Preparation of Alkyl-Substituted Indoles in the Benzene Portion. Part 9.[1] Synthesis of (1a*S*,8b*S*)-1-*tert*-Butyloxycarbonyl-8-formyl-1,1a,2,8b-tetrahydroazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole. Model Study for the Enantiospecific Synthesis of Aziridinomitosenes

Iwao UTSUNOMIYA,[a] Masahiro FUJI,[a] Tomohiro SATO,[b] and Mitsutaka NATSUME*,[a]

Research Foundation Itsuu Laboratory,[a] 2–28–10 Tamagawa, Setagaya-ku, Tokyo 158, Japan and Shionogi Research Laboratories,[b] Sagisu, Fukushima-ku, Osaka 553, Japan. Received October 15, 1992

Effective pathways for an enantiospecific synthesis of (1a*S*,8b*S*)-1-*tert*-butyloxycarbonyl-8-formyl-1,1a,2,8b-tetrahydroazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole (8) were investigated as a preliminary experiment aiming at chiral syntheses of aziridinomitosenes 5 and (1a*S*,8b*S*)-8-[[(aminocarbonyl)oxy]methyl]-5-formyl-7-hydroxy-1,1a,2,8b-tetrahydroazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole (6a). An aldehyde 14, derived from L-serine was condensed with 2-lithio-1-(phenylsulfonyl)indole (10) to afford diastereomers 15a and 15b, whose stereochemistry was unambiguously determined by ^{1}H-NMR studies of the 1,3-dioxane derivatives 17a, 17b, and 18 as well as the X-ray crystallographic analysis of a dihydropyrrolo[1,2-*a*]indole derivative 31a. The latter compound was prepared from 15a *via* the following operations (Chart 5): (i) removal of the acetonide and the indole-protecting groups, followed by acetylation to form 29a, (ii) Vilsmeier reaction to produce 30a, and (iii) hydrolysis of acetyl groups, partial methanesulfonylation (mesylation), and treatment with potassium carbonate in acetonitrile. A diastereomer 31b was obtained from 15b in a similar manner. Both isomers 31a and 31b afforded the desired compound 8 upon treatment with a mesylation reagent followed by potassium *tert*-butoxide in tetrahydrofuran.

Keywords tetrahydroazirinopyrroloindole; aziridinomitosene model; chiral synthesis; chiral aldehyde α-indole substitution; ^{1}H-NMR configuration determination; X-ray crystallographic analysis

In the previous paper of this series, we reported a new synthetic procedure for 4-, 5-, 6-, and 7-hydroxyindoles.[2] This method was applied to a synthesis of indole derivatives having both alkyl and alkoxy groups in the benzene portion of the indole nucleus; for instance, the acid-induced cyclization reaction of (arylsulfonyl)pyrrole derivatives **1** in the presence of an alcohol R^2OH produced 6-alkoxy-4-alkylindoles (**2a**) (Chart 1). Cleavage of the alkoxy group was readily carried out to afford 4-alkyl-6-hydroxyindoles (**2b**) in good overall yields.[2] This indole-forming reaction could become an important key step for the synthesis of aziridinomitosene derivatives **5**, if (i) appropriately substituted pyrroles **3** can be readily prepared, (ii) they can be cyclized as above to 4-alkoxy-6-methylindoles (**4a**) having hetero functions at the C-5 position, (iii) introduction of the five-membered ring is feasible at the indole nitrogen and the C-2 position, and finally (iv) the aziridine ring can be assembled in an enantioselective manner, in parallel with attachment of the carbinol function bearing an aminocarbonyl group at the C-3 position of the parent indole molecule. When starting from compounds **4b**, which carry a masked aldehyde group R^2 without a hetero substituent at C-5, similar transformation would provide a tetrahydroazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole **6a** and its diacetate **6b**, whose structural resemblance to FR 900482 (**7a**) and FK 973 (**7b**)[3,4] led us to anticipate potent anticancer activities. In this paper, we report successful enantiospecific synthesis of (1a*S*,8b*S*)-1-*tert*-butyloxycarbonyl-8-formyl-1,1a,2,8b-tetrahydroazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indole (**8**) as a demonstration of the above operations (iii) and (iv).

Our synthetic plan of **8** consists first in preparation of 2-substituted indoles **9** having a three-carbon side chain, which carries two leaving groups (X and Y) and a nitrogen

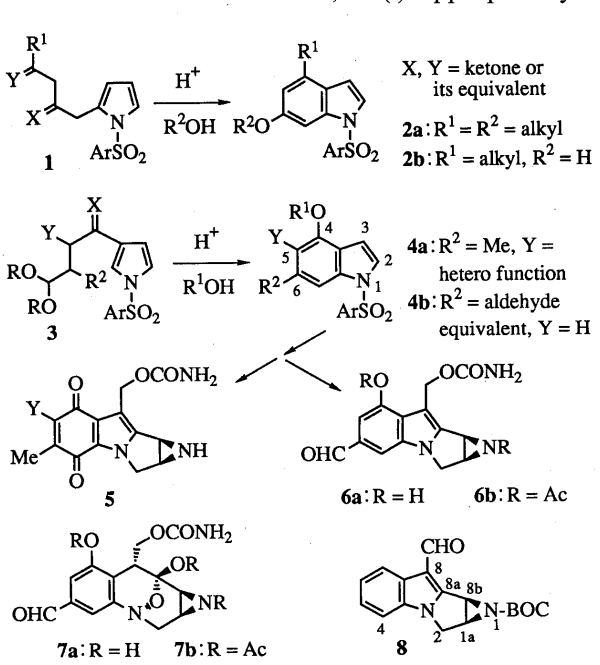


Chart 1

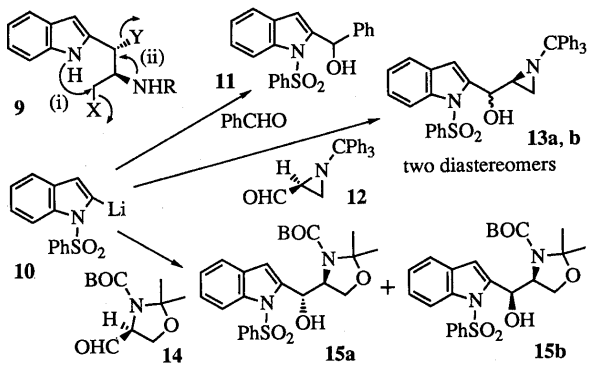


Chart 2

function of defined absolute configuration (Chart 2). The five-membered ring is then constructed between the indole nitrogen and the terminal carbon atom [step (i)], followed by the formation of the aziridine ring using the leaving group Y [step (ii)]. The formyl group may be introduced at any time during these transformations by the Vilsmeier method. In order to get 2-substituted indoles **9** with a substituent Y adjacent to the aromatic ring, condensation of an aldehyde with 2-lithio-1-(phenylsulfonyl)indole (**10**) was attempted, assuming that our indole-forming reaction would produce other more complex 1-(arylsulfonyl)indoles **4a** and **4b** in parallel experiments. For this purpose, *n*-butyllithium was found to be sufficient to generate **10** from 1-(phenylsulfonyl)indole, contrary to the literature procedure using *tert*-butyllithium[5] or lithium diisopropylamide[6] (LDA). Reactions with benzaldehyde, (*S*)-2-formyl-1-triphenylmethylaziridine (**12**) prepared from methyl (*S*)-1-triphenylmethylaziridine-2-carboxylate,[7] and *tert*-butyl (*S*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate[8] (**14**) in tetrahydrofuran (THF) at low temperature afforded **11** (83%),[9] **13a** (44%) and **13b** (15%), and **15a** (57%) and **15b** (14%), respectively. In the cases of **12** and **14**, 1-(phenylsulfonyl)indole was recovered in 20% and 17% yields, probably due to simultaneous protonation of **10** by abstracting the acidic hydrogens from **12** and **14** during these condensations. The stereochemistry of the hydroxy group of **13a** and **13b** remained unknown, whereas the *S* or *R* nature of the hydroxy groups in **15a** and **15b** was determined as follows.

Both diastereomers **15a** and **15b**, obtained as major and minor products respectively, in the condensation reaction of **10** with **14**, were treated with a diluted acid to hydrolyze

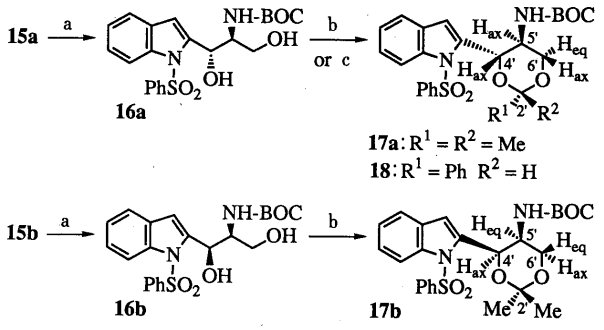


Chart 3

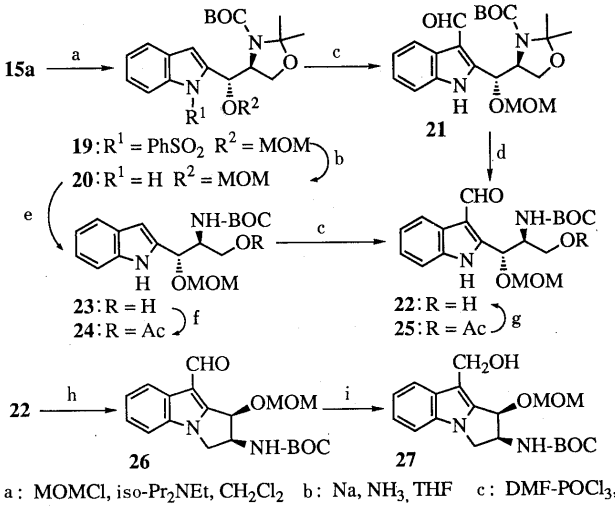
TABLE I. Selected ^{1}H-NMR Spectral Data for **17a**, **17b** and **18**

