Stereoselective Synthesis of Polysubstituted Tetrahydrofurans by Radical Cyclization of Epoxides Using a Transition-Metal Radical Source. Application to the Total Synthesis of (±)-Methylenolactocin and (±)-Protolichesterinic Acid

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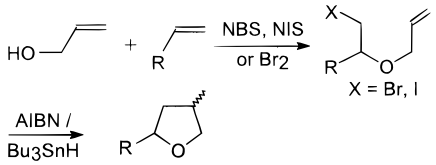
Radical cyclization reactions of substituted α-(prop-2-ynyloxy) epoxides using bis(cyclopentadienyl)-titanium(III) chloride as the radical source resulted in polysubstituted tetrahydrofurans. Titanium(III) species were prepared in situ from commercially available titanocene dichloride and zinc dust in tetrahydrofuran. Upon radical cyclization, 2-aryl epoxides **3a**−**e** afforded only trans products **4a**−**e** whereas the 2-alkyl epoxides **3f**−**h** formed a mixture of isomeric products **4f**−**h** in a ratio of 5:1. Some of the aryl tetrahydrofuran derivatives have already been used for the synthesis of bioactive furofuran lignans. 2-Pentyl-3-(hydroxymethyl)-4-methylenetetrahydrofuran (**4f**) and 2-tridecyl-3-(hydroxymethyl)-4-methylenetetrahydrofuran (**4g**) have been transformed to two antitumor antibiotics (±)-methylenolactocin (**1f**) and (±)-protolichesterinic acid (**1g**), respectively, in good overall yield.

Introduction

The explosive growth in free radical chemistry in recent years reflects its significance as a powerful tool in modern synthetic chemistry.[1] The mildness and regio- and stereoselectivities of the 5-hexenyl radical cyclization have been extensively used[2] for the construction of carbocyclic as well as oxacyclic compounds leading to cyclopentane and tetrahydrofuran derivatives, respectively. Although there are several methods available in the literature for intramolecular radical cyclizations, a bromoalkene or a bromoalkyne has extensively been used as a radical precursor[3] (Scheme 1). Newer methods for the preparation of radical precursors required for the intramolecular radical cyclizations are still desirable.

Scheme 1



Epoxides are vastly used as building blocks for organic synthesis due to their ready availability and facile substitution reactions with predictable stereochemistry.[4] Rajanbabu and Nugent have successfully established[5] the selective one-electron reduction of an epoxide to a radical intermediate which represents an invaluable synthetic tool as the intermediate radical can be trapped in subsequent reactions (Scheme 2).

Thus, epoxides can provide an excellent source of functionalized radicals.[6] The regio- and stereochemistries of the epoxide cleavage via C−O homolysis are guided by the relative stability of the intermediate radicals rather than the ease of approach to the epoxide termini. Very recently Engman and Gupta reported[7] the ring opening of epoxides by arenetellurolate or arene-

(1) For a general review and books, see: (a) Giese, B. *Radical in Organic Synthesis: Formation of C-C bonds*; Pergamon Press: Oxford, 1986. (b) Curran, D. P. *Synthesis* **1988**, p 417 and 489. (c) Regitz, M., Giese, B., Eds. *Houben-Weyl, Methoden der Organischen Chemie*; band E19a, C-Radikale, Teil 1+2; Georg Tieme Verlag: Stuttgart, 1989. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 715 and 779. (e) Motherwell, W. B.; Crich, D. *Free Radical Chain Reactions in Organic Synthesis*; Academic Press: New York, 1992. (f) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley: New York, 1995.

(2) See for example: Ladlow, M.; Pattenden, G. *Tetrahedron Lett.* **1984**, *25*, 4317. Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. Moriya, O.; Kakihana, M.; Urata, Y.; Sugizaki, T.; Kageyama, T.; Ueno, Y.; Endo, T. *J. Chem. Soc., Chem. Commun.* **1985**, 1401. Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. Bhandal, H.; Pattenden, G.; Russell, J. J. *Tetrahedron Lett.* **1986**, *27*, 2299. Pezechk, M.; Brunetiere, A. P.; Lallemand, J. Y. *Tetrahedron Lett.* **1986**, *27*, 3715. Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1351. Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384. Morikawa, T.; Nishiwaki, T.; Iitaka, Y.; Kobayashi, Y. *Tetrhedron Lett.* **1987**, *28*, 671. Hutchinson, J. H.; Pattenden, G.; Myers, P. L. *Tetrahedron Lett.* **1987**, *28*, 1313. Begby, M. J.; Bhandal, H.; Hutchinson, J. H.; Pattenden, G. *Tetrahedron Lett.* **1987**, *28*, 1317. Keck, G. E.; Burnett, D. A. *J. Org. Chem.* **1987**, *52*, 2958. Audin, C.; Lancelin, J.-M.; Beau, J.-M. *Tetrahedron Lett.* **1988**, *29*, 3691. Harrison, T.; Pattenden, G.; Myers, P. L. *Tetrahedron Lett.* **1988**, *29*, 3869. De Mesmalker, A.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* **1989**, *30*, 57. Chapleur, Y.; Moufid, N. *J. Chem. Soc., Chem. Commun.* **1989**, 39. Bonini, C. *Tetrahedron Lett.* **1990**, *31*, 5369. Ishiyama, T.; Murata, M.; Suzuki, A.; Miyaura, N. *J. Chem. Soc., Chem. Commun.* **1995**, 295. Srikrishna, A.; Viswajanani, R.; Sattigeri, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 469. Srikrishna, A.; Viswajanani, R.; Yelamaggad, C. V. *Tetrahedron Lett.* **1995**, *36*, 1127. Giese, B.; Kopping, B.; Gobel, T.; Dickhauf, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301.

