Facile and Efficient Preparation of a C-1 Side Chain Equivalent of Zaragozic Acid C

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An optically pure C-1 side chain equivalent of zaragozic acid C, (4*R*,5*R*)-4-benzyloxy-5-methyl-6-phenyl-1-hexyne, has been synthesized in ten steps from (*E*)-4-phenyl-2-buten-1-ol with an overall yield of 50%, involving a Sharpless asymmetric epoxidation as a key step, followed by regio- and stereocontrolled ring-opening of the epoxide with the trimethylaluminum/*n*-butyllithium system.

Key words zaragozic acid C; C-1 side chain; Sharpless asymmetric epoxidation; epoxide-ring opening

The zaragozic acids and squalestatins, a family of fungal metabolites isolated and characterized by respective researchers at Merck and Glaxo in 1992, have been shown to be picomolar competitive inhibitors of squalene synthase.[2] Structurally, these molecules share a 4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic acid core with an array of six stereogenic centers including contiguous quaternary carbons, and represent considerable variations in the C-1 alkyl and C-6 acyl side chains. Owing to their biomedical significance as intriguing lead compounds for the development of therapeutic agents for hypercholesterolemia, coupled with their novel molecular architecture, zaragozic acids (squalestatins) have presented themselves as unusually attractive and important targets for synthetic investigations,[3,4] wherein efforts of six groups including our group have recently culminated in the total synthesis of these molecules.[5,6]

The key features of our convergent synthesis of zaragozic acid C (**1**) involve a) simultaneous creation of the C-4 and C-5 quaternary carbon centers by $Sn(OTf)_2$-promoted aldol coupling reaction between an α-keto ester and silyl ketene thioacetal derived from L- and D-tartaric acids, respectively, b) direct introduction of the lithium acetylide from (4*R*,5*R*)-4-benzyloxy-5-methyl-6-phenyl-1-hexyne (**3**) as the C-1 side chain equivalent onto the fully functionalized aldehyde **2**, and c) construction of the bicyclic core structure by acid-catalyzed internal ketalization under kinetically controlled conditions (Fig. 1).[6c] Consequently, we required large quantities of optically pure **3** for the syntheses of **1** and its analogs. The C-1 side chain fragments of zaragozic acid C (**1**) have been synthesized by the Merck[7] and Carreira groups,[6a] both of which take advantage of the Evans asymmetric aldol methodology[8] to create the stereogenic centers. From a practical point of view, we have undertaken the synthesis of **3** capitalizing on Sharpless catalytic asymmetric epoxidation.[9]

Results and Discussion

The well known nature of the Sharpless asymmetric epoxidation process, namely that higher enantioselectivies can be achieved with (*E*)-allylic alcohols than with their (*Z*)-counterparts, dictated to us the synthesis of **3** commencing with (*E*)-4-phenyl-2-buten-1-ol (**4**)[10] (Chart 1). Catalytic asymmetric epoxidation of **4** under Sharpless conditions provided the epoxy alcohol **5**, $[\alpha]_D^{27}$ −35.4° (*c*=2.1, $CHCl_3$), in 91% yield, whose enantiomeric purity was determined to be 92% by a chiral stationary phase column (Daicel Chiralcel AD).[11] For enhancement of optical purity, **5** was then acylated with 3,5-dinitrobenzoyl chloride[12] to give crystalline ester **6**, which, upon two recrystallizations from (iso-Pr)$_2$O-toluene (3 : 1), furnished an optically pure material (*vide infra*), mp 96.0—96.5 °C, $[\alpha]_D^{25}$ −25.1° (*c*=1.1, $CHCl_3$), in 76% yield. Transesterification of the thus obtained **6** with methanol reproduced the epoxy alcohol **5**, $[\alpha]_D^{25}$ −39.9° (*c*=1.4, $CHCl_3$), in 96% yield, the homochirality of which was confirmed by the chiral stationary phase column.