Compd.	H-4′	H-5′	H_{eq}-6′	H_{ax}-6′
17a	5.58, d J=10.5	4.14—4.25	4.09, dd J=11, 5	3.74, dd J=11, 11
18	5.59, d J=10	4.47—4.57[a]	4.51, dd J=10, 4.5	3.74, dd J=10, 10
17b[b]	5.86, s, 5.73, s	4.21, dd J=10,[c] 2 4.09, br d J=10[c]	4.32, br d J=12	3.88, dd J=12, 2

Chemical shift, δ ppm; coupling constant, Hz. *a*) Including NHCOO-*tert*-Bu. *b*) Affording two sets of signals due to rotamers of the urethane group in the ratio of *ca.* 2:1 (values in the upper line indicate the main signals). *c*) Coupling constant with NHCOO-*tert*-Bu.

the *N*,*O*-acetonide group, furnishing the diols **16a** and **16b** in 94% and 90% yields (Chart 3). These were converted into the *O*,*O*-acetonides **17a** and **17b** as well as a benzylidene derivative **18** in 75.5%, 83%, and 58% yields, respectively, by treatment with 2,2-dimethoxypropane or benzaldehyde dimethyl acetal[10] in the presence of *p*-toluenesulfonic acid or camphorsulfonic acid. Their ^{1}H-NMR spectra as shown in Table I indicated that the C-5′ protons of **17a** and **18** have axial configuration, judging from the coupling patterns with adjacent equatorial and axial protons at the C-6′ position, and the C-4′ protons were coupled with the C-5′ protons in the *trans*-diaxial manner, on the supposition that the 1,3-dioxane ring was fixed in the chair conformation. This implied that the secondary hydroxy group of **16a** was oriented in the *S* fashion. With this conclusion in hand, ^{1}H-NMR spectral data of **17b** were consistent with an equatorial indolyl group and an axial *tert*-butyloxycarbonylamino group, supporting the *R* configuration of the secondary hydroxy group in **16b**. Thus, the mode of the addition reaction of **10** on **14** obeyed Felkin and Anh's rule and produced predominantly the anti-derivative **15a**.[11]

As the structures of **15a** and **15b** were settled, we started the synthesis by trying to form the five-membered ring, as illustrated by the arrow (i) in **9**, with connection of the indole nitrogen and the terminal carbon atom of the alkyl side chain introduced as above. For this purpose, the secondary hydroxy group of **15a** was protected by a methoxymethyl (MOM) group to form **19** in 74.5% yield,[12] and this was converted into an appropriately modified compound **22** in two ways, *i.e.* **19**→**20** (89%)→**21** (93%)→**22** (62%), and **20**→**23** (65%)→**24** (94%)→**25** (85%)→**22** (88%) (Chart 4). In the former route, removal of the isopropylidene group was effected at a later stage. When this was carried out on a small scale, hydrolysis of **21** proceeded without difficulty, but on a large scale, the yield of **22** decreased due to the formation of intractable by-products even though **21** has an electron-withdrawing group at the C-3 position. On the other hand, in the latter route, the isopropylidene group was eliminated in the beginning. This step **20**→**23** proceeded only in a fair yield



a: MOMCl, iso-Pr_2NEt, CH_2Cl_2 b: Na, NH_3, THF c: DMF-$POCl_3$, CH_2Cl_2 d: 4% HCl in MeOH-H_2O e: 3% HCl in MeOH-H_2O f: Ac_2O, Py g: K_2CO_3, MeOH h: 1) MsCl, Et_3N, CH_2Cl_2; 2) K_2CO_3, CH_3CN i: $NaBH_4$, MeOH

Chart 4

in the absence of the benzenesulfonyl protecting group, compared to the conversion **15**→**16**; nevertheless the latter route was more favorable for routine synthesis. Introduction of the necessary one-carbon unit at the C-3 position of the indole was carried out during these transformations in the form of the formyl group, whose presence enhanced the stability of the molecules and further made it easy to effect the required N–C bond formation under very mild conditions. Thus **22** was converted to its methanesulfonate (mesylate) and treatment of this with potassium carbonate in acetonitrile at 0 °C afforded **26** in 67% yield. The formyl function of **26** was readily reduced with sodium borohydride in methanol at room temperature to give the 3-indolylcarbinol **27** in 66% yield.

Now the stage seemed to be set for the formation of the aziridine ring [step (ii) in **9**]. Surprisingly, however, removal of the MOM group in **26** was unsuccessful, presumably because the environment of the MOM group became congested upon formation of **26** and a variety of conditions of acid-catalyzed hydrolysis only afforded either the recovery of **26** or complete decomposition. Therefore the reaction scheme was reinvestigated from the beginning without protecting the secondary alcohol part with the MOM group.

The benzenesulfonyl group of **15a** and **15b** was reductively split off in 90% and 87% yields, and the resulting **28a** and **28b** were treated with a diluted acid to remove the isopropylidene unit, followed by acetylation to give the diacetates **29a** and **29b** in 59% and 64% yields, respectively (Chart 5). These were also obtained from the above-mentioned diols **16a** and **16b** by removal of the benzenesulfonyl group and subsequent acetylation in 54% and 58% yields. The diacetates **29a** and **29b** were subjected to the Vilsmeier reaction to produce the 3-formylindoles **30a** and **30b** in 81% and 80% yields. Successive three-step operation on **30a** and **30b**, that is, methanolysis of the acetate group, monomesylation of the resulting diols, and treatment with potassium carbonate in acetonitrile, afforded the ring-cyclized compounds **31a** and **31b** in 55% and 52% yields. To regulate the mesylation to occur only at the primary alcohol, intermediary diols were treated with *ca.* 1.4—1.8 molar eq. of methanesulfonyl (mesyl) chloride in the presence of triethylamine in dichloromethane at −75 °C.

Then the final aziridine formation was tested by mesylation of both **31a** and **31b** at 0 °C, followed by treatment with potassium *tert*-butoxide in THF at room temperature. Quite unexpectedly, the same aziridine **8** was obtained in 53% and 32% yields, respectively from **31a** and **31b**. These results were perplexing in that compound **31b**, having a favorable stereochemistry of the leaving oxygen function, gave the product in poor yield, whereas the alcohol **31a** having the opposite situation afforded a fairly good yield of **8**.[13] The latter result was satisfactory in itself, since **31a** had originated from the major condensation product **15a**, but these questions forced us to reconfirm the above assignment of the hydroxy configuration in **15a** and **15b**, because the ^{1}H-NMR argument concerning the stereostructures of **17a**, **17b**, and **18** was based upon the assumption that the 1,3-dioxane ring took a chair conformation in these compounds. If this assumption was not valid in the present case, the stereochemical assignment of the hydroxy groups might be reversed. To clarify the

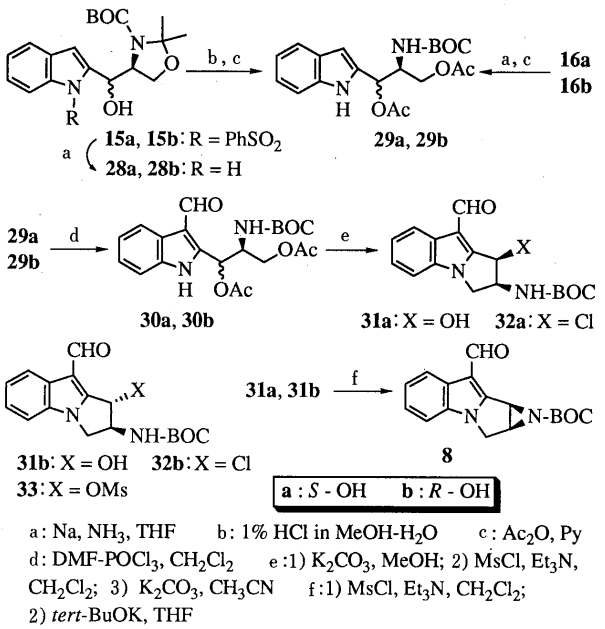


Chart 5

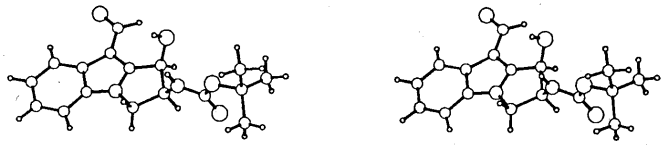


Chart 6

situation, we conducted an X-ray crystallographic analysis on **31a**. Its crystal structure was solved as shown in Experimental and the result shown in Chart 6 at a refinement stage of $R=0.032$ revealed that the chemical structure was indeed expressed as **31a**, meaning that the previous ^{1}H-NMR assignment was correct.

With this conclusion in hand, we considered that the above unusual phenomena could probably be explained in terms of the special location of the hydroxy group adjacent to the indole ring. During the mesylation of **31a** and **31b**, **31a**–mesylate and **33** were reactive enough to suffer partial replacement by chloride anion derived from mesyltriethylammonium chloride, and considerable amounts of chlorides **32b** and **32a** had been contaminating the crude mesylation products, judging from the integration values of the mesyl proton signals in the ^{1}H-NMR specta. Therefore either the chloride **32b**, formed in a considerable amount from **31a**–mesylate, or the mesylate **33**, which remained in a small amount during mesylation of **31b** was responsible for production of the aziridine **8** in the above two cases, explaining why **31a** afforded **8** in a fairly good yield instead of **31b**, which appeared to be the only suitable compound at first glance.

