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Synthetic Studies on Virantmycin. 2. Total Synthesis of Unnatural (+)-Virantmycin and Determination of Its Absolute Stereochemistry[1]

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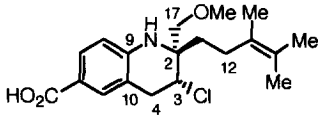
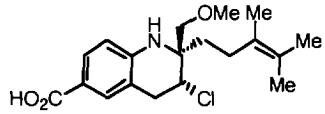
Abstract: The enantioselective total synthesis of (+)-virantmycin (**1**) has been achieved by means of the Sharpless asymmetric epoxidation of allylic alcohol **27** followed by an intramolecular epoxide opening of the *exo* epoxy alcohol **32** which was derived from the *endo* epoxy alcohol **28**. The synthesis of (+)-**1** has established that the absolute configuration of the natural product (-)-**1** is shown to be 2*R*, 3*R* at the two chiral centers. Further, antiviral activities of the virantmycin analogs were also examined against influenza virus. Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

The antibiotic virantmycin (**1**), isolated from the fermentation broth of *Streptomyces nitrosporeus* by Ōmura *et al.* in 1981, has been found to possess antifungal and potent inhibitory activity against various RNA and DNA viruses.[2] Its unique gross structure, which is characterized by the chlorine-containing tetrahydroquinoline skeleton and terminal tetrasubstituted double bond rarely occurring in nature,[3] has been established by chemical and spectroscopic studies.[4] However, the relative and absolute stereochemistry at the two chiral centers (C2 and C3) of **1** has remained to be determined. In the preceding paper we reported the efficient and stereospecific total syntheses of (±)-virantmycin (**1**) and its diastereomer (±)-**2** on the basis of an intramolecular nitrene addition reaction, and the relative stereochemistry of virantmycin has been established as shown in **1**.[5] In this article we describe the enantioselective total synthesis of (+)-virantmycin (**1**) which is an antipode of natural (-)-virantmycin (**1**), the determination of its absolute stereochemistry, and the antiviral activities of virantmycin analogs against influenza virus.



natural (-)-**1**



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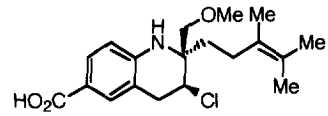


synthetic (+)-**1**

RESULTS AND DISCUSSION

Retrosynthetic analysis of virantmycin is delineated in Fig. 1.[6] In the asymmetric synthesis of virantmycin having unknown stereochemistry, we considered an introduction of chiral carbons into the allylic alcohol such as **6** by Sharpless asymmetric epoxidation[7] because of ready availability of chiral epoxide possessing a predictable absolute configuration, simple procedure, generally high yields, and so on.[8] Although a ring closure of the *endo* epoxy alcohol **4**, an immediate product of the Sharpless epoxidation, through path b will directly give the desired piperidine ring, Baldwin's rule[9] envisaged that path a (5-*exo*-tet) is more favored process than path b (6-

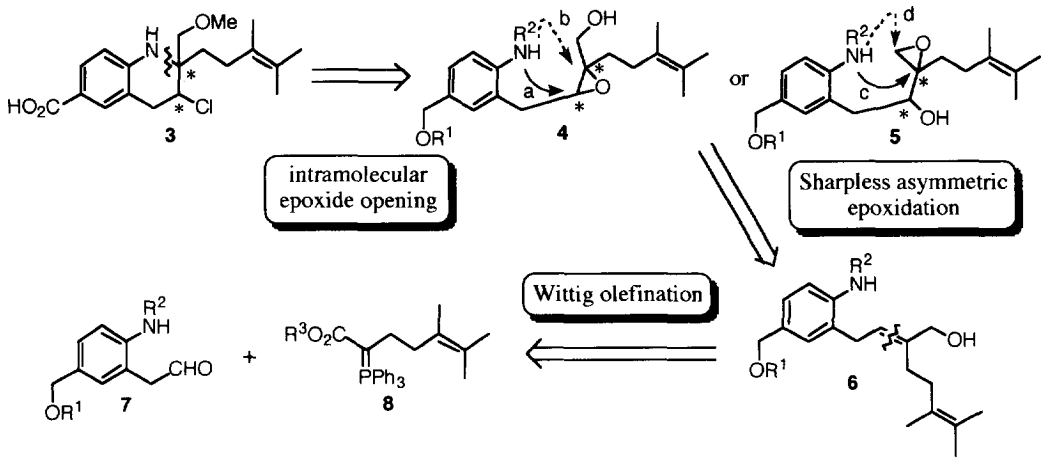
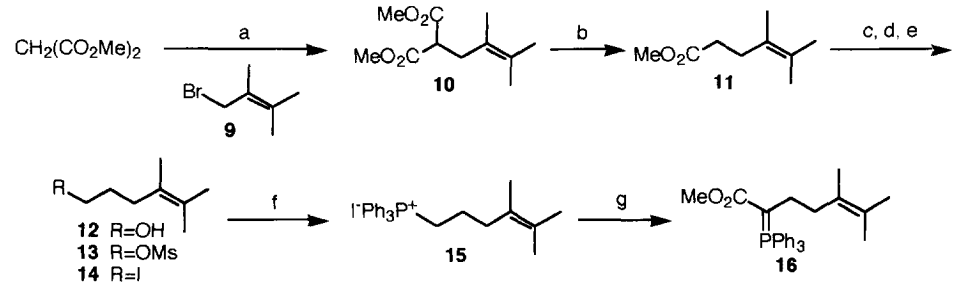


Fig. 1. Retrosynthetic analysis of virantmycin.

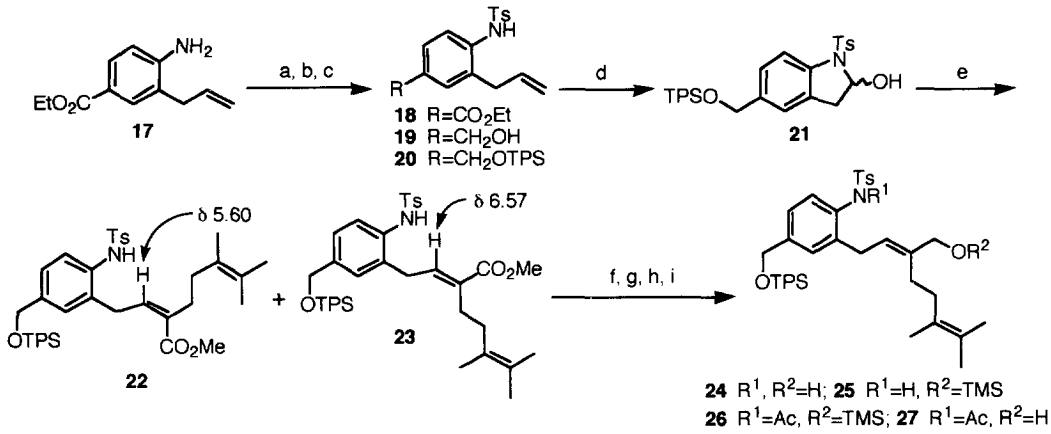
endo-tet).[10a] On the other hand, it was anticipated that in the *exo* epoxy alcohol **5** path c (6-*exo*-tet) is more favored process than path d (7-*endo*-tet)[10b] to afford the desired piperidine ring system. The allylic alcohol **6** required for the Sharpless asymmetric epoxidation will be constructed by Wittig olefination of the aromatic aldehyde **7** with the phosphorane **8**. The following sequences are mentioned on the basis of this retrosynthetic analysis.

The preparation of phosphorane **16** required for Wittig reaction with the aromatic moiety **7** began with an alkylation of dimethyl malonate with 1-bromo-2,3-dimethyl-2-butene (**9**)[11] to give diester **10** (Scheme 1). Demethoxycarbonylation of **10** under Krapcho's condition[12] yielded ester **11** which was reduced to alcohol **12** with lithium aluminum hydride. Mesylate **13** obtained from the alcohol **12** by treatment with methanesulfonyl chloride and triethylamine was consecutively substituted with sodium iodide and triphenylphosphine to afford phosphonium salt **15**. Finally, the desired phosphorane **16** was prepared through the ylide generated from **15** by means of *n*-butyllithium in 98% yield.[13]

Preparation of the aromatic moiety **21** was carried out using readily available ethyl 4-amino-3-(2-propenyl)benzoate (**17**)[5] as a starting material (Scheme 2). After protection of the amino group in **17** as sulfonamide, ester **18** was reduced with lithium aluminum hydride to give alcohol **19** in which the hydroxyl



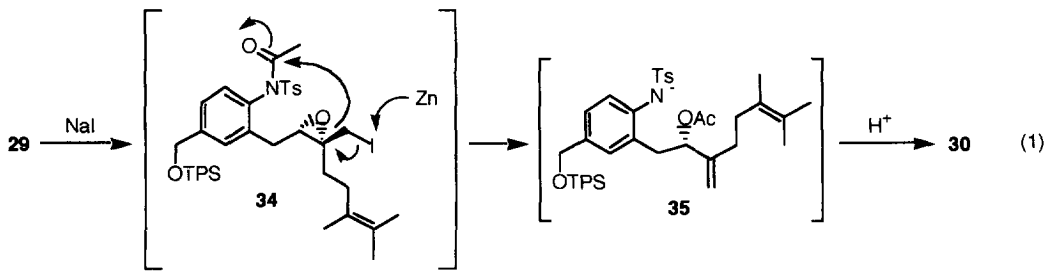
Scheme 1. Reagents and conditions: (a) NaH, THF, 0 °C, 30 min, then **9**,[11] 0 °C→rt, 1 h, 86%; (b) NaCl, H_2O, DMSO, 170 °C, 4.5 h; (c) $LiAlH_4$, THF, 0 °C→rt, 45 min; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 86% (3 steps); (e) NaI, DMF, 80 °C, 3 h; (f) PPh_3, benzene, reflux, 3 d, 89% (2 steps); (g) 2.1 equiv of *n*-BuLi, 1.1 equiv of $HN(TMS)_2$, THF, 0 °C, 30 min, then $ClCO_2Me$, -78 °C, 3 h, 98%.

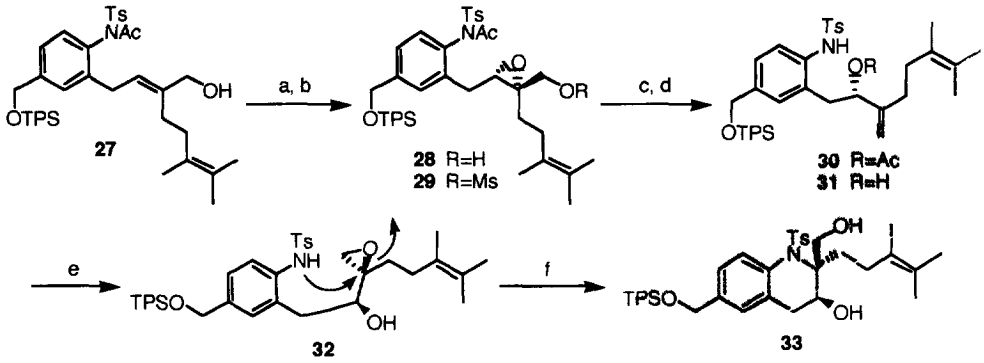


Scheme 2. Reagents and conditions: (a) TsCl, Py, CH_2Cl_2, rt, 17 h, 100%; (b) $LiAlH_4$, THF, 0 °C→rt, 2 h, 95%; (c) TPSCl, imidazole, DMF, 60 °C, 85 h, 82%; (d) OsO_4, THF-H_2O (1:1), rt, 30 min, then $NaIO_4$, 2 h, 89%; (e) **16**, CH_2Cl_2, rt, 52 h, 90% (**22**:**23**=1:30); (f) DIBALH, toluene, -15 °C, 30 min, 92%; (g) TMSCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; (h) AcCl, Et_3N, CH_2Cl_2, 0 °C, 30 min; (i) citric acid, Et_2O-MeOH-H_2O (4:10:1), rt, 50 min, 96% (3 steps).

group was protected as *tert*-butyldiphenylsilyl (TPS) ether. Lemieux-Johnson oxidation[14] of the sulfonamide **20** afforded hemiacetal **21** in high yield as only one tautomer [^{1}H NMR δ 5.87 (1H, dd, *J*=7, 3 Hz, NC*H*OH); IR 3540 cm^{-1} (OH)]. The Wittig reaction of the hemiacetal **21** with phosphorane **16** stereoselectively gave (*E*)-α,β-unsaturated ester **23** and its (*Z*)-isomer **22** with the ratio of 30 : 1, respectively, after chromatography. The stereochemistry of the olefins **22** and **23** was proven by the chemical shifts of their vinyl protons (**22**, δ 5.60; **23**, δ 6.57).[15] The major ester **23** was reduced to allylic alcohol **24** with diisobutylaluminum hydride and *N*-protection of **24** was performed through the following sequence of reactions because of lowering nucleophilicity of nitrogen: (1) silylation of the alcohol, (2) *N*-acetylation, and (3) deprotection of TMS ether.[16] Thus, the allylic alcohol **27**, a substrate of Sharpless asymmetric epoxidation reaction, was prepared from **17** in very high overall yields.

