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Synthetic Studies on Quinocarcin and Its Related Compounds. 2.[1, 2] Synthesis of an Enantiomeric Pair of the ABC Ring System of Quinocarcin

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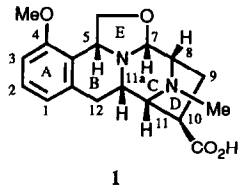
Key words: asymmetric synthesis, quinocarcin, antitumor antibiotic, ABC ring system, diastereoselective reduction, intramolecular N,O-acetal formation

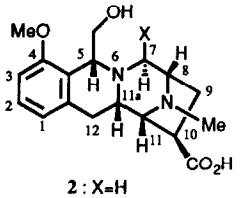
Abstract: *An enantiomeric pair of the ABC ring system (5 and ent-5) of quinocarcin (1), a potent antitumor antibiotic, was synthesized in >95% ee with an aim to disclose novel aspects of the structure-activity relationships of 1. The key features of the synthesis consist of novel diastereoselective reduction of 1,3-disubstituted isoquinoline derivatives 29 and ent-29 to control stereochemistries at the C6 and C11a positions in 5 and ent-5 simultaneously in a single step and intramolecular N,O-acetal formation of amino aldehydes 6 and ent-6 to complete the requisite skeletal framework.*

(–)-Quinocarcin (**1**) isolated from the culture broth of *Streptomyces melanovinaceus* along with pharmacologically inactive quinocarcinol (**2**), shows a notable antitumor activity. DX-52-1 (**3**), the more stable semisynthetic 7-cyano congener of **1**, has been reported to retain significant antitumor activity.[2]

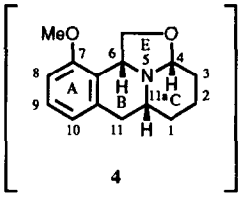
As described in the preceding paper,[2] we have succeeded in developing an efficient synthetic scheme to enantiomeric pairs of the ABE ring system and its analogues of **1**. Based on the results accumulated in these model studies, we next investigated the synthesis of an enantiomeric pair of the ABCE ring system of **1** (**4** and *ent*-**4**). After experimentation, however, **4** turned out to be too labile to be isolated. Therefore, the isolation of **4** was achieved in a form of the corresponding stable cyano derivative **5** (*vide infra*). In the second part of this series of papers, we wish to report full details of the synthesis of an enantiomeric pair of the ABC ring system of **1** (**5** and *ent*-**5**).[1b]



1



2 : X=H
3 : X=CN



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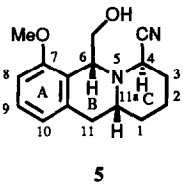

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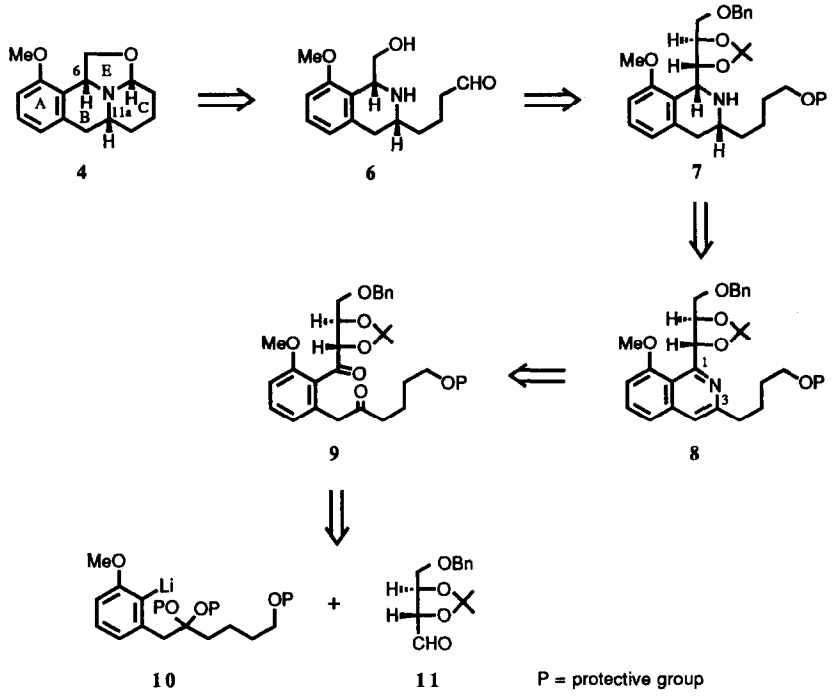
Synthetic Plan

The retrosynthetic plan for **4** was designed as outlined in **Scheme 1**. The key step in this approach is envisaged to be the diastereoselective reduction of isoquinoline derivative **8** to control stereochemistries at the

Scheme 1



C6 and C11a positions (2*H*-benzo[*b*]quinolidine numbering) in **4** simultaneously in a single step. The reduction product **7** could be converted into **4** by sequential functional group manipulations and deprotections or *vice versa* through the reactive amino aldehyde **6**. Interesting possibility for simultaneously constructing both the C and E rings in **4** involves the intramolecular *N*,*O*-acetal formation of **6**. The key substrate **8** is anticipated to be elaborated by the coupling of aryl lithium **10** with threose derivative **11**[2,7] *via* diketone **9**.

