Pergamon

Tetrahedron Vol. 50, No. 21, pp. 6239-6258, 1994
Copyright © 1994 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/94 $7.00+0.00

0040-4020(94)E0228-L

Synthetic Studies on Quinocarcin and Its Related Compounds. 4.[1, 2] Total Synthesis of Enantiomeric Pairs of Quinocarcin and 10-Decarboxyquinocarcin

Tadashi Katoh, Masayuki Kirihara,[3] Yuriko Nagata, Yuko Kobayashi,[4] Katsuko Arai, Junko Minami, Shiro Terashima*

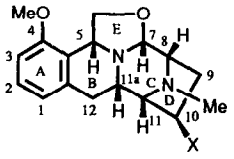
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229, Japan

Key words: total synthesis, quinocarcin, 10-decarboxyquinocarcin, antitumor antibiotic, aldol coupling, diastereoselective reduction, intramolecular aminal formation

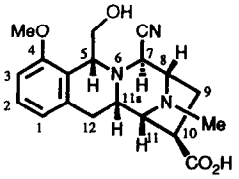
Abstract: *The title synthesis was accomplished by featuring (i) aldol coupling of the 3-methylanisole **11** with 5-substituted- or 3,5-disubstituted- 2-formylpyrrolidine **4** or **5**, (ii) highly diastereoselective reduction of 1,3-disubstituted isoquinolines **14** and **33** to control stereochemistries at the C5 and C11a positions in 10-decarboxyquinocarcin (**2**) and quinocarcin (**1**), respectively, simaultaneously in a single step, and (iii) intramolecular aminal formation of amino aldehydes **21** and **41** to construct the requisite ABCD ring systems **22** and **42** as key steps.*

(–)-Quinocarcin (**1**), isolated from *Streptomyces melanovinaceus* has been the subject of recent synthetic endeavors due to its unique structure and notable antitumor activity. Cyanation of **1** with sodium cyanide or potassium cyanide can produce the more stable 7-cyano congener, DX-52-1 (**3**), which still retains significant antitumor activity. It is also reported that treatment of **3** with silver nitrate can cleanly regenerate **1**.[2a]

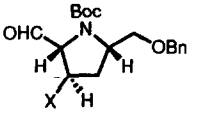
As described in the preceding papers,[2c] we have succeeded in establishing efficient and enantioselective routes to 5-substituted- and 3,5-disubstituted-2-formylpyrrolidines (**4**, *ent*-**4**, **5**, and *ent*-**5**) corresponding to the key D-ring fragments of enantiomeric pairs of 10-decarboxyquinocarcin (**2** and *ent*-**2**) (the ABCDE ring system of **1**) and quinocarcin (**1** and *ent*-**1**). In the fourth part of this series of papers, we wish to report full details of the total synthesis of enantiomeric pairs of **1** and **2** employing **4**, *ent*-**4**, **5**, and *ent*-**5** as the key D-ring fragments.[1d] Our synthetic strategy for **1** and **2** involves the following 3 key steps: (i) aldol coupling of the 2-methylanisole **11** with **4** or **5** (**Scheme 1** and **Scheme 4**) ; (ii) highly diastereoselective reduction of 1,3-disubstituted isoquinolines **14** and **33** to control stereochemistries at the C5 and C11a positions in **2** and **1**, respectively, simultaneously in a single step (**Scheme 1** and **Scheme 4**) ; (iii) intramolecular aminal



1 : X=CO_2H
2 : X=H



3



4 : X=H
5 : X=CH_2OMOM

formation of the amino aldehydes **21** and **41** produced *in situ* by removal of the N_2-protecting group in tetrahydroisoquinolines **20** and **40** to construct the requisite ABCD ring systems **22** and **42**, respectively (**Scheme 1** and **Scheme 4**).

Results and Discussion

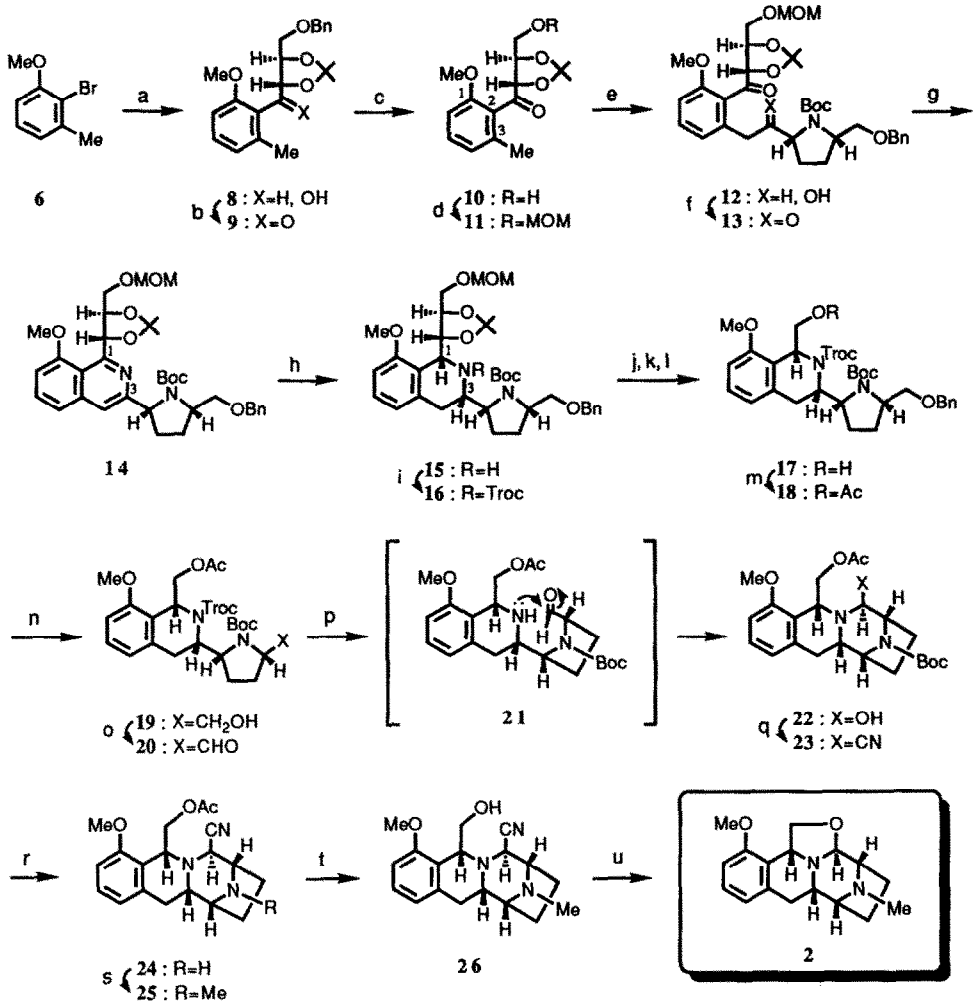
1. Total Synthesis of an Enantiomeric Pair of 10-Decarboxyquinocarcin (2 and *ent*-2)

At first, the total synthesis of 10-decarboxyquinocarcin (**2**) was investigated as shown in **Scheme 1**. Thus, 2-bromo-3-methylanisole (**6**)[2a] was converted to the ketone **9** having a chiral auxiliary by coupling of the aryl lithium generated from **6** with 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose[2a,b] (**7**), followed by Collins oxidation of an epimeric mixture of the resulting secondary alcohol **8**. In order to directly introduce the D-ring fragment **4** into **9**, the aldol coupling of **9** with **4** was examined under various reaction conditions. However, these initial attempts met with failure presumably due to instability of the benzyl protecting group in **9** under the basic conditions.[5] After extensive experimentation, the aldol coupling was finally realized by exchanging the benzyl group in **9** with a methoxymethyl group. Thus, debenzylation of **9** and subsequent protection of the resulting alcohol **10** provided the corresponding methoxymethyl ether **11**. The toluate anion generated *in situ* by treatment of **11** with lithium diisopropylamide (LDA) in tetrahydrofuran at -78°C, was allowed to react with **4** in the presence of *N,N,N',N'*-tetramethylenediamine (TMEDA), providing the desired coupling product **12** as an inseparable diastereomeric mixture in 48% yield along with a recovery of the starting material **11** (46%) and **4** (47%). It is worth mentioning that the chiral auxiliary (4-methoxymethoxymethyl-3,3-dimethyl-1,3-dioxolane-4-carbonyl group) present at the C_2 position in **11** plays a key role for directed metalation of the C_3-methyl group.[6] Oxidation of the highly hindered secondary hydroxyl group in **12** was best achieved by employing Jones reagent, giving rise to diketone **13** in 68% yield.[7] Further treatment of **13** with aqueous ammonia afforded the key isoquinoline derivative **14** in a good yield.

Crucial reduction of **14** with sodium cyanoborohydride in an acidic medium at 0°C proceeded in a completely diastereoselective manner, providing the tetrahydroisoquinoline **15** as a sole product in an almost quantitative yield. The stereostructure of **15** was unambiguously confirmed based on the 400 MHz ^{1}H-NMR spectrum of the 2-oxazolidinone derivative derived from **15** (*vide infra*). Protection of the amino group of **15** with 2,2,2-trichloroethyl chloroformate[8] (TrocCl) in pyridine gave the carbamate **16**, which was further converted to alcohol **17** by sequential acidic hydrolysis of both the acetonide and methoxymethyl groups, oxidative cleavage of the triol moiety, and reduction of the resulting aldehyde.

With the requisite absolute stereochemistries and carbon framework set up, we next focused our attention to construction of the ABCD ring system of **2**. Towards this end, sequential protection of the primary alcohol in **17**, debenzylation of the resulting acetate **18**, and Swern oxidation of the primary alcohol **19** provided aldehyde **20**. The final crucial step was envisaged to be the intramolecular cyclization of the amino aldehyde **21** generated *in situ* by removal of the Troc group of **17**, to furnish the desired tetracyclic ring system **22**. In the event, treatment of **20** with zinc powder in the presence of aqueous acetic acid in tetrahydrofuran[8] at ambient temperature smoothly produced the tetracyclic hemiaminal **22**. While **22** was fairly labile, immediate exposure of **22** to trimethylsilyl cyanide in the presence of zinc chloride[9] resulted in the formation of sturdy amino nitrile **23** in 58% overall yield from **20**. To complete the projected synthesis, removal of the Boc (*tert*-butoxycarbonyl) group in **23** with trifluoroacetic acid followed by reductive

Scheme 1

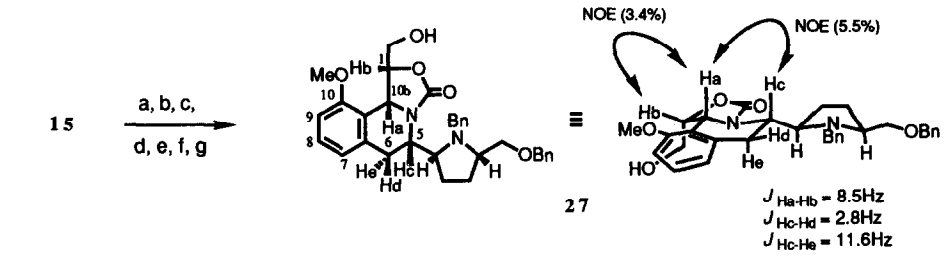


reagents and conditions: a) ^{n}BuLi, Et_2O, -78°C; 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose (7), -78°C, 99% b) Collins oxid., 98% c) H_2, $Pd(OH)_2$-C, MeOH, rt, 98% d) MOMCl, $^{i}Pr_2EtN$, CH_2Cl_2, rt, 92% e) LDA, THF, -78°C; TMEDA; 4, -78°C, 48% f) Jones oxid., 68% g) 14M NH_3, THF, rt, 72% h) $NaBH_3CN$, conc.HCl-MeOH(1:100), 0°C, 98% i) TrocCl, Py,rt, 88% j) 12M HCl, MeOH, rt k) $NaIO_4$, MeOH-H_2O(10:1v/v), rt l) $NaBH_4$, MeOH-H_2O(10:1v/v), rt, 68% (3 steps) m) Ac_2O, DMAP, Py, rt, 100% n) H_2, 10%Pd-C, EtOAc, rt, 86% o) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, 95% p) Zn, THF-H_2O-AcOH(5:1:1v/v/v), rt q) TMSCN $ZnCl_2$, CH_2Cl_2, rt, 58% (2 steps) r) TFA, CH_2Cl_2, rt, 91% s) 37%HCHO, $NaBH_3CN$, MeOH, rt, 72% t) 1M NaOH, MeOH, rt, 83% u) $AgNO_3$, MeOH, rt, 83%

methylation of the resulting amine **24** with a combination of aqueous formaldehyde and sodium cyanoborohydride in methanol,[10] giving rise to the corresponding *N*-methyl derivative **25**. Finally, saponification of **25** afforded 10-decarboxy-DX-52-1 (**26**), which was further treated with silver nitrate according to the reported method,[11] providing 10-decarboxyquinocarcin (**2**) (the ABCDE ring system of **1**).

In order to confirm stereochemistries at the newly formed C1 and C3 positions (isoquinoline numbering)

Scheme 2

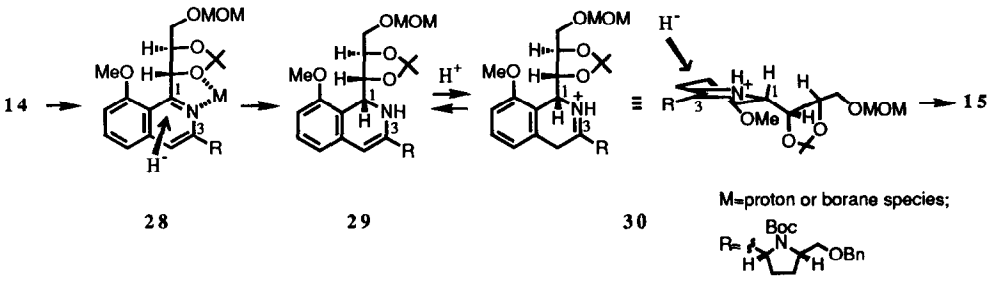


reagents and conditions: a) $ClCO_2Me$, Et_3N, $CHCl_3$, rt b) HCl, MeOH, rt c) KOH, MeOH, rt d) $NaIO_4$, MeOH-H_2O(10:1v/v), rt e) $NaBH_4$, MeOH-H_2O(10:1v/v), rt f) TMSBr, CH_2Cl_2, rt g) BnBr, aq.$NaHCO_3$, CH_2Cl_2, rt, 61%(7 steps)

in **15**, it was converted to the 2-oxazolidinone **27** as shown in **Scheme 2**. The 400 MHz ^{1}H-NMR spectrum of **27** exhibited the coupling constant of 8.5 Hz for Ha and Hb, establishing their *cis*-relationships.[2a,b] NOEs of 3.4% and 5.5% were observed between the signals due to Ha and Hb and between the signals due to Ha and Hc, respectively. These results obviously revealed that the newly formed tetrahydropyridine ring in **27** takes a half-chair conformation and that Ha, Hb, and Hc are all in *cis*-relationships. Moreover, the coupling constant of 2.8Hz (axial-equatorial) was observed for Hc and Hd, and that of 11.6Hz (axial-axial) was recorded for Hc and He. Based on these spectral features, the stereostructure of **15** could be rigorously assigned as depicted.

High diastereoselectivity observed for the reduction of **14** can be accounted for by the sequential 2-step asymmetric induction similar to that described in the preceding paper.[2b] Thus, as shown in **Scheme 3**, the first hydride attack may proceed through the well-known Cram's cyclic model (see, **28**) and second one may occur under an influence of the so-called stereoelectronic effect (see, **30**).