The asymmetric epoxidation[7] of the allylic alcohol **27** by the usual procedure using L-(+)-diethyl tartrate furnished optically active epoxy alcohol **28** (92% ee), $[\alpha]_D^{25}$ -14.9° (*c* 1.00, $CHCl_3$), in 98% yield (Scheme 3). Although several derivatives of the *endo* epoxide **28** were subjected to an intramolecular epoxide opening under acidic or basic conditions as shown in Fig. 1, not surprisingly, obtained products were only indoline compounds following the Baldwin's rule (path a in Fig. 1). Therefore, the *endo* epoxide **28** was transformed to





Scheme 3. Reagents and conditions: (a) L-(+)-DET, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, -20 °C, 1.5 h, 98%; (b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, 95%; (c) 5 equiv of NaI, 2 equiv of Zn, DMF, 100 °C, 15 min, 87%; (d) DIBALH, toluene, -15 °C, 30 min, 98%; (e) TBHP, VO(acac)$_2$, CH_2Cl_2, 0 °C, 2.5 h, 96%; (f) 2 equiv of TFA, toluene, rt, 6 h, 67%.

the *exo* epoxide **32** favored for the Baldwin's rule. Mesylation of the alcohol **28** provided mesylate **29** which was converted into allylic acetate **30** with sodium iodide and zinc metal at 100 °C for 15 minutes in high yield through the plausible mechanism via intermediates **34** and **35** as shown in equation 1.

Diisobutylaluminum hydride reduction of the acetate **30** afforded allylic alcohol **31** which was subjected to the vanadium(V) catalyzed epoxidation[17] to give stereoselectively *erythro* epoxy alcohol **32** as a single diastereomer in very high yield, the stereochemistry of which was confirmed in aziridine **45** (*vide infra*).[18] This complete *erythro* selectivity in the epoxidation of **31** may be rationalized according to the Sharpless' predicted model.[19] In the vanadium(V) catalyzed epoxidation of allylic alcohols the conformation which has an O-C-C=C dihedral angle near 50° in the allyloxy moiety is preferred because of stereoelectronic requirement (**A** and **B** in Fig. 2). Though the model **A** leading to *threo* epoxide experiences a steric interaction between benzylic and homoallylic substituents, there is no such an interaction in the model **B** leading to *erythro* epoxide. Therefore, it is thought that the *erythro* epoxy alcohol **32** was selectively obtained through the transition state resembling the predicted model **B**. Treatment of the *exo* epoxide **32** with trifluoroacetic acid in toluene at room temperature for 6 hours expectedly provided the desired piperidine product **33** following the Baldwin's rule (path c in Fig. 1).

As a construction of the tetrahydroquinoline skeleton could be achieved thus in the stereoselective manner, manipulation of functional groups was performed next (Scheme 4). Oxidation of the benzylic alcohol like **33** into carboxylic acid demanded a circuitous way. After protection of the diol **33** as an acetonide, *tert*-

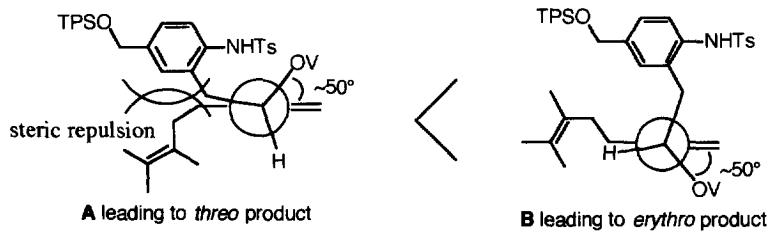
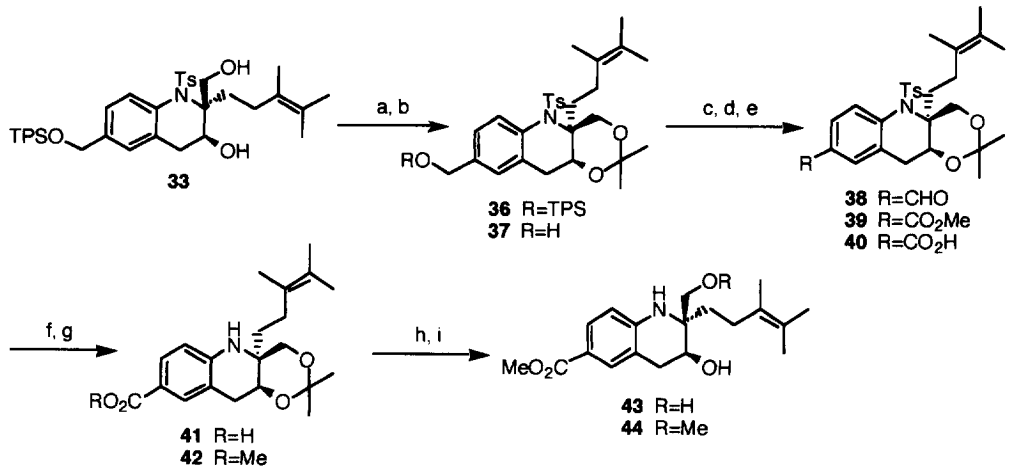
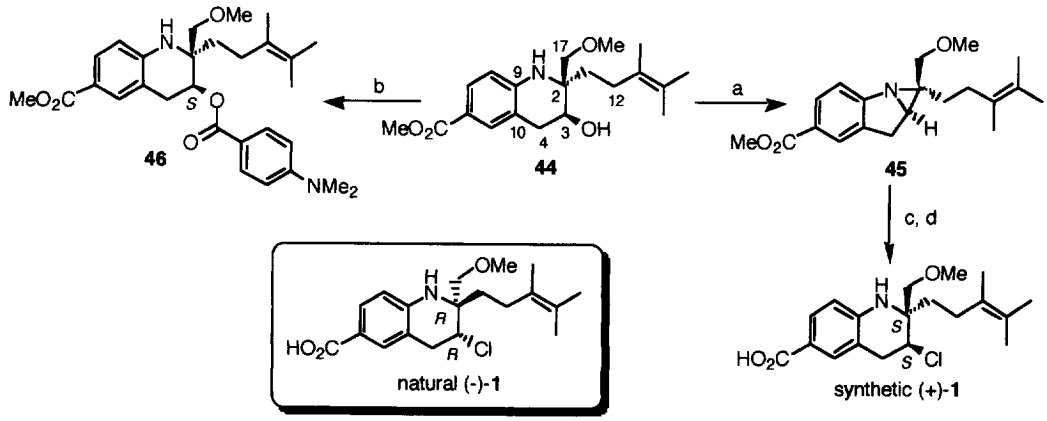


Fig. 2. Predicted models **A** and **B** in the epoxidation of allylic alcohol **31**.



Scheme 4. Reagents and conditions: (a) $Me_2C(OMe)_2$, CSA, acetone, rt, 3 h, 92%; (b) *n*-Bu_4NF, THF, rt, 15 h, 99%; (c) PDC, CH_2Cl_2, rt, 4 h; (d) MnO_2, KCN, AcOH, MeOH-benzene (2:1), rt, 13 h; (e) KOH, Et_2O-MeOH-H_2O (2:2:1), rt, 24 h, 100% (3 steps); (f) Na, naphthalene, DME, -15 °C, 30 min, 100%; (g) CH_2N_2, MeOH, rt, 100%; (h) *p*-TsOH, MeOH-Et_2O (4:1), rt, 18 h, 92%; (i) NaH, *n*-Bu_4NI, THF, 0 °C, 30 min, then 5 equiv of MeI, 2 equiv of HMPA, -15 °C, 1.5 h, 70%.

butyldiphenylsilyl group was removed with tetrabutylammonium fluoride to yield benzylic alcohol **37**. Oxidation of the alcohol to the carboxylic acid **40** was carried out stepwise in quantitative overall yield through the following sequence of reactions: (1) first oxidation to aldehyde **38** with pyridinium dichromate,[20] (2) second oxidation to methyl ester **39** by Corey's method,[21] and (3) saponification of **39**. Amine **41** was regenerated from the sulfonamide **40** by treatment with sodium naphthalene anion radical in 1,2-dimethoxyethane,[22] followed by work-up with diazomethane and removal of the acetonide to provide diol **43**. Methylation of the primary hydroxyl group in **43** gave methyl ether **44** for which the relative and absolute configuration was assigned as described in the next paragraph.



Scheme 5. Reagents and conditions: (a) DEAD, PPh_3, THF, rt, 3 h, 89%; (b) 4-dimethylaminobenzoic acid, 2-chloro-1-methylpyridinium *p*-toluenesulfonate, *n*-Bu_3N, toluene, reflux, 4 h, 54%; (c) NaOH, MeOH, reflux, 39 h; (d) 20 equiv of Et_4NCl, 4 equiv of TFA, CH_2Cl_2, -15 °C, 15 min, 81% (2 steps).

As Mitsunobu reaction[23] of the alcohol **44** afforded aziridine **45** which was identical with the authentic compound reported in the preceding paper,[5] the relative stereochemistry of **44** could be determined as shown in **44** (Scheme 5). In our preliminary communication we assigned the relative configuration between methoxymethyl and hydroxyl groups in **44** *trans* disposition by mistake.[6] Now we would like to review why we mistook the assignment for relative configuration of **44**. When the relative configuration of **44** was previously reported as shown in 2-*epi*-**44**, we judged that the piperidine ring adopted only one conformation because of the diagnostic coupling constants between H3 and $H_2$4 ($J_{3\text{-}4L}$=6 Hz, $J_{3\text{-}4S}$=5 Hz) and presence of NOE between H_L4 (δ 2.84) and $H_2$17 which appeared to be consistent with the stereo-structure of 2-*epi*-**44** (Fig. 3). However, as clarified in the preceding paper[5] later, these coupling constants between H3 and $H_2$4 ($J_{3\text{-}4L}$=6 Hz, $J_{3\text{-}4S}$=5 Hz) in **44** suggested that the conformation of this piperidine ring is very flexible to exist as a mixture equilibrated between two conformers **44a** and **44b**. The NOEs attributed to both half-chair conformers **44a** and **44b** have been practically observed by our and Sanders' groups,[24] independently, but it is unclear why the two groups observed only the different NOEs respectively.[25] Thus, the fast ring inversion must occur in this piperidine ring system of **44**. In conclusion, assuming the conformation of **44** to be only one and hydroxyl at C3 and methoxymethyl at C2 substituents to be axial orientation resulted in the mis-assignment of the relative configuration of **44**.

The absolute stereochemistry of **44** was determined by applying the exciton chirality method[26] to 4-dimethylaminobenzoate **46** which was derived from **44** by Mukaiyama's method[27] (Scheme 5). In the CD spectrum ($\Delta\varepsilon_{320}$=-33.9, $\Delta\varepsilon_{289}$=+17.1, in EtOH) of 4-dimethylaminobenzoate **46** the negative sign of the first Cotton effect was corresponding to the negative chirality (Fig. 4). Thus, the absolute configuration of **44** was assigned to be 2*S*, 3*S* as shown in Fig. 4. The configuration of C3 to be *S* was consistent with the one expected from the Sharpless asymmetric epoxidation (**27** → **28** in Scheme 3). As general combinations of dibenzoates in exciton chirality rule are those of the same direction of dipole moment in the chromophores toward screwness axis (tail to tail), it is very stimulating that the critical result was obtained in a combination of the opposite direction (head to tail) as shown in this case.[26d]

After saponification of methyl ester **45** the highly regio and stereoselective ring opening of aziridine by chloride ion[5] gave only (+)-virantmycin (**1**) having 2*S*, 3*S* configuration whose spectroscopic data (NMR, IR, MS, UV) and chromatographic behavior perfectly coincided with those of natural virantmycin (Scheme 5). The optical rotation of the synthetic (+)-**1** was, however, observed as $[\alpha]_D^{24}$ +11.2° (*c* 0.125, $CHCl_3$) contrary to that of the natural (-)-**1**, $[\alpha]_D^{24}$ -11.1° (*c* 0.175, $CHCl_3$).[28] Thus, the synthesis of antipodal virantmycin revealed that the absolute configuration of the natural product is shown to be 2*R*, 3*R* at the two chiral centers.

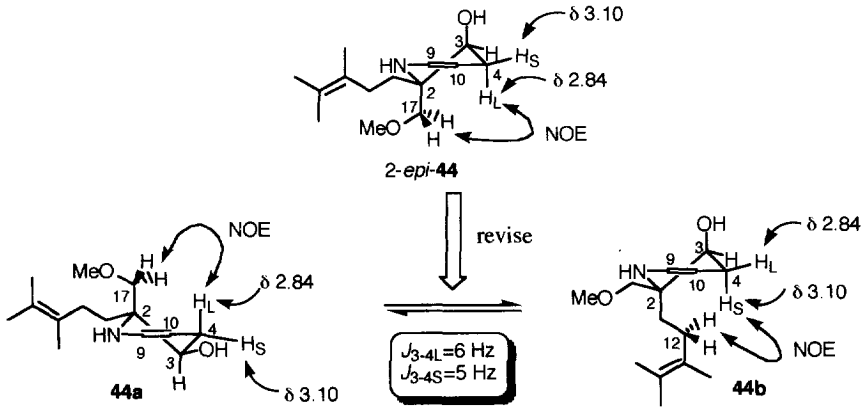


Fig. 3. Wrong and corrected assignment to NMR spectra of **44**.

