Stereocontrolled Synthesis of Exocyclic Olefins Using Arene Tricarbonyl Chromium Complex-Catalyzed Hydrogenation. II. A Catalytic Asymmetric Synthesis of an Anthracycline Intermediate

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A method for the stereospecific synthesis of trisubstituted exocyclic allylic alcohols is described. Using this methodology in combination with the Sharpless catalytic asymmetric epoxidation, an efficient synthesis of (*R*)-(−)-9, an important intermediate for anthracycline synthesis, has been accomplished in 36% overall yield from 14 with 93% ee.

Keywords dienol acetate; 1,4-hydrogenation; arene tricarbonyl chromium complex; exocyclic allylic alcohol; antineoplastic agent

The Sharpless asymmetric epoxidation is one of the most useful and versatile catalytic asymmetric reactions.[1] For the efficient use of this excellent reaction the olefin geometry of allylic alcohols has to be strictly controlled. Although a number of methods for the stereocontrolled synthesis of olefins are known, there is no methodology for the stereospecific synthesis of exocyclic allylic alcohols such as **4**. As described in the preceding paper,[2] we have exploited an extremely efficient method for the stereospecific synthesis of exocyclic tri- and tetrasubstituted olefins using the 1,4-hydrogenation of conjugated dienes catalyzed by arene·$Cr(CO)_3$ complex. This successful result led us to expect that extension of the 1,4-hydrogenation technique to dienol acetates **1** could produce exocyclic allylic alcohols **4** stereospecifically (Chart 1). To test the feasibility of this stereospecific synthesis of exocyclic allylic alcohols, the following asymmetric synthesis of the anthracycline intermediate **9** was undertaken (Chart 2).

4-Demethoxyadriamycin (**7**) and 4-demethoxydaunorubicin (**8**) are expected to be more clinically useful antineoplastic agents than the naturally occurring anthracyclines **5** and **6**.[3] Since these analogues are not available by the fermentation method, quite a number of synthetic studies on **7** and **8** have already been reported, and it has been established that (*R*)-(−)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (**9**) is one of the most useful synthetic intermediates.[4] This account describes a synthesis of (*R*)-(−)-**9** using the above-mentioned methodology, which features a catalytic use of the chiral source.[5]

Regiocontrolled Synthesis of the Dienol Acetate The synthesis of the dienol acetate **13** started with the highly enolizable ketone **14**, which was prepared according to the reported procedure.[6] First we attempted to use the ethynyl-alcohol **16** as an intermediate, obtainable by the reaction of **14** with the ethynylcerium reagent[7] followed by desilylation (tetrabutylammonium fluoride (TBAF) in tetrahydrofuran (THF), 94%). Hydroboration of **16** with disiamylborane and subsequent oxidation[8] afforded the

