ORGANIC LETTERS

2005
Vol. 7, No. 25
5705−5708

Catalytic Asymmetric Claisen Rearrangement in Natural Product Synthesis: Synthetic Studies toward (−)-Xeniolide F

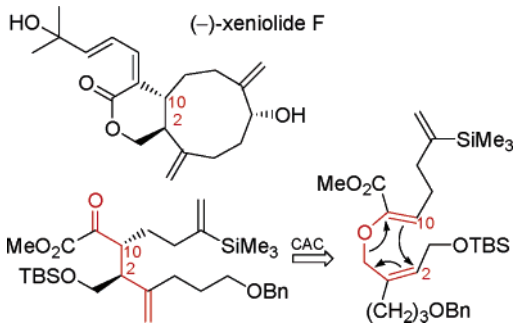
Annett Pollex and Martin Hiersemann*

Institut für Organische Chemie, Technische Universität Dresden, D-01062 Dresden, Germany

martin.hiersemann@chemie.tu-dresden.de

Received October 11, 2005

ABSTRACT



The catalytic asymmetric Claisen rearrangement (CAC) of a highly substituted and functionalized α-alkoxycarbonyl-substituted allyl vinyl ether has been exploited to gain access to an advanced building block for the projected total synthesis of (−)-xeniolide F, the enantiomer of a xenicane diterpene isolated from a coral of the genus *Xenia*.

Xenicane diterpenes are being isolated as bioactive natural products from brown algae and cnidarians. Soft corals of the genus *Xenia* are a particularly rich source of xenicane and related diterpenes.[1] The xenicane framework (**1**, Figure 1) is distinguished by the presence of a single nine membered carbocyclic ring. (+)-Xeniolide F (**2**) was isolated from an unknown *Xenia* species collected near Sulawesi Island (Indonesia) in small amounts (4.7 mg from 300 g of the coral) by Jiménez and co-workers.[2] The gross structure of xeniolide F was determined by NMR and MS studies. The assignment of the relative configuration was based on the analysis of

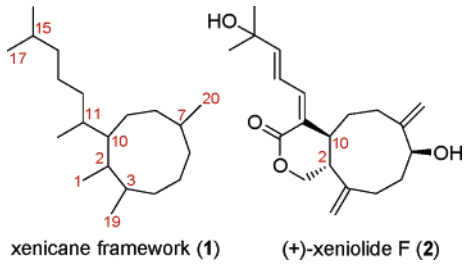


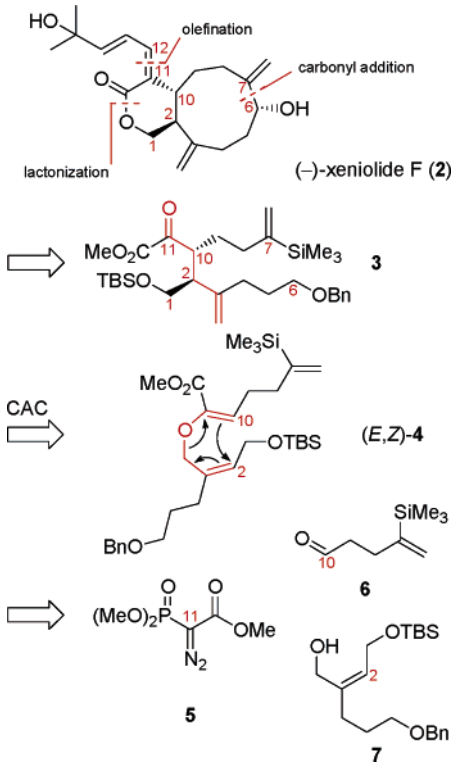
Figure 1. Basic xenicane framework (**1**) and the xenicane diterpene (+)-xeniolide F (**2**). The depicted numbering is used throughout the paper.

