Cascade Cyclization: Synthesis of (+)-Tuberine

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Received December 21, 1993•

Asymmetric dihydroxylation of epoxide **12** led, via biomimetic epoxide opening, to tetrahydrofuran **13**. Acetylation of **13** then gave the antibiotic terpene (+)-tuberine (**14**). In the course of this work, the absolute configuration of (+)-tuberine was corrected.

A variety of physiologically active cyclic ethers, illustrated by (+)-tuberine (**1**),[2] uvaricin (**2**),[3] and CP-96,797 (**3**),[4] have been isolated from natural sources. The current hypothesis is that these ethers are biosynthesized by cyclization of precursor epoxides,[5,6] as exemplified by the transformation of **4** to **5**.[7] We report a biomimetic synthesis of natural (+)-tuberine. In the course of this work, we have established that the correct absolute configuration of (+)-tuberine is that shown in **14** (Scheme 2).

Development of the Cyclization. Successful application of this retrosynthetic analysis in a forward sense depended on the solution of two problems: preparation of the precursor epoxides with absolute as well as relative stereocontrol and the development of regioselectivity in intramolecular epoxide opening. In addition, appropriate initiators and, perhaps, terminators for the cyclization must be developed.

It occurred to us that the ubiquitous 2,5-tetrahydrofurandimethanol motif of **1** and **2** could be readily assembled by combining Sharpless asymmetric epoxidation[8] with Sharpless asymmetric dihydroxylation.[9] As illustrated for geraniol (Scheme 1), these two procedures, applied sequentially, would establish, with absolute stereocontrol, four new stereogenic centers. There remained, however, the question of regioselectivity in the epoxide opening. Either of the two alkoxides could react with either end of the epoxide, so four regioisomeric cyclic ethers were possible.

In fact, exposure (Scheme 1) of the tosylate **7** of geraniol epoxide[7] to AD-mix β[8] (0 °C, then rt, 18 h) led to two new substances by TLC analysis, R_f (40% EtOAc/petroleum ether) = 0.2 and 0.5. Further stirring (72 h, rt) allowed complete conversion to the less polar product, identified as **8** by comparison of spectroscopic data to those of authentic material.[10] As hoped, five-membered cyclic ether formation had dominated over the six-membered and seven-membered alternatives, and the cascade cyclization had proceeded cleanly.

Clearly, had absolute stereocontrol failed at either of the oxygenation steps, cyclization would necessarily have led to a mixture of diastereomers. In fact, we deliberately prepared this mixture, by simple dihydroxylation[11] of tosylate **7**. The epoxide methines of **8** and **9** were cleanly resolved by ^{1}H NMR (δ 3.03 and 3.10, respectively). These

• Abstract published in *Advance ACS Abstracts,* May 15, 1994.

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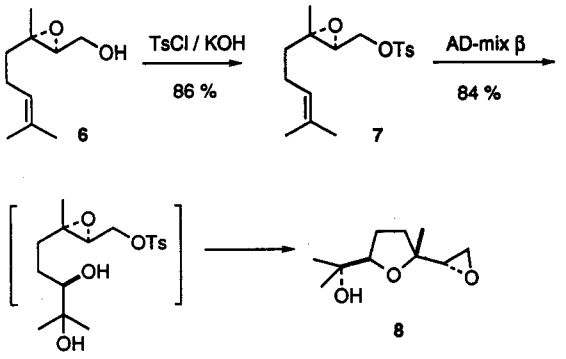
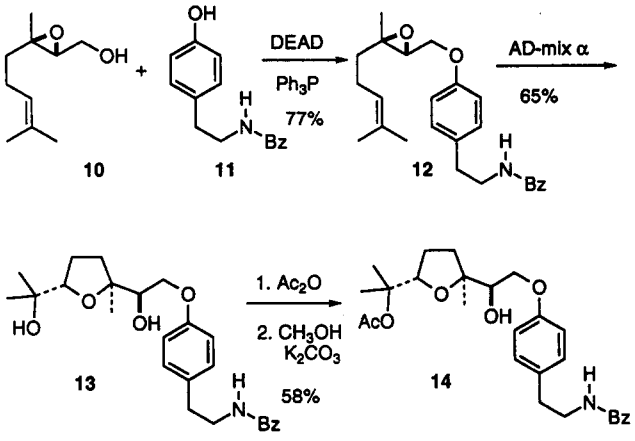
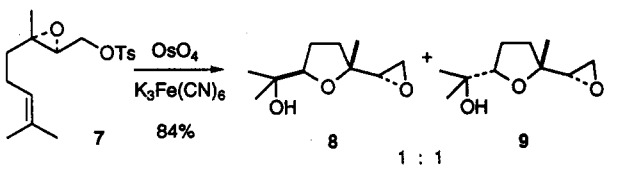
Scheme 1



