Tetrahedron Letters,Vol.26,No.7,pp 847-850,1985
Printed in Great Britain

0040-4039/85 $3.00 + .00

TOTAL SYNTHESIS OF AMAUROMINE

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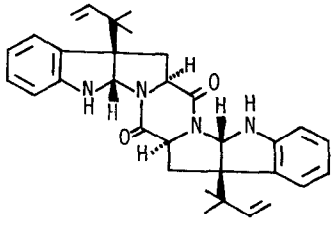
Summary: Total synthesis of amauromine(1), a novel alkaloid possessing two reversed prenyl groups in its molecule, was described.

Amauromine (1) is a recently isolated novel alkaloid with vasodilating activity[1]. In previous papers, we reported its unique structure[2] and the synthesis[3] of a model compound : debromo-8,8a-dihydroflustramine C (2). Herein, we report the first total synthesis of amauromine (1) utilizing thio-Claisen rearrangement reaction in the key step.

Carbobenzyloxy-L-tryptophan was converted to the oxindole derivative (3) by the standard method (DMSO/conc HCl/RT[4], and MeOH/HCl, 53 %). Introduction of the methylthio function at position 2 of indole skeleton was carried out by refluxing of 3 with P_2S_5 in pyridine (3hr, under argon) and subsequent methylation (CH_3I/ K_2CO_3/ RT) to lead to 4 (NMR ($CDCl_3$) δ 8.33 (1H, s),



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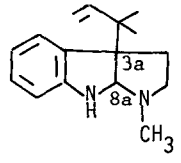

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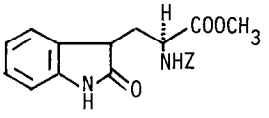

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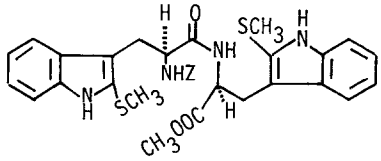

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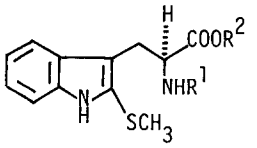
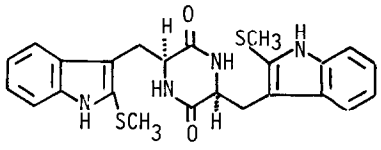


4 $R^1 = COOCH_2C_6H_5$, $R^2 = CH_3$

5 $R^1 = COOCH_2C_6H_5$, $R^2 = H$

6 $R^1 = H$, $R^2 = CH_3$



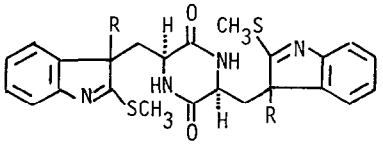
8

7.57-7.00 (9H, m), 5.43 (1H, d, J=8Hz), 5.05 (2H, s), 4.73 (1H, m), 3.63 (3H, s),3.33 (2H, d, J=6Hz), 2.30 (3H, s); 32% from 3). From 4 the corresponding carboxylic acid (5) and amine (6) are prepared quantitatively by alkaline hydrolysis (NaOH / THF-MeOH-H_2O / RT / overnight) and by treatment with 30 % HBr-AcOH (RT / 1hr) respectively. Synthesis of the key precursor (8) was achieved by coupling of 5 and 6, followed by formation of diketopiperazine ring. Thus, the active ester derived from 5 by DCC/HOSu was condensed with 6 at r.t. overnight to provide the dipeptide (7) (NMR ($CDCl_3$) δ 8.13 (2H, s), 7.33-7.00 (13H, m), 6.33 (1H, d, J=8Hz), 5.43 (1H, d, J=8Hz), 4.97 (2H, s), 4.80-4.37 (2H, m), 3.50 (3H, s), 3.30-3.17 (4H, m), 2.20 (6H, s); 52 %). After removal of the Z-group of (7) by treatment with 30 % HBr-AcOH, the resulting amine was dissolved in dry MeOH and saturated with dry ammonia gas at 0°. Standing for 4hr at r.t. resulted in the diketopiperazine 8 (NMR (CD_3OD) δ 7.33-6.83 (8H, m), 4.20-4.00 (2H, m), 3.33-3.17 (4H, m), 2.33 (6H, s); 67 %).