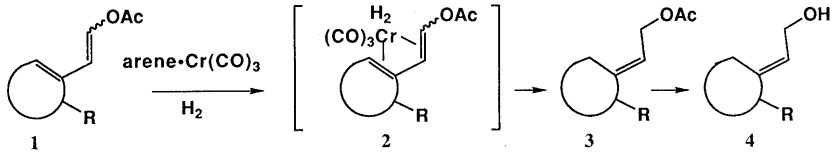

Chart 1

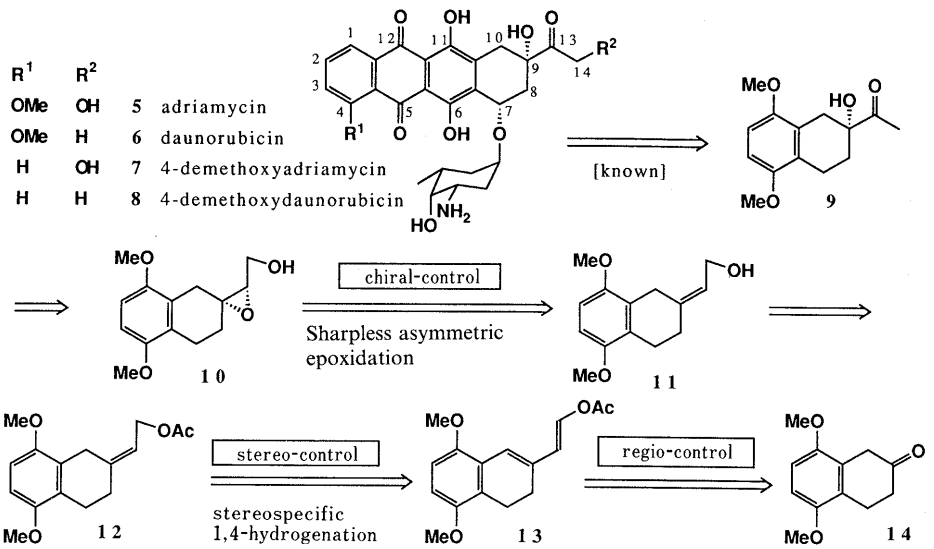

Chart 2

aldehydes **17** and **18**. These aldehydes could be converted to the desired dienol acetate **13** by treatment with acetic anhydride (3.6 eq) and triethylamine (4.0 eq) in toluene at 80 °C. The overall yield of **13** from **15**, however, was only 17% owing to instability of the aldehydes under the oxidation conditions. Furthermore, reproducibility of the reaction was poor.

Therefore, we next turned our attention to the allylic alcohol **19**, which was obtained efficiently from **14** according to the procedure reported by Hiyama *et al.*[9] Treatment of **19** with a catalytic amount of osmium tetroxide and 3 eq of sodium periodate in aqueous ether (ether–H_2O, 3 : 4) at 23 °C afforded the unstable aldehyde **17**, which, without purification, was converted to the dienol acetate **13** regio- and stereospecifically on exposure to acetic anhydride (5 eq), triethylamine (8 eq) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in toluene at 80 °C for 40 min (60% overall yield from **19**).[10] A better overall yield was obtained by the following sequence. Acetylation of **19** (5 eq of Ac_2O, 5 eq of pyridine and a catalytic amount of DMAP in CH_2Cl_2) gave the acetate **20**, which was transformed into the dienol acetate **13** regio- and stereospecifically on exposure to the same reaction conditions as described above in 73% overall yield. The stereochemistry of the disubstituted double bond in the dienol acetate **13** was determined from the proton nuclear magnetic resonance (^{1}H-NMR) spectra. The coupling constant between H_a and H_b was 13 Hz, being in accord with those of *E*-enol acetates.[11]

1,4-Hydrogenation of the Dienol Acetate As expected, the crucial 1,4-hydrogenation of the dienol acetate **13** proceeded smoothly by using naphthalene·$Cr(CO)_3$ as a catalyst to afford the stereochemically homogeneous *Z*-allylic acetate **12** in 91% yield (20 mol% of the catalyst, acetone solvent, 140 kg/cm^2 of H_2 pressure, 45 °C, 13 h) together with recovery of **13** (9%). A part of **12** (4%) was isolated as its chromium complex (**21**), which was easily converted to **12** on exposure to $FeCl_3$/EtOH. The obtained allylic acetate **12** was then converted to the allylic alcohol **11** in quantitative yield by treatment with potassium carbonate in methanol.

Comparison of the ^{1}H-NMR spectra of **12** and **24** showed clearly that the 1,4-hydrogenation product was stereochemically homogeneous. The stereoisomer **24** was synthesized as shown in Chart 5. Furthermore, the stereochemistry of the desired exocyclic allylic alcohol **11** was unequivocally determined to be *Z* by the nuclear Overhauser effect (NOE) experiments.

Thus, we succeeded in the efficient and stereospecific synthesis of the exocyclic allylic alcohol **11**.