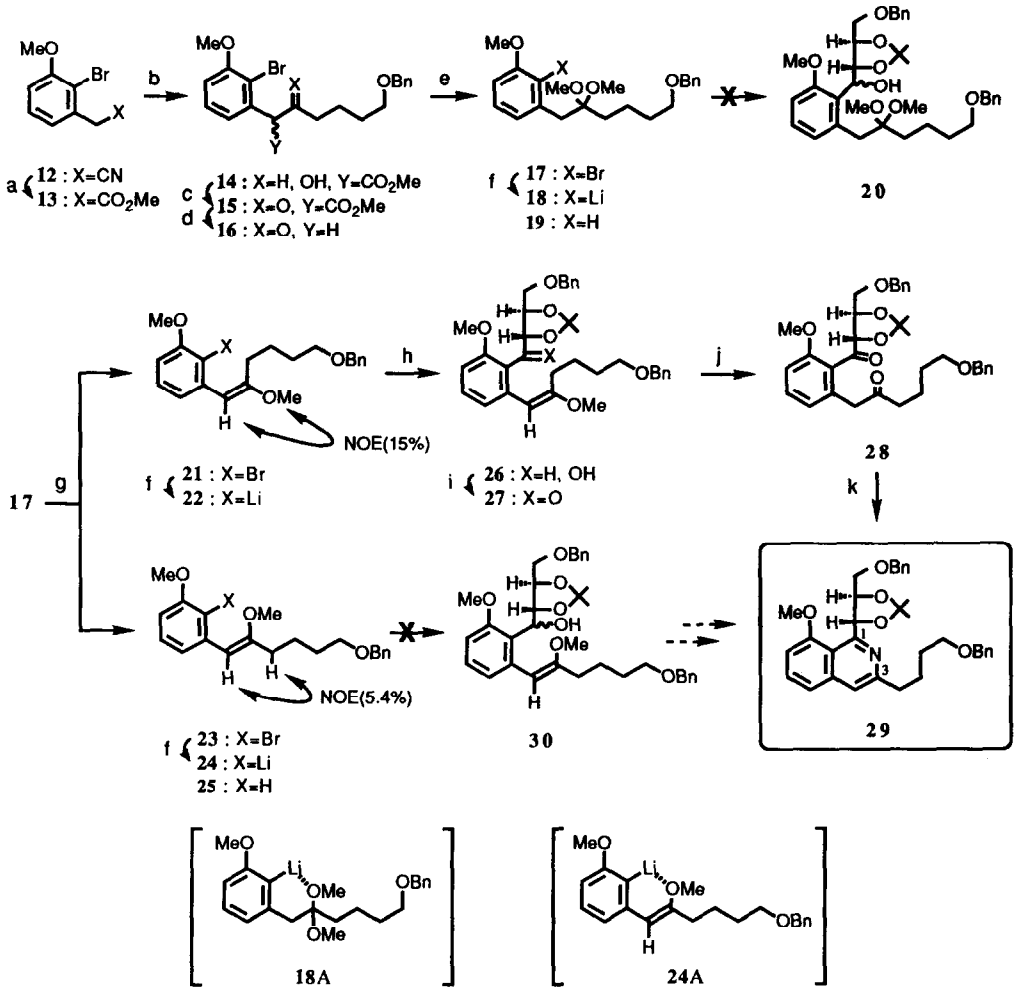
Results and Discussion

1. Preparation of the Key Synthetic Intermediate 29

In order to explore feasibility of the designed synthetic scheme, the preparation of the key 1,3-disubstituted isoquinoline derivative **29** corresponding to **8** was first attempted as shown in **Scheme 2**. Thus, alkaline hydrolysis of (2-bromo-3-methoxyphenyl)acetonitrile[2] (**12**) followed by esterification of the resulting carboxylic acid provided methyl ester **13**. The lithium enolate generated from **13** was allowed to react with 5-benzyloxypentanal[8] in the presence of *N*,*N*,*N*',*N*'-tetramethylenediamine (TMEDA), giving rise to the desired adduct **14** as a diastereomeric mixture. Without separation, Jones oxidation of **14** followed by demethoxycarbonylation of the resulting ketoester **15** yielded the ketone **16**, whose carbonyl group was further protected to afford dimethylacetal **17**.

For introducing a chiral auxiliary, **17** was lithiated, and the generated aryl lithium **18** was allowed to react with 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose **11**[2,7] to provide the debrominated product **19** after standard workup instead of the desired coupling adduct **20**. Various reaction conditions were extensively

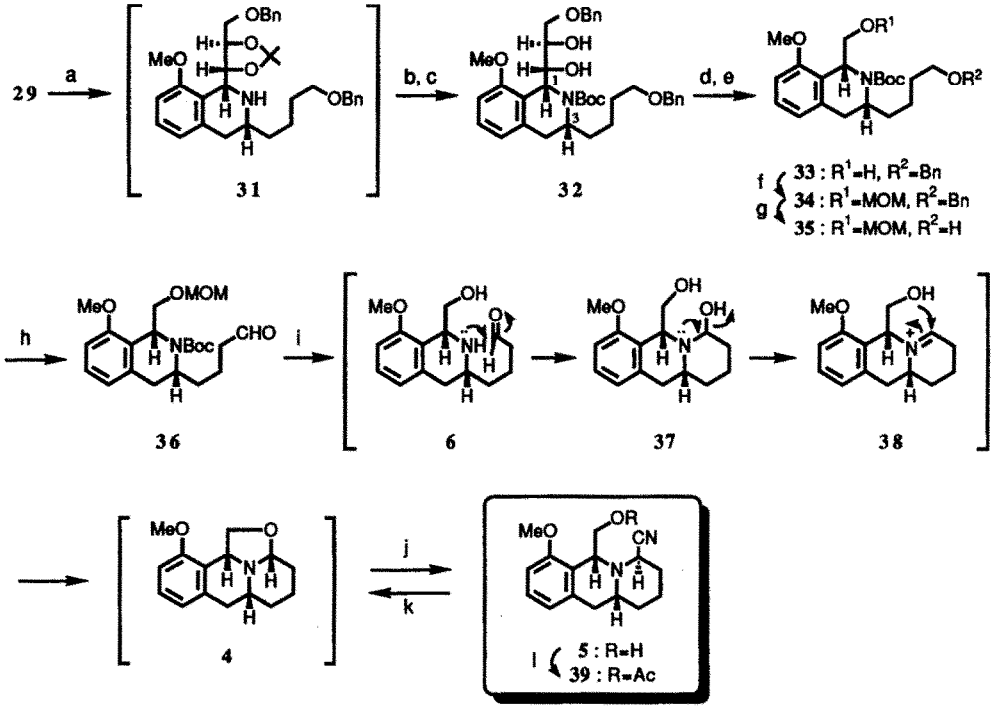
Scheme 2



reagents and conditions : a) NaOH, MeOH, reflux ; CH_2N_2, Et_2O, rt, 86% b) LDA, TMEDA, THF, -78°C ; $BnO(CH_2)_3CHO$, -78°C, 78% c) Jones oxid., 89% d) NaCl, H_2O, DMSO, 140°C, 89%(2 steps) e) $(MeO)_3CH$, CSA, MeOH, rt, 88% f) ^nBuLi, Et_2O, -78°C g) CSA, MeOH, reflux, 85%(21:23=73:27) h) **11**, -78°C, Et_2O, 75% from **21** i) Collins oxid., j) 1M HCl, THF, rt k) 14M NH_4OH, THF, rt, 42%(3 steps)

examined, however, none of **20** was obtained. Consequently, an alternative protecting group for the carbonyl function in **16** was sought to circumvent this problem. Thus, treatment of **17** with *dl*-10-camphorsulfonic acid furnished a mixture of (*E*)- and (*Z*)-methyl enol ether **21** and **23** in a ratio of 73:27. These enol ethers were cleanly separated by column chromatography on silica gel. Assignments of the geometries of enol ether moieties of **21** and **23** were readily achieved by NOE measurements in their 400 MHz ^{1}H-NMR spectra. Thus, NOE between the signals due to olefinic proton and methyl group in **21** was found to be 15%. On the other hand, NOE of 5.4% was observed between the signals due to olefinic proton and allylic methylene in

Scheme 3



reagents and conditions : a) $NaBH_3CN$, conc HCl-MeOH(1:100), 0°C b) HCl, MeOH, rt c) Boc_2O, Et_3N, $CHCl_3$, reflux, 79%(3 steps) d) $NaIO_4$, MeOH-H_2O(10:1v/v), rt e) $NaBH_4$, MeOH-H_2O(10:1v/v), 94%(2 steps), f) MOMCl, $^iPr_2EtN$, THF, rt, 96% g) H_2, 10%Pd-C, MeOH, rt h) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C ; Et_3N, 89%(2 steps) i) TMSBr, CH_2Cl_2, rt j) NaCN, MeOH, rt, 59%(2 steps) k) $AgNO_3$, MeOH, rt l) Ac_2O, DMAP, Py, rt, 83%

23. To our delight, the coupling reaction of **22** with **11** turned out to be effected under the same conditions as described above, giving rise to the adduct **26** in 75% yield. On the other hand, the coupling reaction of **24** with **11** attempted under the same conditions as described for the preparation for **26** gave no desired adduct **30**, resulting in the formation of the debrominated product **25**. These interesting observations can be explained by the formation of six-membered chelates between lithium atom and oxygen atom in **18** and **24** (see, **18A** and **24A**), extremely decreasing reactivity of the corresponding aryl lithiums. To continue the synthesis, **26** was next subjected to Collins oxidation without separation to provide ketone **27**. Acidic hydrolysis of the enol ether moiety in **27** followed by treatment of the resulting diketone **28** with aqueous ammonia in tetrahydrofuran, afforded **29** in 42 % overall yield from **26**.

2. Synthesis of an Enantiomeric Pair of the ABC Ring System (5 and *ent*-5)

With the first key intermediate **29** in hand, we next focused our attention on the crucial reduction of **29.** As shown in **Scheme 3**, highly diastereoselective reduction of **29** turned out to be effected by employing sodium cyanoborohydride in acidic media at 0°C,[9] giving rise to the tetrahydroisoquinoline **31**. This could be isolated in a form of diol carbamate **32** in 79% overall yield from **29**, after removal of the acetonide group in

31 followed by protection of the amino function. It is noteworthy that **32** was found to consist of a single isomer among four possible diastereomers. The stereochemical issue with respect to the newly produced C1 and C3 positions (isoquinoline numbering) in **32** was rigorously corroborated as pictured based on the 400 MHz ^{1}H-NMR spectrum of the 2-oxazolidinone derivative derived from **32** (*vide infra*).