In summary, we have developed a synthetic pathway, mainly as shown in Chart 5, to reach (1a*S*,8b*S*)-1-*tert*-butyloxycarbonyl-8-formyl-1,1a,2,8b-tetrahydroazirino-[2′,3′:3,4]pyrrolo[1,2-*a*]indole (**8**) starting from a simple indole, by using a condensation reaction between 2-lithio-1-(phenylsulfonyl)indole (**10**) and *tert*-butyl (*S*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (**14**). Application of this knowledge to highly substituted indole derivatives such

as **4a** and **4b** is in progress with the aim of synthesizing a variety of optically active aziridinomitosenes **5** and tetrahydroazirino[2′,3′:3,4]pyrrolo[1,2-*a*]indoles **6** of biological interest, which are related to FR 900482.

Experimental

Melting points were determined on Yanagimoto micro-melting point apparatus and are not corrected. MS and high resolution MS (HRMS) were recorded on a Hitachi M-80B spectrometer at an ionizing voltage of 70 eV. IR spectra were measured on a Hitachi 215 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM 390 (90 MHz) spectrometer and a JEOL JMN-GX-400 (400 MHz) spectrometer in $CDCl_3$ with tetramethylsilane as an internal reference. Column chromatography was conducted on silica gel, Fuji Davison BW 200 and preparative TLC (PTLC) was carried out on glass plates (20 × 20 cm) coated with Merck silica gel 60 PF_{254} (1 mm thick). Usual work-up refers to washing of the organic layers with water or brine, drying over anhydrous Na_2SO_4, and evaporating off the solvents under reduced pressure.

Phenyl-[1-(phenylsulfonyl)-2-indolyl]methanol (11) A solution of 15% BuLi in hexane (0.34 ml, 0.53 mmol) was added to a solution of 1-(phenylsulfonyl)indole (69 mg, 0.27 mmol) in Et_2O (5 ml) at −84 °C under an Ar atmosphere. The mixture was stirred at −84——77 °C for 15 min, then benzaldehyde (0.11 ml, 1.1 mmol) was added at −77 °C, and the reaction mixture was stirred at 0 °C for 15 min. Saturated NH_4Cl–H_2O was added, then the whole was extracted with CH_2Cl_2, and the extract was worked up as usual. The residue was purified by PTLC twice using hexane–AcOEt (5:1) and benzene, followed by recrystallization from $CHCl_3$–hexane to afford 81 mg (83%) of **11** as colorless prisms, mp 116.5—117 °C [lit.[5] mp 115.5—117 °C]. *Anal.* Calcd for $C_{21}H_{17}NO_3S$: C, 69.40; H, 4.71; N, 3.85. Found: C, 69.57; H, 4.66; N, 3.89. HRMS Calcd for $C_{21}H_{17}NO_3S$: 363.0928. Found: 363.0913. MS *m/z* (relative intensity): 363 (M^+, 19), 221 (100), 204 (25), 194 (17), 144 (14), 105 (42), 77 (78). ^{1}H-NMR (90 MHz) δ: 3.54 (1H, d, J=5 Hz, OH), 6.19 (1H, s), 6.37 (1H, d, J=5 Hz, changed to s with D_2O), 7.02—7.52 (11H, m), 7.59—7.82 (2H, m), 7.94—8.20 (1H, m).

(*S*)-2-Formyl-1-triphenylmethylaziridine (12) i) (*S*)-1-Triphenylmethylaziridine-2-methanol $LiAlH_4$ (308 mg, 8.11 mmol) was added portionwise to a solution of methyl (*S*)-1-triphenylmethylaziridine-2-carboxylate[7] (2.322 g, 6.77 mmol), prepared according to the procedure for benzyl (*S*)-1-triphenylmethylaziridine-2-carboxylate,[14] in THF (10 ml) at −20 °C. The mixture was stirred at the same temperature for 15 min, then the reaction was quenched with saturated Rochelle salt–H_2O and the whole was filtered through a Celite bed. Extraction of the filtrate with Et_2O, usual work-up, and recrystallization from Et_2O afforded (*S*)-1-triphenylmethylaziridine-2-methanol (2.066 g, 97%) as colorless prisms, mp 127.5—128.5 °C. *Anal.* Calcd for $C_{22}H_{21}NO$: C, 83.77; H, 6.71; N, 4.44. Found: C, 84.01; H, 6.83; N, 4.43. $[\alpha]_D^{24}$ +8.8° (c=1.00, CH_2Cl_2). MS *m/z* (relative intensity): 284 ($M^+ - CH_2OH$, 0.5), 257 (2), 243 (100), 165 (48), 77 (10), 33 (19). ^{1}H-NMR (90 MHz) δ: 1.10 (1H, d, J=6.5 Hz), 1.54 (1H, dddd, J=6.5, 3.5, 3.5, 3 Hz), 1.82 (1H, d, J=3 Hz), 2.22 (1H, dd, J=7.5, 4.5 Hz, OH), 3.64 (1H, ddd, J=11.5, 7.5, 3.5 Hz, changed with D_2O to dd, J=11.5, 3.5 Hz), 3.85 (1H, ddd, J=11.5, 4.5, 3.5 Hz, changed with D_2O to dd, J=11.5, 3.5 Hz), 7.01—7.57 (15H, m).

ii) Oxidation to 12 Dimethyl sulfoxide (0.38 ml, 5.4 mmol) was added to a solution of $(COCl)_2$ (0.23 ml, 2.6 mmol) in CH_2Cl_2 (5 ml) at −60 °C. The mixture was stirred for 5 min, then a solution of the above alcohol (700 mg, 2.22 mmol) in CH_2Cl_2 (7 ml) was added at −60 °C, and the mixture was stirred at the same temperature for 15 min. Et_3N (1.55 ml, 11.1 mmol) was added at −60 °C and the mixture was further stirred at room temperature for 15 min. The reaction was quenched with saturated NH_4Cl–H_2O, and the whole was extracted with Et_2O, and worked up as usual. The residue was purified by column chromatography over silica gel [hexane–EtOAc (10:1)], followed by recrystallization from hexane to give **12** (563 mg, 81%) as colorless prisms, mp 124—126.5 °C. *Anal.* Calcd for $C_{22}H_{19}NO$: C, 84.32; H, 6.11; N, 4.47. Found: C, 84.32; H, 6.12; N, 4.38. HRMS Calcd for $C_{22}H_{19}NO$: 313.1466. Found: 313.1442. $[\alpha]_D^{24}$ −66.5° (c=1.34, $CDCl_3$). MS *m/z* (relative intensity): 313 (M^+, 0.2), 243 (100), 165 (49). IR ($CHCl_3$) cm^{-1}: 1709. ^{1}H-NMR (90 MHz) δ: 1.54 (1H, d, J=7 Hz), 1.94 (1H, ddd, J=7, 7, 3 Hz), 2.30 (1H, d, J=3 Hz), 7.08—7.61 (15H, m), 9.35 (1H, d, J=7 Hz).

(2*S*,α*ξ*)-α-[1-(Phenylsulfonyl)-2-indolyl]-1-triphenylmethyl-2-aziridinemethanols (13a and 13b) A solution of 15% BuLi in hexane (0.15 ml, 0.23 mmol) was added to a solution of 1-(phenylsulfonyl)indole (30 mg, 0.12 mmol) in THF (2 ml) at −86 °C. The mixture was stirred at −86—−80 °C for 20 min, then a solution of **12** (91 mg, 0.29 mmol) in THF (3 ml) was added and the reaction mixture was stirred at −85——48 °C for 1 h and 15 min. Saturated NH_4Cl–H_2O was added, then the whole was extracted with CH_2Cl_2, and worked up as usual. The residue was separated and purified by PTLC twice using hexane–EtOAc (7:1) and hexane–CH_2Cl_2 (2:3) to afford **13a** (29 mg, 44%) as a more polar material and **13b** (10 mg, 15%) as a less polar material, together with the recovery of 1-(phenylsulfonyl)indole (6 mg, 20%). **13a**: Colorless syrup. $[\alpha]_D^{24}$ −146° (c=0.88, $CHCl_3$). MS *m/z* (relative intensity): 327 ($M^+ - CPh_3$, 0.2), 299 (4), 286 (4), 243 (100), 165 (42), 130 (13), 77 (22). ^{1}H-NMR (90 MHz) δ: 1.29 (1H, d, J=6 Hz), 1.98 (1H, d, J=3 Hz), 2.19 (1H, ddd, J=6, 3, 3 Hz), 3.60 (1H, d, J=7 Hz, OH), 5.10—5.40 (1H, m, changed with D_2O to 5.26, d, J=3 Hz), 6.56 (1H, s), 6.91—7.56 (21H, m), 7.56—7.80 (2H, m), 7.80—8.08 (1H, m). **13b**: Colorless syrup, $[\alpha]_D^{24}$ +18.6° (c=0.77, $CHCl_3$). MS *m/z* (relative intensity): 327 ($M^+ - CPh_3$, 0.6), 299 (7), 286 (3), 243 (100), 165 (50), 130 (25), 77 (33). ^{1}H-NMR (90 MHz) δ: 1.13 (1H, d, J=6 Hz), 1.95 (1H, d, J=3 Hz), 2.28 (1H, ddd, J=6, 3, 3 Hz), 3.68—4.07 (1H, s, OH), 5.63 (1H, d, J=3 Hz), 6.63 (1H, s), 7.00—7.63 (21H, m), 7.63—7.86 (2H, m), 7.92—8.19 (1H, m).

