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Enantioselective Synthesis of the C8–C20 Segment of Curvicollide C

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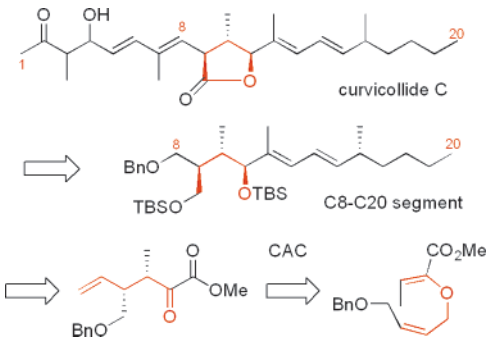
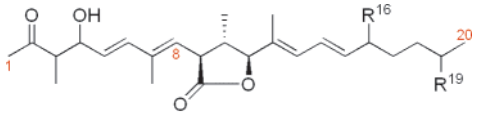
ABSTRACT



The enantioselective synthesis of the C8–C20 fragment of curvicollide C has been accomplished. A catalytic asymmetric Claisen rearrangement (CAC), a diastereoselective methyl cupration of an alkynoate, and a Julia–Kocienski olefination served as key C/C-connecting transformations.

The curvicollides A−C (C_{A-C}, **1**−**3**) are antifungal polyketides that have been isolated in small amounts from a fermentation mixture of *Podospora curvicolla* (Figure 1).[1] The mycoparasitic fungus was originally isolated from a sclerotium of *Aspergillus flavus* that had been buried in an Illinois cornfield for 3 years.



curvicollide	cmpd	R^{16}	R^{19}
A	**1**	CH_2OH	H
B	**2**	CH_3	OH
C	**3**	CH_3	H

Figure 1. Reported constitution and relative configuration of curvicollides A (**1**), B (**2**), and C (**3**).

The relative configuration of the lactone ring in C_A (**1**) was deduced from NOESY data. NMR proton coupling constants are consistent with the assigned relative configuration and the *E*-configuration of the two disubstituted double bonds. The relative configuration of C_B (**2**) and C_C (**3**) was assigned in analogy to C_A (**1**) based on the similarity of the NMR data. The relative configuration of the remaining stereogenic carbon atoms, as well as the absolute configuration of the curvicollides (**1**−**3**), has not yet been established.

The curvicollides possess several synthetically challenging structural features, including the two conjugated diene moieties and the two vicinal non-heteroatom-substituted stereogenic carbon atoms C9 and C10. In this letter, we report a convergent enantioselective synthesis of the C8−C20 segment **4** of curvicollide C (**3**).[2]

Our synthetic strategy was designed to assemble the segments with known and unknown relative configuration in a highly convergent manner (Figure 2). Therefore, the C1−C7 fragment was first disconnected. The resulting building block **4** features the (16*R*)-configuration, arbitrarily

(1) Che, Y.; Gloer, J. B.; Wicklow, D. T. *Org. Lett.* **2004**, *6*, 1249−1252.

(2) For a preliminary account on the synthesis of the C8−C12 segment of C_C (**3**), see: Körner, M.; Hiersemann, M. *Synlett* **2006**, 121−123.

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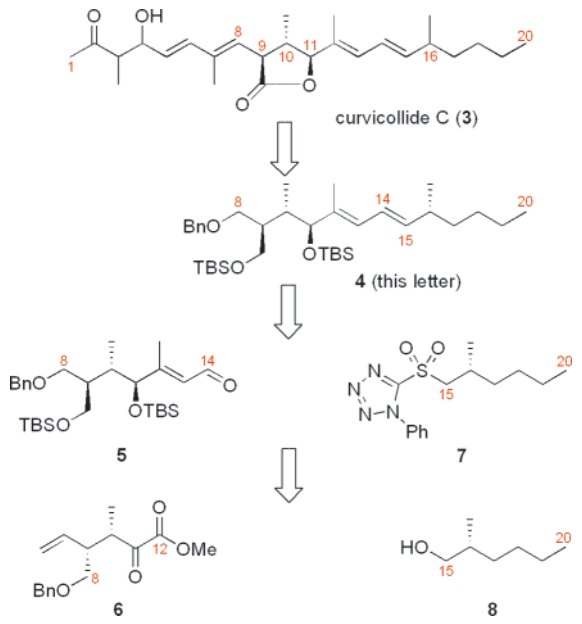


Figure 2. Retrosynthetic analysis of curvicollide C (**3**).

selected and easily reversible. Utilizing an olefination transform to disconnect the C14/C15 double bond afforded the sulfone **7** and the aldehyde **5**. The C15−C20 building block **7** was further simplified to the known alcohol **8**,[3] easily available in both enantiomeric forms.[4] The molecular complexity of **5** is obviously caused by the two vicinal stereogenic carbon atoms C9 and C10. In need of a synthetic strategy that enables the construction of the two pivotal stereogenic carbon atoms in a highly diastereo- and enantioselective fashion, we considered the α-keto ester **6** as suitable building block. **6** represents a γ,δ-unsaturated carbonyl compound, in principle, accessible by a catalytic asymmetric Claisen rearrangement (CAC).[5]

