Tetrahedron Vol. 46, No. 18, pp. 6331-6342, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

SYNTHETIC STUDIES OF MARINE ALKALOIDS HAPALINDOLES. Part 1. TOTAL SYNTHESIS OF (±)-HAPALINDOLES J and M

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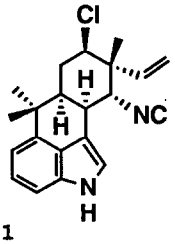
(*Received in Japan* 4 *June* 1990)

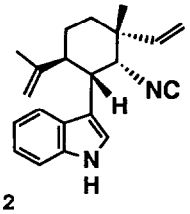
Abstract — The first concise synthesis of marine indole alkaloids (±)-hapalindoles J (**4**) and M (**5**) was achieved in seven or six steps starting from a readily available compound **6** using important key reactions, **6** → **7** → **8** and **35** → **41** or **5**.

Hapalindoles are antibacterial, antimycotic, and antialgal indole alkaloids, isolated from the blue-green alga *Hapalosiphon fontinalis* (Ag.) Bornet (Stigonemataceae).[1,2] They can be devided into two classes depending upon their chemical structures. About fifteen alkaloids have a hitherto unknown tetracyclic frame-work of 2,6,6a,7,8,9,10,10a-octahydronaphth[1,2,3-*cd*]indole, and hapalindoles A (**1**) is a representative of this class of compounds. Five alkaloids such as hapalindole C (**2**) form another class and have structures of typically substituted 3-cyclohexylindoles. These are constructed from tryptamine and two parts of isoprene and correspond to the biogenetic precursors for the tetracyclic alkaloids. This process in nature was traced chemically by treating this class of compounds with an acid to yield the tetracyclic compounds.[3] In either class there are chlorine-containing and non-chlorine-containing alkaloids. Almost at the same time, hapalindolinone A (**3**) has been isolated from the cells of a cultured cyanobacterium belonging to the genus *Fischerella* (ATCC 53558) as an inhibitor of arginine vasopressin binding.[4]

Among these indole derivatives, we selected the tetracyclic non-chlorine-containing hapalindoles for synthesis study, and here we describe the details of our successful synthesis of (±)-hapalindoles J (**4**) and M (**5**).[5] This is the only report of the total synthesis, which was based on three major fundamental reactions (Chart 1): (i) a carbon-carbon bond-forming reaction between the cyclohexanone derivatives and a highly substituted one carbon unit at the 4 position of indole (**6** → **7**); (ii) an unprecedented intramolecular cyclization of 1-tosyl-4-substituted indoles having the ketone group at an appropriate positon (**7** → **8**); and (iii) an extremely unusual and stereoselective lithium aluminum hydride reduction of the electron-rich tetrasubstituted double bond conjugated with the indole nucleus, which is involved in steps **8** → **9**.



1
Hapalindole A



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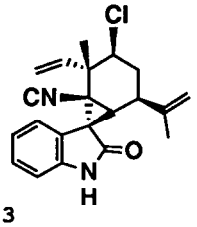
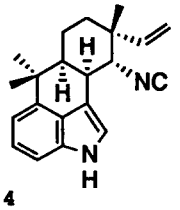
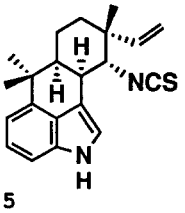
Hapalindole C



3
Hapalindolinone A



4
Hapalindole J



5
Hapalindole M

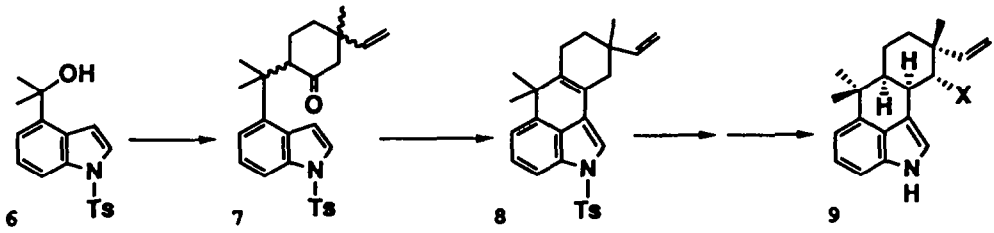


Chart 1

Preliminary Experiments

Our synthesis was initiated by an effort to produce a compound having a substituent of the quaternary carbon center at the 4 position of the indole nucleus. This was the tin (IV) chloride-mediated reaction of the tertiary alcohols (**10**) of the benzyl alcoholic type with trimethylsilyl vinyl ethers (**11**) to yield α-alkylated ketones (**12**) with the tertiary groups (Chart 2). Similar reactions have been reported previously in condensations of the tertiary alkyl halides with trimethylsilyl vinyl ethers in the presence of titanium (IV) chloride.[6,7,8] Our method has synthesis value in that the tertiary alcohols are generally much more readily obtainable than the corresponding halides.

The reaction was carried out by adding 1.5–3 molar equivalents of tin (IV) chloride to a mixture of **10** (one molar equivalent) and **11** (2–3 molar equivalents) in dichloromethane at −75 to 0°C (Chart 2 and Table 1). Then quenching after 10–15 min afforded products **12** and **13** in 69–96% yields (Table 1, Runs 1 — 5). The nucleophiles were extended to allyltrimethylsilane (**15**) and trimethylsilyl cyanide (**16**), and the reaction with 1-phenylcyclohexanol[9]