Scheme 3

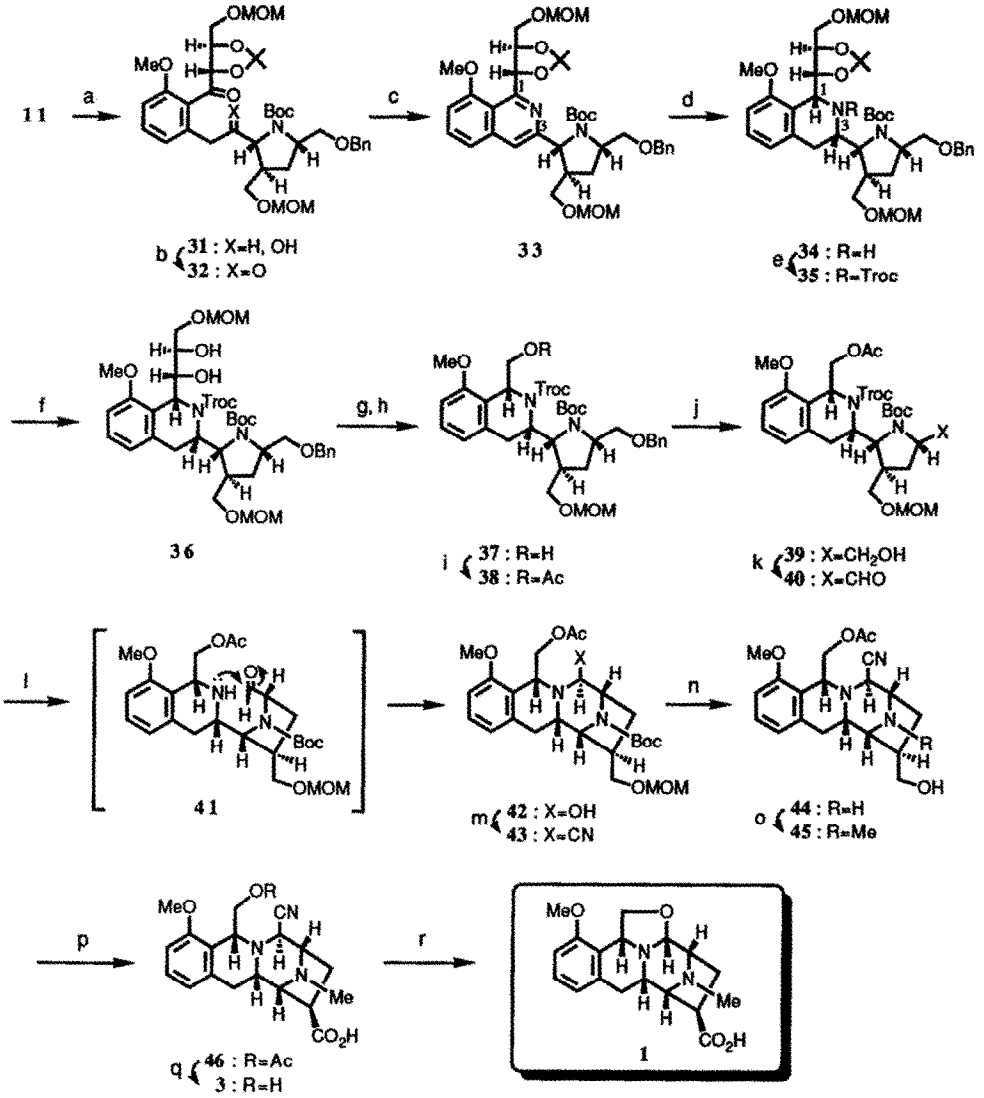


By employing 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose (*ent*-**7**) and (2*S*,5*R*)-5-benzyloxymethyl-2-formylpyrrolidine derivative (*ent*-**4**) instead of the D-isomer (**7**) and the (2*R*,5*S*)-isomer (**4**), respectively, enantiomeric 10-decarboxyquinocarcin (*ent*-**2**) was synthesized in the same manner as described above.

2. Total Synthesis of an Enantiomeric Pair of Quinocarcin (1 and *ent*-1)

Having established the synthetic scheme to an enantiomeric pair of the ABCDE ring system (**2** and *ent*-**2**), we next undertook the total synthesis of an enantiomeric pair of **1** as shown in **Scheme 4.** Thus,

Scheme 4



reagents and conditions: a) LDA, THF, -78°C; TMEDA; 5, -78°C, 51% b) Jones oxid., 42% c)14M NH_3, THF, rt, 67% d) $NaBH_3CN$, conc. HCl-MeOH(1:100), 0°C, 93% e) TrocCl, Py, rt, 85% f) $FeCl_3$-SiO_2, $CHCl_3$, rt, 86% g) $NaIO_4$, MeOH-H_2O (10:1), rt h) $NaBH_4$, MeOH-H_2O(10:1), rt, 84%(2 steps) i) Ac_2O, DMAP, Py, rt, 91% j) H_2, 10%Pd-C, EtOAc, rt, 82% k) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, 99% l) Zn,THF-H_2O-AcOH(5:1:1), rt m) TMSCN, $ZnCl_2$, CH_2Cl_2, rt,39%(2 steps) n) TFA, CH_2Cl_2, rt, 82% o) MeI, $^iPr_2EtN$, MeCN, 38°C, 68% p) Jones oxid., 79% q) 1M NaOH, MeOH, rt, 86% r) $AgNO_3$, MeOH, rt, 81%

employing **5** instead of **4**, the 2,2,2-trichloroethyl carbamate **35** could be produced *via* **31**-**34** starting from **11** by the reaction sequence similar to that described for the preparation of **16**. It is noteworthy that the crucial reduction of **33** took place with complete diastereoselectivity similarly to that of **14**. Chemoselective hydrolysis of the acetonide function in **35** turned out to be effected by employing a combination of ferric

chloride and silica gel developed by Kim *et al.*,[12] giving rise to the desired diol **36** in 86% yield.[13] This was further converted to amino alcohol **44** *via* **37-43** in a fashion analogous to that for the preparation of **24**. To complete the total synthesis of **1**, **44** was next subjected to selective *N*-methylation[9] to afford alcohol **45** in 68% yield. Oxidation of **45** with Jones reagent followed by saponification of the resulting carboxylic acid **46** gave DX-52-1 (**3**). Finally, **3** was treated with silver nitrate under the same conditions as reported,[11] providing **1**, mp 183-226°C (dec.) [lit.,[14] mp >170°C (dec.)], $[\alpha]_D^{22}$ -30.6° (c 0.48, H_2O) [lit.,[14] $[\alpha]_D^{22}$ -32.0° (c 0.50, H_2O)]. The spectroscopic properties (IR, ^{1}H-NMR, MS) were identical with those of authentic sample of (–)-**1** which was kindly provided by Drs. T. Hirata and H. Saito, Kyowa Hakko Kogyo Co., Ltd..

By employing *ent*-**11** prepared from 2-bromo-3-methylanisole (**6**) and 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose (*ent*-**7**), and (2*S*,3*S*,5*R*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-2-formyl-3-methoxymethoxymethylpyrrolidine (*ent*-**5**) instead of **11** and the (2*R*,3*R*,5*S*)-pyrrolidine **5**, respectively, enantiomeric quinocarcin (*ent*-**1**) was synthesized in the same manner as described above.

Results of antitumor activity assay of the synthesized compounds (**23**, *ent*-**23**, **24**, *ent*-**24**, **25**, *ent*-**25**, **26**, *ent*-**26**, **2**, *ent*-**2**, **46**, *ent*-**46**, **3**, *ent*-**3**, **1**, and *ent*-**1**) are the subject of the accompanying paper.[15]

Conclusion

As mentioned above, we have succeeded in completing the total synthesis of enantiomeric pairs of **1** and **2** by featuring (i) aldol coupling of the 3-methylanisoles **11** and *ent*-**11** with the 2-formylpyrrolidines **4** and *ent*-**4** or **5** and *ent*-**5**, (ii) novel diastereoselective reduction of 1,3-disubstituted isoquinolines **14**, *ent*-**14**, **33**, and *ent*-**33** to control stereochemistries at the C_5 and C_{11a} positions in **2** *ent*-**2**, **1**, and *ent*-**1**, respectively, and (iii) intramolecular aminal formation of amino aldehydes **21**, *ent*-**21**, **41**, and *ent*-**41** to complete the requisite tetracyclic ring systems **22**, *ent*-**22**, **42**, and *ent*-**42** as key steps. Since the explored synthetic scheme seems to be highly general and flexible to prepare various structural types of quinocarcin congeners, these studies may open opportunity for developing novel anticancer agents. Further synthetic efforts on various quinocarcin congeners and evaluation of their cytotoxic and antitumor activity are the subject of the accompanying paper.[15]

Experimental

General. All melting points were determined with a Yamato MP-21 micro melting point apparatus and are uncorrected. Measurements of optical rotations were performed with a Horiba SEPA-200 automatic digital polarimeter. ^{1}H-NMR spectra were measured with a Hitachi R-90H (90MHz) and a Brucker AM-400 (400MHz) spectrometer. The chemical shifts were expressed in ppm using tetramethylsilane (δ=0) and/or residual solvents such as chloroform (δ=7.25), benzene (δ=7.20), and CD3OD (δ=3.35) as internal standards. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sixtet (sxt), multiplet (m), and broad (br). Infrared (IR) spectral measurements were carried out with a JASCO A-202 and a JASCO FT/IR-5300 spectrometer. Low resolution mass (MS) spectra were taken with a Hitachi RMU-6MG spectrometer, and high resolution mass (HRMS) spectra were obtained on a Hitachi M-80A spectrometer. Routine monitoring of reactions was carried out using Merk 60 F254 silica gel, glass-supported TLC plates. Unless otherwise noted, flash column chromatography was performed with indicated solvents on Wakogel C-300. Solvents and commercial reagents were dried and purified before use. Ether and tetrahydrofuran were distilled from sodium benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon.

2-[1-[(4*R*,5*R*)-5-Benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-1-hydroxymethyl]-3-methylanisole (8) and Its Enantiomer (*ent*-8)

a) Preparation of **8**: *n*-Butyllithium in hexane (1.65 M solution, 15.6 ml, 26 mmol) was added dropwise to a stirred solution of 2-bromo-3-methylanisole[2a] (**6**) (2.00 g, 10 mmol) in dry ether (150 ml) at -78°C under argon. After 30 min, a solution of 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose[2a,b] (6.22 g, 26 mmol) in dry ether (20 ml) was added slowly, and the mixture was further stirred for 45 min at -78°C and allowed to warm up to 0°C. The reaction was quenched with saturated aqueous ammonium chloride (30 ml), and the mixture was extracted with ethyl acetate (350 ml). The extract was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1→ 2:1) to give **8** (3.68 g, 99%) as a

mixture of two diastereomers. This material was directly used for the next step without separation. In a small scale experiment, this mixture was further separated by column chromatography (hexane-ethyl acetate, 10:1→ 2:1) to give pure samples of less polar and more polar **8** in a ratio of 75:25.

Less polar 8: colorless oil. IR (neat): 3550, 3075, 3050, 3000, 2950, 2875, 1740, 1600, 1585, 1490, 1480, 1450, 1420, 1370, 1250, 1230, 1180, 1170, 1130, 1080, 1050 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.35 (3H, s, acetonide Me), 1.43 (3H, s, acetonide Me), 2.38 (3H, s, Ar*Me*), 3.69 (1H, dd, J=10.4, 6.2 Hz, C*H*2OBn), 3.79 (3H, s, ArO*Me*), 3.80 (1H, dd, J=10.4, 2.9 Hz, C*H*2OBn), 3.96 (1H, d, J=11.0 Hz, OH), 4.22 (1H, dd, J=8.4, 7.9 Hz, CH(OH)C*H*(O-)CH(O-)CH2OBn), 4.41 (1H, ddd, J=7.9, 6.2, 2.9 Hz, CH(OH)CH(O-)C*H*(O-)CH2OBn), 4.64 (2H, s, OC*H*2Ph), 4.88 (1H, dd, J=11.0, 8.4 Hz, C*H*OH), 6.75 (1H, d, J=8.1 Hz, aromatic proton), 6.81 (1H, d, J=8.1 Hz, aromatic proton), 7.14 (1H, t, J=8.1 Hz, aromatic proton), 7.25-7.39 (5H, m, aromatic protons). EIMS m/z: 372 (M^+), 357 [(M-Me)$^+$], 314 [(M-Me2CO)$^+$], 221, 151, 91. HRMS calcd for C22H28O5 (M^+): 372.1935. Found: 372.1943.

More polar 8: colorless oil. IR (neat): 3525, 3075, 3050, 3000, 2950, 2875, 1600, 1585, 1500, 1475, 1450, 1380, 1370, 1250, 1210, 1180, 1170, 1130, 1080, 1050 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.46 (3H, s, acetonide Me), 1.48 (3H, s, acetonide Me), 2.36 (3H, s, Ar*Me*), 3.02 (1H, dd, J=10.9, 10.8 Hz, C*H*2OBn), 3.03 (1H, dd, J=10.9, 10.6 Hz, C*H*2OBn), 3.66-3.78 (1H, m, OH), 3.79 (3H, s, ArOMe), 3.91 (1H, ddd, J=10.8, 8.4, 3.2 Hz, CH(OH)CH(O-)C*H*(O-)CH2OBn), 4.33 (2H, s, OC*H*2Ph), 4.39 (1H, dd, J=8.4, 7.6 Hz, CH(OH)C*H*(O-)CH(O-)CH2OBn), 5.03 (1H, dd, J=9.3, 7.6 Hz, C*H*OH), 6.67 (1H, d, J=8.1 Hz, aromatic proton), 6.75 (1H, d, J=8.1 Hz, aromatic proton), 7.11 (1H, t, J=8.1 Hz, aromatic proton), 7.14-7.34 (5H, m, aromatic protons). EIMS m/z: 372 (M^+), 357 [(M-Me)$^+$], 314 [M-Me2CO)$^+$], 221, 151, 91. HRMS calcd for C22H28O5 (M^+): 372.1934. Found: 372.1918.

b) Preparation of *ent*-**8**: The same treatments of **6** (2.20 g, 11 mmol) and 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose[2a,b] (6.84 g, 27 mmol) as described for the preparation of **8** gave *ent*-**8** (3.87 g, 95%) as a mixture of two diastereomers. This material was directly used for the next step without further separation. In a small scale experiment, this mixture was further separated by column chromatography (hexane-ethyl acetate, 10:1→ 2:1) to give pure samples of less polar and more polar *ent*-**8** in a ratio of 75:25.

Less polar *ent*-8: colorless oil. The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for less polar **8**.

More polar *ent*-8: colorless oil. The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for more polar **8**.

2-[(4*S*,5*R*)-5-Benzyloxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbonyl]-3-methylanisole (9) and Its Enantiomer (*ent*-9)

a) Preparation of **9**: Pyridine (10.4 ml, 0.14 mol) was added dropwise to a stirred suspension of chromium (VI) oxide (5.40 g, 54 mmol) in dry dichloromethane (150 ml) containing dry celite (20 g) at room temperature under argon. After 15 min, a solution of **8** (2.00 g, 5.4 mmol) in dry dichloromethane (30 ml) was added slowly to the above mixture, and stirring was continued for 45 min at room temperature. The resulting mixture was diluted with ether (450 ml) and filtered through a pad of celite. The filtrate was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→ 3:1) to give **9** (1.96 g, 98%) as a colorless oil. [α]D^{20} +3.5° (c 1.03, CHCl3). IR (neat): 3100, 3070, 3025, 2950, 1805, 1710, 1605, 1585, 1500, 1480, 1460, 1440, 1380, 1370, 1270, 1220, 1170, 1100, 1040, 1000 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.34 (3H, s, acetonide Me), 1.46 (3H, s, acetonide Me), 2.23 (3H, s, Ar*Me*), 3.53 (1H, dd, J=10.6, 5.9 Hz, C*H*2OBn), 3.64 (1H, dd, J=10.6, 3.0 Hz, C*H*2OBn), 3.73 (3H, s, ArO*Me*), 4.42 (1H, ddd, J=7.7, 6.0, 3.0 Hz, CH(O-)C*H*(O-)CH2OBn), 4.54 (2H, s, OC*H*2Ph), 4.77 (1H, d, J=7.7 Hz, C*H*(O-)CH(O-)CH2OBn), 6.71 (1H, d, J=8.0 Hz, aromatic proton), 6.78 (1H, d, J=8.0 Hz, aromatic proton), 7.21-7.34 (6H, m, aromatic protons). EIMS m/z: 370 (M^+), 355 [(M-Me)$^+$], 312 [(M-Me2CO)$^+$], 221, 149, 91. HRMS calcd for C22H26O5 (M^+): 370.1804. Found: 370.1779.

b) Preparation of *ent*-**9**: The same treatments of *ent*-**8** (3.85 g, 10 mmol) as described for the preparation of **9** from **8** gave *ent*-**9** (3.71 g, 97%) as a colorless oil. [α]D^{20} -3.2° (c 1.10, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **9**.

2-[(4*S*,5*R*)-5-Hydroxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbonyl]-3-methylanisole (10) and Its Enantiomer (*ent*-10)

a) Preparation of **10**: A mixture of **9** (1.44 g, 3.9 mmol) and 20% palladium hydroxide on carbon (290 mg) in methanol (30 ml) was stirred for 15 h at room temperature under hydrogen atmosphere (1 atm). The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane-ethyl acetate, 3:1) to give **10** (1.07 g, 98%) as a colorless oil. [α]D^{20} +11.3° (c 0.66, CHCl3). IR (neat): 3525, 3025, 2975, 1740, 1710, 1605, 1590, 1475, 1440, 1385, 1300, 1270, 1220, 1170, 1120, 1090, 1050, 1000 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.32 (3H, s, acetonide Me), 1.45 (3H, s, acetonide Me), 2.02 (1H, br s, OH), 2.26 (3H, s, Ar*Me*), 3.62 (1H, br d, J=11.0 Hz, C*H*2OH), 3.81 (3H, s, ArO*Me*), 3.85 (1H, br dd, J=11.0, 3.1 Hz, C*H*2OH), 4.32 (1H, ddd, J=7.6, 4.2, 3.1 Hz, CH(O-)C*H*(O-)CH2OH), 4.83 (1H, d, J=7.6 Hz, C*H*(O-)CH(O-)CH2OH), 6.76 (1H, d, J=8.0 Hz, aromatic proton), 6.82 (1H, d, J=8.0 Hz, aromatic proton), 7.26 (1H, t, J=8.0 Hz, aromatic protons). EIMS m/z: 280 (M^+), 265 [(M-Me)$^+$], 149, 91, 59. HRMS calcd for C15H20O5 (M^+): 280.1309. Found: 280.1319.

b) Preparation of *ent*-**10**: The same treatments of *ent*-**9** (3.65 g, 9.9 mmol) as described for the preparation of **10** from **9** gave *ent*-**10** (2.60 g, 94%) as a colorless oil. [α]D^{20} -12.9° (c 0.88, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **10**.

