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Synthetic Studies on Quinocarcin and Its Related Compounds. 1.[1] Synthesis of Enantiomeric Pairs of the ABE Ring Systems of Quinocarcin

Shoichi Saito,[2] Osamu Tamura,[3] Yuko Kobayashi,[4] Fuyuhiko Matsuda,[5] Tadashi Katoh, Shiro Terashima*

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

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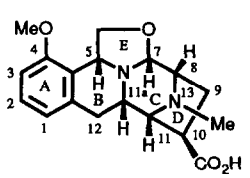
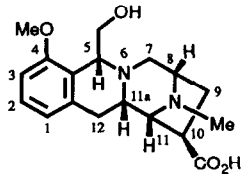
Abstract: *Enantiomeric pairs of the ABE ring system (5 and ent-5) and its analogues (6, ent-6, 7, and ent-7) of quinocarcin (1), a prominent antitumor antibiotic, were synthesized in >95% ee with an aim to elucidate structure-activity relationships of 1. The key step of the synthesis includes novel diastereoselective reduction of 3,4-dihydroisoquinoline derivatives 25 and ent-25, wherein each enantiomer of 4-O-benzyl-2,3-O-isopropylidene-threose (I and ent-I) is employed as a chiral auxiliary.*

(–)-Quinocarcin (**1**) isolated from the culture broth of *Streptomyces melanovinaceus* in 1983,[6] exhibits potent antitumor activity against several types of solid mammalian carcinomas including St-4 gastric carcinoma, M5076 sarcoma, Co-3 human colon carcinoma, B16 melanoma, and MX-1 human mammary carcinoma.[7] Quincarcinol (**2**), the pharmacologically inactive dihydroderivative of **1**, was also isolated from the same culture broth.[6] Cyanation of **1** with sodium cyanide or potassium cyanide can produce the more stable 7-cyano derivative, DX-52-1 (**3**), which still retains significant antitumor activity of **1**.[8] It is also reported that treatment of **3** with silver nitrate or hydrochloric acid can cleanly regenerate **1**.[8] The stereostructure of **1** except absolute configuration was revealed by X-ray diffraction and spectral studies to have a novel 8,11-iminoazepino[1,2-*b*]isoquinoline skeleton with six asymmetric centers.[9] The absolute configuration of **1** depicted below was suggested by Remers *et al.* in 1988 on the basis of computer simulation of binding of **1** to DNA.[10] In 1992, Garner *et al.* completed the asymmetric synthesis of (–)-**1**, leading to confirmation of its absolute configuration.[11]



1



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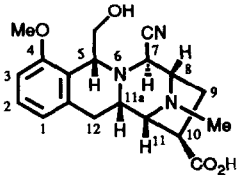

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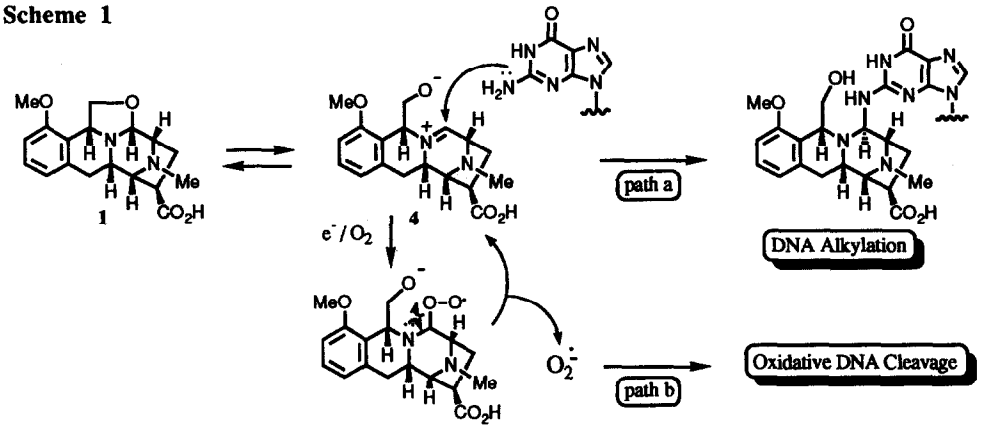
Scheme 1

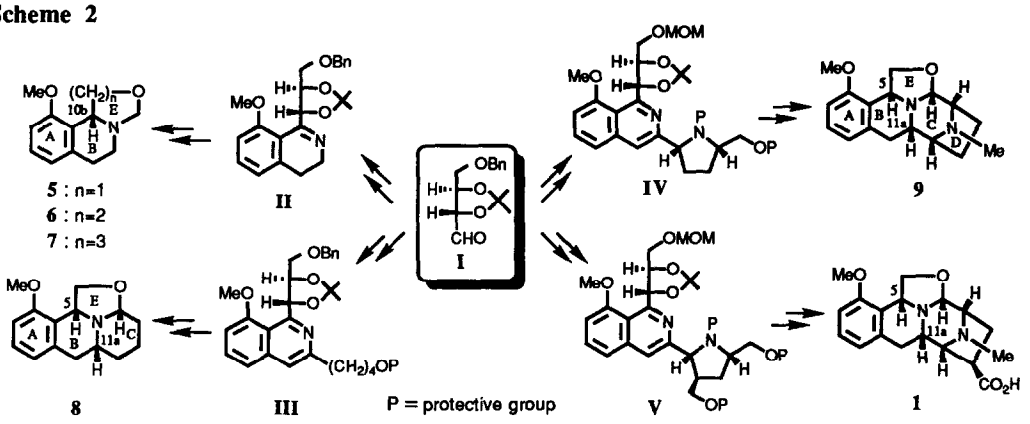


It was reported that **1** inhibits DNA synthesis in preference to RNA and protein synthesis in *Bacillus subtilis*.[7a] Two plausible modes of antitumor actions have hitherto been proposed for **1** as outlined in **Scheme 1**. Thus, one is the alkylation of the 2-amino group of guanine in a minor grove of DNA by the iminium ion **4** generated by opening of the oxazolidine ring in **1** (path a).[10] The other one is the oxidative cleavage of DNA by a superoxide radical anion produced by auto-redox disproportionation of the oxazolidine ring of **1** (path b).[12] These suggestions indicate that the oxazolidine ring (or its equivalent such as an α-cyanoamino group) plays an important role in exhibiting significant antitumor activity, while it is not yet clear which mode of action is responsible for the antitumor properties. Taking into account its unique structural feature and remarkable antitumor activity, we embarked on the total synthesis of optically active **1** with an aim to disclose novel aspects of the structure-activity relationships of **1**.[13-15] Our earnest endeavors culminated in completing the total synthesis of (–)-**1** and in exploring 10-decarboxyquinocarcin congeners which are 10^{1-3} times more cytotoxic than natural **1** and its 7-cyano congeners against P388 murine luekemia.[1d] This series of papers concerns with complete details of the total synthesis of an enantiomeric pair of **1** as well as antitumor activity of various structural types of quinocarcin congeners.[1]

Synthetic Strategy

At the time that this project was initiated, the absolute configuration of **1** was unknown. Therefore, an efficient and flexible synthetic scheme was sought which can provide enantiomeric pairs of **1** and various structural types of quinocarcin congeners with definite absolute configurations. The synthetic route outlined in **Scheme 2** was explored as a unified synthetic strategy applicable to construction of the ABE ring systems (**5**, **6**, and **7**), the ABCE ring system (**8**), the ABCDE ring system (**9**), and **1**. The key feature in our synthetic scheme depends upon diastereoselective reduction of the 3,4-dihydroisoquinoline **II**, and the isoquinolines **III**, **IV**, and **V** to control the stereochemistry(-ies) of asymmetric center(s) at the C_{10b} position (3*H*-oxazolo[4,3-*b*]isoquinoline numbering) of **5**, **6**, and **7** and at the C_5 and C_{11a} positions (quinocarcin numbering) of **8**, **9**, and **1**, respectively, wherein threose derivative **I**[16] can be employed as a common chiral auxiliary. The first part of this series of papers concerns full details of the synthesis of enantiomeric pairs of the ABE ring systems (**5**, *ent*-**5**, **6**, *ent*-**6**, **7**, and *ent*-**7**).[1a]

Scheme 2



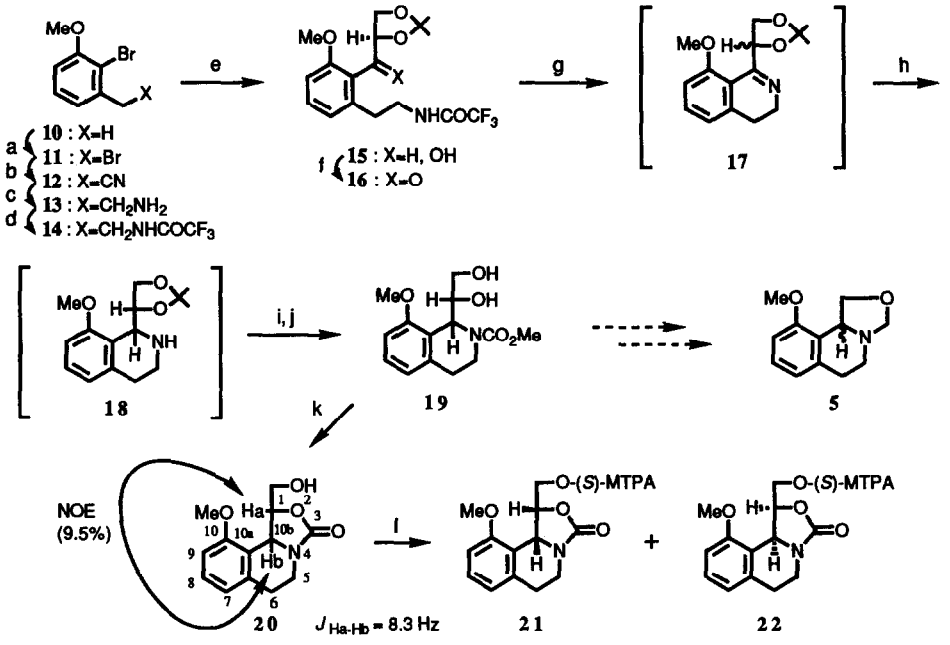
Results and Discussion

1. Initial Attempts to Prepare the ABE Ring System (*ent*-5) in an Optically Active Form by Use of 2,3-*O*-Isopropylidene-L-glyceraldehyde as a Chiral Auxiliary

We initially pursued the preparation of **5** in an optically active form by employing 2,3-*O*-isopropylidene-L-glyceraldehyde[17] as a chiral auxiliary as shown in **Scheme 3**. After considerable experimentation, however, this chiral auxiliary turned out to be useless because complete racemization occurred during formation of the key intermediate **17** (**16**→**17**). Thus, benzylic bromination of 2-bromo-3-methylanisole (**10**) prepared from commercially available 2-methyl-6-nitroaniline according to the reported method,[18] followed by treatment of the resulting benzyl bromide **11** with sodium cyanide provided the benzyl cyanide **12**. After reduction of **12** with borane-tetrahydrofuran complex, protection of the resulting phenethylamine **13** furnished the trifluoroacetamide **14**. The coupling reaction of the aryl lithium generated *in situ* from **14** with 2,3-*O*-isopropylidene-L-glyceraldehyde[17] cleanly took place to afford the desired adduct **15** as an epimeric mixture, which was further subjected to Collins oxidation without separation to give ketone **16**.

