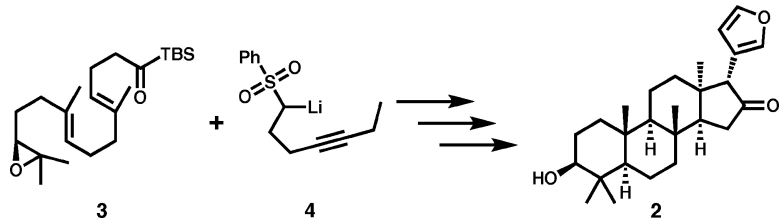
Communication

Simple Enantioselective Approach to Synthetic Limonoids

Douglas C. Behenna, and E. J. Corey

J. Am. Chem. Soc., **2008**, 130 (21), 6720-6721 • DOI: 10.1021/ja802376g • Publication Date (Web): 30 April 2008



More About This Article

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

- Supporting Information
- Links to the 1 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 04/30/2008

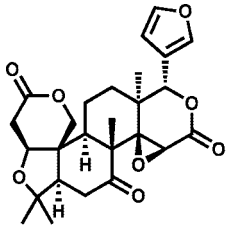
Simple Enantioselective Approach to Synthetic Limonoids

Douglas C. Behenna and E. J. Corey*

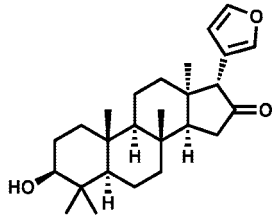
Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

Received April 1, 2008; E-mail: corey@chemistry.harvard.edu

Since the determination of the structure of the citrus bitter principle limonin (**1**) in 1960,[1] the number of structurally defined members of this class of natural products (now called limonoids) has grown to several hundred.[2] Membership in this class is even larger when the numerous glycoside derivatives are counted.