The second key intermediate **36** having the requisite carbon framework and functional groups with correct absolute stereochemistries was elaborated from **32** as follows. Thus, sequential oxidative cleavage of the vicinal diol moiety in **32**, reduction of the resulting aldehyde function and protection of the primary hydroxy group in **33** provided methoxymethyl ether **34**. Debenzylation of **33** followed by Swern oxidation of the resulting alcohol **35** afforded aldehyde **36**. The final crucial step in the synthesis was anticipated to be the intramolecular *N,O*-acetal formation of the amino aldehyde **6** produced *in situ* by simultaneous removal of the MOM and Boc groups in **36**, to furnish the requisite ABCE ring system in **4**. In the event, upon treatment of **36** with bromotrimethylsilane[10] in dichloromethane at ambient temperature, a new single compound deemed to be the desired **4** was observed on TLC analysis. It is presumed that this reaction proceeded through the reactive amino aldehyde **6**, hemiaminal **37**, and iminium ion **38**. All attempts to isolate **4**, however, met with failure presumably due to its chemical instability inherent in the oxazolidine ring (the E ring) of **4**. Therefore, **4** was isolated in a form of the corresponding stable cyano derivative **5** by treatment with sodium cyanide[11] in methanol at ambient temperature in 59% overall yield from **36**. Exposure of **5** to silver nitrate in methanol according to the reported method[11] effected regeneration of **4**. However, all the efforts to isolate **4** were again unsuccessful. The stereostructure of **5** was proven by the 400 MHz ^{1}H-NMR spectral analysis of the acetate **39** derived from **5**.[12]

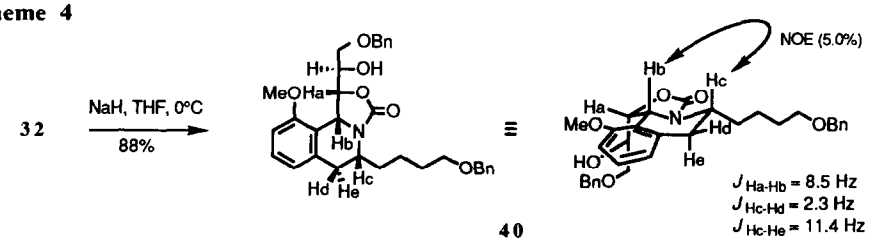
By employing 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose (*ent*-**11**) instead of the D-isomer (**11**), the enantiomeric ABC ring system (*ent*-**5**) and its acetate *ent*-**39** were prepared in the same manner as described above. Finally, both **5** and *ent*-**5** were converted to the corresponding MTPA esters[13] to determine their optical purity. Comparison of their 400 MHz ^{1}H-NMR spectra established that the optical purity of **5** and *ent*-**5** were more than 95% ee.

Results of antitumor activity assay of the synthesized compounds (**5**, *ent*-**5**, **39**, and *ent*-**39**) are the subject in the accompanying paper.[14]

3. Structural Elucidation of the Reduction Product 32

In order to confirm the stereochemistries of asymmetric centers newly produced at the C1 and C3 positions (isoquinoline numbering) in **32**, it was converted to the corresponding 2-oxazolidinone derivative **40** by treatment with sodium hydride in tetrahydrofuran at 0°C as shown in **Scheme 4**. The 400 MHz ^{1}H-

Scheme 4



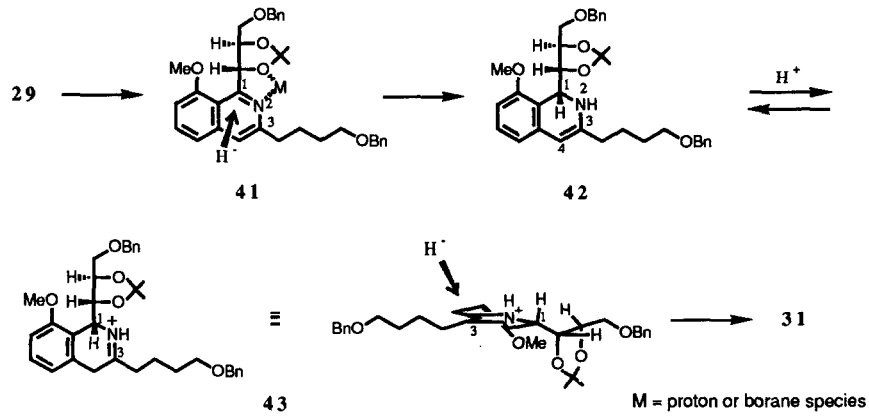
40

NMR spectrum of **40** exhibited the coupling constant of 8.5 Hz for Ha and Hb, establishing their *cis*-relationship.[2] NOE between the signals due to Hb and Hc was found to be 5.0%. These results obviously revealed that the tetrahydropyridine ring of **40** takes a half chair-like conformation and that Ha, Hb, and Hc of **40** are all in *cis*-relationships. Moreover, the coupling constants of 2.3 Hz (axial-equatorial) and 11.4 Hz (axial-axial) were observed for Hc and Hd and for Hc and He, respectively. Based on these spectral features, the stereostructure of **32** could be rigorously assigned as pictured.

4. Mechanistic Considerations on the Highly Diastereoselective Reduction of 29

Complete diastereoselectivity observed for the reduction of **29** with sodium cyanoborohydride in acidic media can be rationalized by sequential 2-step asymmetric induction as shown in **Scheme 5**. Thus, the first hydride attack may proceed through the usual Cram's chelation model (see, **41**) which interacts with the alkoxy group adjacent to the C1, N2-double bond in a similar fashion to that described in the preceding paper,[2] exclusively providing the 1,2-dihydroisoquinoline **42**. Although the enamine function itself in **42** might resist to reduction, rapid and reversible protonation on the C4 position in an acidic medium would generate the readily reducible iminium salt **43**.[9,15] High stereoselectivity subsequently achieved in the reduction of **43** under an influence of the newly produced C1 chiral center, can be rationalized by the stereoelectronic control proposed for stereoselective reduction of tetrahydropyridinium salt with a hydride reagent.[16]

Scheme 5



Conclusion

As mentioned above, an enantiomeric pair of the ABC ring system of **1** (**5** and *ent*-**5**) with definite absolute configuration could be synthesized in more than 95% ee. The key steps in the synthesis include the novel diastereoselective reduction of 1,3-disubstituted isoquinoline derivatives **29** and *ent*-**29** to control stereochemistries at the C6 and C11a positions in **5** and *ent*-**5**, respectively, simultaneously in a single step and the intramolecular *N,O*-acetal formation of amino aldehydes **6** and *ent*-**6** to complete the skeletal framework of requisite ring system. On the basis of the results accumulated in these model studies, we next attempted the total synthesis of enantiomeric pairs of **1** and 10-decarboxyquinocarcin (the ABCDE ring system of **1**). This is the subject of the two accompanying papers.[17]

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 (90 MHz) and a Brucker AM-400 (400 MHz) spectrometer.The chemical shifts were expressed in ppm using tetramethylsilane (δ=0) and/or residual solvents such as chloroform (δ=7.25) and benzene (δ=7.20) as internal standards. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), 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 Merck 60 F254 silica gel, glass-supported TLC plates. 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.

