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Total Synthesis of an Enantiomeric Pair of FR900482. 3.[1] Completion of the Synthesis by Assembling the Two Segments

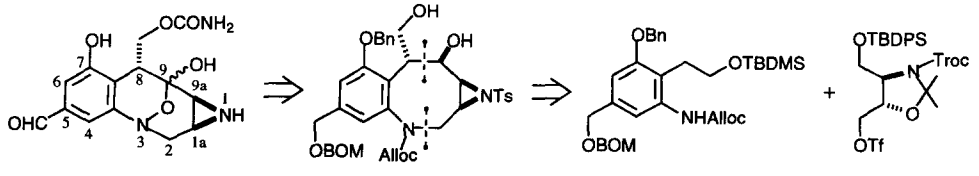
Tadashi Katoh, Yuriko Nagata, Toshiharu Yoshino, Shogo Nakatani, Shiro Terashima*

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

Abstract: *The title synthesis was accomplished by a method which features (i) coupling of the aromatic segment* ***2*** *with the enantiomerically pure aliphatic segment* ***3*** *to install the requisite carbon unit (**2+3→4**); (ii) intramolecular aldol reaction of the highly functionalized dialdehyde* ***10*** *to elaborate the desired eight-membered ring system* ***12*** *(**10→12**); (iii) epimerization at the C-8 position of the hydroxy ketone* ***15*** *to obtain the correct stereochemistry (**15→16**); (iv) internal hemiacetal formation of the N-hydroxylamino ketone* ***25*** *in situ generated from the ketone* ***24*** *to construct the requisite tetracyclic ring system* ***26*** *(**24→25→26**) as the key steps. The in vitro cytotoxicity assay of the synthesized compounds (**1**, **ent-1**, **31**, **ent-31**, **32**, and **ent-32**) against P388 murine leukemia cells disclosed that FR900482 (**1**) and its congeners **31**, **32** bearing natural absolute configuration are 100 times more cytotoxic than the corresponding unnatural enantiomers (**ent-1**, **ent-31**, **ent-32**).* © 1997 Elsevier Science Ltd.

FR900482 (**1**), a natural secondary metabolite produced by *Streptomyces sandaensis* No.6897, has been the subject of recent synthetic endeavors due to its unique structural feature as well as remarkable antitumor activity against several types of mammalian solid tumors.[2] As described in the preceding paper,[3] we have succeeded in preparing the aromatic segment **2** and the enantiomerically pure aliphatic segments **3** and ***ent*-3**, thereby setting the stage for completion of the projected synthesis by assembling these segments (**Scheme 1**). In the third part of this series of papers, we wish to disclose full details of the first enantioselective total synthesis of both enantiomers of **1** in a convergent manner utilizing **2**, **3**, and ***ent*-3** as the key segments. Furthermore, the results of *in vitro* cytotoxicity assay of the synthesized compounds (**1**, ***ent*-1**, **31**, ***ent*-31**, **32**, and ***ent*-32**) against P388 murine leukemia cells are presented, disclosing some novel aspects of the structure-activity relationships.

Scheme 1. Synthetic Plan for FR900482 (**1**)



1 : FR900482 **2** **3**

Our synthetic strategy involves the following four key steps: (i) coupling reaction of **2** with **3** to install the requisite carbon unit (**2+3→4**) (**Scheme 2**); (ii) intramolecular aldol reaction of the highly functionalized dialdehyde **10** to elaborate the desired 1*H*-azirizino[2,3-*c*][1]benzazocine system **12** representing the core

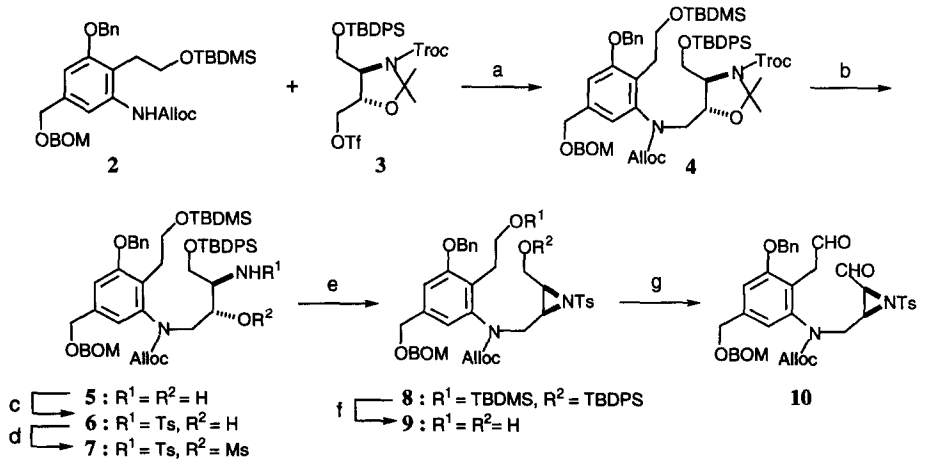
skeleton of **1** (**10**→**12**) (**Scheme 3**); (iii) epimerization at the C-8 position of the hydroxy ketone **15** to obtain the correct stereochemistry (**15**→**16**) (**Scheme 4**); (iv) internal hemiacetal formation of the *N*-hydroxylamino ketone **25**, produced *in situ* by removal of the acetyl group in the acetate **24**, to construct the requisite tetracyclic ring system **26** (**24**→**25**→**26**) (**Scheme 5**).

Results and Discussion

1. Synthesis of the Eight-membered Key Intermediate 17

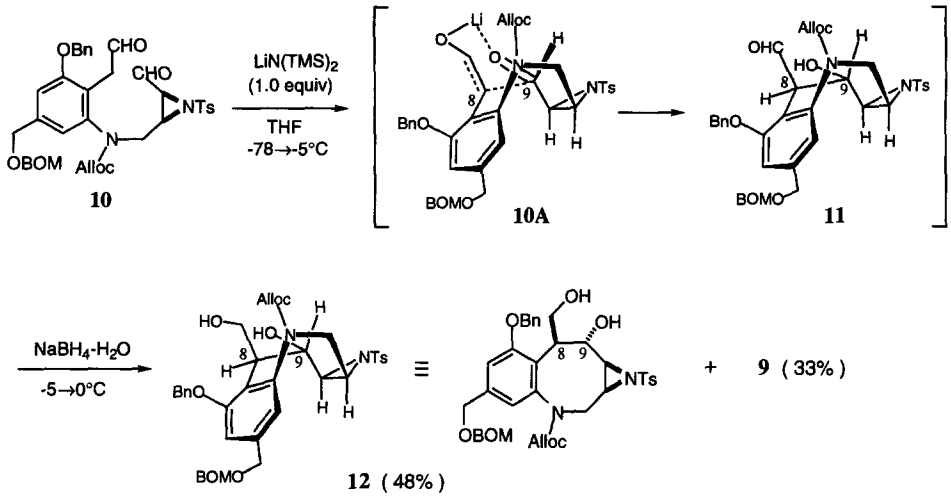
At first, we targeted the synthesis of the eight-membered key intermediate **17** (see, **Scheme 4**) possessing the requisite core skeleton and functional groups with the correct absolute stereochemistries at the C-1a, C-8, and C-9a positions. To this end, our first efforts were directed toward elaboration of the substrate **10** for the key intramolecular aldol reaction as shown in **Scheme 2**. Thus, the critical coupling reaction of the aromatic segment **2**[3] with the enantiomerically pure aliphatic segments **3**[3] was carried out by treating a mixture of these segments in tetrahydrofuran (THF) with sodium hydride at -78°C followed by warming to room temperature, giving rise to the desired coupling product **4** in a quantitative yield. Simultaneous removal of the 2,2,2-trichloroethoxycarbonyl (Troc)[4] group and the acetonide moiety in **4** was achieved by reaction with zinc powder in the presence of acetic acid in THF-H_2O at room temperature, providing the amino alcohol **5**. Subsequent chemoselective tosylation[5] of the amino group in **5** afforded the *N*-protected amino alcohol **6** in 77% overall yield from **4**. Compound **6** was then converted to the aziridine **8** (86%, 2 steps) by mesylation of the secondary hydroxyl group followed by treatment of the resulting mesylate **7** with sodium hydride in the presence of imidazole in refluxing THF.[6] Both of the *tert*-butyldimethylsilyl (TBDMS) and the *tert*-butyldiphenylsilyl (TBDPS) protecting groups in **8** were simultaneously removed by exposure to hydrogen fluoride-pyridine complex[7] in pyridine at 0°C, cleanly furnishing the diol **9** in 99% yield. Further subjection of **9** to

Scheme 2. Synthesis of the Substrate **10** for the Key Intramolecular Aldol Reaction



a) NaH, THF, -78°C→rt, 100% b) Zn, AcOH, THF-H_2O, rt c) TsCl, Et_3N, DMF, 0°C→rt, 77% (2 steps) d) MsCl, Et_3N, CH_2Cl_2, 0°C→rt, 94% e) NaH, imidazole, THF, reflux, 92% f) $(HF)_n$·Py, Py, 0°C, 99% g) Dess-Martin periodinane, CH_2Cl_2, rt, 98%

Scheme 3. The Key Intramolecular Aldol Reaction of the Dialdehyde **10**

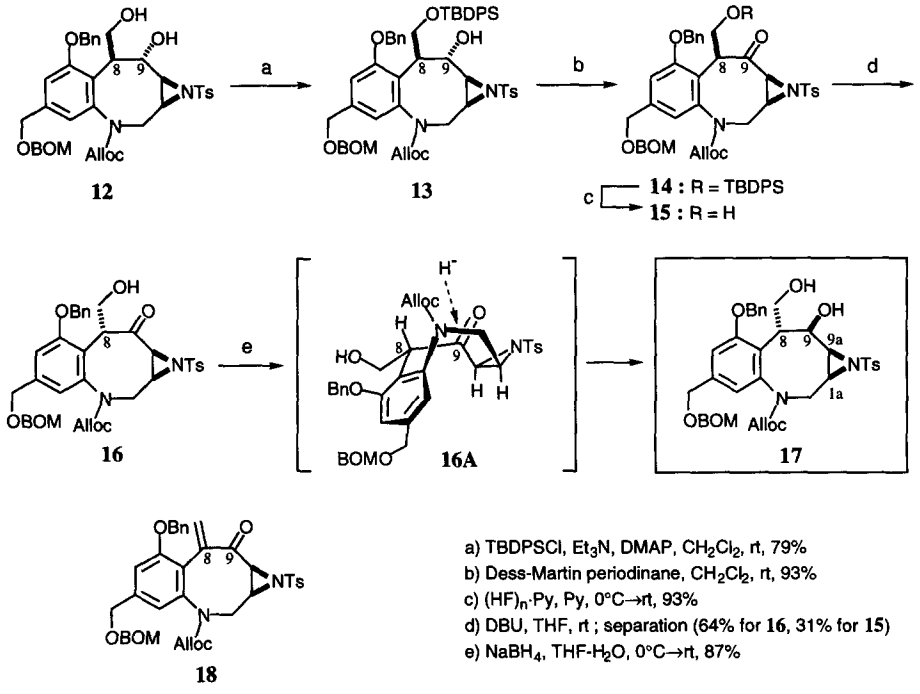


Dess-Martin oxidation[8] gave the key cyclization precursor **10** in 98% yield.

The stage is now set for the crucial intramolecular aldol reaction event. In general, the formation of eight-membered ring systems by intramolecular ring closure reactions is often difficult due to the steric strain and unfavorable entropy factor.[9] However, in the case of **10**, the fused aromatic and aziridine rings can be expected to overcome these barriers. In the event, as shown in **Scheme 3**, the intramolecular aldol cyclization could be accomplished by treating a dilute solution of **10** in THF (0.01 M) with 1.0 equiv of lithium bis(trimethylsilyl)amide [$LiN(TMS)_2$] at -78°C followed by warming to -5°C. After treatment of this mixture with sodium borohydride in H2O,[10] the requisite cyclization product **12** was readily isolated as a sole product in 48% yield along with a recovery of the diol **9** (33%). No other cyclized stereoisomers were obtained from the reaction mixture. The complete structure of **12** including the stereochemistries at the newly formed C-8 and C-9 positions was rigorously confirmed by X-ray diffraction analysis of its bis(*p*-bromobenzoate) derivative.[11] This cyclization might proceed through the transition state such as six-membered chelation intermediate **10A**, exclusively affording the cyclized product **11**. In the intermediate **10A**, the eight-membered ring takes a twist-boat conformation and the C-8 enolate moiety is oriented in quasiaxial positions to avoid an unfavorable allylic 1,3-strain[12] between the enolate moiety and the benzyloxy (BnO) group present in the aromatic ring.