The enantioselective synthesis of the C8−C12 fragment rests on only two stereodifferentiating transformations starting from an achiral substrate (Scheme 1). CAC of the known allyl vinyl ether (*Z*,*Z*)-**9**[2] in the presence of 7.5 mol% of [Cu{(*S*,*S*)-*tert*-Bu-box}]$(H_2O)_2(SbF_6)_2$[6] (**10**) provided the α-keto ester **6**, essentially as an enantio- and diastereomerically pure compound.[7] The relative and absolute configuration was assigned based on the well-established stereochemical course of the CAC.[5] Subsequent reduction of the α-keto ester **6** employing K[(*s*-Bu)$_3$BH][8] provided the α-hydroxy ester **11** as a single diastereomer based on NMR analysis.

(3) For (*R*)-**8**, see: Goldstein, S. W.; Overman, L. E.; Rabinowitz, M. H. *J. Org. Chem.* **1992**, *57*, 1179−1190. Details for the preparation of (*R*)-**8** are reported in the Supporting Information.

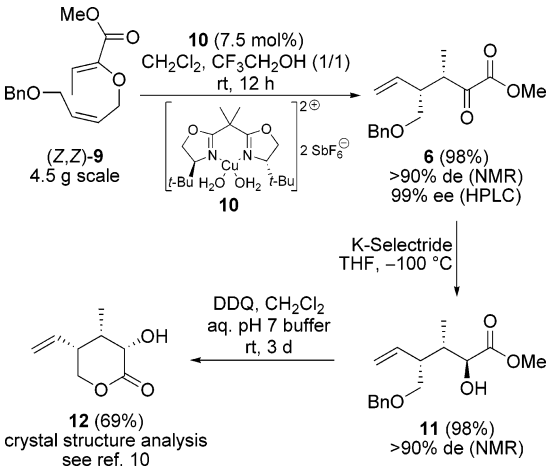
(4) For (*S*)-**8**, see: Fuganti, C.; Grasselli, P.; Servi, S.; Zirotti, C. *Tetrahedron Lett.* **1982**, *23*, 4269−4272. Details for the preparation of (*S*)-**8** are reported in the Supporting Information.

(5) (a) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4700−4703. (b) Abraham, L.; Körner, M.; Schwab, P.; Hiersemann, M. *Adv. Synth. Catal.* **2004**, *346*, 1281−1294.

(6) Evans, D. A.; Miller, S. J.; Lectka, T.; Matt, P. v. *J. Am. Chem. Soc.* **1999**, *121*, 7559−7573.

(7) The yield of the CAC is dependent on an appropriate work-up procedure. See the Supporting Information for details.

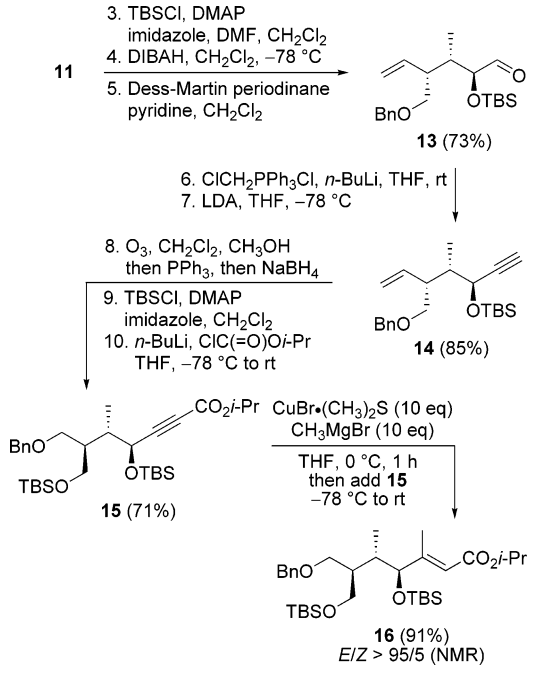
Scheme 1. Sequence of CAC and K-Selectride Reduction Provides the α-Hydroxy Ester **11**



Treatment of the α-hydroxy ester **11** with DDQ[9] removed the benzyl protecting group and induced lactonization to provide the crystalline δ-lactone **12**. A crystal structure analysis of **12** confirmed the original assignment of the relative configuration of **11**.[10]

Having established a scalable access to the crucial central building block **11**, the synthesis of the C8−C14 segment **16** was completed as depicted in Scheme 2. Thus, the α-hydroxy