Methyl (2-bromo-3-methoxyphenyl)acetate (13)

A mixture of (2-bromo-3-methoxyphenyl)acetonitrile[2] (**12**) (37.5 g, 0.17 mol) and 6M sodium hydroxide (200 ml, 1.2 mol) in methanol (400 ml) was heated at reflux for 12 h. After cooling, the mixture was acidified to pH 3 with 37% aqueous hydrochloric acid, and concentrated *in vacuo* to give a residue, which was diluted with ethyl acetate (1300 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave (2-bromo-3-methoxyphenyl)acetic acid (35.8 g), which was suspended in ether (500 ml). The ethereal suspension was treated with diazomethane in ether (0.65 M solution, 292 ml, 0.19 mol) for 1 h at 0°C. The reaction was quenched with acetic acid (10 ml), and the mixture was diluted with ethyl acetate (900 ml). The organic layer was washed with saturated aqueous sodium hydrogen carbonate and brine, then dried over Na2SO4. Evaporation of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 6:1) to give **13** (37.1 g, 86%, 2 steps) as a colorless oil. IR (neat): 2960, 2930, 2830, 1745 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3) δ: 3.71 (3H, s, CO2Me), 3.83 (2H, s, ArC*H2*), 3.90 (3H, s, ArO*Me*), 6.84 (1H, d, J=8.1 Hz, aromatic proton), 6.92 (1H, d, J=8.1 Hz, aromatic proton), 7.26 (1H, t, J=8.1 Hz, aromatic proton). EIMS m/z: 260 [(M+2)$^+$, ^{81}Br], 258 (M$^+$, ^{79}Br), 245 [(M-Me+2)$^+$, ^{81}Br], 243 [(M-Me)$^+$, ^{79}Br].

6-Benzyloxy-1-(2-bromo-3-methoxyphenyl)-2-hexanone (16)

A solution of **13** (10.0 g, 39 mmol) in dry tetrahydrofuran (150 ml) was added to a stirred solution of lithium diisopropylamide (47 mmol) [prepared from *n*-butyllithium in hexane (1.6 M solution, 29.3 ml, 47 mmol) and diisopropylamine (8.25 ml, 59 mmol)] in dry tetrahydrofuran (400 ml) at -78°C under argon. After 1 h, *N,N,N',N'*-tetramethylenediamine (6.98 ml, 46 mmol) was added, and stirring was continued for 30 min at -78°C. A solution of 5-benzyloxypentanal[8] (9.43 g, 49 mmol) in dry tetrahydrofuran (50 ml) was added, and the mixture was further stirred for 2 h at -78°C. The reaction was quenched with saturated aqueous ammonium chloride (50 ml), and the mixture was diluted with ethyl acetate (700 ml). The organic layer 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, 5:1) to give methyl 7-benzyloxy-2-(2-bromo-3-methoxyphenyl)-3-hydroxyheptanoate (**14**) (12.6 g, 78%) as a mixture of two diasteromers. IR (neat): 3350, 2950, 1740, 1595 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3) δ: 1.15-1.88 (6H, m, C4-H2, C5-H2, and C6-H2) 2.55 (0.4H, d, J=6.2 Hz, C3-H), 3.15 (0.6H, d, J=6.2 Hz, C3-H), 3.36-3.58 (2H, m, C7-H2), 3.68 (3H, s, CO2Me), 3.89 (3H, s, ArO*Me*), 4.08-4.39 (1H, m, C2-H), 4.45 (1H, d, J=5.8 Hz, OC*H2*Ph), 4.56 (1H, d, J=5.8 Hz, OC*H2*Ph), 6.76-7.05 (2H, m, aromatic protons), 7.12-7.38 (6H, m, aromatic protons). This material was directly used for the next reaction without further separation.

2.7 M Jones reagent (16.7 ml, 45 mmol) was added dropwise to a stirred solution of **14** (12.6 g, 30 mmol) in acetone (150 ml) at room temperature. After 20 min, 2-propanol (15 ml) and saturated aqueous sodium hydrogen carbonate (30 ml) were added successively, and the mixture was diluted with ethyl acetate (350 ml). The organic layer was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave methyl 7-benzyloxy-2-(2-bromo-3-methoxyphenyl)-3-oxoheptanoate (**15**) (11.5 g). A solution of **15** in dimethyl sulfoxide (120 ml) containing sodium chloride (1.93 g, 33 mmol) and water (1.50 ml, 83 mmol) was heated at 140°C for 2 h under argon. After cooling, the mixture was diluted with ethyl acetate (350 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, 10:1) to give **16** (10.5 g, 89%, 2 steps) as a colorless oil. IR (neat): 2870, 1710, 1590 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3) δ: 1.46-1.88 (4H, m, C4-H2 and C5-H2) 2.50 (2H, br t, J=6.7 Hz, C3-H2), 3.46 (2H, br t, J=6.7 Hz, C6-H2), 3.86 (2H, s, C1-H2), 3.89 (3H, s, ArO*Me*), 4.49 (2H, s, OC*H2*Ph), 6.80 (2H, d, J=8.1 Hz, aromatic protons), 7.23 (1H, t, J=8.1 Hz, aromatic proton), 7.32 (5H, m, aromatic protons). EIMS m/z: 392 [(M+2)$^+$, ^{81}Br], 390 (M$^+$, ^{79}Br), 377 [(M-Me+2)$^+$, ^{81}Br], 375 [(M-Me)$^+$, ^{79}Br].

6-Benzyloxy-1-(2-bromo-3-methoxyphenyl)-2,2-dimethoxyhexane (17)

dl-10-Camphorsulfonic acid (45.0 mg, 0.20 mmol) was added to a stirred solution of **16** (430 mg, 1.1 mmol) in trimethyl orthoformate (6.00 ml, 55 mmol) containing methanol (3.00 ml, 94 mmol) at room temperature. After 10 h, the mixture was

diluted with ethyl acetate (120 ml). The organic layer was washed successively 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, 20:1) to give **17** (423 mg, 88%) as a colorless oil. IR (neat): 2955, 1635, 1590 cm^{-1}. ^1H-NMR (90 MHz, CDCl3) δ: 1.18-1.75 (6H, m, C3-H2, C4-H2, and C5-H2), 3.18 (2H, s, C1-H2), 3.25 (6H, s, C2-OMe x 2), 3.36 (2H, br t, J=6.8 Hz, C6-H2), 3.86 (3H, s, ArO*Me*), 4.43 (2H, s, OC*H*2Ph), 6.70-6.82 (1H, m, aromatic proton), 7.15-7.41 (7H, m, aromatic protons). EIMS m/z: 438 [(M+2)$^+$, ^{81}Br], 436 (M$^+$, ^{79}Br), 406 [(M-MeOH+2)$^+$, ^{81}Br], 404 [(M-MeOH)$^+$, ^{79}Br].

(*E*)-6-Benzyloxy-1-(2-bromo-3-methoxyphenyl)-2-methoxy-1-hexene (21) and Its (Z)-Isomer (23)

A solution of **17** (400 mg, 0.92 mmol) in methanol (20 ml) containing *dl*-10-camphorsulfonic acid (50.0 mg, 0.22 mmol) was heated at reflux for 1 h. After cooling, the mixture was diluted with ethyl acetate (150 ml). The organic layer 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 separated by column chromatography (hexane-ethyl acetate, 50:1→ 10:1) to give **21** (230 mg, 62%) as a less polar product and **23** (85 mg, 23%) as a more polar product.

21: colorless oil. IR (neat): 2950, 1640, 1590 cm^{-1}. ^1H-NMR (90 MHz, CDCl3) δ: 1.42-1.78 (4H, m, C4-H2 and C5-H2), 2.12-2.37 (2H, m, C3-H2), 3.26-3.62 (2H, m, C6-H2), 3.70 (3H, s, C2-OMe), 3.89 (3H, s, ArO*Me*), 4.45 (2H, s, OC*H*2Ph), 5.58 (1H, s, C1-H), 6.73 (1H, d, J=8.2 Hz, aromatic proton), 6.85 (1H, d, J=8.2 Hz, aromatic proton), 7.19 (1H, t, J=8.2 Hz, aromatic proton), 7.31 (5H, br s, aromatic protons). EIMS m/z: 406 [(M+2)$^+$, ^{81}Br], 404 (M$^+$, ^{79}Br), 391 [(M-Me+2)$^+$, ^{81}Br], 389 [(M-Me)$^+$, ^{79}Br].

