, 0.64 mmol), triethylamine (4.4 mL, 32.2 mmol) and *t*-butyldimethylsilyl chloride (TBSCl) (1456 mg, 9.66 mmol) at room temperature. After being stirred overnight at this temperature, the reaction was heated to 40 ^{o}C for additional 5 h. After cooled down to room temperature, the mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by

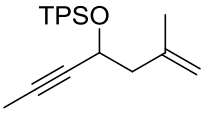
column chromatography using cyclohexane-ethyl acetate (10:1) to give ***rac*-2.22** (1470 mg, 6.17 mmol, 96%) as light yellow oil.

Spectroscopic data of the alcohol ***rac*-2.22**: see experiment **V 2.22**.

tert-Butyl((2-methylhept-1-en-5-yn-4-yl)oxy)diphenylsilane (*rac*-2.24)

V2.24

(ZY-146)



Based on AAV3, to a solution of ***rac*-2.11** (800 mg, 6.45 mmol) in dry DCM (10 mL) was added N,N-dimethylaminopyridine (DMAP) (82 mg, 0.65 mmol), triethylamine (4.4 mL, 32.3 mmol) and *t*-butyldiphenylsilyl chloride (TPSCl) (2.6 mL, 9.68 mmol) at room temperature. After being stirred for 22 h at this temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give ***rac*-2.24** (2.1 g, 5.8 mmol, 90%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77-7.69 (m, 4H), 7.44-7.35 (m, 6H), 4.74 (d, *J* = 22.6 Hz, 2H), 4.44-4.39 (m, 1H), 2.36 (dd, *J* = 6.6, 2.9 Hz, 2H), 1.66 (d, *J* = 2.1 Hz, 3H), 1.59 (s, 3H), 1.07 (s, 9H).

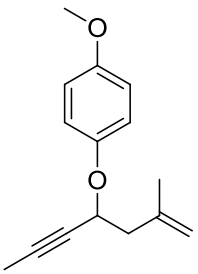
^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 136.3, 136.1, 134.1, 134.0, 129.8, 129.6, 127.6, 127.4, 113.6, 81.4, 80.7, 63.2, 47.2, 27.1, 22.8, 19.4, 3.6.

HRMS: calc'd for $[M+H]^+$: 363.2139, found: 363.2135; calc'd for $[M+Na]^+$: 385.1958, found: 385.1954.

1-Methoxy-4-((2-methylhept-1-en-5-yn-4-yl)oxy)benzene (*rac*-2.26)

V2.25

(ZY-566)



Based on AAV3, to a solution of ***rac*-2.11** (380 mg, 3.06 mmol) in DCM (31 mL) was added 4-methoxyphenol (760 mg, 6.12 mmol), triphenylphosphine (1605 mg, 6.12 mmol) at room temperature. After being stirred for 5 minutes at room temperature and then cooled to 0 ℃, DIAD (1316 mg, 6.12 mmol) was added dropwise and the solution was stirred at room temperature for 24 h. The reaction mixture was quenched with water and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.26** (411 mg, 1.79 mmol, 58%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98-6.94 (m, 2H), 6.85-6.81 (m, 2H), 4.88-4.85 (m, 2H), 4.75-4.69 (m, 1H), 3.77 (s, 3H), 2.69-2.52 (m, 2H), 1.82 (d, *J* = 7.8 Hz, 6H).

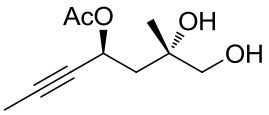
^{13}C NMR (100 MHz, $CDCl_3$):δ = 154.4, 152.0, 141.3, 117.2, 114.6, 113.5, 82.8, 77.9, 68.3, 55.8, 44.4, 23.1, 3.8, 1.2.

HRMS: calc'd for $[M+H]^+$: 231.1380, found: 231.1391; calc'd for $[M+Na]^+$: 253.1199, found: 253.1212.

(2*S*,4*S*)-6, 7-Dihydroxy-6-methylhept-2-yn-4-yl acetate ((2*S*,4*S*)-2.21)

V2.26

(ZY-563)



Based on AAV4, to a suspension of AD-mix-α (4.2 g) in *n*-butanol/H_2O (1:1, 30 mL) **(*S*)-2.17** (500 mg, 3.0 mmol, 90% ee) was added at 0 ℃. After being stirred overnight at 0 ℃, $(DHQ)_2PHAL$ (23.4 mg, 30 umol) was added and stirred for another 10 h. Then, Methanesulfonamide (571 mg, 6.0 mmol), $(DHQ)_2PHAL$ (46.8 mg, 60 umol), and $K_2OsO_2(OH)_4$ (11 mg, 30 umol) were added and continued to stir 23 h at 0 ℃. Na_2SO_3 sodium sulfite (4.5 g) was added and stirred for 50 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give **(2*S*,4*S*)-2.21** (124 mg, 0.62 mmol, 21%, dr = 61:39) as light yellow oil. And **(*S*)-2.17** (110 mg, 22%) recovered as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.76-4.72 (m, 0.39H), 4.69-4.65 (m, 0.61H), 4.08-3.99 (m, 2H), 2.93 (d, J = 13.5 Hz, 2H), 2.10 (d, J = 4.7 Hz, 3H), 2.07-1.93 (m, 2H), 1.83 (d, J = 2.1 Hz, 3H), 1.28 (d, J = 9.5 Hz, 3H).

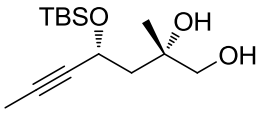
^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.3/171.1, 81.8/81.6, 80.1/80.0, 72.1/71.6, 70.0, 60.1/59.9, 45.2/44.6, 26.1/23.7, 21.0/21.0, 3.7.

The NMR data are consistent with the literature data.[39]

(2*S*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylhept-5-yne-1,2-diol((2*S*,4*R*)-2.23a)

V2.27

(ZY-551)



Based on AAV4, to a suspension of AD-mix-α (15.26 g) in *n*-butanol/H_2O (1:1, 109 mL) **(*R*)-2.22** (2.6 g, 10.9 mmol) was added at 0 ℃. After being stirred overnight at 0 ℃, Na_2SO_3 sodium sulfite (16.35 g) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give **(2*S*,4*R*)-2.23a** (2.53 g, 9.29 mmol, 85%, dr = 77:23) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.75 (d, *J* = 9.6 Hz, 0.77H), 4.70 (s, 0.23H), 3.52-3.38 (m, 2H), 3.05 (bs, 2H), 2.14 (dd, *J* = 14.7, 9.8 Hz, 1H), 1.83-1.71 (m, 3H), 1.70 (dd, *J* = 14.8, 3.3 Hz, 1H), 1.20 (s, 3H), 0.91 (s, 9H), 0.20-0.15 (m, 6H).

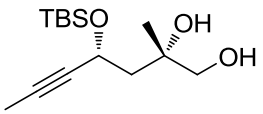
^{13}C NMR (100 MHz, $CDCl_3$): δ = 82.5/82.1, 80.3/80.3, 72.6/72.6, 70.2/69.6, 61.4/61.3, 45.9/45.0, 25.9/25.9, 25.5/23.7, 18.1/18.1, 3.6/3.6, -3.9/-4.1, -4.9/-5.0.

The NMR data are consistent with the literature data.[39]

(2*S*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylhept-5-yne-1,2-diol((2*S*,4*R*)-2.23b)

V2.28

(ZY-533)



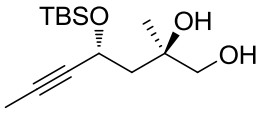
Based on AAV4, to a suspension of AD-mix-α (350 mg) and $(DHQ)_2PHAL$ (3.9 mg, 5 umol) in *n*-butanol/H_2O (1:1, 3 mL) **(*R*)-2.22** (60 mg, 0.25 mmol) was added at 0 ℃. After being stirred overnight at 0 ℃, Na_2SO_3 sodium sulfite (375 mg) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give **(2*S*,4*R*)-2.23b** (52 mg, 191 umol, 76%, dr = 77:23) as light yellow oil.

Spectroscopic data of **(2*S*,4*R*)-2.23**: see experiment **V 2.27**.

(2*R*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylhept-5-yne-1,2-diol((2*R*,4*R*)-2.23)

V2.29

(ZY-213)



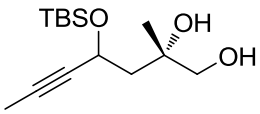
Based on AAV4, to a suspension of AD-mix-β (1.46 g) in *n*-butanol/H_2O (1:1, 10 mL) **(*R*)-2.22** (249 mg, 1.05 mmol) was added at 0 ℃. After being stirred overnight at 0 ℃, Na_2SO_3 sodium sulfite (1.5 g) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give **(2*R*,4*R*)-2.23** (266 mg, 0.98 mmol, 93%, dr = 76:24) as light yellow oil.

Spectroscopic data of **(2*S*, 4*R*)-2.23**: see experiment **V 2.27**.

(2*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylhept-5-yne-1,2-diol ((*S*)-2.23)

V2.30

(ZY-119)



Based on AAV4, to a suspension of AD-mix-α (1.97 g) in *n*-butanol/H_2O (1:1, 14 mL) ***rac*-2.22** (335 mg, 1.41 mmol) was added at 0 ℃. After being stirred 18 h at 0 ℃, Na_2SO_3 sodium sulfite (5.22 g) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and

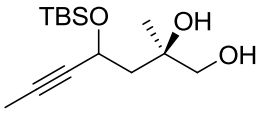
concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give **(*S*)-2.23** (370 mg, 1.35 mmol, 96%, dr = 50:50) as light yellow oil.

Spectroscopic data of **(*S*)-2.23**: see experiment **V 2.27**.

(2*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-methylhept-5-yne-1,2-diol ((*R*)-2.23)

V2.31

(ZY-115)



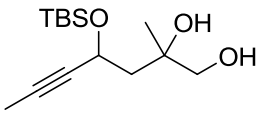
Based on AAV4, to a suspension of AD-mix-β (1.97 g) in *n*-butanol/H_2O (1:1, 14 mL) ***rac*-2.22** (335 mg, 1.41 mmol) was added at 0 ℃. After being stirred 20 h at 0 ℃, Na_2SO_3 sodium sulfite (2.1 g) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give **(*R*)-2.23** (380 mg, 1.4 mmol, 99%, dr = 50:50) as light yellow oil.

Spectroscopic data of **(*R*)-2.23**: see experiment **V 2.27**.

4-((*tert*-Butyldimethylsilyl)oxy)-2-methylhept-5-yne-1,2-diol (*rac*-2.23)

V2.32

(ZY-232)



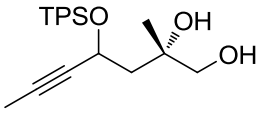
Based on AAV4, to a suspension of AD-mix-α (9.1 g) and AD-mix-β (9.1 g) in *n*-butanol/H_2O (1:1, 130 mL) ***rac*-2.22** (3.1 g, 13.01 mmol) was added at 0 ℃. After being stirred 24 h at room temperature, Na_2SO_3 sodium sulfite (19.5 g) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give ***rac*-2.23** (3.31 g, 12.16 mmol, 93%, dr = 63:37) as light yellow oil.

Spectroscopic data of ***rac*-2.23**: see experiment **V 2.27**.

(2*S*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylhept-5-yne-1,2-diol ((*S*)-2.25)

V2.33

(ZY-150)



Based on AAV4, to a suspension of AD-mix-α (2.3 g) in *n*-butanol/H_2O (1:1, 17 mL) ***rac*-2.24** (600 mg, 1.66 mmol) was added at 0 ℃. After being stirred 30 h at 0 ℃, Na_2SO_3 sodium sulfite (2.49 g) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give **(*S*)-2.25** (630 mg, 1.59 mmol, 96%, dr = 50:50) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76-7.70 (m, 4H), 7.45-7.37 (m, 6H), 4.68-4.62 (m, 1H), 3.51-3.43 (m, 2H), 2.16 (dd, *J* = 14.7, 8.2 Hz, 0.5H), 1.99 (dd, *J* = 14.7, 5.4 Hz, 0.5H), 1.88 (dd, *J* = 14.7, 6.5 Hz, 0.5H), 1.77 (dd, *J* = 14.7, 4.5 Hz, 0.5H), 1.47 (dd, *J* = 59.5, 2.1 Hz, 3H), 1.18 (d, *J* = 9.4 Hz, 3H), 1.07 (d, *J* = 2.7 Hz, 9H).

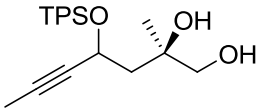
^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.1, 135.9/135.9, 133.5/133.2, 132.8/132.8, 130.1/130.1, 129.8/129.7, 127.9/127.8, 127.4, 127.3, 84.2/83.9, 80.1, 72.7/72.6, 70.5/70.0, 62.4/62.0, 45.6/45.1, 27.0, 25.2/23.9, 19.2, 3.4/3.3.

HRMS: calc'd for $[M+H]^+$: 397.2194, found: 397.2216; calc'd for $[M+Na]^+$: 419.2013, found: 419.2038.

(2*R*)-4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylhept-5-yne-1,2-diol ((*R*)-2.25)

V2.34

(ZY-151)



Based on AAV4, to a suspension of AD-mix-β (2.3 g) in *n*-butanol/H_2O (1:1, 17 mL) ***rac*-2.24** (600 mg, 1.66 mmol) was added at 0 ℃. After being stirred 30 h at 0 ℃, Na_2SO_3

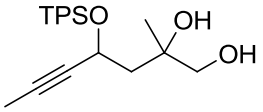
sodium sulfite (2.49 g) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give **(*R*)-2.25** (650 mg, 1.64 mmol, 99%, dr = 50:50) as light yellow oil.

Spectroscopic data of **(*R*)-2.25**: see experiment **V 2.33**.

4-((*tert*-Butyldiphenylsilyl)oxy)-2-methylhept-5-yne-1,2-diol (*rac*-2.25)

V2.35

(ZY-152)



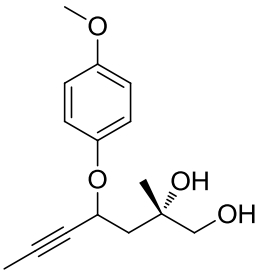
Based on AAV4, to a suspension of AD-mix-α (1.74 g) and AD-mix-β (1.74 g) in *n*-butanol/H_2O (1:1, 25 mL) ***rac*-2.24** (900 mg, 2.48 mmol) was added at 0 ℃. After being stirred 28 h at room temperature, Na_2SO_3 sodium sulfite (3.72 g) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give ***rac*-2.25** (930 mg, 2.35 mmol, 95%, dr = 50:50) as light yellow oil.

Spectroscopic data of ***rac*-2.25**: see experiment **V 2.33**.

(2*S*)-4-(4-methoxyphenoxy)-2-methylhept-5-yne-1,2-diol ((*S*)-2.27)

V2.36

(ZY-567)



Based on AAV4, to a suspension of AD-mix-α (2.31 g) in *n*-butanol/H_2O (1:1, 17 mL) ***rac*-2.26** (380 mg, 1.65 mmol) was added at 0 ℃. After being stirred 28 h at 0 ℃, Na_2SO_3 sodium sulfite (2.5 g) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and

concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give **(*S*)-2.27** (333 mg, 1.26 mmol, 76%, dr = 50:50) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93-6.88 (m, 2H), 6.79-6.77 (m, 2H), 4.90-4.83 (m, 1H), 3.71 (d, *J* = 2.1 Hz, 3H), 3.43-3.39 (m, 2H), 2.38 (bs, 2H), 2.33-1.90 (m, 2H), 1.75 (dd, *J* = 5.0, 2.0 Hz, 3H), 1.19 (d, *J* = 11.1 Hz, 3H).

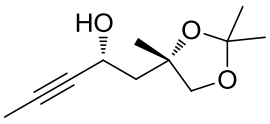
^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9/154.8, 151.0/150.8, 117.5/117.2, 114.7, 83.7/83.6, 77.8/77.6, 72.3, 70.3/70.0, 66.8/66.7, 66.0, 55.8, 44.7/44.4, 24.7/24.5, 15.4/14.3, 3.8/3.8.

HRMS: calc'd for $[M+Na]^+$: 287.1254, found: 287.1251.

(*R*)-1-((*S*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-ol ((2*S*,4*R*)-2.29a)

V2.37

(ZY-552)



To a solution of **(2*S*,4*R*)-2.23a** (2.4 g, 8.82 mmol) in dry acetone (22 mL) was added *p*-toluenesulfonic acid hydrate (336 mg, 1.76 mmol). After being stirred 16.5 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give **(2*S*,4*R*)-2.29a** (1.47 g, 7.42 mmol, 84%, dr = 74:26) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.76-4.69 (m, 0.74H), 4.58-4.55 (m, 0.26H), 3.89 (dd, J = 18.1, 8.6 Hz, 1H), 3.77 (dd, J = 18.6, 8.6 Hz, 1H), 3.24 (bs, 1H), 2.10-1.85 (m, 2H), 1.83-1.82 (m, 3H), 1.42 (d, J = 3.5 Hz, 3H), 1.39 (s, 3H), 1.36 (d, J = 4.7 Hz, 3H).

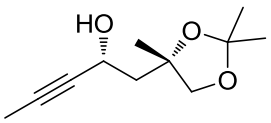
^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.2/109.4, 81.1/81.0, 80.9/80.7, 80.3/80.0, 75.3/74.2, 60.0/59.8, 46.8/46.6, 27.5/27.0/26.9/26.9, 26.1/24.4, 3.7/3.7.

The NMR data are consistent with the literature data.[39]

(*R*)-1-((*S*)-2, 2, 4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-ol ((2*S*,4*R*)-2.29b)

V2.38

(ZY-540)



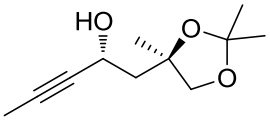
To a solution of **(2*S*,4*R*)-2.23b** (52 mg, 191 umol) in dry acetone (0.5 mL) was added *p*-toluenesulfonic acid hydrate (8.0 mg, 38.2 umol). After being stirred 16.5 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give **(2*S*,4*R*)-2.29b** (19 mg, 95.9 umol, 50%, dr = 74:26) as colorless oil.

Spectroscopic data of **(2*S*,4*R*)-2.29b**: see experiment **V 2.37**.

(*R*)-1-((*R*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-ol ((2*R*,4*R*)-2.29)

V2.39

(ZY-217)



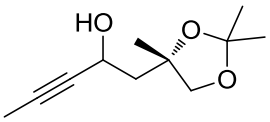
To a solution of **(2*R*,4*R*)-2.23** (255 mg, 0.94 mmol) in dry acetone (2.4 mL) was added *p*-toluenesulfonic acid hydrate (0.19 mmol, 36 mg). After being stirred 22.5 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give **(2*R*,4*R*)-2.29** (146 mg, 0.74 mmol, 78%, dr = 74:26) as colorless oil.

Spectroscopic data of **(2*R*,4*R*)-2.29**: see experiment **V 2.37**.

1-((*S*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-ol ((*S*)-2.29a)

V2.40

(ZY-116)



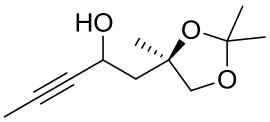
To a solution of **(*S*)-2.23** (335 mg, 0.97 mmol) in dry acetone (3.0 mL) was added *p*-toluenesulfonic acid hydrate (47.5 mg, 0.25 mmol). After being stirred 18 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give **(*S*)-2.29a** (236 mg, 1.19 mmol, 97%, dr = 50:50) as colorless oil.

Spectroscopic data of **(*S*)-2.29a**: see experiment **V 2.37**.

1-((*R*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-ol ((*R*)-2.29a)

V2.41

(ZY-118)



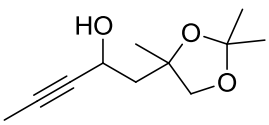
To a solution of **(*R*)-2.23** (360 mg, 1.32 mmol) in dry acetone (3.2 mL) was added *p*-toluenesulfonic acid hydrate (50.3 mg, 0.26 mmol). After being stirred 17.5 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give **(*R*)-2.29a** (172 mg, 0.87 mmol, 66%, dr = 50:50) as colorless oil.

Spectroscopic data of **(*R*)-2.29a**: see experiment **V 2.37**.

1-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-ol (*rac*-2.29a)

V2.42

(ZY-231)



To a solution of ***rac*-2.23** (3.05 g, 11.2 mmol) in dry acetone (28 mL) was added *p*-toluenesulfonic acid hydrate (469 mg, 2.47 mmol). After being stirred 14.5 h at room temperature, another *p*-toluenesulfonic acid hydrate (469 mg, 2.47 mmol) was added again. After being stirred another 24 h at room temperature, the reaction mixture was quenched with

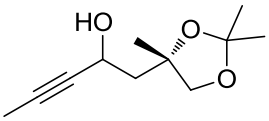
sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-2.29a** (1.58 g, 8.0 mmol, 71%, dr = 63:37) as colorless oil.

Spectroscopic data of ***rac*-2.29a**: see experiment **V 2.37**.

1-((*S*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-ol ((*S*)-2.29b)

V2.43

(ZY-154)



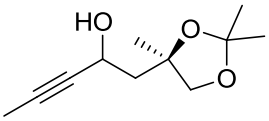
To a solution of **(*S*)-2.25** (290 mg, 0.73 mmol) in dry acetone (2 mL) was added *p*-toluenesulfonic acid hydrate (55.5 mg, 0.29 mmol). After being stirred 15 h at room temperature, another *p*-toluenesulfonic acid hydrate (55.5 mg, 0.29 mmol) was added and continued to stir 72.5 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give **(*S*)-2.29b** (75 mg, 0.38 mmol, 52%, dr = 50:50) as colorless oil.

Spectroscopic data of **(*S*)-2.29b**: see experiment **V 2.37**.

1-((*R*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-ol ((*R*)-2.29b)

V2.44

(ZY-155)



To a solution of **(*R*)-2.25** (290 mg, 0.73 mmol) in dry acetone (2 mL) was added *p*-toluenesulfonic acid hydrate (55.5 mg, 0.29 mmol). After being stirred 15 h at room temperature, another *p*-toluenesulfonic acid hydrate (55.5 mg, 0.29 mmol) was added and continued to stir 72.5 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column

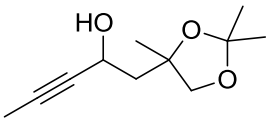
chromatography using cyclohexane-ethyl acetate (4:1) to give **(*R*)-2.29b** (80 mg, 0.40 mmol, 55%, dr = 50:50) as colorless oil.

Spectroscopic data of **(*R*)-2.29b**: see experiment **V 2.37**.

1-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-ol (*rac*-2.29b)

V2.45

(ZY-156)



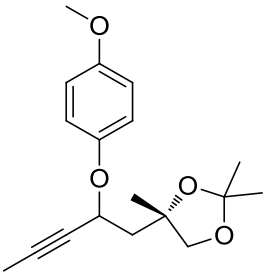
To a solution of ***rac*-2.25** (290 mg, 0.73 mmol) in dry acetone (2 mL) was added *p*-toluenesulfonic acid hydrate (61.1 mg, 0.32 mmol). After being stirred 15.5 h at room temperature, another *p*-toluenesulfonic acid hydrate (61.1 mg, 0.32 mmol) was added and continued to stir 72.5 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-2.29b** (78 mg, 0.39 mmol, 53%, dr = 50:50) as colorless oil.

Spectroscopic data of ***rac* -2.29b**: see experiment **V 2.37**.

(4*S*)-4-(2-(4-Methoxyphenoxy)pent-3-yn-1-yl)-2,2,4-trimethyl-1,3-dioxolane ((*S*)-2.31)

V2.46

(ZY-570)



To a solution of **(*S*)-2.27** (150 mg, 0.57 mmol) in dry acetone (1.3 mL) was added *p*-toluenesulfonic acid hydrate (22 mg, 114 umol). After being stirred 24 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give **(*S*)-2.31** (118 mg, 0.39 mmol, 68%, dr = 50:50) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95-6.93 (m, 2H), 6.84-6.82 (m, 2H), 4.82-4.74 (m, 1H), 4.05 (dd, *J* = 25.8, 8.6 Hz, 1H), 3.77 (d, *J* = 1.4 Hz, 3H), 3.76-3.72 (m, 1H), 2.32-2.27 (m, 1H), 2.19-2.15 (m, 1H), 1.81-1.81 (m, 3H), 1.40-1.38 (m, 6H), 1.30 (d, *J* = 5.7 Hz, 3H).

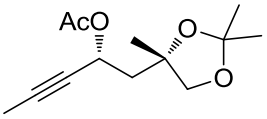
^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.4/154.3, 151.6/151.5, 117.0/116.7, 114.7/114.7/114.6, 83.1/82.7, 80.1/79.8, 78.3/78.1, 75.1, 73.7/72.3, 65.9/65.8, 55.8/55.8, 46.5/45.7, 31.1, 27.4/27.4, 27.2/27.0, 26.2, 24.5/24.5, 3.8.

HRMS: calc'd for $[M+Na]^+$: 327.1567, found: 327.1570; calc'd for $[M+K]^+$: 343.1306, found: 343.1304.

(*R*)-1-((*S*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-yl acetate ((2*S*,4*R*)-2.30a)

V2.47

(ZY-553)



Based on AVV 5, to a solution of **(2*S*,4*R*)-2.29a** (1.4 g, 7.07 mmol) in DCM (110 mL) was added Ac_2O (1.33 mL, 14.14 mmol), Et_3N (2.0 mL, 14.14 mmol) and DMAP (172 mg, 1.41 mmol) at 0 ^{o}C. After being stirred for 22 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **(2*S*,4*R*)-2.30a** (1.52 g, 6.33 mmol, 90%, dr = 74:26) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.49-5.46 (m, 0.74H), 5.43-5.40 (m, 0.26H), 3.98-3.96 (m, 0.76H), 3.92-3.90 (m, 0.24H), 3.72-3.66 (m, 1H), 2.16-1.98 (m, 5H), 1.85-1.82 (m, 3H), 1.37-1.24 (m, 9H).

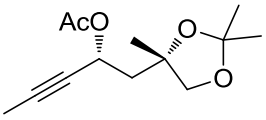
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0/169.9, 109.3/109.2, 82.3/81.9, 79.6/79.4, 77.3/77.2, 74.5/74.0, 61.6/61.5, 45.1/44.8, 27.3/27.0, 27.1/27.0, 25.4/24.8, 21.3/21.3, 3.8/1.2.

The NMR data are consistent with the literature data.[39]

(*R*)-1-((*S*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-yl acetate ((2*S*,4*R*)-2.30b)

V2.48

(ZY-544)



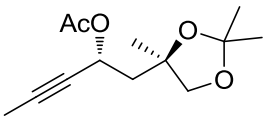
Based on AVV 5, to a solution of **(2*S*,4*R*)-2.29b** (19 mg, 95.9 umol) in DCM (1.5 mL) was added Ac_2O (18 uL, 191.8 umol), Et_3N (26.5 uL, 191.8 umol) and DMAP (2.3 mg, 19.18 umol) at 0 ^oC. After being stirred for 22 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **(2*S*,4*R*)-2.30b** (10 mg, 41.6 umol, 43%, dr = 74:26) as light yellow oil.

Spectroscopic data of **(2*S*,4*R*)-2.30b**: see experiment **V 2.47**.

(*R*)-1-((*R*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-yl acetate ((2*R*,4*R*)-2.30)

V2.49

(ZY-221)



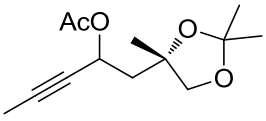
Based on AVV 5, to a solution of **(2*R*,4*R*)-2.29** (140 mg, 0.7 mmol) in DCM (11 mL) was added Ac_2O (131 uL, 1.4 mmol), Et_3N (193 uL, 1.4 mmol) and DMAP (17 mg, 0.14 mmol) at 0 ^oC. After being stirred for 22 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give **(2*R*,4*R*)-2.30** (156 mg, 0.65 mmol, 93%, dr = 74:26) as light yellow oil.

Spectroscopic data of **(2*R*,4*R*)-2.30**: see experiment **V 2.47**.

1-((*S*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-yl acetate ((*S*)-2.30a)

V2.50

(ZY-123)



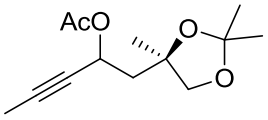
Based on AVV 5, to a solution of **(*S*)-2.29a** (236 mg, 1.19 mmol) in DCM (20 mL) was added Ac_2O (223 uL, 2.38 mmol), Et_3N (330 uL, 2.38 mmol) and DMAP (29.3 mg, 0.24 mmol) at 0 ^oC. After being stirred for 17 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give **(*S*)-2.30a** (247 mg, 1.03 mmol, 86%, dr = 50:50) as light yellow oil.

Spectroscopic data of **(*S*)-2.30a**: see experiment **V 2.47**.

1-((*R*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-yl acetate ((*R*)-2.30a)

V2.51

(ZY-122)



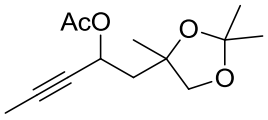
Based on AVV 5, to a solution of **(*R*)-2.29a** (172 mg, 0.87 mmol) in DCM (20 mL) was added Ac_2O (163 uL, 1.74 mmol), Et_3N (240 uL, 1.74 mmol) and DMAP (21.3 mg, 0.17 mmol) at 0 ^oC. After being stirred for 17 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give **(*R*)-2.30a** (182 mg, 0.76 mmol, 87%, dr = 50:50) as light yellow oil.

Spectroscopic data of **(*R*)-2.30a**: see experiment **V 2.47**.

1-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-yl acetate (*rac*-2.30a)

V2.52

(ZY-233)



Based on AVV 5, to a solution of ***rac*-2.29a** (1.58 g, 8 mmol) in DCM (150 mL) was added Ac_2O (1.9 mL, 20 mmol), Et_3N (3.0 mL, 20 mmol) and DMAP (243 mg, 2 mmol) at 0 ^oC. After being stirred for 24 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with

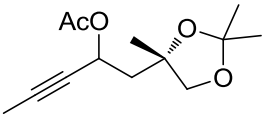
$MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give ***rac*-2.30a** (1.68 g, 7 mmol, 87%, dr = 63:37) as light yellow oil.

Spectroscopic data of ***rac*-2.30a**: see experiment **V 2.47**.

1-((*S*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-yl acetate ((*S*)-2.30b)

V2.53

(ZY-160)



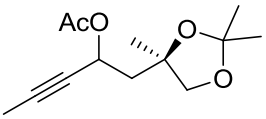
Based on AVV 5, to a solution of **(*S*)-2.29b** (75 mg, 0.38 mmol) in DCM (10 mL) was added Ac_2O (75 uL, 0.76 mmol), Et_3N (110 uL, 0.76 mmol) and DMAP (10 mg, 0.08 mmol) at 0 ^oC. After being stirred for 20 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give **(*S*)-2.30b** (71 mg, 0.3 mmol, 78%, dr = 50:50) as light yellow oil.