Since the configuration at the C-8 position in the cyclization product **12** turned out to be undesired, the inversion of the C-8 stereochemistry was next investigated as shown in **Scheme 4**. Thus, selective silylation of the primary hydroxyl group in **12** followed by Dess-Martin oxidation[8] of the resulting silyl ether **13** furnished the ketone **14** in 73% yield for the two steps. Initial attempts to achieve the epimerization at the C-8 position of **14** under standard basic conditions met with failure, resulting in the formation of the useless exocyclic enone **18** by elimination of the siloxy moiety in an almost quantitative yield. However, success was eventually realized by employing the hydroxy ketone **15**, prepared in 93% yield by desilylation of **14** with hydrogen fluoride-pyridine complex,[7] as the substrate for the epimerization.[13] Thus, **15** was treated with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in THF at room temperature for 2 h, leading to an equilibrium mixture of **15** and **16** in a ratio of *ca.* 1 : 2. Fortunately, this mixture could be readily separated by column

Scheme 4. Epimerization at the C-8 Position of the Cyclization Product **12** and the Synthesis of the Eight-Membered Key Intermediate **17**



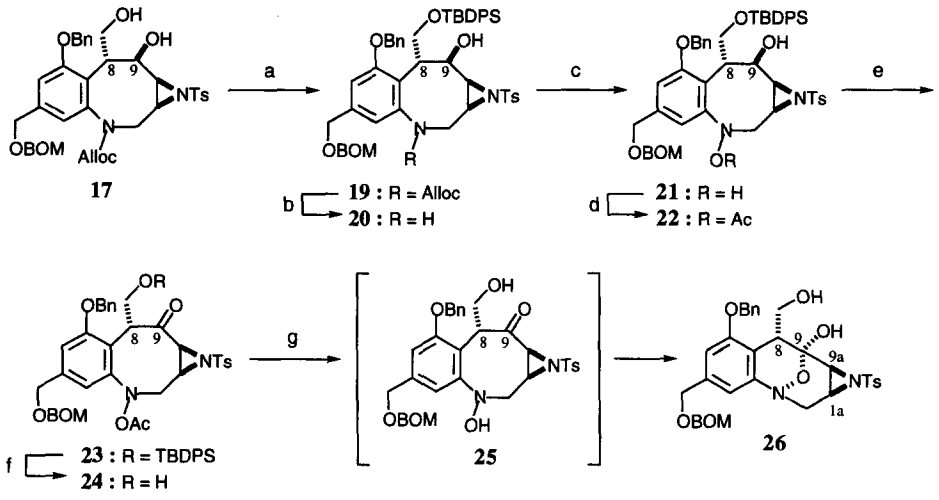
a) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 79%
b) Dess-Martin periodinane, CH_2Cl_2, rt, 93%
c) $(HF)_n$·Py, Py, 0°C→rt, 93%
d) DBU, THF, rt ; separation (64% for **16**, 31% for **15**)
e) $NaBH_4$, THF-H_2O, 0°C→rt, 87%

chromatography on silica gel to give the desired product **16** (64%) possessing the desired configuration at the C-8 position, along with the starting material **15** (31% recovery). Since prolonged reaction times caused dehydration of both **15** and **16** to produce the same enone **18**, the reaction was quenched when approximately a 1:2 mixture of **15** and **16** was generated. Finally, reduction of the carbonyl group in **16** with sodium borohydride furnished the eight-membered key intermediate **17** as a single diastereoisomer in 87% yield, whose stereostructure was unambiguously assigned based on single crystal X-ray analysis of the related bis(*p*-bromobenzoate) derivative.[14] The complete stereoselectivity observed for the reduction can be explained by considering that the hydride attack occurs from the outside of the eight-membered ring system (see, **16A**) owing to steric factor.

2. Total Synthesis of (+)-FR900482 (1) and Its Enantiomer [*ent*-(−)-1]

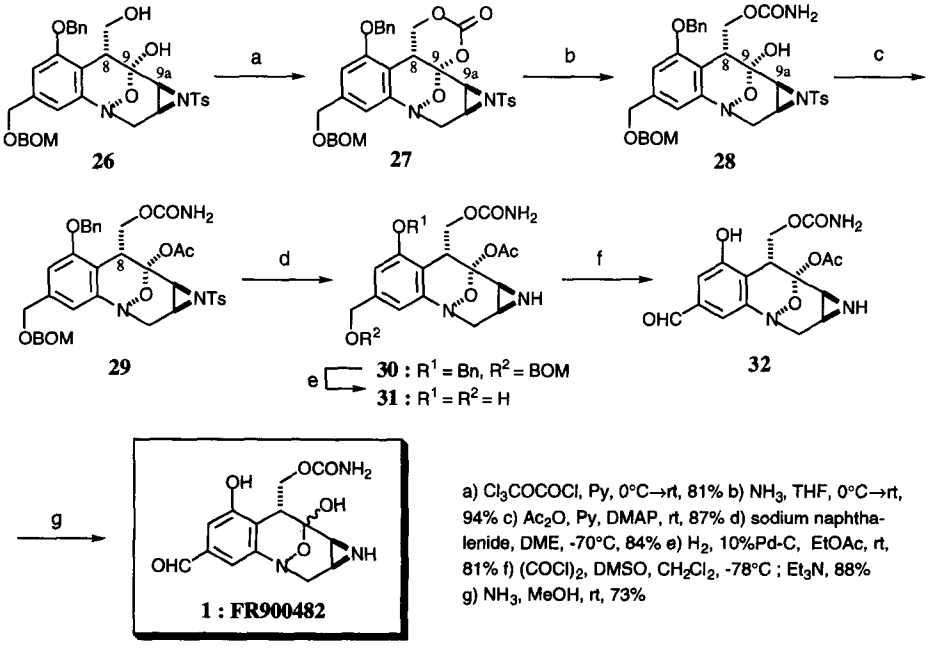
Having obtained the key intermediate **17**, our next efforts were devoted to completion of the total synthesis of **1**. Towards this end, we initially elaborated the bridged tetracyclic compound **26** from **17** as shown in **Scheme 5**. Thus, **17** was converted to the amine **20** (59%, 2 steps) by selective protection of the primary hydroxyl group followed by palladium (0)-catalyzed cleavage of the *N*-allyloxycarbonyl (Alloc)[15] group in the resulting silyl ether **19**. Careful oxidation of the amino moiety in **20** with *m*-chloroperbenzoic acid (MCPBA)[16] at low temperature furnished the labile hydroxylamine **21** in 67% yield. Chemoselective acetylation of **21** was achieved by treatment with acetic anhydride in the presence of sodium hydrogen carbonate, giving rise to the acetate **22** in 69% yield. Compound **22** was further converted to the alcohol **24**

Scheme 5. Synthesis of the Tetracyclic Key intermediate **26**



a) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, rt, 71% b) $Pd(PPh_3)_4$, PPh_3, THF, rt, 83% c) MCPBA, CH_2Cl_2, -5°C, 67% d) Ac_2O, $NaHCO_3$, rt, 69% e) Dess-Martin periodinane, CH_2Cl_2, rt, 88% f) $(HF)_n$·Py, Py, 0°C→rt, 88% g) K_2CO_3, MeOH, 0°C→rt, 89%

Scheme 6. Completion of the Total Synthesis of Natural (+)-FR900482 (**1**)



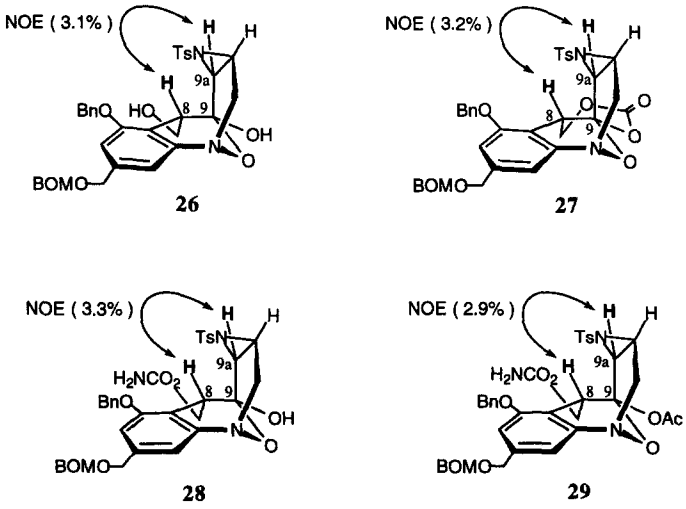
a) $Cl_3COCOCl$, Py, 0°C→rt, 81% b) NH_3, THF, 0°C→rt, 94% c) Ac_2O, Py, DMAP, rt, 87% d) sodium naphthalenide, DME, -70°C, 84% e) H_2, 10%Pd-C, EtOAc, rt, 81% f) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C ; Et_3N, 88% g) NH_3, MeOH, rt, 73%

(77%, 2 steps) by Dess-Martin oxidation[8] followed by deprotection of the TBDPS group in the resulting ketone **23**. One of the critical steps in our synthetic scheme was envisaged to be the internal hemiacetalization[16,17] of the *N*-hydroxylamine **25** generated *in situ* by removal of the acetyl group of **24**, to furnish the requisite tetracyclic compound **26**. In the event, removal of the acetyl group in **24** by reaction with potassium carbonate in methanol cleanly produced **25**, which spontaneously underwent the internal hemiacetalization to give **26** as the sole product in 89% yield. The stereochemical issue with respect to the newly produced C-9 position in **26** was assigned based on NOE measurements (*vide infra*).

The final route that led to the successful synthesis of (+)-FR900482 (**1**) is summarized in **Scheme 6**. Thus, the tetracyclic hemiacetal **26** was allowed to react with phosgene dimer (trichloromethyl chloroformate), and the resulting cyclic carbonate **27** was then subjected to ammonolysis,[16] leading to the formation of the urethane **28** in 76% yield for the two steps. Further acetylation of the hydroxyl group in **28** afforded the key intermediate **29**, mp 129-131°C [lit.,[18] mp 130-132°C], $[\alpha]_D^{20}$ +66.8°(*c* 0.78, $CHCl_3$) [lit.,[18] $[\alpha]_D^{20}$ +68.1° (*c* 0.76, $CHCl_3$)], in 87% yield. The spectroscopic properties (IR, ^{1}H-NMR, MS) of **29** were identical with those of the authentic sample[18] prepared from FK973, the triacetyl derivative of **1**. Finally, **29** was transformed to (+)-FR900482 (**1**), mp 174°C (dec) [lit.,[19] mp 175°C (dec)], $[\alpha]_D^{23}$ +7.9°(*c* 0.97, H_2O) [lit.,[19] $[\alpha]_D^{23}$ +8.0° (*c* 1.00, H_2O)], *via* **30-32** in a similar manner to that described in the preceding paper.[18] The synthesized **1** was identical with a natural sample of **1** in all spectroscopic properties (IR, ^{1}H-NMR, MS).

The stereochemistries at the C-9 position of the bridged tetracyclic compounds **26-29** were proven by NOE measurements in their 400MHz ^{1}H-NMR spectra. As shown in **Figure 1**, NOEs between the signals of C8-H and C9a-H in **26**, **27**, **28**, and **29** were found to be 3.1%, 3.2%, 3.3%, and 2.9%, respectively. Based on these results, their stereostructures could be rigorously assigned as depicted.[20]

Figure 1. Selected NOE Enhancements of the Bridged Tetracyclic Compounds **26-29**



By employing *ent*-**3** instead of **3** as the aliphatic segment, unnatural (–)-FR900482 [*ent*-(–)-**1**], $[\alpha]_D^{23}$ -10°(*c* 0.02, H_2O), was also synthesized in the same manner as described above.

3. *In Vitro* Cytotoxicity of Enantiomeric Pairs of FR900482 (1 and *ent*-1) and Its Congeners (31, *ent*-31, 32, and *ent*-32)

The *in vitro* cytotoxicity assay against P388 murine leukemia was next carried out by employing enantiomeric pairs of FR900482 (**1** and *ent*-**1**) and its congeners (**31**, *ent*-**31**, **32**, and *ent*-**32**) along with FK973,[18] the triacetyl derivative of **1**. The IC_{50} values collected are shown in **Table 1**. These results cleanly disclosed that cytotoxicity of the C9-*O*-acetyl derivatives **31** and **32** is *ca.* 10-100 times more potent than that of **1**.[21] It is noteworthy that **1**, **31**, and **32** bearing natural absolute configuration were found to be approximately 100 time more cytotoxic than the corresponding enantiomers (*ent*-**1**, *ent*-**31**, and *ent*-**32**) possessing unnatural absolute configuration. This result is quite of interest in view of the fact that, as for mitomycin C carrying a similar structure to that of **1**, the unnatural enantiomer shows cytotoxicity being approximately half of that for the natural compound.[22] Taking into accounts the modes of action proposed for mitomycin C and **1** which are very similar each other,[18,22] the natural absolute configuration in **1** might provide a key structural feature for uptake of **1** by cancer cells and/or, more probably, for bioreduction of the *N*-hydroxylamine moiety to produce the benzazocine structure which spontaneously cyclizes to the mitosene derivative. In the case of mitomycin C, bioreduction of the quinoid part to the benzenoid structure followed by the mitosene formation with a loss of methanol might occur more readily, being affected by the absolute configuration less effectively than that of **1**.