***tert*-Butyl (4*S*)-2,2-Dimethyl-4-[(*S*)-hydroxy[1-(phenylsulfonyl)-2-indolyl]methyl]-3-oxazolidinecarboxylate (15a) and *tert*-Butyl (4*S*)-2,2-Dimethyl-4-[(*R*)-hydroxy[1-(phenylsulfonyl)-2-indolyl]methyl]-3-oxazolidinecarboxylate (15b)** A solution of 15% BuLi in hexane (0.26 ml, 0.40 mmol) was added to a solution of 1-(phenylsulfonyl)indole (54 mg, 0.21 mmol) in THF (3 ml) at −86 °C under an Ar atmosphere. The mixture was stirred at −88——82 °C for 20 min, then a solution of **14**[8] (120 mg, 0.524 mmol) in THF (1 ml) was added and the reaction mixture was stirred at −88——75 °C for 30 min. Saturated NH_4Cl–H_2O was added, and the whole was extracted with CH_2Cl_2, and worked up as usual. PTLC [hexane–EtOAc (4:1)] gave recovered 1-(phenylsulfonyl)indole (9 mg, 17%) and a mixture of **15a** and **15b**. The latter was separated by PTLC [benzene–EtOAc (35:1)] to afford **15a** (58.5 mg, 57%) as a more polar material and **15b** (14.5 mg, 14%) as a less polar material. **15a**: Colorless syrup. HRMS Calcd for $C_{25}H_{30}N_2O_6S$: 486.1823. Found: 486.1814. $[\alpha]_D^{22}$ +44.9° (c=1.14, $CHCl_3$). MS *m/z* (relative intensity): 486 (M^+, 0.1), 345 (5), 286 (13), 200 (11), 145 (22), 100 (58), 57 (100). IR ($CHCl_3$) cm^{-1}: 1695. ^{1}H-NMR (90 MHz) δ: 1.49 (15H, s), 3.82—5.04 (br s, OH), 4.01 (1H, dd, J=9, 7 Hz), 4.34 (1H, dd, J=9, 3 Hz), 4.57 (1H, ddd, J=7, 3, 3 Hz), 5.60—5.88 (1H, m, changed with D_2O to 5.72, d, J=3 Hz), 6.61 (1H, s), 7.03—7.56 (6H, m), 7.63—7.88 (2H, m), 7.96—8.20 (1H, m). **15b**: Colorless syrup. HRMS Calcd for $C_{25}H_{30}N_2O_6S$: 486.1823. Found: 486.1848. $[\alpha]_D^{21}$ −65.2° (c=1.09, $CHCl_3$). MS *m/z* (relative intensity): 486 (M^+, 0.07), 3.45 (4), 286 (14), 200 (10), 145 (22), 100 (58), 57 (100). IR ($CHCl_3$) cm^{-1}: 1693, 1657. ^{1}H-NMR (90 MHz, 53 °C) δ: 1.47 (9H, s), 1.57 (3H, s), 1.74 (3H, s), 3.73 (1H, dd, J=9.5, 2.5 Hz), 3.90 (1H, dd, J=9.5, 6 Hz), 4.10—4.83 (br s, OH), 4.61 (1H, ddd, J=8.5, 6, 2.5 Hz), 5.52 (1H, d, J=8.5 Hz), 6.71 (1H, s), 7.11—7.50 (6H, m), 7.76—7.98 (2H, m), 8.06—8.23 (1H, m).

(1*S*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-1-[1-(phenylsulfonyl)-2-indolyl]-1,3-propanediol (16a) A solution of **15a** (44 mg, 0.091 mmol) and 10% HCl–H_2O (0.3 ml) in MeOH (2.7 ml) was stirred at room temperature for 20 min. This was neutralized with saturated $NaHCO_3$–H_2O, NaCl powder was added, and the whole was extracted with 10% MeOH-containing CH_2Cl_2. Usual work-up, followed by PTLC [hexane–EtOAc (2:1)] gave **16a** (38 mg, 94%) as a colorless syrup. $[\alpha]_D^{21}$ +63.5° (c=2.21, $CHCl_3$). MS *m/z* (relative intensity): 372 ($M^+ - tert$-BuOH, 4), 345 (4), 286 (34), 145 (46), 117 (27), 89 (33), 77 (100), 59 (85), 57 (51). IR ($CHCl_3$) cm^{-1}: 1700. ^{1}H-NMR (90 MHz, 55 °C) δ: 1.34 (9H, s), 3.77 (1H, dd, J=12, 4.5 Hz), 3.96 (1H, dd, J=12, 3 Hz), 4.00—4.34 (1H, m), 5.08—5.33 (br s, NH), 5.50 (1H, d, J=6 Hz), 6.87 (1H, s), 7.04—7.57 (6H, m), 7.60—7.83 (2H, m), 7.98—8.23 (1H, m).

(1*R*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-1-[1-(phenylsulfonyl)-2-indolyl]-1,3-propanediol (16b) A solution of **15b** (63 mg, 0.13 mmol) and 10% HCl–H_2O (0.5 ml) in MeOH (4.5 ml) was stirred at room temperature for 1 h. Work-up as above, followed by PTLC [hexane–EtOAc (1:1)] afforded **16b** (52 mg, 90%) as a colorless syrup. $[\alpha]_D^{22}$ −57.2° (c=0.94, $CHCl_3$). MS *m/z* (relative intensity): 428 ($M^+ - H_2O$, 0.8), 372 (13), 286 (32), 145 (46), 117 (28), 77 (61), 60 (100), 57 (95). IR ($CHCl_3$) cm^{-1}: 1695. ^{1}H-NMR (90 MHz, 55 °C) δ: 1.32 (9H, s), 2.43 (1H, br s, OH), 3.60—4.02 (3H, m, 2H and OH), 4.02—4.33 (1H, m), 5.25 (1H, br d, J=9 Hz, NH), 5.60 (1H, br s), 6.80 (1H, s), 7.03—7.55 (6H, m), 7.62—7.80 (2H, m), 7.97—8.17 (1H, m).

(4*S*,5*S*)-5-(*tert*-Butyloxycarbonylamino)-2,2-dimethyl-4-[1-(phenylsulfonyl)-2-indolyl]-1,3-dioxane (17a) A solution of **16a** (17 mg, 0.038 mmol) and *p*-TsOH·H_2O (7 mg, 0.037 mmol) in 2,2-dimethoxypropane (1 ml) was

stirred at room temperature for 30 min. Saturated $NaHCO_3$–H_2O was added, then the mixture was extracted with CH_2Cl_2, and worked up as usual. Purification by PTLC [hexane–EtOAc (2 : 1)] afforded **17a** (14 mg, 75.5%) as a colorless syrup, together with the *N,O*-acetonide **15a** (3 mg, 16%). HRMS Calcd for $C_{25}H_{30}N_2O_6S$: 486.1823. Found: 486.1850. MS *m/z* (relative intensity): 486 (M^+, 0.2), 428 (2), 371 (6), 355 (6), 285 (83), 77 (60), 57 (100). IR ($CHCl_3$) cm^{-1}: 1713. ^{1}H-NMR (400 MHz) δ: 1.33 (9H, s), 1.39 (3H, s), 1.62 (3H, s), 4.58 (1H, br d, J=9 Hz, NH), 7.04 (1H, s), 7.21 (1H, dd, J=8, 8 Hz), 7.29 (1H, dd, J=8, 8 Hz), 7.39 (2H, dd, J=8, 8 Hz), 7.45—7.54 (2H, m), 7.86 (2H, d, J=8 Hz), 8.07 (1H, d, J=8 Hz), and signals shown in Table I.

(4*R*,5*S*)-5-(*tert*-Butyloxycarbonylamino)-2,2-dimethyl-4-[1-(phenylsulfonyl)-2-indolyl]-1,3-dioxane (17b) A solution of **16b** (10 mg, 0.022 mmol) and *p*-TsOH·H_2O (2 mg, 0.01 mmol) in 2,2-dimethoxypropane (1 ml) was stirred at room temperature for 45 min. The same work-up as above afforded **17b** (10 mg, 83%) as a colorless syrup. HRMS Calcd for $C_{25}H_{30}N_2O_6S$: 486.1823. Found: 486.1793. MS *m/z* (relative intensity): 486 (M^+, 1), 428 (2), 371 (7), 355 (6), 285 (58), 77 (34), 57 (100). IR ($CHCl_3$) cm^{-1}: 1704. ^{1}H-NMR (400 MHz) [two rotamers (*ca.* 2 : 1)] δ: (major conformer) 1.17 (9H, s), 1.50 (3H, s), 1.61 (3H, s), 5.30 (1H, d, J=10 Hz, NH), 6.78 (1H, s), 7.15—7.32 (2H, m), 7.35—7.55 (4H, m), 7.75 (2H, d, J=8 Hz), 8.02 (1H, d, J=8 Hz); (minor conformer) 0.99 (9H, s), 1.50 (3H, s), 1.56 (3H, s), 5.15 (1H, d, J=10 Hz, NH), 6.78 (1H, s), 7.15—7.32 (2H, m), 7.35—7.55 (4H, m), 7.70 (2H, d, J=8 Hz), 8.19 (1H, d, J=8 Hz), and signals shown in Table I.

(2*S*,4*S*,5*S*)-5-(*tert*-Butyloxycarbonylamino)-2-phenyl-4-[1-(phenylsulfonyl)-2-indolyl]-1,3-dioxane (18) A solution of **16a** (13 mg, 0.023 mmol) and camphorsulfonic acid (4 mg, 0.02 mmol) in benzaldehyde dimethyl acetal (1.5 ml) was stirred at room temperature for 15 h. Work-up as above, followed by PTLC twice using hexane–EtOAc (2 : 1) and hexane–CH_2Cl_2 (1 : 3) afforded **18** (9 mg, 58%) as a colorless syrup. HRMS Calcd for $C_{29}H_{30}N_2O_6S$: 534.1823. Found: 534.1804. MS *m/z* (relative intensity): 534 (M^+, 0.2), 460 (4), 371 (3), 337 (2), 285 (100), 105 (40), 77 (100), 57 (48). IR ($CHCl_3$) cm^{-1}: 1714. ^{1}H-NMR (400 MHz) δ: 1.37 (9H, s), 5.76 (1H, s), 7.03—7.10 (3H, m), 7.21 (1H, dd, J=8, 8 Hz), 7.29 (1H, dd, J=8, 8 Hz), 7.32—7.39 (4H, m), 7.44—7.52 (3H, m), 7.78 (2H, br d, J=8 Hz), 8.06 (1H, d, J=8 Hz), and signals shown in Table I.