2-[(4*S*,5*R*)-5-Methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbonyl]-3-methylanisole (11) and Its Enantiomer (*ent*-11)

a) Preparation of **11**: Chloromethyl methyl ether (9.19 ml, 0.12 mol) was added to a stirred solution of **10** (3.08 g, 11 mmol) in dry dichloromethane (200 ml) containing *N,N*-diisopropylethylamine (25.1 ml, 0.15 mol) at room temperature under argon. After 17 h, the mixture was diluted with ethyl acetate (600 ml). The organic layer was washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1) to give **11** (3.28 g, 92%) as a colorless oil. $[\alpha]D^{20}$ +6.1° (c 1.24, CHCl3). IR (neat): 3025, 2970, 2920, 1705, 1600, 1590, 1475, 1440, 1385, 1300, 1270, 1220, 1160, 1090, 1040, 1000 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.33 (3H, s, acetonide Me), 1.46 (3H, s, acetonide Me), 2.26 (3H, s, Ar*Me*), 3.31 (3H, s, CH2O*Me*), 3.60 (1H, dd, J=10.9, 6.3 Hz, C*H*2OMOM), 3.72 (1H, dd, J=10.9, 2.9 Hz, C*H*2OMOM), 3.80 (3H, s, ArO*Me*), 4.42 (1H, ddd, J=7.8, 6.3, 2.9 Hz, CH(O-)C*H*(O-)CH2OMOM), 4.61 (1H, d, J=6.8 Hz, OC*H*2OMe), 4.63 (1H, d, J=6.8 Hz, OC*H*2OMe), 4.74 (1H, d, J=7.8 Hz, C*H*(O-)CH(O-)CH2OH), 6.76 (1H, d, J=8.0 Hz, aromatic proton), 6.82 (1H, d, J=8.0 Hz, aromatic proton), 7.25 (1H, t, J=8.0 Hz, aromatic proton). EIMS m/z: 324 (M^+), 309 [(M-Me)$^+$], 266[(M-Me2CO)$^+$], 149, 91, 54. HRMS calcd for C17H24O6 (M^+): 324.1571. Found: 324.1576.

b) Preparation of *ent*-**11**: The same treatments of *ent*-**10** (2.58 g, 9.2 mmol) as described for the preparation of **11** from **10** gave *ent*-**11** (2.81 g, 94%) as a colorless oil. $[\alpha]D^{20}$ -6.0° (c 0.83, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **11**.

(2*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-[[2-[(4*S*,5*R*)-5-methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbonyl]-3-methoxyphenyl]-1-hydroxyethyl]pyrrolidine (12) and Its Enantiomer (*ent*-12)

a) Preparation of **12**: A solution of **11** (2.00 g, 6.2 mmol) in dry tetrahydrofuran (80 ml) was added to a stirred solution of lithium diisopropylamide (62 mmol) [prepared from *n*-butyllithium in hexane (1.6 M solution, 38.8 ml, 62 mmol) and diisopropylamine (10.0 ml, 71 mmol)] in dry tetrahydrofuran (100 ml) at -78°C under argon. After 1 h, *N,N,N',N'*-tetramethylenediamine (11.0 ml, 74 mmol) was added, and stirring was continued for 1 h at -78°C. A solution of (2*R*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-2-formylpyrrolidine (**4**)[2c] (7.36 g, 22.8 mmol) in dry tetrahydrofuran (80 ml) was added, and the mixture was further stirred for 2 h at -78°C. The reaction was quenched with saturated aqueous ammonium chloride (30 ml), and the mixture was allowed to warm up to room temperature. The mixture was extracted with ethyl acetate (800 ml) and the extract was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→ 2:1) to give **12** (pale yellow caramel, 1.91 g, 48%) as a mixture of two diastereomers along with **11** (921 mg, 46% recovery) and **4** (3.46g, 47% recovery). The adduct (**12**) was directly used for the next reaction without further separation. IR (neat): 3475, 3000, 2950, 1740, 1700, 1605, 1590, 1480, 1460, 1380, 1305, 1260, 1250, 1220, 1170, 1130, 1140 cm^{-1}.^{1}H-NMR (90 MHz, CDCl3) δ: 1.42 (15H, br s, ^{t}Bu and acetonide), 1.65-2.20 (4H, m, pyrrolidine ring C3-H2 and pyrrolidine ring C4-H2), 2.36-2.58 (2H, m), 2.62-3.00 (1H, m), 3.13 (3H, br s, CH2OMe), 3.19-4.20 (8H, m), 3.85 (3H, br s, ArOMe), 4.35-4.60 (4H, m, OC*H*2OMe and OC*H*2Ph), 4.78 (1H, br d, J=8.0 Hz, COC*H*(O-)CH(O-)), 6.76 (2H, br d, J=8.0 Hz, aromatic proton), 7.16-7.65 (6H, m, aromatic proton). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening was observed for this ^{1}H-NMR spectrum. EIMS m/z: 644 [(M+1)$^+$], 626 [(M-OH)$^+$], 625 [(M-H2O)$^+$], 570 [(M-OH-C4H8)$^+$], 522, 468, 412, 368, 290, 190, 91, 57. HRMS calcd for C35H47NO9 [(M-H2O)$^+$]: 625.3247. Found: 625.3245.

b) Preparation of *ent*-**12**: The coupling reaction of *ent*-**11** (2.78 g, 8.6 mmol) with (2*S*,5*R*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-2-formylpyrrolidine (*ent*-**4**)[2c] (10.1 g, 31.5 mmol) as described for the preparation of **12** from **11** and **4** gave *ent*-**12** (pale yellow caramel, 2.58 g, 47%) as a mixture of two diastereomers along with *ent*-**11** (1.25 g, 45% recovery) and *ent*-**4** (1.19 g, 46% recovery). The adduct (*ent*-**12**) was directly used for the next reaction without further separation. The IR, ^{1}H-NMR, and mass specra of *ent*-**12** were identical with those recorded for **12**.

(2*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-[2-[(4*S*,5*R*)-5-methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbonyl]-3-methoxyphenyl]acetylpyrrolidine (13) and Its Enantiomer (*ent*-13)

a) Preparation of **13**: 2.6 M Jones reagent (4.80 ml, 12 mmol) was added dropwise to a stirred suspension of **12** (2.16 g, 3.36 mmol) in acetone (180 ml) containing dry celite (5.5 g) at room temperature. After 20 min, 2-propanol (15 ml) and saturated aqueous sodium hydrogen carbonate (80 ml) were added successively, and the mixture was diluted with ethyl acetate (600 ml). The resulting mixture was filtered through a pad of celite, and the filtrate was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1) to give **13** (1.46 g, 68%) as a pale yellow caramel. $[\alpha]D^{20}$ +37.2° (c 0.65, CHCl3). IR (neat): 3000, 2950, 1730, 1700, 1605, 1590, 1480, 1460, 1440, 1390, 1370, 1340, 1300, 1265, 1220, 1170, 1110, 1040 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3) δ: 1.32 (3H, br s, acetonide Me), 1,41 (9H, s, ^{t}Bu), 1.55 (3H, br s, acetonide Me), 1.85-2.20 (4H, m, pyrrolidine ring C3-H2 and pyrrolidine ring C4-H2), 3.32 (3H, s, ArO*Me*), 3.48-4.16 (6H, m, C*H*(O-)C*H*2OMOM, ArC*H*2CO and pyrrolidine ring C5-H), 3.83 (3H, s, ArO*Me*), 4.22-4.48 (1H, m, pyrrolidine ring C2-H), 4.57 (2H, br s OC*H*2Ph), 4.66 (2H, br s, OC*H*2OMe), 4.83 (1H, br d, J=8.0 Hz, COC*H*(O-)CH(O-)), 6.87 (2H, br d, J=8.0 Hz, aromatic protons), 7.22-7.47 (6H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening was observed for this ^{1}H-NMR spectrum. EIMS m/z: 641 (M^+), 626

[(M-Me)$^+$], 610 [(M-OMe)$^+$], 520, 494, 420, 366, 290, 246, 190, 149, 91, 57. HRMS calcd for C34H44NO10 [(M-Me)$^+$]: 626.2963. Found: 626.2967.

b) Preparation of *ent*-**13**: The same treatments of *ent*-**12** (2.56 g, 4.0 mmol) as described for the preparation of **13** from **12** gave *ent*-**13** (1.56 g, 61%) as a pale yellow caramel. [α]D^{20} -36.4° (c 0.45, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **11**.

3-[(2*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonylpyrrolidin-2-yl]-1-[(4*R*,5*R*)-5-methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-8-methoxyisoquinoline (14) and Its Enantiomer (*ent*-14)

a) Preparation of **14**: 38% Aqueous ammonia (7.00 ml, 0.16mol) was added to a stirred solution of **13** (964 mg, 1.5 mmol) in tetrahydrofuran (40 ml) at room temperature. After 15 h, the mixture was extracted with ethyl acetate (200 ml), and the extract was washed with brine and dried over Na2SO4. Concentration of the solvent gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1) to give **14** (690 mg, 72%) as a colorless caramel. [α]D^{20} +65.0° (c 0.77, CHCl3). IR (neat): 3000, 2950, 1700, 1620, 1570, 1460, 1390, 1370, 1310, 1260, 1220, 1170, 1105, 1040 cm^{-1}.^{1}H-NMR (400 MHz, CDCl3) δ: 1.12 (6H, br s, ^{t}Bu), 1.26 (3H, br s, ^{t}Bu), 1.49 (3H, br s, acetonide Me), 1.58 (3H, br s, acetonide Me), 2.02-2.14 (2H, m, pyrrolidine ring C3-H2 or pyrrolidine ring C4-H2), 2.14-2.26 (0.5H, m, pyrrolidine ring C3-H2 or pyrrolidine ring C4-H2), 2.26-2.37 (1.5H, m, pyrrolidine ring C3-H2 or pyrrolidine ring C4-H2), 3.32 (3H, s, OCH2O*Me*), 3.71 (1H, dd, J=10.8, 6.7 Hz, C*H*2OMOM), 3.78-3.94 (2H, m, C*H*2OBn), 3.84 (1H, dd, J=10.8, 2.9 Hz, C*H*2OMOM), 4.00 (3H, s, ArO*Me*), 4.18-4.33 (1H, m, pyrrolidine ring C5-H), 4.62 (2H, br s, OC*H*2Ph), 4.67 (2H, s, OC*H*2OMe), 4.88-5.04 (0.5H, m, pyrrolidine ring C2-H), 5.04-5.12 (0.5H, m, pyrrolidine C2-H), 5.30 (1H, br s, CH(O-)C*H*(O-)CH2OMOM), 6.03 (1H, d, J=8.2 Hz, C*H*(O-)CH(O-)CH2OMOM), 6.89 (1H, d, J=7.9 Hz, C5-H or C7-H), 7.11-7.37 (6H, m, aromatic protons), 7.47 (1H, t, J=7.9 Hz, C6-H), 7.55 (1H, br s, C4-H). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 622 (M$^+$), 607 [(M-Me)$^+$], 591 [(M-OMe)$^+$], 501 [(M-CH2OCH2Ph)$^+$], 401, 389, 297, 229, 190, 170, 114, 91, 57. HRMS calcd for C35H46N2O8 (M$^+$): 622.3231. Found: 622.3225.

b) Preparation of *ent*-**14**: The same treatments of *ent*-**13** (1.52 g, 2.4 mmol) as described for the preparation of **14** from **13** gave *ent*-**14** (1.03 g, 61%) as a colorless caramel. [α]D^{20} -67.4° (c 0.87, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **14**.

(1*R*,3*R*)-3-[(2*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonylpyrrolidin-2-yl]-1-[(4*R*,5*R*)-5-methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-8-methoxy-1,2,3,4-tetrahydroisoquinoline (15) and Its Enantiomer (*ent*-15)

a) Preparation of **15**: Sodium cyanoborohydride (840 mg, 13 mmol) was added in small portions to a stirred solution of **14** (415 mg, 0.66 mmol) in 37% aqueous hydrochloric acid-methanol (1:100) (120 ml) at 0°C. After 2 h, the mixture was made alkaline with 10% aqueous sodium hydroxide and extracted with ethyl acetate (500 ml). The extract was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1) to give **15** (409 mg, 98%) as a colorless caramel. [α]D^{20} -40.8°(c 0.75, CHCl3). IR (neat): 2980, 2950, 1700, 1590, 1470, 1460, 1380, 1260, 1250, 1220, 1170, 1110, 1050 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.41 (9H, s, ^{t}Bu), 1.42 (3H, s, acetonide Me), 1.49 (3H, br s, acetonide Me), 1.62-1.86 (2H, m, pyrrolidine ring C3-H2 or pyrrolidine ring C4-H2), 1.89-1.99 (1H, m, pyrrolidine ring C3-H or pyrrolidine ring C4-H), 2.06-2.25 (1H, m, pyrrolidine ring C3-H or pyrrolidine ring C4-H and NH), 2.51 (1H, dd, J=14.9, 2.2 Hz, C4-H), 2.61 (1H, dd, J=14.9, 11.0 Hz, C4-H), 2.73 (1H, dd, J=10.8, 1.8 Hz, C3-H), 2.94 (1H, dd, J=10.8, 7.5 Hz, pyrrolidine ring C2-H), 3.15 (3H, s, ArO*Me*), 3.32 (1H, br s, pyrrolidine ring C5-H), 3.50-3.67 (2H, m, C*H*2OBn), 3.79 (3H, s, OCH2O*Me*), 3.88-4.40 (2H, m, C*H*2OMOM), 4.32-4.41 (1H, m, CH(O-)C*H*(O-)CH2OMOM), 4.37 (1H, d, J=6.5 Hz, OC*H*2Ph), 4.39 (1H, d, J=6.5 Hz, OC*H*2Ph), 4.47 (1H, dd, J=8.2, 2.9 Hz, C*H*(O-)CH(O-)CH2OMOM), 4.50 (1H, d, J=12.2 Hz, OC*H*2OMe), 4.79 (1H, d, J=12.2 Hz, OC*H*2OMe), 4.79 (1H, br s, C1-H), 6.66 (2H, d, J=7.9 Hz, C5-H and C7-H), 7.10 (1H, t, J=7.9 Hz, C6-H), 7.28 (5H, br s, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 627 [(M+1)$^+$], 611 [(M-Me)$^+$], 451 [(M-CH(OCMe2O)CH-CH2OMOM)$^+$], 351 [(M-CH(OCMe2O)CHCH2OMOM-Boc)$^+$], 336, 229, 190, 160, 91, 57, 43. HRMS calcd for C35H51N2O8 [(M+1)$^+$]: 627.3643. Found: 627.3646.

b) Preparation of *ent*-**15**: The same treatments of *ent*-**14** (1.00 g, 1.6 mmol) as described for the preparation of **15** from **14** gave *ent*-**15** (0.98 g, 97%) as a colorless caramel. [α]D^{20} +41.2°(c 0.75, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **15**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 3-[(2*R*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonylpyrrolidin-2-yl]-1-[(4*R*,5*R*)-5-methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (16) and Its Enantiomer (*ent*-16)

a) Preparation of **16**: 2,2,2-Trichloroethyl chloroformate (0.85 ml, 6.2 mmol) was added dropwise to a stirred solution of **15** (390 mg, 0.62 mmol) in pyridine (24 ml) at room temperature. After 15 h, the mixture was diluted with ethyl acetate (130 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1) to give **16** (438 mg, 88%) as a colorless caramel. [α]D^{20} +8.0°(c 0.50, CHCl3). IR

(neat): 3000, 2950, 1720, 1700, 1600, 1480, 1450, 1370, 1305, 1280, 1260, 1220, 1170, 1160, 1120, 1110, 1050 cm^{-1}. ^1H-NMR (400 MHz, CDCl3) δ: 1.32 (3H, br s, ^{t}Bu), 1.41 (6H, br s, ^{t}Bu), 1.55 (6H, br s, acetonide Me x 2), 1.72-1.89 (1H, m, pyrrolidine ring C3-H or pyrrolidine ring C4-H), 1.89-1.97 (1H, m, pyrrolidine ring C3-H or pyrrolidine ring C4-H), 2.04-2.13 (1H, m, pyrrolidine ring C3-H or C4-H), 2.12-2.28 (1H, m, pyrrolidine ring C3-H or C4-H), 2.80 (1H, br s, C4-H), 3.05-3.60 (4H, m, C*H*2OMOM, C4-H, and C3-H), 3.40 (3H, s, OCH2O*Me*), 3.65 (2H, br s, OC*H*2Ph), 2.51 (1H, dd, J=14.9, 2.2 Hz, C4-H), 2.61 (1H, dd, J=14.9, 11.0 Hz, C4-H), 2.94 (1H, dd, J=10.8, 7.5 Hz, pyrrolidine ring C2-H), 3.78 (4H, s, ArO*Me* and CH(O-)*CH*(O-)CH2OMOM), 4.01 (1H, dd, J=10.9, 1.8 Hz, C*H*(O-)CH(O-)CH2OMOM), 4.16-4.32 (2H, m, pyrrolidine ring C2-H and pyrrolidine ring C5-H), 4.55 (2H, s, OC*H*2Ph), 4.60 (1H, d, J=7.4 Hz, CO2C*H*2CCl3), 4.70 (1H, d, J=6.8 Hz, OC*H*2OMe), 4.72 (1H, d, J=6.8 Hz, OC*H*2OMe), 4.85 (1H, d, J=7.4 Hz, CO2C*H*2CCl3), 5.97 (1H, br s, C1-H), 6.70 (2H, br d, J=7.9 Hz, C5-H and C7-H), 7.17 (1H, t, J=7.9 Hz, C6-H), 7.22-7.35 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^1H-NMR spectrum. EIMS m/z: 802 [(M+2)$^+$, ^{37}Cl , ^{35}Cl x 2], 800 (Me$^+$, ^{35}Cl x 3], 789 [(M-Me+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 787 [(M-Me+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 785 [(M-Me)$^+$, ^{35}Cl x 3], 629 [(M-CH(OCMe2O)CHCH2OMOM+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 627 [(M-CH(OCMe2O)CHCH2OMOM+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 625 [(M-CH(OCMe2O)CHCH2OMOM)$^+$, ^{35}Cl x 3], 573, 571, 569, 529, 527, 525, 456, 454, 452, 424, 422, 420, 338, 336, 334, 290, 190, 91, 57, 43.