(1) For recent reports on the isolation of xenicanes from *Xenia* sp., see: (a) Shen, Y.-C.; Lin, Y.-C.; Ahmed, A. F.; Kuo, Y.-H. *Tetrahedron Lett.* **2005**, *46*, 4793−4796. (b) El-Gamal, A. A. H.; Chiang, C.-Y.; Huang, S.-H.; Wang, S.-K.; Duh, C.-Y. *J. Nat. Prod.* **2005**, *68*, 1336−1340. (c) El-Gamal, A. A. H.; Wang, S.-K.; Duh, C.-Y. *Tetrahedron Lett.* **2005**, *46*, 6095−6096. (d) El-Gamal, A. A. H.; Wang, S.-K.; Duh, C.-Y. *Tetrahedron Lett.* **2005**, *46*, 4499−4500. (e) El-Gamal, A. A. H.; Wang, S.-K.; Duh, C.-Y. *Org. Lett.* **2005**, *7*, 2023−2025.

(2) Anta, C.; González, N.; Santafé, G.; Rodríguez, J.; Jiménez, C. *J. Nat. Prod.* **2002**, *65*, 766−768.

10.1021/ol052462t CCC: $30.25
Published on Web 11/17/2005

Scheme 1. Retrosynthesis of the Key Building Block **3**



coupling constants and NOE studies. Although the absolute configuration of xeniolide F (**2**) was not explicitly determined, the depicted absolute configuration at C2 and C10 is consistent with earlier reports concerning the absolute configuration of xenicane diterpenes from soft corals.[3]

Xenicanes combine unique structural features and interesting biological activities with an unsolved supply issue. However, synthetic efforts toward xenicane diterpenes are rare.[4] Therefore, we have initiated a research program aimed at the total synthesis of members of the xenicane class of diterpenes. Here, we report the efficient enantioselective access to a key building block (**3**) in the projected total synthesis of (−)-xeniolide F (**2**) and we provide a general and enantioselective strategy for the generation of the critical stereogenic carbon atoms C2 and C10 of the xenicane framework.

Our retrosynthetic analysis rests on the availability of the highly substituted acyclic α-keto ester **3** and requires the de novo synthesis of the nine-membered carbocyclic segment (Scheme 1). An intramolecular addition of a vinyl anion at C7 to a carbonyl functionality at C6 may be envisioned for this purpose. The α-keto ester function of building block **3** would be utilized to construct the C11/C12 double bond by olefination and the protected hydroxyl group at C1 should be suitable for the formation of the δ-lactone moiety. To ensure an efficient access to the α-keto ester **3**, the enantioselective generation of the two nonheteroatom-substituted stereogenic carbon atoms C2 and C10 has to be addressed. Recognizing the Claisen rearrangement retron in the α-keto ester **3**, the achiral allyl vinyl ether **4** was selected as the pivotal synthon.

It is well-known that the thermal Claisen rearrangement of acyclic allyl vinyl ethers can be highly diastereoselective based on the concerted nature and chairlike geometry of the corresponding transition state.[5] However, considering the achiral nature of the allyl vinyl ether **4**, an external chiral inductor is required to control the absolute configuration of the rearrangement product.[6] Therefore, our recently implemented protocol for a catalytic asymmetric Claisen rearrangement (CAC) should be ideally suited to solve this problem.[7] However, it was uncertain whether the highly substituted and functionalized allyl vinyl ether **4** would be tolerated as a substrate for our Lewis acid based CAC protocol. Finally, a strategy that addresses the often troublesome diastereoselective generation of an acyclic vinyl ether double bond was required for the synthesis of (*E*,*Z*)-**4**. A convergent approach utilizing the building blocks **5**−**7** was envisioned to take that synthetic hurdle.

Scheme 2 illustrates the synthesis of the *Z*-configured allylic alcohol **7**.

