Pergamon

Tetrahedron, Vol. 52, No. 32, pp. 10609-10630, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00609-6

Synthetic Studies on Virantmycin. 1. Total Synthesis of (±)-Virantmycin and Determination of Its Relative Stereochemistry[1]

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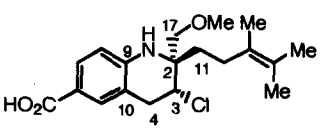
Abstract: The efficient and stereospecific route to the tetrahydroquinoline ring models **3** and **4** of virantmycin has been developed by means of an intramolecular nitrene addition reaction as a key step. In the NOE experiments of **4** and **3** we revealed that a ring inversion occurs in their piperidine ring system and determined the relative stereochemistry by capturing each half-chair conformer as cyclic carbamates **26** and **27**, respectively. Utilizing this protocol total syntheses of (±)-**1** and its diastereomer (±)-**2** have been accomplished and the relative stereochemistry of virantmycin has been established as shown in **1**.

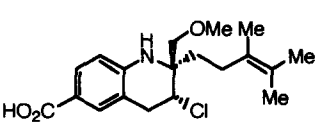
INTRODUCTION

The antibiotic virantmycin (**1**), the unique tetrahydroquinoline alkaloid isolated from the fermentation broth of *Streptomyces nitrosporeus* by Ōmura *et al.* in 1981, has been found to exhibit antifungal and prominent inhibitory activity against various RNA and DNA viruses.[2,3] Although its gross structure was elucidated mainly by NMR studies, the relative and absolute stereochemistry at the two chiral centers (C2 and C3) have remained unknown.[4] We embarked on total synthesis of virantmycin (**1**) with interest in the following subjects: (1) determination of the relative and absolute stereochemistry, (2) construction of the unusual chlorine-containing tetrahydroquinoline ring system rarely occurring in nature, and (3) structure-activity relationships between stereochemistry and biological activity.

While our synthetic study was under investigation, the first total synthesis of (±)-**1** was reported by Raphael and Hill in 1986.[5] However, the relative and absolute stereochemistry at C2 and C3 chiral centers remained to be determined. In 1988, we primarily suggested by mistake that the absolute configuration of virantmycin is 2*S*, 3*R* like **2** through its total synthesis,[6a] but on the other hand Sanders and Pearce reported in 1990 that the stereochemistry at C2 is *R*.[7] In each case, the relative stereochemical assignments were determined by the NOE experiments with **1** and its C3 hydroxyl derivative which were not thought to adopt rigid conformation in the piperidine ring. In order to solve this problem on the assignment of the relative configuration of **1**, we have developed an effective and stereospecific route to a diastereomeric pair of the tetrahydroquinoline ring systems **3** and **4** with definite relative stereochemistry.[6b] Further, according to this synthetic scheme, the stereospecific total syntheses of (±)-**1** and its diastereomer **2** were efficiently achieved without ambiguity in the relative stereochemistry at the two chiral centers (C2 and C3).[6c] Thus, the stereochemistry of **1** was finally established as 2*R*, 3*R*. In this and the accompanying article[8] we report the details of our synthetic and stereochemical studies on virantmycin (**1**).[9]



virantmycin (**1**)



2

3 R^1=CH_2OMe, R^2=Et
4 R^1=Et, R^2=CH_2OMe

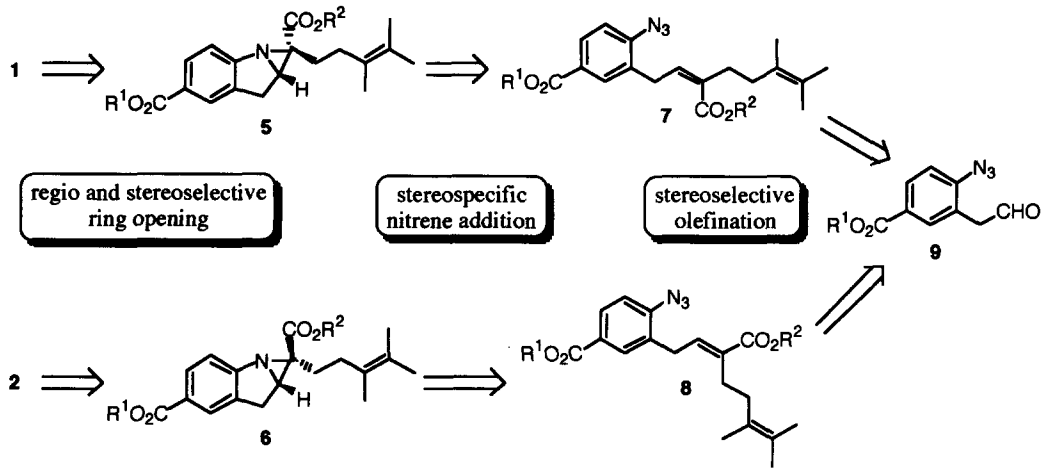
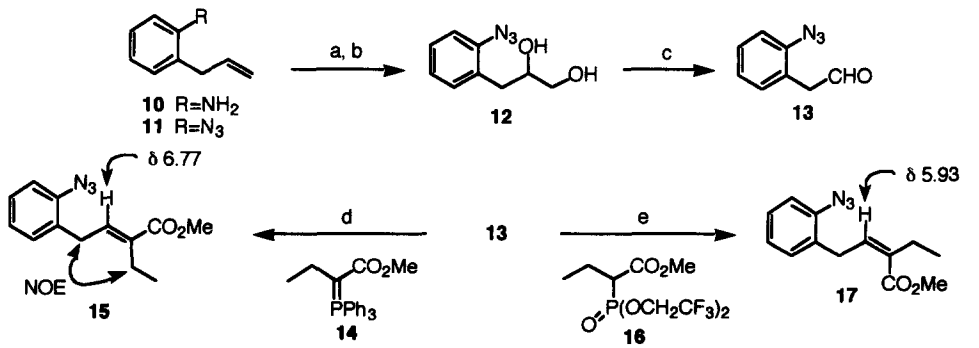


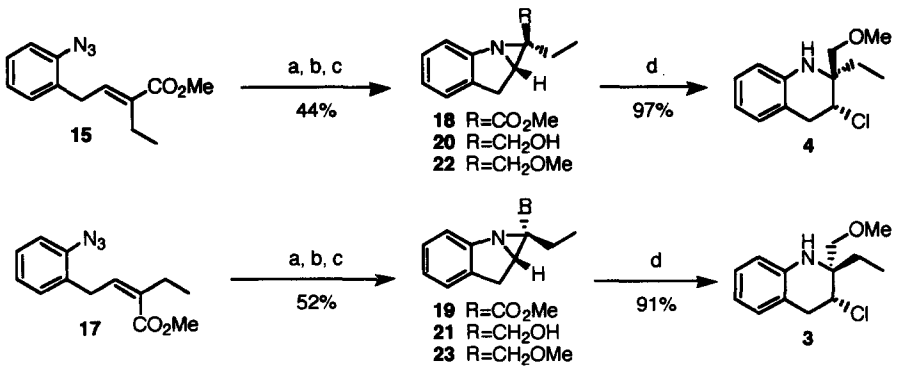
Fig. 1. Retrosynthetic analysis of virantmycin.

RESULTS AND DISCUSSION

Retrosynthetic analysis of two possible diastereomers **1** and **2** of virantmycin is depicted in Fig. 1. It was anticipated that the unusual tetrahydroquinoline ring system would be prepared by a regio and stereoselective ring opening reaction of aziridines **5** and **6** with chloride ion. The aziridines **5** and **6** will be constructed by an intramolecular stereospecific nitrene addition reaction of (*Z*)-olefin **7** and (*E*)-olefin **8**, respectively, via photolysis of azido group which will be provided from aldehyde **9** by stereoselective olefination. Although some stereospecific intermolecular nitrene addition reactions to olefins have been reported,[10] utilization of the nitrene addition reaction for organic syntheses has been limited because of low yields of the desired aziridines. In order to explore whether the key intramolecular nitrene addition reaction stereospecifically proceeds and reasonable yield of the desired aziridine is obtained, we firstly implemented model studies on a diastereomeric pair of the tetrahydroquinoline ring systems **3** and **4**, which brought an important information about conformation of the piperidine ring later.



Scheme 1. Reagents and conditions: (a) HCl, $NaNO_2$, H_2O, 0 °C, 15 min, then NaN_3, 0 °C, 30 min, 83%; (b) OsO_4, *N*-methylmorpholine *N*-oxide (NMO), acetone-H_2O (1:1), rt, 17 h, 89%;[12] (c) $NaIO_4$, THF-H_2O (1:1), rt, 4.5 h, 70%; (d) **14**, CH_2Cl_2, rt, 30 h, 80% (*E*:*Z*=32:1); (e) **16**, $KN(TMS)_2$, 5 equiv of 18-crown-6, THF, -78 °C→rt, 4 h, 50% (*E*:*Z*=1:8).



Scheme 2. Reagents and conditions: (a) *hν*, toluene, rt; (b) $LiAlH_4$, THF, 0 °C; (c) KH, THF, 0 °C, 30 min, then 5 equiv of MeI, -15 °C; (d) 15 equiv of Et_4NCl, TFA, CH_2Cl_2, -15 °C, 20 min.

The syntheses of azido olefins **15** and **17** required for nitrene addition reaction were carried out by stereoselective olefination of the aldehyde **13** easily prepared from known 2-(2-propenyl)aniline (**10**)[11] (Scheme 1). The Wittig reaction of the aldehyde **13** with methyl 2-(triphenylphosphoranylidene)butyrate (**14**),[13] a stable ylide, yielded (*E*)-olefin **15** with the stereoselectivity of 32 : 1. On the other hand, the Horner-Emmons reaction of **13** with methyl 2-[bis(2,2,2-trifluoroethyl)phosphono]butyrate (**16**)[14] under Still's condition[15] provided (*Z*)-olefin **17** with the stereoselectivity of 8 : 1. The stereochemistry of the olefins **15** and **17** was proven by the chemical shifts of their vinyl protons (**15**, δ 6.77; **17**, δ 5.93) and the presence of NOE shown in **15**.

The key nitrene addition reaction expectedly proceeded with complete stereospecificity through nitrene intermediates which were generated by photolysis[16] of the azido olefins **15** and **17** in toluene at room temperature to afford the desired aziridines **18** and **19** in good yields, respectively (Scheme 2). The stereochemistry of the aziridines **18** and **19** was supported from the high field shifts of the protons in the functional groups (CO_2CH_3 or CH_2CH_3) *cis* to an aromatic ring in their ^1H NMR spectra [**18**, δ 3.80 (3H, s, CO_2CH_3), δ 1.50 (1H, dq, *J*=14.7, 7.3 Hz, CH_2CH_3), δ 1.20 (1H, dq, *J*=14.7, 7.3 Hz, CH_2CH_3), δ 0.84 (3H, t, *J*=7.3 Hz, CH_2CH_3); **19**, δ 3.25 (3H, s, CO_2CH_3), δ 2.09 (1H, dq, *J*=14.7, 7.3 Hz, CH_2CH_3), δ 1.66 (1H, dq, *J*=14.7, 7.3 Hz, CH_2CH_3), δ 1.04 (3H, t, *J*=7.3 Hz, CH_2CH_3)], due to its shielding effect (Fig. 2). Reduction of methyl ester in aziridine **18** with lithium aluminum hydride gave alcohol **20** which was subjected to methylation to provide methyl ether **22**. Finally, a ring opening of the aziridine **22** by treatment with an excess of tetraethylammonium chloride and trifluoroacetic acid regio and stereoselectively proceeded in very high yield with inversion[17] to afford the desired model compound **4** which contained the same tetrahydroquinoline ring system as virantmycin. The another diastereomer **3** was also prepared through the same sequence of reactions from the aziridine **19** in comparable yield.

In order to prove the relative stereochemistry of **4** and **3** deduced from the stereospecific reaction sequences, their NOE experiments were performed. Then, in the one (**4**) the NOEs between H_S4 and H_217 and between H_L4 and H_211 were concurrently observed, and in the other (**3**) the NOEs between H_S4 and H_211 and between H_L4 and H_217 (Fig. 3). As a result, it has been found that the conformation of this piperidine ring is

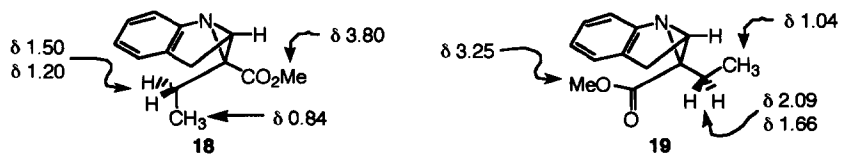


Fig. 2. Stereo-structure of aziridines **18** and **19**.

