Preparation of Alkyl-Substituted Indoles in the Benzene Portion. Part 12.[1] Enantiospecific Synthesis of Hapalindole O

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Received December 15, 1993; accepted January 28, 1994

An important chiral ketone derivative, (3*S*,4*R*)-3-methyl-4-pivaloyloxy-3-vinylcyclohexan-1-one (16) was prepared from (*R*)-(−)-carvone (10) using a stereo-controlled conjugate addition of the vinyl group to (*R*)-3-methyl-6-(1-methylethylidene)-4-pivaloyloxy-2-cyclohexen-1-one (13). The first enantiospecific total synthesis of a terrestrial blue-green alga constituent, hapalindole O (1) was accomplished by condensation of this ketone 16 with α,α-dimethyl-1-(*p*-toluenesulfonyl)-1*H*-indole-4-methanol (6) to construct the fundamental carbon framework of the hapalindole 21, followed by introduction of the nitrogen function, stereoselective reduction of the tetra-substituted double bond with lithium aluminum hydride, and subsequent isothiocyanate formation.

Keywords enantiospecific synthesis; blue-green alga constituent; hapalindole; lithium aluminum hydride unusual reduction

In 1990 we reported[2] successful total syntheses of (±)-hapalindole J (**2**), (±)-hapalindole M (**3**), (±)-hapalindole H (**4**), and (±)-hapalindole U (**5**), isolated from a terrestrial blue-green alga *Hapalosiphon fontinalis*[3] (Chart 1). The hapalindole family contains more than twenty tricyclic and tetracyclic, antibacterial, antifungal indole alkaloids, biogenetically composed of tryptophan and geraniol pyrophosphate. Structurally more complex alkaloids, hapalonamides,[4] hapalindolinones,[5] ambiguine isonitriles[6] and Fischer indole L[7] have also been isolated from other species of blue-green algae. In 1993 Vaillancourt and Albizati announced an enantiospecific synthesis of tricyclic hapalindole Q.[8]

Our previous synthesis consisted of i) preparation of a trimethylsilyl enol ether **7b** (R=H) of 3-methyl-3-vinylcyclohexanone (**7a**, R=H), ii) an acid-catalyzed condensation of **7b** (R=H) with α,α-dimethyl-1-(*p*-toluenesulfonyl)-1*H*-indole-4-methanol (**6**) to construct a tetracyclic framework **8** (R=H), and iii) introduction of a hetero-atom function X at the desired position as well as a mechanistically unique lithium aluminum hydride reduction of the tetra-substituted double bond conjugated with the indole part, creating the stereostructure of hapalindoles **9**. For a ready access to the indole alcohol **6**, our novel procedures for the preparation of alkyl-substituted indoles in the benzene portion provided methyl 1-(*p*-toluenesulfonyl)-1*H*-indole-4-carboxylate,[9] which was converted to **6** with methylmagnesium bromide in an excellent yield.[2b] Through the above synthetic pathway, enantiospecific syntheses of various kinds of tetracyclic hapalindoles would be attainable by selecting appropriate chiral sources as starting materials for the preparation of optically active ketone derivatives **7a** (R=hetero atom). Here we report an enantiospecific synthesis of natural hapalindole O (**1**) starting from (*R*)-(−)-carvone (**10**) by way of a chiral cyclohexanone **7a** (R=acyloxy).

Pure (1*R*,*cis*)-carveol (**11a**) was prepared from (*R*)-(−)-carvone (**10**) and converted to its 2,2-dimethylpropanoyl (pivaloyl) ester (**11b**), according to the literature[10,11] (Chart 2). Oxidation at the allylic position in **11b** was carried out with chromium trioxide in the presence of 3,5-dimethylpyrazole[12] to form an α,β-unsaturated ketone **12** in 35% yield. Conjugate addition of the vinyl function to this enone was tried by reacting vinylmagnesium bromide on **12** in the presence of a complex of cuprous bromide-dimethyl sulfide in tetrahydrofuran (THF). A hardly separable mixture of two diastereomers was obtained in a ratio of 1.2:1, judging from its ^{1}H-NMR spectrum. This mixture was treated with sodium methoxide in methanol to induce migration of the *exo*-methylene double bond in the side chain to the conjugated enone position, followed by separation to afford **14** and **15** in 37% and 35% yields, respectively. The stereochemistry of the vinyl group was unknown at this stage, but the fact that two diastereomers were obtained in almost equal amounts could be explained by looking at the ^{1}H-NMR spectrum of **12**, where the C-6 proton signal adjacent to the ketone group was observed at δ 3.13 at a dd of J=13.5 and 6 Hz, suggesting that the carbon substituent and hence the pivaloyloxy group as well were in pseudo-equatorial orientation. Therefore no appreciable difference of steric hindrance was expected for the approach of the vinyl anion

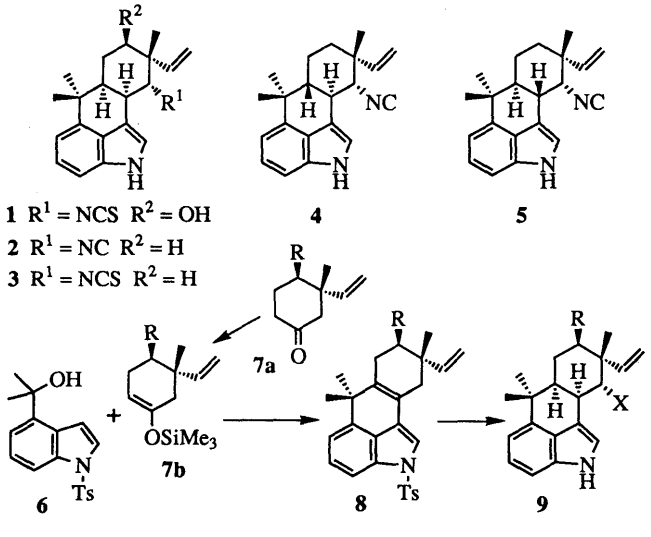

Chart 1

from either side of the enone plane.

To alter the steric situation of the pivaloyloxy group, a doubly conjugated dienone **13** was prepared in 95% yield by treatment of **12** with sodium methoxide. Inspection of the ^{1}H-NMR spectrum of **13** revealed that the C-4 proton signal at δ 5.43 appeared as a dd having $J=7.5$ and 5 Hz, suggesting pseudo-axial nature of the pivaloyloxy function. In fact, the product ratio of **14** and **15** in a mixture obtained in 77% yeild by the conjugate addition reaction of vinylmagnesium bromide to **13** was dramatically improved to 16 : 1, and the stereochemical structure of **14** was assumed to be as shown on the basis of this result, which was ascribed to the back-side attack of the reagent on the pivaloyloxy group. At this stage, the unnecessary isopropylidene side chain was split off by treatment of **14** (containing a trace amount of **15**) with hydrochloric acid in dioxane–water to give the desired ketone **16** in 84% yield. This reaction was explained by assuming that the enone part of **14** was in an equilibrium with the β-hydroxyketone structure *via* acid-catalyzed addition of water, and the latter form could liberate acetone by a retro-aldol type of cleavage reaction to result in the production of **16**.