Table 1. *In Vitro* Cytotoxicity of Enantiomeric Pairs of FR900482 (**1**) and Its Congeners Against P388 Murine Leukemia Cells

Compound	IC_{50} (μg/ml)[a]	Compound	IC_{50} (μg/ml)[a]
1	3.3×10^{-2}	*ent*-**1**	3.1
31	4.7×10^{-3}	*ent*-**31**	3.0×10^{-1}
32	3.6×10^{-4}	*ent*-**32**	4.0×10^{-2}
FK973[b]	9.5×10^{-4}		

a) Concentration required for 50% inhibition of the cell growth after incubation for 96h at 37°C (initial cell density: 1×10^4 cells/ml).
b) The triacetyl derivative of **1**.[18,21]

Conclusion

As described above, we have succeeded in completing the first enantioselective total synthesis of natural (+)- and unnatural (–)-FR900482 (**1** and *ent*-**1**) in a convergent manner starting from commercially available 5-hydroxyisophthalic acid and each enantiomer of diethyl tartrate. The explored synthetic scheme should hold promise for preparing various structural types of FR900482 congeners due to its flexibility. The cytotoxicity assay of **1**, its synthetic intermediates, and their enantiomers disclosed some novel aspects of the structure-activity relationships useful for both investigating the mode of antitumor action of **1** and designing novel FR900482 congeners.

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 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 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 F_{254} 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 1,2-dimethoxyethane were distilled from sodium benzophenone ketyl and dichloromethane was distilled from calcium hydride under argon.

N-Allyloxycarbonyl-*N*-[(4*R*,5*R*)-4-*tert*-butyldiphenylsiloxymethyl-2,2-dimethyl-3-(2,2,2-trichloroethoxycarbonyl)oxazolidine-5-yl]methyl-3-benzyloxy-5-benzyloxymethoxymethyl-2-(2-*tert*-butyldimethylsiloxy)ethylaniline (4) and Its Enantiomer (*ent*-4)

a) Preparation of **4:** Sodium hydride (60% dispersion in mineral oil, 3.50 g, 88 mmol) was added dropwise to a stirred solution of **2** (10.4 g, 18 mmol) and **3** (17.4 g, 25 mmol) in dry tetrahydrofuran (300 ml) at -78°C. The mixture was gradually warmed up to room temperature over 4 h and further stirred for 2 h. The reaction was quenched with saturated aqueous ammonium chloride (10 ml), and the mixture was diluted with ether (1500 ml). The organic layer was washed with water and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetae, 10:1) to give **4** (20.2 g, 100%) as a colorless caramel. $[\alpha]_D^{20}$ -1.3° (c 1.25, $CHCl_3$). IR (neat): 2970, 2950, 2900, 2875, 1720, 1590, 1440, 1410, 1260, 1140, 1120, 1060, 1030, 840, 780, 750, 710 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ -0.05 (6H, s, Me x 2), 0.84 (9H, s, *tert*-Bu), 0.91 (4.5H, s, *tert*-Bu), 0.96 (4.5H, s, *tert*-Bu), 1.43-1.73 (6H, m, acetonide Me), 2.72-3.03 (2H, m, CH_2), 3.24-4.15 (7H, m, CH_2 x 3 and CH), 4.15-4.90 (11H, m, CH_2 x 5 and CH), 4.98-5.42 (4H, m, CH_2 x 2), 5.72-6.04 (1H, m, Alloc-C*H*), 6.86-7.02 (2H, m, C4-H and C6-H), 7.22-7.46 (16H, m, aromatic protons), 7.46-7.68 (4H, m, aromatic protons). Due to the presence of rotamers in the allyl carbamate and 2,2,2-trichloroethyl carbamate groups, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. SIMS (3-NBA+NaCl) m/z: 1169 [$(M+Na)^+$, ^{35}Cl x 3], 1089 [$(M-C_4H_9)^+$, ^{35}Cl x 3]. *Anal.* Calcd for $C_{60}H_{77}Cl_3N_2O_{10}Si_2$: C, 62.73; H, 6.76; N, 2.44; Cl, 9.26%. Found: C, 62.59; H, 6.79; N, 2.31; Cl, 9.18%.

b) Preparation of *ent*-**4:** The same treatments of *ent*-**2** (13.6 g, 23 mmol) and *ent*-**3** (22.8 g, 32 mmol) as described for the preparation of **4** from **2** and **3** gave *ent*-**4** (26.2 g, 99%) as a colorless caramel. $[\alpha]_D^{20}$ +1.9° (c 1.14, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **4**.

N-Allyloxycarbonyl-*N*-[(2*R*,3*R*)-4-*tert*-butyldiphenylsiloxy-2-hydroxy-3-*p*-toluenesulfonamido]butyl-3-benzyloxy-5-benzyloxymethoxymethyl-2-(2-*tert*-butyldimethylsiloxy)ethylaniline (6) and Its Enantiomer (*ent*-6)

a) Preparation of **6:** Zinc powder (34.0 g, 0.52 mol) was added to a stirred solution of **4** (20.0 g, 17 mmol) in tetrahydrofuran (400 ml) containing water (100 ml) and acetic acid (18 ml) at room temperature. After 1 h, the mixture was filtered, and the filtrate was diluted with ether (1500 ml). The organic layer was washed with aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave *N*-allyloxycarbonyl-*N*-[(2*R*,3*R*)-3-amino-4-*tert*-butyldiphenylsiloxy-2-hydroxy]-butyl-3-benzyloxy-5-benzyloxymethoxymethyl-2-(2-*tert*-butyldimethylsiloxy)ethylaniline (**5**) (16.1 g) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): δ -0.07 (3H, br s, Me), -0.06 (3H, br s, Me), 0.81 (4.5H, s, *tert*-Bu), 0.82 (4.5H, s, *tert*-Bu), 0.99 (4.5H, s, *tert*-Bu), 1.0 (4.5H, s, *tert*-Bu), 1.57-1.94 (3H, m, OH and NH_2), 2.64-3.95 (10H, m, CH_2 x 4 and CH x 2), 4.40-5.19 (12H, m, CH_2 x 6), 5.58-5.94 (1H, m, Alloc-C*H*), 6.80-7.02 (2H, m, C4-H and C6-H), 7.24-7.50 (16H, m, aromatic protons), 7.50-7.73 (4H, m, aromatic protons). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. This material was directly used for the next reaction without further purification.

Triethylamine (2.67 ml, 19 mmol) and *p*-toluenesulfonyl chloride (3.33 g, 17 mmol) were successively added to a stirred solution of **5** (16.1g) in dry *N,N*-dimethylformamide (160 ml) at room temperature under argon. After 4 h, the mixture was was diluted with ethyl acetate (1500 ml). The organic layer was washed with water and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 5:1→2:1) to give **6** (14.6 g, 77%, 2 steps) as a colorless caramel. $[\alpha]_D^{20}$ -12.5° (c 1.16, $CHCl_3$).[24] IR (neat): 2970, 2950, 2900, 2870, 1690, 1590, 1440, 1430, 1410, 1330, 1170, 1150, 1120, 1100, 1060, 1030, 840, 750 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ -0.05 (2H, s, Me), -0.04 (4H, s, Me), 0.83 (3H, s, *tert*-Bu), 0.85 (6H, s, *tert*-Bu), 0.95 (6H, s, *tert*-Bu), 0.96 (3H, s, *tert*-Bu), 2.36 (3H, s, Ts-*Me*), 2.50-4.45 (11H, m, CH_2 x 4, CH x 2, and OH), 4.46-5.16 (13H, m, CH_2 x 6 and NH), 5.62-5.88 (1H, m, Alloc-C*H*), 6.75-6.98 (2H, m, C4-H and C6-H), 7.10-7.17 (2H, m, Ts-*H* x 2), 7.24-7.47 (16H, m, aromatic protons), 7.48-7.60 (6H, m, aromatic protons and Ts-*H* x 2). Due to

the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. SIMS (3-NBA+NaCl) m/z: 1100 [(M+Na)$^+$], 1029 [(M-C$_4$H$_9$)$^+$]. *Anal.* Calcd for C$_{61}$H$_{78}$N$_2$O$_{10}$SSi$_2$: C, 67.37; H, 7.23; N, 2.58; S, 2.95%. Found: C, 67.23; H, 7.29; N, 2.47; S, 2.99%.

b) Preparation of *ent*-**6**: Treatments of *ent*-**4** (26.1 g, 23 mmol) in the same manner as described for the preparation of **6** from **4** *via* **5** gave *ent*-**6** (19.5 g, 79%, 2 steps) as a colorless caramel *via ent*-**5** (21.2 g). $[\alpha]_D^{20}$ +11.1° (c 1.01, CHCl$_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **6**.

_N_-Allyloxycarbonyl-_N_-[(2_R_,3_R_)-4-*tert*-butyldiphenylsiloxy-2-methanesulfonyloxy-3-*p*-toluenesulfonamido]butyl-3-benzyloxy-5-benzyloxymethoxymethyl-2-(2-*tert*-butyldimethylsiloxy)ethylaniline (7) and Its Enantiomer (*ent*-7)

a) Preparation of **7**: Methanesulfonyl chloride (2.06 ml, 27 mmol) was added dropwise to a stirred solution of **6** (14.4 g, 13 mmol) in dichloromethame (180 ml) containing triethylamine (5.53 ml, 40 mmol) at 0°C, and stirring was continued for 3 h at room temperature under argon. The reaction was quenched with aqueous sodium hydrogen carbonate (10 ml), and the mixture was diluted with ether (1500 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, 5:1→3:1→2:1) to give **7** (14.5 g, 94%) as a colorless caramel. IR (neat): 2970, 2950, 2900, 2870, 1710, 1580, 1480, 1440, 1340, 1260, 1170, 1150, 1120, 1100, 1060, 750, 710, 670 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ -0.08 (2H, br s, Me), -0.04 (4H, s, Me), 0.84 (3H, s, *tert*-Bu), 0.85 (6H, s, *tert*-Bu), 0.94 (6H, s, *tert*-Bu), 0.97 (3H, br s, *tert*-Bu), 2.32 (3H, s, Ts-*Me*), 2.51-2.64, 2.81-3.83 (11H, m, CH2 x 3, CH x 2, and Ms-*Me*), 4.18-5.60 (15H, m, CH2 x 7 and NH), 5.68-5.90 (1H, brs, W1/2=45.2 Hz, Alloc-C*H*), 6.87-7.17 (4H, m, C4-H, C6-H and Ts-*H* x 2), 7.24-7.66 (24H, m, aromatic protons and Ts-*H* x 2). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. This material was immediately used for the next reaction due to its instability.

b) Preparation of *ent*-**7**: Similar treatments of *ent*-**6** (19.4 g, 18 mmol) to those described for the preparation of **7** from **6** gave *ent*-**7** (19.1 g, 92%) as a colorless caramel. The IR and ^{1}H-NMR spectra of this sample were identical with those recorded for **7**.

(2_S_,3_S_)-2-*tert*-Butyldiphenylsiloxymethyl-3-[_N_-allyloxycarbonyl-3-benzyloxy-5-benzyloxymethoxymethyl-2-(2-*tert*-butyldimethylsiloxy)ethylanilino]methyl-1-*p*-toluenesulfonylaziridine (8) and Its Enantiomer (*ent*-8)

a) Preparation of **8**: Sodium hydride (60% dispersion in mineral oil, 1.47 g, 36 mmol) was added dropwise to a stirred solution of **7** (14.3 g, 12 mmol) in dry tetrahydrofuran (250 ml) containing imidazole (1.67 g, 25 mmol) at room temperature, and the mixture was heated at reflux for 30 min. After colling, the reaction was quenched with saturated aqueous ammonium chloride (10 ml), and the mixture was extracted with ether (3 x 500 ml). The combined extracts were washed with saturated aqueous sodium hydrogen carbonate, water, and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetae, 5:1→3:1) to give **8** (12.1 g, 92%) as a colorless caramel. $[\alpha]_D^{20}$ -6.8° (c 1.20, CHCl3). IR (neat): 3080, 3050, 2970, 2950, 2900, 2870, 1710, 1580, 1470, 1450, 1260, 1170, 1090, 1050, 840, 710, 510 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): δ -0.14-0.04 (6H, m, Me x 2), 0.79 (4.5H, s, *tert*-Bu), 0.80 (4.5H, s, *tert*-Bu), 0.88 (4.5H, s, *tert*-Bu), 0.90 (4.5H, s, *tert*-Bu), 2.32 (1.5H, s, Ts-*Me*), 2.35 (1.5H, s, Ts-*Me*), 2.50-4.30 (10H, m, CH2 x 4 and CH x 2), 4.42-5.26 (12H, m, CH2 x 6), 5.68-5.90 (1H, m, Alloc-C*H*), 6.74 (0.5H, br s, C6-H), 6.78 (0.5H, br s, C6-H), 6.90 (0.5H, br s, C4-H), 6.94 (0.5H, br s, C4-H), 7.16 (1H, d, J=8.0 Hz, Ts-*H*), 7.21 (1H, d, J=8.0 Hz, Ts-*H*), 7.25-7.54 (20H, m, aromatic protons), 7.78 (1H, d, J=8.0 Hz, Ts-*H*), 7.88 (1H, d, J=8.0 Hz, Ts-*H*). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. SIMS (3-NBA+KCl) m/z: 1107 [(M+K)$^+$], 1011 [(M-C4H9)$^+$]. *Anal.* Calcd for C$_{61}$H$_{76}$N$_2$O$_9$SSi$_2$: C, 68.50; H, 7.16; N, 2.62; S, 3.00%. Found: C, 68.62; H, 7.27 N, 2.60; S, 2.99%.

b) Preparation of *ent*-**8**: Treatments of *ent*-**7** (19.0 g, 16 mmol) in a similar manner to that described for the preparation of **8** from **7** gave *ent*-**8** (16.4 g, 94%) as a colorless caramel. $[\alpha]_D^{20}$ +6.3° (c 1.02, CHCl3). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **8**.