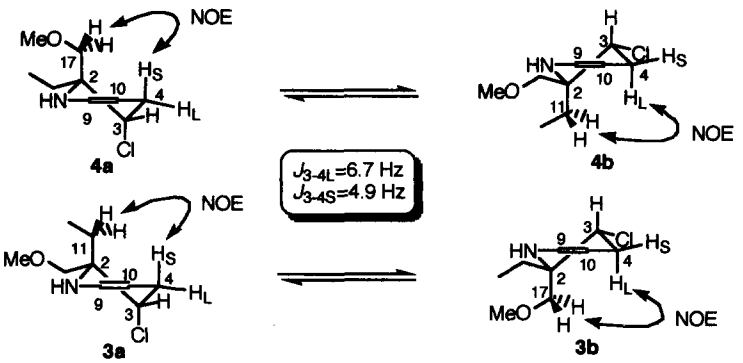
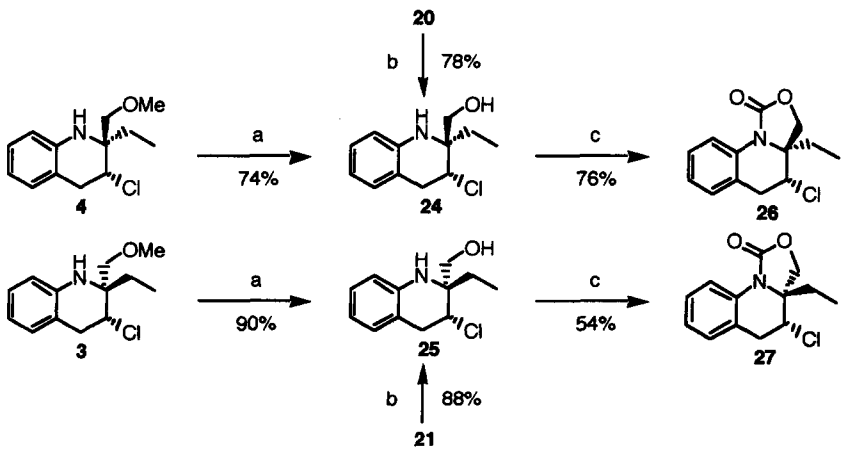


Fig. 3. Conformational aspect of half-chair conformers **a** and **b** in **4** and **3**.

very flexible to exist as a mixture equilibrated between two conformers **a** and **b** at room temperature and the coupling constants between H3 and $H_2$4 (**4**, $J_{3\text{-}4L}$=6.7 Hz, $J_{3\text{-}4S}$=4.9 Hz; **3**, $J_{3\text{-}4L}$=6.7 Hz, $J_{3\text{-}4S}$=4.9 Hz) have been observed as average values of those of the conformers. Therefore, the assignment of each proton of $H_2$4 to equatorial or axial orientation remained unclear.

There, for the purpose of fixing the conformation of the piperidine ring, cyclic carbamates **26** and **27** were derived from **4** and **3**, respectively, through demethylation using Lewis acid-thiol system[18] followed by carbamation of the amino alcohols **24** and **25** which could be also prepared from aziridines **20** and **21**, respectively (Scheme 3). As shown in Fig. 4, coupling constants between H3 and $H_2$4 of the piperidine rings in **26** ($J_{3\text{-}4ax}$=11.6 Hz, $J_{3\text{-}4eq}$=6.7 Hz) and **27** ($J_{3\text{-}4ax}$=4.6 Hz, $J_{3\text{-}4eq}$=1.8 Hz) made it clear that these ring systems of the carbamates adopted only one rigid conformation. Furthermore, the relative stereochemistry of compounds **4** and **3** was unambiguously confirmed from NOE experiments with **26** and **27**, respectively.

We have developed an efficient and stereospecific route to the tetrahydroquinoline ring system of virantmycin utilizing intramolecular nitrene addition reaction as a key step, revealed that very fast ring inversion exists in these piperidine ring systems at room temperature, and established the method of an unequivocal assignment for the relative stereochemistry. The application of this strategy to the total synthesis of natural product and determination of its relative stereochemistry is described in the following paragraphs.



Scheme 3. Reagents and conditions: (a) $AlCl_3$, *n*-PrSH, CH_2Cl_2, rt; (b) 15~20 equiv of Et_4NCl, TFA, CH_2Cl_2, -15 °C, 20 min; (c) 10 equiv of Im_2CO, toluene, 60~100 °C.

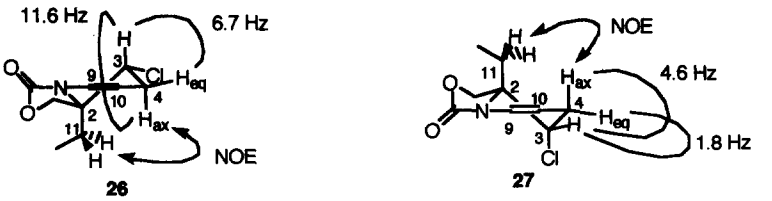
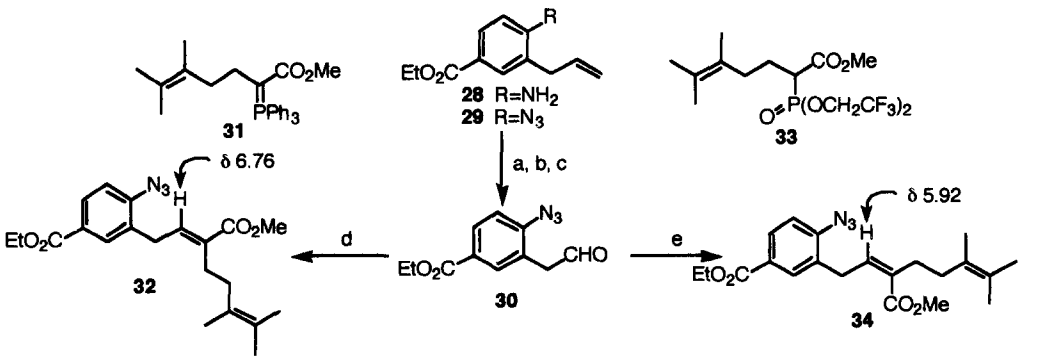


Fig. 4. NOEs and *J* values observed in cyclic carbamates **26** and **27**.

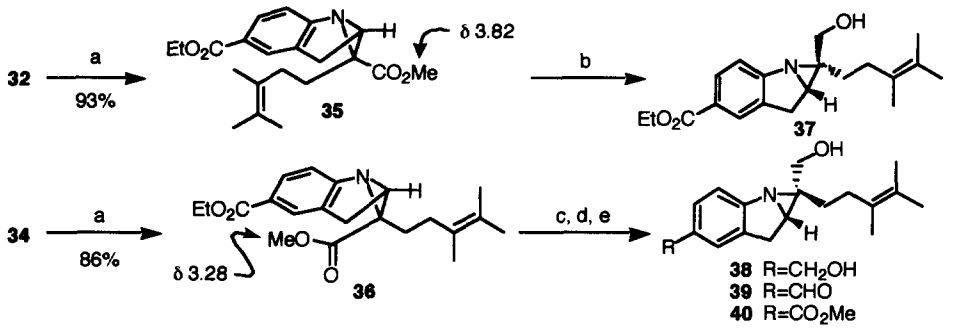
Like the model study, the syntheses of azido olefins **32** and **34** required for the stereospecific nitrene addition reaction were carried out by stereoselective olefination of the aldehyde **30** easily prepared from known ethyl 4-amino-3-(2-propenyl)benzoate (**28**)[19] (Scheme 4). The Wittig reaction of **30** with phosphorane **31**[18] yielded (*E*)-olefin **32** with the stereoselectivity of >50 : 1. On the other hand, the Horner-Emmons reaction of **30** with phosphonate **33** under Still's condition,[15] which was prepared from commercially available methyl bis(2,2,2-trifluoroethyl)phosphonoacetate by alkylation[14] with 1-bromo-3,4-dimethyl-3-pentene,[20] provided (*Z*)-olefin **34** with the stereoselectivity of >50 : 1. The stereochemistry of the olefins **32** and **34** was proven by the chemical shifts of their vinyl protons (**32**, δ 6.76; **34**, δ 5.92) (*cf.* **15** and **17** in Scheme 1).

The intramolecular nitrene addition reaction by photolysis[16] of **32** and **34** proceeded with complete stereospecificity to afford aziridines **35** and **36**, respectively, in high yields (Scheme 5). The stereochemistry of **35** and **36** was supported from the high field shift of methyl ester *cis* to an aromatic ring in their ^{1}H NMR spectra (**35**, δ 3.82; **36**, δ 3.28) due to its shielding effect (*cf.* Fig. 2). In aziridine **35** only methyl ester was chemoselectively reduced by treatment with 4 equivalent of lithium tri-*tert*-butoxyaluminum hydride in tetrahydrofuran at room temperature for 14 hours to give alcohol **37** in 93% yield, but in aziridine **36** the same reduction didn't proceed probably because of steric hindrance. Therefore, both methyl and ethyl esters were reduced with lithium aluminum hydride and then only benzylic alcohol was oxidized to methyl ester with manganese dioxide by Corey's method[21] to provide alcohol **40** in good overall yield.

After methylation of the alcohol **37** and saponification of ethyl ester **41**, the highly regio and stereoselective ring opening of aziridine with inversion[17] gave only (±)-**2**, different from natural product in its chromatographic and spectroscopic properties (Scheme 6). Following the same sequence of reactions, the synthesis of (±)-**1** [mp 138-143 °C (lit.[5] mp 133-139 °C)], identical with natural product in all chromatographic and spectroscopic (NMR, IR, MS, HRMS) properties, was accomplished from alcohol **40**.

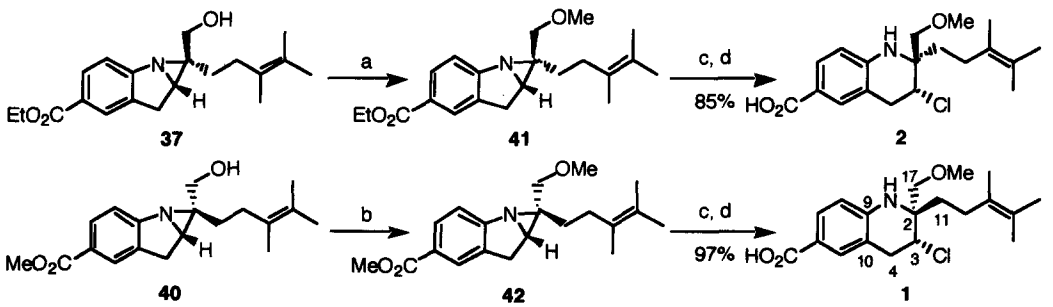


Scheme 4. Reagents and conditions: (a) HCl, $NaNO_2$, H_2O, 0 °C, 15 min, then NaN_3, 0 °C, 1 h 45 min, 81%; (b) OsO_4, NMO, acetone-H_2O (1:1), rt, 17 h;[12] (c) $NaIO_4$, THF-H_2O (1:1), rt, 1 h, 69% (2 steps); (d) **31**, CH_2Cl_2, rt, 38 h, 74%; (e) **33**, $KN(TMS)_2$, 5 equiv of 18-crown-6, THF, -78→-40 °C, 2 h 30 min, 63%.



Scheme 5. Reagnts and conditions: (a) *hν*, toluene, rt, 3 h; (b) 4 equiv of $LiAlH(Ot\text{-}Bu)_3$, THF, rt, 14 h, 93%; (c) $LiAlH_4$, THF, 0 °C, 3 h, 100%; (d) MnO_2, acetone, rt, 46 h; (e) KCN, MnO_2, MeOH, rt, 3.5 h, 82% (2 steps).

Chemical shifts of H3 and $H_2$4 and coupling constants between these protons in **2** and **1** [**2**, δ 4.42 (H3, dd, *J*=6.6, 4.9 Hz), 3.28 (H_S4, dd, *J*=17.1, 4.9 Hz), 3.13 (H_L4, dd, *J*=17.1, 6.6 Hz); **1**, δ 4.36 (H3, dd, *J*=6.1, 4.7 Hz), 3.37 (H_S4, dd, *J*=17.1, 4.7 Hz), 3.11 (H_L4, dd, *J*=17.1, 6.1 Hz)] were well consistent with those in **4** and **3** [**4**, δ 4.45 (H3, dd, *J*=6.7, 4.9 Hz), 3.25 (H_S4, dd, *J*=17.1, 4.9 Hz), 3.08 (H_L4, dd, *J*=17.1, 6.7 Hz); **3**, δ 4.35 (H3, dd, *J*=6.7, 4.9 Hz), 3.31 (H_S4, dd, *J*=17.1, 4.9 Hz), 3.06 (H_L4, dd, *J*=17.1, 6.7 Hz)], respectively.[22] This observation supported the stereo-structures of **2** and **1** expected from the stereospecific reaction sequences and revealed that this pair of the diastereomers also possessed the conformationally flexible piperidine ring systems (Fig. 5). However, though the NOEs proving an equilibrium between two conformers **a** and **b** were observed in model compounds **4** and **3** (Fig. 3), concerning **2** and **1** the only NOE attributed to the conformer **1b** could be detected. In order to capture the two conformers **a** and **b**, measurement of ^{1}H NMR spectra of **1** were performed at low temperatures (0 °C, -20 °C, and -40 °C), but chemical shifts and coupling constants in these spectra were practically the same as those at room temperature. From these facts, the energy barrier for ring inversion between the half-chair conformers **1a** and **1b** may be estimated to be rather low.[23]



Scheme 6. Reagents and conditions: (a) NaH, *n*-Bu_4NI, THF, 0 °C, 30 min, then MeI, HMPA, -15 °C, 2 h, 71%; (b) KH, THF, 0 °C, 30 min, then MeI, -15 °C, 1 h, 53%; (c) NaOH, MeOH, reflux, 3 d; (d) 20 equiv of Et_4NCl, TFA, CH_2Cl_2, -15 °C, 20 min.