With this optically active cyclohexanone **16** in hand, the next task, the coupling reaction of **16** with the indole part **6** to construct the tetracyclic fundamental framework of the objective alkaloids, was effected according to our previous synthetic studies.[2] Treatment of **16** with lithium diisopropylamide (LDA) and chlorotrimethylsilane[13] afforded exclusively the required enol ether **17** in an excellent yield. Crude **17** in dichloromethane was allowed to react with **6** in the presence of tin (IV) chloride at low temperature and separation of the reaction mixture produced **18** in 50% yield based on **16**, along with the recovery of **16** (36%) and **6** (26%) as well as the formation of crude by-products **19** and **20** in 21% and 8% yields, respectively. Compound **18** was obtained in a crystalline state, so that purification by recrystallization made **18** free from impurities derived from a trace of the diastereomer **15**. The stereostructure **18** was depicted as shown on the basis of an analysis of its ^{1}H-NMR spectrum. The next intramolecular Friedel–Crafts type of cyclization was substantiated by treatment of **18** with boron trifluoride etherate in dichloromethane at 0 °C, and an important intermediate **21** was obtained in 66% yield, accompanied by the formation of a by-product **22** in 4% yield.

The necessary nitrogen function was introduced into **21** in the manner developed previously[2] (Chart 3). Allylic bromination was first carried out by refluxing a carbon tetrachloride solution of **21** with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide and then a crude mixture of highly reactive bromo derivatives was treated with sodium azide in dimethylformamide (DMF) at room temperature to produce epimers of the azido compounds **23** and **24** in 39% yield each. The stereostructures of these epimers were uncertain at this stage, but the next experiment suggested the orientation of the azido group in **24** in the *trans* relationship to the pivaloyloxy group. Compound **24** was treated with diisobutylaluminum hydride (DIBAL-H) at low temperature to reductively remove the pivaloyl group in 97% yield.

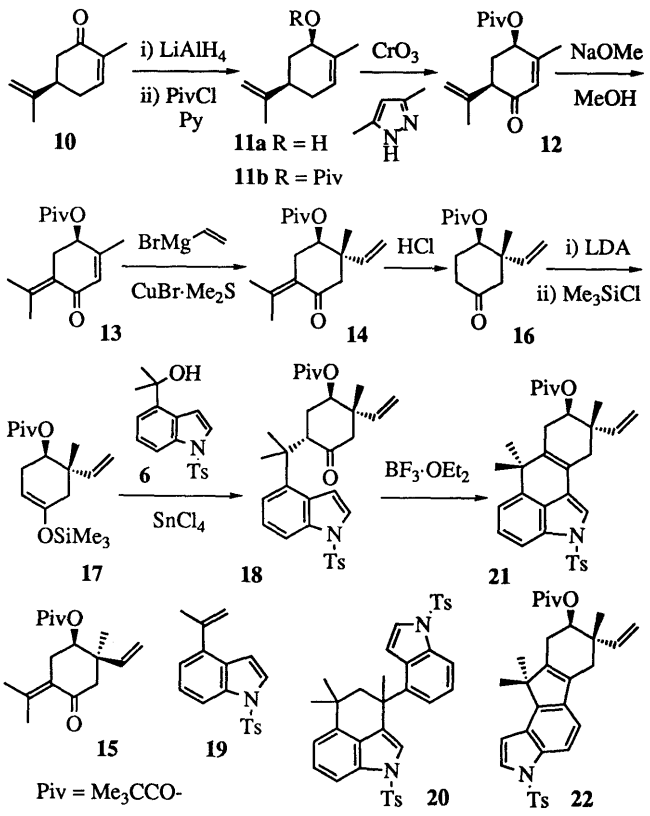

Chart 2

The azido group in the resulting compound **25** was reduced with 1,3-propanedithiol and triethylamine in methanol[14] and the crude amine was formylated by treatment with acetic formic anhydride and pyridine (Py) in dichloromethane, followed by cleavage of the *O*-formyl group by methanolysis with potassium carbonate in a mixture of methanol and dichloromethane, affording **26** in 87% yield. When this formamide **26** was warmed with thionyl chloride in toluene at 50 °C, a facile cyclization took place instead of chlorination, and **27** was isolated as the sole product in 88% yield. This phenomenon was explained in terms of the back-side attack of the formamide group on an activated oxygen function to form a very stable dihydrooxazine ring, suggesting the structure of **24** to be as shown. This assumption was finally verified by completion of the total synthesis using **24** as an intermediate.

To proceed with the synthesis, the hydroxyl group of **25** was protected by either a 2-(trimethylsilyl)ethoxymethyl (SEM) or a 1-ethoxyethyl group as in **28a** (96% yield) or **28b** (95% yield). These were separately submitted to the unusual reduction[2c] with lithium aluminum hydride in THF at 0 °C and the crude products were directly treated with 1,1′-thiocarbonyldiimidazole in dichloromethane. Pairs of reaciton products, **29a** and **30a** as well as **29b** and **30b**, were obtained in 48% and 6% yields and 50% and 16% yields, respectively. Whereas removal of the SEM group of **29a** with tetrabutylammonium fluoride was unattainable without destruction of the isothiocyanate group, mild treatment of **29b** with acetic acid in a mixture of methanol and water at room temperature successfully cleaved the ethoxyethyl protecting group, and hapalindole

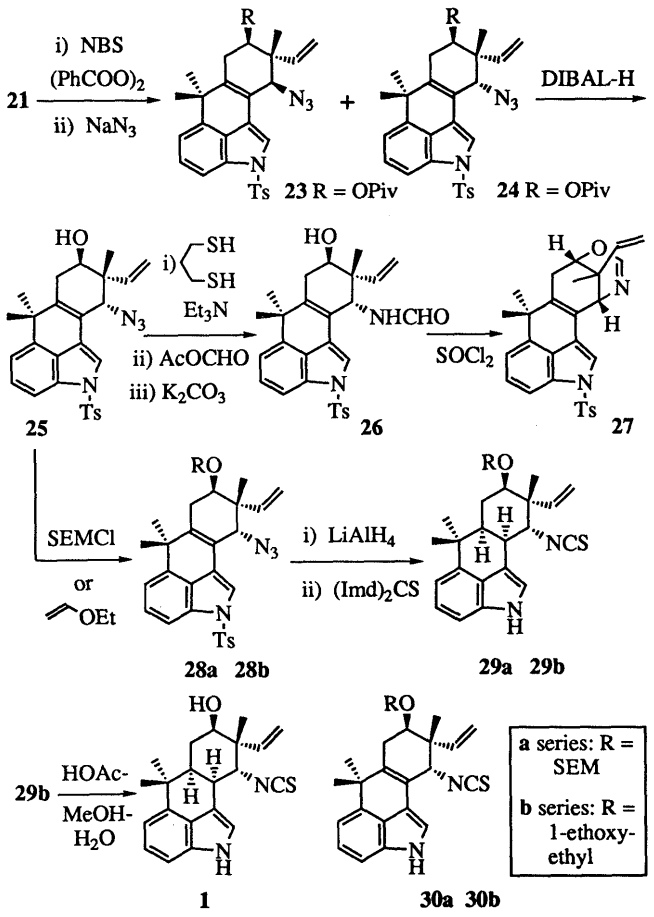

Chart 3

O (**1**) was obtained in 98% yield. Identity of the synthetic material with natural hapalindole O was confirmed by complete agreement of their ^{1}H-NMR and IR spectra. However, a considerable discrepancy of the optical rotational values was observed between our product, $[\alpha]_D^{24}$ $-160°$ ($c=0.51$, chloroform), and the natural product, $[\alpha]_D$ $-106.0°$ ($c=2.4$, chloroform),[3] and the origin of this difference remains unclarified.

