J|A|C|S
COMMUNICATIONS

Published on Web 10/04/2006

# Total Synthesis of (+)-*cis*-Sylvaticin: Double Oxidative Cyclization Reactions Catalyzed by Osmium

Timothy J. Donohoe,*,† Robert M. Harris,† Jeremy Burrows,‡ and Jeremy Parker§

*Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, U.K., AstraZeneca Pharmaceuticals, Department of Medicinal Chemistry R&D, Södertälje, S-151 85, Sweden, and AstraZeneca, Process R&D Avlon/Charnwood, Avlon Works, Severn Road, Hallen, Bristol, BS10 7ZE, U.K.*

Received August 18, 2006; E-mail: timothy.donohoe@chem.ox.ac.uk

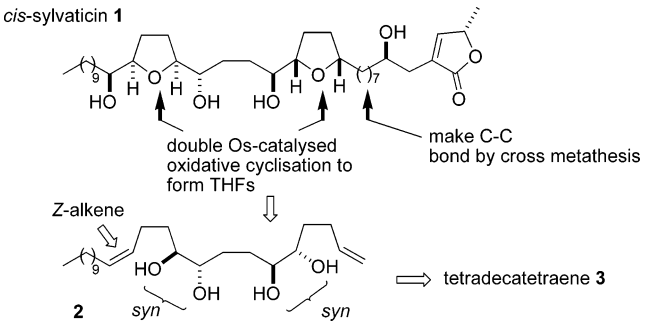
The annonaceous acetogenins are a burgeoning class of natural products that are of interest because of their wide-ranging biological activities.[1] Examples containing multiple tetrahydrofuran (THF) rings are of particular appeal because of the challenges that they pose for synthetic organic chemistry. Within this class of natural product, those containing nonadjacent THF rings are much less commonly studied and only the squamostatins[2] (C and D) and gigantecins[3] (both containing only nonadjacent *trans* disposed THF rings) have been synthesized.

*cis*-Sylvaticin **1**, isolated in 1995 from the leaf extracts of *Rollinia* mucosa (Jacq.) Baill, is an interesting natural product with nonadjacent THF rings (both *cis*, Scheme 1).[4] This compound has not yet been synthesized although the structure was assigned by a comprehensive NMR study by McLaughlin.[4] *cis*-Sylvaticin displays potent activity as an antitumor agent and exhibits nanomolar cytotoxicity toward human solid tumor cell lines: its mode of action is thought to include inhibition of ATP production via blockage of mitochondrial complex I.

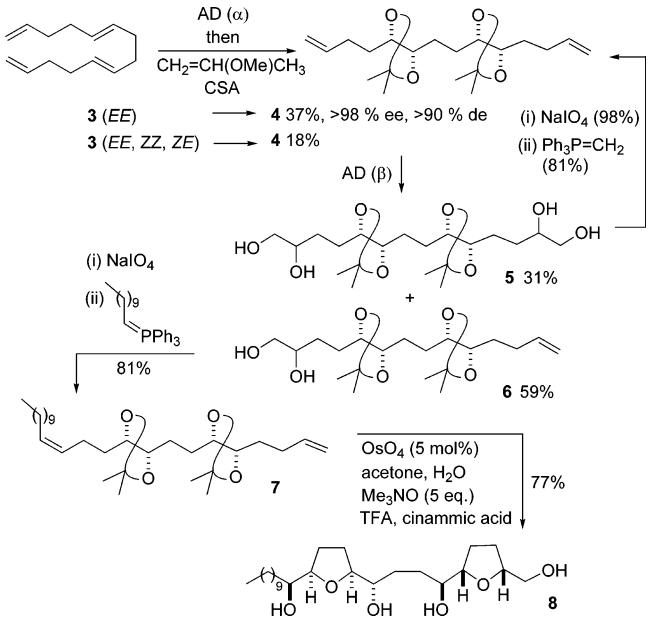
Our synthetic strategy for this target was to divide the molecule into two sections, Scheme 1. The right-hand side containing the butenolide and alkyl chain was to be prepared separately and joined to the main fragment (containing two THF rings) by cross metathesis. The remainder of the molecule would be constructed by double oxidative cyclization on acyclic precursor **2**. This key oxidative cyclization to form two THF rings is based upon methodology that we have reported recently and should proceed with reliable stereospecificity (syn addition across a pendant alkene) and stereoselectivity (*cis*-2,5-THFs are formed).[5] The notion of a *double* oxidative cyclization to form two rings in one reaction would present a serious test of this new method.