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(5) Rajanbabu, T. V.; Nugent, W. A. *J. Am. Chem. Soc.* **1994**, *116*, 986 and references therein.

(6) Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181. Merlic, C. A.; Xu, D. *J. Am. Chem. Soc.* **1991**, *113*, 9855. Rawal, V. H.; Dufour, C. *J. Am. Chem. Soc.* **1994**, *116*, 2613.

(7) Engman, L.; Gupta, V. *J. Org. Chem.* **1997**, *62*, 157.

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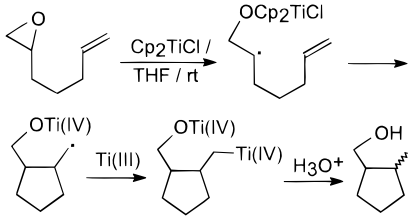
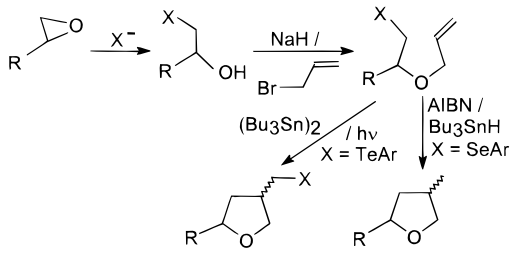
Scheme 2

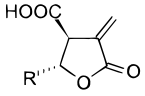


Scheme 3



selenide ion and the preparation of tetrahydrofuran derivatives by a hexabutyltin/light-induced group transfer cyclization reaction of the O-allylated telluride and Bu_3SnH-induced radical cyclization of selenide precursors (Scheme 3).

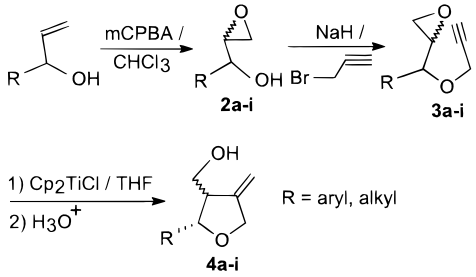
Although the intramolecular radical cyclizations of epoxides using a titanium radical source were reported for the synthesis of cyclopentane derivatives years ago,[5] application toward the stereoselective preparation of polysubstituted tetrahydrofuran derivatives or natural products are still unexplored. We report here a full account[8] of the stereoselective synthesis of polysubstituted tetrahydrofuran derivatives some of which are valuable precursors for biologically active furano lignans.[9] This epoxide radical cyclization strategy has also been applied to the total synthesis of two densely functionalized antitumor antibiotics, (±)-methylenolactocin (**1f**)[10] and (±)-protolichesterinic acid (**1g**).[11] Compound **1f** was



1f, R = C_5H_{11}; Methylenolactocin
1g, R = $C_{13}H_{27}$; Protolichesterinic acid

isolated from the culture filtrate of *Pencillium* sp., and it shows selective antibacterial activity against Gram-positive bacteria.[12] Protolichesterinic acid (**1g**) was isolated from various types of moss Cetraria[13] and found to be effective in inhibiting the growth of Gram-positive bacteria.

Scheme 4



Results and Discussion

Preparation of Epoxides and Propargylation of Epoxy Alcohols. Epoxy alcohols **2** were prepared from the corresponding vinyl alcohols by treatment with MCPBA in $CHCl_3$.[14] The epoxides **2a**−**h** were found to be a mixture of two isomers in a ratio of 1:1. The ratio was determined from the ^1H NMR signals for the proton adjacent to the hydroxy group, e.g., for **2a** the particular signals appeared as two multiplets at δ 4.88 for one isomer and at δ 4.44 for the other. Epoxide **2i** was isolated as a single isomer. Since the isomers in **2a**−**h** could not be separated by usual chromatographic methods, the mixture of isomers was used for the propargylation step (Scheme 4). The epoxy alcohols **2a**−**i** were O-prop-2-ynylated by treatment with propargyl bromide in the presence of NaH in THF−DMSO (10:1) to furnish **3a**−**h** (Table 1) as an inseparable mixture of two isomers in a ratio of 1:1 and **3i** as a single isomer. These prop-2-ynylated derivatives **3a**−**i** were used as precursors to 3-oxa-5-hexynyl radicals finally leading to polysubstituted tetrahydrofurans. Since the isomers could not be separated by usual chromatographic methods, the crude isomeric mixtures were used for the radical cyclization reactions.