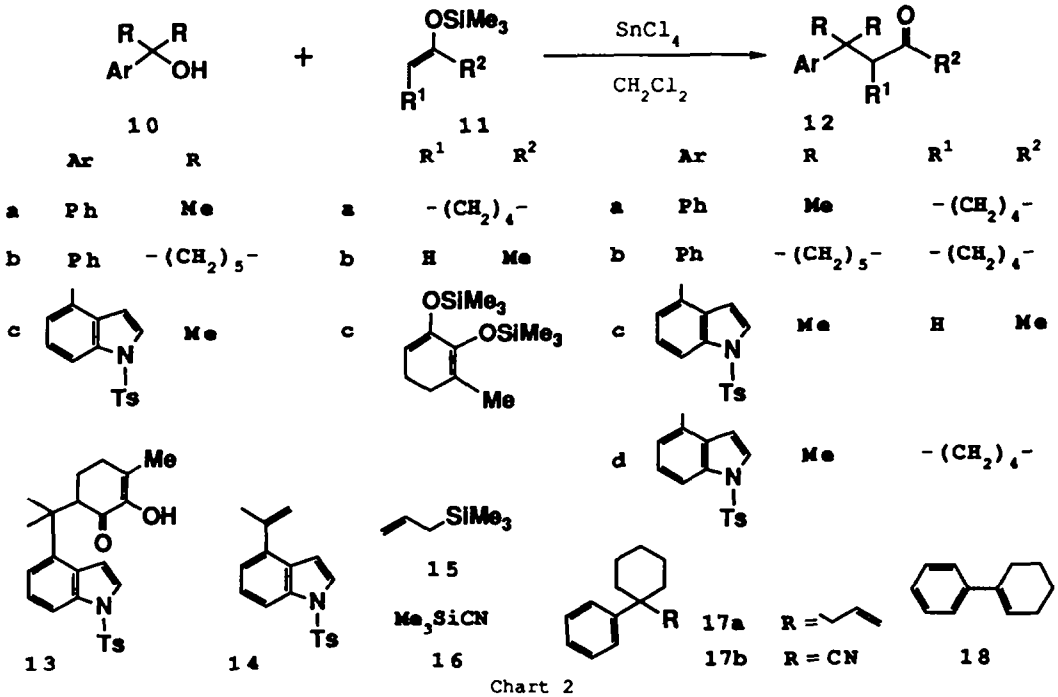


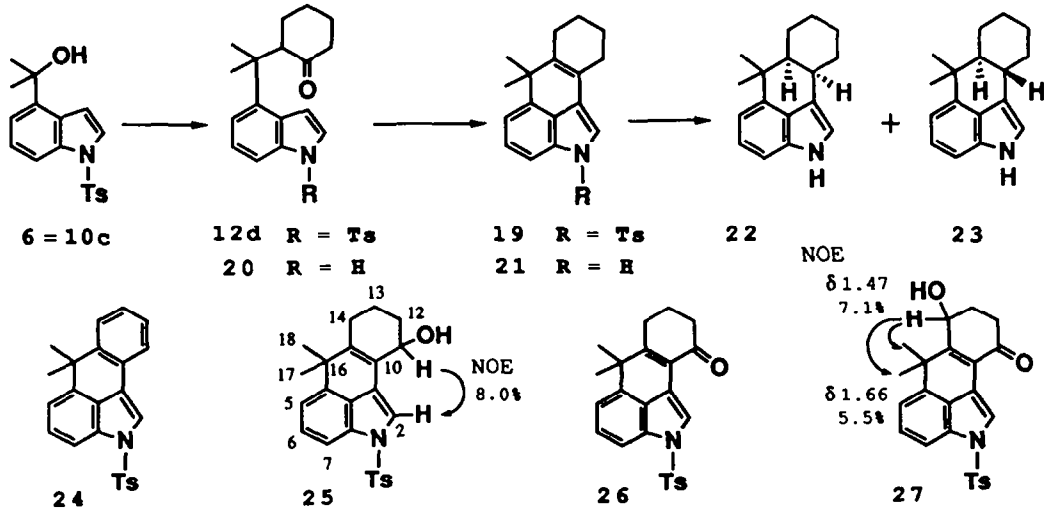
Chart 2

Table 1

Run	Tertiary Alcohol	Nucleophile (equiv.)	$SnCl_4$ equiv.	Teperature °C	Time min	Product	(% Yield)		
1	**10a**	**11a** (3)	1.5	-68	10	**12a**	(96)		
2	**10b**	**11a** (3)	1.5	0	10	**12b**	(95)		
3	**10c-6**	**11b** (2.2)	3	0	10	**12c**	(96)		
4	**10c-6**	**11a** (2)	2	-65	10	**12d**	(95)		
5	**10c-6**	**11c** (3)	3	-75	15	**13**	(69)	**14**	(8)
6	**10b**	**15** (3)	1.5	-71	10	**17a**	(91)		
7	**10b**	**16** (3)	1.5	0	10	**17b**	(91)	**18**	(6)

(**10b**) afforded **17a** and **17b** in 91% yield each (Runs 6 and 7). The unsaturated compounds **14** and **18**[10] were sometimes obtained as the recovery of the starting tertiary alcohols, probably due to poor reactivity of the nucleophiles (Runs 5 and 7).

When the reaction between **10c** and **11a** was carried out at about 0°C, a certain amount of a new product **19** was produced in the impure state in addition to **12d** (Chart 3). This implied that the ketone group of **12d** behaved as an electrophile in the presence of tin (IV) chloride and attacked intramolecularly the 3 position of the 1-tosylindole nucleus to afford the unexpected cyclized compound. Originally we planned a sequence of steps **12d** → **20** → **21** → **22** and **23** for the framework of hapalindole alkaloids, and in fact these steps were readily



6 = **10c** **12d** R = Ts **19** R = Ts **22** **23**
20 R = H **21** R = H

24 **25** **26** **27**

Chart 3

realized as follows. Removal of the tosyl group from **12d** was carried out in 93% yield by treating with magnesium in methanol[11] and the resulting **20** was cyclized to the tetracyclic compound **21** by reaction with the Lawesson's reagent[12] in refuxing tetrahydrofuran in 77% yield. The very unstable compound **21** was then reduced with sodium cyanoborohydride in acidic methanol to give **22** and **23** in 44% yield each, whose assignment as cis and trans compounds was obtained from the half height width ($W_{1/2}$= 10 and 22 Hz) of the H-10 signals in their proton NMR spectra. However, the unexpected cyclization reaction did really happen even with the electron-withdrawing tosyl group present at the indole nitrogen atom. So the reaction condition for producing the pure **19** in the preparative scale was investigated next. Treatment of **12d** with boron trifluoride etherate in dichloromethane gave the best result and **19** was obtained in 80% yield as a stable crystalline compound. Thus the tetracyclic compound **19** having the same carbon frame-work as hapalindoles was formed in only two steps from the readily accessible compound **6**.

Cleavage of the tosyl group from **19** was possible by reduction with sodium in liquid ammonia to afford **21** in 76% yield, but this was so unstable that the oxidative introduction of the functional groups into the fourth ring of the hapalindole skeleton was studied using the tosylated compound **19**. The selenium dioxide oxidation of **19** in refluxing dioxane afforded a complex mixture of reaction products, and four compounds, **24**, **25**, **26**, and **27** were isolated in 16%, 26%, 19%, and 14% yields, respectively, accompanied by the recovery of **19** in 4% yield. On the other hand, *N*-bromosuccinimide treatment of **19** in the presence of benzoyl peroxide gave a better result, and **24** and **25** were obtained in 15% and 50% yields after the hydrolysis during the silica gel separation. The Swern oxidation[13] of **25** afforded **26** in 84% yield. Structural proof of **25** and **27** was secured by inspection of their proton NMR spectra, where the nuclear Overhauser effect (NOE) was observed as shown in Chart 3 between proton signals of H-2 and H-11 of the hydroxylated compound **25** and those of H-14 and geminal dimethyl groups of the hydroxyketone compound **27**.

The Natural Product Synthesis

3-Methyl-3-vinylcyclohexanone[14] (**28**) was converted to its trimethylsilyl enol ethers **29** and **30** with lithium diisopropylamide and chlorotrimethylsilane, according to the procedure[15] to minimize the formation of the undesired ether **30** (Chart 4). The ratio of **29** and **30** in

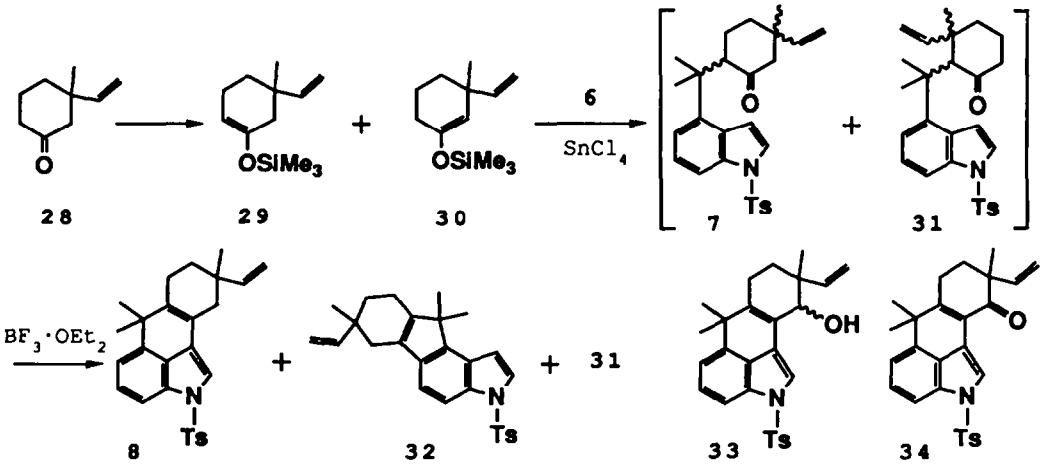


Chart 4

the mixture was determined to be 5:2 by looking at the C-3 methyl proton signals of the NMR spectrum. The mixture was allowed to react with the tertiary alcohol **6** ~ **10c** using tin (IV) chloride as a catalyst in dichloromethane at -78°C for 10 min. A crude reaction mixture containing **7** and **31** was then subjected to treatment with boron trifluoride etherate in dicloromethane at room temperature for 1.5 h. The expected compound **8** was obtained in 57% yield, accompanied by a by-product **32** in 4.5% yield, calculated respectively from **6**, and the impure **31**. The compound **31**, a mixture of the diastereomers, remained uncyclized probably due to the steric congestion around the dimethyl group and the quaternary carbon substituents on the cyclohexanone in the close situation.