(2_S_,3_S_)-3-[_N_-Allyloxycarbonyl-3-benzyloxy-5-benzyloxymethoxymethyl-2-(2-hydroxyethyl)anilino]-methyl-1-*p*-toluenesulfonyl-2-aziridinemethanol (9) and Its Enantiomer (*ent*-9)

a) Preparation of **9**: Hydrogen fluoride-pyridine complex (110 ml, 41 mol) was added dropwise to a stirred solution of **8** (12.0 g, 11 mmol) in pyridine (320 ml) at -10°C. After 40 min, the reaction mixture was diluted with ether (1500 ml). The organic layer was washed successively with water, 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 acetae, 3:2→2:1) to give **9** (7.96 g, 99%) as a colorless caramel. $[\alpha]_D^{20}$ -10.9° (c 1.16, CHCl3). IR (neat): 3450, 2950, 2900, 1710, 1700, 1580, 1460, 1450, 1410, 1330, 1310, 1280, 1170, 1050, 750, 700, 680, 580 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): 2.41 (1.5H, s, Ts-*Me*), 2.43 (1.5H, s, Ts-*Me*), 2.66-4.80 (12H, m, CH2 x 4, CH x 2, and OH x 2), 4.48-5.16 (12H, m, CH2 x 6), 5.70-6.05 (1H, m, Alloc-C*H*), 6.74 (0.5H, br s, C6-H), 6.78 (0.5H, br s, C6-H), 6.90 (0.5H, br s, C4-H), 6.94 (0.5H, br s, C4-H), 7.24-7.46 (12H, m, aromatic protons

and Ts-*H* x 2), 7.74 (1H, d, J=8.0 Hz, Ts-*H*), 7.80 (1H, d, J=8.0 Hz, Ts-*H*). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. SIMS (3-NBA+NaCl) m/z: 739 [(M+Na)$^+$], 717 [(M+H)$^+$], 659 [(M-C_3H_5O)$^+$]. HRMS calcd for $C_{36}H_{38}N_2O_8S$[(M-C_3H_6O)$^+$]: 658.2346. Found: 658.2356.

b) Preparation of *ent*-**9**: The same treatments of *ent*-**8** (16.3 g, 15 mmol) as described for the preparation of **9** from **8** gave *ent*-**9** (10.7 g, 98%) as a colorless caramel. [α]$_D^{20}$ +10.7° (c 0.97, $CHCl_3$). The IR, ^{1}H-NMR, mass spectra of this sample were identical with those recorded for **9**.

(2*S*,3*S*)-3-[*N*-Allyloxycarbonyl-3-benzyloxy-5-benzyloxymethoxymethyl-2-(2-formylmethyl)anilino]-methyl-1-*p*-toluenesulfonylaziridine-2-carboxaldehyde (10) and Its Enantiomer (*ent*-10)

a) Preparation of **10**: Dess-Martin periodinane (18.6 g, 44 mmol) was added in small portions to a stirred solution of **9** (7.86 g, 11 mmol) in dry dichloromethane (210 ml) at room temperature. After 1 h, the mixture was diluted with ether (1300 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetae, 2:1→1:1) to give **10** (7.66 g, 98%) as a colorless caramel. [α]$_D^{20}$ -2.6° (c 0.91, $CHCl_3$). IR (neat): 1730, 1710, 1620, 1500, 1450, 1410, 1390, 1330, 1310, 1280, 1210, 1170, 1100, 1050, 990, 850, 820, 750, 700, 680, 590 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.42 (1.5H, s, Ts-*Me*), 2.44 (1.5H, s, Ts-*Me*), 3.21-3.28 (1H, m, C3-H), 3.34-3.88 (2H, m, C*H*$_2$CHO or AllocNC*H*$_2$), 4.01-4.15 (2H, m, C*H*$_2$CHO or AllocNC*H*$_2$), 3.54 (1H, d, J=12.6 Hz, C2-H), 4.48 (2H, br s, W$_{1/2}$=44 Hz, Alloc-C*H*$_2$), 4.63 (2H, d, J=4.6 Hz, C*H*$_2$OBOM), 4.66 (2H, d, J=2.5 Hz, PhC*H*$_2$OCH$_2$O), 4.86 (2H, d, J=1.5 Hz, PhCH$_2$OC*H*$_2$O), 5.07 (2H, d, J=6.7 Hz, PhC*H*$_2$O), 5.09 (2H, br s, W$_{1/2}$=40 Hz, Alloc-terminal C*H*$_2$), 5.76 (1H, br s, W$_{1/2}$=28 Hz, Alloc-C*H*), 6.76 (0.5H, br s, aniline C6-H), 6.88 (0.5H, br s, aniline C6-H), 6.98 (0.5H, br s, aniline C4-H), 7.00 (0.5H, br s, aniline C4-H), 7.24-7.46 (12H, m, aromatic protons and Ts-*H* x 2), 7.80 (1H, d, J=8.0 Hz, Ts-*H*), 7.81 (1H, d, J=8.0 Hz, Ts-*H*), 9.06 (1H, br s, CHO), 9.57 (0.5H, s, CHO), 9.60 (0.5H, s, CHO). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. CIMS (isobutane) m/z: 713 [(M+H)$^+$], 695 [(M+H-H_2O)$^+$], 683 [(M-CHO)$^+$], 665 [(M-CHO-H_2O)$^+$]. *Anal.* Calcd for $C_{39}H_{40}N_2O_9S$: C, 65.72; H, 5.66; N, 3.93; S, 4.50%. Found: C, 65.50; H, 5.90; N, 3.83; S, 4.46%.

b) Preparation of *ent*-**10**: Treatments of *ent*-**9** (10.5 g, 15 mmol) in the same manner as described for the preparation of **10** from **9** gave *ent*-**10** (9.97 g, 95%) as a colorless caramel. [α]$_D^{20}$ +3.9° (c 1.12, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **10**.

(1a*S*,8*S*,9*S*,9a*S*)-3-Allyloxycarbonyl-7-benzyloxy-5-benzyloxymethoxymethyl-1a,2,3,8,9,9a-hexahydro-9-hydroxy-8-hydroxymethyl-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (12) and Its Enantiomer (*ent*-12)

a) Preparation of **12**: Lithium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M solution, 3.90 ml, 3.9 mmol) was added dropwise to a stirred solution of **10** (2.79 g, 3.9 mmol) in dry tetrahydrofuran (490 ml) at -78°C, and the mixture was gradually warmed up to -5°C over 3 h. Sodium borohydride (740 mg, 20 mmol) in water (10 ml) was added slowly at -5°C, and stirring was continued fo 20 min at 0°C. The mixture was poured into saturated aqueous ammonium chloride (100 ml) and extracted with ether (3 x 500 ml). The combined extracts were washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 3:2→1:2) to give **12** (colorless caramel, 1.34 g, 48%) along with **9** (926 mg, 33% recovery). [α]$_D^{20}$ +103° (c 0.72, $CHCl_3$). IR (neat): 2950, 2900, 1710, 1620, 1610, 1580, 1500, 1460, 1440, 1400, 1390, 1330, 1250, 1170, 1100, 1050, 990, 970, 880, 820, 750, 700, 680, 580, 550 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.11-2.61 (2H, m, OH x 2), 2.45 (3H, s, Ts-*Me*), 2.76 (2H, br s, W$_{1/2}$=28 Hz, C1a-H and C9a-H), 3.78(4H, br s, W$_{1/2}$=88 Hz, C2-H$_2$, C8-H, and C9-H), 4.26-4.75 (4H, m, C*H*$_2$OH and Alloc-C*H*$_2$), 4.60 (2H, s, C*H*$_2$OBOM), 4.65 (2H, s, PhC*H*$_2$OCH$_2$O), 4.85 (2H, s, PhCH$_2$OC*H*$_2$O), 5.10 (2H, s, PhC*H*$_2$O), 4.98-5.42 (2H, m, Alloc-terminal C*H*$_2$), 5.75 (0.5H, br s, W$_{1/2}$=20 Hz, Alloc-C*H*), 5.92 (0.5H, br s, W$_{1/2}$=20 Hz, Alloc-C*H*), 6.66 (1H, br s, W$_{1/2}$=28 Hz, C4-H), 7.00 (1H, s, C6-H), 7.24-7.51 (12H, m, aromatic protons and Ts-*H* x 2), 7.83 (2H, d, J=8.2 Hz, Ts-*H* x 2). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. CIMS (isobutane) m/z: 715 [(M+H)$^+$], 697 [(M+H-H_2O)$^+$]. *Anal.* Calcd for $C_{39}H_{42}N_2O_9S$: C, 65.53; H, 5.92; N, 3.92; S, 4.49%. Found: C, 65.34; H, 6.01; N, 3.80; S, 4.45%.

b) Preparation of *ent*-**12**: Similar treatments of *ent*-**10** (2.88 g, 4.0 mmol) to those described for the preparation of **12** from **10** gave *ent*-**12** (colorless caramel, 1.36 g, 47%), [α]$_D^{20}$ -99.2° (c 0.99, $CHCl_3$), along with *ent*-**9** (898 mg, 31% recovery). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **12**.

(1a*S*,8*S*,9*S*,9a*S*)-3-Allyloxycarbonyl-7-benzyloxy-5-benzyloxymethoxymethyl-8-*tert*-butyldiphenylsiloxymethyl-1a,2,3,8,9,9a-hexahydro-9-hydroxy-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (13) and Its Enantiomer (*ent*-13)

a) Preparation of **13:** *tert*-Butyldiphenylsilyl chloride (3.04 ml, 12 mmol) was added to a stirred solution of **12** (2.78 g, 4.0 mmol) in dry dichloromethane (200 ml) containing triethylamine (2.71 ml, 20 mmol) and 4-dimethylaminopyridine (732 mg, 6.0 mmol) at room temperature. After 5 h, the mixture was diluted with ether (1000 ml). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1→3:1→1:1) to give **13** (2.93 g, 79%) as a colorless caramel. $[\alpha]_D^{20}$ +92.1° (c 1.03, $CHCl_3$). IR (neat): 2950, 2900, 1710, 1620, 1580, 1500, 1460, 1440, 1400, 1330, 1260, 1230, 1160, 1140, 1110, 1100, 1060, 1030, 990, 880, 820, 750, 710, 680, 580, 510 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.99 (9H, s, *tert*-Bu), 2.45 (3H, s, Ts-*Me*), 2.63 (1H, dd, J=12.6, 7.1 Hz, C1a-H), 2.95 (1H, dd, J=9.2, 8.1 Hz, C9a-H), 3.74 (4H, br s, W1/2=74 Hz, C2-H2 and Alloc-C*H*2), 4.06-4.17 (1H, m, C8-H), 4.22 (2H, dd, J=14.2, 5.2 Hz, C*H*2OTBDPS), 4.29 (1H, s, OH), 4.40 (1H, t, J=9.2 Hz, C9-H), 4.53 (2H, s, C*H*2OBOM), 4.60 (2H, s, PhC*H*2OCH2O), 4.78 (2H, s, PhCH2OC*H*2O), 4.46-4.85 (2H, m, Alloc-terminal C*H*2), 5.02 (1H, d, J=11.9 Hz, PhC*H*2O), 5.10 (1H, d, J=11.9 Hz PhC*H*2O), 5.31 (1H, br s, W1/2=48 Hz, Alloc-C*H*), 6.58 (1H, br s, W1/2=32 Hz, C4-H), 6.89 (1H, d, J=1.3 Hz, C6-H), 7.17 (1H, d, J=7.6 Hz, Ts-*H*), 7.20 (1H, d, J=7.6 Hz, Ts-*H*), 7.23-7.48 (16H, m, aromatic protons), 7.50-7.61 (4H, m, aromatic protons), 7.90 (2H, d, J=7.6, Ts-*H* x 2). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. SIMS (3-NBA+NaCl) m/z: 975 [(M+Na)$^+$], 935 [(M+H-H2O)$^+$], 895 [(M-*tert*-Bu)$^+$]. *Anal.* Calcd for $C_{55}H_{60}N_2O_9SSi$: C, 69.30; H, 6.34; N, 2.94; S, 3.36%. Found: C, 69.46; H, 6.50; N, 2.75; S, 3.31%.

b) Preparation of *ent*-**13:** Treatments of *ent*-**12** (4.68 g, 6.6 mmol) in a simmilar manner to that described for the preparation of **13** from **12** gave *ent*-**13** (4.99 g, 80%) as a colorless caramel. $[\alpha]_D^{20}$ -93.6° (c 1.04, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **13**.