b) Preparation of *ent*-**16**: The same treatments of *ent*-**15** (0.96 g, 1.5 mmol) as described for the preparation of **16** from **15** gave *ent*-**16** (1.12 g, 91%) as a colorless caramel. [α]D^{20} -7.9°(c 0.61, CHCl3). The IR, ^1H-NMR, and mass specra of this sample were identical with those recorded for **16**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 3-[(2*R*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonylpyrrolidin-2-yl]-1-hydroxymethyl-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (17) and Its Enantiomer (*ent*-17)

a) Preparation of **17**: 37% Aqueous hydrochloric acid (5.00 ml, 51 mmol) was added to a stirred solution of **16** (400 mg, 0.50 mmol) in methanol (45 ml) at room temperature. After 5 h, the mixture was neutralized with 10% aqueous sodium hydroxide and diluted with ethyl acetate (200 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, whose solution in in methanol-water (10:1) (70 ml) was treated with sodium periodate (1.10g, 5.1 mmol) for 15 h at room temperature. Sodium borohydride (195 mg, 5.1 mmol) was added, and stirring was continued for 30 min at room temperature. The reaction was quenched with 3% aqueous hydrochloric acid (5 ml), and the mixture was extracted with ethyl acetate (200 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1) to give **17** (328 mg, 68%, 3 steps) as a colorless caramel. [α]D^{20} +13.9° (c 0.72, CHCl3). IR (neat): 3450, 2950, 2930, 1680, 1590, 1470, 1450, 1420, 1380, 1300, 1260, 1160, 1120, 1080, 1050 cm^{-1}. ^1H-NMR (400 MHz, CDCl3) δ: 1.29 (4H, br s, ^{t}Bu), 1.35 (5H, br s, ^{t}Bu), 1.74-1.99 (1H, m, pyrrolidine ring C3-H or pyrrolidine ring C4-H), 1.99-2.18 (2H, m, pyrrolidine ring C3-H and/or pyrrolidine ring C4-H), 2.18-2.40 (1H, m, pyrrolidine ring C3-H or pyrrolidine ring C4-H), 2.75 (1H, br dd, J=16.4, 6.7 Hz, C4-H), 2.99 (1H, br d, J=16.4 Hz, C4-H), 3.67 (5H, br s, C*H*2OBn, C*H*2OH and C3-H), 3.83 (3H, s, ArO*Me*), 4.01 (1H, br s, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.43 (1H, br s, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.54 (2H, br s, OC*H*2Ph), 4.78-4.90 (2H, m, CO2C*H*2CCl3), 5.73 (1H, br s, C1-H), 6.68 (1H, br d, J=7.9 Hz, C5-H or C7-H), 6.72 (1H, br d, J=7.9 Hz, C5-H or C7-H), 7.16 (1H, t, J=7.9 Hz, C6-H), 7.29-7.39 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^1H-NMR spectrum. EIMS m/z: 629 [(M-CH2OH+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 627 [(M-CH2OH+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 625 [(M-CH2OH)$^+$, ^{35}Cl x 3], 573 [(M-CH2OH-C4H8+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 571 [(M-CH2OH-C4H8+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 569 [(M-CH2OH-C4H8)$^+$, ^{35}Cl x 3], 529 [(M-CH2OH-Boc+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 527 [(M-CH2OH-Boc+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 525 [(M-CH2OH-Boc)$^+$, ^{35}Cl x 3], 352, 350, 348, 338, 336, 334, 287, 190, 91, 57. HRMS calcd for C30H36Cl3N2O6 [(M-CH2OH)$^+$, ^{35}Cl x 3]: 625.1636. Found: 625.1617.

b) Preparation of *ent*-**17**: The same treatments of *ent*-**16** (1.10 g, 1.4 mmol) as described for the preparation of **17** from **16** gave *ent*-**17** (640 mg, 71%, 3 steps) as a colorless caramel. [α]D^{20}-14.0° (c 1.01, CHCl3). HRMS calcd for C30H36Cl3N2O6 [(M-CH2OH)$^+$, ^{35}Cl x 3]: 625.1636. Found: 625.1652. The IR, ^1H-NMR, and mass specra of this sample were identical with those recorded for **16**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 1-acetoxymethyl-3-[(2*R*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonylpyrrolidin-2-yl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (18) and Its Enantiomer (*ent*-18)

a) Preparation of **18**: Acetic anhydride (1.50 ml, 16 mmol) was added dropwise to a stirred solution of **17** (149 mg, 0.23 mmol) in pyridine (10 ml) containing a catalytic amount of 4-dimethylaminopyridine (15.0 mg, 0.12 mmol) at room temperature under argon. After 12 h, the mixture was diluted with ethyl acetate (100 ml). The organic layer was washed successively with 3% aqeous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1) to give **18** (159 mg, 100%) as a colorless caramel. [α]D^{20} +31.7° (c 0.52, CHCl3). IR (neat): 2960, 2920, 2850, 1740, 1710, 1690, 1590, 1470, 1450, 1420, 1380, 1360, 1320, 1290, 1270, 1250, 1230, 1170, 1120, 1090, 1050 cm^{-1}. ^1H-NMR (400 MHz, CDCl3) δ: 1.28 (9H, br s, ^{t}Bu), 1.59-1.75 (1H, m, pyrrolidine ring C3-H or pyrrolidine ring C4-H), 1.93-2.15 (2H, m, pyrrolidine ring C3-H and/or pyrrolidine ring C4-H), 2.02 (1.5H, s, Ac), 2.04 (1.5H, s, Ac), 2.28-2.48 (1H, m, pyrrolidine ring C3-H or pyrrolidine ring C4-H), 2.77 (1H, br dd, J=16.8, 7.0 Hz, C4-H), 2.99 (1H, br d, J=16.8 Hz, C4-H), 3.68 (2H, br s, C*H*2OBn), 3.83 (3H, s, ArO*Me*), 4.01 (1.5H, br

s, 1H of pyrrolidine ring C2-H or pyrrolidine ring C5-H and 0.5H of C3-H), 4.17-4.33 (1.5H, m, 1H of pyrrolidine ring C2-H or C5-H and 0.5H of C3-H), 4.55 (2H, br s, OC*H*2Ph or C*H*2OAc), 4.60 (2H, br s, OC*H*2Ph or C*H*2OAc), 4.81 (1H, br t, J=9.6 Hz, CO2C*H*2CCl3), 4.90 (0.5H, br d, J=9.6 Hz, CO2C*H*2CCl3), 4.97 (0.5H, br d, J=9.6 Hz, CO2C*H*2CCl3), 5.73 (1H, br d, J=9.6 Hz, C1-H), 6.70 (2H, br d, J=7.9 Hz, C5-H and C7-H), 7.18 (1H, t, J=7.9 Hz, C6-H), 7.25-7.39 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 702 [(M+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 700 [(M+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 698 (M$^+$, ^{35}Cl x 3), 629 [(M-CH2OAc+4)$^+$, ^{37}Cl x 2, ^{35}C], 627 [(M-CH2OAc+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 625 [(M-CH2OAc)$^+$, ^{35}Cl x 3], 352, 350, 348, 338, 336, 334, 290, 190, 91, 57.

b) Preparation of *ent*-**18**: The same treatments of *ent*-**17** (632 mg, 0.96 mmol) as described for the preparation of **18** from **17** gave *ent*-**18** (639 mg, 95%) as a colorless caramel. [α]D^{20} -31.6° (c 0.52, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **18**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 1-acetoxymethyl-3-[(2*R*,5*S*)-1-*tert*-butoxycarbonyl-5-hydroxymethylpyrrolidin-2-yl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (19) and Its Enantiomer (*ent*-19)

a) Preparation of **19**: A mixture of **18** (175 mg, 0.25 mmol) and 10% palladium on carbon (500 mg) in ethyl acetate (40 ml) was stirred for 15 min at room temperature under hydrogen atmosphere (1 atm). The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1) to give **19** (131 mg, 86%) as a colorless caramel. [α]D^{20} +46.7° (c 2.85, CHCl3). IR (neat): 3450, 2960, 2930, 2830, 1740, 1710, 1690, 1590, 1470, 1450, 1420, 1380, 1360, 1330, 1310, 1300, 1270, 1250, 1230, 1160, 1120, 1080, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.24 (3H, br s, ^{t}Bu), 1.25 (1.5H, br s, ^{t}Bu), 1.27 (4.5H, br s, ^{t}Bu), 1.70 (1H, br s, pyrrolidine ring C3-H or C4-H), 1.93 (1.5H, br s, pyrrolidine ring C3-H and/or pyrrolidine ring C4-H), 2.02 (3H, s, Ac), 2.02-2.14 (1.5H, m, pyrrolidine ring C3-H and/or pyrrolidine ring C4-H), 3.06 (2H, br s, C4-H2), 3.58 (1H, br s, C*H*2OH), 3.80 (1H, br s, C*H*2OH), 3.84 (3H, s, ArO*Me*), 4.06 (1.5H, br s, 1H of pyrrolidine ring C2-H or pyrrolidine ring C5-H and 0.5H of C3-H), 4.32 (1.5H, m, 1H of pyrrolidine ring C2-H or C5-H and 0.5H of C3-H), 4.48 (1H, br t, J=7.6 Hz, C*H*2OAc), 4.53-4.70 (1H, m, C*H*2OAc), 4.70-4.94 (2H, m, CO2C*H*2CCl3), 5.85 (1H, br d, J=6.8 Hz, C1-H), 6.73 (1H, d, J=7.9 Hz, C5-H or C7-H), 6.78 (1H, d, J=7.9 Hz, C5-H or C7-H), 7.22 (1H, t, J=7.9 Hz, C6-H). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 612 [(M+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 610 [(M+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 608 (M$^+$, ^{35}Cl x 3), 539 [(M-CH2OAc+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 537 [(M-CH2OAc+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 535 [(M-CH2OAc)$^+$, ^{35}Cl x 3], 483 [(M-CH2OAc-C4H8+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 481 [(M-CH2OAc-C4H8+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 479 [(M-CH2OAc-C4H8)$^+$, ^{35}Cl x 3], 352, 350, 348, 338, 336, 334, 287, 200, 173, 160, 144, 100, 57. HRMS calcd for C24H28Cl3N2O8 [(M-CH2OAc)$^+$, ^{35}Cl x 3]: 535.1166. Found: 533.1161.

b) Preparation of *ent*-**19**: The same treatments of *ent*-**18** (631 mg, 0.90 mmol) as described for the preparation of **19** from **18** gave *ent*-**19** (451 mg, 82%) as a colorless caramel. [α]D^{20} -50.4° (c 0.69, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **19**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 1-acetoxymethyl-3-[(2*R*,5*S*)-1-*tert*-butoxycarbonyl-5-formylpyrrolidin-2-yl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (20) and Its Enantiomer (*ent*-20)

a) Preparation of **20**: Dimethyl sulfoxide (0.242 ml, 3.4 mmol) in dry dichloromethane (2 ml) was added dropwise to a stirred solution of oxalyl chloride (0.149 ml, 1.7 mmol) in dry dichloromethane (10 ml) at -78°C under argon. After 10 min, a solution of **19** (112 mg, 0.18 mmol) in dry dichloromethane (4 ml) was added slowly, and stirring was continued for 15 min at -78°C. After addition of triethylamine (0.474 ml, 3.4 mmol), the mixture was gradually warmed up to -25°C and further stirred for 30 min. The resulting mixture was diluted with water (5 ml) and then extracted with ethyl acetate (80 ml). The extract was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1→2:1) to give **20** (106 mg, 95%) as a colorless caramel. [α]D^{20} +42.7° (c 0.94, CHCl3). IR (neat): 2970, 2930, 2810, 1730, 1710, 1590, 1470, 1450, 1410, 1380, 1360, 1320, 1250, 1170, 1190, 1030cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.32 (3H, br s, ^{t}Bu), 1.43 (6H, br s, ^{t}Bu), 1.83 (1H, br s, pyrrolidine ring C3-H or pyrrolidine ring C4-H), 2.02-2.30 (3H, m, pyrrolidine ring C3-H2 and/or pyrrolidine ring C4-H2), 2.03 (3H, s, Ac), 3.03 (1H, br s, C4-H), 3.22 (1H, br t, J=15.3 Hz, C4-H), 3.84 (3H, s, ArO*Me*), 4.22 (0.5H, br s, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.40 (2H, br s, C*H*2OAc), 4.55 (0.5H, br s, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.78 (1.5H, br s, 1H of CO2C*H*2CCl3 and 0.5H of pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.92 (1H, br s, CO2C*H*2CCl3), 5.87 (1H, br s, C1-H), 6.74 (1H, d, J=7.9 Hz, C5-H or C7-H), 6.79 (1H, br d, J=7.9 Hz, C5-H or C7-H), 7.24 (1H, t, J=7.9 Hz, C6-H), 9.54 (0.7H, br s, CHO), 9.65 (0.3H, br s, CHO). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 537 [(M-CH2OAc+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 535 [(M-CH2OAc+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 533 [(M-CH2OAc)$^+$, ^{35}Cl x 3], 481 [(M-CH2OAc-C4H8+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 479 [(M-CH2OAc-C4H8+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 477 [(M-CH2OAc-C4H8)$^+$, ^{35}Cl x 3], 412, 410, 408, 352, 350, 348, 338, 336, 334, 173, 160, 98, 57. HRMS calcd for C23H28Cl3N2O6 [(M-CH2OAc)$^+$, ^{35}Cl x 3]: 533.1011. Found: 533.0987.

b) Preparation of *ent*-**20**: The same treatments of *ent*-**19** (448 mg, 0.74 mmol) as described for the preparation of **20** from **19** gave *ent*-**20** (438 mg, 98%) as a colorless caramel. [α]D^{20} -45.0° (c 0.57, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **20**.

(5*R*,7*R*,8*S*,11*R*,11a*S*)-5-Acetoxymethyl-13-*tert*-butoxycarbonyl-7-cyano-4-methoxy-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline (23) and Its Enantiomer (*ent*-23)

a) Preparation of **23**: Zinc powder (565 mg, 8.7 mmol) was added to a stirred solution of **20** (65.8 mg, 0.11 mmol) in tetrahydrofuran-acetic acid-water (5:1:1) (30 ml) at room temperature under argon. After 30 min, the mixture was neutralized with saturated aqueous sodium hydrogen carbonate and diluted with ethyl acetate (120 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave (5*R*,7*R*,8*S*,11*R*,11a*S*)-5-acetoxymethyl-13-*tert*-butoxycarbonyl-7-hydroxy-4-methoxy-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline (**22**) (62.8 mg), which was dissolved in dry dichloromethane (7 ml). The dichloromethane solution was treated with trimethylsillyl cyanide (22.0 µl, 0.16mmol) and zinc chloride (16.2 mg, 0.12mmol) for 10 min at room temperature. The mixture was diluted with saturated aqueous sodium hydrogen carbonate (3 ml) and ethyl acetate (60 ml), and the organic layer was washed with brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1→ 2:1) to give **23** (27.7 mg, 58%, 2 steps) as a colorless caramel. $[\alpha]D^{20}$ +21.7° (c 0.62 , CHCl3). IR (neat): 2970, 2930, 2830, 2350, 1720, 1695, 1590, 1460, 1410, 1380, 1360, 1320, 1260, 1230, 1160, 1100, 1080, 1050, 1030 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.48 (9H, br s, ^{t}Bu), 1.63-1.78 (1H, m, C9-H or C10-H), 1.84 (1H, br d, J=10.8 Hz, C9-H or C10-H), 1.94 (2H, br td, J=10.8, 3.5 Hz, C9-H2 and/or C10-H2), 2.04 (3H, s, Ac), 2.51-2.64 (2H, m, C12-H2), 3.00 (1H, br dd, J=8.8, 4.6Hz, C11a-H), 3.82 (3H, s, ArO*Me*), 3.96 (1H, dd, J=11.3, 6.6 Hz, C*H*2OAc), 3.98 (1H, br s, C7-H), 4.21 (1H, br s, C8-H or C11-H), 4.35-4.43 (2H, m, C5-H and C*H*2OAc), 4.50 (1H, br s, C8-H or C11-H), 6.71 (1H, br d, J=7.9 Hz, C1-H or C3-H), 6.74 (1H, d, J=7.9 Hz, C1-H or C3-H), 7.17 (1H, t, J=7.9 Hz, C2-H). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 368 [(M-CH2OAc)$^+$], 312 [(M-CH2OAc-C4H8)$^+$], 268 [(M-CH2OAc-Boc)$^+$], 98, 57. CIMS (isobutane) m/z: 442 [(M+H)$^+$]. HRMS calcd for C21H26N3O3 [(M-CH2OAc)$^+$]: 368.1972. Found: 368.1962.

b) Preparation of *ent*-**23**: The same treatments of *ent*-**20** (431 mg, 0.71 mmol) as described for the preparation of **23** from **20** gave *ent*-**23** (198 mg, 63%, 2 steps) as a colorless caramel *via ent*-**22**. $[\alpha]D^{20}$ -21.4° (c 0.51 , CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **23**.

