The Catalytic Asymmetric Claisen Rearrangement (CAC) in Natural Product Synthesis: Synthetic Studies toward Curvicollides A–C

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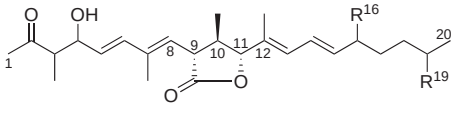
Abstract: A catalytic asymmetric Claisen rearrangement has been utilized as key C–C connecting transformation for the synthesis of a building block in the projected total synthesis of the fungicidal polyketides curvicollide A–C.

Key words: total synthesis, natural products, asymmetric catalysis, pericyclic reactions, Lewis acids

The curvicollides A–C (**1a**–**c**) have been isolated in small quantities (**1a**: 6.5 mg, **1b**: 2.1 mg, **1c**: 3.0 mg) from an organic extract of solid substrate fermentation cultures of an isolate of *Podospora curvicolla* that was originally obtained from the surface of a sclerotium of *Aspergillus flavus* buried in an Illinois cornfield for three years.[1] NMR studies enabled the assignment of the gross structure of these polyketides (Figure 1). The relative configuration of the C9–C11 stereotriad of curvicollide A (**1a**) was deduced from NOESY data. The relative configuration of curvicollide B (**1b**) and C (**1c**) was then assigned in analogy based on the similarity of the corresponding NMR spectra. Neither the relative configuration of the remaining stereogenic carbon atoms nor the absolute configuration of the curvicollides could be established. Curvicollide A (**1a**) exerted antifungal activity against *Aspergillus flavus* and *Fusarium verticillioides*. Due to sample limitations, the fungicidal properties of curvicollides B (**1b**) and C (**1c**) could not be evaluated.



Compd	Curvicollide	R^{16}	R^{19}
1a	A	CH_2OH	H
1b	B	CH_3	OH
1c	C	CH_3	H

Figure 1 Curvicollides A–C **1a**–**c**, fungicidal polyketides from *Podospora curvicolla*.

In light of the interesting structure and biological activity of the curvicollides **1a**–**c**, we have initiated a research program aimed at the unambiguous assignment of the absolute configuration of the curvicollides **1a**–**c** by enantioselective total synthesis. Furthermore, considering the unsolved supply issue, an efficient synthetic access to the natural products and non-natural diastereomers thereof could enable the comprehensive evaluation of the curvicollides **1a**–**c** as potential fungicidal lead compounds. In this paper, we report the enantioselective synthesis of a C8–C12 building block utilizing a catalytic asymmetric Claisen rearrangement (CAC) as the key C–C connecting transformation.

Our synthetic approach toward the curvicollides **1a**–**c** relies on a convergent retrosynthetic analysis that requires the enantioselective access to the central C8–C12 segment of known relative configuration (Figure 2). We envision connecting the C1–C7 and the C13–C20 moieties to the central segment by olefination chemistry. Based on this analysis, we have identified the highly substituted ketone **2** as suitable building block. Building block **2** features three contiguous stereogenic carbon atoms including the secondary hydroxyl group at C11, which we envisioned to establish by a diastereoselective reduction of the α-keto ester *anti*-**3**. From the outset, we intended to generate the crucial non-heteroatom-substituted stereogenic carbon atoms C9 and C10 in *anti*-**3** by a Claisen rearrangement of the allyl vinyl ether (*E*,*Z*)-**4**. Based on a chair-like transition state geometry for the Claisen rearrangement,[2] the relative configuration of the rearrangement product *anti*-**3** was expected to be determined by the double bond configuration of the allyl vinyl ether (*E*,*Z*)-**4**. However, since the allyl vinyl ether (*E*,*Z*)-**4** is achiral, this approach requires an external chiral inductor to control the absolute configuration of the rearrangement product *anti*-**3**.[3] Relying on our previously developed catalytic asymmetric Claisen rearrangement (CAC),[4] we set out to identify a suitable chiral Lewis acid that would fulfill the role as a chiral inductor in catalytic amounts, thereby establishing the CAC as the key C–C connecting transformation in the synthesis of the central building block **2**. The projected CAC requires an efficient and diastereoselective synthesis of the *E*,*Z*-configured allyl vinyl ether **4**. The diastereoselective synthesis of a vinyl ether double bond that is not part of a ring system is often troublesome and no general solution to this problem exists. We envisioned utilizing an inherently *E*-selective olefination reaction between the phosphonate **5** and acetaldehyde for this purpose.

