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TOTAL SYNTHESIS OF MARINE ALKALOIDS (±)-HAPALINDOLES J AND M

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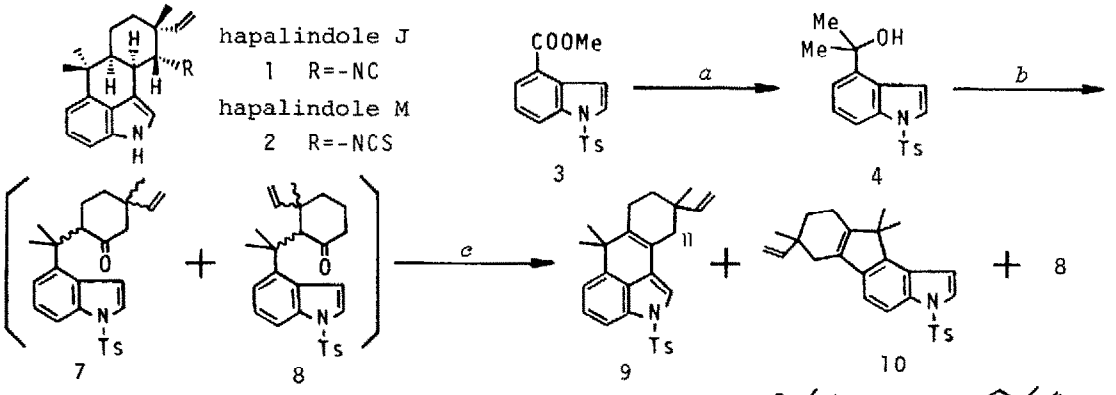
Abstract : Marine alkaloids hapalindoles J 1 and M 2 were concisely synthesized in the racemic form from a tertiary alcohol 4 by way of 7, 9, 11, and 17, using unusual $LiAlH_4$ reduction of 11 as a key reaction step.

Hapalindoles and related indole derivatives are antibacterial and antimycotic alkaloids obtained from the blue-green alga *Hapalosiphon fontinalis* by Moore and co-laborators.[1,2,3] Recently indolinones, having similar structures, have been isolated from the cells of a cultured cyanobacterium belonging to the genus *Fischerella* as inhibitors of arginine vasopressin binding.[4] In this communication, we report the first and concise total synthesis of hapalindoles J 1 and M 2, representatives of non-chlorine-containing alkaloids among the 24 above-mentioned natural products. Our success in the synthesis of 1 and 2 stems from three novel findings: (i) the $SnCl_4$-mediated carbon-carbon bond forming reaction (4 → 7), whose details have been reported elsewhere,[5] (ii) unprecedented intramolecular cyclization of the indolic C-4 substituent to the C-3 position (7 → 9), and (iii) unusual and stereoselective reduction of the electron-rich tetrasubstituted double bond of 11 with $LiAlH_4$ (LAH) to give the otherwise unattainable compound 17.

The synthesis commenced with the tertiary alcohol 4,[9] readily available from methyl 1-(*p*-toluenesulfonyl)-4-indolylcarboxylate 3[6] in 98% yield (Chart 1).

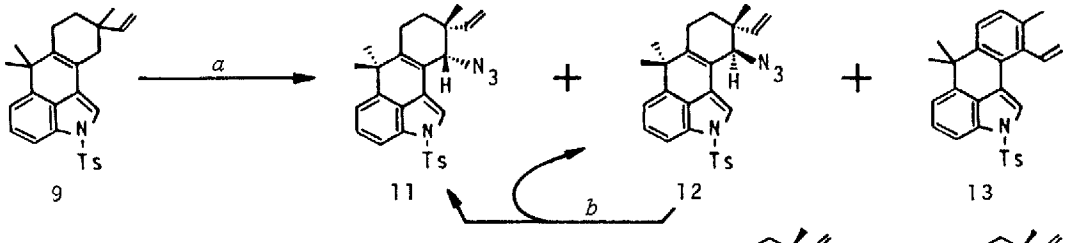


a: MeMgI, Et_2O-THF, 0°C → r.t., 30 min.
b: 5 + 6 (5:2), $SnCl_4$, CH_2Cl_2, -78°C, 10 min.
c: $BF_3 \cdot Et_2O$, CH_2Cl_2, 18°C, 1.5 h.