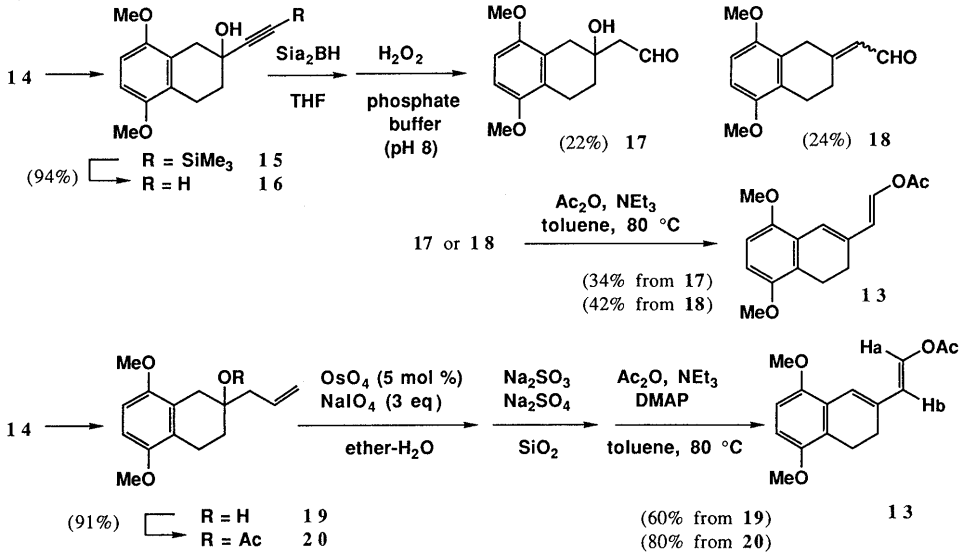

Chart 3

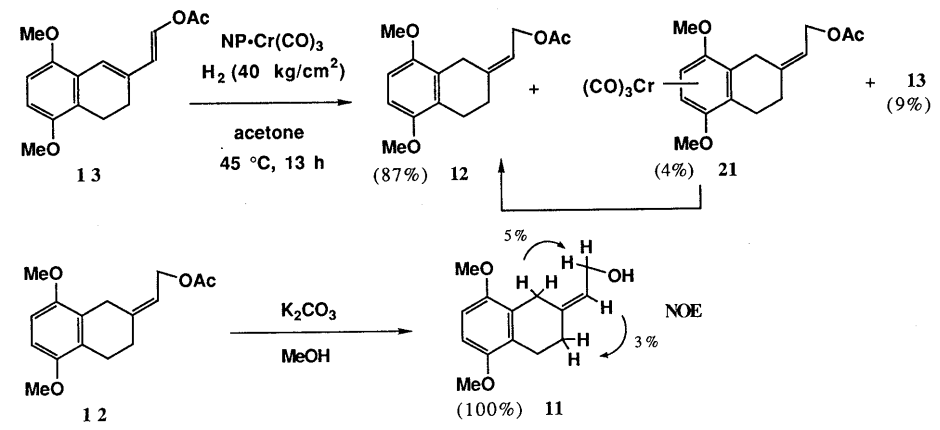

Chart 4

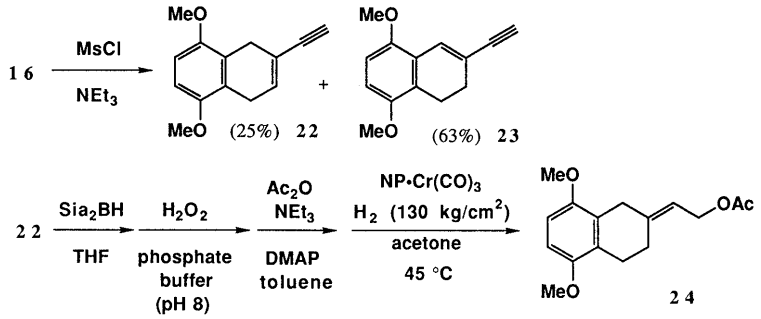

Chart 5

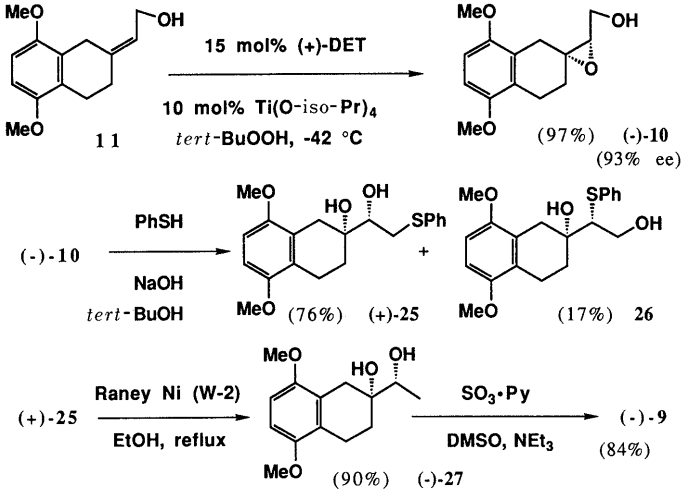

Chart 6

Asymmetric Synthesis of the Anthracycline Intermediate Next we turned our attention to the transformation of **11** into (*R*)-(−)-**9**. The Sharpless catalytic asymmetric epoxidation[1] of **11** proceeded smoothly (5 mol% of (+)-diethyl tartrate, 10 mol% of titanium(IV) isopropoxide, 2 eq of *tert*-butyl hydroperoxide, molecular sieves 4A, −42 °C, 2.5 h), providing the optically active and crystalline epoxy-alcohol **10** in 97% yield. The enantiomeric excess was determined to be 93% by ^{1}H-NMR analysis (400 MHz) of the corresponding MTPA ester.[12] Recrystallization of this sample from CH_2Cl_2–hexane gave optically pure (−)-**10** (yield, 43%).