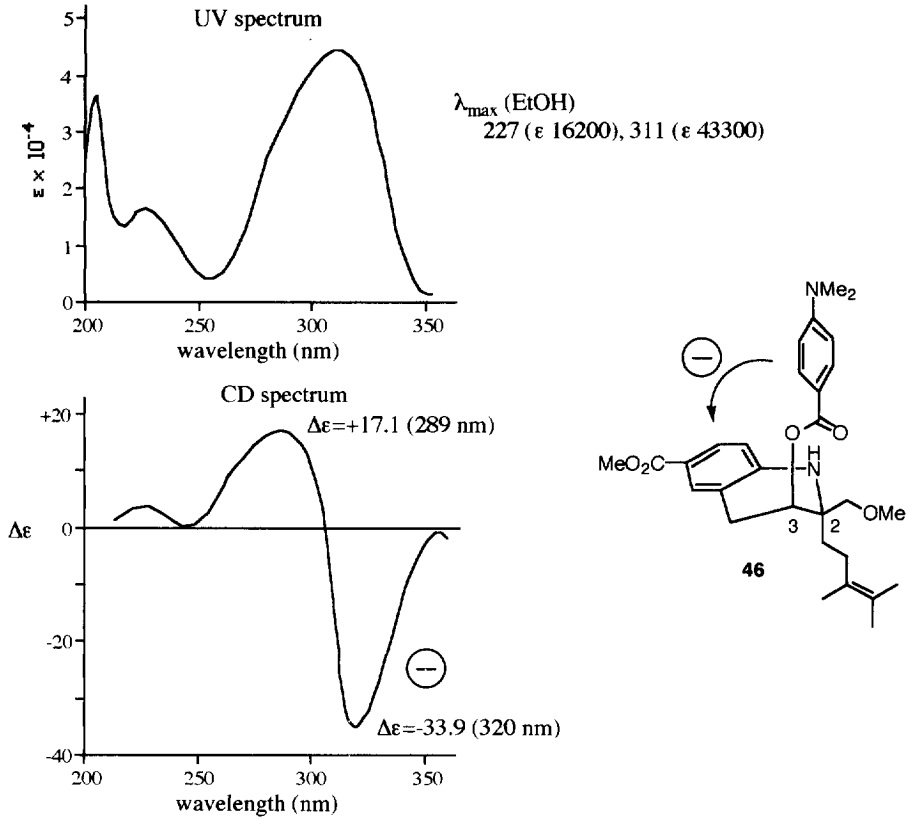
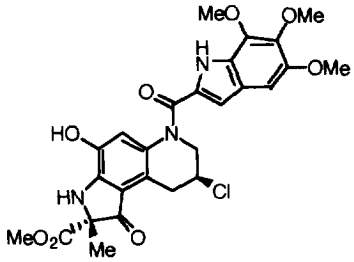
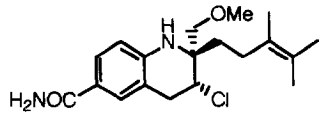


Fig. 4. UV and CD spectra of 4-dimethylaminobenzoate **46**.

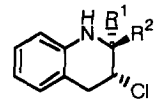
Recently, it has been reported that some natural products possessing the chlorine-bearing tetrahydroquinoline skeleton such as virantmycin produced by *Streptomyces sp.* show a wide variety of biological activities. For example, it has been found that virantmycin exhibits antiviral and antifungal activity[2] as mentioned in introduction and duocarmycin C_1 (**47**) does antitumor and antimicrobial one.[29] More recently, benzastatin C (**48**) whose structure is closely related to **1** has been isolated from the same *Streptomyces sp.* as the producing organism of **1** and disclosed an inhibitory activity against glutamate toxicity and lipid peroxidation.[3a] From the above facts it was intensely considered that the chlorine-containing tetrahydroquinoline ring system might play an indispensable role for a broad spectrum of their biological activities. Thus, we took an interest in the structure-activity relationships between virantmycin analogs **1**, **2**, **49**, and **50** which we have synthesized in this and the preceding papers[5] and would like to report the results on their antiviral activities against influenza virus.



duocarmycin C_1 (**47**)



benzastatin C (**48**)



49 R^1=CH_2OMe, R^2=Et
50 R^1=Et, R^2=CH_2OMe

Table 1. Antiviral Activities of Virantmycin Analogs against Influenza Virus.

entry	substrate (dose = 2 μg/mL)	HA value[a]
1	natural (-)-**1**	<2
2	(±)-**1**	<2
3	synthetic (+)-**1**	128
4	(±)-**2**	64
5	(±)-**49**	128
6	(±)-**50**	64
7	control	256

[a]HA value = haemagultinin value.

The antiviral activities of the virantmycin analogs were tested by a growth inhibition of influenza virus which was performed by measuring population of haemagultinin existing on its surface. The results are listed in Table 1. Both natural (-)-**1** and synthetic (±)-**1** revealed outstanding antiviral activity (entries 1 and 2), but on the other hand the synthetic (+)-enantiomer **1** and (±)-diastereomer **2** of natural virantmycin did not show meaningful one (entries 3 and 4). Thus, it was found that only (-)-enantiomer is responsible for the antiviral activity of (±)-**1**. Furthermore, an analog **49** having the same relative configuration as the natural product but not carboxylic group and terminal tetrasubstituted double bond was also examined to indicate negligible activity (entry 5). These suggested that not only the stereochemistry of the tetrahydroquinoline ring moiety but also carboxylic group or terminal tetrasubstituted double bond must play an important role for occurrence of the antiviral activity. After all among four possible stereoisomers of virantmycin only (-)-**1** having an absolute stereochemistry of 2*R*, 3*R* exhibited an effective antiviral activity.

In conclusion we have accomplished the enantioselective total synthesis of unnatural (+)-virantmycin (**1**) through the following sequence of reactions: (1) stereoselective preparation of the trisubstituted double bond in **23**, (2) an introduction of chiral carbons into the allylic alcohol **27** by Sharpless asymmetric epoxidation, and (3) regio and stereoselective construction of the piperidine ring system **33** by an intramolecular epoxide opening (6-*exo*-tet) of **32**. The unknown absolute stereochemistry of natural product has been determined to be 2*R*, 3*R* at the two chiral centers through an application of the exciton chirality method to 4-dimethylaminobenzoate **46**. Finally, we have revealed that among four possible stereoisomers of virantmycin only natural (-)-**1** possesses an effective antiviral activity against influenza virus.

EXPERIMENTAL SECTION

General Procedures

Melting points are uncorrected. ^{1}H NMR spectra were recorded in deuteriochloroform on Hitachi R-90H (90 MHz), JEOL model JNM-GX 270 (270 MHz), and FX-500 (500 MHz) spectrometers. Chemical shifts were reported in ppm down field from the peak of tetramethylsilane as an internal standard. The data are reported as follows: chemical shift, number of proton, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broadened), and coupling constants. Infrared (IR) spectra were recorded on a JASCO IR-S spectrophotometer. Optical rotations were determined on a JASCO DIP-360 digital polarimeter using the sodium D line (λ=589 nm) at the temperature indicated and are reported as follows: $[\alpha]_D^{temp}$, concentration (c=g/100 mL), and solvent. CD spectra were obtained by a JASCO J-20-A automatic recording spectropolarimeter. UV spectra were recorded on a HITACHI model 200-10 spectrophotometer. Low (EI and FD) and high (EI and FI) resolution mass spectra were determined on JEOL model JMS-DX 300, JMS-DX 303, and 01SG-2 spectrometers.

Analytical and preparative thin layer chromatographies were carried out by precoated silica gel (Macherey-Nagel DC-Fertigplatten SIL G-25 UV_{254} and Merck DC-Fertigplatten Kieselgel 60 F_{254}). Silica gels used for column chromatographies were Wako Wakogel C-200, Merck kieselgel 60 Art 7734, and Amicon Matrex® silica Si chromatography medium. All reactions were performed in oven-dried glassware.

Tetrahydrofuran (THF), diethyl ether (Et_2O), and 1,2-dimethoxyethane (DME) were distilled from sodium metal / benzophenone ketyl. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), benzene, pyridine (Py), toluene, and acetonitrile (CH_3CN) were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium methoxide. Acetone was distilled from potassium permanganate. Acetyl chloride (AcCl) was distilled from *N*,*N*-dimethylaniline. Dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), and tributylamine (n-Bu_3N) were distilled from calcium hydride at reduced pressure. p-Toluenesulfonyl chloride (p-TsCl) was recrystallized from ether. 1-Bromo-2,3-dimethyl-2-butene (**9**),[11] ethyl 4-amino-3-(2-propenyl)benzoate (**17**),[5] 5 M solution of *tert*-butyl hydroperoxide (TBHP) in CH_2Cl_2,[30] active manganese dioxide (MnO_2),[31b] and a solution of diazomethane in diethyl ether[31c] were prepared according to literature methods. 1.0 M Solution of sodium naphthalenide in 1,2-dimethoxyethane was prepared by stirring sodium metal and naphthalene (recrystallized from ethanol) in absolute dry 1,2-dimethoxyethane at room temperature for 1-2 h.

Dimethyl 2,3-dimethyl-2-butenylmalonate (10)

To a suspension of sodium hydride (155 mg, 6.44 mmol, washed with hexane) in 10 mL of THF was added slowly 0.736 mL (6.44 mmol) of dimethyl malonate (freshly distilled under reduced pressure) at 0 °C under Ar. After the mixture was stirred at 0 °C for 30 min, 0.794 mL (6.13 mmol) of 1-bromo-2,3-dimethyl-2-butene (**9**)[11] was added to the solution at the same temperature. The solution was allowed to warm to room temperature and further stirred for 1 h. After quenching with 1 mL of saturated aqueous NH_4Cl, the reaction mixture was poured into 40 mL of water and extracted with ether (30 mL × 3). The ethereal layer was washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (4% EtOAc/hexane) on 30 g of silica gel to give the diester **10** as a clear oil (1.13 g, 86% yield): ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.71 (6H, s), 3.50 (1H, t, J=8 Hz), 2.66 (2H, d, J=8 Hz), 1.64 (9H, s); IR (neat) 2990, 2960, 1760, 1445, 1350, 1240, 1200, 1160, 1040 cm^{-1}; EI-MS *m/z* (relative intensity) 214 (M^+, 4.7), 83 (33), 55 (32), 44 (100), 41 (26); EI-HRMS calcd for $C_{11}H_{18}O_4$ (M^+) 214.1205, found 214.1213.

Methyl 4,5-dimethyl-4-hexenoate (11)

A solution of diester **10** (4.52 g, 21.1 mmol), 1.36 g (23.2 mmol) of sodium chloride, and 0.760 mL (42.2 mmol) of water in 22.6 mL of DMSO was stirred at 170 °C for 4.5 h and then cooled to room temperature. 5 mL of saturated aqueous NH_4Cl was slowly added to the reaction vessel with stirring. The resulting mixture was poured into 100 mL of water and extracted with ether (100 mL × 3). The ethereal layer was washed with

200 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* under 20 °C to afford the ester **11** which was used directly in the next reaction. A small sample of **11** was purified by column chromatography (2% ether/hexane) on silica gel and characterized: ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.63 (3H, s), 2.33 (4H, s), 1.62 (9H, s); IR (neat) 2915, 2870, 1745, 1440, 1368, 1301, 1259, 1170, 1120 cm^{-1}; EI-MS *m/z* (relative intensity) 156 (M^+, 18), 95 (31), 83 (79), 81 (30), 57 (38), 55 (100), 44 (47), 43 (50), 41 (70), 40 (31); EI-HRMS calcd for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1192.

4,5-Dimethyl-4-hexen-1-ol (12)

To a solution of lithium aluminum hydride (801 mg, 21.1 mmol) in 40 mL of THF at 0 °C was added dropwise ester **11** (3.30 g, 21.1 mmol) dissolved in 20 mL of THF under Ar. After the addition the solution was allowed to warm to room temperature and stirred for 45 min. The reaction was carefully quenched with 0.801 mL of water, followed by 0.801 mL of 15% aqueous NaOH, and then 2.40 mL of water. The resulting solution was stirred vigorously for 10 min, treated with anhydrous Na_2SO_4 for another 20 min, then filtered through a pad of Celite *in suction*, and evaporated *in vacuo* under 20 °C to give the alcohol **12** which was used directly in the next reaction. A small sample of **12** was purified by column chromatography (4% EtOAc/benzene) on silica gel and characterized: ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.61 (2H, t, *J*=6 Hz), 2.30-1.95 (2H, m), 1.63 (9H, s), 1.85-1.50 (2H, m); IR (neat) 3370, 2930, 2880, 1447, 1374, 1054 cm^{-1}; FI-MS *m/z* (relative intensity) 129 (M^++H, 13), 128 (M^+, 100); FI-HRMS calcd for $C_8H_{16}O$ (M^+) 128.1200, found 128.1197.

4,5-Dimethyl-4-hexenyl methanesulfonate (13)

To a solution of alcohol **12** (2.71 g, 21.1 mmol) in 27.1 mL of CH_2Cl_2 at 0 °C under Ar were added sequentially 6.47 mL (46.4 mmol) of triethylamine and 1.80 mL (23.2 mmol) of methanesulfonyl chloride, and then the mixture was stirred for 30 min. The reaction mixture was poured into 40 mL of water and extracted with CH_2Cl_2 (30 mL × 3). The extracted organic layer was washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residual oil was subjected to column chromatography (16% EtOAc/hexane) on 100 g of silica gel to give pure mesylate **13** as a colorless oil (3.72 g, 86% overall yield from diester **10**): ^{1}H NMR (90 MHz, $CDCl_3$) δ 4.17 (2H, t, *J*=6 Hz), 2.98 (3H, s), 2.25-1.95 (2H, m), 1.96-1.60 (2H, m), 1.64 (9H, s); IR (neat) 2920, 2870, 1457, 1355, 1175, 972, 956, 923, 836 cm^{-1}; EI-MS *m/z* (relative intensity) 206 (M^+, 14), 110 (26), 95 (100), 83 (18), 82 (24), 69 (15), 67 (36), 55 (40), 41 (30); EI-HRMS calcd for $C_9H_{18}SO_3$ (M^+) 206.0977, found 206.0990.

