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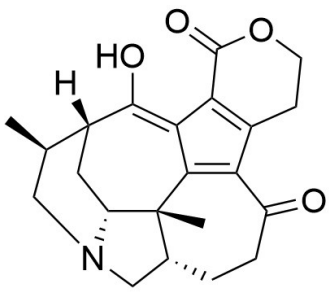
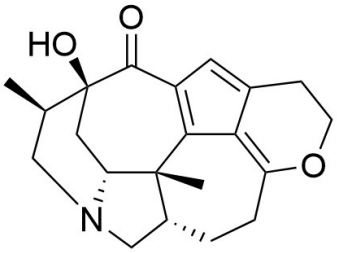
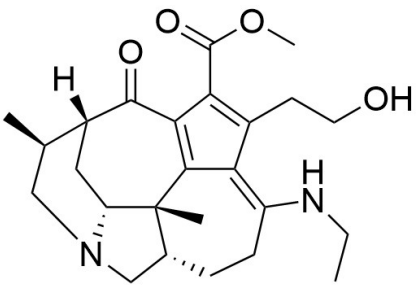
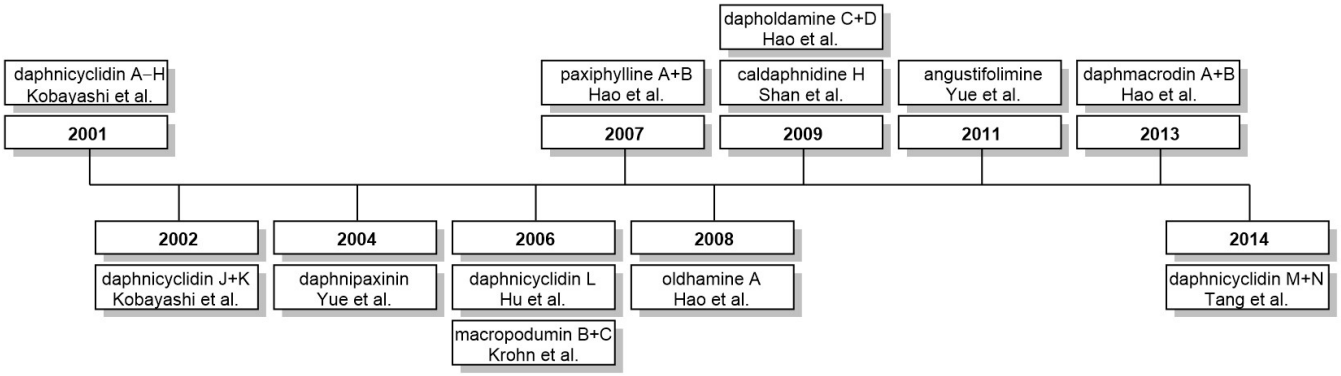
Daphnicyclidin Alkaloids 2001–2023

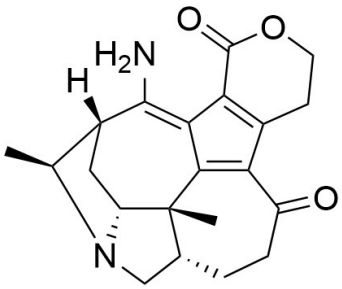
Jan Gierok[a] and Martin Hiersemann*[a]

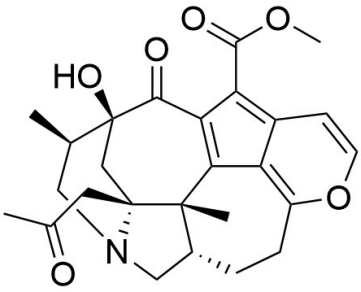


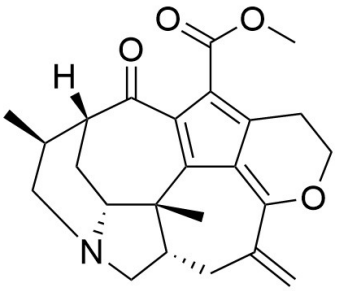












Review
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The *Daphniphyllum* alkaloids represent a particularly diverse class of complex diterpene alkaloids, which are characterized by their enormous structural diversity. The daphnicyclidins, a subgroup of these alkaloids, stand out due to their unique pentafulvene structural motif. This review article gives an overview of the compounds that have been isolated so far and can be assigned to this subgroup. Furthermore, all synthesis approaches and total syntheses published to date are presented.

1. Introduction

The *Daphniphyllum* alkaloids[1a–j] constitute an extraordinarily unique and structurally sophisticated class of natural products. Taming structural diversity, *daphniphyllum* alkaloids are often classified according to signature structural motifs and the proposed biosynthesis. The polycyclic, cage-like daphnicyclidine alkaloids form a particularly fascinating branch within the *Daphniphyllum* alkaloid family. Daphnicyclidine alkaloids are distinguished by the presence of an embedded pentafulvene[2] motif. The first part of this review provides an overview of the status quo of the isolation of the various daphnicyclidine alkaloids.

The intricated molecular architecture of *daphniphyllum* alkaloids in general and daphnicyclidin alkaloids in particular represents a major challenge for total synthesis. Enormous efforts have been undertaken to establish a producer-independent synthetic access to daphnicyclidin alkaloids and derivatives. The second part of our overview summarizes these synthetic efforts of the last 15 years in chronological order.

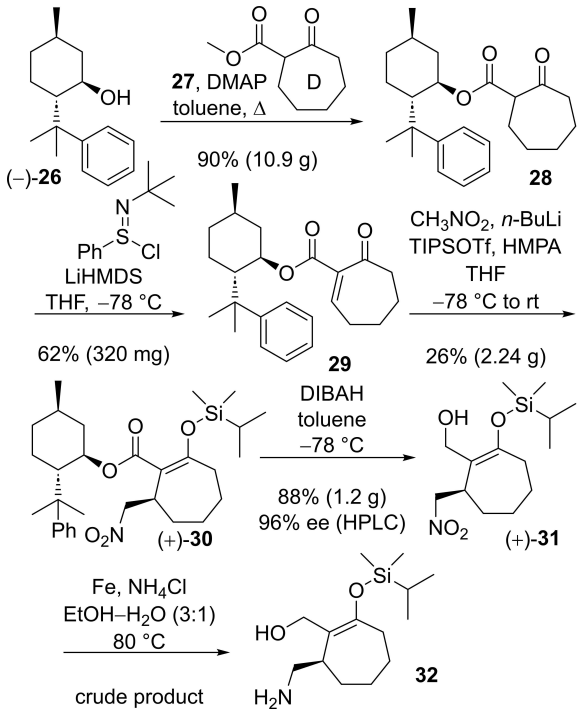
2. Isolation

Figure 1 illustrates a timeline for the isolation and the structural elucidation of daphnicyclidine alkaloids from plants of the genus *Daphniphyllum*. In 2001, Kobayashi and coworkers[3] reported the isolation and structural elucidation of the daphnicyclidins A–H ($D_{A–H}$, **1**–**8**) from *D. teijsmanni* and *D. humile*. Daphnicyclidins are characterized by a pentafulvene embedded into a penta- or hexacyclic, cage-like structure. To the best of our knowledge, the pentafulvene motif has not been found in any other natural product. Therefore, we consider the presence of the pentafulvene motif to be the defining structural feature of members of the family of daphnicyclidin alkaloids.

In 2002, the group of Kobayashi reported the isolation and structural elucidation of D_J (**9**) and D_K (**10**) from *D. humile*.[4] Yue and colleagues succeeded in isolating daphnipaxinine (**11**) from *D. paxianum* in 2004.[5] In 2006, Hu *et al.* described the isolation of D_L (**12**)[6] from *D. macropodum MIQ* and Krohn *et al.* the isolation of macropodumin B (**13**) and C (**14**) from *D. macropodum MIQ*.[7] Hao and coworkers isolated paxiphylline A (**15**) and B (**16**) from *D. paxianum* in 2007.[8] In 2008, Hao *et al.* described the isolation of oldhamine A (**17**) from *D. oldhami*[9] and one year later[10] the two dapholdamines C (**18**) and D (**19**) also from *D. oldhami*. Also in 2008, Shan *et al.* described caldaphnidine H (**20**) from *D. calycinum*.[11] In 2011, Yue and colleagues described the angustifolimine (**21**) isolated from *D. angustifolium*.[12] In 2013, Hao *et al.* isolated daphmacrodin A (**22**) and B (**23**) from *D. macropodum*[13] which appear to be the conjugated Brønsted acids of D_A **1** (daphmacrodin B **23**) and D_B **2** (daphmacrodine A **22**). The publication even erroneously refers to daphnicyclidin B at one point. In the last publication on the isolation of daphnicyclidins to date, Tang *et al.* reported 2014[14] the structures of daphnicyclidin N (**24**) and M (**25**) also isolated from from *D. macropodum*.

3. Synthetic Efforts

In 2009, Iwabuchi *et al.* reported the convergent asymmetric synthesis of an BCD-tricyclic building block for the non-natural enantiomer of daphnicyclidin A (+)-**1** (Scheme 1–3).[15] The



Scheme 1. Synthesis of an BCD-tricyclic backbone of ent-(−)-daphnicyclidin A ent-(−)-**1** according to Iwabuchi *et al.* (Part I).