Crucial reduction of the 3,4-dihydroisoquinoline **17** produced *in situ* by removal of the trifluoroacetyl group in **16** with potassium carbonate in methanol, with sodium cyanoborohydride[19] provided the tetrahydroisoquinoline **18**. This could be isolated in a form of diol carbamate **19** after sequential acidic hydrolysis of the acetonide group and protection of the amino group. The 400 MHz ^{1}H-NMR spectrum of the 2-oxazolidinone **20** derived from **19** exhibited the coupling constant of 8.3 Hz[20] for Ha and Hb and NOE (9.5%) between the signals due to Ha and Hb, establishing their *cis*-relationships. At this stage, the possible racemization was concerned under the basic treatment required in the step for **16**→**17** because **16** includes only one asymmetric center at the α-position of carbonyl group. Therefore, we decided to determine the optical purity of **20**. As concerned, treatment of **20** with (*S*)-MTPA chloride in pyridine[21] gave the corresponding two separable (*S*)-MTPA esters **21** and **22** in a ratio of *ca.*1:1. These observations definitely disclosed that the reduction of **17** took place in a highly diastereoselective manner while **16** or less possibly **17** underwent complete racemization under the basic reaction conditions. Although the initial attempts to prepare optically active **5** turned out to be unsuccessful, the results obtained here proved to be very useful in the subsequent investigations.

Scheme 3



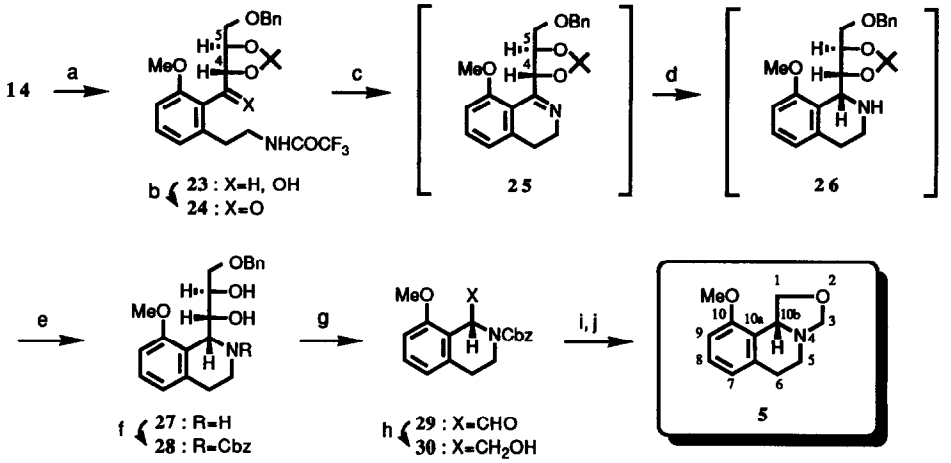
reagents and conditions : a) Br_2, CCl_4, 0°C b) NaCN, DMSO, rt, 67%(2 steps) c) BH_3•THF, THF, reflux d) CF_3CO_2Et, Et_3N, MeOH, rt, 78%(2 steps) e) ^{n}BuLi, Et_2O, -78°C ; 2,3-*O*-isopropylidene-L-glyceraldehyde, -78→0°C, 85% f) Collins oxid., 84% g) K_2CO_3, MeOH-H_2O(5:2v/v), rt h) $NaBH_3CN$, MeOH-H_2O(5:2v/v), rt i) HCl, MeOH, rt, j) $ClCO_2Me$, 1M NaOH, CH_2Cl_2, rt, 86%(4 steps) k) 10%KOH-MeOH, rt, 86% l) (*S*)-MTPACl, Py, rt, 85%

2. Synthesis of an Enantiomeric Pair of the ABE Ring System (5 and *ent*-5) by Use of 4-*O*-Benzyl-2,3-*O*-isopropylidene-D-threose as a Chiral Auxiliary

The racemization problem mentioned above was found to be completely circumvented by using 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose[16] (**I**) instead of glyceraldehyde derivative as a chiral auxiliary. Being different from **16** and **17** bearing the 4-monosubstituted-1,3-dioxolane systems, it was anticipated that, in the synthetic intermediates **24** and **25** readily accessible from **I** similarly to **16** and **17**, possible epimerization of the C4 positions in *trans*-4,5-disubstituted-1,3-dioxolane systems would be prohibited due to the presence of benzyloxymethyl group at the C5 positions. Thus, even if deprotonation at the C4 positions of *trans*-4,5-disubstituted-1,3-dioxolane systems in **24** and **25** takes place under basic conditions, subsequent protonation under thermodynamically and/or kinetically controlled conditions can smoothly regenerate the initial *trans*-4,5-disubstituted systems. It was also expected that the benzyloxymethyl group could be deleted by oxidative cleavage at the later steps. This expectation turned out to be the case as shown in **Scheme 4**.

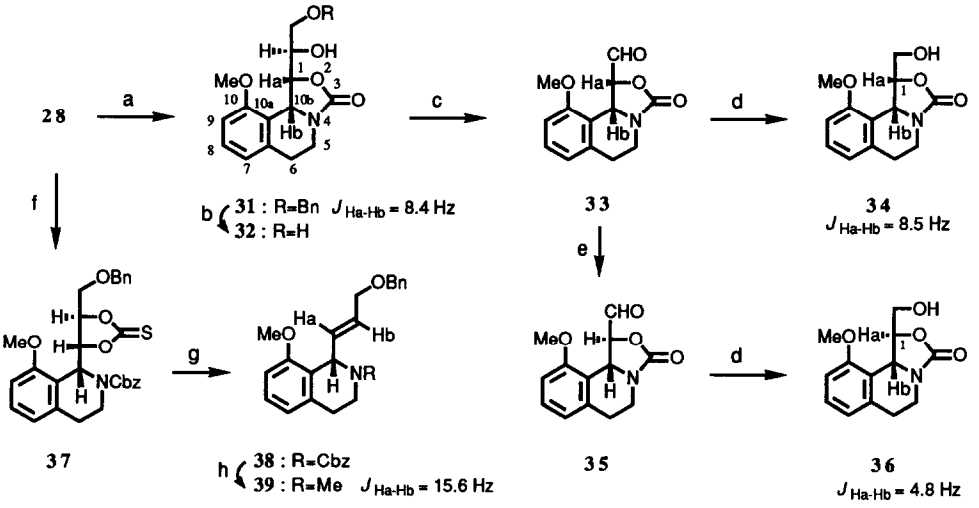
By employing the reaction sequence similar to that described for the preparation of **19**, **14** was converted to diol carbamate **28** *via* **23**-**27**. The stereostructure of **28** was unambiguously confirmed based on the 400 MHz ^{1}H-NMR spectra of the 2-oxazolidinone derivatives derived from **28** (*vide infra*). Additionally, we were delighted to find that the optical purity of **27** was more than 95% ee (*vide infra*). The final task remaining to complete the synthesis of **5** was the construction of the E ring in **5**. Thus, oxidative cleavage of the vicinal diol moiety of **28** provided aldehyde **29**, which was immediately reduced with sodium borohydride

Scheme 4



reagents and conditions : a) ^{n}BuLi, Et_2O, -78°C ; 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose, -78→0°C, 88% b) Collins oxid., 83% c) K_2CO_3, MeOH-H_2O(5:2 v/v), rt d) $NaBH_3CN$, MeOH-H_2O(5:2 v/v), 0°C e) HCl, MeOH, rt, f) CbzCl, 1M NaOH, CH_2Cl_2, rt, 83%(4 steps) g) $NaIO_4$, MeOH-H_2O(10:1 v/v), rt, 94% h) $NaBH_4$, MeOH-H_2O(10:1 v/v), rt, 98% (2 steps) i) H_2, 10%Pd-C, MeOH, rt j) 35% HCHO, MeOH, rt, 73%(2 steps)

Scheme 5



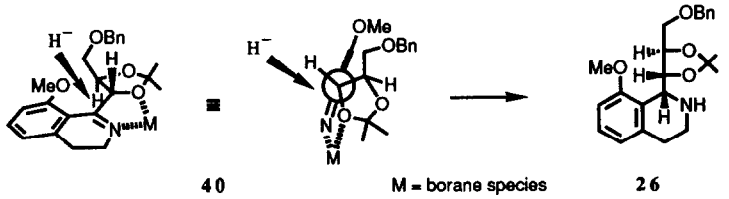
reagents and conditions : a) 10%KOH-MeOH, rt, 96% b) H_2, 10%Pd-C, MeOH, rt, 88% c) $NaIO_4$, MeOH-H_2O(10:1 v/v), 91% d)$NaBH_4$, MeOH-H_2O(10:1 v/v), 96% for 33, 93%(2 steps) for 35 e) K_2CO_3, MeOH, rt f) thiocarbonyldiimidazole, toluene, reflux, 78% g) $(MeO)_3P$, reflux, 79% h) $LiAlH_4$, Et_2O, rt, 85%

to give alcohol **30**. Removal of the Cbz (benzyloxycarbonyl) group in **30** followed by treatment of the resulting amino alcohol with aqueous formaldehyde in methanol furnished **5**, >95% ee (*vide infra*).

