Iron-Catalyzed Cross-Coupling Reactions and Total Synthesis of Myxovirescin A_1

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Keywords: iron-catalyzed cross-coupling reactions; total synthesis of Myxovirescin A_1; ring closing alkyne metathesis; (*E*)-selective semi-reduction.

Part 1: Iron-Catalyzed Cross-Coupling Reactions

The iron-catalyzed sp^3-sp^2 cross-coupling between alkyl GRIGNARD reagents and alkenyl bromides was described in 1971 by KOCHI.[1] Recently, FÜRSTNER showed that this method can be applied for the arylation and alkylation of substituted aryl chlorides and aryl sulfonates by using cheap, readily available, air stable, nontoxic, and environmentally benign $Fe(acac)_3$ as precatalyst.[2] Despite some scattered reports on the efficiency of iron salts as catalysts for the cross-coupling of GRIGNARD reagents with acid chlorides,[3] the relevance of this method has not been fully explored. Due to the good compatibility of iron-catalyzed processes in general with a variety of functional groups in both reaction partners, we anticipated that the scope of this particular ketone synthesis might extend beyond the barely functionalized cases previously reported in the literature.

As can be seen from some extended results compiled in Scheme 1, a host of aromatic and aliphatic acid chlorides react with various alkyl- as well as arylmagnesium halides to give the corresponding ketones in good to excellent yields.[4] The reactions proceed very rapidly at −78 °C (<15 min), require only a low catalyst loading, and can also be performed by "inverse addition" (a solution of the acid chloride is added to a cold solution containing $Fe(acac)_3$ and the GRIGNARD reagent). Under these conditions, the uncatalyzed attack of the GRIGNARD reagent to

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[1] M. Tamura, J. Kochi, *J. Am. Chem. Soc.* **1971**, *93*, 1487-1489; M. Tamura, J. Kochi, *Synthesis* **1971**, *6*, 303-305.

[2] A. Fürstner, A. Leitner, *Angew. Chem., Int. Ed.* **2002**, *41*, 609-612; A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856-13863; A. Fürstner, R. Martin, *Chem. Lett.* **2005**, *34*, 624-629.

[3] W. C. Percival, R. B. Wagner, N. C. Cook, *J. Am. Chem. Soc.* **1953**, *75*, 3731-3734; V. Fiandanese, G. Marchese, V. Martina, L. Ronzini, *Tetrahedron Lett.* **1984**, *25*, 4805-4808; M. M. Dell´Anna, P. Mastrorilli, C. F. Nobile, G. Marchese, M. R. Taurino, *J. Mol. Catal. A: Chem.* **2000**, *161*, 239-243; C. K. Reddy, P. Knochel, *Angew. Chem., Int. Ed.* **1996**, *34*, 1700-1701; K. Ritter, M. Hanack, *Tetrahedron Lett.* **1985**, *26*, 1285-1288; C. Cardellicchio, V. Fiandanese, G. Marchese, L. Ronzini, *Tetrahedron Lett.* **1987**, *28*, 2053-2056. For a general review on the acylation of organometallic reagents, see: Dieter, R. K. *Tetrahedron* **1999**, *55*, 4177.

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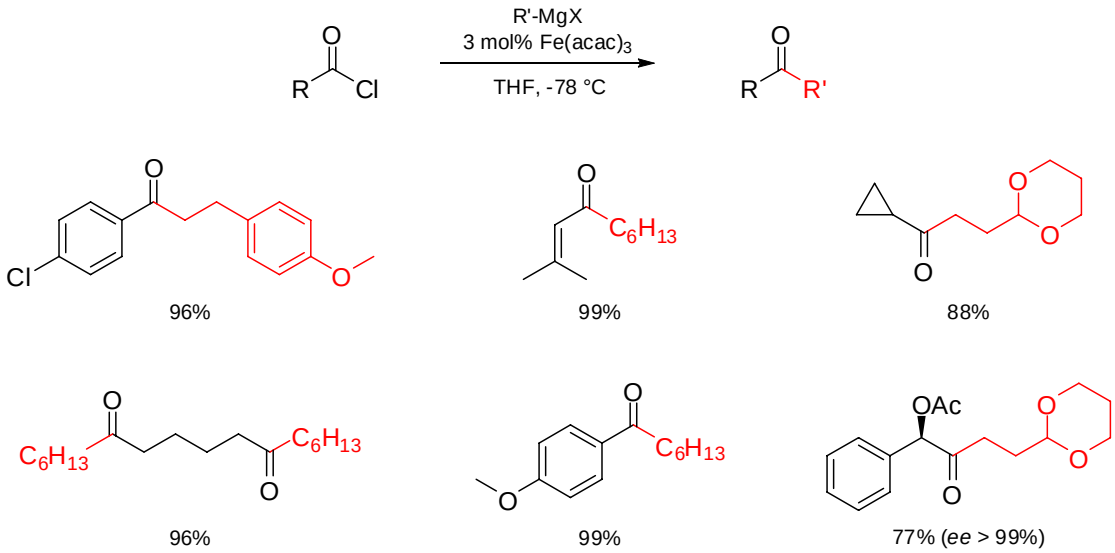
the resulting ketone is negligible. The integrity of the cyclopropyl group makes radical intermediates rather unlikely. Notable is the fact that even chloride or bromide substituents in the substrates do not interfere, thus showing that the iron-catalyzed reaction of an acid chloride is even faster than the otherwise very rapid cross-coupling of aryl halides.[5] Since different functional groups turned out to be compatible and stereogenic centers in the substrate are not racemized, the method should qualify for target-oriented synthesis (see Part 2: Total Synthesis of Myxovirescin A_1).