For introduction of the functional group at the 11 position, selenium dioxide oxidation of **8** was tried again with a limited amount of the oxidizing agent. Over-oxidation, however, was inevitable and the single hydroxy compound **33** with the unknown stereochemical arrangement and the ketone compound **34** were the only isolable products, in 16% and 11% yields respectively, besides the recovery of **8** in 30% yield. The rest of the products were more polar compounds probably due to the extra oxidation of the vinyl group. Evidence of the oxidation site in **33** and **34** is described in the discussion in the following report.[16]

Compound **8** was brominated with *N*-bromosuccinimide in the presence of benzoyl peroxide in refluxing carbon tetrachloride (Chart 5) and the crude reaction mixture was directly treated with sodium azide in dimethylformamide to replace the highly reactive bromine atom by the stable azide function to give **35** and **36** in 34% and 29% yields, together with the formation of **37** in 7% yield. The structure of by-product **37** was verified by its NMR spectrum including the NOE experiment between H-2 and the vinyl protons as shown in Chart 5. The stereochemistry of the azide group of **35** and **36** remained unknown at this stage but was made clear after completion of the natural product synthesis. Conversion of the configuration of the azide group was partially attained by reduction of **36** with tin (II) chloride in methanol[17] to give a mixture of the solvolysis products **38** and **39**, which was further treated with

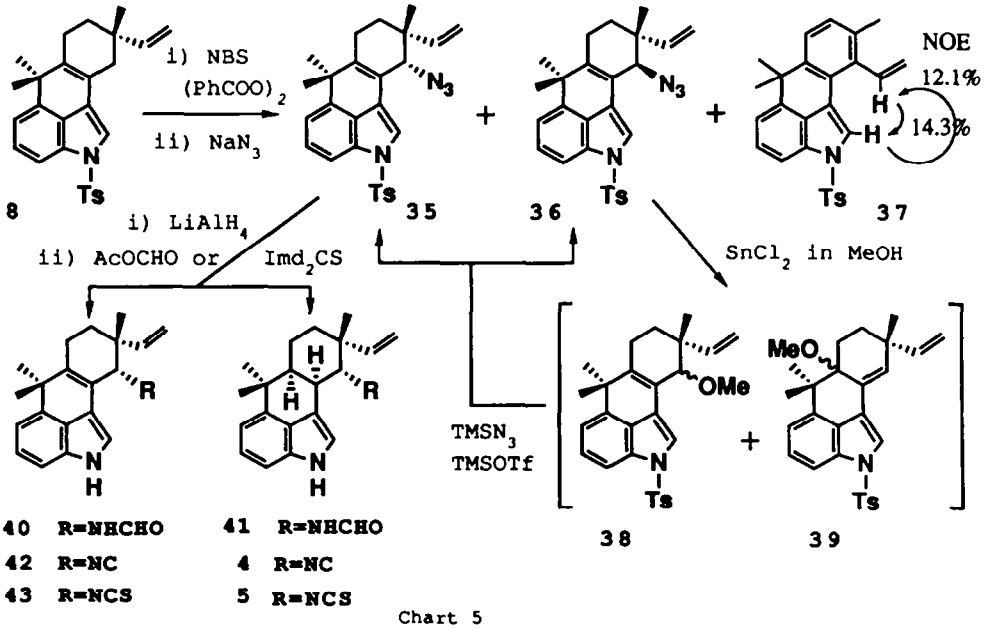


Chart 5

trimethylsilylazide in the presence of trimethylsilyl triflate to recycle to **35** and **36** in 23% and 53% yields. Thus the undesired compound **36** was changed in part to the useful compound **35**.

Our initial intention for the next steps was to remove the tosyl group from **35**, reduce the azide function, formylate the resulting amine to afford the compound **40**, and finally saturate the double bond in **40** with sodium cyanoborohydride in an acidic medium to yield **41** by analogy with the reduction of **21** to give **22** and **23** (Chart 3). To effect the first two reactions together, the tosylated azide compound **35** was treated with lithium aluminum hydride in tetrahydrofuran at room temperature for 15 h and the products were isolated after formylation with acetic formic anhydride and pyridine in dichlormethane. Formation of the expected compound **40** did occur in 23% yield, but a major product **41** obtained in 41% yield was an over-reduction compound of the tetrasubstituted double bond. That was the compound we really wanted. The structure of **41** including the requisite stereochemical arrangement was verified by completing the synthesis of the natural product. Treating **41** with phosphorus oxychloride in pyridine at -20°C afforded (±)-hapalindole J (**4**) in 76% yield. The same isonitrile formation from **40** was also carried out and the compound **42** obtained in 73% yield corresponds to unnatural dechlorohapalindole K. Synthesis of (±)-hapalindole M (**5**) was achieved similarly by reducing **35** with lithium aluminum hydride and this time the reduction mixture was treated with 1,1'-thiocarbonyldiimidazole in dichloromethane[18] to afford **43** and (±)-**5** in 9% and 35% yields. Identity of the synthetic materials with the natural **4** and **5** was confirmed by comparison of their proton NMR and IR spectra. Thus the first total synthesis of hapalindoles J and M was accomplished in seven and six steps from the readily available compound **6**. The assumed reaction mechanism concerning the unusual lithium aluminum hydride reduction of the electron-rich double bond is discussed in the following paper. Without this unexpected reaction, the present synthesis of hapalindoles would not be successful, since the conventional reduction of the compound **40** with sodium cyanoborohydride was found to afford nothing but the starting material, probably due to the enhanced steric congestion, compared to the simpler case of the compound **21**.

EXPERIMENTAL

Melting points were determined on Yanagimoto micro-melting point apparatus and are not corrected. Mass spectra (MS) were taken on Hitachi RMS-4 spectrometer. High resolution mass spectra (HRMS) were measured on JEOL JMS-DX-300 spectrometer. Infrared spectra (IR) were recorded on Hitachi 215 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained on Varian EM 390 spectrometer unless otherwise specified. ^{1}H NMR spectra at 400 MHz and NOE difference spectra were recorded on JEOL JMN GX-400 spectrometer. ^{1}H NMR spectra at 300 MHz were taken on Varian XL-300 spectrometer. ^{13}C NMR spectra were measured on Hitachi R-26 or Varian XL-300 (75 MHz) spectrometer. The carbon numbering for the NMR assignment is depicted in Chart 3. Axial and equatorial hydrogens at the X position are expressed as H-Xa and H-Xe. Coupling constants (J) are shown in Hz. Column chromatography was conducted on silica gel, Fuji Davison BW 200, and preparative thin-layer chromatography (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 the organic layers with water or brine, drying over anhydrous sodium sulfate and evaporating the solvents under reduced pressure.

