SYNTHESIS OF DEBROMO-8,8a-DIHYDROFLUSTRAMINE C. A MODEL EXPERIMENT RELATED TO THE TOTAL SYNTHESIS OF AMAUROMINE

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Abstract — A derivative (1) from marine alkaloid, flustramine C, was synthesized utilizing thio-Claisen rearrangement at the key step. The method of the synthesis would be applied to synthesis of alkaloids possessing the reversed prenyl group at 3a position of hexahydropyrrolo[2,3-b]indole skeleton such as amauromine.

During the last decade, several alkaloids which possess the reversed prenyl group at 3a position of hexahydropyrrolo[2,3-b]indole skeleton have been isolated from micro-organism and marine sources. The mode of introduction of the inverted isoprene unit in vivo into those alkaloids can be accounted by a feasible
explanation reported by Bycroft et al, who developed thio-Claisen rearrangement reaction of dimethylallyl 2-indolyl sulphonium salts, giving possible implications in indole alkaloid biosynthesis.

Recently we reported the structure of a new alkaloid, amauromine, which is a fungal metabolite with potent vasodilating activity. In order to explore a method toward total synthesis of this alkaloid possessing two reversed prenyl groups in its molecule, we intended to conduct synthesis of a model compound. Debromo-8,8a-dihydroflustramine C (1) is a compound derived from bromo-substituted marine alkaloid, flustramine C, by lithium aluminum hydride reduction. In this communication, we report the synthesis of the model compound (1) utilizing thio-Claisen rearrangement and successive ring closure with desulfurization by base. 8-Indole acetic acid was oxidized with DMSO (10 eq) and conc HCl (20 eq, room temperature, 30 min.) into 2 (60 %, mp 146°C, lit, mp 147°C), which was methylated with MeOH-HCl (74 %), and subsequently treated with P2S5 (reflux, 3 h) to give thione (3) (65 %). After methylation of 3 with MeI, the yielded 2-methylthio indole derivative (4) was subjected to the thio-Claisen rearrangement reaction by being stirred with prenyl bromide (2.5 eq), K2CO3.
(3.5 eq) in dioxane-DMF (20 : 1) for 48 h at room temperature. The products obtained after usual work up were shown by analysis of $^1$H-NMR spectrum to involve the compound (5) as the major product accompanied by a minor product (6) (5 : 6 = 8 : 1) $^7$ which were hydrolysed with aq. NaOH to provide the crystalline rearranged compound (7) $^8$. The isolated yield of 7 from 3 was 30 %. The position 2 of the compound (7) was expected to work as a good electrophilic center for attack of amide anion leading to cyclization. Then 7 was converted to N-methylamide (8) $^9$ (65 %) through mixed anhydride (Et$_3$N, ClCOOEt) followed by treatment with aq. methylamine. Abstraction of amide hydrogen in 8 by NaH resulted in clean cyclization with concurrent elimination of methylthio group to give 9 in the yield of 80 %. Reduction of 9 with DIBAL in ether afforded the hexahydropyrrolo [2,3-b]indole derivative (1) (52 %). PMR, CMR and Mass spectral data of this synthetic compound were in accord with those of debromo-8,8a-dihydroflustramine C prepared from flustramine C by Carlé et al. $^4$ The synthesis achieved here would be an efficient method to synthesize hexahydropyrrolo[2,3-b]indole skeleton substituted with 1,1-dimethyl-2-propenyl group at position 3a. Application of this methodology to total synthesis of amauromine is being conducted, and the details will be reported elsewhere.

REFERENCES AND NOTES


7. The ratio was determined from NMR data on the integral of respective methyl signals of inverted prenyl and prenyl groups in 5 and 6.
8. The structure of the intermediates was confirmed by the following physical evidence.

2: IR (Nujol) 3300-2500, 1720, 1690, 1650, 1620 cm⁻¹; PMR (DMSO-d₆) 12.30 (1H, s), 10.33 (1H, s), 7.33-6.80 (4H, m), 3.66 (1H, dd, J=6.6 and 4.8 Hz), 2.90 (1H, dd, J=16.8 and 4.8 Hz), 2.73 (1H, dd, J=16.8 and 6.6 Hz) ppm; MS m/z 191 (M⁺); mp 146°C.

4: IR (CHCl₃) 3460, 3000, 2950, 2920, 1730, 1450, 1340, 1160, 1020 cm⁻¹; PMR (CDCl₃) 8.40 (1H, s), 7.63-7.50 (1H, m), 7.20-7.00 (3H, m), 3.89 (2H, s), 3.63 (3H, s), 2.29 (3H, s) ppm; MS m/z 235 (M⁺).

7: IR (CHCl₃) 3400-2500, 1710, 1500, 1380, 1360, 920 cm⁻¹; PMR (CDCl₃-CD₃OD) 7.40-7.00 (4H, m), 6.00 (1H, dd, J=11.0 and 17.0 Hz), 5.30-4.87 (2H, m), 3.03 (2H, s), 2.63 (3H, s), 1.07 (3H, s), 1.00 (3H, s) ppm; MS m/z 289 (M⁺).

8: IR (CHCl₃) 3420, 2980, 1660, 1380, 1360, 920 cm⁻¹; PMR (CD₃OD) 7.43-7.00 (4H, m), 6.03 (1H, dd, J=11.0 and 16.0 Hz), 5.27-4.87 (2H, m), 2.97 (2H, s), 2.67 (3H, s), 2.33 (3H, s), 1.07 (3H, s), 1.00 (3H, s) ppm; MS m/z 302 (M⁺).

9: IR (CHCl₃) 1740, 1630, 1590, 1380, 1360, 920 cm⁻¹; PMR (CDCl₃) 7.44-6.90 (4H, m), 5.76 (1H, dd, J=11.0 and 16.0 Hz), 5.16-4.94 (2H, m), 3.20 (3H, s), 3.02 (1H, d, J=16.0 Hz), 2.40 (1H, d, J=16.0 Hz), 0.96 (3H, s), 0.80 (3H, s) ppm; MS m/z 254 (M⁺).

Received, 19th July, 1984