Spectroscopic data of **(*S*)-2.30b**: see experiment **V 2.47**.

1-((*R*)-2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-yl acetate ((*R*)-2.30b)

V2.54

(ZY-161)



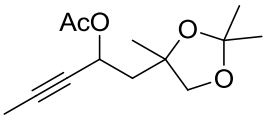
Based on AVV 5, to a solution of **(*R*)-2.29b** (80 mg, 0.4 mmol) in DCM (10 mL) was added Ac_2O (75 uL, 0.8 mmol), Et_3N (110 uL, 0.8 mmol) and DMAP (10 mg, 0.08 mmol) at 0 ^oC. After being stirred for 20 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give **(*R*)-2.30b** (70 mg, 0.29 mmol, 73%, dr = 50:50) as light yellow oil.

Spectroscopic data of **(*R*)-2.30b**: see experiment **V 2.47**.

1-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-yl acetate (*rac*-2.30b)

V2.55

(ZY-162)



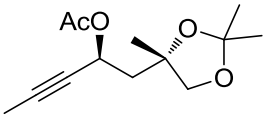
Based on AVV 5, to a solution of ***rac*-2.29b** (78 mg, 0.39 mmol) in DCM (10 mL) was added Ac_2O (95 uL, 1.0 mmol), Et_3N (140 uL, 1.0 mmol) and DMAP (12 mg, 0.1 mmol) at 0 ^oC. After being stirred for 20 h at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give ***rac*-2.30b** (86 mg, 0.36 mmol, 92%, dr = 50:50) as light yellow oil.

Spectroscopic data of ***rac*-2.30b**: see experiment **V 2.47**.

(*S*)-1-((*S*)-2, 2,4-Trimethyl-1,3-dioxolan-4-yl)pent-3-yn-2-yl acetate ((2*S*,4*S*)-2.30)

V2.56

(ZY-564)



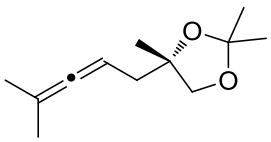
Based on AVV 5, to a solution of **(2*S*,4*S*)-2.21** (108 mg, 0.54 mmol) in dry acetone (1.2 mL) was added *p*-toluenesulfonic acid hydrate (20.5 mg, 108 umol). After being stirred 23 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with ethyl acetate. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give **(2*S*,4*S*)-2.30** (54 mg, 0.22 mmol, 41%, dr = 61:39) as light yellow oil.

Spectroscopic data of **(2*S*,4*S*)-2.30**: see experiment **V 2.47**.

(*S*)-2,2,4-Trimethyl-4-(4-methylpenta-2,3-dien-1-yl)-1,3-dioxolane ((*S*)-2.32)

V2.57

(ZY-579)



Based on AVV 6, to a suspension of CuCN (4.78 g, 52.9 mmol) in dry THF (130 mL) was added dropwise *n*-Bu_3P (13.2 mL, 52.9 mmol). The mixture was stirred at room temperature until the solution was homogeneous and then cooled to -40 ^oC. MeMgCl (17.8 mL, 52.9 mmol, 3 M in THF) was added dropwise, the mixture was stirred for a further 30 min during -40 ^oC to -30 ^oC. A solution of **(2*S*,4*R*)-2.30a** (1.27 g, 5.29 mmol) in 20 mL dry THF was added dropwise and the reaction mixture was stirred at this temperature for 2.5 h. Saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes while warming to room temperature. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(*S*)-2.32** (830 mg, 4.23 mmol, 80%) as light yellow oil.

The ee was determined by chiral GC: start temperature, 40 ^oC; flow rate, 0.5 $^oC\ min^{-1}$ to 80 ^oC; retention time, (*R*)-**6** 70.5 min, (*S*)-**6** 72.6 min.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.94-4.90 (m, 1H), 3.87 (d, *J* = 8.3 Hz, 1H), 3.69 (d, *J* = 8.3 Hz, 1H), 2.21 (d, *J* = 7.6 Hz, 2H), 1.67 (d, *J* = 2.9 Hz, 6H), 1.42 (s, 3H), 1.40 (s, 3H), 1.30 (s, 3H).

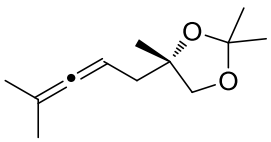
^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.8, 109.3, 94.6, 84.3, 81.3, 73.4, 40.4, 27.3, 27.1, 24.8, 20.7, 20.6.

ee = 55%.

The NMR data are consistent with the literature data.[39]

V2.58

(ZY-556)



Based on AVV 6, to a suspension of CuCN (188 mg, 2.1 mmol) in dry THF (6 mL) was added dropwise $(EtO)_3P$ (370 uL, 2.1 mmol). The mixture was stirred at room temperature

until the solution was homogeneous and then cooled to -40 °C. MeMgCl (0.7 mL, 2.1 mmol, 3 M in THF) was added dropwise, the mixture was stirred for a further 30 min during -40 °C to -30 °C. A solution of **(2*S*,4*R*)-2.30a** (50 mg, 0.21 mmol) in 2 mL dry THF was added dropwise and the reaction mixture was stirred at this temperature for 2.5 h. Saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes while warming to room temperature. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(*S*)-2.32** (10 mg, 51 umol, 24%, 42% ee) as light yellow oil.

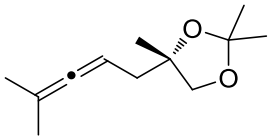
The ee was determined by chiral GC: see experiment **V 2.57**.

ee = 42%.

Spectroscopic data of **(*S*)-2.32**: see experiment **V 2.57**.

V2.59

(ZY-580)



Based on AVV 6, to a suspension of CuCN (37.6 mg, 416 umol) in dry THF (3 mL) was added dropwise *n*-Bu_3P (104 uL, 416 umol). The mixture was stirred at room temperature until the solution was homogeneous and then cooled to -40 °C. MeMgCl (140 uL, 416 umol, 3 M in THF) was added dropwise, the mixture was stirred for a further 30 min during -40 °C to -30 °C. A solution of **(2*S*,4*R*)-2.30b** (10 mg, 41.6 umol) in 20 mL dry THF was added dropwise and the reaction mixture was stirred at this temperature for 2.5 h. Saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes while warming to room temperature. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(*S*)-2.32** (3 mg, 15.3 umol, 37%) as light yellow oil.

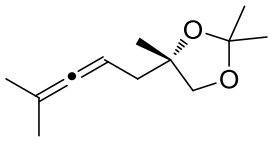
The ee was determined by chiral GC: see experiment **V 2.57**.

ee = 52%.

Spectroscopic data of **(*S*)-2.32**: see experiment **V 2.57**.

V2.60

(ZY-134)



Based on AVV 6, to a flask LiBr (285 mg, 3.3 mmol) were added and heated under vacuum at about 300 ^{o}C for 5 minutes and cooled under argon to room temperature. Then, copper (I) iodide (623 mg, 3.3 mmol) and dry THF (10 mL) was added at room temperature and cooled at ice bath. Methyl magnesium chloride (1.1 mL, 3.3 mmol, 3 M in THF) was slowly added dropwise at 0 ℃. It was stirred at this temperature for 30 minutes. To the yellow solution **(*S*)-2.30a** (80 mg, 0.33 mmol) in 3 mL dry THF was added dropwise. After being stirred for 48 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(*S*)-2.32** (58 mg, 0.3 mmol, 90%) as light yellow oil.

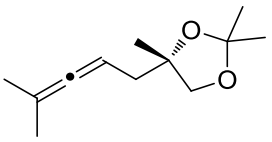
The ee was determined by chiral GC: see experiment **V 2.57**.

ee = 54%.

Spectroscopic data of **(*S*)-2.32**: see experiment **V 2.57**.

V2.61

(ZY-215)



Based on AVV 6, to a flask LiBr (145 mg, 1.7 mmol) were added and heated under vacuum at about 300 ^{o}C for 5 minutes and cooled under argon to room temperature. Then, copper (I) iodide (323 mg, 1.7 mmol) and dry THF (6 mL) was added at room temperature and cooled at ice bath. Methyl magnesium chloride (0.85 mL, 1.7 mmol, 2 M in THF) was slowly added dropwise at 0 ℃. It was stirred at this temperature for 30 minutes. To the yellow solution **(*S*)-2.30b** (40 mg, 0.17 mmol) in 2 mL dry THF was added dropwise. After being stirred for 48 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column

chromatography using pentane-Et_2O (20:1) to give **(*S*)-2.32** (22 mg, 0.11 mmol, 66%) as light yellow oil.

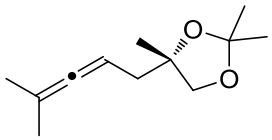
The ee was determined by HPLC: see experiment **V 2.60**.

ee = 67%.

Spectroscopic data of **(*S*)-2.32**: see experiment **V 2.57**.

V2.62

(ZY-578)



Based on AVV 6, to a suspension of CuCN (94 mg, 1.0 mmol) in dry THF (6 mL) was added dropwise *n*-Bu_3P (260 uL, 1.0 mmol). The mixture was stirred at room temperature until the solution was homogeneous and then cooled to -40 ^oC. MeMgCl (0.35 mL, 1.0 mmol, 3 M in THF) was added dropwise, the mixture was stirred for a further 30 min during -40 ^oC to -30 ^oC. A solution of **(2*S*,4*S*)-2.30** (25 mg, 0.1 mmol) in 1 mL dry THF was added dropwise and the reaction mixture was stirred at this temperature for 2.5 h. Saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes while warming to room temperature. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(*S*)-2.32** (10 mg, 0.04 mmol, 40%) as light yellow oil.

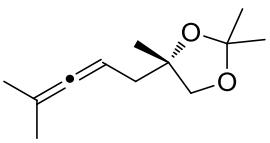
The ee was determined by chiral GC: see experiment **V 2.57**.

ee = 37%.

Spectroscopic data of **(*S*)-2.32**: see experiment **V 2.57**.

V2.63

(ZY-571)



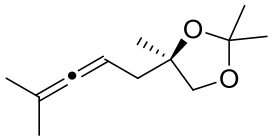
Based on AVV 6, to a suspension of CuCN (94 mg, 1.0 mmol) in dry THF (6 mL) was added dropwise *n*-Bu_3P (260 uL, 1.0 mmol). The mixture was stirred at room temperature until the solution was homogeneous and then cooled to -40 ^oC. MeMgCl (0.34 mL, 1.0 mmol, 3 M in

THF) was added dropwise, the mixture was stirred for a further 30 min during -40 °C to -30 °C. A solution of **(*S*)-2.31** (31 mg, 0.1 mmol) in 1 mL dry THF was added dropwise and the reaction mixture was stirred at this temperature for 0.5 h. Then it was warmed up to -10 °C in 1 h. It was still no reaction and ended with saturated aqueous NH_4Cl solution.

(*R*)-2,2,4-Trimethyl-4-(4-methylpenta-2,3-dien-1-yl)-1,3-dioxolane ((*R*)-2.32)

V2.64

(ZY-225)



Based on AVV 6, to a flask LiBr (145 mg, 1.7 mmol) were added and heated under vacuum at about 300 °C for 5 minutes and cooled under argon to room temperature. Then, copper (I) iodide (323 mg, 1.7 mmol) and dry THF (6 mL) was added at room temperature and cooled at ice bath. Methyl magnesium chloride (0.85 mL, 1.7 mmol, 2 M in THF) was slowly added dropwise at 0 ℃. It was stirred at this temperature for 30 minutes. To the yellow solution **(2*R*,4*R*)-2.30** (40 mg, 0.17 mmol) in 2 mL dry THF was added dropwise. After being stirred for 52 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(*R*)-2.32** (11 mg, 0.06 mmol, 33%) as light yellow oil.

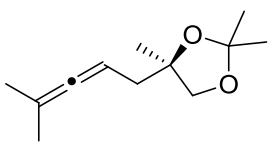
The ee was determined by chiral HPLC: *i*-PrOH : *n*-heptane = 3 : 97; flow rate, 0.3 mL min^{-1}; 25 ℃; retention time, **(*S*)-2.32** 11.2 min, **(*R*)-2.32** 12.3 min.

ee = 17%.

Spectroscopic data of **(*R*)-2.32**: see experiment **V 2.57**.

V2.65

(ZY-138)



Based on AVV 6, to a flask LiBr (345 mg, 4 mmol) were added and heated under vacuum at about 300 °C for 5 minutes and cooled under argon to room temperature. Then, copper (I)

iodide (755 mg, 4 mmol) and dry THF (12 mL) was added at room temperature and cooled at ice bath. Methyl magnesium chloride (1.3 mL, 4 mmol, 3 M in THF) was slowly added dropwise at 0 ℃. It was stirred at this temperature for 30 minutes. To the yellow solution **(*R*)-2.30a** (96 mg, 0.4 mmol) in 4 mL dry THF was added dropwise. After being stirred for 48 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(*R*)-2.32** (67 mg, 0.34 mmol, 85%) as light yellow oil.

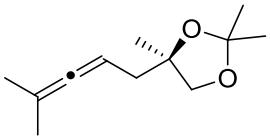
The ee was determined by HPLC: see experiment **V 2.60**.

ee = 63%.

Spectroscopic data of **(*R*)-2.32**: see experiment **V 2.57**.

V2.66

(ZY-200)



Based on AVV 6, to a flask LiBr (243 mg, 2.8 mmol) were added and heated under vacuum at about 300 ^oC for 5 minutes and cooled under argon to room temperature. Then, copper (I) iodide (532 mg, 2.8 mmol) and dry THF (10 mL) was added at room temperature and cooled at ice bath. Methyl magnesium chloride (1.1 mL, 2.8 mmol, 2.5 M in THF) was slowly added dropwise at 0 ℃. It was stirred at this temperature for 30 minutes. To the yellow solution **(*R*)-2.30b** (68 mg, 0.28 mmol) in 3 mL dry THF was added dropwise. After being stirred for 46 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(*R*)-2.32** (30 mg, 0.15 mmol, 55%) as light yellow oil.

The ee was determined by HPLC: see experiment **V 2.60**.

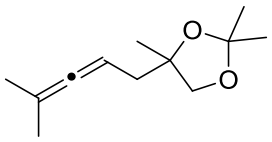
ee = 58%.

Spectroscopic data of **(*R*)-2.32**: see experiment **V 2.57**.

2,2,4-Trimethyl-4-(4-methylpenta-2,3-dien-1-yl)-1,3-dioxolane (*rac*-2.32)

V2.67

(ZY-424)

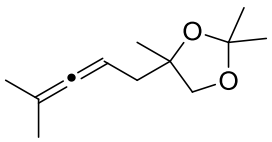


Based on AVV 6, to a suspension of CuCN (3.76 g, 41.6 mmol) in dry THF (130 mL) was added dropwise *n*-Bu_3P (10.4 mL, 41.6 mmol). The mixture was stirred at room temperature until the solution was homogeneous and then cooled to -40 ^oC. MeMgCl (14 mL, 41.6 mmol, 3 M in THF) was added dropwise, the mixture was stirred for a further 30 min during -40 ^oC to -30 ^oC. A solution of ***rac*-2.30a** (1.0 g, 4.16 mmol) in 20 mL dry THF was added dropwise and the reaction mixture was stirred at this temperature for 2.5 h. Saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes while warming to room temperature. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.32** (620 mg, 3.16 mmol, 76%) as light yellow oil.

Spectroscopic data of ***rac*-2.32**: see experiment **V 2.57**.

V2.68

(ZY-234)



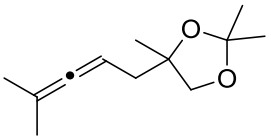
Based on AVV 6, to a flask LiBr (3.61 g, 41.6 mmol) were added and heated under vacuum at about 300 ^oC for 5 minutes and cooled under argon to room temperature. Then, copper (I) iodide (7.93 g, 41.6 mmol) and dry THF (125 mL) was added at room temperature and cooled at ice bath. Methyl magnesium chloride (13.9 mL, 41.6 mmol, 3 M in THF) was slowly added dropwise at 0 ℃. It was stirred at this temperature for 30 minutes. To the yellow solution ***rac*-2.30a** (1.0 g, 4.16 mmol) in 21 mL dry THF was added dropwise. After being stirred for 24 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by

column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.32** (624 mg, 3.18 mmol, 76%) as light yellow oil.

Spectroscopic data of ***rac*-2.32**: see experiment **V 2.57**.

V2.69

(ZY-168)



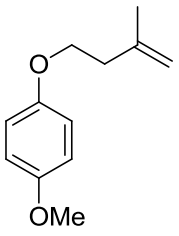
Based on AVV 6, to a flask LiBr (310 mg, 3.6 mmol) were added and heated under vacuum at about 300 ^oC for 5 minutes and cooled under argon to room temperature. Then, copper (I) iodide (680 mg, 3.6 mmol) and dry THF (11 mL) was added at room temperature and cooled at ice bath. Methyl magnesium chloride (1.2 mL, 3.6 mmol, 3 M in THF) was slowly added dropwise at 0 ℃. It was stirred at this temperature for 30 minutes. To the yellow solution ***rac*-2.30b** (86 mg, 0.36 mmol) in 3 mL dry THF was added dropwise. After being stirred for 24 h at room temperature, saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, The residue was purified by column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.32** (30 mg, 0.15 mmol, 42%) as light yellow oil.

Spectroscopic data of ***rac*-2.32**: see experiment **V 2.57**.

1-Methoxy-4-((3-methylbut-3-en-1-yl)oxy)benzene (2.61)

V2.70

(ZY-581)



Based on AVV2, to a solution of 3-methyl-3-buten-1-ol **2.60** (4.31 g, 50.0 mmol) in DCM (500 mL) was added 4-methoxyphenol (19.24 g, 155.0 mmol), triphenylphosphine (18.00 g, 68.5 mmol) at room temperature. After being stirred for 5 minutes at room temperature and then cooled to 0 ℃, DIAD (14.74 g, 68.5 mmol) was added dropwise and the solution was stirred at room temperature for three hours. The reaction mixture was quenched with water and extracted three times with DCM. The organic layer was washed with brine, dried with

$MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **2.61** (9.41 g, 49.0 mmol, 98%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88-6.80 (m, 4H), 4.84 (s, 1H), 4.80 (s, 1H), 4.03 (t, *J* = 6.9 Hz, 2H), 3.77 (s, 3H), 2.48 (t, *J* = 6.9 Hz, 2H), 1.81 (s, 3H).

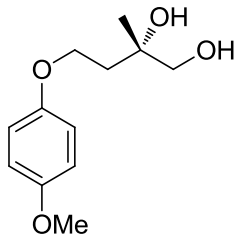
^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 153.2, 142.5, 115.7, 114.7, 112.0, 67.3, 55.9, 37.5, 23.0.

The NMR data are consistent with the literature data.[53]

(*S*)-4-(4-Methoxyphenoxy)-2-methylbutane-1,2-diol ((*S*)-2.62)

V2.71

(ZY-600)



Based on AVV4, to a suspension of $(DHQ)_2PHAL$ (299 mg, 0.38 mmol), $K_3Fe(CN)_6$ (37.92 g, 114.9 mmol), K_2CO_3 (16.10 g, 114.9 mmol) and $K_2OsO_2(OH)_4$ (54 mg, 153.2 umol) in *n*-butanol/H_2O (1:1, 384 mL) was added **2.61** (7.35 g, 38.3 mmol) at 0 ℃. After being stirred 17 hours at this temperature, Na_2SO_3 sodium sulfite (57.45 g) was added and then warmed to room temperature and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give **(*S*)-2.62** (8.26 g, 36.5 mmol, 95%, 95% ee). After recrystallization from cyclohexane-AcOEt, enantiomerically pure **(*S*)-2.62** (7.11 g, 31.4 mmol, 86%) was obtained as colorless solid.

The ee was determined by chiral HPLC: *i*-PrOH : *n*-heptane = 10:90; flow rate, 1.2 mL min^{-1}; room temperature; retention time, **(*S*)-2.62** 16.0 min, **(*R*)-2.62** 17.1 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87-6.82 (m, 4H), 4.20-4.07 (m, 2H), 3.77 (s, 3H), 3.54 (d, *J* = 11.1 Hz, 1H), 3.47 (d, *J* = 11.1 Hz, 1H), 2.55 (brs, 2H), 2.15-2.05 (m, 1H), 1.97-1.86 (m, 1H), 1.25 (s, 3H).

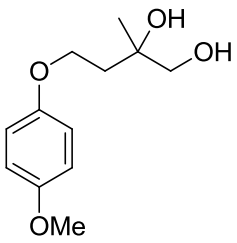
^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4, 152.4, 115.7, 114.8, 72.5, 70.2, 65.6, 55.9, 37.7, 24.3.

ee = >99%.

$[\alpha]_D^{20}$ = +11.8 (*c* = 2.00, $CHCl_3$).

The NMR data are consistent with the literature data.[36]

4-(4-Methoxyphenoxy)-2-methylbutane-1,2-diol (*rac*-2.62)



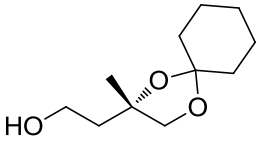
V2.72

(ZY-576)

Based on AVV4, to a suspension of AD-mix-α (2.8 g) and AD-mix-β (2.8 g) in *n*-butanol/H_2O (1:1, 40 mL) **2.61** (768 mg, 4.0 mmol) was added at 0 ℃. After being stirred overnight at room temperature, Na_2SO_3 sodium sulfite (6.0 g) was added and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give ***rac*-2.62** (801 mg, 3.54 mmol, 89%) as colorless solid.

Spectroscopic data of ***rac*-2.62**: see experiment **V 2.71**.

(*S*)-2-(2-Methyl-1,4-dioxaspiro[4.5]decan-2-yl)ethanol ((*S*)-2.64)



V2.73

(ZY-607)

To a solution of **(*S*)-2.62** (4.00 g, 17.7 mmol) in cyclohexanone (50 mL) was added *p*-TsOH·H_2O (673 mg, 3.54 mmol) at room temperature under argon. After being stirred for 30 min, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum

to give the crude cyclohexylidene ketal. This was dissolved in a 4 : 1-mixture of CH_3CN and H_2O (175 mL) and CAN (19.4 g, 35.4 mmol) was added at 0 °C under air. After being stirred for 1 hour, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give **(*S*)-2.64** (3.42 g, 17.1 mmol, 97%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94-3.87 (m, 1H), 3.83 (d, *J* = 8.4 Hz, 1H), 3.79-3.73 (m, 2H), 2.60 (brs, 1H), 1.96-1.85 (m, 1H), 1.78-1.69 (m, 1H), 1.63 (dd, *J* = 21.8, 14.7 Hz, 8H), 1.45-1.36 (m, 2H), 1.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.5, 81.2, 74.5, 59.7, 41.1, 36.8, 36.5, 25.4, 25.2, 24.1, 24.0.

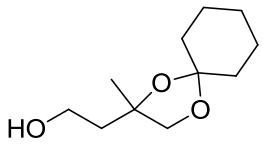
$[\alpha]_D^{20}$ = -12.6 (*c* = 1.40, $CHCl_3$).

The NMR data are consistent with the literature data.[36]

2-(2-Methyl-1,4-dioxaspiro[4.5]decan-2-yl)ethanol (*rac*-2.64)

V2.74

(ZY-582)



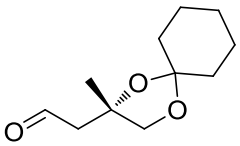
To a solution of ***rac*-2.62** (786 mg, 3.48 mmol) in cyclohexanone (9.8 mL) was added *p*-TsOH H_2O (132.4 mg, 0.7 mmol) at room temperature under argon. After being stirred for 5 min, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum to give the crude cyclohexylidene ketal. This was dissolved in a 4 : 1-mixture of CH_3CN and H_2O (35 mL) and CAN (3.81 g, 6.96 mmol) was added at 0 °C under air. After being stirred for 5 min, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give ***rac*-2.64** (550 mg, 2.75 mmol, 79%) as yellow oil.

Spectroscopic data of ***rac*-2.64**: see experiment **V 2.73**.

(*S*)-2-(2-Methyl-1,4-dioxaspiro[4.5]decan-2-yl)acetaldehyde ((*S*)-2.65)

V2.75

(ZY-609)



Based on AVV9, to a solution of **(*S*)-2.64** (2.20 g, 11.0 mmol) in DCM (100 mL) was added Dess–Martin periodinane (5.60 g, 13.2 mmol) at room temperature under air, and the reaction mixture was heated up to 40 ^{o}C for 1 h. After cooling to room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with DCM The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give **(*S*)-2.65** (1.92 g, 9.65 mmol, 88%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (t, *J* = 2.4 Hz, 1H), 3.87 (d, *J* = 8.8 Hz, 1H), 3.81 (d, *J* = 8.8 Hz, 1H), 2.73 (dd, *J* = 15.6, 2.2 Hz, 1H), 2.59 (dd, *J* = 15.6, 2.6 Hz, 1H), 1.66-1.56 (m, 8H), 1.47-1.40 (m, 1H), 1.39 (s, 3H), 1.35 (dd, *J* = 11.7, 5.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.6, 110.5, 78.4, 73.8, 53.6, 36.8, 36.5, 25.9, 25.2, 24.0, 24.0.

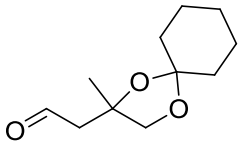
$[\alpha]_D^{20}$ = -34.6 (*c* = 1.10, $CHCl_3$).

The NMR data are consistent with the literature data.[36]

2-(2-Methyl-1,4-dioxaspiro[4.5]decan-2-yl)acetaldehyde (*rac*-2.65)

V2.76

(ZY-585)



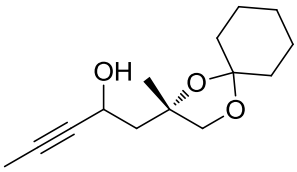
Based on AVV9, to a solution of ***rac*-2.64** (250 mg, 1.25 mmol) in DCM (12 mL) was added Dess–Martin periodinane (636 mg, 1.5 mmol) at room temperature under air, and the reaction mixture was heated up to 40 ^{o}C for 1 h. After cooling to room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give ***rac*-2.65** (180 mg, 0.91 mmol, 73%) as yellow oil.

Spectroscopic data of ***rac*-2.65**: see experiment **V 2.75**.

1-((*S*)-2-Methyl-1, 4-dioxaspiro[4.5]decan-2-yl)pent-3-yn-2-ol ((*S*)-2.66)

V2.77

(ZY-611)



To a solution of propyne (1.0 M in THF; 12.1 mL, 12.12 mmol) in dry THF (60 mL) was added *n*-BuLi (2.5 M in hexane; 5.7 mL, 14.14 mmol) at -80 ^{o}C under argon. After being stirred for 30 min at -80 ^{o}C, to reaction mixture was added the solution of **(*S*)-2.65** (2.00 g, 10.10 mmol) in dry THF (40 mL) at -80 ^{o}C under argon. After warming up to -40 ^{o}C for 1 h, the reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **(*S*)-2.66** (1.97 g, 8.27 mmol, 82%, dr = 62:38) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78-4.53 (m, 1H), 3.87 (dd, *J* = 18.5, 8.6 Hz, 1H), 3.76 (ddd, *J* = 22.3, 8.6, 1.2 Hz, 1H), 2.94 (brs, 1H), 2.14-1.91 (m, 2H), 1.87-1.80 (m, 3H), 1.62 (ddt, *J* = 23.9, 18.4, 8.8 Hz, 8H), 1.46-1.30 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.9, 110.2, 81.0, 80.6, 80.5, 80.3, 80.1, 75.0, 73.7, 60.0, 59.9, 46.9, 46.4, 37.0, 36.4, 36.4, 26.6, 25.2, 24.5, 24.1, 24.1, 24.0, 23.9, 3.7.

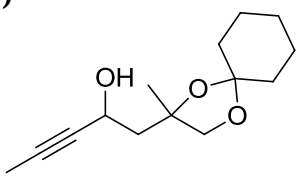
IR (ν cm^{-1}): 3441, 2933, 2861, 2360, 2342.

HRMS: calc'd for $[M+H]^+$: 239.1642, found: 239.1643.

1-(2-Methyl-1,4-dioxaspiro[4.5]decan-2-yl)pent-3-yn-2-ol (*rac*-2.66)

V2.78

(ZY-590)



To a solution of propyne (1.0 M in THF; 0.46 mL, 0.46 mmol) in dry THF (4 mL) was added *n*-BuLi (2.5 M in hexane; 0.26 mL, 0.64 mmol) at -80 ^{o}C under argon. After being stirred for 30 min at -80 ^{o}C, to reaction mixture was added the solution of ***rac*-2.65** (100 mg, 0.5 mmol)

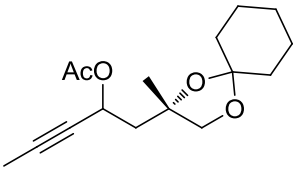
in dry THF (3 mL) at -80 °C under argon. After warming up to -40 °C for 2.5 h, the reaction mixture was quenched with H_2O and extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give ***rac*-2.66** (70 mg, 0.29 mmol, 64%, dr = 62:38) as yellow oil.

Spectroscopic data of ***rac*-2.66**: see experiment **V 2.77**.

1-((*S*)-2-Methyl-1,4-dioxaspiro[4.5]decan-2-yl)pent-3-yn-2-yl acetate ((*S*)-2.67)

V2.79

(ZY-613)



Based on AVV 5, to a solution of **(*S*)-2.66** (2.30 g, 9.66 mmol) in DCM (53 mL) was added Ac_2O (1.84 mL, 19.32 mmol), Et_3N (2.76 mL, 19.32 mmol) and DMAP (72.5 mg, 0.48 mmol) at 0 °C. After being stirred for 30 min at this temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **(*S*)-2.67** (2.60 g, 9.28 mmol, 96%, dr = 62:38) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50-5.40 (m, 1H), 3.92 (dd, *J* = 30.5, 8.5 Hz, 1H), 3.67 (dd, *J* = 20.4, 8.5 Hz, 1H), 2.16-1.98 (m, 5H), 1.86-1.79 (m, 3H), 1.56-1.62 (m, 8H), 1.39-1.28 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 109.9, 109.8, 82.3, 81.9, 79.0, 78.9, 77.3, 74.2, 73.7, 61.7, 61.6, 45.3, 45.1, 36.8, 36.7, 36.5, 25.7, 25.3, 25.2, 25.1, 24.1, 24.0, 21.3, 21.3, 3.8.