In summary, a straightforward pathway for the preparation of the chirality-defined cyclohexanone **16** from (*R*)-(−)-carvone (**10**) was developed and its utilization for natural product synthesis was exemplified by an enantiospecific synthesis of hapalindole O (**1**). Two successive acid-catalyzed carbon–carbon connecting reactions (**17**→**18**→**21**) were applied to **16** and an indolyl alcohol **6** to construct the fundamental tetracyclic structure **21** of hapalindoles. Furthermore, the previous finding concerning the unusual lithium aluminum hydride reaction was effectively applied to the stereo-controlled reduction of the double bond in **28**, making it possible to generate the otherwise unattainable carbon skeleton of the tetracyclic hapalindole **29**. Extension of this study to the synthesis of other hapalindoles is planned.

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 inonizing voltage of 70 eV, and figures in parentheses indicate the relative intensities. IR spectra were measured on a Hitachi 215 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM 390 (90 MHz) spectrometer, unless otherwise specified, in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference. ^{1}H-NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were measured on a JEOL JMN-GX-400 spectrometer. 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.

(4*R*,6*R*)-3-Methyl-4-pivaloyloxy-6-(1-methylethenyl)-2-cyclohexen-1-one (12) 3,5-Dimethylpyrazole (3.05 g, 31.8 mmol) was added to a slurry of CrO_3 (3.18 g, 31.8 mmol) in CH_2Cl_2 (16 ml) at −20 °C and the mixture was stirred for 20 min. A CH_2Cl_2 solution (5 ml) of **11b** (500 mg, 2.12 mmol) was added dropwise to this at −20 °C and the whole was further stirred at −20—0 °C for 15 h. After addition of Et_2O (50 ml) and powdered $NaHCO_3$ (6.68 g, 79.5 mmol), the mixture was filtered through a Celite bed and the Celite was washed thoroughly with Et_2O. The Et_2O layer was washed successively with saturated $NaHCO_3$–H_2O, 2% HCl–H_2O, and saturated $NaHCO_3$–H_2O, and was treated as usual. Purification by column chromatography [hexane–EtOAc (10 : 1)] afforded **12** (185 mg, 35%) as a colorless oil. GC-HRMS Calcd for $C_{15}H_{22}O_3$: 250.1568. Found: 250.1560. GC-MS *m/z*: 250 (M^+, 12), 166 (23), 148 (14), 133 (9), 98 (74), 57 (100). $[\alpha]_D^{24}$ −40.3° ($c=1.34$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1725, 1670. ^{1}H-NMR δ: 1.27 (9H, s), 1.75 (3H, s), 1.90—2.00 (3H, m), 2.13—2.40 (2H, m), 3.13 (1H, dd, $J=13.5$, 6 Hz), 4.75—4.88 (1H, m), 4.91—5.07 (1H, m), 5.56—5.85 (1H, m), 5.87—6.03 (1H, m).

(*R*)-3-Methyl-6-(1-methylethylidene)-4-pivaloyloxy-2-cyclohexen-1-one (13) A solution of **12** (75 mg, 0.30 mmol) and NaOMe (15 mg, 0.28 mmol) in MeOH (1.5 ml) was stirred at 0 °C for 1.5 h. The mixture was poured into saturated NH_4Cl–H_2O and the whole was extracted with Et_2O. Usual work-up and purification by PTLC [hexane–EtOAc (8 : 1)] afforded **13** (71 mg, 95%) as a colorless oil. GC-MS *m/z*: 166 ($M^+-C_5H_8O$, 1), 148 (100), 133 (40), 105 (19), 57 (45), 41 (40). $[\alpha]_D^{23}$ +70.6° ($c=1.25$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1725, 1665, 1610. ^{1}H-NMR δ: 1.22 (9H, s), 1.83 (3H, s), 1.90 (3H, d, $J=1$ Hz), 2.13 (3H, s), 2.67 (1H, dd, $J=14$, 7.5 Hz), 3.00 (1H, dd, $J=14$, 5 Hz), 5.43 (1H, br dd, $J=7.5$, 5 Hz), 5.92—6.02 (1H, m).

(4*R*,5*S*)-5-Methyl-2-(1-methylethylidene)-4-pivaloyloxy-5-vinylcyclohexan-1-one (14) (a) A THF solution (?.8 ml) of **13** (70 mg, 0.28 mmol) was added dropwise to a cooled solution (−40 °C) of 1 M vinylmagnesium bromide (0.84 ml, 0.84 mmol) and CuBr·Me_2S (6 mg, 0.029 mmol) in THF (2 ml), and the mixture was stirred at −40—−30 °C for 30 min. The mixture was poured into saturated NH_4Cl–H_2O and the whole was extracted with Et_2O. Usual work-up and purification by column chromatography [hexane–EtOAc (15 : 1)] gave **14** (60 mg, 77%) as a colorless oil, along with the recovery of **13** (3 mg, 4%). The compound obtained here contained about 6% of **15**, as estimated from the ^{1}H-NMR spectrum. GC-MS *m/z*: 176 (M^+ − *tert*-BuCOOH, 100), 161 (11), 133 (28), 57 (82), 41 (43). $[\alpha]_D^{22}$ −48.2° ($c=0.988$, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1720, 1680. ^{1}H-NMR (400 MHz) δ: 1.09 (3H, s), 1.20 (9H, s), 1.75 (3H, s), 2.03 (3H, s), 2.52 (1H, d, $J=15.5$ Hz), 2.55 (1H, d, $J=15.5$ Hz), 2.65—2.71 (2H, m), 4.95 (1H, dd, $J=5$, 5 Hz), 5.09 (1H, d, $J=17.5$ Hz), 5.10 (1H, d, $J=10.5$ Hz), 5.77 (1H, dd, $J=17.5$, 10.5 Hz). ^{13}C-NMR δ: 22.1 (q), 22.4 (q), 23.1 (q), 27.1 (q), 31.0 (t), 39.0 (s), 42.8 (s), 49.1 (t), 73.9 (d), 114.5 (t), 127.2 (s), 142.7 (d), 145.8 (s), 177.6 (s), 201.0 (s).