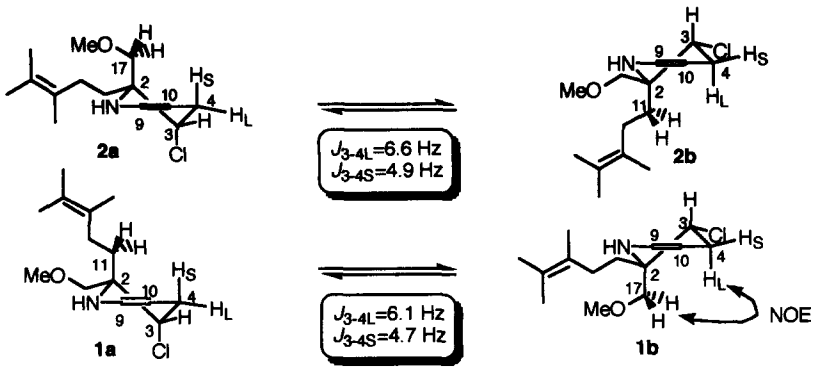
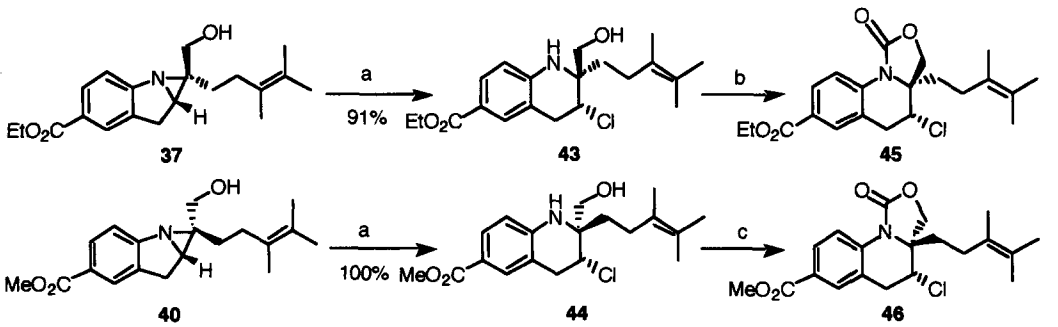


Fig. 5. Ring inversion between half-chair conformers **a** and **b** in **2** and **1**.

For the purpose of further confirmation of the deduced stereochemistry of **2** and **1**, cyclic carbamates **45** and **46** were derived from **37** and **40**, respectively, like the model study (Scheme 7). As shown in Fig. 6, coupling constants between H3 and H_24 of the piperidine rings in **45** ($J_{3\text{-}4ax}$=11.6 Hz, $J_{3\text{-}4eq}$=6.7 Hz) and **46** ($J_{3\text{-}4ax}$=4.9 Hz, $J_{3\text{-}4eq}$=1.8 Hz)[22] made it clear that these ring systems of the carbamates adopted only one rigid conformation. Furthermore, the relative stereochemistry of compounds **2** and **1** was unambiguously confirmed from NOE experiments with **45** and **46**, respectively (Fig. 6). Thus, it has been found that the relative stereochemistry at the two chiral centers of virantmycin (**1**) has *cis* relationship between methoxymethyl and chloro groups.



Scheme 7. Reagents and conditions: (a) 15 equiv of Et_4NCl, TFA, CH_2Cl_2, -15 °C, 20 min; (b) 10 equiv of Im_2CO, toluene, 90 °C, 9 h, 54%; (c) 10 equiv of Im_2CO, toluene, reflux, 20 h, 46%.

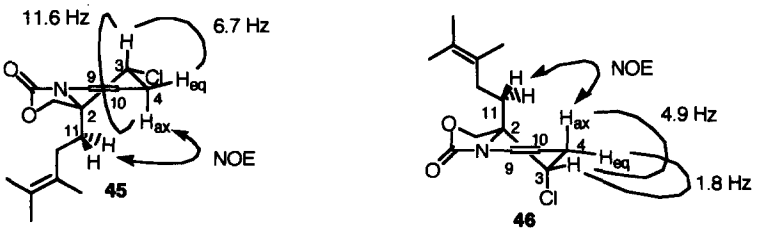


Fig. 6. NOEs and *J* values observed in cyclic carbamates **45** and **46**.

In summary we have developed an efficient and stereospecific route to the tetrahydroquinoline ring system of virantmycin by means of an intramolecular nitrene addition reaction as a key step. In the NOE experiments of model compounds we revealed that fast ring inversion occurs in their piperidine ring systems and explicitly determined the relative stereochemistry by capturing each half-chair conformer as a cyclic carbamate. Utilizing the protocol we have accomplished total syntheses of (±)-**1** and its diastereomer (±)-**2** and established the relative stereochemistry of virantmycin as shown in **1**. Another enantioselective total synthesis of (+)-virantmycin and determination of its absolute stereochemistry are reported in the accompanying paper.

EXPERIMENTAL SECTION

General Procedures

Melting points are uncorrected. ^{1}H NMR spectra were recorded in deuteriochloroform on Hitachi R-90H (90 MHz), R-250H (250 MHz), JEOL model JNM-GX 270 (270 MHz), and Bruker AM-400 (400 MHz) spectrometers. ^{13}C NMR spectra were measured in deuteriochloroform on JEOL model JNM-GX 270 (68 MHz) spectrometer. 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. Low and high resolution mass spectra (EI) were determined on JEOL model JMS-DX 303 and JMS-HX 110 spectrometers. Photo-irradiation was carried out on 300 W medium pressure mercury arc (Eikosha Ltd.).

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 Merck kieselgel 60 Art 7734 and Amicon Matrex® silica Si chromatography medium. Medium pressured column chromatography was performed employing Lobar® Größe B (310-25) LiChroprep® Si 60 (40-63 μm) (Merck) equipped with a FMI LAB POMP MODEL RP SY. All reactions were performed in oven-dried glassware.

Tetrahydrofuran (THF) was distilled from sodium metal / benzophenone ketyl. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium methoxide. Acetone was distilled from potassium permanganate. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride at reduced pressure. 2-(2-Propenyl)aniline (**10**),[11] methyl 2-(triphenylphosphoranylidene)butyrate (**14**),[13] ethyl 4-amino-3-(2-propenyl)benzoate (**28**),[19] 1-bromo-3,4-dimethyl-3-pentene,[20] and active manganese dioxide[24] were prepared according to literature methods. 1 M and 0.5 M solutions of potassium hexamethyldisilazide in tetrahydrofuran were prepared from potassium hydride (35% dispersion in mineral oil), 1,1,1,3,3,3-hexamethyldisilazane (freshly distilled from calcium hydride), and absolute dry tetrahydrofuran.

1-Azido-2-(2-propenyl)benzene (11)

To a solution of 2-(2-propenyl)aniline (**10**)[11] (3.66 g, 27.5 mmol) in 110 mL of water at 0 °C were added successively 11.0 mL of concentrated hydrochloric acid (12 N) and 2.28 g (33.0 mmol) of sodium nitrite in 13.8 mL of water and the mixture was stirred for 15 min. Sodium azide (90% purity, 2.98 g, 41.3 mmol) in 13.8 mL of water was added to the solution at 0 °C and the mixture was further stirred at the same temperature for additional 30 min. The reaction mixture was transfered to a separatory funnel 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*. The residual oil was purified by column chromatography (100% hexane) on 100 g of silica gel to give azide **11** as a pale yellow oil (3.64 g, 83% yield): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.34-6.87 (4H, m), 5.91 (1H, ddt, *J*=18, 10, 6 Hz), 5.01 (1H, dd, *J*=10, 2 Hz), 4.98 (1H, dd, *J*=18, 2 Hz), 3.31 (2H, d, *J*=6 Hz); IR (neat) 3070, 2920, 2150, 1641, 1586, 1492, 1454, 1434, 1294, 1149, 995, 915, 753 cm^{-1}; EI-MS *m/z* (relative intensity) 159 (M^+, 4.8), 149 (70), 97 (36), 85 (39), 83 (41), 81 (32), 71 (60), 69 (63), 57 (100), 55 (57), 43 (69), 41 (51).

3-(2-Azidophenyl)-1,2-propanediol (12)

To a solution of azide **11** (748 mg, 4.70 mmol) and *N*-methylmorpholine *N*-oxide (826 mg, 7.05 mmol) in each 7 mL of acetone and water at room temperature was added osmium tetroxide (23.9 mg, 94.0 μmol). The reaction was slightly exothermic initially and was maintained at room temperature with a water bath. The reaction was complete after stirring for 17 h at room temperature under Ar. The reaction mixture was poured into 50 mL of water and extracted with CH_2Cl_2 (30 mL × 3). The combined organic 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 (4% acetone/$CHCl_3$) on 25 g of silica gel to afford diol **12** (810 mg, 89% yield): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.42-6.87 (4H, m), 3.93 (1H, dq, *J*=4, 7 Hz), 3.64 (1H, dd, *J*=11, 4 Hz), 3.44 (1H, dd, *J*=11, 7 Hz), 2.83 (1H, dd, *J*=14, 6 Hz), 2.67 (1H, dd, *J*=14, 6 Hz), 2.13 (2H, s); IR (neat) 3370, 2930, 2870, 2165, 1583, 1492, 1453, 1286, 1100, 1071, 1035, 900, 866, 756 cm^{-1}; EI-MS *m/z* (relative intensity) 193 (M^+, 21), 134 (81), 106 (91), 105 (50), 104 (100), 91 (33), 79 (41), 78 (96), 77 (64), 61 (39), 51 (42), 43 (53), 39 (36); EI-HRMS calcd for $C_9H_{11}O_2N_3$ (M^+) 193.0851, found 193.0875.

2-Azidophenylacetaldehyde (13)

To a solution of diol **12** (809 mg, 4.19 mmol) in each 8.09 mL of THF and water at room temperature was added a portion of sodium metaperiodate (1.08 g, 5.03 mmol) and the mixture was stirred vigorously at the same temperature for 4.5 h. The reaction mixture was filtered *in suction*, poured into 30 mL of water, and extracted with ether (30 mL × 3). The extracted organic layers were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Purification of the residue by column chromatography (2% EtOAc/hexane) on 25 g of silica gel provided unstable aldehyde **13** (475 mg, 70% yield): ^{1}H NMR (90 MHz, $CDCl_3$) δ 9.64 (1H, t, *J*=2 Hz), 7.52-6.80 (4H, m), 3.63 (2H, d, *J*=2 Hz); IR (neat) 2845, 2740, 2150, 1730, 1588, 1494, 1459, 1411, 1392, 1291, 1155, 1097, 1048, 1038, 934, 756 cm^{-1}; EI-MS *m/z* (relative intensity) 161 (M^+, 59), 106 (25), 105 (68), 104 (100), 79 (21), 78 (81), 77 (68), 52 (31), 51 (50), 50 (21), 39 (33); EI-HRMS calcd for $C_8H_7ON_3$ (M^+) 161.0589, found 161.0563.

Methyl (2*E*)-4-(2-azidophenyl)-2-ethyl-2-butenoate (15)

To a solution of methyl 2-(triphenylphosphoranylidene)butyrate (**14**)[13] (1.02 g, 2.81 mmol) in 3 mL of CH_2Cl_2 at 0 °C under Ar was added 348 mg (2.16 mmol) of aldehyde **13** in 4 mL of CH_2Cl_2 and the solution was allowed to warm to room temperature. After stirring at room temperature for 30 h, organic solvent was evaporated *in vacuo* and the reaction mixture was chromatographed on 10 g of silica gel eluting with 100% benzene to furnish crude products. Purification of the crude products by column chromatography on 20 g of silica gel yielded mixture of (2*Z*)- and (2*E*)-α,β-unsaturated esters (68 mg, 13% yield) eluting with 1.5% ether/hexane and pure (2*E*)-α,β-unsaturated ester **15** (356 mg, 67% yield) eluting with 2% ether/hexane. The former mixture (68 mg) was further subjected to medium pressured column chromatography (15% ether/hexane) to give pure (2*Z*)-α,β-unsaturated ester **17** (12.8 mg, 2.4% yield) and (2*E*)-α,β-unsaturated ester **15** (55.2 mg, 10% yield). (2*Z*)-α,β-unsaturated ester **17** will be characterized later. (2*E*)-α,β-unsaturated ester **15**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.28 (1H, m), 7.16-7.05 (3H, m), 6.77 (1H, t, *J*=7.3 Hz), 3.73 (3H, s), 3.47 (2H, d, *J*=7.3 Hz), 2.45 (2H, q, *J*=7.3 Hz), 1.07 (3H, t, *J*=7.3 Hz); IR (neat) 2980, 2180, 1715, 1645, 1588, 1493, 1455, 1439, 1295, 1242, 1196, 1129, 1097, 1068, 1033, 997, 913, 808, 755 cm^{-1}; EI-MS *m/z* (relative intensity) 245 (M^+, 0.14), 217 (M^+–N_2, 3.8), 158 (100), 157 (21), 156 (31), 143 (55), 142 (60), 130 (39), 128 (24), 117 (38), 115 (21), 91 (24), 77 (26), 51 (22), 39 (26); EI-HRMS calcd for $C_{13}H_{15}NO_2$ (M^+–N_2) 217.1103, found 217.1093.

Methyl 2-[bis(2,2,2-trifluoroethyl)phosphono]butyrate (16)

To a suspension of sodium hydride (37.7 mg, 1.57 mmol, washed with hexane) in 3 mL of DMSO at room temperature under Ar was added dropwise 500 mg (1.57 mmol) of commercially available methyl bis(2,2,2-trifluoroethyl)phosphonoacetate in 3 mL of DMSO and the mixture was stirred for 10 min. Ethyl iodide (0.377 mL, 4.71 mmol) was added to the solution and the mixture was further stirred at room

temperature for 48 h. The reaction was quenched with 1 mL of saturated aqueous NH_4Cl and the resulting mixtures were poured into 50 mL of water, followed by extracting with ether (30 mL × 3). The ethereal layer was washed sequentially with each 50 mL of 10% aqueous $Na_2S_2O_3$ and brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (6% EtOAc/benzene) on 25 g of silica gel to afford Horner-Emmons' reagent **16** as a clear oil (461 mg, 85% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.60-4.25 (4H, m), 3.79 (3H, s), 3.05 (1H, ddd, *J*=21.7, 8.9, 5.5 Hz), 2.14-1.84 (2H, m), 1.03 (3H, t, *J*=7.3 Hz); IR (neat) 2985, 1744, 1460, 1441, 1422, 1295, 1259, 1172, 1100, 1069, 960, 896, 872, 845, 800, 737 cm^{-1}; EI-MS *m/z* (relative intensity) 347 (M^++H, 33), 346 (M^+, 7.4), 318 (46), 315 (40), 287 (70), 257 (22), 219 (21), 101 (73), 69 (55), 59 (32), 55 (33), 41 (100), 39 (28); EI-HRMS calcd for $C_9H_{14}O_5F_6P$ (M^++H) 347.0482, found 347.0464 and $C_9H_{13}O_5F_6P$ (M^+) 346.0404, found 346.0430.

