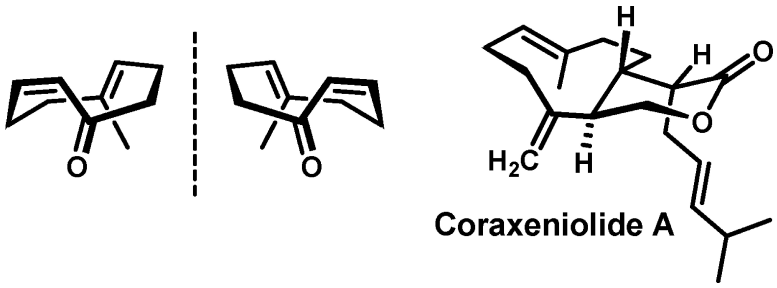
Communication

An Unconventional Approach to the Enantioselective Synthesis of Caryophylloids

Oleg V. Larionov, and E. J. Corey

J. Am. Chem. Soc., **2008**, 130 (10), 2954-2955 • DOI: 10.1021/ja8003705



Coraxeniolide A

More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

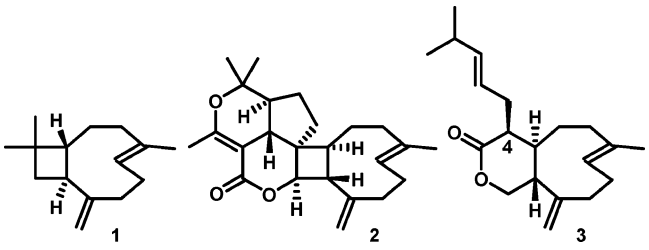
Published on Web 02/16/2008

An Unconventional Approach to the Enantioselective Synthesis of Caryophylloids

Oleg V. Larionov and E. J. Corey*
Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

Received January 19, 2008; E-mail: corey@chemistry.harvard.edu

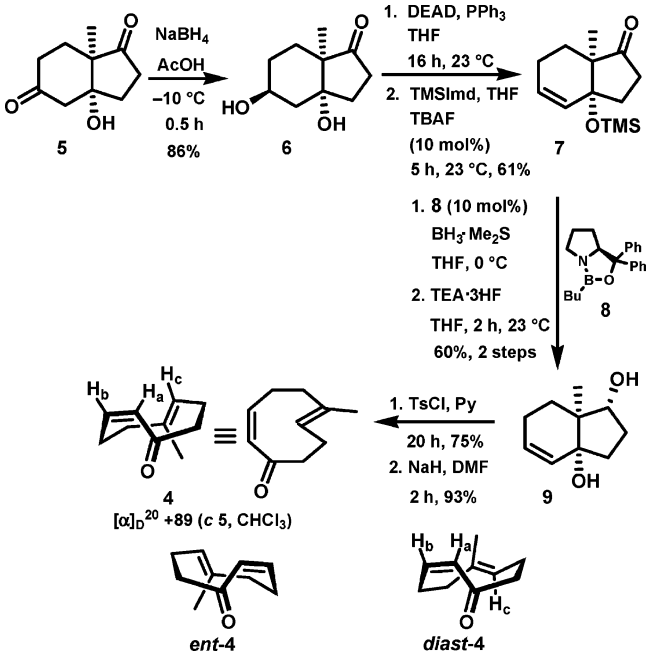
Since the appearance of the unusual 4/9-fused ring nucleus of β-caryophyllene (**1**),[1] many natural products have been discovered that either contain or are derived from this subunit, for instance antheliolide A (**2**)[2] and coraxeniolide A (**3**).[3] This whole family of caryophylloids has presented a real challenge to synthetic chemistry, and most members have either not been synthesized or been made only recently.[4] We describe herein a novel strategy for the synthesis of caryophylloids, which depends on the accessibility of the hitherto unknown chiral dienone **4** and its enantiomer, *ent*-**4**.