***tert*-Butyl (4*S*)-2,2-Dimethyl-4-[(*S*)-(methoxymethoxy)[1-(phenylsulfonyl)-2-indolyl]methyl]-3-oxazolidinecarboxylate (19)** Methoxymethyl chloride (0.30 ml) was added to a solution of **15a** (101 mg, 0.208 mmol) and diisopropylethylamine (0.5 ml) in CH_2Cl_2 (5 ml) at 0 °C and the mixture was stirred at room temperature for 14 h. Saturated $NaHCO_3$–H_2O was added to this, the whole was extracted with CH_2Cl_2, and the extract was successively washed with saturated $CuSO_4$–H_2O, H_2O, saturated $NaHCO_3$–H_2O and H_2O, and worked up as usual. Purification by PTLC [hexane–EtOAc (4 : 1)] afforded **19** (82 mg, 74.5%) as a colorless syrup, together with the recovery of **15a** (13 mg, 13%). HRMS Calcd for $C_{27}H_{34}N_2O_7S$: 530.2086. Found: 530.2068. $[\alpha]_D^{23}$ +95.6° (c=1.12, $CHCl_3$). MS *m/z* (relative intensity): 530 (M^+, 0.4), 330 (8), 270 (27), 200 (15), 158 (20), 100 (52), 57 (100). IR ($CHCl_3$) cm^{-1}: 1694. ^{1}H-NMR (90 MHz, 55 °C) δ: 1.50 (12H, s), 1.65 (3H, s), 3.33 (3H, s), 3.67 (1H, dd, J=9, 7.5 Hz), 3.98 (1H, dd, J=9, 3 Hz), 4.47—4.90 (3H, m), 5.98 (1H, d, J=4.5 Hz), 6.83 (1H, s), 7.04—7.54 (6H, m), 7.70—7.90 (2H, m), 8.05—8.27 (1H, m).

***tert*-Butyl (4*S*)-2,2-Dimethyl-4-[(*S*)-(2-indolyl)(methoxymethoxy)methyl]-3-oxazolidinecarboxylate (20)** Na (23 mg, 1.0 mg atom) was added to a solution of **19** (61 mg, 0.12 mmol) in THF (3 ml) and liquid NH_3 (5 ml) at −70 °C. The mixture was stirred at the same temperature for 10 min, NH_4Cl powder (0.5 g) was added, and NH_3 gas was evaporated off at room temperature. The residue was extracted with 10% MeOH-containing CH_2Cl_2 and worked up as usual. Purification by PTLC [hexane–EtOAc (4 : 1)] gave **20** (40 mg, 89%) as a colorless syrup. HRMS Calcd for $C_{21}H_{30}N_2O_5$: 390.2153. Found: 390.2137. $[\alpha]_D^{23}$ −50.6° (c=1.65, $CHCl_3$). MS *m/z* (relative intensity): 390 (M^+, 7), 190 (10), 130 (22), 100 (32), 57 (100). IR ($CHCl_3$) cm^{-1}: 1696. ^{1}H-NMR (90 MHz, 55 °C) δ: 1.30 (9H, s), 1.50 (3H, s), 1.62 (3H, s), 3.38 (3H, s), 3.90 (1H, dd, J=9, 6 Hz), 4.07—4.37 (2H, m), 4.60 (1H, d, J=6 Hz), 4.71 (1H, d, J=6 Hz), 5.16 (1H, d, J=5.5 Hz), 6.36 (1H, s), 6.93—7.37 (3H, m), 7.42—7.62 (1H, m), 8.49 (1H, br s, NH).

***tert*-Butyl (4*S*)-2,2-Dimethyl-4-[(*S*)-(3-formyl-2-indolyl)(methoxymethoxy)methyl]-3-oxazolidinecarboxylate (21)** A solution of *N,N*-dimethylformamide (DMF) (0.3 ml, 4 mmol) and $POCl_3$ (0.10 ml, 1.1 mmol) in CH_2Cl_2 (2 ml) was stirred at 0 °C for 15 min, and a solution of **20** (56 mg, 0.14 mmol) in CH_2Cl_2 (2.5 ml) was added to this at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, then a suspension of $NaHCO_3$ powder in saturated $NaHCO_3$–H_2O was added, and the whole was stirred at room temperature for 30 min. This was extracted with CH_2Cl_2 and worked up as usual. Purification by PTLC [hexane–EtOAc (2 : 1)], followed by recrystallization from MeOH afforded **21** (56 mg, 93%) as colorless prisms, mp 185—186 °C. *Anal.* Calcd for $C_{22}H_{30}N_2O_6$: C, 63.14; H, 7.23; N, 6.69. Found: C, 62.79; H, 7.19; N, 6.65. HRMS Calcd for $C_{22}H_{30}N_2O_6$: 418.2102. Found: 418.2120. $[\alpha]_D^{21}$ −75.4° (c=1.58, $CHCl_3$). MS *m/z* (relative intensity): 418 (M^+, 2), 301 (1), 219 (15), 174 (32), 100 (31), 57 (100). IR (KBr) cm^{-1}: 1687, 1628. ^{1}H-NMR (90 MHz, 55°C) δ: 1.30 (9H, s), 1.50 (3H, s), 1.60 (3H, s), 3.37 (3H, s), 3.91 (1H, dd, J=9, 6 Hz), 4.11 (1H, dd, J=9, 3 Hz), 4.40 (1H, ddd, J=6, 6, 3 Hz), 4.67 (1H, d, J=6 Hz), 4.72 (1H, d, J=6 Hz), 5.60 (1H, d, J=6 Hz), 7.13—7.43 (3H, m), 8.14—8.37 (1H, m), 9.15 (1H, br s, NH), 10.29 (1H, s).

2-[(1*S*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-3-hydroxy-1-(methoxymethoxy)propyl]-3-formylindole (22) A solution of **21** (39 mg, 0.093 mmol) and 10% HCl–H_2O (4 ml) in MeOH (6 ml) was stirred at room temperature for 1 h. This mixture was neutralized with saturated $NaHCO_3$–H_2O, saturated with NaCl powder, extracted with 10% MeOH-containing CH_2Cl_2 and worked up as usual. Purification by PTLC [hexane–EtOAc (1 : 1)] gave **22** (22 mg, 62%) as a colorless glass. HRMS Calcd for $C_{19}H_{26}N_2O_6$: 378.1789. Found 378.1773. $[\alpha]_D^{21}$ −129° (c=1.11, $CHCl_3$). MS *m/z* (relative intensity): 378 (M^+, 1), 333 (1), 219 (60), 174 (100), 57 (50), 45 (94). IR ($CHCl_3$) cm^{-1}: 1696, 1648. ^{1}H-NMR (90 MHz, 55 °C) δ: 1.17 (9H, s), 3.34 (3H, s), 3.68—4.37 (3H, m), 4.63 (2H, s), 5.45 (1H, br d, J=10 Hz, NH), 5.56 (1H, d, J=8 Hz), 7.03—7.37 (3H, m), 8.02—8.25 (1H, m), 10.15—10.38 (1H, br s, NH), 10.27 (1H, s).

2-[(1*S*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-3-hydroxy-1-(methoxymethoxy)propyl]indole (23) A solution of **20** (154 mg, 0.395 mmol) and 10% HCl–H_2O (3 ml) in MeOH (7 ml) was stirred at room temperature for 20 h. The same work-up as above and purification by PTLC [hexane–EtOAc (1 : 1)], followed by recrystallization from benzene–hexane afforded **23** (90 mg, 65%) as colorless prisms, mp 156—157 °C, together with recovered **20** (13 mg, 8%). *Anal.* Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 8.00. Found: C, 61.80; H, 7.44; N, 7.87. HRMS Calcd for $C_{18}H_{26}N_2O_5$: 350.1840. Found: 350.1849. $[\alpha]_D^{21}$ −95.8° (c=1.53, $CHCl_3$). MS *m/z* (relative intensity): 350 (M^+, 10), 219 (7), 190 (37), 130 (59), 57 (41), 45 (100). ^{1}H-NMR (90 MHz, 55 °C) δ: 1.36 (9H, s), 2.37 (1H, br s, OH), 3.40 (3H, s), 3.55—4.13 (3H, m), 4.61 (1H, d, J=7.5 Hz), 4.69 (1H, d, J=7.5 Hz), 4.93—5.20 (1H, br s, NH), 5.05 (1H, d, J=6 Hz), 6.46 (1H, br s), 6.93—7.42 (3H, m), 7.42—7.64 (1H, m), 8.57 (1H, br s, NH).

2-[(1*S*,2*S*)-3-Acetoxy-2-(*tert*-butyloxycarbonylamino)-1-(methoxymethoxy)propyl]indole (24) A solution of **23** (78 mg, 0.22 mmol) and Ac_2O (0.3 ml) in pyridine (0.5 ml) was stirred at room temperature for a sufficient time. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. The extract was successively washed with saturated $CuSO_4$–H_2O, H_2O, saturated $NaHCO_3$–H_2O and H_2O, and worked up as usual. Purification by PTLC [hexane–EtOAc (2 : 1)] and recrystallization from benzene–hexane afforded **24** (82 mg, 94%) as colorless needles, mp 154—155 °C. *Anal.* Calcd for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.14. Found: C, 60.85; H, 7.12; N, 7.08. HRMS Calcd for $C_{20}H_{28}N_2O_6$: 392.1946. Found: 392.1938. $[\alpha]_D^{22}$ −69.9° (c=1.20, $CHCl_3$). MS *m/z* (relative intensity): 392 (M^+, 8), 190 (40), 130 (49), 57 (42), 45 (100). IR (KBr) cm^{-1}: 1755, 1694. ^{1}H-NMR (90 MHz, 55 °C) δ: 1.32 (9H, s), 2.01 (3H, s), 3.35 (3H, s), 4.07—4.53 (3H, m), 4.53 (1H, d, J=6 Hz), 4.63 (1H, d, J=6 Hz), 4.80 (1H, br d, J=9 Hz, NH), 4.93 (1H, d, J=6 Hz), 6.44 (1H, br s), 6.90—7.40 (3H, m), 7.40—7.65 (1H, m), 8.57 (1H, br s, NH).

