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SYNTHESIS OF DEBROMO-8,8a-DIHYDROFLUSTRAMINE C[1], A MODEL SYNTHESIS TOWARD AMAUROMINE

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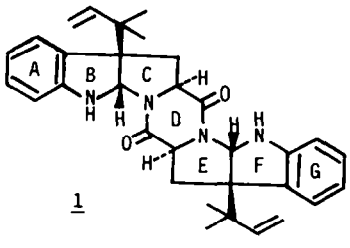
Abstract - Debromo-8,8a-dihydroflustramine C (4), a model compound of amauromine(1), was synthesized utilizing thio-Claisen rearrangement of a sulphonium cation at the key step. This is the first synthesis of hexahydropyrrolo-[2,3-b]indole skeleton substituted with inverted prenyl group at position 3a.

Amauromine (1) is a novel alkaloid isolated as a potent vasodilator from the culture broth of Amauroascus sp. No. 6237[2]. In the previous paper[3], the detailed process of structure elucidation of amauromine including the absolute configuration was presented by us. Amauromine (1) encompasses 3a-substituted physostigmine skeleton and is a dimeric alkaloid possessing a C_2 symmetry axis in the center of diketopiperazine (D ring). To our knowledge, none of synthesis of hexahydropyrrolo[2,3-b]indole skeleton, i.e. physostigmine skeleton with reversed prenyl group at 3a-position, has so far been reported[4]. In order to explore a method toward total synthesis of amauromine, thus firstly, we intended to synthesize a model compound comprising of this physostigmine skeleton 3a-substituted with reversed prenyl group. Recently, marine alkaloids, flustramine C[5] (2) and dihydroflustramine C[6] (3), have been isolated from natural sources. Carlé and Christophersen[5] obtained debromo-8,8a-dihydroflustramine C (4) by lithium aluminium hydride reduction of 2. The compound 4 was considered to be a suitable model compound for synthetic study of amauromine. In the present paper, we describe a full account of synthesis[1] of the model compound 4 which corresponds to the monomeric part (ABC and EFG rings) of 1.



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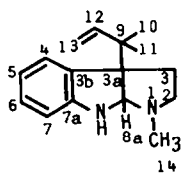

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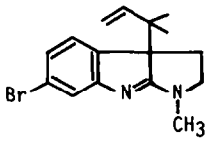

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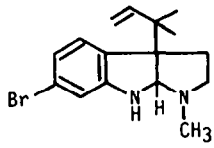

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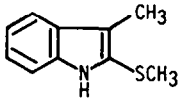
In 1970, a new type of thio-Claisen rearrangement reaction was developed by Bycroft and Landon[7], who treated 3-substituted indolyl sulphide 5 with prenyl bromide in the presence of potassium carbonate to get compound 6 having inverted prenyl group at position 3 as a major product, together with concomitantly produced minor product 7 in which dimethylallyl group was directly inserted to 3-position. The rearrangement into the major product 6 is supposed to have taken place through 3,3-sigmatropic process after formation of 2-indolyl sulphonium cation, from the machanistic consideration. It is thought that this new rearrangement reaction would be applicable to introduction of inverted prenyl group in the synthesis of 4. The intended compound 12* for the key rearrangement reaction was synthesized as follows (Scheme 1).



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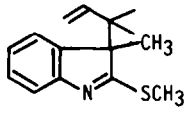

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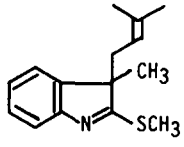

