

Enantioselective Synthesis of the  
C8–C20 Segment of Curvicollide C

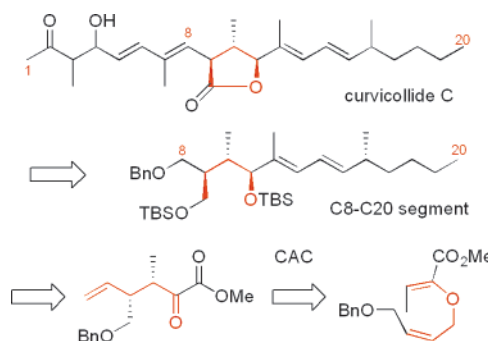
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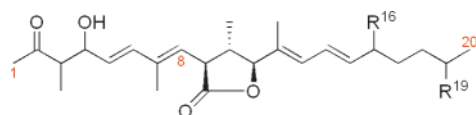
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## ABSTRACT



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).<sup>1</sup> The myco-



curvicollide	compd	R <sup>16</sup>	R <sup>19</sup>
A	1	CH <sub>2</sub> OH	H
B	2	CH <sub>3</sub>	OH
C	3	CH <sub>3</sub>	H

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

parasitic fungus was originally isolated from a sclerotium of *Aspergillus flavus* that had been buried in an Illinois cornfield for 3 years.

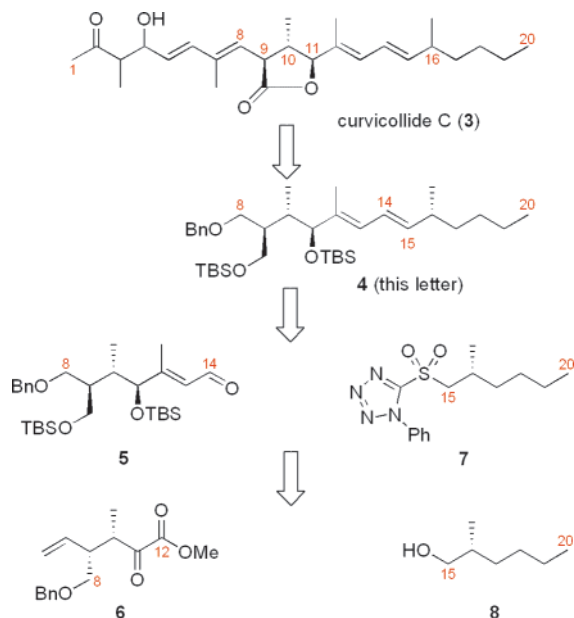
The relative configuration of the lactone ring in  $C_A$  (**1**) was deduced from NOESY data. NMR proton coupling constants are consistent with the assigned relative configuration and the *E*-configuration of the two disubstituted double bonds. The relative configuration of  $C_B$  (**2**) and  $C_C$  (**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**).<sup>2</sup>

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.



**Figure 2.** Retrosynthetic analysis of curvicolide 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**,<sup>3</sup> easily available in both enantiomeric forms.<sup>4</sup> 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  $\alpha$ -keto ester **6** as suitable building block. **6** represents a  $\gamma,\delta$ -unsaturated carbonyl compound, in principle, accessible by a catalytic asymmetric Claisen rearrangement (CAC).<sup>5</sup>

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**<sup>2</sup> in the presence of 7.5 mol% of  $[\text{Cu}\{(S,S)\text{-tert-Bu-box}\}](\text{H}_2\text{O})_2(\text{SbF}_6)_2$  (**10**) provided the  $\alpha$ -keto ester **6**, essentially as an enantio- and diastereomerically pure compound.<sup>7</sup> The relative and absolute configuration was assigned based on the well-established stereochemical course of the CAC.<sup>5</sup> Subsequent reduction of the  $\alpha$ -keto ester **6** employing  $\text{K}[(s\text{-Bu})_3\text{BH}]$ <sup>8</sup> provided the  $\alpha$ -hydroxy ester **11** as a single diastereomer based on NMR analysis.

