ORGANIC LETTERS

2002
Vol. 4, No. 4
593−595

Concise, Regioselective Synthesis of the ABC Tristetrahydropyran of Thyrsiferol and Venustatriol

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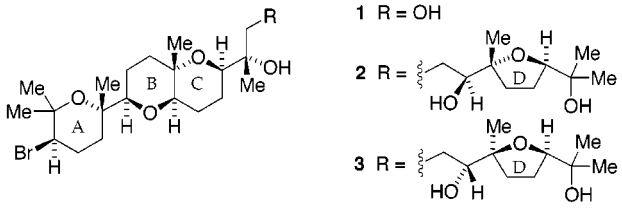
Received December 8, 2001

ABSTRACT



The ABC tristetrahydropyran substructure 1 of the natural products thyrsiferol (2) and venustatriol (3) has been synthesized in 14 steps from farnesyl acetate, with effective control of all aspects of regio- and stereoselectivity in the formation of each tetrahydropyran ring.

The marine natural product polycyclic ethers thyrsiferol[1] and venustatriol,[2] isolated from the red algae genus *Laurencia* from both Pacific and Atlantic Ocean sources, exhibit interesting biological activities ranging from antiviral to potent cytotoxic activities. These compounds and a host of recently characterized congeners[3] are biogenetically derived from the parent C_{30} triterpene squalene, with cyclic ether formation arising from a variety of brominative or oxidative cyclizations of this polyene precursor. These natural product structures have been the subject of synthetic activity, with total syntheses recorded by the laboratories of Corey,[4] Shirahama,[5] and Forsyth.[6]

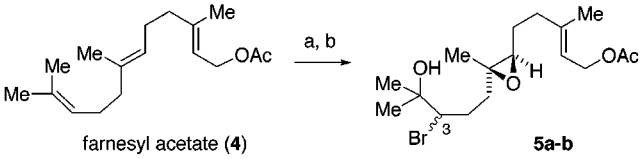
A challenge not completely solved in these syntheses or related synthetic approaches[7] includes regioselective synthesis of the bromotetrahydropyran A ring. Despite encouraging precedents in methodology developed by Kato,[8] which described the use of 2,2,6,6-tetrabromocyclohexa-2,5-dien-1-one for brominative *endo*-regioselective cyclization of hydroxyalkenes, the application of this reagent to similar ring formation of the A ring of thyrsiferol/venustatriol has consistently resulted in poor regioselectivity and modest stereoselectivity.[9] In line with our long-standing interests in regio- and stereoselective oxacyclizations of hydroxyalkene[10] and hydroxyepoxide[11] compounds, we have explored a novel strategy for the synthesis of the thyrsiferol and venustatriol natural products.

The substrate required for synthesis of the A and B rings was prepared from commercially available farnesyl acetate (**4**), by regioselective synthesis of the racemic bromohydrin[12]

(1) Blunt, J. W.; Hartshorn, M. P.; McLennan, T. J.; Munro, M. H. G.; Robinson, W. T.; Yorke, S. C. *Tetrahedron Lett.* **1978**, *19*, 69.
(2) Sakemi, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1986**, *27*, 4287.
(3) For a review, see: Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235.
(4) Corey, E. J.; Ha, D.-C. *Tetrahedron Lett.* **1988**, *29*, 3171.
(5) Hashimoto, M.; Kan, T.; Nozaki, K.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *J. Org. Chem.* **1990**, *55*, 5088.
(6) González, I. C.; Forsyth, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 9099.
(7) (a) Jung, M. E.; Fahr, B. T.; D'Amico, D. C. *J. Org. Chem.* **1998**, *63*, 2982. (b) Broka, C. A.; Lin, Y. T. *J. Org. Chem.* **1988**, *53*, 5876.
(8) Kato, T.; Ichinose, I.; Hosogai, T.; Kitahara, Y. *Chem. Lett.* **1976**, 1187.
(9) González and Forsyth (ref 6) reported oxymercuration of a racemic cyanohydrin-alkene substrate, resulting in regio- and diastereoselective synthesis of racemic bromotetrahydropyran A ring.
(10) McDonald, F. E.; Towne, T. B.; Schultz, C. C. *Pure Appl. Chem.* **1998**, *70*, 355.
(11) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917.