The realization of our initial strategy for the synthesis of the allyl vinyl ether **4** is depicted in Scheme 1. Trimethyl diazophosphonoacetate (**6**)[5] was converted into the

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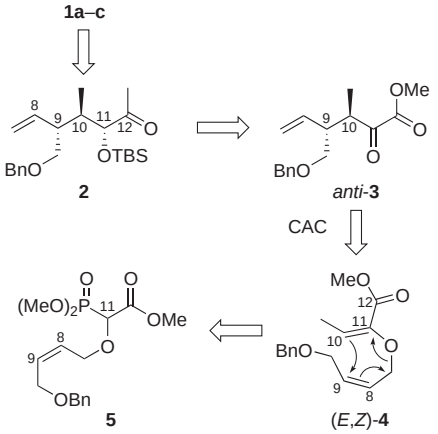
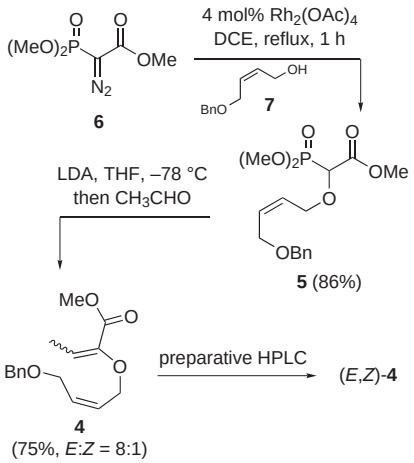


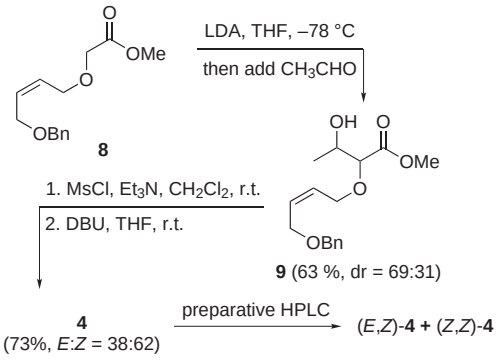
Figure 2 Retrosynthetic analysis of the central segment of the curvicollides.

2-(allyloxy)phosphonoacetate (**5**) by a rhodium(II)-catalyzed OH insertion[6] using the allylic alcohol **7**.[7] The reaction afforded the phosphonate **5** in excellent yield on a small scale (1.8 mmol of **7**). However, the yield decreased significantly when the reaction was performed on a gram scale. The subsequent Horner–Wadsworth–Emmons reaction of the phosphonate **5** with acetaldehyde provided the desired allyl vinyl ether (*E*,*Z*)-**4**[8] as a 8:1 mixture with (*Z*,*Z*)-**4** that was removed by chromatography.[9,10]



Scheme 1 Synthesis of the allyl vinyl ether (*E*,*Z*)-**4**.

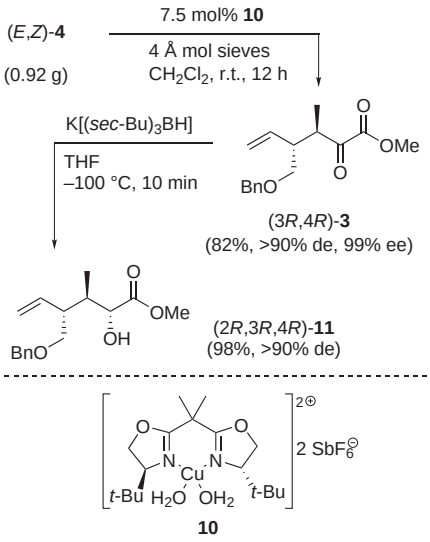
Though the discussed route provided a diastereoselective access to the desired *E*,*Z*-configured allyl vinyl ether **4**, it was hampered by our inability to scale up the Rh^{II}-catalyzed OH-insertion and by the expensiveness of the Rh^{II} catalyst. Therefore, we utilized an alternative route to the allyl vinyl ether **4** which can easily be performed on large scale (Scheme 2).[11] In the event, aldol addition of the enolate of the allyloxy-substituted acetic acid ester **8** with acetaldehyde afforded the β-hydroxy ester **9** in moderate non-optimized yield as a mixture of diastereomers. Mesylation of **9** followed by DBU-mediated elimination provided the desired allyl vinyl ether **4** as mixture of vinyl ether double bond isomers that were conveniently separated by preparative HPLC.[9]



