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SYNTHETIC STUDIES OF MARINE ALKALOIDS HAPALINDOLES. Part 2. LITHIUM ALUMINUM HYDRIDE REDUCTION OF THE ELECTRON-RICH CARBON-CARBON DOUBLE BOND CONJUGATED WITH THE INDOLE NUCLEUS

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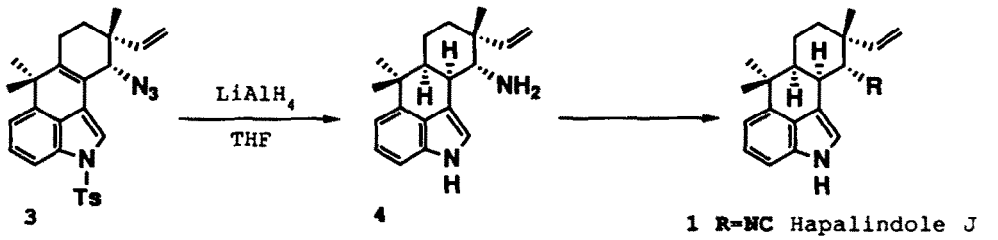
Abstract — A reaction mechanism is proposed for an unusual reduction of the electron-rich C-C double bond with lithium aluminum hydride in the indole derivatives such as **3**. Liberation of an aluminum hydride anion from 1-indolylaluminum intermediates, *i.e.*, **27** may play an important rôle for the inversion of the polarity at the 15 position.

In the previous paper, we reported a successful synthesis of hapalindoles J (**1**) and M (**2**) making use of the reduction of the azide compound **3** with lithium aluminum hydride (LAH).[1] This single operation effects the following three reactions simultaneously to yield the amino compound **4**: (i) reductive cleavage of the tosyl group from the indole nitrogen atom, (ii) reduction of the azide group, and (iii) stereoselective reduction of the double bond conjugated with the indole nucleus. Of these, the third reaction is extremely unusual in that the electron-rich tetrasubstituted double bond easily accepts the hydride attack originating from LAH in a very mild condition, *i.e.*, stirring in tetrahydrofuran at room temperature. A first glance at the structure of the substrate **3** for this reduction raised some questions into our mind. Is the tosyl group playing a rôle in initiating the reduction of the double bond? Is participation of the neighboring heteroatom, such as the nitrogen here, necessary for anchoring the reducing agent? How does the hydride attack proceed as a whole? To answer these questions, we carried out several experiments including reduction with lithium aluminum deuteride, and we here propose a hypothesis for the reaction mechanism.



3 **4**

1 R=NC Hapalindole J
2 R=NCS Hapalindole M

Chart 1

The compound **5** was a by-product obtained together with the important intermediate **3** in the previous report. Now this is a compound for testing the stereoselectivity observed at the LAH reduction (Chart 2). The reaction was carried out as before by treating **5** with 15 molar equivalents of LAH in tetrahydrofuran at room temperature for 15 h and a crude reaction mixture was formylated with acetic formic anhydride and pyridine in dichloromethane. The unsaturated and saturated compounds **6** and **7** were obtained in 35% and 31% yields, completely analogous to the previous case of the hapalindole J synthesis. The stereochemical structure of compound **7** was not identified at this stage, because in its proton NMR spectrum **7** behaved