With the optically pure epoxide **5** in hand, the stage was now set for the introduction of a methyl group *via* a regio- and stereocontrolled ring-opening of **5**. Of several methods reported,[13] the procedure of Oshima and Nozaki[14] with trimethylaluminum seemed to be the method of choice for this purpose. However, it was reported by Lentz and Peet that reaction of **5** with trimethylaluminum proceeded through the intermediacy of a phenonium ion.[10a] For a related transformation in the synthesis of the C-1 side chain of zaragozic acid A, Nicolaou and co-workers recently demonstrated a distinct advantage latent in the Pfaltz protocol[15] wherein a regioselective ring-opening of 1-benzyloxy-2,3-epoxybutane was achieved by the use of trimethylaluminum in the presence of a catalytic amount of *n*-butyllithium.[5a] Indeed, protection of **5** as a *p*-methoxybenzyl (MPM) ether and subse-

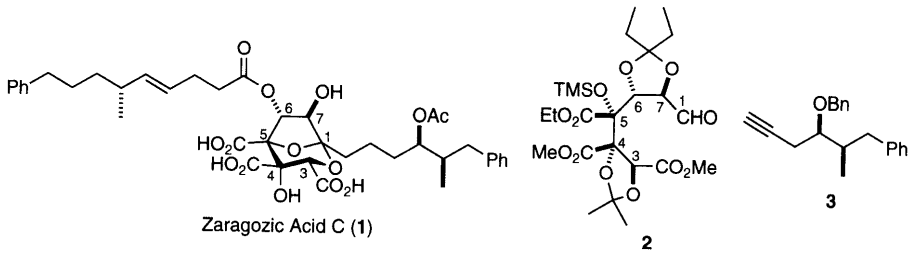

Fig. 1. Zaragozic Acid C and Key Compounds Used in Our Total Synthesis

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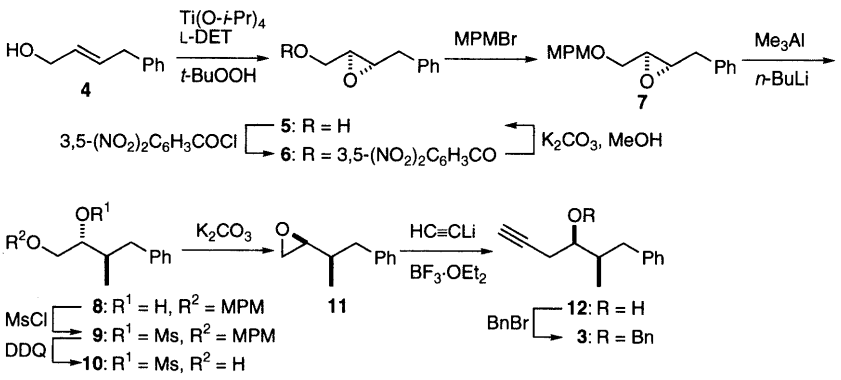

Chart 1

quent ring-opening of the epoxide **7** under Pfaltz conditions produced exclusively the desired alcohol **8**, $[\alpha]_D^{26}$ −2.55° (c=5.2, $CHCl_3$), in 92% yield. Methanesulfonylation of **8** followed by oxidative deprotection of the MPM ether[16] afforded the alcohol **10**, $[\alpha]_D^{26}$ −12.3° (c=3.1, $CHCl_3$), in 90% yield, which, upon exposure to methanolic potassium carbonate, underwent intramolecular S_N2 displacement to give the volatile epoxide **11**, $[\alpha]_D^{25}$ −19.9° (c=1.0, $CHCl_3$) in 96% yield. Finally, a regioselective ring-opening of **11** with lithium acetylide[17] according to the Yamaguchi protocol[18] and subsequent protection of the liberated alcohol as a benzyl ether furnished the target alkyne **3**, $[\alpha]_D^{25}$ −30.3° (c=2.0, $CHCl_3$), in 95% yield.

In summary, we have achieved a practical synthesis of the optically pure C-1 side chain equivalent of zaragozic acid C with an overall yield of 50% for the ten-step sequence, wherein a previously unrecognized property of the Pfaltz protocol has proven to be crucial for a regio- and stereocontrolled epoxide ring-opening.