Chart 1

3-Methyl-3-vinylcyclohexanone[7] was treated with LDA and Me_3SiCl[8] and the resulting mixture of enol ethers 5 and 6 (5:2) was allowed to react with 4 in the presence of $SnCl_4$.[5] A crude reaction mixture containing 7 and 8 was further treated with $BF_3 \cdot Et_2O$ to give tetracyclic compounds 9[9] and 10[9] in 57% and 4.5% yields respectively, calculated from the tertiary alcohol 4, accompanied by 8 with inseparable contaminants. The geminal dimethyl group may play an important rôle to make the ketone group of 7 approach the C-3 position of the indole nucleus, whereas in the case of 8, steric congestion of the dimethyl group and the quaternary carbon side chain on the cyclohexanone prohibits the formation of the corresponding tetracyclic compound. Thus an important intermediate 9 having the same carbon frame-work as hapalindoles was obtained from a readily accessible compound 4 in only two steps.

To introduce a nitrogen function at the desired C-11 position of 9, it was treated with N-bromosuccinimide in the presence of benzoyl peroxide to give a mixture of epimeric bromides, followed by replacement with sodium azide in DMF to produce two compounds 11[9] and 12[9] in 34% and 29% yields respectively, whose stereochemistry remained unknown at this stage (Chart 2). An aromatic compound 13[9] was obtained as a by-product in 7% yield. When the azide 12 was subjected to a reduction condition with $SnCl_2$ in MeOH,[10] solvolysis of an intermediary allylic nitrogen species took place and reaction products were probably a mixture of 14 and 15, judging from its PMR spectrum. Without separation, this was treated with trimethylsilylazide in the presence of trimethylsilyl triflate to recycle to 11 and 12 in 23% and 53% yields, respectively, converting the undesired 12 in part into 11.



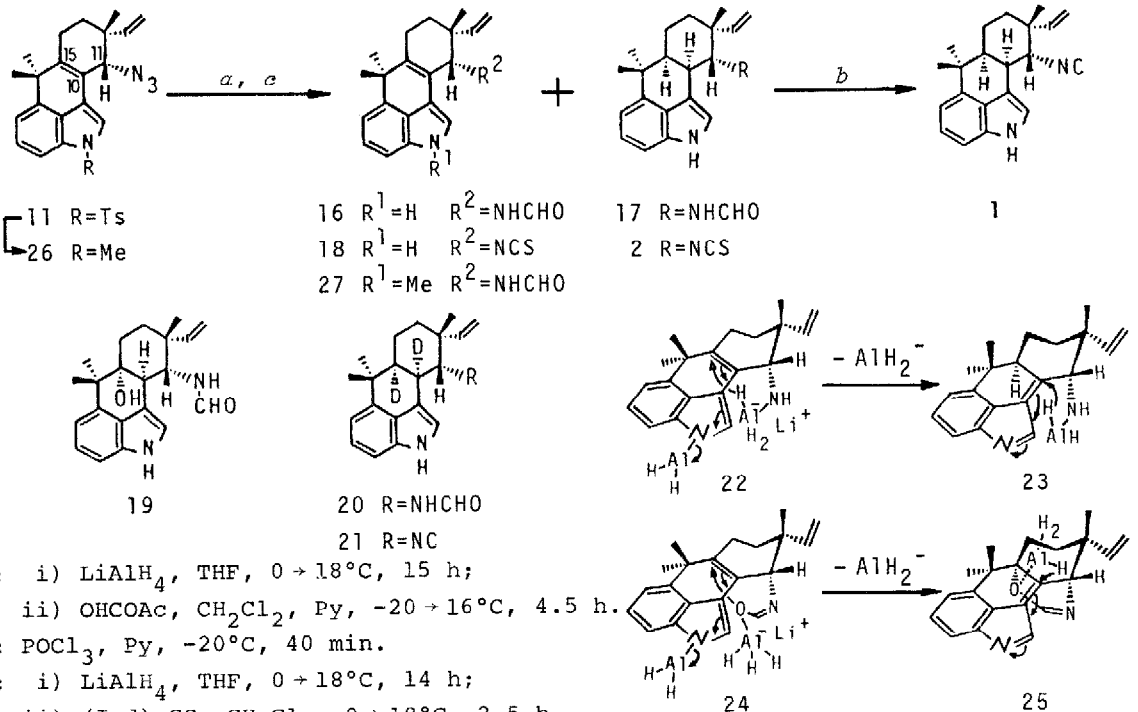
9 11 12 13 14 15

a: i) NBS, BPO, CCl_4, reflux, 30 min.
ii) NaN_3, DMF, 20°C, 16 h.
b: i) $SnCl_2$, MeOH, reflux, 2h.
ii) $TMSN_3$, TMSOTf, CH_2Cl_2, -20 – 12°C, 18h.