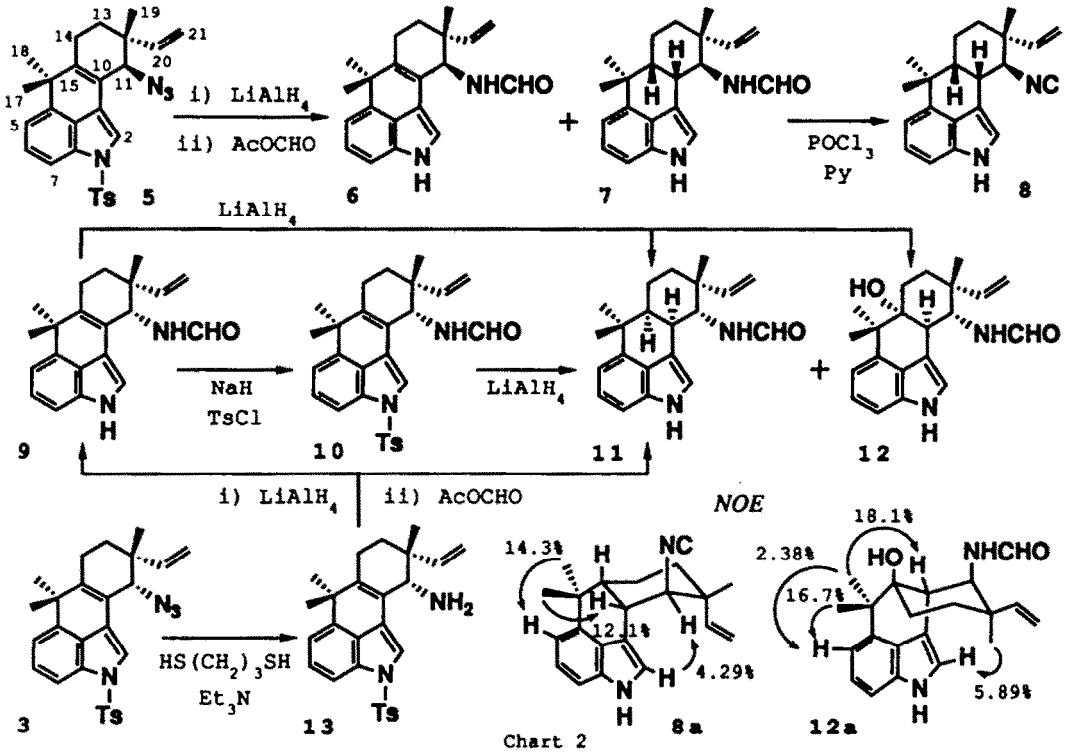


Chart 2

as two rotational isomers due to the presence of the formamide function. So this was converted to the isonitrile derivative **8** with phosphorus oxychloride in pyridine in 71% yield. As shown in the formula **8a**, the nuclear Overhauser effect (NOE) experiment made clear the vicinity of H-2 to H-11, of C-17 methyl hydrogens to H-10, and of C-18 methyl hydrogens to H-5, and supported the stereostructure of **7**. Therefore it is established that the two hydrogens at the cis ring juncture of the perhydronaphthalene part came from the same side as the azide group during the LAH reduction.

To make sure about this stereoeffective participation of the heteroatom adjacent to the tetrasubstituted double bond, the tosylate **10** was prepared from **9**[1] and reduced with LAH. The expected compound **11**[1] having the ring juncture hydrogens cis to the formamide group was certainly produced in 46% yield, but parallel to the formation of **11**, a new compound **12** with the hydroxyl function was obtained in 12% yield. As the amino compound **13** obtained from **3** by treatment with propane-1,3-dithiol and triethylamine in methanol,[2] afforded only **9** and **11** by the LAH reduction and subsequent formylation, the formamide function in **10** is necessary for the formation of **12**. The structure of **12**, especially the location and stereochemical arrangement of the hydroxyl group was clarified by the analysis of its proton NMR spectrum including the presence of the A_2B_2 pattern of the four protons at 13 and 14 positions and the allylic coupling pattern between H-2 and H-10, as well as the NOE result depicted in **12a**. The cis stereochemical relationship between formamide and the newly introduced hydroxyl group clearly indicated the participation of the neighboring group during the LAH reduction. Introduction of the hydroxyl group at the 15 position is quite remarkable in that the 15 position of the double bond is an electron-rich site due to the conjugation with the indole nucleus. Therefore a certain factor which inverts the polarity from the electron-donating position to the electron-attracting position may be operating during the reduction. The tosyl group is

not involved in the inversion of the polarity, because compound **9** gave similarly **11** and **12** in 12% and 40% yields upon LAH reduction. So we must establish a reaction mechanism for the unusual LAH reduction taking these factors into consideration.

We next examined what happens without the heteroatoms (Chart 3). Compounds **14**, **17**, and **20**, the latter being prepared from **17** with magnesium in methanol in 85% yield, were submitted to the LAH reduction. The trans and cis derivatives,[1] **15** and **16**, were obtained in 25% and 43% yields from **14**, and a hardly separable mixture of the two cis derivatives **18** and **19** was produced from **17** and **20** in 66% and 69% yields, respectively. We tried to sparate this mixture by column chromatography over silica gel and only a trace amount of **18** was obtained in the pure state. The proton NMR spectrum (Table 1) exhibiting $J_{10,15}$ = 4 Hz, $W_{1/2}$ = 12 Hz of H-10, and the NOE result shown in **18a** supported the cis structure of **18** having the vinyl function spacially close to the indole moiety. The corresponding proton NMR signal of H-10 of the impure **19** was found at δ 3.59-3.66 ppm with the half height value equal to 12 Hz, so that **19** was assigned to have another type of the cis structure. Thus it was made clear that the minimum structural unit for the unusual LAH reduction is just the carbon-carbon double bond conjugated with the indole nucleus.

To get further insight into the reaction mechanism, compounds **14**, **17**, and **3** were reduced with lithium aluminum deuteride. Deuterated compounds **21**, **22**, and **23+24** were produced in 26%, 55%, and 80% yields respectively from the first two compounds, and **26** was obtained via **25** in 29% overall yield from **3**. All these products carried two deuteriums in their molecules and the sites of deuterium incorporation were unambiguously found to be the 10 and 15 positions by comparison of the proton NMR spectra of **23**, **24**, and **26** with those of **18**, **19**, and **1** (Table 1). Incorporation of the deuterium at the 15 position reminds us of the formation of **12** and