2-(1-Methyl-1-phenylethyl)cyclohexanone (12a) (A typical example) — $SnCl_4$ (0.16 ml) was added to a cooled (-68°C) CH_2Cl_2 solution (5 ml) of 2-phenyl-2-propanol (**10a**) (123 mg) and 1-(trimethylsilyloxy)cyclohexene (**11a**) (463 mg) with stirring under Ar atmosphere. After 10 min, the mixture was poured into sat. $NaHCO_3$-H_2O and the whole was filtered through a celite

bed. The celite was washed with CH_2Cl_2 and the organic layers were combined. Usual work-up and PTLC [hexane–EtOAc (29:1)] afforded **12a** (187 mg, 96%) as colorless syrup. MS *m/z*: 216 (M^+). IR (neat) cm^{-1}: 1711. ^1H NMR ($CDCl_3$) δ: 1.38 (3H, s), 1.44 (3H, s), 1.24-2.39 (8H, m), 2.57-2.86 (1H, m), 6.99-7.45 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 24.1, 26.1, 27.2, 28.5, 30.4, 39.7, 44.3, 60.5, 125.1 (×3), 127.4 (×2), 148.9, 209.2. 2,4-Dinitrophenylhydrazone: Orange needles, mp 167-168°C (MeOH–CH_2Cl_2). Anal. Calcd for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N, 14.14. Found: C, 63.59; H, 6.03; N, 14.18.

2-(1-Phenylcyclohexyl)cyclohexanone (12b) — Colorless syrup. MS *m/z*: 256 (M^+). IR (neat) cm^{-1}: 1710. ^{13}C NMR ($CDCl_3$) δ: 22.5 (×2), 25.2, 26.7, 27.6, 28.7, 32.0, 34.2, 43.9, 44.1, 61.4, 125.0, 127.0 (×2), 128.0 (×2), 142.2, 209.8. 2,4-Dinitrophenylhydrazone: Orange prisms, mp 161-162.5°C (MeOH–CH_2Cl_2). Anal. Calcd for $C_{24}H_{28}N_4O_4$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.76; H, 6.36; N, 12.73.

2-(1-*p*-Toluenesulfonyl-4-indolyl)-2-propanol (6=10c) — To an ice-cooled Et_2O solution (10 ml) of MeMgI prepared from Mg (219 mg) and MeI (0.60 ml) was added dropwise a THF solution (7 ml) of methyl 1-*p*-toluenesulfonyl-4-indolylcarboxylate[11] (597 mg) during 5 min under N_2 atmosphere. After being stirred at 0°C for 10 min and at room temperature for 20 min, the reaction was quenched with sat. NH_4Cl–H_2O and the mixture was extracted with Et_2O. Usual work-up gave crystals, which were purifed by recrystallization from Et_2O and PTLC [hexane–CH_2Cl_2 (1:3)], affording **6** (=10c) (585 mg, 98%) as colorless prisms, mp 108.5-109.5°C. Anal. Calcd for $C_{18}H_{19}NO_3S$: C, 65.63; H, 5.81; N, 4.25. Found: C, 65.37; H, 5.59; N, 4.26. MS *m/z*: 329 (M^+). ^1H NMR ($CDCl_3$) δ: 1.57 (6H, s), 2.04 (1H, br s, OH), 2.23 (3H, s), 6.98-7.25 (5H, m), 7.50 (1H, d, J=4, H-2), 7.70 ($\underline{A}_2B_2$, J=8.5), *ca.* 7.77-7.98 (1H, m, H-7).

4-Methyl-4-(1-*p*-toluenesulfonyl-4-indolyl)-2-pentanone (12c) — Colorless syrup. MS *m/z*: 369 (M^+). IR (neat) cm^{-1}: 1705. ^1H NMR ($CDCl_3$) δ: 1.47 (6H, s), 1.54 (3H, s), 2.23 (3H, s), 2.88 (2H, s), 6.86 (1H, d, J=4.5, H-3), 6.99-7.26 (4H, m), 7.57 (1H, d, J=4.5, H-2), 7.71 ($\underline{A}_2B_2$, J=8.5), 7.87 (1H, d, J=7.5, H-7). ^{13}C NMR ($CDCl_3$) δ: 21.6, 29.0 (×2), 31.4, 38.5, 55.2, 108.8, 111.8, 120.1, 123.9, 125.1, 126.2 (×2), 127.5, 129.1 (×2), 134.6, 135.2, 140.5, 144.0, 205.4.

2-[1-Methyl-1-(1-*p*-toluenesulfonyl-4-indolyl)ethyl]cyclohexanone (12d) — Colorless syrup. MS *m/z*: 409 (M^+). IR ($CHCl_3$) cm^{-1}: 1702. ^1H NMR ($CDCl_3$) δ: 1.21-2.41 (8H, m), 1.48 (3H, s), 1.58 (3H, s), 2.27 (3H, s), 3.01-3.28 (1H, m), 6.87 (1H, d, J=4, H-3), 7.06-7.36 (4H, m), 7.58 (1H, d, J=4, H-2), 7.75 ($\underline{A}_2B_2$, J=8.5), *ca.* 7.75-7.99 (1H, m, H-7). ^{13}C NMR ($CDCl_3$) δ: 21.7, 24.1, 26.1, 26.9, 28.3, 30.4, 41.1, 44.3, 58.2, 108.9, 111.2, 120.6, 123.6, 124.5, 126.2 (×2), 127.0, 129.1 (×2), 135.0 (×2), 142.1, 143.9, 208.9.

3-Methyl-6-[1-methyl-1-(1-*p*-toluenesulfonyl-4-indolyl)ethyl]-1,2-cyclohexanedione (13) — *O,O*-Bis(trimethylsilyl)-3-methyl-4,5-dihydrocatechol (**11c**) was prepared according to the Corey's procedure[15] from 3-methyl-1,2-cyclohexanedione[19] (3 equiv. to **6**) and the crude product was used without further purification. Crude **11c**: Colorless oil. ^1H NMR ($CDCl_3$) δ: 0.20 (9H, s), 0.24 (9H, s), 1.69 (3H, s), 1.96-2.23 (4H, m), 4.68-4.87 (1H, m). **13**: Colorless syrup. HRMS Calcd for $C_{25}H_{27}NO_4S$: 437.166. Found: 437.166. IR ($CHCl_3$) cm^{-1}: 1680, 1640. ^1H NMR ($CDCl_3$) δ: 1.23-1.60 (2H, m), 1.43 (3H, s), 1.67 (3H, s), 1.79 (3H, s), 1.94-2.20 (2H, m), 2.27 (3H, s), 3.16 (1H, dd, J=10.5, 5.5), 6.22 (1H, s, OH), 6.85 (1H, d, J=4, H-3), 7.05-7.37 (4H, m), 7.58 (1H, d, J=4, H-2), 7.74 ($\underline{A}_2B_2$, J=8.5), 7.90 (1H, dd, J=6.5, 2, H-7). **14**: Colorless syrup. MS *m/z*: 311 (M^+). IR ($CHCl_3$) cm^{-1}: 1630. ^1H NMR ($CDCl_3$) δ: 2.12 (3H, s), 2.21 (3H, s), 5.14 (1H, br s), 5.22 (1H, br s), 6.80 (1H, d, J=4, H-3), *ca.* 6.99-7.25 (1H, m, H-5), 7.11 and 7.74 (A_2B_2, J=8.5), 7.25 (1H, dd, J=7.5, 7.5, H-6), 7.56 (1H, d, J=4, H-2), 7.93 (1H, d, J=7.5, H-7).

1-Allyl-1-phenylcyclohexane (17a) — Colorless oil. MS *m/z*: 159 ($M^+ - CH_2{=}CH{-}CH_2\cdot$). IR (neat) cm^{-1}: 1638. ^1H NMR ($CDCl_3$) δ: 1.13-1.81 (8H, m), 1.81-2.24 (2H, m), 2.24 (2H, d, J=7), 4.67-4.99 (2H, m), 5.14-5.65 (1H, m), 6.97-7.39 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 22.5 (×2), 26.8, 36.1 (×2), 41.5, 48.6, 116.2, 125.0, 126.4 (×2), 127.6 (×2), 134.4, 145.9.