Radical Cyclizations of Epoxides Using a Titanium Radical Source. For homolytic cleavage of epoxides, a titanium(III) reagent, bis(cyclopentadienyl)-titanium(III) chloride,[5] was used at room temperature. The reagent was easily generated in situ from inexpensive Cp_2TiCl_2 and is compatible with many organic functional groups. A satisfactory reagent can be prepared by stirring a red THF solution of Cp_2TiCl_2 with activated Zn dust (eq 1). After 15 min, the solution turns lime green and the formation of Cp_2TiCl is complete.

$$2Cp_2TiCl_2 + Zn \rightarrow 2Cp_2TiCl + ZnCl_2 \qquad (1)$$

In a preliminary experiment, 2 molar equiv of Cp_2TiCl in THF was added dropwise to a THF solution of the epoxide **3a**. The initial green color of the titanium(III) species instantly discharged to red upon exposure to the epoxide. Quenching the mixture with 10% H_2SO_4 in H_2O afforded the tetrahydrofuran **4a** in 71% yield as a single isolable product (Scheme 5). This cyclization/protonolysis was applied to a series of substituted epoxyalkynes containing synthetically useful functionalities. The results are tabulated in Table 1. It is noteworthy that the α-aryl epoxides **3a**−**e** upon radical cyclization formed only trans products (**4a**−**e**) whereas the α-alkyl epoxides **3f**−**h** led to an inseparable mixture of two isomeric products (**4f**−**h**), in a ratio of 5:1. The ratio of the isomers

(8) For preliminary communication, see: Maiti, G.; Roy, S. C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 403.
(9) Adhikari, S.; Roy, S. *Tetrahedron Lett.* **1992**, *33*, 6025. Maiti, G.; Adhikari, S.; Roy, S. C. *Tetrahedron Lett.* **1994**, *35*, 3985. Maiti, G.; Adhikari, S.; Roy, S. C. *Tetrahedron Lett.* **1994**, *35*, 6731. Maiti, G.; Adhikari, S.; Roy, S. C. *Tetrahedron* **1995**, *51*, 8389.
(10) (a) Azevedo, de M. B. M.; Murta, M. M.; Greene, A. E. *J. Org. Chem.* **1992**, *57*, 4567. (b) Zhu, G.; Lu, X. *J. Org. Chem.* **1995**, *60*, 1087. (c) Vaupel, A.; Knochel, P. *Tetrahedron Lett.* **1995**, *36*, 231. Sarkar, S.; Ghosh, S. *Tetrahedron Lett.* **1996**, *37*, 4809.
(11) (a) Murta, M. M.; Azevedo, de M. B. M.; Greene, A. E. *J. Org. Chem.* **1993**, *58*, 7587. (b) Sibi, M. P.; Despande, P. K.; Loggia, La A. J. *Synlett* **1996**, 343.
(12) Park, B. K.; Nakagawa, M.; Hirota, A.; Nakayama, M. *J. Antibiot.* **1988**, *41*, 751.
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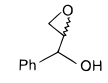
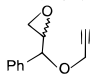
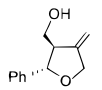
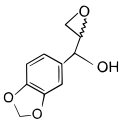
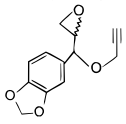
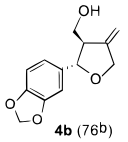
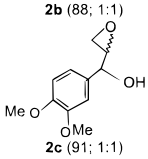
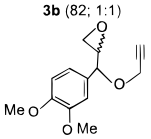
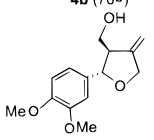
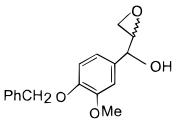
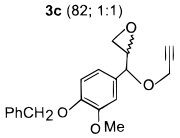
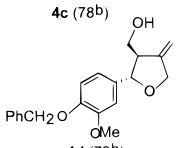
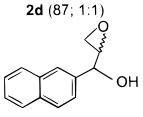
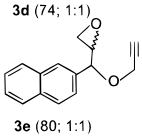
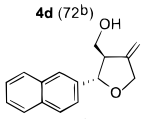
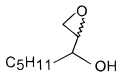
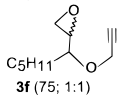
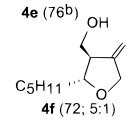
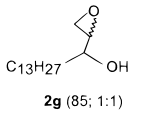
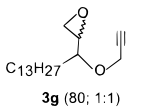
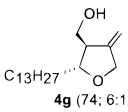
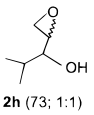
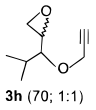
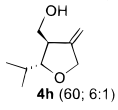
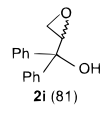
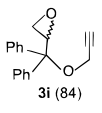
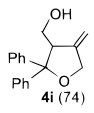
(14) Chavdarian, C. G.; Heathcock, C. H. *Synth. Commun.* **1996**, *6*, 277.