Treatment of optically pure **10** with thiophenol under basic conditions (slow dropping of thiophenol into a solution of **10** in 0.5 N aqueous NaOH–*tert*-butanol (3 : 2) at 85—90 °C)[13] afforded the desired dihydroxy-sulfide **25** *via* Payne rearrangement[14] in 76% yield together with a small amount of the regioisomer **26** (17%). Hydrogenolysis of the carbon-sulfur bond of **25** was carried out with Raney Ni (W-2) in boiling ethanol, giving the diol **27** in 90% yield. Finally the diol **27** was converted to (*R*)-(−)-**9** in 84% yield on exposure to 10 eq of sulfur trioxide–pyridine complex and 30 eq of triethylamine in dimethyl sulfoxide (DMSO). The values of the optical rotation ($[\alpha]_D^{20}$ −48.7° (c=0.825, $CHCl_3$) and the melting point (128—129 °C) of **9** thus obtained were in good agreement with those reported in the literature (lit. 4*i* $[\alpha]_D^{20}$ −48.8° (c=1, $CHCl_3$), mp 128—129 °C, lit. 4*l* $[\alpha]_D^{20}$ −47.6° (c=1.02, $CHCl_3$), mp 129.5—130 °C, lit. 4*d* $[\alpha]_D^{20}$ −48.2° (c=0.982, $CHCl_3$), mp 128—129 °C).

In summary, we have accomplished an asymmetric synthesis of (*R*)-(−)-**9**, a well-known intermediate for the synthesis of anthracyclines, in 36% overall yield starting with **14**. The synthesis presented above involves a new and efficient method for the stereospecific synthesis of exocyclic allylic alcohols and a catalytic asymmetric induction process. The aforementioned methodology should be advantageous for synthesizing a variety of compounds.[15]

Experimental

General Methods Infrared (IR) spectra were measured on a JASCO A-202 diffraction grating infrared spectrophotometer. ^{1}H-NMR spectra were recorded with a Varian EM 390 NMR spectrometer or a Hitachi R-90H Fourier-transform NMR spectrometer or a Brucker AN-400 spectrometer with tetramethylsilane as an internal standard. Low-resolution mass spectra (MS) were obtained with a Hitachi RUM-6MG mass spectrometer. Optical rotation was measured on a Horiba SEPA-200 high-sensitivity polarimeter. In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned.

2-Ethynyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (16) Tetrabutylammonium fluoride (1 M solution in THF, 3.59 ml) was added to a solution of **15**[7] (729 mg, 2.39 mmol) in THF (10 ml), and the mixture was stirred for 10 min at 23 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction of the mixture with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 1 : 2) to give the alcohol **16** (522 mg, 94%) as colorless prisms. IR (KBr): 3310, 3260, 2110, 1605, 1258, 805 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.05 (t, J=7 Hz, 2H), 2.11 (s, 1H), 2.40 (s, 1H), 2.85 (t, J=7 Hz, 2H), 2.92 (d, J=16 Hz, 1H), 3.16 (d, J=16 Hz, 1H), 3.78 (s, 6H), 6.64 (s, 2H). MS m/z: 332 (base peak, M^+), 214 ($M^+ - H_2O$), 199, 183, 175, 164, 149, 165, 159, 121, 91, 77. *Anal.* Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.34; H, 6.92. mp 104—105 °C (recryst. from ether–CH_2Cl_2).

2-Acetoxy-2-allyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (20) Pyridine (4.48 ml, 55 mmol), acetic anhydride (5.22 ml, 55 mmol) and a catalytic amount of DMAP were added to a stirred solution of the alcohol **19**[9] (2.75 g, 11 mmol) in methylene chloride (20 ml), and the mixture was stirred at 23 °C overnight. After evaporation of the solvent and the excess reagents, the residue was purified by silica gel column chromatography (ether–hexane, 1 : 5) to give **20** (2.91 g. 91%) as colorless prisms. IR (KBr): 1730, 1640, 1605, 1490, 1258 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (s, 3H), 2.20—3.00 (m, 7H), 3.17 (d, J=17 Hz, 1H), 3.77 (s, 6H), 5.12 (m, 2H), 5.80 (m, 1H), 6.60 (s, 2H). MS m/z: 290 (M^+), 249 (M^+ − allyl), 230 (base peak), 215, 207, 199, 189, 174, 158, 115, 91, 43. *Anal.* Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.02; H, 7.48. mp 92—94 °C (recryst. from benzene–hexane).