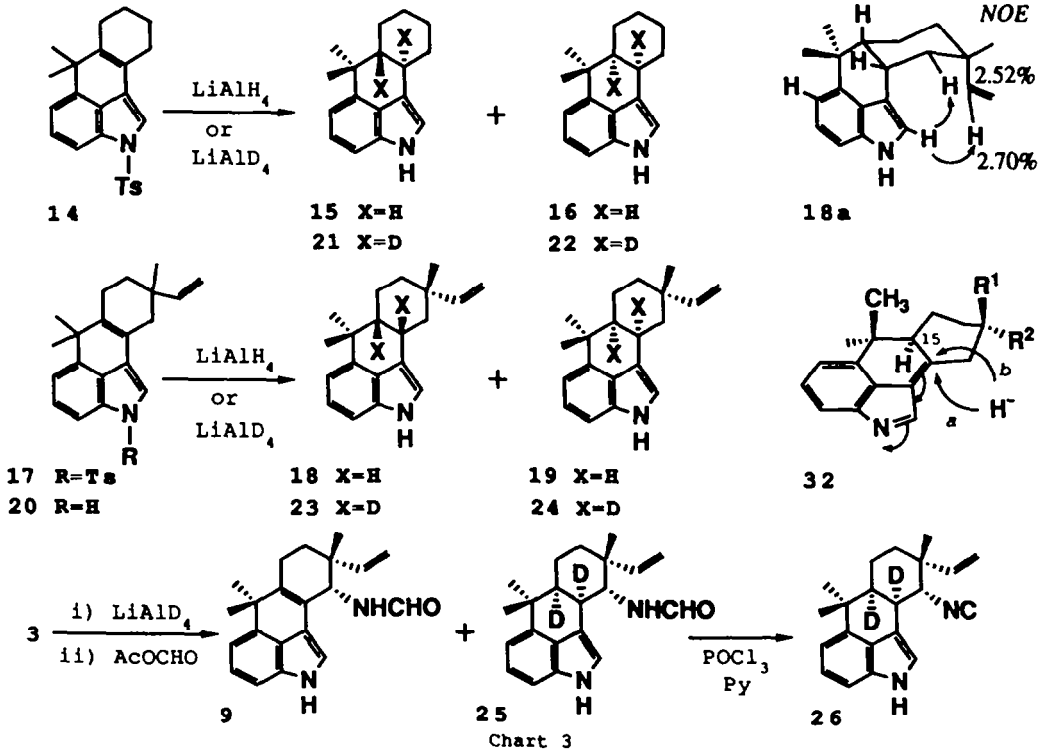
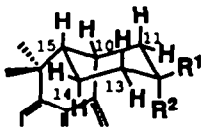


Chart 3

Table 1. Proton NMR Spectra (Chemical shift: δ ppm; Coupling constant: Hz)



Comp.	H-10	H-11 (eq)	H-11 (ax)	H-13 (eq)	H-13 (ax)	H-14 (eq)	H-14 (ax)	H-15
18	3.53-3.60	2.33, ddd	1.79, dd	1.66, dddd	1.27, ddd	1.51, ddddd	1.02, dddd	1.63, ddd
	$W_{1/2}$=12	J=14, 2.5, 2.5	14, 5.5	13.5, 3.5, 3, 2.5	13.5, 13.5, 3.5	13.5, 3.5, 3.5, 3.5, 1.5	13.5, 13.5, 12.5, 3	12.5, 4, 3.5
23	D	2.32, dd	1.78, d	1.66, dddd	1.27, ddd	1.51, ddd	0.97-1.06	D
		14, 2.5	14	13.5, 3.5, 3, 2.5	13.5, 13.5, 3.5	13.5, 3.5, 3.5		
19*	3.59-3.66	2.20, br d	1.83, dd	1.50-1.69	1.32-1.45	1.32-1.45	0.96-1.08	1.50-1.69
	$W_{1/2}$=12	14	14, 5.5					
24*	D	2.19, d	1.83, d	1.50-1.69	1.32-1.45	1.32-1.45	0.97-1.07	D
		14	14					
1	3.80-3.90	4.12-4.22	-N=C	1.37, ddd	1.89, ddd	1.73, dddd	1.05-1.20	2.11, ddd
				13.5, 4, 4	13.5, 13.5, 4	14, 4, 4, 4		12, 4.5, 4
26	D	4.17 br s	-N=C	1.38, ddd	1.90, ddd	1.73, ddd	1.06-1.20	D
				13.5, 4, 4	13.5, 13.5, 4	14, 4, 4		

* These compounds contain small amounts of **18** and **23** respectively as unavoidable impurities.

points out the problem to be solved regarding the inversion of the polarity.

To explain this unbelievable fact, we propose the following reaction mechanism for the LAH reduction (Chart 4).[3] When the compound **3** was reduced, reduction of the azide group and reductive cleavage of the tosyl group caused the formation of a 1-indolylaluminum derivative **27** with an aluminum-chelated nitrogen function at the 11 position. The electron-sufficient double bond donated the electron to the aluminium at the indole nitrogen atom to liberate an aluminum hydride anion, accompanied by a simultaneous hydride attack at the 15 position by the chelated reducing species to form an α,β-unsaturated indolenine derivative **28**. This may have been further reduced intramolecularly at the 10 position to produce the final indole derivative **4**. Thus the two hydrogens at the 10 and 15 positions were situated in the relation cis to the heteroatom at the 11 position.