6-Iodo-2,3-dimethyl-2-hexene (14)

A solution of mesylate **13** (3.68 g, 17.8 mmol) and sodium iodide (13.3 g, 89.0 mmol) in 49.1 mL of DMF under Ar was heated at 80 °C with stirring. After 3 h, an oil bath was removed and the reaction vessel was cooled to room temperature. The reaction mixture was poured into 250 mL of 10% aqueous $Na_2S_2O_3$ and extracted with ether (200 mL × 3). The ethereal layer was washed with 300 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* under 20 °C to give iodide **14** which was used directly in the next reaction. A small sample of **14** was purified by column chromatography (100% hexane) on silica gel and characterized: ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.13 (2H, t, *J*=7 Hz), 2.34-1.70 (4H, m), 1.61 (9H, s); IR (neat) 2920, 2870, 1446, 1380, 1226, 1171 cm^{-1}; EI-MS *m/z* (relative intensity) 238 (M^+, 100), 83 (79), 69 (27), 55 (56), 42 (37); EI-HRMS calcd for $C_8H_{15}I$ (M^+) 238.0218, found 238.0205.

4,5-Dimethyl-4-hexenyltriphenylphosphonium iodide (15)

To a solution of triphenylphosphine (4.67 g, 17.8 mmol) in 20 mL of benzene was added iodide **14** (4.24 g, 17.8 mmol) in 8.3 mL of benzene with stirring and the solution was refluxed for 3 days under Ar. An oil bath was removed and the reaction vessel was cooled to room temperature. The precipitated product was filtered *in suction*, washed with ether (20 mL × 5), and dried in desicator under reduced pressure for several hours to afford the phosphonium salt **15** as a white solid (7.92 g, 89% overall yield from mesylate **13**): mp 134-139 °C;

^{1}H NMR (90 MHz, $CDCl_3$) δ 8.01-7.47 (15H, m), 3.88-3.39 (2H, m), 2.37 (2H, br t, *J*=7 Hz), 1.97-1.31 (2H, m), 1.61 (6H, s), 1.50 (3H, s); IR ($CHCl_3$) 2940, 2890, 1592, 1490, 1440, 1116, 999, 754, 728, 691 cm^{-1}; EI-MS *m/z* (relative intensity) 373 {[Me_2C=C(Me)$(CH_2)_3PPh_3$]$^+$, 4.2}, 262 (100), 183 (81), 108 (56), 83 (29), 69 (27), 55 (45), 41 (37); EI-HRMS calcd for $C_{26}H_{30}P$ {[Me_2C=C(Me)$(CH_2)_3PPh_3$]$^+$} 373.2085, found 373.2068.

Methyl 5,6-dimethyl-2-triphenylphosphoranylidene-5-heptenoate (16)

To a solution of phosphonium salt **15** (4.00 g, 7.99 mmol) in 40 mL of THF at 0 °C under Ar were added successively 1.86 mL (8.79 mmol) of 1,1,1, 3, 3, 3-hexamethyldisilazane (freshly distilled from calcium hydride) and 10.4 mL (16.8 mmol) of *n*-butyllithium (1.62 M in hexane), and then the mixture was stirred for 30 min at the same temperature followed by cooling to -78 °C. To the red-orange solution was added dropwise 0.679 mL (8.79 mmol) of freshly distilled methyl chloroformate and the resulting mixture was stirred at -78 °C for 3 h. After quenching with 5 mL of saturated aqueous $NaHCO_3$ at -78 °C, the reaction mixture was allowed to warm to room temperature, poured into 100 mL of water, and extracted with CH_2Cl_2 (80 mL × 3). The combined organic layers were washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (0:100 to 60:40 MeOH/$CHCl_3$) on 80 g of silica gel to afford the desired phosphorane **16** (3.38 g, 98% yield): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.95-7.25 (15H, m), 3.38 (3H, s), 2.29-1.60 (4H, m), 1.52 (3H, s), 1.47 (3H, s), 1.37 (3H, s); IR (neat) 2940, 1627, 1602, 1441, 1324, 1292, 1184, 1165, 1115, 719, 691 cm^{-1}; EI-MS *m/z* (relative intensity) 430 (M^+, 0.7), 348 (27), 347 (100), 278 (25), 277 (52), 183 (26); EI-HRMS calcd for $C_{28}H_{31}O_2P$ (M^+) 430.2059, found 430.2059.

Ethyl 3-(2-propenyl)-4-(*p*-toluenesulfonyl)aminobenzoate (18)

To a solution of ethyl 4-amino-3-(2-propenyl)benzoate (**17**)[5] (4.78 g, 23.3 mmol) and pyridine (4.15 mL, 51.3 mmol) in 27.8 mL of CH_2Cl_2 at room temperature under Ar was added slowly 4.88 g (25.6 mmol) of *p*-toluenesulfonyl chloride in 20 mL of CH_2Cl_2. The resulting mixture was stirred at the same temperature for 17 h and poured into 80 mL of water. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 2). The combined organics were washed successively with each 100 mL of saturated aqueous $CuSO_4$ and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (16% EtOAc/hexane) on 150 g of silica gel to give sulfonamide **18** (8.40 g, 100% yield) as a pale yellow oil: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.85 (1H, dd, *J*=9, 2 Hz), 7.72 (1H, d, *J*=2 Hz), 7.62 (2H, d, *J*=8 Hz), 7.50 (1H, d, *J*=9 Hz), 7.20 (2H, d, *J*=8 Hz), 6.80 (1H, br s), 5.78 (1H, ddt, *J*=17, 11, 6 Hz), 5.14 (1H, dd, *J*=11, 2 Hz), 4.94 (1H, dd, *J*=17, 2 Hz), 4.32 (2H, q, *J*=8 Hz), 3.13 (2H, d, *J*=6 Hz), 2.38 (3H, s), 1.37 (3H, t, *J*=8 Hz); IR (neat) 3280, 2990, 2940, 1705, 1638, 1610, 1496, 1396, 1335, 1275, 1160, 1118, 1090, 1020, 905, 819, 771 cm^{-1}; EI-MS *m/z* (relative intensity) 359 (M^+, 9.5), 204 (100), 202 (37), 176 (21), 174 (20), 158 (24), 132 (47), 131 (56), 130 (63), 91 (42); EI-HRMS calcd for $C_{19}H_{21}NO_4S$ (M^+) 359.1191, found 359.1204.

3-(2-Propenyl)-4-(*p*-toluenesulfonyl)aminophenylmethanol (19)

To a solution of lithium aluminum hydride (204 mg, 5.37 mmol) in 38.6 mL of THF at 0 °C under Ar was added dropwise ester **18** (1.93 g, 5.37 mmol) dissolved in 10 mL of THF. After the addition the solution was allowed to warm to room temperature and stirred for 2 h. The reaction was carefully quenched with 0.204 mL of water, followed by 0.204 mL of 15% aqueous NaOH, and then 0.612 mL of water. The resulting solution was stirred vigorously for 10 min, treated with anhydrous Na_2SO_4 for another 20 min, then filtered through a pad of Celite *in suction*, and evaporated *in vacuo*. Column chromatography (32% EtOAc/benzene) of the residual oil on silica gel (60 g) gave 1.62 g (95% yield) of pure alcohol **19**: ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.53 (2H, d, *J*=8 Hz), 7.24 (1H, d, *J*=8 Hz), 7.16 (1H, d, *J*=8 Hz), 7.15 (2H, d, *J*=8 Hz), 7.01 (1H, s), 6.71 (1H, br s), 5.72 (1H, ddt, *J*=17, 11, 6 Hz), 5.03 (1H, dd, *J*=11, 2 Hz), 4.86 (1H, dd, *J*=17, 2 Hz), 4.55 (2H, s), 3.02 (2H, d, *J*=6 Hz), 2.37 (1H, br s), 2.37 (3H, s); IR (neat) 3480, 3290, 2940, 1601, 1499, 1396, 1328, 1158, 1094,

914, 821, 757 cm^{-1}; EI-MS *m/z* (relative intensity) 317 (M^+, 18), 162 (67), 160 (54), 144 (30), 132 (100), 130 (34), 117 (20), 91 (29); EI-HRMS calcd for $C_{17}H_{19}NO_3S$ (M^+) 317.1086, found 317.1086.

4-(*tert*-Butyldiphenylsilyl)oxymethyl-2-(2-propenyl)-*N*-(*p*-toluenesulfonyl)aniline (20)

To a solution of alcohol **19** (5.44 g, 17.1 mmol) and imidazole (3.72 g, 54.7 mmol) in 27.2 mL of DMF at room temperature under Ar was added 6.68 mL (25.7 mmol) of *tert*-butyldiphenylsilyl chloride. The solution was allowed to warm to 60 °C and stirred for 85 h. After stirring an oil bath was removed and the reaction vessel was cooled to room temperature. The reaction mixture was poured into 100 mL of water and extracted with ether (100 mL × 3). The ethereal layer was washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residual oil was subjected to column chromatography on 170 g of silica gel eluting with 16% and 50% EtOAc/hexane to afford desired silyl ether **20** (7.74 g, 82% yield) and recovered alcohol **19** (867 mg, 16% yield), respectively. Data for silyl ether **20**: ^1H NMR (90 MHz, $CDCl_3$) δ 7.77-7.35 (6H, m), 7.45-6.95 (10H, m), 6.96 (1H, br s), 6.42 (1H, br s), 5.72 (1H, ddt, *J*=17, 11, 6 Hz), 5.03 (1H, dd, *J*=11, 2 Hz), 4.87 (1H, dd, *J*=17, 2 Hz), 4.66 (2H, s), 2.98 (2H, d, *J*=6 Hz), 2.38 (3H, s), 1.09 (9H, s); IR (neat) 3320, 3080, 2900, 2870, 1596, 1499, 1429, 1332, 1164, 1116, 1089, 910, 818, 741, 698 cm^{-1}; EI-MS *m/z* (relative intensity) 555 (M^+, 0.21), 499 (20), 498 (55), 300 (12), 200 (18), 199 (100), 144 (15), 91 (21), 77 (15), 45 (11); EI-HRMS calcd for $C_{33}H_{37}NO_3SSi$ (M^+) 555.2262, found 555.2227.

5-(*tert*-Butyldiphenylsilyl)oxymethyl-1-(*p*-toluenesulfonyl)-2-indolinol (21)

To a solution of silyl ether **20** (3.87 g, 6.96 mmol) in each 38.7 mL of THF and water at room temperature was added osmium tetroxide (17.7 mg, 69.6 μmol) and the solution was stirred at the same temperature. After 30 min a portion of sodium metaperiodate (4.47 g, 20.9 mmol) was added to the solution and the resulting mixture was stirred vigorously for additional 2 h. The reaction mixture was filtered *in suction*, poured into 50 mL of water, and extracted with ether (80 mL × 3). The organic layers were washed with 150 mL of brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (2% EtOAc/benzene) on 120 g of silica gel to give hemiacetal **21** as a colorless oil (3.45 g, 89% yield): ^1H NMR (90 MHz, $CDCl_3$) δ 7.77-7.35 (6H, m), 7.45-7.00 (10H, m), 7.00 (1H, s), 5.87 (1H, dd, *J*=7, 3 Hz), 4.62 (2H, s), 3.47 (1H, br s), 3.17 (1H, dd, *J*=17, 7 Hz), 2.87 (1H, dd, *J*=17, 3 Hz), 2.35 (3H, s), 1.07 (9H, s); IR (neat) 3540, 3060, 2890, 2860, 1595, 1486, 1426, 1349, 1256, 1161, 1111, 1078, 1024, 977, 909, 818, 735, 699 cm^{-1}; FD-MS *m/z* (relative intensity) 557 (M^+, 100), 391 (21), 385 (27), 256 (27), 157 (22), 156 (75), 155 (34); FI-HRMS calcd for $C_{32}H_{35}NO_4SSi$ (M^+) 557.2056, found 557.2072.

Methyl (2*E*)-2-[2-[5-(*tert*-butyldiphenylsilyl)oxymethyl-2-(*p*-toluenesulfonyl)aminophenyl]-ethylidene]-5,6-dimethyl-5-heptenoate (23) and its (2*Z*)-isomer (22)

To a solution of hemiacetal **21** (3.47 g, 6.22 mmol) in 10 mL of CH_2Cl_2 at room temperature under Ar was added 2.94 g (6.84 mmol) of phosphorane **16** in 7.4 mL of CH_2Cl_2 and stirred for 52 h. Dichloromethane was evaporated *in vacuo* and the residue was subjected to column chromatography on 110 g of silica gel eluting with 8% and 12% EtOAc/hexane to afford (*E*)-α,β-unsaturated ester **23** (3.86 g, 87% yield) and its (*Z*)-ismer **22** (128 mg, 2.9% yield), respectively.

(*E*)-isomer **23**: ^1H NMR (90 MHz, $CDCl_3$) δ 7.81-7.35 (6H, m), 7.50-6.85 (11H, m), 6.57 (1H, t, *J*=7 Hz), 6.41 (1H, br s), 4.68 (2H, s), 3.69 (3H, s), 3.34 (2H, d, *J*=7 Hz), 2.38 (3H, s), 2.53-1.83 (4H, m), 1.62 (9H, s), 1.06 (9H, s); IR (neat) 3280, 2950, 2870, 1713, 1646, 1601, 1498, 1430, 1331, 1255, 1200, 1163, 1114, 1089, 907, 818, 758, 699 cm^{-1}; EI-MS *m/z* (relative intensity) 709 (M^+, 14), 652 (47), 554 (35), 482 (70), 454 (65), 284 (88), 199 (96), 135 (38), 130 (100), 91 (58), 44 (34); EI-HRMS calcd for $C_{42}H_{51}NO_5SSi$ (M^+) 709.3257, found 709.3241.