Methyl (2*Z*)-4-(2-azidophenyl)-2-ethyl-2-butenoate (17)

To a solution of 18-crown-6 (6.50 g, 24.6 mmol) and methyl 2-[bis(2,2,2-trifluoroethyl)phosphono]butyrate (**16**) (1.70 g, 4.91 mmol) in 15 mL of THF at -78 °C under Ar were added successively potassium hexamethyldisilazide (1 M in THF, 4.91 mL, 4.91 mmol) and 791 mg (4.91 mmol) of aldehyde **13** in 3 mL of THF, and then the mixture was stirred at -78 °C to room temperature over 4 h. The reaction was quenched with 3 mL of saturated aqueous NH_4Cl and the resulting mixtures were poured into 80 mL of water, followed by extracting 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 chromatographed on 25 g of silica gel eluting with 100% benzene to furnish crude products. Purification of the crude products by column chromatography on 50 g of silica gel yielded pure (2*Z*)-α,β-unsaturated ester **17** (450 mg, 38% yield) eluting with 1.5% ether/hexane, mixture of (2*Z*)-**17** and (2*E*)-**15** (123 mg, 10% yield) eluting with 1.5% ether/hexane, and pure (2*E*)-α,β-unsaturated ester **15** (27 mg, 2.3% yield) eluting with 2% ether/hexane. The mixture (123 mg) was further subjected to medium pressured column chromatography (15% ether/hexane) to provide pure (2*Z*)-α,β-unsaturated ester **17** (83 mg, 6.9% yield) and (2*E*)-α,β-unsaturated ester **15** (40 mg, 3.3% yield). (2*Z*)-α,β-unsaturated ester **17**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35-6.95 (4H, m), 5.93 (1H, tt, *J*=7.3, 1.2 Hz), 3.79 (3H, s), 3.72 (2H, d, *J*=7.3 Hz), 2.30 (2H, dq, *J*=1.2, 7.3 Hz), 1.03 (3H, t, *J*=7.3 Hz); IR (neat) 2970, 2170, 1718, 1491, 1453, 1438, 1376, 1290, 1235, 1200, 1130, 1089, 756 cm^{-1}; EI-MS *m/z* (relative intensity) 245 (M^+, 6.3), 158 (100), 156 (39), 143 (69), 142 (76), 130 (46), 128 (35), 117 (39), 115 (32), 77 (32), 57 (32), 41 (30); EI-HRMS calcd for $C_{13}H_{15}N_3O_2$ (M^+) 245.1165, found 245.1154. (2*E*)-α,β-unsaturated ester **15** has been already characterized (*vide supra*).

(2*S)-1,2-[(*S**)-1-Ethyl-1-(methoxycarbonyl)methylene]indoline (18)**

A solution of azido olefin **15** (336 mg, 1.37 mmol) in 7 mL of toluene at room temperature under Ar was stirred for 33 h under photo-irradiation by medium pressure mercury arc through Pyrex filter and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (4% EtOAc/benzene) on 15 g of silica gel to give aziridine **18** (254 mg, 86% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34 (1H, m), 7.22-7.01 (3H, m), 3.80 (3H, s), 3.48-3.25 (2H, m), 3.17 (1H, m), 1.50 (1H, dq, *J*=14.7, 7.3 Hz), 1.20 (1H, dq, *J*=14.7, 7.3 Hz), 0.84 (3H, t, *J*=7.3 Hz); IR (neat) 2970, 1731, 1609, 1591, 1477, 1461, 1439, 1382, 1325, 1310, 1275, 1240, 1215, 1190, 1156, 1141, 1067, 1053, 1019, 1001, 954, 909, 894, 883, 841, 805, 775, 728 cm^{-1}; EI-MS *m/z* (relative intensity) 217 (M^+, 19), 202 (26), 188 (11), 186 (13), 159 (16), 158 (100), 156 (17), 143 (37), 142 (49), 130 (24), 128 (17), 117 (15), 115 (11), 91 (11), 89 (12), 77 (18), 39 (10); EI-HRMS calcd for $C_{13}H_{15}NO_2$ (M^+) 217.1103, found 217.1112.

(2*S)-1,2-[(*R**)-1-Ethyl-1-(methoxycarbonyl)methylene]indoline (19)**

A solution of azido olefin **17** (71 mg, 0.289 mmol) in 5 mL of toluene at room temperature under Ar was stirred for 20 h under photo-irradiation by medium pressure mercury arc through Pyrex filter and concentrated *in vacuo*. Purification of the residue by column chromatography (8% EtOAc/hexane) on 5 g of silica gel afforded aziridine **19** (47 mg, 75% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.26 (1H, dd, *J*=7.3, 1.2 Hz), 7.12 (1H, dt,

J=1.2, 7.3 Hz), 7.11 (1H, dd, *J*=7.3, 1.2 Hz), 7.01 (1H, dt, *J*=1.2, 7.3 Hz), 3.56 (1H, dd, *J*=17.1, 1.2 Hz), 3.29 (1H, dd, *J*=17.1, 7.3 Hz), 3.25 (3H, s), 3.00 (1H, dd, *J*=7.3, 1.2 Hz), 2.09 (1H, dq, *J*=14.7, 7.3 Hz), 1.66 (1H, dq, *J*=14.7, 7.3 Hz), 1.04 (3H, t, *J*=7.3 Hz); IR (neat) 2990, 2950, 1740, 1610, 1479, 1463, 1440, 1341, 1235, 1216, 1195, 1167, 1141, 1099, 988, 978, 814, 776, 725 cm^{-1}; EI-MS *m/z* (relative intensity) 217 (M^+, 18), 202 (24), 158 (100), 143 (37), 142 (46), 130 (23), 85 (29), 77 (20), 73 (21), 69 (21), 57 (33), 55 (23), 43 (29), 41 (28); EI-HRMS calcd for $C_{13}H_{15}O_2N$ (M^+) 217.1102, found 217.1104.

(2*S)-1,2-[(*S**)-1-Ethyl-1-(hydroxymethyl)methylene]indoline (20)**

To a solution of lithium aluminum hydride (18.3 mg, 0.483 mmol) in 1 mL of THF at 0 °C under Ar was added dropwise 105 mg (0.483 mmol) of ester **18** dissolved in 2.5 mL of THF and the solution was stirred at the same temperature for 50 min. The reaction was carefully quenched with 18.3 μL of water, followed by 18.3 μL of 15% aqueous NaOH, and then 54.9 μL 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*. The residue was subjected to column chromatography (4% acetone/$CHCl_3$) on 5 g of silica gel to furnish alcohol **20** (56.5 mg, 62% yield): ^1H NMR (250 MHz, $CDCl_3$) δ 7.21-6.92 (4H, m), 3.82 (1H, d, *J*=11.0 Hz), 3.62 (1H, d, *J*=11.0 Hz), 3.30 (1H, dd, *J*=17.1, 7.9 Hz), 3.08 (1H, dd, *J*=17.1, 1.8 Hz), 3.06 (1H, dd, *J*=7.9, 1.8 Hz), 2.86 (1H, br s), 1.21 (1H, dq, *J*=14.7, 7.3 Hz), 1.03 (1H, dq, *J*=14.7, 7.3 Hz), 0.86 (3H, t, *J*=7.3 Hz); IR (neat) 3180, 2980, 2935, 2880, 1608, 1594, 1481, 1463, 1437, 1382, 1240, 1220, 1156, 1099, 1078, 1047, 1018, 1001, 937, 896, 843, 824, 794, 756, 721 cm^{-1}; EI-MS *m/z* (relative intensity) 189 (M^+, 52), 188 (15), 172 (45), 159 (19), 158 (100), 156 (25), 144 (18), 143 (38), 130 (38), 118 (99), 117 (56), 91 (25), 90 (20), 89 (17), 77 (23); EI-HRMS calcd for $C_{12}H_{15}ON$ (M^+) 189.1154, found 189.1155.

(2*S)-1,2-[(*R**)-1-Ethyl-1-(hydroxymethyl)methylene]indoline (21)**

To a solution of lithium aluminum hydride (20.7 mg, 0.545 mmol) in 1 mL of THF at 0 °C under Ar was added dropwise 158 mg (0.727 mmol) of ester **19** dissolved in 3 mL of THF and the solution was stirred at the same temperature for 2 h. The reaction was carefully quenched with 20.7 μL of water, followed by 20.7 μL of 15% aqueous NaOH, and then 62.1 μL 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*. The residue was purified by column chromatography (4% acetone/$CHCl_3$) on 8 g of silica gel to yield alcohol **21** (117 mg, 85% yield): ^1H NMR (250 MHz, $CDCl_3$) δ 7.22 (1H, dd, *J*=7.3, 1.2 Hz), 7.12 (1H, dt, *J*=1.2, 7.3 Hz), 7.11 (1H, dd, *J*=7.3, 1.2 Hz), 7.02 (1H, dt, *J*=1.2, 7.3 Hz), 3.48 (1H, dd, *J*=12.2, 7.9 Hz), 3.29 (1H, dd, *J*=17.1, 7.9 Hz), 3.22 (1H, dd, *J*=12.2, 4.3 Hz), 3.09 (1H, dd, *J*=17.1, 1.8 Hz), 2.88 (1H, dd, *J*=7.9, 1.8 Hz), 2.05 (1H, dq, *J*=14.7, 7.3 Hz), 1.45 (1H, dq, *J*=14.7, 7.3 Hz), 1.19 (1H, m), 1.04 (3H, t, *J*=7.3 Hz); IR (neat) 3275, 2975, 2935, 2885, 1606, 1590, 1477, 1462, 1440, 1380, 1260, 1230, 1151, 1098, 1040, 1018, 945, 921, 906, 894, 823, 797, 764, 723 cm^{-1}; EI-MS *m/z* (ralative intensity) 189 (M^+, 43), 172 (45), 158 (100), 156 (30), 143 (45), 130 (45), 118 (81), 117 (56), 91 (30), 90 (23), 89 (22), 77 (28), 41 (21); EI-HRMS calcd for $C_{12}H_{15}NO$ (M^+) 189.1154, found 189.1173.

(2*S)-1,2-[(*S**)-1-Ethyl-1-(methoxymethyl)methylene]indoline (22)**

To a suspension of potassium hydride (35% dispersion in mineral oil, 72.6 mg, 0.634 mmol) in 2 mL of THF at 0 °C under Ar was added 60 mg (0.317 mmol) of alcohol **20** in 2 mL of THF and the solution was stirred at the same temperature for 30 min. After the mixture was cooled to -15 °C, 99.1 μL (1.59 mmol) of freshly distilled methyl iodide was added to the solution and the resulting mixture was stirred at the same temperature for 3 h. The reaction was quenched with 1 mL of saturated aqueous NH_4Cl and the reaction mixture was poured into 25 mL of water, followed by extracting with ether (20 mL × 3). The combined ethereal layers were washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (100% $CHCl_3$) on 5 g of silica gel to provide methyl ether **22** (53.5 mg, 83% yield): ^1H NMR (250 MHz, $CDCl_3$) δ 7.21 (1H, br d, *J*=7.3 Hz), 7.18-7.00 (2H, m), 7.01

(1H, br t, *J*=7.3 Hz), 3.63 (1H, d, *J*=10.4 Hz), 3.42 (3H, s), 3.31 (1H, d, *J*=10.4 Hz), 3.28 (1H, dd, *J*=17.1, 7.3 Hz), 3.09 (1H, d, *J*=17.1 Hz), 2.94 (1H, d, *J*=7.3 Hz), 1.27 (1H, dq, *J*=14.7, 7.3 Hz), 1.08 (1H, dq, *J*=14.7, 7.3 Hz), 0.82 (3H, t, *J*=7.3 Hz); IR (neat) 2980, 2940, 2890, 1606, 1478, 1463, 1378, 1290, 1239, 1195, 1109, 1017, 945, 888, 818, 780, 758, 726 cm^{-1}; EI-MS *m/z* (relative intensity) 203 (M^+, 33), 173 (18), 172 (100), 158 (47), 156 (17), 143 (23), 130 (21), 118 (59), 117 (34), 91 (16), 86 (30), 71 (45), 45 (26); EI-HRMS calcd for $C_{13}H_{17}ON$ (M^+) 203.1310, found 203.1294.

(2*S)-1,2-[(*R**)-1-Ethyl-1-(methoxymethyl)methylene]indoline (23)**

To a suspension of potassium hydride (35% dispersion in mineral oil, 141 mg, 1.23 mmol) in 2 mL of THF at 0 °C under Ar was added 116 mg (0.613 mmol) of alcohol **21** in 4 mL of THF and the solution was stirred at the same temperature for 30 min. After the temperature was cooled to -15 °C, 0.191 mL (3.07 mmol) of freshly distilled methyl iodide was added to the solution and the resulting mixture was stirred at the same temperature for 40 min. The reaction was quenched with 1 mL of saturated aqueous NH_4Cl and the reaction mixture was poured into 25 mL of water, followed by extracting with ether (20 mL × 3). The ethereal layer was washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Purification of the residue by column chromatography (8% EtOAc/benzene) on 6 g of silica gel produced methyl ether **23** (101 mg, 81% yield): ^1H NMR (250 MHz, $CDCl_3$) δ 7.20 (1H, br d, *J*=7.3 Hz), 7.11 (1H, br t, *J*=7.3 Hz), 7.10 (1H, br d, *J*=7.3 Hz), 7.01 (1H, br t, *J*=7.3 Hz), 3.27 (1H, dd, *J*=17.1, 7.9 Hz), 3.17 (1H, d, *J*=11.0 Hz), 3.08 (1H, dd, *J*=17.1, 1.8 Hz), 3.04 (3H, s), 2.89 (1H, d, *J*=11.0 Hz), 2.87 (1H, dd, *J*=7.9, 1.8 Hz), 1.85 (1H, dq, *J*=14.7, 7.3 Hz), 1.52 (1H, dq, *J*=14.7, 7.3 Hz), 1.04 (3H, t, *J*=7.3 Hz); IR (neat) 2980, 2930, 1607, 1591, 1478, 1462, 1379, 1271, 1230, 1194, 1152, 1107, 1018, 969, 946, 918, 887, 841, 819, 801, 776, 766, 725 cm^{-1}; EI-MS *m/z* (relative intensity) 203 (M^+, 4.4), 172 (21), 118 (21), 97 (21), 95 (20), 83 (28), 81 (50), 73 (28), 71 (33), 70 (20), 69 (100), 67 (21), 60 (26), 57 (67), 56 (20), 55 (57), 43 (60), 41 (67); EI-HRMS calcd for $C_{13}H_{17}ON$ (M^+) 203.1310, found 203.1291.