10.1021/ol0171968 CCC: $22.00
Published on Web 01/29/2002

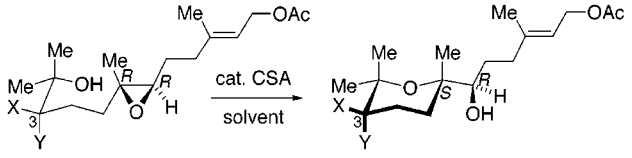
Scheme 1. Synthesis of Bromohydrin-Epoxide **5a-b**[a]



[a] (a) NBS, THF−H_2O (4:1), 0 °C (67%). (b) 0.3 equiv Shi catalyst, Oxone, DMM−MeCN−H_2O, pH 10.5, −10 °C (58%).

followed by regioselective and enantioselective epoxidation[13] of the internal alkene to give bromohydrin-epoxide **5a-b** as an inseparable mixture of diastereomers (Scheme 1).[14] Acid-catalyzed cyclization of **5a-b** proceeded with complete *exo*-regioselectivity for tetrahydropyran formation. Although cyclization in polar solvents such as acetone or THF provided a diastereomeric mixture of the bromotetrahydropyrans **6a** and **6b** (Table 1), we could achieve effective kinetic

Table 1. Solvent Effects on Kinetic Resolution/Cyclization of Bromohydrin-Epoxide **5a-b** to Bromotetrahydrofuranyl Alcohol **6a**

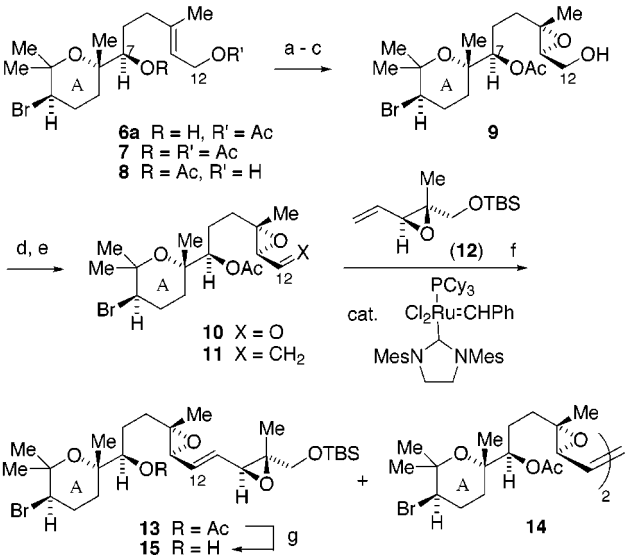


solvent	temp (°C)	ratio **6a**:**6b**	yield of **6** (%)
acetone	22	50:50	65
THF	22	75:25	48
diethyl ether	22	90:10	41
diethyl ether	19	100:0	50

resolution when the acid-catalyzed cyclization of **5a-b** was conducted in diethyl ether. Careful control of the reaction temperature and time resulted in the formation of only one diastereomer, **6a**, which was produced in the maximum theoretical yield (50% isolated yield).[15]

The A ring cyclization product **6a** was converted into the epoxyalcohol **9** by a straightforward sequence of acylation of the secondary alcohol, selective saponification of the primary acetate, and Sharpless asymmetric epoxidation[16]

Scheme 2. Preparation of Diepoxy-*trans*-Alkene **15**[a]



[a] (a) Ac_2O, Et_3N (92%). (b) LiOH, MeOH−H_2O (93%). (c) *t*-BuOOH, cat. Ti(O-*i*-Pr)$_4$, cat. (+)-diethyl tartrate, CH_2Cl_2, −20 °C (99%). (d) SO_3-py, DMSO, Et_3N (85%). (e) $Ph_3P{=}CH_2$, THF (84%). (f) 3 equiv **12**, 10% Ru catalyst, CH_2Cl_2 (44% + 20% with recycle). (g) LiOH, MeOH−H_2O (79%).

(Scheme 2). The diastereomeric purity of **9** was determined to be >95%, indicating that both the Sharpless and Shi epoxidations proceeded with high enantioselectivity. To favor *endo*-regioselectivity in the formation of the B ring and to provide a handle for alkene metathesis homologation leading to the C ring, the alcohol of **9** was oxidized to the aldehyde **10**, which was converted into the vinyl epoxide **11**. Alkene cross-metathesis[17,18] of **11** with 3 equiv of the vinyl epoxide **12**[19] proceeded to provide the diepoxy-*trans*-alkene **13** (44%) along with the metathesis homodimer **14** and unreacted **11**. The total isolated yield of **13** was increased to 64% by reacting the recovered mixture of **11** and homodimer **14** with additional **12** in the presence of the metathesis catalyst to provide 20% additional yield of **13**. Saponification of the acetate of **13** provided the hydroxydiepoxide **15**.