In order to determine the stereostructure of **28**, it was converted to 2-oxazolidinone derivatives **31**, **34**, and **36** as shown in **Scheme 5**. Thus, treatment of **28** with potassium hydroxide in methanol cleanly afforded the 2-oxazolidinone **31**. Debenzylation of **31** followed by oxidative cleavage of the resulting diol **32** furnished aldehyde **33**. Immediate reduction of **33** with sodium borohydride provided the *cis*-2-oxazolidinone **34**. On the other hand, treatment of **33** with potassium carbonate in methanol at ambient temperature effected epimerization to the thermodynamically more stable aldehyde **35**, which was immediately reduced to furnish the *trans*-2-oxazolidinone **36** being epimeric at the C1 position in **34**. The 400 MHz ^{1}H-NMR spectra of **31** and **34** showed the coupling constants of 8.4 Hz and 8.5 Hz between Ha and Hb, respectively, supporting their 4,5-*cis*-disubstituted-2-oxazolidinone systems.[20] On the other hand, the corresponding coupling constant in the 400 MHz ^{1}H-NMR spectrum of **36** was 4.8 Hz, assigning its *trans* arrangement.[20] Moreover, **28** was subjected to stereospecific olefin formation[22] providing olefin **38** *via* thiocarbonate **37**, which was further reduced with lithium aluminium hydride to give the *N*-methylamine **39**. The (*E*)-configuration of **39** was rigorously confirmed by the observation of the coupling constant of 15.6 Hz between Ha and Hb in its 400 MHz ^{1}H-NMR spectrum, establishing *trans*-configuration of the diol functionality in **28**. These spectral features unambiguously disclosed that the stereostructure of **28** can be assigned as depicted and that no epimerization occurs during formation of the key intermediates **24** and **25**, being different from the cases for **16** and **17**.

The remarkable diastereoselectivity observed for the reduction of **25** can be explained by the well-known Cram's chelation model[23] as shown in **Figure 1**. Thus, the hydride attack exclusively takes place from the least hindered side through the five-membered cyclic chelating transition state (see, **40**) which might be produced by the chelation with a borane species. In this transition state, the stereochemistry at the α-position of imine moiety can play a key role for the crucial 1,2-asymmetric induction.

Figure 1



40 M = borane species **26**

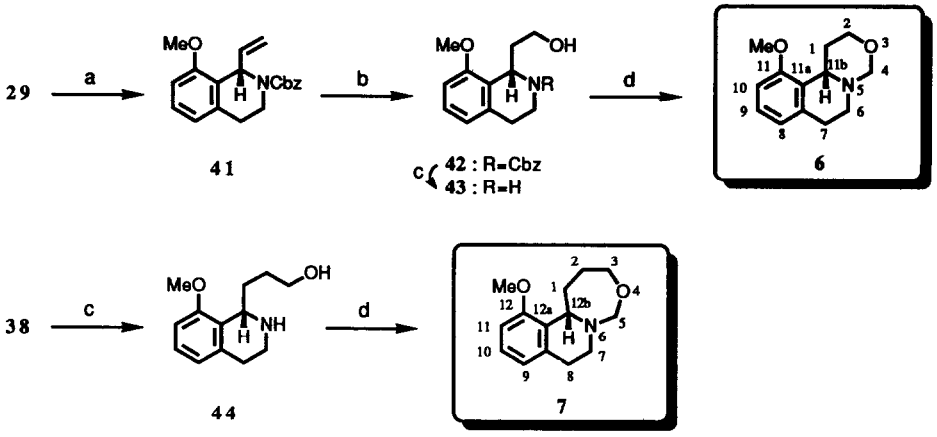
By employing 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose[16] (*ent*-**I**) instead of **I**, the enantiomeric ABE ring system (*ent*-**5**) was synthesized in the same reaction sequence as described above *via ent*-**23**-*ent*-**30**.

Finally, in order to determine the optical purity of both **5** and *ent*-**5**, two sorts of the *N*-protected amino alcohols **30** and *ent*-**30** were converted to the corresponding MTPA esters.[21] Comparison of their 400 MHz ^{1}H-NMR spectra established that the optical purity of both **5** and *ent*-**5** were more than 95% ee.

3. Synthesis of Enantiomeric Pairs of Analogues of the ABE Ring System (6, *ent*-6, 7, and *ent*-7)

We became interested in the modification of the E ring in **5**, because the E ring in **1** plays an important role for its remarkable antitumor activity as stated earlier. Accordingly, as shown in **Scheme 6**, we next

Scheme 6



reagents and conditions : a) CH_2I_2, Zn, Me_3Al, rt, 97% b) BH_3•SMe_2, THF, rt ; H_2O_2, NaOH, 48%, c) H_2, 10%Pd-C, AcOEt, rt d) 35% HCHO, MeOH, rt, 78%(2 steps) for **6**, 52%(2 steps) for **7**

addressed on the synthesis of analogues **6** and **7**, in which the E ring of **5** is replaced with larger six- and seven-membered rings, respectively. These analogues (**6** and **7**) were designed by expecting their superior cytotoxicity to that of **5**. Thus, olefination of **29** was best achieved by employing a combination of diiodomethane, zinc powder, and trimethylaluminium developed by Oshima *et al.*,[24] giving rise to olefin **41** in 97% yield. Several initial attempts on the olefination employing Wittig reagent resulted in poor yields (15-37%) of **41**, presumably due to steric hindrance of the carbonyl group in **29**. Hydroboration of **41** followed by treatment with alkaline hydrogen peroxide afforded alcohol **42**. Hydrogenolysis of **42** produced amino alcohol **43**, which was further treated with aqueous formaldehyde in methanol without purification to furnish the six-membered cyclic amino acetal **6**, >95% ee.[25] On the other hand, simultaneous hydrogenolysis and hydrogenation of **38** provided amino alcohol **44**, which was similarly treated with aqueous formaldehyde to give the seven-membered cyclic amino acetal **7**, >95% ee.

The enantiomeric cyclic amino acetals *ent*-**6** and *ent*-**7** (both >95% ee) were synthesized in the same manners as described above by employing 4-*O*-benzyl-2,3-*O*-isopropylidene -L-threose[16] (*ent*-**I**) instead of **I**.

Results of antitumor activity assay of the synthesized compounds (**5**, *ent*-**5**, **6**, *ent*-**6**, **7**, and *ent*-**7**) are the subject of the accompanying paper.[26]

Conclusion

We have succeeded in developing an efficient synthetic scheme to enantiomeric pairs of the ABE ring system of **1** (**5** and *ent*-**5**) and their congeners (**6**, *ent*-**6**, **7**, and *ent*-**7**) with definite absolute configurations by employing each enantiomer of 4-*O*-benzyl-2,3-*O*-isopropylidenethreose (**I** and *ent*-**I**) as a chiral auxiliary and featuring a novel diastereoselective reduction of 3,4-dihydroisoquinoline derivatives **25** and *ent*-**25**. In order to further assess feasibility of the explored synthetic methodology, we next investigated the synthesis of an enantiomeric pair of the ABCE ring system (**8** and *ent*-**8**). This is the subject of the accompanying paper.[27]

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), a Bruker AC-200 (200 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, tetrahydrofuran, and toluene were distilled from sodium benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon.

(2-Bromo-3-methoxyphenyl)acetonitrile (12)

A solution of bromine (12.8 ml, 0.25 mol) in carbon tetrachloride (80 ml) was added slowly to a stirred solution of 2-bromo-3-methylanisole[18] (**10**) (50.0 g, 0.25 mol) in carbon tetrachloride (500 ml) at 0°C. After 3 h, the mixture was diluted with chloroform (550 ml). The organic layer was washed successively with saturated aqueous sodium hydrogen carbonate, saturated aqueous sodium thiosulfate, water, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave 2-bromo-3-methoxybenzyl bromide (**11**) (67.4 g) as a pale yellow solid. IR (KBr): 2960, 2930, 2830, 1570 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3): δ 3.90 (3H, s, OMe), 4.64 (2H, s, CH2Br), 6.60-7.60 (3H, m, aromatic protons). EIMS m/z: 282 [(M+4)$^+$, ^{81}Br x 2], 280 [(M+2)$^+$, ^{81}Br, ^{79}Br], 278 (M$^+$, ^{79}Br x 2), 201 [(M-Br+2)$^+$, ^{81}Br, ^{79}Br], 199 [(M-Br)$^+$, ^{79}Br x 2]. This material was directly used for the next reaction without further purification.

Sodium cyanide (12.3 g, 0.25 mol) was added to a stirred solution of crude **11** (67.4 g) in dimethyl sulfoxide (300 ml) at room temperature under argon. After 1 h, the mixture was diluted with ethyl acetate (1500 ml). The organic layer was washed with water, and brine, then dried over Na2SO4. Evaporation of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 8:1→ 4:1) to give **12** (37.5 g, 67%, 2 steps) as a white solid. Recrystallization from hexane-ether afforded an analytical sample of **12** as colorless prisms, mp 56-57 °C. IR (KBr): 2210, 1585, 1570, 1465, 1425, 1285, 1060, 1020 cm^{-1}.^{1}H-NMR (200 MHz, CDCl3): δ 3.87 (2H, s, CH2CN), 3.92 (3H, s, OMe), 6.90 (1H, d, J=7.9 Hz, aromatic proton), 7.16 (1H, d, J=7.9 Hz, aromatic proton), 7.33 (1H, t, J=7.9 Hz, aromatic proton). EIMS m/z: 227 [(M+2)$^+$, ^{81}Br], 225 (M$^+$, ^{79}Br), 146, 103. *Anal.* Calcd for C9H8BrNO: C, 47.82; H, 3.57, N, 6.20%. Found: C, 47.84; H, 3.46, N, 6.09%.

***N*-Trifluoroacetyl-2-(2-bromo-3-methoxyphenyl)ethylamine (14)**

A solution of **12** (9.27 g, 41 mmol) in dry tetrahydrofuran (100 ml) was added to borane-tetrahydrofuran complex in tetrahydrofuran (1.0 M solution, 243 ml, 0.24 mol), and the mixture was heated at reflux for 1 h under argon. After cooling, methanol (80 ml) and 1M hydrochloric acid (30 ml) were added successively to the mixture, and stirring was continued for 15 min at room temperature. The resulting mixture was neutralized with 1M sodium hydroxide and extracted with ethyl acetate (550 ml), and the extract was washed with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* gave 2-(2-bromo-3-methoxypheny)ethylamine (**13**) (9.25 g) as a colorless oil. ^{1}H-NMR (90 MHz, CDCl3): δ 2.96 (2H, br s, NH2), 3.52-3.76 (4H, m, CH2CH2), 3.90 (3H, s, OMe), 6.62-7.43 (3H, m, aromatic protons). This material was directly used for the next reaction without further purification.