(*Z*)-isomer **22**: ^1H NMR (90 MHz, $CDCl_3$) δ 8.25 (1H, br s), 7.74-7.44 (6H, m), 7.45-7.00 (10H, m), 6.94 (1H, br s), 5.60 (1H, t, *J*=8 Hz), 4.65 (2H, s), 3.85 (3H, s), 3.31 (2H, d, *J*=8 Hz), 2.33 (3H, s), 2.46-1.87 (4H, m), 1.55 (9H, s), 1.08 (9H, s); IR (neat) 3260, 2960, 2930, 2860, 1712, 1643, 1600, 1497, 1427, 1375, 1337, 1249, 1164, 1112, 1090, 901, 818, 745, 703 cm^{-1}; EI-MS *m/z* (relative intensity) 709 (M^+, 0.44), 284

(17), 200 (21), 199 (100), 147 (14), 135 (10), 130 (24), 91 (37), 77 (13), 44 (16); EI-HRMS calcd for $C_{42}H_{51}NO_5SSi$ (M^+) 709.3257, found 709.3273.

(2*E*)-2-[2-[5-(*tert*-Butyldiphenylsilyl)oxymethyl-2-(*p*-toluenesulfonyl)aminophenyl]-ethylidene]-5,6-dimethyl-5-hepten-1-ol (24)

To a solution of (*E*)-α,β-unsaturated ester **23** (3.86 g, 5.44 mmol) in 19.3 mL of toluene at -15 °C under Ar was added slowly diisobutylaluminum hydride (1 M in hexane, 19.0 mL, 19.0 mmol) and the mixture was stirred at the same temperature for 30 min. The reaction was quenched carefully with each appropriate amount of MeOH and water, and then the temperature was allowed to warm to room temperature. After vigorously stirring for 20 min, the resulting mixture was filtered through a pad of Celite *in suction* and the filtrates were concentrated under reduced pressure. The residue was purified by column chromatography (16% EtOAc/benzene) on 120 g of silica gel to give allylic alcohol **24** (3.40 g, 92% yield): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.80-7.44 (6H, m), 7.50-7.06 (10H, m), 7.01 (1H, s), 6.35 (1H, br s), 5.26 (1H, t, *J*=7 Hz), 4.66 (2H, s), 4.04 (2H, s), 3.11 (2H, d, *J*=7 Hz), 2.38 (3H, s), 2.14 (4H, br s), 1.62 (9H, s), 1.06 (9H, s); IR (neat) 3550, 3310, 3060, 2930, 2870, 1596, 1496, 1460, 1428, 1380, 1335, 1162, 1118, 1089, 1028, 998, 907, 817, 736, 697 cm^{-1}; FD-MS *m/z* (relative intensity) 681 (M^+, 100), 680 (16), 679 (21), 665 (17), 664 (29), 663 (42), 646 (11), 528 (27), 527 (36), 156 (25); FI-HRMS calcd for $C_{41}H_{51}NO_4SSi$ (M^+) 681.3307, found 681.3287.

(2*E*)-2-[2-[2-Acetyl(*p*-toluenesulfonyl)amino-5-(*tert*-butyldiphenylsilyl)oxymethylphenyl]-ethylidene]-5,6-dimethyl-5-hepten-1-ol (27)

To a solution of allylic alcohol **24** (2.39 g, 3.50 mmol) in 23.9 mL of CH_2Cl_2 at 0 °C under Ar was added 1.17 mL (8.40 mmol) of triethylamine. To the solution was added dropwise 0.533 mL (4.20 mmol) of chlorotrimethylsilane and the resulting mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into 50 mL of water and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (30 mL × 2). The combined organic layer was washed with 80 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to furnish crude TMS ether **25** which was used directly in the next reaction.

To a solution of the above TMS ether **25** (2.64 g, 3.50 mmol) in 26.4 mL of CH_2Cl_2 at 0 °C under Ar was added 1.17 mL (8.40 mmol) of triethylamine. To the solution was added dropwise 0.299 mL (4.20 mmol) of acetyl chloride and the resulting mixture was stirred at the same temperature for 30 min. The reaction mixture was poured into 50 mL of water and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (30 mL × 2). The combined organic layer was washed with 80 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude acetamide **26** which was employed immediately in the following reaction.

To a solution of the above acetamide **26** (2.79 g, 3.50 mmol) in 5.08 mL of diethyl ether, 12.7 mL of MeOH, and 1.27 mL of water at room temperature was added a portion of citric acid monohydrate (368 mg, 1.75 mmol), and then the resulting mixture was stirred at the same temperature for 50 min. The reaction mixture was poured into 70 mL of water and extracted with ether (50 mL × 3). The ethereal layer was washed with 100 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (4% EtOAc/benzene) on 85 g of silica gel to produce desired allylic alcohol **27** as an oil (2.44 g, 96% overall yield from the allylic alcohol **24**): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.90 (2H, d, *J*=8 Hz), 7.73-7.44 (5H, m), 7.44-7.00 (9H, m), 6.91 (1H, d, *J*=8 Hz), 5.50 (1H, br t, *J*=7 Hz), 4.76 (2H, s), 4.04 (2H, br s), 3.00 (2H, d, *J*=7 Hz), 2.41 (3H, s), 2.16 (4H, br s), 1.80 (3H, s), 1.65 (6H, s), 1.61 (3H, s), 1.11 (9H, s); IR (neat) 3490, 2930, 2870, 1712, 1600, 1492, 1460, 1430, 1367, 1267, 1228, 1169, 1110, 1088, 1013, 887, 817, 738, 698 cm^{-1}; FD-MS *m/z* (relative intensity) 723 (M^+, 92), 722 (36), 706 (20), 571 (21), 570 (30), 569 (46), 568 (28), 453 (22), 368 (23), 239 (27), 156 (100), 139 (20); FI-HRMS calcd for $C_{43}H_{53}NO_5SSi$ (M^+) 723.3413, found 723.3435.

(2*S*,3*S*)-4-[2-Acetyl(*p*-toluenesulfonyl)amino-5-(*tert*-butyldiphenylsilyl)oxymethylphenyl]-2-(3,4-dimethyl-3-pentenyl)-2,3-epoxy-1-butanol (28)

To a solution of allylic alcohol **27** (1.45 g, 2.00 mmol) and L-(+)-diethyl tartrate (495 mg, 2.40 mmol) in 14.5 mL of CH_2Cl_2 at -20 °C under Ar was added 0.596 mL (2.00 mmol) of titanium tetraisopropoxide (freshly distilled under reduced pressure) and the mixture was stirred for 15 min. Then, *tert*-butyl hydroperoxide (5 M in CH_2Cl_2, 0.8 mL, 4.00 mmol)[30] was added to the solution and the resulting mixtures were stirred at the same temperature for 1.5 h. 10 mL of 10% aqueous tartaric acid was added to the reaction vessel and the solution was stirred for 15 min. After the temperature was allowed to warm to room temperature, the solution was stirred for another 30 min. The reaction mixture was poured into 30 mL of 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2 (30 mL × 3). The organic layer was washed with 80 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residual mixtures were purified by column chromatography (8% EtOAc/benzene) on 100 g of silica gel to give an optically active epoxy alcohol **28** as an oil (1.45 g, 98% yield): $[\alpha]_D^{25}$ -14.9° (*c* 1.00, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.89 (2H, d, *J*=8 Hz), 7.74-7.00 (14H, m), 6.93 (1H, d, *J*=8 Hz), 4.79 (2H, s), 3.75-3.50 (2H, m), 3.02 (1H, m), 2.42 (3H, s), 2.40-1.90 (4H, m), 1.84 (3H, s), 1.90-1.50 (2H, m), 1.65 (9H, s), 1.11 (9H, s); IR (neat) 3540, 2940, 2860, 1714, 1597, 1496, 1462, 1430, 1365, 1266, 1227, 1171, 1113, 1087, 1016, 886, 819, 745, 700 cm^{-1}; EI-MS *m/z* (relative intensity) 739 (M^+, 0.18), 386 (31), 328 (44), 284 (26), 199 (56), 135 (21), 131 (22), 130 (100), 91 (34), 83 (29), 55 (24); EI-HRMS calcd for $C_{43}H_{53}NO_6SSi$ (M^+) 739.3361, found 739.3339.

(2*S*,3*S*)-4-[2-Acetyl(*p*-toluenesulfonyl)amino-5-(*tert*-butyldiphenylsilyl)oxymethylphenyl]-2-(3,4-dimethyl-3-pentenyl)-2,3-epoxybutyl methanesulfonate (29)

To a solution of epoxy alcohol **28** (247 mg, 0.334 mmol) in 5 mL of CH_2Cl_2 at 0 °C under Ar was added sequentially 0.116 mL (0.835 mmol) of triethylamine and 31.0 μL (0.401 mmol) of methanesulfonyl chloride, and the solution was stirred at the same temperature for 30 min. The reaction mixture was poured into 20 mL of water and extracted with CH_2Cl_2 (20 mL × 3). The extracts were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Purification of the residue was carried out by column chromatography (4% EtOAc/benzene) on 15 g of silica gel to afford mesylate **29** (260 mg, 95% yield): $[\alpha]_D^{26}$ -15.3° (*c* 1.00, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.88 (2H, d, *J*=8 Hz), 7.73-7.00 (14H, m), 6.93 (1H, d, *J*=8 Hz), 4.79 (2H, s), 4.36 (1H, d, *J*=11 Hz), 4.10 (1H, d, *J*=11 Hz), 3.20 (1H, m), 2.97 (3H, s), 2.42 (3H, s), 2.50-1.95 (4H, m), 1.82 (3H, s), 2.00-1.50 (2H, m), 1.68 (9H, br s), 1.12 (9H, s); IR (neat) 2970, 2940, 2870, 1713, 1598, 1430, 1362, 1170, 1114, 1087, 956, 819, 757, 702 cm^{-1}; FD-MS *m/z* (relative intensity) 817 (M^+, 100), 816 (33), 776 (40), 775 (53), 762 (36), 761 (49), 760 (61), 664 (52), 663 (56), 368 (36), 353 (33), 156 (64).

(1*S*)-1-[5-(*tert*-Butyldiphenylsilyl)oxymethyl-2-(*p*-toluenesulfonyl)aminophenylmethyl]-5,6-dimethyl-2-methylene-5-heptenyl acetate (30)

To a solution of mesylate **29** (1.26 g, 1.54 mmol) and 201 mg (3.08 mmol) of zinc powder (activated by washing with 1 N HCl, water, MeOH, and ether and drying under high vacuum)[31a] in 20 mL of DMF at room temperature was added a portion of sodium iodide (1.15 g, 7.70 mmol) and the resulting mixture was stirred vigorously at 100 °C for 15 min under Ar. An oil bath was removed and the mixture was cooled to room temperature. To the reaction vessel was added 5 mL of saturated aqueous NH_4Cl and the mixture was poured into 100 mL of 10% aqueous $Na_2S_2O_3$, followed by extracting with ether (60 mL × 3). The ethereal layer was washed with 100 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (16% EtOAc/hexane) on 40 g of silica gel to provide allylic acetate **30** (970 mg, 87% yield) as an oil: $[\alpha]_D^{27}$ -25.5° (*c* 0.350, $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.73-6.95 (16H, m), 6.89 (1H, br s), 4.97 (1H, br t, *J*=6 Hz), 4.84 (1H, br s), 4.76 (1H, s), 4.64 (2H, s), 2.54 (2H, br d, *J*=6 Hz), 2.36 (3H, s), 2.08 (3H, s), 2.05 (4H, br s), 1.60 (9H, br s), 1.09 (9H, s); IR (neat) 3280, 2930, 2870, 1718, 1601, 1497, 1430, 1367, 1231, 1166, 1113, 1088, 889, 818, 744, 700 cm^{-1}; EI-MS *m/z* (relative intensity) 723 (M^+, 0.16), 409 (32), 408 (100), 253 (51), 252 (40), 199 (97), 170 (32), 135 (30), 130 (59), 91 (47); EI-HRMS calcd for $C_{43}H_{53}NO_5SSi$ (M^+) 723.3413, found 723.3448.

(2*S*)-1-[5-(*tert*-Butyldiphenylsilyl)oxymethyl-2-(*p*-toluenesulfonyl)aminophenyl]-6,7-dimethyl-3-methylene-6-octen-2-ol (31)

To a solution of allylic acetate **30** (208 mg, 0.287 mmol) in 4 mL of toluene at -15 °C under Ar was added slowly diisobutylaluminum hydride (1 M in hexane, 1.00 mL, 1.00 mmol) and the mixture was stirred at the same temperature for 30 min. The reaction was quenched carefully with each appropriate amount of MeOH and water, and then the temperature was allowed to warm to room temperature. After stirring vigorously for 20 min, the resulting mixture was filtered through a pad of Celite *in suction* and the filtrates were concentrated under reduced pressure. The residue was purified by column chromatography (16% EtOAc/hexane) on 11 g of silica gel to furnish *exo* allylic alcohol **31** (192 mg, 98% yield): $[\alpha]_D^{26}$ -26.9° (*c* 1.00, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 8.79 (1H, br s), 7.75-7.00 (16H, m), 6.90 (1H, br s), 4.96 (1H, br s), 4.81 (1H, br s), 4.68 (2H, s), 4.18 (1H, br t, *J*=6 Hz), 2.36 (3H, s), 2.30 (2H, br d, *J*=6 Hz), 2.25-1.80 (4H, m), 1.62 (9H, s), 1.05 (9H, s); IR (neat) 3530, 3200, 3070, 2930, 2870, 1601, 1500, 1430, 1376, 1337, 1162, 1110, 1092, 907, 817, 737, 698 cm^{-1}; FD-MS *m/z* (relative intensity) 681 (M^+, 100), 528 (20), 527 (33), 157 (10), 156 (21); FI-HRMS calcd for $C_{41}H_{51}NO_4SSi$ (M^+) 681.3308, found 681.3323.