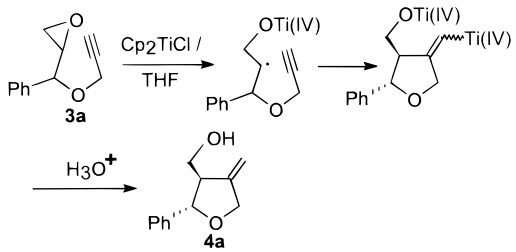
Table 1. Radical Cyclization of Epoxides Using Titanium(III) Radical Source

Epoxy alcohols **2** (% yield[a]; threo/erythro ratio)	O-prop-2-ynylated epoxides **3** (% yield[a]; threo/erythro ratio)	Radical cyclization products **4** (yield[a]; trans/cis ratio)
 **2a** (90; 1:1)	 **3a** (76; 1:1)	 **4a** (71[b])
 **2b** (88; 1:1)	 **3b** (82; 1:1)	 **4b** (76[b])
 **2c** (91; 1:1)	 **3c** (82; 1:1)	 **4c** (78[b])
 **2d** (87; 1:1)	 **3d** (74; 1:1)	 **4d** (72[b])
 **2e** (88; 1:1)	 **3e** (80; 1:1)	 **4e** (76[b])
 **2f** (80; 1:1)	 **3f** (75; 1:1)	 **4f** (72; 5:1)
 **2g** (85; 1:1)	 **3g** (80; 1:1)	 **4g** (74; 6:1)
 **2h** (73; 1:1)	 **3h** (70; 1:1)	 **4h** (60; 6:1)
 **2i** (81)	 **3i** (84)	 **4i** (74)

[a]yields refer to chromatographically pure isolated products. [b]isolated as a pure single isomer.

in **4f**−**h** was determined from two distinguishable multiplets in the ^{1}H NMR spectra for 3-H, e.g., for **4h** two multiplets centered at δ 2.45 for the major isomer and at δ 2.65 for the minor one.

Scheme 5



Since two isomers could not be separated, it was not clear at this stage which isomer is which. The observed stereochemistries of the products can be rationalized by invoking well-known conformational effects in the intermediates.[15,16] It is well established that the intimate

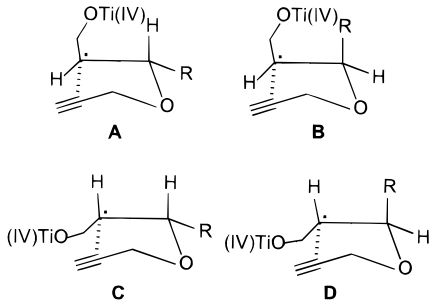


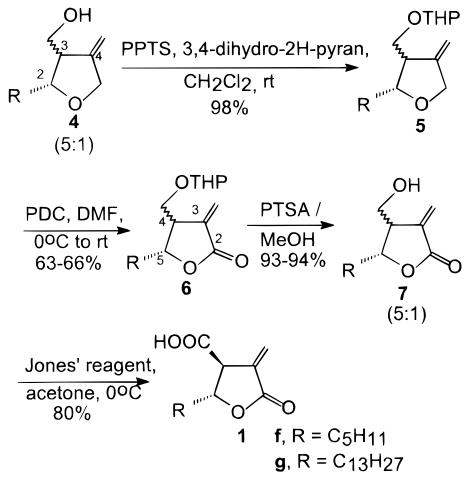
Figure 1.

transition complex for 1,5-intramolecular addition in hex-5-enyl radical will comprise a structure somewhat similar in dimensions to cyclohexane and existing preferentially in a chairlike conformation. Consequently, in our case, for 1,5-ring closure of 2-substituted hex-5-ynyl radical, four "chairlike" transition complexes, **A** and **B** where $CH_2OTi(IV)$ moiety lies up and **C** and **D** where $CH_2OTi(IV)$ lies down, are possible (Figure 1). Here, the transition complexes **A** and **C** which are equatorially substituted α to the radical should be of lower free energy than the axially substituted complexes **B** and **D**. Since the α-substituent R and $CH_2OTi(IV)$ in the complex **C** are cis, they will have some steric interactions as we observe from the difference in the product distributions upon cyclization by changing R from an aryl to an alkyl group. It seems from the model that there might also be some steric interaction between $CH_2OTi(IV)$ and $OCH_2C{\equiv}CH$ moieties since they come closer in the complex **C** compared to **A**. The transition complex **A** will have the lower free energy than **C** and therefore lies on the pathway to the more stable product. Thus, preferential formation of trans product **4a**−**e** derived from **A** should occur. When the aryl group is replaced by an alkyl group in **3f**−**h**, a mixture of isomeric products in **4f**−**h** is formed, probably through transition complexes such as **A** and **C**, though one isomer always predominated. Therefore, the radical cyclization occurs without retention of the stereochemistry of the epoxide. The trans stereochemistry in **4b**−**c** is precedented in our earlier work[9] and also from the published literature.[17] The tetrahydrofurans **4b**−**c** prepared by other methods in our laboratory have already been used for the total synthesis of furofuran lignans.[9]

Stereoselective Total Synthesis of (±)-Methylenolactocin (1f) and (±)-Protolichesterinic Acid (1 g). The crude tetrahydrofuran derivatives **4f** and **4g** were converted to two antitumor antibiotics, (±)-methylenolactocin (**1f**) and (±)-protolichesterinic acid (**1g**), respectively, in good overall yield. The inseparable isomeric mixtures were used for this purpose (Scheme 6). It seemed to us that probably the oxidation of the hydroxymethyl group as well as allylic oxidation of **4** might occur in one pot, giving rise to the target molecules **1**. However, various methods for double oxidation were unsuccessful, resulting only in an intractable mass. For the successful approach, the free alcohol in **4** was protected with 3,4-dihydro-2*H*-pyran in the presence of a catalytic amount of pyridinium toluene-*p*-sulfonate

(15) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545.
(16) Rajanbabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139.
(17) Andrey, O.; Ducry, L.; Landais, Y.; Planchenault, D.; Weber, V. *Tetrahedron* **1997**, *53*, 4339.