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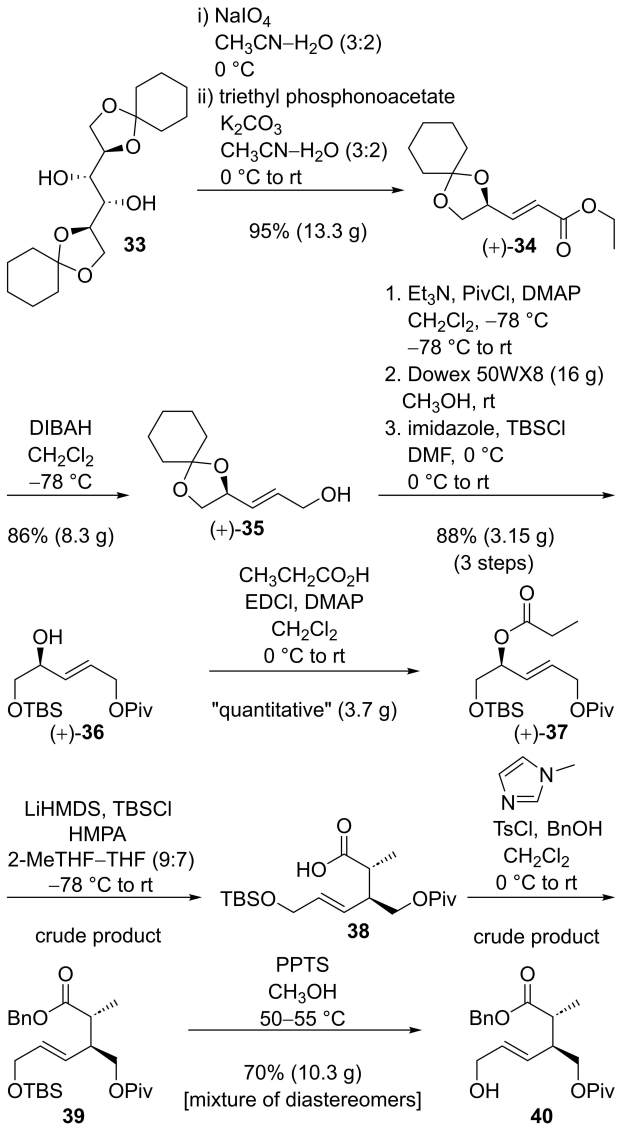
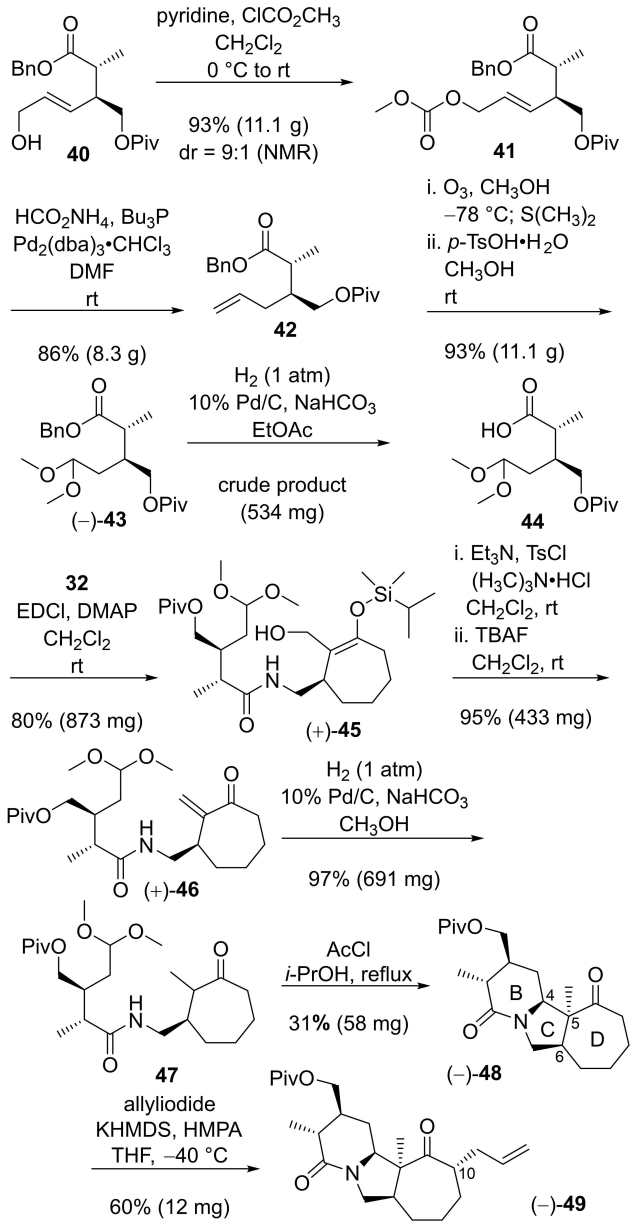


Scheme 2. Synthesis of an BCD-tricyclic backbone of ent-(−)-daphnicyclidin A ent-(−)-**1** according to Iwabuchi *et al.* (Part II).



Scheme 3. Synthesis of an BCD-tricyclic backbone of ent-(−)-daphnicyclidin A ent-(−)-**1** according to Iwabuchi *et al.* (Part III).

Jan Gierok was born in Wickede, Germany in 1993. He started to study chemistry at the Technical University of Dortmund in 2013 and completed his Master studies in 2018 supervised by Martin Hiersemann and is currently carrying out his Ph.D. studies about the total synthesis of daphniphyllum alkaloids within the same workgroup.

Martin Hiersemann was born in Berlin-Steglitz, Germany. He studied Chemistry at the FU Berlin and graduated with the degree Diplomchemiker in 1991. He went on to study Organic Chemistry with Johann Mulzer (Berlin), Gary Molander (Boulder), and Hans-Ullrich Reißig (Dresden). Short stays in the working groups of David Evans (Cambridge, MA), Paul Grieco (Bozeman) and Akira Hosomi (Tsukuba) set the course for his further development. As a member of a faculty with a strong focus on Chemical Biology, he is Professor of Organic Chemistry at the TU Dortmund and remains active in the developement and application of synthetic methods as well as in natural product total synthesis.

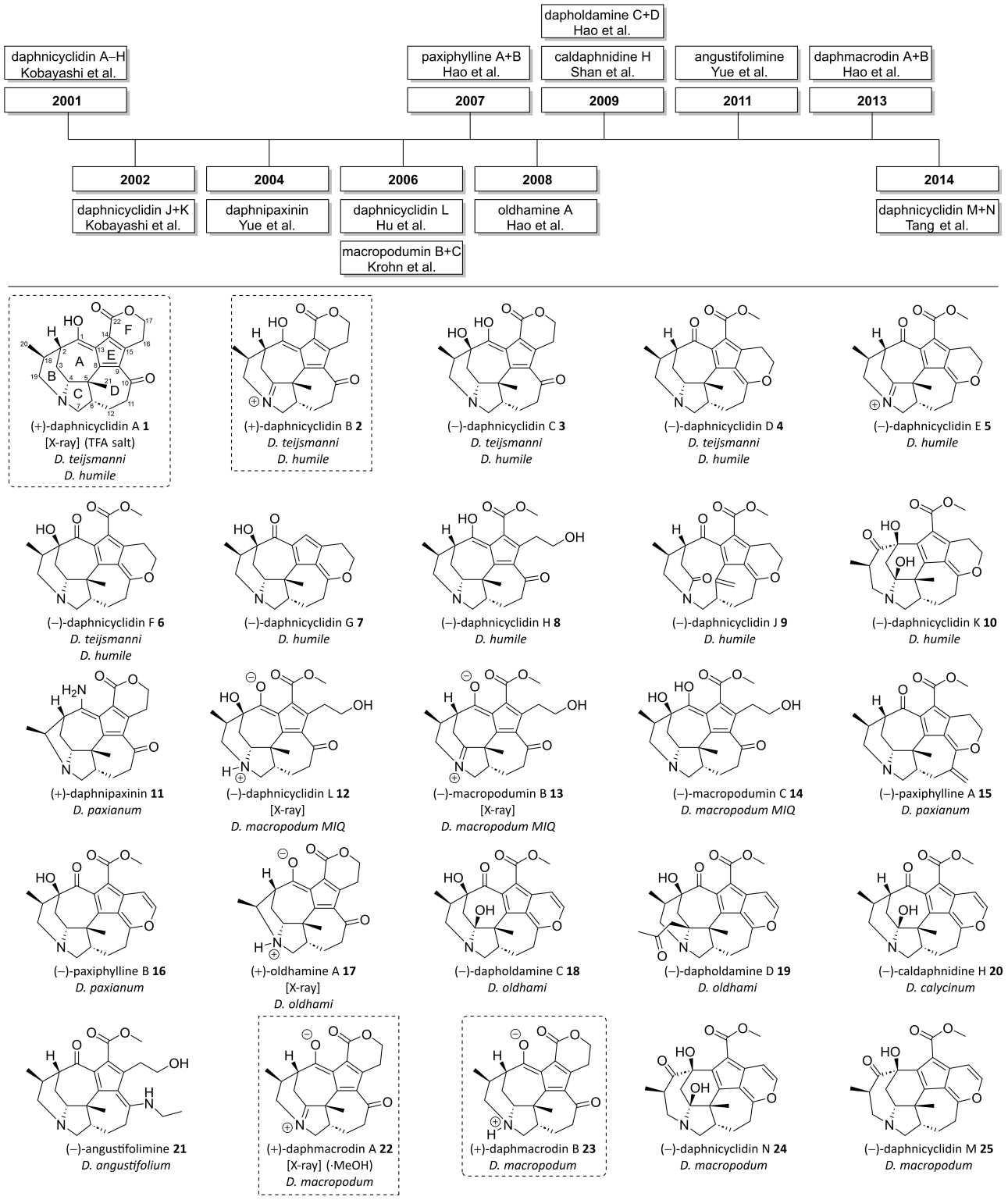


Figure 1. Timeline for publications on the isolation of daphnicyclidin alkaloids and structural formulae. The order of the publications visualized in the timeline corresponds to the compounds **1**–**25** shown from left to right and top to bottom.

asymmetric synthesis of the D ring building block **32** embarked with the introduction of the chiral auxiliary (−)-8-phenylmenthol **26** by transesterification of the cyclic β-ketoester **27** to the β-ketoester **28** (Scheme 1). Mukaiyama–Matsuo dehydrogenation of **27** afforded the chiral Michael acceptor **29** in moderate yield. Subsequent Michael addition of lithiated nitromethane and trapping of the resulting enolate with triisopropylsilyltriflate (TIPSOTf) afforded the silyl enol ether **30**.

Reductive removal of the chiral auxiliary with diisobutylaluminum hydride (DIBAH) yielded the primary alcohol **31** in very good yield and with an enantiomeric excess of 96%. The chiral auxiliary (−)-8-phenylmenthol **26** was recovered in 90% yield. The reduction of the nitro group to the primary amine **32** could be realized with a combination of iron powder and ammonium chloride in a mixture of ethanol and water. To prevent decomposition, **32** was further processed as a stock solution stabilized with pyridine (Scheme 1).

Iwabuchi continued his endeavor by the ex-chiral-pool synthesis of the acyclic building block **40** (Scheme 2). Mannitol-derived C_2 dissymmetric diol **33** was subjected to glycol cleavage and subsequent Horner–Wadsworth-Emmons reaction to yield the α,β-unsaturated ester **34**. DIBAH reduction of **34** delivered the primary allylic alcohol **35**[16] which was further elaborated by functional group interconversion to the secondary allylic alcohol **36**. Steglich type esterification delivered the propionic acid ester **37** of the allylic alcohol **36**. As expected, the Ireland–Claisen rearrangement of the allylic propionate **37** proceeded reliably under self-immolative 1,3-chirality transfer, yielding the crude γ,δ-unsaturated carboxylic acid **38** at the decagram scale. Formation of the crude benzyl ester **39** and cleavage of the allylic silyl ether finalized a routine robust synthesis of the building block **40**, albeit as a mixture of two not specified diastereomers.

The allylic alcohol **40** was further elaborated to the BCD-tricyclic building block **49** as outlined in Scheme 3.

Reductive isomerization of the allylic alcohol **40** to the δ,ε-unsaturated ester **42** was accomplished by a Pd-catalyzed reductive allylic substitution of the carbonate **41**.[17]

A sequence of functional group interconversions set the stage for fragment coupling. Ozonolysis of the terminal double bond of **42** and subsequent formation of the dimethylacetal **43** preceded hydrogenolytic removal of the benzyl ester to yield the acid **44**.

The chiral non-racemic D-ring building block **32** was coupled with the chiral non-racemic acid **44** using EDCI and DMAP to yield the secondary amide **45**.