(2*S*,3*R*)-1-[5-(*tert*-Butyldiphenylsilyl)oxymethyl-2-(*p*-toluenesulfonyl)aminophenyl]-3-(3,4-dimethyl-3-pentenyl)-3,4-epoxy-2-butanol (32)

To a blue solution of allylic alcohol **31** (508 mg, 0.745 mmol) and vanadyl acetylacetonate (19.8 mg, 74.5 μmol) in 5.08 mL of CH_2Cl_2 at 0 °C under Ar was added *tert*-butyl hydroperoxide (5 M in CH_2Cl_2, 0.298 mL, 1.49 mmol)[30] and the red-brown solution was stirred at the same temperature for 2.5 h. The reaction mixture was poured into 20 mL of 10% aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residual oil was subjected to column chromatography (16% EtOAc/hexane) on 25 g of silica gel to give purified epoxy alcohol **32** (499 mg, 96% yield) as a single diastereomer: $[\alpha]_D^{26}$ -2.11° (*c* 1.00, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 8.65 (1H, s), 7.80-7.57 (6H, m), 7.48-7.31 (7H, m), 7.21 (2H, d, *J*=8.1 Hz), 7.17 (1H, dd, *J*=7.3, 1.8 Hz), 6.97 (1H, d, *J*=1.8 Hz), 4.68 (2H, s), 3.95 (1H, dd, *J*=7.3, 2.2 Hz), 2.68 (1H, s), 2.56 (1H, d, *J*=4.4 Hz), 2.55 (1H, dd, *J*=15.0, 2.2 Hz), 2.48 (1H, d, *J*=4.4 Hz), 2.40 (3H, s), 2.33 (1H, dd, *J*=15.0, 7.3 Hz), 2.03 (2H, m), 1.82 (1H, ddd, *J*=14.5, 10.6, 6.0 Hz), 1.60 (6H, br s), 1.56 (3H, s), 1.53 (1H, m), 1.07 (9H, s); IR (neat) 3520, 3220, 2940, 2870, 1601, 1497, 1428, 1375, 1336, 1251, 1217, 1160, 1108, 1092, 918, 818, 757 cm^{-1}; EI-MS *m/z* (relative intensity) 697 (M^+, 2.0), 640 (35), 622 (31), 485 (67), 467 (56), 424 (35), 268 (31), 199 (100), 144 (48), 135 (46), 132 (40), 130 (57), 91 (61), 83 (46), 55 (58), 44 (61); EI-HRMS calcd for $C_{41}H_{51}NO_5SSi$ (M^+) 697.3257, found 697.3264.

(2*S*,3*S*)-6-(*tert*-Butyldiphenylsilyl)oxymethyl-2-(3,4-dimethyl-3-pentenyl)-2-hydroxymethyl-1-(*p*-toluenesulfonyl)-1,2,3,4-tetrahydroquinolin-3-ol (33)

To a solution of epoxy alcohol **32** (366 mg, 0.524 mmol) in 7 mL of toluene at room temperature under Ar was added slowly 81.1 μL (1.05 mmol) of trifluoroacetic acid and the solution was stirred at the same temperature for 6 h. After stirring for 6 h, the reaction was quenched with 3 mL of saturated aqueous $NaHCO_3$. The resulting mixtures were poured into 20 mL of water and extracted with ether (20 mL × 3). The extracted ethereal layers were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification of the residue by column chromatography (8% EtOAc/benzene) on 20 g of silica gel afforded diol **33** (245 mg, 67% yield): $[\alpha]_D^{26}$ -31.1° (*c* 0.525, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.80-6.95 (14H, m), 7.18 (2H, d, *J*=8 Hz), 6.96 (1H, s), 4.68 (2H, s), 4.13-3.53 (3H, m), 3.02 (1H, dd, *J*=16, 6 Hz), 2.60 (1H, dd, *J*=16, 5 Hz), 2.38 (3H, s), 2.25-1.88 (2H, m), 1.80-1.10 (2H, m), 1.52 (3H, s), 1.43 (3H, s), 1.39 (3H, br s), 1.08 (9H, s); IR (neat) 3540, 3070, 2930, 2870, 1601, 1494, 1461, 1430, 1342, 1258, 1158, 1111, 1088, 1041, 816, 744, 701 cm^{-1}; EI-MS *m/z* (relative intensity) 697 (M^+, 0.35), 386 (11), 328 (13), 200 (20), 199 (100), 130 (33), 91 (14), 83 (13), 77 (15), 55 (12), 45 (11); EI-HRMS calcd for $C_{41}H_{51}NO_5SSi$ (M^+) 697.3257, found 697.3270.

(4a*S*,9a*S*)-6-(*tert*-Butyldiphenylsilyl)oxymethyl-9a-(3,4-dimethyl-3-pentenyl)-3,3-dimethyl-9-(*p*-toluenesulfonyl)-9-aza-2,4-dioxa-1,2,3,4,4a,10,9,9a-octahydroanthracene (36)

To a solution of diol **33** (395 mg, 0.566 mmol) and 0.348 mL (2.83 mmol) of 2,2-dimethoxypropane in 4.5 mL of acetone at room temperature was added a portion of camphorsulfonic acid (13.1 mg, 56.6 μmol) and the mixture was stirred for 3 h under Ar. The reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ and the resulting mixtures were poured into 25 mL of water, followed by extracting with ether (20 mL × 3). The ethereal layer was washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (4% EtOAc/hexane) on 20 g of silica gel to provide acetonide **36** (383 mg, 92% yield): $[\alpha]_D^{26}$ -4.04° (*c* 1.48, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.80-7.00 (16H, m), 6.97 (1H, br s), 4.72 (2H, s), 4.42 (1H, br d, *J*=11 Hz), 4.12 (1H, d, *J*=11 Hz), 3.59 (1H, dd, *J*=10, 7 Hz), 2.52 (1H, dd, *J*=15, 7 Hz), 2.37 (3H, s), 2.40-1.98 (3H, m), 1.98-1.30 (2H, m), 1.54 (6H, br s), 1.47 (3H, br s), 1.30 (3H, s), 1.24 (3H, s), 1.08 (9H, s); IR (neat) 2920, 2860, 1601, 1493, 1460, 1430, 1380, 1355, 1285, 1226, 1167, 1114, 1088, 874, 817, 758, 701 cm^{-1}; EI-MS *m/z* (relative intensity) 737 (M^+, 4.9), 487 (38), 486 (100), 428 (53), 238 (36), 199 (65), 156 (47), 135 (32), 130 (34), 91 (50), 83 (43), 55 (52); EI-HRMS calcd for $C_{44}H_{55}NO_5SSi$ (M^+) 737.3570, found 737.3608.

(4a*S*,9a*S*)-9a-(3,4-Dimethyl-3-pentenyl)-6-hydroxymethyl-3,3-dimethyl-9-(*p*-toluenesulfonyl)-9-aza-2,4-dioxa-1,2,3,4,4a,10,9,9a-octahydroanthracene (37)

To a solution of acetonide **36** (383 mg, 0.519 mmol) in 4 mL of THF at room temperature under Ar was added tetrabutylammonium fluoride (1.0 M in THF, 1.04 mL, 1.04 mmol) and the mixture was stirred at the same temperature for 15 h. The reaction was quenched with 1 mL of saturated aqueous NH_4Cl and the reaction mixtures were poured into 20 mL of water, followed by extracting with ether (20 mL × 3). The combined ethereal layers were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography (8% EtOAc/benzene) on 20 g of silica gel to produce deprotected benzylic alcohol **37** (256 mg, 99% yield): $[\alpha]_D^{26}$ -31.2° (*c* 0.700, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.62 (1H, d, *J*=8 Hz), 7.45 (2H, d, *J*=8 Hz), 7.35-6.95 (2H, m), 7.13 (2H, d, *J*=8 Hz), 4.65 (2H, s), 4.40 (1H, dd, *J*=11, 1 Hz), 4.10 (1H, d, *J*=11 Hz), 3.58 (1H, dd, *J*=10, 7 Hz), 2.58 (1H, dd, *J*=15, 7 Hz), 2.35 (3H, s), 2.50-1.30 (5H, m), 1.53 (6H, s), 1.45 (3H, br s), 1.30 (3H, s), 1.23 (3H, s); IR (neat) 3520, 2920, 2860, 1600, 1495, 1450, 1380, 1351, 1290, 1228, 1167, 1127, 1092, 1064, 1041, 875, 817, 759 cm^{-1}; EI-MS *m/z* (relative intensity) 499 (M^+, 4.9), 344 (23), 286 (22), 256 (24), 248 (100), 190 (65), 139 (20), 91 (25), 83 (25), 55 (37), 44 (41); EI-HRMS calcd for $C_{28}H_{37}NO_5S$ (M^+) 499.2392, found 499.2427.

(4a*S*,9a*S*)-9a-(3,4-Dimethyl-3-pentenyl)-3,3-dimethyl-9-(*p*-toluenesulfonyl)-9-aza-2,4-dioxa-1,2,3,4,4a,10,9,9a-octahydroanthracene-6-carbaldehyde (38)

To a solution of benzylic alcohol **37** (215 mg, 0.430 mmol) in 4.3 mL of CH_2Cl_2 at room temperature was added a portion of pyridinium dichromate (324 mg, 0.860 mmol) and the resulting mixture was stirred for 4 h under Ar. After diluted with 10 mL of ether, the reaction mixtures were filtered through a pad of Celite *in suction* and the filtrates were evaporated under reduced pressure to give the aldehyde **38** which was used directly in the next reaction. A small sample of the aldehyde **38** was purified by column chromatography (8% EtOAc/hexane) on silica gel and characterized: $[\alpha]_D^{26}$ -55.5° (*c* 0.550, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 9.92 (1H, s), 7.86 (1H, d, *J*=8 Hz), 7.72 (1H, br d, *J*=8 Hz), 7.60 (1H, br s), 7.52 (2H, d, *J*=8 Hz), 7.17 (2H, d, *J*=8 Hz), 4.43 (1H, br d, *J*=11 Hz), 4.12 (1H, d, *J*=11 Hz), 3.71 (1H, dd, *J*=9, 7 Hz), 2.76 (1H, dd, *J*=16, 7 Hz), 2.38 (3H, s), 2.40-1.30 (5H, m), 1.53 (6H, br s), 1.46 (3H, br s), 1.28 (6H, s); IR (neat) 2920, 2870, 1699, 1610, 1492, 1443, 1380, 1354, 1228, 1167, 1126, 1090, 874, 816, 757 cm^{-1}; EI-MS *m/z* (relative intensity) 497 (M^+, 0.52), 342 (22), 284 (33), 246 (92), 188 (100), 155 (26), 91 (65), 83 (38), 55 (63), 41 (33); EI-HRMS calcd for $C_{28}H_{35}NO_5S$ (M^+) 497.2236, found 497.2256.

(4a*S*,9a*S*)-9a-(3,4-Dimethyl-3-pentenyl)-6-methoxycarbonyl-3,3-dimethyl-9-(*p*-toluenesulfonyl)-9-aza-2,4-dioxa-1,2,3,4,4a,10,9,9a-octahydroanthracene (39)

To a solution of the aldehyde **38** (214 mg, 0.430 mmol), potassium cyanide (95% purity, 147 mg, 2.15 mmol), and active manganese dioxide (748 mg, 8.60 mmol)[31b] in 4 mL of MeOH and 2 mL of benzene at room temperature under Ar was added 39.4 μL (0.688 mmol) of acetic acid, and then the mixture was stirred for 13 h. The reaction mixture was filtered through a pad of Celite *in suction* and poured into 30 mL of saturated aqueous $NaHCO_3$, followed by extracting with ether (20 mL × 3). The combined organic layers were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo* to afford the methyl ester **39** which was used directly in the following reaction. A small sample of **39** was purified by column chromatography (8% EtOAc/hexane) on silica gel and characterized: $[\alpha]_D^{29}$ -48.7° (*c* 0.500, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.93 (1H, dd, *J*=9, 2 Hz), 7.73 (1H, d, *J*=2 Hz), 7.73 (1H, d, *J*=9 Hz), 7.47 (2H, d, *J*=8 Hz), 7.15 (2H, d, *J*=8 Hz), 4.42 (1H, br d, *J*=12 Hz), 4.11 (1H, d, *J*=12 Hz), 3.89 (3H, s), 3.66 (1H, dd, *J*=10, 7 Hz), 2.69 (1H, dd, *J*=15, 7 Hz), 2.37 (3H, s), 2.40-1.30 (5H, m), 1.52 (6H, br s), 1.44 (3H, br s), 1.29 (3H, s), 1.25 (3H, s); IR (neat) 2930, 1726, 1608, 1494, 1444, 1356, 1278, 1225, 1199, 1164, 1124, 1090, 1062, 1039, 997, 875, 822, 807, 764, 714 cm^{-1}; EI-MS *m/z* (relative intensity) 527 (M^+, 1.2), 372 (25), 314 (33), 276 (100), 218 (94), 197 (24), 139 (42), 97 (24), 91 (62), 83 (75), 71 (21), 69 (32), 57 (43), 55 (95), 43 (44), 41 (48); EI-HRMS calcd for $C_{29}H_{37}NO_6S$ (M^+) 527.2342, found 527.2350.