Scheme 1: Iron-catalyzed cross-coupling reactions of acid chlorides and GRIGNARD reagents.

Part 2: Total Synthesis of Myxovirescin A_1

Myxovirescin A_1 (TROWITZSCH, 1982),[6] also referred to as Antibiotic TA (ROSENBERG, 1973)[7] or Megovalicin C (MIYASHIRO, 1988)[8] (Scheme 2) is a broad spectrum antibiotic produced by gliding bacteria of the *Myxococcus* species. It represents a new class of antibiotic, unrelated to existing agents and having a unique mode of action.[9] The natural product contains a 28-membered macrocyclic lactam-lacton-ringsystem with seven stereogenic centers as well as a characteristic triol- and (*E*,*Z*)-diene-subunit.[10]

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[5] A. Fürstner, A. Leitner, *Angew. Chem., Int. Ed.* **2002**, *41*, 609-612; A. Fürstner, A. Leitner, M. Méndez, H. Krause, *J. Am. Chem. Soc.* **2002**, *124*, 13856-13863.
[6] K. Gerth, H. Irschik, H. Reichenbach, W. Trowitzsch, *J. Antibiot.* **1982**, *35*, 1454-1459.
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[9] E. Rosenberg, J. M. Porter, P. N. Nathan, A. Manor, M. Varon, *Bio/Technology*, **1984**, *2*, 796-799.
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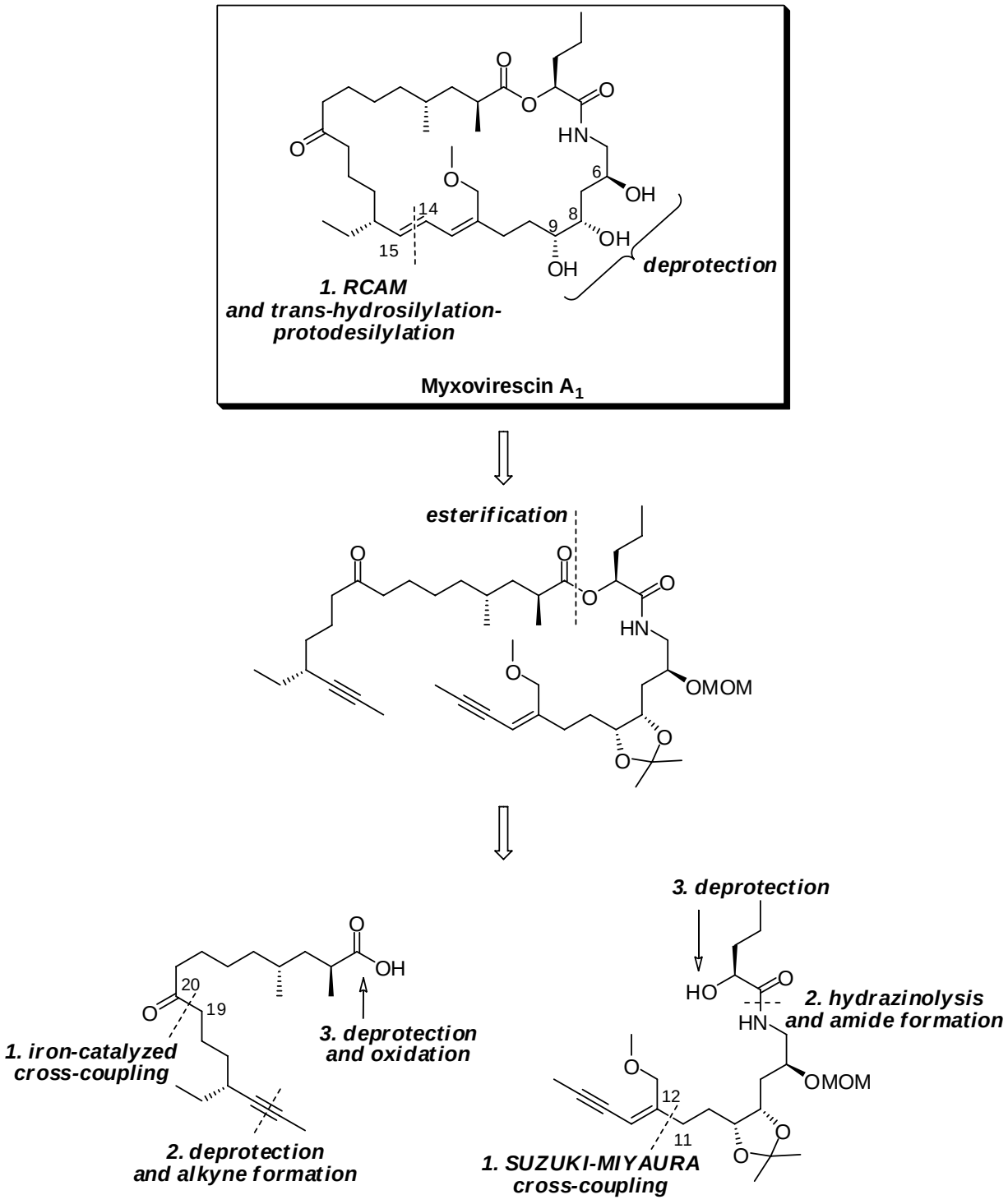