(5*R*,7*R*,8*S*,11*R*,11a*S*)-5-Acetoxymethyl-7-cyano-4-methoxy-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline (24) and Its Enantiomer (*ent*-24)

a) Preparation of **24**: Trifluoroacetic acid (85.0 µl, 1.1 mmol) was added dropwise to a stirred solution of **23** (48.5 mg, 0.11 mmol) in dichloromethane (10 ml) at room temperature under argon. After 5 h, the mixture was made alkaline with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (50 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (ethyl acetate) to give **24** (34.1 mg, 91%) as a colorless caramel. IR (neat): 3300, 2950, 2840, 2380, 2340, 1740, 1659, 1595, 1470, 1460, 1440, 1420, 1380, 1320, 1260, 1230, 1200, 1060, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.61-1.71 (1H, m, C9-H or C10-H), 1.76-1.95 (3H, m, C9-H2 or C10-H2), 2.04 (3H, s, Ac), 2.46 (1H, dd, J=14.7, 2.6 Hz, C12-H), 2.57 (1H, dd, J=14.7, 11.4 Hz, C12-H), 2.86 (1H, dt, J=9.4, 1.8 Hz, C11a-H), 3.32 (1H, d, J=6.4 Hz, C8-H or C11-H), 3.67 (1H, dd, J=6.4, 2.5 Hz, C8-H or C11-H), 3.82 (3H, s, ArO*Me*), 3.85 (1H, s, NH), 3.96 (1H, s, C7-H), 3.97 (1H, dd, J=10.8, 5.8 Hz, C*H*2OAc), 4.32 (1H, dd, J=10.8, 2.9 Hz, C*H*2OAc), 4.40 (1H, dd, J=5.8, 2.9 Hz, C5-H), 6.71 (1H, d, J=7.9 Hz, C3-H), 6.73 (1H, d, J=7.9 Hz, C1-H), 7.16 (1H, t, J=7.9 Hz, C2-H). EIMS m/z: 341 (M$^+$), 315 [(M-CN)$^+$], 268 [(M-CH2OAc)$^+$], 199, 149, 68, 43. HRMS calcd for C19H23N3O3 (M$^+$): 341.1738. Found: 341.1742.

b) Preparation of *ent*-**24**: The same treatments of *ent*-**23** (181 mg, 0.41 mmol) as described for the preparation of **24** from **23** gave *ent*-**24** (122 mg, 87%) as a colorless caramel. The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **23**.

(5*R*,7*R*,8*S*,11*R*,11a*S*)-5-Acetoxymethyl-7-cyano-4-methoxy-13-methyl-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline (25) and Its Enantiomer (*ent*-25)

a) Preparation of **25**: Sodium cyanoborohydride (4.35 mg, 69 µmol) was added to a stirred solution of **24** (33.8 mg, 99 µmol) in methanol (3 ml) containing 37% aqueous formaldehyde (8.23µl, 0.10 mmol) at room temperature. After 1 h, the mixture was diluted with ethyl acetate (50 ml), and the organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1) to give **25** (25.3 mg, 72%) as a colorless caramel. Recrystallization from hexane-ethyl acetate gave an analytical sample of **25** as colorless prisms, mp 61-62.5 °C and $[\alpha]D^{20}$ +16.0° (c 0.20, CHCl3). IR (neat): 2940, 2900, 2840, 2350, 1730, 1590, 1470, 1440, 1300, 1260, 1230, 1150, 1130, 1100, 1070, 1050 cm^{-1}. ^{1}H-NMR (400 MHz, C6D6) δ: 1.45-1.57 (4H, m, C9-H2 and C10-H2), 1.57 (3H, s, Ac), 1.97 (3H, s, NMe), 2.01 (1H, dd, J=14.3, 2.1 Hz, C12-Heq), 2.35 (1H, dd, J=14.3, 11.8 Hz, C12-Hax), 2.47 (1H, dt, J=6.3, 1.0 Hz, C11-H), 2.76 (1H, ddd, J=5.4, 3.0, 2.1 Hz, C8-H), 3.03 (1H, dt, J=11.8, 2.1 Hz, C11a-H), 3.12 (3H, s, ArO*Me*), 3.54 (1H, d, J=3.0 Hz, C7-H), 4.12 (1H, dd, J=10.8, 4.7 Hz, C*H*2OAc), 4.51 (1H, dd, J=10.8, 2.9 Hz, C*H*2OAc), 4.63 (1H, dd, J=4.7, 2.9 Hz, C5-H), 6.32 (1H, d, J=7.9 Hz, C3-H), 6.58 (1H, d, J=7.9 Hz, C1-H), 7.00 (1H, t, J=7.9 Hz, C2-H). EIMS m/z: 355 (M$^+$), 329 [(M-CN)$^+$], 296 [(M-OAc)$^+$], 282 [(M-CH2OAc)$^+$], 201, 122, 82, 43. HRMS calcd for C20H25N3O3 (M$^+$): 355.1894. Found: 355.1880.

b) Preparation of *ent*-**25**: The same treatments of *ent*-**24** (116 mg, 0.34 mmol) as described for the preparation of **25** from **24** gave *ent*-**25** (83.4 mg, 69%) as a colorless caramel. Recrystallization from hexane-ethyl acetate gave an analytical sample of **25** as

colorless prisms, mp 61-62 °C and $[\alpha]D^{20}$ -13.8° (c 0.25, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **25**.

(5*R*,7*R*,8*S*,11*R*,11a*S*)-7-Cyano-5-hydroxymethyl-4-methoxy-13-methyl-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline (10-decarboxy-DX-52-1) (26) and Its Enantiomer (*ent*-26)

a) Preparation of **26**: 1M Sodium hydroxide (0.70 ml, 0.70 mmol) was added dropwise to a stirred solution of **25** (33.5 mg, 94 μmol) in methanol (4 ml) at room temperature. After 2 h, the mixture was diluted with ethyl acetate (50 ml), and the organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1) to give **26** (24.5 mg, 83%) as a colorless caramel. $[\alpha]D^{20}$ +27.3° (c 0.13, CHCl3). IR (neat): 3400, 2940, 2870, 1590, 1470, 1440, 1380, 1370, 1290, 1260, 1150, 1120, 1070, 1040, 1020 cm^{-1}. ^{1}H-NMR (400 MHz, C6D6) δ: 1.17-1.35 (2H, m, C9-H2), 1.37-1.52 (2H, m, C10-H2), 1.79 (1H, br s, OH), 1.94 (3H, s, NMe), 1.96 (1H, dd, J=15.1, 2.6 Hz, C12-Heq), 2.34 (1H, dd, J=15.1, 12.6 Hz, C12-Hax), 2.43 (1H, dt, J=6.0, 1.2 Hz, C11-H), 2.71 (1H, ddd, J=5.6, 2.9, 1.6 Hz, C8-H), 3.02 (1H, dt, J=11.8, 2.0 Hz, C11a-H), 3.13 (3H, s, ArO*Me*), 3.41 (1H, d, J=3.0 Hz, C7-H), 3.69 (1H, br d, J=11.5 Hz, C*H*2OH), 3.72 (1H, br d, J=11.5 Hz, C*H*2OH), 4.49 (1H, t, J=3.5, Hz, C5-H), 6.15 (1H, d, J=8.1 Hz, C3-H), 6.58 (1H, d, J=8.1 Hz, C1-H), 7.01 (1H, t, J=8.1 Hz, C2-H). EIMS m/z: 313 (M^+), 282 [(M-CH2OH)$^+$], 201, 122, 82, 42. HRMS calcd for C18H23N3O2 (M^+): 313.1788. Found: 313.1784.

b) Preparation of *ent*-**26**: The same treatments of *ent*-**25** (73.2 mg, 0.21 mmol) as described for the preparation of **26** from **25** gave *ent*-**26** (56.1 mg, 87%) as a colorless caramel. $[\alpha]D^{20}$ -25.9° (c 0.33, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **26**.

10-Decarboxyquinocarcin (2) and Its Enantiomer (*ent*-2)

a) Preparation of **2**: Silver nitrate (11.8 mg, 70 μmol) was added to a stirred solution of **26** (19.8 mg, 63 μmol) in methanol (2 ml) at room temperature under argon. After 1 h, the mixture was concentrated *in vacuo* to give a residue, which was purified by column chromatography (ethyl acetate-methanol, 3:1) to give **2** (15.0 mg, 83%) as a colorless amorphous powder. $[\alpha]D^{20}$ -13.0° (c 0.23, MeOH). IR (KBr): 2925, 2850, 1580, 1470, 1260, 1180, 1140, 1090, 1060, 1030 cm^{-1}. ^{1}H-NMR (400 MHz, C6D6) δ: 2.02-2.23 (2H, m, C9-H2), 2.27-2.42 (2H, m, C10-H2), 2.53 (1H, dd, J=12.3, 2.6 Hz, C12-Heq), 2.34 (1H, dd, J=15.1, 12.6 Hz, C12-Hax), 2.43 (1H, dt, J=6.0, 1.2 Hz, C11-H), 2.71 (1H, ddd, J=5.6, 2.9, 1.6 Hz, C8-H), 3.02 (1H, dt, J=12.3, 11.1 Hz, C11a-H), 2.81 (3H, s, NMe), 3.35-3.37 (1H, m, C8-H), 3.39 (1H, dd, J=10.7, 7.2 Hz, C6-H), 3.69 (1H, dd, J=10.7, 2.8 Hz, C6-H), 3.78 (1H, br d, J=6.3 Hz, C11-H), 3.81 (3H, s, ArO*Me*), 4.03-4.09 (1H, m, 11a-H), 4.54 (1H, dd, J=7.3, 2.8 Hz, C5-H), 4.55 (1H, d, J=3.1 Hz, C7-H), 6.74 (1H, d, J=7.8 Hz, C3-H), 6.84 (1H, d, J=7.8 Hz, C1-H), 7.16 (1H, t, J=7.8 Hz, C2-H). EIMS m/z: 286 (M^+), 257[(M-CHO)$^+$], 256 [(M-CH2O)$^+$], 230, 204, 149, 69. HRMS calcd for C17H22N2O2 (M^+): 286.1679. Found: 286.1652.

b) Preparation of *ent*-**2**: The same treatments of *ent*-**26** (51.2 mg, 0.16 mmol) as described for the preparation of **2** from **26** gave *ent*-**2** (37.4 mg, 80%) as a colorless caramel. $[\alpha]D^{20}$ +12.0° (c 0.43, MeOH). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **2**.

(1*R*,5*R*,10b*R*)-5-[(2*R*,5*S*)-1-Benzyl-5-benzyloxymethylpyrrolidin-2-yl]-1-hydroxymethyl-10-methoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (27)

Methyl chloroformate (24.1 μl, 0.31 mmol) was added dropwise to a stirred solution of **15** (39.0 mg, 62 μmol) in chloroform (1.5 ml) containing triethylamine (52.0 μl, 0.37 mmol) at room temperature. After 3 h, the mixture was concentrated *in vacuo* to give a residue, which was dissolved in methanol (1.8 ml). 37% Aqueous hydrochloric acid (0.30 ml, 3.1 mmol) was added to the methanolic solution at 0 °C, and the mixture was stirred for 3 h at room temperature. The mixture was neutralized with 10% aqueous sodium hydroxide and diluted with ethyl acetate (20 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was dissolved in methanol (2 ml). The methanolic solution was treated with sodium hydroxide (34.9 mg, 0.62 mmol) for 3 h at room temperature. The mixture was neutrized with 3% aqueous hydrochloric acid and extracted with ethyl acetate (20 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was dissolved in methanol-water (10:1) (2 ml). The methanolic solution was treated with sodium periodate (66.7 mg, 0.31 mmol) for 13 h at room temperature. Sodium borohydride (11.8 mg, 0.31 mmol) was added, and stirring was continued for 30 min at room temperature. The reaction was quenched with 3% aqueous hydrochloric acid (0.2 ml), and the mixture was extracted with ethyl acetate (20 ml). The extract was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was dissolved in dichloromethane (1.8 ml). Bromotrimethylsilane (40.9 μl, 0.31 mmol) was added to the above dichloromethane solution, and stirring was continued for 1 h at room temperature. The mixture was concentrated *in vacuo* to give a residue, which was dissolved in dichloromethane (1.5 ml) containing saturated aqueous sodium hydrogen carbonate (0.5 ml). The mixture was treated with benzyl bromide (0.149 ml, 1.2 mmol) for 15 h at room temperature. The mixture was diluted with ethyl acetate (20 ml), and the organic layer was washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na2SO4. Concentrration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1→ 1:1) to give **27** (20.1 mg, 61%, 7 steps) as a colorless caranel. IR (neat): 3430, 3030, 2930, 2850, 1750, 1600, 1580, 1490, 1470, 1450, 1440, 1410, 1380, 1360, 1335, 1300, 1260, 1230, 1210, 1170, 1070, 1045 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.62-1.70 (1H, m, pyrrolidine ring C4-H), 1.91-2.02 (2H, m, pyrrolidine ring C3-H and pyrrolidine ring C4-H), 2.02-2.14 (1H, m, pyrrolidine ring C3-H), 2.62 (1H, dd, J=16.1 Hz, C6-

Hax), 2.86 (1H, dd, J=16.1, 2.8 Hz, C6-Heq), 2.99 (1H, ddd, J=11.6, 10.2, 2.8 Hz, C5-H), 3.05-3.20 (3H, m, pyrrolidine ring C5-H, C*H*2OH, and C*H*2OBn), 3.28 (1H, dd, J=12.2, 5.6 Hz, C*H*2OH), 3.31 (1H, dd, J=8.4, 4.1 Hz, C*H*2OBn), 3.80 (3H, s, C10-OMe), 3.86 (1H, d, J=13.5 Hz, NC*H*2Bn), 3.94 (1H, d, J=13.5 Hz, NC*H*2Bn), 4.10 (1H, ddd, J=10.2, 7.4, 3.4 Hz, pyrrolidine ring C2-H), 4.33 (1H, d, J=12.1 Hz, OC*H*2Ph), 4.37 (1H, d, J=12.1 Hz, OC*H*2Ph), 5.03 (1H, ddd, J=8.4, 5.7, 2.6 Hz, C1-H), 5.25 (1H, d=8.4 Hz, C10b-H), 6.62 (1H, d, J=8.2 Hz, C7-H or C9-H), 6.72 (1H, d, J=8.2 Hz, C7-H or C9-H), 7.15-7.38 (11H, m, C8-H and Ph x 2). EIMS m/z: 528 (M^+), 511 [(M-OH)$^+$]. HRMS calcd for C32H36N2O5 (M^+): 528.2769. Found: 528.2766.

(2*R*,3*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-[[2-[(4*S*,5*R*)-5-methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbonyl]-3-methoxyphenyl]-1-hydroxyethyl]-3-methoxymethoxymethylpyrrolidine (31) and Its Enantiomer (*ent*-31)

a) Preparation of **31**: Coupling reaction of **11** (2.78 g, 8.5 mmol) with (2*R*,3*R*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-2-formyl-3-methoxymethoxymethylpyrrolidine (**5**)[2c] (11.9 g, 30 mmol) under the same conditions as described for the preparation of **12** gave **31** (pale yellow caramel, 3.14 g, 51%) as a mixture of two diastereomers along with **11** (1.25 g, 45% recovery) and **5** (5.11 g, 43% recovery) after purification by column chromatography (hexane-ethyl acetate, 10:1→ 1:1). The adduct (**31**) was directly used for the next step without further separation. IR (neat): 3420, 2970, 2930, 2880, 1740, 1690, 1580, 1465, 1450, 1380, 1360, 1335, 1300, 1255, 1210, 1165, 1150, 1105 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3) δ: 1.42 (15H, br s, ^{t}Bu and acetonide Me x 2), 2.02-2.22 (2H, m, pyrrolidine ring C4-H2), 2.70-3.06 (1H, m, pyrrolidine ring C3-H), 3.17 (3H, s, OCH2O*Me*), 3.36 (3H, s, OCH2O*Me*), 3.27-4.35 (11H, m, C*H*2OBn, C*H*2OMOM x 2, ArC*H*2CH(O*H*), pyrrolidine ring C2-H, and pyrrolidine ring C5-H), 3.87 (3H, s, ArO*Me*), 4.38-4.95 (3H, m, COC*H*(O-)C*H*(O-)CH2OMOM and C*H*(OH)), 4.56 (2H, br s, OC*H*2Ph), 4.60 (2H, br s, OC*H*2OMe), 4.63 (2H, br s, OC*H*2OMe), 6.62-6.95 (2H, m, aromatic protons), 7.10-7.42 (6H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening was observed for this ^{1}H-NMR spectrum. EIMS m/z: 700 [(M-OH)$^+$], 699 [(M-H2O)$^+$], 641 [(M-H2O-Me2O)$^+$], 585, 524, 480, 435, 264, 202, 161, 91, 57, 45. CIMS (isobutane) m/z: 718 [(M+H)$^+$]. HRMS calcd for C38H54NO11 [(M-H2O)$^+$]: 699.3615. Found: 699.3641.

b) Preparation of *ent*-**31**: The same treatments of *ent*-**11** (3.12 g, 9.6 mmol) and (2*S*,3*S*,5*R*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-2-formyl-3-methoxymethoxymethylpyrrolidine (*ent*-**5**)[2c] (13.2 g, 34 mmol) as described for the preparation of **31** from **11** and **5** gave *ent*-**31** (pale yellow caramel, 3.66 g, 53%) as a mixture of two diastereomers along with *ent*-**11** (1.34 g, 43% recovery) and *ent*-**5** (5.41 g, 41% recovery). The adduct (*ent*-**31**) was directly used for the next step without further separation. The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **31**.