Ethyl trifluoroacetate (19.5 ml, 0.16 mol) was added to a stirred solution of crude **13** (9.25 g) in methanol (160 ml) containing triethylamine (11.4 ml, 82 mmol) at room temperature under argon. After 30 min, concentration of the mixture *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 10:1→ 6:1) to give **14** (10.4 g, 78%, 2 steps) as a white solid. Recrystallization from chloroform-hexane afforded an analytical sample of **14** as colorless prisms, mp 113-114 °C. IR (KBr): 3350, 1708, 1580, 1465 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3): δ 3.12 (2H, t, J=6.0 Hz, CH2), 3.68 (2H, q, J=6.0 Hz, CH2), 3.91 (3H, s, OMe), 6.38 (1H, br s, NH), 6.83 (2H, d, J=8.0 Hz, aromatic protons), 7.27 (1H, t, J=8.0 Hz, aromatic proton). EIMS m/z: 327 [(M+2)$^+$, ^{81}Br], 325 (M$^+$, ^{79}Br). *Anal.* Calcd for C11H11BrF3NO2: C, 40.51; H, 3.40, N, 4.30%. Found: C, 40.68; H, 3.32, N, 4.28%.

***N*-Trifluoroacetyl-2-[3-methoxy-2-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-carbonyl]phenyl]ethylamine (16)**

n-Butyllithium in hexane (1.6 M solution, 4.50 ml, 7.2 mmol) was added dropwise to a stirred solution of **14** (750 mg, 2.3 mmol) in dry ether (100 ml) at -78°C under argon. After 30 min, a solution of 2,3-*O*-isopropylidene-L-glyceraldehyde[17] (1.81 g, 7.3 mmol) in dry ether (15 ml) was added slowly, and the mixture was further stirred for 1 h at -78°C and then allowed to warm up to 0°C. The resulting mixture was quenched with saturated aqueous ammonium chloride (25 ml) and diluted with ethyl acetate (150 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, 6:1→ 2:1) to give *N*-trifluoroacetyl-2-[3-methoxy-2-[1-hydroxy-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl]phenyl]ethylamine (**15**) (737 mg, 85%) as a mixture of two diastereomers. This material was directly used for the next reaction without further separation.

Pyridine (4.03 ml, 50 mmol) was added dropwise to a stirred suspension of chromium (III) oxide (2.00 g, 20 mmol) in dry dichloromethane (25 ml) containing dry celite (5 g) at room temperature under argon. After 20 min, a solution of **15** (737 mg, 2.0 mmol) in dry dichloromethane (15 ml) was added slowly to the above mixture. After 1 h, the resulting mixture was diluted with ether (50 ml) and 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 a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1→ 3:1) to give **16** (630 mg, 84%) as a colorless oil. $[\alpha]D^{20}$ +16.1° (c 1.38, CHCl3). ^{1}H-NMR (90 MHz, CDCl3): δ 1.31 (3H, s, acetonide Me), 1.36 (3H, s, acetonide Me), 2.75 (2H, t, J=6.0 Hz, CH2C*H2*NHCOCF3), 3.61 (2H, q, J=6.0 Hz, C*H2*CH2NHCOCF3), 3.87 (3H, s, ArO*Me*), 4.23 (2H, d, J=6.0 Hz, COCH(O-)C*H2*O-), 5.11 (1H, d, J=6.0 Hz, COC*H*(O-)CH2O-), 6.90 (1H, d, J=8.0 Hz, aromatic proton), 6.93 (1H, d, J=8.0 Hz, aromatic proton), 7.42 (1H, t, J=8.0 Hz, aromatic proton). EIMS m/z: 375 (M^+), 360 [$(M\text{-}Me)^+$], 274.

Methyl 1-(1,2-dihydroxyethyl)-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (19)

Potassium carbonate (179 mg, 3.3 mmol) was added to a stirred solution of **16** (500 mg, 1.3 mmol) in methanol-water (5:2) (20 ml) at room temperature. After 2 h, sodium cyanoborohydride (816 mg, 13 mmol) was added in small portions to the above mixture, and stirring was continued for 30 min at room temperature. The resulting mixture was diluted with ethyl acetate (50 ml), and 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 1-(2,2-dimethyl-1,3-dioxolan-4-yl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**18**) (331 mg), which was dissolved in methanol (15 ml). The methanolic solution was treated with 37% aqueous hydrochloric acid (0.5 ml) for 15 h at room temperature. The mixture was concentrated *in vacuo* to give a residue, which was dissolved in dichloromethane (10 ml). 1M Sodium hydroxide (10 ml) and methyl chloroformate (3.01 ml, 39 mmol) was added to the above solution, and the resulting mixture was stirred for 1.5 h at room temperature. The mixture was diluted with ethyl acetate (30 ml), and 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, 1:1→ 1:3) to give **19** (322 mg, 86%, 3 steps) as a colorless caramel. ^{1}H-NMR (90 MHz, CDCl3): δ 2.62-3.23 (3H, m, OCH2CHO), 3.33-3.92 (4H, m, C3-H2 and C4-H2), 3.77 (3H, s, CO2Me), 3.87 (3H, s, ArO*Me*), 5.60 (1H, br s, OH), 6.83 (2H, d, J=8.0 Hz, aromatic protons), 7.25 (1H, t, J=8.0 Hz, aromatic proton). EIMS m/z: 250 [$(M\text{-}CH2OH)^+$], 220 [$(M\text{-}CH(OH)CH2OH)^+$].

1-Hydroxymethyl-10-methoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (20)

Potassium hydroxide (1.20 g, 21 mmol) was added to a stirred solution of **19** (300 mg, 1.1 mmol) in methanol (15 ml) at room temperature. After 10 min, the mixture was neutralized with 10% aqueous hydrochloric acid and extracted with ethyl acetate (100 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, 1:1→1:2) to give **20** (229 mg, 86%) as a colorless caramel. ^{1}H-NMR (400 MHz, CDCl3): δ 2.02 (1H, br s, OH), 2.73 (1H, ddd, J=15.4, 3.3, 1.3 Hz, C6-H), 2.92 (1H, ddd, J=15.4, 12.9, 5.6 Hz, C6-H), 3.03 (1H, dt, J=12.9, 3.3 Hz, C5-H), 3.28 (1H, m, C*H2*OH), 3.43 (1H, m, C*H2*OH), 3.85 (3H, s, ArO*Me*), 4.14 (1H, ddd, J=12.9, 5.6, 1.3 Hz, C5-H), 5.04 (1H, ddd, J=8.3, 6.5, 2.9 Hz, C1-H), 5.19 (1H, d, J=8.3 Hz, C10b-H), 6.76 (1H, d, J=8.2 Hz, aromatic proton), 6.79 (1H, d, J=8.2 Hz, aromatic proton), 7.23 (1H, t, J=8.2 Hz, aromatic proton). EIMS m/z: 249 (M^+), 231 [$(M\text{-}H2O)^+$], 218 [$(M\text{-}CH2OH)^+$].

(*S*)-[10-Methoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinolin-1-yl]methyl α-methoxy-α-(trifluoromethyl)phenylacetates [(*S*)-MTPA Esters of 20] (21 and 22)

(*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride [(*S*)-MTPA Cl] (91.4 μl, 0.49 mmol) was added to a stirred solution of **20** (94.0 mg, 0.38 mmol) in pyridine (5 ml) at 0°C. After 30 min, 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 two products, which were separated by column chromatography (hexane-ethyl acetate, 6:1→3:1) to give a less polar product (**21** or **22**) (73.7 mg, 42%) and a more polar product (**22** or **21**) (75.5 mg, 43%) both as a colorless caramel.

Less polar product : ^{1}H-NMR (400 MHz, CDCl3): δ 2.37 (1H, ddd, J=15.7, 3.2, 1.2 Hz, C6-H), 2.63 (1H, ddd, J=15.7, 12.7, 5.9 Hz, C6-H), 2.94 (1H, dt, J=12.7, 3.2 Hz, C5-H), 3.54 (3H, d, J=1.3 Hz, C-OMe),3.80 (1H, dd, J=12.3, 4.0 Hz, OCH2), 3.84 (3H, s, ArO*Me*), 4.06 (1H, ddd, J=12.7, 5.9, 1.2 Hz, C5-H), 4.37 (1H, dd, J=12.3, 2.7 Hz, OCH2), 5.17 (1H, d, J=8.5 Hz, C10b-H), 5.23 (1H, ddd, J=8.5, 4.0, 2.0 Hz, C1-H), 6.21 (1H, d, J=8.1 Hz, C7-H or C9-H), 6.66 (1H, d, J=8.1 Hz, C7-H or C9-H), 6.99 (1H, t, J=8.1 Hz, C8-H), 7.27-7.41 (5H, m, aromatic protons). EIMS m/z: 465 (M^+), 232 [$(M\text{-}OCOC(OMe)(CF3)Ph)^+$].

More polar product : ^{1}H-NMR (400 MHz, CDCl3): δ 2.65 (1H, ddd, J=16.0, 3.7, 1.2 Hz, C6-H), 2.80 (1H, ddd, J=16.0, 12.1, 6.0 Hz, C6-H), 3.00 (1H, dt, J=12.3, 3.6 Hz, C5-H), 3.37 (3H, d, J=1.1 Hz, C-OMe), 3.85 (3H, s, ArO*Me*), 4.02 (1H, dd, J=12.1, 6.1 Hz, OCH2), 4.03 (1H, ddd, J=12.3, 6.0, 1.2 Hz, C5-H), 4.19 (1H, dd, J=12.1, 1.5 Hz, OCH2), 5.17 (1H, d, J=8.5 Hz, C10b-H), 5.22 (1H, ddd, J=8.5, 6.1, 1.5 Hz, C1-H), 6.76 (1H, d, J=8.2 Hz, C7-H or C9-H), 6.79 (1H, d, J=8.2 Hz, C7-H or C9-H), 7.23 (1H, t, J=8.2 Hz, C8-H), 7.37-7.41 (5H, m, aromatic protons). EIMS m/z: 465 (M^+), 232 [(M-OCOC(OMe)-(CF3)Ph)$^+$].