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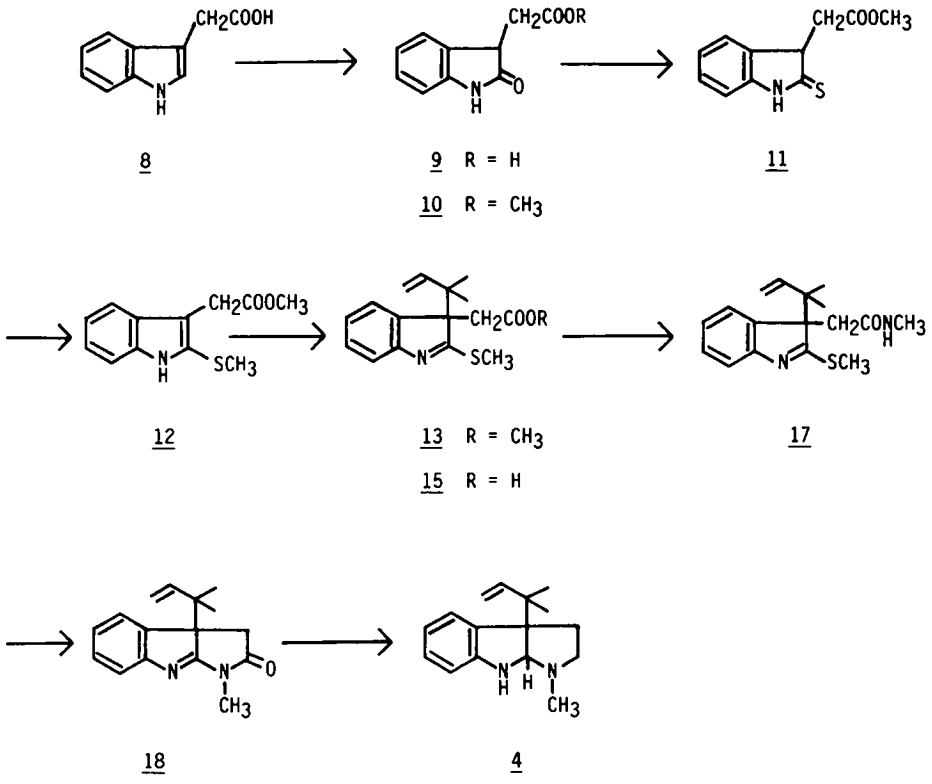
Indole-3-acetic acid (8) was oxidized with DMSO and conc HCl at room temperature[9] into oxindole-3-acetic acid (9), which was methylated with MeOH-HCl to give 10. Conversion of methyl ester 10 into thione 11 was effected by refluxing with phosphorus pentasulfide in pyridine for 3 hours. S-Methylation of 11 with methyl iodide (1.1eq) in the presence of potassium carbonate led quantitatively to the objective 2-methylthioindole derivative 12, which turned out to be rather unstable for isolation. The thio-Claisen rearrangement reaction through sulphonium cation for 12 was examined, therefore without isolation of 12, by one pot reaction using thione 11 as the starting material on the same solvent system. Thus, after the mixture of 11, methyl iodide (1.1eq) and potassium carbonate (3.6eq) in a solvent was stirred at room temperature for 5 minutes, prenyl bromide (2.5eq) was added, and the whole mixture was stirred under argon atmosphere at ambient temperature. Although in any solvent system the desired product 13 was always accompanied by the side reaction product 14 as in the case of Bycroft's experiment, the ratio of 13 and 14 was found to be influenced by

*Compound 12 was also prepared by the reaction of methyl indole-3-acetate and methylsulphenyl chloride according to the method by Wieland et al.[8] but the yield was not satisfactory.



8 9 R = H 10 R = CH_3 11

12 13 R = CH_3 15 R = H 17

18 4

Scheme - 1.

solvents used as shown in Table 1. Among the tested solvents dioxane-DMF (20:1) was the solvent system of our choice, while dioxane alone is still promising one provided the reaction time is extended more. The mixed oil of 13 and 14 (8:1), which was inseparable by chromatography, was subjected to alkaline hydrolysis (1N NaOH, MeOH-THF). Fortunatelly, direct crystallization of the crude products from diisopropyl ether led to isolation of the desired carboxylic acid 15 as a crystalline form. The overall yield of 15 from 11 was 30%.

The position 2 of indolenine 15 containing thus successfully introduced inverted prenyl group at position 3, was anticipated to be quite electrophilic and susceptible to intramolecular substitution by such a nucleophile as amide anion. Thus, the carboxyl group of 15 was converted to N-methylamide 17 through mixed anhydride (Et_3N, ClCOOEt) followed by addition of aq. methylamine. Generation of amide anion from 17 by treatment with sodium hydride in THF resulted in clean cyclization with concurrent elimination of methylthio group to provide the lactam 18 in the yield of 80%. Selective reduction of imine and lactam functions of 18 was effected with diisobutylaluminum hydride in ether to afford 3a-(1,1-dimethyl-2-propenyl)-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (4). ^1H, ^{13}C NMR and mass spectral data of this synthetic compound 4 are identical with those of debromo-8,8a-dihydroflustramine C prepared from flustramine C by Carlé and Christophersen[5]. The first synthesis of