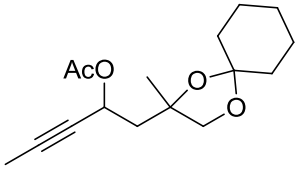
IR (ν cm^{-1}): 2934, 2862, 2248, 1740.

HRMS: calc'd for $[M+H]^+$: 281.1747, found: 281.1747.

1-(2-Methyl-1,4-dioxaspiro[4.5]decan-2-yl)pent-3-yn-2-yl acetate (*rac*-2.67)

V2.80

(ZY-596)



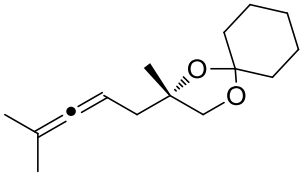
To a solution of ***rac*-2.66** (130 mg, 0.55 mmol) in DCM (3 mL) was added Ac_2O (63 uL, 0.66 mmol), Et_3N (100 uL, 0.72 mmol) and DMAP (4.1 mg, 0.03 mmol) at 0 ^oC. After being stirred for 30 min at this temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give ***rac*-2.67** (127 mg, 0.45 mmol, 82%, dr = 62:38) as light yellow oil.

Spectroscopic data of ***rac*-2.67**: see experiment **V 2.79**.

(*S*)-2-Methyl-2-(4-methylpenta-2, 3-dien-1-yl)-1,4-dioxaspiro[4.5]decane ((*S*)-2.68)

V2.81

(ZY-615)



Based on AVV 6, to a suspension of CuCN (6.40 g, 71.4 mmol) in dry THF (200 mL) was added dropwise *n*-Bu_3P (17.8 mL, 71.4 mmol). The mixture was stirred at room temperature until the solution was homogeneous and then cooled to -40 ^oC. MeMgCl (23.8 mL, 71.4 mmol, 3 M in THF) was added dropwise, the mixture was stirred for a further 30 min during -40 ^oC to -30 ^oC. A solution of **(*S*)-2.67** (2.00 g, 7.14 mmol) in 40 Ml dry THF was added dropwise and the reaction mixture was stirred at this temperature for two hours. Saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes while warming to room temperature. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, the residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(*S*)-2.68** (1.37 g, 5.80 mmol, 81%) as light yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.93 (dddd, *J* = 10.4, 7.6, 5.8, 2.9 Hz, 1H), 3.85 (d, *J* = 8.3 Hz, 1H), 3.67 (d, *J* = 8.3 Hz, 1H), 2.21 (d, *J* = 7.5 Hz, 2H), 1.67 (d, *J* = 2.9 Hz, 6H), 1.64-1.33 (m, 10H), 1.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.7, 109.9, 94.6, 84.4, 80.8, 73.0, 40.6, 36.9, 25.3, 25.1, 24.1, 20.7, 20.6.

IR (ν cm^{-1}): 2976, 2933, 2861, 1969.

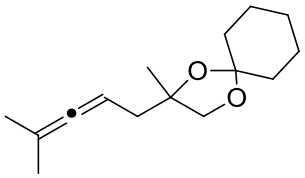
HRMS: calc'd for $[M+H]^+$: 237.1849, found: 237.1849.

$[\alpha]_D^{20}$ = +5.5 (c = 2.10, $CHCl_3$).

2-Methyl-2-(4-methylpenta-2,3-dien-1-yl)-1,4-dioxaspiro[4.5]decane (*rac*-2.68)

V2.82

(ZY-597)



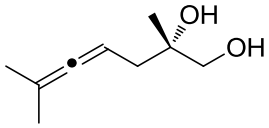
Based on AVV 6, to a suspension of CuCN (225 mg, 2.5 mmol) in dry THF (10 mL) was added dropwise *n*-Bu_3P (0.62 mL, 2.5 mmol). The mixture was stirred at room temperature until the solution was homogeneous and then cooled to -40 ^{o}C. MeMgCl (0.84 mL, 2.5 mmol, 3 M in THF) was added dropwise, the mixture was stirred for a further 30 min during -40 ^{o}C to -30 ^{o}C. A solution of ***rac*-2.67** (70 mg, 0.25 mmol) in dry THF (2 mL) was added dropwise and the reaction mixture was stirred at this temperature for two hours. Saturated aqueous NH_4Cl solution was added and the mixture was hydrolyzed and stirred for another 15 minutes while warming to room temperature. Subsequent filtration through celite, drying with $MgSO_4$, and concentrated under vacuum, the residue was purified by column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.68** (57 mg, 241 umol, 97%) as light yellow oil.

Spectroscopic data of ***rac*-2.68**: see experiment **V 2.81**.

(*S*)-2,6-Dimethylhepta-4,5-diene-1,2-diol ((*S*)-2.33)

V2.83

(ZY-617)



To a solution of **(*S*)-2.68** (2.50 g, 10.58 mmol) in dry MeOH (250 mL) was added *p*-TsOH (2.01 g, 10.58 mmol) at room temperature under argon. After being stirred for 24 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with Et_2O. The organic

layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give **(*S*)-2.33** (1.49 g, 9.55 mmol, 90%) as well as recovered starting material **(*S*)-2.68** (130 mg, 0.55 mmol, 5%) as light yellow oil.

^{1}H NMR (400 MHz, C_6D_6) δ = 5.04 (tp, *J* = 8.6, 2.9 Hz, 1H), 3.35-3.21 (m, 2H), 2.22-2.04 (m, 2H), 1.90 (brs, 1H), 1.75 (brs, 1H), 1.58 (dd, *J* = 2.8, 1.6 Hz, 6H), 1.07 (s, 3H).

^{13}C NMR (100 MHz, C_6D_6) δ = 204.2, 94.4, 84.5, 72.7, 69.6, 39.3, 30.5, 23.5, 20.6.

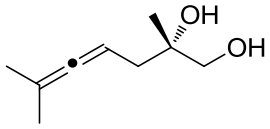
IR (ν cm^{-1}): 3363, 2976, 2933, 2873, 1968, 1721.

HRMS: calc'd for $[M+Na]^+$: 179.1043, found: 179.1043.

$[\alpha]_D^{20}$ = -2.5 (*c* = 2.05, $CHCl_3$).

V2.84

(ZY-584)



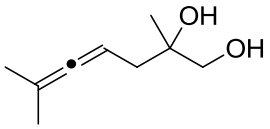
To a solution of **(*S*)-2.32** (830 mg, 4.23 mmol) in THF (8.2 mL) and H_2O (82 mL) was added concentrated acetic acid (205 mL) at room temperature under air. After being stirred for 24 h, the solvent was removed in vacuum using toluene as entrainer. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give **(*S*)-2.33** (590 mg, 3.78 mmol, 89%) as light yellow oil.

Spectroscopic data of **(*S*)-2.33**: see experiment **V 2.83**.

2,6-Dimethylhepta-4,5-diene-1,2-diol (*rac*-2.33)

V2.85

(ZY-598)



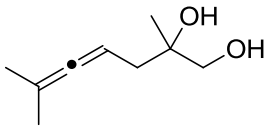
To a solution of ***rac*-2.68** (30 mg, 127 umol) in dry MeOH (3.3 mL) was added *p*-TsOH·H_2O (24 mg, 127 umol) at room temperature under argon. After being stirred for 24 h, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was

purified by column chromatography using pentane-Et_2O (1:1) to give ***rac*-2.33** (15 mg, 96 umol, 76 %) as light yellow oil.

Spectroscopic data of ***rac*-2.33**: see experiment **V 2.83**.

V2.86

(ZY-429)



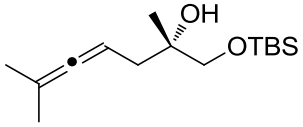
To a solution of ***rac*-2.32** (1 g, 5.1 mmol) in THF (10 mL) and H_2O (100 mL) was added concentrated acetic acid (250 mL) at room temperature under air. After being stirred for 24 h, the solvent was removed in vacuum using toluene as entrainer. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give ***rac*-2.33** (702 mg, 4.5 mmol, 88%) as light yellow oil.

Spectroscopic data of ***rac*-2.33**: see experiment **V 2.83**.

(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylhepta-4,5-dien-2-ol ((*S*)-2.34)

V2.87

(ZY-618)



Based on AVV3, to a solution of **(*S*)-2.33** (1.60 g, 10.25 mmol) in 15 mL dry DCM was added *N*,*N*-dimethylaminopyridine (DMAP) (52 mg, 0.41 mmol), triethylamine (1.7 mL, 12.3 mmol) and *t*-butyldimethylsilyl chloride (TBSCl) (1.62 g, 10.76 mmol) at room temperature. After being stirred for 14 h at this temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **(*S*)-2.34** (2.42 g, 8.94 mmol, 87%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.97-4.89 (m, 1H), 3.48 (d, *J* = 9.4 Hz, 1H), 3.39 (d, *J* = 9.5 Hz, 1H), 2.42 (s, 1H), 2.18-2.08 (m, 2H), 1.68 (d, *J* = 2.9 Hz, 6H), 1.14 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.8, 94.3, 84.2, 72.6, 69.6, 39.0, 26.0, 23.2, 20.8, 20.7, 18.4, -5.3.

IR (ν cm^{-1}): 3570, 3461, 2955, 2930, 2907, 2857, 2711, 1969.

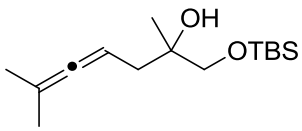
HRMS: calc'd for $[M+H]^+$: 271.2088, found: 271.2088.

$[\alpha]_D^{20}$ = -9.3 (c = 2.03, $CHCl_3$).

1-((*tert*-Butyldimethylsilyl)oxy)-2,6-dimethylhepta-4,5-dien-2-ol (*rac*-2.34)

V2.88

(ZY-432)



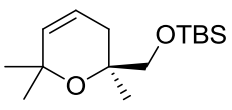
Based on AVV3, to a solution of ***rac*-2.33** (1000 mg, 6.4 mmol) in 10 mL dry DCM was added DMAP (32 mg, 0.26 mmol), triethylamine (1063 uL, 7.68 mmol) and TBSCl (1013 mg, 6.72 mmol) at room temperature. After being stirred for 18 h at this temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give ***rac*-2.34** (1405 mg, 5.2 mmol, 81%) as light yellow oil.

Spectroscopic data of ***rac*-2.34**: see experiment **V 2.87**.

(*S*)-*tert*-Butyldimethyl((2,6,6-trimethyl-3,6-dihydro-2*H*-pyran-2-yl)methoxy)silane ((*S*)-2.35)

V2.89

(ZY-620)



Based on AVV7, to a solution of **(*S*)-2.34** (2.10 g, 7.77 mmol) in 125 mL dry toluene was added Triphenylphosphingold (I) chloride (96.1 mg, 194.3 umol), silver tetrafluoroborate (37.8 mg, 194.3 umol) at room temperature under argon. After being stirred for 6 h, the reaction mixture was filtrated through Celite and the filtrate was concentrated under vacuum.

The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(*S*)-2.35** (1.77 g, 6.54 mmol, 84%) as colorless oil.

The ee was determined by chiral GC: start temperature, 40 ^oC; flow rate, 0.5 $^oC\ min^{-1}$ to 80 ^oC; retention time, **(*S*)-2.35** 65.5 min, **(*R*)-2.35** 69.2 min.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.77-5.58 (m, 2H), 3.51 (d, *J* = 9.2 Hz, 1H), 3.34 (d, *J* = 9.2 Hz, 1H), 2.10 (ddd, *J* = 17.2, 3.7, 1.4 Hz, 1H), 1.91-1.82 (m, 1H), 1.25 (s, 3H), 1.20 (d, *J* = 2.9 Hz, 6H), 0.89 (s, 9H), 0.03 (d, *J* = 2.1 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.2, 120.8, 73.5, 71.6, 69.8, 31.0, 31.0, 30.3, 26.1, 24.9, 18.4, -5.3.

IR (ν cm^{-1}): 3032, 2971, 2956, 2929, 2896, 2858, 2710, 1666.

HRMS: calc'd for $[M+H]^+$: 271.2088, found: 271.2088.

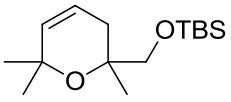
ee = >99%.

$[\alpha]_D^{20}$ = -3.3 (*c* = 2.27, $CHCl_3$).

tert-Butyldimethyl((2,6,6-trimethyl-3,6-dihydro-2*H*-pyran-2-yl)methoxy)silane (*rac*-2.35)

V2.90

(ZY-437)



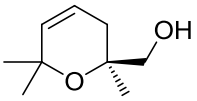
Based on AVV7, to a solution of ***rac*-2.34** (1000 mg, 3.7 mmol) in 60 mL dry toluene was added Triphenylphosphingold (I) chloride (45.8 mg, 92.5 umol), silver tetrafluoroborate (18 mg, 92.5 umol) at room temperature under argon. After being stirred for 8 h, the reaction mixture was filtrated through Celite and the filtrate was concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.35** (842 mg, 3.1 mmol, 84%) as colorless oil.

Spectroscopic data of ***rac*-2.35**: see experiment **V 2.89**.

(*S*)-(2,6,6-Trimethyl-3,6-dihydro-2*H*-pyran-2-yl)methanol ((*S*)-2.37)

V2.91

(ZY-623)



To a solution of (***S*)-2.35** (1.00 g, 3.7 mmol) in 36 mL THF was added tetrabutylammonium fluoride trihydrate (2.34 g, 7.4 mmol) at room temperature. Then the solution was heated at reflux for 7.5 h. After cooled to room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, filtered through celite, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give (***S*)-2.37** (546 mg, 3.5 mmol, 95%) as light yellow oil.

The ee was determined by chiral GC: start temperature, 40 ^oC; flow rate, 0.5 $^oC\ min^{-1}$ to 65 ^oC; retention time, (***R*)-2.37** 37.6 min, (***S*)-2.37** 46.5 min.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.74-5.64 (m, 2H), 3.44-3.34 (m, 2H), 2.29 (d, *J* = 16.9 Hz, 1H), 2.10 (bs, 1H), 1.74 (dd, *J* = 16.9, 5.3 Hz, 1H), 1.28 (s, 3H), 1.23 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.6, 120.6, 72.8, 72.1, 69.9, 31.1, 30.0, 29.5, 24.3.

IR ($\nu\ cm^{-1}$): 3441, 3031, 2972, 2929, 1663.

HRMS: calc'd for $[M+H]^+$: 157.1223, found: 157.1223.

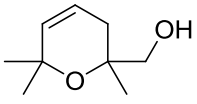
ee = >99%.

$[\alpha]_D^{20}$ = -11.8 (*c* = 1.27, $CHCl_3$).

(2,6,6-Trimethyl-3,6-dihydro-2*H*-pyran-2-yl)methanol (*rac*-2.37)

V2.92

(ZY-446)



To a solution of ***rac*-2.35** (1000 mg, 3.7 mmol) in 38 mL THF was added tetrabutylammonium fluoride trihydrate (2335 mg, 7.4 mmol) at room temperature. Then the solution was heated at reflux for 7.5 h. After cooled to room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, filtered through celite, and

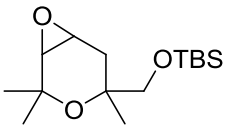
concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give ***rac*-2.37** (531 mg, 3.4 mmol, 92%) as light yellow oil.

Spectroscopic data of ***rac*-2.37**: see experiment **V 2.91**.

tert-Butyldimethyl((2,2,4-trimethyl-3,7-dioxabicyclo[4.1.0]heptan-4-yl)methoxy)silane (*rac*-2.36)

V2.93

(ZY-530)



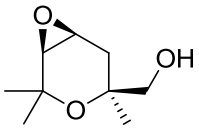
Based on AVV8, to a solution of ***rac*-2.35** (100 mg, 0.37 mmol) in 6 mL dry DCM was added disodium hydrogen phosphate (105 mg, 0.74 mmol) and *m*-CPBA (70%-75% in water, 182 mg, 0.74 mmol,) at 0 ℃. After being stirred for 41 h at room temperature, the reaction mixture was quenched with sat. aq. Na_2CO_3 and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (2:1) to give ***rac*-2.36** (87 mg, 0.3 mmol, 82%, dr = 1:1) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.56-3.33 (m, 1H), 3.41-3.40 (m, 0.5H), 3.38-3.36 (m, 0.5H), 3.27 (dd, J = 30.7, 9.3 Hz, 1H), 2.93 (dd, J = 13.8, 4.4 Hz, 1H), 2.05-1.96 (m, 1H), 1.83-1.70 (m, 1H), 1.34 (s, 3H), 1.28 (d, J = 2.3 Hz, 3H), 1.18 (d, J = 38.7 Hz, 3H), 0.88 (d, J = 1.5 Hz, 9H), 0.03 (t, J = 3.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.0/72.8, 71.8/70.4, 69.9/69.8, 56.6/55.9, 51.5/50.8, 29.9/29.7, 29.0/28.5, 28.2/27.7, 27.1/27.0, 26.0/26.0/25.9, 18.4/18.4, -5.3/-5.3.

HRMS: calc'd for $[M+H]^+$: 287.2037, found: 287.2039; calc'd for $[M+Na]^+$: 309.1856, found: 309.1858.

((2*S*,4*S*,5*S*)-2,2,4-Trimethyl-3,7-dioxabicyclo[4.1.0]heptan-4-yl)methanol ((2*S*,4*S*,5*S*)-2.38)



V2.94

(ZY-625)

Based on AVV8, to a solution of (***S*)-2.37** (496 mg, 3.18 mmol) in 30 mL dry DCM was added disodium hydrogen phosphate (677 mg, 4.77 mmol) and *m*CPBA (70%-75% in water, 1.18 g, 4.77 mmol,) at 0 ℃. After being stirred for 48 h at room temperature, the reaction mixture was quenched with sat. aq. Na_2CO_3 and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (2:1) to give (2***S*,4*S*,5*S*)-2.38** (427 mg, 2.48 mmol, 78%, dr = 6.3:1.0) as yellow oil.

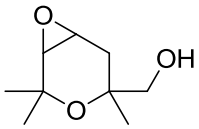
^{1}H NMR (400 MHz, $CDCl_3$): δ =4.47-4.45/3.41-3.39 (m, 1H), 3.34-3.28 (m, 2H), 2.95 (d, *J* = 4.4 Hz, 1H), 2.18 (ddd, *J* = 15.4, 6.1, 1.8 Hz, 1H), 1.80 (dd, *J* = 15.4, 3.6 Hz, 1H), 1.36 (s, 3H), 1.31 (s, 3H), 1.15 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.4/72.3, 71.1/70.9, 70.5/69.8, 56.8/55.5, 52.2/50.6, 29.6/29.2, 28.3/28.0, 27.4/27.2, 26.9/25.2.

IR (*v* cm^{-1}): 3441, 2975, 2933, 2875, 2360, 1722, 1649, 1575.

HRMS: calc'd for $[M+H]^+$: 173.1172, found: 173.1172.

2,2,4-Trimethyl-3,7-dioxabicyclo[4.1.0]heptan-4-yl)methanol (*rac*-2.38)



V2.95

(ZY-595)

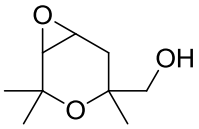
Based on AVV8, to a solution of ***rac*-2.37** (680 mg, 4.36 mmol) in 43 mL dry DCM was added disodium hydrogen phosphate (1237 mg, 8.72 mmol) and *m*CPBA (70%-75% in water, 2148 mg, 8.72 mmol,) at 0 ℃. After being stirred for 48 h at room temperature, the reaction mixture was quenched with sat. aq. Na_2CO_3 and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum.

The residue was purified by column chromatography using pentane-Et_2O (2:1) to give ***rac*-2.38** (550 mg, 3.20 mmol, 73%, dr = 4.0:1.0) as yellow oil.

Spectroscopic data of ***rac*-2.38**: see experiment **V 2.94**.

V2.96

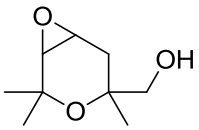
(ZY-252)



Based on AVV8, to a solution of ***rac*-2.37** (48 mg, 0.31 mmol) in 3 mL dry DCM was added disodium hydrogen phosphate (65 mg, 0.46 mmol) and *m*CPBA (70%-75% in water, 113 mg, 0.46 mmol,) at 0 ℃. After being stirred for 5 days at 0 ℃, the reaction mixture was quenched with sat. aq. Na_2CO_3 and extracted three times with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (2:1) to give ***rac*-2.38** (20 mg, 116 umol, 37%, dr = 4.0:1.0) and recovered A14 (10 mg, 64 umol, 20%) as yellow oil.

V2.97

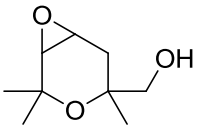
(ZY-259)



Based on AVV8, to a solution of ***rac*-2.37** (166 mg, 1.06 mmol) in 12 mL dry DCM was added disodium hydrogen phosphate (452 mg, 3.18 mmol) and *m*CPBA (70%-75% in water, 784 mg, 3.18 mmol,) at 0 ℃. After being stirred for 44 h at room temperature, the reaction mixture was quenched with sat. aq. Na_2CO_3 and extracted three times with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (2:1) to give ***rac*-2.38** (30 mg, 174 umol, 16%, dr = 4.0:1.0) as yellow oil.

V2.98

(ZY-476)

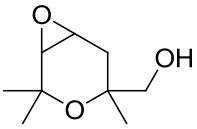


Based on AVV8, to a solution of ***rac*-2.37** (110 mg, 0.7 mmol) in 10 mL dry DCM was added *m*CPBA (70%-75% in water, 345 mg, 1.4 mmol,) at 0 ℃. After being stirred for 39 h at room

temperature, the reaction mixture was quenched with sat. aq. Na_2CO_3 and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (2:1) to give ***rac*-2.38** (61 mg, 0.354 mmol, 51%, dr = 4.0:1.0) as yellow oil.

V2.99

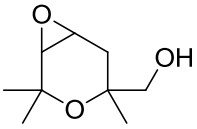
(ZY-536)



Based on AVV8, to a solution of ***rac*-2.36** (40 mg, 0.14 mmol, dr = 1:1) in 1.5 mL THF was added tetrabutylammonium fluoride trihydrate (88 mg, 0.28 mmol) at room temperature. Then the solution was heated at reflux for 7.5 h. After cooled to room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, filtered through celite, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give ***rac*-2.38** (23 mg, 134 umol, 96%, dr = 1:1) as light yellow oil.

V2.100

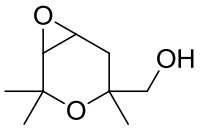
(ZY-248)



To a suspension of $VO(acac)_2$ (1.4 mg, 5.3 umol) in 2 mL Toluene was added ***rac*-2.37** (24.6 mg, 157.6 umol) and TBHP (50 uL, 275umol, 5.5 M in decane) at room temperature. The reaction was stirred at MW irradiation (113 ^oC, 150 W max) for 100 min. After being cooled to room temperature, the mixture was quenched with sat. aq. $Na_2S_2O_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (2:1) to give ***rac*-2.37** (20 mg, 128 umol, 81%) as light yellow oil and trace ***rac*-2.38**.

V2.101

(ZY-244)

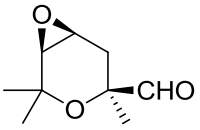


To a suspension of $VO(acac)_2$ (0.3 mg, 0.96 umol) in 2 mL DCM was added ***rac*-2.37** (10 mg, 64.1 umol) and TBHP (17.5 uL, 96.1 umol, 5.5 M in decane) at 0 ^{o}C. After being stirred about 5 days at room temperature, it still had a lot of ***rac*-2.37** and trace ***rac*-2.38**.

(2*S*,4*S*,5*S*)-2,2,4-Trimethyl-3,7-dioxabicyclo[4.1.0]heptane-4-carbaldehyde ((2*S*,4*S*,5*S*)-2.59)

V2.102

(ZY-629)



Based on AVV9, to a solution of (2***S*,4*S*,5*S*)-2.38** (50 mg, 0.29 mmol) in 3.0 mL DCM was added Dess–Martin periodinane (148 mg, 0.35 mmol) at room temperature under argon. After being stirred for 2.5 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give (2***S*,4*R*,5*R*)-2.59** (3 mg, 17.6 umol, 6%) and (2***S*,4*S*,5*S*)-2.59** (22 mg, 129.3 umol, 45%) as light yellow oil.

(2***S*,4*S*,5*S*)-2.59**:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, J = 1.4 Hz, 1H), 3.34 (t, J = 3.9 Hz, 1H), 2.99 (d, J = 4.5 Hz, 1H), 2.74 (dd, J = 14.7, 3.4 Hz, 1H), 1.94 (dt, J = 14.7, 1.0 Hz, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.08 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.1, 78.1, 70.7, 57.1, 50.6, 32.9, 28.7, 28.4, 24.8.

IR (ν cm^{-1}): 2981, 2973, 2951, 2929, 2870, 2810, 2687, 2361, 2342, 1806, 1721.

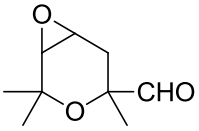
HRMS: calc'd for $[M+Na]^+$: 193.0835, found: 193.0822.

$[\alpha]_D^{20}$ = +33.4 (c = 0.70, $CHCl_3$).

2,2,4-Trimethyl-3,7-dioxabicyclo[4.1.0]heptane-4-carbaldehyde (*rac*-2.59)

V2.103

(ZY-485)



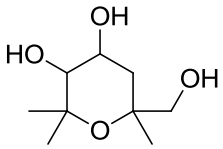
Based on AVV9, to a solution of ***rac*-2.38** (60 mg, 0.35 mmol) in 4 mL DCM was added Dess–Martin periodinane (178 mg, 0.42 mmol) at room temperature under argon. After being stirred for 1 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give ***rac*-2.59** (42 mg, 0.25 mmol, 71%) as light yellow oil.

Spectroscopic data of ***rac*-2.59**: see experiment **V 2.102**.

6-(Hydroxymethyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diol (*rac*-2.39)

V2.104

(ZY-324)



To a solution of ***rac*-2.42** (87 mg, 0.27 mmol) in 5 mL MeOH/DCM (3:2) was added $PdCl_2$ (58 mg, 0.33 mmol) at room temperature. After being stirred for 40 min at room temperature, the mixture was filtered through celite and saturated aqueous NaCl was added. The aqueous phase was extracted four times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was dissolved in MeOH (5 mL) and Pd/C (30 mg) was added. The suspension was stirred for 2 h under hydrogen atmosphere at room temperature. The mixture was filtered through celite and the solvent was removed in vacuo. The residue was purified by column chromatography using DCM-MeOH (20:1) to give ***rac*-2.39** (30 mg, 157.8 umol, 58%) as colorless viscous oil.

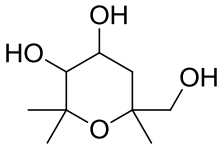
^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 3.98-3.97 (m, 1H), 3.82-3.75 (m, 1H), 3.73-3.71 (m, 1H), 3.52-3.45 (m, 2H), 3.37 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.13-3.10 (m, 1H), 2.13 (dd, *J* = 13.2, 4.8 Hz, 1H), 1.37-1.29 (m, 1H), 1.21 (s, 3H), 1.19 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (100 MHz, $(CD_3)_2CO$): δ = 80.9/80.9/80.8/80.8, 76.9/76.0, 68.0/67.9, 67.1/67.0, 41.4/41.3, 31.2, 28.7, 23.6/23.6.

HRMS: calc'd for $[M+Na]^+$: 213.1097, found: 213.1094.