(b) In the same manner as above, a THF solution (3 ml) of **12** (75 mg, 0.30 mmol) was added to a solution of 1 M vinylmagnesium bromide (0.90 ml, 0.90 mmol) and CuBr·Me_2S (6 mg, 0.029 mmol) in THF (2 ml) at −40 °C. The mixture was stirred at the same temperature for 30 min, then saturated NH_4Cl–H_2O was added and the whole was extracted with Et_2O. Usual work-up and purification by column chromatography [hexane–EtOAc (20 : 1)] gave a mixture of two diastereomers (1.2 : 1, 67 mg, 80%) as a colorless oil. A solution of this mixture (67 mg, 0.24 mmol) in MeOH (1.5 ml) was stirred with NaOMe (15 mg, 0.28 mmol) at 0 °C for 1.5 h. This was poured into saturated NH_4Cl–H_2O and extracted with Et_2O. Usual work-up and separation by PTLC [hexane–EtOAc (25 : 1)] afforded **14** (31 mg, 37%) and (4*R*,5*R*)-5-methyl-2-(1-methylethylidene)-4-pivaloyloxy-5-vinylcyclohexan-1-one (**15**) (29 mg, 35%) in order of increasing polarity. **15**: Colorless oil. MS

m/z: 176 ($M^+ - tert$-BuCOOH, 92), 161 (70), 133 (34), 57 (100), 41 (59). $[\alpha]_D^{22}$ −70.1° (*c*=0.75, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1720, 1680. ^{1}H-NMR (400 MHz) δ: 1.09 (3H, s), 1.20 (9H, s), 1.77 (3H, s), 2.04 (3H, s), 2.31 (1H, d, *J*=16 Hz), 2.55 (1H, dd, *J*=16, 7.5 Hz), *ca.* 2.71—2.78 (1H, m), 2.76 (1H, d, *J*=16 Hz), 4.95 (1H, dd, *J*=7.5, 4.5 Hz), 5.04 (1H, d, *J*=17.5 Hz), 5.11 (1H, d, *J*=11 Hz), 5.89 (1H, dd, *J*=17.5, 11 Hz).

(3*S*,4*R*)-3-Methyl-4-pivaloyloxy-3-vinylcyclohexan-1-one (16) A solution of **14** (500 mg, 1.80 mmol) in dioxane (12 ml) and concentrated HCl (6 ml) was stirred at 90 °C for 4 h and 20 min. After cooling, the mixture was poured into brine and the whole was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$–H_2O and worked up as usual. Purification by column chromatography [hexane–EtOAc (8 : 1)] gave **16** (360 mg, 84%) as a colorless oil. GC-HRMS Calcd for $C_{14}H_{22}O_3$: 238.1568. Found: 238.1582. GC-MS *m/z*: 238 (M^+, 0.6), 154 (6), 136 (20), 85 (23), 57 (100). $[\alpha]_D^{23}$ −30.3° (*c*=1.07, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1730, 1715. ^{1}H-NMR δ: 1.08 (3H, s), 1.25 (9H, s), 1.87—2.43 (4H, m), 2.47 (2H, s), 4.87—5.07 (1H, m), 5.03 (1H, d, *J*=18 Hz), 5.07 (1H, d, *J*=10 Hz), 5.72 (1H, dd, *J*=18, 10 Hz).

(4*R*,5*S*)-5-Methyl-4-pivaloyloxy-1-trimethylsilyloxy-5-vinyl-1-cyclohexene (17) Me_3SiCl (0.88 ml, 6.94 mmol) in THF (3.5 ml) and a THF solution (1.5 ml) of **16** (330 mg, 1.39 mmol) were successively added under an Ar atmosphere to a cooled (−73 °C) solution of LDA, prepared from diisopropylamine (0.33 ml, 2.36 mmol) and 15% BuLi–hexane (1.30 ml, 2.03 mmol). The mixture was stirred at −73 °C for 10 min, then Et_3N (1.50 ml, 10.8 mmol) was added and stirring was continued for 3 min. The mixture was poured into saturated $NaHCO_3$–H_2O and the whole was extracted with hexane. The organic layer was successively washed with H_2O, 0.1 N citric acid–H_2O, saturated $NaHCO_3$–H_2O, and H_2O, and then worked up as usual to afford crude **17** (425 mg) as an oil. ^{1}H-NMR δ: 0.23 (9H, s), 1.10 (3H, s), 1.22 (9H, s), *ca.* 1.78—2.58 (4H, m), 4.53—4.85 (2H, m), 4.98 (1H, d, *J*=10 Hz), 5.02 (1H, d, *J*=17.5 Hz), 5.75 (1H, dd, *J*=17.5, 10 Hz).

(2*S*,4*R*,5*S*)-5-Methyl-2-[1-methyl-1-[1-(*p*-toluenesulfonyl)-4-indolyl]-ethyl]-4-pivaloyloxy-5-vinyl-1-cyclohexanone (18) $SnCl_4$ (49 μl, 0.42 mmol) was added to a mixture of the above crude **17** (109 mg) and **6** (133 mg, 0.404 mmol) in CH_2Cl_2 (3.5 ml) at −78 °C under an Ar atmosphere, and the mixture was stirred for 15 min at the same temperature. Saturated $NaHCO_3$–H_2O was added and the whole was filtered through a Celite bed. The Celite was washed with CH_2Cl_2 and the combined organic layer was worked up as usual. Purification by PTLC [hexane–EtOAc (8 : 1)] afforded **19** (26 mg, 21% based on **6**), recovered **16** (30 mg, 36%), **18** (98 mg, 50% calculated from **16**), **20** (10 mg, 8% based on **6**), and recovered **6** (35 mg, 26%) in order of increasing polarity. **18**: Colorless needles, mp 168—169 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{32}H_{39}NO_5S$: C, 69.92; H, 7.15; N, 2.55. Found: C, 69.91; H, 7.15; N, 2.59. MS *m/z*: 549 (M^+, 5), 312 (100), 158 (17), 155 (12), 91 (27), 57 (26). $[\alpha]_D^{24}$ −97.3° (*c*=1.16, $CHCl_3$). IR (KBr) cm^{-1}: 1714, 1640. ^{1}H-NMR (400 MHz) δ: 0.95 (3H, s), 1.06 (9H, s), 1.41 (3H, s), 1.45—1.56 (1H, m), 1.64 (3H, s), 1.83 (1H, ddd, *J*=14.5, 13, 2 Hz), 2.35 (3H, s), 2.35 (1H, d, *J*=14 Hz), 2.55 (1H, d, *J*=14 Hz), 3.32 (1H, dd, *J*=13, 5.5 Hz), 4.85 (1H, br s), 5.10 (1H, d, *J*=17.5 Hz), 5.11 (1H, d, *J*=11 Hz), 5.63 (1H, dd, *J*=17.5, 11 Hz), 6.80 (1H, d, *J*=3.5 Hz), 7.12 (1H, d, *J*=8 Hz), 7.21 (1H, dd, *J*=8, 8 Hz), 7.24 and 7.77 (A_2B_2, *J*=8.5 Hz), 7.55 (1H, d, *J*=3.5 Hz), 7.83 (1H, d, *J*=8 Hz). **19**: Colorless syrup, whose spectral data were already reported.[2b] **20**: Colorless syrup. HRMS Calcd for $C_{36}H_{34}N_2O_4S_2$: 622.1958. Found: 622.1964. MS *m/z*: 622 (M^+, 22), 607 (10), 468 (21), 467 (17), 453 (18), 297 (29), 155 (15), 91 (100), 65 (29). ^{1}H-NMR (60 °C) δ: 0.54 (3H, s), 1.28 (3H, s), 1.83 (3H, s), 1.91 (1H, d, *J*=14 Hz), 2.30 (3H, s), 2.37 (3H, s), 2.59 (1H, d, *J*=14 Hz), 6.31 (1H, d, *J*=4 Hz), 6.64 (1H, d, *J*=8 Hz), 6.91 (1H, d, *J*=8 Hz), *ca.* 6.91—7.39 (8H, m), 7.53—7.90 (6H, m).