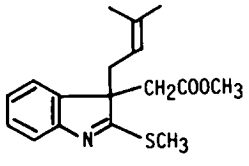


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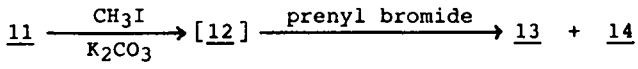
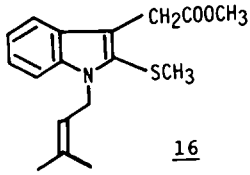
Table 1. Influence of solvent on the reaction



Entry	Solvent	Reaction time[a]	Combined yield of 13 and 14	(13/14)[b]	Other isolated products (yield)
1	DMF	6 hr	45%	(0.3/1)	16 (20%)[c]
2	acetone	48 hr	51%	(6/1)	
3	dioxane-DMF (20:1)	48 hr	56%	(8/1)	
4	dioxane	72 hr	18%	(8.6/1)	12 (43%)

a: after addition of prenyl bromide.
b: the ratio was determined *in situ* by ^{1}H NMR analysis (see Experimental section).
c: structural assignment for 16 was made by analysis of the spectral data (see Experimental section).

hexahydropyrrolo[2,3-b]indole (physostigmine) skeleton substituted with inverted prenyl group at position 3a, achieved here, would be a method widely applicable to synthesis of such indole alkaloids encompassing the same physostigmine nucleus as amauromine, flustramine A[10], flustramide A[11], roquefortine[12], aszonalenin[13], and LL-S490β[14]. Actually, we achieved a total synthesis[15] of amauromine (1) essentially following the methodology used in this model synthesis, and the details are the subject of the succeeding paper[16].



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EXPERIMENTAL

Melting points were taken on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 60 MHz (Jeol JNM-PMX 60), 100MHz (Jeol MH-100) or 400MHz (Bruker AM400) as indicated. ^{13}C NMR spectra and two-dimensional ^{1}H-^{13}C shift correlated spectrum were measured with Bruker AM400. Multiplicities of carbon signals were determined by DEPT technique[17]. The chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (δ 0.00) as an internal standard. Coupling constants are reported in hertz (Hz). IR spectra were recorded on a JASCO A-102 infrared spectrometer and are reported in wave numbers (cm^{-1}). Low-resolution mass spectra were measured on a Jeol JMS-D300 spectrometer. High-resolution mass spectra

(HRMS) were obtained on a VG ZAB-SE mass spectrometer. Medium pressure LC was performed by using Lobar pre-packed column (Merck), F.M.I. pump and UV detector UVILOG-10V (Yamazen). Column chromatography was performed with Merck 70-230 mesh silica gel (Art 7734) and preparative TLC with pre-coated silica gel plates (Merck, Art 5744).

2-(2-Oxo-3-indolinyl)acetic acid (9). To a solution of indole-3-acetic acid (100 g, 0.57 mole) in dimethyl sulfoxide (405 ml, 5.7 mole) was added conc HCl (960ml) over 10 min with stirring. After the addition was completed, the mixture was stirred at room temperature for 15min. The mixture was diluted with water and extracted with ethyl acetate (3x1l) and the combined organic extracts were washed with water, brine and dried over magnesium sulfate. Removal of the solvent left a powder which was recrystallized from acetone-benzene to yield 66 g (60.4%) of 9 as colorless needles: m.p. 146°C (lit[18]., 147°C); IR (Nujol) 3200-2500, 1720, 1690, 1650, 1620 cm^{-1}; ^1H NMR (100MHz,DMSO-d_6) δ 12.30 (1H,s), 10.33 (1H,s), 7.33-6.80 (4H,m), 3.66 (1H,dd,J=6.6 and 4.8Hz), 2.90 (1H,dd,J=16.8 and 4.8Hz), 2.73 (1H,dd,J=16.8 and 6.6Hz); MS m/z 191 (M^+).