The next stage, the introduction of two reversed prenyl groups on 8, was

realized by thio-Claisen rearrangement reaction. Thus, 8, prenyl bromide (8eq) and K_2CO_3 (4eq) were stirred in dioxane at r.t. for 7 days under argon atmosphere. Separation of the products by medium pressure LC (1.5% MeOH-$CHCl_3$) and PTLC (ethyl acetate) afforded the key compound (9) (18% yield) and (10) (15% yield), 9 : NMR ($CDCl_3$) δ 7.56-7.02 (8H, m), 6.06 (2H, dd, J=10.5 and 17Hz), 5.20 (2H, dd, J=10.5 and 1Hz), 5.08 (2H, dd, J=17 and 1Hz), 4.88 (2H, d, J=3Hz), 3.24-3.04 (2H, m), 2.72 (6H, s), 2.80-2.70 (4H, m), 1.08 (6H, s), 1.04 (6H, s), MS m/z 600 (M^+) ; 10 : NMR ($CDCl_3$) δ 7.48-7.04 (8H, m), 5.96 (2H,dd, J=11 and 16Hz), 5.12 (2H, dd, J=11 and 1Hz), 5.00 (2H, dd, J=16 and 1Hz), 4.52 (2H, d, J=3Hz), 3.20-3.10 (2H, m), 2.72 (2H, d, J=16Hz), 2.60 (6H, s), 2.16 (2H, dd, J=16 and 8Hz), 1.08 (6H, s), 0.92 (6H, s), MS m/z 600 (M^+).

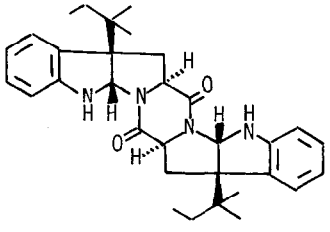
The stereochemistry of 9 and 10 was determined as follows. The compound 11 obtained from 9 by catalytic reduction (PtO_2 / AcOEt / 1 atm, 86 %) was treated with deactivated Ra-Ni (acetone / reflux / 70 min) to effect reductive cyclization giving the compound (41 %) all identical with tetrahydro-amauromine[2] (12). Through the same reaction sequences as above, the compound



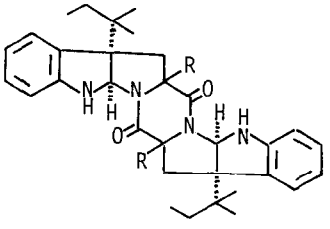
9 R =

10 R =

11 R =



12



13 R = ····H

14 R = ▬H

10 was transformed to 13 (NMR ($CDCl_3$) δ 7.10 (2H, d, J=8Hz), 7.00 (2H, t, J=8Hz), 6.70 (2H, t, J=8Hz), 6.28(2H, d, J=8Hz), 5.30 (2H, s), 5.08 (2H, s), 4.14 (2H, t, J=8Hz), 2.72 (2H, dd, J=14 and 8Hz), 2.68 (2H, dd, J=14 and 8Hz), 1.68-1.12 (4H, m), 0.92 (6H, s), 0.88 (6H, s), 0.80 (6H, t, J=8Hz), MS m/z 512 (M^+); over all yield 33 %), which was converted to 14 ($[\alpha]_D^{23}$ + 552°, c=0.5, $CHCl_3$), the antipode of tetrahydroamauromine (12), on alkaline treatment (Na_2CO_3 / MeOH / reflux).

Although cyclization of (9) by the method used for the model compound (2) was unsuccessful, reductive desulfurization of 9 with the combined use of $TiCl_4$ and $LiAlH_4$[5] directly afforded the compound (15%) identical with amauromine (1)[2] in all respects : synthetic, $[\alpha]_D^{23}$ -581° (c=0.65, $CHCl_3$) ; natural, $[\alpha]_D^{23}$ -583° (c=1.0, $CHCl_3$)[6].

references and notes

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6) Since the $[\alpha]_D$ value of the synthetic compound was in accord with that of the natural amauromine, it is understood that no epimerization occurred during the present synthesis.

(Received in Japan 18 October 1984)