2-(*E*-2-Acetoxyvinyl)-3,4-dihydro-5,8-dimethoxynaphthalene (13) From **16**: A solution of disiamylborane in THF (0.93 M, 1.11 ml, 1.03 mmol) was added to a stirred solution of **16** (100 mg, 0.43 mmol) in THF (1 ml) at 0 °C, and the mixture was stirred at 23 °C for 20 min. Then the reaction mixture was poured into a mixture of phosphate buffer (NaH_2PO_4 3.8 mmol, NaOH 3.3 mmol in 10 ml of H_2O, pH 8) and 30% H_2O_2 (0.351 ml, 3.10 mmol), and the whole reaction mixture was stirred at 23 °C for 40 min, then extracted with ether. The combined organic layers were washed with $Na_2S_2O_3$ and brine and dried over $MgSO_4$. Removal of the solvent gave the oily residue, which was purified by silica gel column

chromatography (ether–hexane, 1 : 1) to afford the aldehyde **17** (24 mg, 22%) and **18** (24 mg, 24%). Owing to the instability of these aldehydes, only the NMR spectra were measured. **17**: ^{1}H-NMR ($CDCl_3$) δ: 1.86 (m, 2H), 2.64 (d, J=2 Hz, 2H), 2.80 (m, 5H), 3.78 (s, 6H), 6.64 (s, 2H), 9.97 (t, J=2 Hz, 1H). **18**: ^{1}H-NMR ($CDCl_3$) δ: 2.30—3.20 (m, 6H), 6.02 (m, 1H), 3.78 (s, 6H), 6.65 (s, 2H), 10.10, 10.20 (each d, J=6 Hz, total 1H). Triethylamine (0.054 ml, 0.384 mmol), acetic anhydride (0.033 ml, 0.345 mmol) and a catalytic amount of DMAP were added to a stirred solution of the aldehyde **17** (24 mg, 0.096 mmol) in toluene (1.3 ml), and the mixture was stirred at 80 °C for 10 min, then allowed to cool to room temperature. The reaction was quenched by the addition of brine, followed by extraction of the mixture with ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 1 : 4) to afford the dienol acetate **13** (9 mg, 34%). In a similar manner, **18** was converted to **13** in 42% yield.

From **20**: A solution of osmium tetroxide in ether (0.1% (w/v), 1.8 ml, 0.7 mmol) was added to a solution of the acetate **20** (2.05 g, 7.0 mmol) in ether (26 ml). To this solution, an aqueous solution of $NaIO_4$ (4.49 g, 21 mmol in 35 ml of H_2O) was added over 5 min, and the mixture was stirred at 23 °C for 6.5 h. The separated ether layer was filtered through a pad of Na_2SO_4–Na_2SO_3–SiO_2. Removal of the solvent from the filtrate gave the crude aldehyde **17**. Triethylamine (7.8 ml, 56 mmol), acetic anhydride (3.3 ml, 35 mmol) and a catalytic amount of DMAP were added to a stirred solution of the crude aldehyde **17** in toluene (40 ml), and the mixture was stirred at 80 °C for 50 min, then allowed to cool to room temperature. The reaction was quenched by the addition of brine, followed by extraction of the mixture with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 1 : 4) to afford the dienol acetate **13** (1.54 g, 80%) as colorless prisms. IR (KBr): 1757, 1640, 1618, 1598, 1490, 1215 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (s, 3H), 2.33 (t, J=8 Hz, 2H), 2.83 (t, J=8 Hz, 2H), 3.80 (s, 6H), 6.29 (d, J=13 Hz, 1H), 6.66 (s, 2H), 6.76 (s, 1H), 7.52 (d, J=13 Hz, 1H). MS m/z: 274 (M^+), 232 (base peak), 43. *Anal.* Calcd for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.99; H, 6.67. mp 115—116 °C (recryst. from CH_2Cl_2–hexane).