To access the α-methylenecycloheptanone **46** by a two-step one-pot procedure, the hydroxymethyl-substituted silyl enol ether **45** was converted to the corresponding tosylate. Supposedly, trimethylamine is formed in situ from trimethylammonium chloride by Brønsted acid/base reaction and serves a nucleophilic organocatalyst for sulfonylation. Adding TBAF to the reaction mixture of the sulfonylation triggered silyl enol ether cleavage and tosylate elimination to yield **46**. Hydrogenation of the α-methylenecycloheptanone **46** delivered the α-methylcycloheptanone **47** envisioned as competent for a Brønsted acid-mediated intramolecular Mannich reaction.

With the *N*-acylated γ-amino ketone **47** in hand, the annulative Mannich reaction was realized next. Hence, subjecting **47** to Brønsted acid triggered cyclization to the corresponding *N*-acyliminium cation and enolization of the cycloheptanone function. Concomitant intramolecular nucleophilic addition of the enol to the *N*-acyliminium cation afforded the desired Mannich base **48** as mixture of diastereomers. Unfortunately, only the minor diastereomer of the BCD-tricyclic building block **48** possessed the required relative configuration of the carbon atoms C4, C5, and C6 of daphnicyclidin A.

The BCD-tricyclic building block **48** was further elaborated by diastereoselective enolate allylation to yield α-allylated cycloheptanone **49**, thus introducing an expandable three-carbon handle at the carbon atom C10. However, all attempts to utilize **49** as an advanced building block for the total synthesis of daphnicyclidin A failed.[18] Particularly, the D-ring resisted target-oriented C/C-connecting transformations, e.g. nucleophilic addition of organometallic reagents or cross-couplings with the corresponding cycloheptenyltriflate.

Also, in 2019, Overman *et al.*[19] revealed the synthesis of a ABCD-tetracyclic building block **70** for daphnipaxinin (**11**) using their signature 2-azonia-Cope rearrangement-Mannich reaction (Scheme 4 and 5).

The synthesis of **70** started with the organocatalytic asymmetric Diels–Alder reaction between the diene **51** and acrolein to deliver the non-racemic cyclohexanecarbaldehyde **52** on gram-scale. Catalyst-induced enantioselectivity was achieved in the presence of a MacMillan catalyst.[20]

To introduce C20 and to set the required absolute configuration of C18 (vide infra), Overman *et al.* turned to transition metal catalysis. Thus, nickel-catalyzed nucleophilic methyl transfer[21] to the cyclohexanecarbaldehyde **52** in the presence of the chiral phosphoramidite **53** yielded the secondary alcohol **54** as a mixture of diastereomers at C18.

Silyl ether protection of the secondary alcohol **54** and oxidative cleavage of the vinyl acetate delivered the α,β-cyclohexenone **56**.

Diastereoselective α-amination of **56** was accomplished by a three-step procedure. Formation of the cross-conjugated silyl enol ether **57** enabled subsequent diastereoface-differentiating (dr = 6 : 1) nitroso-Diels–Alder reaction to afford the 2-oxa-3-azabicyclo[2.2.2]oct-5-ene **58** possessing the undesired absolute configuration at C4. At this point, the minor diastereomer from the nucleophilic methylation was removed by chromatography. One-pot reductive cleavage of the N/O-σ-bond with molybdenum hexacarbonyl in acetonitrile and elimination yielded the α′-amino-α,β-cyclohexenone **59**.

The α,β-enone of **59** moiety was utilized to introduce a masked hydroxyl group at C1. Thus, fully diastereoselective diethylzinc-mediated nucleophilic addition of (dimethyl(phenyl)silyl)lithium delivered the α-amino cyclohexanone (4*S*)-**60**, still as mixture of epimers with respect to C4.

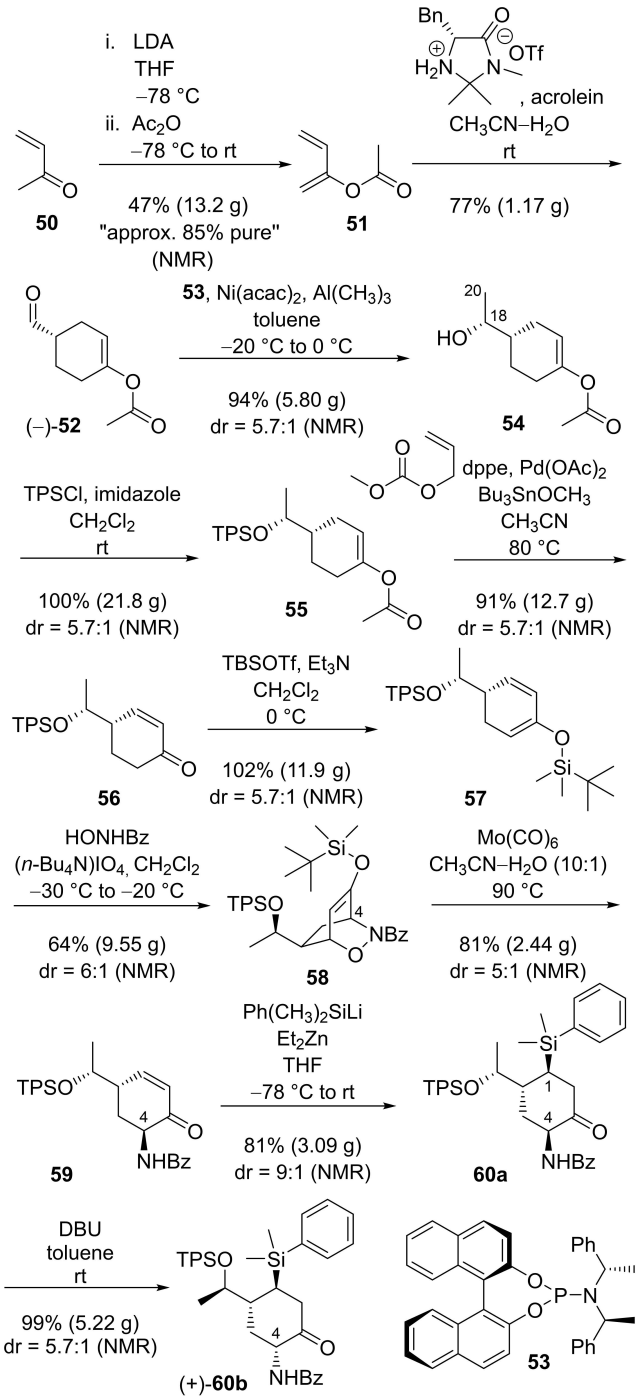
To gain access to the required epimer (4*R*)-**60** (vide infra), the α-amino cyclohexanone (4*S*)-**60** was subjected to a Brønsted base-mediated epimerization.

The following steps were devoted to the synthesis of the substrate **64** for the signature 2-azonia-Cope rearrangement-Mannich reaction (Scheme 5).

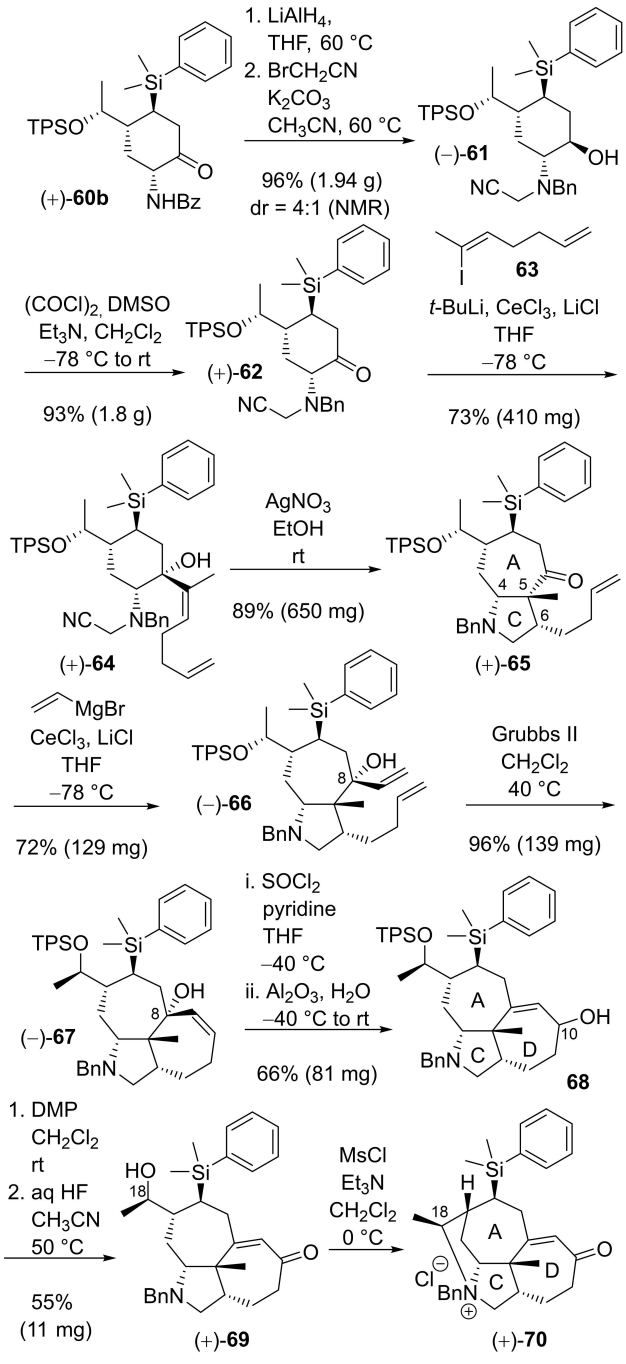
Diastereoselective reduction of the amino ketone (4*R*)-**60** yielded the corresponding amino alcohol.

Subsequent *N*-alkylation delivered the α-amino nitrile **61**, which serves as a latent iminium cation.

Oxidation to the α-amino cyclohexanone **62** allowed preparation of the homoallylic amine **64** by diastereoselective nucleophilic addition of the vinyl anion accessible from **63**.



Scheme 4. Synthesis of an ABCD-tetracyclic building block of daphnipaxinin **11** according to Overman *et al.* (Part I).



Scheme 5. Synthesis of an ABCD-tetracyclic building block of daphnipaxinin **11** according to Overman *et al.* (Part II).

The stage was now set for the crucial 2-azonia-Cope rearrangement-Mannich reaction. Hence, subjecting the α-amino nitrile **64** to silver nitrate triggered formation of the corresponding iminium cation. The in situ-formed iminium cation underwent diastereoface-differentiating and ring-enlarging 2-azonia-Cope rearrangement followed by transannular Mannich reaction to yield the perhydrocyclohepta[*b*]pyrrol-4-one **65** in excellent yield. The Mannich base **65** possessed the required relative configuration at C4, C5 and C6 of daphnipaxinine (**11**).

Having made available the AC-bicyclic building block **65**, Overman *et al.* turned their attention to the synthesis the seven-membered D ring by ring-closing metathesis. The required vinyl moiety was introduced at C8 by diastereoface-differentiating nucleophilic vinylation to yield the 1,8-diene **66**. Subjecting **66** to the Grubbs II pre-catalyst complex at elevated temperature triggered formation of the ACD-tricyclic building block **67** by RCM in excellent yield.