(2*S,3*R**)-3-Chloro-2-ethyl-2-methoxymethyl-1,2,3,4-tetrahydroquinoline (4)**

To a solution of methyl ether **22** (46.5 mg, 0.229 mmol) and tetraethylammonium chloride (570 mg, 3.44 mmol) in 4 mL of CH_2Cl_2 at -15 °C under Ar was added 21.2 μL (0.275 mmol) of trifluoroacetic acid and the solution was stirred at the same temperature for 20 min. The reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ and the reaction mixture was poured into 20 mL of water, followed by extracting with ether (20 mL × 3). The ethereal layer was washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography (2% EtOAc/hexane) on 3 g of silica gel to give the desired chlorine-containing piperidine **4** (53 mg, 97% yield): ^1H NMR (250 MHz, $CDCl_3$) δ 7.02 (1H, t, *J*=7.9 Hz), 6.97 (1H, d, *J*=7.9 Hz), 6.68 (1H, t, *J*=7.9 Hz), 6.58 (1H, d, *J*=7.9 Hz), 4.45 (1H, dd, *J*=6.7, 4.9 Hz), 3.41 (2H, s), 3.35 (3H, s), 3.33 (1H, br s), 3.25 (1H, dd, *J*=17.1, 4.9 Hz), 3.08 (1H, dd, *J*=17.1, 6.7 Hz), 1.82 (1H, dq, *J*=14.7, 7.3 Hz), 1.72 (1H, dq, *J*=14.7, 7.3 Hz), 0.94 (3H, t, *J*=7.3 Hz); ^{13}C NMR (68 MHz, $CDCl_3$) δ 142.2, 129.4, 127.4, 118.0, 117.8, 115.1, 75.3, 59.4, 58.1, 57.6, 34.1, 25.5, 7.5; IR (neat) 3390, 2935, 2900, 1611, 1591, 1488, 1390, 1320, 1311, 1286, 1263, 1196, 1175, 1156, 1110, 961, 829, 750 cm^{-1}; EI-MS *m/z* (relative intensity) 239 (M^+, 13), 197 (5.2), 196 (38), 195 (16), 194 (100), 159 (8.9), 158 (43), 149 (6.4), 143 (12), 142 (6.3), 130 (8.9), 118 (6.1), 77 (5.1), 45 (8.1); EI-HRMS calcd for $C_{13}H_{18}ONCl$ (M^+) 239.1077, found 239.1103.

(2*R,3*R**)-3-Chloro-2-ethyl-2-methoxymethyl-1,2,3,4-tetrahydroquinoline (3)**

To a solution of methyl ether **23** (101 mg, 0.497 mmol) and tetraethylammonium chloride (1.24 g, 7.46 mmol) in 5 mL of CH_2Cl_2 at -15 °C under Ar was added 45.9 μL (0.596 mmol) of trifluoroacetic acid and the solution was stirred at the same temperature for 20 min. The reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ and the reaction mixture was poured into 25 mL of water, followed by extracting with ether (20 mL × 3). The extracts were washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (4% ether/hexane) on 5 g of silica

gel to afford the desired chlorine-containing piperidine **3** (108 mg, 91% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.03 (1H, t, *J*=7.9 Hz), 6.97 (1H, d, *J*=7.9 Hz), 6.67 (1H, t, *J*=7.9 Hz), 6.56 (1H, d, *J*=7.9 Hz), 4.35 (1H, dd, *J*=6.7, 4.9 Hz), 4.01 (1H, br s), 3.54 (1H, d, *J*=9.2 Hz), 3.49 (1H, d, *J*=9.2 Hz), 3.37 (3H, s), 3.31 (1H, dd, *J*=17.1, 4.9 Hz), 3.06 (1H, dd, *J*=17.1, 6.7 Hz), 1.76 (1H, dq, *J*=14.7, 7.3 Hz), 1.66 (1H, dq, *J*=14.7, 7.3 Hz), 0.93 (3H, t, *J*=7.3 Hz); ^{13}C NMR (68MHz, $CDCl_3$) δ 142.3, 129.3, 127.5, 117.6, 117.3, 114.8, 73.6, 59.4, 57.6, 57.1, 34.0, 27.3, 7.1; IR (neat) 3400, 2980, 2930, 2835, 1609, 1590, 1486, 1386, 1314, 1292, 1258, 1195, 1156, 1110, 1043, 1015, 978, 958, 910, 886, 836, 786, 749 cm^{-1}; EI-MS *m/z* (relative intensity) 239 (M^+, 4.7), 194 (45), 167 (38), 158 (32), 149 (100), 97 (22), 85 (21), 83 (29), 81 (20), 71 (52), 70 (28), 69 (40), 57 (82), 55 (46), 43 (62), 41 (50); EI-HRMS calcd for $C_{13}H_{18}NOCl$ (M^+) 239.1077, found 239.1093.

(2*S,3*R**)-3-Chloro-2-ethyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoline (24)**

Preparation from amine **4**.

To a solution of amine **4** (10 mg, 41.7 μmol) and 0.1 mL (1.10 mmol) of propanethiol in 1 mL of CH_2Cl_2 at room temperature was added a portion of aluminum chloride (27.9 mg, 0.209 mmol) and the solution was stirred at the same temperature under Ar for 46 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 (10 mL × 3). The ethereal layer was 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 provided amino alcohol **24** (7 mg, 74% yield): *Rf*=0.53 (30% EtOAc/hexane on silica gel); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.03 (1H, t, *J*=7.3 Hz), 6.98 (1H, d, *J*=7.3 Hz), 6.71 (1H, t, *J*=7.3 Hz), 6.60 (1H, d, *J*=7.3 Hz), 4.46 (1H, dd, *J*=7.3, 5.5 Hz), 3.68 (1H, d, *J*=11.0 Hz), 3.66 (1H, br s), 3.56 (1H, d, *J*=11.0 Hz), 3.25 (1H, dd, *J*=16.5, 5.5 Hz), 3.10 (1H, dd, *J*=16.5, 7.3 Hz), 1.85 (1H, br s), 1.77 (1H, dq, *J*=14.7, 7.3 Hz), 1.76 (1H, dq, *J*=14.7, 7.3 Hz), 0.92 (3H, t, *J*=7.3 Hz); IR (neat) 3560 (sh), 3380, 3060, 2980, 2900, 1611, 1591, 1491, 1463, 1388, 1310, 1261, 1154, 1129, 1075, 1049, 983, 960, 932, 828, 779, 751 cm^{-1}; EI-MS *m/z* (relative intensity) 225 (M^+, 16), 196 (41), 195 (16), 194 (100), 159 (13), 158 (62), 143 (19), 142 (10), 130 (15), 118 (31), 117 (11); EI-HRMS calcd for $C_{12}H_{16}ONCl$ (M^+) 225.0920, found 225.0918.

Preparation from aziridine **20**.

To a solution of aziridine **20** (73 mg, 0.386 mmol) and tetraethylammonium chloride (959 mg, 5.79 mmol) in 5 mL of CH_2Cl_2 at -15 °C under Ar was added 35.7 μL (0.463 mmol) of trifluoroacetic acid and the solution was stirred at the same temperature for 20 min. The reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ and the reaction mixture was poured into 20 mL of water, followed by extracting with ether (20 mL × 3). The ethereal layer was washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (4% EtOAc/benzene) on 4 g of silica gel to yield amino alcohol **24**, identical with the product prepared from **4**, (68 mg, 78% yield).

(2*R,3*R**)-3-Chloro-2-ethyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoline (25)**

Preparation from amine **3**.

To a solution of amine **3** (20 mg, 83.4 μmol) and 0.1 mL (1.10 mmol) of propanethiol in 1 mL of CH_2Cl_2 at room temperature was added a portion of aluminum chloride (55.6 mg, 0.417 mmol) and the solution was stirred at the same temperature under Ar for 21 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 (10 mL × 3). The extracts were washed with 20 mL of brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Preparative thin layer chromatography (silica gel) of the residue with 30% EtOAc/hexane furnished amino alcohol **25** (17 mg, 90% yield): *Rf*=0.52 (30% EtOAc/hexane on silica gel); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.02 (1H, t, *J*=7.3 Hz), 6.96 (1H, d, *J*=7.3 Hz), 6.66 (1H, t, *J*=7.3 Hz), 6.56 (1H, d, *J*=7.3 Hz), 4.33 (1H, dd, *J*=7.9, 5.5 Hz), 3.83 (1H, br s), 3.74 (2H, s), 3.27 (1H, dd, *J*=17.1, 5.5 Hz), 3.11 (1H, dd, *J*=17.1, 7.9 Hz), 1.78 (1H, dq, *J*=14.7, 7.3 Hz), 1.76 (1H, br s), 1.68 (1H, dq, *J*=14.7, 7.3 Hz), 0.95 (3H, t, *J*=7.3 Hz); IR (neat) 3595 (sh), 3395, 2975, 1610, 1590, 1491, 1460, 1400, 1388, 1317, 1291, 1262,

1192, 1168, 1149, 1119, 1044, 877, 834, 791, 756 cm^{-1}; EI-MS *m/z* (relative intensity) 225 (M^+, 17), 196 (49), 195 (14), 194 (100), 159 (13), 158 (68), 143 (23), 142 (19), 130 (17), 118 (24), 69 (11), 57 (18), 55 (11), 43 (13), 41 (12); EI-HRMS calcd for $C_{12}H_{16}ONCl$ (M^+) 225.0920, found 225.0909.

Preparation from aziridine **21**.

To a solution of aziridine **21** (40.9 mg, 0.216 mmol) and tetraethylammonium chloride (716 mg, 4.32 mmol) in 4 mL of CH_2Cl_2 at -15 °C under Ar was added 20.0 μL (0.260 mmol) of trifluoroacetic acid and the solution was stirred at the same temperature for 20 min. The reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ and the reaction mixture was poured into 20 mL of water, followed by extracting with ether (20 mL × 3). The ethereal layer was washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by column chromatography (4% EtOAc/benzene) on 3 g of silica gel gave the amino alcohol **25**, consistent with the product prepared from **3**, (43 mg, 88% yield).

(3a*S,4*R**)-4-Chloro-3a-ethyl-9b-aza-2-oxabenzo[*q*]perhydroinden-1-one (26)**

To a solution of amino alcohol **24** (10 mg, 44.3 μmol) in 3 mL of toluene at room temperature was added a portion of carbonyl diimidazole (71.8 mg, 0.443 mmol) and the solution was heated to 60 °C. After stirring at 60 °C under Ar for 35 h, an oil bath was removed and the mixture was cooled to room temperature. The reaction mixture was poured into 10 mL of water and extracted with ether (10 mL × 3). The ethereal layer was washed with 20 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was subjected to column chromatography (6% EtOAc/hexane) on 2 g of silica gel to afford cyclic carbamate **26** (8.5 mg, 76% yield): mp 138-140 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 8.04 (1H, d, *J*=8.5 Hz), 7.28 (1H, m), 7.20-7.05 (2H, m), 4.37 (1H, d, *J*=9.2 Hz), 4.35 (1H, dd, *J*=11.6, 6.7 Hz), 4.31 (1H, d, *J*=9.2 Hz), 3.37 (1H, dd, *J*=17.1, 6.7 Hz), 3.20 (1H, dd, *J*=17.1, 11.6 Hz), 1.87 (1H, dq, *J*=14.7, 7.3 Hz), 1.67 (1H, dq, *J*=14.7, 7.3 Hz), 0.93 (3H, t, *J*=7.3 Hz); IR (CCl_4) 2980, 2940, 1773, 1498, 1462, 1389, 1370, 1336, 1290, 1189, 1158, 1130, 1111, 1081, 1055, 966 cm^{-1}; EI-MS *m/z* (relative intensity) 253 (16), 251 (M^+, 46), 224 (36), 223 (14), 222 (100), 216 (21), 180 (10), 178 (30), 144 (10), 143 (36), 142 (68), 130 (14), 117 (10), 116 (14), 115 (18), 77 (18); EI-HRMS calcd for $C_{13}H_{14}O_2NCl$ (M^+) 251.0713, found 251.0721.