1-Cyano-1-phenylcyclohexane (17b) — Colorless oil. MS *m/z*: 185 (M^+). IR (neat) cm^{-1}: 2230. ^1H NMR ($CDCl_3$) δ: 0.98-2.37 (10H, m), 7.15-7.61 (5H, m). ^{13}C NMR ($CDCl_3$) δ: 23.7

(×2), 25.3, 37.4 (×2), 44.3, 121.7, 124.6 (×2), 126.9, 128.0 (×2), 140.5.

2-[1-(4-Indolyl)-1-methylethyl]cyclohexanone (20) — Mg (173 mg) was added to a solution of **12d** (246 mg) in MeOH (8 ml) and the mixture was stirred at room temperature for 15 min to initiate the reaction. It was cooled to 0°C and further stirred for 3.5 h. Quenching with sat. NH_4Cl-H_2O, extraction with CH_2Cl_2, usual work-up, and PTLC [hexane-EtOAc (5:1)] afforded **20** (143 mg, 93%) as colorless syrup. MS *m/z*: 255 (M^+). IR ($CHCl_3$) cm^{-1}: 1708. ^1H NMR ($CDCl_3$) δ: 1.09-2.47 (6H, m), 1.56 (3H, s), 1.69 (3H, s), 3.26-3.55 (1H, m), 6.54-6.73 (1H, m, H-3), 6.91-7.25 (4H, m), 8.43 (1H, br s).

2,6,7,8,9,10-Hexahydro-6,6-dimethylnaphth[1,2,3-*cd*]indole (21) — A solution of **20** (45 mg) and Lawesson's reagent (72 mg) in THF (3 ml) was stirred under reflux for 20 h under Ar atmosphere. After cooling, sat. $NaHCO_3$-H_2O was added and the mixture was extracted with Et_2O. Usual work-up and PTLC [hexane-EtOAc (9:1)] gave **21** (32 mg, 77%) as an unstable crystalline material, which turned brown in refrigerator. MS *m/z*: 237 (M^+). ^1H NMR ($CDCl_3$) δ: 1.42 (6H, s), 1.56-1.93 (4H, m), 2.10-2.62 (4H, m), 6.71 (1H, d, J=2, changed to s with D_2O, H-2), 6.90-7.32 (3H, m), 7.52 (1H, br s).

2,6,6a,7,8,9,10,10a-Octahydro-6,6-dimethylnaphth[1,2,3-*cd*]indoles (22 and 23) — To a solution of **21** (25 mg) in THF (1 ml) and MeOH (0.5 ml) was added successively 95% $NaBH_3CN$ (17 mg) and 1*N* HCl in MeOH-H_2O (9:1) (0.5 ml) at 0°C and the mixture was stirred at the same temperature for 20 min. Sat. $NaHCO_3$-H_2O was added and the mixture was extracted with Et_2O. Usual work-up and PTLC [hexane-CH_2Cl_2 (9:1)] provided a less polar compound **22** (11 mg, 44%) and a more polar compound **23** (11 mg, 44%). **22**: Colorless prisms, mp 104-105°C (MeOH-H_2O). Anal. Calcd for $C_{17}H_{21}N$: C, 85.30; H, 8.85; N, 5.85. Found: C, 85.32; H, 8.89; N, 5.81. MS *m/z*: 239 (M^+). ^1H NMR ($CDCl_3$) δ: 1.22 (3H, s), 1.43 (3H, s), 2.31 (1H, br d, J=12, H-11e), 3.41-3.65 (1H, m, H-10), 6.81 (1H, dd, J=2, 2, H-2), *ca.* 6,81-7.03 (1H, m, H-5), 7.08-7.20 (2H, m, H-6 and H-7), 7.81 (1H, br s). **23**: Colorless needles, mp 152-153°C (CH_2Cl_2-hexane). Anal. Calcd for $C_{17}H_{21}N$: C, 85.30; H, 8.85; N, 5.85. Found: C, 85.19; H, 8.80; N, 5.77. MS *m/z*: 239 (M^+). ^1H NMR ($CDCl_3$) δ: 1.09 (3H, s), 1.42 (3H, s), 2.19-2.54 (1H, m, H-11e), 2.48-2.85 (1H, m, H-10), 6.79 (1H, dd, J=1.5, 1.5, H-2), 6.93-7.27 (3H, m), 7.76 (1H, br s).

2,6,7,8,9,10-Hexahydro-6,6-dimethyl-2-*p*-toluenesulfonylnaphth[1,2,3-*cd*]-indole (19) — A solution of **12d** (68 mg) in CH_2Cl_2 (3 ml) was stirred with BF_3·OEt_2 (0.04 ml) at -20°C for 30 min and then at room temperature for 2 h. Quenching with sat. $NaHCO_3$-H_2O, extraction with CH_2Cl_2, and usual work-up yielded a crystalline material, which was purified by recrystallization and column chromatography [hexane-EtOAc (19:1)] to give **19** (52 mg, 80%) as colorless prisms, mp 203-205°C (CH_2Cl_2-MeOH). Anal. Calcd for $C_{24}H_{25}NO_2S$: C, 73.62; H, 6.44; N, 3.58. Found: C, 73.57; H, 6.38; N, 3.56. MS *m/z*: 391 (M^+). IR (KBr) cm^{-1}: 1632. ^1H NMR ($CDCl_3$) δ: 1.35 (6H, s), 1.59-1.92 (4H, m), 2.06-2.57 (4H, m), 2.30 (3H, s), 7.10 (1H, s, H-2), 7.10 (1H, dd, J=7.5, 1, H-5), 7.15 and 7.76 (A_2B_2, J=8.5), 7.29 (1H, dd, J=7.5, 7.5, H-6), 7.66 (1H, dd, J=7.5, 1, H-7).

Reductive Deprotection of the Compound 19 to Form the Compound 21 — Na (32 mg) was added to a solution of **19** (54 mg) in THF (2 ml) and liquid NH_3 (3 ml) at -70°C under Ar atmosphere. After being stirred at -70 – -62°C for 40 min, NH_4Cl (60 mg) was added and the mixture was stirred at room temperature for 20 min. Addition of sat. NH_4Cl-H_2O, extraction with Et_2O, usual work-up, and PTLC [hexane-EtOAc (14:1)] afforded **21** (25 mg, 76%).

Selenium Dioxide Oxidation of the Compound 19 — SeO_2 (10 mg) was added to a solution of **19** (26 mg) in dioxane (1.5 ml) and the mixture was refluxed with stirring for 30 min. After cooling, H_2O was added to this and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane-EtOAc (6:1)] afforded **24** (4 mg, 16%) and a mixture (21 mg) containing **25**, **26**, and **27** along with the recovery of **19** (1 mg, 4%). The mixture was purified by PTLC [hexane-CH_2Cl_2 (1:3)] to yield **25** (7 mg, 26%), **26** (5 mg, 19%), and **27** (4 mg, 14%). **24**: Slightly yellow syrup. HRMS Calcd for $C_{24}H_{21}NO_2S$: 387.129. Found: 387.128. ^1H NMR ($CDCl_3$) δ: 1.62 (6H, s), 2.30 (3H, s), 7.39-7.89 (12H, m). **25**: Colorless prisms, mp 207-209°C (CH_2Cl_2-MeOH). Anal. Calcd for $C_{24}H_{25}NO_3S$: C, 70.73; H, 6.18; N, 3.44. Found: C, 70.73; H, 6.23; N, 3.51. MS *m/z*: 407 (M^+). IR (KBr) cm^{-1}: 1632. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (3H, s), 1.40 (3H, s), 1.67-