The synthetic route, by which we have synthesized coraxeniolide A (**3**) and the key intermediate **4**, is outlined in Schemes 1 and 2. The known chiral hydroxy dione **5** was synthesized by the Hajos-Parrish procedure[5] and reduced selectively to the dihydroxy ketone **6** by in situ generated $NaBH(OAc)_3$ (see Scheme 1). Selective dehydration by Mitsunobu activation of the secondary hydroxyl group of **6** afforded, after silylation of the remaining hydroxyl, the trimethylsiloxy ketone **7**. Diastereoselective reduction of **7** by $Me_2S\cdot BH_3$ in the presence of 10 mol % of the (*S*)-oxazaborolidine **8**[6] produced the diol **9** ($NaBH_4$ reduction, in contrast, was nonselective). Selective tosylation of the secondary hydroxyl group of **9** followed by deprotonation and alkoxide-driven, carbonyl-forming elimination[7] gave the chiral *E*,*Z*-dienone **4**, $[\alpha]_D^{20}$ +89 (*c* 5, $CHCl_3$), as an enantiomerically pure, colorless liquid that was configurationally stable when stored at −20 °C for over 1 month. The dissymmetry of **4**, which lacks any carbon stereocenters, arises because of restricted C−C bond rotation in the nine-membered ring, which prevents racemization at 23 °C or below.

The synthesis of of *ent*-**4** was also carried out by a route parallel to that described in Scheme 1 for **4**, except that the starting point was *ent*-**5**[5] and the chiral catalyst used to generate *ent*-**9** was the (*R*)-proline-derived oxazaborolidine, *ent*-**8**. The spectral data for **4** and *ent*-**4** are identical except for the opposite sign of optical rotation. The cis relationship between the olefinic hydrogens H_a and H_b is clear from the coupling constant between them in the ^1H NMR spectrum ($^3J = 12$ Hz) and from the observation of an NOE interaction between them. There is also a transannular NOE between these hydrogens and H_c on the remote double bond, which demonstrates the three-dimensional geometry expressed by the stereoformula for **4**, which appears in Scheme 1. The NOE data allow the further conclusion that the *diastereomeric* form of **4** shown at the bottom of Scheme 1 (*diast*-**4**), which should be capable of independent existence and which should be preparable, can be excluded. Finally, the infrared spectrum of **4** exhibits a carbonyl stretching band at 1687 cm^{-1}, indicating π-conjugation. If the α,β-double bond were trans, its π-bond would be nearly orthogonal to the C=O π-bond, and the stretching frequency would be higher (ca. 1700 cm^{-1}).

Scheme 1. Synthesis of Chiral Dienone **4**



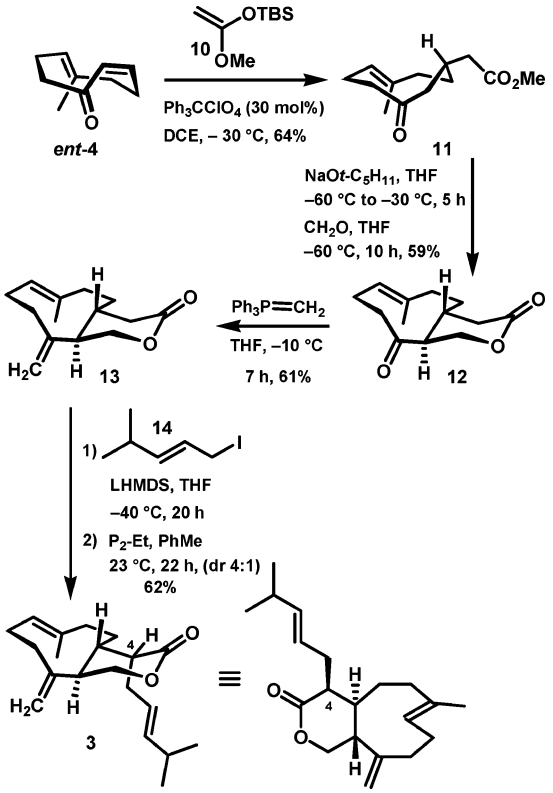
The selective formation of **4** instead of *diast*-**4** in the carbonyl-forming elimination of the tosylate of **4** is easy to understand, because the three-dimensional proximity of the methyl group and carbonyl oxygen of **4** reflects a least motion pathway from cis arrangement of the hydroxy and methyl groups in the tosylate of **9**. The *E*-arrangement of the unconjugated double bond in **4** follows from previous studies that demonstrated a concerted *anti*-periplanar E2 elimination pathway for such a process.[7]