When the formamide function is located close to the 10,15-double bond, the reduction of **9** and **10** may be started in part by an intramolecular attack of the formamide oxygen, instead of the hydride approach at the 15 position as depicted in **29**, to yield the α,β-unsaturated indolenine derivative **30** having a dihydro-1,3-oxazine ring. The subsequent hydride attack at the 10 position of **30** by the reducing agent, probably chelated at the formamide oxygen, may produce an intermediate **31**, which is hydrolyzed during the work-up to form the hydroxylated compound **12**. In cases of the simpler substrates **14**, **17**, and **20**, the 1-indolylaluminum intermediates receive intermolecularly the hydride attack of LAH at the 15 position to afford indolenine derivatives **32** (Chart 3). When R^1 and R^2 are either methyl or vinyl group, the opposite side of the H-15 is so crowded with the two pseudoaxial groups of methyl and R^1 that the second approach of LAH is limited to occur only from the path *a*, yielding the compounds **18** and **19** with the cis ring juncture. If R^1 and R^2 do not exist, the hydride attack from the *b* side is partially possible, resulting in the formation of cis and trans compounds, **16** and **15** in the ratio of 2:1.

All of these mechanisms rely on the assumption that the 1-indolylaluminium linkage is formed

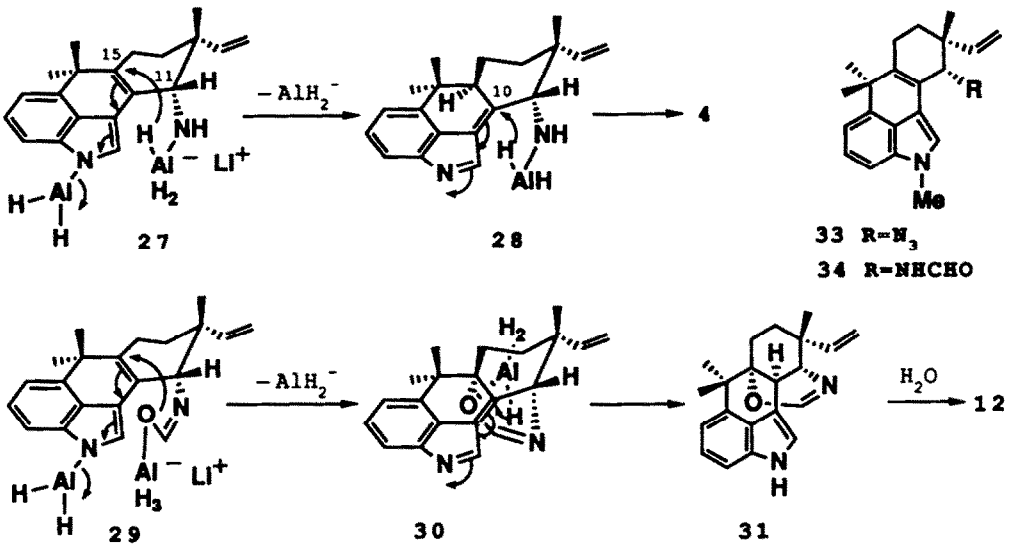


Chart 4

in the beginning and liberation of an aluminum hydride initiates the unusual reaction of inversion of the polarity. So we questioned what occurs if the formation of the indolyl-aluminium linkage is blocked. 1-Methylindole derivative **33** was prepared from **3** by removal of the tosyl group with warming alkali in 71% yield, followed by the methylation with sodium hydride and iodomethane in 83% yield. Then **33** was submitted to successive treatment with LAH and the formylating reagent. No saturated compounds were produced and the compound **34** was the sole product obtained in 44% yield, thus supporting our reduction mechanism. Further synthesis of hapalindoles using this reaction is reported in the following paper.

EXPERIMENTAL

For the general description, refer to that in the preceding paper.

[9*R-(9α,10β)]-10-Formamido-2,6,7,8,9,10-hexahydro-6,6,9-trimethyl-9-vinylnaphth[1,2,3-*cd*]indole (6) and [6a*R**-(6aβ,9α,10β,10aβ)]-10-Formamido-2,6,6a,7,8,9,10,10a-octahydro-6,6,9-trimethyl-9-vinylnaphth[1,2,3-*cd*]indole (7)** – To a THF solution (5 ml) of **5** (81 mg) was added $LiAlH_4$ (LAH) (98 mg) at 0°C under Ar atmosphere and the mixture was stirred at 0°C to room temperature for 15 h. After cooling in an ice bath, it was quenched with sat. Roschell salt in H_2O and the mixture was extracted with Et_2O. After usual work-up, the resulting residue was dissolved in CH_2Cl_2 (2 ml) and pyridine (0.6 ml) and the solution was cooled at -20°C. A CH_2Cl_2 solution (1 ml) of acetic formic anhydride (0.3 ml) was added dropwise to this and the mixture was stirred at -20°C to room temperature for 4.5 h. Quenching with sat. $NaHCO_3$-H_2O, extraction with Et_2O, usual work-up, and PTLC [hexane-EtOAc (2:1)] gave **6** (19 mg, 35%) and the crude **7**. The latter was further purified by PTLC (0.5% MeOH-CH_2Cl_2) to yield **7** (17 mg, 31%). **6**: Colorless syrup. MS *m/z*: 320 (M^+). IR ($CHCl_3$) cm^{-1}: 1678. ^1H NMR ($CDCl_3$) of major and minor rotamers δ: 1.10 (3H, s), 1.40 (3H, s), 1.44 (3H, s), 1.44-1.87 (2H, m, H-13), 2.21-2.51 (2H, m, H-14), *ca.* 4.84-5.16 and 4.05 (1H, m and d, J=10, H-11), 4.97 (1H, dd, J=10.5, 1), 5.03 (1H, dd, J=17.5, 1), 5.51-5.78 (1H, m, NHCHO), 5.84 and 5.82 (1H, dd each, J=17.5, 10.5), 6.70-7.32 (4H, m), 7.99 (1H, br s, indole NH), 8.23 and 8.12 (1H, s each, CHO). **7**: Colorless prisms, mp 241-243°C (CH_2Cl_2-hexane). Anal. Calcd for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.02; H, 8.10; N, 8.59. MS *m/z*: 322 (M^+). IR ($CHCl_3$) cm^{-1}: 1685. ^1H NMR ($CDCl_3$) of major and minor rotamers δ: 0.99 and 1.02 (3H, s each), 1.13 and 1.19 (3H, s each), 1.46 (3H, s), 3.40-3.58 (1H, m,