(3a*R,4*R**)-4-Chloro-3a-ethyl-9b-aza-2-oxabenzo[*q*]perhydroinden-1-one (27)**

To a solution of amino alcohol **25** (10 mg, 44.3 μmol) in 3 mL of toluene at room temperature was added a portion of carbonyl diimidazole (71.8 mg, 0.443 mmol) and the solition was heated to 100 °C. After stirring at 100 °C under Ar for 23 h, an oil bath was removed and the mixture was cooled to room temperature. The reaction mixture was poured into 10 mL of water and extracted with ether (10 mL × 3). The ethereal layer was washed with 20 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Preparative thin layer chromatography (silica gel) of the residue with 30% EtOAc/hexane provided cyclic carbamate **27** (6.0 mg, 54% yield): mp 124-127 °C; *Rf*=0.37 (30% EtOAc/hexane on silica gel); ^1H NMR (250 MHz, $CDCl_3$) δ 8.07 (1H, d, *J*=8.6 Hz), 7.30 (1H, dt, *J*=1.8, 8.6 Hz), 7.14 (1H, dd, *J*=7.9, 1.8 Hz), 7.09 (1H, t, *J*=7.9 Hz), 4.55 (1H, d, *J*=9.2 Hz), 4.39 (1H, dd, *J*=4.6, 1.8 Hz), 4.26 (1H, d, *J*=9.2 Hz), 3.46 (1H, dd, *J*=18.3, 4.6 Hz), 3.22 (1H, dd, *J*=18.3, 1.8 Hz), 1.80 (1H, dq, *J*=14.7, 7.3 Hz), 1.61 (1H, dq, *J*=14.7, 7.3 Hz), 0.97 (1H, t, *J*=7.3 Hz); IR (CCl_4) 2980, 1775, 1498, 1464, 1399, 1370, 1335, 1305, 1220, 1188, 1161, 1139, 1111, 1081, 1055, 960 cm^{-1}; EI-MS *m/z* (relative intensity) 253 (10), 251 (M^+, 29), 224 (26), 222 (70), 178 (33), 143 (50), 142 (100), 130 (18), 116 (21), 115 (29), 77 (29), 51 (16), 39 (16); EI-HRMS calcd for $C_{13}H_{14}O_2NCl$ (M^+) 251.0713, found 251.0715.

Ethyl 4-azido-3-(2-propenyl)benzoate (29)

To a solution of ethyl 4-amino-3-(2-propenyl)benzoate (**28**)[19] (1.00 g, 4.87 mmol) in 19.5 mL of water at 0 °C were added sequentially 1.95 mL of concentrated (12 N) hydrochloric acid and 403 mg (5.84 mmol) of sodium nitrite in 2.45 mL of water and the mixture was stirred for 15 min. Sodium azide (90% purity, 528 mg, 7.31 mmol) in 2.45 mL of water was added to the solution at 0 °C and the mixture was further stirred at the same temperature for additional 1 h 45 min. The reaction mixture was transfered into a separatory funnel and

extracted with ether (30 mL × 3). The ethereal layer was washed with 50 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residual oil was purified by column chromatography (2% ether/hexane) on 30 g of silica gel to give azide **29** (916 mg, 81% yield): ^{1}H NMR (90 MHz, $CDCl_3$) δ 7.96 (1H, dd, *J*=8, 2 Hz), 7.91 (1H, d, *J*=2 Hz), 7.19 (1H, d, *J*=8 Hz), 5.96 (1H, ddt, *J*=16, 11, 7 Hz), 5.09 (1H, dd, *J*=11, 2 Hz), 5.03 (1H, dd, *J*=16, 2 Hz), 4.36 (2H, q, *J*=7 Hz), 3.36 (2H, d, *J*=7 Hz), 1.40 (3H, t, *J*=7 Hz); IR (neat) 3070, 2990, 2165, 2115, 1721, 1643, 1605, 1584, 1496, 1424, 1396, 1372, 1293, 1258, 1188, 1152, 1118, 1021, 997, 917, 867, 836, 768 cm^{-1}; EI-MS *m/z* (relative intensity) 231 (M^+, 1.8), 174 (44), 158 (40), 131 (15), 130 (100), 129 (14), 128 (11), 104 (10), 103 (27), 102 (14), 77 (28), 76 (10), 63 (12), 51 (19), 39 (14); EI-HRMS calcd for $C_{12}H_{13}O_2N_3$ (M^+) 231.1008, found 231.0982.

Ethyl 4-azido-3-formylmethylbenzoate (30)

To a solution of azide **29** (3.71 g, 16.0 mmol) and *N*-methylmorpholine *N*-oxide (2.25 g, 19.2 mmol) in each 15 mL of acetone and water at room temperature was added osmium tetroxide (40.7 mg, 0.160 mmol). The reaction was slightly exothermic initially and was maintained at room temperature with a water bath. The reaction was complete after stirring for 17 h at room temperature under Ar. The reaction mixture was poured into 100 mL of water and extracted with ether (70 mL × 3). The combined organic layers were washed with 150 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was subjected to column chromatography (2% MeOH/$CHCl_3$) on 110 g of silica gel to afford diol contaminated with impurity which was used directly in the next reaction.

To a solution of the above diol (4.24 g, 16.0 mmol) in each 42.4 mL of THF and water at room temperature was added a portion of sodium metaperiodate (4.11 g, 19.2 mmol) and the mixture was stirred vigorously at the same temperature for 1 h. The reaction mixture was filtered *in suction*, poured into 100 mL of water, and extracted with ether (100 mL × 3). The extracted organic layers were washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. Purification of the residue by column chromatography (12% EtOAc/hexane) on 130 g of silica gel provided unstable aldehyde **30** (2.57 g, 69% yield from azide **29**): ^{1}H NMR (90 MHz, $CDCl_3$) δ 9.71 (1H, t, *J*=1 Hz), 8.03 (1H, dd, *J*=8, 2 Hz), 7.87 (1H, d, *J*=2 Hz), 7.22 (1H, d, *J*=8 Hz), 4.36 (2H, q, *J*=8 Hz), 3.71 (2H, d, *J*=1 Hz), 1.40 (3H, t, *J*=8 Hz); IR (neat) 3410, 2990, 2170, 1720, 1605, 1583, 1495, 1426, 1394, 1372, 1293, 1261, 1190, 1152, 1119, 1022, 866, 836, 768 cm^{-1}; EI-MS *m/z* (relative intensity) 233 (M^+, 17), 188 (19), 177 (34), 176 (17), 161 (19), 160 (100), 149 (19), 148 (34), 144 (11), 132 (50), 105 (18), 104 (22), 103 (12), 77 (20), 76 (12), 51 (12); EI-HRMS calcd for $C_{11}H_{11}O_3N_3$ (M^+) 233.0800, found 233.0795.

Ethyl 4-azido-3-[(2*E*)-3-methoxycarbonyl-6,7-dimethyl-2,6-octadienyl]benzoate (32)

To a solution of phosphorane **31**[8] (3.38 g, 7.85 mmol) in 8 mL of CH_2Cl_2 at 0 °C under Ar was added 1.30 g (5.57 mmol) of aldehyde **30** in 5 mL of CH_2Cl_2 and the solution was allowed to warm to room temperature. After stirring at room temperature for 38 h, organic solvent was evaporated *in vacuo* and the reaction mixture was chromatographed on 40 g of silica gel with 4% EtOAc/hexane to furnish crude product. Purification of the crude product by column chromatography (2% EtOAc/hexane) on 40 g of silica gel yielded (*E*)-α,β-unsaturated ester **32** (1.59 g, 74% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.97 (1H, dd, *J*=8.5, 1.8 Hz), 7.85 (1H, d, *J*=1.8 Hz), 7.18 (1H, d, *J*=8.5 Hz), 6.76 (1H, t, *J*=7.3 Hz), 4.36 (2H, q, *J*=7.3 Hz), 3.74 (3H, s), 3.50 (2H, d, *J*=7.3 Hz), 2.55-2.42 (2H, m), 2.24-2.12 (2H, m), 1.71 (3H, br s), 1.69 (3H, br s), 1.64 (3H, br s), 1.39 (3H, t, *J*=7.3 Hz); IR (neat) 2990, 2950, 2180, 1716, 1643, 1606, 1584, 1495, 1438, 1366, 1290, 1258, 1189, 1152, 1111, 1050, 1022, 831, 768 cm^{-1}; EI-MS *m/z* (relative intensity) 385 (M^+, 28), 357 (22), 314 (23), 298 (35), 229 (30), 228 (39), 215 (20), 214 (41), 213 (20), 202 (24), 201 (23), 190 (20), 186 (20), 170 (30), 144 (22), 142 (32), 83 (100), 55 (41), 41 (25); EI-HRMS calcd for $C_{21}H_{27}O_4N_3$ (M^+) 385.2001, found 385.1990.

Methyl 2-[bis(2,2,2-trifluoroethyl)phosphono]-5,6-dimethyl-5-heptenoate (33)

To a suspension of sodium hydride (302 mg, 12.6 mmol, washed with hexane) in 15 mL of DMSO at room temperature under Ar was added dropwise 4.00 g (12.6 mmol) of commercially available methyl bis(2,2,2-trifluoroethyl)phosphonoacetate in 5 mL of DMSO and the mixture was further stirred for 10 min. 1-Bromo-3,4-dimethyl-3-pentene[20] (6.69 g, 37.8 mmol) in 5 mL of DMSO was added to the solution and the mixture was further stirred at room temperature for 3 days. The reaction was quenched with 5 mL of saturated aqueous NH_4Cl and the resulting mixtures were poured into 150 mL of water, followed by extracting with ether (100 mL × 3). The ethereal layer was washed with 200 mL of brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The residue was purified by column chromatography (4% EtOAc/benzene) on 160 g of silica gel to afford Horner-Emmons' reagent **33** (2.78 g, 53% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.58-4.26 (4H, m), 3.76 (3H, s), 3.10 (1H, m), 2.22-1.81 (4H, m), 1.63 (3H, br s), 1.60 (6H, br s); IR (neat) 2970, 2930, 2885, 1745, 1453, 1441, 1423, 1381, 1298, 1260, 1166, 1099, 1069, 961, 876, 846 cm^{-1}; EI-MS *m/z* (relative intensity) 414 (M^+, 5.0), 331 (13), 319 (23), 318 (16), 287 (20), 286 (16), 219 (13), 97 (17), 96 (100), 83 (11), 82 (33), 81 (19), 67 (11), 55 (16), 41 (18); EI-HRMS calcd for $C_{14}H_{21}O_5F_6P$ (M^+) 414.1031, found 414.1010.

Ethyl 4-azido-3-[(2*Z*)-3-methoxycarbonyl-6,7-dimethyl-2,6-octadienyl]benzoate (34)

To a solution of 18-crown-6 (2.29 g, 8.65 mmol) and phosphonate **33** (717 mg, 1.73 mmol) in 13 mL of THF at -78 °C under Ar were added successively potassium hexamethyldisilazide (0.5 M in THF, 3.46 mL, 1.73 mmol) and 403 mg (1.73 mmol) of aldehyde **30** in 5 mL of THF, and then the mixture was stirred at -78 °C to -40 °C over 2 h 30 min. The reaction was quenched with 5 mL of saturated aqueous NH_4Cl and the resulting mixtures were poured into 80 mL of water, followed by extracting 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 (3% EtOAc/hexane) on 25 g of silica gel to provide (*Z*)-α,β-unsaturated ester **34** (419 mg, 63% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.95 (1H, d, *J*=8.6 Hz), 7.89 (1H, s), 7.18 (1H, d, *J*=8.6 Hz), 5.92 (1H, t, *J*=7.3 Hz), 4.36 (2H, q, *J*=7.3 Hz), 3.80 (3H, s), 3.77 (2H, d, *J*=7.3 Hz), 2.42-2.22 (2H, m), 2.22-2.03 (2H, m), 1.60 (6H, s), 1.59 (3H, s), 1.39 (3H, t, *J*=7.3 Hz); IR (neat) 2990, 2940, 2870, 2160, 1722, 1644, 1607, 1583, 1497, 1442, 1372, 1292, 1260, 1230, 1190, 1153, 1112, 1021, 998, 910, 829, 769 cm^{-1}; EI-MS *m/z* (relative intensity) 385 (M^+, 2.8), 274 (25), 273 (20), 261 (24), 229 (30), 214 (26), 170 (22), 142 (30), 83 (100), 69 (27), 55 (81), 43 (24), 41 (71); EI-HRMS calcd for $C_{21}H_{27}O_4N_3$ (M^+) 385.2001, found 385.1979.

(2*S)-1,2-[(*S**)-1-(3,4-Dimethyl-3-pentenyl)-1-(methoxycarbonyl)methylene]-5-ethoxycarbonylindoline (35)**

A solution of azido olefin **32** (1.58 g, 4.10 mmol) in 150 mL of toluene at room temperature under Ar was stirred for 3 h under photo-irradiation by medium pressure mercury arc through Pyrex filter and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (4% EtOAc/benzene) on 50 g of silica gel to give aziridine **35** (1.37 g, 93% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.90 (1H, d, *J*=8.6 Hz), 7.85 (1H, s), 7.39 (1H, d, *J*=8.6 Hz), 4.35 (2H, q, *J*=7.3 Hz), 3.82 (3H, s), 3.50-3.32 (2H, m), 3.20 (1H, m), 2.12 (1H, dt, *J*=4.9, 11.6 Hz), 1.83 (1H, dt, *J*=4.9, 11.6 Hz), 1.60 (1H, ddd, *J*=14.0, 11.6, 4.9 Hz), 1.50 (3H, s), 1.38 (3H, t, *J*=7.3 Hz), 1.38 (3H, s), 1.30 (3H, s), 1.12 (1H, ddd, *J*=14.0, 11.6, 4.9 Hz); IR (neat) 2990, 2940, 2880, 1722, 1614, 1438, 1372, 1328, 1289, 1268, 1236, 1200, 1178, 1151, 1115, 1097, 1079, 1058, 1020, 946, 898, 877, 853, 785 cm^{-1}; EI-MS *m/z* (relative intensity) 357 (M^+, 41), 298 (29), 275 (28), 274 (100), 228 (29), 214 (32), 202 (21), 201 (20), 186 (16), 170 (37), 142 (37), 83 (16), 55 (17); EI-HRMS calcd for $C_{21}H_{27}O_4N$ (M^+) 357.1940, found 357.1938.

