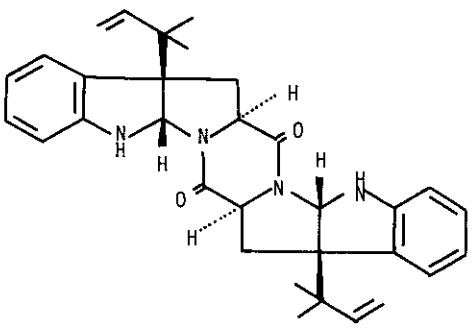
SYNTHESIS OF DEBROMO-8,8a-DIHYDROFLUSTRAMINE C. A MODEL EXPERIMENT RELATED TO THE TOTAL SYNTHESIS OF AMAUROMINE

Shigehiro Takase, Itsuo Uchida, Hirokazu Tanaka, and Hatsuo Aoki

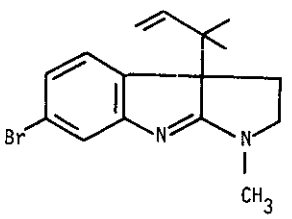
Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd. 1-6, 2-chome, Kashima, Yodogawa-ku, Osaka 532, Japan

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.

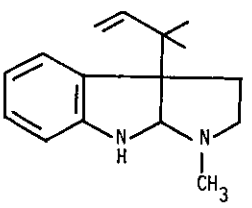
During the last decade, several alkaloids which possess the reversed prenyl group at 3a position of hexahydropyrrolo[2,3-b]indole skeleton have been isolated from micro-organism and marine sources.[1] The mode of introduction of the inverted isoprene unit in vivo into those alkaloids can be accounted by a feasible



Amauromine



Flustramine C



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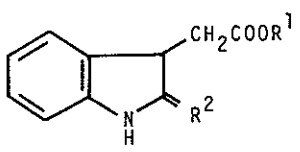
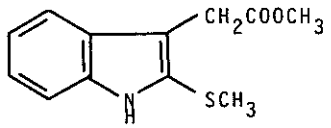
explanation reported by Bycroft et al[2], who developed thio-Claisen rearrangement reaction of dimethylallyl 2-indolyl sulphonium salts, giving possible implications in indole alkaloid biosynthesis.

Recently we reported the structure of a new alkaloid, amauromine[3], 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[4]. In this communication, we report the synthesis of the model compound (1) utilizing thio-Claisen rearrangement and successive ring closure with desulfurization by base.

ß-Indole acetic acid was oxidized with DMSO (10 eq) and conc HCl (20 eq, room temperature, 30 min.)[5] into 2 (60 %, mp 146°C, lit[6], mp 147°C)[8], which was methylated with MeOH-HCl (74 %), and subsequently treated with P_2S_5 (reflux. 3 h) to give thione (3) (65 %). After methylation of 3 with MeI, the yielded 2-methylthio indole derivative (4)[8] was subjected to the thio-Claisen rearrangement reaction by being stirred with prenyl bromide (2.5 eq), K_2CO_3



2 R^1=H, R^2=O
3 R^1=CH_3, R^2=S



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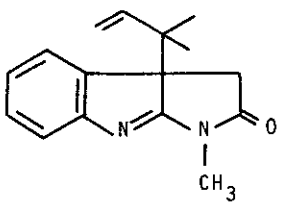

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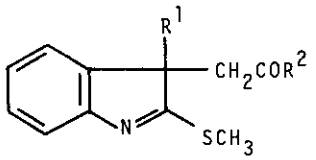

5 R^1=  , R^2=OCH_3

6 R^1=  , R^2=OCH_3

7 R^1=  , R^2=OH

8 R^1=  , R^2=$NHCH_3$

(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)[8] (65 %) through mixed anhydride (Et_3N, 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[8] 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.

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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-d_6) 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 ($CHCl_3$) 3460, 3000, 2950, 2920, 1730, 1450, 1340, 1160, 1020 cm^{-1} ; PMR ($CDCl_3$) 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 ($CHCl_3$) 3400-2500, 1710, 1500, 1380, 1360, 920 cm^{-1} ; PMR ($CDCl_3$-CD_3OD) 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 ($CHCl_3$) 3420, 2980, 1660, 1380, 1360, 920 cm^{-1} ; PMR (CD_3OD) 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 ($CHCl_3$) 1740, 1630, 1590, 1380, 1360, 920 cm^{-1} ; PMR ($CDCl_3$) 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^+).

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