(4a*S*,9a*S*)-9a-(3,4-Dimethyl-3-pentenyl)-3,3-dimethyl-9-(*p*-toluenesulfonyl)-9-aza-2,4-dioxa-1,2,3,4,4a,10,9,9a-octahydroanthracene-6-carboxylic acid (40)

To a solution of methyl ester **39** (227 mg, 0.430 mmol) in 2 mL of diethyl ether, 2 mL of MeOH, and 1 mL of water at room temperature was added potassium hydroxide (2 M in water, 1.08 mL, 2.15 mmol) and the solution was stirred at the same temperature for 24 h. The reaction mixture was poured into 15 mL of water and the aqueous layer was acidified to pH 3-4 with 1 N aqueous HCl, followed by extracting with CH_2Cl_2 (20 mL × 3). The extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (4% MeOH/$CHCl_3$) on 15 g of silica gel to provide carboxylic acid **40** (221 mg, 100% overall yield from the aldehyde **38**): $[\alpha]_D^{28}$ -47.1° (*c* 0.500, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.99 (1H, br d, *J*=9 Hz), 7.81 (1H, s), 7.77 (1H, d, *J*=9 Hz), 7.52 (2H, d, *J*=8 Hz), 7.18 (2H, d, *J*=8 Hz), 4.44 (1H, br d, *J*=12 Hz), 4.13 (1H, d, *J*=12 Hz), 3.71 (1H, dd, *J*=10, 7 Hz), 2.73 (1H, dd, *J*=15, 7 Hz), 2.38 (3H, s), 2.40-1.30 (5H, m), 1.55 (6H, br s), 1.47 (3H, br s), 1.29 (6H, br s); IR (neat) 3710-2310, 2920, 2860, 1694, 1613, 1442, 1380, 1355, 1285, 1225, 1163, 1128, 1089, 1060, 1038, 994, 872, 815, 757 cm^{-1}; EI-MS *m/z* (relative intensity) 513 (M^+, 0.53), 358 (23), 300 (36), 262 (89), 204 (100), 197 (20), 186 (22), 139 (42), 91 (51), 83 (65), 55 (72), 43 (22), 41 (30); EI-HRMS calcd for $C_{28}H_{35}NO_6S$ (M^+) 513.2185, found 513.2207.

(4a*S*,9a*S*)-9a-(3,4-Dimethyl-3-pentenyl)-3,3-dimethyl-9-aza-2,4-dioxa-1,2,3,4,4a,10,9,9a-octahydroanthracene-6-carboxylic acid (41)

To a solution of sulfonamide **40** (98.5 mg, 0.192 mmol) in 4 mL of 1,2-dimethoxyethane at -15 °C under Ar was added sodium naphthalenide (1.0 M in 1,2-dimethoxyethane, 0.576 mL, 0.576 mmol) and the dark-blue solution was stirred at the same temperature for 30 min. The reaction was quenched with 1 mL of saturated aqueous NH_4Cl and the reaction mixture was poured into 15 mL of water. The aqueous layer was acidified to pH 3-4 with 1 N aqueous HCl and extracted with CH_2Cl_2 (20 mL × 3). The organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was subjected to column chromatography (4% MeOH/$CHCl_3$) on 6 g of silica gel to give purified carboxylic acid **41** (69 mg, 100% yield): $[\alpha]_D^{27}$ -42.4° (*c* 0.500, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (1H, s), 7.75 (1H, d, *J*=9 Hz), 6.55 (1H, d, *J*=9 Hz), 4.12 (1H, dd, *J*=3, 1 Hz), 3.95 (1H, d, *J*=11 Hz), 3.66 (1H, d, *J*=11 Hz), 3.08 (1H, dd, *J*=17, 3 Hz), 2.74 (1H, dd, *J*=17, 1 Hz), 2.11 (1H, dt, *J*=5, 12 Hz), 1.95 (1H, dt, *J*=5, 12 Hz), 1.70-1.40 (1H, dt, *J*=5, 12 Hz), 1.60 (3H, s), 1.58 (3H, s), 1.55 (3H, s), 1.49 (3H, s), 1.35 (1H, dt, *J*=5, 12 Hz), 1.30 (3H, s); IR (neat) 3700-2200, 3394, 2920, 1675, 1605, 1525, 1445, 1385, 1295, 1255, 1205, 1161, 1076, 901, 826, 756 cm^{-1}; EI-MS *m/z* (relative intensity) 359 (M^+, 61), 270 (41), 262 (45), 205 (92), 204 (100), 203 (61), 189 (74), 176

(40), 174 (30), 162 (62), 83 (61), 73 (61), 55 (82), 43 (37), 41 (47); EI-HRMS calcd for $C_{21}H_{29}NO_4$ (M^+) 359.2097, found 359.2081.

(4a*S*,9a*S*)-9a-(3,4-Dimethyl-3-pentenyl)-6-methoxycarbonyl-3,3-dimethyl-9-aza-2,4-dioxa-1,2,3,4,4a,10,9,9a-octahydroanthracene (42)

To a solution of carboxylic acid **41** (48.9 mg, 0.136 mmol) in 4 mL of MeOH at room temperature was added a solution of diazomethane in diethyl ether[31c] till generation of nitrogen was over, and then the yellow mixtures were evaporated under reduced pressure. The residue was purified by column chromatography (16% EtOAc/hexane) on 5 g of silica gel to afford methyl ester **42** (50.8 mg, 100% yield): $[\alpha]_D^{27}$ -32.2° (*c* 0.250, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.66 (1H, br s), 7.63 (1H, d, *J*=8 Hz), 6.48 (1H, d, *J*=8 Hz), 4.22 (1H, br s), 4.06 (1H, dd, *J*=3, 1 Hz), 3.92 (1H, d, *J*=12 Hz), 3.80 (3H, s), 3.58 (1H, d, *J*=12 Hz), 3.05 (1H, dd, *J*=17, 3 Hz), 2.67 (1H, dd, *J*=17, 1 Hz), 2.30-1.70 (2H, m), 1.70-1.20 (2H, m), 1.57 (9H, br s), 1.48 (3H, s), 1.29 (3H, s); IR (neat) 3375, 3000, 2940, 1692, 1613, 1515, 1438, 1381, 1333, 1288, 1248, 1198, 1112, 1075, 900, 832, 762 cm^{-1}; EI-MS *m/z* (relative intensity) 373 (M^+, 60), 284 (48), 276 (42), 219 (83), 218 (100), 217 (63), 203 (65), 190 (36), 83 (31), 73 (49), 55 (57), 41 (34); EI-HRMS calcd for $C_{22}H_{31}NO_4$ (M^+) 373.2253, found 373.2215.

(2*S*,3*S*)-2-(3,4-Dimethyl-3-pentenyl)-2-hydroxymethyl-6-methoxycarbonyl-1,2,3,4-tetrahydroquinolin-3-ol (43)

To a solution of methyl ester **42** (34 mg, 91.0 μmol) in 0.5 mL of diethyl ether and 2 mL of MeOH at room temperature was added a portion of *p*-toluenesulfonic acid monohydrate (17.3 mg, 91.0 μmol) and the mixture was stirred at the same temperature for 18 h. The reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ and the reaction mixture was poured into 10 mL of water, followed by extracting with ether (15 mL × 3). The ethereal layer was washed with 30 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by column chromatography (4% MeOH/$CHCl_3$) on 3 g of silica gel provided deprotected diol **43** (28 mg, 92% yield): $[\alpha]_D^{27}$ +44.2° (*c* 0.250, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.67 (1H, d, *J*=1 Hz), 7.63 (1H, dd, *J*=9, 1 Hz), 6.45 (1H, d, *J*=9 Hz), 4.02 (1H, dd, *J*=5, 4 Hz), 3.84 (1H, d, *J*=12 Hz), 3.80 (3H, s), 3.68 (1H, d, *J*=12 Hz), 3.09 (1H, dd, *J*=16, 4 Hz), 2.78 (1H, dd, *J*=16, 5 Hz), 2.70 (1H, br s), 2.30-1.70 (2H, m), 1.70-1.30 (2H, m), 1.60 (9H, br s); IR (neat) 3390, 2930, 1703, 1611, 1512, 1435, 1331, 1288, 1196, 1137, 1102, 1067, 1053, 986, 900, 831, 775, 751 cm^{-1}; EI-MS *m/z* (relative intensity) 333 (M^+, 14), 303 (23), 302 (100), 284 (10), 236 (26), 220 (41), 206 (10), 204 (12), 202 (11), 188 (12), 176 (11), 144 (13), 83 (71), 55 (47), 41 (24); EI-HRMS calcd for $C_{19}H_{27}NO_4$ (M^+) 333.1940, found 333.1944.

(2*S*,3*S*)-2-(3,4-Dimethyl-3-pentenyl)-6-methoxycarbonyl-2-methoxymethyl-1,2,3,4-tetrahydroquinolin-3-ol (44)

To a solution of diol **43** (29.0 mg, 87.0 μmol) and tetrabutylammonium iodide (16.1 mg, 43.5 μmol) in 2 mL of THF at 0 °C was added a portion of sodium hydride (6.26 mg, 0.261 mmol, washed with hexane) and the solution was stirred at the same temperature for 30 min under Ar. After the temperature was cooled to -15 °C, 27.1 μL (0.435 mmol) of freshly distilled methyl iodide and 30.3 μL (0.174 mmol) of hexamethylphosphoric triamide (freshly distilled from calcium hydride under reduced pressure) were added successively to the solution and the resulting mixtures were stirred at the same temperature for additional 1.5 h. The reaction was quenched with 1 mL of saturated aqueous NH_4Cl and the reaction mixture was poured into 10 mL of water, followed by extracting with ether (15 mL × 3). The combined ethereal layers were washed with 30 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was subjected to column chromatography on 3 g of silica gel to give 4.4 mg (14% yield) of dimethyl ether (eluted with 4% EtOAc/benzene), 21 mg (70% yield) of desired monomethyl ether **44** (eluted with 16% EtOAc/benzene), and 4.6 mg (16% yield) of recovered diol **43** (eluted with 4% MeOH/$CHCl_3$).

Dimethyl ether: $[\alpha]_D^{21}$ +45.6° (*c* 0.250, $CHCl_3$); CD (*c* 2.77×10^{-5} M, EtOH at 23 °C) $\Delta\varepsilon_{215}$=-2.08, $\Delta\varepsilon_{315}$=-1.75; UV λ_{max} (EtOH) 230 (ε 8200), 311 (ε 22600); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.66 (1H, d, *J*=1 Hz), 7.62 (1H, dd, *J*=9, 1 Hz), 6.42 (1H, d, *J*=9 Hz), 4.46 (1H, br s), 3.80 (3H, s), 3.65-3.20 (3H, m), 3.36 (3H, s), 3.33 (3H, s), 3.02-2.77 (2H, m), 2.30-1.85 (2H, m), 1.85-1.30 (2H, m), 1.60 (9H, br s); EI-MS *m/z* (relative intensity) 361 (M^+, 11), 317 (24), 316 (100), 234 (27), 202 (23), 190 (94), 189 (21), 158 (38), 131 (23), 83 (51), 55 (43), 41 (22); EI-HRMS calcd for $C_{21}H_{31}NO_4$ (M^+) 361.2253, found 361.2251.

Monomethyl ether **44**: $[\alpha]_D^{26}$ +36.2° (*c* 0.250, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (1H, d, *J*=2 Hz), 7.69 (1H, dd, *J*=8, 2 Hz), 6.49 (1H, d, *J*=8 Hz), 3.97 (1H, dd, *J*=6, 5 Hz), 3.84 (3H, s), 3.66 (1H, d, *J*=9 Hz), 3.48 (1H, d, *J*=9 Hz), 3.40 (3H, s), 3.10 (1H, dd, *J*=17, 5 Hz), 2.84 (1H, dd, *J*=17, 6 Hz), 2.09 (1H, dt, *J*=5, 12 Hz), 2.05 (1H, br s), 2.03 (1H, dt, *J*=5, 12 Hz), 1.81 (1H, ddd, *J*=14, 12, 5 Hz), 1.62 (3H, s), 1.61 (6H, s), 1.57 (1H, ddd, *J*=14, 12, 5 Hz); IR (neat) 3470, 3390, 2930, 1703, 1611, 1511, 1433, 1380, 1333, 1287, 1252, 1197, 1128, 1103, 1066, 980, 831, 774 cm^{-1}; EI-MS *m/z* (relative intensity) 347 (M^+, 9.9), 316 (22), 303 (20), 302 (100), 284 (12), 250 (16), 232 (12), 220 (39), 218 (10), 204 (13), 202 (12), 188 (11), 144 (10), 83 (68), 55 (46), 45 (15), 41 (21); EI-HRMS calcd for $C_{20}H_{29}NO_4$ (M^+) 347.2097, found 347.2078.

(2*S*,3*S*)-3-(4-Dimethylaminobenzoyloxy)-2-(3,4-dimethyl-3-pentenyl)-6-methoxycarbonyl-2-methoxymethyl-1,2,3,4-tetrahydroquinoline (46)

To a solution of methyl ether **44** (4.5 mg, 13.0 μmol), 4.29 mg (26.0 μmol) of 4-dimethylaminobenzoic acid, and 9.35 mg (31.2 μmol) of 2-chloro-1-methylpyridinium *p*-toluenesulfonate in 3 mL of toluene at room temperature under Ar was added 14.9 μL (62.4 μmol) of tributylamine and the mixture was heated to reflux. After stirred at the same temperature for 4 h, an oil bath was removed and the reaction vessel was cooled to room temperature. The reaction mixture was poured into 10 mL of water and extracted with ether (10 mL × 3). The organic layers were washed with 20 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Preparative thin layer chromatography (silica gel) of the residue with 30% EtOAc/hexane yielded benzoate **46** (3.5 mg, 54% yield): *Rf*=0.40 (30% EtOAc/hexane on silica gel); $[\alpha]_D^{19}$ -56.2° (*c* 0.175, $CHCl_3$); CD (*c* 4.04×10^{-5} M, EtOH at 23 °C) $\Delta\varepsilon_{289}$=+17.1, $\Delta\varepsilon_{320}$=-33.9; UV λ_{max} (EtOH) 227 (ε 16200), 311 (ε 43300); ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.78 (2H, d, *J*=9 Hz), 7.77 (1H, d, *J*=9 Hz), 7.63 (1H, s), 6.57 (2H, d, *J*=9 Hz), 6.49 (1H, d, *J*=9 Hz), 5.41 (1H, t, *J*=5 Hz), 3.80 (3H, s), 3.57 (1H, d, *J*=9 Hz), 3.42 (1H, d, *J*=9 Hz), 3.32 (3H, s), 3.20-2.70 (2H, m), 2.99 (6H, s), 2.35-1.10 (4H, m), 1.59 (9H, br s); EI-MS *m/z* (relative intensity) 494 (M^+, 5.0), 465 (18), 447 (16), 300 (25), 285 (15), 284 (65), 283 (15), 282 (62), 232 (39), 216 (16), 166 (32), 165 (18), 164 (24), 148 (100); EI-HRMS calcd for $C_{29}H_{38}N_2O_5$ (M^+) 494.2779, found 494.2749.