(2*R*,3*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-2-[[2-[(4*S*,5*R*)-5-methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbonyl]-3-methoxyphenyl]acetyl]-3-methoxymethoxymethylpyrrolidine (32) and Its Enantiomer (*ent*-32)

a) Preparation of **32**: Treatments of **31** (3.02 g, 4.2 mmol) in a similar manner to that described for the preparation of **13** from **12** gave **32** (1.27 mg, 42%) as a colorless caramel after purification by column chromatography (hexane-ethyl acetate, 2:3). [α]D^{20} -12.1° (c 0.83, CHCl3). IR (neat): 2950, 2930, 2880, 1730, 1690, 1585, 1470, 1450, 1380, 1365, 1300, 1260, 1210, 1170, 1150, 1110, 1070, 1040 cm^{-1}.^{1}H-NMR (90 MHz, CDCl3) δ: 1.44 (15H, br s, ^{t}Bu and acetonide Me x 2), 1.85-2.33 (2H, m, pyrrolidine ring C4-H2), 2.65-3.05 (1H, m, pyrrolidine ring C3-H), 3.33-4.33 (10H, m, C*H*2OBn, C*H*2OMOM x 2, ArC*H*2CO, pyrrolidine ring C2-H, and pyrrolidine ring C5-H), 3.35 (3H, s, OCH2O*Me*), 3.38 (3H, s, OCH2O*Me*), 3.85 (3H, s, ArO*Me*), 4.35-4.90 (2H, m, COC*H*(O-)C*H*(O-)CH2OMOM), 4.55 (2H, br s, OC*H*2Ph), 4.64 (4H, br s, OC*H*2OMe x 2), 6.62-6.95 (2H, m, aromatic protons), 7.20-7.45 (6H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening was observed for this ^{1}H-NMR spectrum. EIMS m/z: 700 [(M-Me)$^+$], 684 [(M-OMe)$^+$], 628 [(M-OMe-C4H8)$^+$], 594, 494, 440, 364, 264, 202, 148, 91, 57, 45. CIMS (isobutane) m/z: 716 [(M+H)$^+$]. HRMS calcd for C37H50NO12 [(M-Me)$^+$]: 700.3329. Found: 700.3330.

b) Preparation of *ent*-**32**: The same treatments of *ent*-**31** (3.52 g, 4.9 mmol) as described for the preparation of **32** from **31** gave *ent*-**32** (1.44 g, 41%) as a pale yellow caramel. [α]D^{20} +13.0° (c 1.11, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **32**.

3-[(2*R*,3*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-3-methoxymethoxymethylpyrrolidin-2-yl]-1-[(4*R*,5*R*)-5-methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbonyl]-8-methoxyisoquinoline (33) and Its Enantiomer (*ent*-33)

a) Preparation of **33**: Treatments of **32** (1.23 g, 1.7 mmol) in a similar manner to that described for the preparation of **14** from **13** gave **33** (805 mg, 67%) as a colorless caramel after purification by column chromatography (hexane-ethyl acetate, 2:3). [α]D^{20} +23.1° (c 0.78, CHCl3). IR (neat): 2975, 2930, 2880, 1690, 1620, 1560, 1455, 1380, 1365, 1310, 1260, 1210, 1170, 1150, 1110, 1070, 1040, 1000 cm^{-1}.^{1}H-NMR (90 MHz, CDCl3) δ: 1.28 (3H, br s, ^{t}Bu or acetonide Me), 1.46 (6H, br s, ^{t}Bu or acetonide Me), 1.55 (3H, br s, ^{t}Bu or acetonide Me), 1.75 (3H, br s, ^{t}Bu or acetonide Me), 1.90-2.30 (2H, m, pyrrolidine ring C4-H2), 2.65-3.05 (1H, m, pyrrolidine ring C3-H), 3.05-4.18 (7H, m, C*H*2OBn, C*H*2OMOM x 2, and pyrrolidine ring C5-H), 3.12 (3H, s, OCH2O*Me*), 3.36 (3H, s, OCH2O*Me*), 4.02 (3H, s, ArO*Me*), 4.10-4.95 (2H, m, pyrrolidine ring C2-H and CH(O-)C*H*(O-)CH2OMOM), 4.25 (2H, br s, OC*H*2Ph), 4.60 (2H, s, OC*H*2OMe), 4.65 (2H, s, OC*H*2OMe), 6.50 (1H, d, J=8.2 Hz, C*H*(O-)CH(O-)CH2OMOM), 6.89 (1H, br d, J=7.9 Hz, C5-H or C7-H), 7.10-7.62 (8H, m, aromatic protons and C4-H). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were

observed for this ^{1}H-NMR spectrum. EIMS m/z: 696 (M^+), 681 [(M-Me)$^+$], 665 [(M-OMe)$^+$], 605 [(M-CH2Ph)$^+$], 575 [(M-CH2OCH2Ph)$^+$], 552, 475, 451, 355, 264, 202, 91, 57, 45. HRMS calcd for C38H52N2O10 (M^+): 696.3619. Found: 696.3619.

b) Preparation of *ent*-**33**: The same treatments of *ent*-**32** (1.42 g, 2.0 mmol) as described for the preparation of **33** from **32** gave *ent*-**33** (843 mg, 61%) as a colorless caramel. [α]D^{20} -24.7° (c 1.38, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **33**.

(1*R*,3*R*)-3-[(2*R*,3*R*,5*S*)-5-Benzyloxymethyl-1-*tert*-butoxycarbonyl-3-methoxymethoxymethylpyrrolidin-2-yl]-1-[(4*R*,5*R*)-5-methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-8-methoxy-1,2,3,4-tetrahydroisoquinoline (34) and Its Enantiomer (*ent*-34)

a) Preparation of **34**: Treatments of **33** (789 mg, 1.1 mmol) in a similar manner to that described for the preparation of **15** from **14** gave **34** (738 mg, 93%) as a colorless caramel after purification by column chromatography (hexane-ethyl acetate, 1:3). IR (neat): 3350, 2920, 2850, 1690, 1580, 1470, 1450, 1380, 1370, 1330, 1300, 1250, 1210, 1170, 1150, 1100, 1070, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.38 (3H, br s, ^{t}Bu or acetonide Me), 1.42 (9H, br s, ^{t}Bu and/or acetonide Me), 1.53 (3H, br s, ^{t}Bu and/or acetonide Me), 1.92-2.16 (2H, m, pyrrolidine ring C4-H2), 2.28-2.38 (1H, m, pyrrolidine ring C3-H), 2.47 (1H, br s, NH), 2.66 (2H, br s, C4-H2), 2.90 (1H, br s, C3-H), 3.18 (3H, s, OCH2O*Me*), 3.33 (1H, dd, J=10.5, 2.4 Hz, C*H*2OMOM), 3.35-3.44 (2H, m, C*H*2OMOM), 3.37 (3H, s, OCH2O*Me*), 3.67 (1H, dd, J=10.5, 3.2 Hz, C*H*2OMOM), 3.72-3.78 (1.5H, m, C*H*2OBn and pyrrolidine ring C2-H or pyrrolidine ring C5-H), 3.79 (3H, s, ArO*Me*), 3.88 (0.5H, br s, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 3.93 (1H, br dd, J=10.7, 9.31 Hz, C*H*2OBn), 4.00 (0.5H, br s, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.07 (0.5H, br t, J=6.8 Hz, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.10-4.18 (1H, m, CH(O-)C*H*(O-)CH2OMOM), 4.46 (1H, d, J=6.7 Hz, OC*H*2Ph), 4.52 (1H, d, J=6.7 Hz, OC*H*2Ph), 4.54 (1H, d, J=4.8 Hz, C*H*2OMOM), 4.55 (1H, d, J=4.8 Hz, C*H*2OMOM), 4.57-4.66 (1H, m, C*H*(O-)CH(O-)CH2OMOM), 4.61 (1H, d, J=6.5 Hz, C*H*2OMOM), 4.63 (1H, d, J=6.4 Hz, C*H*2OMOM), 5.16 (1H, br s, C1-H), 6.64 (1H, br d, J=7.9 Hz, C5-H or C7-H), 6.68 (1H, d, J=7.9 Hz, C5-H or C7-H), 7.10 (1H, t, J=7.9 Hz, C6-H), 7.28-7.34 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 701 [(M+1)$^+$], 525 [(M-CH(OCMe2O)CHCH2OMOM)$^+$], 469 [(M-CH(OCMe2O)CHCH2OMOM-C4H8)$^+$], 425 [(M-CH(OCMe2O)CHCH2OMOM-Boc)$^+$], 336, 264, 202, 160, 91, 57. HRMS calcd for C30H41N2O8 [(M-CH(OCMe2O)CHCH2-OMOM)$^+$]: 525.2961. Found: 525.2948.

b) Preparation of *ent*-**34**: The same treatments of *ent*-**33** (835 mg, 1.2 mmol) as described for the preparation of **34** from **33** gave *ent*-**34** (756 mg, 91%) as a colorless caramel. The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **34**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 3-[(2*R*,3*R*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-3-methoxymethoxymethylpyrrolidin-2-yl]-1-[(4*R*,5*R*)-5-methoxymethoxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (35) and Its Enantiomer (*ent*-35)

a) Preparation of **35**: Treatments of **34** (735 mg, 1.0 mmol) in a similar manner to that described for the preparation of **16** from **15** gave **35** (781 mg, 85%) as a colorless caramel after purification by column chromatography (hexane-ethyl acetate, 2:1). [α]D^{20} -21.2°(c 1.25, CHCl3). IR (neat): 2970, 2930, 2880, 1710, 1685, 1590, 1470, 1450, 1380, 1330, 1275, 1210, 1165, 1150, 1105, 1160, 1705, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.23 (6H, br s, ^{t}Bu or/and acetonide Me), 1.42 (9H, br s, ^{t}Bu or/and acetonide Me), 2.01-2.10 (1H, m, pyrrolidine ring C4-H), 2.11-2.22 (1H, m, pyrrolidine ring C4-H), 2.58 (1H, br s, pyrrolidine ring C3-H), 2.86 (1H, br s, C4-H), 3.05 (1H, br t, J=10.6 Hz, C4-H), 3.25-3.38 (1H, m, C3-H), 3.38-3.44 (2H, m C*H*2OMOM), 3.36 (3H, s, OCH2O*Me*), 3.39 (3H, s, OCH2O*Me*), 3.59-3.78 (1H, m, C*H*2OBn or C*H*2OMOM), 3.80 (3H, s, ArO*Me*), 3.82-3.92 (1H, m, C*H*2OBn or C*H*2OMOM), 3.97-4.33 (5H, m, C*H*2OBn or C*H*2OMOM, pyrrolidine ring C2-H, pyrrolidine ring C5-H, and CH(O-)C*H*(O-)CH2OMOM), 4.38-4.69 (2H, m, C*H*(O-)CH(O-)CH2OMOM and NCO2C*H*2CCl3), 4.56 (2H, br s, OC*H*2Ph), 4.61 (2H, s, OC*H*2OMe), 4.71 (1H, d, J=6.4 Hz, OC*H*2OMe), 4.75 (1H, d, J=6.4 Hz, OC*H*2OMe), 4.90 (1H, d, J=11.9 Hz, NCO2C*H*2CCl3), 5.94 (1H, br s, C1-H), 6.65 (1H, br d, J=7.9 Hz, C5-H or C7-H), 6.72 (1H, br d, J=7.9 Hz, C5-H or C7-H), 7.15 (1H, t, J=7.9 Hz, C6-H), 7.22-7.35 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 863 [(M-Me+4)$^+$, ^{37}Cl x 2,^{35}Cl], 861 [(M-Me+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 859 [(M-Me)$^+$, ^{35}Cl x 3], 703 [(M-CH(OCMe2O)CHCH2OMOM+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 701 [(M-CH(OCMe2O)CHCH2O-MOM+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 699 [(M-CH(OCMe2O)CHCH2OMOM)$^+$, ^{35}Cl x 3], 647, 645, 643, 603, 601, 599, 481, 479, 477, 451, 364, 338, 336, 334, 264, 202, 160, 91, 57, 45. CIMS (isobutane) m/z: 879 [(M+H+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 877 ((M+H+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 875 [(M+H)$^+$, ^{35}Cl x 3]. HRMS calcd for C33H42Cl3N2O8 [(M-CH(OCMe2O)-CHCH2OMOM)$^+$]: 699.2004. Found: 699.1992.

b) Preparation of *ent*-**35**: The same treatments of *ent*-**34** (750 mg, 1.1 mmol) as described for the preparation of **35** from **34** gave *ent*-**35** (824 mg, 88%) as a colorless caramel. [α]D^{20} +22.6°(c 1.01, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **35**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 3-[(2*R*,3*R*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-3-methoxymethoxymethylpyrrolidin-2-yl]-1-[(1*R*,2*R*)-1,2-dihydroxy-3-methoxymethoxypropyl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (36) and Its Enantiomer (*ent*-36)

a) Preparation of **36**: Ferric chloride adsorbed on silica gel[12] (769 mg, 0.30 mmol) was added to a stirred solution of **35** (795 mg, 0.90 mmol) in chloroform (70 ml) at room temperature. After 15 h, the mixture was diluted with ethyl acetate (270 ml) and

filtered. The filtrate was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:2) to give **36** (652 mg, 86%) as a colorless caramel. $[\alpha]D^{20}$ +5.7°(c 1.01, CHCl3). IR (neat): 3450, 2930, 2880, 1710, 1695, 1595, 1470, 1470, 1450, 1385, 1370, 1335, 1290, 1260, 1210, 1170, 1150, 1110, 1080, 1045 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.41 (9H, s, ^{t}Bu), 2.14 (1H, br s, pyrrolidine ring C4-H), 2.18-2.27 (1H, m, pyrrolidine ring C4-H), 2.58 (1H, br s, pyrrolidine ring C3-H), 2.86 (1H, br s, C4-H), 3.24-3.62 (6H, m, C4-H, C3-H, C*H*2OBn, and C*H*2OMOM), 3.35 (3H, s, OCH2O*Me*), 3.36 (3H, s, OCH2O*Me*), 3.63-3.78 (1H, m, C*H*2OMOM), 3.81-4.00 (2H, m, pyrrolidine ring C2-H or pyrrolidine ring C5-H and CH(OH)C*H*(OH)CH2OMOM), 3.86 (3H, s, ArO*Me*), 4.08-4.22 (2H, m, pyrrolidine ring C2-H or pyrrolidine ring C5-H and C*H*(OH)CH(OH)CH2OMOM), 4.51 (1H, br d, J=12.2 Hz, NCO2C*H*2CCl3), 4.54 (1H, d, J=12.0 Hz, C*H*2OBn or C*H*2OMOM), 4.57 (1H, d, J=12.0 Hz, C*H*2OBn or C*H*2OMOM), 4.59 (1H, d. J=8.7 Hz, C*H*2OBn or C*H*2OMOM), 4.62 (1H, d. J=8.7 Hz, C*H*2OBn or C*H*2OMOM), 4.66 (2H, s, OC*H*2OMe), 4.92 (1H, br d, J=12.2 Hz, NCO2C*H*2CCl3), 5.31 (1H, br s, OH), 6.10 (1H, br d, J=2.6 Hz, C1-H), 6.78 (2H, br d, J=8.2 Hz, C5-H and C7-H), 7.20 (1H, t, J=8.1 Hz, C6-H), 7.24-7.36 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 703 [(M-CH(OH)CH(OH)CH2OMOM+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 701 [(M-CH(OH)CH(OH)CH2OMOM+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 699 [(M-CH(OH)CH(OH)CH2OMOM)$^+$, ^{35}Cl x 3], 645, 643, 641, 603, 601, 599, 451, 364, 264, 202, 160, 91, 57, 45, 31. CIMS (isobutane) m/z: 839 [(M+H+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 837 ((M+H+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 835 [(M+H)$^+$, ^{35}Cl x 3]. HRMS calcd for C33H42Cl3N2O8 [M-CH(OH)CH(OH)CHCH2O-MOM)$^+$]: 699.2003. Found: 699.1978.