(2*S)-1,2-[(*R**)-1-(3,4-Dimethyl-3-pentenyl)-1-(methoxycarbonyl)methylene]-5-ethoxycarbonylindoline (36)**

A solution of azido olefin **34** (173 mg, 0.449 mmol) in 7 mL of toluene at room temperature under Ar was stirred for 3 h under photo-irradiation by medium pressure mercury arc through Pyrex filter and concentrated *in*

vacuo. Purification of the residue by column chromatography (6% EtOAc/hexane) on 10 g of silica gel afforded aziridine **36** (138 mg, 86% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.86 (1H, d, *J*=8.5 Hz), 7.82 (1H, s), 7.29 (1H, d, *J*=8.5 Hz), 4.33 (2H, q, *J*=7.3 Hz), 3.60 (1H, dd, *J*=17.1, 1.2 Hz), 3.31 (1H, dd, *J*=17.1, 7.3 Hz), 3.28 (3H, s), 3.10 (1H, dd, *J*=7.3, 1.2 Hz), 2.28-2.04 (4H, m), 1.64 (9H, br s), 1.37 (3H, t, *J*=7.3 Hz); IR (neat) 2980, 2925, 2870, 1739, 1717, 1610, 1478, 1436, 1368, 1322, 1289, 1271, 1237, 1208, 1196, 1158, 1107, 1085, 1020, 986, 851, 785, 729 cm^{-1}; EI-MS *m/z* (relative intensity) 357 (M^+, 23), 298 (63), 275 (30), 274 (90), 228 (51), 214 (55), 202 (39), 201 (36), 190 (64), 186 (32), 170 (80), 144 (36), 142 (100), 118 (32), 83 (63), 55 (91), 41 (93); EI-HRMS calcd for $C_{21}H_{27}O_4N$ (M^+) 357.1940, found 357.1930.

(2*S)-1,2-[(*S**)-1-(3,4-Dimethyl-3-pentenyl)-1-(hydroxymethyl)methylene]-5-ethoxycarbonylindoline (37)**

To a solution of lithium tri-*tert*-butoxyaluminum hydride (636 mg, 2.50 mmol) in 3 mL of THF at room temperature under Ar was added 223 mg (0.624 mmol) of diester **35** in 4 mL of THF and the solution was stirred at the same temperature for 14 h. The reaction was quenched carefully with each appropriate amount of MeOH and water and the mixture was stirred vigorously for 10 min. The resulting mixture was filtered through a pad of Celite *in suction* and the filtrates were concentrated under reduced pressure. The residue was subjected to column chromatography (2% acetone/$CHCl_3$) on 10 g of silica gel to provide alcohol **37** (191 mg, 93% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 (1H, d, *J*=8.6 Hz), 7.83 (1H, s), 7.22 (1H, d, *J*=8.6 Hz), 4.35 (2H, q, *J*=7.3 Hz), 3.86 (1H, d, *J*=11.6 Hz), 3.68 (1H, m), 3.35 (1H, dd, *J*=17.1, 7.3 Hz), 3.21 (1H, dd, *J*=7.3, 1.2 Hz), 3.14 (1H, dd, *J*=17.1, 1.2 Hz), 2.63 (1H, br s), 2.05 (1H, dt, *J*=6.1, 11.9 Hz), 1.91 (1H, dt, *J*=6.1, 11.9 Hz), 1.70-1.20 (1H, dt, *J*=6.1, 10.7 Hz), 1.51 (3H, s), 1.39 (3H, s), 1.38 (3H, t, *J*=7.3 Hz), 1.34 (3H, s), 1.13 (1H, dt, *J*=6.1, 10.7 Hz); IR (neat) 3370, 2930, 2880, 1703, 1612, 1443, 1393, 1370, 1326, 1269, 1210, 1180, 1151, 1107, 1023, 898, 774 cm^{-1}; EI-MS *m/z* (relative intensity) 329 (M^+, 71), 298 (30), 284 (36), 247 (37), 246 (52), 190 (100), 144 (60), 118 (59), 117 (42), 83 (37), 55 (33); EI-HRMS calcd for $C_{20}H_{27}O_3N$ (M^+) 329.1991, found 329.1995.

(2*S)-1,2-[(*R**)-1-(3,4-Dimethyl-3-pentenyl)-1-(hydroxymethyl)methylene]-5-hydroxymethylindoline (38)**

To a solution of lithium aluminum hydride (18.8 mg, 0.496 mmol) in 2 mL of THF at 0 °C under Ar was added dropwise 88.5 mg (0.248 mmol) of diester **36** dissolved in 2 mL of THF and the solution was stirred at the same temperature for 3 h. The reaction was carefully quenched with 18.8 μL of water, followed by 18.8 μL of 15% aqueous NaOH, and then 56.4 μL 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*. The residue was purified by column chromatography (2% MeOH/$CHCl_3$) on 5 g of silica gel to furnish diol **38** (71 mg, 100% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.13 (1H, br d, *J*=7.9 Hz), 7.12 (1H, br s), 7.07 (1H, br d, *J*=7.9 Hz), 4.58 (2H, d, *J*=5.5 Hz), 3.50 (1H, dd, *J*=12.2, 7.3 Hz), 3.24 (1H, dd, *J*=17.7, 7.9 Hz), 3.18 (1H, dd, *J*=12.2, 4.3 Hz), 3.05 (1H, dd, *J*=17.7, 1.8 Hz), 2.90 (1H, dd, *J*=7.9, 1.8 Hz), 2.39 (1H, br s), 2.34-1.99 (3H, m), 1.68 (6H, s), 1.65 (3H, s), 1.50-1.20 (2H, m); IR (neat) 3310, 2930, 2860, 1615, 1488, 1440, 1375, 1240, 1188, 1157, 1129, 1101, 1034, 936, 881, 836, 806, 756 cm^{-1}; EI-MS *m/z* (relative intensity) 287 (M^+, 29), 256 (34), 205 (30), 204 (50), 186 (35), 174 (51), 173 (32), 156 (100), 148 (58), 130 (45), 118 (97), 83 (44), 55 (52), 41 (56); EI-HRMS calcd for $C_{18}H_{25}O_2N$ (M^+) 287.1885, found 287.1859.

(2*S)-1,2-[(*R**)-1-(3,4-Dimethyl-3-pentenyl)-1-(hydroxymethyl)methylene]-5-methoxycarbonylindoline (40)**

To a solution of diol **38** (70.5 mg, 0.245 mmol) in 4 mL of acetone at room temperature was added a portion of active manganese dioxide[24] (213 mg, 2.45 mmol) and the mixture was stirred at the same temperature under Ar for 46 h. The reaction mixture was filtered through a pad of Celite *in suction* and the filtrates were evaporated under reduced pressure to yield aldehyde **39** which was used directly in the next reaction.

To a solution of the above aldehyde **39** (69.9 mg, 0.245 mmol) and potassium cyanide (95% purity, 84.3 mg, 1.23 mmol) in 4 mL of MeOH at room temperature was added a portion of active manganese dioxide[24] (213 mg, 2.45 mmol) and the solution was stirred at the same temperature under Ar for 3 h 30 min. The reaction mixture was filtered through a pad of Celite *in suction*, poured into 25 mL of water, and extracted with ether (20 mL × 3). The ethereal layer was washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by column chromatography (16% EtOAc/benzene) on 5 g of silica gel gave methyl ester **40** (63.5 mg, 82% overall yield from diol **38**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.87 (1H, d, *J*=7.9 Hz), 7.82 (1H, s), 7.27 (1H, d, *J*=7.9 Hz), 3.89 (3H, s), 3.53 (1H, dd, *J*=12.8, 7.3 Hz), 3.32 (1H, dd, *J*=17.7, 7.9 Hz), 3.22 (1H, dd, *J*=12.8, 4.3 Hz), 3.12 (1H, dd, *J*=17.7, 1.8 Hz), 3.00 (1H, dd, *J*=7.9, 1.8 Hz), 2.40-1.98 (4H, m), 1.68 (6H, br s), 1.65 (3H, br s), 1.80-1.40 (1H, m); IR (CH_2Cl_2) 3430, 2860, 1718, 1611, 1380, 1353, 1098, 1073, 1042, 1023, 930, 846 cm^{-1}; EI-MS *m/z* (relative intensity) 315 (M^+, 30), 284 (54), 233 (44), 232 (75), 214 (45), 202 (32), 201 (44), 200 (41), 182 (65), 176 (100), 155 (33), 154 (33), 144 (98), 117 (48), 116 (30), 83 (76), 59 (31), 55 (79), 41 (80); EI-HRMS calcd for $C_{19}H_{25}O_3N$ (M^+) 315.1835, found 315.1862.

(2*S)-1,2-[(*S**)-1-(3,4-Dimethyl-3-pentenyl)-1-(methoxymethyl)methylene]-5-ethoxycarbonylindoline (41)**

To a solution of alcohol **37** (47 mg, 0.143 mmol) and tetrabutylammonium iodide (15.8 mg, 42.9 μmol) in 3 mL of THF at 0 °C was added a portion of sodium hydride (4.13 mg, 0.172 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, 44.3 μL (0.715 mmol) of freshly distilled methyl iodide and 49.8 μL (0.286 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 2 h. The reaction was quenched with 1 mL of saturated aqueous NH_4Cl and the reaction mixture was poured into 20 mL of water, followed by extracting with ether (20 mL × 3). The combined ethereal layers were washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was subjected to column chromatography (8% EtOAc/benzene) on 3 g of silica gel to give methyl ether **41** (35 mg, 71% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.86 (1H, d, *J*=7.9 Hz), 7.81 (1H, s), 7.26 (1H, d, *J*=7.9 Hz), 4.34 (2H, q, *J*=7.3 Hz), 3.68 (1H, d, *J*=10.4 Hz), 3.43 (3H, s), 3.33 (1H, d, *J*=10.4 Hz), 3.32 (1H, dd, *J*=17.1, 7.9 Hz), 3.13 (1H, dd, *J*=17.1, 1.8 Hz), 3.06 (1H, dd, *J*=7.9, 1.8 Hz), 2.09 (1H, dt, *J*=4.9, 12.5 Hz), 1.84 (1H, dt, *J*=4.9, 12.5 Hz), 1.70-1.20 (1H, ddd, *J*=14.0, 12.2, 4.3 Hz), 1.50 (3H, br s), 1.37 (3H, t, *J*=7.3 Hz), 1.36 (3H, br s), 1.29 (3H, br s), 1.03 (1H, ddd, *J*=14.0, 12.2, 4.3 Hz); IR (neat) 2940, 1708, 1613, 1449, 1393, 1369, 1324, 1288, 1268, 1209, 1183, 1149, 1110, 1048, 1020, 848, 757, 727 cm^{-1}; EI-MS *m/z* (relative intensity) 343 (M^+, 12), 260 (28), 156 (22), 149 (23), 144 (22), 83 (48), 71 (100), 55 (60), 45 (31), 43 (26), 41 (56); EI-HRMS calcd for $C_{21}H_{29}NO_3$ (M^+) 343.2148, found 343.2167.

(2*S)-1,2-[(*R**)-1-(3,4-Dimethyl-3-pentenyl)-1-(methoxymethyl)methylene]-5-methoxycarbonylindoline (42)**

To a suspension of potassium hydride (35% dispersion in mineral oil, 17.8 mg, 0.155 mmol) in 0.5 mL of THF at 0 °C under Ar was added 24.5 mg (77.7 μmol) of alcohol **40** in 2 mL of THF and the solution was stirred at the same temperature for 30 min. After the mixture was cooled to -15 °C, 24.2 μL (0.389 mmol) of freshly distilled methyl iodide was added to the solution and the resulting mixture was stirred at the same temperature for 1 h. The reaction was quenched with 1 mL of saturated aqueous NH_4Cl and the reaction mixture was poured into 25 mL of water, followed by extracting with ether (20 mL × 3). The combined ethereal layers were washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (12% EtOAc/hexane) on 2.5 g of silica gel to provide methyl ether **42** (13.5 mg, 53% yield): ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.86 (1H, d, *J*=7.9 Hz), 7.81 (1H, s), 7.25 (1H, d, *J*=7.9 Hz), 3.89 (3H, s), 3.30 (1H, dd, *J*=17.7, 7.9 Hz), 3.22 (1H, d, *J*=11.6 Hz), 3.11 (1H, dd, *J*=17.7, 1.8 Hz), 3.03 (3H, s), 2.97 (1H, dd, *J*=7.9, 1.8 Hz), 2.86 (1H, d, *J*=11.6 Hz), 2.24 (1H, dt,

J=6.1, 11.6 Hz), 2.14 (1H, dt, *J*=5.5, 10.4 Hz), 1.94 (1H, ddd, *J*=13.4, 10.4, 6.1 Hz), 1.66 (6H, br s), 1.63 (3H, br s), 1.49 (1H, ddd, *J*=13.4, 11.6, 5.5 Hz); IR (neat) 2930, 2870, 1721, 1611, 1484, 1440, 1378, 1327, 1288, 1269, 1236, 1194, 1150, 1108, 1087, 1052, 978, 944, 904, 848, 784, 728 cm^{-1}; EI-MS *m/z* (relative intensity) 329 (M^+, 14), 284 (28), 246 (39), 214 (43), 201 (22), 182 (41), 176 (40), 155 (21), 154 (24), 144 (41), 117 (21), 83 (38), 71 (100), 55 (50), 45 (38), 41 (68); EI-HRMS calcd for $C_{20}H_{27}O_3N$ (M^+) 329.1991, found 329.1983.

(2*S,3*R**)-3-Chloro-2-(3,4-dimethyl-3-pentenyl)-2-methoxymethyl-1,2,3,4-tetrahydroquinoline-6-carboxylic acid (2)**

To a solution of aziridine **41** (40 mg, 0.116 mmol) in 4 mL of MeOH at room temperature was added 58.0 μL (0.232 mmol) of 4 N aqueous sodium hydroxide and the mixture was heated to reflux. After stirring at the same temperature for 3 days, 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 which was used directly in the next reaction.