The synthesis began with commercial tetradecatetraene **3**, Scheme 2. This compound was available as a mixture of the three possible geometric isomers which could be separated by chromatography on silica gel doped with $AgNO_3$. Oxidation of the pure *EE* isomer under AD conditions gave a tetraol which was immediately converted into bisacetonide **4** in 37% overall yield.[6] The outcome of the AD reaction has its origins in the preferential oxidation of 1,2-*trans*-alkenes over monosubstituted alkenes.[7] This success led us to perform the AD reaction on the commercially available mixture of tetraenes, in the knowledge that *cis*-alkenes are dihydroxylated approximately 11 times slower than *trans*-alkenes.[7] In this case we were able to form the desired tetraol with reasonable selectivity (although the compound could not be fully purified until it was derivatized as bisacetonide **4**). The yield for the two steps to **4** was 18% from

***Scheme 1***




***Scheme 2***



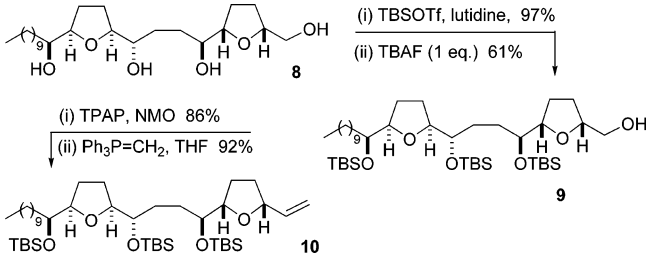

the mixture, but this reaction could be run easily on a multigram scale.

Our next task was to cleave one alkene unit within **4** in the presence of another, which was difficult because they are homotopic. Eventually, oxidation under AD conditions gave 59% of diol **6** and 31% of tetraol **5**, Scheme 2. The undesired tetraol **5** was recycled back into **4** by double oxidative cleavage and methylenation. Meanwhile, diol **6** was cleaved and olefinated to give *Z*-**7** in 81% yield. The key double oxidative cyclization was then attempted on bisacetonide **7**, in the hope that in situ double deprotection would occur allowing cyclization to take place. Pleasingly, bis-THF **8** formed in 77% yield and as a single diastereoisomer.[5] Subsequently, the bis-THF was prepared for cross metathesis by global protection

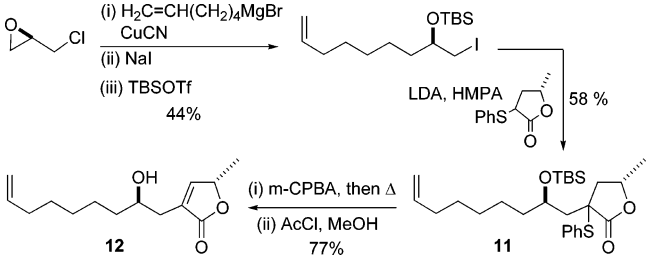
† University of Oxford.
‡ AstraZeneca Pharmaceuticals.
§ AstraZeneca.


10.1021/ja0660148 CCC: $33.50 

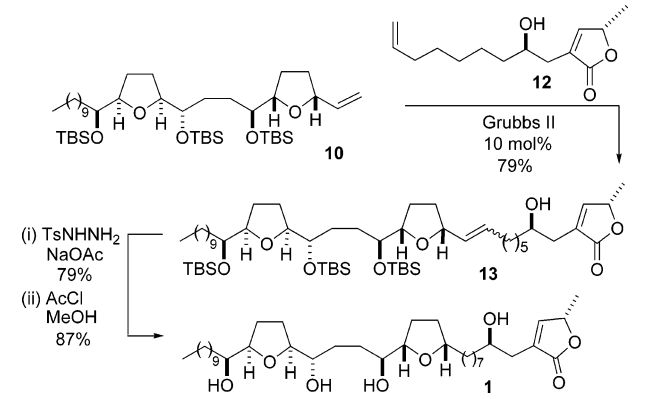
***Scheme 3***




***Scheme 4***




***Scheme 5***




and selective deprotection **9**, followed by oxidation and olefination to furnish **10**, Scheme 3.

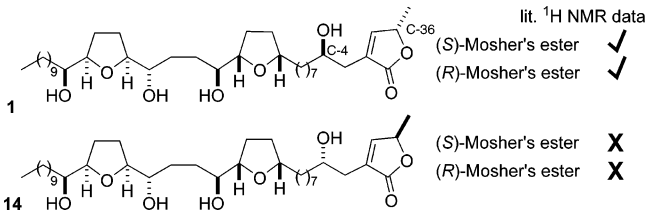
The butenolide fragment of the target was prepared according to the work of Lee, which transformed (*R*)-epichlorohydrin into compound **11** in four steps, Scheme 4.[8] After synthesizing **11**, we prepared **12** for cross-metathesis by introducing the butenolide (thermal elimination) and deprotection of the OTBS group.