Scheme 2. Synthesis of the C8−C14 Segment

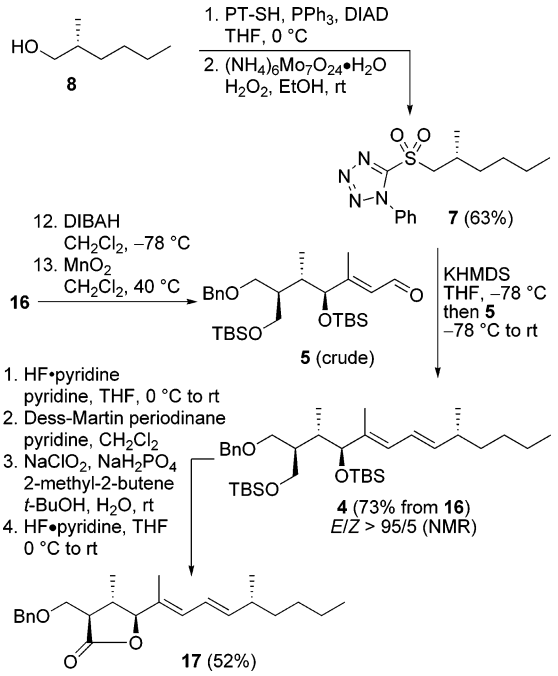


ester **11** was first protected as a TBS ether and then converted into the aldehyde **13** by a redox sequence.[11,12] The α-chiral aldehyde **13** was sufficiently stable to be purified and characterized. One-carbon homologation of **13** was ac-

complished by chloromethylenation[13] and a subsequent Fritsch−Buttenberg−Wiechell[14] rearrangement to afford the alkyne **14**.[15] The double bond was then cleaved chemoselectively by ozonolysis followed by a reductive workup[16] to provide a primary alcohol which was protected as a TBS ether. The trisubstituted C12/C13 double bond was established next. For this purpose, the terminal triple bond was lithiated and treated with isopropyl chloroformate to provide the alkynoate **15**.

Subsequent methylcupration of **15** in the presence of superstoichiometric amounts of copper(I) bromide and methylmagnesium bromide provided the *E*-configured α,*β*-unsaturated ester **16**.[17−19] In accordance with a report by Williams,[19] we found that the presence of the sterically demanding isopropyl ester and the bulky TBS protecting group at C11 in combination with a slow warming process prior to protic quench was essential for a very high *E*/*Z* diastereoselectivity. The synthesis of the sulfone **7** and the fragment coupling to provide the C8−C20 building block **4** is outlined in Scheme 3.

Scheme 3. Synthesis of the C8−C20 Segment



The known alcohol **8**[3] was converted into the sulfone **7** by a Mitsunobu reaction[20] employing 1-phenyl-1*H*-tetrazole-5-thiol (PT-SH) as the nucleophile and a subsequent Mo(VI)-catalyzed oxidation[21] of the intermediate sulfide. Utilizing the robust and reliable procedure reported by Kocienski,[22] the sulfone **7** was deprotonated with potassium bis(trimethylsilyl)amide (KHMDS) and treated with the crude aldehyde **5** to afford the (12*E*,14*E*)-configured diene **4**.[23] The α,*β*-unsaturated aldehyde **5** had been prepared from the α,*β*-unsaturated ester **16** by a two-step redox sequence and was used without further purification.[24]

At this point, we had established an enantioselective synthetic access to the C8−C20 building block **4** featuring a longest linear sequence of 14 steps from the allyl vinyl ether (*Z*,*Z*)-**9** with an overall yield of 28%. To substantiate the feasibility of our synthetic strategy toward C_C (**3**), we set out to prepare the *γ*-lactone in **17** from the protected diol **4** in the presence of the potentially sensitive diene moiety (Scheme 3). Relying on a more conventional, stepwise line of events, we first chemoselectively cleaved the primary TBS ether in **4** to afford a primary alcohol which was oxidized to the corresponding carboxylic acid by a two-step procedure.[12,25] Subsequent treatment of the acid with HF in pyridine[26] without an excess of pyridine deprotected the secondary alcohol and induced lactonization to afford the desired C8−C20 segment **17** of C_C (**3**).

In summary, we have demonstrated the utility of the catalytic asymmetric Claisen rearrangement (CAC) in natural product synthesis.[27] The CAC provides scalable access to the α-keto ester **6** as a single stereoisomer, thereby paving the way for an efficient synthetic approach to the C8−C20 building block **4**. Further work aimed at the completion of the synthesis and, thereby, the elucidation of the relative and absolute configuration of curvicollide C (**3**) is well underway and will be reported in due course.

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Supporting Information Available: Experimental details and copies of NMR spectra for all compounds including the preparation of **8**, (*Z*,*Z*)-**9**, and **10**. Details of the determination of enantioselectivities by HPLC. This material is available free of charge via the Internet at http://pubs.acs.org.

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