(1a*S*,8*S*,9a*S*)-3-Allyloxycarbonyl-7-benzyloxy-5-benzyloxymethoxymethyl-8-*tert*-butyldiphenylsiloxymethyl-1a,2,3,8,9,9a-hexahydro-9-oxo-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (14) and Its Enantiomer (*ent*-14)

a) Preparation of **14:** Dess-Martin periodinane (8.83 g, 21 mmol) was added in small portions to a stirred solution of **13** (3.55 g, 3.7 mmol) in dry dichloromethane (110 ml) at room temperature. After 1 h, the mixture was diluted with ether (800 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetae, 5:1→2:1) to give **14** (3.29 g, 93%) as a colorless caramel. $[\alpha]_D^{20}$ +11.3° (c 0.99, $CHCl_3$). IR (KBr): 2950, 2900, 2870, 1740, 1720, 1620, 1580, 1460, 1440, 1390, 1340, 1300, 1250, 1170, 1110, 1060, 1030, 990, 830, 750, 710, 570, 510 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.93 (9H, s, *tert*-Bu), 2.44 (3H, s, Ts-*Me*), 2.95 (1H, ddd, J=8.2, 6.2, 4.1 Hz, C1a-H), 3.52 (1H, d, J=8.1 Hz, C9a-H), 3.46-3.68 (2H, m, C2-H2), 3.68-4.46 (4H, m, C*H*2OTBDPS, C8-H, and Alloc-C*H*2), 4.56 (1H, dd, J=8.1, 3.4 Hz, C*H*2OTBDPS), 4.60 (2H, s, C*H*2OBOM), 4.63 (2H, s, PhC*H*2OCH2O), 4.84 (2H, s, PhCH2OC*H*2O), 4.52-4.96 (2H, m, Alloc-terminal C*H*2), 5.10 (1H, d, J=11.6 Hz, PhC*H*2O), 5.15 (1H, d, J=11.6 Hz, PhC*H*2O), 5.24-5.80 (1H, m, Alloc-C*H*), 6.66 (1H, s, C4-H), 7.00 (1H, d, J=1.0 Hz, C6-H), 7.18 (1H, d, J=7.9 Hz, Ts-*H*), 7.20 (1H, d, J=7.9 Hz, Ts-*H*), 7.24-7.50 (16H, m, aromatic protons), 7.55 (2H, dd, J=8.0, 1.3 Hz, aromatic protons), 7.72 (2H, dd, J=8.0, 1.3 Hz, aromatic protons), 7.90 (2H, d, J=7.9 Hz, Ts-*H* x 2). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. CIMS (isobutane) m/z: 951 [(M+H)$^+$], 933 [(M+H-H2O)$^+$], 893[(M-*tert*-Bu)$^+$], 893 [(M-Ph)$^+$]. *Anal.* Calcd for $C_{55}H_{58}N_2O_9SSi$: C, 69.45; H, 6.15; N, 2.94; S, 3.37%. Found: C, 69.43; H, 6.13; N, 2.92; S, 3.39%.

b) Preparation of *ent*-**14:** The same treatments of *ent*-**13** (4.93 g, 5.2 mmol) as described for the preparation of **14** from **13** gave *ent*-**14** (4.68 g, 95%) as a colorless caramel. $[\alpha]_D^{20}$ -12.2° (c 0.98, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **14**.

(1a*S*,8*S*,9a*S*)-3-Allyloxycarbonyl-7-benzyloxy-5-benzyloxymethoxymethyl-1a,2,3,8,9,9a-hexahydro-8-hydroxymethyl-9-oxo-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (15) and Its Enantiomer (*ent*-15)

a) Preparation of **15:** Hydrogen fluoride-pyridine complex (33 ml, 1.2 mol) was added dropwise to a stirred solution of **14** (3.14 g, 3.3 mmol) in pyridine (100 ml) at -10°C, and the mixture was allowed to warm up to room temperature. After 1 h, the reaction mixture was diluted with ether (1000 ml). The organic layer was washed successively with water, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetae, 3:1→1:1) to give **15** (2.19 g, 93%) as a colorless caramel. $[\alpha]_D^{20}$ +16.1° (c 1.02, $CHCl_3$).[24] IR (neat): 2950, 2900, 1730, 1620, 1590, 1450, 1390, 1340, 1300, 1250, 1190, 1170, 1110, 1100, 1050, 980, 760, 700, 680, 570 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.44 (3H, s, Ts-*Me*), 2.67 (1H, dd, J=10.4, 4.2 Hz, OH), 3.03 (1H, ddd, J=8.1, 6.1, 3.6 Hz, C1a-H), 3.38 (1H, d, J=8.1 Hz, C9a-H), 3.51-3.70 (2H, m, C2-H2), 4.05 (1H, dd, J=12.0, 3.7 Hz, C8-H), 4.32-4.44 (2H, m, C*H*2OH), 4.50 (2H, br s, W1/2=32 Hz, Alloc-C*H*2), 4.63 (2H, s, C*H*2OBOM), 4.65 (2H, s, PhC*H*2OCH2O), 4.86 (2H, s,

PhCH2OC*H2*O), 5.14 (1H, d, J=11.6 Hz, PhC*H2*O), 5.18 (1H, d, J=11.6 Hz, PhC*H2*O), 5.06-5.25 (2H, m, Alloc-terminal C*H2*), 5.81 (1H, br s, W1/2=48 Hz, Alloc-C*H*), 6.73 (1H, s, C4-H), 7.05 (1H, d, J=1.1 Hz, C6-H), 7.24-7.47 (12H, m, aromatic protons and Ts-*H* x 2), 7.86 (2H, dd, J=7.6, 1.3 Hz, Ts-*H* x 2). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. SIMS (3-NBA+NaCl) m/z: 735 [(M+Na)$^+$], 713 [(M+H)$^+$], 695[(M+H-H2O)$^+$], 682 [(M+H-CH2OH)$^+$]. *Anal.* Calcd for C39H40N2O9S: C, 65.72; H, 5.66; N, 3.93; S, 4.50%. Found: C, 65.92; H, 5.76; N, 3.83; S, 4.30%.

b) Preparation of *ent*-**15:** Similar treatments of *ent*-**14** (4.03 g, 4.2 mmol) to those described for the preparation of **14** from **13** gave *ent*-**15** (2.84 g, 94%) as a colorless caramel. [α]D^{20} -16.4° (c 1.09, CHCl3). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **15**.

(1a*S*,8*R*,9a*S*)-3-Allyloxycarbonyl-7-benzyloxy-5-benzyloxymethoxymethyl-1a,2,3,8,9,9a-hexahydro-8-hydroxymethyl-9-oxo-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (16) and Its Enantiomer (*ent*-16)

a) Preparation of **16:** A solution of **15** (2.08 g, 2.9 mmol) in tetrahydrofuran (200 ml) containing 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) (1.32 ml, 8.8 mmol) was stirred for 3 h at room temperature. The mixture was diluted with ether (600 ml). The organic layer was washed with aqueous sodium hydrogen carbonate and brine, then dried over Na2SO4. Concentration of the solvent *in vacuo* afforded a residue, which was separated by column chromatography (benzene-ethyl acetae, 5:1) to give more polar **16** (colorless caramel, 1.33 g, 64%) and less polar **15** (645 mg, 31% recovery). [α]D^{20} +4.3° (c 1.07, CHCl3).[24] IR (neat): 2950, 2900, 1720, 1590, 1460, 1440, 1390, 1330, 1290, 1250, 1190, 1170, 1100, 1050, 990, 900, 890, 820, 740, 700, 680, 570, 540 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): 2.12 (3H, s, Ts-*Me*), 2.52 (1H, brs, W1/2=28 Hz, OH), 3.43 (1H, d, J=2.0 Hz, C9a-H), 3.35-3.68 (3H, m, C1a-H and C2-H2), 3.91 (1H, dd, J=8.8, 2.8 Hz, C*H2*OH), 4.01 (1H, br s, W1/2=36 Hz, C*H2*OH), 4.51 (2H, br s, W1/2=32 Hz, Alloc-C*H2*), 4.63 (2H, s, C*H2*OBOM), 4.67 (2H, s, PhC*H2*OCH2O), 4.86 (2H, s, PhCH2OC*H2*O), 4.60-4.82 (1H, m, C8-H), 5.12 (1H, d, J=12.0 Hz PhC*H2*O), 5.16 (1H, d, J=12.0 Hz, PhC*H2*O), 5.03-5.25 (2H, m, Alloc-terminal C*H2*), 5.82 (1H, br s, W1/2=40 Hz, Alloc-C*H*), 6.63 (1H, s, C4-H), 7.00 (1H, s, C6-H), 7.00 (1H, d, J=8.0 Hz, Ts-*H*), 7.03 (1H, d, J=8.0 Hz, Ts-*H*), 7.25-7.44 (12H, m, aromatic protons and Ts-*H* x 2). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. CIMS (isobutane) m/z: 713 [(M+H)$^+$], 695 [(M+H-H2O)$^+$], 683[(M+H-CH2O)$^+$], 665 [(M+H-H2O-CH2O)$^+$]. *Anal.* Calcd for C39H40N2O9S: C, 65.72; H, 5.66; N, 3.93; S, 4.50%. Found: C, 65.44; H, 5.70; N, 3.84; S, 4.41%.

b) Preparation of *ent*-**16:** Treatments of *ent*-**15** (2.65 g, 3.7 mmol) in a similar manner to that described for the preparation of **16** from **15** gave *ent*-**16** (colorless caramel, 1.67 g, 63%), [α]D^{20} -5.2° (c 1.15, CHCl3), along with recovery of *ent*-**15** (848 mg, 32%). The ^{1}H-NMR spectrum of *ent*-**16** was identical with that recorded for **16**.

(1a*S*,8*R*,9*R*,9a*S*)-3-Allyloxycarbonyl-7-benzyloxy-5-benzyloxymethoxymethyl-1a,2,3,8,9,9a-hexahydro-9-hydroxy-8-hydroxymethyl-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (17) and Its Enantiomer (*ent*-17)

a) Preparation of **17:** Sodium borohydride (334 mg, 8.8 mmol) in water (15 ml) was added to a stirred solution of **16** (1.25 g, 1.76 mmol) in tetrahydrofuran (150 ml) at 0°C, and the mixture was allowed to warm up to room temperature. After 1 h, the reaction was quenched with saturated aqueous ammonium chloride (15 ml), and the reaction mixture was diluted with ethyl acetate (300 ml). The organic layer was washed successively with brine and dried over Na2SO4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetate, 2:1→1:1) to give **17** (1.09 g, 87%) as a colorless caramel. [α]D^{20} -40.1° (c 1.21, CHCl3). IR (neat): 2950, 2900, 1720, 1690, 1620, 1580, 1500, 1460, 1440, 1410, 1380, 1330, 1270, 1220, 1190, 1170, 1090, 1050, 990, 930, 850, 820, 770, 740, 700, 670, 550 cm^{-1}. ^{1}H-NMR (400 MHz, CDCl3): 2.34-2.51 (3H, m, Ts-*Me*), 2.51-2.73 (1H, m, OH), 3.17-3.43 (1H, m, CH), 3.43-4.42 (7H, m, CH x 2, CH2 x 2, OH), 4.47-4.86 (8H, m, C*H2*OBOM PhC*H2*OC*H2*O, Alloc-C*H2*), 5.00-5.45 (5H, m, CH, PhC*H2*O, Alloc-terminal C*H2*), 5.71-5.99 (1H, m, Alloc-C*H*), 6.48-6.70 (1H, m, C4-H), 6.87-6.98 (1H, m, C6-H), 7.24-7.58 (12H, m, aromatic protons and Ts-*H* x 2), 7.73-7.89 (2H, m, Ts-*H* x 2). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. CIMS (isobutane) m/z: 715 [(M+H)$^+$], 697 [(M+H-H2O)$^+$], 685 [(M+H-CH2O)$^+$]. *Anal.* Calcd for C39H42N2O9S: C, 65.53; H, 5.92; N, 3.92; S, 4.49%. Found: C, 65.43; H, 5.93; N, 3.82; S, 4.43%.

b) Preparation of *ent*-**17:** The same treatments of *ent*-**16** (1.60 g, 2.2 mmol) as described for the preparation of **17** from **16** gave *ent*-**17** (1.41 g, 88%) as a colorless caramel. [α]D^{20} +39.5° (c 1.07, CHCl3). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **17**.