Methyl 2-(2-oxo-3-indolinyl)acetate (10). Dry hydrogen chloride was bubbled into a solution of 2-(2-oxo-3-indolinyl)acetic acid (9) (65g) in anhydrous methanol (500ml) at 5°C for 10 min with stirring and the mixture was allowed to stand at room temperature for 1 hr. The solution was evaporated to dryness under reduced pressure to give an oil which was dissolved in methanol and the solution was concentrated to dryness under reduced pressure. This operation was repeated twice. Recrystallization of the residue from hot methanol afforded 52 g (74.5%) of 10 as white needles: m.p. 164-167°C ; IR (Nujol) 3150, 1720, 1700, 1620 cm^{-1}; ^1H NMR (60MHz,DMSO-d_6) δ 10.40 (1H,s), 7.33-6.73 (4H,m), 3.63 (1H,m), 3.53 (3H,s), 2.97-2.60 (2H,m); MS m/z 145 (base peak), 205 (M^+).

Methyl 2-(2-thioxo-3-indolinyl)acetate (11). Phosphorus pentasulfide (11.8g) was added to a solution of 10 (20g) in pyridine (214ml), and the mixture was refluxed for 3 hr under argon atmosphere. After cooled to room temperature, the mixture was poured into an ice water (1500ml) containing conc HCl (250ml) and extracted with ethyl acetate. The organic extract was washed with water, brine and dried over magnesium sulfate. Removal of the solvent gave an oil which was triturated with ether to afford 14 g (64.9%) of 11 as a colorless powder: IR (Nujol) 3150, 1725, 1620, 1500 cm^{-1}; MS m/z 221 (M^+).

Methyl 2-(2-methylthio-3-indolyl)acetate (12). To a solution of methyl 2-(2-thioxo-3-indolinyl)acetate (11) (100 mg, 0.45 mmole) in acetone (5ml) was added potassium carbonate (125 mg, 0.9 mmole) and methyl iodide (34 μl, 0.5 mmole) at room temperature under argon atmosphere. The mixture was stirred for 5 min and then filtered and the filtrate was concentrated under reduced pressure keeping the temperature below 30°C. The obtained oil was purified by medium pressure LC ($CHCl_3$) to give 90 mg (85%) of 12 as an oil whose spectral data were measured immediately. IR ($CHCl_3$) 3460, 3000, 2950, 2920, 1730, 1450, 1340, 1160, 1020 cm^{-1}; ^1H NMR (100MHz,$CDCl_3$) δ 8.40 (1H,s), 7.56 (1H,m), 7.20-7.00 (3H,m), 3.89 (2H,s), 3.63 (3H,s), 2.29 (3H,s); MS m/z 235 (M^+).

2-(3-(1,1-Dimethyl-2-propenyl)-2-methylthio-3H-indol-3-yl)acetic acid (15). To a solution of methyl 2-(2-thioxo-3-indolinyl)acetate (11) (2 g, 9.1 mmole) in a mixture of dioxane (10ml) and DMF (0.5ml) were added potassium carbonate (4.38g)

and methyl iodide (0.62ml). The mixture was stirred at room temperature for 5 min under argon atmosphere. Prenyl bromide (1-bromo-3-methyl-2-butene) (2.65 ml, 22 mmole) was added thereto and the mixture was stirred at room temperature for 2 days under argon atmosphere. The reaction mixture was diluted with ethyl acetate, and the mixture was washed with water, brine and dried over magnesium sulfate. Removal of the solvent gave an oil which was subjected to silica gel column chromatography. The column was eluted with chloroform to give 1.66g of oil, which is a mixture of methyl 2-(3-(1,1-dimethyl-2-propenyl)-2-methylthio-3H-indol-3-yl)-acetate (13) and methyl 2-(3-(3-methyl-2-butenyl)-2-methylthio-3H-indol-3-yl)-acetate (14) in the ratio of 8:1, judging from the ^{1}H NMR spectrum. To the oil (1.66g) dissolved in a mixture of methanol (5ml) and THF (5ml), 1N NaOH (6.6ml) was added, and the mixture was stirred at room temperature overnight under argon atmosphere. The reaction mixture was diluted with water and washed with ether. The aqueous solution was adjusted to pH 4 with 5% citric acid and extracted with ethyl acetate. The extract was washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. Crystallization of the residue from hot diisopropyl ether gave 790 mg (30% from 11) of 15 as a white powder: IR ($CHCl_3$) 3400-2500, 1710, 1500, 1380, 1360, 920 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$) δ 10.24 (1H,br s,exchangeable), 7.22-7.13 (3H,m), 7.02 (1H,td,J=7.5 and 1Hz), 5.94 (1H,dd,J=17 and 10.5Hz), 5.15 (1H,d,J=10.5Hz), 5.01 (1H,d,J=17Hz), 2.98 (1H,d,J=14Hz), 2.96 (1H,d,J=14Hz), 2.39 (3H,s), 0.99 (3H,s), 0.91 (3H,s); ^{13}C NMR (100MHz, $CDCl_3$) δ 186.4 (C), 173.1 (C), 154.7 (C), 142.9 (CH), 139.0 (C), 128.2 (CH), 124.2 (CH), 123.1 (CH), 118.0 (CH), 114.9 (CH_2), 66.1 (C), 40.8 (C), 38.3 (CH_2), 22.7 (CH_3), 22.3 (CH_3), 14.9 (CH_3); MS m/z 176 (base peak), 221, 289 (M^+); HRMS m/z 289.1112 ($C_{16}H_{19}NO_2S$ requires 289.1137).