H-10), 4.77 and 3.82 (1H, br d, J=10.5 and dd, J=10.5, 4; changed to br s and d, J=4 with D_2O, H-11), 4.59 (1H, d, J=17.5), 4.88 (1H, d, J=10.5), 5.69 and 5.67 (1H, dd each, J=17.5, 10.5), 6.07 and 6.34 (1H, br d each, J=10.5, NHCHO), 6.72-7.18 (4H, m), 8.03 (1H, br s, indole NH), 8.30 and 8.16 (1H, s each, CHO).

[6aR*-(6aβ,9α,10β,10aβ)]-2,6,6a,7,8,9,10,10a-Octahydro-10-isocyano-6,6,9-trimethyl-9-vinylnaphth[1,2,3-*cd*]indole (8) — To a cooled (-20°C) solution of 7 (18 mg) in pyridine (0.5 ml) was added $POCl_3$ (26 μl) under Ar atmosphere. After being stirred at that temperature for 40 min, sat. $NaHCO_3$-H_2O was added and the mixture was extracted with 10% MeOH-CH_2Cl_2. Usual work-up and PTLC [hexane-EtOAc (4:1)] afforded **8** (12 mg, 71%) as colorless prisms, mp 167.5-168.5°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, 82.91; H, 7.92; N, 9.15. MS *m/z*: 304 (M^+). IR (KBr) cm^{-1}: 2160, 1641. ^1H NMR ($CDCl_3$, 400MHz) δ: *ca.* 1.01-1.20 (1H, m, H-14a), 1.22 (3H, s, H-17), 1.23 (3H, s, H-19), 1.47-1.74 (3H, m, H-13 and H-14e), 1.50 (3H, s, H-18), 2.10 (1H, ddd, J=12, 4, 4, H-15), 3.83 (1H, br s, H-10), 4.21 (1H, br s, H-11), 4.61 (1H, d, J=11, H-21*E*), 4.75 (1H, d, J=17.5, H-21*Z*) 5.58 (1H, dd, J=17.5, 11, H-20), 6.77 (1H, br s, H-2), 6.92-6.97 (1H, m, H-5), 7.13-7.19 (2H, m, H-6 and H-7), 7.97 (1H, br s, NH).

Tosylation of the Compound 9 to Form the Compound 10 — To a solution of **9** (12 mg) in THF (1.5 ml) and DMF (0.5 ml) was added 50% NaH in mineral oil (16 mg) at -20°C under Ar atmosphere and the mixture was stirred for 15 min. After addition of *p*-TsCl (21 mg), stirring was continued at -20°C for 1 h. Addition of sat. NH_4Cl-H_2O, extraction with Et_2O, usual work-up, and PTLC [hexane-EtOAc (3:2)] gave **10** (15 mg, 84%) as colorless syrup. MS *m/z*: 474 (M^+). IR ($CHCl_3$) cm^{-1}: 1678, 1638. ^1H NMR ($CDCl_3$) of two rotamers δ: 1.05 (3H, s), 1.38 (3H, s), 1.41 (3H, s), *ca.* 1.41-1.92 (2H, m, H-13), *ca.* 2.17-2.73 (2H, m, H-14), 2.30 (3H, s), 3.90 (minor) and 4.78 (major) (1H, d each, J=9 and 10.5, H-11), 5.00 (1H, dd, J=18, 1), 5.05 (1H, dd, J=10.5, 1), 5.50 (1H, br d, J=10.5, NHCHO), 5.80-6.20 (1H, m, H-20), 7.03-7.42 (3H, m, H-2, H-5, and H-6), 7.18 and 7.80 (A_2B_2, J=8.5), 7.70 (1H, d, J=8, H-7), 8.17 (1H, s, CHO).