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

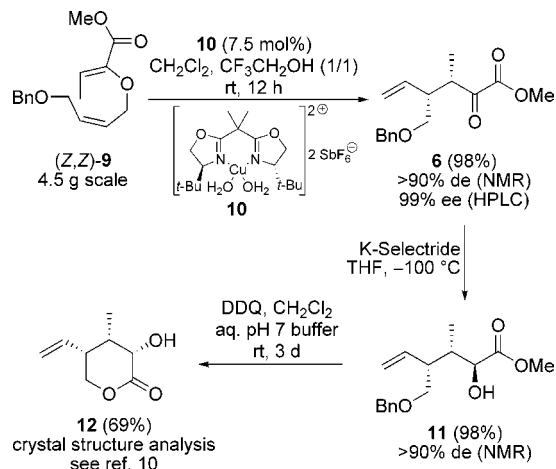
(4) For (*S*)-**8**, see: Fuganti, C.; Grasselli, P.; Servi, S.; Zirotti, C. *Tetrahedron Lett.* **1982**, *23*, 4269–4272. Details for the preparation of (*S*)-**8** are reported in the Supporting Information.

(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.

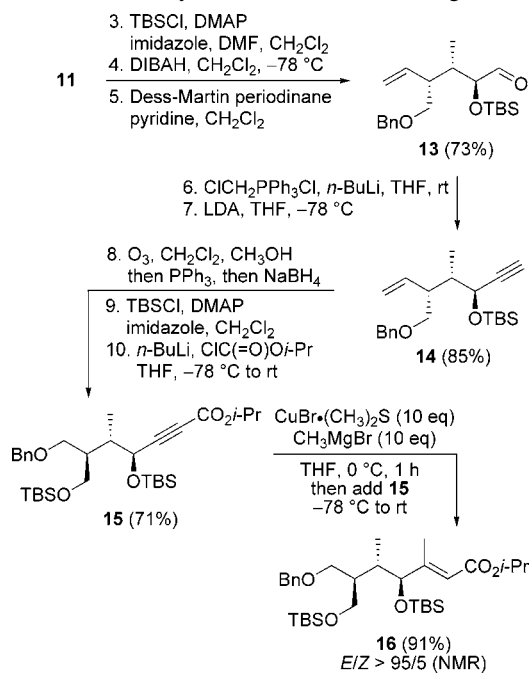
**Scheme 1.** Sequence of CAC and K-Selectride Reduction Provides the  $\alpha$ -Hydroxy Ester **11**



Treatment of the  $\alpha$ -hydroxy ester **11** with DDQ<sup>9</sup> removed the benzyl protecting group and induced lactonization to provide the crystalline  $\delta$ -lactone **12**. A crystal structure analysis of **12** confirmed the original assignment of the relative configuration of **11**.<sup>10</sup>

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  $\alpha$ -hydroxy

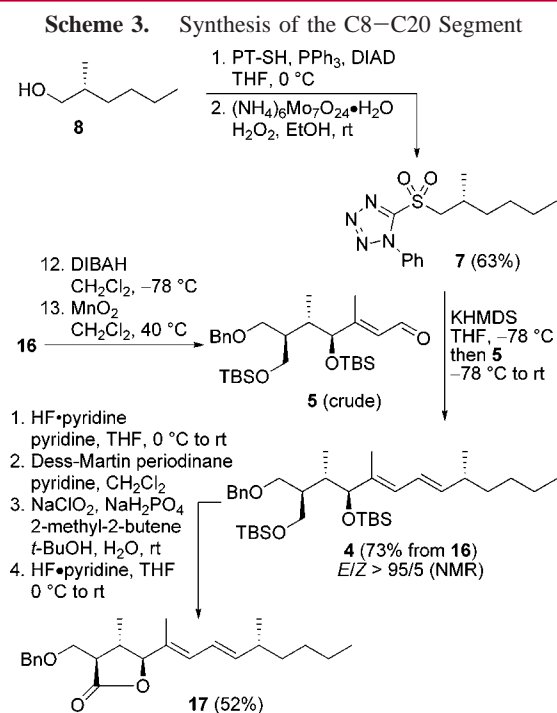
**Scheme 2.** Synthesis of the C8–C14 Segment