The union of the two halves was accomplished by a cross metathesis reaction between **10** and **12**, Scheme 5.[9] Following the work of Lee,[8] we required a 4-fold excess of compound **12** to eradicate homodimerization of bis-THF **10** (at the expense of homodimerization of **12**). Here, our rationale for early removal of the TBS group from **11** becomes clear, because the homodimer of **12** is more polar than the desired compound **13** and thus easy to separate. In addition, the dimerized derivative of **12** can be reused in the cross-metathesis reaction to give **13** in 54% yield.

The synthesis was completed by a diimide reduction of the more symmetrical alkene within **13** and acid promoted deprotection of the three OTBS groups, to furnish *cis*-sylvaticin **1** in 69% yield from **13**. The synthetic material had spectroscopic data ($^1$H and $^{13}$C NMR, $[\alpha]_D$, HRMS) identical to that reported.[4]

As part of final studies to confirm the structure of the natural product and relate the stereochemistry of the bis-THF portion to that of the butenolide, we prepared a series of diastereoisomers of the structure **1**, varying stereochemistry of the butenolide at both C-4 and C-36, Scheme 6.[10] Of the four possible stereoisomers,

***Scheme 6***




compound **14** also had NMR spectra that matched the synthetic and natural product data exactly.[10] However, preparation of both (*R*)- and (*S*)-tetra-Mosher's ester derivatives of **14** and comparison with literature values confirmed that neither it nor its enantiomer was the natural product. Conversely, the tetra-(*R*) and tetra-(*S*) Mosher's ester derivatives of **1** exhibited NMR data that matched that reported in ref 4.

To conclude we have reported the first total synthesis of the natural product *cis*-sylvaticin in a route that is exceptionally concise (13 linear steps and 19 chemical operations in total). The key step in our synthesis was a novel double oxidative cyclization of a tetraol onto two pendant alkene units; this was promoted by catalytic amounts of osmium and the reaction gave complete stereoselectivity and stereospecificity for the double THF product.

**Acknowledgment.** We thank the EPSRC and AstraZeneca for supporting this project. Merck, AstraZeneca, Pfizer, and Novartis are thanked for unrestricted funding. N. Wagner is thanked for assistance and J. L. McLaughlin is thanked for providing copies of the NMR spectra of *cis*-sylvaticin.

**Supporting Information Available:** Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) For a review see (a) Bermejo, A.; Figadére, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, *22*, 269. For recent examples of syntheses see (b) Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 3557. (c) Narayan, R. S.; Borhan, B. *J. Org Chem.* **2006**, *71*, 1416. (d) Tominaga, H.; Maezaki, N.; Yanai, M.; Kojima, N.; Urabe, D.; Ueki, R.; Tanaka, T. *Eur. J. Org. Chem.* **2006**, 1422.

(2) (a) Marshall, J.; Jiang, H. *J. Org. Chem.* **1998**, *63*, 7066. (b) Zhu, L.; Mootoo, D. R. *J. Org. Chem.* **2004**, *69*, 3154.

(3) (a) Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **1998**, *54*, 6329. (b) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790. (c) Hoye, T. R.; Eklov, B. M.; Jeon, J.; Khoroosi, M. *Org. Lett.* **2006**, *8*, 3383.

(4) Shi, G.; Zeng, L.; Gu. Z.; MacDougal, J. M.; McLaughlin, J. L. *Heterocycles* **1995**, *41*, 1785.

(5) (a) Donohoe T. J.; Butterworth, S. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 4766. A sacrificial alkene is added to these cyclizations to dihydroxylate Os(VIII) and form Os(VI), which is a more competent catalyst, in situ. Cinnamic acid was used here because the diol formed from it is polar and easy to separate. See also (b) Walba, D. M.; Stoudt, G. *Tetrahedron Lett.* **1982**, *23*, 727.

(6) The tetrol was analysed as its tetra Mosher's ester and found to be >98% ee; comparison with an authentic sample of a meso tetraol confirmed that it was >95:5 dr in favour of the $C_2$ symmetrical compound.

(7) Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7047. We devised a computer programme which predicted that the maximum yield attainable for double dihydroxylation of the two internal alkenes of *E*,*E*-**3** was 45%, which is close to our best yield of 37%. This model assumes a 7:1 rate difference between the two classes of alkene and a lack of cooperative effects upon rates after a single dihydroxylation.

(8) (a) Keum, G.; Hwang, C. H.; Kang, S. B.; Kim, Y.; Lee, E. *J. Am. Chem. Soc.* **2005**, *127*, 10396. (b) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991. (c) Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876. (d) Avediaaian, H.; Sinha, S. C.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035.

(9) Chatterjee. A. K.; Choi, T. L.-; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

(10) (a) Hoye, T. R.; Hanson, P. R.; Hasenwinkel, L. E.; Ramirez, E. A.; Zhuang, Z. *Tetrahedron Lett.* **1994**, *35*, 8529. (b) Curran, D. P.; Zhang, Q.; Lu, H.; Gudipati, V. *J. Am. Chem. Soc.* **2006**, *128*, 9943.

JA0660148