***N*-Trifluoroacetyl-2-[2-[(4*S*,5*R*)-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-carbonyl]-3-methoxyphenyl]ethylamine (24) and Its Enantiomer (*ent*-24)**

a) Preparation of **24**: **14** (208 mg, 0.64 mmol) and 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose[16] (325 mg, 1.3 mmol) were treated in the same manner as described for the preparation of **16** from **14** to give **24** (231 mg, 73%, 2 steps) as a white solid after purification by column chromatography (hexane-ethyl acetate, 4:1) *via N*-trifluoroacetyl-2-[2-[(4*R*,5*R*)-5-benzyloxymethyl-1,3-dioxolan-4-yl]-1-hydroxymethyl]-3-methoxyphenyl]ethylamine (**23**). Recrystallization from hexane gave an analytical sample of **24** as colorless needles, mp 66-67.5 °C and [α]D^{20} +18.5° (c 1.09, CHCl3). IR (KBr): 3350, 1710, 1680, 1580, 1555 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3): δ 1.30 (3H, s, acetonide Me), 1.42 (3H, s, acetonide Me), 2.69 (2H, dd, J=6.8, 5.4 Hz, C*H*2NHCOCF3), 3.42-3.75 (4H, m, C*H*2OBn and C*H*2Ar), 3.81 (3H, s, ArO*Me*), 4.32-4.54 (1H, m, C*H*CH2OBn), 4.55 (1H, d, J=5.2 Hz, OC*H*2Ph), 5.01 (1H, d, J=5.2 Hz, OC*H*2Ph), 4.91 (1H, d, J=8.6 Hz, ArCO-C*H*), 6.83 (1H, d, J=8.1 Hz, aromatic proton), 6.87 (1H, d, J=8.1 Hz, aromatic proton), 7.31 (5H, br s, OCH2*Ph*), 7.40 (1H, t, J=8.1 Hz, aromatic proton), 7.75 (1H, br s, NHCOCF3). EIMS m/z: 495 (M^+), 480 [(M-Me)$^+$], 437 [(M-Me2CO)$^+$]. *Anal.* Calcd for C25H28F3NO6: C, 60.60; H, 5.70; N, 2.83%. Found: C, 60.44; H, 5.83; N, 2.85%.

b) Preparation of *ent*-**24**: The same treatments of **14** (240mg, 0.74 mmol) and 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose[16] (375 mg, 1.5 mmol) as described for the preparation of **24** from **14** and 4-*O*-benzyl-2,3-*O*-isopropylidene-D-threose gave *ent*-**24** (284 mg, 78%, 2 steps) as colorless needles *via ent*-**23**. mp 66.5-67 °C. [α]D^{20} -17.9° (c 1.00, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **24**.

(*R*)-Benzyl 1-[(1*R*,2*R*)-3-benzyloxy-1,2-dihydroxypropyl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (28) and Its Enantiomer (*ent*-28)

a) Preparation of **28**: Potassium carbonate (158 mg, 1.1 mmol) was added to a stirred solution of **24** (350 mg, 0.71 mmol) in methanol-water (5:2) (10 ml) at room temperature. After 4 h, sodium cyanoborohydride (509 mg, 8.1 mmol) was added in small portions to the above methanolic solution of **25** at 0°C, and stirring was continued for 1 h at 0°C. The resulting mixture was diluted with ethyl acetate (30 ml), and 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 (*R*)-1-[(4*R*,5*R*)-5-benzyloxymethyl-2,2-dimethyl-1,3-dioxolan-4-yl]-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**26**) (279 mg), which was dissolved in methanol-water (5:2) (30 ml). The methanolic solution was treated with 37% aqueous hydrochloric acid (2.5 ml) for 12 h at room temperature. The solvent was concentrated *in vacuo* to give (*R*)-1-[(1*R*,2*R*)-3-benzyloxy-1,2-dihydroxyproyl]-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**27**) (235 mg), which was dissolved in dichloromethane (20 ml). The dichloromethane solution was further treated with benzyl chloroformate (0.50 ml, 3.5 ml) and 1M sodium hydroxide (10 ml) for 1 h at room temperature. The mixture was neutralized with 3% aqueous hydrochloric acid and diluted with ethyl acetate (40 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 **28** (280 mg, 83%, 3 steps) as a colorless oil. [α]D^{20} -17.1°(c 1.00, CHCl3). IR (neat): 3350, 2950, 1670, 1590, 1480, 1410 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 2.65 (1H, d, J=10.1 Hz, OH), 2.78 (1H, br dt, J=15.5, 3.4 Hz, C4-H), 2.98 (1H, br ddd, J=15.5, 12.2, 6.2 Hz, C4-H), 3.41 (1H, br dt, J=12.1, 5.2 Hz, C3-H), 3.58-3.70 (2H, m, C*H*2OBn), 3.71-3.79 (1H, m, C*H*CH2OBn), 3.83 (3H, s, ArO*Me*), 3.89 (1H, ddd, J=12.1, 6.2, 1.2 Hz, C3-H), 4.31 (1H, d, J=4.1 Hz, OH), 4.52 (1H, d, J=12.0 Hz, CH2OC*H*2Ph), 4.57 (1H, d, J=12.0 Hz, CH2OC*H*2Ph), 5.13 (1H, d, J=12.5 Hz, NCO2C*H*2Ph), 5.18 (1H, d, J=12.5 Hz, NCO2C*H*2Ph), 5.61 (1H, d, J=9.8 Hz, C1-H), 6.79 (2H, d, J=7.8 Hz, C5-H and C7-H), 7.19 (1H, t, J=7.8 Hz, C6-H), 7.26-7.38 (10H, m, aromatic protons). Due to the presence of rotamers in the benzyl carbamate group, line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 478 [(M+1)$^+$], 370 [(M-OBn)$^+$], 296 [(M-CH(OH)CH(OH)CH2OBn)$^+$]. HRMS calcd for C28H32NO6 [(M+1)$^+$]: 478.2163. Found: 478.2195.

b) Preparation of *ent*-**28**: The same treatments of *ent*-**24** (385mg, 0.81 mmol) as described for the preparation of **28** from **24** gave *ent*-**28** (303 mg, 78%, 3 steps) as a colorless oil *via ent*-**25**-*ent*-**27**. [α]D^{20} +16.5° (c 1.03, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **28**.

(*R*)-Benzyl 1-formyl-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (29) and Its Enantiomer (*ent*-29)

a) Preparation of **29**: Sodium periodate (118 mg, 0.55 mmol) was added to a stirred solution of **28** (167 mg, 0.35 mmol) in methanol-water (10:1) (10 ml) at 0°C. After 5 h, the mixture was diluted with water (6 ml) and extracted with ethyl acetate (25

ml). The extract was washed successively with saturated aqueous thiosulfate, 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 **29** (103 mg, 94%) as a colorless oil. $[\alpha]D^{20}$ -144° (c 0.65, CHCl3). IR (CHCl3): 1735, 1700, 1590, 1480, 1420 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 2.66-2.78 (1H, m, C4-H), 2.79-2.93 (1H, m, C4-H), 3.38 (0.5H, ddd, J=13.0, 8.9, 4.5 Hz, C3-H), 3.48 (0.5H, ddd, J=13.0, 8.9, 4.5 Hz, C3-H), 3.88 (1.5H, s, ArO*Me*), 3.89 (1.5H, s, ArO*Me*), 3.94 (1H, dt, J=13.0, 4.5 Hz, C3-H), 4.06 (1H, dt, J=13.0, 4.5 Hz, C3-H), 5.17 (0.5H, d, J=12.4 Hz, NCO2C*H*2Ph), 5.20 (0.5H, d, J=12.4 Hz, NCO2C*H*2Ph), 5.23 (0.5H, d, J=12.4 Hz, NCO2C*H*2Ph), 5.24 (0.5H, d, J=12.4 Hz, NCO2C*H*2Ph), 5.95 (0.5H, br s, C1-H), 6.12 (0.5H, br s, C1-H), 6.79 (1H, br d, J=8.0 Hz, C5-H or C7-H), 6.81 (1H, br d, J=8.0 Hz, C5-H or C7-H), 7.28 (0.5H, br t, J=8.0 Hz, C6-H), 7.29 (0.5H, br t, J=8.0 Hz, C6-H), 7.29-7.42 (5H, m, aromatic protons), 9.61 (0.5H, br s, CHO), 9.71 (0.5H, br s, CHO). Due to the presence of rotamers in the benzyl carbamate group, line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 296 [(M-CHO)$^+$]. HRMS calcd for C19H19NO4 [(M-CHO)$^+$]: 296.1280. Found: 296.1288.

b) Preparation of *ent*-**29**: The same treatments of *ent*-**28** (301 mg, 0.63 mmol) as described for the preparation **29** from **28** gave *ent*-**29** (195 mg, 95%) as a colorless oil. $[\alpha]D^{20}$ +160° (c 1.16, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **29**.

(*R*)-Benzyl 1-hydroxymethyl-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (30) and Its Enantiomer (*ent*-30)

a) Preparation of **30**: Sodium borohydride (21.0 mg, 0.54 mmol) was added to a stirred solution of **29** (103 mg, 0.32 mmol) in methanol-water (10:1) (5 ml) at room temperature. After 15 min, the reaction was quenched with 3% aqueous hydrochloric acid (1 ml), and the mixture was extracted with ethyl acetate (13 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, 2:1) to give **30** (102 mg, 92%) as a colorless oil. $[\alpha]D^{20}$ +60.0° (c 1.12, CHCl3). IR (neat): 3450, 2950, 1680, 1520, 1430 cm^{-1}. ^{1}H-NMR (90 MHz, CDCl3): δ 2.55 (1H, br s, OH), 2.73-2.97 (2H, m, C4-H2), 3.23-4.41 (4H, m, C*H*2OH and C3-H2), 3.83 (3H, s, ArO*Me*), 5.26 (2H, br s, OC*H*2Ph), 5.63 (1H, m, C1-H), 6.73 (2H, d, J=8.3 Hz, C5-H or C7-H), 7.16 (1H, t, J=8.3 Hz, C6-H), 7.35 (5H, br s, aromatic protons). EIMS m/z: 328 [(M+1)$^+$], 296 [(M-CH2OH)$^+$]. HRMS calcd for C19H22NO4[(M+1)$^+$]: 328.1578. Found: 328.1564.

b) Preparation of *ent*-**30**: The same treatments of *ent*-**29** (188 mg, 0.58 mmol) as described for the preparation of **30** from **29** gave *ent*-**30** (183 mg, 96%) as a colorless caramel. $[\alpha]D^{20}$ -59.7° (c 1.11, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **30**.