The synthesis was initiated with a Pd^0-catalyzed hydrostannation of 2-butyne-1,4-diol **8** to afford the vinylstannane **9** in excellent yield.[8] Protection of the sterically less hindered hydroxy group[9] followed by iododestannation and protection of the remaining hydroxy group as a TMS ether provided the vinyl iodide **10**. Initial attempts to perform the subsequent cross coupling reaction in the absence of the TMS protecting group were unsuccessful. However, the *B*-alkyl Suzuki−Miyaura coupling[10] between the in situ generated borane[11] from allyl benzyl ether (**11**) and 9-BBN[12] as well as the vinyl iodide **10** afforded the fully protected allylic alcohol **12** along with varying amounts of the monodeprotected allylic alcohol **7**. Complete cleavage of the TMS ether was subsequently achieved by treatment of **12** with K_2CO_3 in methanol to afford the desired allylic alcohol **7** in 60% overall yield for the cross coupling/deprotection sequence as a single *Z*-configured diastereomer.

(3) (a) Vanderah, D. J.; Steudler, P. A.; Ciereszko, L. S.; Schmitz, F. J.; Ekstrand, J. D.; Helm, D. V. d. *J. Am. Chem. Soc.* **1977**, *99*, 5780−5784. (b) Miyaoka, H.; Mitome, H.; Nakano, M.; Yamada, Y. *Tetrahedron* **2000**, *56*, 7737−7740. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096. (c) Ohtani, I.; Kusumi, T.; Ishitsuka, M. O.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 3147−3150.

(4) For the total synthesis of (+)-coraxeniolide A, see: (a) Renneberg, D.; Pfander, H.; Leumann, C. J. *J. Org. Chem.* **2000**, *65*, 9069−9079. (b) Liu, G.; Smith, T. C.; Pfander, H. *Tetrahedron Lett.* **1995**, *36*, 4979−4982.

(5) (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423−1452. (b) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939−3002.

(6) (a) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847−1882. (b) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43−50. (c) Nubbemeyer, U. *Synthesis* **2003**, 961−1008.

(7) (a) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4700−4703. (b) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461−1471. (c) Abraham, L.; Körner, M.; Schwab, P.; Hiersemann, M. *Adv. Synth. Catal.* **2004**, *346*, 1281−1294. (d) Abraham, L.; Körner, M.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 3647−3650.

(8) Commeiras, L.; Santelli, M.; Parrain, J.-L. *Org. Lett.* **2001**, *3*, 1713−1715.

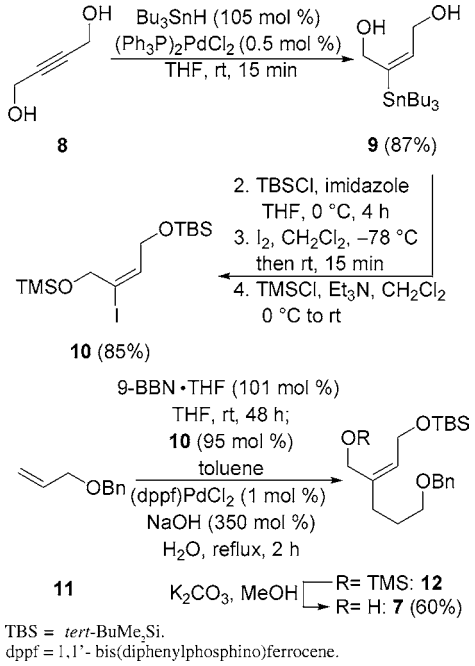
(9) Barrett, A. G. M.; Barta, T. E.; Flygare, J. A. *J. Org. Chem.* **1989**, *54*, 4246−4249.

(10) Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* **1986**, *27*, 6369−6372.

(11) Bo, Z.; Schlüter, A. D. *J. Org. Chem.* **2002**, *67*, 5327−5332.

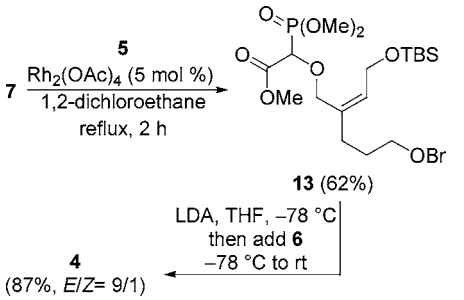
(12) Brown, H. C.; Knights, E. F.; Scouten, C. G. *J. Am. Chem. Soc.* **1974**, *96*, 7765−7770.