23: colorless oil. IR (neat): 2950, 1640, 1590 cm^{-1}. ^1H-NMR (90 MHz, CDCl3) δ: 1.48-1.88 (4H, m, C4-H2 and C5-H2), 2.11-2.47 (2H, m, C3-H2), 3.38-3.61 (2H, m, C6-H2), 3.56 (3H, s, C2-OMe), 3.87 (3H, s, ArO*Me*), 4.52 (2H, s, OC*H*2Ph), 5.72 (1H, s, C1-H), 6.70 (1H, d, J=8.3 Hz, aromatic proton), 7.16 (1H, t, J=8.3 Hz, aromatic proton), 7.31 (5H, s, aromatic protons), 7.45 (1H, d, J=8.3 Hz, aromatic proton). EIMS m/z: 406 [(M+2)$^+$, ^{81}Br], 404 (M$^+$, ^{79}Br), 391 [(M-Me+2)$^+$, ^{81}Br], 389 [(M-Me)$^+$, ^{79}Br].

(*E*)-6-Benzyloxy-1-[2-[1-[(4*S*,5*R*)-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-1-hydroxymethyl]-3-methoxyphenyl]-2-methoxy-1-hexene (26) and Its Enantiomer (*ent*-26)

a) Preparation of **26**: *n*-Butyllithium in hexane (1.6 M solution, 1.08 ml, 1.7 mmol) was added dropwise to a stirred solution of **21** (292 mg, 0.72 mmol) in dry ether (50 ml) at -78°C under argon. After 30 min, a solution of 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose[2,7] (447 mg, 1.8 mmol) in dry ether (10 ml) was added slowly. The mixture was further stirred for 1 h at -78°C, and then allowed to warm up to 0°C. The reaction was quenched with saturated aqueous ammonium chloride (10 ml), and the mixture was extracted with ethyl acetate (200 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 **26** (309 mg, 75%) as a mixture of two diastereomers. This mixture 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, 8:1→ 2:1) to give pure samples of less polar and more polar **26** in a ratio of 76:24.

Less polar 26: colorless caramel. [α]D^{20} -48.7° (c 1.04, CHCl3). IR (neat): 3550, 2950, 2875, 1640, 1590, 1450, 1370, 1260 cm^{-1}. ^1H-NMR (400 MHz, CDCl3) δ: 1.33 (3H, s, acetonide Me), 1.38 (3H, s, acetonide Me), 1.54-1.62 (4H, m, C4-H2 and C5-H2), 2.08-2.20 (2H, m, C3-H2), 3.37-3.42 (2H, m, C6-H2), 3.61 (3H, s, C2-OMe), 3.68 (1H, dd, J=10.3, 6.2 Hz, C*H*2OBn), 3.80 (3H, s, ArO*Me*), 3.80 (1H, dd, J=10.3, 2.8 Hz, C*H*2OBn), 3.85 (1H, d, J=11.0 Hz, OH), 4.23 (1H, t, J=8.0 Hz, C*H*(O-)CH(O-)CH2OBn), 4.35 (1H, ddd, J=8.0, 6.2, 2.8 Hz, CH(O-)C*H*(O-)CH2OBn), 4.44 (2H, s, OC*H*2Ph), 4.64 (2H, s, OC*H*2Ph), 4.95 (1H, dd, J=11.0, 8.6 Hz, C*H*OH), 5.62 (1H, s, C1-H), 6.76 (1H, d, J=7.9 Hz, aromatic proton), 6.77 (1H, d, J=7.9 Hz, aromatic proton), 7.15 (1H, t, J=7.9 Hz, aromatic proton), 7.22-7.38 (10H, m, aromatic protons). EIMS m/z: 561 [(M-Me)$^+$], 545 [M-OMe)$^+$]. HRMS calcd for C34H41O7 [(M-Me)$^+$]: 561.2853. Found: 561.2839.

More polar 26: colorless caramel. [α]D^{20} -38.2° (c 1.34, CHCl3). IR (neat): 3550, 3000, 2950, 2875, 1640, 1600, 1575, 1450, 1370, 1265 cm^{-1}. ^1H-NMR (400 MHz, CDCl3) δ: 1.45 (3H, s, acetonide Me), 1.46 (3H, s, acetonide Me), 1.52-1.62 (4H, m, C4-H2 and C5-H2), 2.10-2.16 (2H, m, C3-H2), 2.96-3.04 (2H, m, C6-H2), 3.39 (2H,m, C*H*2OBn), 3.60 (3H, s, C2-OMe), 3.72 (1H, d, J=10.3 Hz, OH), 3.74 (3H, s, ArO*Me*), 3.89 (1H, ddd, J=7.5, 4.8, 2.3 Hz, CH(O-)C*H*(O-)CH2OBn), 4.33 (1H, t, J=7.5 Hz, C*H*(O-)CH(O-)CH2OBn), 4.33 (1H, d, J=12.4 Hz, OC*H*2Ph), 4.34 (1H, d, J=12.4 Hz, OC*H*2Ph), 4.44 (2H, s, OC*H*2Ph), 5.07 (1H, dd, J=10.3, 8.0 Hz, C*H*OH), 5.58 (1H, s, C1-H), 6.69 (1H, d, J=7.9 Hz, aromatic proton), 6.73 (1H, d, J=7.9 Hz, aromatic proton), 7.13 (1H, t, J=7.9 Hz, aromatic proton), 7.15-7.36 (10H, m, aromatic protons). EIMS m/z: 577 [(M+1)$^+$], 545 [M-OMe)$^+$]. HRMS calcd for C35H45O7 [(M+1)$^+$]: 577.3166. Found: 577.3162.

b) Preparation of *ent*-**26**: The same treatments of **21** (313 mg, 0.77 mmol) and 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose[2,7] (480 mg, 1.9 mmol) as described for the preparation of **26** gave *ent*-**26** (353 mg, 79%) as a mixture of two diastereomers, which was directly used for the next reaction without separation. Further separation of this mixture by column chromatography (hexane-ethyl acetate, 8:1→2:1) gave pure samples of less polar and more polar *ent*-**26** in a ratio of 74:26.

Less polar *ent*-26: colorless caramel. $[\alpha]D^{20}$ +52.3° (c 1.04, CHCl3). The IR, ^{1}H-NMR, mass spectra of this sample were identical with those recorded for less polar **26**.

More polar *ent*-26: colorless caramel. $[\alpha]D^{20}$ +38.9° (c 1.31, CHCl3). The IR, ^{1}H-NMR, mass spectra of this sample were identical with those recorded for more polar **26**.

3-(4-Benzyloxybutyl)-1-[(4*R*,5*R*)-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-8-methoxyisoquinoline (29) and Its Enantiomer (*ent*-29)

a) Preparation of **29**: Pyridine (2.55 ml, 32 mmol) was added dropwise to a stirred suspension of chromium (VI) oxide (1.28 g, 13 mmol) in dry dichloromethane (25 ml) containing dry celite (5 g) at room temperature under argon. After 20 min, a solution of **26** (365 mg, 0.64 mmol) in dry dichloromethane (15 ml) was added slowly to the above mixture, and stirring was continued for 1 h at room temperature. The resulting mixture was diluted with ether (50 ml), then 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 (*E*)-6-benzyloxy-1-[2-[(4*R*,5*R*)-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbonyl]-3-methoxyphenyl]-2-methoxy-1-hexene (**27**) (361 mg) as a pale yellow oil. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.32 (3H, s, acetonide Me), 1.45 (3H, s, acetonide Me), 1.51-1.65 (4H, m, C4-H2 and C5-H2), 2.18 (2H, br t, J=7.0 Hz, C3-H2), 3.37-3.47 (3H, m, C6-H2 and C*H*2OBn), 3.52-3.57 (1H,m, C*H*2OBn), 3.53 (3H, s, C2-OMe), 3.74 (3H, s, ArOMe), 4.36 (1H, ddd, J=8.4, 6.1, 3.2 Hz, CH(O-)C*H*(O-)CH2OBn), 4.46 (2H, s, OC*H*2Ph), 4.49 (2H, s, OC*H*2Ph), 4.72 (1H, d, J=8.4 Hz, C*H*(O-)CH(O-)CH2OBn), 5.47 (1H, s, C1-H), 6.71 (1H, d, J=8.3 Hz, aromatic proton), 6.78 (1H, d, J=8.3 Hz, aromatic proton), 7.21-7.35 (11H, m, aromatic protons). This material was directly used for the next step without further purification.