[6aR*-(6aα,9α,10α,10aα)]-10-Formamido-2,6,6a,7,8,9,10,10a-octahydro-6a-hydroxy-6,6,9-trimethyl-9-vinylnaphth[1,2,3-*cd*]indole (12) and the Compound 11 — Reduction of **10** (45 mg) with LAH (73 mg) in THF (5 ml) was carried out as above. Usual work-up and PTLC [hexane-EtOAc (3:2)] afforded **11**[1] (14 mg, 46%) and **12** (4 mg, 12%). **12**: Colorless scales, mp 245-247°C (CH_2Cl_2-hexane). Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.25; H, 7.75; N, 8.30. MS *m/z*: 320 (M^+-H_2O). IR (KBr) cm^{-1}: 1655. ^1H NMR [$CDCl_3$-CD_3OD (4:1), 400 MHz] of major and minor rotamers δ: 0.67 (3H, s, H-19), 1.14 (3H, s, H-18), 1.19 (1H, br d, J=13.5, H-13e), 1.47 (3H, s, H-17), 1.50 (1H, ddd, J=13.5, 13.5, 4, H-14a), 1.70 (1H, br d, J=13.5, H-14e), 2.04 (1H, ddd, J=13.5, 13.5, 4, H-13a), 3.41 and 3.55 (1H, br d each, J=1.5, H-10), 4.70 and 4.00 (1H, s each, H-11), 4.89 and 4.97 (1H, dd, J=17.5, 1, and d, J=17.5, H-21*Z*), 4.90 and 5.04 (1H, dd, J=11, 1, and d, J=11, H-21*E*), 5.98 and 5.81 (1H, dd each, J=17.5, 11, H-20), 6.91 (1H, d, J=7.5, H-5 or H-7), 7.09 and 6.98 (1H, d each, J=1.5, H-2), 7.13 (1H, dd, J=7.5, 7.5, H-6), 7.20 (1H, d, J=7.5, H-7 or H-5), 8.07 and 7.97 (1H, s each, CHO).

[9R*-(9α,10α)]-10-Amino-2,6,7,8,9,10-hexahydro-6,6,9-trimethyl-9-vinylnaphth[1,2,3-*cd*]indole (13) — A solution of **3** (84 mg), propane-1,3-dithiol (0.40 ml), and Et_3N (0.8 ml) in MeOH (4 ml) was stirred under reflux for 6 h. After cooling, H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and PTLC (4% MeOH-CH_2Cl_2) afforded **13** (73 mg, 92%) as colorless syrup. HRMS Calcd for $C_{27}H_{30}N_2O_2S$: 446.203. Found: 446.201. IR ($CHCl_3$) cm^{-1}: 1638. ^1H NMR ($CDCl_3$) δ: 0.97 (3H, s), 1.37 (3H, s), 1.40 (3H, s), 1.64 (2H, s, NH_2), 2.19 (3H, s), 3.38 (1H, s, H-11), 5.04 (1H, dd, J=17, 1.5), 5.11 (1H, dd, J=11, 1.5), 5.95 (1H, dd, J=17, 11), 6.96-7.17 (1H, m, H-5), 7.05 and 7.76 (A_2B_2, J=8.5), 7.28 (1H, dd, J=7.5, 7.5, H-6), 7.36 (1H, s, H-2), 7.67 (1H, d, J=7.5, H-7).

Transformation of the Compound 13 to the Compounds 9 and 11 — Applying the procedure for converting **5** to **6** and **7**, **13** (26 mg) afforded **9**[1] (3 mg, 16%) and **11**[1] (9 mg, 48%) after purification by PTLC [hexane-EtOAc (3:2)].

LAH Reduction of the Compound 9 — In the same manner as above, **9** (40 mg) was converted

with LAH (73 mg) in THF (5 ml) to **11** (5 mg, 12%) and **12** (17 mg, 40%), colorless scales, mp 245-247°C (CH_2Cl_2-hexane).

2,6,7,8,9,10-Hexahydro-6,6,9-trimethyl-9-vinylnaphth[1,2,3-*cd*]indole (20) — To a suspension of **17** (81 mg) in MeOH (5 ml) was added Mg (113 mg) at room temperature and the mixture was stirred for 14 h. Addition of sat. NH_4Cl-H_2O, extraction with CH_2Cl_2, usual work-up, and PTLC [hexane-EtOAc (9:1)] gave **20** (44 mg, 85%) as colorless syrup. MS *m/z*: 277 (M^+). IR ($CHCl_3$) cm^{-1}: 1638. ^1H NMR ($CDCl_3$) δ: 1.08 (3H, s), 1.41 (3H, s), 1.43 (3H, s), 1.50-1.78 (2H, m, H-13), *ca.* 1.78-2.70 (2H, m, H-14), 2.22 and 2.49 (1H each, d each, J=16.5, H-11), 4.91 (1H, dd, J=10.5, 1.5), 4.95 (1H, dd, J=17.5, 1.5), 5.88 (1H, dd, J=17.5, 10.5), 6.77 (1H, br s, H-2), 6.90-7.31 (3H, m), 7.59 (1H, br s, NH).