V2.105

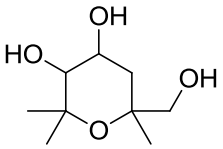
(ZY-253)



To a solution of ***rac*-2.38** (4 mg, 23.2 umol) in 1.5 mL H_2O concentrated acetic acid (0.5 mL) was added. After being stirred overnight at room temperature, another concentrated acetic acid (1.0 mL) was added. After being stirred 10 h at room temperature, another concentrated acetic acid (4.5 mL) was added again. It was continued to stir 4 days and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.106

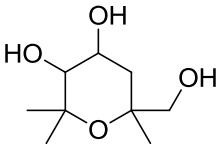
(ZY-263)



To a solution of ***rac*-2.38** (20 mg, 116 umol) in 7 mL H_2O concentrated acetic acid (28 mL) was added. After being stirred 22 h at room temperature, another concentrated acetic acid (7 mL) was added. It was continued to stir 74 and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.107

(ZY-257)

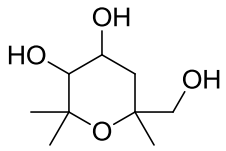


To a solution of ***rac*-2.38** (2.5 mg, 14.5 umol) in 0.1 mL H_2O and 2 mL THF three drops $HClO_4$ (60% in water) was added. After being stirred 23 h at room temperature, another three drops $HClO_4$ (60% in water) was added. After being stirred 46 h at room temperature, another four drops $HClO_4$ (60% in water) was added again. It was continued to stir 2.5 h and

monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.108

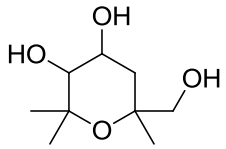
(ZY-258)



To a solution of ***rac*-2.38** (2.5 mg, 14.5 umol) in 1 mL acetone H_2SO_4 (0.5 mL, 1M in water) was added. After being stirred 23 h at room temperature, another H_2SO_4 (0.5 mL, 1M in water) was added. After being stirred 46 h at room temperature, another H_2SO_4 (0.5 mL, 1M in water) was added again. It was continued to stir 2.5 h and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.109

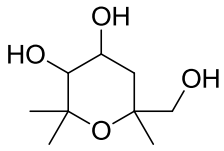
(ZY-266)



To a solution of ***rac*-2.38** (3 mg, 17.4 umol) NaOH (0.5 mL, 10% in water) was added at room temperature. It was stirred 48 h and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.110

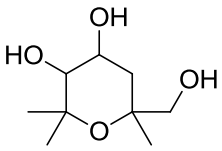
(ZY-267)



To a solution of ***rac*-2.38** (3 mg, 17.4 umol) in 0.5 ml acetone NaOH (0.5 mL, 10% in water) was added at room temperature. It was stirred 48 h and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.111

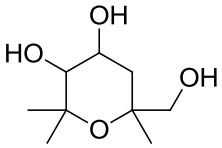
(ZY-268)



To a solution of ***rac*-2.38** (3 mg, 17.4 umol) H_2SO_4 (0.5 mL, 2M in water) was added. It was stirred 48 h and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.112

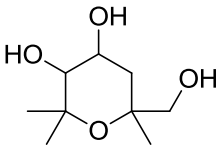
(ZY-269)



To a solution of ***rac*-2.38** (3 mg, 17.4 umol) in 0.5 mL acetone H_2SO_4 (0.5 mL, 2M in water) was added. It was stirred 48 h and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.113

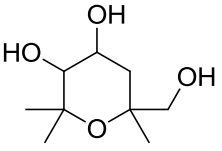
(ZY-280)



To a solution of ***rac*-2.38** (2 mg, 11.6 umol) in 1 mL THF H_2SO_4 (0.2 mL, 2M in water) was added at room temperature. It was stirred 24 h at 65 ^oC and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.114

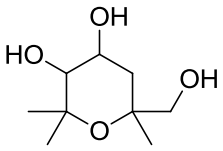
(ZY-282)



To a solution of ***rac*-2.38** (14 mg, 81.3 umol) in 1 mL THF H_2SO_4 (0.2 mL, 2M in water) was added at room temperature. It was stirred 19 h at 65 ^oC and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.115

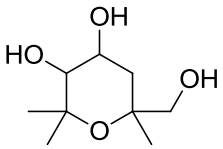
(ZY-281)



To a solution of ***rac*-2.38** (2 mg, 11.6 umol) in 1 mL THF and 0.1 mL H_2O $HClO_4$ (0.1 mL, 60% in water) was added at room temperature. It was stirred 48 h at 65 ^oC and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.116

(ZY-285)

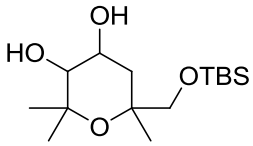


To a solution of ***rac*-2.38** (6 mg, 34.9 umol) in 1 mL THF and 0.1 mL H_2O $HClO_4$ (0.1 mL, 60% in water) was added at room temperature. It was stirred 46 h at 65 ^oC and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

6-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diol (*rac*-2.40)

V2.117

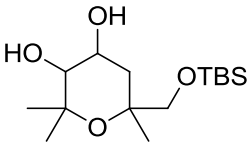
(ZY-270)



To a solution of ***rac*-2.36** (2 mg, 6.6 umol) NaOH (0.5 mL, 10% in water) was added at room temperature. It was stirred 48 h and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.118

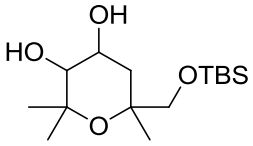
(ZY-271)



To a solution of ***rac*-2.36** (2 mg, 6.6 umol) in 0.5 mL acetone NaOH (0.5 mL, 10% in water) was added at room temperature. It was stirred 48 h and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.119

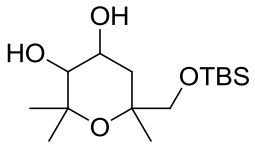
(ZY-272)



To a solution of ***rac*-2.36** (2 mg, 6.6 umol) H_2SO_4 (0.5 mL, 2M in water) was added at room temperature. It was stirred 2 h and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.120

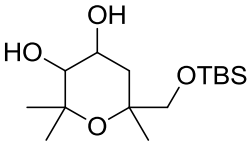
(ZY-273)



To a solution of ***rac*-2.36** (2 mg, 6.6 umol) in 0.5 mL acetone H_2SO_4 (0.5 mL, 2M in water) was added at room temperature. It was stirred 2 h and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.121

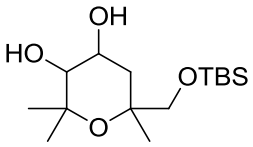
(ZY-283)



To a solution of ***rac*-2.36** (2 mg, 6.6 umol) in 1mL THF H_2SO_4 (0.2 mL, 2M in water) was added at room temperature. It was stirred 48 h at 65 ^oC and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

V2.122

(ZY-284)

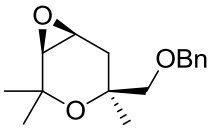


To a solution of ***rac*-2.36** (2 mg, 6.6 umol) in 1 mL THF and 0.1 mL H_2O $HClO_4$ (0.1 mL, 60% in water) was added at room temperature. It was stirred 48 h at 65 ^oC and monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

(2*S*,4*S*,5*S*)-4-((Benzyloxy)methyl)-2,2,4-trimethyl-3,7-dioxabicyclo[4.1.0]heptane ((2*S*,4*S*,5*S*)-2.41)**

V2.123

(ZY-635)



Based on AVV10, to a solution of (2***S*,4*S*,5*S*)-2.38** (320 mg, 1.86 mmol) in 20 mL THF/DMF (3:1) was added NaH (165 mg, 4.09 mmol) was added and stirred for 30 min at 0 ^oC. BnBr (0.47 mL, 3.91 mmol) was added dropwise to the solution. After being stirred for 6 h at room temperature, the reaction mixture was quenched with water carefully and the aqueous phase was extracted five times with ethyl acetate. The organic layers were dried with $MgSO_4$, the solvent was removed. Toluene (3 x 60 mL) was added and removed in vacuum to remove traces of DMF. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give (2***S*,4*S*,5*S*)-2.41** (439 mg, 1.67 mmol, 90%, dr = 4.5:1.0) as light yellow oil.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.26 (m, 5H), 4.57-4.51 (m, 2H), 3.41-3.35/3.25-3.20 (m, 2H), 3.39-3.37 (m, 1H), 2.95 (d, *J* = 4.4 Hz, 1H), 2.07 (dd, *J* = 15.3, 2.0 Hz, 1H), 1.77 (dd, *J* = 15.3, 3.5 Hz, 1H), 1.35 (d, *J* = 5.1 Hz, 3H), 1.31 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.9/138.7, 128.5, 128.4/128.4, 127.7/127.7, 127.6/127.6, 127.6/127.5, 78.7/78.5, 73.5/73.4, 72.5/72.1, 70.0/69.9, 56.4/56.0, 51.4/50.9, 30.5/30.3, 28.8/28.7, 28.0/27.7, 27.6/26.4.

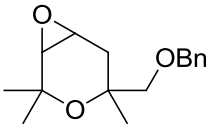
IR (ν cm^{-1}): 3029, 2975, 2929, 2861, 2360, 2116, 1952, 1812, 1737, 1605, 1497, 1454.

HRMS: calc'd for $[M+Na]^+$: 285.1461, found: 285.1471.

4-((Benzyloxy)methyl)-2,2,4-trimethyl-3,7-dioxabicyclo[4.1.0]heptane (*rac*-2.41)

V2.124

(ZY-477)

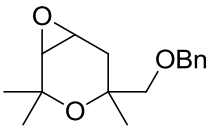


Based on AVV10, to a solution of ***rac*-2.38** (240 mg, 1.39 mmol) in 16 mL THF/DMF (3:1) was added NaH (122.4 mg, 3.06 mmol) was added and stirred for 30 min at 0 ^{o}C. BnBr (355 uL, 2.92 mmol) was added dropwise to the solution. After being stirred for 4 h at room temperature, the reaction mixture was quenched with water carefully and the aqueous phase was extracted five times with ethyl acetate. The organic layers were dried with MgSO4, the solvent was removed. Toluene (3 x 10 mL) was added and removed in vacuum to remove traces of DMF. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give ***rac*-2.41** (300 mg, 1.14 mmol, 82%) as light yellow oil.

Spectroscopic data of ***rac*-2.41**: see experiment **V 2.123**.

V2.125

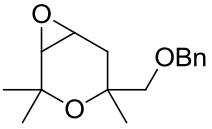
(ZY-439)



Based on AVV10, to a solution of ***rac*-2.38** (160 mg, 0.93 mmol) in 16 mL THF/DMF (1:1) was added NaH (81.6 mg, 2.04 mmol) was added and stirred for 30 min at 0 ^{o}C. BnBr (237 uL, 1.95 mmol) was added dropwise to the solution. After being stirred for 23.5 h at room temperature, the reaction mixture was quenched with water carefully and the aqueous phase was extracted five times with ethyl acetate. The organic layers were dried with MgSO4, the solvent was removed. Toluene (3 x 10 mL) was added and removed in vacuum to remove traces of DMF. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give ***rac*-2.41** (163 mg, 0.62 mmol, 67%) as light yellow oil.

V2.126

(ZY-311)

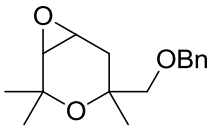


Based on AVV10, to a solution of ***rac*-2.38** (20 mg, 116 umol) in 2 mL THF/DMF (1:1) was added NaH (10.6 mg, 264 umol) was added and stirred for 30 min at 0 ^{o}C. BnBr (30 uL, 252

umol) and TBAI (2.2 mg, 6 umol) were added to the solution. After being stirred for 47.5 h at room temperature, the reaction mixture was quenched with water carefully and the aqueous phase was extracted five times with ethyl acetate. The organic layers were dried with MgSO4, the solvent was removed. Toluene (3 x 10 mL) was added and removed in vacuum to remove traces of DMF. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give ***rac*-2.41** (19.8 mg, 75.5 umol, 65%) as light yellow oil.

V2.127

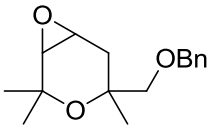
(ZY-308)



Based on AVV10, to a solution of ***rac*-2.38** (4 mg, 23.2 umol) in 1 mL DMF was added NaH (2.1 mg, 51 umol) was added and stirred for 30 min at 0 ^{o}C. BnBr (6 uL, 48.7 umol) was added dropwise to the solution. After being stirred for 22 h at room temperature, there is no any product and the reaction mixture was quenched with water carefully.

V2.128

(ZY-295)

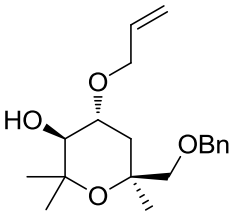


Based on AVV10, to a solution of ***rac*-2.38** (10 mg, 0.06 mmol) in 2 mL THF was added NaH (4.8 mg, 0.12 mmol) was added and stirred for 25 min at 0 ^{o}C and 30 min at room temperature. BnBr (14 uL, 0.12 mmol) and some TBAI were added dropwise to the solution. After being stirred for 1h at room temperature, 2 mL DMF was added. It was continued to stir about three days, the product was still very weak.

(2*S*,4*R*,5*S*)-4-(Allyloxy)-6-((benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3-ol ((2*S*,4*R*,5*S*)-2.42)

V2.129

(ZY-636)



To a solution of (2***S*,4*S*,5*S*)-2.41** (400 mg, 1.53 mmol) in 20 mL allyl alcohol was added $HClO_4$ (70% in water, 0.46 mL, 7.65 mmol) was added slowly at 0 ℃. The reaction mixture

was stirred at 0 ℃ for 2 h, then at room temperature for 5 h. The solution was diluted with DCM and sat. aq. $NaHCO_3$ was added. The aqueous solution was extracted five times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **(2*S*,4*R*,5*S*)-2.42** (353 mg, 1.10 mmol, 72%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.28 (m, 5H), 5.91 (ddd, *J* = 22.8, 10.5, 5.7 Hz, 1H), 5.28-5.17 (m, 2H), 4.59-4.47 (m, 2H), 4.10 (dd, *J* = 12.6, 5.5 Hz, 1H), 3.92 (dd, *J* = 12.6, 5.8 Hz, 1H), 3.52 (ddd, *J* = 11.1, 9.0, 4.8 Hz, 1H), 3.47 (d, *J* = 9.1 Hz, 1H), 3.31 (d, *J* = 4.9 Hz, 1H), 3.30 (d, *J* = 4.8 Hz, 1H), 2.51 (brs, 1H), 2.30 (dd, *J* = 13.1, 4.8 Hz, 1H), 1.35-1.33 (m, 1H), 1.31 (s, 3H), 1.26 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 135.0, 128.5, 127.8, 117.2, 78.2, 76.2, 75.7, 75.0, 74.8, 73.5, 69.9, 37.3, 30.6, 29.2, 23.4.

IR (ν cm^{-1}): 3472, 2976, 2930, 2863, 2362, 1873, 1647, 1605, 1587, 1496, 1454.

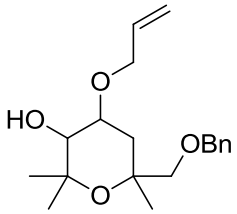
HRMS: calc'd for $[M+Na]^+$: 343.1880, found: 343.1900.

$[\alpha]_D^{20}$ = -37.8 (*c* = 2.05, $CHCl_3$).

4-(Allyloxy)-6-((benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3-ol(*rac*-2.42)

V2.130

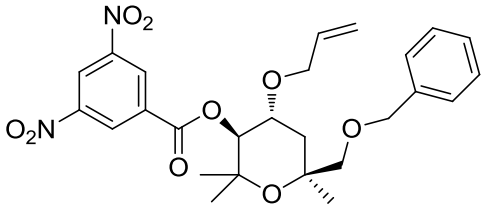
(ZY-604)



To a solution of ***rac*-2.41** (490 mg, 1.87 mmol) in 27 mL allyl alcohol was added $HClO_4$ (70% in water, 556 uL, 9.35 mmol) was added slowly at 0 ℃. The reaction mixture was stirred at 0 ℃ for 2 h, then at room temperature for 4 h. The solution was diluted with DCM and sat. aq. $NaHCO_3$ was added. The aqueous solution was extracted five times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10 : 1) to give ***rac*-2.42** (419 mg, 1.31 mmol, 70%) as yellow oil.

Spectroscopic data of ***rac*-2.42**: see experiment **V 2.129**.

(2*S*,4*R*,5*S*)-4-(Allyloxy)-6-((benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3-yl 3,5-dinitrobenzoate ((2*S*,4*R*,5*S*)-2.70)



V2.131

(ZY-642)

To a solution of **(2*S*,4*R*,5*S*)-2.42** (8.0 mg, 25 umol) in pyridine (1.6 mL) 3,5-dinitrobenzoyl chloride (28.8 mg, 125 umol) was added at room temperature. The yellow solution was stirred for 1 h. sat. aq. NH_4Cl (15 mL) was added and the aqueous layer was extracted with DCM (4 x 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(2*S*,4*R*,5*S*)-2.70** (12.7 mg, 24.7 umol, 99%) as white solid.

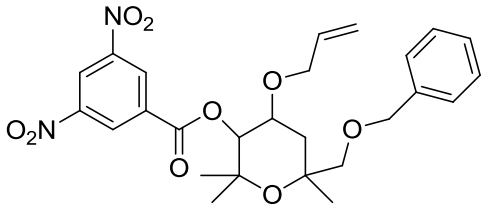
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.24 (t, *J* = 2.1 Hz, 1H), 9.12 (d, *J* = 2.1 Hz, 2H), 7.36-7.34 (m, 4H), 7.32-7.29 (m, 1H), 5.75-5.68 (m, 1H), 5.14-5.10 (m, 2H), 5.06-5.04 (m, 1H), 4.63-4.55 (m, 2H), 4.07-4.04 (m, 1H), 3.91-3.84 (m, 2H), 3.50 (d, *J* = 9.3 Hz, 1H), 3.39 (d, *J* = 9.3 Hz, 1H), 2.40 (dd, *J* = 13.6, 4.9 Hz, 1H), 1.61 (dd, *J* = 13.6, 10.3 Hz, 1H), 1.35 (s, 3H), 1.34 (s, 3H), 1.32 (s, 3H).

^{13}C NMR (100 MHz, CDCl3): δ = 162.1, 148.9, 138.2, 134.6, 134.1, 129.5, 128.6, 127.9, 127.8, 122.6, 117.0, 80.3, 76.2, 75.0, 74.9, 73.6, 72.6, 69.9, 37.1, 30.3, 28.6, 24.8.

HRMS: calc'd for $[M+H]^+$: 515.2024, found: 515.2026; calc'd for $[M+Na]^+$: 537.1844, found: 537.1841.

$[\alpha]_D^{20}$ = -19.3 (*c* = 1.13, $CHCl_3$).

4-(Allyloxy)-6-((benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3-yl 3,5-dinitrobenzoate (*rac*-2.70)



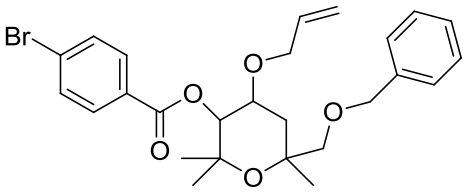
V2.132

(ZY-507)

To a solution of ***rac*-2.42** (20 mg, 62.5 umol) in pyridine (4 mL) 3, 5 -dinitrobenzoyl chloride (72 mg, 312.5 umol) was added at room temperature. The yellow solution was stirred for 1 h. Sat. aq. NH_4Cl (15 mL) was added and the aqueous layer was extracted with CH2Cl2 (4 x 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.70** (29 mg, 56.4 umol, 90%) as white solid.

Spectroscopic data of ***rac*-2.70**: see experiment **V 2.131**.

4-(Allyloxy)-6-((benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3-yl 4-bromobenzoate (*rac*-2.72)



V2.133

(ZY-538)

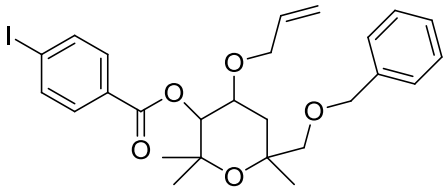
To a solution of ***rac*-2.42** (10 mg, 31.2 umol) in pyridine (2 mL) 4-bromobenzoyl chloride (34 mg, 156 umol) was added at room temperature. The yellow solution was stirred for 23.5 h. Sat. aq. NH_4Cl (15 mL) was added and the aqueous layer was extracted with DCM (4 x 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuum. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.72** (13 mg, 25.9 umol, 83%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 4.3 Hz, 4H), 7.30 (dt, J = 8.7, 4.0 Hz, 1H), 5.74 (ddd, J = 22.6, 10.6, 5.4 Hz, 1H), 5.16-5.12 (m, 1H), 5.07-5.03 (m, 2H), 4.62-4.55 (m, 2H), 4.03 (dd, J = 13.1, 5.3 Hz, 1H), 3.91 (dd, J = 12.4, 4.8 Hz, 1H), 3.81-3.76 (m, 1H), 3.42 (dd, J = 49.5, 9.4 Hz, 2H), 2.31 (dd, J = 13.7, 4.8 Hz, 1H), 1.64 -1.59 (m, 1H), 1.34 (s, 3H), 1.31 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 138.5, 134.9, 131.9, 131.3, 129.2, 128.5, 128.3, 127.8, 127.8, 116.7, 77.6, 76.6, 75.0, 74.7, 73.6, 72.9, 70.3, 36.5, 29.9, 28.2, 25.2.

HRMS: calc'd for $[M+H]^+$: 503.1428, found: 503.1432; calc'd for $[M+Na]^+$: 525.1247, found: 525.1249; calc'd for $[M+K]^+$: 541.0987, found: 541.0990.

4-(Allyloxy)-6-((benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3-yl 4-iodobenzoate (*rac*-2.74)

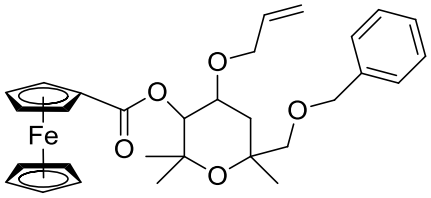


V2.134

(ZY-547)

To a solution of ***rac*-2.42** (10 mg, 31.2 umol) in pyridine (2 mL) 4-iodobenzoyl chloride (41.5 mg, 156 umol) was added at room temperature. After being stirred for 11 h, DMAP (7.6 mg, 62.4 umol) was added. It was continued to stir for 60 h and monitored by thin layer chromatography. No conversion was observed and the reaction was terminated.

Ferrocenecarboxylic ester (*rac*-2.76)



V2.135

(ZY-628)

To a solution of ***rac*-2.42** (10 mg, 31.2 mmol) in 1 mL DCM was added ferrocenecarboxylic acid **2.75** (71.8 mg, 312 umol), DCC (64.4 mg, 312 umol) and DMAP (38.1 mg, 312 umol) at room temperature. After being stirred for 48 hours at room temperature, the resulting slurry was filtered through celite and concentrated under reduced pressure. The residue was dissolved in ether and filtered through celite again and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give ***rac*-2.76** (10 mg, 18.8 umol, 60%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, J = 4.3 Hz, 4H), 7.31 (dt, J = 8.6, 4.1 Hz, 1H), 5.86 (ddt, J = 15.8, 10.5, 5.3 Hz, 1H), 5.24 (d, J = 17.2 Hz, 1H), 5.12 (d, J = 10.3 Hz, 1H), 4.96 (d, J = 7.5 Hz, 1H), 4.80 (s, 2H), 4.60 (s, 2H), 4.40 (s, 2H), 4.23 (s, 5H), 4.10-4.00 (m, 2H), 3.76

(td, J = 8.5, 4.9 Hz, 1H), 3.58-3.35 (m, 2H), 2.33-2.27 (m, 1H), 1.60 (dd, J = 13.7, 8.9 Hz, 1H), 1.36 (d, J = 7.6 Hz, 6H), 1.29 (s, 3H).

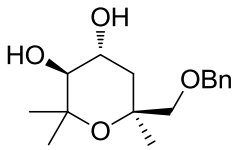
^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 138.6, 135.0, 128.5, 127.7, 127.7, 116.8, 75.8, 74.8, 74.4, 73.6, 72.8, 71.7, 70.5, 70.4, 70.0, 35.8, 30.4, 29.9, 28.0, 25.7.

HRMS: calc'd for $[M+H]^+$: 533.1985, found: 533.1981; calc'd for $[M+Na]^+$: 555.1804, found: 555.1809.

(2*S*,4*R*,5*S*)-6-((Benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diol ((2*S*,4*R*,5*S*)-2.50)

V2.136

(ZY-641)



To a solution of **(2*S*,4*R*,5*S*)-2.42** (300 mg, 0.94 mmol) in 30 mL MeOH/DCM (1:1) was added $PdCl_2$ (16.5 mg, 0.09 mmol) at room temperature. After being stirred for 2 hours at room temperature, the mixture was filtered through celite and saturated aqueous NaCl was added. The aqueous phase was extracted four times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give **(2*S*,4*R*,5*S*)-2.50** (189 mg, 0.67 mmol, 72%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.27 (m, 5H), 4.56 (d, J = 12.2 Hz, 1H), 4.50 (d, J = 12.2 Hz, 1H), 3.80 (ddd, J = 11.6, 9.4, 4.9 Hz, 1H), 3.44 (d, J = 9.2 Hz, 1H), 3.36 (d, J = 9.2 Hz, 1H), 3.20 (d, J = 9.4 Hz, 1H), 2.27 (brs, 2H), 2.19 (dd, J = 13.1, 4.8 Hz, 1H), 1.42 (dd, J = 13.0, 11.8 Hz, 1H), 1.29 (s, 3H), 1.26 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 128.5, 127.9, 127.8, 80.5, 76.3, 75.3, 74.8, 73.6, 67.3, 41.0, 30.7, 29.1, 22.9.

IR (ν cm^{-1}): 3375, 2976, 2933, 2864, 2352, 1605, 1587, 1496, 1454.

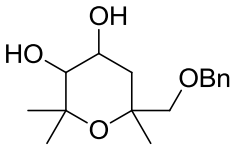
HRMS: calc'd for $[M+H]^+$: 281.1747, found: 281.1753.

$[\alpha]_D^{20}$ = -17.4 (c = 1.05, $CHCl_3$).

6-((Benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diol (*rac*-2.50)

V2.137

(ZY-605)

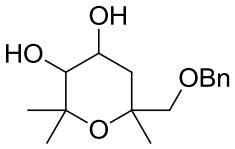


To a solution of ***rac*-2.42** (320 mg, 1.0 mmol) in 32 mL MeOH/DCM (1:1) was added $PdCl_2$ (17.7 mg, 0.1 mmol) at room temperature. After being stirred for 2 hours at room temperature, The mixture was filtered through celite and saturated aqueous NaCl was added. The aqueous phase was extracted four times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give ***rac*-2.50** (200 mg, 0.71 mmol, 71%) as colorless oil.

Spectroscopic data of ***rac*-2.50**: see experiment **V 2.136**

V2.138

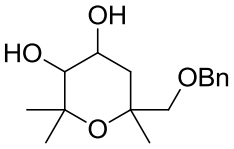
(ZY-460)



To a solution of ***rac*-2.42** (100 mg, 0.31 mmol) in 5 mL MeOH/DCM (3:2) was added $PdCl_2$ (5.5 mg, 31 umol) at room temperature. After being stirred for 2 hours at room temperature, The mixture was filtered through celite and saturated aqueous NaCl was added. The aqueous phase was extracted four times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give ***rac*-2.50** (53 mg, 189 umol, 61%) as colorless oil.

V2.139

(ZY-443)

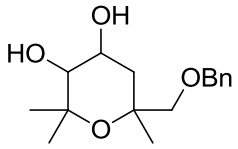


To a solution of ***rac*-2.42** (32 mg, 0.1 mmol) in 2 mL MeOH/DCM (3:2) was added $PdCl_2$ (21 mg, 0.12 mmol) at room temperature. After being stirred for 20 min at room temperature, the mixture was filtered through celite and saturated aqueous NaCl was added. The aqueous phase was extracted four times with DCM. The organic layer was washed with brine, dried

with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give ***rac*-2.50** (10.9 mg, 39 umol, 39%) as colorless oil.

V2.140

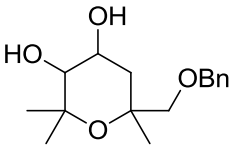
(ZY-444)



To a solution of ***rac*-2.42** (150 mg, 0.47 mmol) in 10 mL MeOH/DCM (3:2) was added $PdCl_2$ (83 mg, 0.47 mmol) at 0 ^oC. After being stirred for 10 min at 0 ^oC and 25 min at room temperature, the mixture was filtered through celite and saturated aqueous NaCl was added. The aqueous phase was extracted four times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give ***rac*-2.50** (51.1 mg, 182 umol, 39%) as colorless oil.

V2.141

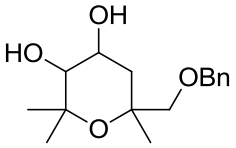
(ZY-481)



To a solution of ***rac*-2.42** (20 mg, 62.5 umol) in 1.5 mL MeOH/DCM (1:2) was added $PdCl_2$ (1.1 mg, 6.25 umol) at room temperature. After being stirred for 40 min at room temperature, the mixture was filtered through celite and saturated aqueous NaCl was added. The aqueous phase was extracted four times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give ***rac*-2.50** (10 mg, 35.7 umol, 57%) as colorless oil.

V2.142

(ZY-482)



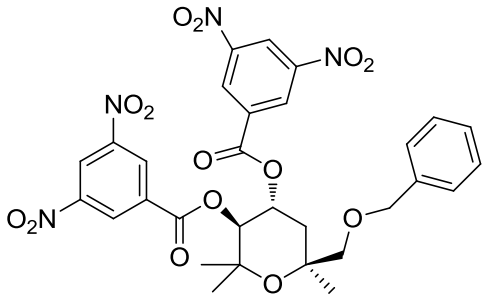
To a solution of ***rac*-2.42** (23 mg, 71.8 umol) in 2.0 mL MeOH was added $PdCl_2$ (1.1 mg, 6.25 umol) at room temperature. After being stirred for 15 min at room temperature, 1.0 mL

DCM was added. After being stirred for another 20 min, $PdCl_2$ (1.1 mg, 6.25 umol) was added. After being stirred for another 25 min, 1.0 mL DCM was added again. The mixture was filtered through celite and saturated aqueous NaCl was added. The aqueous phase was extracted four times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (1:1) to give ***rac*-2.50** (18 mg, 64.2 umol, 89%) as colorless oil.

(2*S*,4*R*,5*S*)-6-((Benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diyl bis(3,5-dinitrobenzoate) ((2*S*,4*R*,5*S*)-2.77)

V2.143

(ZY-643)



To a solution of **(2*S*,4*R*,5*S*)-2.50** (10 mg, 35.7 umol) in pyridine (2.3 mL) 3,5-dinitrobenzoyl chloride (123.3 mg, 535.5 umol) was added at room temperature. The yellow solution was stirred for 1 h. sat. aq. NH_4Cl (15 mL) was added and the aqueous layer was extracted with DCM (4 x 10 mL). The combined organic layers were dried with Na_2SO_4 and the solvent was removed in vacuo. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **(2*S*,4*R*,5*S*)-2.77** (23.6 mg, 35.3 umol, 99%) as colorless viscous oil.

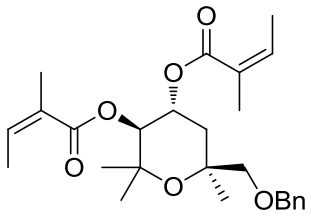
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.20-9.19 (m, 1H), 9.17 (t, J = 2.1 Hz, 1H), 9.07 (d, J = 2.1 Hz, 2H), 9.03 (d, J = 2.1 Hz, 2H), 7.41-7.37 (m, 4H), 7.31 (t, J = 7.1 Hz, 1H), 5.78 (ddd, J = 11.0, 9.6, 5.3 Hz, 1H), 5.42 (d, J = 9.5 Hz, 1H), 4.64 (s, 2H), 3.63 (d, J = 9.6 Hz, 1H), 3.52 (d, J = 9.0 Hz, 1H), 2.65 (dd, J = 13.3, 5.3 Hz, 1H), 1.95 (dd, J = 13.2, 11.1 Hz, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.26 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.3, 162.0, 148.9, 148.9, 137.9, 133.3, 133.0, 130.0, 129.5, 129.5, 128.6, 128.0, 127.8, 123.0, 122.8, 79.5, 75.8, 75.3, 75.2, 73.7, 71.9, 38.0, 30.6, 28.9, 24.0.

HRMS: calc'd for $[M+Na]^+$: 691.1494, found: 691.1467.

$[\alpha]_D^{20}$ = -34.1 (*c* = 1.23, $CHCl_3$).

(2*Z*,2'*Z*)-(2*S*,4*R*,5*S*)-6-((Benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diyl bis(2-methylbut-2-enoate) ((2*S*,4*R*,5*S*)-2.51)



V2.144

(ZY-634)

To a solution of **(2*S*,4*R*,5*S*)-2.50** (128 mg, 0.46 mmol) in 25 mL DCM was added angelic acid (184 mg, 1.84 mmol), DCC (380 mg, 1.84 mmol) and DMAP (112 mg, 0.92 mmol) at room temperature. After being stirred for 48 hours at 40 ℃ and then cooled to room temperature. The resulting slurry was filtered through celite and concentrated under reduced pressure. The residue was dissolved in ether and filtered through celite again and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **(2*S*,4*R*,5*S*)-2.51** (161 mg, 0.36 mmol, 79%, *Z*/*E* = 4.7:1.0) as light yellow oil.