A solution of crude **27** (361 mg) in tetrahydrofuran (20 ml) was treated with 1M hydrochloric acid (2.50 ml, 2.5 mmol) for 2 h at room temperature. The mixture was neutralized with saturated aqueous sodium hydrogen carbonate and extracted with ethyl acetate (200 ml). The extract was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave 6-benzyloxy-1-[2-[(4*R*,5*R*)-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolane-4-carbonyl]-3-methoxyphenyl]-2-hexanone (**28**) (328 mg) as pale yellow oil. ^{1}H-NMR (90 MHz, CDCl3) δ: 1.31 (3H, s, acetonide Me), 1.43 (3H, s, acetonide Me), 1.48-1.75 (4H, m, C4-H2 and C5-H2), 2.48 (2H, br t, J=7.0 Hz, C3-H2), 3.28-3.97 (6H, m, C1-H2, C6-H2, and C*H*2OBn), 3.75 (3H, s, ArO*Me*), 4.27 (1H, m, CH(O-)C*H*(O-)CH2OBn), 4.48 (2H, s, OC*H*2Ph), 4.57 (2H, s, OC*H*2Ph), 4.84 (1H, d, J=7.9 Hz, C*H*(O-)CH(O-)CH2OBn), 6.81 (2H, d, J=8.1 Hz, aromatic proton), 7.20-7.42 (11H, m, aromatic protons). This material was directly used for the next reaction without further purification.

38% Aqueous ammonia (5.00 ml, 0.11mol) was added to a stirred solution of crude **28** (328 mg) in tetrahydrofuran (20 ml) at room temperature. After 5 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, 8:1) to give **29** (145 mg, 42%, 3 steps) as a colorless oil. $[\alpha]D^{20}$ +59.7° (c 1.02, CHCl3). IR (neat): 2950, 2875, 1620, 1565, 1455, 1370, 1310 cm^{-1}.^{1}H-NMR (400 MHz, CDCl3) δ: 1.56 (3H, s, acetonide Me), 1.59 (3H, s, acetonide Me), 1.63-1.72 (2H, m, CH2CH2C*H*2CH2OBn), 1.83-1.92 (2H, m, CH2C*H*2CH2CH2OBn), 2.85 (1H, dd, J=14.4, 7.5 Hz, C*H*2CH2CH2CH2OBn), 2.93 (1H, dd, J=14.4, 7.5 Hz, C*H*2CH2CH2CH2OBn), 3.49 (2H, t, J=6.5 Hz, CH2CH2CH2C*H*2OBn), 3.70 (1H, dd, J=10.7, 6.2 Hz, C*H*2OBn), 3.77 (1H,dd, J=10.7, 2.9 Hz, C*H*2OBn), 3.95 (3H, s, ArO*Me*), 4.48 (2H, s, OC*H*2Ph), 4.59 (2H, s, OC*H*2Ph), 5.22 (1H, ddd, J=8.2, 6.2, 2.9 Hz, CH(O-)C*H*(O-)CH2OBn), 6.07 (1H, d, J=8.2 Hz, C*H*(O-)CH(O-)CH2OBn), 6.84 (1H, d, J=7.9 Hz, C5-H or C7-H), 7.16-7.35 (11H, m, aromatic protons), 7.48 (1H, t, J=7.9 Hz, C6-H). EIMS m/z: 542 [(M+1)$^+$], 526 [M-Me)$^+$], 483 [(M-MeCOMe)$^+$]. HRMS calcd for C34H40NO5 [(M+1)$^+$]: 542.2908. Found: 542.2915.

b) Preparation of *ent*-**29**: The same treatments of *ent*-**26** (327 mg, 0.57 mmol) as described for the preparation of **29** from **26** gave *ent*-**29** (150 mg, 49%, 3 steps) as a colorless oil *via ent*-**27** and *ent*-**28**. $[\alpha]D^{20}$ -60.4° (c 1.02, CHCl3). The IR, ^{1}H-NMR, mass spectra of this sample were identical with those recorded for **29**.

(1*R*,3*R*)-*tert*-Butyl 3-(4-benzyloxybutyl)-1-[(1*R*,2*R*)-3-benzyloxy-1,2-dihydroxypropyl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (32) and Its Enantiomer (*ent*-32)

a) Preparation of **32**: Sodium cyanoborohydride (487 mg, 7.8 mmol) was added in small portions to a stirred solution of **29** (280 mg, 0.52 mmol) in 37% aqueous hydrochloric acid-methanol (1:100) (25 ml) at 0°C. After 1 h, 37% aqueous hydrochloric acid (4 ml) was added, and stirring was continued for 10 h at room temperature. The mixture was neutralized with 10% aqueous sodium hydroxide and extracted with ethyl acetate (200 ml). The extract was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave a residue (255 mg), which was dissolved in chloroform (10 ml) containing di-*tert*-butyl dicarbonate (226 mg, 1.0 mmol) and triethylamine (0.288 ml, 2.0 mmol). The mixture was heated at reflux for 5 h. After cooling, the mixture was concentrated *in vacuo* to give a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→ 4:1) to give **32** (247 mg, 79%, 3 steps) as a colorless oil. $[\alpha]D^{20}$ -19.4°(c 0.99, CHCl3). IR (neat): 3450, 2950, 2870, 1660, 1600, 1480, 1450, 1400, 1365, 1335 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.49 (9H, s, ^{t}Bu), 1.35-1.70 (5H, m, C*H*2C*H*2C*H*2CH2OBn), 1.96-2.10 (1H, m, C*H*2CH2CH2CH2OBn), 2.34-3.42 (2H, m, OH x 2), 2.67 (1H, dd, J=15.3, 11.5 Hz, C4-H), 3.03 (1H, dd, J=15.3, 6.5 Hz, C4-H), 3.45-3.50 (2H, m, C*H*2OBn), 3.63-3.37 (4H,m, C*H*2OBn and C*H*(OH)C*H*(OH), 3.83 (3H, s, ArO*Me*), 3.99-4.06 (1H, m, C3-H), 4.50 (1H, d, J=12.0 Hz, OC*H*2Ph), 4.51 (1H, d, J=12.0 Hz, OC*H*2Ph), 4.57

(1H, d, J=12.0 Hz, OC*H*2Ph), 4.59 (1H, d, J=12.0 Hz, OC*H*2Ph), 5.68 (1H, d, J=10.9 Hz, C1-H), 6.76 (iH, d, J=8.2 Hz, C5-H or C7-H), 6.79 (1H, d, J=8.2 Hz, C5-H or C7-H), 7.19 (1H, t, J=8.2 Hz, C6-H). EIMS m/z: 424 [(M-CH(OH)CH(OH)-CH2OBn)$^+$].

b) Preparation of *ent*-**32**: The same treatments of *ent*-**29** (230mg, 0.42 mmol) as described for the preparation of **32** from **29** gave *ent*-**32** (189 mg, 74%, 3 steps) as a colorless oil. [α]D^{20} +19.4° (c 1.04, CHCl3). The IR, ^{1}H-NMR, mass spectra of this sample were identical with those recorded for **32**.