(*Z*)-2-(2-Acetoxyethylidene)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (12) The dienol acetate **13** (410 mg, 1.49 mmol) and naphthalene·$Cr(CO)_3$ (80 mg, 0.3 mmol) were dissolved in acetone (10 ml). The solution was degassed by three freeze-pump-thaw cycles, and then transferred into an autoclave with a glass insert (100 ml) under an argon atmosphere. The autoclave was purged repeatedly with hydrogen. The solution was stirred at 45 °C for 13 h under 140 kg/cm^2 of hydrogen pressure. After cooling to room temperature, the reaction mixture was exposed to air and light to decompose the catalyst. Removal of the solvent gave a dark green residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 5) to afford the desired exocyclic allylic acetate **12** (359 mg, 87%) as a more polar fraction and the starting material **13** (39 mg, 9%) as a less polar fraction. Furthermore, elution with ether afforded the unstable chromium complex **21** (28 mg, IR (KBr): 2940, 1952, 1865, 1735 cm^{-1}) as a yellow caramel. This complex was partially decomposed on exposure to air and light. A solution of $FeCl_3$ in wet ethanol was added to **21**, and the mixture was stirred at 23 °C for 1 h. Removal of the solvent and purification of the residue by silica gel column chromatography (ether–hexane, 1 : 5) afforded **12** (16 mg, 4%). Spectral data of **12**: IR (KBr): 2950, 1740, 1675, 1602, 1485, 1258, 1090 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.06 (s, 3H), 2.40 (t, J=7 Hz, 2H), 2.75 (t, J=7 Hz, 2H), 3.43 (br s, 2H), 3.75 (s, 3H), 3.78 (s, 3H), 4.68 (d, J=7 Hz, 2H), 5.48 (t, J=7 Hz, 1H), 6.62 (s, 2H). MS m/z: 276 (M^+), 218, 217, 216 (base peak), 201, 189, 175, 173, 115, 43. HR-MS m/z: (M^+) Calcd for $C_{16}H_{20}O_4$ 276.1359, Found 276.1357.

(*Z*)-2-(2-Hydroxyethylidene)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (11) Potassium carbonate (151 mg, 1.09 mmol) was added to a solution of the acetate **12** (151 mg, 0.55 mmol) in methanol (8 ml), and the mixture was stirred at 23 °C for 1 h. Evaporation of methanol, dilution of the residue with ether, and filtration through a silica gel pad afforded the desired alcohol **11** (128 mg, 100%) as a colorless solid. Recrystallization from ether–hexane gave colorless needles. IR (KBr): 3400, 1678, 1602, 1482, 1255, 1082, 790 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (s, 1H), 2.39 (t, J=7 Hz, 2H), 2.77 (t, J=7 Hz, 2H), 3.43 (s, 2H), 3.76 (s, 3H), 3.80 (s, 3H), 4.26 (d, J=7 Hz, 2H), 5.55 (t, J=7 Hz, 1H), 6.63 (s, 2H). MS m/z: 234 (M^+), 217, 216 (base peak), 203, 201, 189, 188, 185, 173, 159, 128, 115, 91, 77, 61, 45, 43, 29. *Anal.* Calcd for $C_{14}H_{18}O_3$: C, 70.32; H, 7.64. Found: C, 70.02; H, 7.48. mp 63.5—65.0 °C (recryst. from ether–hexane).

2-Ethynyl-5,8-dimethoxy-1,4-dihydronaphthalene (22) Triethylamine (13.5 ml, 96.9 mmol) and mesyl chloride (2.5 ml, 32.3 mmol) were added to a solution of **16** (1.5 g, 6.46 mmol) in methylene chloride (40 ml) at 0 °C, and the mixture was stirred at 0—23 °C for 1.5 h. The reaction was quenched by the addition of brine, followed by extraction of the mixture wih ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 1 : 20) to give **22** (345 mg, 25%) as a less polar fraction and **23** (864 mg, 63%) as a more polar fraction. Spectral data of **22**: IR (neat): 3265, 2950, 2110, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.84 (s, 1H), 3.37 (s, 4H), 3.78 (s, 6H), 6.32 (br s, 1H), 6.62 (s, 2H). MS m/z: 214 (base peak, M^+), 199, 189, 183, 164, 149. HR-MS m/z: (M^+) Calcd for $C_{14}H_{14}O_2$ 214.0994, Found 214.0998. Spectral data of **23**: IR (neat): 3265, 2940, 2110, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.37 (br t, J=8 Hz, 2H), 2.80 (br t, J=8 Hz, 2H), 3.10 (s, 1H), 3.78 (s, 6H), 6.65 (s, 1H), 6.68 (s, 1H), 7.24 (s, 1H). MS m/z: 214 (base peak, M^+), 199, 189, 183. HR-MS m/z: (M^+) Calcd for $C_{14}H_{14}O_2$ 214.0994, Found 214.0982.

(*E*)-2-(2-Acetoxyethylidene)-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (24) In a similar manner to that used for the synthesis of **12** from **16**, the stereoisomer of **12** (**24**) was synthesized. Spectral data of **24**: IR (neat): 2950, 1740, 1675, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.19 (s, 3H), 2.48 (t, J=7 Hz, 2H), 2.78 (t, J=7 Hz, 2H), 3.38 (br s, 2H), 3.75 (s, 6H), 4.65 (d, J=7 Hz, 2H), 5.55 (t, J=7 Hz, 1H), 6.61 (s, 2H). MS m/z: 276 (M^+), 217, 216 (base peak), 201, 175, 115, 43. HR-MS m/z: (M^+) Calcd for $C_{16}H_{20}O_4$ 276.1359, Found 276.1368.