Scheme 2



diastereomers ran together on TLC. The ^{1}H NMR of the cyclization product from asymmetric dihydroxylation of **7** in fact showed both diastereomers, **8** and **9**, in a ratio of 15:1. Simple algebra demonstrated that the two oxygenation steps had proceeded with an average enantioselectivity of 30:1.



Synthesis of (+)-Tuberine. We had originally envisioned that tuberine (1) could be prepared by opening of epoxide 8 with an appropriate phenolic nucleophile. When initial attempts to achieve such an opening were not successful, we adopted an alternative plan (Scheme 2). This strategy was initially effected starting with epoxide 6 (Scheme 1). However, this led to *ent*-tuberine (1), identical to the natural product in all respects except rotation ($[\alpha]_D = -6.3°$). The absolute configuration[2] of (+)-tuberine must therefore be revised to that shown in 14 (Scheme 2). This necessitated repeating the synthesis in the enantiomeric series, starting from epoxide 10[8] (Scheme 2).

Mitsunobu coupling[12] of **10** with *N*-benzoyltyramine (**11**)[13,14] proceeded smoothly to give the crystalline ether **12**. Unfortunately, amide **12** was not soluble in the usual tBuOH/H_2O asymmetric dihydroxylation reaction mixture. The reaction was therefore carried out in 1:1:1 acetone/tBuOH/H_2O. Using this mixture, starting material was consumed, and two new substances appeared, TLC R_f (20% acetone/CH_2Cl_2) = 0.12 and 0.23. After the reaction mixture was stirred at rt for 3days, the lower-R_f material was substantially diminished. Workup and chromatography at this stage then provided **13**.

The relative configuration of **13** was confirmed by conversion (acetylation, followed by selective transesterification of the sterically more accesible of the two acetates) to (+)-tuberine (**14**), identical (TLC, ^{1}H NMR, ^{13}C NMR) with natural material. The synthetic material (13 mg, chromatographed but not recrystallized) showed $[\alpha]_D$ = +6.3°, compared to +7.8° for the natural sample.

Conclusion. The strategy outlined here, coupling asymmetric epoxidation with asymmetric dihydroxylation, should allow construction of naturally occurring cyclic ethers, including acetogenins such as **2**, with control of both relative and absolute configuration.[15] Further, asymmetric dihydroxylation has been established to be a useful initiator for epoxide cyclization.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-250 spectrometer. Chemical shifts are reported relative to tetramethylsilane at 0.0 ppm. Infrared spectra were determined on a Nicolet 5DXB System FT IR and are reported in wavenumbers (cm^{-1}). High resolution mass spectrometry (HRMS) was performed on a VG 70-70 mass spectrometer. Low resolution mass spectra (LRMS) were obtained on a Hewlett Packard 5890 gas chromatograph-mass spectrometer (GC-MS). Optical rotations were measured on a Rudolph Research Autopol III polarimeter, using concentrations expressed in grams per 100 mL. Thin layer chromatography (TLC) was run using Analtech, Inc. 2.5 × 10 cm, 250-μm analytical plates coated with silica gel GF. Column chromatography was done under air pressure on TLC grade 60-Å silica gel.[16] The solvent mixtures indicated for TLC are volume/volume mixtures.