Scheme 2 An aldol strategy toward the 2-alkoxycarbonyl-substituted allyl vinyl ether **4**. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

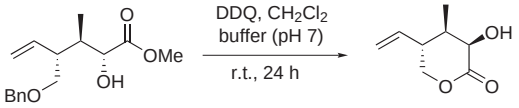
Having successfully established a synthetic access to the allyl vinyl ether (*E*,*Z*)-**4** on a multigram scale, the pivotal CAC of (*E*,*Z*)-**4** was investigated (Scheme 3). Under carefully optimized conditions, (*E*,*Z*)-**4** underwent the desired Claisen rearrangement in the presence of 7.5 mol% [Cu{(*S*,*S*)-*tert*-Bu-box}]$(H_2O)_2(SbF_6)_2$ (**10**)[12] to provide the α-keto ester (3*R*,4*R*)-**3**[13] as a single diastereomer (based on ^{1}H NMR analysis) and enantiomer (based on HPLC analysis, Chiracel OD 14025, *n*-hexane–*i*-PrOH 99.8:0.2, 1 mL/min) in good yield even on a gram scale. The absolute configuration of **3** was assigned in analogy to the previously established stereochemical course of the Cu(box)-catalyzed Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ether.[4]

We have recently reported that K-Selectride is particularly useful to reduce 3-substituted 2-oxo ester with a high diastereoselectivity in favor of the corresponding 2,3-*anti*-configured α-hydroxy ester.[4c] Accordingly, treatment of the α-keto ester **3** with K-Selectride provided the α-hydroxy ester (2*R*,3*R*,4*R*)-**11** as a single diastereomer (based on ^{1}H NMR analysis) in very good yield. As reported previously,[4c] the stereochemical course of the reduction can be explained by the application of the Cram–Felkin–Anh model.[14]



Scheme 3 The sequence of the two stereodifferentiating reactions.

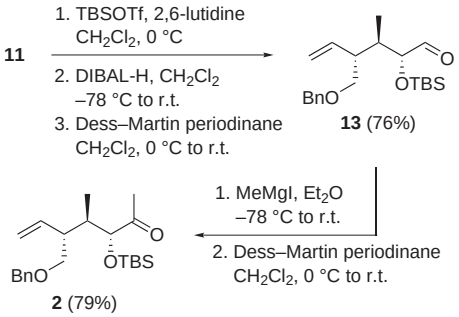
In order to verify the assumed relative configuration of (2*R*,3*R*,4*R*)-**11**, the δ-lactone (2*R*,3*R*,4*R*)-**12** was prepared in situ under the conditions of the oxidative removal[15] of the benzyl protecting group (Equation 1). NOESY on the δ-lactone **12** provided NOE that unambiguously support our mechanism-based assignment of the relative configuration of (2*R*,3*R*,4*R*)-**11**.



(2*R*,3*R*,4*R*)-**11** (2*R*,3*R*,4*R*)-**12** (81%)

Equation 1 Validation of the relative configuration of **11** is based on NOESY studies of the δ-lactone (2*R*,3*R*,4*R*)-**12**.

The synthesis of the key building block **2** was concluded by a five-step sequence from **11** as depicted in Scheme 4. Thus, the protection of the secondary hydroxyl group as a silyl ether[16] was followed by the reduction of the ester function to the primary alcohol and a subsequent Dess–Martin oxidation[17] to afford the aldehyde **13**. Grignard reaction between the aldehyde **13** and methylmagnesium iodide followed by Dess–Martin oxidation[17] provided the desired ketone **2**.[18]



Scheme 4 Final steps toward the desired building block **2**.

In conclusion, we have established a highly enantioselective access to the ketone **2**, the central C8–C12 synthon in the projected total synthesis of the curvicollides **1a**–**c**. We have demonstrated the efficiency of the catalytic asymmetric Claisen rearrangement (CAC) in target-oriented synthesis. Based on the availability of the building block **2**, efforts aimed at the completion of the total synthesis of the curvicollides **1a**–**c** are currently underway in our laboratory.