(*R*)-10-Methoxy-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (5) and Its Enantiomer (*ent*-5)

a) Preparation of **5**: A mixture of **30** (50.2 mg, 0.15 mmol) and 10% palladium on carbon (25 mg) in methanol (8 ml) was stirred for 30 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 dissolved in methanol (5 ml). The methanolic solution was treated with 35% aqueous formaldehyde (0.13 ml, 1.5 mmol) for 5 min at room temperature. Concentration of the mixture *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1) to give **5** (23 mg, 73%, 2 steps) as a colorless caramel. $[\alpha]D^{20}$ -91.5° (c 1.22, CHCl3). IR (KBr): 3000, 2900, 2850, 1590, 1478, 1350, 1260 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 2.74 (1H, dt, J=15.9, 2.5 Hz, C6-H), 2.82-2.98 (2H, m, C6-H and C5-H), 3.10 (1H, ddd, J=16.4, 10.8, 5.2 Hz, C6-H), 3.44 (1H, dd, J=9.0, 7.3 Hz, C1-H), 4.20 (1H, dd, J=8.6 Hz, ArO*Me*), 4.41 (1H, t, J=8.6 Hz, C10b-H), 4.57 (1H, d, J=6.4 Hz, C3-H), 4.64 (1H, d, J=6.4 Hz, C3-H), 6.71 (1H, d, J=8.2 Hz, C7-H or C9-H), 6.78 (1H, d, J=8.2 Hz, C7-H or C9-H), 7.13 (1H, t, J=8.2 Hz, C8-H). EIMS m/z: 205 (M$^+$), 175 [(M-CH2O)$^+$]. HRMS calcd for C12H15NO2 (M$^+$): 205.1103. Found: 205.1101.

b) Preparation of *ent*-**5**: The same treatments of *ent*-**30** (175 mg, 0.52 mmol) as described for the preparation of **5** from **30** gave *ent*-**5** (74.0 mg, 69%, 2 steps) as a colorless caramel. $[\alpha]D^{20}$ +90.3° (c 1.10, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **5**.

(1*R*,10b*R*)-1-[(*R*)-2-Benzyloxy-1-hydroxyethyl]-10-methoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (31)

Treatments of **28** (78.0 mg, 0.16 mmol) in a similar manner to that described for the preparation of **20** from **19** gave **31** (57.8 mg, 96%) as a colorless caramel after purification by column chromatography (hexane-ethyl acetate, 3:1). $[\alpha]D^{20}$ -248° (c 1.15, CHCl3). IR (neat): 3425, 2950, 2875, 1740, 1590, 1480, 1465, 1420 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.72 (1H, d, J=4.3 Hz, OH), 2.62-2.73 (1H, m, C6-H), 2.93-3.06 (2H, m, C5-H and C6-H), 3.50-3.64 (3H, m, C*H*(OH)C*H*2OBn), 3.81 (3H, s, ArO*Me*), 4.10-4.20 (1H, m, C5-H), 4.47 (1H, d, J=11.7 Hz, OC*H*2Ph), 4.52 (1H, d, J=11.7 Hz, OC*H*2Ph), 4.94 (1H, d, J=8.5 Hz, C1-H), 5.24 (1H, d, J=8.5 Hz, C10b-H), 6.75 (1H, d, J=8.1 Hz, C7-H or C9-H), 6.78 (1H, d, J=8.1 Hz, C7-H or C9-H), 7.21 (1H, t, J=8.1 Hz, C8-H), 7.24-7.36 (5H, m, aromatic protons). EIMS m/z: 369 (M$^+$), 262 [(M-OBn)$^+$], 218 [(M-CH(OH)CH2OBn)$^+$]. HRMS Calcd for C21H23NO5 (M$^+$): 369.1576. Found. 369.1526.

(1*R*,10b*R*)-1-[(*R*)-1,2-Dihydroxyethyl]-10-methoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (32)

A mixture of **31** (106 mg, 0.29 mmol) and 10% palladium on carbon (65 mg) in methanol (9 ml) was stirred for 4 h 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 (ethyl acetate) to give **32** (70.5 mg, 88%) as a white solid. Recrystallization from ethyl acetate afforded an analytical sample of **32** as colorless prisms, mp 216-217.5 °C and $[\alpha]D^{20}$ -328° (c 1.25, CHCl3). IR (KBr): 3450, 2900, 1700, 1590, 1420 cm^{-1}. ^{1}H-NMR (90 MHz): δ 1.80 (2H, br s, OH x 2), 2.55-3.15 (3H, m, C5-H and C6-H2), 3.20-3.79 (3H, m, C*H*(OH)C*H2*OH), 4.13 (1H, br d, J=8.9 Hz, C5-H), 4.95 (1H, d, J=8.6 Hz, C1-H), 5.26 (1H, d, J=8.6 Hz, C10b-H), 6.79 (1H, d, J=8.1 Hz, C7-H or C9-H), 6.81 (1H, d, J=8.1 Hz, C7-H or C9-H), 7.25 (1H, t, J=8.1 Hz, C8-H). EIMS m/z: 279 (M^+). *Anal.* Calcd for C14H17NO5: C, 60.21; H, 6.14; N, 5.02%. Found: C, 60.25; H, 6.12; N, 4.96%.

(1*R*,10b*R*)-1-Hydroxymethyl-10-methoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (34)

Sodium periodate (108 mg, 0.51 mmol) was added to a stirred solution of **32** (70.5 mg, 0.25 mmol) in methanol-water (10:1) (10 ml) at room temperature. After 2 h, the mixture was diluted with water (4 ml) and extracted with ethyl acetate (50 ml). The extract was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, saturated aqueous thiosulfate, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* gave (1*R*,10b*R*)-1-formyl-10-methoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*] isoquinoline (**33**) (56.8 mg), which was dissolved in methanol-water (10:1) (5 ml). The methanolic solution was treated with sodium borohydride (17.4 mg, 0.46 mmol) for 30 min at room temperature. The reaction was quenched with 3% aqueous hydrochloric acid (1 ml) and then extracted with ethyl acetate (40 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, 1:1) to give **34** (55.0 mg, 96%, 2 steps) as a white solid. Recrystallization from hexane-ethyl acetate gave an analytical sample of **34** as colorless needles, mp 148.5-149 °C and $[\alpha]D^{20}$ -368° (c 1.55, CHCl3). IR (KBr): 3420, 1730, 1590 1415, 1320 cm^{-1}. ^{1}H-NMR (400 MHz, CD3OD): δ 2.74 (1H, ddd, J=15.5, 2.8, 1.1 Hz, C6-H), 2.89 (1H, ddd, J=15.5, 12.8, 5.6 Hz, C6-H), 3.04 (1H, dt, J=12.5, 3.4 Hz, C5-H), 3.20 (1H, dd, J=12.4, 5.7 Hz, C*H2*OH), 3.43 (1H, dd, J=12.4, 2.6 Hz, C*H2*OH), 3.86 (3H, s, ArO*Me*), 4.04 (1H, ddd, J=12.5, 5.6, 1.1 Hz, C5-H), 5.02 (1H, ddd, J=8.3, 5.7, 2.6 Hz, C1-H), 5.22 (1H, d, J=8.3 Hz, C10b-H), 6.70 (1H, d, J=8.1 Hz, C7-H or C9-H), 6.79 (1H, d, J=8.1 Hz, C7-H or C9-H), 7.23 (1H, t, J=8.2 Hz, C8-H). EIMS m/z: 249 (M^+), 231 [(M-H2O)$^+$], 218 [(M-CH2OH)$^+$]. *Anal.* Calcd for C13H15NO4: C, 62.64; H, 6.07; N, 5.62%. Found: C, 62.42; H, 6.05; N, 5.55%.

(1*S*,10b*R*)-1-Hydroxymethyl-10-methoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*]isoquinoline (36)

Potassium carbonate (121mg, 0.88 mmol) was added to a stirred solution of crude **33** (53.4 mg, 0.22 mmol) in methanol-water (10:1) (5 ml) at room temperature. After 4 h, the mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo* to give (1*S*,10b*R*)-1-formyl-10-methoxy-3-oxo-1,5,6,10b-tetrahydro-3*H*-oxazolo[4,3-*a*] isoquinoline (**35**) (53.1 mg), which was dissolved in methanol-water (10:1) (3 ml). The methanolic solution was treated with sodium borohydride (14.4 mg, 0.38 mmol) for 20 min at room temperature. The reaction was quenched with 3% aqueous hydrochloric acid (0.8 ml), and the mixture was extracted with ethyl acetate (40 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, 1:1) to give **36** (50.0 mg, 93%, 2 steps) as a white solid. Recrystallization from ethyl acetate afforded an analytical sample of **36** as colorless needles, mp 176.5-178 °C and $[\alpha]D^{20}$ -218° (c 1.08, CHCl3). IR (KBr): 3415, 1730, 1595, 1415, 1320 cm^{-1}. ^{1}H-NMR (400 MHz, CD3OD): δ 2.66 (1H, br ddd, J=16.3, 3.7, 0.8 Hz, C6-H), 2.93 (1H, br ddd, J=16.3, 12.6, 6.0 Hz, C6-H), 3.14 (1H, ddd, J=12.6, 3.7, 1.3 Hz, C5-H), 3.83 (3H, s, ArO*Me*), 3.94 (1H, dd, J=12.4, 4.3 Hz, C*H2*OH), 4.00 (1H, ddd, J=12.6, 6.0, 1.0 Hz, C5-H), 4.01 (1H, dd, J=12.4, 2.2 Hz, C*H2*OH), 4.41 (1H, ddd, J=4.8, 4.4, 2.2 Hz, C1-H), 4.88 (1H, d, J=4.8 Hz, C10b-H), 6.76 (1H, d, J=7.9 Hz, C7-H or C9-H), 6.86 (1H, d, J=7.9 Hz, C7-H or C9-H), 7.21 (1H, t, J=7.9 Hz, C8-H). EIMS m/z: 249 (M^+), 231 [(M-H2O)$^+$], 218 [(M-CH2OH)$^+$]. *Anal.* Calcd for C13H15NO4: C, 62.64; H, 6.07; N, 5.62%. Found: C, 62.67; H, 5.95; N, 5.52%.