(2*R*,3′*S*)-5,8-Dimethoxy-1,2,3,4-tetrahydronaphthalene-2-spiro-3′-hydroxymethyl-2′-oxirane (10) Titanium tetraisopropoxide (0.036 ml, 0.12 mmol) was added to a suspension of powdered molecular sieves 4A (60 mg, dried at 220 °C under vacuum) in methylene chloride (6 ml) at −22 °C, and the mixture was stirred at the same temperature for 10 min. L-(+)-Diethyl tartrate (0.033 ml, 0.19 mmol) was added, and this mixture was stirred at −22 °C for 15 min. A solution of *tert*-butyl hydroperoxide (6.1 M solution in CH_2Cl_2, 0.41 ml, 2.48 mmol) was added to this suspension, and the reaction mixture was stirred at the same temperature for 40 min. A solution of the allylic alcohol **11** (290 mg, 1.24 mmol) in methylene chloride (8 ml) was then added at −42 °C, and the whole mixture was stirred at −42 °C for 2.5 h. The reaction was quenched by addition of 10% aqueous sodium hydroxide solution saturated with sodium chloride (0.29 ml) at −42 °C, and the mixture was diluted with ether (5 ml), removed from the cold bath, allowed to warm to 10 °C with vigorous stirring, and filtered through a Celite pad. The clear filtrate was treated again with 10% aqueous sodium hydroxide solution saturated with sodium chloride (0.29 ml) at 23 °C for 10 min. A solution of phosphate buffer (0.2 ml) [Na_2HPO_4 (1.5 mol) and KH_2PO_4 (1.5 mol) were dissolved in H_2O (1 l), and the pH was adjusted to 7 by addition of NaOH], Celite (1 g), and $MgSO_4$ (1 g) were then added, and the whole mixture was filtered through a Celite pad. Evaporation of the solvent gave a pale yellow solid. Purification by silica gel column chromatography (ether–methylene chloride, 1 : 5) afforded the epoxy alcohol **10** (301 mg, 97%, $[\alpha]_D^{20}$ −18.1° (c=1.34, $CHCl_3$)) as a colorless solid. For analysis of the enantiomeric purity, **10** was converted to the corresponding methoxytrifluoromethylphenylacetate (MTPA ester). Thus, (−)-MTPA chloride (5 μl) was added to a solution of **10** (3 mg, 0.01 mmol) in pyridine (0.1 ml), and the mixture was stirred at 23 °C for 2 h. The reaction mixture was diluted with ether, followed by filtration through a silica gel pad. Purification by silica gel column chromatography provided the MTPA ester. Analysis was accomplished by the use of 400 MHz ^{1}H-NMR ($CDCl_3$). Diastereomeric excess was determined to be 93.2% from the ratio of the two peaks (δ 3.518 ppm, (−)-MTPA-(−)-**10**, and δ 3.543 ppm, (−)-MTPA-(+)-**10**, 96.6 : 3.4). Optically pure (−)-**10** (colorless fine needles, $[\alpha]_D^{20}$ −21.7° (c=0.725, $CHCl_3$), mp 145—146 °C) was obtained by single recrystallization from methylene chloride–hexane (recovery, 46%). The optical purity of this sample was determined to be >97% ee by ^{1}H-NMR (400 MHz) analysis of its MTPA ester. IR (KBr): 3390, 3310, 2960, 1605, 1485, 1255, 1085, 795, 715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.78 (m, 2H), 2.02 (t, J=6 Hz, 1H), 2.50—3.00 (m, 4H), 3.01 (t, J=6 Hz, 1H), 3.50—4.00 (m, 2H), 3.74 (s, 3H), 3.76 (s, 3H), 6.62 (s, 2H). MS m/z: 250 (M^+, base peak), 232, 220, 219, 217, 206, 191, 190, 189, 177, 175, 174, 160, 159, 115, 91, 77. *Anal.* Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.05; H, 7.33.

