JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Highly Enantioselective Proton-Initiated Polycyclization of Polyenes

Karavadhi Surendra and E. J. Corey*

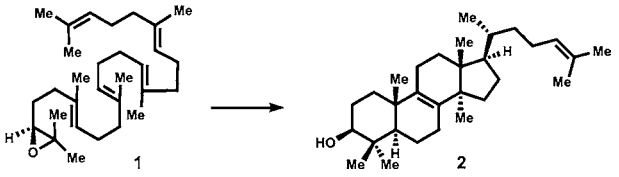
Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138, United States

Supporting Information

ABSTRACT: This report describes the synthesis of a range of chiral polycyclic molecules (tricyclic to pentacyclic) from achiral polyene precursors by enantioselective proton-initiated polycyclization promoted by the 1:1 complex of *o*,*o*′-dichloro-BINOL and $SbCl_5$. Excellent yields (ca. 90% per ring formed) and enantioselectivety (20:1 to 50:1) were obtained. The process is practical as well as efficient, because the chiral ligand is both readily prepared from *R*,*R*- or *S*,*S*-BINOL and easily recovered from the reaction mixture by extraction.

The unmatched synthetic power of the enzymatic conversion of (*S*)-2,3-oxidosqualene (**1**) to polycyclic triterpenoids, as exemplified by the one-step biosynthesis of lanosterol (**2**) shown in Scheme 1, has provided inspiration and challenge to synthetic chemistry.[1,2] Although the synthesis of many polycyclic terpenoids, for instance, the pentacyclic triterpenoid lupeol,[3] has been greatly facilitated by the application of cation−olefin polycyclization, the area clearly requires further development to achieve its full potential.[4]

Scheme 1. Biosynthesis of Lanosterol

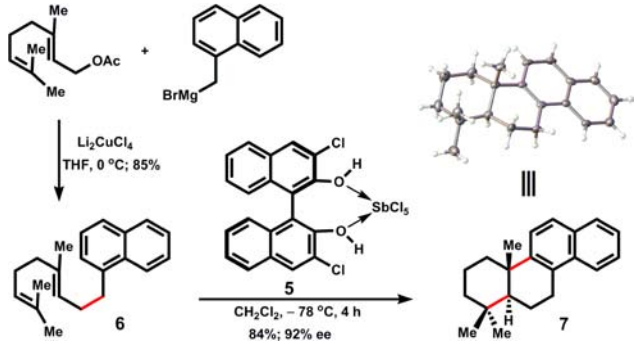


We recently reported that indium(III) iodide or bromide can selectively activate C−C triple bonds and initiate cation−olefin polycyclization, as exemplified by the one-step process **3** → **4** shown in Scheme 2.[5] In this transformation In(III) functions as a proton equivalent, and the initiating propargylic stereocenter controls the absolute configuration of the product, which is formed with complete diastereoselectivity. As a result of this research we were encouraged to search for a strongly acidic, chiral proton source that might both selectively activate the terminal C−C double bond of a polyene and control the absolute configuration of the product. We were aware of the findings of Yamamoto's group that complexes of the BINOL monoether type with $SnCl_4$ can initiate cation−olefin cyclization with modest enantioselectivity.[6]

Scheme 2. In(III)-Catalyzed Enantioselective Cationic Polycyclization

Our approach was guided by the conjecture that the enantioselectivity and terminal C=C selectivity of cation−polyolefin cyclization might be improved by the use of a bulkier and stronger Lewis acid than $SnCl_4$. It was also surmised that there might be additional benefit in increasing the acidity of the BINOL derivative. Thus, we arrived at *o*,*o*′-dichloro-BINOL[7] as ligand and $SbCl_5$ as the Lewis acid **5**. We were very gratified to find that the 1:1 complex of these simple components was indeed a much stronger and more enantioselective polycyclization catalyst than those previously studied. The reactions reported herein with the new catalyst occurred rapidly at −78 °C and provided the polycyclic product with remarkable enantioselectivity, generally in the range 20−50:1. A typical example of such cyclization is shown in Scheme 3.

Scheme 3. Synthesis of Chiral Tetracycle



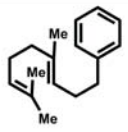
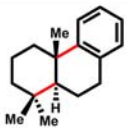
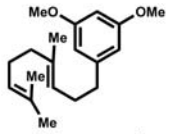
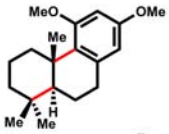
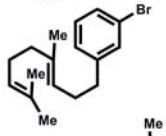
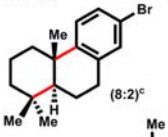
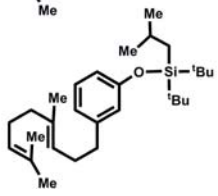
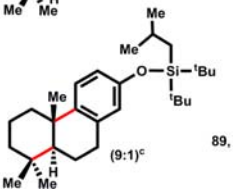
The results for the *R*,*R*-**5**-catalyzed cyclization of an additional eight substrates are summarized in Table 1 for four cases of bicyclization and Table 2 for four tricyclization reactions. Absolute stereochemistry was established by X-ray crystallographic analysis of the tetracyclic reaction product, mp 110−112 °C, which was formed diastereoselectively in 84% yield.[8] The absolute configurations for the other products shown in Tables 1 and 2 (all from *R*,*R*-**5**) were assigned by analogy. In addition, the optical rotation of the product in Table 1, entry 1, was close to that reported for a 4-methylphenyl analogue of **6**.[6]