(*S*)-Benzyl 1-[(*E*)-3-benzyloxy-1-propenyl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (38) and Its Enantiomer (*ent*-38)

a) Preparation of **38**: A solution of **28** (182 mg, 0.38 mmol) in dry toluene (20 ml) containing 1,1'-thiocarbonyldiimidazole (0.60 ml, 3.4 mmol) was heated at reflux for 2 h under argon. After cooling, the mixture was diluted with ethyl acetate (80 ml), and 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, 4:1) to give (*R*)-benzyl 1-[(4*R*,5*R*)-5-benzyloxymethyl-2-thioxo-1,3-dioxolan-4-yl]-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (**37**) (155 mg) as a pale yellow oil. ^{1}H-NMR (400 MHz, CDCl3): δ 2.78

(0.7H, br d, J=15.8 Hz, C4-H), 2.80-2.89 (0.3H, m, C4-H), 3.01-3.09 (0.3H, m, C4-H), 3.08-3.24 (0.7H, m, C4-H), 3.31-3.38 (0.3H, m, C3-H), 3.44 (0.7H, br dt, J=10.7, 2.5 Hz, C3-H), 3.50-3.56 (0.3H, m, C3-H), 3.61-3.72 (0.7H, m, C3-H), 3.67 (1H, br d, J=10.6 Hz, C*H*2OBn), 3.77 (1H, br d, J=10.6 Hz, C*H*2OBn), 3.80 (3H, s, ArO*Me*), 4.38-4.54 (0.3H, m, OC*H*2Ph), 4.56 (0.7H, br d, J=12.0 Hz, OC*H*2Ph), 4.59 (1H, br d, J=12.0 Hz, OC*H*2Ph), 4.98 (0.3H, br s, C*H*(O-)C*H*(O-)CH2OBn), 5.02-5.09 (0.7H, m, C*H*(O-)C*H*(O-)CH2OBn), 5.13 (1H, br s, C*H*(O-)C*H*(O-)CH2OBn), 5.14 (1H, br t, J=12.8 Hz, NCO2C*H*2Ph), 5.19 (1H, br t, J=12.8 Hz, NCO2C*H*2Ph), 5.64 (0.3H, br s, C1-H), 5.71 (0.7H, br s, C1-H), 6.77 (1H, d, J=8.2 Hz, C5-H or C7-H), 6.82 (1H, d, J=8.2 Hz, C5-H or C7-H), 7.25 (1H, t, J=8.2 Hz, C6-H), 7.26-7.39 (10H, m, aromatic protons). Due to the presence of rotamers in the benzyl carbamate group, line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum.

A solution of **37** (155 mg) in trimethyl phosphite (6.00 ml, 51 mmol) was heated at reflux for 26 h under argon. After cooling, the mixture was concentrated *in vacuo* to give a residue, which was purified by column chromatography (hexane-ethyl acetate, 8:1) to give **38** (102 mg, 79%, 2 steps) as a colorless oil. $[\alpha]D^{20}$ +57.0° (c 0.91, CHCl3). IR (neat): 3400, 3030, 2940, 2850, 1700, 1590, 1470, 1460, 1425, 1420 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 2.71-2.79 (1H, m, C4-H), 2.81-2.98 (1H, m, C4-H), 3.29-3.39 (0.5H, m, C3-H), 3.40-3.48 (0.5H, m, C3-H), 3.81 (3H, s, ArO*Me*),3.91-3.98 (0.5H, m, C3-H), 3.94-4.04 (2H, m, C*H*2OBn), 4.03-4.12 (0.5H, m, C3-H), 4.43 (1H, d, J=12.1 Hz, CH2OC*H*2Ph), 4.47 (1H, d, J=12.1 Hz, CH2OC*H*2Ph), 5.13 (0.5H, d, J=12.5 Hz, CO2C*H*2Ph), 5.15 (0.5H, d, J=9.7 Hz, CO2C*H*2Ph), 5.19 (0.5H, d, J=9.7 Hz, NCO2C*H*2Ph), 6.26 (0.5H, d, J=12.5 Hz, NCO2C*H*2Ph), 5.42-5.53 (1H, m, C1-H), 5.81-6.20 (2H, m, C*H*=C*H*), 6.72 (1H, br d, J=8.1 Hz, C5-H or C7-H), 6.75 (1H, br d, J=8.1 Hz, C5-H or C7-H), 7.16 (1H, br t, J=8.1 Hz, C6-H), 7.23-7.39 (10H, m, aromatic protons). Due to the presence of rotamers in the benzyl carbamate group, line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 443 (M^+), 352 [(M-Bn)$^+$], 308 [(M-CO2Bn)$^+$]. HRMS Calcd for C28H29NO4: 443.1251. Found: 443.1273.

b) Preparation of *ent*-**38**: The same treatments of *ent*-**28** (223 mg, 0.47 mmol) as described for the preparation of **38** from **28** gave *ent*-**38** (166 mg, 80%, 2 steps) as a colorless oil *via ent*-**37**. $[\alpha]D^{20}$ -57.0° (c 0.94, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **38**.

(*S*)-1-[(*E*)-3-Benzyloxy-1-propenyl]-8-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (39)

Lithium aluminium hydride (20.0 mg, 0.52 mmol) was added in small portions to a stirred solution of **38** (14.2 mg, 32 μmol) in dry ether (3 ml) at room temperature under argon. After 30 min, the reaction was quenched with 25% aqueous sodium hydroxide (0.25 ml), and the mixture was extracted with ethyl acetate (40 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 (ethyl acetate-methanol, 20:1) to give **39** (8.80 mg, 85%) as a colorless oil. $[\alpha]D^{20}$ +11.2° (c 0.87, CHCl3). IR (neat): 3020, 2940, 2850, 1590, 1465, 1360, 1340 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 2.49 (3H, s, NMe), 2.66-2.78 (2H, m, C4-H2), 2.94-3.10 (2H, m, C3-H2), 3.75 (3H, s, ArO*Me*), 4.02 (1H, d, J=12.4 Hz, , C*H*2OBn), 4.03 (1H, d, J=12.4 Hz, , C*H*2OBn), 4.42 (1H, d, J=6.1 Hz, C1-H), 4.46 (1H, d, J=12.1 Hz, OC*H*2Ph), 4.47 (1H, d, J=12.1 Hz, OC*H*2Ph), 5.58 (1H, ddt, J=15.6, 6.1, 0.9 Hz, C*H*=CHCH2), 5.82 (1H, ddt, J=15.6, 6.1, 0.9 Hz, CH=C*H*CH2), 6.66 (1H, d, J=8.0 Hz, C5-H or C7-H), 6.74 (1H, d, J=8.0 Hz, C5-H or C7-H), 7.13 (1H, t, J=8.1 Hz, C6-H), 7.24-7.34 (5H, m, aromatic protons). EIMS m/z: 323 (M^+), 232 [(M-Bn)$^+$], 176 [(M-CH=CHCH2OBn)$^+$]. HRMS Calcd for C21H25NO2: 323.1833. Found: 323.1850.

(*S*)-Benzyl 8-methoxy-1-vinyl-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (41) and Its Enantiomer (*ent*-41)

a) Preparation of **41**: Trimethylaluminum in hexane (2.0 M solution, 0.25 ml, 0.5 mmol) was added dropwise to a stirred suspension of zinc powder (486 mg, 7.4 mmol) and diiodomethane (0.20 ml, 2.5 mmol) in dry tetrahydrofuran (4 ml) at room temperature under argon. After 10 min, a solution of **29** (82.8 mg, 0.25 mmol) in dry tetrahydrofuran (3 ml) was added slowly to the above mixture, and stirring was continued for 15 min. The reaction was quenched with saturated aqueous ammonium chloride (2 ml), and the mixture was extracted with ethyl acetate (70 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 **41** (79.8 mg, 97%) as a colorless oil. $[\alpha]D^{20}$ +53.3° (c 1.15, CHCl3). IR (CHCl3): 1690, 1590, 1475, 1430, 1260 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 2.71-2.79 (1H, m, C4-H), 2.80-2.98 (1H, m, C4-H), 3.35 (0.5H, ddd, J=12.9, 10.3, 4.7 Hz, C3-H), 3.46 (0.5H, ddd, J=12.9, 9.5, 4.9 Hz, C3-H), 3.80 (1.5H, s, ArO*Me*), 3.81 (1.5H, s, ArO*Me*), 3.94 (0.5H, dt, J=12.9, 5.3 Hz, C3-H), 4.09 (0.5H, dt, J=12.9, 5.3 Hz, C3-H), 4.90 (0.5H, br d, J=17.6 Hz, CH=C*H*2), 4.93 (0.5H, br d, J=17.6 Hz, CH=C*H*2), 5.09 (0.5H, br d, J=9.4 Hz, CH=C*H*2), 5.11 (0.5H, br d, J=9.4 Hz, CH=C*H*2), 5.14 (0.5H, br d, J=12.4 Hz, OC*H*2Ph), 5.17 (0.5H, br d, J=9.2 Hz, OC*H*2Ph), 5.20 (0.5H, br d, J=9.2 Hz, OC*H*2PhH), 5.26 (0.5H, br d, J=12.4 Hz, OC*H*2Ph), 5.88-6.04 (2H, m, C*H*=CH2 and C1-H), 6.73 (1H, d, J=8.2 Hz, C5-H or C7-H), 6.76 (1H, d, J=8.2 Hz, C5-H or C7-H), 7.15 (0.5H, d, J=8.2 Hz, C6-H), 7.16 (0.5H, t, J=8.2 Hz, C6-H), 7.27-7.40 (5H, m, aromatic protons). Due to the presence of rotamers in the benzyl carbamate group, line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 296 [(M-CH=CH2)$^+$], 232 [(M-CH2Ph)$^+$]. HRMS Calcd for C20H21NO3 [(M-CH=CH2)$^+$]: 296.1285. Found: 296.1278.

b) Preparation of *ent*-**41**: The same treatments of *ent*-**29** (115 mg, 0.35 mmol) as described for the preparation of **41** from **29** gave *ent*-**41** (107 mg, 94%) as a colorless oil. $[\alpha]D^{20}$ -57.4° (c 1.78, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **41**.