b) Preparation of *ent*-**36**: The same treatments of *ent*-**35** (815 mg, 0.93 mmol) as described for the preparation of **36** from **35** gave *ent*-**36** (684 mg, 88%) as a colorless caramel. $[\alpha]D^{20}$ -6.5°(c 1.01, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **36**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 3-[(2*R*,3*R*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-3-methoxymethoxymethylpyrrolidin-2-yl]-1-hydroxymethyl-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (37) and Its Enantiomer (*ent*-37)

a) Preparation of **37**: Sodium periodate (1.66 g, 7.7 mmol) was added to a stirred solution of **36** (645 mg, 0.77 mmol) in methanol-water (10:1) (100 ml) at room temperature. After 12 h, sodium borohydride (293 mg, 7.7 mmol) was added in small portions, and stirring was continued for 30 min at room temperature. The reaction was quenched with 3% aqueous hydrochloric acid (10 ml), and the mixture was diluted with ethyl acetate (200 ml). The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate, saturated aqueous thiosulfate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1) to give **37** (472 mg, 84%) as a colorless caramel. $[\alpha]D^{20}$ -5.1° (c 0.73, CHCl3). IR (neat): 3400, 2945, 2930, 1710, 1675, 1595, 1475, 1455, 1410, 1395, 1365, 1340, 1310, 1270, 1255, 1235, 1215, 1165, 1150, 1130, 1090, 1045 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.41 (9H, s, ^{t}Bu), 2.11 (2H, br s, pyrrolidine ring C4-H2), 2.50 (1H, br s, pyrrolidine ring C3-H), 2.83 (1H, br dd, J=15.8, 10.6 Hz, C4-H), 2.99 (1H, br dd, J=15.8, 8.1 Hz, C4-H), 3.35 (3H, s, OCH2O*Me*), 3.33-3.44 (1H, m, C*H*2OBn), 3.51-3.61 (1H, m, C*H*2OBn), 3.73 (1H, br t, J=9.0 Hz, C*H*2OH), 3.79 (3H, s, ArO*Me*), 3.85-4.06 (3H, m, C*H*2OMOM and C*H*2OH), 4.21 (1H, br s, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.42-4.54 (2H, m, pyrrolidine ring C2-H or pyrrolidine ring C5-H and CO2C*H*2CCl3), 4.60 (1H, d, J=11.8 Hz, OC*H*2Ph), 4.58 (1H, d, J=11.8 Hz, OC*H*2Ph), 4.59 (1H, d, J=3.5 Hz, OC*H*2OMe), 4.62 (1H, d, J=3.5 Hz, OC*H*2OMe), 4.90 (1H, br s, CO2C*H*2CCl3), 5.76 (1H, br s, OH), 6.11 (1H, br d, J=7.4 Hz, C1-H), 6.68 (1H, br d, J=7.9 Hz, C5-H or C7-H), 6.72 (1H, br d, J=7.9 Hz, C5-H or C7-H), 7.15 (1H, t, J=7.9 Hz, C6-H), 7.29-7.36 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 703 [(M-CH2OH+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 701 [(M-CH2OH+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 699 [(M-CH2OH)$^+$, ^{35}Cl x 3], 646 [(M-CH2OH-C4H9+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 645 [(M-CH2OH-C4H9+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 643 [(M-CH2OH-C4H9)$^+$, ^{35}Cl x 3], 603 [(M-CH2OH-Boc+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 601 [(M-CH2OH-Boc+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 599 [(M-CH2OH-Boc)$^+$, ^{35}Cl x 3], 364, 338, 336, 334, 264, 202, 160, 91, 57, 45. CIMS (isobutane) m/z: 735 [(M+H+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 733 [(M+H+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 731 [(M+H)$^+$, ^{35}Cl x 3]. HRMS calcd for C33H42Cl3N2O8 [(M-CH2OH)$^+$, ^{35}Cl x 3]: 699.2004. Found: 699.1994.

b) Preparation of *ent*-**37**: The same treatments of *ent*-**36** (67.5 mg, 81 μmol) as described for the preparation of **37** from **36** gave *ent*-**37** (52.0 mg, 88%) as a colorless caramel. $[\alpha]D^{20}$ +5.6° (c 0.82, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **37**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 1-acetoxymethyl-3-[(2*R*,3*R*,5*S*)-5-benzyloxymethyl-1-*tert*-butoxycarbonyl-3-methoxymethoxymethylpyrrolidin-2-yl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (38) and Its Enantiomer (*ent*-38)

a) Preparation of **38**: Treatments of **37** (467 mg, 0.64 mmol) in a similar manner to that described for the preparation of **18** from **17** gave **38** (449 mg, 91%) as a colorless caramel after purification by column chromatography (hexane-ethyl acetate, 2:1). $[\alpha]D^{20}$ -29.3° (c 0.86, CHCl3). IR (neat): 2940, 2930, 2890, 2850, 1720, 1710, 1690, 1590, 1470, 1450, 1420, 1380, 1360, 1310, 1290, 1250, 1220, 1170, 1110, 1100, 1090, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.45 (9H, s, ^{t}Bu), 1.98-2.06 (1H, m, pyrrolidine ring C4-H), 1.99 (3H, s, Ac), 2.11-2.21 (1H, m, pyrrolidine ring C4-H), 2.57 (1H, br s, pyrrolidine ring C3-H),

2.86 (2H, br d, J=8.7 Hz, C3-H2), 3.34 (3H, s, OCH2O*Me*), 3.40 (1H, br dd, J=10.2, 7.6 Hz, C*H*2OBn), 3.48-3.59 (2H, m, C*H*2OBn and C3-H), 3.63-3.74 (1H, m, C*H*2OMOM), 3.74-3.79 (1H, m, C*H*2OMOM), 3.82 (3H, br s, ArO*Me*), 4.10 (1H, br s, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.25 (1H, m, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.45-4.61 (1H, m, OC*H*2Ac), 4.45 (2H, br s, OC*H*2Ph or C*H*2OMOM), 4.57 (2H, br s, OC*H*2Ph or C*H*2OMOM), 4.67 (1H, br t, J=5.1 Hz, OC*H*2Ac), 4.76 (2H, br s, CO2C*H*2CCl3), 6.08 (1H, br dd, J=7.5, 5.1 Hz, C1-H), 6.62 (1H, br d, J=7.9 Hz, C5-H or C7-H), 6.76 (1H, br d, J=7.9 Hz, C5-H or C7-H), 7.19 (1H, t, J=7.9 Hz, C6-H), 7.25-7.38 (5H, m, aromatic protons). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 739 [(M-Cl+2)$^+$, ^{37}Cl, ^{35}Cl], 737 [(M-Cl)$^+$, ^{35}Cl x 2], 703 [(M-CH2OAc+4)$^+$, ^{37}Cl x 2, ^{35}C], 701 [(M-CH2OAc+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 699 [(M-CH2OAc)$^+$, ^{35}Cl x 3], 646 [(M-CH2OAc-^{t}Bu+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 645 [(M-CH2OAc-^{t}Bu+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 643 [(M-CH2OAc-^{t}Bu)$^+$, ^{35}Cl x 3], 603 [(M-CH2OAc-Boc+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 601 [(M-CH2OAc-Boc+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 599 [(M-CH2OAc-Boc)$^+$, ^{35}Cl x 3], 481, 479, 477, 451, 364, 264, 202, 160, 91, 57. CIMS (isobutane) m/z: 773 [(M+H+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 775 ((M+H+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 773 [(M+H)$^+$, ^{35}Cl x 3]. HRMS calcd for C36H47Cl2N2O10 [(M-Cl)$^+$, ^{35}Cl x 2]: 737.2614. Found: 737.2633.

b) Preparation of *ent*-**38**: The same treatments of *ent*-**37** (51.5 mg, 71 μmol) as described for the preparation of **38** from **37** gave *ent*-**38** (53.3 mg, 89%) as a colorless caramel. [α]D^{20} +30.7° (c 0.86, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **38**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 1-acetoxymethyl-3-[(2*R*,3*R*,5*S*)-1-*tert*-butoxycarbonyl-5-hydroxymethyl-3-methoxymethoxymethylpyrrolidin-2-yl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (39) and Its Enantiomer (*ent*-39)

a) Preparation of **39**: Treatments of **38** (441 mg, 0.57 mmol) in a similar manner to that described for the preparation of **19** from **18** gave **39** (320 mg, 82%) as a colorless caramel after purification by column chromatography (hexane-ethyl acetate, 3:2). [α]D^{20} -22.8° (c 0.49, CHCl3). IR (neat): 3430, 2960, 2880, 1740, 1700, 1690, 1590, 1470, 1450, 1430, 1380, 1360, 1320, 1240, 1230, 1170, 1130, 1110, 1090, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.46 (9H, s, ^{t}Bu), 1.50-1.72 (2H, m, pyrrolidine ring C4-H2), 1.99 (3H, s, Ac), 2.52 (1H, br s, pyrrolidine ring C3-H), 2.89 (1H, br s, C4-H), 3.00 (1H, br s, C4-H), 3.31-3.62 (6H, m, C3-H, C*H*2O*H* and OC*H*2OMOM), 3.35 (3H, s, OCH2O*Me*), 3.81 (3H, s, ArO*Me*), 4.12 (1H, br s, pyrrolidine ring C2-H or pyrrolidine ring C5-H), 4.32-4.48 (3H, m, pyrrolidine ring C2-H or pyrrolidine ring C5-H and C*H*2OAc), 4.59 (1H, d, J=6.6 Hz, OC*H*2OMe), 4.62 (1H, d, J=6.6 Hz, OC*H*2OMe), 4.85 (1H, br s, CO2C*H*2CCl3), 4.97 (1H, br s, CO2C*H*2CCl3), 6.22 (1H, br s, C1-H), 6.75 (2H, br d, J=8.1 Hz, C5-H and C7-H), 7.21 (1H, br t, J=8.1 Hz, C6-H). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 687 [(M+H+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 685 [(M+H+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 683 ((M+H)$^+$, ^{35}Cl x 3), 649 [(M-Cl+2)$^+$, ^{37}Cl, ^{35}Cl], 647 [(M-Cl)$^+$, ^{35}Cl x 2], 613 [(M-CH2OAc+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 611 [(M-CH2OAc+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 609 [(M-CH2OAc)$^+$, ^{35}Cl x 3], 555 [(M-CH2OAc-C4H9+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 553 [(M-CH2OAc-C4H9+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 551 [(M-CH2OAc-C4H9)$^+$, ^{35}Cl x 3], 481, 479, 477, 352, 350, 348, 338, 336, 334, 274, 174, 160, 114, 57. HRMS calcd for C29H41Cl3N2O10 [(M+H)$^+$, ^{35}Cl x 3]: 683.1903. Found: 683.1933.

b) Preparation of *ent*-**39**: The same treatments of *ent*-**38** (52.5 mg, 68 μmol) as described for the preparation of **39** from **38** gave *ent*-**39** (39. 4 mg, 85%) as a colorless caramel. [α]D^{20} +24.2° (c 0.81, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **39**.

(1*R*,3*R*)-2,2,2-Trichloroethyl 1-acetoxymethyl-3-[(2*R*,3*R*,5*S*)-1-*tert*-butoxycarbonyl-5-formyl-3-methoxymethoxymethylpyrrolidin-2-yl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (40) and Its Enantiomer (*ent*-40)

a) Preparation of **40**: Treatments of **39** (320 mg, 0.47 mmol) in a similar manner to that described for the preparation of **20** from **19** gave **40** (316 mg, 99%) as a colorless caramel after purification by column chromatography (hexane-ethyl acetate, 3:2). [α]D^{20} -19.5° (c 0.41, CHCl3). IR (neat): 2930, 2880, 2850, 1740, 1710, 1590, 1470, 1450, 1440, 1380, 1360, 1310, 1270, 1260, 1230, 1170, 1130, 1080, 1040cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.45 (9H, br s, ^{t}Bu), 2.00 (3H, s, Ac), 2.02-2.20 (2H, m, pyrrolidine ring C4-H2), 2.50-2.92 (2H, br, pyrrolidine ring C3-H and C4-H), 3.01 (1H, br s, C4-H), 3.36 (3H, s, OCH2O*Me*), 3.38-3.56 (3H, m, C*H*2OMOM and C3-H), 3.83 (3H, s, ArO*Me*), 4.08-4.75 (4H, br, C*H*2OAc, pyrrolidine ring C2-H, and pyrrolidine ring C5-H), 4.82 (2H, br s, CO2C*H*2CCl3), 6.14 (1H, br s, C1-H), 6.78 (2H, br s, C5-H and C7-H), 7.21 (1H, br s, C6-H), 9.70 (1H, br s, CHO). Due to the presence of rotamers in the *tert*-butyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 645 [(M-Cl)$^+$, ^{35}Cl x 2], 611 [(M-CH2OAc+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 609 [(M-CH2OAc+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 607 [(M-CH2OAc)$^+$, ^{35}Cl x 3], 555 [(M-CH2OAc-C4H8+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 553 [(M-CH2OAc-C4H8+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 551 [(M-CH2OAc-C4H8)$^+$, ^{35}Cl x 3], 511 [(M-CH2OAc-Boc+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 509 [(M-CH2OAc-Boc+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 507 [(M-CH2OAc-Boc)$^+$, ^{35}Cl x 3], 410, 408, 406, 352, 350, 348, 338, 336, 334, 272, 218, 173, 160, 110, 57. CIMS (isobutane) m/z: 685 [(M+H+4)$^+$, ^{37}Cl x 2, ^{35}Cl], 683 ((M+H+2)$^+$, ^{37}Cl, ^{35}Cl x 2], 681 [(M+H)$^+$, ^{35}Cl x 3]. HRMS calcd for C26H34Cl3N2O8 [(M-CH2OAc)$^+$, ^{35}Cl x 3]: 607.1378. Found: 607.1351.

b) Preparation of *ent*-**40**: The same treatments of *ent*-**39** (30.8 mg, 45 μmol) as described for the preparation of **40** from **39** gave *ent*-**40** (30.7 mg, 100%) as a colorless caramel. $[\alpha]D^{20}$ +20.9° (c 0.65, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **40**.

(5*R*,7*R*,8*S*,10*R*,11*R*,11a*S*)-5-Acetoxymethyl-13-*tert*-butoxycarbonyl-7-cyano-4-methoxy-10-methoxymethoxymethyl-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline (43) and Its Enantiomer (*ent*-43)

a) Preparation of **43**: Treatments of **40** (301 mg, 0.44 mmol) in a similar manner to that described for the preparation of **23** from **20** gave **43** (88.8 mg, 39%, 2 steps) as a colorless amorphous powder *via* (5*R*,7*R*,8*S*,10*R*,11*R*,11a*S*)-5-acetoxymethyl-13-*tert*-butoxycarbonyl-7-hydroxy-4-methoxy-10-methoxymethoxymethyl-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline (**42**) after purification by column chromatography (hexane-ethyl acetate, 4:1→ 2:1). $[\alpha]D^{20}$ +10.9° (c 0.41 , CHCl3). IR (neat): 2960, 2930, 2830, 1730, 1690, 1590, 1470, 1410, 1380, 1320, 1260, 1230, 1160, 1100, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.46 (3H, br s, ^{t}Bu), 1.48 (6H, br s, ^{t}Bu), 1.90-2.06 (2H, m, C9-H2), 2.03 (3H, s, Ac), 2.04 (1H, s, Ac), 2.51-2.60 (1H, m, C10-H), 2.60-2.72 (2H, m, C12-H2), 3.01 (1H, br d, J=9.2, 5.3 Hz, C11a-H), 3.19-3.34 (2H, m, C*H*2OMOM), 3.38 (3H, s, OCH2O*Me*), 3.81 (3H, s, ArO*Me*), 3.95 (1H, dd, J=11.0, 6.5 Hz, C*H*2OAc), 3.97-4.03 (1H, m, C7-H), 4.12 (1H, br s, C11-H), 4.35-4.44 (2H, m, C*H*2OAc and C7-H), 4.52 (1H, br d, J=6.3 Hz, C8-H), 4.62 (2H, br s, OC*H*2OMe), 4.67 (1H, br d, J=7.3 Hz, C5-H), 6.71 (1H, br d, J=7.9 Hz, C1-H or C3-H), 6.74 (1H, d, J=7.9 Hz, C1-H or C3-H), 7.17 (1H, br t, J=7.9 Hz, C2-H). Due to the presence of rotamers in the *tert*-butyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 442 [(M-CH2OAc)$^+$], 386 [(M-CH2OAc-C4H8)$^+$], 342 [(M-CH2OAc-Boc)$^+$], 199, 160, 80, 57. CIMS (isobutane) m/z: 516 [(M+H)$^+$]. HRMS calcd for C24H32N3O5 [(M-CH2OAc)$^+$]: 442.2340. Found: 442.2340.

b) Preparation of *ent*-**43**: The same treatments of *ent*-**40** (30.2 mg, 44 μmol) as described for the preparation of **43** from **40** gave *ent*-**43** (9.6 mg, 42%) as a colorless amorphous powder. $[\alpha]D^{20}$ -9.3° (c 0.96, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **43**.