[8*R*-(8β,9α)]-2,6,7,8,9,10-Hexahydro-6,6,9-trimethyl-8-pivaloyloxy-2-(*p*-toluenesulfonyl)-9-vinylnaphth[1,2,3-*cd*]indole (21) $BF_3 \cdot OEt_2$ (0.45 ml, 3.66 mmol) was added to a stirred solution of **18** (400 mg, 0.729 mmol) in CH_2Cl_2 (7.3 ml) at 0 °C and the mixture was stirred at the same temperature for 24 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2, and then worked up as usual. Separation by PTLC [hexane–EtOAc (15 : 1)] afforded **21** (254 mg, 66%), **22** (13 mg, 4%) and recovered **18** (39 mg, 10%) in order of increasing polarity. **21**: Colorless glass. HRMS Calcd for $C_{32}H_{37}NO_4S$: 531.2441. Found: 531.2463. MS *m/z*: 531 (M^+, 10), 516 (33), 429 (74), 414 (100), 274 (22), 155 (15), 91 (72), 57 (90). $[\alpha]_D^{24}$ −2.0° (*c*=1.02, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1717, 1637. ^{1}H-NMR δ: 1.11 (3H, s), 1.17 (9H, s), 1.33 (6H, s), 2.30 (3H, s), 2.35—2.60 (4H, m), 4.81—5.02 (1H, m), 4.97 (1H, d, *J*=10 Hz), 4.98 (1H, d, *J*=17 Hz), 5.77 (1H, dd, *J*=17, 10 Hz), 7.07 (1H, d, *J*=7.5 Hz), 7.11 (1H, s), 7.17 and 7.78 (A_2B_2, *J*=8 Hz), 7.25 (1H, dd, *J*=7.5, 7.5 Hz), 7.63 (1H, d, *J*=7.5 Hz). **22**: Colorless prisms, mp 217.5—219 °C (MeOH–H_2O). *Anal.* Calcd for $C_{32}H_{37}NO_4S$: C, 72.29; H, 7.01; N, 2.63. Found: C, 71.96; H, 6.91; N, 2.61. HRMS Calcd for $C_{32}H_{37}NO_4S$: 531.2441. Found: 531.2412. MS *m/z*: 531 (M^+, 5), 516 (4), 429 (100), 414 (20), 274 (19), 259 (18), 244 (20), 155 (9), 91 (31), 57 (61). $[\alpha]_D^{23}$ −48.7° (*c*=0.407, $CHCl_3$). IR (KBr) cm^{-1}: 1728, 1638. ^{1}H-NMR δ: 1.17 (12H, s), 1.32 (6H, s), 2.03—2.08 (4H, m), 2.28 (3H, s), 4.93—5.03 (1H, m), 4.97 (1H, d, *J*=10.5 Hz), 5.03 (1H, d, *J*=17 Hz), 5.80 (1H, dd, *J*=17, 10.5 Hz), 6.72 (1H, d, *J*=4 Hz), 7.13 (1H, d, *J*=8 Hz), 7.17 and 7.75 (A_2B_2, *J*=8 Hz), 7.58 (1H, d, *J*=4 Hz), 7.88 (1H, d, *J*=8 Hz).

[8*R*-(8β,9α,10β)]- and [8*R*-(8β,9α,10α)]-10-Azido-2,6,7,8,9,10-hexahydro-6,6,9-trimethyl-8-pivaloyloxy-2-(*p*-toluenesulfonyl)-9-vinylnaphth-[1,2,3-*cd*]indoles (23 and 24) A solution of **21** (106 mg, 0.200 mmol) in CCl_4 (5 ml) was refluxed with NBS (40 mg, 0.225 mmol) and benzoyl peroxide (17 mg, 0.070 mmol) for 15 min. It was then cooled in an ice bath, saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up gave a residue (155 mg). A DMF solution (3 ml) of this was stirred with NaN_3 (195 mg, 3.00 mmol) at room temperature for 3.5 h. H_2O was added and the whole was extracted with Et_2O, and then worked up as usual. Separation by PTLC [hexane–EtOAc (20 : 1)] afforded **23** (45 mg, 39%) and **24** (45 mg, 39%) in order of decreasing polarity. **23**: Colorless glass. HRMS Calcd for $C_{32}H_{36}N_4O_4S$: 572.2455. Found: 572.2461. MS *m/z*: 572 (M^+, 0.5), 557 (2), 544 (3), 529 (20), 470 (14), 442 (45), 273 (17), 155 (13), 91 (76), 57 (100). $[\alpha]_D^{23}$ −98.9° (*c*=1.05, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2115, 1725, 1640. ^{1}H-NMR (400 MHz) δ: 1.21 (9H, s), 1.28 (3H, s), 1.38 (3H, s), 1.41 (3H, s), 2.34 (3H, s), 2.49 (1H, dd, *J*=18.5, 4.5 Hz), 2.65 (1H, dd, *J*=18.5, 4.5 Hz), 4.13 (1H, s), 5.03 (1H, dd, *J*=4.5, 4.5 Hz), 5.16 (1H, d, *J*=11 Hz), 5.19 (1H, d, *J*=17.5 Hz), 5.75 (1H, dd, *J*=17.5, 11 Hz), 7.14 (1H, d, *J*=7.5 Hz), 7.23 and 7.80 (A_2B_2, *J*=8 Hz), 7.34 (1H, dd, *J*=8, 7.5 Hz), 7.43 (1H, s), 7.69 (1H, d, *J*=8 Hz). **24**: Colorless glass. HRMS Calcd for $C_{32}H_{36}N_4O_4S$: 572.2455. Found: 572.2478. MS *m/z*: 572 (M^+, 2), 557 (3), 544 (4), 529 (22), 470 (8), 442 (11), 427 (35), 273 (19), 155 (11), 91 (61), 57 (100). $[\alpha]_D^{24}$ +48.8° (*c*=1.21, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2100, 1722, 1640. ^{1}H-NMR (400 MHz) δ: 1.17 (3H, s), 1.18 (9H, s), 1.45 (6H, s), 2.28 (1H, dd, *J*=18, 9 Hz), 2.34 (3H, s), 2.87 (1H, dd, *J*=18, 6 Hz), 4.02 (1H, s), 5.22 (1H, dd, *J*=9, 6 Hz), 5.27 (1H, dd, *J*=17.5, 1 Hz), 5.31 (1H, dd, *J*=11, 1 Hz), 6.08 (1H, dd, *J*=17.5, 11 Hz), 7.14 (1H, d, *J*=7.5 Hz), 7.22 and 7.80 (A_2B_2, *J*=8 Hz), 7.32 (1H, s), 7.34 (1H, dd, *J*=8, 7.5 Hz), 7.69 (1H, d, *J*=8 Hz).