LAH or $LiAlD_4$ reduction of the Compounds 14, 17, and 20 — Procedure was the same as above using 15 fold of LAH or 98 atom% $LiAlD_4$. The compond **14** afforded **15**[1] (25%), colorless needles, mp 151-153°C (CH_2Cl_2-hexane) and **16**[1] (43%), colorless prisms, mp 103-105°C (MeOH-H_2O), or **21** (26%, the more polar isomer) and **22** (55%, the less polar isomer) after PTLC [hexane-CH_2Cl_2 (11:1)]. **21**: Colorless needles, mp 152-153.5°C (CH_2Cl_2-hexane). Anal. Calcd for $C_{17}H_{19}D_2N$: C, 84.59; H, 7.94; D, 1.67; N, 5.80. Found: C, 84.44; H, 7.96; D, 1.76; N, 5.80. MS *m/z*: 241 (M^+). IR (KBr) cm^{-1}: 2110, 2080. ^1H NMR ($CDCl_3$) δ: 1.08 (3H, s), 1.40 (3H, s), 2.38 (1H, br d, J=10, H-11e), 6.76 (1H, d, J=1.5, H-2), 6.90-7.25 (3H, m), 7.72 (1H, br s, NH). **22**: Colorless prisms, mp 103-105°C (MeOH-H_2O). Anal. Calcd for $C_{17}H_{19}D_2N$: C, 84.59; H, 7.94; D, 1.67; N, 5.80. Found: C, 84.55; H, 8.03; D, 1.78; N, 5.83. MS *m/z*: 241 (M^+). IR (KBr) cm^{-1}: 2130, 2105, 2090. ^1H NMR ($CDCl_3$) δ: 1.20 (3H, s), 1.39 (3H, s), 2.29 (1H, br d, J=12, H-11e), 6.76 (1H, d, J=2, H-2), *ca.* 6.76-7.00 (1H, m, H-5), 7.00-7.18 (2H, m), 7.72 (1H, br s, NH). About a 3:2 mixture of **18** and **19** was obtained from either **17** or **20** in 66% or 69% yield. This mixture was repeatedly separated by column chromatography [hexane-Et_2O (19:1)] to afford samples for ^1H NMR analysis. **18** (the less polar isomer): Colorless scales, mp 119-120.5°C (MeOH-H_2O). Anal. Calcd for $C_{20}H_{25}N$: C, 85.97; H, 9.02; N, 5.01. Found: C, 85.61; H, 8.96; N, 5.08. MS *m/z*: 279 (M^+). IR (KBr) cm^{-1}: 1634. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.01 (3H, s), 1.21 (3H, s), 1.47 (3H, s), 4.47 (1H, dd, J=11, 1.5), 4.61 (1H, dd, J=17.5, 1.5), 5.77 (1H, dd, J=17.5, 11), 6.78 (1H, dd, J=2, 2, H-2), 6.87-6.94 (1H, m, H-5), 7.09-7.17 (2H, m, H-6 and H-7), 7.85 (1H, br s, NH), others in Table 1. **19** (the more polar isomer): Colorless syrup. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.77 (3H, s), 1.21 (3H, s), 1.49 (3H, s), 4.87 (1H, dd, J=10.5, 1.5), 4.93 (1H, dd, J=17.5, 1.5), 5.83 (1H, dd, J=17.5, 10.5), 6.87 (1H, dd, J=2, 2, H-2), 6.90-6.97 (1H, m, H-5), 7.10-7.19 (2H, m, H-6 and H-7), 7.90 (1H, br s, NH), others in Table 1. The mixture of **23** and **24** (*ca.* 3:2), obtained from **17** in 80% yield, was purified in the same manner as above. **23** (the less polar isomer): Colorless scales, mp 118-119°C (MeOH-H_2O). Anal. Calcd for $C_{20}H_{23}D_2N$: C, 85.35; H, 8.24; D, 1.43; N, 4.98. Found: C, 84.82; H, 8.12; D, 1.41; N, 4.92. MS *m/z*: 281 (M^+). IR (KBr) cm^{-1}: 2120, 1633. ^1H NMR ($CDCl_3$, 400 MHz) δ: 1.01 (3H, s), 1.20 (3H, s), 1.47 (3H, s), 4.47 (1H, dd, J=11, 1.5), 4.61 (1H, dd, J=17.5, 1.5), 5.77 (1H, dd, J=17.5, 11), 6.78 (1H, d, J=2, H-2), 6.87-6.94 (1H, m, H-5), 7.09-7.17 (2H, m, H-6 and H-7), 7.85 (1H, br s, NH), others in Table 1. **24** (the more polar isomer): Colorless syrup. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.77 (3H, s), 1.20 (3H, s), 1.48 (3H, s), 4.87 (1H, dd, J=10.5, 1.5), 4.93 (1H, dd, J=17.5, 1.5), 5.83 (1H, dd, J=17.5, 10.5), 6.87 (1H, d, J=2, H-2), 6.90-6.97 (1H, m, H-5), 7.10-7.20 (2H, m, H-6 and H-7), 7.92 (1H, br s, NH), others in Table 1.

[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-6a,10a-d_2 (25)** — In a similar manner as above, reduction of **3** (55 mg) in THF (5 ml) with $LiAlD_4$ (147 mg), followed by formylation with acetic formic anhydride (0.3 ml) in CH_2Cl_2 (3 ml) and pyridine (0.6 ml) afforded the crude **9** and the crude **25** after PTLC [hexane-EtOAc (4:3)]. Both were further purified by PTLC (1% MeOH-CH_2Cl_2) to yield **9** (6 mg, 16%) and **25** (15 mg, 40%). **25**: Colorless syrup. MS *m/z*: 324 (M^+). IR ($CHCl_3$) cm^{-1}: 2115, 1673. ^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), 1.46 (3H, s), 4.62 and 3.76 (1H, d each, J=9 and 9.5, H-11), 4.84 (1H, dd, J=17.5, 1.5), 4.92 (1H, dd, J=11, 1.5), 5.64-6.12 (1H, m, NHCHO),

5.86 (1H, dd, J=17.5, 11), 6.74-7.17 (4H, m), 8.24 (1H, br s, indole NH), 8.15 and 7.91 (1H, s each, CHO).