Scheme 2. Synthesis of the Allylic Alcohol **7**



With the functionalized allylic alcohol **7** in hand, the allyl vinyl ether synthesis was realized in a two-step sequence (Scheme 3).[13] In the event, a Rh^{II}-catalyzed OH-insertion[14]

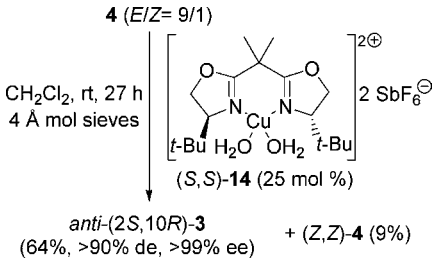
Scheme 3. Sequential OH Insertion/Olefination[13]



reaction between trimethyl diazophosphonoacetate **5**[15] and the alcohol **7** followed by a Horner−Wadsworth−Emmons olefination[16] of the aldehyde **6**[17] with the resulting phosphonate **13** afforded the allyl vinyl ether **4** in good overall yield as an $E/Z = 9/1$ mixture of vinyl ether double-bond isomers.[18]

The critical CAC of the allyl vinyl ether **4** was investigated

Scheme 4. Catalytic Asymmetric Claisen Rearrangement (CAC)



next (Scheme 4). After some experimentation, we found that treatment of the $E/Z = 9/1$ mixture of **4** with substoichiometric amounts of the chiral Cu^{II} Lewis acid [Cu{(*S*,*S*)-*t*-Bu-box}]$(H_2O)_2(SbF_6)_2$ (*S*,*S*)-**14**[19] in the presence of freshly activated 4 Å molecular sieves in CH_2Cl_2 at room temperature afforded the desired rearrangement product *anti*-(2*S*,10*R*)-**3** in 64% yield as a single diastereo- and enantiomer based on NMR and HPLC analysis.[20] The minor (*Z*,*Z*)-configured allyl vinyl ether **4** did not rearrange under these conditions and was reisolated as a single double bond isomer. Subsequent treatment of (*Z*,*Z*)-**4** even with stoichiometric amounts of (*S*,*S*)-**14** did not afford the corresponding rearrangement product but led to extensive cleavage of the TBS ether. Significantly, the (*S*,*S*)-**14**-catalyzed rearrangement of pure (*E*,*Z*)-**4** was substantially faster and provided *anti*-(2*S*,10*R*)-**3** in >80% yield as a single stereoisomer. The thermal Claisen rearrangement (1,2-dichloroethane, 80 °C, 32 h) of the $E/Z = 9/1$ mixture of **4** provided the rearrangement product (±)-*anti*-**3** in mediocre yield (50%) along with unreacted (*Z*,*Z*)-**4**.

A proposal for the stereochemical course of the rearrangement and the different reactivity of (*E*,*Z*)- and (*Z*,*Z*)-**4** is depicted in Figure 2. The model rests on the previously established privileged topicity of the (*S*,*S*)-**14**-catalyzed Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers.[21] It is therefore feasible to assume that the substrate **4** is coordinated to the catalyst (*S*,*S*)-**14** in a bidentate fashion and that the relative configuration of the rearrangement product **3** is a consequence of a chairlike transition state geometry for the catalyzed rearrangement. A qualitative analysis of substrate-catalyst complex **15** indicates a severe 1,3-diaxial interaction between the substituents at C10 and C3. Consequently, (*Z*,*Z*)-**4** did not rearrange either in the presence of (*S*,*S*)-**14** or under thermal

(13) 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*, 6787−6788. (b) Pawlak, J. L.; Berchtold, G. A. *J. Org. Chem.* **1987**, *52*, 1765−1771. (c) Lesuisse, D.; Berchtold, G. A. *J. Org. Chem.* **1988**, *53*, 4992−4997. (d) Wood, H. B.; Buser, H. P.; Ganem, B. *J. Org. Chem.* **1992**, *57*, 178−184. (e) Mattia, K. M.; Ganem, B. *J. Org. Chem.* **1994**, *59*, 720−728.