[8*R*-(8β,9α,10α)]-10-Azido-2,6,7,8,9,10-hexahydro-8-hydroxy-6,6,9-trimethyl-2-(*p*-toluenesulfonyl)-9-vinylnaphth[1,2,3-*cd*]indole (25) A solution of **24** (108 mg, 0.189 mmol) in toluene (3 ml) was cooled to −78 °C and 1.5 M DIBAL-H in toluene (0.33 ml, 0.495 mmol) was added to it. The mixture was stirred for 10 min at the same temperature, MeOH was added and the whole was gradually warmed up to room temperature. It was filtered through a Celite bed and the Celite was washed with EtOAc. Usual work-up of the combined organic layer gave a residue (113 mg). To a THF solution (2 ml) of this, 1 N HCl (0.6 ml) was added and the mixture was stirred at room temperature for 5 min, and then poured into saturated NH_4Cl–H_2O. The whole was extracted with EtOAc and worked up as usual. Purification by PTLC [hexane–EtOAc (3 : 1)] afforded **25** (89 mg, 97%) as a colorless syrup. HRMS Calcd for $C_{27}H_{28}N_4O_3S$: 488.1880. Found: 488.1907. MS *m/z*: 488 (M^+, 13), 473 (35), 445 (28), 442 (30), 427 (55), 287 (44), 271 (58), 155 (16), 91 (100). $[\alpha]_D^{24}$ +41.7° (*c*=0.895, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2100, 1637. ^{1}H-NMR δ: 1.05 (3H, s), 1.43 (3H, s), 1.45 (3H, s), 1.78 (1H, br s, OH), 2.22 (1H, dd, *J*=18, 10 Hz), 2.28 (3H, s), 2.87 (1H, dd, *J*=18, 6 Hz), 4.00 (1H, s), 4.03 (1H, dd, *J*=10, 6 Hz), 5.32 (1H, dd, *J*=17, 1 Hz), 5.52 (1H, dd, *J*=10.5, 1 Hz), 6.22 (1H, dd, *J*=17, 10.5 Hz), 7.10 (1H, d, *J*=7.5 Hz), 7.13 and 7.75 (A_2B_2, *J*=8 Hz), 7.23 (1H, s), 7.31 (1H, dd, *J*=7.5, 7.5 Hz), 7.67 (1H, d, *J*=7.5 Hz).

[8*R*-(8β,9α,10α)]-10-Formamido-2,6,7,8,9,10-hexahydro-8-hydroxy-6,6,9-trimethyl-2-(*p*-toluenesulfonyl)-9-vinylnaphth[1,2,3-*cd*]indole (26) An MeOH solution (1 ml) of **25** (20 mg, 0.041 mmol), 1,3-propanedithiol (83 μl, 0.83 mmol) and Et_3N (170 μl, 1.22 mmol) was refluxed with stirring for 5 h. After cooling, the mixture was poured into H_2O and the whole was extracted with CH_2Cl_2. Usual work-up gave a residue (40 mg). AcOCHO (0.3 ml) was added to a cooled (−20 °C) solution of the residue (40 mg) in CH_2Cl_2 (1.8 ml) and pyridine (0.6 ml), and the mixture was stirred at −20—0 °C for 5 h. It was poured into 2% HCl–H_2O and the

whole was extracted with CH_2Cl_2, and then worked up as usual to afford a residue (43 mg). This in a mixture of CH_2Cl_2 (0.5 ml) and MeOH (0.5 ml) was stirred with K_2CO_3 (19 mg, 0.072 mmol) at room temperature for 10 min. Saturated NH_4Cl–H_2O was added and the mixture was extracted with CH_2Cl_2, and then worked up as usual. Purification by PTLC [hexane–EtOAc (2 : 3)] gave **26** (17.5 mg, 87%) as a colorless syrup. HRMS Calcd for $C_{28}H_{30}N_2O_4S$: 490.1925. Found: 490.1896. MS *m/z*: 490 (M^+, 28), 475 (100), 445 (18), 430 (50), 321 (27), 275 (14), 155 (17), 91 (99). IR ($CHCl_3$) cm^{-1}: 1695. ^{1}H-NMR δ: 1.03 (3H, s), 1.40 (3H, s), 1.43 (3H, s), 2.23 (1H, dd, J=18.5, 9 Hz), 2.28 (3H, s), 2.83 (1H, dd, J=18.5, 6 Hz), 3.92 (1H, dd, J=9, 6 Hz), 4.88 (1H, d, J=10.5 Hz), 5.23 (1H, d, J=18 Hz), 5.28 (1H, d, J=12 Hz), 5.82 (1H, br d, J=10.5 Hz, NH), 5.90 (1H, dd, J=18, 12 Hz), 7.05 (1H, d, J=7.5 Hz), 7.13 and 7.73 (A_2B_2, J=8 Hz), 7.15 (1H, s), 7.27 (1H, dd, J=7.5, 7.5 Hz), 7.63 (1H, d, J=7.5 Hz), 8.16 (1H, br s).

(8*S*,12*R*,13*R*)-6,7,8,12-Tetrahydro-6,6,13-trimethyl-2-(*p*-toluenesulfonyl)-13-vinyl-8,12-methano-2*H*-indolo[4,3-*ij*][4,2]benzoxazocine (27) $SOCl_2$ (34 μl, 0.466 mmol) was added to a solution of **26** (33 mg, 0.057 mmol) in toluene (3 ml) and the mixture was stirred at 50 °C for 1 h. After cooling, the mixture was poured into saturated $NaHCO_3$–H_2O and the whole was extracted with EtOAc. Usual work-up followed by purification by PTLC [hexane–EtOAc (3 : 1)] afforded **27** (28 mg, 88%) as a colorless syrup. HRMS Calcd for $C_{28}H_{28}N_2O_3S$: 472.1819. Found: 472.1815. MS *m/z*: 472 (M^+, 16), 457 (100), 303 (9), 258 (18), 155 (9), 91 (55). IR ($CHCl_3$) cm^{-1}: 1645. ^{1}H-NMR δ: 1.03 (3H, s), 1.38 (3H, s), 1.43 (3H, s), 2.28 (3H, s), *ca.* 2.60—3.00 (2H, m), 4.06 (1H, d, J=3 Hz), 4.58 (1H, ddd, J=3, 3, 3 Hz), 5.17 (1H, d, J=10.5 Hz), 5.28 (1H, d, J=17 Hz), 5.92 (1H, dd, J=17, 10.5 Hz), 6.88 (1H, s), 7.03 (1H, d, J=8 Hz), 7.12 and 7.82 (A_2B_2, J=8 Hz), 7.28 (1H, dd, J=8, 8 Hz), 7.48 (1H, s), 7.68 (1H, d, J=8 Hz).