Toluene-4-sulfonic Acid, [3-Methyl-3-(4-methylpent-3-enyl)oxiran-2-yl]methyl Ester (7). Potassium hydroxide (450 mg, 8.0 mmol) was added to a solution of epoxy alcohol **6** (685 mg, 3.7 mmol) in ether (50 mL) at −78 °C and the resulting mixture was stirred for 10 min. Tosyl chloride (975 mg, 5.11 mmol) was added and the reaction was allowed to warm to rt and then stirred for a total of 18 h. Ether (20 mL) followed by 10% HCl (1 mL) was added and the resulting mixture was stirred until the solids dissolved. This ethereal solution was washed with saturated brine (20 mL), dried (K_2CO_3), filtered, concentrated, and chromatographed to give the epoxy tosylate **7** (1.02 g, 86% yield) as a colorless oil: R_f (40% EtOAc/petroleum ether) = 0.75; ^{1}H NMR (δ) 7.80 (2H, d, J = 8.2 Hz), 7.36 (2H, d, J = 8.2 Hz), 5.03 (1H, m), 4.11 (2H, m), 2.97 (1H, t, J = 5.8 Hz), 2.44 (3H, s), 2.03 (2H, dd, J = 7.4, 3.8 Hz), 1.67 (3H, s), 1.68–1.2 (2H, m), 1.58 (3H, s), 1.20 (3H, s); ^{13}C NMR δ μ: 144.9, 132.6, 132.0, 68.5, 60.6, 37.86 23.3; d: 129.8, 127.7, 122.9, 58.5, 25.4, 21.4, 17.4, 16.5; MS (*m/z*, rel intensity) 269 (17), 227 (29), 168 (90), 143 (38), 127 (100), 109 (29).

2-(5-Methyl-5-oxiran-2-yltetrahydrofuran-2-yl)propan-2-ol (8). A solution of the epoxy tosylate **7** (1.49 g, 4.6 mmol) in tBuOH/H_2O (5 mL, 1/1) was added to a mixture of AD-mix β (7.8 g) and methanesulfonamide (0.270 g, 2.8 mmol) in tBuOH/H_2O (45 mL, 1/1) at 0 °C. The resulting heterogeneous mixture was stirred for 72 h at rt. This reaction mixture was directly extracted with three 75-mL portions of ethyl acetate. The combined organic extract was washed with half-saturated aqueous

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Na_2SO_3, dried (Na_2SO_4), concentrated, and chromatographed to give the oxiranyltetrahydrofuran **8** (722 mg, 84% yield) as a colorless oil: R_f (40% EtOAc/petroleum ether) = 0.31; ^{1}H NMR (δ) 3.70 (1H, t, J = 6.6 Hz), 2.95 (1H, dd, J = 4.1, 2.8 Hz), 2.66 (1H, t, J = 4.5 Hz), 2.50 (1H, dd, J = 4.9, 2.7 Hz), 2.20 (1H, bs), 1.78 (3H, m), 1.54 (1H, m), 1.19 (3H, s), 1.16 (3H, s), 1.14 (3H, s); ^{13}C NMR δ μ: 80.7, 70.1, 43.1, 32.1, 25.7, d: 86.2, 56.4, 23.4, 23.8, 23.6. $[\alpha]_D = -2.45°$ (c = 6.72, $CHCl_3$); MS (m/z, rel intensity) 171 (15), 143 (100), 127 (84), 109 (36); HRMS calcd for $C_9H_{15}O_3$ ($M^+ - CH_3$) 171.1021, found 171.1044.

***N*-Benzoyltyramine (11).** *N*-Benzoyltyramine was prepared by a variation of the literature[13,14] procedure. Thus, benzoyl chloride (8.4 mL, 74.7 mmol) was added slowly to a solution of tyramine (4.8 g, 35.0 mmol) in pyridine (16 mL). After an initial exothermic reaction, the solidified mixture was heated to 100 °C for 40 min. After cooling, the reaction mixture was partitioned between water and $CHCl_3$. The combined organic extracts were concentrated to give tan solid. This was recrystallized from hot acetonitrile to give dibenzoyltyramine (8.8 g, 73% yield) as white crystalline needles: mp 172–174 °C (lit.[13] mp = 172–173 °C): R_f (35% EtOAc/petroleum ether) = 0.55; ^{1}H NMR δ 8.20 (2H, d, J = 8.4 Hz), 7.72 (2H, d, J = 8.4 Hz), 7.70–7.32 (6H, m), 7.28 (2H, d, J = 8.4 Hz), 7.18 (2H, d, J = 8.2 Hz), 6.34 (1H, bs), 3.74 (2H, q, J = 7.1 Hz), 2.97 (2H, t, J = 7.1 H).