(14) Miller, D. J.; Moody, C. J. *Tetrahedron* **1995**, *51*, 10811−10843.

(15) Prepared according to Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2003**, 3798−3810.

(16) (a) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klahre, G. *Chem. Ber.* **1959**, *92*, 2499−2507. (b) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733−1738.

(17) Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248−2256.

(18) The *E*/*Z* diastereomers may be separated by preparative HPLC. See the Supporting Information for details.

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

(20) A second stereoisomer could not be detected by NMR or chiral HPLC. See the Supporting Information for details.

(21) Application of (*S*,*S*)-**14** leads preferentially to a *Si*-face approach of the allylic ether moiety to the (*E*)-configured vinyl ether double bond: (*E*,*S*,*S*,*Si*)-topicity (*E-like*). See ref 7c for details.

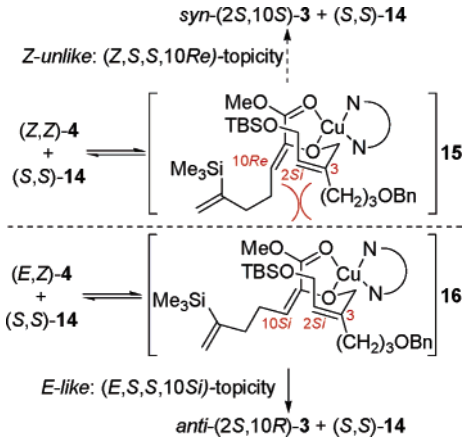
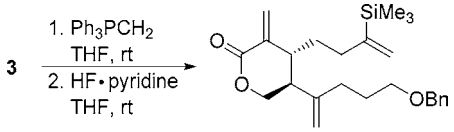


Figure 2. Stereochemical course of the CAC.

reaction conditions. The observation that the (*S*,*S*)-**14**-catalyzed rearrangement of (*E*,*Z*)-**4** is slower in the presence of (*Z*,*Z*)-**4** than in its absence may indicate that (*S*,*S*)-**14** indeed coordinates to (*Z*,*Z*)-**4**. The decisive destabilizing 1,3-diaxial interaction is absent in the complex **16** between (*S*,*S*)-**14** and (*E*,*Z*)-**4** and the catalyzed Claisen rearrangement afforded the rearrangement product *anti*-(2*S*,10*R*)-**3**. The configuration of the rearrangement product *anti*-(2*S*,10*R*)-**3** is a consequence of the chairlike transition-state geometry and the privileged topicity of the (*S*,*S*)-**14**-catalyzed rearrangement of an allyl vinyl ether containing an (*E*)-configured vinyl ether double bond.

Having established access to the crucial building block *anti*-(2*S*,10*R*)-**3** as originally envisioned, a two-step sequence was realized in order to support the viability of our synthetic strategy toward (−)-xeniolide F (**2**). Thus, treatment of the

Scheme 5. α-Keto Ester Olefination and Lactonization



17 (52%)

α-keto ester **3** with the methylene Wittig reagent led to the formation of an α,β-unsaturated ester which was transformed into the δ-lactone **17** by silyl ether cleavage and subsequent in situ lactonization. The analysis of the NOE data of the δ-lactone **17** supports our assignment of the relative configuration of the initial rearrangement product *anti*-(2*S*,10*R*)-**3** (Scheme 5).

In summary, we have established an efficient and enantioselective access to the α-keto ester building block *anti*-(2*S*,10*R*)-**3** utilizing the catalytic asymmetric Claisen rearrangement (CAC) of the highly substituted and functionalized allyl vinyl ether (*E*,*Z*)-**4**. Further work aimed at the completion of the total synthesis of (−)-xeniolide F (**2**) and other xenicane diterpenes is currently underway in our laboratory.

Acknowledgment. Financial support from the DFG and the FCI is gratefully acknowledged. M.H. is a Heisenberg fellow of the DFG. We are indebted to Prof. Carloz Jiménez for providing NMR spectra of natural xeniolide F and a picture of the *Xenia* sp. from which the natural product was originally isolated.

Supporting Information Available: Experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052462T