[8*R*-(8β,9α,10α)]-10-Azido-2,6,7,8,9,10-hexahydro-6,6,9-trimethyl-2-(*p*-toluenesulfonyl)-8-[(2-trimethylsilyl)ethoxy]methoxy-9-vinylnaphth-[1,2,3-*cd*]indole (28a) A solution of **25** (57 mg, 0.117 mmol), SEMCl (109 μl, 0.617 mmol), iso-Pr_2NEt (122 μl, 0.702 mmol), and 4-dimethylaminopyridine (14 mg, 0.115 mmol) in 1,2-dichloroethane (1 ml) was stirred at 50 °C for 12 h. It was then cooled, saturated $CuSO_4$–H_2O was added and the whole was extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$–H_2O and worked up as usual. Purification by PTLC [hexane–EtOAc (15 : 1)] gave **28a** (69 mg, 96%) as a colorless syrup. MS *m/z*: 618 (M^+, 2), 603 (7), 590 (3), 575 (24), 427 (12), 155 (42), 91 (68), 75 (46), 73 (100). IR ($CHCl_3$) cm^{-1}: 2100. ^{1}H-NMR δ: 0.03 (9H, s), 0.90 (2H, t, J=8 Hz), 1.10 (3H, s), 1.40 (6H, s), 2.25 (3H, s), 2.25 (1H, dd, J=18, 9 Hz), 2.83 (1H, dd, J=18, 6 Hz), 3.58 (2H, t, J=8 Hz), 3.88 (1H, dd, J=9, 6 Hz), 3.90 (1H, s), 4.56 (1H, d, J=6 Hz), 4.72 (1H, d, J=6 Hz), 5.17 (1H, d, J=18 Hz), 5.20 (1H, d, J=10.5 Hz), 6.08 (1H, dd, J=18, 10.5 Hz), 7.00 (1H, d, J=8 Hz), 7.07 and 7.67 (A_2B_2, J=8 Hz), 7.15 (1H, s), 7.22 (1H, dd, J=8, 8 Hz), 7.57 (1H, d, J=8 Hz).

[8*R*-(8β,9α,10α)]-10-Azido-8-[1-(ξ)-(ethoxy)ethoxy]-2,6,7,8,9,10-hexahydro-6,6,9-trimethyl-2-(*p*-toluenesulfonyl)-9-vinylnaphth[1,2,3-*cd*]-indole (28b) Pyridinium *p*-toluenesulfonate (3 mg, 0.01 mmol) was added to a solution of **25** (54 mg, 0.111 mmol) and ethyl vinyl ether (106 μl, 1.11 mmol) in CH_2Cl_2 (2 ml), and the mixture was stirred at room temperature for 10 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2 and then worked up as usual. Purification by PTLC [hexane–EtOAc (12 : 1)] afforded **28b** (59 mg, 95%) as a colorless syrup. HRMS Calcd for $C_{31}H_{36}N_4O_4S$: 560.2455. Found: 560.2427. MS *m/z*: 560 (M^+, 5), 545 (9), 517 (11), 445 (9), 427 (6), 273 (7), 155 (7), 91 (34), 73 (88), 45 (100). IR ($CHCl_3$) cm^{-1}: 2100. ^{1}H-NMR of two diastereomers δ: 1.08 and 1.12 (total 3H, s each), 1.20 (3H, t, J=7 Hz), 1.26 and 1.32 (total 3H, d each, J=5 Hz), 1.43 (6H, s), 2.10—2.55 (1H, m), 2.30 (3H, s), 2.82 and 2.88 (total 1H, dd each, J=18, 6 Hz), 3.57 (2H, q, J=7 Hz), 3.90 and 4.00 (total 1H, dd each, J=9, 6 Hz), 3.97 (1H, s), 4.72 and 4.83 (total 1H, q each, J=5 Hz), 5.23 (1H, d, J=18 Hz), 5.28 (1H, d, J=10.5 Hz), 6.18 (1H, dd, J=18, 10.5 Hz), 7.12 (1H, d, J=7.5 Hz), 7.18 and 7.77 (A_2B_2, J=8 Hz), 7.26—7.27 (1H, m), 7.32 (1H, dd, J=7.5, 7.5 Hz), 7.67 (1H, d, J=7.5 Hz).

***O*-[(2-Trimethylsilyl)ethoxy]methylhapalindole O (29a)** $LiAlH_4$ (61 mg, 1.61 mmol) was added to a cooled (0 °C) solution of **28a** (40 mg, 0.065 mmol) in THF (8.5 ml) and the mixture was stirred at 0 °C for 8 h. Excess $LiAlH_4$ was gradually decomposed by addition of H_2O-saturated Et_2O and then of H_2O itself with vigorous stirring at room temperature. The whole was filtered through a Celite bed and the Celite was washed with Et_2O. The organic layer was worked up as usual to leave a residue (42 mg), which was dissolved in CH_2Cl_2 (2 ml) and the solution was cooled to 0 °C. Thiocarbonyldiimidazole (90% purity, 19 mg, 0.096 mmol) was added to this and the mixture was stirred at 0 °C—room temperature for 12 h. The solvent was evaporated *in vacuo* and the residue was separated by PTLC [hexane–EtOAc (12 : 1)] to afford **29a** (15 mg, 48%) and **30a** (2 mg, 6%) in order of decreasing polarity. **29a**: Colorless syrup. HRMS Calcd for $C_{27}H_{38}N_2O_2SSi$: 482.2421. Found: 482.2434. MS *m/z*: 482 (M^+, 40), 234 (15), 182 (16), 168 (29), 73 (100). IR ($CHCl_3$) cm^{-1}: 2150, 2070. ^{1}H-NMR δ: 0.00 (9H, s), 0.73 (3H, s), 0.90—1.10 (2H, m), 1.18 (3H, s), 1.47 (3H, s), 1.78—2.30 (2H, m), 3.30—3.57 (2H, m), 3.60—3.80 (1H, m), 3.78 (1H, dd, J=13, 4 Hz), 4.33 (1H, d, J=2 Hz), 4.42 (1H, d, J=7 Hz), 4.57 (1H, d, J=7 Hz), 5.05 (1H, d, J=17 Hz), 5.17 (1H, d, J=11 Hz), 6.00 (1H, dd, J=17, 11 Hz), 6.68—6.77 (1H, m), 6.76—6.97 (1H, m), 6.97—7.12 (2H, m), 7.88 (1H, br s, NH). **30a**: Colorless syrup. HRMS Calcd for $C_{27}H_{36}N_2O_2SSi$: 480.2265. Found: 480.2277. MS *m/z*: 480 (M^+, 12), 465 (15), 406 (13), 347 (16), 317 (14), 260 (25), 258 (21), 73 (100). IR ($CHCl_3$) cm^{-1}: 2150, 2075. ^{1}H-NMR δ: 0.93 (2H, t, J=8 Hz), 1.13 (3H, s), 1.47 (6H, s), 3.63 (2H, t, J=8 Hz), 3.93 (1H, dd, J=8, 6 Hz), 4.58 (1H, s), 4.68 (1H, d, J=6 Hz), 4.80 (1H, d, J=6 Hz), 5.27 (1H, d, J=18 Hz), 5.31 (1H, d, J=10 Hz), 6.13 (1H, dd, J=18, 10 Hz), 6.90—7.37 (4H, m), 7.88 (1H, br s, NH).