Introduction of the carbonyl group at C10 was initiated by oxidative transposition of the tertiary allylic hydroxyl group of **67** and delivered the secondary allylic alcohol **68**. Subsequent oxidation yielded the corresponding α,β-cycloheptenone and fluoride-mediated silyl ether cleavage afforded the δ-amino alcohol **69**.

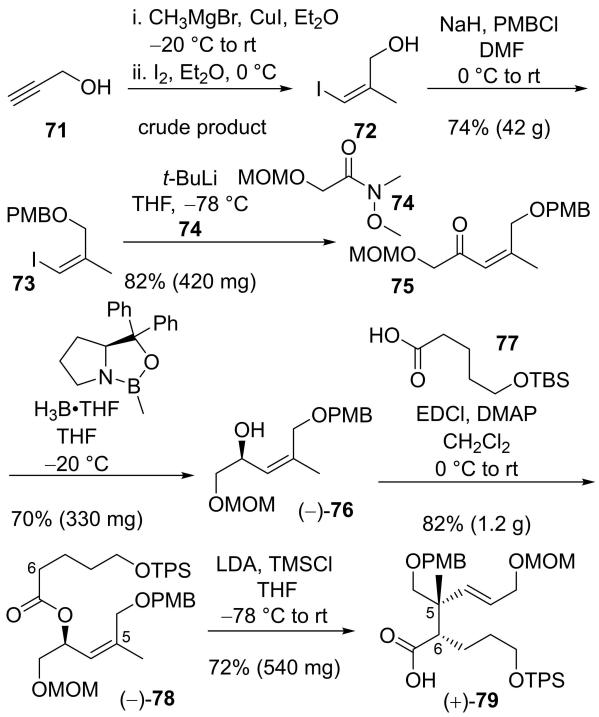
Mesylation of the secondary hydroxyl group at C18 enabled the ring-closure of the bridging B ring by intramolecular nucleophilic substitution at C18. The stereospecific S_Ni proceeded under Walden inversion at C18 and yielded the ABCD-tetracyclic building block **70** for daphnipaxinin (**11**) as an ammonium salt.

The asymmetric synthesis of the ABC-tricyclic building block **97** for daphnicyclidin A (**1**) was reported in 2014 by Williams *et al.* (Scheme 6–8).[22]

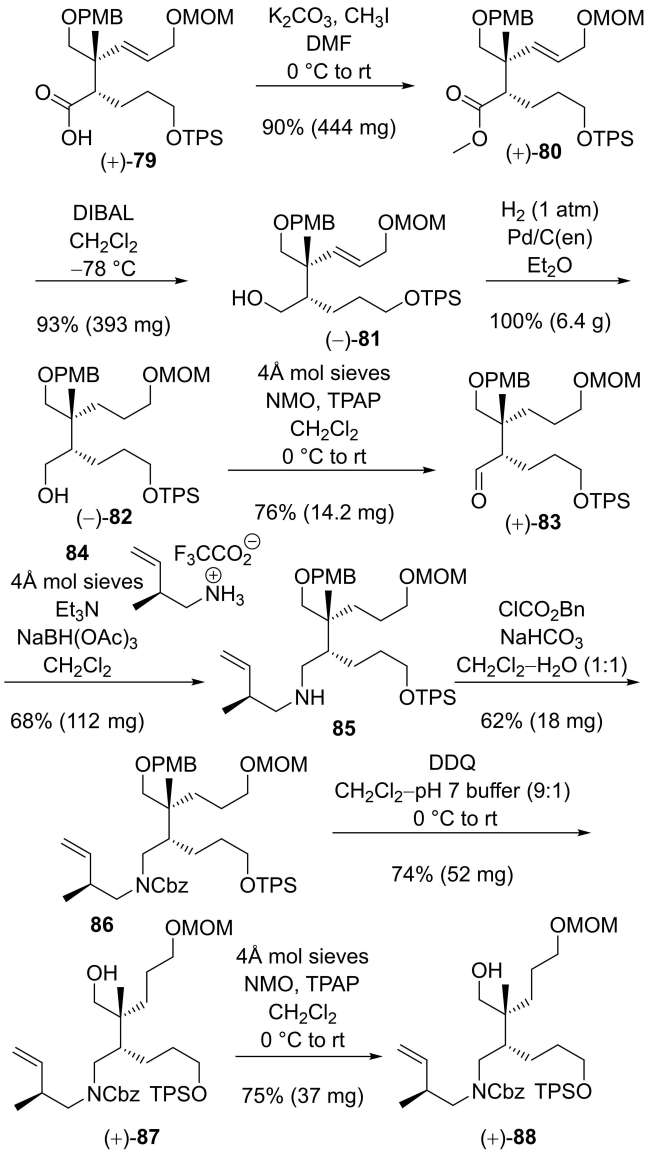
Scheme 6 illustrates the application of an Ireland−Claisen rearrangement for the asymmetric synthesis of the building block **79** featuring the all-carbon-substituted chiral carbon atoms C5 and C6 of daphnicyclidine A. To fully exploit the self-immolative chirality transfer of an Ireland–Claisen rearrangement, access to the chiral allylic alcohol **76** featuring a trisubstituted *Z*-configured double bond was required.

The synthesis of **76** started from propargyl alcohol by *cis*-methylcupration and stereoretentive iodo-decupration to yield vinyl iodide **72**. Subsequent etherification delivered the *p*-methoxybenzyl ether **73**[23a,b] on a decagram scale.

The vinyl iodide **73** was subjected to iodine-lithium exchange and the corresponding vinyl lithium species was treated with the Weinreb amide **74**[24] to deliver the α,β-enone **75**.



Scheme 6. Synthesis of an ABC-tricyclic backbone of (+)-daphnicyclidin A (+)-**1** according to Williams *et al.* (Part I).



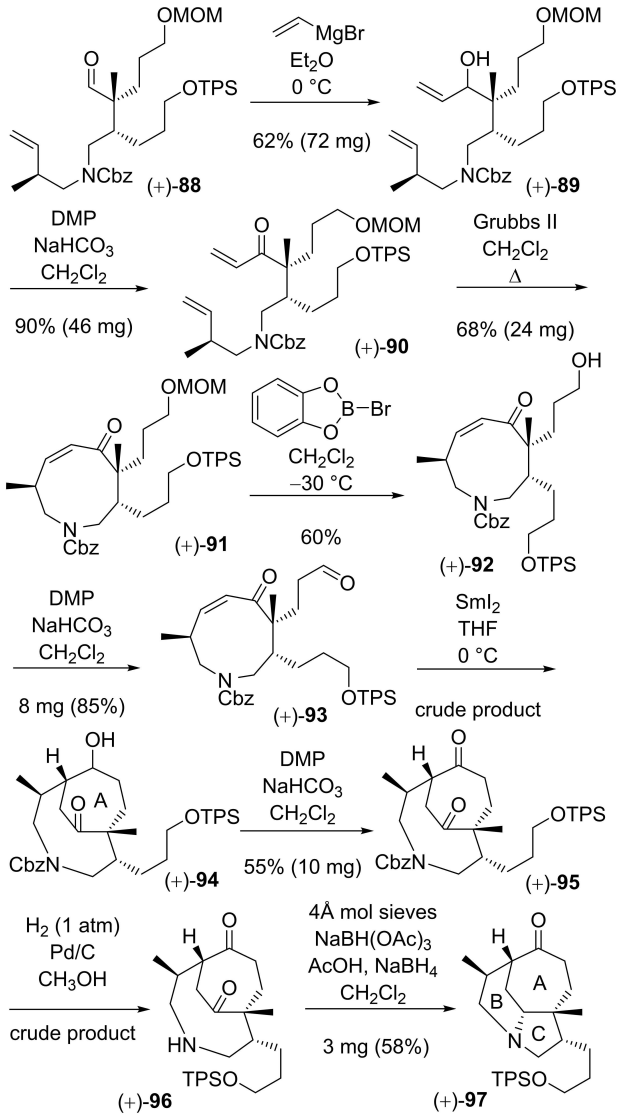
Scheme 7. Synthesis of an ABC-tricyclic backbone of (+)-daphnicyclidin A (+)-**1** according to Williams *et al.* (Part II).

Enantioface-differentiating CBS reduction of the α,β-enone **75** finally delivered the chiral non-racemic allylic alcohol **76**. Subsequent esterification of **76** with the carboxylic acid **77**[22] set the stage for the crucial Ireland–Claisen rearrangement.

Ireland−Claisen rearrangement of **76** was triggered the usual way by formation of the corresponding *E*-configured silyl ketene acetal and proceeded via a chair-like transition-state structure to deliver the γ,δ-unsaturated carboxylic acid **79** in very good yield on a larger scale. The self-immolative chirality transfer of the Claisen rearrangement was utilized to set the absolute configuration of C5 and C6 in predictable way.

The chiral non-racemic carboxylic acid **79** was further elaborated as outline in Scheme 7.

Methyl ester formation was followed by reduction to the primary alcohol **81** and double bond hydrogenation to yield the orthogonally tris-protected tetrol **82**.



Scheme 8. Synthesis of an ABC-tricyclic backbone of (+)-daphnicyclidin A (+)-**1** according to Williams *et al.* (Part III).

Oxidation of the primary alcohol **82** enabled reductive amination using the primary amine **85**[22] to deliver the secondary amine **85**. Introduction of the Cbz protecting group was followed by oxidative cleavage of the PMB ether to yield the primary alcohol **87**.

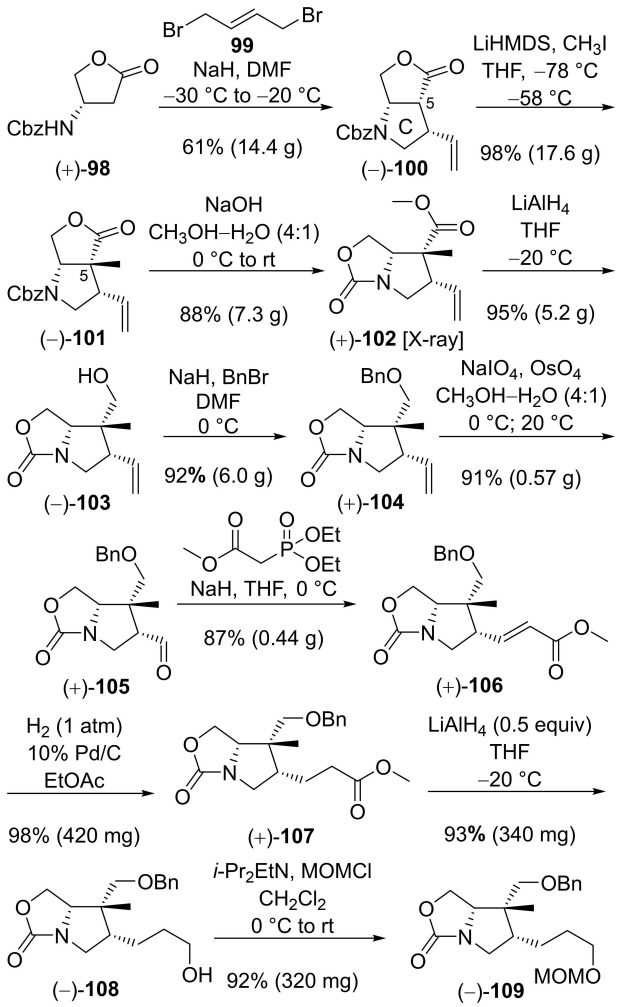
Oxidation of the primary alcohol **87** to the aldehyde **88** finalized the elaboration of the γ,δ-unsaturated carboxylic acid **79** to the γ-amino aldehyde **88** by functional group interconversion.