Experimental

Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. NMR spectra were recorded on a JEOL JNM-EX270 spectrometer, ^1H at 270 MHz and ^{13}C at 67.8 MHz, with tetramethylsilane (δ 0.0, ^1H) or chloroform-d_1 (δ 77.0, ^{13}C) as an internal standard. Infrared spectra were recorded on a Jasco FT/IR-5300 spectrometer. Optical rotations were measured on a Jasco DIP-370 digital polarimeter. Electron impact (EI) mass spectra were obtained on a JEOL JMS-DX303 spectrometer, operating with an ionization energy of 70 eV. FAB-MS were obtained on a JEOL JMS-HX110 spectrometer. Column chromatography was performed on Merck silica gel 60 (70—230 mesh). Dichloromethane (CH_2Cl_2) was distilled from P_2O_5 and stored over 4A molecular sieves. Toluene was distilled from sodium metal and stored over 4A molecular sieves. Triethylamine was distilled from calcium hydride. A stock solution of *tert*-butyl hydroperoxide in CH_2Cl_2 (4.0 M)[9a] and 4-methoxybenzyl bromide[19] were prepared according to literature procedures. All other commercially obtained reagents were used as received.

(2*S*,3*S*)-2,3-Epoxy-4-phenyl-1-butanol (5) (92% ee) Titanium isopropoxide (1.5 ml, 5.04 mmol) was added to a stirred mixture of powdered 4A molecular sieves (3.20 g) and diethyl L-tartrate (1.25 g, 6.06 mmol) in CH_2Cl_2 (200 ml) at −20 °C. A 4.0 M solution of *tert*-butyl hydroperoxide in CH_2Cl_2 (25 ml, 100 mmol) was added and the mixture was stirred for 30 min. A solution of allyl alcohol **4** (7.29 g, 49.2 mmol) in CH_2Cl_2 (15 ml) was added over a 20-min period, and the whole was stirred at −20 °C for 4 h. The solution was quenched with water (30 ml) and allowed to warm to 0 °C. After 30 min at 0 °C, 30% aqueous NaOH in brine (6 ml) was added and the resulting mixture was stirred at room temperature for a further 30 min. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×100 ml). The combined organic extracts were washed with brine (2×50 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (8.85 g), which was purified by column chromatography (silica gel 200 g, 3 : 1→2 : 1 hexane/EtOAc) to give epoxy alcohol **5** (7.32 g, 91%) as a colorless oil. The enantiomeric excess was determined to be 92% by a chiral stationary phase column, $[\alpha]_D^{27}$ −35.4° (c=2.1, $CHCl_3$). IR (film) cm^{-1}: 3420, 2986, 1605, 1497, 1454, 1229, 1076, 1030, 922. ^1H-NMR ($CDCl_3$) δ: 2.89 (1H, dd, J=5.3, 14.5 Hz, $ArCH_2$), 2.94 (1H, dd, J=5.3, 14.5 Hz, $ArCH_2$), 3.00 (1H, ddd, J=2.0, 2.6, 4.0 Hz, $HOCH_2CHO$), 3.22 (1H, dt, J=2.0, 5.3 Hz, $ArCH_2CHO$), 3.65 (1H, dd, J=4.0, 12.5 Hz, CH_2O), 3.92 (1H, dd, J=2.6, 12.5 Hz, CH_2O), 7.21—7.37 (5H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 37.6 (CH_2), 55.9 (CH), 58.3 (CH), 61.4 (CH_2), 126.5 (CH), 128.3 (CH), 128.8 (CH), 136.8 (C). EI-MS *m/z* (rel. int. %): 164 (M^+, 31), 133 (47), 121 (44), 103 (45), 91 (100). HR-EI-MS *m/z*: 164.0842 (Calcd for $C_{10}H_{12}O_2$: 164.0837). HPLC t_R (2*S*,3*S*)-isomer, 19.5 min (96.0%); t_R (2*R*,3*R*)-isomer, 22.9 min (4.0%) (Daicel Chiralcel AD, 20 : 1 hexane/iso-PrOH, 0.8 ml/min).