1.95 (4H, m), 1.72 (1H, br s, OH), 2.15-2.26 (1H, m, H-14a), 2.31 (3H, s), 2.40 (1H, ddd, J=17.5, 4.5, 4.5, H-14e), 4.62 (1H, dd, J=4.5, 4.5, H-11), 7.12 (1H, d, J=7.5, H-5), 7.17 and 7.78 (A_2B_2, J=8), 7.31 (1H, dd, J=7.5, 7.5, H-6), 7.41 (1H, s, H-2), 7.68 (1H, d, J=7.5, H-7). **26**: Colorless needles, mp 248-250°C (CH_2Cl_2-hexane). Anal. Calcd for $C_{24}H_{23}NO_3S$: C, 71.08; H, 5.72; N, 3.46. Found: C, 70.59; H, 5.75; N, 3.27. MS *m/z*: 405 (M^+). IR (KBr) cm^{-1}: 1660. ^1H NMR ($CDCl_3$) δ: 1.48 (6H, s) 1.89-2.22 (2H, m, H-13), 2.31 (3H, s), 2.44-2.72 (4H, m, H-12 and H-14), 7.03-7.42 (4H, m), 7.72 (1H, dd, J=7.5, 1, H-7), 7.81 (A_2B_2, J=8), 8.08 (1H, s, H-2). **27**: Slightly yellow syrup. MS *m/z*: 421 (M^+). IR ($CHCl_3$) cm^{-1}: 1677. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.44 (3H, s), 1.66 (3H, s), 1.79 (1H, br s, OH), 2.14 (1H, dddd, J=13.5, 13.5, 5, 2.5, H-13a), 2.32 (3H, s), 2.35 (1H, dddd, J=13.5, 5.5, 3.5, 2, H-13e), 2.58 (1H, ddd, J=18, 5, 2, H-12e), 3.04 (1H, ddd, J=18, 13.5, 5.5, H-12a), 4.79 (1H, dd, J=3.5, 2.5, H-14), 7.15 (1H, d, J=7.5, H-5), 7.20 and 7.81 (A_2B_2, J=8), 7.34 (1H, dd, J=7.5, 7.5, H-6), 7.74 (1H, d, J=7.5, H-7), 8.15 (1H, s).

MBS Oxidation of the Compound 19 — A CCl_4 solution (3 ml) of **19** (48 mg), NBS (23 mg), and benzoyl peroxide (8 mg) was gently refluxed with stirring for 30 min. After cooling in an ice bath, sat. $NaHCO_3$-H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and PTLC (CH_2Cl_2) afforded **24** (7 mg, 15%) and **25** (25 mg, 50%), colorless prisms, mp 207-209°C (CH_2Cl_2-MeOH).

Swern Oxidation of the Compound 25 — To a cooled (-70°C) solution of 10% v/v $(COCl)_2$/CH_2Cl_2 (0.26 ml) in CH_2Cl_2 (1 ml) was added 10% v/v DMSO/CH_2Cl_2 (0.63 ml) under Ar atmosphere and the mixture was stirred at the same temperature for 3 min. A CH_2Cl_2 solution (3 ml) of **25** (30 mg) was added dropwise to this and stirring was continued at -70 – -68°C for 20 min. After addition of Et_3N (0.20 ml), the mixture was stirred at -68°C for 5 min, and at -20°C for 30 min. Quenching with sat. $NaHCO_3$-H_2O, extraction with Et_2O, usual work-up, and PTLC [hexane-CH_2Cl_2 (2:3)] afforded **26** (25 mg, 84%), colorless needles, mp 248-250°C (CH_2Cl_2-hexane).

$\Delta^{1,6}$ and $\Delta^{1,2}$-1-Trimethylsilyloxy-3-methyl-3-vinylcyclohexenes (29) and (30) — 3-Methyl-3-vinylcyclohexanone[14] (323 mg) in THF (3 ml) was added dropwise to a cooled (-73°C) solution of LDA, prepared from diisopropylamine (0.43 ml) and 15% BuLi-hexane (1.88 ml), and chlorotrimethylsilane (1.48 ml) under Ar atmosphere. After being stirred at -73°C for 5 min, Et_3N (2.50 ml) was added and the mixture was stirred for 3 min. It was poured into sat. $NaHCO_3$-H_2O and the whole was extracted with hexane. Successive washing of the organic layer with H_2O, 0.1 *N* citric acid, sat. $NaHCO_3$-H_2O, and H_2O, followed by usual work-up afforded an oil (520 mg) of **29** and **30**, which was used without further purification. ^1H NMR ($CDCl_3$) of **29** δ: 0.18 (9H, s), 1.00 (3H, s), 5.74 (1H, dd, J=18, 10.5). ^1H NMR ($CDCl_3$) of **30** δ: 0.18 (9H, s), 1.03 (3H, s), 5.66 (1H, dd, J=18, 10). The ratio of **29** and **30** (5:2) was estimated by the integrated values of the Me signals at 1.00 and 1.03 ppm.

2,6,7,8,9,10-Hexahydro-6,6,9-trimethyl-2-*p*-toluenesulfonyl-9-vinylnaphth-[1,2,3-*cd*]indole (8) — $SnCl_4$ (0.19 ml) was added to a CH_2Cl_2 solution (6 ml) of **6** (218 mg) and the above mixture (520 mg) of **29** and **30** at -78°C under Ar atmosphere and the whole was stirred for 10 min. After the same treatment as for the preparation of **12**, the residue was roughly separated by PTLC [hexane-EtOAc (9:1)] to yield a mixture (267 mg) of the crude **7** and **31**, which was dissolved in CH_2Cl_2 (5 ml) and stirred with $BF_3 \cdot OEt_2$ (0.22 ml) at room temperature for 1.5 h. The mixture was poured into ice-cooled sat. $NaHCO_3$-H_2O and the whole was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane-EtOAc (29:1)] gave **8** (162 mg, 57%) and **32** (13 mg, 4.5%). **8**: Colorless syrup. HRMS Calcd for $C_{27}H_{29}NO_2S$: 431.192. Found: 431.194. IR ($CHCl_3$) cm^{-1}: 1638. ^1H NMR ($CDCl_3$) δ: 1.06 (3H, s), 1.34 (3H, s), 1.36 (3H, s), 1.46-1.77 (2H, m, H-13), 2.02-2.63 (4H, m), 2.23 (3H, s), 4.90 (1H, dd, J=10.5, 1), 4.91 (1H, dd, J=18, 1), 5.84 (1H, dd, J=18, 10.5), 7.01-7.19 (1H, m, H-5), 7.12 and 7.78 (A_2B_2, J=8.5), 7.16 (1H, s, H-2), 7.30 (1H, dd, J=7.5, 7.5, H-6), 7.69 (1H, d, J=7.5, H-7). **32**: Colorless syrup. HRMS Calcd for $C_{27}H_{29}NO_2S$: 431.192. Found: 431.189. IR ($CHCl_3$) cm^{-1}: 1638. ^1H NMR ($CDCl_3$) δ: 1.07 (3H, s), 1.22 (3H, s), 1.25 (3H, s), 2.29 (3H, s), 4.89 (1H, dd, J=10.5, 1.5), 4.93 (1H, dd,

J=18, 1.5), 5.87 (1H, dd, J=18, 10.5), 6.75 (1H, d, J=4, H-3), 7.14 (1H, d, J=8, H-6), 7.19 and 7.79 (A_2B_2, J=8.5), 7.61 (1H, d, J=4, H-2), 7.89 (1H, d, J=8, H-7).