(1a*S*,9a*S*)-3-Allyloxycarbonyl-7-benzyloxy-5-benzyloxymethoxymethyl-1a,2,3,8,9,9a-hexahydro-8-methylene-9-oxo-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (18)

The 1*H*-azirizino[2,3-*c*][1]benzazocine **15** (30.7 mg, 43.1 μmol) was treated for 13 h under the same conditions as described for the preparation of **16** from **15** to afford **18** (29.0 mg, 97%) as a colorless caramel after purification by column chromatography (hexane-ethyl acetate, 3:1). [α]D^{20} +39.8° (c 1.35, CHCl3). IR (neat): 1720, 1680, 1570, 1440, 1390, 1330, 1250, 1160, 1090,

1050, 990, 900, 740, 700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.13 (3H, br s, $W_{1/2}$=18 Hz, Ts-*Me*), 2.44 (1H, br s, $W_{1/2}$=28 Hz), 3.01 (0.5H, br s, $W_{1/2}$=20 Hz), 3.27-3.51 (1.5H, m), 3.57-3.67 (1H, m), 3.80-3.95 (0.5H, br s, $W_{1/2}$=20 Hz), 4.28-4.60 (1.5H, m), 4.66 (2H, s, C*H*$_2$OBOM), 4.68 (2H, s, PhC*H*$_2$OCH$_2$O), 4.70-4.85 (2H, m), 4.88 (2H, s, PhCH$_2$OC*H*$_2$O), 5.61-5.76 (1H, br s, $W_{1/2}$=28 Hz), 5.84-5.92 (0.5H, br s, $W_{1/2}$=20 Hz), 6.03-6.11 (0.5H, br s, $W_{1/2}$=20 Hz), 6.19-6.24 (0.5H, br s, $W_{1/2}$=14 Hz), 6.36-6.42 (0.5H, br s, $W_{1/2}$=12 Hz), 6.81-6.88 (0.5H, br s, $W_{1/2}$=18 Hz), 6.68 (1H, s, C4-H), 6.98-7.12 (3H, m, C6-H and Ts-*H* x 2), 7.28-7.45 (11.5H, m aromatic protons), 7.83-7.91 (0.5H, br s, $W_{1/2}$=20 Hz). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. EIMS m/z: 694 (M^+), 653 [(M-CH_2=CH_2)$^+$]. HRMS calcd for $C_{39}H_{38}N_2O_8S$ (M^+): 694.2346. Found: 694.2359.

(1a*S*,8*R*,9*R*,9a*S*)-3-Allyloxycarbonyl-7-benzyloxy-5-benzyloxymethoxymethyl-8-*tert*-butyldiphenylsiloxymethyl-1a,2,3,8,9,9a-hexahydro-9-hydroxy-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (19) and Its Enantiomer (*ent*-19)

a) Preparation of **19:** *tert*-Butyldiphenylsilyl chloride (1.11 ml, 4.3 mmol) was added to a stirred solution of **17** (1.02 g, 1.4 mmol) in dry dichloromethane (80 ml) containing triethylamine (1.00 ml, 7.1 mmol) and 4-dimethylaminopyridine (87 mg, 0.70 mmol) at room temperature. After 7 h, the mixture was diluted with ether (200 ml). The organic layer was washed with brine and dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetate, 4:1→2:1) to give **19** (966 mg, 71%) as a colorless caramel. $[\alpha]_D^{20}$ -28.9° (c 1.02, $CHCl_3$). IR (KBr): 2950, 2900, 2870, 1710, 1620, 1580, 1500, 1470, 1460, 1440, 1400, 1330, 1310, 1270, 1230, 1170, 1110, 1100. 1050, 1030, 1000, 980, 940, 900, 820, 720, 700, 580, 510 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.07 (6H, s, *tert*-Bu), 1.09 (3H, s, *tert*-Bu), 2.41 (2H, s, Ts-*Me*), 2.43 (1H, s, Ts-*Me*), 2.48-2.80 (1H, m, OH), 3.37-3.50 (1H, br t, J=7.8 Hz), 3.58-3.72 (2H, m), 3.78-3.89 (1H, m), 3.94-4.40 (0.7H, dd, J=14.0, 5.2Hz), 4.10 (0.3H, br s, $W_{1/2}$=20 Hz), 4.20 (1H, br t, J=11.5Hz), 4.32 (1H, br dd, J=14.0, 5.2Hz), 4.43-4.97 (6H, m), 4.47 (2H, s, C*H*$_2$OBOM), 4.56 (2H, s, PhC*H*$_2$OCH$_2$O), 5.01 (2H, s, PhCH$_2$OC*H*$_2$O), 5.00 (1H, d, J=11.9 Hz, PhC*H*$_2$O), 5.06 (1H, d, J=11.9 Hz, PhC*H*$_2$O), 5.20-5.48 (1H, m, Alloc-C*H*), 6.51 (1H, s, C4-H), 6.83 (1H, s, C6-H), 7.12-7.53 (16H, m, aromatic protons and Ts-*H* x 2), 7.53-7.69 (4H, m, aromatic protons), 7.85 (2H, d, J=8.3 Hz, Ts-*H* x 2). Due to the presence of rotamers in the allyl carbamate group, extensive line broadening and, in some instances, doubling of signals were observed for this ^{1}H-NMR spectrum. CIMS (isobutane) m/z: 953 [(M+H)$^+$], 935[(M+H-H_2O)$^+$], 895 [(M-*tert*-Bu)$^+$], 875 [(M-Ph)$^+$]. *Anal.* Calcd for $C_{55}H_{60}N_2O_9SSi$: C, 69.30; H, 6.34; N, 2.94; S, 3.36%. Found: C, 69.06; H, 6.36; N, 2.84; S, 3.36%.

b) Preparation of *ent*-**19:** Treatments of *ent*-**17** (1.33 g, 1.9 mmol) in the same manner described for the preparation of **19** from **17** gave *ent*-**19** (1.33 g, 75%) as a colorless caramel. $[\alpha]_D^{20}$ +29.8° (c 1.12, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **19**.

(1a*S*,8*R*,9*R*,9a*S*)-7-Benzyloxy-5-benzyloxymethoxymethyl-8-*tert*-butyldiphenylsiloxymethyl-1a,2,3,8,9,9a-hexahydro-9-hydroxy-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (20) and Its Enantiomer (*ent*-20)

a) Preparation of **20:** Triphenylphosphine (262 mg, 1.0 mmol), tetrakis(triphenylphosphine)palladium(0) (277 mg, 0.24 mmol), and octanoic acid (0.80 ml, 5.0 mmol) were successively added to a stirred solution of **19** (952 mg, 1.0 mmol) in dry tetrahydrofuran (100 ml) at room temperature. After 2 h, the mixture was diluted with ether (300 ml). The organic layer was washed with aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (benzene-ethyl acetate, 15:1→6:1) to give **20** (720 mg, 83%) as a colorless caramel. $[\alpha]_D^{20}$ +47.4° (c 0.91, $CHCl_3$). IR (KBr): 2950, 2900, 2860, 1620, 1590, 1460, 1430, 1380, 1370, 1330, 1250, 1230, 1160, 1140, 1120, 1100, 1050, 1000, 960, 930, 880, 820, 740, 700, 620, 570, 510 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.03 (9H, br s, $W_{1/2}$=70 Hz, *tert*-Bu), 2.41 (3H, s, Ts-*Me*), 2.62-5.08 (10H, m, C*H*$_2$ x 2, C*H* x 4, NH and OH), 4,49 (2H, s, C*H*$_2$OBOM), 4.61 (2H, s, PhC*H*$_2$OCH$_2$O), 4.78 (2H, s, PhCH$_2$OC*H*$_2$O), 4.95 (2H, s, PhC*H*$_2$O), 6.30 (1H, br s, $W_{1/2}$=40 Hz, C4-H), 6.50 (1H, s, C6-H), 7.14-7.75 (22H, m, aromatic protons and Ts-*H* x 2), 7.84 (2H, d, J=7.0, Hz, Ts-*H* x 2). CIMS (isobutane) m/z: 869 [(M+H)$^+$], 851 [(M+H-H_2O)$^+$], 811 [(M-*tert*-Bu)$^+$]. *Anal.* Calcd for $C_{51}H_{56}N_2O_7SSi$: C, 70.48; H, 6.49; N, 3.22; S, 3.69%. Found: C, 70.72; H, 6.63; N, 3.11; S, 3.65%.

b) Preparation of *ent*-**20:** Similar treatments of *ent*-**19** (1.25 g, 1.3 mmol) to those described for the preparation of **20** from **19** gave *ent*-**20** (969 mg, 85%) as a colorless caramel. $[\alpha]_D^{20}$ -50.1° (c 1.01, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **20**.

(1a*S*,8*R*,9*R*,9a*S*)-7-Benzyloxy-5-benzyloxymethoxymethyl-8-*tert*-butyldiphenylsiloxymethyl-1a,2,3,8,9,9a-hexahydro-3,9-dihydroxy-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (21) and Its Enantiomer (*ent*-21)

a) Preparation of **21:** A solution of *m*-chloroperbenzoic acid (211 mg, 1.2 mmol) in dichloromethane (14 ml) was added dropwise to a stirred solution of **20** (705 mg, 0.81 mmol) in dichloromethane (70 ml) at 0°C. After 30 min, the reaction was quenched with methyl sulfide (40 μl), and the mixture was diluted with ether (200 ml). The organic layer was washed with water and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (benzene-

ethyl acetate, 20:1→10:1→5:1) to give **21** (481 mg, 67%) as a colorless caramel. IR (KBr): 3450, 2930, 2900, 2860, 1620, 1600, 1590, 1500, 1470, 1460, 1430, 1330, 1270, 1160, 1110, 1100, 1050, 990, 850, 820, 740, 700, 670, 620, 510 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.80-1.16 (9H, m, *tert*-Bu), 2.20-2.50 (3H, m, Ts-*Me*), 2.30-2.68 (1H, m, N-OH), 2.94-4.30 (7H, m, CH and CH_2), 4.51 (2H, s, C*H*$_2$OBOM), 4.52-4.72 (2H, m, PhC*H*$_2$OCH$_2$O), 4.77 (2H, s, PhCH$_2$OC*H*$_2$O), 4.35-4.93 (1H, m, CH or C*H*$_2$), 4.97 (2H, br s, $W_{1/2}$=36 Hz, PhC*H*$_2$O), 5.63-6.04 (1H, m, OH,), 6.55-6.77 (1H, m, aromatic protons), 6.97-7.93 (25H, m, aromatic protons). SIMS (3-NBA+NaCl) m/z: 907 [$(M+Na)^+$], 867 [$(M+H-H_2O)^+$]; (3-NBA+KCl) m/z: 923 [$(M+K)]^+$, 867 [$(M+H-H_2O^+)$]. This material was immediately used for the next reaction due to its instability.

b) Preparation of *ent*-**21:** Treatments of *ent*-**20** (903 mg, 1.0 mmol) in a similar manner to those described for the preparation of **21** from **20** gave *ent*-**21** (607 mg, 66%) as a colorless caramel. The ^{1}H-NMR spectrum of this sample was identical with that recorded for **21**.