(2*S*,3*S*)-2,3-Epoxy-4-phenylbutyl 3,5-Dinitrobenzoate (6) To a solution of alcohol **5** (7.26 g, 44.2 mmol) in pyridine (90 ml) at 0 °C was added 3,5-dinitrobenzoyl chloride (15.34 g, 66.5 mmol) in one portion. After 1 h at 0 °C, the reaction was quenched by addition of 5 pieces of ice. The resulting mixture was partitioned between water (200 ml) and EtOAc (300 ml). The organic layer was washed successively with 3 N aqueous HCl (300 ml), water (150 ml), saturated aqueous $NaHCO_3$ (150 ml), and brine (2×80 ml), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The yellow solid (16.02 g) thus obtained was purified by column chromatography (silica gel 320 g, 5 : 6 : 1 hexane/toluene/EtOAc) to give ester **6** (15.38 g, 97%) as a colorless solid, which was recrystallized twice from (iso-Pr)$_2$O–toluene (3 : 1, 400 ml) to afford optically pure ester (12.00 g, 78%) as colorless fine needles, mp 96.0—96.5 °C, $[\alpha]_D^{25}$ −25.1° (c=1.1, $CHCl_3$). IR (nujol) cm^{-1}: 2924, 1732, 1460, 1343, 1277, 1167. ^1H-NMR ($CDCl_3$) δ: 2.92 (1H, dd, J=5.3, 14.5 Hz, $ArCH_2$), 3.01 (1H, dd, J=5.3, 14.5 Hz, $ArCH_2$), 3.17—3.25 (2H, m, CHO×2), 4.30 (1H, dd, J=6.6, 11.9 Hz, CH_2O), 4.75 (1H, dd, J=3.3, 11.9 Hz, CH_2O), 7.21—7.37 (5H, m, ArH), 9.15 (2H, d, J=2.0 Hz, ArH), 9.24 (1H, t, J=2.0 Hz, ArH). ^{13}C-NMR ($CDCl_3$) δ: 37.4 (CH_2), 54.4 (CH), 56.3 (CH), 66.6 (CH_2), 122.3 (CH), 126.6 (CH), 128.3 (CH), 128.7 (CH), 129.2 (CH), 133.0 (C), 136.2 (C), 148.3 (C), 162.1 (C=O). EI-MS *m/z* (rel. int. %): 358 (M^+, 1.3), 267 (39), 195 (100), 91 (53). HR-EI-MS *m/z*: 358.0800 (Calcd for $C_{17}H_{14}N_2O_7$: 358.0801). *Anal.* Calcd for $C_{17}H_{14}N_2O_7$: C, 56.99; H, 3.94; N, 7.82. Found: C, 56.75; H, 4.03; N, 7.74.

(2*S*,3*S*)-2,3-Epoxy-4-phenyl-1-butanol (5) (100% ee) Potassium carbonate (486 mg, 3.52 mmol) was added to a stirred solution of ester **6** (11.95 g, 33.4 mmol) in 2 : 1 tetrahydrofuran (THF)/methanol (210 ml) at 0 °C. After 10 min, the reaction mixture was poured into brine (100 ml) and the whole was extracted with EtOAc (3×100 ml). The combined organic extracts were washed with brine (2×50 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (12.82 g), which was purified by column chromatography (silica gel 200 g, 2 : 1 hexane/EtOAc) to give alcohol **5** (5.24 g, 96%) as a colorless oil. The homochirality of this sample was judged by HPLC analysis using a chiral stationary phase column, $[\alpha]_D^{25}$ −39.9° (c=1.4, $CHCl_3$).

(2*S*,3*S*)-2,3-Epoxy-1-(4-methoxybenzyl)oxy-4-phenylbutane (7) Sodium hydride (993 mg, 41.4 mmol) was added to a mixture of alcohol **5** (5.17 g, 31.5 mmol) and 4-methoxybenzyl bromide (8.25 g, 41.0 mmol) in 3 : 1 THF/*N*,*N*-dimethylformamide (DMF) (60 ml) at 0 °C. After 20 h at room temperature, the reaction was quenched by addition of methanol (1 ml) at 0 °C, followed by stirring at 0 °C for 1 h. Saturated aqueous NH_4Cl (30 ml) and water (20 ml) were added and the whole was extracted with EtOAc (2×50 ml). The combined organic extracts were washed with brine (2×20 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in*