The conversion of the acyclic γ-amino aldehyde **88** to the ABC-tricyclic building block **97** for daphnicyclidin A continued as outlined in Scheme 8. Treating the acyclic γ-amino aldehyde **88** with vinylmagnesium bromide delivered the allylic alcohol **89** which was oxidized to yield the [9]-RCM competent diene **90**.

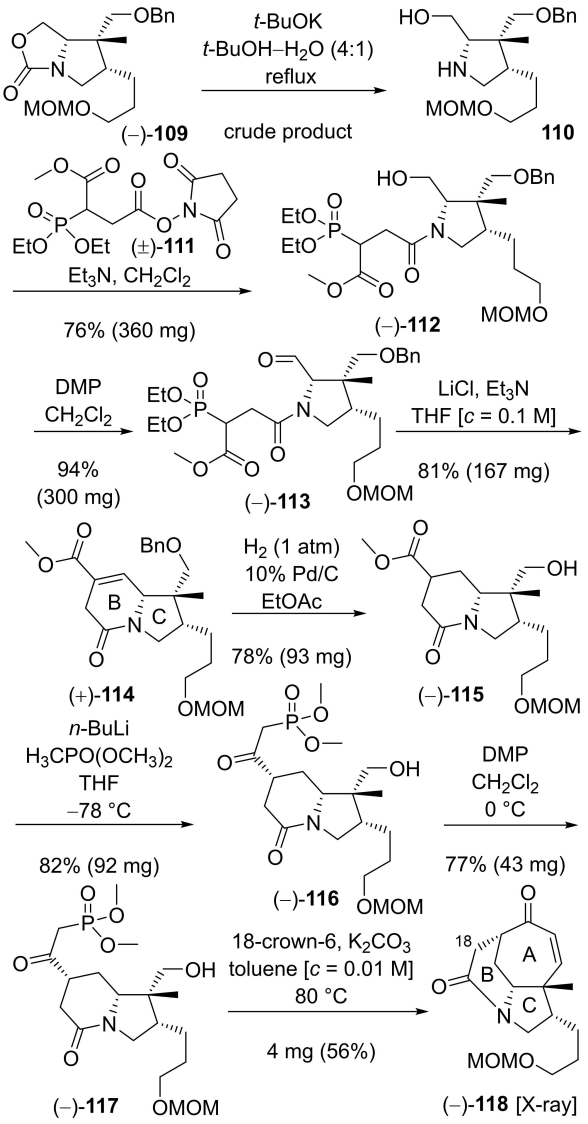
The rapid assembly of molecular complexity started with the [9]-RCM of the 5-aza-1,10-diene **90** to yield the hexahydroazonin-5-one **91**. Removal of the MOMO protecting and Dess–Martin oxidation of the primary alcohol delivered the α,β-enonal **93**. Subjecting **93** to SmI_2 enabled formation of the γ-hydroxyketone **94** which was oxidized to deliver the bicyclic diketone **95**. The seven-membered C-ring of the ABC tricyclic building block **97** for daphnicyclidin A is thus formed in an original fashion by two-carbon bridging of an azonane.

The synthesis of the ABC tricycle building block **97** is then concluded by a transannular reductive amination. In preparation of the intramolecular reductive amination of **95**, the Cbz protecting group is removed by hydrogenolytic cleavage to afford the bicyclic amino diketone **96**. The transannular reductive amination of **96** proceeded in moderate yield and delivered the ABC tricyclic building block **97** for daphnicyclidin A on a single digit milligram scale.

The synthesis of the ABC tricyclic building block **118** for daphnicyclidin A was reported in 2017 by Yang *et al.* (Scheme 9 and 10).[25] Notably, **118** lacks the crucial methyl group at C18 of daphnicyclidin A. The C-ring-first strategy of Yang *et al.* relies heavily on phosphonate chemistry to assemble and to cyclize the carbon backbone of **197**.



Scheme 9. Synthesis of an ABC-tricyclic backbone of (+)-daphnicyclidin A (+)-**1** according to Yang *et al.* (Part I).



Scheme 10. Synthesis of an ABC-tricyclic backbone of (+)-daphnicyclidin A (+)-**1** according to Yang *et al.* (Part II).

Starting from the commercially available (*S*)-3-Cbz-amino-γ-butyrolactone (+)-**98**, The pyrrolidine ring was constructed by sequential alkylation using 1,4-dibromobut-2-ene **99** as a 1,2-dielectrophile (Scheme 9).

Subsequent lactone enolate methylation delivered the pyrrolidine lactone **101** as a single diastereomer with respect to the quaternary chirality center at C5. Having introduced the angular methyl group at C5, hydroxide-triggered functional group interconversion enabled formation of the cyclic carbamate **102**. Constitution and configuration of **102** was secured by X-ray crystal structure analysis.

Subsequently hydroxymethylation of the terminal double bond of **102** to provide the primary alcohol **108** required several steps. Reduction of the methyl ester and subsequent benzylation converted the ester **102** to the vinyl pyrrolidine **104**. Oxidative cleavage of the terminal double of **104** was followed by Horner–Wadsworth–Emmons (HWE) reaction to deliver the α,β-unsaturated ester **106**. Hydrogenation and reduction of the α,β-unsaturated ester delivered the primary alcohol **108** which was subsequently endowed with a MOM protecting group.

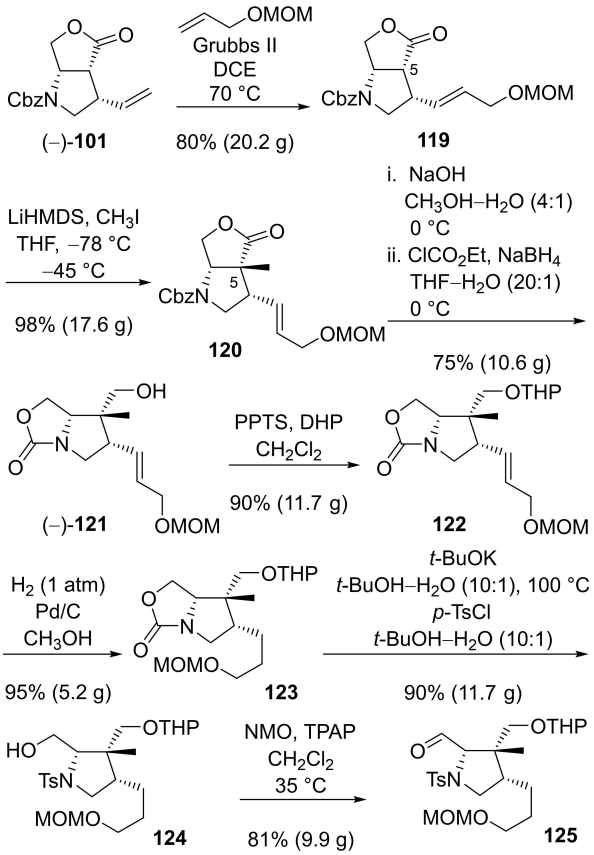
The C-ring building block **109** was further elaborated as outlined in Scheme 10. Cleavage of the cyclic carbamate delivered the highly substituted pyrrolidine **110** which underwent *N*-acylation with the active ester **111** to yield the phosphonate **112**.

Oxidation of the primary alcohol **112** delivered the aldehyde **113** Intramolecular HWE reaction of **113** using conditions according to Rathke and Nowak yielded the BC-bicyclic building block **114** at ambient temperature. Subsequent hydrogenation of **114** afforded the indolizidinone **115**.

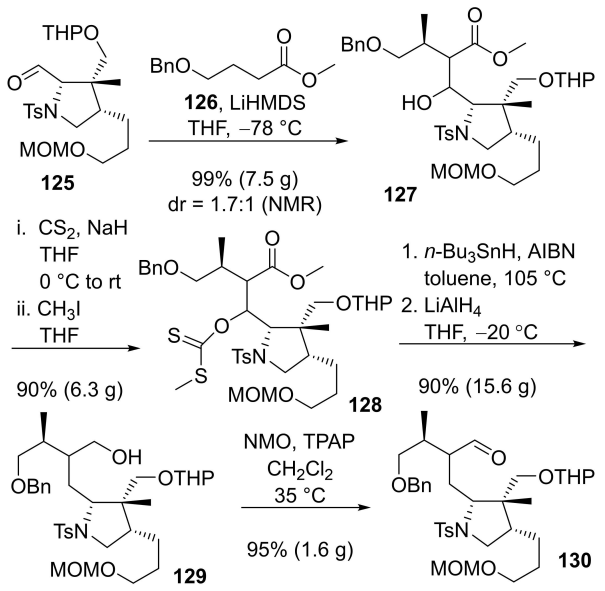
The methyl ester function installed by the first HWE reaction was exploited for the formation of the β-keto phosphonate **116** by Claisen condensation between **115** and lithiated dimethyl methylphosphonate.

Oxidation of the primary alcohol **116** delivered the aldehyde **117**. An amazing intramolecular HWE reaction to the ABC tricyclic building block **118** for daphnicyclidin A was realized under "naked enolate" conditions at elevated temperature.