(1a*S*,8*R*,9*R*,9a*S*)-3-Acetoxy-7-benzyloxy-5-benzyloxymethoxymethyl-8-*tert*-butyldiphenylsiloxymethyl-1a,2,3,8,9,9a-hexahydro-9-hydroxy-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (22) and Its Enantiomer (*ent*-22)

a) Preparation of **22:** Acetic anhydride (53.3 ml, 0.57 mol) was added dropwise to a stirred mixture of **21** (471 mg, 0.53 mmol) and sodium hydrogen carbonate (40.6 g, 0.48 mol) at -5°C. The reaction mixture was gradually warmed up to 10°C over 5 h and then diluted with ether (300 ml). The organic layer was washed with aqueous sodium hydrogen carbonate and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (benzene-ethyl acetate, 4:1→2:1) to give **22** (340 mg, 69%) as a colorless caramel. $[\alpha]_D^{20}$ +4.3° (c 0.74, $CHCl_3$).[24] IR (neat): 3400, 2950, 2860, 1770, 1720, 1620, 1590, 1460, 1430, 1390, 1370, 1330, 1310, 1290, 1270, 1200, 1160, 1110, 1050, 1030, 990, 940, 910, 850, 820, 740, 700, 670, 510 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.02 (9H, s, *tert*-Bu), 1.99 (3H, s, Ts-*Me*), 2.20 (3H, s, Ac), 3.13 (1H, br s, $W_{1/2}$=44 Hz, CH or C*H*$_2$), 3.42 (1H, br d, J=24 Hz, CH or C*H*$_2$), 3.52 (1H, br s, $W_{1/2}$=32 Hz, CH or C*H*$_2$), 3.64 (1H, br s, $W_{1/2}$=32 Hz, CH or C*H*$_2$), 3.82 (1H, br d, J=24 Hz, CH or C*H*$_2$), 3.90 (1H, br s, $W_{1/2}$=32 Hz, CH or C*H*$_2$), 4.22 (1H, br t, J=12 Hz, CH or C*H*$_2$), 4.56 (2H, s, C*H*$_2$OBOM), 4.62 (2H, s, PhC*H*$_2$OCH$_2$O), 4.80 (2H, s, PhCH$_2$OC*H*$_2$O), 4.82 (1H, br s, $W_{1/2}$=28 Hz, CH or C*H*$_2$), 4.95 (1H, d, J=12.1 Hz, PhC*H*$_2$O), 5.01 (1H, d, J=12.1 Hz, PhC*H*$_2$O), 5.63 (1H, br s, $W_{1/2}$=32 Hz, OH), 6.77 (1H, s, C4-H), 6.97 (1H, s, C6-H), 7.06 (1H, br d, J=8.0 Hz, Ts-*H*), 7,18 (2H, t, J=7.0 Hz, Ts-*H* x 2), 7.23-7.43 (16H, m, aromatic protons), 7.57 (2H, d, J=8.0 Hz, aromatic protons or Ts-*H* x 2), 7.74 (2H, br d, J=8.0 Hz, aromatic protons or Ts-*H* x 2). SIMS (3-NBA) m/z: 926 (M^+), 867 [$(M-MeCO_2)^+$]; (3-NBA+NaCl): 949 [$(M+Na)^+$], 927 [$(M+H)^+$], 867 [$(M-MeCO_2)^+$]. *Anal.* Calcd for $C_{53}H_{58}N_2O_9SSi$: C, 68.66; H, 6.30; N, 3.02; S, 3.46%. Found: C, 68.83; H, 6.45; N, 2.90; S, 3.48%.

b) Preparation of *ent*-**22:** The same treatments of *ent*-**21** (572 mg, 0.65 mmol) as described for the preparation of **22** from **21** gave *ent*-**22** (395 mg, 66%) as a colorless caramel. $[\alpha]_D^{20}$ -4.5° (c 1.07, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **22**.

(1a*S*,8*R*,9a*S*)-3-Acetoxy-7-benzyloxy-5-benzyloxymethoxymethyl-8-*tert*-butyldiphenylsiloxymethyl-1a,2,3,8,9,9a-hexahydro-9-oxo-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (23) and Its Enantiomer (*ent*-23)

a) Preparation of **23:** Dess-Martin periodinane (497 mg, 1.2 mmol) was added in small portions to a stirred solution of **22** (330 mg, 0.36 mmol) in dry dichloromethane (35 ml) at room temperature. After 20 min, the mixture was diluted with ether (300 ml). The organic layer was washed successively with 20% aqueous sodium thiosulfate, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (hexane-ethyl acetae, 2:1) to give **23** (290 mg, 88%) as a colorless caramel. $[\alpha]_D^{20}$ +34.7° (c 0.91, $CHCl_3$). IR (neat): 2950, 2900, 2860, 1780, 1720, 1620, 1590, 1500, 1460, 1430, 1330, 1290, 1270, 1200, 1160, 1110, 1100, 1050, 1030, 1000, 900, 880, 830, 740, 710, 680 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90 (9H, s, *tert*-Bu), 1.74 (3H, s, Ts-*Me*), 2.10 (3H, s, Ac), 3.34 (1H, dd, J=7.9, 3.9 Hz, C_{1a}-H), 3.50 (1H, d, J=7.9 Hz, C_{9a}-H), 3.60 (1H, d, J=13.2 Hz, C2-H), 3.72 (1H, dd, J=13.2, 3.9 Hz, C2-H), 3.76 (1H, dd, J=9.8, 4.0 Hz, C*H*$_2$OTBDPS), 3.97 (1H, dd, J=6.7, 4.0 Hz, C8-H), 4.43 (1H, dd, J=9.8, 6.7 Hz, C*H*$_2$OTBDPS), 4.66 (2H, s, C*H*$_2$OBOM), 4.68 (2H, s, PhC*H*$_2$OCH$_2$O), 4.85 (2H, s, PhCH$_2$OC*H*$_2$O), 4.97 (1H, d, J=12.0 Hz, PhC*H*$_2$O), 5.02 (1H, d, J=12.0 Hz, PhC*H*$_2$O), 6.91 (1H, s, C4-H), 6.99 (2H, d, J=8.3 Hz, Ts-*H* x 2), 7.01 (1H, s, C6-H), 7.18 (2H, t, J=7.3 Hz, aromatic protons), 7.23-7.41 (16H, m, aromatic protons), 7.45 (2H, dd, J=8.0, 1.4 Hz, aromatic protons), 7.59 (2H, dd, J=8.0, 1.4 Hz, aromatic protons). SIMS (3-NBA+NaCl): 947 [$(M+Na)^+$], 866 [$(M+H-MeCO_2)^+$]. *Anal.* Calcd for $C_{53}H_{56}N_2O_9SSi$: C, 68.81; H, 6.10; N, 3.03; S, 3.47%. Found: C, 68.90; H, 6.38; N, 2.96; S, 3.35%.

b) Preparation of *ent*-**23:** The same treatments of *ent*-**22** (361 mg, 0.39 mmol) as described for the preparation of **23** from **22** gave *ent*-**23** (324 mg, 90%) as a colorless caramel. $[\alpha]_D^{20}$ -36.3° (c 1.26, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **23**.

(1a*S*,8*R*,9a*S*)-3-Acetoxy-7-benzyloxy-5-benzyloxymethoxymethyl-1a,2,3,8,9,9a-hexahydro-8-hydroxymethyl-9-oxo-1-*p*-toluenesulfonyl-1*H*-azirino[2,3-*c*][1]benzazocine (24) and Its Enantiomer (*ent*-24)

a) Preparation of **24:** Hydrogen fluoride-pyridine complex (6.0 ml, 0.22 mol) was added dropwise to a stirred solution of **23** (280 mg, 0.30 mmol) in pyridine (15 ml) at -10°C, and the mixture was allowed to warm up to room temperature. After 2 h, the reaction mixture was diluted with ether (300 ml). The organic layer was washed successively with water, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetae, 3:2→1:1) to give **24** (183 mg, 88%) as a colorless caramel. $[\alpha]_D^{20}$ +35.1° (c 1.03, $CHCl_3$). IR (KBr): 3520, 3450, 2950, 2900, 1770, 1700, 1620, 1600, 1500, 1460, 1440, 1340, 1290, 1200, 1160, 1110, 1100, 1050, 1030, 1000, 890, 820, 740, 700, 680, 560 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.95 (3H, s, Ts-*Me*), 2.14 (3H, s, Ac), 2.93 (1H, dd, J=8.4, 6.0 Hz, C8-H), 3.40 (1H, dt, J=7.9, 2.2 Hz, C1a-H), 3.47 (1H, d, J=7.9 Hz, C9a-H), 3.68-3.73 (3H, m, C2-H2 and OH), 3.88 (1H, ddd, J=11.3, 8.4, 5.4 Hz, C*H*2OH), 4.04 (1H, ddd, J=11.3, 6.0, 2.4 Hz, C*H*2OH), 4.66 (2H, s, C*H*2OBOM), 4.69 (2H, s, PhC*H*2OCH2O), 4.87 (2H, s, PhCH2OC*H*2O), 5.10 (2H, s, PhC*H*2O), 6.96 (1H, d, J=1.1 Hz, C4-H), 7.02 (1H, d, J=1.1 Hz, C6-H), 7.02 (2H, d, J=8.0 Hz, Ts-*H* x 2), 7.29-7.42 (12H, m, aromatic protons and Ts-*H* x 2). EIMS m/z: 626 [(M-AcOH)$^+$]. CIMS (isobutane) m/z: 687 [(M+H)$^+$], 686 (M$^+$), 670 [(M+H-OH)$^+$], 628 [(M+H-AcO)$^+$]. HRMS Calcd for $C_{35}H_{34}N_2O_7S$ [(M-AcOH)$^+$]: 626.2085. Found: 626.2098.

b) Preparation of *ent*-**24:** Treatments of *ent*-**23** (301 mg, 0.33 mmol) in the same manner described for the preparation of **24** from **23** gave *ent*-**24** (190 mg, 85%) as a colorless caramel. $[\alpha]_D^{20}$ -36.2° (c 1.16, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **24**.

(1a*S*,3S,8*R*,9S,9a*S*)-7-Benzyloxy-5-benzyloxymethoxymethyl-1a,2,3,8,9,9a-hexahydro-9-hydroxy-8-hydroxymethyl-1-*p*-toluenesulfonyl-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine (26) and Its Enantiomer (*ent*-26)

a) Preparation of **26:** Potassium carbonate (42.2 mg, 31 mmol) in water (4 ml) was added dropwise to a stirred solution of **24** (175 mg, 0.26 mmol) in methanol (40 ml) at 0°C, and the mixture was allowed to warm up to room temperature. After 30 min, the reaction mixture was diluted with ether (200 ml). The organic layer was washed successively with water, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetae, 3:2→1:1) to give **26** (146 mg, 89%) as a colorless caramel. $[\alpha]_D^{20}$ +57.3° (c 0.72, $CHCl_3$). IR (neat): 3350, 2950, 2900, 2360, 2350, 1620, 1590, 1500, 1460, 1440, 1380, 1330, 1270, 1230, 1190, 1160, 1120, 1100, 1050, 990, 940, 900, 890, 860, 820, 740, 700, 680, 600, 570, 550 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.14 (3H, s, Ts-*Me*), 2.19 (1H, dd, J=5.8, 4.1 Hz, CH2O*H*), 3.07 (1H, dd, J=7.4, 2.1 Hz, C1a-H), 3.11 (1H, dd, J=9.7, 3.3 Hz, C8-H), 3.53 (1H, d, J=7.4 Hz, C9a-H), 3.53 (1H, d, J=14.9 Hz, C2β-H), 3.90 (1H, dd, J=14.9, 2.1 Hz, C2α-H), 3.98 (1H, ddd, J=10.6, 9.7, 6.0 Hz, C*H*2OH3.98), (1H, ddd, J=10.6, 4.1,3.3 Hz, C*H*2OH), 4.58 (2H, s, C*H*2OBOM), 4.66 (2H, s, PhC*H*2OCH2O), 4.82 (2H, s, PhCH2OC*H*2O), 5.05 (1H, d, J=12.7 Hz, PhC*H*2O), 5.09 (1H, d, J=12.7 Hz, PhC*H*2O), 6.35 (1H, d, J=1.0 Hz, C4-H), 6.63 (1H, d, J=1.0 Hz, C6-H), 7.00 (1H, s, OH), 7.06 (2H, d, J=8.0 Hz, Ts-*H* x 2), 7.24-7.43 (12H, m, aromatic protons and Ts-*H* x 2). EIMS m/z: 644 (M$^+$), 628 [(M-OH)$^+$]. CIMS (isobutane) m/z: 645 [(M+H)$^+$], 628 [(M-OH)]$^+$. HRMS Calcd for $C_{35}H_{36}N_2O_8S$ (M$^+$): 644.2189. Found: 644.2167.

b) Preparation of *ent*-**26:** Similar treatments of *ent*-**24** (170 mg, 0.25 mmol) to those described for the preparation of **26** from **24** gave *ent*-**26** (141 mg, 88%) as a colorless caramel. $[\alpha]_D^{20}$ -59.5° (c 0.87, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **26**.