(±)-Hapalindole J-6a,10a-d_2 (26) — Stirring of **25** (13 mg) in pyridine (0.5 ml) with $POCl_3$ (19 µl) at -20°C for 40 min under Ar atmosphere as before, followed by usual work-up and PTLC [hexane-EtOAc (4:1)] afforded **26** (9 mg, 73%) as colorless prisms, mp 180-181.5°C (CH_2Cl_2-hexane). Anal. Calcd for $C_{21}H_{22}D_2N_2$: C, 82.31; H, 7.24; D, 1.31; N, 9.14. Found: C, 82.09; H, 7.33; D, 1.40; N, 9.04. MS *m/z*: 306 (M^+). IR (KBr) cm^{-1}: 2150, 1640. ^1H NMR ($CDCl_3$, 400 MHz) δ: 0.82 (3H, s, H-19), 1.22 (3H, s, H-18), 1.52 (3H, s, H-17), 5.08 (1H, d, J=17, H-21*Z*), 5.14 (1H, d, J=11, H-21*E*), 6.05 (1H, dd, J=17, 11, H-20), 6.89 (1H, br s, H-2), 6.93-7.01 (1H, m, H-5), 7.13-7.22 (2H, m, H-6 and H-7), 8.00 (1H, br s, NH), others in Table 1.

[9*R-(9α,10α)]-10-Azido-2,6,7,8,9,10-hexahydro-2,6,6,9-tetramethyl-9-vinylnaphth[1,2,3-*cd*]indole (33)** — A solution of **3** (50 mg) in 10% KOH in DME-MeOH-H_2O (2:1:1) (4 ml) was warmed at 55-60°C with stirring for 8 h. After cooling in an ice bath, sat. NH_4Cl-H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane-EtOAc (6:1)] afforded the detosylated compound (24 mg, 71%) as slightly yellow syrup. MS *m/z*: 318 (M^+). IR ($CHCl_3$) cm^{-1}: 2090, 1638. ^1H NMR ($CDCl_3$) δ: 1.03 (3H, s), 1.46 (3H, s), 1.49 (3H, s), 3.78 (1H, s, H-11), 5.10 (1H, dd, J=18, 1.5), 5.12 (1H, dd, J=10.5, 1.5), 6.09 (1H, dd, J=18, 10.5), 6.83 (1H, d, J=2, H-2), 6.90-7.32 (3H, m), 7.71 (1H, br s, NH). To an ice-cooled solution of this detosylated compound (22 mg) in THF (2 ml) and DMF (0.5 ml) were added successively MeI (0.05 ml) and 50% NaH (7 mg) with stirring under Ar atmosphere. The mixture was further stirred at 0°C for 30 min. Quenching with sat. NH_4Cl-H_2O, extraction with Et_2O, usual work-up, and PTLC [hexane-EtOAC (29:1)] gave **33** (19 mg, 83%) as colorless syrup. MS *m/z*: 332 (M^+). IR ($CHCl_3$) cm^{-1}: 2100, 1640. ^1H NMR ($CDCl_3$) δ: 1.04 (3H, s), 1.47 (3H, s), 1.49 (3H, s), 3.69 (3H, s, NCH_3), 3.75 (1H, s, H-11), 5.09 (1H, dd, J=18, 1), 5.12 (1H, dd, J=10.5, 1), 6.08 (1H, dd, J=18, 10.5), 6.76 (1H, s, H-2), 6.88-7.35 (3H, m).

[9*R-(9α,10α)]-10-Formamido-2,6,7,8,9,10-hexahydro-2,6,6,9-tetramethyl-9-vinylnaphth[1,2,3-*cd*]indole (34)** — Compound **33** (18 mg) in THF (4 ml) was reduced with LAH (40 mg) at 0-26°C for 16 h. After the usual work-up, the residue (18 mg) was stirred with acetic formic anhydride (0.2 ml) in CH_2Cl_2 (2 ml) and pyridine (0.4 ml) at -20°C to room temperature for 7 h. The same work-up as before and PTLC [hexane-CH_2Cl_2 (1:2)] afforded **34** (8 mg, 44%) as slightly yellow syrup. HRMS Calcd for $C_{22}H_{26}N_2O$: 334.205. Found: 334.206. IR ($CHCl_3$) cm^{-1}: 1675. ^1H NMR ($CDCl_3$) of major and minor rotamers δ: 1.09 (3H, s), 1.43 (3H, s), 1.46 (3H, s), *ca.* 1.46-1.94 (2H, m, H-13), *ca.* 2.13-2.71 (2H, m, H-14), 3.66 (3H, s, NCH_3), 4.78 (1H, d, J=10.5, H-11), 4.99 (1H, dd, J=18, 1), 5.02 (1H, dd, J=10.5, 1), 5.49 (1H, br d, J=10.5, N<u>H</u>CHO), 5.79-6.20 (1H, m, H-20), 6.82 and 6.63 (1H, s each, H-2), 6.86-7.33 (3H, m), 8.14 and 8.20 (1H, s each, CHO).

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