(*S*)-Benzyl 1-(2-hydroxyethyl)-8-methoxy-3,4-dihydro-2(1*H*)-isoquinolinecarboxylate (42) and Its Enantiomer (*ent*-42)

a) Preparation of **42**: Borane-methyl sulfide complex in tetrahydrofuran (2.0 M solution, 0.25 ml, 0.50 mmol) was added dropwise to a stirred solution of **41** (40.3 mg, 0.12 mmol) in dry tetrahydrofuran (1 ml) at 0°C under argon. After 24 h, water (0.1 ml), 35% aqueous hydrgen peroxide (0.5 ml), and 2M sodium hydroxide (0.75 ml) were successively added, and stirring was continued for 1.5 h at room temperature. The resulting mixture was extracted with ethyl acetate (50 ml), and 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 **42** (20.3 mg, 48%) as a colorless oil. $[\alpha]D^{20}$ +59.1° (c 1.08, CHCl3). IR (CHCl3): 3475, 3030, 2960, 1680, 1590, 1475, 1440, 1340, 1260 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.54-1.68 (0.7H, m, C*H*2CH2OH), 1.74-1.84 (0.3H, m, C*H*2CH2OH), 2.09-2.20 (0.3H, m, C*H*2CH2OH), 2.20-2.29 (0.7H, m, C*H*2CH2OH), 2.78 (1H, br dt, J=16.3, 4.7 Hz, C4-H), 2.89 (0.7H, br ddd, J=16.3, 3.6, 1.0 Hz, C4-H), 2.92 (0.3H, br ddd, J=16.3, 3.6, 1.0 Hz, C4-H), 3.32-3.31 (0.3H, m, C3-H), 3.34 (0.7H, ddd, J=13.1, 9.9, 4.9 Hz, C3-H), 3.53-3.74 (3H, m, CH2OH), 3.84 (3H, s, ArO*Me*), 4.03 (0.7H, dt, J=13.1, 4.9, C3-H), 5.09 (0.3H, br d, J=12.7 Hz, OC*H*2Ph), 5.17 (0.7H, d, J=12.4 Hz, OC*H*2Ph), 5.22 (0.7H, d, J=12.4 Hz, OC*H*2Ph), 5.28 (0.3H, br d, J=12.7 Hz, OC*H*2PhH), 5.46 (0.3H, br d, J=11.2 Hz, C1-H), 5.57 (0.7H, dd, J=11.2, 3.0 Hz, C1-H), 6.73 (2H, d, J=8.2 Hz, C5-H and C7-H), 7.15 (1H, t, J=8.2 Hz, C6-H), 7.25-7.45 (5H, m, aromatic protons). Due to the presence of rotamers in the benzyl carbamate group, line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 342 [(M+1)$^+$], 296 [(M-CH2CH2OH)$^+$], 252 [(M-CH2CH2OH-CO2)$^+$]., HRMS Calcd for C18H18NO3 [(M-CH2CH2OH)$^+$]: 296.1285. Found: 296.1285.

b) Preparation of *ent*-**42**: The same treatments of *ent*-**41** (144 mg, 0.45 mmol) as described for the preparation of **42** from **41** gave *ent*-**42** (91.8 mg, 60%) as a colorless oil. $[\alpha]D^{20}$ -59.7° (c 1.08, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **5**.

(*S*)-11-Methoxy-1,6,7,11b-tetrahydro-2*H*,4*H*-1,3-oxazino[4,3-*a*]isoquinoline (6) and Its Enantiomer (*ent*-6)

a) A mixture of **42** (13.0 mg, 38 μmol) and 10% palladium on carbon (15 mg) in ethyl acetate (2 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 (*S*)-1-(2-hydroxyethyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**43**) (6.20 mg) as a pale yellow oil. ^{1}H-NMR (200 MHz, CDCl3): δ.1.75-2.15 (2H, m, C*H*2CH2OH), 2.60-2.90 (2H, m, C4-H2), 3.08 (1H, dt, J=13.2, 4.1 Hz, C3-H), 3.14-3.37 (1H, m, C3-H), 3.41-3.90 (3H, m, CH2C*H*2O*H* and N*H*), 3.80 (3H, s, OMe), 4.01 (1H, dt, J=10.7, 3.0 Hz, CH2C*H*2OH), 4.33 (1H, dd, J=9.6, 3.4 Hz, C1-H), 6.68 (1H, d, J=8.1 Hz, C5-H or C7-H), 6.72 (1H, d, J=8.1 Hz, C5-H or C7-H), 7.13 (1H, t, J=8.1 Hz, C5-H or C7-H). This material was directly used for the next reaction without further purification.

35% Aqueous formaldehyde (30 μl, 0.35 mmol) was added to a stirred solution of crude **43** (6.2 mg) in methanol (1 ml) at room temperature. After 30 min, the mixture was concentrated *in vacuo* to give a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1) to give **6** (6.51 mg, 78%, 2 steps) as a white solid. Recrystallization from hexane gave an analytical sample of **6** as colorless prisms, mp 84-86 °C and $[\alpha]D^{20}$ +15.3° (c 0.78, CHCl3). IR (CHCl3): 2980, 2950, 2870, 1595, 1470, 1380, 1265, 1140, 1090 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.79 (1H, dddd, J=12.6, 3.0, 2.6, 1.0 Hz, C1-H), 2.05 (1H, dddd, J=14.0, 12.6, 11.4, 4.8 Hz, C1-H), 2.79 (1H, dd, J=16.0, 4.0 Hz, C7-H), 2.91 (1H, dd, J=11.8, 8.6 Hz, C6-H), 3.05 (1H, ddd, J=16.0, 11.8, 6.6 Hz, C7-H), 3.54 (1H, dt, J=11.8, 4.0 Hz, C6-H), 3.80 (3H, s, OMe), 3.87 (1H, ddd, J=14.0, 11.3, 2.6 Hz, C2-H), 4.08 (1H, ddt, J=11.3, 4.8, 1.0 Hz, C2-H), 4.38 (1H, dd, J=11.4, 3.0 Hz, C11b-H), 4.61 (1H, d, J=10.6 Hz, C4-H), 4.74 (1H, d, J=10.6 Hz, C4-H), 6.68 (1H, d, J=7.9 Hz, C8-H or C10-H), 6.75 (1H, d, J=7.9 Hz, C8-H or C10-H), 7.12 (1H, t, J=7.9 Hz, C9-H). MS m/z: 219 (M$^+$), 190 [(M-C2H5)$^+$], 160 [(M-C2H5-CHO)$^+$]. HRMS calcd for C13H17NO2 (M$^+$): 219.1258. Found: 219.1284.

b) Preparation of *ent*-**6**: The same treatments of *ent*-**42** (27.0 mg, 79 μmol) as described for the preparation of **6** from **42** gave *ent*-**6** (10.8 mg, 62%, 2 steps) as colorless prisms *via ent*-**43**. mp 84-85.5 °C (hexane). $[\alpha]D^{20}$ -15.0° (c 0.40, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **6**.

(*S*)-12-Methoxy-1,2,3,7,8,12b-hexahydro-5*H*-1,3-oxazepino[4,3-*a*]isoquinoline (7) and Its Enantiomer (*ent*-7)

a) Preparation of **7**: A mixture of **38** (199 mg, 0.45 mmol) and 20% palladium hydroxide on carbon (48 mg) in methanol (5 ml) was stirred for 16 h at room temperature under hydrogen atmosphere (1 atm). The catalyst was filtered off and the filtrate was concentrated *in vacuo* to give (*S*)-1-(3-hydroxyproyl)-8-methoxy-1,2,3,4-tetrahydroisoquinoline (**44**) (78.2 mg) as a colorless oil. ^{1}H-NMR (400 MHz, CDCl3): δ.1.70-1.84 (2H, m, CH2C*H*2CH2OH), 1.80-1.92 (1H, m, C*H*2CH2CH2OH), 1.99-2.10 (1H, m, C*H*2CH2CH2OH), 2.62-2.95 (2H, m, C4-H, NH, and OH), 3.10-3.24 (2H, m, C3-H2), 3.56 (1H, ddd, J=1H, 11.3, 9.0, 2.7 Hz,

C*H*2OH), 3.76 (1H, ddd, J=1H, 11.3, 4.8, 3.1 Hz, C*H*2OH), 3.82 (3H, s, ArO*Me*), 4.11 (1H, dd, J=9.6, 2.2 Hz, C1-H), 6.70 (1H, d, J=7.9 Hz, C5-H or C7-H), 6.71 (1H, d, J=7.9 Hz, C5-H or C7-H), 7.13 (1H, t, J=7.9 Hz, C6-H). This material was directly used for the next reaction without further purification.

35% Aqueous formaldehyde (70 µl, 0.82 mmol) was added to a stirred solution of crude **44** (78.2 mg) in methanol (1 ml) at room temperature. After 10 min, the mixture was concentrated *in vacuo* to give a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:1) to give **7** (54.4 mg, 52%, 2 steps) as a white solid. Recrystallization from hexane-ethyl acetate afforded an analytical sample of **7** as colorless plates, mp 104-106 °C and $[\alpha]D^{20}$ -28.7° (c 1.15, CHCl3). IR (KBr): 2950, 2880, 2855, 1592, 1470, 1440, 1380, 1370, 1340, 1260, 1235, 1150, 1080, 1050, 995 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ 1.84-2.10 (4H, m, C1-H2 and C2-H2), 2.72-2.80 (1H, m, C7-H), 2.90-3.04 (2H, m, C8-H2), 3.24-3.32 (1H, m, C7-H), 3.76-3.88 (1H, m, C3-H), 3.82 (3H, s, ArO*Me*), 3.94-4.02 (1H, m, C3-H), 4.14 (1H, br d, J=8.2 Hz, C12b-H), 4.55 (1H, d, J=11.5 Hz, C5-H), 4.61 (1H, d, J=11.5 Hz, C5-H), 6.68 (1H, d, J=8.1 Hz, C9-H or C11-H), 6.73 (1H, d, J=8.1 Hz, C9-H or C11-H), 7.11 (1H, d, t=8.1 Hz, C10-H). MS m/z: 233 (M^+), 190, 175, 162. *Anal.* Calcd for C14H19NO2: C, 72.07; H, 8.21; N, 6.00%. Found: C, 72.30; H, 8.40; N, 6.03%.

b) Preparation of *ent*-**7**: The same treatments of *ent*-**38** (100 mg, 0.23 mmol) as described for the preparation of **7** from **38** gave *ent*-**7** (13.2 mg, 28%, 2 steps) as colorless plates *via ent*-**44**. mp 104.5-106.5 °C (hexane-ethyl acetate). $[\alpha]D^{20}$ +28.6° (c 0.44, CHCl3). The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those recorded for **7**.

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2. Present address: Faculty of Pharmaceutical Sciences, University of Tokyo, Bunkyo, Tokyo 113, Japan.
3. Present address: Meiji College of Pharmacy, Setagaya, Tokyo 154, Japan.
4. Present address: Organic Chemistry Laboratories, Tanabe Seiyaku Co., Ltd., Toda, Saitama 335, Japan.
5. Present address: Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 006, Japan.
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