trans-Cyclooctene is quite stable at ambient temperature,[8] in contrast to *trans*-cycloheptene, which rapidly converts to the *cis*-isomer even at 0 °C.[9] *trans*-Cyclooctene was the first chiral cycloolefin to be made in enantiomerically pure form, having been made either by resolution of the Pt(II) complex[10] or by direct synthesis.[11] Surprisingly, since the work nearly a half-century ago, there has been little or no use of such chiral cycloolefins in the planned synthesis of complex naturally occurring compounds. *trans*-Cyclononene has been resolved as the Pt(II) complex but racemizes in less than a few minutes at ambient temperature.[12] Clearly, the enantiomeric stability of **4** depends on the presence of *two* double bonds and possibly also the methyl substituent on the *E*-olefinic linkage.

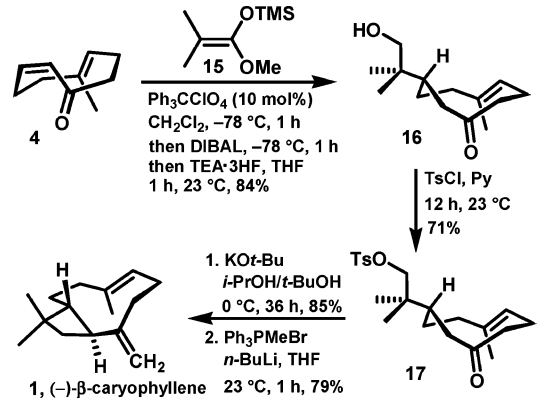
The synthetic utility of **4** and *ent*-**4** is demonstrated in Schemes 2 and 3, featuring syntheses of coraxeniolide A (**3**) and β-caryo-

10.1021/ja8003705 CCC: $40.75

Scheme 2. Synthesis of Coraxeniolide a (**3**) from *ent*-**4**



Scheme 3. Synthesis of β-caryophyllene (**1**) from **4**



phyllene (**1**), respectively. Thus, trityl perchlorate-catalyzed[13] conjugate addition of silyl ketene acetal **10** to the enone *ent*-**4** produced ketoester **11**. Position-selective deprotonation of **11** under carefully chosen conditions (sodium *tert*-pentoxide in THF), followed by subsequent trapping of the enolate with formaldehyde (as a freshly prepared solution[14] in THF), yielded lactone **12** in a regio- and stereoselective fashion. Methylenation of **12** proved to be difficult to achieve by the standard protocols (e.g., Ph_3PMeBr/*n*-BuLi in THF, or $CH_2Br_2/TiCl_4/Zn$).[15] This problem was circumvented by using crystallized, salt-free methylenetriphenylphosphorane[16] (made and maintained in inert atmosphere) in THF solution. The success of this technique is due to the enhanced reactivity of the salt-free ylide. α-Alkylation of lactone **13** was effected by the addition of lithium hexamethyldisilazide to a mixture of iodide **14** and lactone **13** which produced coraxeniolide A (**3**) and the 4-epimer (ratio 1:6). Subsequent base-mediated (Schwesinger phosphazene P_2−Et, Aldrich) equilibration reversed the ratio to 4:1 in favor of coraxeniolide A (**3**), which was separated from the 4-epimer by column chromatography. The spectroscopic and polarimetric data of the synthetic samples of **3** and 4-*epi*-**3** were in complete agreement with the values previously reported for these compounds.[3,15]

A new enantioselective synthesis of β-caryophyllene (**1**) from dienone **4** was carried out as shown in Scheme 3, the initial step being the trityl perchlorate-catalyzed[13] conjugate addition of silyl ketene acetal **15** to the dienone **4**. The ester group in the in situ-generated silyl enol ether was then selectively reduced to CH_2OH. Desilation with Et_3NH^+ $H_2F_3^-$ afforded ketone **16**. These three transformations were carried out efficiently in one flask without isolation of the intermediates. Primary alcohol **16** was then converted into tosylate **17**. Position-selective deprotonation (KO*t*-Bu in *i*-PrOH − *t*-BuOH) of **17** and intramolecular α-alkylation forged the cyclobutane ring and the caryophylloid ring system stereoselectively.[17] Finally, Wittig methylenation of the intermediate ketone (Ph_3PMeBr/*n*-BuLi in THF)[7] afforded synthetic β-caryophyllene (**1**), which was fully identical with a sample of the natural β-caryophyllene. This is the first fully executed enantioselective synthesis of β-caryophyllene.