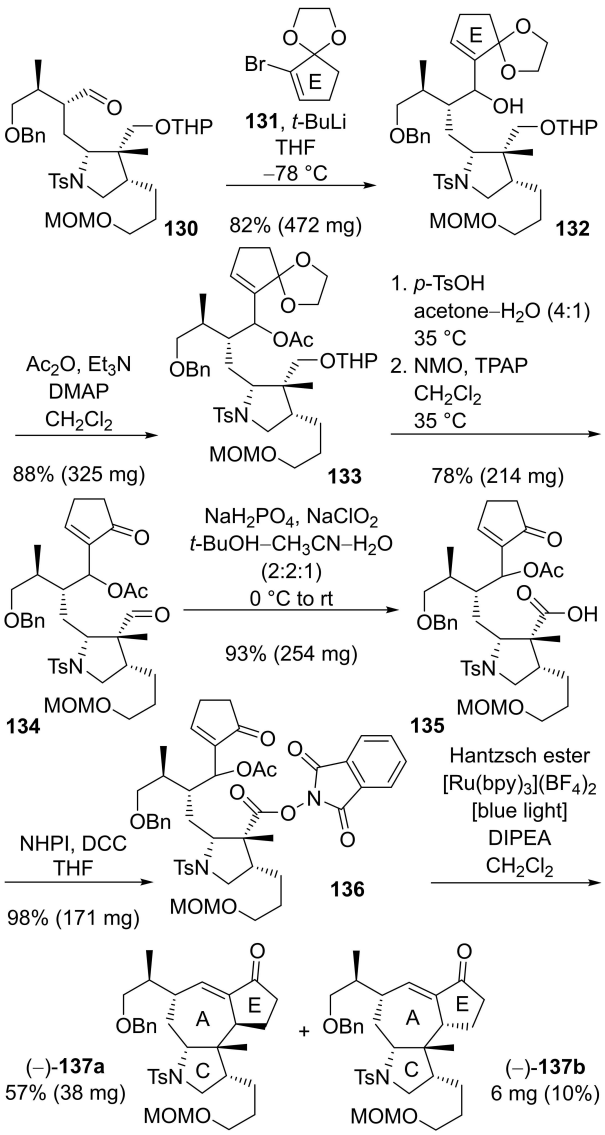
Without resorting to phosphonate chemistry, Yang *et al.* reported the synthesis of an ACE-tricyclic building block **137** for daphnicyclidin A in 2019 (Scheme 11–13).[26] Using the previously synthesized pyrrolidine lactone **101**, cross-metathesis



Scheme 11. Synthesis of an ACE-tricyclic backbone of (+)-daphnicyclidin A (+)-**1** according to Yang *et al.* (Part I).



Scheme 12. Synthesis of an ACE-tricyclic backbone of (+)-daphnicyclidin A (+)-**1** according to Yang *et al.* (Part II).



Scheme 13. Synthesis of an ACE-tricyclic backbone of (+)-daphnicyclidin A (+)-**1** according to Yang *et al.* (Part II).

(CM) with MOM-protected allylic alcohol afforded the allylic alcohol **119**. Subsequent diastereoselective formation of the quaternary chirality center C5 was accomplished by electrophilic methylation of the enolate of the γ-lactone **119**. Downstream chemistry is then devoted to protecting group chemistry and functional group interconversion by redox manipulations. Hence, saponification of the γ-lactone **120** triggered formation of a cyclic carbamate and enabled reduction of the activated acid to yield the bicyclic building block **121**. Introduction of the THP acetal completed the orthogonal protection of the triol **122**. Hydrogenation of the superfluous double bond from CM delivered the bicyclic carbamate **123**. One-pot cleavage of the carbamate by hydroxide at elevated temperature and *N*-tosylation delivered the β-Amino alcohol that was oxidized to the pyrrolidine-2-carbaldehyde **125**.

With all necessary functional groups in place the C-ring building block **125** was further elaborated as outlined in Scheme 11.

A diastereoface–diastereoface-differentiating ester enolate aldol addition between the methyl ester **126** and the pyrrolidine-2-carbaldehyde **125** delivered the aldol **127** in excellent yield as mixture of two diastereomers. Removal of the aldol's β-hydroxyl group was realized according to Barton and McCombie. Thus, the xanthogenate **128** was synthesized and defunctionalized under conditions that support a radical chain process. Redox chemistry converted the desoxygenated ester to the α,β-branched aldehyde **130**. Note that the aldehyde **130** should be isolated as a mixture of diastereomers because of the induced diastereoselectivity of the upstream ester enolate aldol addition.

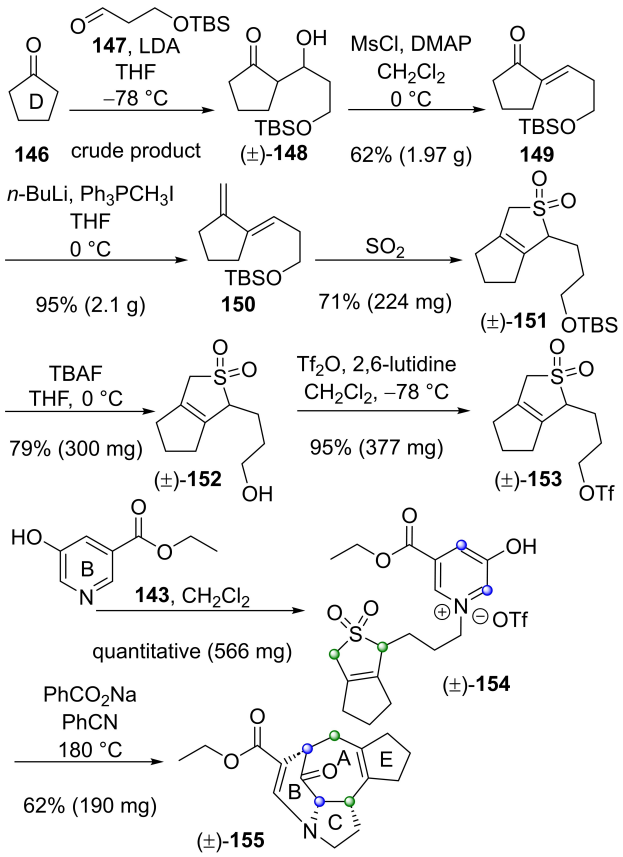
On the final stage of the multi-step synthesis of the ACE-tricyclic building block **137** for daphnicyclidin A, molecular complexity is rapidly build-up starting from the diastereomerically pure aldehyde **130** (Scheme 13).

1,3-Dioxolane-protected 2-bromocyclopent-2-en-1-one **131** served as the synthon for the E-ring. **131** was attached to the aldehyde **130** by nucleophilic addition of the corresponding cyclopent-1-ene-1-yllithium prepared from **131** by bromo-lithium exchange. The resulting allylic alcohol **132** was converted to the corresponding acetate **133**.

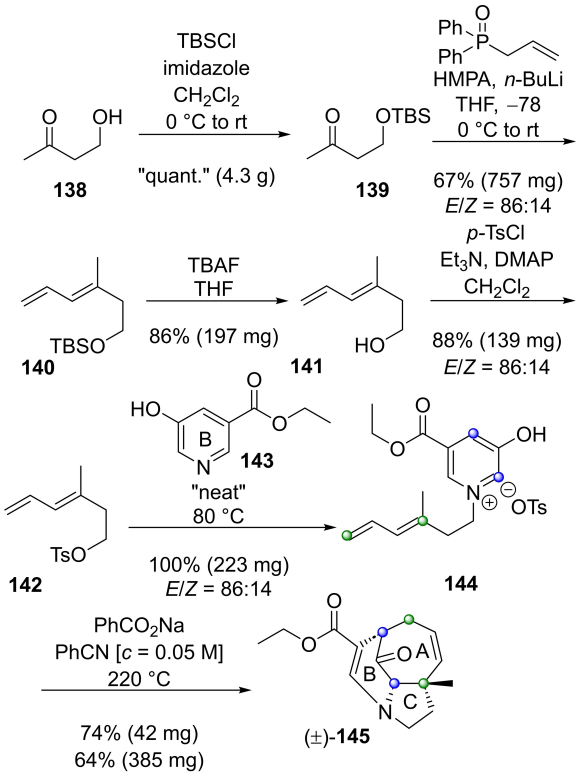
In preparation for the pivotal radical ring closure of the seven membered A-ring of the ACE-tricyclic building block **137**, **133** was further elaborated by THP hydrolysis and oxidation to provide the acid **135**. Esterification of the acid with *N*-hydroxyphthalimide (NHPI) delivered the *N*-acyloxyphthalimid **136** suitable for a photoredox-catalyzed intramolecular Michael reaction. Based on a procedure originally reported by Okada[27] and later promoted by Overman,[28a,b] **136** underwent cyclization and elimination in the presence of tris(bipyridine)ruthenium(II) tetrafluoroborate, Hantzsch ester and Hünig base to deliver a mixture of the two diastereomeric α,β-enones **137a** and **137b**.

In 2022, Harmata *et al.* reported the comparatively short synthesis of the ABC-tricyclic building block **145** for daphnicyclidin A (Scheme 14).[29] An intramolecular (4+3) cycloaddition of the 3-hydroxypyridinium cation **144** at high temperature on a preparative scale enabled a rapid build-up of the required molecular complexity. The convergent synthesis of the hydroxypyridinium cation **144** was accomplished by *N*-alkylation of ethyl 5-hydroxynicotinate **143** with the tosylate **142**. The tosylate **142** was synthesized from 4-hydroxybutan-2-one **138** in short sequence consisting of silyl ether formation to **139**, Horner olefination to **140**, silyl ether cleavage to **141**, and finally tosylation to yield the fragile **142**.

The even more elaborated 3-hydroxypyridinium cation **154** was also qualified for the intramolecular (4+3) cycloaddition (Scheme 15).[30] In the event, the fragile 1,3-diene moiety was masked as 3-sulfolene. Using high temperature conditions, cycloelimination of sulfur dioxide exposed the corresponding 1,3-diene and enabled formation of the ABCE-tricyclic building block **155** for daphnicyclidin A by intramolecular (4+3) cycloaddition. Notably, however, **155** lacks the crucial C21-methyl group at C5 of daphnicyclidin A. The 3-hydroxypyridinium cation **154** was synthesized in a convergent manner from the decomposable triflate **153** and ethyl 5-hydroxynicotinate **143** by *N*-alkylation. The triflate was accessed via a short sequence from cyclopentanone **146** as the E ring synthone. Aldol condensation between **146** and **147** delivered the α,β-enone **149**. Subsequent methylidenation by Wittig reaction delivered the 1,3-diene **150**. Protection of the delicate 1,3-diene by cheleotropic [4+2] cycloaddition with sulfur dioxide delivered



Scheme 15. Synthesis of an ABCE-tetracyclic backbone of (±)-daphnicyclidin A (±)-**1** by Harmata *et al.*



Scheme 14. Synthesis of an ABC-tricyclic backbone of (±)-daphnicyclidin A (±)-**1** according to Harmata *et al.*

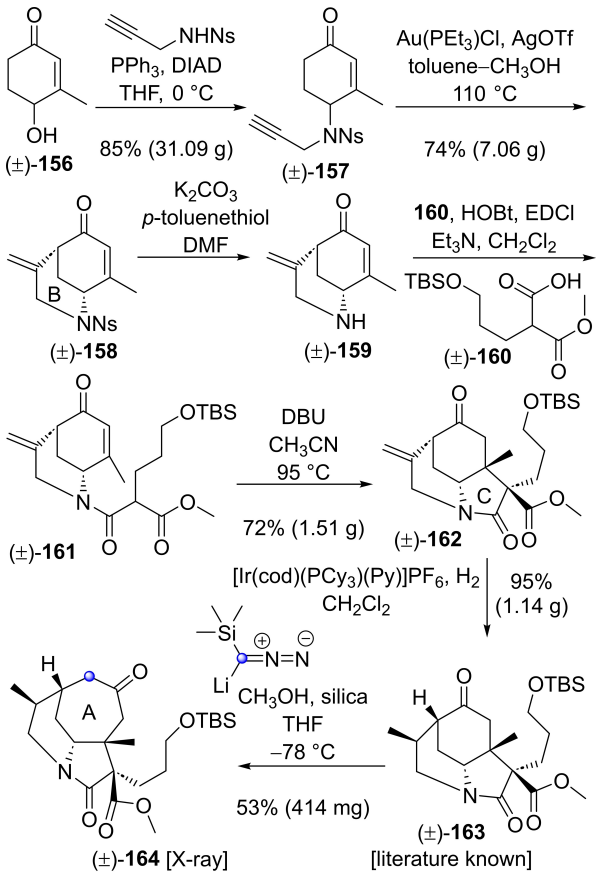
the bicyclic sulfolene **151**. Cleavage of the silyl ether and triflation finally yielded the alkylating triflate **153**.