Potassium carbonate (250 mg, 1.8 mmol) was added to *N,O*-dibenzoyltyramine (860 mg, 2.5 mmol) in methanol (10 mL), and the resulting heterogeneous reaction mixture was stirred for 30 min. The mixture was partitioned between 10% aqueous HCl and chloroform, and the combined organic extract was dried (Na_2SO_4) and concentrated to give **11** as white solid. Recrystallization from acetonitrile then gave **11** (512 mg, 85% yield) as shiny white and flaky crystals: mp 163–164 °C (lit.[14] mp 164.5–165.5 °C); R_f (35% EtOAc/petroleum ether) = 0.45; ^{1}H NMR δ 7.85 (2H, m), 7.48 (3H, m), 7.08 (2H, d, J = 8.4 Hz), 6.76 (2H, d, J = 8.4 Hz), 6.60 (1H, bs), 5.01 (1H, bs), 3.56 (2H, q, J = 7.1 Hz), 2.90 (2H, t, J = 7.1 Hz).

N-[2-[4-[[3-Methyl-3-(4-methylpent-3-enyl)oxiranyl-2-yl]-methoxy]phenyl]ethyl]benzamide (12). A solution of DEAD (487 mg, 2.8 mmol) in THF (1 mL) was added to a mixture of epoxy alcohol **10** (342 mg, 2 mmol), *N*-benzoyltyramine **11** (635 mg, 2.7 mmol), and triphenylphosphine (689 mg, 2.7 mmol) in THF (1 mL) at −10 °C. This yellow reaction mixture was stirred for 24 h (until TLC showed no starting material), during which time the reaction turned light pink. The reaction mixture was partitioned between dichloromethane and water. The organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the ether **12** (606 mg, 77% yield) as a white solid: mp 107–108 °C: R_f (40% EtOAc/petroleum ether) = 0.63; ^{1}H NMR δ 7.73 (2H, d, J = 6.8 Hz), 7.48 (3H, m), 7.21 (2H, d, J = 8.5 Hz), 6.95 (2H, d, J = 8.5 Hz), 6.18 (1H, bs), 5.15 (1H, bt, J = 4.2 Hz), 4.13 (2H, m), 3.73 (2H, dd, J = 12.9, 6.7 Hz), 2.92 (1H, t, J = 6.7 Hz), 2.14 (2H, dd, J = 15.1, 7.4 Hz), 1.80–1.40 (1H, m), 1.74 (3H, s), 1.66 (3H, s), 1.39 (3H, s); ^{13}C NMR δ u: 167.4, 157.2, 134.6, 132.0, 131.3, 66.9, 41.2, 38.1, 34.6, 23.5; d: 131.1, 129.6, 128.3, 126.7, 123.2, 114.7, 60.4, 25.5, 17.5, 16.8. $[\alpha]_D = +9.6°$ (c = 1.0, $CHCl_3$); MS (m/z, rel intensity) 192 (4), 148 (100), 120 (67), 105 (55); HRMS calcd for $C_{25}H_{31}NO_3$ 393.2303, found 393.2304. Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94. Found: C, 75.91; H, 8.02.

***N*-[2-[4-[2-Hydroxy-2-[5-(1-hydroxy-1-methylethyl)-2-methyltetrahydrofuran-2-yl]ethoxy]phenyl]ethyl]benzamide (13).** A solution of ether **12** (235 mg, 0.6 mmol) in acetone (5 mL) was added to a heterogeneous mixture of AD-mix α (721 mg) and methanesulfonamide (40 mg, 0.4 mmol) in $tBuOH/H_2O$ (5mL/5mL) at 0 °C. The resulting yellow mixture was allowed to warm to room temperature and then was stirred vigorously for 4 days. Saturated aqueous sodium sulfite solution (10 mL) was added, and the mixture was stirred until it was white and then extracted with three 10-mL portions of ethyl acetate. The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed to give starting ether **12** (125 mg) and the diol **13** (78 mg, 65% yield based on **12** not recovered) as a viscous oil: R_f (20% EtOAc/petroleum ether) = 0.3; ^{1}H NMR δ 7.69 (2H, d, J = 8.4 Hz), 7.43 (3H, m), 7.13 (2H, d, J = 8.6 Hz), 6.86 (2H, d, J = 8.6 Hz), 6.34 (1H, bs), 4.18–3.93 (3H, m), 3.80 (1H, m), 3.66 (2H, dd, J = 12.9, 6.8 Hz), 2.86 (2H, t, J = 6.8 Hz), 2.67 (1H, bs), 2.2–1.2 (5H, m), 1.24 (3H, s), 1.22 (3H, s), 1.14 (3H, s); ^{13}C NMR δ u: 167.5, 157.3, 134.6, 131.3, 84.0, 69.2, 41.3, 34.7, 34.1, 26.3; d: 131.3, 129.7, 128.4, 126.8, 114.8, 87.2, 75.1, 27.1, 23.0, 22.9. MS (m/z, rel intensity) 306 (1), 288 (6), 143 (90), 125 (60), 120 (64), 105 (100); HRMS calcd for $C_{24}H_{30}NO_5$ 412.2123, found 412.2143.