Received: June 19, 2012
Published: July 10, 2012

ACS Publications © 2012 American Chemical Society

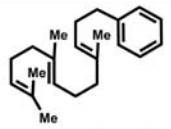
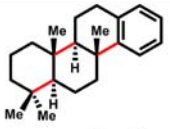
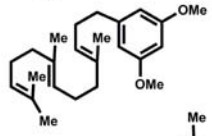
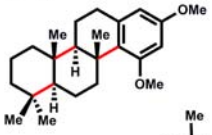
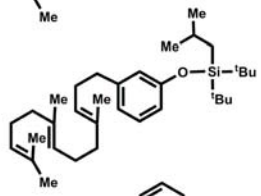
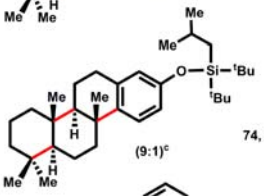
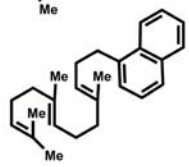
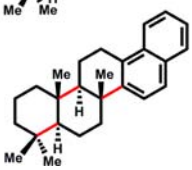
dx.doi.org/10.1021/ja305851h | *J. Am. Chem. Soc.* 2012, 134, 11992−11994

Table 1. (*R*)-BINOL-$SbCl_5$ (0.5 equiv)-Catalyzed Polycyclization in CH_2Cl_2 at −78 °C

Entry	Substrate	Product	Yield,[a] ee,%[b]
1			80, 91
2			85, 87
3		 (8:2)[c]	82, 90
4		 (9:1)[c]	89, 92

[a]Isolated yields of products fully characterized by NMR and MS. [b]ee determined by HPLC analysis using a Chiralcel OD-H column. [c]Cyclization occurred both *para* and *ortho* to Br.

Table 2. (*R*)-BINOL-$SbCl_5$ (1.0 equiv)-Catalyzed Polycyclization in CH_2Cl_2 at −78 °C

Entry	Substrate	Product	Yield,[a] ee,%[b]
1			70, 90
2			76, 84
3		 (9:1)[c]	74, 90
4			78, 86

[a]Isolated yields of products fully characterized by NMR and MS. [b]ee determined by HPLC analysis using a Chiralcel OD-H column. [c]Cyclization occurred both *para* and *ortho* to OR.

The various substrates for these cyclization studies were obtained starting with geraniol or farnesol acetate by the type of copper-catalyzed cross-coupling shown in Scheme 3 for the synthesis of the cyclization precursor **6**. Cyclizations were carried out at −78 °C in CH_2Cl_2 with reaction times in the range of 4−6 h, using thin-layer chromatographic analysis to follow the progress of the reaction. From 50 to 100 mol % of catalyst was used. The ligand for **5** was easily removed from the crude cyclization product by extraction with aqueous sodium hydroxide, and recovered (>95%) simply by acidification and extraction. Thus, the use of *o*,*o*′-dichloro-BINOL, which is readily made from BINOL,[7] is practical even at 100 mol %.

The $SbCl_5$ complex **5** is far superior as an enantioselective proton donor in the type of cyclization described herein to the corresponding complexes with In(III), Al(III), or Ti(IV) in terms of reaction rate and enantioselectivity. It was also ascertained that *o*,*o*′-dimethyl-BINOL and *o*,*o*′-diphenyl-BINOL were unsatisfactory as catalysts, leading to much diminished enantioselectivities.

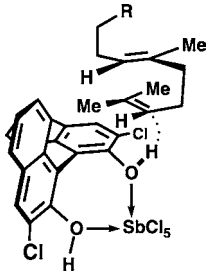


Figure 1. Pre-transition-state assembly for the cationic cyclization initiated by proton transfer from catalyst **5**.

The $SbCl_5$ complex **5** may be of value for other proton-accelerated reactions in which stereocenters are created from achiral starting materials, and studies along these lines are in progress. The absolute stereochemical course of the cyclizations described herein can be explained rationally in terms of a concerted protonation and cyclization process[9] in which the terminal C=C is protonated *π*-face-selectively by **5** with a *π*−*π* intraction between the developing cation and one of the naphthyl subunits of **5** (see Figure 1).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^1H and ^{13}C NMR spectra and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

corey@chemistry.harvard.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Pfizer Inc. for a postdoctoral fellowship to K. S. and to Dr. S.-L. Zheng from Harvard University and Dr. Y.-S. Chen at ChemMatCARS, APS, for the X-ray crystallographic analysis.

■ REFERENCES

(1) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812.

(2) For a recent discussion, see: Kürti, L.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 9031.

(3) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 13928.

(4) For recent reviews, see: (a) Corey, E. J.; Kürti, L. *Enantioselective Chemical Synthesis*; Direct Book Publishing: http://

directbookpublishing.com/, 2010; pp 276−311. (b) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.
(5) Surendra, K.; Qiu, W.-W.; Corey, E. J. *J. Am. Chem. Soc.* **2011**, *133*, 9724.
(6) (a) Ishihara, K.; Nakamura, S.; Yamamoto, H *J. Am. Chem. Soc.* **1999**, *121*, 4906. (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H *J. Am. Chem. Soc.* **2001**, *123*, 1505. (c) Ishibashi, H.; Ishihara, K.; Yamamoto, H *J. Am. Chem. Soc.* **2004**, *126*, 11122.
(7) Turner, H, M.; Patel, J.; Niljianskul, N.; Chong, J. M. *Org. Lett.* **2011**, *13*, 5796.
(8) See the Supporting Information for details.
(9) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc.* **1998**, *120*, 3526.