In 2023, She *et al.*[31] published the synthesis of the ABC-tricyclic platform molecule **164** prepared from Li's established building block **163**[32] (Scheme 16), and its elaboration to the advanced building block **175** for daphnicyclidin A (Scheme 17).

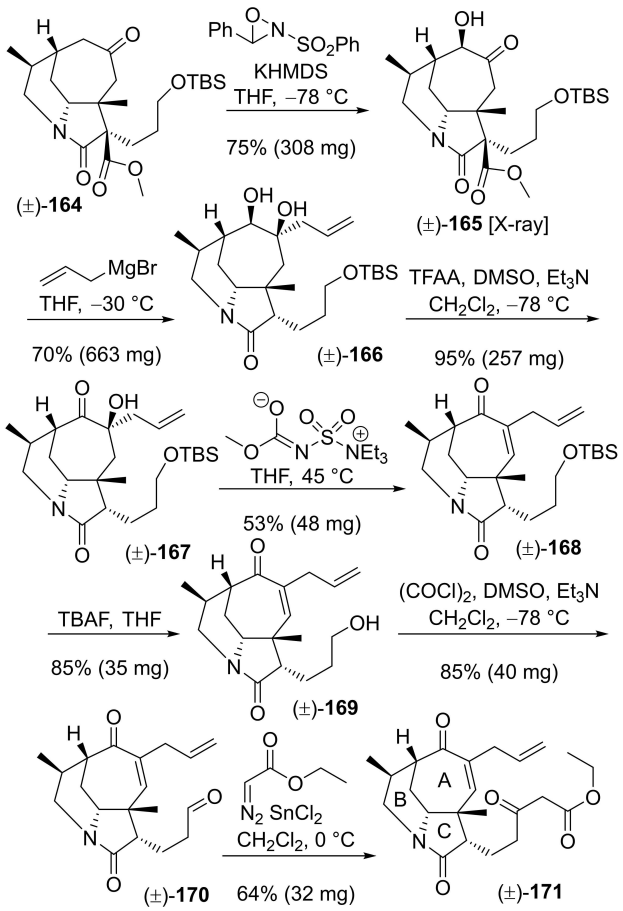
The ring-by-ring synthesis of **164** initially followed an established route[32] which was slightly modified from the known A ring synthon **156**.[33a,b] Thus, coupling **156** with protected propargylic amine by Mitsunobu reaction to yield racemic **157**. The bridging B ring was formed by a gold(I) catalyzed Conia ene reaction to deliver the 2-azabicyclo[3.3.1]-nonane **158**. In the event, the triple bond represents the (formal) enophile and the in situ formed enol of the α,β-enone **157** the (formal) ene. Notably, this procedure circumvents the prior formation of the silyl enol ether of **157** for the purpose of B ring formation by (formal) intramolecular Conia ene reaction.

In preparation of C ring formation, the nitrogen atom of **158** was deprotected and the resulting secondary amine **159** was subjected to the active ester derived from the malonic acid mono ester **160** to provide the malonic ester amide **161**.

The stage was now set to execute the ring closure of the C ring by intramolecular Michael addition. Hence, **161** was subjected to Brønsted base at elevated temperature to deliver the perhydro-1,6-ethanoindol **162** diastereoselectively.



Scheme 16. Synthesis of an ABC-tricyclic backbone of (±)-daphnicyclidin A (±)-**1** according to She *et al.* (Part I).



Scheme 17. Synthesis of an ABC-tricyclic backbone of (±)-daphnicyclidin A (±)-**1** according to She *et al.* (Part II).

Lactam carbonyl-directed hydrogenation of the exocyclic double bond using Crabtree's catalyst provided the cyclohexanone **163**[32] diastereoselectively.

Next, a position-selective one-carbon ring-expansion was required to convert **163** to the ABC-tricyclic platform molecule **164**. In the event, a Tiffaneau–Demjanov-type ring expansion using the Colvin reagent as nucleophilic one-carbon insertion unit (blue highlighted) was utilized and enabled access to the desired ABC-tricyclic **164**. Note that the higher substituted α-carbon atom migrates preferentially during the ring-expansion by nucleophilic [1,2] rearrangement.

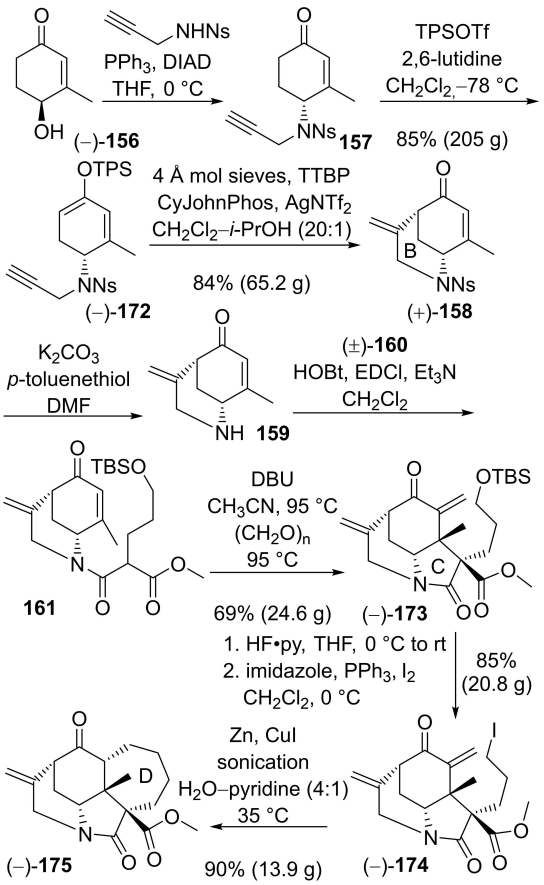
In contrast to the approaches discussed above, She et al. utilized the ABD-tricyclic platform molecule **164** to further advance the synthesis towards daphnicyclidin A (Scheme 17).

To move the carbonyl group at the seven-membered A ring counterclockwise and to introduce a handle for E ring synthesis, **164** was subjected to a positional-selective Davis α-hydroxylation. The resulting α-hydroxy ketone **165** was treated with allylmagnesium bromide to yield the unexpected glycol **166**. In a fortunate turn of events, the residual malonic ester amide moiety of **165** underwent formal demethoxycarbonylation under the conditions of the Grignard reaction (large excess of Grignard reagent). Albright-Goldman oxidation converted the 1,2-diol **166** to the α-hydroxy ketone **167** and a Burgess reagent-mediated elimination delivered the α,β-enone **168**.

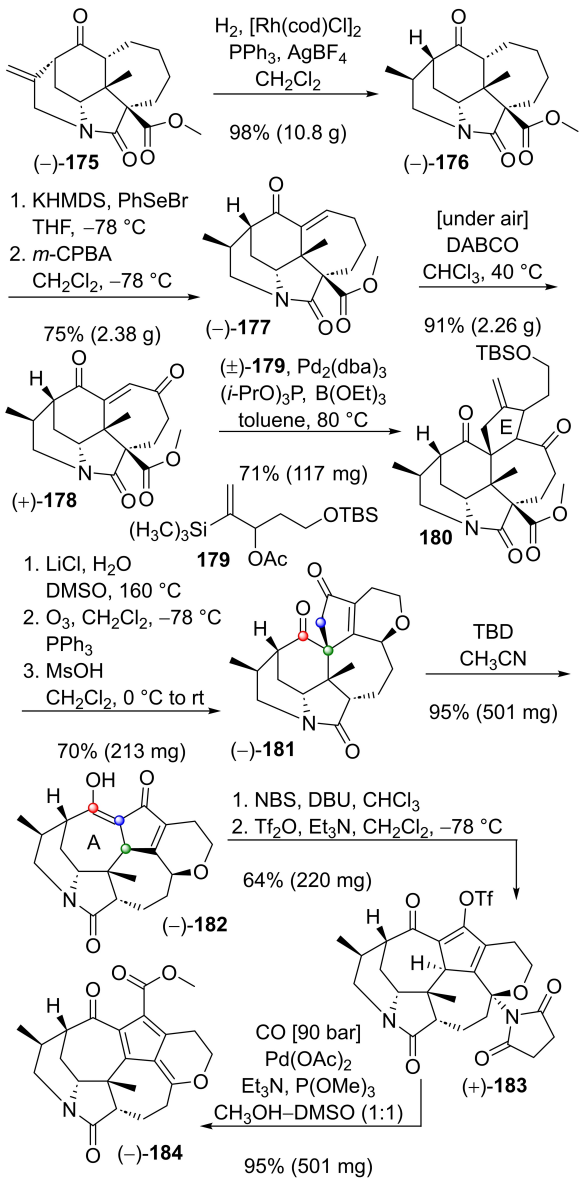
The ring-by-ring strategy of She *et al.* called for an intramolecular Michael reaction for the formation of the seven-membered D ring. Thus, the silyl ether of **168** was cleaved and the resulting alcohol **169** was oxidized to deliver the aldehyde **170**. Holmquist–Roskamp reaction converted **170** to the β-keto ester **171**. However, all published attempts to close the seven-membered D ring by intramolecular Michael reaction of **171** in the presence of various bases were futile.

The numerous inventive syntheses of building blocks for daphnicyclidin A finally culminated in the first successful natural product syntheses of four daphnicyclidins in 2023. Relying and ring-by-ring synthetic strategy, Li *et al.* successfully completed the total synthesis of (+)-daphnicyclidin A (**1**), (−)-daphnicyclidin D (**4**), (−)-daphnicyclidin F (**6**) and (−)-daphnicyclidin K (**10**).[35]

Riding a previously published route from their own lab,[36a,b] non-racemic **156**[33a,b,34] was subjected to Mitsunobu reaction to yield the propargylic amine **157** (Scheme 18). Since six-membered **156** is used as an A ring building block, a downstream one-carbon ring expansion is required. Subsequent conversion of **157** to the silyl enol ether **172** enabled Ag(I)-catalyzed cyclization to deliver the azabicyclo[3.3.1]nonane **158**. Removal of the 4-nitrobenzenesulfonamide (nosyl, Ns) protecting group of **158** afforded the secondary amine **159** that was converted to



Scheme 18. Synthesis of four daphnicyclidins according to Li *et al.* (Part I).