The work described above entails a number of noteworthy developments including (1) the implementation of a new strategy involving the use of a chiral cycloolefin in the synthesis of caryophylloids, (2) a simple synthesis of the chiral cyclononadienones **4** and *ent*-**4**, (3) the 4-step conversion of *ent*-**4** to coraxeniolide A, and (4) the rapid and stereocontrolled transformation of **4** to β-caryophyllene. The configurational stability and utility of **4** and *ent*-**4** are especially striking in view of the almost instantaneous racemization[12] of the prototype *trans*-cyclononene.

Supporting Information Available: Experimental and characterization data for all the compounds prepared in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Dawson, T. L.; Ramage, G. R. *J. Chem. Soc.* **1951**, 3382−3386. (b) Robertson, J. M.; Todd, G. *J. Chem. Soc.* **1955**, 1254−1263. (c) Clunie, J. S.; Robertson, J. M. *Proc. Chem. Soc.* **1960**, 82−83. (d) Barton, D. H. R.; Nickon, A. *J. Chem. Soc.* **1954**, 4665−4669.
(2) (a) Green, D.; Carmely, S.; Benayahu, Y.; Kashman, Y. *Tetrahedron Lett.*
(3) Schwartz, R. E.; Scheuer, P. J.; Zabel, V.; Watson, W. H. *Tetrahedron* **1981**, *37*, 2725−2733.
(4) For reviews on some other naturally occuring caryophylloids, see: (a) Hooper, G. J.; Davies-Coleman, M. T. *J. Nat. Prod.* **1997**, *60*, 889−893. (b) Miyaoka, H.; Nakano, M.; Iguchi, K.; Yamada, Y. *Heterocycles* **2003**, *61*, 189−196.
(5) Hajos, Z. G.; Parish, D. R. *Org. Synth. Col.* **1990**, *7*, 363−368.
(6) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *31*, 1986−2012.
(7) (a) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1963**, *85*, 362−363. (b) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Org. Chem.* **1964**, *86*, 485−492.
(8) (a) Ziegler, K.; Sauer, H.; Brunt, L.; Froitzhelm-Külhorn, H.; Schneider, J. *Ann. Chem.* **1954**, *589*, 122−162. (b) Ziegler, K.; Wilms, H. *Ann. Chemi.* **1950**, *561*, 1−45. (c) Cope A. C.; Pike, R. A.; Spencer, C. F. *J. Am. Chem. Soc.* **1953**, *75*, 3213−3215.
(9) Corey, E. J.; Carey, F. A.; Winter, R. A. E. *J. Am. Chem. Soc.* **1965**, *81*, 934−935.
(10) (a) Cope A. C.; Ganellin, C. R.; Johnson, H. W., Jr.; Van Aulsen, T. V.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1963**, *85*, 3216−3219. (b) Cope, A. C.; Mehta, A. S. *J. Am. Chem. Soc.* **1964**, *86*, 5626−5630.
(11) Corey, E. J.; Schulman, J. I. *Tetrahedron Lett.* **1968**, *9*, 3655−3658.
(12) Cope, A. C.; Banholze, K.; Keller, H.; Pawson, B. A.; Whang, J. J.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1965**, *87*, 3644−3649.
(13) Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1817−1820.
(14) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, *11*, 704.
(15) See Renneberg, D.; Pfander, H.; Leumann, C. J. *J. Org. Chem.* **2000**, *65*, 9069−9079.
(16) Schmidbaur, H.; Stühler, H.; Vornberger, W. *Chem. Ber.* **1972**, *105*, 1084−1086.
(17) For other recent enantioselective approaches to β-caryophyllene, see: (a) Liu, D.; Hong, S.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 8160−8161. (b) Shen R. C.; Corey E. J. *Org. Lett.* **2007**, *6*, 1057−1059.

JA8003705