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SYNTHESIS OF THE NECINE BASE PLATYNECINE FROM GLUCOSE

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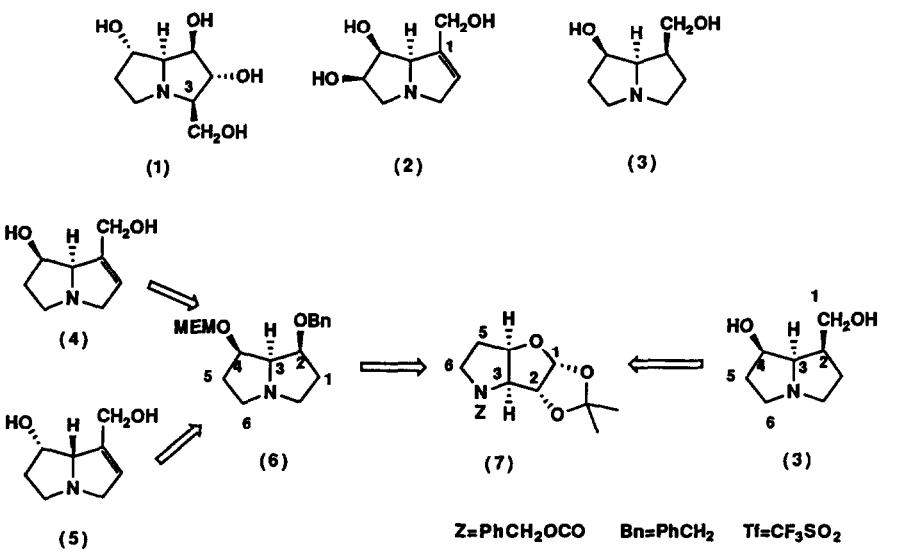
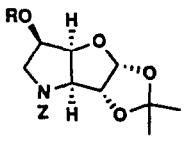
A synthesis of platynecine from an intermediate is described which has previously been used for the synthesis of the enantiomers of retronecine; the stereochemistry of the necine base is determined by the formation of a tricyclic amide intermediate.

Two classes of pyrrolizidines occur in natural products; the alexines [such as alexine (1)[1]] with a one carbon branch at C-3[2] and the necine bases [such as crotanecine (2)[3]] with a one carbon branch at C-1 of the pyrrolizidine nucleus.[4] Although to date there has been relatively little interest in the synthesis of alexines,[5] necines are[6] and have been for some time[7] attractive targets for synthetic chemists. For the more oxygenated heterocycles, carbohydrates are attractive as a starting point,[8] due both to the number of contiguous chiral centres and to the highly functionalised nature of the nitrogen base. The linear 8 carbon chain in the alexines [with a branch at C-3 of the pyrrolizidine] means that the carbon framework of the alkaloids can be constructed by a two carbon extension from C-1 or C-6 of a hexose. However, the carbon chain in the necines is branched so that, while the number of synthetic strategies is greater, carbon-carbon bonds must at some stage be introduced into the sugar, usually at C-2, C-3 or C-4. This paper reports an enantiospecific synthesis of platynecine (3) from glucose.

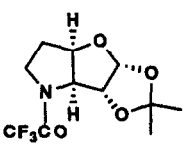


A synthesis of retronecine (4) and its enantiomer (5) from the protected amine (7) has been reported[9] in which the sugar was first elaborated, after a one carbon extension at C-1, to the bicyclic amine (6). Retronecine (4) then required a one carbon extension from C-2 of the original sugar whereas the enantiomer (5) required the exocyclic

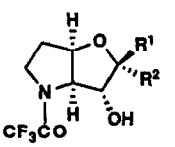
carbon in the product to be introduced at C-4 of the sugar. In the strategy adopted in this synthesis of platynecine (3), the exocyclic carbon is derived from C-1 of the carbohydrate and a two carbon chain is introduced at C-2 of the sugar by a Wittig reaction.