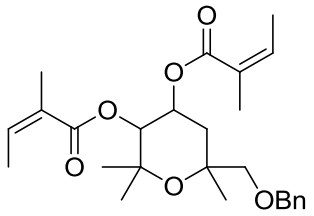
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.33 (m, 4H), 7.29-7.27 (m, 1H), 6.82-6.75 (m, 2 H), 5.30-5.26 (m, 1H), 5.04 (dd, *J* = 9.7, 4.5 Hz, 1H), 4.61-4.55 (m, 2H), 3.50-3.45 (m, 2H), 2.36-2.32 (m, 1H), 1.93-1.74 (m, 12H), 1.68-1.63 (m, 1H), 1.30 (t, *J* = 5.9 Hz, 6H), 1.24 (d, *J* = 3.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5/167.3, 167.2/167.1, 138.4/138.2, 137.8/137.8, 137.7, 128.4, 128.3, 127.7, 127.6, 76.3/76.2, 75.5/75.4, 75.3/75.2, 74.7/74.7, 73.5, 68.3/67.7, 38.1/38.0, 30.2/30.2, 28.5/28.4, 23.9/23.8, 14.4, 12.1, 11.9.

IR (ν cm^{-1}): 2980, 2930, 2857, 2364, 1711, 1651, 1519, 1497, 1453.

HRMS: calc'd for $[M+H]^+$: 445.2585, found: 445.2579; calc'd for $[M+Na]^+$: 467.2404, found: 467.2388.

(2*Z*,2'*Z*) -6-((Benzyloxy)methyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diyl bis(2-methylbut-2-enoate) (*rac*-2.51)



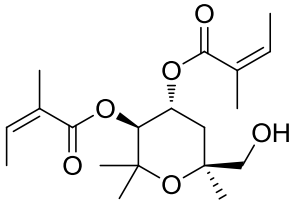
V2.145

(ZY-631)

To a solution of ***rac*-2.50** (150 mg, 0.54 mmol) in 30 mL DCM was added angelic acid (216 mg, 2.16 mmol), DCC (446 mg, 2.16 mmol) and DMAP (132 mg, 1.08 mmol) at room temperature. After being stirred for 48 hours at 40 ℃ and then cooled to room temperature. The resulting slurry was filtered through celite and concentrated under reduced pressure. The residue was dissolved in ether and filtered through celite again and the filtrate concentrated under reduced pressure. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give ***rac*-2.51** (171 mg, 0.38 mmol, 72%, *Z*/*E* = 4.0:1.0) as light yellow oil.

Spectroscopic data of ***rac*-2.51**: see experiment **V 2.144**.

(2*Z*,2'*Z*)-(2*S*,4*R*,5*S*)-6-(Hydroxymethyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diyl bis(2-methylbut-2-enoate) ((2*S*,4*R*,5*S*)-2.53)



V2.146

(ZY-648)

To a solution of **(2*S*,4*R*,5*S*)-2.51** (100 mg, 0.23 mmol) in 20 mL DCM/H_2O (9:1) was added DDQ (204 mg, 0.9 mmol) at room temperature. After being stirred for 24 hours at 40 ℃ and then cooled to room temperature. Saturated aqueous $NaHCO_3$ was added and the resulting dark red solution was stirred vigorously for 2 h. The layers were separated and the aqueous layer was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give **(2*S*,4*R*,5*S*)-2.53** (15 mg, 42.3 umol, 19%, *Z*/*E* = 1:1) and **(2*S*,4*R*,5*S*)-2.53** (40 mg, 113 umol, 50%) as colorless viscous oil.

(2*S*,4*R*,5*S*)-2.53:

1H NMR (400 MHz, $CDCl_3$): δ = 6.84-6.76 (m, 2H), 5.21 (td, J = 8.8, 5.1 Hz, 1H), 5.05 (d, J = 8.5 Hz, 1H), 3.66 (d, J = 11.2 Hz, 1H), 3.39 (d, J = 11.2 Hz, 1H), 2.28 (dd, J = 13.9, 5.1 Hz,

1H), 1.99-1.92 (m, 1H), 1.80-1.75 (m, 11H), 1.69 (dd, J = 13.9, 9.0 Hz, 1H), 1.31 (d, J = 4.0 Hz, 6H), 1.28 (s, 3H), 1.25 (s, 1H).

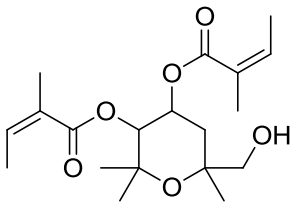
13C NMR (100 MHz, $CDCl_3$): δ = 167.5, 167.1, 138.3, 138.2, 128.3, 128.3, 75.2, 74.7, 74.7, 68.5, 68.3, 36.0, 29.6, 27.4, 24.7, 14.6, 12.2, 12.1.

IR (ν cm^{-1}):3431, 2987, 2929, 2858, 2809, 2360, 2325, 1704, 1653.

HRMS: calc'd for $[M+H]^+$: 355.2115, found: 355.2118; calc'd for $[M+Na]^+$: 377.1935, found: 377.1937.

$[\alpha]_D^{20}$ = -41.1 (c = 0.65, $CHCl_3$).

(2*Z*,2'*Z*)-6-(Hydroxymethyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diyl bis(2-methylbut-2-enoate) (*rac*-2.53)

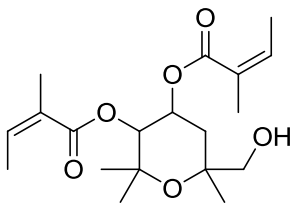


V2.147

(ZY-637)

To a solution of ***rac*-2.51** (150 mg, 0.34 mmol) in 30 mL DCM/H_2O (9:1) was added DDQ (309 mg, 1.36 mmol) at room temperature. After being stirred for 48 hours at 40 ℃ and then cooled to room temperature. Saturated aqueous $NaHCO_3$ was added and the resulting dark red solution was stirred vigorously for 2 h. The layers were separated and the aqueous layer was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give ***rac*-2.53** (96 mg, 0.27 mmol, 80%, *Z*/*E* = 4:1) as colorless viscous oil.

Spectroscopic data of ***rac*-2.53**: see experiment **V 2.146**.



V2.148

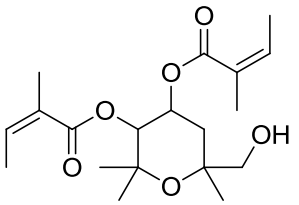
(ZY-464)

To a solution of ***rac*-2.51** (3.8 mg, 8.6 umol) in 2.2 mL DCM/H_2O (10:1) was added DDQ (2.3 mg, 10.3 umol) at 0 ℃. After being stirred for 1 h at 0 ℃ and 1 h at room temperature,

DDQ (2.3 mg, 10.3 umol) was added again. After being stirred for another 17.5 h at room temperature, sat. aq. $NaHCO_3$ was added and the resulting dark red solution was stirred vigorously for 2 h. The layers were separated and the aqueous layer was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to recover ***rac*-2.51** (2.5 mg, 5.6 umol, 66%) as light yellow oil and give trace ***rac*-2.53**.

V2.149

(ZY-465)

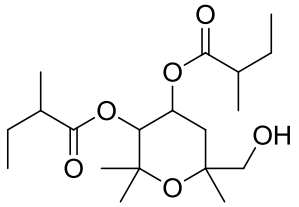


To a solution of ***rac*-2.51** (10 mg, 22.5 umol) in 5 mL DCM was added BCl_3 (33.8 umol, 33.8 umol, 1 M in DCM) at -78 ℃. The reaction mixture was stirred for 6.5 h while the temperature was slowly warmed from -80 ℃ to -50 ℃. 1 mL MeOH was added stirred for 2 h. The layers were separated and the aqueous layer was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give ***rac*-2.53** (5 mg, 14.1 umol, 63%, *Z*/*E* = 4:1) as colorless viscous oil.

6-(Hydroxymethyl)-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diyl bis(2-methylbutanoate) (*rac*-2.52)

V2.150

(ZY-459)



To a solution of ***rac*-2.51** (52 mg, 117 umol) in 15 mL MeOH was added $Pd(OH)_2$ (15 mg, mmol) under hydrogen atmosphere at room temperature. After being stirred for 24 h at room temperature, $Pd(OH)_2$ (10 mg, mmol) was added again. It was continued to stir 7 h under hydrogen atmosphere at room temperature. The mixture was filtered through celite and the solvent was removed in vacuum. The residue was purified by column chromatography using pentane-Et_2O (4:1) to give ***rac*-2.52** (27 mg, 75.4 umol, 64%) as colorless viscous oil.

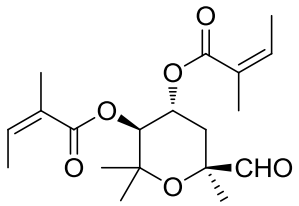
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.14 (ddd, J = 14.8, 9.0, 5.7 Hz, 1H), 4.97 (d, J = 8.8 Hz, 1H), 3.65 (dd, J = 11.2, 3.7 Hz, 1H), 3.38 (d, J = 11.2 Hz, 1H), 2.38-2.30 (m, 2H), 2.25-2.21

(m, 1H), 1.97 (s, 1H), 1.69-1.60 (m, 3H), 1.47-1.42 (m, 2H), 1.29 (s, 3H), 1.26 (s, 6H), 1.11 (dt, J = 14.6, 7.2 Hz, 6H), 0.91-0.86 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.2/176.0/175.7/175.6/175.6, 75.2/75.2, 74.7/74.7/74.7/74.6/74.5/74.4, 68.3/68.3/68.2, 67.9, 41.4/41.4/41.3/41.2/41.0, 36.4/36.4/36.3/36.2, 29.8/29.8, 27.5/27.5/27.5, 26.9/26.8/26.7/26.6/26.5, 24.4/24.4, 16.8/16.5/16.4, 11.7/11.8/11.7.

HRMS: calc'd for $[M+H]^+$: 359.2428, found: 359.2431; calc'd for $[M+Na]^+$: 381.2248, found: 381.2249.

(2*Z*,2'*Z*)-(2*S*,4*R*,5*S*)-6-Formyl-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diyl bis(2-methylbut-2-enoate) ((2*S*,4*R*,5*S*)-2.54)



V2.151

(ZY-671)

Based on AVV9, to a solution of **(2*S*,4*R*,5*S*)-2.53** (38 mg, 107.3 umol) in 1.2 mL DCM was added Dess-Martin periodinane (54.3 mg, 128.8 mmol) at room temperature under argon. After being stirred for 1 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give **(2*S*,4*R*,5*S*)-2.54** (29 mg, 82.3 umol, 77%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, *J* = 1.7 Hz, 1H), 6.78-6.71 (m, 2H), 5.14-5.08 (m, 1H), 5.01 (d, *J* = 10.3 Hz, 1H), 2.82 (dd, *J* = 12.9, 5.2 Hz, 1H), 1.75-1.73 (m, 12H), 1.63-1.57 (m, 1H), 1.25 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H).

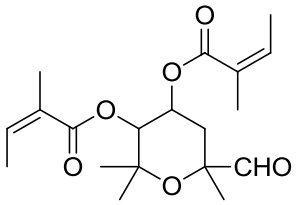
^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.1, 167.2, 138.3, 138.0, 128.3, 128.2, 79.2, 76.9, 75.7, 67.1, 35.5, 28.9, 24.3, 22.2, 14.6, 12.2, 12.0.

IR (ν cm^{-1}):2983, 2931, 2860, 2799, 1716, 1650.

HRMS: calc'd for $[M+H]^+$: 353.1959, found: 353.1965. calc'd for $[M+Na]^+$: 375.1778, found: 375.1781.

$[\alpha]_D^{20}$ = -2.2 (*c* = 0.58, $CHCl_3$).

(2*Z*,2'*Z*)-6-Formyl-2,2,6-trimethyltetrahydro-2*H*-pyran-3,4-diyl bis(2-methylbut-2-enoate) (*rac*-2.54)



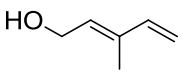
V2.152

(ZY-639)

Based on AVV9, to a solution of ***rac*-2.53** (80 mg, 0.23 mmol) in 2.4 mL DCM was added Dess–Martin periodinane (119 mg, 0.28 mmol) at room temperature under argon. After being stirred for 1 h at room temperature, the reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (10:1) to give ***rac*-2.54** (62 mg, 0.18 mmol, 78%) as light yellow oil.

Spectroscopic data of ***rac*-2.54**: see experiment **V 2.151**.

(*E*)-3-Methylpenta-2, 4-dien-1-ol ((*E*)-2.44)



V2.153

(ZY-207)

To a solution of (*E*)-3-methylpent-2-en-4-yn-1-ol **(*E*)-2.43** (800 mg, 8.3 mmol) in 25 ml of abs. Methanol, Lindlar catalyst (191 mg) was added. While the solution was stirred under a hydrogen atmosphere (H_2 balloon. 1 atm.) at room temperature for 90 minutes, the reaction was monitored by gas chromatography (1 min 40 ℃, then 5 ℃/min to 280 ℃, Rt (starting material) = 5.99 min, Rt (product) = 6.20 min). Followed by filtration through celite, evaporation of the solvent in vacuum (200 mbar minimal) and distillation (1.4 mbar, 43 ℃) to give **(*E*)-2.44** (550 mg, 68%) as colorless viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.39 (dd, J = 17.4, 10.7 Hz, 1H), 5.67 (t, J = 6.8 Hz, 1H), 5.22 (d, J = 17.4 Hz, 1H), 5.06 (d, J = 10.7 Hz, 1H), 4.29 (d, J = 6.8 Hz, 2H), 1.79 (s, 3H).

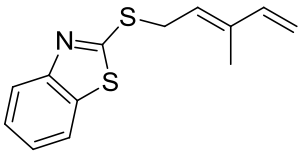
^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 136.6, 130.5, 113.3, 59.5, 12.0.

The NMR data are consistent with the literature data.[39]

(*E*)-2-((3-Methylpenta-2,4-dien-1-yl)thio)benzo[*d*]thiazole ((*E*)-2.45)

V2.154

(ZY-209)



To a solution of **(*E*)-2.44** (260 mg, 2.65 mmol) in 16 mL abs. THF, 2-mercaptobenzothiazole (665 mg, 3.98 mmol) and triphenylphosphine (1114 mg, 4.24 mmol) were added. After cooling to 0 ℃, Diisopropylazodicarboxylate (DIAD) (840 uL, 3.98 mmol) dissolved in 5 mL abs. THF was added dropwise. After being stirring 30 minutes at this temperature, the solvent was removed in vacuum and the crude product was purified by column chromatography using cyclohexane/ethyl acetate (30:1) to give **(*E*)-2.45** (620 mg, 2.51 mmol, 95%, *E*/*Z* = 95:5) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.44-7.40 (m, 1H), 7.32-7.28 (m, 1H), 6.92-6.85 (m, 0.05H), 6.38 (dd, J = 17.4, 10.7 Hz, 0.95H), 5.73 (t, J = 8.0 Hz, 0.95H), 5.63 (t, J = 8.2 Hz, 0.05H), 5.23 (d, J = 17.4 Hz, 1H), 5.07 (d, J = 10.7 Hz, 1H), 4.15 (d, J = 8.0 Hz, 2H), 1.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 166.6, 153.4, 140.5, 138.9, 135.5, 126.2, 125.2, 124.4, 121.7, 121.1, 113.7, 31.9, 12.1.

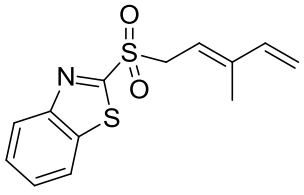
IR (ν cm^{-1}): 3060, 2962, 2923, 2857, 1678, 1640, 1606, 1591, 1560, 1456.

HRMS: calc'd for $[M+H]^+$: 248.0562, found: 248.0569.

(*E*)-2-((3-Methylpenta-2,4-dien-1-yl)sulfonyl)benzo[*d*]thiazole ((*E*)-2.46)

V2.155

(ZY-621)



To a solution of **(*E*)-2.45** (300 mg, 1.21 mmol) in 15 mL normal ethanol, ammonium molybdate tetrahydrate (300 mg, 0.24 mmol) in 5.2 ml hydrogen peroxide (35% in water) was added slowly. After being stirring 25 minutes at room temperature, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with diethyl ether. The organic layer was washed with water, dried with Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane/ethyl acetate (30:1-10:1) to give **(*E*)-2.46** (240 mg, 0.86 mmol, 71%, *E*/*Z* = 83:17) as light yellow viscous oil.

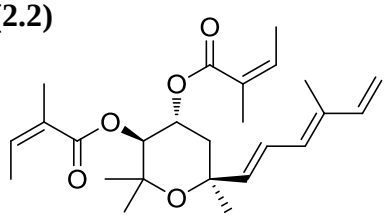
^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24-8.21 (m, 1H), 8.02-7.98 (m, 1H), 7.66-7.57 (m, 2H), 6.55 (dd, J = 17.5, 11.2 Hz, 0.17H), 6.35 (dd, J = 17.3, 10.9 Hz, 0.83H), 5.52 (t, J = 8.2 Hz, 0.83H), 5.45 (t, J = 8.2 Hz, 0.17H), 5.25-5.19 (dd, J = 17.2, 5.4 Hz, 1H), 5.12-5.08 (m, 1H), 4.38 (d, J = 8.1 Hz, 2H), 1.70 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.8, 152.8, 144.2, 139.7, 137.2, 128.1, 127.8, 125.6, 122.5, 115.6, 114.8, 55.0, 12.4.

IR (ν cm^{-1}): 3065, 2926, 2858, 2361, 2342, 2292, 2251,1684, 1607, 1554, 1471, 1459.

HRMS: calc'd for $[M+H]^+$: 280.0461, found: 280.0462.

(2*Z*,2'*Z*)-(2*S*,4*R*,5*S*)-2,2,6-Trimethyl-6-((1*E*,3*E*)-4-methylhexa-1,3,5-trien-1-yl)tetrahydro-2*H*-pyran-3,4-diyl bis(2-methylbut-2-enoate) (2.2)



V2.156

(ZY-647)

To a solution of **(*E*)-2.46** (44.5 mg, 159.5 umol) in 1.2 ml dry THF was added Sodium bis(trimethylsilyl)amide NaHMDS (1 M in THF, 164.5 umol, 164.5 uL) at -80 ^{o}C. After being stirred for 30 minutes from -80 ^{o}C to -65 ^{o}C, A solution of **(2*S*,4*R*,5*S*)-2.54** (29 mg, 82.3 umol) in 0.4 mL dry THF was added dropwise and the reaction mixture was stirred for 4 h while the temperature was slowly warmed from -80 ℃ to 0 ℃. The reaction is still stirring under 0 ℃ for 1 h. Then, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted three times with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **2.2** (19 mg, 45.6 umol, 55%, *E*/*Z* = 83:17) as colorless oil.

1H NMR (400 MHz, $CDCl_3$): δ = 6.81-6.72 (m, 3H), 6.43 (dd, J = 17.3, 10.7 Hz, 1H), 6.07 (d, J = 10.9 Hz, 0.78H), 5.99 (d, J = 11.0 Hz, 0.22H), 5.82 (d, J = 15.9 Hz, 1H), 5.27-5.23 (m, 1H), 5.19-5.14 (m, 1H), 5.07 (d, J = 1.9 Hz, 1H), 5.05 (d, J = 2.2 Hz, 1H), 2.72 (dd, J = 13.0, 4.3 Hz, 1H), 1.98 (s, 2H), 1.91 (s, 1H), 1.76 (t, J = 7.9 Hz, 12H), 1.72-1.68 (m, 1H), 1.26 (d, J = 4.4 Hz, 6H), 1.19 (s, 3H).

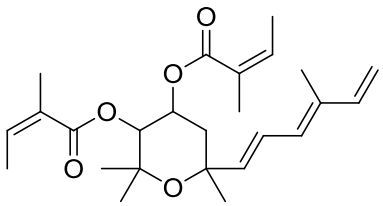
^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9/167.9, 167.4, 141.3, 141.0, 138.0, 137.8, 136.2, 134.7, 133.6, 130.9, 129.4, 128.5, 128.5, 124.0, 123.1, 113.0, 76.5, 76.4, 75.1, 69.1, 38.9, 32.0, 30.0, 23.2, 20.0, 16.9, 14.6, 14.5, 12.3, 12.2, 12.0.

IR (ν cm^{-1}): 2977, 2954, 2926, 2856, 1714, 1651.

HRMS: calc'd for $[M+Na]^+$: 439.2455, found: 439.2449.

$[\alpha]_D^{20}$ = -20.1 (c = 0.50, $CHCl_3$).

(2*Z*,2'*Z*)-2,2,6-Trimethyl-6-((1*E*,3*E*)-4-methylhexa-1,3,5-trien-1-yl)tetrahydro-2*H*-pyran-3,4-diyl bis(2-methylbut-2-enoate) (*rac*-2.2)



V2.157

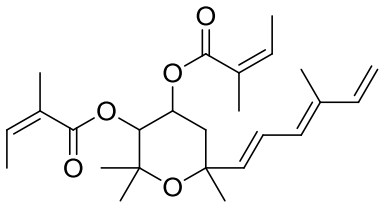
(ZY-644)

To a solution of **(*E*)-2.46** (24 mg, 85.2 umol) in 0.8 ml dry THF was added Sodium bis(trimethylsilyl)amide NaHMDS (1 M in THF, 85.2 umol, 85.2 uL) at -80 ^oC. After being stirred for 30 minutes from -80 ^oC to -65 ^oC, a solution of ***rac*-2.54** (20 mg, 56.8 umol) in 0.4 mL dry THF was added dropwise and the reaction mixture was stirred for 4 h while the temperature was slowly warmed from -80 ℃ to -20 ℃. Then, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted three times with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.2** (12.4 mg, 29.8 umol, 53%) as colorless oil.

Spectroscopic data of ***rac*-2.2**: see experiment **V 2.156**.

V2.158

(ZY-492)

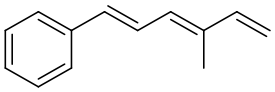


To a solution of **(*E*)-2.46** (9.5 mg, 34.1 umol) and ***rac*-2.54** (8 mg, 22.7 umol) in 1 ml dry THF was added Sodium bis(trimethylsilyl)amide NaHMDS (2 M in THF, 34.1 umol, 17 uL) at -80 ^{o}C. The reaction mixture was stirred for 3 h while the temperature was slowly warmed from -80 ℃ to 7 ℃. Then, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted three times with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.2** (2 mg, 4.8 umol, 21%) as colorless oil.

4-Methylhexa-1,3,5-trien-1-yl)benzene (2.56)

V2.159

(ZY-487)



To a solution of **(*E*)-2.46** (19.7 mg, 70.7 umol) and benzaldehyde **2.55** (5 mg, 47.1 umol) in 1 ml dry THF was added Sodium bis(trimethylsilyl)amide NaHMDS (2 M in THF, 70.7 umol, 35.4 uL) at -80 ^{o}C. The reaction mixture was stirred for 1.5 h while the temperature was slowly warmed from -80 ℃ to -19 ℃. Then, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted three times with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give **2.56** (6 mg, 35.3 umol, 75%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, J = 4.4 Hz, 4H), 7.27-7.22 (m, 1H), 6.60-6.42 (m, 4H), 5.28 (d, J = 17.3 Hz, 1H), 5.08 (d, J = 10.6 Hz, 1H), 1.98/1.98/1.95/1.93 (4s, 3H).

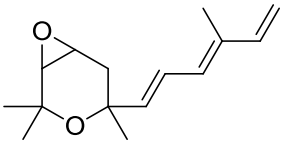
^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.5/141.3, 137.9/137.7, 130.6, 129.3/128.8, 128.4/128.3, 127.6/127.6, 127.1/127.1, 126.5/126.2, 113.3/113.1, 12.4/12.1.

The NMR data are consistent with the literature data.[39]

2,2,4-Trimethyl-4-((1*E*,3*E*)-4-methylhexa-1,3,5-trien-1-yl)-3,7-dioxabicyclo[4.1.0]heptane (*rac*-2.57)

V2.160

(ZY-488)



To a solution of **(*E*)-2.46** (25 mg, 89.6 umol) and ***rac*-2.59** (10 mg, 58.8 umol) in 1 ml dry THF was added Sodium bis(trimethylsilyl)amide NaHMDS (2 M in THF, 89.6 umol, 44 uL) at -80 ^{o}C. The reaction mixture was stirred for 4 h while the temperature was slowly warmed from -80 ℃ to -10 ℃. Then, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted three times with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using pentane-Et_2O (20:1) to give ***rac*-2.57** (5 mg, 21.3 umol, 36%) as colorless oil.

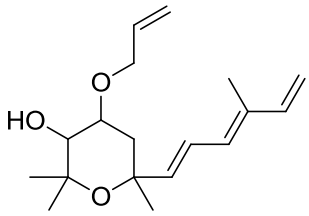
^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81-6.37 (m, 2H), 6.23-6.02 (m, 1H), 5.91-5.61 (m, 1H), 5.23-5.00 (m, 2H), 3.43-3.42 (m, 1H), 2.94 (d, J = 5.5 Hz, 1H), 2.20-2.15 (m, 1H), 1.93-1.87 (m, 1H), 1.84 (d, J = 17.7 Hz, 3H), 1.34 (d, J = 6.4 Hz, 6H), 1.27 (d, J = 8.9 Hz, 3H).

The NMR data are consistent with the literature data.[39]

4-(Allyloxy)-2,2,6-trimethyl-6-((1*E*,3*E*)-4-methylhexa-1,3,5-trien-1-yl)tetrahydro-2*H*-pyran-3-ol (*rac*-2.58)

V2.161

(ZY-490)



To a solution of ***rac*-2.57** (5 mg, 21.3 umol) in 0.5 mL allyl alcohol was added $HClO_4$ (70% in water, 2.5 uL, 42.6 umol) was added slowly at 0 ℃. The reaction mixture was stirred at 0 ℃ for 2 h, then at room temperature for 24 h. And the reaction was monitored by thin layer chromatography. A low conversion was observed, however starting materials was complete decomposition and the reaction was terminated.

Chapter 3. Studies on the total synthesis of (+)-3-*O*-Feruloylcassine

3.1 Introduction

After the total synthesis of 9α,10β-Bisangeloyloxy-agerafastin, which contains an O-containing 6-membered ring as the main building block, the second natural product with an N-containing 6-membered ring was selected. The 6-membered nitrogen heterocycles are particularly attractive for us because the preparation of them could start from β-aminoallenes, and the cycloisomerization of these allenes has been rarely studied so far. The gold-catalyzed cycloisomerization of β-aminoallenes to produce 6-membered nitrogen heterocycles was previously examined by *Gockel*[39] and *Sun*[77] from our group. Compared to the synthesis of a 5-membered nitrogen heterocycle in this way, the synthesis of 6-membered nitrogen heterocycles is more challenging.

(+)-3-*O*-Feruloylcassine **3.1** was first isolated by *Nair et al*. from the green fruits of *Senna* spectabilis in 2007.[78] The structure was determined by HRMS, EA, IR, NMR (^{1}H-, ^{13}C-, COSY-, HMBC- and NOSY NMR) and the relative configuration by NOSY experiments and comparison of coupling constants with structurally similar compounds **3.2** and **3.3**[79] detected (Figure 3.1). Besides the interesting structure, this new alkaloid has broad biological activities including lipoperoxidation inhibitory, cyclooxygenase enzymes inhibitory, antioxidant and anti-inflammatory activities.[78]

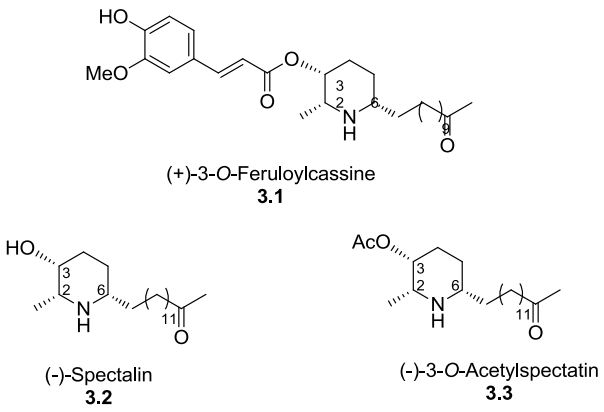


Figure 3.1

[77] T. Sun, PhD Thesis, TU Dortmund, **2011**.

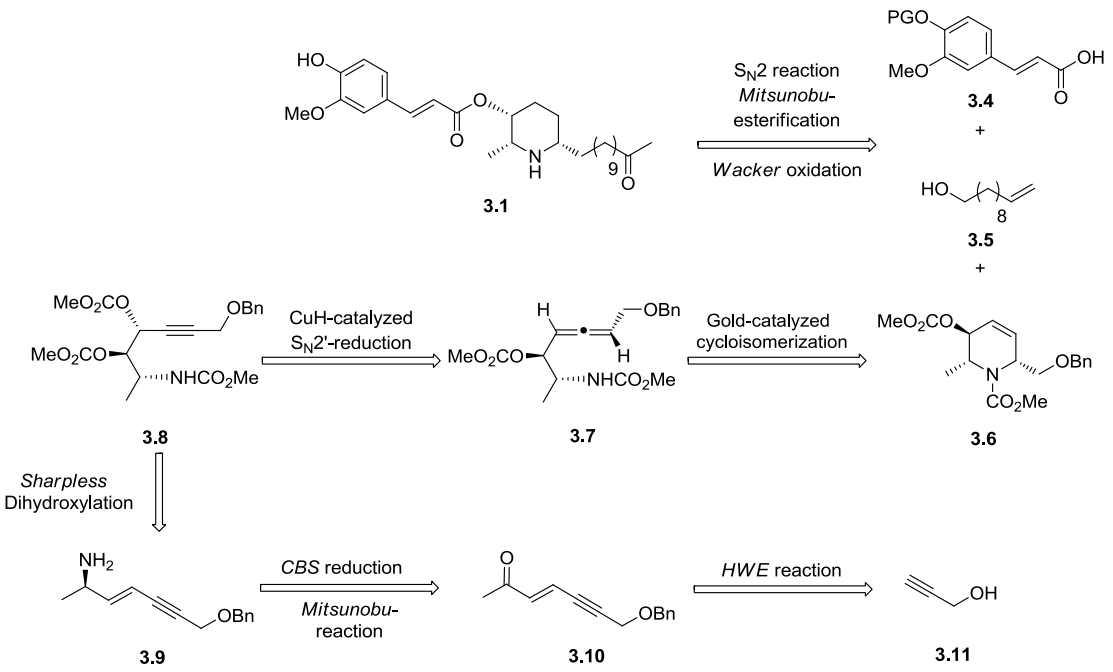
[78] J. C. Viegas, D. H. S. Silva, M. Pivatto, A. de Rezende, I. Castro-Gamboa, V. S. Bolzani, M. G. Nair, *J. Nat. Prod.* **2007**, *70*, 2026-2028.