Scheme 19. Synthesis of four daphnicyclidins according to Li *et al.* (Part II).

the malonic ester amide **161**. An intramolecular Michael reaction was combined with an methylidenation by aldol condensation with formic aldehyde to deliver the tricyclic building block **173** diastereoselectively. In preparation of the ring-closure of the seven-membered D ring by intramolecular nucleophilic 1,4-addition to the α,β-enone function, the silyl ether of **161** was cleaved and the hydroxyl group was substituted by iodide by an Appel reaction to afford **174**. Subjecting **174** to a large excess of Zn dust (15 equiv.) and CuI (5 equiv.) in a solvent mixture consisting of pyridine and water at slightly elevated temperature yielded the desired tetracyclic building block **175**.

The tetracyclic building block **175** was further elaborated as outlined in Scheme 19. The all-important diastereoselective hydrogenation of the exo-methylene double bond was accomplished by a lactam carbonyl-directed rhodium(I)-catalyzed process to yield the ketone **176**.[36a,b] To prepare for the annulation of the five-membered E ring, ketone **176** was oxidized to the α,β-enone **177** by a two-step procedure via the intermediate formation of a selenoxide. DABCO-mediated γ-oxidation of the α,β-enone **177** under ambient atmosphere delivered the en-1,4-dione **178**. Annulation of the five-membered E ring was then realized by a positional-selective Pd-catalyzed trimethylenemethane (3 + 2) cycloaddition[37,38] of **178** with **179** and delivered the pentacyclic building block **180** as a mixture of four diastereomers.

To remove the superfluous methoxycarbonyl function of the malonic ester amide moiety, **180** was subjected to the conditions of a Krapcho reaction. Concomitantly, the primary silyl ether was cleaved under the strongly silaphilic conditions. The resulting alcohol was subjected to an ozonolysis to access the cyclopentenone E ring. Finally, the dihydropyrane F ring was closed by an Brønsted acid mediated cyclocondensation with successive isomerization of the enol ether double into π-conjugation to yield the hexacyclic building block **181**.

Next on the agenda was the decisive isomerizing one-carbon ring expansion of the still six-membered A ring of the 1,4-diketone **181**. The electrophilic [1,2] migration of the acyl carbon atom from carbon atom 8 to carbon atom 13 was accomplished in the presence of the Brønsted base 1,5,7-

triazabicyclo[4.4.0]dec-5-ene (TBD) and delivered the expected ABCDEF-hexacyclic 1,3-diketone in its enol form **182**. This amazingly efficient isomerization is probably initiated by a strain-building intramolecular aldol addition followed by a retro-aldolization. The resulting E ring dienolate is protonated at carbon atom 8 in a diastereoface-differentiating manner.

The following three steps completed the construction of the characteristic pentafulvene motif of all daphnicyclidin alkaloids. To extent the cross-conjugated π-system of **182** to the fully conjugated π-system of the pentafulvene π-system of **184**, succinimidyl and triflate nucleofuges were incorporated to deliver **183**. Palladium-catalyzed methoxycarbonylation of **183** replaced the triflate and triggered elimination of the succinimidate nucleofuge to yield the relay building block **184**.

With the multi-purpose building block **184** in hand, daphnicyclidin D (**4**) was synthesized by a two-step one-pot reduction of the pyrrolidinone carbonyl function according to Nagashima using Vaska's complex (Scheme 20). Daphnicyclidin A (**1**) was accessed from daphnicyclidin D (**4**) by a hydroxide-triggered transesterification/saponification of the doubly vinylogous carbonate segment of **4** with successive tautomerization of the pentafulvene π-system.

Taking advantage of the utility of the building block **184**, the total synthesis of daphnicyclidin F (**6**) and K (**10**) was also finalized (Scheme 20). Regio- and diastereoselective ketone enolate α-hydroxylation afforded the α-hydroxyketone **185**. Tow-step one-pot lactam reduction converted **185** to daphnicyclidin F (**6**). The synthesis of daphnicyclidin K required a skeletal rearrangement of the hexacyclic building block **185**. The α-ketol rearrangement of the AB-segment of **185** in the presence of the oxygen chelator dibutyltin oxide at elevated temperature served this purpose and provided access to **186**. The tricarbonyl compound **186** was reduced to the dicarbonyl compound **187**. After a longest linear sequence of 24 steps, the building block **187** was then oxidized at the most highly substituted α-carbon atom to the nitrogen atom of the pyrrolidine segment to deliver daphnicyclidin K (**10**) after an aqueous work-up.

4. Summary and Outlook

During the last two decades, 23 structurally distinct daphnicyclidins featuring the signature pentafulvene motif have been isolated, purified and characterized. Inspired by the intricate polycyclic architecture of these plant metabolites, significant efforts were devoted to engineer a chemosynthetic access to the daphnicyclidine alkaloids. During the past 15 years, a half dozen research groups were committed to the total synthesis of daphnicylidin alkaloids. Intriguingly diverse synthetic strategies were brought to practice and several tri- or even tetracyclic building blocks were accessed (Scheme 21).

Iwabuchi *et al.* prepared building block **49** relying on an Ireland–Claisen rearrangement with self-immolative chirality transfer and an intramolecular Mannich reaction.[15]

Overman *et al.* synthesized building block **70** utilizing (4 + 2) cycloadditions, a 2-azonia-Cope rearrangement-Mannich reaction and a [7]-RCM.[19]

Williams *et al.* employed an Ireland–Claisen rearrangement with self-immolative chirality transfer, a [9]-RCM, an intramolecular ketyl radical anion cyclization and a transannular reductive amination to access the building block **97**.[22]

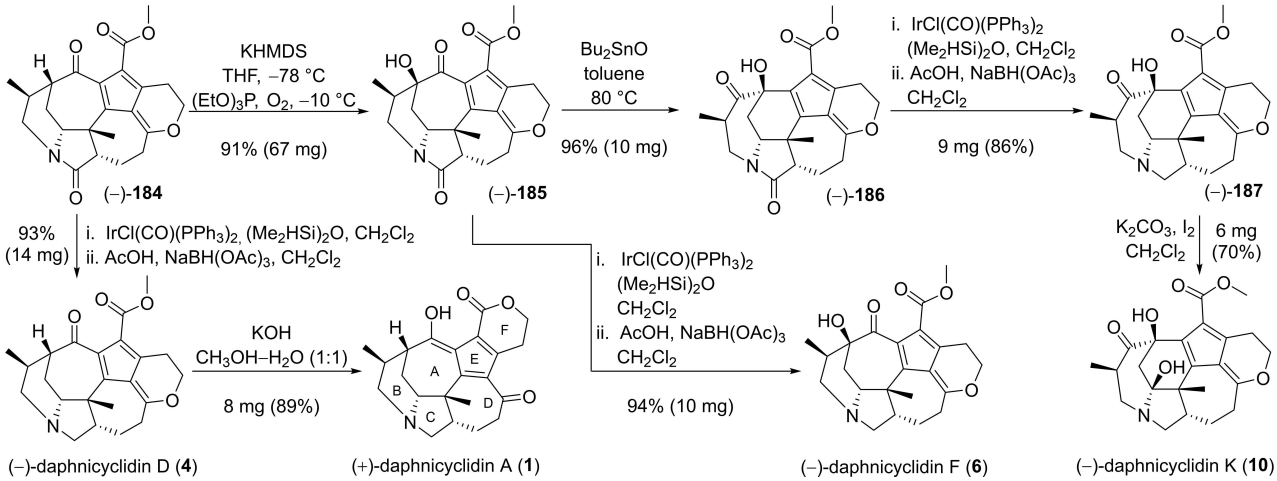
Yang *et al.* accomplished the synthesis of the building block **118** utilizing cyclizing Horner–Wadsworth–Emmons reactions.[25]

The synthesis of the building block **137** by Yang *et al.* is highlighted by a late-stage photoredox-catalyzed intramolecular Michael reaction.[26]

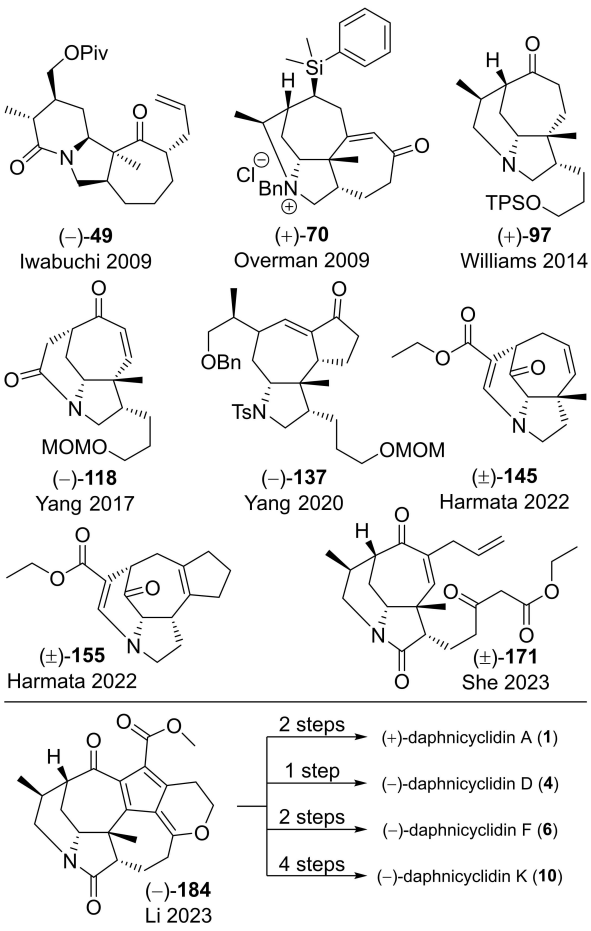
An intramolecular (4 + 3) cycloaddition was exploited to prepare the building blocks **145** and **155** by Harmata *et al.*[27,28]

She *et al.* synthesized the building block **171** one-carbon ring-expanding Tiffeneau-Demjanow reaction of the known **163**;[32–34] Their synthesis of **163** is highlighted by an Au-catalyzed ynenol cyclization.

In 2023, two decades of natural product chemistry and natural product total synthesis reached their preliminary climax when Li *et al.* reported the total synthesis of daphnicyclidins A (**1**), D (**4**), F (**6**) and K (**10**). In the event, ABCDEF-hexacyclic **184** serves as a versatile relay building block.[35,36a,b] The synthetic



Scheme 20. Synthesis of four daphnicyclidins according to Li *et al.* (Part III).



Scheme 21. Overview of the synthesized polycyclic synthesis building blocks and the already totally synthesized daphnicyclidins.

sequence to **184** utilizes inter alia intermolecular Michael reactions, a Brønsted base-mediated skeletal rearrangement, and a Pd-catalyzed trimethylenemethane (3 + 2) cycloaddition. The relay function of **184** is enabled by a scaffold-isomerizing α-ketol rearrangement.

Looking ahead, we can expect that further conceptually novel approaches to daphincyclidins will be sought and found. The story of the daphnicyclidins underlines that the total synthesis of natural products has lost none of its relevance, its fascination, and its innovative power.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Research data are not shared.

Keywords: daphniphyllum alkaloids · total synthesis · pentafulvenes · isolation · daphnicyclidin-type alkaloids

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