2-[(1*S*,2*S*)-3-Acetoxy-2-(*tert*-butyloxycarbonylamino)-1-(methoxymethoxy)propyl]-3-formylindole (25) A solution of DMF (0.2 ml, 3 mmol) and $POCl_3$ (60 μl, 0.64 mmol) in CH_2Cl_2 (2 ml) was stirred at 0 °C for 20 min. A solution of **24** (64 mg, 0.16 mmol) in CH_2Cl_2 (2.5 ml) was added to this at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. A suspension of $NaHCO_3$ powder in saturated $NaHCO_3$–H_2O was added and the whole was stirred at room temperature for 10 min, then extracted with CH_2Cl_2 and worked up as usual. Purification by PTLC [hexane–EtOAc (1 : 1)] gave **25** (58 mg, 85%) as a colorless glass. HRMS Calcd for $C_{21}H_{28}N_2O_7$: 420.1895. Found: 420.1872. $[\alpha]_D^{22}$ −118° (c=1.21, $CHCl_3$). MS *m/z* (relative intensity): 420 (M^+, 1), 375 (1), 346 (2), 319 (1), 219 (45), 174 (72), 57 (68), 45 (100). IR ($CHCl_3$) cm^{-1}: 1743, 1702, 1656. ^{1}H-NMR (90 MHz, 55 °C) δ: 1.18 (9H, s), 2.07 (3H, s), 3.33 (3H, s), 4.13—4.70 (3H, m), 4.60 (2H, s), 5.25 (1H, br d, J=9 Hz, NH), 5.54 (1H, d, J=7.5 Hz), 7.08—7.37 (3H, m), 8.01—8.23 (1H, m), 10.07 (1H, br s, NH), 10.31 (1H, s).

2-[(1*S*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-3-hydroxy-1-(methoxymethoxy)propyl]-3-formylindole (22) from 25 A mixture of **25** (49 mg, 0.12 mmol) and K_2CO_3 (39 mg, 0.28 mmol) in MeOH (5 ml) was stirred

at room temperature for 30 min. Saturated NH_4Cl–H_2O was added and the mixture was extracted with 10% MeOH-containing CH_2Cl_2. Usual work-up and purification by PTLC [hexane–EtOAc (3 : 2)] gave **22** (39 mg, 88%) as a colorless glass.

(1*S*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-9-formyl-1-(methoxymethoxy)-1*H*-pyrrolo[1,2-*a*]indole (26) $MeSO_2Cl$ (0.05 ml, 0.6 mmol) was added to a cooled solution of **22** (36 mg, 0.095 mmol) and Et_3N (0.4 ml, 3 mmol) in CH_2Cl_2 (4 ml) at 0 °C, and the mixture was stirred at 0 °C for 10 min. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. The extract was successively washed with saturated $CuSO_4$–H_2O, H_2O, saturated $NaHCO_3$–H_2O and H_2O, and worked up as usual. The residue (51 mg) was dissolved in MeCN (3 ml), K_2CO_3 (45 mg, 0.33 mmol) was added to this, and the reaction mixture was stirred at room temperature for 3.5 h. Saturated NH_4Cl–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [hexane–EtOAc (3 : 1)] afforded **26** (23 mg, 67%) as a colorless syrup. HRMS Calcd for $C_{19}H_{24}N_2O_5$: 360.1684. Found: 360.1661. $[\alpha]_D^{24}$ +37.1° (c=1.27, $CHCl_3$). MS m/z (relative intensity): 360 (M^+, 15), 286 (6), 259 (36), 57 (86), 45 (100). IR ($CHCl_3$) cm^{-1}: 1714, 1658. ^{1}H-NMR (90 MHz) δ: 1.48 (9H, s), 3.40 (3H, s), 3.90 (1H, dd, J=10.5, 7.5 Hz), 4.49 (1H, dd, J=10.5, 7.5 Hz), 4.71 (1H, d, J=7 Hz), 4.90 (1H, d, J=7 Hz), 4.80—5.11 (1H, m), 5.34 (1H, d, J=5.5 Hz), 5.50 (1H, br d, J=9 Hz, NH), 7.20—7.42 (3H, m), 8.17—8.42 (1H, m), 10.15 (1H, s).

(1*S*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-9-(hydroxymethyl)-1-(methoxymethoxy)-1*H*-pyrrolo[1,2-*a*]indole (27) $NaBH_4$ (4 mg, 0.1 mmol) was added to a solution of **26** (6 mg, 0.02 mmol) in MeOH (2 ml) at room temperature and the mixture was stirred for 1 h and 20 min. Saturated NH_4Cl–H_2O was added, and the whole was extracted with CH_2Cl_2, and worked up as usual. Purification by PTLC [hexane–EtOAc (2 : 1)] afforded **27** (4 mg, 66%) as a colorless syrup. HRMS Calcd for $C_{19}H_{26}N_2O_5$: 362.1840. Found: 362.1833. MS m/z (relative intensity): 362 (M^+, 49), 288 (28), 243 (75), 227 (71), 199 (26), 183 (63), 57 (71), 45 (100). IR ($CHCl_3$) cm^{-1}: 1715. ^{1}H-NMR (90 MHz) δ: 1.50 (9H, s), 2.58 (1H, br s, OH), 3.37 (3H, s), 3.82 (1H, dd, J=9, 9 Hz), 4.45 (1H, dd, J=9, 7 Hz), 4.70 (1H, d, J=7 Hz), 4.85 (1H, d, J=7 Hz), 5.11 (1H, d, J=5.5 Hz), 5.44 (1H, br s, NH), 6.98—7.30 (3H, m), 7.57—7.77 (1H, m).

***tert*-Butyl (4*S*)-2,2-Dimethyl-4-[(*S*)-hydroxy(2-indolyl)methyl]-3-oxazolidinecarboxylate (28a)** Na (69 mg, 3.0 mg atom) was added to a solution of **15a** (221 mg, 0.455 mmol) in THF (5 ml) and liquid NH_3 (10 ml) at −70 °C. The mixture was stirred at the same temperature for 10 min, then NH_4Cl powder (0.3 g) was added and the whole was worked up as in the case of **20**. Purification by PTLC [hexane–EtOAc (3 : 2)] gave **28a** (141 mg, 90%) as a colorless syrup. HRMS Calcd for $C_{19}H_{26}N_2O_4$: 346.1891. Found: 346.1897. $[\alpha]_D^{22}$ −22.1° (c=1.24, $CHCl_3$). MS m/z (relative intensity): 346 (M^+, 7), 146 (33), 100 (33), 57 (100). IR ($CHCl_3$) cm^{-1}: 1695. ^{1}H-NMR (90 MHz, 55 °C) δ: 1.38 (12H, s), 1.45 (3H, s), 3.63 (1H, br s, OH), 3.87 (1H, dd, J=9, 6 Hz), 4.03 (1H, dd, J=9, 3 Hz), 4.27 (1H, ddd, J=6, 3, 3 Hz), 5.16 (1H, d, J=3 Hz), 6.27 (1H, br s), 6.88—7.32 (3H, m), 7.40—7.60 (1H, m), 8.61 (1H, br s, NH).

***tert*-Butyl (4*S*)-2,2-Dimethyl-4-[(*R*)-hydroxy(2-indolyl)methyl]-3-oxazolidinecarboxylate (28b)** Na (72 mg, 3.1 mg atom) was added to a solution of **15b** (197 mg, 0.405 mmol) in THF (5 ml) and liquid NH_3 (8 ml) at −78 °C. The mixture was stirred at the same temperature for 10 min, then NH_4Cl powder (1 g) was added and the whole was worked up as above. Purification by PTLC [hexane–EtOAc (2 : 1)] afforded **28b** (122 mg, 87%) as a colorless syrup. HRMS Calcd for $C_{19}H_{26}N_2O_4$: 346.1891. Found: 346.1888. $[\alpha]_D^{22}$ +7.0° (c=1.21, $CHCl_3$). MS m/z (relative intensity): 346 (M^+, 7), 146 (31), 100 (34), 57 (100). IR ($CHCl_3$) cm^{-1}: 1660. ^{1}H-NMR (90 MHz) δ: 1.50 (15H, s), 3.72 (1H, dd, J=10.5, 6 Hz), 3.87 (1H, dd, J=10.5, 2 Hz), 4.10—4.37 (1H, m), 4.96 (1H, d, J=9 Hz), 5.44 (1H, br s, OH), 6.37 (1H, br s), 6.91—7.37 (3H, m), 7.42—7.65 (1H, m), 8.85 (1H, br s, NH).