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(8) (*E*,*Z*)-**4**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (d, 3 H, *J* = 7.4 Hz), 3.78 (s, 3 H), 4.09 (d, 2 H, *J* = 4.2 Hz), 4.31 (d, 2 H, *J* = 4.0 Hz), 4.50 (s, 2 H), 5.36 (q, 1 H, *J* = 7.4 Hz), 5.78–5.81 (m, 2 H), 7.31–7.34 (m, 5 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 12.6, 51.8, 65.0, 65.8, 72.4, 112.9, 127.7, 127.8, 128.0, 128.4, 129.7, 138.0, 144.8, 164.1. IR (neat): 3035–3030, 2950–2860, 1725 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.21; H, 7.39.
(9) Preparative HPLC: Nu 50-7, 32 × 250 mm, heptane–EtOAc 9:1, 30 ml/min, t_R (*Z*) = 7 min, t_R (*E*) = 9 min, baseline separation with 400 mg/injection.
(10) The sequence of OH-insertion and olefination was originally developed and utilized by Ganem and Berchtold for the synthesis of chorismate und its derivatives, see: (a) Ganem, B.; Ikota, N.; Muralidharan, V. B.; Wade, W. S.; Young, S. D.; Yukimoto, Y. *J. Am. Chem. Soc.* **1982**, *104*, 6787. (b) Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765. (c) Lesuisse, D.; Berchtold, G. A. *J. Org. Chem.* **1988**, *53*, 4992. (d) Wood, H. B.; Buser, H. P.; Ganem, B. *J. Org. Chem.* **1992**, *57*, 178. (e) Mattia, K. M.; Ganem, B. *J. Org. Chem.* **1994**, *59*, 720. (f) For an intramolecular application, see: Kim, S.; Sutton, S. C.; Guo, C.; LaCour, T. G.; Fuchs, P. L. *J. Am. Chem. Soc.* **1999**, *121*, 2056.
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(13) (3*R*,4*R*)-**3**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, 3 H, *J* = 6.9 Hz), 2.83 (m, 1 H), 3.31–3.39 (m, 2 H), 3.45 (dd^{AB}, 1 H, *J* = 9.6, 4.9 Hz), 3.62 (s, 3 H), 4.33 (d^{AB}, 1 H, *J* = 12.0 Hz), 4.37 (d^{AB}, 1 H, *J* = 12.0 Hz), 5.12–5.17 (m, 2 H), 5.45–5.58 (m, 1 H), 7.22–7.34 (m, 5 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4, 43.1, 48.4, 52.5, 72.4, 72.7, 118.7, 127.6, 128.3, 135.3, 137.5, 161.5, 195.6. IR (neat): ν = 3300–3150, 2950–2870, 1728 cm^{-1}. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.28; H, 7.38. $[\alpha]^{25}_D$ +39.7 (*c* 0.89, $CHCl_3$).
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(18) (3*R*,4*R*,5*R*)-**2**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.00 (s, 3 H), 0.05 (s, 3 H), 0.75 (d, 3 H, *J* = 7.1 Hz), 0.94 (s, 9 H), 2.03–2.12 (m, 1 H), 2.14 (s, 3 H), 2.71–2.79 (m, 1 H), 3.46 (dd^{AB}, 1 H, *J* = 9.7, 7.2 Hz), 3.53 (dd^{AB}, 1 H, *J* = 9.7, 6.1 Hz), 3.79 (d, 1 H, *J* = 7.7 Hz), 4.45 (d^{AB}, 1 H, *J* = 12.1 Hz), 4.55 (d^{AB}, 1 H, *J* = 12.1 Hz), 5.04–5.14 (m, 2 H), 5.71 (ddd, 1 H, *J* = 17.2, 10.5, 8.8 Hz), 7.29–7.41 (m, 5 H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = –5.0, –4.8, 11.3, 18.1, 25.3, 25.8, 37.0, 42.8, 71.6, 72.6, 81.4, 117.5, 127.5, 127.6, 128.3, 136.2, 138.5, 211.7. IR (neat): ν = 3100–3060, 2970–2860, 1716 cm^{-1}. Anal. Calcd for $C_{22}H_{36}O_3Si$: C, 70.16; H, 9.63. Found: C, 70.30; H, 9.72. $[\alpha]^{25}_D$ +38.3 (*c* 0.90, $CHCl_3$).