ester **11** was first protected as a TBS ether and then converted into the aldehyde **13** by a redox sequence.<sup>11,12</sup> The  $\alpha$ -chiral aldehyde **13** was sufficiently stable to be purified and characterized. One-carbon homologation of **13** was ac-

complished by chloromethylenation<sup>13</sup> and a subsequent Fritsch–Buttenberg–Wiechell<sup>14</sup> rearrangement to afford the alkyne **14**.<sup>15</sup> The double bond was then cleaved chemoselectively by ozonolysis followed by a reductive workup<sup>16</sup> 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  $\alpha,\beta$ -unsaturated ester **16**.<sup>17–19</sup> In accordance with a report by Williams,<sup>19</sup> 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.



The known alcohol **8**<sup>3</sup> was converted into the sulfone **7** by a Mitsunobu reaction<sup>20</sup> employing 1-phenyl-1*H*-tetrazole-

5-thiol (PT-SH) as the nucleophile and a subsequent Mo-(VI)-catalyzed oxidation<sup>21</sup> of the intermediate sulfide. Utilizing the robust and reliable procedure reported by Kocienski,<sup>22</sup> 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**.<sup>23</sup> The  $\alpha,\beta$ -unsaturated aldehyde **5** had been prepared from the  $\alpha,\beta$ -unsaturated ester **16** by a two-step redox sequence and was used without further purification.<sup>24</sup>

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<sub>C</sub> (**3**), we set out to prepare the  $\gamma$ -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.<sup>12,25</sup> Subsequent treatment of the acid with HF in pyridine<sup>26</sup> without an excess of pyridine deprotected the secondary alcohol and induced lactonization to afford the desired C8–C20 segment **17** of C<sub>C</sub> (**3**).

In summary, we have demonstrated the utility of the catalytic asymmetric Claisen rearrangement (CAC) in natural product synthesis.<sup>27</sup> The CAC provides scalable access to the  $\alpha$ -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 curvicolide C (**3**) is well underway and will be reported in due course.

(15) The Ohira–Bestmann procedure failed to provide the desired alkyne **14**; see: (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521–522.

(16) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1952**, *74*, 3855–3860.

(17) NOE studies on both double bond isomers support the assignment of the double bond configuration. See the Supporting Information for details.

(18) (a) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851–1852. (b) Siddall, J. B.; Biskup, M.; Fried, J. H. *J. Am. Chem. Soc.* **1969**, *91*, 1853–1854. For a mechanistic study, see: (c) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem.–Eur. J.* **1998**, *4*, 2051–2058.

(19) Williams, D. R.; Fromhold, M. G.; Earley, J. D. *Org. Lett.* **2001**, *3*, 2721–2724.

(20) Mitsunobu, O.; Yamada, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380–2382.

(21) Schultz, H. S.; Freyermuth, H. B.; Buc, S. R. *J. Org. Chem.* **1963**, *28*, 1140–1142.

(22) (a) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28. (b) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585.

(23) The <sup>3</sup>J<sub>HH</sub>-based configurational analysis and NOE studies support the assignment of the *E*-configuration to the newly generated C13/C14 double bond. See the Supporting Information for details.

(24) For MnO<sub>2</sub>-mediated oxidation, see: Gritter, R. J.; Wallace, T. J. *J. Org. Chem.* **1959**, *24*, 1051–1056.

(25) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.

(26) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011–4013.

(27) For previous applications, see: (a) Pollex, A.; Hiersemann, M. *Org. Lett.* **2005**, *7*, 5705–5708. (b) Wang, Q.; Millet, A.; Hiersemann, M. *Synlett* **2007**, 1683–1686.

- (8) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100–4102.  
(9) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885–888.  
(10) Körner, M.; Schürmann, M.; Preut, H.; Hiersemann, M. *Acta Crystallogr.* **2007**, *E63*, o3012.  
(11) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.  
(12) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.  
(13) Seyferth, D.; Grim, S. O.; Read, T. O. *J. Am. Chem. Soc.* **1961**, *83*, 1617–1620.  
(14) Knorr, R. *Chem. Rev.* **2004**, *104*, 3795–3850.

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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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