Acid-catalyzed cyclization of the hydroxydiepoxide **15** proceeded with excellent *endo*-regioselectivity for the tetrahydropyran B ring. The desired regioselectivity in product **16** is undoubtably facilitated by the C_{12}-alkene (Scheme 3).[20] Diimide hydrogenation[21] of the alkene followed by removal of the silyl ether afforded the epoxydiol **18**, which underwent cyclization of the C ring to provide tricyclic product **1** by

(12) (a) van Tamelen, E. E.; Stormi, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.* **1963**, *85*, 3295. (b) Hanzlik, R. P. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 560. (c) Gonzalez, A. G.; Martin, J. D.; Perez, C.; Ramirez, M. A.; Ravelo, F. *Tetrahedron Lett.* **1980**, 187.

(13) Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

(14) The unreacted alkene of **5a-b** is deactivated towards epoxidation by the electron-withdrawing acetoxymethylene substituent.

(15) The unreacted 3*S*,6*R*,7*R*-diastereomer **5b** was easily separated from cyclization product **6a** and was isolated in 30% yield.

(16) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(17) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58.

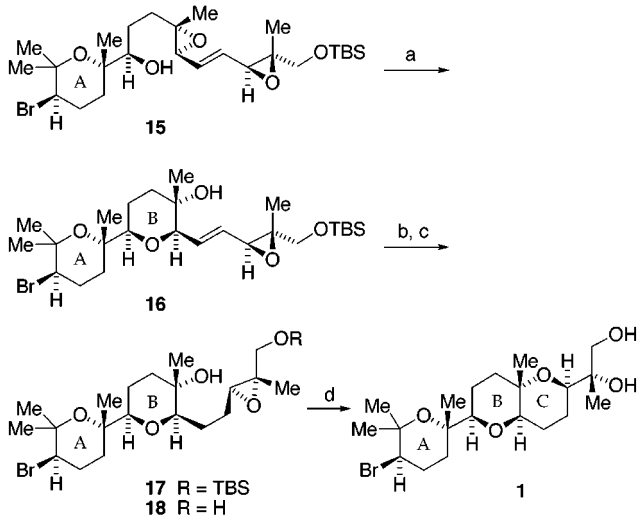
(18) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831.

(19) Vinylepoxide **12** was prepared in two steps from 2-methyl-2,4-pentadien-1-ol (Piers, E.; Jung, G. L.; Ruediger, E. H. *Can. J. Chem.* **1987**, *65*, 670): (a) *t*-BuOOH, cat. Ti(O-*i*-Pr)$_4$, cat. (+)-diethyl tartrate, CH_2Cl_2, −20 °C (89%); (b) TBDMSCl, imidazole, DMF (100%).

(20) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(21) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91.

Scheme 3. Cyclizations of the B and C rings of tricyclic **1**



[a] (a) cat. PPTs, CH_2Cl_2, 0 °C, 1 h (70%). (b) H_2NNH_2, H_2O_2, EtOH, 30 h (70%). (c) Bu_4NF, THF (90%). (d) Ti(O-*i*-Pr)$_4$, toluene, 50 °C, 2 h (58%).

activation of the glycidol moiety of **18** with titanium tetraisopropoxide.[5,22] Our synthetic product **1** matched the spectral data reported for the same compound prepared earlier by the laboratory of Shirahama.[5]

In conclusion, we have developed a synthetic approach that forms each of the three tetrahydropyran rings of thyrsiferol/venustatriol with excellent control of all aspects of regio- and stereoselectivity. The synthesis of advanced synthetic intermediate **1** proceeds in 14 steps from commercially available farnesyl acetate (1.5% overall yield), with several notable transformations including the apparently unprecedented kinetic resolution-cyclization of one diastereomer of the bromohydrin-epoxide **5a** and the cross-metathesis coupling of vinyl epoxides **11** and **12**.

Acknowledgment. We thank the National Science Foundation (CHE-9982400) for support of this research. We also acknowledge the use of shared instrumentation (NMR spectroscopy, mass spectrometry) provided by grants from the National Institute of Health, National Science Foundation, and the Georgia Research Alliance.

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

OL0171968

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