1



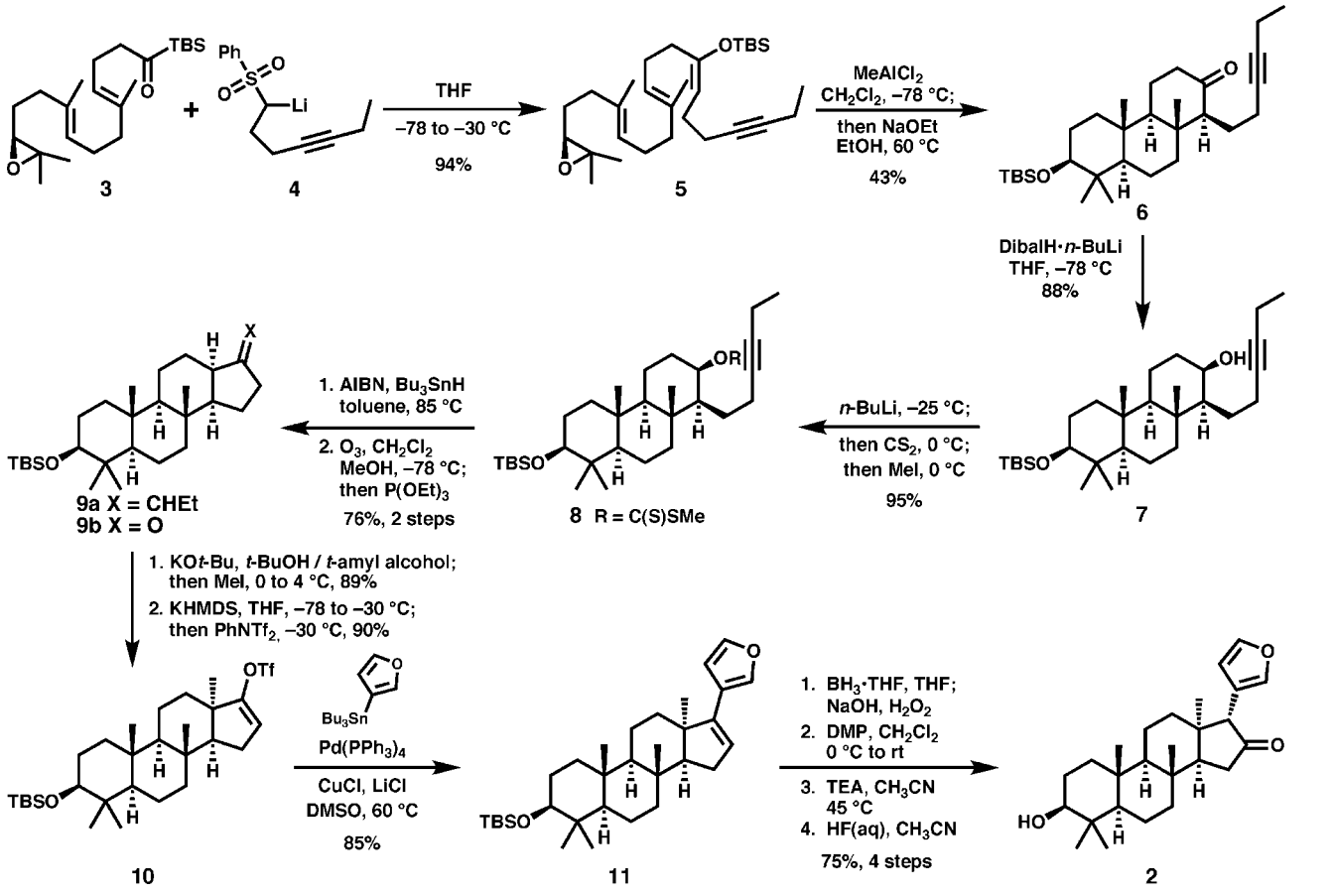
2

The various limonoids represent a structurally very diverse group since they are extensively modified from a simpler precursor in terms of degree and location(s) of oxygenation, ring cleavage, and C−C rearrangement. However, all of these compounds are derivable by such biosynthetic processes from the simpler predecessor **2**. Relatively little effort has been invested in the synthesis of limonoids, which is somewhat surprising in view of their variety, widespread occurrence, and significant biological activity.[3,4]

Some years ago, we published a stereocontrolled synthesis of the racemic limonoid azadiradione.[5] More recently, Ley and coworkers have achieved a noteworthy total synthesis of azadirachtin from the chiral starting material galactose.[6,7] We describe herein the first enantioselective synthesis of a limonoid, the protolimonoid **2**, by a route which is both short and stereocontrolled (Scheme 1).

Our synthesis commences with a one-flask carbonyl addition/Brook rearrangement/elimination[8] reaction to unite all the carbons required for the synthesis of the A−D rings. The known acylsilane **3**,[9] which was generated by a uniquely site-selective and enantioselective dihydroxylation reaction,[10] underwent sequential nucleophilic addition, Brook rearrangement, and elimination upon low temperature reaction with α-lithiosulfone **4**.[11] Epoxy silyl enol ether **5** was produced in excellent yield as a 10:1 mixture (by ^{1}H NMR analysis) favoring the (*E*)-silyl enol ether.[12] Brief exposure of

Scheme 1. Synthesis of Protolimonoid **2**



10.1021/ja802376g CCC: $40.75

epoxide **5** to 1.2 equiv of $MeAlCl_2$ at −78 °C provided two diastereomeric tricyclic ketones in a 1.5:1.0 ratio with ketone **6** as the minor component. The predominating diastereomer in the mixture, in which the appendage α to the carbonyl is axially oriented, could be isomerized to **6** by treatment of the crude mixture with sodium ethoxide in ethanol. Overall, the cationic cyclization and epimerization permit the rapid stereoselective establishment of three rings and five stereocenters in 43% yield.[13]

We next turned our attention to the efficient construction of the D ring. First, ketone **6** was diastereoselectively reduced with the aluminum ate complex formed from DibalH and *n*-BuLi.[14] This reagent provided significantly higher yields of alcohol **7** than DibalH alone (by about 20%). Alcohol **7** was converted to xanthate **8** under standard conditions. Slow addition of a solution of AIBN and Bu_3SnH to a heated solution of xanthate **8** resulted in smooth radical-mediated 5-*exo*-dig cyclization to form **9a** (2:1 ratio of *E/Z* isomers). Ozonolysis of **9a** gave a single ketone, **9b** (*cis* C/D ring junction).

When ketone **9b** was deprotonated under reversible conditions favoring the more stable Δ(13−17) enolate (KO*t*-Bu in *t*-BuOH solvent, 23 °C) and treated with methyl iodide, the required angular methylation occurred with the *cis* C/D fused product predominating (5:1).[15] This selectivity improved to 10:1 when the methylation was performed at a lower temperature (0−4 °C) with *t*-amyl alcohol as solvent. *The dependence of diastereoselectivity on temperature for this methylation is noteworthy.* The angularly methylated tetracyclic ketone was transformed into the corresponding vinyl triflate **10** by deprotonation and subsequent reaction with *N*-phenyl triflimide. Standard Stille coupling conditions were unsatisfactory for attachment of the furan appendage to the hindered vinyl triflate **10**. However, the Cu(I)-promoted Stille reaction developed in these laboratories[16] proved uniquely effective in providing an excellent yield of the required pentacyclic furan **11**.

Introduction of the limonoid carbonyl at C(16) by an epoxidation/rearrangement combination[7a] did not proceed in high yield so we used a hydroboration/oxidation sequence,[17] which provided consistently better yields of the desired ketone. The diastereomeric mixture of α-furyl ketones thus formed was equilibrated under mild basic conditions to give exclusively the desired 17-α-oriented furan. Clean desilylation of the 3-oxygen was achieved with HF to afford protolimonoid **2** in 75% yield overall from furan **11**.