Scheme 6



(PPTS) to afford the tetrahydropyranyl (THP) ether **5** as an inseparable diastereomeric mixture in 98% yield. Crude **5** was oxidized with pyridinium dichromate (PDC) in DMF[18] to give the lactone **6** (63−66% yield) which was treated with toluene-*p*-sulfonic acid (PTSA) in MeOH to afford the lactone **7** in 93−94% yield as an inseparable mixture of two diastereomers in a ratio of 5:1. The presence of the γ-lactone moiety was confirmed by a strong absorption at 1770 cm^{-1} for **7f** and at 1760 cm^{-1} for **7g** in the IR spectra. The ratio of the isomers in crude **7f** was determined from the distinctive signals in the ^1H NMR spectrum for 4-H and 5-H which appeared as multiplets centered at δ 2.87 and 4.38 for the major isomer and at δ 3.22 and 4.57 for the minor isomer, respectively. The ratio of isomers in **7g** was determined from four distinguishable doublets for the two olefinic protons in the ^1H NMR spectrum at δ 5.71 and 6.33 (J = 2.7 Hz) for the major isomer and at δ 5.69 and 6.29 (J = 2.1 Hz) for the minor isomer, respectively. All attempts to separate the isomers at every stage by usual chromatographic methods were unsuccessful, and NOE experiments or decoupling techniques could not help to elucidate the stereochemistry of the two isomers of crude **7**. Interestingly, on Jones oxidation, the crude lactone **7f** afforded **1f** as the only isolable product in 80% yield. Similarly, the crude lactone **7g**, upon Jones oxidation, furnished only **1g** as isolable compound in 80% yield. Probably, isomerization of the epimerizable C-4 centers in **7f** and **7g** under the strongly acidic Jones oxidation conditions produced only the thermodynamically more stable isomers of methylenolactocin **1f** and protolichesterinic acid **1g**, respectively, which were spectroscopically and chromatographically identical with previously reported samples.[12,13]

Conclusions

In the present paper, we have demonstrated the use of radical cyclization of epoxides using a transition-metal radical source for the construction of a variety of polysubstituted tetrahydrofuran derivatives. The radical cyclization reactions are stereo- and regioselective in nature. Although simple-looking, this radical cyclization sequence has, to the best of our knowledge, not been previously applied to the preparation of polysubstituted tetrahydrofuran derivatives. Aryl epoxides **3a**−**e** on radical cyclization afforded the trans products **4a**−**e** as the only isolable compounds, whereas alkyl epoxides **3f**−**h** led to a mixture of isomeric products **4f**−**h** in a ratio of 5:1. Some of these 2-aryl-3-(hydroxymethyl)-4-methylenetetrahydrofuran derivatives are important precursors for biologically active natural lignans.[8] We also demonstrated here the use of tetrahydrofuran derivatives **4f** and **4g** by converting them to antitumor antibiotics (±)-methylenolactocin (**1f**) and (±)-protolichesterinic acid (**1g**), respectively, in good overall yield. Since α-substituted enantiomerically pure epoxides can be easily prepared by Sharpless epoxidation, enantioselective synthesis of several tetrahydrofuran derivatives as well as oxacyclic natural products will not be very difficult. Work in this direction is already ongoing in our laboratories.

Experimental Section

The compounds described are all racemates. Melting points were determined in open capillary tubes and are uncorrected. Although some of the epoxides used are commercially available, we prepared all epoxides in our laboratory from the corresponding vinyl alcohols according to the published procedure.[14] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on 300 and 200 MHz NMR spectrometers. Diethyl ether and tetrahydrofuran were distilled from sodium−benzophenone ketyl. Dimethyl sulfoxide was freshly distilled from calcium hydride. Elemental analyses were performed in our analytical laboratories. Light petroleum of boiling range 60−80 °C was used for chromatography.