(*R*)-2-[1(*S*)-Hydroxy-2-phenylthioethyl]-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (25) A solution of thiophenol (0.092 ml, 0.9 mmol) in *tert*-butanol (6 ml) was added to a stirred solution of (−)-**10** (150 mg, 0.6 mmol) in *tert*-butanol (6 ml) and 0.5 N aqueous NaOH at 85—90 °C over 3.2 h. After cooling of the mixture to 23 °C, the reaction was quenched by the addition of water, followed by extraction with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and con-

centrated. The residue was purified by silica gel column chromatography (ether–methylene chloride, 1:10) to give **25** (163 mg, 76%) as a less polar fraction and **26** (37 mg, 17%) as a more polar fraction. Recrystallization from chloroform–hexane gave colorless needles. Spectral data of **25**: IR (KBr): 3550, 3225, 2950, 1600, 1585, 1485, 1250, 1100, 1050, 802, 735 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50—2.00 (m, 2H), 2.18 (s, 1H), 2.60—3.80 (m, 8H), 3.74 (s, 3H), 3.76 (s, 3H), 6.60 (s, 2H), 7.30 (m, 5H). MS *m/z*: 360 (M^+), 219, 218, 207, 206 (base peak), 191, 190, 189, 177, 175, 165, 164, 149, 91, 45. *Anal.* Calcd for $C_{20}H_{24}O_4S$: C, 66.64; H,6.71; S, 8.89. Found: C, 66.76; H, 6.80; S, 8.90. $[\alpha]_D^{20}$ +23.9° (*c*=0.750, $CHCl_3$). mp 135—136 °C (recryst. from chloroform–hexane). Spectral data of **26**: IR (KBr): 3350, 2940, 1605, 1585, 1482, 1262, 1115, 1070, 802 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (m, 2H), 2.65—3.20 (m, 6H), 3.34 (t, *J*=6 Hz, 1H), 3.73 (s, 3H), 3.77 (s, 3H), 4.03 (d, *J*=6 Hz, 2H), 6.62 (s, 2H), 7.30 (m, 5H). MS *m/z*: 360 (M^+), 233, 207, 206 (base peak), 189, 164, 136. HR-MS *m/z*: (M^+) Calcd for $C_{20}H_{24}O_4S$ 360.1396, Found 360.1364.

(*R*)-2-[1(*R*)-Hydroxyethyl]-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (27) A suspension of Raney Ni (W-2) in ethanol was added to a stirred solution of (+)-**25** (65 mg, 0.18 mmol) in ethanol (5 ml), and the mixture was stirred under reflux for 4.5 h. After disappearance of the starting material (determined by thin layer chromatography (TLC), SiO_2, ether–hexane, 3:2), the reaction mixture was filtered through a pad of Celite. Removal of the solvent and purification of the residue by silica gel column chromatography (ether–hexane, 3:1) afforded the diol **27** (41 mg, 90%) as a colorless caramel. IR (KBr): 3430, 2950, 1605, 1485, 1255, 1090, 795, 715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (d, *J*=6 Hz, 3H), 1.30—2.10 (m, 2H), 2.17 (s, 2H), 2.74 (m, 4H), 3.65 (m, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 6.62 (s, 2H). MS *m/z*: 252 (M^+), 208, 207 (base peak), 206, 192, 190, 189, 177, 176, 175, 165, 164, 149. HR-MS *m/z*: (M^+) Calcd for $C_{14}H_{20}O_4$ 252.1359, Found 252.1342. $[\alpha]_D^{20}$ −43.2° (*c*=0.905, EtOH).

(*R*)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (9) A solution of SO_3–pyridine complex (223 mg, 1.4 mmol) in DMSO (0.8 ml) was added to a stirred solution of the diol **27** (36 mg, 0.14 mmol) and triethylamine (0.59 ml, 4.2 mmol) in DMSO (0.4 ml), and the mixture was stirred at 23 °C for 75 min. The reaction was quenched by the addition of 10% aqueous HCl (7 ml), followed by extraction with ether. The combined ether extracts were washed with water and brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (ether–hexane, 5:6) to give the hydroxyketone **9** (30 mg, 84%) as a colorless solid. Recrystallization of this sample from ether–hexane afforded **9** as colorless prisms. The spectral data of **9** thus obtained were identical with those reported in the literature.[4] IR (KBr): 3500, 2950, 1705, 1605, 1485, 1260, 1105, 1090, 1080, 970, 810 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.10 (m, 2H), 2.31 (s, 3H), 2.60—3.10 (m, 4H), 3.44 (s, 1H), 3.75 (s, 3H), 3.77 (s, 3H), 6.64 (s, 2H). MS *m/z*: 250 (M^+), 232, 207 (base peak), 189, 176, 174, 164, 158, 147, 43. HR-MS *m/z*: (M^+) Calcd for $C_{14}H_{18}O_4$ 250.1205, Found 250.1180. $[\alpha]_D^{20}$ −48.7° (*c*=0.825, $CHCl_3$). mp 128—129 °C (recryst. from ether–hexane).

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