(1R,3*R*)-*tert*-Butyl 3-(4-benzyloxybutyl)-1-hydroxymethyl-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (33) and Its Enantiomer (*ent*-33)

a) Preparation of **33**: Sodium periodate (278 mg, 1.3 mmol) was added to a stirred solution of **32** (167 mg, 0.35 mmol) in methanol-water (10:1) (12 ml) at room temperature. After 5 h, sodium borohydride (21.0 mg, 0.54 mmol) was added, and stirring was continued for 30 min at room temperature. The reaction was quenched with 3% aqueous hydrochloric acid (2 ml), and the mixture was diluted with ethyl acetate (200 ml). The organic layer 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 **33** (155 mg, 94%) as a colorless oil. [α]D^{20} +10.5° (c 1.05, CHCl3). IR (neat): 3450, 2940, 2860, 1670, 1590, 1460, 1390, 1360, 1260 cm^{-1}.^{1}H-NMR (400 MHz, CDCl3) δ: 1.47 (9H, s, ^{t}Bu), 1.44-1.72 (5H, m, C*H*2C*H*2C*H*2CH2OBn), 1.86-1.96 (1H, m, C*H*2CH2CH2CH2OBn), 2.71 (1H, dd, J=15.9, 7.2 Hz, C4-H), 2.99 (1H, dd, J=15.9, 7.2 Hz, C4-H), 3.49 (2H, m, C*H*2OBn), 3.59 (1H,dd, J=10.5, 9.3 Hz, C*H*2OH), 3.83 (3H, s, ArO*Me*), 3.92 (1H,dd, J=10.5, 9.3 Hz, C*H*2OH), 4.15 (1H, br s, C3-H), 4.50 (2H, s, OC*H*2Ph), 5.66 (1H, br s, C1-H), 6.74 (2H, d, J=7.9 Hz, C5-H and C7-H), 7.17 (1H, t, J=7.9 Hz, C6-H), 7.24-7.36 (5H, 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: 424 [(M-CH2OH)$^+$]. HRMS calcd for C26H34NO4 [(M-CH2OH)$^+$]: 424.2489. Found: 424.2496.

b) Preparation of *ent*-**33**: The same treatments of *ent*-**32** (190mg, 0.40 mmol) as described for the preparation of **33** from **32** gave *ent*-**33** (142 mg, 99%) as a colorless oil. [α]D^{20} -10.6° (c 1.02, CHCl3). The IR, ^{1}H-NMR, mass spectra of this sample were identical with those recorded for **33**.

(1*R*,3*R*)-*tert*-Butyl 3-(4-benzyloxybutyl)-8-methoxy-1-methoxymethoxymethyl-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (34) and Its Enantiomer (*ent*-34)

a) Preparation of **34**: Chloromethyl methyl ether (0.76 ml, 10 mmol) was added to a stirred solution of **33** (125 mg, 0.27 mmol) in dry tetrahydrofuran (2 ml) containing *N*,*N*-diisopropylethylamine (1.80 ml, 10 mmol) at room temperature under argon. After 1 h, the mixture was diluted with ethyl acetate (100 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, 6:1) to give **34** (132 mg, 96%) as a colorless oil. [α]D^{20} -8.8° (c 1.18, CHCl3). IR (neat): 3450, 2950, 2870, 1690, 1590, 1470, 1390, 1365, 1260 cm^{-1}.^{1}H-NMR (400 MHz, CDCl3) δ: 1.45 (9H, s, ^{t}Bu), 1.40-1.82 (5H, m, C*H*2C*H*2C*H*2CH2OBn), 1.96-2.08 (1H, m, C*H*2CH2CH2CH2OBn), 2.75 (1H, dd, J=15.9, 8.3 Hz, C4-H), 2.99 (1H, br dd, J=15.9, 6,9 Hz, C4-H), 3.26 (3H, s, CH2O*Me*), 3.49 (2H, t, J=6.5 Hz, C*H*2OBn), 3.63-3.69 (1H, m, C*H*2OMOM), 3.71-3.77 (1H, m, C*H*2OMOM), 3.82 (3H, s, ArOMe), 3.90-4.16 (1H, m, C3-H), 4.50 (2H, s, OC*H*2Ph), 4.57 (1H, d, J=6.5 Hz, OC*H*2OMe), 4.64 (1H, d, J=6.5 Hz, OC*H*2OMe), 5.83 (1H, br s, C1-H), 6.73 (2H, d, J=7.9 Hz, C5-H and C7-H), 7.15 (1H, t, J=7.9 Hz, C6-H), 7.24-7.36 (5H, 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: 499 (M$^+$), 424 [(M-CH2OMOM)$^+$]. HRMS calcd for C29H41NO6 (M$^+$): 499.2935. Found: 499.2931.

b) Preparation of *ent*-**34**: The same treatments of *ent*-**33** (162mg, 0.37 mmol) as described for the preparation of **34** from **33** gave *ent*-**34** (167 mg, 90%) as a colorless oil. [α]D^{20} +8.8° (c 1.18, CHCl3). The IR, ^{1}H-NMR, mass spectra of this sample were identical with those recorded for **34**.

(4*R*,6*R*,11a*R*)-4-Cyano-6-hydroxymethyl-7-methoxy-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizine (5) and Its Enantiomer (*ent*-5)

a) Preparation of **5**: A mixture of **34** (85.0 mg, 0.17 mmol) and 10% palladium on carbon (30 mg) in methanol (10 ml) was stirred for 1 h at room temperature under hydrogen atmosphere (1 atm). The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give (1*R*,3*R*)-*tert*-butyl 3-(4-hydroxybutyl)-8-methoxy-1-methoxymethoxymethyl-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (**35**) (68 mg) as a colorless oil. ^{1}H-NMR (90 MHz, CDCl3) δ: 1.48 (9H, s, ^{t}Bu), 1.40-1.78 (5H, m, C*H*2C*H*2C*H*2CH2OH), 1.85-2.07 (1H, m, C*H*2CH2CH2CH2OH), 2.88 (1H, dd, J=12.8, 7.9 Hz, C4-H), 3.22 (1H, dd, J=12.8, 6.5 Hz, C4-H), 3.31 (3H, s, CH2O*Me*), 3.52-3.93 (4H, m, C*H*2OH and C*H*2OMOM), 3.83 (3H, s, ArO*Me*), 3.99-4.31 (1H, m, C3-H), 4.59 (1H, d, J=6.8 Hz, OC*H*2OMe), 4.72 (1H, d, J=6.8 Hz, OC*H*2OMe), 5.82 (1H, br t, J=6.7 Hz, C1-H), 6.76 (2H, d, J=8.1 Hz, C5-H and C7-H), 7.20 (1H, t, J=8.1 Hz, C6-H). This material was directly used for the next reaction without further purification.

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 crude **35** (68 mg) 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 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, 2:1) to give (1*R*,3*R*)-*tert*-butyl 3-(3-formylpropyl)-8-methoxy-1-methoxymethoxymethyl-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (**36**) (61.7 mg, 89%) as a colorless oil. ^{1}H-NMR (90 MHz, CDCl3) δ: 1.49 (9H, s, ^{t}Bu), 1.36-1.88 (5H, m, C*H*2C*H*2C*H*2CH2OH), 1.88-2.17 (1H, m, C*H*2CH2CH2CH2OH), 2.53 (1H, br t, J=12.8 Hz, C4-H), 2.92 (1H, dd, J=12.8, 7.8 Hz, C4-H), 3.29 (3H, s, CH2O*Me*), 3.62-3.89 (2H, m, C*H*2OMOM), , 3.81 (3H, s, ArO*Me*), 3.97-4.28 (1H, m, C3-H), 4.56 (1H, d, J=6.6 Hz, OC*H*2OMe), 4.68 (1H, d, J=6.6 Hz, OC*H*2OMe), 5.88 (1H, br dd, J=8.9, 5.7 Hz, C1-H), 6.77 (2H, d, J=8.1 Hz, C5-H and C7-H), 7.18 (1H, t, J=8.1 Hz, C6-H), 9.79(1H, br t, J=1.6 Hz, CHO). This material was immediately used for the next step to avoid decomposition.