To a solution of the above sodium carboxylate (39.1 mg, 0.116 mmol) and 384 mg (2.32 mmol) of tetraethylammonium chloride in 5 mL of CH_2Cl_2 at -15 °C under Ar was added 35.7 μL (0.464 mmol) of trifluoroacetic acid and the solution was stirred at the same temperature for 20 min. The reaction was quenched with 0.3 mL of saturated aqueous $NaHCO_3$ and the reaction mixture was poured into 20 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 combined organic layers were dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residue was purified by column chromatography (100% $CHCl_3$) on 2.5 g of silica gel to give carboxylic acid **2**, one of the two possible diastereomers of virantmycin, (34.5 mg, 85% overall yield from aziridine **41**): ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (1H, dd, *J*=8.6, 1.7 Hz), 7.75 (1H, d, *J*=1.7 Hz), 6.52 (1H, d, *J*=8.6 Hz), 4.42 (1H, dd, *J*=6.6, 4.9 Hz), 3.47 (1H, d, *J*=9.3 Hz), 3.42 (1H, d, *J*=9.3 Hz), 3.38 (3H, s), 3.28 (1H, dd, *J*=17.1, 4.9 Hz), 3.13 (1H, dd, *J*=17.1, 6.6 Hz), 2.09 (2H, t, *J*=8.5 Hz), 1.85 (1H, m), 1.72 (1H, m), 1.62 (9H, s); IR ($CHCl_3$) 3730-2130, 3410, 2940, 1670, 1605, 1518, 1431, 1332, 1288, 1248, 1213, 1191, 1105, 958, 828, 758 cm^{-1}; EI-MS *m/z* (relative intensity) 351 (M^+, 2.8), 306 (33), 83 (87), 81 (32), 71 (39), 69 (57), 67 (33), 57 (72), 55 (100), 45 (32), 43 (82), 41 (100); EI-HRMS calcd for $C_{19}H_{26}O_3NCl$ (M^+) 351.1601, found 351.1580.

(±)-Virantmycin (1)

To a solution of aziridine **42** (50.5 mg, 0.153 mmol) in 4 mL of MeOH at room temperature was added 76.5 μL (0.306 mmol) of 4 N aqueous sodium hydroxide and the mixture was heated to reflux. After stirring at the same temperature for 3 days, an oil bath was removed and the mixture was cooled to room temperature. The reaction mixture was concetrated *in vacuo* and residual water was azeotropically evaporated with benzene under reduced pressure to afford sodium carboxylate which was used directly in the next reaction.

To a solution of the above sodium carboxylate (51.6 mg, 0.153 mmol) and 507 mg (3.06 mmol) of tetraethylammonium chloride in 6 mL of CH_2Cl_2 at -15 °C under Ar was added 47.2 μL (0.612 mmol) of trifluoroacetic acid and the solution was stirred at the same temperature for 20 min. The reaction was quenched with 0.3 mL of saturated aqueous $NaHCO_3$ and the reaction mixture was poured into 20 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 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 3 g of silica gel to provide the desired synthetic (±)-virantmycin (**1**), identical with natural product, (52 mg, 97% overall yield from aziridine **42**): mp 138-143 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (1H, dd, *J*=8.2, 1.9 Hz), 7.76 (1H, d, *J*=1.9 Hz), 6.54 (1H, d, *J*=8.2 Hz), 4.36 (1H, dd, *J*=6.1, 4.7 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, 4.7 Hz), 3.11 (1H, dd, *J*=17.1, 6.1 Hz), 2.09 (1H, dt, *J*=5.0, 12.4 Hz), 2.00 (1H, dt, *J*=5.0, 12.4 Hz), 1.81 (1H, ddd, *J*=13.9, 12.4, 5.0 Hz), 1.63 (1H, ddd, *J*=13.9, 12.4, 5.0 Hz), 1.63 (3H, s), 1.61 (6H, s); IR (CCl_4) 3500-2300, 3430, 2930, 1679, 1611, 1516, 1475, 1430, 1411, 1329, 1289, 1249, 1192,

1111, 933 cm^{-1}; EI-MS *m/z* (relative intensity) 351 (M^+, 9.1), 308 (29), 306 (76), 292 (30), 270 (20), 224 (42), 200 (20), 187 (24), 162 (30), 83 (100), 71 (28), 69 (38), 55 (56), 45 (30), 41 (57); EI-HRMS calcd for $C_{19}H_{26}O_3NCl$ (M^+) 351.1601, found 351.1614.

(2*S,3*R**)-3-Chloro-2-(3,4-dimethyl-3-pentenyl)-6-ethoxycarbonyl-2-hydroxymethyl-1,2,3,4-tetrahydroquinoline (43)**

To a solution of aziridine **37** (101 mg, 0.308 mmol) and tetraethylammonium chloride (766 mg, 4.62 mmol) in 6 mL of CH_2Cl_2 at -15 °C under Ar was added 28.5 μL (0.370 mmol) of trifluoroacetic acid and the solution was stirred at the same temperature for 20 min. The reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ and the reaction mixture was poured into 20 mL of water, followed by extracting with ether (20 mL × 3). The ethereal layer was washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was purified by column chromatography (8% EtOAc/benzene) on 5 g of silica gel to yield amino alcohol **43** (103 mg, 91% yield): ^1H NMR (250 MHz, $CDCl_3$) δ 7.71 (1H, d, *J*=7.9 Hz), 7.70 (1H, s), 6.53 (1H, d, *J*=7.9 Hz), 4.43 (1H, dd, *J*=7.3, 4.9 Hz), 4.30 (2H, q, *J*=7.3 Hz), 3.72 (1H, d, *J*=11.0 Hz), 3.65 (1H, d, *J*=11.0 Hz), 3.29 (1H, dd, *J*=17.1, 4.9 Hz), 3.12 (1H, dd, *J*=17.1, 7.3 Hz), 2.07 (2H, t, *J*=8.5 Hz), 1.90-1.50 (2H, m), 1.60 (9H, br s), 1.35 (3H, t, *J*=7.3 Hz); IR (neat) 3370, 2970, 2930, 2870, 1680, 1610, 1590, 1514, 1440, 1390, 1370, 1331, 1288, 1251, 1187, 1128, 1099, 1040, 965, 907, 828, 773, 735 cm^{-1}; EI-MS *m/z* (relative intensity) 365 (M^+, 6.2), 190 (33), 189 (21), 144 (60), 118 (23), 117 (22), 116 (25), 83 (100), 69 (21), 57 (23), 55 (67), 44 (22), 43 (27), 41 (39); EI-HRMS calcd for $C_{20}H_{28}O_3NCl$ (M^+) 365.1758, found 365.1777.

(2*R,3*R**)-3-Chloro-2-(3,4-dimethyl-3-pentenyl)-2-hydroxymethyl-6-methoxycarbonyl-1,2,3,4-tetrahydroquinoline (44)**

To a solution of aziridine **40** (63 mg, 0.200 mmol) and tetraethylammonium chloride (497 mg, 3.00 mmol) in 5 mL of CH_2Cl_2 at -15 °C under Ar was added 18.5 μL (0.240 mmol) of trifluoroacetic acid and the solution was stirred at the same temperature for 20 min. The reaction was quenched with 1 mL of saturated aqueous $NaHCO_3$ and the reaction mixture was poured into 20 mL of water, followed by extracting with ether (20 mL × 3). The ethereal layer was washed with 40 mL of brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Purification of the residue by column chromatography (8% EtOAc/benzene) on 4 g of silica gel gave amino alcohol **44** (70.5 mg, 100% yield): ^1H NMR (250 MHz, $CDCl_3$) δ 7.70 (1H, d, *J*=8.6 Hz), 7.69 (1H, s), 6.53 (1H, d, *J*=8.6 Hz), 4.36 (1H, dd, *J*=6.7, 4.9 Hz), 3.83 (3H, s), 3.81 (2H, s), 3.33 (1H, dd, *J*=17.1, 4.9 Hz), 3.13 (1H, dd, *J*=17.1, 6.7 Hz), 2.14 (1H, dt, *J*=5.0, 12.4 Hz), 2.03 (1H, dt, *J*=5.0, 12.4 Hz), 1.88-1.50 (2H, m), 1.61 (9H, br s); IR (neat) 3370, 2950, 1690, 1612, 1591, 1514, 1440, 1379, 1333, 1288, 1250, 1213, 1197, 1130, 1101, 1047, 828, 759 cm^{-1}; EI-MS *m/z* (relative intensity) 351 (M^+, 15), 322 (38), 321 (24), 320 (100), 306 (49), 254 (51), 250 (21), 240 (24), 238 (63), 83 (80), 69 (35), 55 (44), 41 (34); EI-HRMS calcd for $C_{19}H_{26}O_3NCl$ (M^+) 351.1601, found 351.1628.

(3a*S,4*R**)-4-Chloro-3a-(3,4-dimethyl-3-pentenyl)-7-ethoxycarbonyl-9b-aza-2-oxabenzo[*q*]perhydroinden-1-one (45)**

To a solution of amino alcohol **43** (31 mg, 84.7 μmol) in 4 mL of toluene at room temperature was added a portion of carbonyl diimidazole (137 mg, 0.847 mmol) and the solution was heated to 90 °C. After stirring at 90 °C under Ar for 9 h, an oil bath was removed and the mixture was cooled to room temperature. The reaction mixture was poured into 10 mL of water and extracted with ether (10 mL × 3). The ethereal layer was 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 20% EtOAc/hexane provided cyclic carbamate **45** (18 mg, 54% yield): *Rf*=0.64 (30% EtOAc/hexane on silica gel); ^1H NMR (250 MHz, $CDCl_3$) δ 8.16 (1H, d, *J*=8.6 Hz), 7.94 (1H, br d, *J*=8.6 Hz), 7.84 (1H, br s), 4.45 (1H, d, *J*=9.2 Hz), 4.36 (2H, q, *J*=7.3 Hz), 4.35 (1H, d, *J*=9.2 Hz), 4.34 (1H, dd, *J*=11.6, 6.7 Hz), 3.42 (1H, dd, *J*=17.1, 6.7 Hz), 3.23 (1H, dd, *J*=17.1, 11.6 Hz), 2.15-1.83 (3H, m), 1.64-1.48 (1H, m), 1.54 (3H, s), 1.46 (3H, s), 1.38 (3H, t, *J*=7.3 Hz), 1.37 (3H,

s); IR (neat) 2980, 2940, 2920, 1767, 1714, 1614, 1584, 1503, 1440, 1390, 1370, 1341, 1286, 1271, 1229, 1207, 1166, 1120, 1100, 1069, 1058, 1020, 980, 846, 828, 757 cm^{-1}; EI-MS *m/z* (relative intensity) 391 (M^+, 25), 296 (38), 295 (19), 294 (100), 259 (26), 258 (39), 214 (33), 142 (46), 115 (19), 83 (26), 55 (78), 43 (18), 41 (56), 39 (16); EI-HRMS calcd for $C_{21}H_{26}O_4NCl$ (M^+) 391.1550, found 391.1547.

(3a*R,4*R**)-4-Chloro-3a-(3,4-dimethyl-3-pentenyl)-7-methoxycarbonyl-9b-aza-2-oxabenzo[*q*]perhydroinden-1-one (46)**

To a solution of amino alcohol **44** (30.5 mg, 86.7 μmol) in 4 mL of toluene at room temperature was added a portion of carbonyl diimidazole (141 mg, 0.867 mmol) and the solution was heated to reflux. After stirring at reflux under Ar for 20 h, an oil bath was removed and the mixture was cooled to room temperature. The reaction mixture was poured into 10 mL of water and extracted with ether (10 mL × 3). The ethereal layer was washed with 20 mL of brine, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. Preparative thin layer chromatography (silica gel) of the residue with 30% EtOAc/hexane gave cyclic carbamate **46** (15 mg, 46% yield): *Rf*=0.48 (30% EtOAc/hexane on silica gel); ^1H NMR (250 MHz, $CDCl_3$) δ 8.21 (1H, d, *J*=8.6 Hz), 7.96 (1H, dd, *J*=8.6, 1.8 Hz), 7.88 (1H, d, *J*=1.8 Hz), 4.61 (1H, d, *J*=8.6 Hz), 4.43 (1H, dd, *J*=4.9, 1.8 Hz), 4.34 (1H, d, *J*=8.6 Hz), 3.90 (3H, s), 3.51 (1H, dd, *J*=18.3, 4.9 Hz), 3.30 (1H, dd, *J*=18.3, 1.8 Hz), 2.19-1.92 (2H, m), 1.83-1.56 (2H, m), 1.56 (3H, br s), 1.50 (6H, br s); IR (neat) 2940, 2870, 1760, 1722, 1614, 1585, 1502, 1440, 1397, 1372, 1282, 1210, 1151, 1100, 1060, 1029, 989, 872, 846, 757 cm^{-1}; EI-MS *m/z* (relative intensity) 377 (M^+, 39), 282 (32), 280 (100), 245 (26), 244 (72), 200 (66), 142 (43), 115 (25), 83 (20), 59 (61), 55 (77), 43 (21), 41 (62); EI-HRMS calcd for $C_{20}H_{24}O_4NCl$ (M^+) 377.1394, found 377.1399.

Acknowledgments

We thank Prof. S. Ōmura (The Kitasato Institute) for providing us with an authentic sample of natural virantmycin, and Prof. R. A. Raphael and Prof. J. K. M. Sanders (University Chemical Laboratory, Cambridge) for the detailed information on the results of their studies and their friendly exchange of views.

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(*Received in Japan* 20 *May* 1996; *accepted* 28 *June* 1996)