The reactions listed in Table 1 and by-product 16. The reactions were conducted in the scale of 1/10 in various solvents. The reaction mixtures were worked up by usual way and the obtained oils were purified by medium pressure LC ($CHCl_3$). Compound 13 and 14 have same Rf value on TLC and could not be separated. The ratio of 13 and 14 was determined by measurement of ^{1}H NMR spectra of the mixed oil of 13 and 14: chemical shifts due to methyl signals of 1,1-dimethyl-2-propenyl group in 13 are δ 1.06 and 0.96, and those of 3-methyl-2-butenyl group in 14 are δ 1.54 and 1.48, respectively. Compound 16: IR ($CHCl_3$) 3000, 2920, 1725, 1450, 1430, 1160 cm^{-1}; ^{1}H NMR (100MHz, $CDCl_3$) δ 7.56 (1H,m), 7.32-6.98 (3H,m), 5.20 (1H,t,J=7Hz), 4.92 (2H,d,J=7Hz), 3.96 (2H,s), 3.68 (3H,s), 2.28 (3H,s), 1.88 (3H,s), 1.68 (3H,s); MS m/z 176 (base peak), 235, 303 (M^+).

N-Methyl-2-(3-(1,1-dimethyl-2-propenyl)-2-methylthio-3H-indol-3-yl)acetamide (17). Triethylamine (0.22ml) was added to a solution of 2-(3-(1,1-dimethyl-2-propenyl)-2-methylthio-3H-indol-3-yl)acetic acid (15) (460 mg, 1.6 mmole) in THF (50ml). To this solution was added ethyl chloroformate (0.15ml) at -18°C and the mixture was stirred at the same temperature for 1hr. After the mixture was cooled to -60°C, methylamine (0.4 ml, 40% in water) was added thereto, and the resultant mixture was stirred at the same temperature for 1hr. After the temperature of the mixture rose to room temperature, the mixture was diluted with ethyl acetate, washed with water, brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was triturated with diisopropyl ether to give 315 mg (65.5%) of 17 as a white powder: IR ($CHCl_3$) 3420, 2980, 1660, 1380, 1360, 920 cm^{-1}; ^{1}H NMR (400MHz, CD_3OD) δ 7.45 (1H,dd,J=7.5 and 1Hz), 7.31-7.27 (2H,m), 7.10 (1H,td,J=7.5 and 1Hz), 6.00 (1H,dd,J=17 and 10.5Hz), 5.17 (1H,dd,J=10.5 and 1Hz), 5.05 (1H,dd,J=17 and 1Hz), 2.90 (1H,d,J=14Hz), 2.88 (1H,d,J=14Hz), 2.70 (3H,s),

2.36 (3H,s), 1.07 (3H,s), 0.98 (3H,s); ^{13}C NMR (100MHz, CD_3OD) δ 184.9 (C), 169.3 (C), 155.2 (C), 143.2 (CH), 139.3 (C), 128.4 (CH), 124.8 (CH), 123.3 (CH), 118.7 (CH), 114.8 (CH_2), 67.2 (C), 40.9 (C), 40.1 (CH_2), 26.1 (CH_3), 22.8 (CH_3), 22.5 (CH_3), 14.9 (CH_3); MS m/z 176 (base peak), 234, 302 (M^+); HRMS m/z 302.1442 ($C_{17}H_{22}N_2OS$ requires 302.1453).