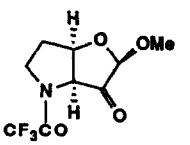
(8) R=H
(9) R=Tf



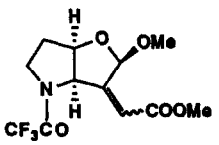
(10)



(11α) R^1=H;R^2=OMe
(11β) R^1=OMe;R^2=H



(12)



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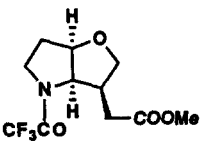

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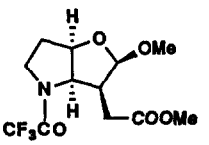

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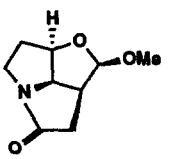

(16)

The protected amine (8), readily available from diacetone glucose, has been used in the synthesis of pyrrolidines and indolizidines.[10] Reaction of (8) with triflic anhydride in dichloromethane in the presence of pyridine at -30°C gave the corresponding triflate (9) [95% yield] which, with sodium borohydride in acetonitrile,[11] gave a highly efficient deoxygenation to the key intermediate (7) [96% yield]. The Barton deoxygenations[12] of thionocarbonate derivatives of the alcohol (8) with tributyltin hydride gave lower yields and were unsatisfactory on a large scale. The synthesis at a later stage required a nitrogen protecting group which was not susceptible to hydrogenolytic cleavage; thus the Z-group was removed by hydrogenolysis in methanol and ethyl acetate in the presence of palladium black to give an amine in which the nitrogen was immediately reprotected by treatment with trifluoroacetic anhydride to give the tertiary amide (10) in 94% yield. Methanolysis of the the acetonide (10) with methanolic hydrogen chloride gave the methyl furanosides (11) [87% yield, α:β ratio 1:13] in which only the C-2 hydroxyl is unprotected. A two carbon extension was achieved by oxidation of the major anomer (11β) with pyridinium chlorochromate to the corresponding ketone (12) which with the stabilised Wittig reagent, carboxymethylenetriphenylphosphorane, afforded a mixture of the α,β-unsaturated esters (13) [67% yield].

Hydrogenation of the unsaturated esters (13) in ethanol in the presence of palladium black resulted in both reduction of the double bond, together with unwanted hydrogenolysis of the anomeric substituent to give the tetrahydrofuran (14) in 92% yield. However, hydrogenation of (13) in ethyl acetate in the presence of 10% palladium on charcoal gave a highly stereoselective reduction to a single isomer (15) in quantitative yield. Treatment of (15) with sodium methoxide in methanol caused removal of the trifluoroacetamide protecting group and cyclisation of the resulting amine on to the ester carbonyl group to afford the tricyclic amide (16) in 52% yield. Hydrolysis of the methyl furanoside (16) with aqueous trifluoroacetic acid, followed by reduction of the resulting lactol with lithium aluminum hydride in tetrahydrofuran gave platynecine in 78% yield [20% overall yield from the protected amine (8)].

EXPERIMENTAL M. p. s. were recorded on a Kofler block. Infra red spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^1H NMR spectra were run at 300 MHz on a Bruker WH 300 spectrometer (500 MHz on a Bruker AM 500 spectrometer); ^{13}C NMR spectra were performed on a Bruker AM 250 (62.9 MHz) or a Bruker AM 500 (125.0 MHz) spectrometer. Mass spectra were recorded on VG Micromass ZAB 1F or MM 30F spectrometers. Microanalyses were recorded by the microanalytical services of the Dyson Perrins Laboratory. TLC was performed on glass plates coated with silica gel Blend 41, and compounds were visualised with a spray of 5% v/v sulphuric acid in methanol or a solution of 5% dodecamolybdophosphoric acid in ethanol. Flash chromatography was carried out using Merck Kieselgel 60, 230-400 mesh; the petroleum ether used was that fraction with b. p. 60°-80°C. Tetrahydrofuran and benzene were distilled from a solution dried with sodium in the presence of benzophenone under dry nitrogen; dichloromethane was distilled from phosphorous pentoxide, acetonitrile from calcium hydride and pyridine from potassium hydroxide. N-Benzyloxycarbonyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (8) was prepared as previously described.[10]