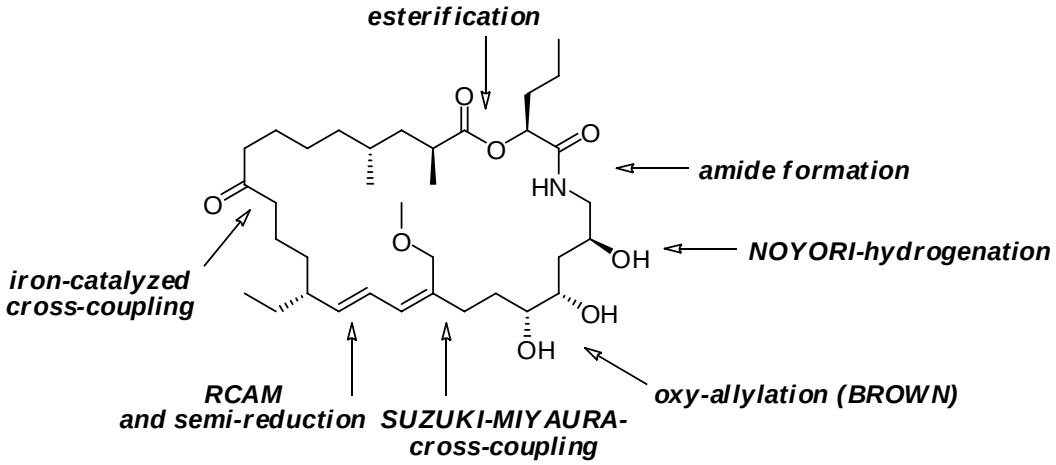
Myxovirescin A_1 was synthesized in 26 steps (longest linear sequence) with an overall yield of 0.2%. Furthermore the (*Z*,*Z*)-configured analog was isolated in an overall yield of 0.1%. The total amount of steps adds up to 55. The retrosynthetic approach is shown in Scheme 2.



Scheme 2: Retrosynthesis of Myxovirescin A_1.

Notably, the oxy-allylation by BROWN and the *trans*-selective hydrosilylation and protodesilylation were used for the first in natural product synthesis (Scheme 3). The first one should be improved concerning the yields, whereas the latter one shows an unexpected isomerization of the double bond. Nevertheless, the iron-catalyzed cross-coupling for the formation of the ketone, the NOYORI-hydrogenation, the Pd-mediated SUZUKI-MIYAURA cross-coupling for the introduction of the ene-yne as well as the ene-yne ring closing metathesis by using the FÜRSTNER-CUMMINS catalyst were applied as key steps in good yields (Scheme 3).



Scheme 3: Key steps for the total synthesis of Myxovirescin A_1.

In summary, the total synthesis of myxovirescin A_1 was successfully completed. With regard to the results obtained further methodological studies are recommended especially for the semi-reduction.