Bromotrimethylsilane (0.200 ml, 1.5 mmol) was added dropwise to a stirred solution of **36** (61.7 mg, 0.15 mmol) in dry dichloromethane (3.5 ml) at room temperature under argon. After 10 min, the mixture was concentrated *in vacuo* to give a residue, which was dissolved in methanol (3 ml). The methanolic solution was treated with sodium cyanide (74.2 mg, 1.5 mmol) for 1 h at room temperature. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 1:1) to give **5** (24.3 mg, 59%, 3 steps) as a colorless caramel. [α]D^{20} -17.7° (c 1.39, CHCl3). IR (neat): 3500, 2950, 2220, 1590, 1475, 1385, 1260, 1080, 1060, 750 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.38 (1H, tdd, J=12.7, 10.7, 4.6 Hz, C1-H), 1.70-2.06 (5H, m, C1-H, C2-H2, and C3-H2), 2.38 (1H, dd, J=7.9, 4.2 Hz, OH), 2.59 (1H, d, J=14.7 Hz, C11-H), 2.63 (1H, d, J=14.7 Hz, C11-H), 2.72-2.81 (1H, m, C11a-H), 3.56 (1H, ddd, 10.4, 7.9, 4.1 Hz, C*H*2OH), 3.75 (1H, dt, 10.4, 4.1 Hz, C*H*2OH), 3.82 (3H, s, ArO*Me*), 4.19-4.23 (2H, m, C4-H and C10-H), 6.68 (1H, d, J=7.9 Hz, C8-H or C10-H), 6.73 (1H, d, J=7.9 Hz, C8-H or C10-H), 7.13 (1H, t, J=7.9 Hz, C9-H). EIMS m/z: 273 [(M+1)$^+$], 241 [(M-CH2OH)$^+$]. HRMS calcd for C16H21N2O2 [(M+1)$^+$]: 273.1604. Found: 273.1619.

In order to determine the optical purity of **5**, it was derived to (*R*)-[(4*R*, 6*R*, 11a*R*)-4-cyano-7-methoxy-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizin-6-yl]methyl α-methoxy-α-(trifluoromethyl)phenylacetate [(*R*)-MTPA ester] and (*S*)-[(4*R*, 6*R*, 11a*R*)-4-cyano-7-methoxy-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizin-6-yl]methyl α-methoxy-α-(trifluoromethyl)phenyl acetate [(*S*)-MTPA ester] by treatments with (*R*)- and (S)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*R*)- and (*S*)-MTPACl] in pyridine for 1 h at room temperature under argon (88% and 91% yields, respectively). Comparison of the 400 MHz ^{1}H-NMR spectra of (*R*)- and (*S*)-MTPA esters obviously disclosed that the optical purity of **4** is more than 95% ee.

b) Preparation of *ent*-**5**: The same treatments of *ent*-**34** (56.1mg, 0.11 mmol) as described for the preparation of **5** from **34** gave *ent*-**5** (19.3 mg, 63%) as a colorless caramel *via ent*-**35** and *ent*-**36**. [α]D^{20} +17.4° (c 1.37, CHCl3). The IR, ^{1}H-NMR, mass spectra of this sample were identical with those recorded for **5**.

The optical purity of *ent*-**5** was determined as more than 95% ee in a similar manner to that described in a).

[(4*R*,6*R*,11a*R*)-4-Cyano-7-methoxy-1,3,4,6,11,11a-hexahydro-2*H*-benzo[*b*]quinolizin-6-yl]methyl acetate (39) and Its Enantiomer (*ent*-39)

a) Preparation of **39**: Acetic anhydride (0.139 ml, 1.5 mmol) was added dropwise to a stirred solution of **5** (20.0 mg, 74 μmol) in pyridine (1 ml) containing a catalytic amount of 4-dimethylaminopyridine (2.70 mg, 22 μmol) at room temperature under argon. After 12 h, the mixture was diluted with ethyl acetate (50 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, 2:1) to give **39** (19.2 mg, 83%) as a colorless caramel. [α]D^{20} +16.3° (c 0.56, MeOH). IR (neat): 2950, 1740, 1595, 1460, 1380, 1260, 1225, 1095, 1060, 780 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3) δ: 1.31 (1H, tdd, J=12.9, 10.4, 4.4 Hz, C1-H), 1.60-1.99 (5H, m, C1-H, C2-H2, and C3-H2), 2.02 (3H, s, OAc), 2.55-2.65 (2H, m, C11-H2), 2.66-2.75 (1H, m, C11a-H), 3.81 (3H, s, ArO*Me*), 4.00 (1H, dd, 11.4, 6.8 Hz, C*H*2OAc), 4.24 (1H, br t, J=3.5 Hz, C4-H), 4.28-4.35 (2H, m, C*H*2OAc and C6-H), 6.69 (1H, d, J=7.9 Hz, C8-H or C10-H), 6.72 (1H, d, J=7.9 Hz, C8-H or C10-H), 7.15 (1H, t, J=7.9 Hz, C9-H). MS m/z: 287 [(M-HCN)$^+$], 241 [(M-CH2OAc)$^+$].

b) Preparation of *ent*-**39**: The same treatments of *ent*-**5** (19.1mg, 72 μmol) as described for the preparation of **39** from **5** gave *ent*-**39** (20.0 mg, 91%) as a colorless caramel. [α]D^{20} -16.5° (c 0.84, MeOH). The IR, ^{1}H-NMR, mass spectra of this sample were identical with those recorded for **39**.

(1*R*, 5*R*, 10b*R*)-1-[(*R*)-2-Benzyloxy-1-hydroxyethyl]-5-(4-benzyloxybutyl)-10-methoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (40)

Sodium hydride (60% dispersion in mineral oil, 13.8 mg, 0.35 mmol) was added to a stirred solution of **32** (19.5 mg, 32 μmol) in dry tetrahydrofuran (2 ml) at room temperature under argon. After 1 h, the reaction was quenched with 3% aqueous hydrochloric acid (0.5 ml), and the mixture was diluted with ethyl acetate (50 ml). The organic layer 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 **40** (15.1 mg, 88%) as a colorless oil. $[\alpha]D^{20}$ -144° (c 1.18, CHCl3). IR (neat): 3400, 2925, 2860, 1740, 1590, 1470, 1450, 1430, 1350, 1300, 1250 cm^{-1}.^{1}H-NMR (400 MHz, CDCl3) δ: 1.58-1.78 (4H, m, CH2C*H2*C*H2*CH2OBn), 1.88 (1H, ddt, J=14.3, 7.5, 0.8 Hz, C*H2*CH2CH2CH2OBn), 2.62 (1H, ddt, J=14.3, 7.5, 0.8 Hz, C*H2*CH2CH2CH2OBn), 2.73 (1H, dd, J=15.3, 2.4 Hz, C6-H), 2.86 (1H, br dd, J=15.3, 11.5 Hz, C6-H), 3.25 (1H, ddt, J=11.5, 7.5, 2.4 Hz, C5-H), 3.48-3.56 (5H, m, C*H2*OBn x 2 and C*H*OH), 3.60 (3H, s, ArO*Me*), 4.47 (1H, d, J=11.7 Hz, OC*H2*Ph), 4.50 (2H, s, OC*H2*Ph), 4.51 (1H, d, J=11.7 Hz, OC*H2*Ph), 4.84 (1H, d, J=8.6 Hz, C1-H), 5.29 (1H, d, J=8.6 Hz, C10b-H), 6.73 (1H, d, J=8.0 Hz, C7-H or C9-H), 6.75 (1H, d, J=8.0 Hz, C7-H or C9-H), 7.19 (1H, t, J=8.0 Hz, C8-H), 7.24-7.36 (10H, m, aromatic protons). MS m/z: 531 (M^+), 440 [$(M-Bn)^+$]. HRMS calcd for C32H37NO6 (M^+): 531.2622. Found: 531.2600.

References and Notes

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