Chart 2

The azide 11 was reduced with LAH, followed by formylation to get 16 in the expectation that further treatment with $NaBH_3CN$ might induce reduction of the tetrasubstituted double bond (Chart 3). Actually, the expected reduction with LAH did happen, but a major product was an over-reduction compound 17,[9] obtained in 41% yield, accompanied by 16[9] in 23% yield. The structure of 17 including a wanted stereochemical arrangement was easily verified by completion of the synthesis of (±)-hapalindole J 1,[9] mp 182-184°C (hexane-CH_2Cl_2), in 76%

yield. Similarly the LAH-reduction mixture of 11 was treated with 1,1'-thiocarbonyldiimidazole[11] to afford (±)-hapalindole M 2,[9] in 35% yield, accompanied by 18[9] in 9% yield from 11. Identity of the synthetic (±)-1 and (±)-2 was confirmed by comparing their PMR (400 MHz, $CDCl_3$) and IR ($CHCl_3$) spectra with those of the natural products. Hence the first total synthesis of (±)-1 and (±)-2 was achieved in seven and six steps from 4 thanks to an unexpected, stereoselective unusual reaction with LAH. The $NaBH_3CN$ reduction of 16 afforded nothing but the starting material.



a: i) $LiAlH_4$, THF, 0 → 18°C, 15 h;
ii) OHCOAc, CH_2Cl_2, Py, -20 → 16°C, 4.5 h.
b: $POCl_3$, Py, -20°C, 40 min.
e: i) $LiAlH_4$, THF, 0 → 18°C, 14 h;
ii) $(Imd)_2CS$, CH_2Cl_2, 0 → 18°C, 2.5 h.
d: i) 10% KOH in DME-MeOH-H_2O (2:1:1), 55 – 60°C, 8 h;
ii) MeI, NaH, THF-DMF (4:1), 0°C, 30 min.

Chart 3

Next we examined how to understand the LAH reduction of the electron-rich double bond conjugated with the indole moiety. Firstly, no deuterium incorporation was observed when the LAH reduction mixture was quenched with D_2O, meaning that a stable carbanion salt does not exist during the reaction course. Secondly, the *p*-toluenesulfonyl group at the indole nitrogen atom was hardly involved in the reduction, since the indole derivative 16 also afforded the reduction compound 17 in 12% yield. But a main product obtained in 46% yield was a hydroxylated compound 19[9] at the most electron-sufficient position of the α,β-unsaturated indole molecule 16. Stereochemistry of the hydroxyl group is noteworthy in that it has the same configuration as the formamide function. Therefore, the $LiAlD_4$ reduction of 11 was carried out to shed further light on the reaction mechanism. After formylation as usual, a compound 20[9] carrying two deuterium atoms at the 10 and 15 positions was obtained in 40% yield with

16 in 16% yield. The structure of 20 was unambiguously determined by converting it into 21[9] ($POCl_3$, Py, 73% yield) and by assigning all PMR signals of 21 (400 MHz), compared with those of 1. Thus the nucleophilic attack at the 15 position of 11 and 16 with the deuterium and hydroxyl anions is characteristic of the present reduction.

A plausible mechanism deduced from this is as follows. Reductive cleavage of the *p*-toluenesulfonyl group may form a 1-indolylaluminum compound 22 having in addition an aluminum-chelated nitrogen function originating from the azide group. The electron-rich double bond donates the electron to the aluminium at the indole nitrogen to liberate aluminum hydride anion, with a simultaneous attack of the hydride at the 15 position by the chelated reducing species, producing an intermediary indolenine derivative 23. This may be further reduced by an intramolecular approach of the hydride to the 10 position to form the fully reduced compound, whose formylation ends up with the stereoselective formation of 17 bearing the required cis configuration at the 10 and 15 positions. When the formamide group is situated close to the double bond as in 16, the LAH reduction may take place partially by way of an intramolecular attack of the formamide oxygen instead of the hydride at the 15 position (24 → 25), and subsequent reduction at the 10 position of 25, followed by hydrolysis of a dihydro-1,3-oxazine ring during the work-up, affords a hydroxylated compound 19. To support the above reaction mechanism initiating from the 1-indolylaluminum compound, the tosylate 11 was transformed to the 1-methyl derivative 26 by alkalline hydrolysis, followed by methylation in 59% yield, and 26 was submitted to the successive treatment with LAH and the formylating reagent. Only one product 27 was obtained in 44% yield, implying that blocking of the indole nitrogen prevents the formation of the over-reduction product.

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