vacuo furnished the crude product (10.56 g), which was purified by column chromatography (silica gel 220 g, 10 : 1 hexane/EtOAc) to afford ether **7** (8.71 g, 97%) as a colorless oil, $[\alpha]_D^{24}$ −9.49° (*c*=3.0, $CHCl_3$). IR (film) cm^{-1}: 2911, 1613, 1512, 1454, 1364, 1248, 1175, 1100. ^{1}H-NMR ($CDCl_3$) δ: 2.85 (1H, dd, *J*=5.3, 14.5 Hz, $ArCH_2$), 2.92 (1H, dd, *J*=5.3, 14.5 Hz, $ArCH_2$), 2.98—3.10 (2H, m, CHO×2), 3.46 (1H, dd, *J*=5.6, 11.9 Hz, CH_2O), 3.67 (1H, dd, *J*=3.6, 11.9 Hz, CH_2O), 3.80 (3H, s, Ar-OCH_3), 4.45 (1H, d, *J*=11.2 Hz, OCH_2Ar), 4.49 (1H, d, *J*=11.2 Hz, OCH_2Ar), 6.88 (2H, m, ArH), 7.19—7.35 (7H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 37.7 (CH_2), 54.8 (CH_3), 55.7 (CH), 56.5 (CH), 69.6 (CH_2), 72.5 (CH_2), 113.5 (CH), 126.3 (CH), 128.2 (CH), 128.7 (CH), 129.0 (CH), 129.8 (C), 136.9 (C), 159.0 (C). EI-MS *m/z* (rel. int. %): 284 (M^+, 4.2), 192 (26), 175 (13), 137 (73), 121 (100). HR-EI-MS *m/z*: 284.1432 (Calcd for $C_{18}H_{20}O_3$: 284.1412).

(2*R*,3*R*)-1-(4-Methoxybenzyl)oxy-3-methyl-4-phenyl-2-butanol (8) Trimethylaluminum in hexane (1.01 M, 60 ml, 60.6 mmol) was diluted with toluene (150 ml). The solution was cooled to −20 °C and *n*-butyllithium in hexane (1.61 M, 5.7 ml, 9.18 mmol) was added dropwise. A solution of epoxide **7** (8.66 g, 30.4 mmol) in toluene (20 ml) was added to the solution over a 30-min period. After 24 h at −20 °C, the reaction mixture was quenched with 2 N aqueous HCl (120 ml) and diluted with EtOAc (100 ml). The layers were separated, and the organic layer was washed successively with water (60 ml), saturated aqueous $NaHCO_3$ (60 ml) and brine (2×30 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* provided the crude product (9.31 g), which was purified by column chromatography (silica gel 200 g, 7 : 1→4:1 hexane/EtOAc) to give alcohol **8** (8.70 g, 95%) as a colorless oil, $[\alpha]_D^{26}$ −2.55° (*c*=5.2, $CHCl_3$). IR (film) cm^{-1}: 3457, 2911, 1613, 1514, 1454, 1302, 1248, 1175, 1094, 1036. ^{1}H-NMR ($CDCl_3$) δ: 0.79 (3H, d, *J*=7.3 Hz, $CHCH_3$), 1.91 (1H, m, $CHCH_3$), 2.38 (1H, dd, *J*=9.6, 13.5 Hz, $ArCH_2$), 2.45 (1H, d, *J*=3.3 Hz, OH), 2.99 (1H, dd, *J*=4.3, 13.5 Hz, $ArCH_2$), 3.41 (1H, dd, *J*=7.9, 9.2 Hz, CH_2O), 3.59 (1H, dd, *J*=2.6, 9.2 Hz, CH_2O), 3.63 (1H, m, CHO), 3.81 (3H, s, Ar-OCH_3), 4.48 (1H, d, *J*=11.2 Hz, OCH_2Ar), 4.49 (1H, d, *J*=11.2 Hz, OCH_2Ar), 6.89 (2H, m, ArH), 7.13—7.31 (7H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 15.0 (CH_3), 38.0 (CH), 38.7 (CH_2), 55.2 (CH_3), 72.2 (CH_2), 73.0 (CH_2), 73.7 (CH), 113.8 (CH), 125.7 (CH), 128.1 (CH), 129.3 (CH×2), 130.0 (C), 140.7 (C), 159.3 (C). EI-MS *m/z* (rel. int. %): 300 (M^+, 5.2), 121 (100), 91 (31). HR-EI-MS *m/z*: 300.1699 (Calcd for $C_{19}H_{24}O_3$: 300.1726).