There are a number of aspects of the synthesis of limonoid **2** that require comment, apart from the obvious brevity of the overall process. The tetracyclic core is generated rapidly by a novel combination of cationic triple annulation and free-radical-induced ring closure with control of stereochemistry. The substrate for this highly effective process (**5**) is assembled in a single step from the readily available components **3** and **4**. The chiral component **3**, which contains the critical initiating stereocenter, can be made from achiral ingredients by a highly effective catalytic asymmetric reaction. The difficult problem of ensuring the required *cis* C/D ring fusion is solved in an effective and simple way, as is the stereoselective introduction of the 17-furyl appendage. The value of the powerful bimetallic (Cu, Pd) coupling[16] to overcome the steric barrier to traditional Stille coupling is dramatically illustrated by the formation of **11**. Further, the highly effective introduction of the 16-keto group in **2** provides a solution to the challenge of selective oxidation in the presence of the easily oxidizable 3-furyl appendage. The synthetic technology residing in the sequence outlined in Scheme 1 may be applicable to many other synthetic problems, including the stereocontrolled construction of a range of other limonoids. We call attention to these features of the present synthesis because, so far, very few laboratories have taken advantage of the powerful synthetic tools that have been applied in the present study. In our view, the tandem combination of cationic and radical cyclization can potentially lead to short syntheses of numerous interesting polycyclic molecules.

Supporting Information Available: Experimental procedures for the steps shown in Scheme 1 are given along with characterization data for each product and selected NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Arigoni, D.; Barton, D. H. R.; Corey, E. J.; Jeger, O.; Caglioti, L.; Dev, S.; Ferrini, P. G.; Glazier, E. R.; Melera, A.; Pradhan, S. K.; Schaffner, K.; Sternhell, S.; Templeton, J. F.; Tobinaga, S. *Experientia* **1960**, *16*, 41–49. (b) Arnott, S.; Davie, A. W.; Robertson, J. M.; Sim, G. A.; Watson, D. G. *Experientia* **1960**, *16*, 49–51.

(2) For reviews on the large family of limonoids, see: (a) Roy, A.; Saraf, S. *Biol. Pharm. Bull.* **2006**, *29*, 191–201. (b) Taylor, D. A. H. *Prog. Chem. Org. Nat. Prod.* **1984**, *45*, 1–102. (c) Connolly, J. D.; Overton, K. H.; Polonsky, J. *Prog. Phytochem.* **1970**, *2*, 385–455. (d) Dreyer, D. L. *Prog. Chem. Org. Nat. Prog.* **1968**, *26*, 190–244.

(3) Various limonoids have been reported to possess anti-proliferative, pro-apoptotic, anti-inflammatory, antibiotic, antiviral, antioxidant, insecticidal, and insect antifeedent activity. See, for example: Champagne, D. E.; Koul, O.; Isman, M. B.; Scudder, G. G. E.; Towers, G. H. N. *Phytochemistry* **1992**, *31*, 377–394.

(4) Substantial quantities of limonoids, such as limonoid glycosides, are injested by humans who eat citrus fruits without ill effects.

(5) (a) Corey, E. J.; Reid, J. G.; Myers, A. G.; Hahl, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 918–919. (b) Corey, E. J.; Hahl, R. W. *Tetrahedron Lett.* **1989**, *30*, 3023–3026.

(6) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem., Int. Ed.* **2007**, *46*, 7629–7632.

(7) Fernández-Mateos and his group have described the synthesis of several limonoid analogues and fragments from natural products. See, for example: (a) Fernández-Mateos, A.; Coca, G. P.; Rubio González, R. *Tetrahedron* **2005**, *61*, 8699–8704. (b) Fernández-Mateos, A.; Ramos Silvo, A. I.; Rubio González, R.; Simmonds, M. S. J. *Tetrahedron* **2006**, *62*, 7809–7816. (c) Fernández-Mateos, A.; López Barba, A. M.; Martín de le Nava, E.; Coca; G, P.; Pérez Alonso, J. J.; Ramos Silvo, A. I.; Rubio González, R. *Tetrahedron* **1997**, *53*, 14131–14140.

(8) For previous examples of the Brook rearrangement/olefination sequence, see: (a) Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 9927–9928. (b) Corey, E. J.; Luo, G.; Lin, L. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 1126–1128. (c) Zhang, J.; Corey, E. J. *Org. Lett.* **2001**, *3*, 3215–3216. (d) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290–11291.

(9) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999–10003.

(10) Corey, E. J.; Zhang, J. *Org. Lett.* **2001**, *3*, 3211–3214.

(11) For details involving the synthesis of compound **4**, see Supporting Information.

(12) The *E* geometry of the silyl enol ether **5** was inferred from the synthesis of analogous (*Z*)-silyl enol ethers via a chelated *Z*-allylic lithium reagent; for an example of (*Z*)-silyl enol ether formation, see ref 8d.

(13) The phenylethynyl analogue of substrate **5** was also prepared and subjected to cationic cyclization. However, the cyclization results were considerably inferior to those with **5**.

(14) Kim, S.; Han Ahn, K. *J. Org. Chem.* **1984**, *49*, 1717–1724.

(15) Audouin, M.; Levisalles, *J. Bull. Soc. Chim. Fr.* **1975**, 695–701.

(16) (a) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605. (b) Stoltz, B. M.; Kano, T.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9044–9045.

(17) Brown, H. C.; Gupta, A. K.; Prasad, J. V. N. V. *Bull. Chem. Soc. Jpn.* **1998**, *61*, 93–100.

JA802376G