(2*R*)-1,2-[(*S*)-1-(3,4-Dimethyl-3-pentenyl)-1-(methoxymethyl)methylene]-5-methoxycarbonylindoline (45)

To a solution of alcohol **44** (13 mg, 37.4 μmol) and 29.4 mg (0.112 mmol) of triphenylphosphine in 2 mL of THF at room temperature under Ar was added 17.6 μL (0.112 mmol) of diethyl azodicarboxylate (freshly distilled under reduced pressure) and the resulting orange solution was stirred at the same temperature for 3 h. The reaction mixture was poured into 10 mL of water and extracted with ether (10 mL × 3). The combined organic layers were washed with 20 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (16% EtOAc/hexane) on 3 g of silica gel to afford aziridine **45** (11 mg, 89% yield): $[\alpha]_D^{26}$ -135° (*c* 0.300, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.86 (1H, dd, *J*=8.1, 1.5 Hz), 7.81 (1H, d, *J*=1.5 Hz), 7.25 (1H, d, *J*=8.1 Hz), 3.89 (3H, s), 3.31 (1H, dd, *J*=17.6, 8.1 Hz), 3.23 (1H, d, *J*=11.4 Hz), 3.12 (1H, dd, *J*=17.6, 2.2 Hz), 3.05 (3H, s), 2.99 (1H, dd, *J*=8.1, 2.2 Hz), 2.87 (1H, d, *J*=11.4 Hz), 2.23 (1H, dt, *J*=5.9, 11.0 Hz), 2.16 (1H, dt, *J*=5.5, 10.3 Hz), 1.96 (1H, ddd, *J*=13.6, 10.4, 5.7 Hz), 1.68 (3H, s), 1.65 (3H, s), 1.62 (3H, s), 1.51 (1H, ddd, *J*=13.6, 11.2, 5.5 Hz); IR (neat) 2920, 2860, 1720, 1612, 1436, 1379, 1324, 1290, 1270, 1197, 1155, 1108, 979, 904, 850, 774, 729 cm^{-1}; EI-MS *m/z* (relative intensity) 329 (M^+, 15), 176 (29), 167 (46), 149 (100), 144 (36), 113 (21), 83 (44), 71 (69), 70 (29), 57 (56), 55 (49), 43 (42), 41 (49); EI-HRMS calcd for $C_{20}H_{27}NO_3$ (M^+) 329.1991, found 329.1982.

(+)-(2*S*,3*S*)-Virantmycin (1)

To a solution of aziridine **45** (11.5 mg, 34.9 μmol) in 3 mL of MeOH at room temperature was added 69.8 μL (69.8 μmol) of 1 N aqueous sodium hydroxide and the mixture was heated to reflux. After stirring at the same temperature for 39 h, an oil bath was removed and the mixture was cooled to room temperature. The reaction mixture was concentrated *in vacuo* and residual water was azeotropically evaporated with benzene under reduced pressure to furnish sodium carboxylate.

To a solution of the above sodium carboxylate (11.8 mg, 34.9 μmol) and 116 mg (0.698 mmol) of tetraethylammonium chloride in 3 mL of CH_2Cl_2 at -15 °C under Ar was added 10.8 μL (0.140 mmol) of trifluoroacetic acid and the solution was stirred at the same temperature for 15 min. The reaction was quenched with 0.3 mL of saturated aqueous $NaHCO_3$ and the reaction mixture was poured into 10 mL of water and the aqueous layer was acidified to pH 3-4 with 1 N aqueous HCl, followed by extracting with CH_2Cl_2 (10 mL × 3). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography (2% acetone/$CHCl_3$) on 2 g of silica gel to give the (+)-(2*S*,3*S*)-virantmycin (**1**) (10 mg, 81% overall yield from the aziridine **45**) which was coincided with natural (-)-virantmycin (**1**) except for the sign of the optical rotation: *Rf*=0.51 (50% EtOAc/hexane + trace of acetic acid on silica gel), 0.23 (30% EtOAc/hexane on silica gel); $[\alpha]_D^{24}$ +11.2° (*c* 0.125, $CHCl_3$); CD (*c* 6.83×10^{-5} M, EtOH at 23 °C) $\Delta\varepsilon_{284}$=+0.776, $\Delta\varepsilon_{315}$=-1.73; UV λ_{max} (EtOH) 225 (ε 10600, sh), 286 (ε 13000), 302 (ε 12700, sh); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (1H, dd, *J*=8.3, 1.8 Hz), 7.75 (1H, d, *J*=1.8 Hz), 6.53 (1H, d, *J*=8.3 Hz), 4.64 (1H, br s), 4.36 (1H, dd, *J*=6.1, 4.9 Hz), 3.57 (1H, d, *J*=9.3 Hz), 3.55 (1H, d, *J*=9.3 Hz), 3.39 (3H, s), 3.37 (1H, dd, *J*=17.1, 4.9 Hz), 3.11 (1H, dd, *J*=17.1, 6.1 Hz), 2.09 (1H, dt, *J*=4.7, 12.6 Hz), 2.01 (1H, dt, *J*=4.4, 12.2 Hz), 1.81 (1H, ddd, *J*=14.0, 12.0, 5.0 Hz), 1.63 (1H, ddd, *J*=14.0, 12.6, 4.4 Hz), 1.63 (3H, s), 1.61 (6H, s); IR (CCl_4) 3440, 3380-2400, 2940, 1679, 1612, 1472, 1429, 1411, 1331, 1289, 1251, 1193, 1112 cm^{-1}; EI-MS *m/z* (relative intensity) 351 (M^+, 5.2), 306 (58), 254 (31), 162 (45), 138 (52), 121 (43), 118 (30), 83 (100), 71 (30), 57 (43), 55 (68), 45 (52), 43 (35), 41 (48), 36 (37); EI-HRMS calcd for $C_{19}H_{26}NO_3Cl$ (M^+) 351.1602, found 351.1604.

(-)-(2*R*,3*R*)-Natural virantmycin (**1**): mp 59 °C; *Rf*=0.51 (50% EtOAc/hexane + trace of acetic acid on silica gel), 0.23 (30% EtOAc/hexane on silica gel); $[\alpha]_D^{24}$ -11.1° (*c* 0.175, $CHCl_3$); CD (*c* 7.73×10^{-5} M, EtOH at 23 °C) $\Delta\varepsilon_{285}$=-0.988, $\Delta\varepsilon_{316}$=+1.78; UV λ_{max} (EtOH) 223 (ε 9900, sh), 283 (ε 14900), 300 (ε 14000, sh); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (1H, dd, *J*=8.3, 2.0 Hz), 7.76 (1H, d, *J*=2.0 Hz), 6.53 (1H, d, *J*=8.3 Hz), 4.63 (1H, br s), 4.36 (1H, dd, *J*=5.9, 4.9 Hz), 3.58 (1H, d, *J*=9.2 Hz), 3.55 (1H, d, *J*=9.2 Hz), 3.39 (3H, s), 3.37 (1H, dd, *J*=17.1, 4.9 Hz), 3.11 (1H, dd, *J*=17.1, 5.9 Hz), 2.09 (1H, dt, *J*=4.9, 12.2 Hz), 2.01 (1H, dt, *J*=4.9, 12.2 Hz), 1.81 (1H, ddd, *J*=13.7, 12.2, 4.9 Hz), 1.63 (1H, ddd, *J*=13.7, 12.2, 4.9 Hz), 1.63 (3H, s), 1.61 (6H, s); IR (CCl_4) 3520-2400, 3440, 2920, 1677, 1610, 1474, 1430, 1410, 1333, 1290, 1252, 1195, 1115 cm^{-1}; EI-MS *m/z* (relative intensity) 351 (M^+, 4.0), 306 (45), 270 (30), 224 (21), 187 (26), 162 (30), 161 (21), 144 (23), 118 (21), 83 (100), 71 (45), 55 (61), 45 (27), 44 (31), 41 (53), 40 (32), 36 (35); EI-HRMS calcd for $C_{19}H_{26}NO_3Cl$ (M^+) 351.1601, found 351.1604.

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REFERENCES AND NOTES

1. This work was carried out at Hokkaido University.
2. (a) Ōmura, S.; Nakagawa, A.; Hashimoto, H.; Oiwa, R.; Iwai, Y.; Hirano, A.; Shibukawa, N.; Kojima, Y. *J. Antibiotics* **1980**, *33*, 1395-1396. (b) Nakagawa, A.; Iwai, Y.; Hashimoto, H.; Miyazaki, N.; Oiwa, R.; Takahashi, Y.; Hirano, A.; Shibukawa, N.; Kojima, Y.; Ōmura, S. *ibid.* **1981**, *34*, 1408-1415.
3. For biological activities and structures of benzastatins closely related to **1**, see: (a) Kim, W.-G.; Kim, J.-P.; Kim, C.-J.; Lee, K.-H.; Yoo, I.-D. *J. Antibiotics* **1996**, *49*, 20-25. (b) Kim, W.-G.; Kim, J.-P.; Yoo, I.-D. *ibid.* **1996**, *49*, 26-30.
4. Ōmura, S.; Nakagawa, A. *Tetrahedron Lett.* **1981**, *22*, 2199-2202.
5. Morimoto, Y.; Matsuda, F.; Shirahama, H. *Tetrahedron*, the preceding paper.
6. When we began the studies on asymmetric synthesis of virantmycin, its relative and absolute stereochemistry was unknown. For our preliminary communication, see: Morimoto, Y.; Oda, K.; Shirahama, H.; Matsumoto, T.; Ōmura, S. *Chem. Lett.* **1988**, 909-912.
7. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.
8. For a review on wide applications of the Sharpless epoxidation to organic syntheses, see: Pfenninger, A. *Synthesis* **1986**, 89-116.
9. Baldwin, J. E. *J. Chem. Soc. Chem. Commun.* **1976**, 734-736.
10. For activation of 6-*endo* over 5-*exo* hydroxy epoxide openings, see: (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330-5334. For activation of 7-*endo* over 6-*exo* epoxide openings, see: (b) Idem *ibid.* **1989**, *111*, 5335-5340.
11. Ruzicka, L.; Schinz, H. *Helv. Chim. Acta* **1940**, *23*, 959-974.
12. (a) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, 957-960. (b) Krapcho, A. P.; Jahngen, Jr., E. G. E.; Lovey, A. J. *ibid.* **1974**, 1091-1094.
13. Bestmann, H. J.; Schulz, H. *Liebigs Ann. Chem.* **1964**, *674*, 11-17.
14. Pappo, R.; Allen, D. S. Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478-479.
15. Concerning chemical shifts of the vinyl protons in trisubstituted α,β-unsaturated esters, (*E*)-isomers appear generally in much lower field than its (*Z*)-isomers. See ref. 5.
16. Bundy, G. L.; Peterson, D. C. *Tetrahedron Lett.* **1978**, 41-44.
17. Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254-5255.
18. In our preliminary communication[6] we mistook the product of this vanadium(V) catalyzed epoxidation of the allylic alcohol **31** for *threo* epoxide. Consequently, the stereochemistries of compounds in ref. 6 must be revised as shown in this paper.
19. Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63-74.
20. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399-402.
21. Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616-5617.
22. Sungchul Ji; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311-5312.
23. (a) Carlock, J. T.; Mack, M. P. *Tetrahedron Lett.* **1978**, 5153-5156. (b) Mitsunobu, O. *Synthesis* **1981**, 1-28.
24. Pearce, C. M.; Sanders, J. K. M. *J. Chem. Soc. Perkin Trans. 1* **1990**, 409-411.
25. More recently, the concurrent NOEs proving an equilibrium between the two half-chair conformers **44a** and **44b** have been observed by Yoo's group.[3b]
26. (a) Harada, N.; Nakanishi, K.; Tatsuoka, S. *J. Am. Chem. Soc.* **1969**, *91*, 5896-5898. (b) Marumo, S.; Harada, N.; Nakanishi, K.; Nishida, T. *Chem. Commun.* **1970**, 1693-1694. (c) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257-263. (d) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy*; University Science Books: Mill Valley, CA, 1983.

27. Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045-1048.
28. The optical rotation of natural (-)-**1** was reexamined and this value was obtained.
29. Ichimura, M.; Muroi, K.; Asano, K.; Kawamoto, I.; Tomita, F.; Morimoto, M.; Nakano, H. *J. Antibiotics* **1988**, *41*, 1285-1288.
30. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.
31. (a) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1967; Vol. 1, pp. 1276-1284. (b) Idem *ibid.* 1967; Vol. 1, pp. 637-643. (c) Idem *ibid.* 1967; Vol. 1, pp. 191-195.

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