2-[(1*S*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-1,3-(diacetoxy)propyl]indole (29a) A solution of **28a** (129 mg, 0.373 mmol) and 10% HCl–H_2O (1 ml) in MeOH (9 ml) was stirred at room temperature for 1.5 h. This mixture was neutralized with powdered K_2CO_3 and diluted with brine. The whole was extracted with 10% MeOH-containing CH_2Cl_2 and worked up as usual. Dried residue (113 mg) was acetylated with Ac_2O (0.7 ml) in pyridine (1 ml) by stirring at room temperature for a sufficient time, and the mixture was worked up as in the case of **24**. Purification by PTLC [hexane–EtOAc (5 : 3)], followed by recrystallization from benzene–hexane afforded **29a** (86 mg, 59%) as colorless needles, mp 150—151.5 °C. *Anal.* Calcd for $C_{20}H_{26}N_2O_6$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.75; H, 6.73; N, 7.01. HRMS Calcd for $C_{20}N_{26}N_2O_6$: 390.1789. Found: 390.1803. $[\alpha]_D^{21}$ −49.4° (c=1.56, $CHCl_3$). MS m/z (relative intensity): 390 (M^+, 10), 274 (10), 215 (4), 188 (14), 146 (100), 102 (30), 57 (74). IR (KBr) cm^{-1}: 1740, 1717, 1687. ^{1}H-NMR (90 MHz, 55 °C) δ: 1.36 (9H, s), 2.06 (3H, s), 2.09 (3H, s), 4.02—4.87 (3H, m), 4.75 (1H, br d, J=9 Hz, NH), 6.06 (1H, d, J=6 Hz), 6.54 (1H, br s), 6.90—7.43 (3H, m), 7.43—7.63 (1H, m), 8.59 (1H, br s, NH).

2-[(1*R*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-1,3-(diacetoxy)propyl]indole (29b) A solution of **28b** (53 mg, 0.22 mmol) and 10% HCl–H_2O (0.5 ml) in MeOH (4.5 ml) was stirred at room temperature for 1 h. Then the mixture was treated as above, and the dried residue (51 mg) was acetylated with Ac_2O (0.3 ml) in pyridine (0.5 ml) by stirring at room temperature for a sufficient time. The same work-up as in the case of **24**, followed by purification by PTLC [hexane–EtOAc (3 : 2)] and recrystallization from benzene–hexane afforded **29b** (38 mg, 64%) as colorless needles, mp 155.5—156.5 °C. *Anal.* Calcd for $C_{20}H_{26}N_2O_6$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.40; H, 6.73; N, 7.13. HRMS Calcd for $C_{20}H_{26}N_2O_6$: 390.1789. Found: 390.1798. $[\alpha]_D^{22}$ +86.1° (c=1.28, $CHCl_3$). MS m/z (relative intensity): 390 (M^+, 11), 274 (10), 215 (5), 188 (15), 146 (100), 102 (33), 57 (79). IR (KBr) cm^{-1}: 1742, 1725, 1685. ^{1}H-NMR (90 MHz) δ: 1.48 (9H, s), 2.02 (3H, s), 2.10 (3H, s), 4.06 (1H, dd, J=12, 6 Hz), 4.19 (1H, dd, J=12, 6 Hz), 4.48 (1H, dddd, J=9, 6, 6, 6 Hz), 4.88 (1H, br d, J=9 Hz, NH), 6.07 (1H, d, J=6 Hz), 6.52 (1H, br s), 6.92—7.40 (3H, m), 7.45—7.63 (1H, m), 8.61 (1H, br s, NH).

2-[(1*S*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-1,3-(diacetoxy)propyl]indole (29a) from 16a Na (89 mg, 3.9 mg atom) was added to a solution of **16a** (287 mg, 0.643 mmol) in THF (7 ml) and liquid NH_3 (16 ml) at −70 °C. The mixture was stirred at the same temperature for 10 min, then NH_4Cl powder (1 g) was added and the whole was worked up as in the case of **20**. The resulting residue (203 mg) was acetylated with Ac_2O (0.5 ml) in pyridine (0.7 ml) by stirring at room temperature for a sufficient time, and the mixture was worked up as in the case of **24**. Purification by PTLC [hexane–EtOAc (2 : 1)] and recrystallization from benzene–hexane gave **29a** (135 mg, 54%) as colorless needles, mp 149—151 °C.

2-[(1*R*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-1,3-(diacetoxy)propyl]indole (29b) from 16b The diol **16b** (95 mg, 0.21 mmol) was treated with Na (31 mg, 1.4 mg atom) in THF (3 ml) and liquid NH_3 (8 ml) at −70 °C as above for 10 min. A similar work-up afforded the residue (79 mg), which was acetylated with Ac_2O (0.3 ml) in pyridine (0.5 ml) as above. Purification by PTLC [hexane–EtOAc (2 : 1)] and recrystallization from benzene–hexane gave **29b** (48 mg, 58%) as colorless needles, mp 155—156 °C.

2-[(1*S*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-1,3-(diacetoxy)propyl]-3-formylindole (30a) A solution of DMF (0.3 ml, 4 mmol) and $POCl_3$ (0.10 ml, 1.1 mmol) in CH_2Cl_2 (4 ml) was stirred at 0 °C for 15 min, and a solution of **29a** (111 mg, 0.285 mmol) in CH_2Cl_2 (4 ml) was added to this at 0 °C. The reaction mixture was stirred at 0 °C for 1 h, then a suspension of $NaHCO_3$ powder in saturated $NaHCO_3$–H_2O was added, the whole was stirred at room temperature for 20 min, extracted with CH_2Cl_2, and worked up as usual. Purification by PTLC [hexane–EtOAc (1 : 1)] afforded **30a** (96 mg, 81%) as a colorless glass. HRMS Calcd for $C_{21}H_{26}N_2O_7$: 418.1738. Found: 418.1746. $[\alpha]_D^{23}$ −33.5° (c=1.04, $CHCl_3$). MS m/z (relative intensity): 418 (M^+, 5), 302 (6), 217 (91), 175 (97), 144 (12), 102 (21), 57 (100). IR ($CHCl_3$) cm^{-1}: 1746, 1696, 1654. ^{1}H-NMR (90 MHz, 55 °C) δ: 1.23 (9H, s), 2.08 (6H, s), 4.17 (1H, dd, J=13.5, 5 Hz), 4.47 (1H, dd, J=13.5, 4.5 Hz), 4.33—4.68 (1H, m), 5.17 (1H, br d, J=9 Hz, NH), 6.59 (1H, d, J=7.5 Hz), 7.10—7.37 (3H, m), 8.04—8.25 (1H, m), 9.73 (1H, br s, NH), 10.37 (1H, s).

2-[(1*R*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-1,3-(diacetoxy)propyl]-3-formylindole (30b) A solution of **29b** (42 mg, 0.11 mmol) in CH_2Cl_2 (3 ml) was treated with the reagent prepared from DMF (0.15 ml, 1.9 mmol) and $POCl_3$ (60 μl, 0.63 mmol) in CH_2Cl_2 (1 ml) as above. Purification by PTLC [hexane–EtOAc (1 : 1)] afforded **30b** (36 mg, 80%) as a colorless glass. HRMS Calcd for $C_{21}H_{26}N_2O_7$: 418.1738. Found: 418.1746. $[\alpha]_D^{24}$ +95.4° (c=1.16, $CHCl_3$). MS m/z (relative intensity): 418 (M^+, 4), 302 (5), 217 (95), 175 (96), 144 (13), 102 (22), 57 (100). IR ($CHCl_3$) cm^{-1}: 1745, 1710, 1655. ^{1}H-NMR (90 MHz, 50 °C), δ: 1.30 (9H, s), 1.99 (3H, s), 2.10 (3H, s), 4.15 (2H, d, J=5 Hz), 4.33—4.67 (1H, m), 5.12—5.43 (1H, br s, NH), 6.67 (1H, d, J=5 Hz), 7.10—7.45 (3H, m), 8.07—8.30 (1H, m), 10.11 (1H, br s, NH), 10.33 (1H, s).

(1*S*,2S)-2-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-9-formyl-1-hydroxy-1*H*-pyrrolo[1,2-*a*]indole (31a) A mixture of **30a** (77 mg, 0.18 mmol) and K_2CO_3 (27 mg, 0.19 mmol) in MeOH (4 ml) was stirred at room temperature for 30 min. Saturated NaCl–H_2O was added, the whole was extracted with 10% MeOH-containing CH_2Cl_2, and the extract was worked up as usual. The dried residue (58 mg) was dissolved in CH_2Cl_2 (3 ml) containing Et_3N (0.2 ml, 1.4 mmol), and $MeSO_2Cl$ (20 μl, 0.26 mmol) was added to this at −75 °C. The reaction mixture was stirred at −75 °C for

1 h, and then quenched by addition of saturated $NaHCO_3$–H_2O. The whole was extracted with CH_2Cl_2, and the extract was washed successively with saturated $CuSO_4$–H_2O, H_2O, saturated $NaHCO_3$–H_2O and H_2O, and worked up as usual. The resulting residue (68 mg) in MeCN (2 ml) was stirred with K_2CO_3 (46 mg, 0.32 mmol) at room temperature for 2 h under an Ar atmosphere. Saturated NH_4Cl–H_2O was added, and the whole was extracted with CH_2Cl_2, and worked up as usual. Purification by PTLC [hexane–EtOAc (1 : 1)] and recrystallization from MeOH afforded **31a** (32 mg, 55%) as colorless plates, mp 204—205 °C (dec.). *Anal.* Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.27; H, 6.35; N, 8.64. HRMS Calcd for $C_{17}H_{20}N_2O_4$: 316.1422. Found: 316.1420. $[\alpha]_D^{22}$ +221° (c=1.18, $CHCl_3$). MS m/z (relative intensity): 316 (M^+, 16), 260 (40), 242 (58), 199 (43), 174 (37), 145 (37), 57 (100). IR (KBr) cm^{-1}: 1662, 1648. ^{1}H-NMR (90 MHz) δ: 1.46 (9H, s), 4.19 (1H, dd, J=12, 4.5 Hz), 4.40 (1H, dd, J=12, 6 Hz), 4.67—5.00 (1H, m), 5.16 (1H, br s, OH), 5.55 (1H, br d, J=6 Hz), 5.68 (1H, br d, J=5 Hz, NH), 7.17—7.40 (3H, m), 7.85—8.07 (1H, m), 10.06 (1H, s).