Typical Procedure for the Preparation of Epoxy Alcohols. Preparation of 1-(3,4-(Methylenedioxy)phenyl)-2,3-epoxypropan-1-ol (2b). To a stirred solution of 3-(3,4-(methylenedioxy)phenyl)-1-propen-3-ol (1 g, 5.6 mmol) in chloroform (30 mL) at 0 °C was added portionwise *m*-chloroperoxybenzoic acid (3.1 g, 40%, 7.3 mmol) over 30 min. The resulting mixture was stirred at 0 °C for an additional 1 h and then left overnight at room temperature. It was diluted with chloroform (20 mL), washed with a 10% aqueous sodium sulfite solution (3 × 25 mL) followed by saturated aqueous sodium bicarbonate (3 × 25 mL), and dried (Na_2SO_4). Solvent was removed under reduced pressure and the residue obtained was chromatographed over silica gel (15% ethyl acetate/light petroleum) to yield the epoxide **2b** (0.95 g, 88%) as a viscous liquid: IR (neat) 3420 (br), 1500 cm^{-1}; ^1H NMR δ 2.61−2.91 (m, 2H), 3.05−3.09 (m, 1H), 4.25 (t, J = 5 Hz, 1/2 H for one isomer), 4.69 (s, 1/2 H for the other isomer), 5.85 (s, 2H), 6.68−6.82 (m, 3H).

Compounds 1-phenyl-2,3-epoxypropan-1-ol (**2a**), 1-(3,4-dimethoxyphenyl)-2,3-epoxypropan-1-ol (**2c**), 1-(3-methoxy-4-(benzyloxy)phenyl)-2,3-epoxypropan-1-ol (**2d**), 1-naphthyl-2,3-epoxypropan-1-ol (**2e**), 1-pentyl-2,3-epoxypropan-1-ol (**2f**), 1-tridecyl-2,3-epoxypropan-1-ol (**2g**), 1-isopropyl-2,3-epoxypropan-1-ol (**2h**), and 1,1-diphenyl-2,3-epoxypropan-1-ol (**2i**) were prepared by the same procedure. For yields, see Table 1.

Typical Procedure for O-Prop-2-ynylation of Epoxy Alcohols. Preparation of 1-(3,4-(Methylenedioxy)phenyl)-1-(prop-2-ynyloxy)-2,3-epoxypropane (3b). To a stirred suspension of sodium hydride (0.32 g, 60% dispersion, 6.70 mmol) in dry tetrahydrofuran−dimethyl sulfoxide (10:1) (20 mL) was added dropwise a solution of epoxy alcohol **2b** (1 g, 5.14 mmol) in dry tetrahydrofuran (10 mL) at room temperature under nitrogen. After evolution of hydrogen ceased, a solution of propargyl bromide (0.74 g, 6.16 mmol) in dry tetrahydrofuran (10 mL) was added dropwise at 0 °C over 30 min. The reaction mixture was then stirred at room temperature for 4 h and carefully quenched with ice−water. After removal of most of the tetrahydrofuran under reduced pressure, the resulting residue was extracted with diethyl ether (3 × 30 mL). The ether extract was washed with saturated brine and dried (Na_2SO_4). Removal of solvent under reduced

(18) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

pressure afforded a viscous liquid which was purified by column chromatography over silica gel (5% ethyl acetate/light petroleum) to furnish **3b** (0.85 g, 82%) as a viscous liquid: IR (neat) 1600, 1490, 1440 cm^{-1}; ^1H NMR δ 2.43−2.44 (m, 1H), 2.61−2.82 (m, 2H), 3.16−3.20 (m, 1H), 3.93−4.08 (m, 1H), 4.16−4.29 (m, 11/2 H), 4.48 (d, J = 4.2 Hz, 1/2 H), 5.85 (s, 2H), 6.68−6.83 (m, 3H). Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.37; H, 5.37.

Compounds 1-phenyl-1-(prop-2-ynyloxy)-2,3-epoxypropane (**3a**), 1-(3,4-dimethoxyphenyl)-1-(prop-2-ynyloxy)-2,3-epoxypropane (**3c**), 1-(3-methoxy-4-(benzyloxy)phenyl)-1-(prop-2-ynyloxy)-2,3-epoxypropane (**3d**), 1-naphthyl-1-(prop-2-ynyloxy)-2,3-epoxypropane (**3e**), 1-pentyl-1-(prop-2-ynyloxy)-2,3-epoxypropane (**3f**), 1-tridecyl-1-(prop-2-ynyloxy)-2,3-epoxypropane (**3g**), 1-isoprpyl-1-(prop-2-ynyloxy)-2,3-epoxypropane (**3h**), and 1,1-diphenyl-1-(prop-2-ynyloxy)-2,3-epoxypropane (**3i**) were prepared by the same procedure. For yields, see Table 1.