(+)-Tuberine (14). Acetic anhydride (0.06 mL, 0.63 mmol) and DMAP (4 mg, 0.033 mmol) were added to the diol (25 mg, 0.058 mmol) in triethylamine (0.2 mL), and the resulting mixture was stirred for 8 h at rt. The reaction mixture was partitioned between ether and, sequentially, water (5 mL), 1% aqueous HCl (5 mL), and saturated aqueous sodium bicarbonate (5 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give the diacetate (22 mg, 73% yield) as a viscous oil: R_f (15% acetone/dichloromethane) = 0.72; ^{1}H NMR δ 7.68 (2H, d, J = 8.4 Hz), 7.42 (3H, m), 7.12 (2H, d, J = 8.6 Hz), 6.84 (2H, d, 8.6), 6.09 (1H, bs), 5.27 (1H, dd, J = 8.6, 2.4 Hz), 4.28 (1H, dd, J = 10.6, 2.4 Hz), 4.06 (2H, m), 3.66 (2H, dd, J = 12.8, 6.8 Hz), 2.85 (2H, t, 6.8 Hz), 2.35–1.5 (4H, m), 2.07 (3H, s), 1.95 (3H, s), 1.45 (3H, s), 1.42 (3H, s) 1.25 (3H, s); ^{13}C NMR δ u: 170.4, 167.4, 157.4, 134.7, 131.3, 83.2, 82.4, 67.3, 41.3, 35.1, 34.8, 26.3; d: 131.3, 129.7, 128.5, 126.8, 114.0, 85.2, 83.2, 82.4, 75.5, 22.9, 22.4, 21.7, 21.1.

Potassium carbonate (5.3 mg, 0.04 mmol) was added to a solution of the diacetate (15 mg, 0.03 mmol), in dichloromethane/methanol (0.5 mL/0.5 mL) at 0 °C, and the resulting mixture was stirred for 3 h as it was allowed to warm to rt. Additional methanol (0.5 mL) was added, and the mixture was stirred for a total of 8 h. The reaction was quenched with 5% aqueous acetic acid, and then partitioned between dichloromethane and 10% aqueous sodium bicarbonate. The combined organic extract was dried (Na_2SO_4), concentrated, and chromatographed to give (+)-tuberine (**14**) (11 mg, 80% yield) as a white solid: R_f (20% acetone/dichloromethane) = 0.59; $[\alpha]_D = +6.3°$ (c = 1.1, $CHCl_3$); ^{1}H NMR δ 7.68 (2H, d, J = 8.3 Hz), 7.43 (3H, m), 7.16 (2H, d, J = 8.6 Hz), 6.89 (2H, d, J = 8.6 Hz), 6.09 (1H, bs), 4.10 (2H, dt, J = 16.6, 6.5 Hz), 3.94 (m, 2H), 3.69 (2H, dd, J = 12.8, 6.8 Hz), 2.88 (2H, t, J = 6.8 Hz), 2.57 (1H, d, J = 2.1 Hz), 2.3–1.6 (4H, m), 1.99 (3H, s), 1.49 (3H,s), 1.46 (3H, s), 1.25 (3H, s); ^{13}C NMR δ u: 167.4, 157.5, 134.8, 131.3, 84.4, 82.5, 69.2, 41.3, 30.8, 33.7, 26.6; d: 131.4, 129.8, 128.6, 126.8, 114.9, 85.6, 75.1, 22.9, 22.5, 22.2, 21.9. MS (m/z, rel intensity) 469 (20), 409 (6), 368 (6), 348 (20), 288 (24), 185 (100), 143 (30), 125 (54), 105 (46); HRMS calcd for $C_{27}H_{35}NO_6$ 469.2464, found 469.2468.

Acknowledgment. We thank the NIH (GM46762) for support of this work. We also thank F. S. El-Feraly for providing an authentic sample of (+)-tuberine (**14**).

Supplementary Material Available: ^{1}H NMR spectra for compounds **7**, **8**, and **11–14** (6 pages). This material is contained in many 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.