X-Ray Crystallographic Analysis of 31a Crystal data: monoclinic, $P2_1$, a=13.356(1), b=11.479(1), c=5.290(1) Å, β=94.60(1), V=808.4(1) Å^3, Z=2, D_c=1.300 g cm^{-3}, CuK_α radiation, λ=1.54178 Å, μ=0.78 mm^{-1}, $F(000)$=336. A colorless plate crystal of dimensions 0.25 × 0.25 × 0.10 mm was used for X-ray measurement at 295 K on a Rigaku AFC5 diffractometer equipped with a graphite monochromator. Cell constants were determined from 24 well centered reflections in the range $45 < 2\theta < 55°$. Intensity data were collected to a maximum 2θ of 130° by the $\omega/2\theta$ scan technique. The total number of independent reflections measured was 1456, of which 1403 were considered to be observed [$F \geq 4\sigma(F)$]. No absorption correction was applied. The structure was solved by direct methods and all H atoms were located in a difference Fourier map. The structure was refined by a full-matrix least-squares procedure, with anisotropic temperature factors for non-H atoms and isotropic temperature factors for H atoms. The weighting scheme employed was w=1. The refinement converged to R=0.032, wR=0.031. The residual densities were in the range of −0.11—0.12 eÅ^{-3}. All crystallographic calculations were made on a VAX 3100 workstation using the program system *Xtal3.0* (S. R. Hall and J. M. Stewart, eds., *Xtal3.0 Reference Manual*, 1990, Univs. of Western Australia, Australia, and Maryland, U.S.A.) with the scattering factors as included in the program.

(1*R*,2*S*)-2-(*tert*-Butyloxycarbonylamino)-2,3-dihydro-9-formyl-1-hydroxy-1*H*-pyrrolo[1,2-*a*]indole (31b) A mixture of **30b** (28 mg, 0.067 mmol) and K_2CO_3 (21 mg, 0.15 mmol) in MeOH (3 ml) was stirred at room temperature for 30 min. The mixture was worked up as above. A solution of the dried residue (23 mg) and Et_3N (0.2 ml, 1.4 mmol) in CH_2Cl_2 (2 ml) was stirred with $MeSO_2Cl$ (10 μl, 0.13 mmol) at −75 °C for 45 min. After being worked up as above, the resulting residue (25 mg) in MeCN (1 ml) was stirred with K_2CO_3 (18 mg, 0.13 mmol) at room temperature for 2 h under an Ar atmosphere. The same work-up as above, followed by purification by PTLC [hexane–EtOAc (3 : 2)] afforded **31b** (11 mg, 52%) as a colorless syrup. HRMS Calcd for $C_{17}H_{20}N_2O_4$: 316.1422. Found: 316.1430. $[\alpha]_D^{24}$ −1.0° (c=0.95, $CHCl_3$). MS m/z (relative intensity): 316 (M^+, 5), 260 (57), 242 (9), 199 (98), 174 (21), 145 (36), 57 (100). IR ($CHCl_3$) cm^{-1}: 1712, 1638. ^{1}H-NMR (90 MHz) δ: 1.50 (9H, s), 4.02 (1H, dd, J=13.5, 10.5 Hz), 4.64 (1H, dd, J=13.5, 7.5 Hz), 4.40—4.73 (1H, m), 5.00 (1H, br s, OH), 5.23—5.42 (1H, br s, NH), 5.45 (1H, d, J=6 Hz), 7.18—7.38 (3H, m), 7.78—8.10 (1H, m), 10.09 (1H, s).

(1a*S*,8b*S*)-1-*tert*-Butyloxycarbonyl-8-formyl-1,1a,2,8b-tetrahydroazirino[2′,3′ : 3,4]pyrrolo[1,2-*a*]indole (8) $MeSO_2Cl$ (30 μl, 0.13 mmol) was added to a solution of **31a** (10 mg, 0.032 mmol) and Et_3N (0.3 ml, 2 mmol) in CH_2Cl_2 (2 ml) at 0 °C, and the mixture was stirred at 0 °C for 2 h. Saturated $NaHCO_3$–H_2O was added, and the whole was extracted with CH_2Cl_2. The extract was washed successively with saturated $CuSO_4$–H_2O, H_2O, saturated $NaHCO_3$–H_2O, and H_2O. The extract was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* below 40 °C. A solution of the dried residue (15 mg) and *tert*-BuOK (9 mg, 0.08 mmol) in THF (2 ml) was stirred at room temperature for 1 h under an Ar atmosphere. Saturated NH_4Cl–H_2O was added, and the whole was extracted with CH_2Cl_2, and worked up as usual. Purification by PTLC [hexane–EtOAc (2 : 1)] afforded **8** (5 mg, 53%) as a colorless glass. HRMS Calcd for $C_{17}H_{18}N_2O_3$: 298.1316. Found: 298.1313. $[\alpha]_D^{26}$ +84.2° (c=0.31, $CHCl_3$). MS m/z (relative intensity): 298 (M^+, 7), 242 (20), 225 (11), 198 (36), 169 (17), 154 (13), 57 (100). IR ($CHCl_3$) cm^{-1}: 1715, 1660. ^{1}H-NMR (400 MHz) δ: 1.04 (9H, s), 4.02 (1H, dd, J=3.5, 3.5 Hz), 4.18 (1H, dd, J=12.5, 3.5 Hz), 4.23 (1H, dd, J=3.5, 1 Hz), 4.72 (1H, dd, J=12.5, 1 Hz), 7.18—7.23 (1H, m), 7.25—7.31 (2H, m), 8.22—8.27 (1H, m), 10.19 (1H, s).

(1a*S*,8b*S*)-1-*tert*-Butyloxycarbonyl-8-formyl-1,1a,2,8b-tetrahydroazirino[2′,3′ : 3,4]pyrrolo[1,2-*a*]indole (8) from 31b $MeSO_2Cl$ (30 μl, 0.13 mmol) was added to a solution of **31b** (10 mg, 0.032 mmol) and Et_3N (0.2 ml, 1 mmol) in CH_2Cl_2 (2 ml) at 0 °C, and the mixture was stirred at 0 °C for 1.5 h, then worked up in the same manner as above. A solution of the dried residue (14 mg) and *tert*-BuOK (15 mg, 0.13 mmol) in THF (2 ml) was stirred at room temperature for 1 h under an Ar atmosphere. The reaction mixture was worked up as above, and purification by PTLC [hexane–EtOAc (2 : 1)] afforded **8** (3 mg, 32%) as a colorless glass.

Acknowledgment The author's thanks are due to the Research Laboratories, Shionogi & Co., Ltd., for elemental analysis. This work was supported by a Grant-in-Aid from the Ministry of Education, Science and Culture.

References and Notes

1) Part 8: I. Utsunomiya, H. Muratake, and M. Natsume, *Chem. Pharm. Bull.*, **40**, 2358 (1992).
2) M. Fuji, H. Muratake, and M. Natsume, *Chem. Pharm. Bull.*, **40**, 2344 (1992).
3) Isolation and biological activity: S. Kiyoto, T. Shibata, M. Yamashita, T. Komori, M. Okuhara, H. Terano, M. Kohsaka, H. Aoki, and H. Imanaka, *J. Antibiot.*, **40**, 594 (1987). Chemical structure: I. Uchida, S. Takase, H. Kayakiri, S. Kiyoto, M. Hashimoto, T. Tada, S. Koda, and Y. Morimoto, *J. Am. Chem. Soc.*, **109**, 4108 (1987). Total synthesis: T. Fukuyama, L. Xu, and S. Goto, *ibid.*, **114**, 383 (1992).
4) The possible relationship between **6** and **7** from the viewpoint of the anticancer activities was discussed. *a*) T. Fukuyama and S. Goto, *Tetrahedron Lett.*, **30**, 6491 (1989); *b*) K. F. McClure and S. J. Danishefsky, *J. Org. Chem.*, **56**, 850 (1991); *c*) R. M. Williams and S. R. Rajski, *Tetrahedron Lett.*, **33**, 2929 (1992).
5) R. J. Sundberg and H. F. Russell, *J. Org. Chem.*, **38**, 3324 (1973).
6) M. G. Saulnier and G. W. Gribble, *J. Org. Chem.*, **47**, 757 (1982).
7) K. Nakajima, T. Tanaka, K. Morita, and K. Okawa, *Pept. Chem.*, **15**, 127 (1978) [*Chem. Abstr.*, **93**, 168584*n* (1980)].
8) P. Garner and J. M. Park, *J. Org. Chem.*, **52**, 2361 (1987).
9) In the literature, **11** was obtained in 55% yield.[5]
10) K. C. Nicolaou, R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis, and T. K. Chakraborty, *J. Am. Chem. Soc.*, **109**, 2205 (1987).
11) M. Chérest, H. Felkin, and N. Prudent, *Tetrahedron Lett.*, **1968**, 2199; N. T. Anh, *Top. Curr. Chem.*, **88**, 145 (1980); R. S. Coleman and A. J. Carpenter, *Tetrahedron Lett.*, **33**, 1697 (1992),
12) Accompanied by the recovery of **15a** in 13% yield. Forcing conditions to complete the reaction resulted in the isolation of **19** in much lower yields.
13) For the *S*$_N$2 intramolecular displacement mechanism in the aziridine formation, see: "Ethylenimine and other Aziridines," ed. by O. C. Dermer and G. E. Ham, Academic Press, New York, 1969, pp. 26—28.
14) K. Nakajima, F. Takai, T. Tanaka, and K. Okawa, *Bull. Chem. Soc. Jpn.*, **51**, 1577 (1978).