Typical Procedure for Radical Cyclization Reaction. Preparation of 2-(3,4-(Methylenedioxy)phenyl)-3-(hydroxymethyl)-4-methylenetetrahydrofuran (4b). A solution of titanocene dichloride (1 g, 4.02 mmol) in dry tetrahydrofuran (50 mL) was stirred with activated zinc dust (0.8 g, 12.1 mmol) for 1 h under argon (activated zinc dust was prepared by washing 20 g of commercially available zinc dust with 60 mL of 4 N HCl and thorough washing with water and finally with dry acetone and then drying in vacuo). The resulting green solution was then added dropwise to a stirred solution of the epoxide **3b** (0.47 g, 2 mmol) in dry tetrahydrofuran (50 mL) at room temperature under argon during 30 min. The reaction mixture was stirred for an additional 1 h and decomposed with 10% H_2SO_4 (100 mL). Most of the solvent was removed under reduced pressure, and the residue was extracted with diethyl ether (4 × 30 mL). The ether layer was washed with saturated $NaHCO_3$ (2 × 25 mL) and dried (Na_2SO_4). After removal of solvent, the crude residue was purified by column chromatography over silica gel (20% ethyl acetate/light petroleum) to afford the alcohol **4b** (0.36 g, 76%) as a viscous liquid: IR (neat) 3420 (br), 1610, 1490 cm^{-1}; ^1H NMR δ 1.81 (brs, OH), 2.71−2.73 (m, 1H), 3.76 (dq, J = 11.1, 4.8 Hz, 2H), 4.49 (q, J = 12.6 Hz, 2H), 4.75 (d, J = 7.2 Hz, 1H), 5.04−5.09 (m, 2H), 5.93 (s, 2H), 6.75−6.89 (m, 3H); ^{13}C NMR δ 53.9, 61.8, 71.2, 83.2, 100.9, 104.9, 106.6, 108.0, 119.8, 134.9, 147.1, 147.8, 148.5. This compound (**4b**) is identical with the authentic sample prepared earlier in our laboratory.[9]

Compounds 2-phenyl-3-(hydroxymethyl)-4-methylenetetrahydrofuran (**4a**), 2-(3,4-dimethoxyphenyl)-3-(hydroxymethyl)-4-methylenetetrahydrofuran (**4c**),[9] 2-(3-methoxy-4-(benzyloxy)-phenyl)-3-(hydroxymethyl)-4-methylenetetrahydrofuran (**4d**), 2-naphthyl-3-(hydroxymethyl)-4-methylenetetrahydrofuran (**4e**), 2-pentyl-3-(hydroxymethyl)-4-methylenetetrahydrofuran (**4f**), 2-tridecyl-3-(hydroxymethyl)-4-methylenetetrahydrofuran (**4g**), 2-isopropyl-3-(hydroxymethyl)-4-methylenetetrahydrofuran (**4h**), and 2,2-diphenyl-3-(hydroxymethyl)-4-methylenetetrahydrofuran (**4i**) were prepared by the same procedure. For yields, see Table 1.

Preparation of 2-Pentyl-3-((tetrahydropyranyloxy)-methyl)-4-methylenetetrahydrofuran (5f). A solution of the alcohol **4f** (0.7 g, 3.8 mmol), 3,4-dihydro-2*H*-pyran (0.48 g, 5.7 mmol), and pyridinium-*p*-toluenesulfonate (95 mg, 0.38 mmol) in dry methylene chloride (15 mL) was stirred for 5 h at room temperature under nitrogen. The resulting reaction mixture was diluted with methylene chloride, washed with saturated $NaHCO_3$ (3 × 25 mL), and dried (Na_2SO_4). After evaporation of the solvent, the crude residue was purified by column chromatography over silica gel (2% ethyl acetate/light petroleum) to afford **5f** (1 g, 98%) as a viscous liquid: IR (neat) 1470, 1450 cm^{-1}; ^1H NMR δ 0.87 (t, J = 6.6 Hz, 3H), 1.16−1.83 (m, 14H), 2.49−2.58 (m, 1H), 3.45−3.52 (m, 2H), 3.73−3.87 (m, 3H), 4.29 (dq, J = 10.6, 2.1 Hz, 2H), 4.54−4.82 (m, 1H), 4.93−5.01 (m, 2H); ^{13}C NMR δ 13.9, 19.1, 19.3, 19.7, 22.5, 22.6, 25.3, 25.4, 25.6, 25.7, 30.4, 30.5, 30.6, 31.7, 31.8, 34.5, 34.6, 48.5, 48.8, 61.7, 62.1, 62.8, 68.6, 68.8, 70.4, 70.5, 83.3, 83.6, 94.5, 98.3, 99.0, 104.6, 104.8, 149.6, 149.7. Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.51. Found: C, 71.28; H, 10.45.

Preparation of 2-Tridecyl-3-((tetrahydropyranyloxy)-methyl)-4-methylenetetrahydrofuran (5g). Compound **5g** was prepared from **4g** using a procedure similar to that described for **5f**. Yield 98%.

Preparation of 4-((Tetrahydropyranyloxy)methyl)-3-methylene-5-pentyltetrahydrofuran-2-one (6f). To a stirred solution of tetrahydropyranyl ether **5f** (0.6 g, 2.24 mmol) in dry DMF (18 mL) was added pyridinium dichromate (8.43 g, 22.4 mmol) portionwise at room temperature during 1 h. The reaction mixture was further stirred for 24 h, diluted with water (25 mL), and extracted with ethyl acetate (4 × 25 mL). The organic layer was washed with water (3 × 25 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue obtained was chromatographed over silica gel (10% ethyl acetate/light petroleum) to furnish the lactone **6f** (0.4 g, 63%) as a light yellow viscous liquid: IR (neat) 1770, 1470 cm^{-1}; ^1H NMR δ 0.89 (t, J = 6.4 Hz, 3H), 1.16−1.76 (several peaks, 14H), 2.90−3.0 (m, 1H), 3.37−3.57 (m, 2H), 3.70−3.94 (m, 2H), 4.30−4.38 (m, 1H), 4.55−4.63 (m, 1H), 5.65−5.72 (m, 1H), 6.24−6.30 (m, 1H). Anal. Calcd for $C_{16}H_{26}O_2$: C, 68.05; H, 9.28. Found: C, 67.95; H, 9.22.