***O*-[1-(ξ)-Ethoxy]ethylhapalindole O (29b)** In the same manner as above, **28b** (33 mg, 0.059 mmol) was reduced with $LiAlH_4$ (56 mg, 1.47 mmol) and the resulting residue (34 mg) was stirred with 90% thiocarbonyldiimidazole (18 mg, 0.091 mmol) in CH_2Cl_2 (1 ml) at 0 °C for 12 h. The same work-up as above and separation by PTLC [hexane–EtOAc (10 : 1)] afforded **29b** (12.5 mg, 50%) and **30b** (4 mg, 16%) in order of decreasing polarity. **29b**: Colorless syrup. HRMS Calcd for $C_{25}H_{32}N_2O_2S$: 424.2183. Found: 424.2155. MS *m/z*: 424 (M^+, 27), 293 (5), 234 (8), 168 (14), 73 (100), 45 (68). IR ($CHCl_3$) cm^{-1}: 2155, 2070. ^{1}H-NMR of two diastereomers δ: 0.73 and 0.76 (total 3H, s each), 1.07—1.28 (10H, m), 1.53 (3H, s), 1.78—2.35 (2H, m), 3.27—3.60 (2H, m), 3.72—3.87 (1H, m), 3.73 and 3.88 (total 1H, dd each, J=11, 4 Hz), 4.40 (1H, d, J=2 Hz), 4.65 and 4.73 (total 1H, q each, J=5 Hz), 5.12 and 5.18 (total 1H, d each, J=17 Hz), 5.22 (1H, d, J=11 Hz), 6.08 and 6.15 (total 1H, dd each, J=17, 11 Hz), 6.75—6.83 (1H, m), 6.80—7.05 (1H, m), 7.08—7.18 (2H, m), 8.03 (1H, br s, NH). **30b**: Colorless syrup. HRMS Calcd for $C_{25}H_{30}N_2O_2S$: 422.2026. Found: 422.2036. MS *m/z*: 422 (M^+, 12), 407 (11), 361 (5), 332 (5), 317 (14), 276 (16), 73 (100), 45 (71). IR ($CHCl_3$) cm^{-1}: 2150, 2080. ^{1}H-NMR of two diastereomers δ: 1.13—1.38 (9H, m), 1.48 (6H, s), 2.40—3.00 (2H, m), 3.42—3.72 (2H, m), 3.87 and 3.92 (total 1H, dd each, J=10, 7 Hz), 4.53 and 4.58 (total 1H, s each), 4.73 and 4.83 (total 1H, q each, J=5 Hz), 5.15—5.47 (2H, m), 6.12 (1H, dd, J=18, 10.5 Hz), 6.92—7.30 (4H, m), 7.88 (1H, br s, NH).

Hapalindole O (1) Acetic acid (0.1 ml) was added to a solution of **29b** (8 mg, 0.019 mmol) in MeOH (0.9 ml) and H_2O (0.3 ml) and the mixture was stirred at room temperature for 6 h. It was then poured into saturated $NaHCO_3$–H_2O and the whole was extracted with CH_2Cl_2. Usual work-up followed by purification by PTLC [hexane–EtOAc (1 : 2)] afforded **1** (6.5 mg, 98%) as a colorless syrup. HRMS Calcd for $C_{21}H_{24}N_2OS$: 352.1608. Found: 352.1602. MS *m/z*: 352 (M^+, 100), 337 (96), 196 (17), 182 (26), 168 (77). $[\alpha]_D^{24}$ −160° (*c*=0.506, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3490, 2155, 2075, 1440. ^{1}H-NMR (400 MHz) δ: 0.75 (3H, s), 1.13 (1H, ddd, J=13, 13, 11.5 Hz), 1.22 (3H, s), 1.38 (1H, br s, OH), 1.56 (3H, s), 1.92 (1H, dddd, J=13, 4.5, 4, 1 Hz), 2.22 (1H, ddd, J=13, 4.5, 4 Hz), 3.84—3.97 (1H, m), 4.00 (1H, dd, J=11.5, 4.5 Hz), 4.46 (1H, d, J=2 Hz), 5.37 (1H, dd, J=17.5, 0.5 Hz), 5.47 (1H, dd, J=11, 0.5 Hz), 6.09 (1H, dd, J=17.5, 11 Hz), 6.86 (1H, dd, J=2, 2 Hz), 6.94—6.99 (1H, m), 7.16—7.20 (2H, m), 8.03 (1H, br s, NH). ^{13}C-NMR (100 MHz) δ: 17.7 (q), 24.5 (q), 28.1 (t), 32.0 (q), 37.7 (d), 38.0 (s), 44.1 (d), 46.0 (s), 66.1 (d), 71.3 (d), 108.4 (d), 111.4 (s), 113.9 (d), 116.6 (t), 118.5 (d), 123.5 (d), 124.0 (s), 131.8 (s), 133.5 (s), 138.3 (s), 143.4 (d).

Acknowledgment We wish to thank Professor R. E. Moore, University of Hawaii, for his generous gift of the spectral data of hapalindole O. The authors' thanks are due to the Research Laboratories, Shionogi & Co., Ltd., for elemental analysis. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture.

References and Notes

1) Part 11: H. Muratake, A. Mikawa, T. Seino, M. Natsume, *Chem. Pharm. Bull.*, **42**, 854 (1994).

2) *a*) H. Muratake, M. Natsume, *Tetrahedron Lett.*, **30**, 1815 (1989); *b*) *Idem*, *Tetrahedron*, **46**, 6331 (1990); *c*) *Idem*, *ibid.*, **46**, 6343 (1990); *d*) H. Muratake, H. Kumagami, M. Natsume, *ibid.*, **46**, 6351 (1990).
3) R. E. Moore, C. Cheuk, X.-Q. G. Yang, G. M. L. Patterson, R. Bonjouklian, T. A. Smitka, J. S. Mynderse, R. S. Foster, N. D. Jones, J. K. Swartzendruber, J. B. Deeter, *J. Org. Chem.*, **52**, 1036 (1987).
4) R. E. Moore, X.-Q. G. Yang, G. M. L. Patterson, R. Bonjouklian, T. A. Smitka, *Phytochemistry*, **28**, 1565 (1989).
5) R. E. Schwartz, C. F. Hirsch, J. P. Springer, D. J. Pettibone, D. L. Zink, *J. Org. Chem.*, **52**, 3704 (1987).
6) T. A. Smitka, R. Bonjouklian, L. Doolin, N. D. Jones, J. B. Deeter, W. Y. Yoshida, M. R. Prinsep, R. E. Moore, G. M. L. Patterson, *J. Org. Chem.*, **57**, 857 (1992).
7) A. Park, R. E. Moore, G. M. L. Patterson, *Tetrahedron Lett.*, **33**, 3257 (1992).
8) V. Vaillancourt, K. F. Albizati, *J. Am. Chem. Soc.*, **115**, 3499 (1993).
9) M. Fuji, H. Muratake, M. Natsume, *Chem. Pharm. Bull.*, **40**, 2338 (1992).
10) R. Grandi, U. M. Pagnoni, R. Trave, L. Garanti, *Tetrahedron*, **30**, 4037 (1974).
11) L. Garver, P. van Eikeren, J. E. Byrd, *J. Org. Chem.*, **41**, 2773 (1976).
12) W. G. Salmond, M. A. Barta, J. L. Havens, *J. Org. Chem.*, **43**, 2057 (1978).
13) E. J. Corey, A. W. Gross, *Tetrahedron Lett.*, **25**, 495 (1984).
14) H. Bayley, D. N. Standring, J. R. Knowles, *Tetrahedron Lett.*, **1978**, 3633.