(2*R*,3*R*)-2-(Methanesulfonyl)oxy-1-(4-methoxybenzyl)oxy-3-methyl-4-phenylbutane (9) Methanesulfonyl chloride (3.1 ml, 40.1 mmol) was added to a solution of alcohol **8** (8.65 g, 28.8 mmol) and triethylamine (10 ml, 71.7 mmol) in CH_2Cl_2 (80 ml) at 0 °C. After stirring at 0 °C for 6 h, 3 pieces of ice were added and the mixture partitioned between 8 : 1 Et_2O/hexane (90 ml) and saturated aqueous NH_4Cl (50 ml). The aqueous layer was extracted with EtOAc (2×50 ml), and the combined organic extracts were washed with brine (2×20 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (11.69 g), which was purified by column chromatography (silica gel 250 g, 8 : 1→4 : 1 hexane/EtOAc) to provide methanesulfonate **9** (10.14 g, 93%) as a colorless oil, $[\alpha]_D^{24}$ −23.8° (*c*=2.0, $CHCl_3$). IR (film) cm^{-1}: 2938, 1613, 1515, 1456, 1350, 1248, 1173, 1101. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, *J*=6.6 Hz, $CHCH_3$), 2.23 (1H, m, $CHCH_3$), 2.37 (1H, dd, *J*=9.9, 13.2 Hz, $ArCH_2$), 2.89 (1H, dd, *J*=4.6, 13.2 Hz, $ArCH_2$), 3.01 (3H, s, SO_2CH_3), 3.66 (2H, d, *J*=6.0 Hz, CH_2O), 3.81 (3H, s, Ar-OCH_3), 4.46 (1H, d, *J*=11.9 Hz, OCH_2Ar), 4.48 (1H, d, *J*=11.9 Hz, OCH_2Ar), 4.74 (1H, dt, *J*=10.6, 6.0 Hz, CHO), 6.89 (2H, m, ArH), 7.11—7.32 (7H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 15.1 (CH_3), 37.1 (CH), 38.3 (CH_2), 38.6 (CH_3), 55.2 (CH_3), 69.3 (CH_2), 72.9 (CH_2), 85.9 (CH), 113.8 (CH), 126.1 (CH), 128.3 (CH), 129.0 (CH), 129.4 (CH), 139.5 (C), 159.4 (C). EI-MS *m/z* (rel. int. %): 378 (M^+, 2.6), 136 (17), 121 (100). HR-EI-MS *m/z*: 378.1475 (Calcd for $C_{20}H_{26}O_5S$: 378.1501).

(2*R*,3*R*)-2-(Methanesulfonyl)oxy-3-methyl-4-phenyl-1-butanol (10) To a biphasic mixture of MPM ether **9** (10.09 g, 26.6 mmol) in 18 : 1 CH_2Cl_2/H_2O (76 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (9.08 g, 40.0 mmol) in one portion at room temperature. After stirring at room temperature for 3.5 h, the black reaction mixture was filtered through a Celite pad and the filtrate partitioned between Et_2O (100 ml) and saturated aqueous $NaHCO_3$ (70 ml). The aqueous layer was extracted with EtOAc (50 ml), and the combined organic extracts washed successively with saturated aqueous $NaHCO_3$ (70 ml) and brine (2×40 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* afforded the crude product (10.85 g), which was purified by column chromatography (silica gel 220 g, 2 : 1→3 : 2 hexane/EtOAc) to provide alcohol **10** (6.69 g, 97%) as a yellow oil, $[\alpha]_D^{26}$ −12.3° (*c*=3.1, $CHCl_3$). IR (film) cm^{-1}: 3534, 2969, 1603, 1454, 1335, 1171, 1073, 1019. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, d, *J*=6.9 Hz, $CHCH_3$), 2.26 (1H, m, $CHCH_3$), 2.41 (1H, dd, *J*=9.8, 13.4 Hz, $ArCH_2$), 2.91 (1H, dd, *J*=4.8, 13.4 Hz, $ArCH_2$), 3.09 (3H, s, SO_2CH_3), 3.84 (1H, dd, *J*=6.9, 12.5 Hz, CH_2O), 3.91 (1H, dd, *J*=3.0, 12.5 Hz, CH_2O), 4.69 (1H, ddd, *J*=3.0, 5.6, 6.9 Hz, CHO), 7.13—7.33 (5H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 15.0 (CH_3), 36.8 (CH), 38.3 (CH_2, CH_3), 62.3 (CH_2), 88.0 (CH), 126.2 (CH), 128.3 (CH), 128.9 (CH), 139.4 (C). FAB-MS *m/z* (rel. int. %): 259 (M^++H, 12), 163 (19), 145 (100). HR-FAB-MS *m/z*: 259.0997 (Calcd for $C_{12}H_{19}O_4S$: 259.1004).