Selenium Dioxide Oxidation of the Compound 8 — A solution of **8** (30 mg) in dioxane (2 ml) was refluxed with SeO_2 (8 mg) for 30 min. After ice-cooling, H_2O was added and the mixture was extracted with Et_2O. Usual work-up and PTLC [hexane-EtOAc (5:1)] gave **33** (5.5 mg, 16%) and **34** (3.5 mg, 11%) along with the recovery of **8** (9 mg, 30%). **33**: Colorless syrup. MS *m/z*: 447 (M^+). IR ($CHCl_3$) cm^{-1}: 1637. ^1H NMR ($CDCl_3$) δ: 1.13 (3H, s), 1.38 (6H, s), *ca.* 1.38-1.99 (2H, m, H-13), 1.63 (1H, br s, OH), 2.21-2.48 (2H, m, H-14), 2.33 (3H, s), 4.32 (1H, br s, H-11), 5.02 (1H, dd, J=10.5, 1.5), 5.03 (1H, dd, J=18, 1.5), 5.83 (1H, dd, J=18, 10.5), 7.12 (1H, d, J=8, H-5), 7.20 and 7.82 (A_2B_2, J=8.5), 7.32 (1H, dd, J=8, 8, H-6), 7.46 (1H, s, H-2), 7.70 (1H, d, J=8, H-7). **34**: Colorless prisms, mp 166-168°C (CH_2Cl_2-MeOH). Anal. Calcd for $C_{27}H_{27}NO_3S$: C, 72.78; H, 6.11; N, 3.14. Found: C, 72.75; H, 6.16; N, 3.13. MS *m/z*: 445 (M^+). IR ($CHCl_3$) cm^{-1}: 1665. ^1H NMR ($CDCl_3$) δ: 1.28 (3H, s), 1.48 (6H, s), *ca.* 1.77-2.22 (2H, m, H-13), 2.31 (3H, s), 2.64 (2H, dd, J=6, 6, H-14), 4.97 (1H, d, J=17), 5.09 (1H, d, J=10.5), 5.95 (1H, dd, J=17, 10.5), 7.05-7.45 (4H, m), 7.76 (1H, d, J=8, H-7), 7.86 (A_2B_2, J=8.5), 8.15 (1H, s, H-2).

[9*R-(9α,10α)]- and [9*R**-(9α,10β)]-10-Azido-2,6,7,8,9,10-hexahydro-6,6,9-trimethyl-2-*p*-toluenesulfonyl-9-vinylnaphth[1,2,3-*cd*]indoles (35 and 36)** — A solution of **8** (98 mg) in CCl_4 (5 ml) was refluxed with NBS (43 mg) and benzoyl peroxide (18 mg) for 30 min. After cooling in an ice bath, sat. $NaHCO_3$-H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up gave a residue (146 mg). This in DMF (3 ml) was stirred with NaN_3 (222 mg) at room temperature for 16 h. Addition of H_2O, extraction with Et_2O, usual work-up, and PTLC [hexane-benzene (5:2)] afforded **35** (37 mg, 34%), **36** (31 mg, 29%), and **37** (7 mg, 7%). **35**: Colorless syrup. HRMS Calcd for $C_{27}H_{28}N_4O_2S$: 472.193. Found: 472.193. IR ($CHCl_3$) cm^{-1}: 2100, 1640. ^1H NMR ($CDCl_3$, 400MHz) δ: 1.04 (3H, s), 1.45 (3H, s), 1.47 (3H, s), 1.64 (1H, dddd, J=13.5, 6.5, 2, 2, H-13e), 1.88 (1H, ddd, J=13.5, 11.5, 6, H-13a), 2.32 (3H, s), 2.37 (1H, ddd, J=18, 11.5, 6.5, H-14a), 2.56 (1H, ddd, J=18, 6, 2, H-14e), 3.80 (1H, s, H-11), 5.15 (1H, dd, J=17.5, 1), 5.18 (1H, dd, J=11, 1), 6.08 (1H, dd, J=17.5, 11), 7.15 (1H, d, J=7.5, H-5), 7.21 and 7.80 (A_2B_2, J=8.5), 7.29 (1H, s, H-2), 7.34 (1H, dd, J=7.5, 7.5, H-6), 7.68 (1H, d, J=7.5, H-7). **36**: Colorless syrup. HRMS Calcd for $C_{27}H_{28}N_4O_2S$: 472.193. Found: 472.192. IR ($CHCl_3$) cm^{-1}: 2100, 1640. ^1H NMR ($CDCl_3$) δ: 1.21 (3H, s), 1.37 (3H, s), 1.41 (3H, s), *ca.* 1.41-1.96 (2H, m, H-13), *ca.* 2.04-2.67 (2H, m, H-14), 2.28 (3H, s), 3.94 (1H, s, H-11), 4.96 (1H, dd, J=10.5, 1), 4.96 (1H, dd, J=18, 1), 5.75 (1H, dd, J=18, 10.5), 7.04-7.46 (2H, m, H-5 and H-6), 7.19 and 7.80 (A_2B_2, J=8), 7.34 (1H, s, H-2), 7.70 (1H, d, J=8). **37**: Colorless syrup. MS *m/z*: 427 (M^+). ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.63 (6H, s), 2.32 (3H, s), 2.35 (3H, s), 5.43 (1H, dd, J=18, 2), 5.82 (1H, dd, J=11.5, 2), 6.93 (1H, dd, J=18, 11.5), 7.20 (1H, d, J=8, H-13), 7.20 and 7.78 (A_2B_2, J=8), 7.24 (1H, d, J=7.5, H-5), 7.37 (1H, dd, J=7.5, 7.5, H-6), 7.44 (1H, d, J=8, H-14), 7.74 (1H, d, J=7.5, H-7), 7.90 (1H, s, H-2).

Transformation of the Compound 36 to the Compound 35 — To a solution of **36** (40 mg) in MeOH (3 ml) was added $SnCl_2$ (135 mg) and the mixture was refluxed for 2 h. After cooling at 0°C, sat. $NaHCO_3$-H_2O was added and the mixture was filtered through a celite bed. The celite was washed with CH_2Cl_2 and the combined organic layer was treated as usual to leave a residue (44 mg) containing **38** and **39**. This and $TMSN_3$ (0.11 ml) were dissolved in CH_2Cl_2 (3 ml) and TMSOTf (50 μl) was added at -20°C under Ar atmosphere. Stirring was continued for 18 h at -20 – 12°C and the reaction was stopped with sat. $NaHCO_3$-H_2O. Extraction with CH_2Cl_2, usual work-up, and PTLC [hexane-benzene (2:1)] afforded **35** (9 mg, 23%) and the recovered **36** (21 mg, 53%).

[6a*S-(6aα,9α,10α,10aα)]-10-Formamido-2,6,6a,7,8,9,10,10a-octahydro-6,6,9-trimethyl-9-vinylnaphth[1,2,3-*cd*]indole (41) and [9*R**-(9α,10α)]-10-Formamido-2,6,7,8,9,10-hexahydro-6,6,9-trimethyl-9-vinylnaphth[1,2,3-*cd*]indole (40)** — To a solution of **35** (32 mg) in THF (3 ml) was added $LiAlH_4$ (39 mg) at 0°C under Ar atmosphere and the mixture was stirred at 0 – 18°C for 15 h. After cooling at 0°C, the reaction was quenched with sat. Roschell salt in H_2O. Extraction with Et_2O followed by usual work-up gave a residue