[79] (a) M. S. A. Moreira, C. Jr. Virgas, A. L. P. de Miranda, V. S. Bolzani, E. J. Barreiro, *Planta Med.* **2003**, *69*, 795-799; (b) C. Jr. Virgas, V. S. Bolzani, M. Furlan, E. J. Barreiro, M. C. M. Young, D. Tomazela, M. N. Eberlin, *J. Nat. Prod.* **2004**, *67*, 908-910.

As a 2,3,6-trisubstituted piperidine alkaloid, Feruloylcassine **3.1** is a suitable target for testing our methods, the gold-catalyzed cycloisomerization of aminoallenes and the CuH-catalyzed S_N2'-reduction to synthesize aminoallenes. However, the total synthesis and absolute configuration is not yet known. Therefore, we have chosen 3-*O*-Feruloylcassine **3.1** with the absolute configuration (2*R*,3*R*,6*S*) as the target for our total synthesis.

3.2 Retrosynthetic Analysis

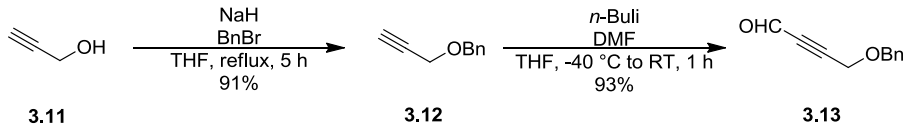
Based on previous work of *Sun*,[77] the retrosynthetic analysis is shown in Scheme 3.1. The (+)-3-*O*-Feruloylcassine **3.1** could be obtained from acid **3.4**, commercially available 10-undecene-1-ol **3.5** and tetrahydropyridine derivative **3.6** by means of a sequence of S_N2-reaction/*Mitsunobu* esterification/*Wacker* oxidation. The key intermediate **3.6** could be synthesized from the protected β-aminoallene **3.7** by gold-catalyzed cycloisomerization. The CuH-catalyzed S_N2'-reduction of propargyl dicarbonate **3.8** should provide the β-aminoallene **3.7**. The propargyl dicarbonate **3.8** should be accessible from the aminoenyne **3.9** that could be synthesized by the enynone **3.10** resulting from the propargyl alcohol **3.11**.



Scheme 3.1: Retrosynthesis of (2*R*,3*R*,6*S*)-3-*O*-Feruloylcassine **3.1**.

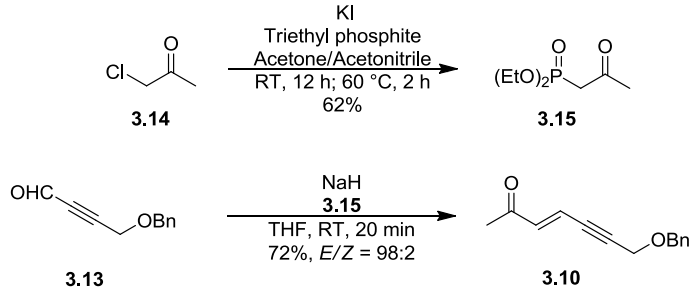
3.3 Synthesis of β-aminoallene

According to the retrosynthetic analysis of 3-*O*-Feruloylcassine **3.1**, starting from propargyl alcohol **3.11**, the protected propargyl alcohol **3.12** was obtained with high yield. Next, **3.12** was reacted with *n*-butyllithium and DMF to provide the aldehyde **3.13** efficiently (Scheme 3.2).



Scheme 3.2: Synthesis of aldehyde **3.13**.

The phosphonate **3.15** was prepared from commercially available chloroacetone **3.14** and triethyl phosphite by a means of a modified *Arbuzov* reaction[80] with a moderate yield of 62% (Scheme 3.3). Subsequent *Horner-Wadsworth-Emmons* (*HWE*) reaction[81] transferred **3.13** and **3.15** to the ketone **3.10** in good yield of 72% and excellent 98:2 *E*/*Z* ratio (Scheme 3.3).



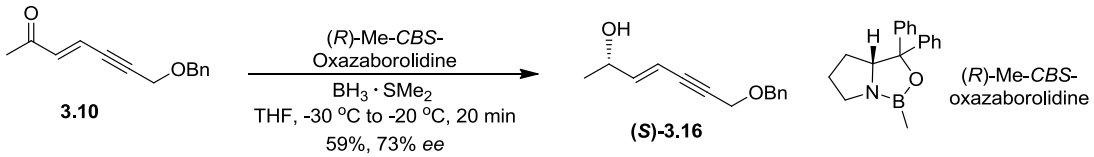
Scheme 3.3: Synthesis of ketone **3.10**.

The asymmetric reduction of ketone **3.10** was performed with 20 mol% (*R*)-Me-*CBS*-oxazaborolidine[82] and 1 equivalent of borane-dimethylsulfide-complex at -30 ℃ to -20 ℃ to afford the product **(*S*)-3.16** only with a moderate yield and enantiomeric excess (ee) because the borane-dimethylsulfide-complex was old (***rac*-3.16**: 99%) (Scheme 3.4). The new borane-dimethylsulfide-complex will be utilized later and good result should be obtained based on *Sun*'s work.

[80] (a) M. Kitamura, M. Tokunaga, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 2931-2932; (b) J. Pietruszka, A. Witt, *Synthesis* **2006**, 4266-4268.

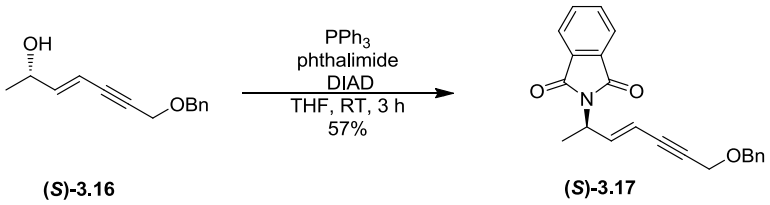
[81] J. Villieras, M. Rambaud, *Synthesis* **1983**, 300-303.

[82] (a) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986-2012; (b) C. Ohta, S.-i. Kuwabe, T. Shiraishi, S. Ohuchida, T. Seko, *Org. Process Res. Dev.* **2009**, *13*, 933-935.



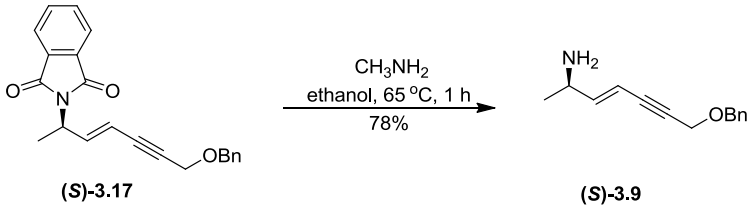
Scheme 3.4: Synthesis of alcohol **(*S*)-3.16**.

The alcohol **(*S*)-3.16** was used in a *Mitsunobu* reaction[49] to give phthalimide **(*S*)-3.17** with a moderate yield of 57% (***rac*-3.17**: 55%) (Scheme 3.5).



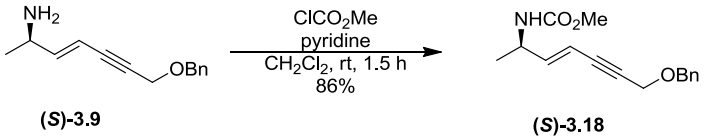
Scheme 3.5: Synthesis of phthalimide **(*S*)-3.17**.

Then, phthalimide **(*S*)-3.17** was reacted with 30 equivalents of methylamine[83] to provide the desired product aminoenyne **(*S*)-3.9** in good yield of 78% (***rac*-3.9**: 70%).



Scheme 3.6: Synthesis of enamine **(*S*)-3.9**.

Protection of the amino group of **(*S*)-3.9** produced carbamate **(*S*)-3.18** in good yield (***rac*-3.18**: 75%) (Scheme 3.7).

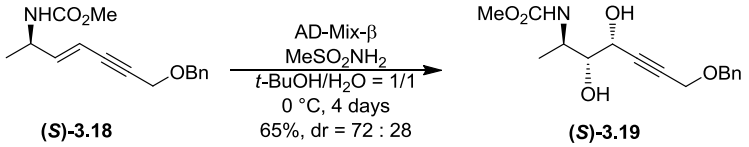


Scheme 3.7: Synthesis of carbamate **(*S*)-3.18**.

The carbamate **(*S*)-3.18** treated in a *Sharpless* dihydroxylation[50] with AD-Mix-β and 2 equivalents of methane sulfonamide, which was used for accelerating the reaction, at 0 ℃ to

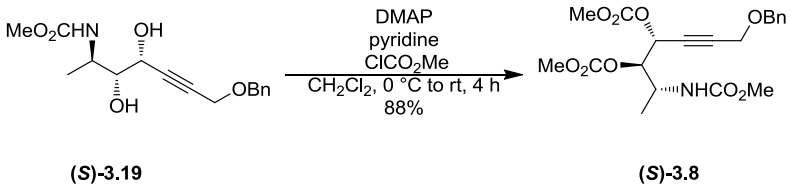
[83] D. Oves, M. Ferrero, S. Fernández, V. Gotor, *J. Org. Chem.* **2003**, *68*, 1154-1157.

afford the mixture diol **(*S*)-3.19** with moderate yield of 65% (***rac*-3.19**: 71%) (Scheme 3.8). However, this reaction was stirred four days which it is very time-consuming. Therefore, additional catalyst $K_2OsO_2(OH)_4$ and chiral ligand $(DHQD)_2PHAL$, as well as additional methane sulfonamide need be added to make the reaction more efficient.



Scheme 3.8: Synthesis of diol **(*S*)-3.19**.

Reaction of the diol **(*S*)-3.19** with 4 equivalents of DMAP, 30 equivalents of pyridine and 10 equivalents of methyl chloroformate afforded the desired product **(*S*)-3.8** with a good yield of 88% (***rac*-3.8**: 83%) (Scheme 3.9).

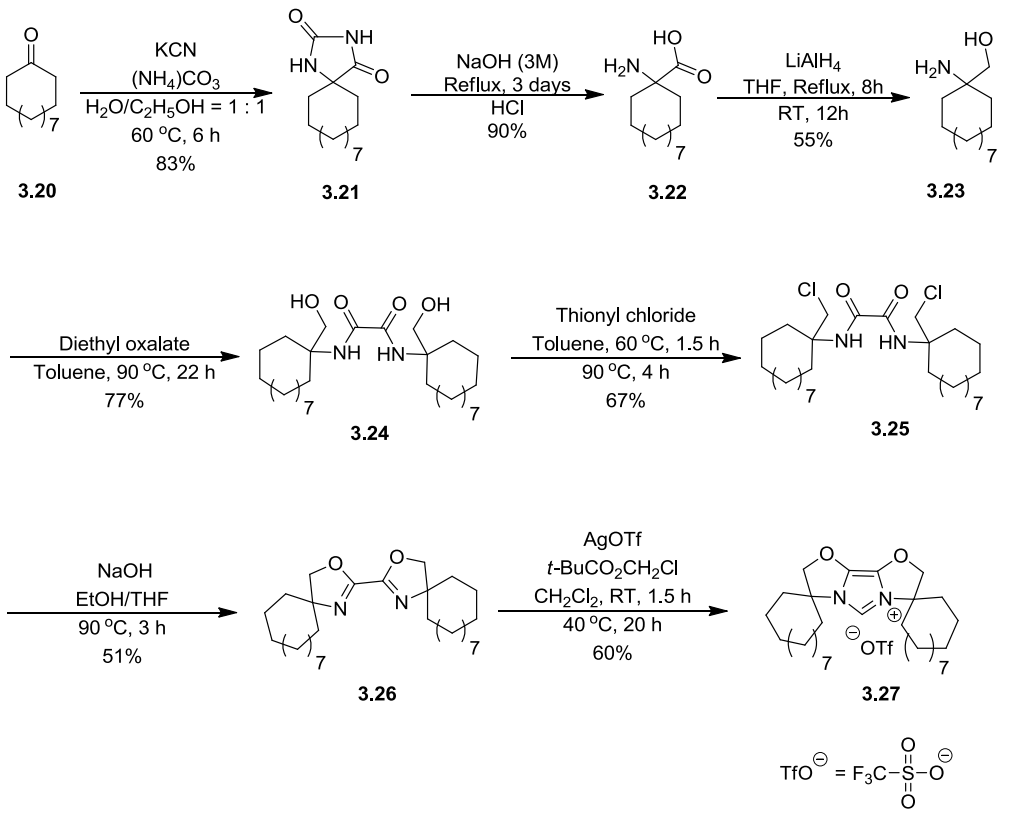


Scheme 3.9: Synthesis of carbamate **(*S*)-3.8**.

With synthesizing propargyl dicarbonate **(*S*)-3.8** successfully, the next step should be the CuH-catalyzed S_N2'-reduction to provide the significant key intermediate, β-aminoallene **3.7 (**Scheme 3.1**)**. Before performing of CuH-catalyzed S_N2'-reduction, the required N-heterocyclic carbene NHC ligand needed to be synthesized.

As shown in Scheme 3.10, the synthesis route[84] started from cyclododecanone **3.20** through seven steps to give the desired NHC ligand **3.27** which is the most suitable NHC ligand for the CuH-catalyzed S_N2'-reduction.[19,20]

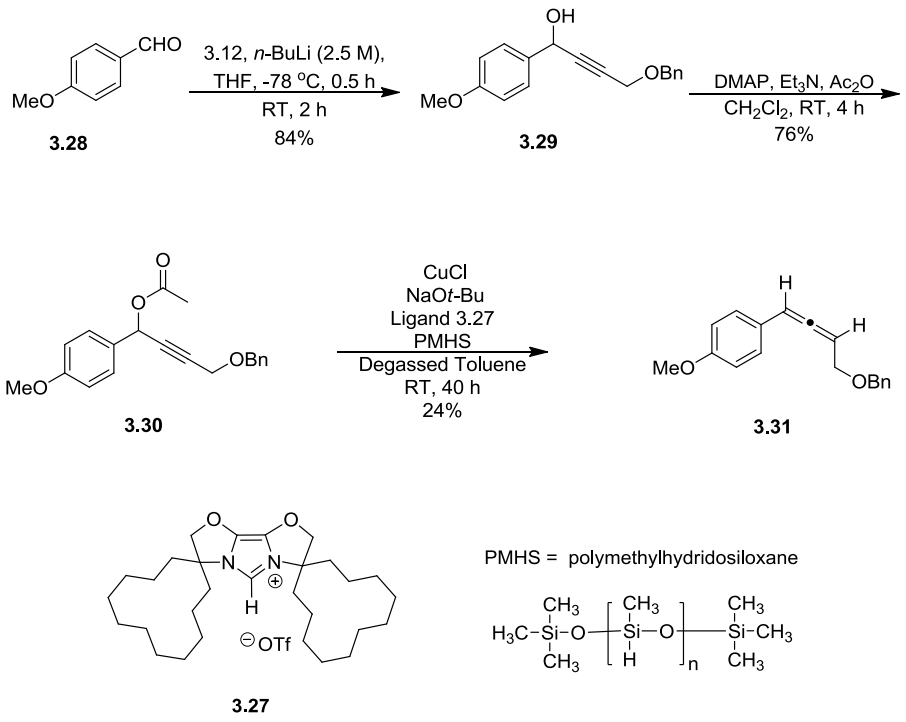
[84] G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195-15201.



Scheme 3.10: Synthesis of NHC Ligand **3.27**.

Then, a test reaction[85] for the CuH-catalyzed S_N2'-reduction was performed because this reaction is very sensitive and easily fails. Firstly, the propargyl acetate **3.30** was obtained from the propargyl alcohol **3.29** which was synthesized from 4-methoxybenzyl aldehyde **3.28** and benzyl propargyl ether **3.12** with *n*-BuLi. Subsequent CuH-catalyzed S_N2'-reduction of propargyl acetate **3.30** was performed with 3 mol% copper(I) chloride, 9 mol% sodium *tert*-butoxide, 3 mol% NHC ligand **3.27** and 2 equivalents of PMHS to give the desired allene **3.31 (**Scheme 3.11**)**, albeit in low yield of 24%.

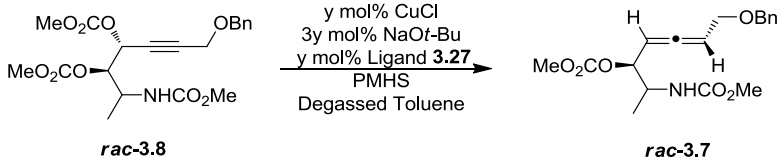
[85] C. Deutsch, PhD Thesis, TU Dortmund, **2008**.



Scheme 3.11: Test reaction of CuH-catalyzed S_N2'-reduction.

Furthermore, the CuH-catalyzed S_N2'-reduction of propargyl dicarbonate ***rac*-3.8** was performed to afford the desired allene ***rac*-3.7** successfully. The reaction conditions of CuH-catalyzed S_N2'-reduction were optimized and results are shown in Table 3.1.

Table 3.1: The CuH-catalyzed S_N2'-reduction of propargyl dicarbonate ***rac*-3.8**.



***rac*-3.8** ***rac*-3.7**

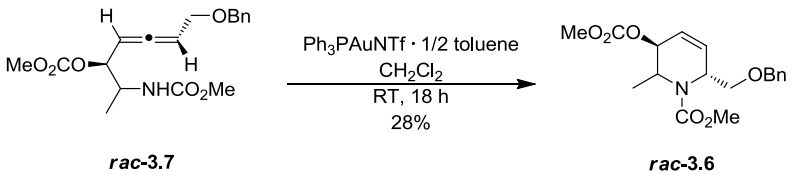
Entry	L-CuH/mol%	PMHS/eq.	T/°C	t/h	Yield%[a]
1	5	2	35 to RT	88	30
2	5	2	RT	86	40
3	5	2	RT	115	29
4	5	4	60	24	53
5	5	4	80	24	49
6	10	4	RT	24	30
7	10	4	RT	41	38
8	10	4	RT	96	53
9	10	4	15	72	45

[a] Isolated yield of ***rac*-3.7**.

It is obvious that an excess of the hydride source PMHS can improve the reaction yield and the best yield was 53% (Table 3.1, Entry 4 and 8). Different reaction temperatures have not influenced the reaction strongly. Considering the efficiency of reaction, the CuH-catalyzed S_N2'-reduction of propargyl dicarbonate ***rac*-3.8** should be performed with 5 mol% catalyst NHC-CuCl and 4 equivalents of PMHS at 60 °C for 24 h to synthesize allene ***rac*-3.7** for the further study (V3.27). Based on *Sun*'s work, the reason why the reaction yield is not good is the formation of a vinyl carbonate. An other disadvantage is the similar polarity of the substrate and the by-product. Therefore, it is not possible to estimate the turnover by thin layer chromatography and to separate the two compounds by column chromatography.

3.4 Gold catalyzed cycloisomerization of β-aminoallene

With the isolated β-aminoallene ***rac*-3.7** in hand, the gold-catalyzed cycloisomerization was investigated. According to *Sun*'s work,[77] it is possible to obtain the desired piperidine ***rac*-3.6** with 28% yield by using 15 mol% $Ph_3PAuNTf_2$ ·1/2 toluene as catalyst for 18 h reaction time (Scheme 3.12). When 5 mol% $Ph_3PAuNTf_2$ ·1/2 toluene was used, the reaction yield was 31% after 10 days reaction time. Therefore, this reaction needs to be further studied.



***rac*-3.7** ***rac*-3.6**

Scheme 3.12: Synthesis ***rac*-3.6** by gold-catalyzed cycloisomerization of ***rac*-3.7**.

In order to optimize the gold-catalyzed cycloisomerization, large amounts of allene ***rac*-3.7** are required. For reasons of time, the study was not continued at this point.

3.5 Summary and outlook

In this chapter, a study on the total synthesis of natural product (+)-3-*O*-Feruloylcassine was carried out. The β-aminoallene ***rac*-3.7** was synthesized by CuH-catalyzed S_N2'-reduction with 53% yield. The gold-catalyzed cycloisomerization of β-aminoallene should be optimized by using more active gold catalysts.

3.6 Experimental Part

3.6.1 General Information

The working techniques and analytical devices used are described in chapter 2.14.1. Unless otherwise stated, the reagents used were from those mentioned in chapter 2.14.1.

3.6.2 General procedures

AVV11: General procedure for the CuH-catalyzed S_N2'-reduction of propargyl dicarbonates

In a Schlenk flask, 5 mol% CuCl, 15 mol% NaO*t*-Bu, and 5 mol% IBiox12 ·HOTf were suspended in dry toluene (4 mL/mol). The mixture was heated to 40 ℃ for 1 h and allowed to cool to room temperature or heated to 100 ℃ for 4 min and cooled to room temperature for 1 h. PMHS was added and the mixture was stirred for 5 min at room temperature. After addition of 1 eq. of the substrate ***rac*-3.8** (85 mg, 0.2 mmol) in dry toluene (2.5 mL/mol), the mixture was stirred at room temperature for 96 h. It was poured into a stirred mixture of saturated aqueous Na_2CO_3 (100 mL/mol) and diethyl ether (100 mL/mol). After stirring for 1 h at room temperature, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with MgSO4, and the solvent was removed in vacuo. The crude product is purified by flash column chromatography on silica gel.

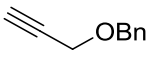
The solvent toluene is carefully degassed by twice repeating the cycle of freezing in liquid nitrogen under argon, evacuating under fine vacuum and then thawing without cooling bath under argon. The silane PMHS is also to be degassed by evacuating under fine vacuum.

3.6.3 The total synthesis of 3-*O*-Feruloylcassine

((Prop-2-yn-1-yloxy)methyl)benzene (3.12)

V3.1

(ZY-2)



To a suspension of sodium hydride (60% in mineral oil, 13.2 g, 0.33 mol) in 400 mL THF freshly distilled propargyl alcohol **3.11** (17.5 mL, 0.3 mmol) was added at 0 ℃. The mixture was stirred until no more gas was monitored (30 minutes). Benzyl bromide (33 mL, 0.278

mol) was added and the solution heated under reflux for five hours. The reaction was quenched with sat. aq. NH_4Cl and extracted three times with diethyl ether. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (20:1) to give **3.12** (36.8 g, 0.252 mol, 91%) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39-7.29 (m, 5H), 4.62 (s, 2H), 4.19 (d, J = 2.4 Hz, 2H), 2.48 (t, J = 2.4 Hz, 1H).

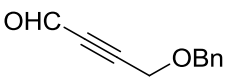
^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 128.6, 128.3, 128.1, 79.8, 74.7, 71.7, 57.2.

The NMR data are consistent with the literature data.[77]

4-(Benzyloxy)but-2-ynal (3.13)

V3.2

(ZY-18)



To a solution of the protected propargyl **3.12** (2.92 g, 20 mmol) in 50 ml of THF, *n*-butyllithium (2.5 M in hexane, 9.6 ml, 24 mmol) was added dropwise at -40 ℃. Subsequently, DMF (N, N-Dimethylformamid) (3.4 mL, 27.4 mmol) was added dropwise at this temperature and the solution was thawed for one hour at room temperature. The reaction mixture was added to a mixture of sodium dihydrogen phosphate monohydrate (26.5 g, 192 mmol, 8 eq., based on *n*-butyllithium) in 192 mL of water and 200 mL diethyl ether pre-cooled to 0 ℃. After stirring for five minutes the phases were separated and the aqueous phase extracted three times with diethyl ether. The combined organic phases were washed with water, dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give **3.13** (3.25 g, 18.67 mmol, 93%) as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.25 (s, 1H), 7.39-7.32 (m, 5H), 4.63 (s, 2H), 4.37 (s, 2H).

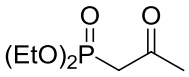
^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 136.6, 128.7, 128.4, 128.3, 92.3, 85.8, 72.4, 57.0.

The NMR data are consistent with the literature data.[77]

Diethyl (2-oxopropyl)phosphonate (3.15) [137]

V3.3

(ZY-3)



To a suspension of potassium iodide (8.2 g, 49 mmol) in 10 ml acetone (dried over $MgSO_4$) and 12.5 ml dried acetonitrile, chloroacetone **3.14** (3.9 mL, 49 mmol) was added. After being stirred for 1 h at room temperature, triethyl phosphite (8.4 mL, 49 mmol) was added slowly. The reaction mixture was stirred for 12 h at room temperature and stirred for 2 h at 60 °C. After cooling, the solid was filtered through celite and rinsed with acetone (dried over $MgSO_4$). After concentration of the solvent under vacuum, the crude product was purified by column chromatography using cyclohexane-ethyl acetate (1:3 to EA) to give **3.15** (5.92 g, 30.5 mmol, 62%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.18-4.09 (m, 4H), 3.09 (s, 1H), 3.04 (s, 1H), 2.30 (s, 3H), 1.32 (t, J = 7.1 Hz, 6H).

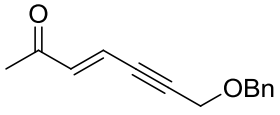
^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.1/200.0, 62.7/62.6, 44.1/42.9, 31.5, 16.4/16.4.

The NMR data are consistent with the literature data. [77]

(*E*)-7-(Benzyloxy)hept-3-en-5-yn-2-one (3.10) [141]

V3.4

(ZY-20)



To a suspension of sodium hydride (60% in mineral oil, 1.8 g, 44.8 mmol) in 180 ml of THF, phosphonate **3.15** (8.70 g, 44.8 mmol) was added slowly at 0 ^{o}C. The mixture was stirred at 0 ^{o}C until no more gas was monitored (ten minutes). To this solution aldehyde **3.13** (6.50 g, 37.3 mmol) dissolved in 75 mL THF was added slowly at 0 ^{o}C. The solution was stirred for 20 minutes at room temperature before the reaction was quenched with sat. aq. NH_4Cl. The aqueous phase was extracted three times with diethyl ether. The combined organic phases was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give **3.10** (5.74 g, 26.8 mmol, 72%, *E*/*Z* = 98:2) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.30 (m, 5H), 6.64 (d, J = 16.1 Hz, 1H), 6.50 (d, J = 16.1 Hz, 1H), 4.61 (s, 2H), 4.35 (s, 2H), 2.28 (s, 3H).

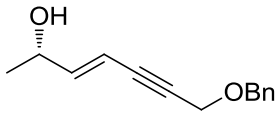
^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 138.7, 137.2, 128.6, 128.3, 128.2, 123.3, 95.8, 83.7, 72.1, 57.9, 27.8.

The NMR data are consistent with the literature data. [77]

(*S*,*E*)-7-(Benzyloxy)hept-3-en-5-yn-2-ol ((*S*)-3.16)

V3.5

(ZY-25)



To a suspension of (*R*)-Me-*CBS*-oxazaborolidine (1 M in toluene, 0.6 mL, 0.6 mmol) in 18 mL THF borane-dimethylsulfide-complex (0.08 mL, 0.9 mmol) was added at -30 ^{o}C. Then, Eninketon **3.10** (642 mg, 3 mmol) in 4 mL THF and borane-dimethylsulfide complex (0.19 mL, 2.1 mmol) were added dropwise at the same time within 30 minutes. After being stirred 30 minutes at -30 ^{o}C to -20 ^{o}C, 5 mL methanol was added and stirred for 15 minutes at room temperature. The solvent was removed in vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (5:1) to give **(*S*)-3.16** (590 mg, 2.73 mmol, 59%) as light yellow oil.

The ee was determined by chiral HPLC: n-heptane/i-PrOH = 95/5, flow rate: 0.6 mL/min, room temperature; retention time, **(*S*)-3.16** 36.0 min, **(*R*)-3.16** 39.5 min.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.28 (m, 5H), 6.21 (dd, J = 15.9, 5.7 Hz, 1H), 5.75 (dd, J = 15.9, 1.6 Hz, 1H), 4.61 (s, 2H), 4.39-4.34 (m, 1H), 4.29 (d, J = 1.8 Hz, 2H), 1.65 (bs, 1H), 1.29 (d, J = 6.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.3, 137.5, 128.6, 128.2, 128.0, 108.6, 85.9, 84.4, 71.7, 68.3, 57.9, 23.1.

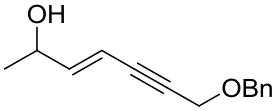
ee = 73%.

The NMR data are consistent with the literature data.[77]

(*E*)-7-(Benzyloxy)hept-3-en-5-yn-2-ol (*rac*-3.16)

V3.6

(ZY-21)



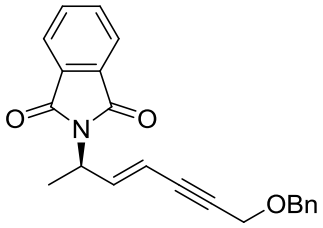
To a suspension of lithium aluminum hydride (372 mg, 9.8 mmol) in 20 mL diethyl ether, ketone 3.10 (2.1 g, 9.8 mmol) dissolved in 10 mL diethyl ether was added dropwise at -60 ^{o}C. After being stirred for 1 h at -60 ^{o}C to -50 ^{o}C, the reaction was quenched with 20 mL sat. aq. NH_4Cl and extracted three times with diethyl ether. The combined organic phases was dried with $MgSO_4$ and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (5:1) to give ***rac*-3.16** (2.1 g, 9.72 mmol, 99%) as light yellow oil.

Spectroscopic data of ***rac*-3.16**: see experiment **V 3.5**.

(*R*,*E*)-2-(7-(Benzyloxy)hept-3-en-5-yn-2-yl)isoindoline-1,3-dione ((*S*)-3.17)

V3.7

(ZY-26)



Based on AAV2, to a solution of **(*S*)-3.16** (720 mg, 3.33 mmol) in THF (28 mL) was added phthalimide (980 mg, 6.66 mmol), triphenylphosphine (1.75 g, 6.66 mmol) at room temperature. After being stirred for 5 minutes at room temperature and then cooled to 0 ℃, DIAD (1.4 mL, 6.66 mmol) was added dropwise and the solution was stirred at this temperature for 1 h and another 2 h at room temperature. The reaction mixture was quenched with water and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (20:1) to give **(*S*)-3.17** (660 mg, 1.91 mmol, 57%) as yellow viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (td, J = 5.3, 2.1 Hz, 2H), 7.72 (td, J = 5.2, 2.1 Hz, 2H), 7.35-7.27 (m, 5H), 6.52 (dd, J = 15.9, 7.5 Hz, 1H), 5.76-5.72 (m, 1H), 5.03-4.94 (m, 1H), 4.58 (s, 2H), 4.26 (d, J = 1.6 Hz, 2H), 1.59 (d, J = 7.1 Hz, 3H).

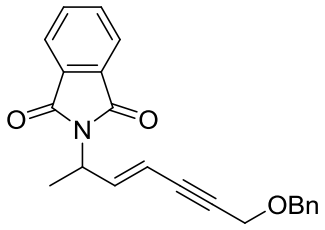
^{13}C NMR (100 MHz, CDCl3): δ = 167.8, 141.8, 137.5, 134.2, 132.0, 128.5, 128.2, 128.0, 123.4, 111.6, 86.5, 84.0, 71.7, 57.8, 48.3, 18.4.