Preparation of 4-((Tetrahydropyranyloxy)methyl)-3-methylene-5-tridecyltetrahydrofuran-2-one (6g). Compound **6g** was prepared from **5g** by using a procedure similar to that described for **6f**. Yield 66%.

Preparation of 4-(Hydroxymethyl)-3-methylene-5-pentyltetrahydrofuran-2-one (7f). To a stirred solution of lactone **6f** (0.2 g, 0.71 mmol) in methanol (4 mL) was added *p*-toluenesulfonic acid monohydrate (15 mg, 0.08 mmol), and the reaction mixture was stirred for 3 h at room temperature. Most of the solvent was removed in vacuo, and the residue was diluted with water (3 mL) and extracted with diethyl ether (3 × 20 mL). The ether extract was washed with saturated $NaHCO_3$ and brine and dried (Na_2SO_4).

After removal of solvent, the residue obtained was purified by column chromatography over silica gel (20% ethyl acetate/light petroleum) to afford the hydroxy lactone **7f** (0.13 g, 93%) as a viscous oil: IR (neat) 3450 (br), 1770, 1470 cm^{-1}; ^1H NMR δ 0.89 (t, J = 6.6 Hz, 3H), 1.27−1.77 (m, 8H), 2.82−2.92 (m, 5/6 H), 3.18−3.30 (m, 1/6 H), 3.75 (d, J = 6.2 Hz, 2H), 4.35−4.41 (m, 5/6 H), 4.55−4.64 (m, 1/6 H), 5.69 (d, J = 2.4 Hz, 1/6 H), 5.71 (d, J = 2.3 Hz, 5/6 H), 6.30 (d, J = 2.4 Hz, 1/6 H), 6.34 (d, J = 2.4 Hz, 5/6 H). Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.51; H, 9.13.

Preparation of 4-(Hydroxymethyl)-3-methylene-5-tridecyltetrahydrofuran-2-one (7g). Compound **7g** was prepared from **6g** by using a procedure similar to that described for **7f**. Yield 94%.

Preparation of (±)-Methylenolactocin (1f). A solution of the hydroxy lactone **7f** (90 mg, 0.45 mmol) in acetone (3 mL) was treated with freshly prepared Jones reagent at 0 °C until a persistent orange color was observed. After 2 h of stirring at 0 °C (progress of the reaction was monitored by TLC), 2-propanol was added to destroy the excess reagent. The reaction mixture was diluted with water (2 mL), and acetone was removed under reduced pressure. The residue was extracted with methylene chloride (4 × 10 mL). The organic extract was washed with brine and dried (Na_2SO_4). Evaporation of the solvent afforded a residue which was purified by a short column of silica gel (chloroform−ethyl acetate−acetic acid, 90:8:2) to give methylenolactocin (**1f**) (77 mg, 80%) as a thick liquid: IR (neat) 3460, 1750, 1660, 1470 cm^{-1}; ^1H NMR δ 0.80 (t, J = 6.6 Hz, 3H), 1.15−1.55 (m, 6H), 1.62−1.74 (m, 2H), 3.54−3.59 (m, 1H), 4.75 (q, J = 6 Hz, 1H), 5.96 (d, J = 2.6 Hz, 1H), 6.39 (d, J = 3 Hz, 1H); ^{13}C NMR δ 13.8, 22.3, 24.4, 31.3, 35.6, 49.5, 79.0, 125.8, 132.5, 168.4, 173.9.

Preparation of (±)-Protolichesterinic Acid (1 g). Compound **1g** was prepared from **7g** by using a procedure similar to that described for **1f**. Yield 80%. **1f**: crystalline solid; mp 105−107 °C; IR (KBr) 3460, 1750, 1660 cm^{-1}; ^1H NMR δ 0.87 (t, J = 6.3 Hz, 3H), 1.25 (brs, 22H), 1.67−1.77 (m, 2H), 3.60−3.64 (m, 1H), 4.80 (q, J = 6 Hz, 1H), 6.01 (d, J = 2.7 Hz, 1H), 6.46 (d, J = 3 Hz, 1H); ^{13}C NMR δ 13.9, 22.5, 24.6, 29.1, 29.2, 29.3, 29.5, 31.8, 35.6, 49.3, 78.7, 125.5, 132.4, 168.0, 173.1.

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Supporting Information Available: ^{1}H NMR spectral data for compounds **1f**−**g**, **2a**, **2c**−**i**, **3a**, **3c**−**i**, **4a**, **4c**−**i**, **5f**−**g**, **6f**−**g**, and **7f**−**g** and ^{13}C NMR spectral data of compounds **1f**−**g**, **3f**−**g**, **4a**, **4c**−**i**, **5f**−**g**, and **7g** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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