(2*S*,3*R*)-1,2-Epoxy-3-methyl-4-phenylbutane (11) Potassium carbonate (3.91 g, 28.3 mmol) was added to a solution of alcohol **10** (6.64 g, 25.7 mmol) in methanol (100 ml) at 0 °C, and the whole was stirred at 0 °C for 1 h and at room temperature for 4 h. The mixture was partitioned between Et_2O (100 ml) and water (80 ml). The aqueous layer was saturated with NaCl, and then extracted with EtOAc (60 ml). The combined organic extracts were washed with brine (2×30 ml) and dried over anhydrous Na_2SO_4. Filtration and concentration by atmospheric fractional distillation furnished the crude product (4.34 g), which was purified by column chromatography (silica gel 45 g, 30 : 1 hexane/Et_2O) to give epoxide **11** (3.99 g, 96%) as a colorless oil, $[\alpha]_D^{25}$ −19.9° (*c*=1.0, $CHCl_3$). IR (film) cm^{-1}: 2967, 1603, 1495, 1454, 1375, 1258, 1030. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, d, *J*=6.6 Hz, $CHCH_3$), 1.62 (1H, m, $CHCH_3$), 2.33 (1H, dd, *J*=2.6, 4.6 Hz, CH_2O), 2.57 (1H, dd, *J*=7.3, 13.2 Hz, $ArCH_2$), 2.64 (1H, dd, *J*=3.9, 4.6 Hz, CH_2O), 2.72 (1H, dd, *J*=7.9, 13.2 Hz, $ArCH_2$), 2.76 (1H, m, CHO), 7.13—7.32 (5H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 16.6 (CH_3), 38.1 (CH), 39.9 (CH_2), 46.5 (CH_2), 56.2 (CH), 125.8 (CH), 128.1 (CH), 128.8 (CH), 139.8 (C). EI-MS *m/z* (rel. int. %): 162 (M^+, 3.3), 131 (78), 117 (21), 91 (100). HR-EI-MS *m/z*: 162.1048 (Calcd for $C_{11}H_{14}O$: 162.1045).

(2*R*,3*R*)-2-Methyl-1-phenyl-5-hexyn-3-ol (12) Dry acetylene gas was bubbled through THF (150 ml) at −78 °C for 15 min and *n*-butyllithium in hexane (3.04 M, 24 ml, 73.0 mmol) was added over a 15-min period with passage of dry acetylene. After 10 min, boron trifluoride diethyl etherate (9.3 ml, 73.4 mmol) was added, and the resulting solution was stirred for 15 min. A solution of epoxide **11** (3.94 g, 24.3 mmol) in THF (15 ml) was added by cannula. After being stirred at −78 °C for 0.5 h, the reaction mixture was poured into a well-stirred mixture of Et_2O (50 ml) and saturated aqueous NH_4Cl (200 ml) at 0 °C. Additional Et_2O (50 ml) and water (100 ml) were added, and the layers were separated. The aqueous layer was extracted with EtOAc (100 ml), and the combined organic extracts were washed with brine (2×50 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* afforded the crude product (5.49 g), which was purified by column chromatography (silica gel 80 g, 8 : 1 hexane/EtOAc) to provide alcohol **12** (4.38 g, 96%) as a yellow oil, $[\alpha]_D^{23}$ −12.4° (*c*=3.0, $CHCl_3$). IR (film) cm^{-1}: 3439, 3299, 2967, 2118, 1603, 1495, 1454, 1250, 1096, 1055. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, d, *J*=6.6 Hz, $CHCH_3$), 1.87 (1H, d, *J*=4.6 Hz, OH), 1.97 (1H, m, $CHCH_3$), 2.05 (1H, t, *J*=2.6 Hz, C≡CH), 2.37 (1H, ddd, *J*=2.6, 5.3, 16.5 Hz, $CH_2C{\equiv}C$), 2.45 (1H, dd, *J*=8.8, 13.6 Hz, $ArCH_2$), 2.45 (1H, m, $CH_2C{\equiv}C$), 2.82 (1H, dd, *J*=6.6, 13.6 Hz, $ArCH_2$), 3.71 (1H, m, CHOH), 7.15—7.33 (5H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 13.1 (CH_3), 25.0 (CH_2), 39.3 (CH), 39.7 (CH_2), 70.6 (C), 72.1 (CH), 81.2 (CH), 125.9 (CH), 128.2 (CH), 129.1 (CH), 140.6 (C). EI-MS *m/z* (rel. int. %): 188 (M^+, 0.6), 149 (12), 131 (25), 91 (100). HR-EI-MS *m/z*: 188.1209 (Calcd for $C_{13}H_{16}O$: 188.1201).