(4a*R*,9*S*,10a*S*,11a*S*,11b*S*)-5-Benzyloxy-7-benzyloxymethoxymethyl-4,4a,10,10a,11,11a-hexahydro-2-oxo-11-*p*-toluenesulfonyl-9,11b-epoxyazirino[2,3-*c*]-1,3-dioxino[4,5-*e*][1]benzazocine (27) and Its Enantiomer (*ent*-27)

a) Preparation of **27:** Trichloromethyl chloroformate (0.63 ml, 3.2 mmol) was added dropwise to a stirred solution of **26** (136 mg, 0.21 mmol) in pyridine (30 ml) at 0°C, and the mixture was allowed to warm up to room temperature. After 2 h, the mixture was diluted with ether (180 ml). The organic layer was washed successively with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* gave a residue, which was purified by column chromatography (hexane-ethyl acetae, 2:1) to give **27** (115 mg, 81%) as a colorless caramel. $[\alpha]_D^{20}$ +18.0° (c 0.97, $CHCl_3$).[24] IR (neat): 3050, 2950, 2900, 1790, 1620, 1590, 1500, 1470, 1460, 1440, 1390, 1340, 1290, 1280, 1260, 1230, 1170, 1140, 1110, 1050, 970, 880, 840, 770, 750, 700, 670 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.16 (3H, s, Ts-*Me*), 3.13 (1H, dd, J=11.6, 5.2 Hz, C4a-H), 3.20 (1H, dd, J=7.2, 2.1 Hz, C10a-H), 3.60 (1H, d, J=7.2 Hz, C11a-H), 3.64 (1H, d, J=15.0 Hz, C10β-H), 4.01 (1H, dd, J=15.0, 2.1 Hz, C10α-H), 4.20 (1H, dd, J=11.6, 10.9 Hz, C*H*2OCO), 4.59 (1H, dd, J=10.9, 5.2 Hz, C*H*2OCO), 4.60 (2H, s, C*H*2OBOM), 4.67 (2H, s, PhC*H*2OCH2O), 4.84 (2H, s, PhCH2OC*H*2O), 5.05 (1H, d, J=11.8 Hz, PhC*H*2O), 5.11 (1H, d, J=11.8 Hz, PhC*H*2O), 6.40 (1H, d, J=1.0 Hz, C4-H), 6.68 (1H, d, J=1.0 Hz, C6-H), 7.09 (2H, d, J=8.0 Hz, Ts-*H* x 2), 7.30-7.44 (12H, m, aromatic protons and Ts-*H* x 2). EIMS m/z: 670 (M$^+$), 626 [(M-CO2)$^+$]. HRMS Calcd for $C_{36}H_{34}N_2O_9S$ (M$^+$): 670.1982. Found: 670.1959.

b) Preparation of *ent*-**27:** Treatments of *ent*-**26** (170 mg, 0.25 mmol) in a similar manner to those described for the preparation of **27** from **26** gave *ent*-**27** (141 mg, 88%) as a colorless caramel. $[\alpha]_D^{20}$ -18.4° (c 0.71, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **27**.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-7-Benzyloxy-5-benzyloxymethoxymethyl-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-9-hydroxy-1-*p*-toluenesulfonyl-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine (28) and Its Enantiomer (*ent*-28)

a) Preparation of **28:** Gaseous ammonia was induced to a stirred solution of **27** (100 mg, 0.15 mmol) in tetrahydrofuran (30 ml) for 5 min at 0°C, and the mixture was allowed to warm up to room temperature. After 8 h, the reaction mixture was concentrated *in vacuo*. Purification of the residue by column chromatography (hexane-ethyl acetae, 1:2) afforded **28** (96.3 mg, 94%) as a colorless caramel. $[\alpha]_D^{20}$ -16.7° (c 0.77, $CHCl_3$). IR (neat): 3470, 3350, 3200, 3040, 2950, 2900, 1500, 1460, 1440, 1350, 1330, 1270, 1160, 1130, 1090, 1050, 1000, 960, 890, 820, 740, 680, 580, 560 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.14 (3H, s, Ts-*Me*), 2.33 (1H, dd, J=3.9, 1.1 Hz, C8-H), 3.06 (1H, dd, J=7.4, 2.0 Hz, C1a-H), 3.46 (1H, d, J=7.4 Hz, C9a-H), 3.53 (1H, d, J=14.8 Hz, C2β-H), 3.87 (1H, dd, J=14.8, 2.0 Hz, C2α-H), 4.52 (1H, dd, J=12.6, 3.9 Hz, C*H*$_2$OCONH$_2$), 4.60 (2H, s, C*H*$_2$OBOM), 4.67 (2H, s, PhC*H*$_2$OCH$_2$O), 4.67 (2H, br s, W1/2=16 Hz, CONH$_2$), 4.85 (2H, s, PhCH$_2$OC*H*$_2$O), 4.92 (1H, dd, J=12.6, 1.1 Hz, C*H*$_2$OCONH$_2$), 5.06 (1H, d, J=11.8 Hz, PhC*H*$_2$O), 5.12 (1H, d, J=11.8 Hz, PhC*H*$_2$O), 6.38 (1H, d, J=1.0 Hz, C4-H), 6.63 (1H, d, J=1.0 Hz, C6-H), 7.02 (1H, s, OH), 7.05 (2H, d, J=8.0 Hz, Ts-*H* x 2), 7.26-7.41 (12H, m, aromatic protons and Ts-*H* x 2). EIMS m/z: 687 (M^+), 644 [(M-CONH$_2$+H)$^+$], 626 [(M-OCONH$_2$-H)$^+$], 610 [(M-OCONH$_2$-OH)$^+$]. HRMS Calcd for $C_{36}H_{37}N_3O_9S$ (M^+): 687.2248. Found: 687.2272.

b) Preparation of *ent*-**28:** The same treatments of *ent*-**27** (98.0 mg, 0.15 mmol) as described for the preparation of **28** from **27** gave *ent*-**28** (93.4 mg, 93%) as a colorless caramel. $[\alpha]_D^{20}$ +15.6° (c 1.04, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **28**.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-7-benzyloxy-5-benzyloxymethoxymethyl-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-1-*p*-toluenesulfonyl-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine (29) and Its Enantiomer (*ent*-29)

a) Preparation of **29:** Acetic anhydride (0.37 ml, 3.9 mmol) was added to a stirred solution of **28** (900 mg, 0.13 mmol) in pyridine (3.7 ml) containing 4-dimethylaminopyridine (16 mg, 0.13 mmol) at room temperature. After 15 h, the mixture was diluted with ether (50 ml). The organic layer was washed with 3% aqueous hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and brine, then dried over Na_2SO_4. Concentration of the solvent *in vacuo* afforded a residue, which was purified by column chromatography (benzene-ethyl acetate, 8:5) to give **29** (83.0 mg, 87%) as a white solid. Recrystallization from ether-hexane afforded an analytical sample of **29** as colorless needles, mp 129-131°C [lit.,[18] mp 130-132°C] and $[\alpha]_D^{20}$ +72.3° (c 1.13, $CHCl_3$) [lit.,[18] $[\alpha]_D^{20}$ +68.1° (c 0.76, $CHCl_3$)]. These IR, ^{1}H-NMR, and mass spectra of this sample were identical with those reported in the preceding paper.[18]

b) Preparation of *ent*-**29:** Treatments of *ent*-**28** (85.3 mg, 0.12 mmol) in the same manner described for the preparation of **29** from **28** gave *ent*-**29** (76.9 mg, 85%) as a white powder. $[\alpha]_D^{20}$ -73.7° (c 0.91, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **29**.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-7-benzyloxy-5-benzyloxymethoxymethyl-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine (30) and Its Enantiomer (*ent*-30)

a) Preparation of **30:** Treatment of **29** (82.0 mg, 0.11 mmol) with sodium naphthalenide in 1,2-dimethoxyethane (0.2 M solution, 1.69 ml, 0.34 mmol) in the same manner as described in the preceding paper[18] gave **30** (54.3 mg, 84%) as a white powder after purification by column chromatography (hexane-ethyl acetae, 1:1). $[\alpha]_D^{20}$ +88.1° (c 0.88, $CHCl_3$) [lit.,[17] $[\alpha]_D^{20}$ +89.3° (c 0.62, $CHCl_3$)]. IR (neat): 3400, 2940, 1730, 1620, 1590, 1500, 1460, 1440, 1400, 1380, 1340, 1280, 1240, 1160, 1120, 1080, 1040, 990, 840, 740, 700 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.49 (1H, br s, W1/2=26 Hz, NH), 2.20 (3H, s, Ac), 2.32 (1H, br d, J=6.0 Hz, C1a-H), 3.13 (1H, br s, W1/2=21 Hz, C9a-H), 3.60 (1H, d, J=14.1 Hz, C2β-H), 3.86 (1H, dd, J=7.0, 1.6 Hz, C8-H), 3.94 (1H, d, J=14.1 Hz, C2α-H), 4.36 (1H, dd, J=11.2, 1.6 Hz, C*H*$_2$OCONH$_2$), 4.52 (1H, dd, J=11.2, 7.0 Hz, C*H*$_2$OCONH$_2$), 4.54 (2H, br s, W1/2=22 Hz, CONH$_2$), 4.58 (2H, s, C*H*$_2$OBOM), 4.63 (2H, s, PhC*H*$_2$OCH$_2$O), 4.82 (2H, s, PhCH$_2$OC*H*$_2$O), 5.09 (2H, s, PhC*H*$_2$O), 6.41 (1H, s, C4-H), 6.64 (1H, s, C6-H), 7.29-7.44 (10H, m, aromatic protons). EIMS m/z: 575 (M^+), 516 [(M-OAc)$^+$], 455 [(M-OAc-OCONH$_2$-H)$^+$]. HRMS Calcd for $C_{31}H_{33}N_3O_8$ (M^+): 575.2269. Found: 575.2291. The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those reported in the preceding paper.[18]

b) Preparation of *ent*-**30:** Similar treatments of *ent*-**29** (76.9 mg, 0.11 mmol) to those described for the preparation of **30** from **29** gave *ent*-**30** (37.0 mg, 61%) as a white powder, $[\alpha]_D^{20}$ -85.4° (c 0.84, $CHCl_3$). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **30**.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-7-hydroxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-methanol (31) and Its Enantiomer (*ent*-31)

a) Preparation of **31:** The same treatments of **30** (54.1 mg, 94 μmol) as described in the preceding paper[18] gave **31** (27.8 mg, 81%) as a white solid after purification by column chromatography (chloroform-methanol, 10:1). Recrystallization from ethyl acetate-hexane afforded an analytical sample of **31** as colorless needles, mp 130-132°C [lit.,[18] mp 130-132°C] and $[\alpha]_D^{20}$ +83.5° (c 0.21, MeOH) [lit.,[18] $[\alpha]_D^{20}$ +81.3° (c 0.13, MeOH)]. The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those reported in the preceding paper.[18]

b) Preparation of *ent*-**31:** Treatments of *ent*-**30** (34.0 mg, 59 μmol) in a similar manner to those described for the preparation of **31** from **30** gave *ent*-**31** (15.5 mg, 72%) as a white solid, $[\alpha]_D^{20}$ -85.2° (c 0.20, MeOH). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **31**.

(1a*S*,3*S*,8*R*,9*S*,9a*S*)-9-Acetoxy-8-carbamoyloxymethyl-1,1a,2,8,9,9a-hexahydro-7-hydroxy-3,9-epoxy-3*H*-azirino[2,3-*c*][1]benzazocine-5-carboxaldehyde (32) and Its Enantiomer (*ent*-32)

a) Preparation of **32:** Treatments of **31** (25.0 mg, 68 μmol) in a similar manner to those described in the preceding paper[18] gave **32** (21.8 mg, 88%) as a white solid after purification by column chromatography (chloroform-methanol, 10:1). Recrystallization from ethyl acetate-hexane afforded an analytical sample of **32** as colorless needles, mp 230°C (dec) [lit.,[18] mp 230°C (dec)] and $[\alpha]_D^{20}$ +130° (c 0.41, acetone) [lit.,[18] $[\alpha]_D^{20}$ +129° (c 0.40, acetone)]. The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those reported in the preceding paper.[18]

b) Preparation of *ent*-**32:** The same treatments of *ent*-**31** (6.8 mg, 19 μmol) as described for the preparation of **32** from **31** gave *ent*-**32** (4.7 mg, 73%) a white solid, $[\alpha]_D^{20}$ -127° (c 0.09, acetone). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **32**.

(+)-FR900482 (1) and (−)-FR900482 (*ent*-1)

a) Preparation of **1:** The same treatments of **32** (30.0 mg, 83 μmol) as described in the preceding paper[18] gave **1** (19.4 mg, 73%) as a white solid after purification by column chromatography (chloroform-methanol, 10:1). Recrystallization from ethyl acetate-hexane afforded an analytical sample of **1** as a white powder, mp 174°C (dec) [lit.,[19] mp 175°C (dec)] and $[\alpha]_D^{23}$ +7.9° (c 0.97, H_2O) [lit.,[19] $[\alpha]_D^{23}$ +8.0° (c 1.00, H_2O)]. The IR, ^{1}H-NMR, and mass spectra of this sample were identical with those of an authentic sample of (+)-FR900482.

b) Preparation of *ent*-**1:** Treatments of *ent*-**32** (1.6 mg, 4.4 μmol) in the same manner described for the preparation of **1** from **32** gave *ent*-**1** (0.8 mg, 58%) as a white powder, $[\alpha]_D^{20}$ -10° (c 0.02, H_2O). The ^{1}H-NMR spectrum of this sample was identical with that recorded for **1**.

***In vitro* cytotoxicity assay**

Murine P388 cells (1×10^4/ml) were seeded in the RPMI-1640 medium containing 10% fetal bovine serum and 0.1 mg/ml of kanamycin. Compounds to be tested were added in graded concentrations, and the cultures were incubated for 96 h at 37°C in a humidified atmosphere of 5% carbon dioxide. The tumor cells were counted by MTT method,[23] and the IC_{50} value (concentration required for 50% inhibition of the cell growth) was determined by means of the growth carve.

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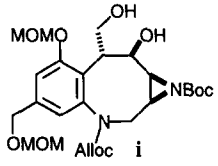

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24. The $[\alpha]_D$ value of this compound was erroneously reported in the preliminary communication[1c] due to the unexpected technical problems met for measuring an optical rotation.

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