(5*R*,7*R*,8*S*,10*R*,11*R*,11a*S*)-5-Acetoxymethyl-7-cyano-10-hydroxymethyl-4-methoxy-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline (44) and Its Enantiomer (*ent*-44)

a) Preparation of **44**: Treatments of **43** (87.4 mg, 0.17 mmol) in a similar manner to that described for the preparation of **24** from **23** gave **44** (51.6 mg, 81%) as a colorless amorphous powder after purification by column chromatography (ethyl acetate-methanol, 10:1). $[\alpha]D^{20}$ +27.6° (c 0.42 , CHCl3). IR (neat): 3380, 3350, 2930, 2830, 1730, 1590, 1470, 1430, 1380, 1260, 1230, 1130, 1100, , 1050, 1040, 1030 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 0.90 (1H, br s, OH), 1.77 (1H, ddd, J=12.4, 6.6, 4,1 Hz, C9-H), 1.82 (1H, br s, NH), 1.98 (1H, dd, J=12.4, 8.9 Hz, C9-H), 2.04 (3H, s, Ac), 2.41 (1H, sxt, J=4.2 Hz, C10-H), 2.53 (1H, dd, J=14.7, 2.6 Hz, C12-H), 2.63 (1H, dd, J=14.7, 11.4 Hz, C12-H), 2.83 (1H, br dt, J=11.4, 1.0 Hz, C11a-H), 3.24 (1H, s, C11-H), 3.56 (1H, , dd, J=10.0, 5.7 Hz, C*H*2OH), 3.71 (1H, , dd, J=10.0, 4.1 Hz, C*H*2OH), 3.74 (1H, dd, J=6.6, 2.3 Hz, C8-H), 3.82 (3H, s, ArO*Me*), 3.94 (1H, dd, J=10.7, 6.0 Hz, C*H*2OAc), 4.10 (1H, d, J=2.3 Hz, C7-H), 4.34 (1H, dd, J=6.0, 2.8 Hz, C5-H), 4.38 (1H, dd, J=10.7, 2.9 Hz, C*H*2OAc), 6.72 (1H, d, J=7.9 Hz, C3-H), 6.75 (1H, d, J=7.9 Hz, C1-H), 7.18 (1H, t, J=7.9 Hz, C2-H). EIMS m/z: 371 (M$^+$), 298 [(M-CH2OAc)$^+$], 199, 160, 68, 43. HRMS calcd for C20H25N3O4 (M$^+$): 371.1843. Found: 371.1858.

b) Preparation of *ent*-**44**: The same treatments of *ent*-**43** (9.5 mg, 18 μmol) as described for the preparation of **44** from **43** gave *ent*-**44** (6.0 mg, 88%) as a colorless amorphous powder. $[\alpha]D^{20}$ -27.1° (c 0.60, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **44**.

(5*R*,7*R*,8*S*,10*R*,11*R*,11a*S*)-5-Acetoxymethyl-7-cyano-10-hydroxymethyl-4-methoxy-13-methyl-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline (45) and Its Enantiomer (*ent*-45)

a) Preparation of **45**: A stirred solution of **44** (47.6 mg, 0.13 mmol) in acetonitrile (16 ml) containing iodomethane (0.162 ml, 2.6 mmol) and *N*,*N*-diisopropylethylamine (0.670 ml, 3.8 mmol) was heated at 60°C for 3 h. After cooling, the mixture was diluted with ethyl acetate (70 ml), and the organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:3) to give **45** (33.6 mg, 68%) as a colorless amorphous powder. $[\alpha]D^{20}$ +28.8° (c 0.63, CHCl3). IR (neat): 3450, 2950, 2900, 2860, 1740, 1600, 1470, 1480, 1450, 1380, 1360, 1290, 1260, 1230, 1180, 1140, 1090, 1070, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, C6D6) δ: 1.18 (1H, br s, OH), 1.41 (1H, ddd, J=12.8, 6.4, 5.5 Hz, C9-H), 1.60 (3H, s, Ac), 1.64 (1H, dd, J=12.8, 9.0 Hz, C9-H), 2.13 (1H, dd, 14.5, 2.3 Hz, C12-Heq), 2.23 (1H, quint, J=7.6 Hz, C10-H2), 2.30 (3H, s, NMe), 2.47 (1H, dd, J=14.5, 12.0 Hz, C12-Hax), 2.61 (1H, s, C11a-H), 2.87 (1H, br dt, J=6.4, 1.0 Hz, C8-H), 3.09 (1H, br dt, J=12.0, 1.0 Hz, C11a-H), 3.14 (3H, s, ArO*Me*), 3.27 (1H, dd, J=9.9, 7.8 Hz, C*H*2OH), 3.34 (1H, dd, J=9.9, 6.5 Hz, C*H*2OH), 3.51 (1H, d, J=2.4 Hz, C7-H), 4.12 (1H, dd, J=10.9, 4.9 Hz, C*H*2OAc), 4.52 (1H, dd, J=10.9, 3.0 Hz, C*H*2OAc), 4.65 (1H, dd, J=4.9, 3.0 Hz, C5-H), 6.33 (1H, d, J=8.0 Hz, C3-H), 6.61 (1H, d, J=8.0 Hz, C1-H), 7.01 (1H, t, J=8.0 Hz, C2-H). EIMS m/z: 385 (M$^+$), 312 [(M-CH2OAc)$^+$], 201, 152, 112, 82, 43. HRMS calcd for C21H27N3O4 (M$^+$): 385.2000. Found: 385.2007.

b) Preparation of *ent*-**45**: The same treatments of *ent*-**44** (6.0 mg, 16 μmol) as described for the preparation of **45** from **44** gave *ent*-**45** (4.6 mg, 75%) as a colorless amorphous powder. $[\alpha]D^{20}$ -27.6° (c 0.46, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **45**.

(5*R*,7*R*,8*S*,10*R*,11*R*,11a*S*)-5-Acetoxymethyl-7-cyano-4-methoxy-13-methyl-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline-10-carboxylic acid (46) and Its Enantiomer (*ent*-46)

a) Preparation of **46**: 2.6 M Jones reagent (322 µl, 0.84 mmol) was added dropwise to a stirred suspension of **45** (32.3 mg, 84 µmol) in acetone (4 ml) containing dry celite (300 mg) at room temperature. After 30 min, 2-propanol (1 ml) and was added, and the mixture was diluted with ethyl acetate (30 ml) and filtered through a pad of celite. The filtrate was dried over Na2SO4 and concentrated *in vacuo*. The residue was purified by column chromatography (ethyl acetate-chloroform, 10:1) to give **46** (26.4 mg, 79%) as a colorless amorphous powder. $[\alpha]D^{20}$ +18.4° (c 0.38, CHCl3). IR (neat): 3440, 2900, 2830, 1730, 1590, 1470, 1380, 1330, 1260, 1230, 1130, 1090, 1070, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, C6D6) δ: 1.54 (3H, s, Ac), 1.73 (1H, dd, J=13.2, 9.7 Hz, C9-H), 2.14 (3H, s, NMe), 2.24 (1H, d, J=14.7 Hz, C12-H), 2.43 (2H, br quint, J=10.6Hz, C9-H and C12-H), 2.80 (1H, br d, J=5.0 Hz, C8-H), 2.98-3.03 (2H, m, C10-H and C11a-H), 3.13 (3H, s, ArO*Me*), 3.30 (1H, br s, C11-H), 3.46 (1H, d, J=1.9 Hz, C7-H), 4.06 (1H, dd, J=10.9, 4.9 Hz, C*H*2OAc), 4.45 (1H, dd, J=10.9, 3.0 Hz, C*H*2OAc), 4.60 (1H, dd, J=4.9, 3.0 Hz, C5-H), 6.31 (1H, d, J=8.0 Hz, C3-H), 6.55 (1H, d, J=8.0 Hz, C1-H), 6.98 (1H, t, J=8.0 Hz, C2-H). EIMS m/z: 399 (M^+), 373 [(M-CN)$^+$], 326 [(M-CH2OAc)$^+$], 234, 201, 174, 126, 82, 42. HRMS calcd for C21H25N3O5 (M^+): 399.1792. Found: 399.1789.

b) Preparation of *ent*-**46**: The same treatments of *ent*-**45** (4.6 mg, 12 µmol) as described for the preparation of **46** from **45** gave *ent*-**46** (4.0 mg, 83%) as a colorless amorphous powder. $[\alpha]D^{20}$ -18.8° (c 0.40, CHCl3). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **46**.

(5*R*,7*R*,8*S*,10*R*,11*R*,11a*S*)-7-Cyano-5-hydroxymethyl-4-methoxy-13-methyl-5,7,8,9,10,11,11a,12-octahydro-8,11-iminoazepino[1,2-*b*]isoquinoline-10-carboxylic acid (DX-52-1) (3) and Its Enantiomer (*ent*-3)

a) Preparation of **3**: Treatments of **46** (26.3 mg, 66 µmol) in a similar manner to that described for the preparation of **26** from **25** gave **3** (20.7 mg, 88%) as a colorless amorphous powder after purification by column chromatography (ethyl acetate-methanol, 5:1). Recrystallization from ether-methanol gave an analytical sample of **3** as a white solid, mp 202-205 °C (dec.) [lit.,[11a] 190-195 °C (dec.)] and $[\alpha]D^{20}$ +24.7° (c 0.32, MeOH). IR (KBr): 3400, 2900, 2830, 1580, 1465, 1380, 1330, 1260, 1230, 1120, 1090, 1070, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CD3OD) δ: 2.15 (1H, dd, J=13.2, 9.7 Hz, C9-H), 2.34 (3H, s, NMe), 2.56-2.64 (2H, m, C9-H and C12-H), 2.24 (1H, d, J=14.7 Hz, C12-H), 2.71 (1H, dd, J=14.6, 11.6 Hz, C12-H), 2.89 (1H, d, J=11.6 Hz, C11a-H), 3.29 (1H, dd, J=9.7, 5.8 Hz, C10-H), 3.44 (1H, dd, J=10.7, 6.7 Hz, C*H*2OH), 3.49 (2H, br s, C8-H, C11-H), 3.77 (1H, dd, J=10.7, 2.6 Hz, C*H*2OH), 3.84 (3H, s, ArO*Me*), 4.20 (1H, dd, J=6.6, 2.5 Hz, C5-H), 4.32 (1H, d, J=2.5 Hz, C7-H), 6.75 (1H, d, J=8.0 Hz, C3-H), 6.83 (1H, d, J=8.0 Hz, C1-H), 7.16 (1H, t, J=8.0 Hz, C2-H). EIMS m/z: 326 [(M-CH2OH)$^+$], 274, 204, 160, 82, 28. These spectra were identical with those of an authentic sample of (+)-DX-52-1 kindly provided by Drs. T. Hirata and H. Saito, Kyowa Hakko Kogyo Co., Ltd..

b) Preparation of *ent*-**3**: The same treatments of *ent*-**46** (3.9 mg, 9.7 µmol) as described for the preparation of **3** from **47** gave *ent*-**46** (3.0 mg, 89%) as a colorless amorphous powder. $[\alpha]D^{20}$ -25.8° (c 0.31, MeOH). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **3**.

(–)-Quinocarcin (1) and (+)-Quinocarcin (*ent*-1)

a) Preparation of **1**: Treatments of **3** (20.0 mg, 56 µmol) in a similar manner to that described for the preparation of **2** from **26** gave **1** (14.9 mg, 81%) as a colorless amorphous powder after purification by column chromatography (Diaion CHP-20P, water-methanol, 10:1). Recrystallization from ether-methanol gave an analytical sample of **1** as a white solid, mp 183-226 °C (dec.) [lit.,[14] mp >170 °C (dec.)] and $[\alpha]D^{22}$ -30.6° (c 0.48, H2O) [lit.,[14] $[\alpha]D^{22}$ -32.0° (c 0.50, H2O)]. IR (KBr): 3350, 2900, 2830, 1740, 1590, 1470, 1390, 1350, 1260, 1230, 1120, 1090, 1070, 1040 cm^{-1}. ^{1}H-NMR (400 MHz, CD3OD) δ: 2.50 (1H, dd, J=13.5, 10.3 Hz, C9-H), 2.65 (2H, br dd, J=14.6, 2.6 Hz, C9-H and C12-H), 2.74-2.84 (1H, m, C12-H), 2.79 (3H, s, NMe), 3.35-3.46 (2H, m, C10-H and C11a-H), 3.40 (1H, dd, J=10.7, 7.2 Hz, C*H*2OH), 3.68 (1H, dd, J=10.7, 2.9 Hz, C*H*2OH), 3.83 (3H, s, ArO*Me*), 4.10 (2H, br s, C8-H and C11-H), 4.56 (1H, dd, J=7.2, 2.8 Hz, C5-H), 4.59 (1H, d, J=3.1 Hz, C7-H), 6.77 (1H, d, J=8.0 Hz, C3-H), 6.85 (1H, d, J=8.0 Hz, C1-H), 7.17 (1H, t, J=8.0 Hz, C2-H). EIMS m/z: 302 [M-CO], 301 [(M-CHO)$^+$]. SIMS m/z: 331 [M+H]. These spectra were identical with those of an authentic sample of (–)-quinocarcin (**1**) kindly provided by Drs. T. Hirata and H. Saito, Kyowa Hakko Kogyo Co., Ltd..

b) Preparation of *ent*-**1**: The same treatments of *ent*-**3** (3.0 mg, 8.4 µmol) as described for the preparation of **1** from **3** gave *ent*-**1** (2.3 mg, 84%) as a colorless amorphous powder. $[\alpha]D^{20}$ +29.8° (c 0.23, H2O). The IR, ^{1}H-NMR, and mass specra of this sample were identical with those recorded for **1**.

Acknowledgement

We are grateful to Drs. T. Hirata and H. Saito, Kyowa Hakko Kogyo Co., Ltd., for providing us with authentic samples of **1** and **3**.

References and Notes

1. Parts of this series of papers have been the subjects of five preliminary communications: a) Saito, S.; Matsuda, F.; Terashima, S., *Tetrahedron Lett.*, **1988**, *29*, 6301. b) Saito, S.; Tanaka, K.; Nakatani, K.;

Matsuda, F.; Terashima, S., *ibid.*, **1989**, *30*, 7423. c) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S., *ibid.*, **1993**, *34*, 5743. d) Katoh, T.; Kirihara, M.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S., *ibid.*, **1993**, *34*, 5747. e) Katoh, T.; Kirihara, M.; Yoshino, T.; Terashima, S., *ibid.*, **1993**, *34*, 5751.

2. a) Part 1: Saito, S.; Tamura, O.; Kobayashi, Y.; Matsuda, F.; Katoh, T.; Terashima, S., *Tetrahedron*, the preceding paper. b) Part 2: Saito, S.; Tanaka, K.; Nakatani, K.; Matsuda, F.; Katoh, T.; Terashima, S., *Tetrahedron*, the preceding paper. c) Part 3: Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S., *Tetrahedron*, the preceding paper.
3. Present address: Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmceutical University, Sugitani, Toyama 930-01, Japan.
4. Present address: Organic Chemistry Laboratories, Tanabe Seiyaku Co., Ltd., Toda, Saitama 335, Japan.
5. All the attempts on aldol coupling of **9** with **4** carried out under various reaction conditions (*e.g.*, base: LDA, LiHMDS, KHMDS, *tert*-BuLi, *sec*-BuLi ; solvent: THF, Et_2O, DME ; additive: DABCO, TMEDA, HMPA; temp.: $-100°C \rightarrow rt$, etc.)[6] gave no desired aldol adduct, but resulted in almost complete decomposition of **9**.
6. For related aldol coupling reactions involving deprotonation of the methyl group at *ortho* position of other directing groups, see, a) Gschwend, H. W.; Rodriguez, H. R., *Org. Reactions*, **1979**, 26. b) Carpenter, T. A.; Evans, G. E.; Leeper, F. J.; Staunton, J.; Wilkinson, M. R., *J. Chem. Soc. Perkin Trans. I*, **1984**, 1043. c) Watanabe, M.; Sahara, M.; Furukawa, S.; Billedeau, R.; Snieckus, V., *Tetrahedron Lett.*, **1982**, *23*, 1647. d) Broka, C. A., *Tetrahedron Lett.* **1991**, *32*, 859.
7. The coupling product **12** turned out to be extremely reluctant to oxidation with other standard reagents (*e.g.*, CrO_3•2Py, CrO_3/AcOH, PCC, PDC, TPAP, DMSO/SO_3•Py, DMSO/$(COCl)_2$, etc.).
8. Windholz, T. B.; Johnston, D. B. R., *Tetrahedron Lett.*, **1967**, *27*, 2555.
9. Fukuyama, T.; Nunes, J. J., *J. Am. Chem. Soc.*, **1988**, *110*, 5196.
10. Saito, H.; Hirata, T., *Tetrahedron Lett.*, **1987**, *28*, 4065.
11. a) Saito, H.; Kobayashi, S.; Uosaki, Y.; Sato, A.; Fujimoto, K.; Miyoshi, K.; Morimoto, M.; Hirata, T., *Chem. Pharm. Bull.*, **1990**, *38*, 1278. b) Saito, H.; Sato, A.; Ashizawa, T.; Morimoto, M.; Hirata, T., *Chem. Pharm. Bull.*, **1990**, *38*, 3202.
12. Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S., *J. Org. Chem.*, **1986**, *51*, 404.
13. When **35** was treated with a protic acid such as hydrochloric acid, acetic acid, *p*-toluenesulfonic acid, or camphorsulfonic acid, both the acetonide and the methoxymethyl groups were found to be simultaneously hydrolyzed, giving rise to the useless tetraol.
14. Takahashi, T.; Tomita, F., *J. Antibiot.*, **1983**, 468.
15. Katoh, T.; Kirihara, M.; Yoshino, T.; Tamura, O.; Ikeuchi, F.; Nakatani, K.; Matsuda, F.; Yamada, K.; Gomi, K.; Ashizawa, T,; Terashima, S., *Tetrahedron*, the accompanying paper.

(*Received in Japan* 4 *February* 1994; *accepted* 22 *February* 1994)