(24 mg). It was dissolved in CH_2Cl_2 (1.5 ml) and pyridine (0.40 ml), and to this was added dropwise a CH_2Cl_2 solution (0.5 ml) of acetic formic anhydride (0.20 ml) at -20°C. After being stirred at -20 – 16°C for 4.5 h, sat. $NaHCO_3$-H_2O was added and the mixture was extracted with Et_2O. Usual work-up and PTLC [hexane-EtOAc (3:2)] afforded **40** (5 mg, 23%) and **41** (9 mg, 41%). **40**: Colorless amorphous compound. HRMS Calcd for $C_{21}H_{24}N_2O$: 320.189. Found: 320.190. IR ($CHCl_3$) cm^{-1}: 1680, 1640. ^1H NMR ($CDCl_3$) of two rotamers δ: 1.09 (3H, s), 1.44 (3H, s), 1.46 (3H, s), 1.55-1.83 (2H, m, H-13), 2.13-2.73 (2H, m, H-14), 3.96 (minor) and 4.82 (major) (1H, d each, J=10 and 11, H-11), 5.01 (1H, dd, J=17.5, 1), 5.04 (1H, dd, J=10.5, 1), 5.52 (1H, br d, J=11, NHCHO), 5.83-6.20 (1H, m), 6.74-7.31 (4H, m), 7.90 (1H, br s), 8.15 (1H, s, CHO). **41**: Colorless syrup. HRMS Calcd for $C_{21}H_{26}N_2O$: 322.205. Found: 322.207. IR ($CHCl_3$) cm^{-1}: 1680, 1639. ^1H NMR ($CDCl_3$) of major and minor rotamers δ: 0.79 and 0.87 (3H, s each), 1.10 and 1.21 (3H, s each), 1.45 (3H, s), 3.54-3.72 and 3.37-3.54 (1H, m each, H-10), 4.65 (1H, dd, J=9, 1.5, H-11), 4.86 (1H, dd, J=17.5, 1), 4.94 (1H, dd, J=11, 1), ca. 5.67-6.00 (1H, m, NHCHO), 5.88 (1H, dd, J=17.5, 11), 6.76-7.20 (4H, m), 7.97-8.33 (1H, m, NH), 8.17 and 7.93 (1H, s each, CHO).

(±)-Hapalindole J (4) — A solution of **41** (16 mg) in pyridine (0.5 ml) was stirred with $POCl_3$ (23 µl) under Ar atmosphere at -20°C for 40 min. Addition of sat. $NaHCO_3$-H_2O, extraction with 10% MeOH-CH_2Cl_2, usual work-up, and PTLC [hexane-EtOAc (4:1)] afforded (±)-hapalindole J (**4**) (11.5 mg, 76%) as colorless prisms, mp 182-184°C (CH_2Cl_2-hexane). Anal. Calcd for $C_{21}H_{24}N_2$: C, 82.85; H, 7.95; N, 9.20. Found: C, 82.85; H, 7.91; N, 9.07. MS *m/z* (relative intensity): 304 (M^+, 96), 289 (100), 262 (13), 207 (17), 182 (19), 168 (31). IR (KBr) cm^{-1}: 2150, 1642. IR ($CHCl_3$) cm^{-1}: 2145, 1641. ^1H NMR ($CDCl_3$, 300 MHz) δ: 0.80 (3H, s), ca. 0.99-1.21 (1H, m, H-14a), 1.21 (3H, s), 1.37 (1H, br ddd, J=13, 4, 4, H-13e), 1,52 (3H, s), 1.73 (1H, br dddd, J=14, 4, 4, 4, H-14e), 1.89 (1H, ddd, J=13, 13, 4, H-13a), 2.10 (1H, ddd, J=12, 4.5, 4, H-15), 3.80-3.90 (1H, m, H-10), 4.11-4.23 (1H, m, H-11), 5.07 (1H, d, J=17), 5.13 (1H, d, J=11), 6.05 (1H, dd, J=17, 11), 6.85-6.92 (1H, m, H-2), 6.93-7.01 (1H, m, H-5), 7.14-7.22 (2H, m, H-6 and H-7), 8.01 (1H, br s, NH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 19.72 (t), 24.76 (q), 25.17 (q), 30.83 (t), 31.61 (q), 36.98 (d), 37.89 (s), 39.06 (s), 43.58 (d), 62.19 (d), 108.14 (d), 111.88 (s), 112.67 (t), 113.70 (d), 118.46 (d), 123.23 (d), 124.24 (s), 133.44 (s), 138.94 (s), 146.07 (d), 155.63 (s).

[9R*-(9α,10α)]-2,6,7,8,9,10-Hexahydro-10-isocyano-6,6,9-trimethyl-9-vinylnaphth[1,2,3-cd]indole (42) — The same treatment of **40** (13 mg) as above with $POCl_3$ (19 µl) in pyridine (0.5 ml) for 50 min and purification by PTLC [hexane-EtOAc (6:1)] gave **42** (9 mg, 73%) as colorless needles, mp 181-183°C (CH_2Cl_2-hexane). Anal. Calcd for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.27. Found: C, 83.29; H, 7.34; N, 9.38. MS *m/z*: 302 (M^+). IR (KBr) cm^{-1}: 2130, 1640. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (3H, s), 1.49 (3H, s), 1.50 (3H, s), 1.65 (1H, ddd, J=14, 6, 5, H-13e), 2.03 (1H, ddd, J=14, 10, 6, H-13a), 2.41 (1H, ddd, J=18, 10, 6, H-14a), 2.58 (1H, ddd, J=18, 6, 5, H-14e), 4.20 (1H, s, H-11), 5.24 (1H, dd, J=17.5, 1), 5.26 (1H, dd, J=11, 1), 6.12 (1H, dd, J=17.5, 11), 7.02 (1H, d, J=7.5, H-5), 7.10 (1H, d, J=2, H-2), 7.13 (1H, d, J=7.5, H-7), 7.24 (1H, dd, J=7.5, 7.5, H-6), 7.89 (1H, br s, NH).

(±)-Hapalindole M (5) and the Compound 43 — The same reduction of **35** (48 mg) as above with $LiAlH_4$ (58 mg) in THF (4 ml) at 0 – 18°C for 14 h gave a residue (40 mg), which was dissolved in CH_2Cl_2 (3 ml) and this was stirred with 90% 1,1'-thiocarbonyldiimidazole (26 mg) at 0 – 18°C for 2.5 h. Evaporation of CH_2Cl_2 followed by PTLC [hexane-EtOAc (9:1)] afforded **43** (3 mg, 9%) and crude (±)-**5** (13 mg). The latter was purified by PTLC [hexane-CH_2Cl_2 (3:2)] to give (±)-hapalindole M (**5**) (12 mg, 35%) as colorless syrup. HRMS Calcd for $C_{21}H_{24}N_2S$: 336.166. Found: 336.166. IR ($CHCl_3$) cm^{-1}: 2155, 2125, 2075. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.79 (3H, s), 1.05-1.21 (1H, m, H-14a), 1.22 (3H, s), 1.41 (1H, br d, J=13, H-13e), 1.52 (3H, s), 1.75 (1H, dddd, J=13.5, 4, 4, 4, H-14e), 1.84 (1H, ddd, J= 13, 13, 4, H-13a), 2.02 (1H, ddd, J=12.5, 4.5, 4, H-15), 3.78-3.91 (1H, m, H-10), 4.21-4.35 (1H, m, H-11), 5.06 (1H, d, J=17.5), 5.13 (1H, d, J=11), 5.99 (1H, dd, J=17.5, 11), 6.86-6.91 (1H, m, H-2), 6.94-7.00 (1H, m, H-5), 7.15-7.21 (2H, m, H-6 and H-7), 7.99 (1H, br s NH). **43**: Colorless syrup. HRMS Calcd for $C_{21}H_{22}N_2S$: 334.150. Found: 334.150. IR ($CHCl_3$) cm^{-1}: 2170, 2140. ^1H NMR ($CDCl_3$) δ: 1.11 (3H, s), 1.48

(6H, s), 4.30 (1H, s, H-11), 5.18 (1H, d, J=17), 5.21 (1H, d, J=11), 5.89-6.28 (1H, m), 6.88-7.29 (4H, m), 7.84 (1H, br s).

ACKNOWLEDGMENT

We wish to thank Professor R. E. Moore, University of Hawaii for his generous supply of the spectral data of hapalindoles J and M. Authors' thanks are due to Research Laboratories, Shionogi & Co. Ltd. for the measurement of elemental analysis. This work was supported by a Grant-in-Aid from the Ministry of Education, Science and Culture, which is gratefully acknowledged.

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