The NMR data are consistent with the literature data. [77]

(*E*)-2-(7-(Benzyloxy)hept-3-en-5-yn-2-yl)isoindoline-1,3-dione (*rac*-3.17)

V3.8

(ZY-22)



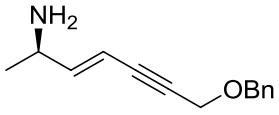
Based on AAV2, to a solution of ***rac*-3.16** (3.52 g, 16.3 mmol) in THF (140 mL) was added phthalimide (3.6 g, 24.5 mmol), triphenylphosphine (6.41 g, 24.5 mmol) at room temperature. After being stirred for 5 minutes at room temperature and then cooled to 0 ℃, DIAD (4.9 mL, 24.5 mmol) was added dropwise and the solution was stirred at this temperature for 1 h and another 2 h at room temperature. The reaction mixture was quenched with water and extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (20:1) to give ***rac*-3.17** (3.54 g, 10.3 mmol, 63%) as yellow viscous oil.

Spectroscopic data of ***rac*-3.17**: see experiment **V 3.7**.

(*R*,*E*)-7-(Benzyloxy)hept-3-en-5-yn-2-amine ((*S*)-3.9)

V3.9

(ZY-27)



To a solution of **(*S*)-3.17** (650 mg, 1.88 mmol) in fresh distilled ethanol (7.5 mL) methylamine (4.8 mL, 40% in water, 56.4 mmol) was added at room temperature. After being stirred for 1 h at 65 ℃, the reaction mixture was quenched with water and extracted three times with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and

concentrated under vacuum. The residue was purified by column chromatography using DCM-MeOH (20:1) to give **(*S*)-3.9** (317 mg, 1.47 mmol, 78%) as yellow viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37-7.27 (m, 5H), 6.16 (dd, J = 15.9, 6.5 Hz, 1H), 5.63 (dd, J = 15.9, 1.5 Hz, 1H), 4.60 (s, 2H), 4.28 (s, 2H), 3.57-3.52 (m, 1H), 1.38 (bs, 2H), 1.18 (d, J = 6.6 Hz, 3H).

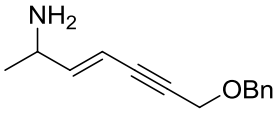
^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1, 137.6, 128.5, 128.2, 128.0, 107.3, 85.0, 84.8, 71.7, 58.0, 49.2, 23.4.

The NMR data are consistent with the literature data.[77]

(*E*)-7-(Benzyloxy)hept-3-en-5-yn-2-amine (*rac*-3.9)

V3.10

(ZY-19)



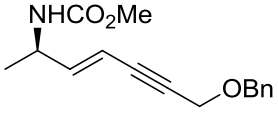
To a solution of ***rac*-3.17** (1.29 g, 3.74 mmol) in fresh distilled ethanol (15 mL) methylamine (9.8 mL, 40% in water, 112.2 mmol) was added at room temperature. After being stirred for 2 h at room temperature, the reaction mixture was quenched with water and extracted three times with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using DCM-MeOH (20:1) to give ***rac*-3.9** (560 mg, 2.6 mmol, 70%) as yellow viscous oil.

Spectroscopic data of ***rac*-3.9**: see experiment **V 3.9**.

(*R*,*E*)-Methyl (7-(benzyloxy)hept-3-en-5-yn-2-yl)carbamate ((*S*)-3.18)

V3.11

(ZY-28)



To a solution of **(*S*)-3.9** (310 mg, 1.44 mmol) in DCM (15 mL) methyl chloroformate (0.14 mL, 1.73 mmol) and pyridine (2.8 mL, 34.6 mmol) were added at room temperature. After being stirred for 1 h at room temperature, the reaction mixture was quenched with water and extracted three times with a mixture of cyclohexane and DCM (1/1). The organic layer was

washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (20:1) to give **(*S*)-3.18** (338 mg, 1.24 mmol, 86%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.28 (m, 5H), 6.10 (dd, J = 16.0, 5.6 Hz, 1H), 5.67 (d, J = 15.9 Hz, 1H), 4.64 (bs, 1H), 4.59 (s, 2H), 4.35-4.34 (m, 1H), 4.27 (d, J = 1.7 Hz, 2H), 3.67 (s, 3H), 1.25 (d, J = 6.9 Hz, 3H).

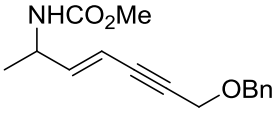
^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 145.1, 137.5, 128.6, 128.2, 128.0, 109.2, 85.9, 84.3, 71.7, 57.9, 52.3, 48.2, 20.7.

The NMR data are consistent with the literature data.[77]

(*E*)-Methyl (7-(benzyloxy)hept-3-en-5-yn-2-yl)carbamate (*rac*-3.18)

V3.12

(ZY-29)



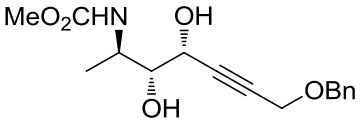
To a solution of ***rac*-3.9** (800 mg, 3.72 mmol) in DCM (37 mL) methyl chloroformate (0.35 mL, 4.46 mmol) and pyridine (7.3 mL, 89.28 mmol) were added at room temperature. After being stirred for 1 h at room temperature, the reaction mixture was quenched with water and extracted three times with a mixture of cyclohexane and DCM (1/1). The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (20:1) to give ***rac*-3.18** (758 mg, 2.78 mmol, 75%) as yellow oil.

Spectroscopic data of ***rac*-3.18**: see experiment **V 3.11**.

Methyl *N*-((2*R*,3*R*,4*R*)-7-(benzyloxy)-3,4-dihydroxyhept-5-yn-2-yl) carbamate ((*S*)-3.19)

V3.13

(ZY-31)



To a suspension of AD-mix-β (1.69 g) in *n*-butanol/H_2O (1:1, 15 mL), $K_3Fe(CN)_6$ (1.19 g, 3.6 mmol) and methane sulfonamide (230 mg, 2.4 mmol) were added. The mixture was

stirred until all the solids were dissolved about 15 minutes. To the solution, **(*S*)-3.18** (330 mg, 1.2 mmol) was added at 0 ℃. The mixture was stirred at this temperature until the reaction was complete. Na_2SO_3 sodium sulfite (1.8 g) was added and then warmed to room temperature and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give **(*S*)-3.19** (240 mg, 0.78 mmol, 65%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.28 (m, 5H), 5.22 (dd, J = 25.1, 8.7 Hz, 1H), 4.58 (s, 2H), 4.38-4.33 (m, 1H), 4.20 (d, J = 1.3 Hz, 2H), 3.92-3.88 (m, 1H), 3.66 (s, 3H), 3.54 (s, 1H), 3.45 (bs, 1H), 2.24 (bs, 1H), 1.25-1.19 (m, 3H).

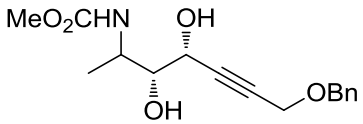
^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4/157.3, 137.2, 128.6, 128.2, 128.1, 84.4/84.3, 82.7/82.3, 73.7/73.5, 71.9, 63.8/63.2, 57.5, 52.5, 48.4, 16.1.

The NMR data are consistent with the literature data.[77]

Methyl *N*-((3*R*,4*R*)-7-(benzyloxy)-3,4-dihydroxyhept-5-yn-2-yl) carbamate (*rac*-3.19)

V3.14

(ZY-70)



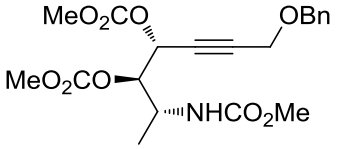
To a mixed solvent of *n*-butanol/H_2O (1:1, 32 mL), $(DHQD)_2PHAL$ (75 mg, 95.7 umol), $K_3Fe(CN)_6$ (3.15 g, 9.57 mmol), K_2CO_3 (1.32 g, 9.57 mmol) and $K_2OsO_2(OH)_4$ (14.1 mg, 38.3 umol) was added. After being stirred 5 minutes at room temperature, methane sulfonamide (607 mg, 6.38 mmol) was added. The mixture was stirred until all the solids were dissolved about 15 minutes. To the solution, ***rac*-3.18** (870 mg, 3.19 mmol) was added at 0 ℃. The mixture was stirred at this temperature until the reaction was complete. Na_2SO_3 sodium sulfite (4.8 g) was added and then warmed to room temperature and stirred for 30 min. The mixture was extracted three times with DCM. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (1:1) to give ***rac*-3.19** (700 mg, 2.28 mmol, 71%) as light yellow oil.

Spectroscopic data of ***rac*-3.19**: see experiment **V 3.13**.

Methyl((2*R*,3*R*,4*R*)-7-(benzyloxy)-3,4-bis((methoxycarbonyl)oxy)hept-5-yn-2-yl)carbamate ((*S*)-3.8)

V3.15

(ZY-33)



To a solution of **(*S*)-3.19** (240 mg, 0.78 mmol) in DCM (5 mL) DMAP (382 mg, 3.12 mmol), pyridine (1.9 mL, 23.43 mmol) and methyl chloroformate (0.62 mL, 7.81 mmol) were added 0 ℃. After being stirred for 4 h at room temperature, the reaction mixture was quenched with sat. aq. NaCl and extracted three times with DCM. The organic layer was washed twice with water, dried with $MgSO_4$, and concentrated under vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (2:1) to give **(*S*)-3.8** (290 mg, 0.69 mmol, 88%) as light yellow viscous oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35-7.28 (m, 5H), 5.39 (d, J = 6.7 Hz, 1H), 5.08 (dd, J = 6.7, 4.6 Hz, 1H), 4.87 (d, J = 8.4 Hz, 1H), 4.57 (s, 2H), 4.29-4.27 (m, 1H), 4.21 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H), 3.65 (s, 3H), 1.25 (d, J = 7.2 Hz, 3H).

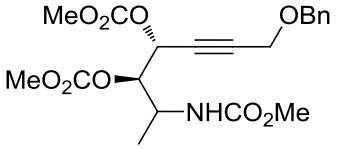
^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 155.4, 154.7, 137.2, 128.6, 128.3, 128.1, 85.3, 79.2, 78.8, 71.7, 67.0, 57.2, 55.5/55.5, 52.4, 46.9, 15.7.

The NMR data are consistent with the literature data. [77]

Methyl((3*R*,4*R*)-7-(benzyloxy)-3,4-bis((methoxycarbonyl)oxy)hept-5-yn-2-yl)carbamate (*rac*-3.8)

V3.16

(ZY-75)

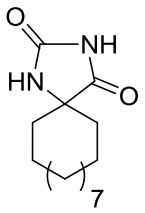


To a solution of **(*rac*)-3.19** (700 mg, 2.28 mmol) in DCM (15 mL) DMAP (1.11 g, 9.12 mmol), pyridine (5.6 mL, 68.4 mmol) and methyl chloroformate (1.8 mL, 22.8 mmol) were added 0 ℃. After being stirred for 4 h at room temperature, the reaction mixture was quenched with sat. aq. NaCl and extracted three times with DCM. The organic layer was washed twice with water, dried with $MgSO_4$, and concentrated under vacuum. The residue

was purified by column chromatography using cyclohexane-ethyl acetate (2:1) to give **(*rac*)-3.8** (800 mg, 1.89 mmol, 83%) as light yellow viscous oil.

Spectroscopic data of ***rac*-3.8**: see experiment **V 3.15**.

1,3-Diazaspiro[4.5]decane-2, 4-dione (3.21)



V3.17

(ZY-39)

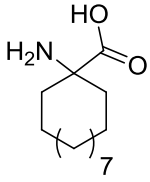
To a suspension of potassium cyanide (9.8 g, 150 mmol) and ammonium carbonate (31.2 g, 325 mmol) in a mixture solvent of 62.5 mL water and 62.5 mL ethanol at room temperature, cyclododecanone **3.20** (13.7 g, 75 mmol) was added. After being stirred for 6 hours at 60 ^{o}C, the alcohol was distilled. The precipitated solid was filtered and washed with cold water. Drying overnight in the air and subsequent azeotropic distillation with toluene at high vacuum to give **3.21** (15.69 g, 62.3 mmol, 83%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.47 (s, 1H), 7.98 (s, 1H), 1.64-1.48 (m, 4H), 1.39-1.25 (m, 18H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 178.3, 156.3, 63.8, 31.0, 25.8, 25.3, 22.4, 21.9, 18.8.

The NMR data are consistent with the literature data. [84]

1-Aminocyclohexanecarboxylic acid (3.22)

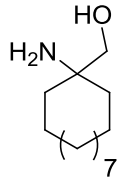


V3.18

(ZY-40)

L1 (6.2 g, 24.6 mmol) and 28 mL 3 M NaOH was stirred for 3 days under reflux. Then, the reaction mixture was acidified with concentrated hydrochloric acid to pH 6. The precipitated solid was filtered and washed with cold water. After drying overnight in the air, subsequent azeotropic distillation with toluene at high vacuum to give **3.22** (5.03 g, 22.1 mmol, 90%) as a white solid, which was used without further characterization in the following step.

(1-Aminocyclododecyl)methanol (3.23)



V3.19

(ZY-44)

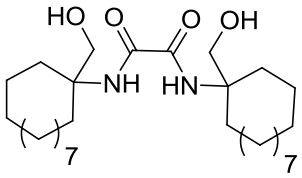
To a suspension of lithium aluminum hydride ($LiAlH_4$) (2.94 g, 77.3 mmol) in 140 ml dried THF, L2 (7.03 g, 30.9 mmol) was added in small portions within one hour at 0 ^oC. The reaction mixture was stirred for 8 hours under reflux and additional 12 hours at room temperature. After hydrolysis with 50 mL 2 N NaOH, the phases were separated and the aqueous phase extracted three times with 30 mL diethyl ether. The combined organic phase was dried with $MgSO_4$ and the solvent was removed in a vacuum to give **3.23** (3.6 g, 17.0 mmol, 55%) as white solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.24 (s, 2H), 2.39 (s, 3H), 1.31-1.30 (m, 22H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.6, 55.7, 31.8, 26.5, 26.1, 22.5, 22.0, 19.0.

The NMR data are consistent with the literature data. [84]

***N*^{1},*N*^{2}-Bis(1-(hydroxymethyl)cyclododecyl)oxalamide (3.24)**



V3.20

(ZY-45)

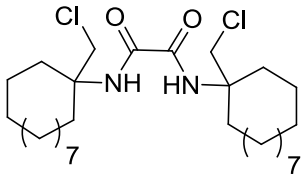
3.23 (1.57 g, 7.36 mmol) and diethyl oxalate (0.49 mL, 3.5 mmol) were stirred at 90 ℃ in 18 mL toluene for 22 h. The **3.24** was crystallized while cooling to room temperature. Decantation of the supernatant and washing of the crystals with cold toluene followed by washing with hexane gave the **3.24** (1.3g, 2.7 mmol, 77%) as white powder.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 2H), 4.10 (s, 2H), 3.66 (s, 4H), 1.67-1.59 (m, 8H), 1.53-1.45 (m, 4H), 1.35 (s, 32H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 66.9, 62.5, 29.0, 26.3, 26.1, 22.6, 22.0, 18.7.

The NMR data are consistent with the literature data. [84]

N^1,N^2-Bis (1-(chloromethyl) cyclododecyl) oxalamide (3.25)



V3.21

(ZY-46)

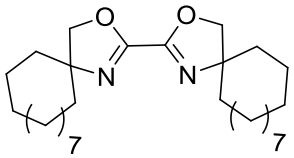
To a suspension of **3.24** (1.26 g, 2.62 mmol) in 26 mL toluene, thionyl chloride (0.56 mL, 7.6 mmol) was added dropwise slowly at 60 ℃. The reaction was stirred at this temperature for 1.5 h and additional 4 h at 90 ℃. Then, the excess thionyl chloride was distilled under water pump vacuum and the residual solvent removed on a rotary evaporator and dried the solid under high vacuum. This gave **3.25** (910 mg, 1.76 mmol, 67%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (s, 2H), 3.85 (s, 4H), 1.88-1.83 (m, 4H), 1.58-1.53 (m, 4H), 1.44-1.24 (m, 36H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 60.0, 46.8, 29.1, 26.1, 26.0, 22.3, 21.9, 18.7.

The NMR data are consistent with the literature data.[84]

Bioxazoline (3.26)



V3.22

(ZY-47)

To a solution of **3.25** (910 mg, 1.76mmol) in 35 mL THF, a solution of NaOH in ethanol (0.4 M; 9.3 mL) was added dropwise. After stirring at room temperature for 30 min, the mixture was heated at 90 ℃ for 3 h. The solvent was evaporated and the residue taken up in chloroform, washed with sat. aq. Na_2CO_3 and the organic phase dried over Na_2SO_4. Evaporation of the solvent and the residue was purified by column chromatography using DCM-MeOH (100:1) to give **3.26** (400 mg, 0.9 mmol, 51%) as white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.06 (s, 4H), 1.80-1.74 (m, 4H), 1.56-1.50 (m, 4H), 1.48-1.36 (m, 36H).

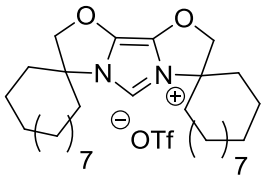
^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 78.6, 74.9, 34.1, 26.5, 26.0, 22.7, 22.3, 19.2.

The NMR data are consistent with the literature data.[84]

IBiox12 ŀHOTf (3.27)

V3.23

(ZY-496)



To a suspension of silver triflate AgOTf (550 mg, 2.14 mmol) in 5 ml dried dichloromethane, Chloromethyl pivalate (318.5 mg, 2.1 mmol) was added and the mixture was stirred vigorously in the dark for 90 minutes. The supernatant was transferred via syringe to the bioxazoline (650 mg, 1.45 mmol) and the resulting solution was stirred in a sealed tube in the dark at 40 ℃ for 20 h. After the solution was cooled to room temperature, the reaction was quenched with methanol and the solvent evaporated in vacuum. The resulting oil was purified by column chromatographed using DCM-MeOH (100:1). Subsequent crystallisation from DCM/diethylether gave the imidazolium triflate **3.27** (520 mg, 0.86 mmol, 59%) as colorless crystals.

^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.68 (s, 1H), 4.73 (s, 4H), 2.25-2.19 (m, 4H), 1.87-1.81 (m, 4H), 1.63-1.57 (m, 12H), 1.45-1.26 (m, 24H).

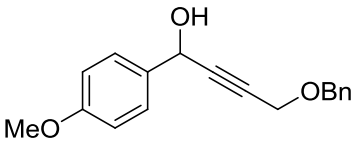
^{13}C NMR (100 MHz, CD_2Cl_2): δ = 125.1, 117.9, 114.3, 87.2, 70.8, 30.6, 25.8, 22.2, 21.7, 19.3.

The NMR data are consistent with the literature data. [84]

4-(Benzyloxy)-1-(4-methoxyphenyl)but-2-yn-1-ol (3.29)

V3.24

(ZY-36)



To a solution of benzyl propargyl ether **3.12** (500 mg, 3.42 mmol) in 18 ml dried THF, *n*-butyllithium (2.3 M in hexane, 1.5 mL, 3.42 mmol) was added dropwise at -78 ^{o}C. The mixture was deprotonated within 30 minutes at this temperature. To the solution, 4-Methoxybenzyl aldehyde **3.28** (475 mg, 3.42 mmol) dissolved in 2.5 ml THF was added slowly. The reaction was stirred for two hours while warming to room temperature. The reaction was hydrolyzed with sat. aq. NH_4Cl and extracted three times with diethyl ether. The combined organic phase was dried with $MgSO_4$ and concentrated. The residue was purified

by column chromatography using cyclohexane-ethyl acetate (4:1) to give **3.29** (810 mg, 2.87 mmol, 84%) as orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, J = 8.6 Hz, 2H), 7.36-7.29 (m, 5H), 6.91 (d, J = 8.7 Hz, 2H), 5.48 (d, J = 5.6 Hz, 1H), 4.61 (s, 2H), 4.27 (d, J = 1.7 Hz, 2H), 3.82 (s, 3H), 2.23 (bs, 1H).

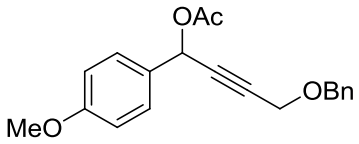
^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 137.5, 132.9, 128.6, 128.2/128.2, 128.0, 114.1, 86.6, 82.6, 71.9, 64.4, 57.6, 55.5.

The NMR data are consistent with the literature data. [85]

4-(Benzyloxy)-1-(4-methoxyphenyl)but-2-yn-1-yl acetate (3.30)

V3.25

(ZY-64)



To a solution of **3.29** (250 mg, 0.89 mmol) in 10 mL dichloromethane, triethylamine (0.19 mL, 1.34 mmol), acetic anhydride (0.17 mL, 1.78 mmol) and N,N-dimethylaminopyridine (DMAP) (5.5 mg, 45 umol) was added at 0 ^{o}C. After stirring for 4 hours at room temperature, the reaction was hydrolyzed with sat. aq. NH_4Cl and extracted three times with diethyl ether. The combined organic phase was dried with $MgSO_4$ and concentrated. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give **3.30** (220 mg, 0.68 mmol, 76%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, J = 8.7 Hz, 2H), 7.35-7.29 (m, 5H), 6.91 (d, J = 8.7 Hz, 2H), 6.48 (s, 1H), 4.60 (s, 2H), 4.26 (s, 2H), 3.82 (s, 3H), 2.09 (s, 3H).

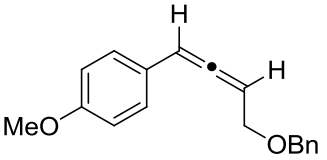
^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 160.2, 137.4, 129.5, 129.2, 128.6, 128.3, 128.1, 114.1, 83.5, 83.2, 71.8, 65.5, 57.5, 55.5, 21.3.

The NMR data are consistent with the literature data.[85]

1-(4-(Benzyloxy)buta-1, 2-dien-1-yl)-4-methoxybenzene (3.31)

V3.26

(ZY-72)



Based on AVV11, to a suspension of copper (I) chloride (1 mg, 0.01 mmol) and sodium *tert*-butoxide (3 mg, 0.03 mmol) in 1 ml toluene, IBiox12 ꞏHOTf (6 mg, 0.01 mmol) was added and stirred for 1 h at 40 ^{o}C. After cooling to room temperature, PMHS (33 uL, 0.5 mmol) was added. After stirring five minutes, the yellow solution was cooled to 0 ^{o}C and **3.30** (100 mg, 0.31 mmol) was added slowly. The mixture was stirred for 40 h at room temperature and quenched with a 1:1 mixed solvent of sat. aq. Na_2CO_3 and diethyl ether. The mixture stirred for an hour violently and the aqueous phase was extracted three times with diethyl ether. The combined organic phases are dried over MgSO4 and the solvent removed in vacuum. The residue was purified by column chromatography using cyclohexane-ethyl acetate (10:1) to give **3.31** (20 mg, 75.2 umol, 24%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.27 (m, 5H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.23 (dt, *J* = 6.0, 2.1 Hz, 1H), 5.70 (q, *J* = 6.6 Hz, 1H), 4.62-4.55 (m, 2H), 4.19-4.12 (m, 2H), 3.81 (s, 3H).

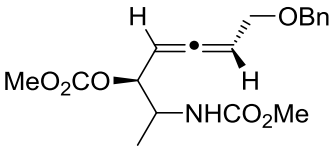
^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.7, 159.1, 138.2, 128.6, 128.1, 128.0, 127.8, 126.3, 114.3, 95.1, 92.6, 72.1, 68.3, 55.5.

The NMR data are consistent with the literature data. [85]

Methyl((3*S*,5*S*)-7-(benzyloxy)-3-((methoxycarbonyl)oxy)hepta-4,5-dien-2-yl)carbamate (*rac*-3.7)

V3.27

(ZY-347)



Based on AVV11, in a Schlenk flask, CuCl (1 mg, 0.01 mmol), NaO*t*-Bu (3 mg, 0.03 mmol), and IBiox12 ꞏHOTf (6 mg, 0.01 mmol) were suspended in dry toluene (0.8 mL). The mixture was heated to 40 ℃ for 1 h and allowed to cool to room temperature. PMHS (25 µL, 0.4 mmol) was added and the mixture was stirred for 5 min at room temperature. After addition

of ***rac*-3.8** (85 mg, 0.2 mmol) in 0.5 mL of dry toluene, the mixture was stirred at 35 ^{o}C for 48 h and another 40 h at room temperature. It was poured into a stirred mixture of saturated aqueous Na_2CO_3 (20 mL) and diethyl ether (20 mL). After stirring for 1 h at room temperature, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with MgSO4, and the solvent was removed in vacuo. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-3.7** (21 mg, 60.1 umol, 30%) as yellow oil.

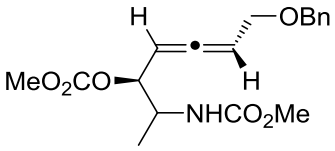
^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.27 (m, 5H), 5.47-5.41 (m, 1H), 5.30-5.28 (m, 1H), 5.11-5.10 (m, 1H), 5.06-4.84 (m, 1H), 4.55-4.51 (m, 2H), 4.09-4.04 (m, 3H), 3.76 (s, 3H), 3.64 (s, 3H), 1.18 (dd, J = 27.7, 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.5/205.0, 156.6/156.4/155.1/155.1, 138.2/138.1, 128.5/128.0/127.9/127.8/127.8, 92.1/91.7/89.3, 77.8/77.2, 72.1/71.9, 67.7/67.2, 55.1/55.0, 52.3/52.2, 49.6/49.4, 17.8/15.8.

The NMR data are consistent with the literature data. [77]

V3.28

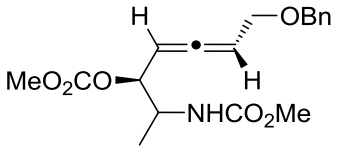
(ZY-355)



Based on AVV11, in a Schlenk flask, CuCl (1 mg, 0.01 mmol), NaO*t*-Bu (3 mg, 0.03 mmol), and IBiox12 ⊣HOTf (6 mg, 0.01 mmol) were suspended in dry toluene (0.8 mL). The mixture was heated to 40 ℃ for 1.5 h and allowed to cool to room temperature. PMHS (25 μL, 0.4 mmol) was added and the mixture was stirred for 5 min at room temperature. After addition of ***rac*-3.8** (85 mg, 0.2 mmol) in 0.5 mL of dry toluene, the mixture was stirred at room temperature for 86 h. It was poured into a stirred mixture of saturated aqueous Na_2CO_3 (20 mL) and diethyl ether (20 mL). After stirring for 1 h at room temperature, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with MgSO4, and the solvent was removed in vacuo. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-3.7** (28 mg, 80.2 umol, 40%) as yellow oil.

V3.29

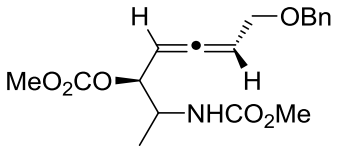
(ZY-369)



Based on AVV11, in a Schlenk flask, CuCl (1 mg, 0.01 mmol), NaO*t*-Bu (3 mg, 0.03 mmol), and IBiox12 ⊣HOTf (6 mg, 0.01 mmol) were suspended in dry toluene (0.8 mL). The mixture was heated to 40 ℃ for 1 h and allowed to cool to room temperature. PMHS (25 μL, 0.4 mmol) was added and the mixture was stirred for 5 min at room temperature. After addition of ***rac*-3.8** (85 mg, 0.2 mmol) in 0.5 mL of dry toluene, the mixture was stirred at room temperature for 115 h. It was poured into a stirred mixture of saturated aqueous Na_2CO_3 (20 mL) and diethyl ether (20 mL). After stirring for 1 h at room temperature, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with MgSO4, and the solvent was removed in vacuo. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-3.7** (20 mg, 57.3 umol, 29%) as yellow oil.

V3.30

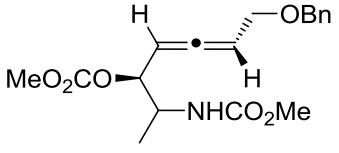
(ZY-743)



Based on AVV11, in a Schlenk flask, CuCl (1 mg, 0.01 mmol), NaO*t*-Bu (3 mg, 0.03 mmol), and IBiox12 ⊣HOTf (6 mg, 0.01 mmol) were suspended in dry toluene (1 mL). The mixture was heated to 100 ℃ for 4 min and cooled to room temperature for 1 h. PMHS (50 μL, 0.8 mmol) was added and the mixture was stirred for 5 min at room temperature. After addition of ***rac*-3.8** (85 mg, 0.2 mmol) in 0.5 mL of dry toluene, the mixture was stirred at 60 ^{o}C for 24 h. After cooling to room temperature, it was poured into a stirred mixture of saturated aqueous Na_2CO_3 (20 mL) and diethyl ether (20 mL). After stirring for 1 h at room temperature, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with MgSO4, and the solvent was removed in vacuo. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-3.7** (36.9 mg, 105.7 umol, 53%) as yellow oil.

V3.31

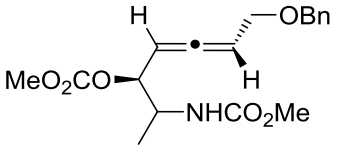
(ZY-745)



Based on AVV11, in a Schlenk flask, CuCl (1 mg, 0.01 mmol), NaO*t*-Bu (3 mg, 0.03 mmol), and IBiox12 ǂHOTf (6 mg, 0.01 mmol) were suspended in dry toluene (1 mL). The mixture was heated to 100 ℃ for 4 min and cooled to room temperature for 1 h. PMHS (50 µL, 0.8 mmol) was added and the mixture was stirred for 5 min at room temperature. After addition of ***rac*-3.8** (85 mg, 0.2 mmol) in 0.5 mL of dry toluene, the mixture was stirred at 80 ^{o}C for 24 h. After cooling to room temperature, it was poured into a stirred mixture of saturated aqueous Na_2CO_3 (20 mL) and diethyl ether (20 mL). After stirring for 1 h at room temperature, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with MgSO4, and the solvent was removed in vacuo. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-3.7** (34.4 mg, 98.5 umol, 49%) as yellow oil.