(4*R*,5*R*)-4-Benzyloxy-5-methyl-6-phenyl-1-hexyne (3) To a suspension of sodium hydride (676 mg, 28.2 mmol) in 3 : 2 THF/DMF (20 ml) at 0 °C was added a solution of alcohol **12** (4.32 g, 22.9 mmol) in THF (12 ml), followed by addition of benzyl bromide (3.3 ml, 27.7 mmol) and tetrabutylammonium iodide (85 mg, 0.23 mmol). After stirring at room temperature for 10 h, the reaction was quenched with saturated aqueous NH_4Cl (8 ml). The whole was partitioned between 10 : 1 Et_2O/hexane (30 ml) and water (10 ml), and the organic layer was washed with brine (2×10 ml) and dried over anhydrous Na_2SO_4. Filtration and evaporation *in vacuo* furnished the crude product (7.41 g), which was purified by column chromatography (silica gel 100 g, 50 : 1 hexane/Et_2O) to afford benzyl ether **3** (6.35 g, 99%) as a colorless oil, $[\alpha]_D^{25}$ −30.3° (*c*=2.0, $CHCl_3$). IR (film) cm^{-1}: 3301, 2967, 2118, 1603, 1495, 1454, 1354, 1069, 1028. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, *J*=6.6 Hz, $CHCH_3$), 1.99 (1H, t, *J*=2.6 Hz, C≡CH), 2.19 (1H, m, $CHCH_3$), 2.42 (1H, ddd, *J*=2.6, 6.6, 16.5 Hz, $CH_2C{\equiv}C$), 2.47 (1H, dd, *J*=9.2, 13.2 Hz, $ArCH_2$), 2.56 (1H, ddd, *J*=2.6, 5.9, 16.5 Hz, $CH_2C{\equiv}C$), 2.82 (1H, dd, *J*=5.9, 13.2 Hz, $ArCH_2$), 3.50 (1H, ddd, *J*=3.3, 5.9, 6.6 Hz, CHO), 4.50 (1H, d, *J*=11.2 Hz, $ArCH_2O$), 4.71 (1H, d, *J*=11.2 Hz, $ArCH_2O$), 7.10—7.42 (10H, m, ArH). ^{13}C-NMR ($CDCl_3$) δ: 13.5 (CH_3), 21.3 (CH_2), 38.2 (CH), 39.6 (CH_2), 69.9 (C), 71.9 (CH_2), 79.8 (CH), 81.5 (CH), 125.7 (CH), 127.4 (CH), 127.5 (CH), 128.1 (CH), 128.2 (CH), 129.0 (CH), 138.6 (C), 140.9 (C). EI-MS *m/z* (rel. int. %): 278 (M^+, 0.1), 170 (9.9), 131 (20), 119 (8.0), 91 (100). HR-EI-MS *m/z*: 278.1650 (Calcd for

$C_{20}H_{22}O$: 278.1671).

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