3a-(1,1-Dimethyl-2-propenyl)-1-methyl-3,3a-dihydropyrrolo[2,3-b]indole-2(1H)-one (18). Sodium hydride (29 mg, 60% oil suspension) was added at 0°C to a solution of 17 (178mg) in anhydrous THF (10ml) and the mixture was stirred at room temperature for 2 hr. After excess sodium hydride was decomposed by careful addition of ice water, the mixture was diluted with ethyl acetate, and the solution was washed with water, brine and dried over magnesium sulfate. Removal of the solvent left a residue which was crystallized from diisopropyl ether to give 120 mg (80%) of 18 as a white powder: IR ($CHCl_3$) 2960, 1740, 1630, 1590, 1380, 1360, 920 cm^{-1}; ^{1}H NMR (100MHz, $CDCl_3$) δ 7.44-6.90 (4H,m), 5.76 (1H,dd,J=11 and 16 Hz), 5.16-4.94 (2H,m), 3.20 (3H,s), 3.02 (1H,d,J=16Hz), 2.40 (1H,d,J=16Hz), 0.96 (3H,s), 0.80 (3H,s); MS m/z 186 (base peak), 254 (M^+).

3a-(1,1-Dimethyl-2-propenyl)-1-methyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole (4). A solution of 18 (20mg) in anhydrous ether (5ml) was added slowly to a solution of diisobutylaluminum hydride (0.68 ml, 1.0M solution in hexane) in anhydrous ether (5ml) under reflux with stirring. After the addition was completed, the mixture was refluxed for additional 30 min under nitrogen atmosphere. The reaction mixture was cooled to 5°C and diluted with ethyl acetate. The solution was washed with brine and dried over magnesium sulfate. Removal of the solvent left an oil which was purified by preparative TLC ($CHCl_3$-MeOH 20:1) to give 10 mg (52%) of 4 as a colorless oil: IR ($CHCl_3$) 3420, 2960, 1600, 1480, 1465, 1380, 1360, 1240, 1150, 920 cm^{-1}; HRMS m/z 242.1743 ($C_{16}H_{22}N_2$ requires 242.1784). ^{1}H NMR, ^{13}C NMR and MS spectral data of 4 were in good agreement with those of debromo-8,8a-dihydroflustramine C derived from flustramine C by Carlé and Christophersen[5]. Since the reported NMR data of debromo-8,8a-dihydroflustramine C[5] lacked in part and the assignment was incomplete, the NMR data of 4 were presented below. The assignment was unequivocally made with the aid of heteronuclear two dimensional shift correlation experiment. Compound 4: ^{1}H NMR (400MHz, $CDCl_3$) δ 7.12 (1H,dd,J=7.5 and 1Hz,H-4), 7.03 (1H,td,J=7.5 and 1Hz,H-6), 6.70 (1H,td,J=7.5 and 1Hz,H-5), 6.59 (1H,broad d,J=7.5Hz,H-7), 5.99 (1H,dd,J=17 and 11Hz,H-12), 5.08 (1H,dd,J=11 and 1Hz,H_2-13), 5.02 (1H,dd,J=17 and 1Hz,H_2-13), 4.46 (1H,s,H-8a), 4.40 (1H,broad s,exchangeable,H-8), 2.65 (1H,m,H_2-2), 2.55 (1H,m,H_2-2), 2.42 (3H,s,H_3-14), 2.33 (1H,m,H_2-3), 1.89 (1H,m,H_2-3), 1.08 (3H,s,H_3-10), 1.00 (3H,s,H_3-11); ^{13}C NMR (100.6MHz, $CDCl_3$) δ 150.5 (C-7a), 144.9 (C-12), 133.3 (C-3b), 127.8 (C-6), 125.2 (C-4), 118.4 (C-5), 113.0 (C-13), 109.1 (C-7), 84.4 (C-8a), 64.4 (C-3a), 53.2 (C-2), 41.4 (C-9), 36.9 (C-14), 34.6 (C-3), 23.2 (C-11), 22.5 (C-10).

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