V3.32

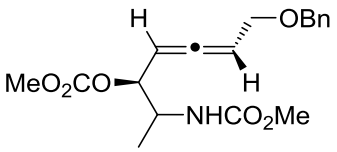
(ZY-739)



Based on AVV11, in a Schlenk flask, CuCl (2 mg, 0.02 mmol), NaO*t*-Bu (6 mg, 0.06 mmol), and IBiox12 ǂHOTf (12 mg, 0.02 mmol) were suspended in dry toluene (1 mL). The mixture was heated to 100 ℃ for 4 min and cooled to room temperature for 1 h. PMHS (48 µL, 0.8 mmol) was added and the mixture was stirred for 5 min at room temperature. After addition of ***rac*-3.8** (85 mg, 0.2 mmol) in 0.5 mL of dry toluene, the mixture was stirred at room temperature for 24 h. It was poured into a stirred mixture of saturated aqueous Na_2CO_3 (20 mL) and diethyl ether (20 mL). After stirring for 1 h at room temperature, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with MgSO4, and the solvent was removed in vacuo. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-3.7** (21 mg, 60.1 umol, 30%) as yellow oil.

V3.33

(ZY-739)

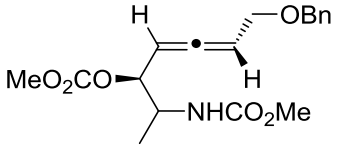


Based on AVV11, in a Schlenk flask, CuCl (2 mg, 0.02 mmol), NaO*t*-Bu (6 mg, 0.06 mmol), and IBiox12 ǂHOTf (12 mg, 0.02 mmol) were suspended in dry toluene (1 mL). The mixture

was heated to 100 ℃ for 4 min and cooled to room temperature for 1 h. PMHS (48 μL, 0.8 mmol) was added and the mixture was stirred for 5 min at room temperature. After addition of ***rac*-3.8** (85 mg, 0.2 mmol) in 0.5 mL of dry toluene, the mixture was stirred at room temperature for 41 h. It was poured into a stirred mixture of saturated aqueous Na_2CO_3 (20 mL) and diethyl ether (20 mL). After stirring for 1 h at room temperature, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with MgSO4, and the solvent was removed in vacuo. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-3.7** (27 mg, 77.3 umol, 38%) as yellow oil.

V3.34

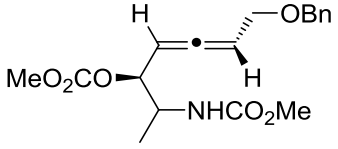
(ZY-742)



Based on AVV11, in a Schlenk flask, CuCl (2 mg, 0.02 mmol), NaO*t*-Bu (6 mg, 0.06 mmol), and IBiox12 ⊣HOTf (12 mg, 0.02 mmol) were suspended in dry toluene (1 mL). The mixture was heated to 100 ℃ for 4 min and cooled to room temperature for 1 h. PMHS (48 μL, 0.8 mmol) was added and the mixture was stirred for 5 min at room temperature. After addition of ***rac*-3.8** (85 mg, 0.2 mmol) in 0.5 mL of dry toluene, the mixture was stirred at room temperature for 96 h. It was poured into a stirred mixture of saturated aqueous Na_2CO_3 (20 mL) and diethyl ether (20 mL). After stirring for 1 h at room temperature, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with MgSO4, and the solvent was removed in vacuo. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-3.7** (37.4 mg, 107.1 umol, 53%) as yellow oil.

V3.35

(ZY-741)



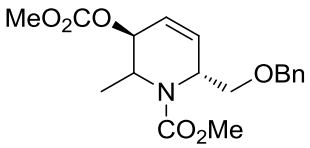
Based on AVV11, in a Schlenk flask, CuCl (2 mg, 0.02 mmol), NaO*t*-Bu (6 mg, 0.06 mmol), and IBiox12 ⊣HOTf (12 mg, 0.02 mmol) were suspended in dry toluene (1 mL). The mixture was heated to 100 ℃ for 4 min and cooled to room temperature for 1 h. PMHS (48 μL, 0.8 mmol) was added and the mixture was stirred for 5 min at room temperature. After addition

of ***rac*-3.8** (85 mg, 0.2 mmol) in 0.5 mL of dry toluene, the mixture was stirred at 15 ^{o}C for 72 h. It was poured into a stirred mixture of saturated aqueous Na_2CO_3 (20 mL) and diethyl ether (20 mL). After stirring for 1 h at room temperature, the layers were separated and the aqueous layer was extracted with diethyl ether. The combined organic extracts were dried with MgSO4, and the solvent was removed in vacuo. The residue was purified by column chromatography using cyclohexane-ethyl acetate (4:1) to give ***rac*-3.7** (31.5 mg, 90.2 umol, 45%) as yellow oil.

(2*R*,5*S*)-Methyl2-((benzyloxy)methyl)-5-((methoxycarbonyl)oxy)-6-methyl-5,6-dihydropyridine-1(2*H*)-carboxylate (*rac*-3.6)

V3.36

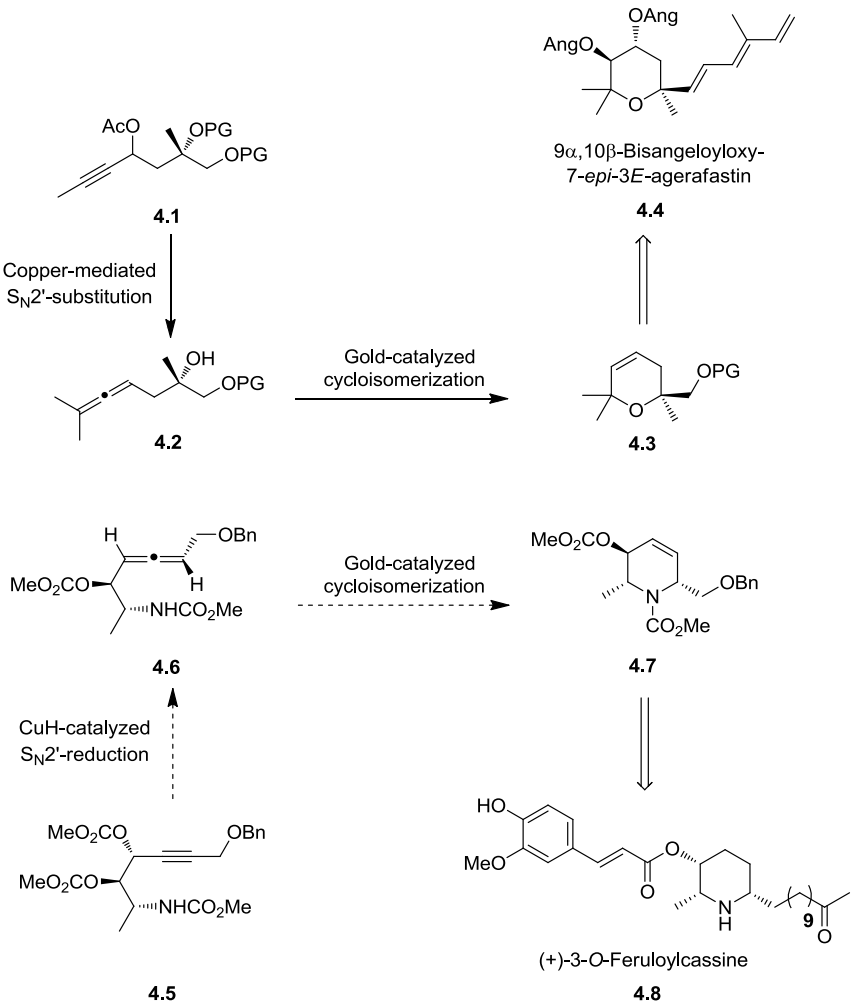
(ZY-497)



To a solution of β-Aminoallene ***rac*-3.7** (48 mg, 137 umol) in 1.5 mL DCM Ph_3PAu-NTf_2 ·1/2 toluene (5.4 mg, 6.9 umol) was added. After being stirred for 21 h, the reaction mixture was filtrated through Celite and the filtrate was concentrated under vacuum. The crude product was purified by flash column chromatography on silica gel to give no product.

Chapter 4. Summary and Perspective

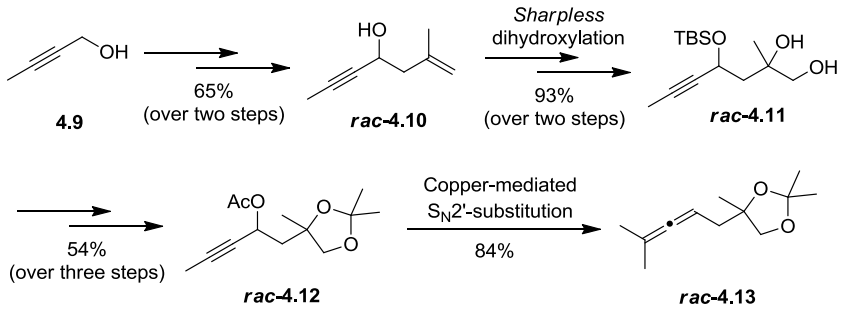
Based on the work described in this thesis, the copper-mediated nucleophilic substitution and the gold-catalyzed cycloisomerization were applied to study the synthesis of natural products containing 6-membered heterocycles, 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin **4.4** and (+)-3-*O*-Feruloylcassine **4.8** (Scheme 4.1).



Scheme 4.1: The application of the copper-catalyzed nucleophilic substitution and the gold-catalyzed cycloisomerization in natural products synthesis.

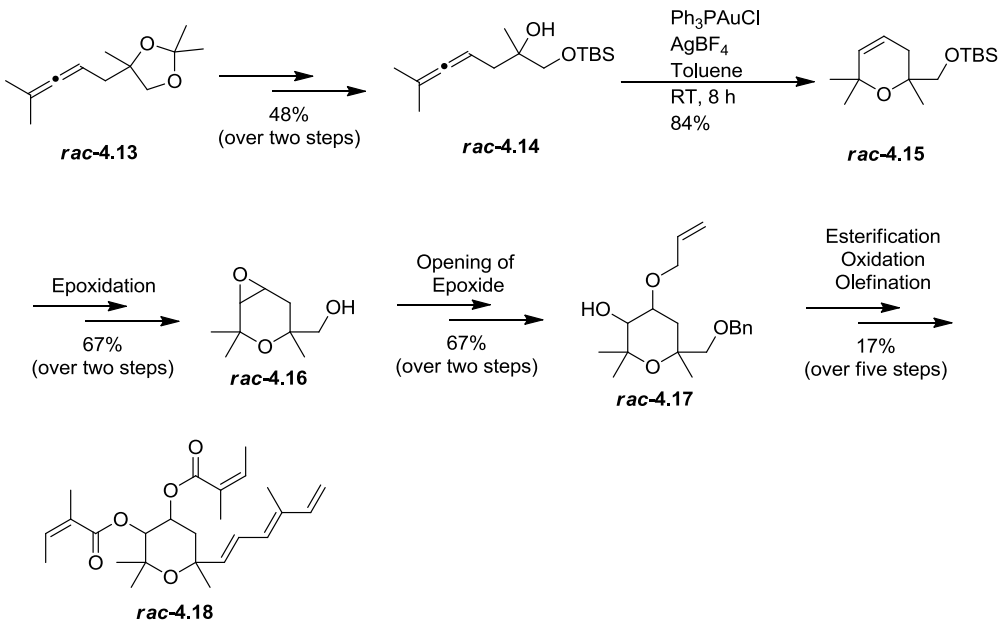
In chapter 2, the first total synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin was demonstrated. Based on *Gockel's* work,[39] homoallylic alcohol ***rac*-4.10** was synthesized from alcohol **4.9**. After protecting the hydroxyl group of ***rac*-4.10**, the diol ***rac*-4.11** was obtained through *Sharpless* dihydroxylation with a 1:1 mixture of AD-mix-α and AD-mix-β. Then, the propargyl acetate ***rac*-4.12** was provided in three steps with a total yield of 54%. The first key step, the copper-mediated S_N2'-substitution of propargyl acetate ***rac*-4.12**, was performed in two ways to provide the allene ***rac*-4.13** with good yield of 84% (Scheme 4.2). In this route, different protecting groups, as well as different reaction conditions for the

asymmetric *Sharpless* dihydroxylation were tested for obtaining the (*S*)- and (*R*)-configured diols with higher selectivity, which will determine the ee of allene **4.13**. However, the enantiomeric excess was still not satisfactory (17%-67%).



Sheme 4.2: Synthesis of β-hydroxyallene ***rac*-2.32**.

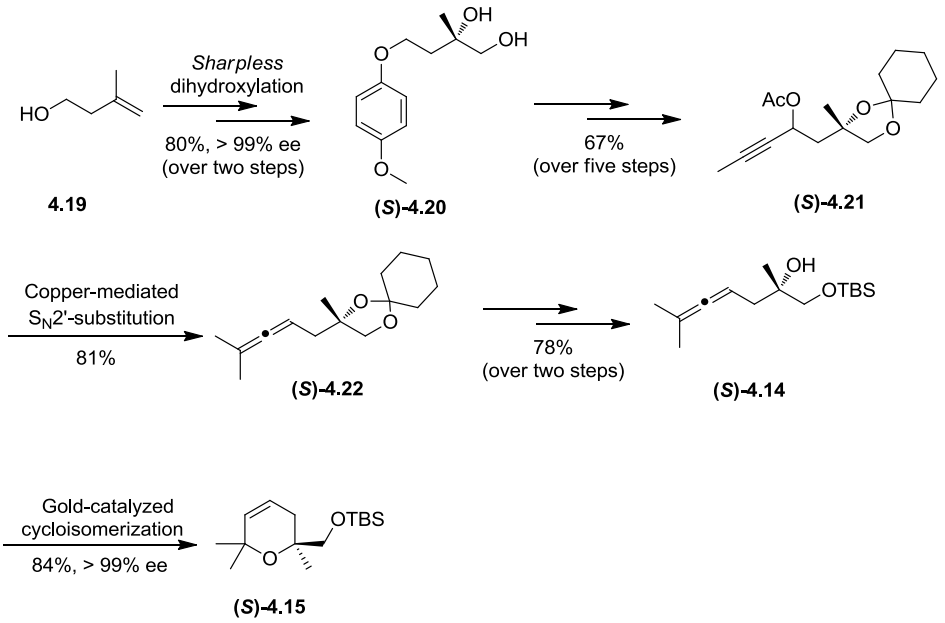
With the gold-catalyzed cycloisomerization of β-hydroxyallene ***rac*-4.14**, the significant intermediate dihydropyran ***rac*-4.15** was obtained with good yield. After epoxidation, various acids and bases were tested to open the epoxide ***rac*-4.16**. Finally, a regio- and stereoselective opening of the epoxide with allyl alcohol and $HClO_4$ was successful to give ***rac*-4.17** with good yield. Fortunately, through a sequence of esterification/oxidation/olefination, the desired racemic agerafastin ***rac*-4.18** was obtained (Scheme 4.3).



Sheme 4.3: Total synthesis of ***rac*-4.18**.

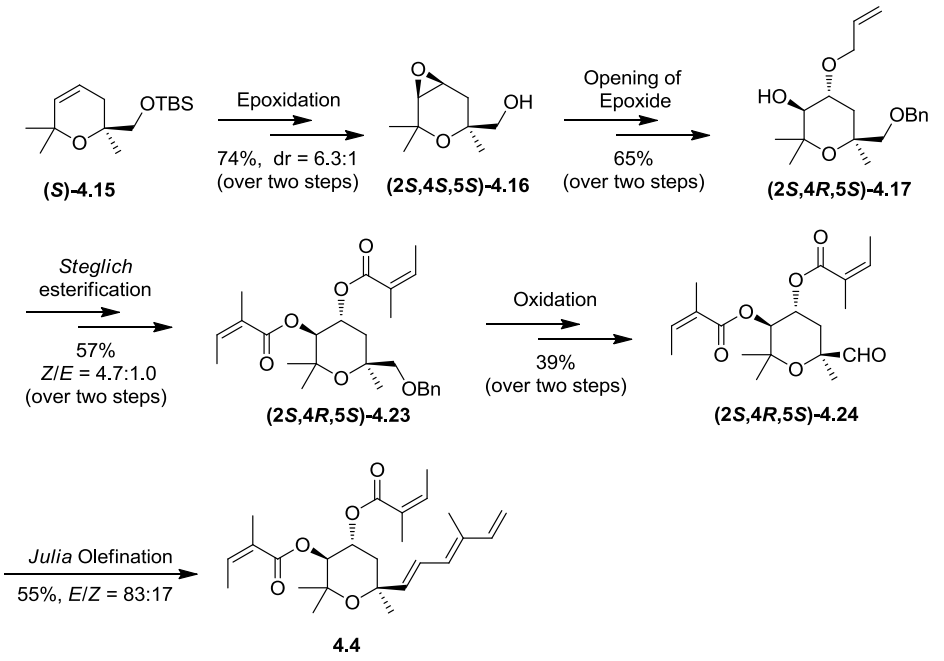
Based on the racemic synthesis route, the homoallylic alcohol **4.10** was not a good substrate for the *Sharpless* dihydroxylation. Then, alcohol **4.19** was chosen as starting material and the

enantiomerically pure diol **(*S*)-4.20** was obtained in 8-gram scale. After five steps, the desired propargyl acetate **(*S*)-4.21** was synthesized. The copper-mediated S_N2'-substitution of propargyl acetate **(*S*)-4.21** was carried out to give the allene **(*S*)-4.22** in good yield of 81% in gram scale. After that, the gold-catalyzed cycloisomerization of β-hydroxyallene **(*S*)-4.14** was performed to provide the key intermediate **(*S*)-4.15** with a yield of 84% and >99% ee, which means the axis-to-center chirality transfer was perfect in this efficient gold-catalyzed cycloisomerization (Scheme 4.4).



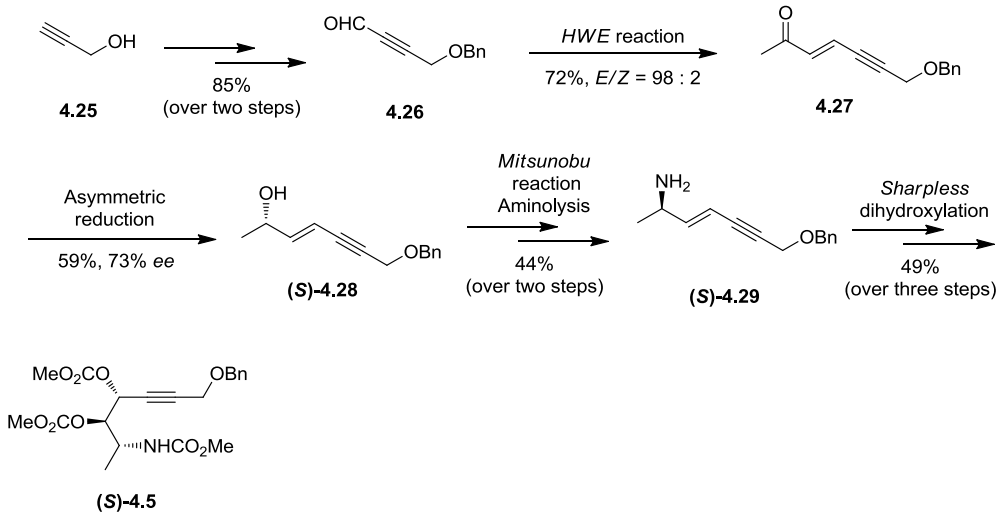
Sheme 4.4: Synthesis of the dihydropyran **(*S*)-4.15**.

Next, the diastereoselective epoxidation directed by the free hydroxyl group was conducted to give the tetrahydropyran (2***S*,4*S*,5*S*)-4.16** in good yield and good selectivity. After protecting the hydroxyl group of (2***S*,4*S*,5*S*)-4.16**, the regio- and stereoselective opening of the epoxide was carried out with allyl alcohol and $HClO_4$ to provide the optically pure tetrahydropyran **(2*S*,4*R*,5*S*)-4.17**. Then, the deprotection of the allyl group of **(2*S*,4*R*,5*S*)-4.17** proceeded to give the diol, which was transformed to the ester **(2*S*,4*R*,5*S*)-4.23** by means of Steglich esterification with good *Z*/*E* ratio (4.7:1.0). After the deprotection of the benzyl group of **(2*S*,4*R*,5*S*)-4.23**, the pure *Z*-isomer was separated by column chromatography successfully. The optically pure aldehyde **(2*S*,4*R*,5*S*)-4.24** was obtained by oxidation with *Dess-Martin* periodinane. The last step, the modified *Julia* olefination, was performed to provide the final product 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin **4.4** with a moderate yield of 55% and good *Z*/*E* ratio (83:17) (Scheme 4.5).



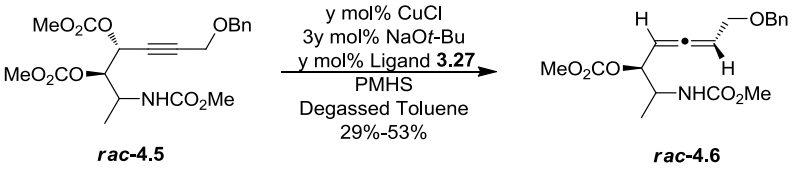
Sheme 4.5: Synthesis of the natural product **4.4**.

In chapter 3, the objective is the total synthesis of natural product (+)-3-*O*-Feruloylcassine. Based on *Sun*'s work,[77] the synthetic route shown in Scheme 4.6 was chosen to study this project. The propargyl dicarbonate **(*S*)-4.5** was obtained successfully.



Scheme 4.6: Synthesis of carbamate **(*S*)-4.5**.

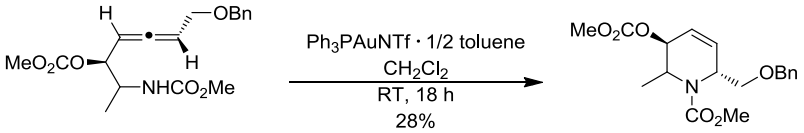
Next, ***rac*-4.5** was used for the further study. The desired β-aminoallene ***rac*-4.6** was obtained by CuH-catalyzed S_N2'-reduction. After optimization of this reaction, the best yield was 53% (Scheme 4.7).



***rac*-4.5** ***rac*-4.6**

Scheme 4.7: Synthesis ***rac*-4.6** by CuH-catalyzed S_N2'-reduction of propargyl dicarbonate ***rac*-4.5**.

With the β-aminoallene ***rac*-4.6** in hand, the plan was to optimize the gold-catalyzed cycloisomerization to obtain a higher yield of the desired tetrahydropyridine. According to *Sun*'s work, it is possible to obtain ***rac*-4.7** with 28% yield after 18 h reaction time (Scheme 4.8).[77] Further optimization of this step is required for an efficient synthesis of (+)-3-*O*-Feruloylcassine.



***rac*-4.6** ***rac*-4.7**

Scheme 4.8: Synthesis ***rac*-4.7** by gold-catalyzed cycloisomerization of ***rac*-4.6**.

Therefore, a more active gold catalysts for synthesizing the tetrahydropyridine should be tested. Recently, new cationic gold catalyst system was developed by *Malhotra* and *Xu*.[86] The new gold complex L1-AuCl (Figure 4.1) can catalyze common types of gold-catalyzed reactions including intra- and intermolecular X-H (X = C, N, O) additions to alkynes and cycloisomerizations efficiently. Then, different ligands, silver salts and reaction conditions can be chosen to optimize the gold-catalyzed cycloisomerization.

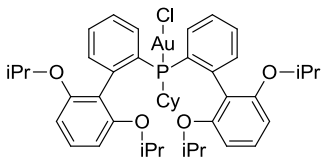


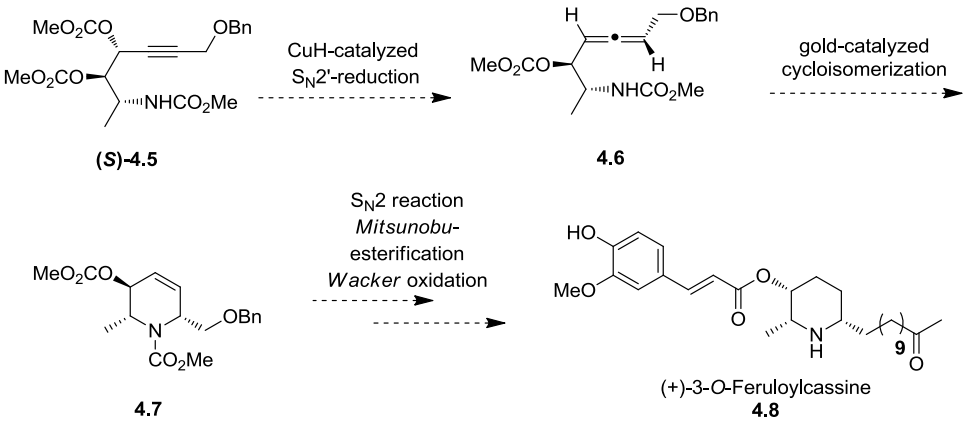
Figure 4.1

[86] D. Malhotra, M. S. Mashuta, G. B. Hammond, B. Xu, *Angew. Chem. Int. Ed.* **2014**, *53*, 4456-4459.

[87] H. Muratake, I. Abe, M. Natsume, *Chem. Pharm. Bull.* **1996**, *44*, 67-79.

[88] (a) J. Tsuji, *Synthesis* **1984**, 369-384; (b) D. A. Evans, P. Nagorny, K. J. McRae, L.-S. Sonntag, D. J. Reynolds, F. Vounatsos, *Angew. Chem. Int. Ed.* **2007**, *46*, 545-548.

After optimizing the gold-catalyzed cycloisomerization, the total synthesis of (+)-3-*O*-Feruloylcassine should be continued as shown in Scheme 4.9.[87-88]



Scheme 4.9: The plan of total synthesis of (+)-3-*O*-Feruloylcassine **4.8**.

I. Abbreviations

Ac	Acyl
AD	Asymmetric dihydroxylation
aq	Aqueous
Ar	Aryl
Bn	Benzyl
Bu	Butyl
Calcd	Calculated
CAN	Ceric ammonium nitrate
CAL-B	Lipase B from *Candida antarctica*
CBS	*Corey-Bakshi-Shibata*
$CDCl_3$	Deuterated chloroform
$CHCl_3$	Chloroform
COSY	(^{1}H-^{1}H) correlated spectroscopy
d	Day
DCC	Dicyclohexylcarbodiimde
DCM	Dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethylazodicarboxylate
DKR	Dynamic kinetic resolution
DMAP	4-*N*,*N*-dimethylaminopyridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMP	*Dess-Martin* periodinane
DIAD	Diisopropylazodicarboxylate
dr	Diastereomeric ratio
ee	Enantiomeric excess
Eq.	Equivalent
ESI	Electron spray inonisation

Et_2O	Diethylether
Et	Ethyl
Et_3N	triethylamine
GC	Gas chromatography
h	Hour
HMBC	Heteronuclear multiple bond correlation
HOTf	Trifluoromethanesulfonic
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
HWE	*Horner-Wadsworth-Emmons*
Hz	Hertz
i-Pr	isopropyl
IR	Infrared spectroscopy
J	Coupling constant
KR	Kinetic resolution
L	Ligand
$LiAlH_4$	Lithium aluminum hydride
M	Metal
m-CPBA	3-Chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
MeOH	Methanol
min	Minute
n-Bu	*n*-Butyl
n-BuLi	*n*-Butyllithium
NHC	N-Heterocyclic carbene
NMR	Nuclear manetic resonance
NOE	Nucler Overhauser effect
NOESY	Nuclear Overhauser enhancement spectroscopy
PG	Protecting group

Ph	Phenyl
PMHS	Polymethylhydridosiloxane
p-TsOH	*p*-Toluenesulfonic acid
RT	Room temperature
S_N	Nucleophilic substitution
Sat.	Saturated
t	*tert*
t	Time
T	Temperature
TBAF	Tetra-*n*-butyl ammonium fluoride
TBAI	Tetra-*n*-butylammonium
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
Tf	Trifluoromethanesulfonyl
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin Layer Chromatography

II. Acknowledgements

First and foremost, I would like to express my sincere gratitude to my PhD supervisor, Prof. Dr. *Norbert Krause*, for his support, education and inspiration on a daily basis and keeping me on the right track over the last four years. I would also thank Prof. Dr. *Ralf Weberskirch* for agreeing to be my second examiner of my PhD thesis.

For my dear colleagues, it's my honor to thank them here not only for cooperation, but also for the help, motivation, and inspiration. Especially I would like to give my sincere thanks to Dr. *Nanaji Arisetti*, *Justin Schieven*, *Martin Körner*, *Indre Versinskaite*, *Maximilian Düser*, *Johannes Rath*, *Katharina Müller*, *Monika Ballmann*, *Anja Wiegand*, *Hülya Sak*, for all the scientific and nonscientific discussions and the helpful suggestions. Special thanks go to associate Prof. Dr. *Gen Onodera* for the NMR analysis. Besides, I thank all the other lab mates in the university, including *Rujin Li*, *Bin Chen*, *Philipp Baumann*, *Hanne Petersen*, *Florian Pätzold*, *Christian Gramse*, *Marvin Diete*, *Yasin Kuzu*, *Felix Langenohl*. I also acknowledge all other members of college, especially those working in the department of organic chemistry, as well as the colleagues in MS measurement, NMR measurement. The collaborative working environment and the enjoyable working atmosphere in our department leave a fantastic memory to me and I shall never forget.

My sincere gratitude also goes to our secretaries *Silvia Lessing* and *Kim-Alexander Vogt*. Life became way much easier here in Dortmund owing to their help.

Many thanks to all of my friends that I met in Germany, for helping me enjoying the life here outside the lab, and also leaving me space when I started to focus on my work.

Further I would like to acknowledge the financial support by CSC (the China Schoolarship Council) to give me a chance to go abroad.

Last but not least, my deep gratitude goes to my family for allowing me to stay abroad for years without any complain. Special thanks to my beloved wife Meijun Ming, I would have never arrived here without her endless support and love over years.

III. Curriculum Vitae

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Nationality: P.R China

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Topic: Study of Total Synthesis of 9α,10β-Bisangeloyloxy-7-*epi*-3*E*-agerafastin and 3-*O*-Feruloylcassine by Copper-mediated Nucleophilic Substitution and Gold-catalyzed Cycloisomerization
Fellowship: CSC (the China Schoolarship Council)

09/2012-06/2015 **Master of Science in Organic Chemistry**

College of Chemistry of Sichuan University
Supervisor: Associate Prof. Dr. Na Wang
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09/2008-06/2012 **Bachelor of Science in Chemicobiology and Double Degree of Project Management**

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Poster

Yang Zhang, Sun Sun, Norbert Krause

"Total Synthesis of the Natural Product (+)-3-*O*-Feruloylcassine"

Münster Symposium, Münster, 03. 2018

Yang Zhang, Birgit Gockel, Norbert Krause

"Total Synthesis of the Natural Products 9α,10β-Bisangeloyloxy agerafastins"

ORCHEM 2018, Berlin, 09. 2018

Presentation

02.2019 Chemistry day of the Technical University of Dortmund
"Total Synthesis of the Natural Products 9α,10β-Bisangeloyloxy agerafastins"

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