N-Benzyloxycarbonyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-5-O-trifluoromethanesulphonyl-α-D-glucofuranose (9). Trifluoromethanesulphonic anhydride (4.77 ml, 28.4 mmol) was added to a solution of protected amine (8) (8.90 g, 26.5 mmol) and pyridine (3.2 ml, 39.5 mmol) in dichloromethane (100 ml) at -30°C; the reaction was maintained at -30°C for 1 h, at -15°C for 2 h, and then allowed to warm to room temperature. The solution was washed with water (20 ml), dilute aqueous hydrochloric acid (20 ml), and then water (20 ml); the organic layer was dried (sodium sulphate), the solvent removed and the residue purified by flash chromatography (ethyl acetate:petroleum ether, 1:5) to give *N-benzyloxycarbonyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-5-O-trifluoromethanesulphonyl-α-D-glucofuranose (9),* (11.61 g, 95%), m. p. 124.5°-126°C (hexane/ether), $[\alpha]^{20}$ -21.9° (c, 1.67 in $CHCl_3$), ν_{max} (KBr): 2995, 1720 (CO), 1415 (SO), 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.39 (5H, br s, ArH), 5.95 (1H, d, H-1, J 3.5 Hz), 5.19 (2H, m, $ArCH_2$), 5.09 (1H, dt, H-5, $J_{4,5}$ 3.7 Hz, $J_{5,6}$= $J_{5,6'}$= 8.3 Hz), 4.97 (1H, br t, H-4, $J_{3,4}$= $J_{4,5}$= 3.7 Hz), 4.87 and 4.71 (2 x 0.5H, br s, H-2), 4.37 (1H, br s, H-3), 4.12 (1H, m, H-6), 3.53 (1H, br t, H-6', J 9.7 Hz), 1.57 (3H, s, CMe), 1.53 and 1.34 (2 x 1.5H, 2s, CMe). ^{13}C NMR ($CDCl_3$) δ 26.74 (q, CMe), 27.52 (q, CMe), 47.11 (t, C-6), 66.08 (d, C-3), 67.98 (t, $ArCH_2$), 79.66, 80.66, 80.96, 83.59, and 84.70 (5d, C-2, C-4 and C-5), 107.06 (d, C-1), 113.31 (s, Me_2C), 118.57 (CF_3), 128.26, 128.62, 128.81 and 135.92 (Ar), and 154.25 (s, C=O). m/z (DCI, NH_3): 485 (57%, $M+NH_4^+$), 468 (8%, $M+H^+$), 410 (57%, $M-CF_3^+$), 91 (100%). (Found C, 46.22; H, 4.49; N, 2.74. $C_{18}H_{20}NO_8F_3S$ requires C, 46.25; H, 4.31; N, 2.99%).

3,6-Imino-1,2-O-isopropylidene-3,5,6-trideoxy-N-trifluoroacetyl-α-D-glucofuranose (10). Sodium borohydride (4.76 g, 114 mmol) was added to a solution of the triflate (9) (11.0 g, 23.6 mmol) in acetonitrile (100 ml) and the reaction mixture was stirred at room temperature under nitrogen for 3 days. The solvent was removed and the residue was treated with chloroform (100 ml) and dilute aqueous hydrochloric acid (20 ml) was added to adjust the aqueous phase to pH 5. The organic layer was then washed with brine (50 ml), dried (sodium sulphate) and the solvent removed. The residue was purified by flash chromatography (ethyl acetate:petroleum ether, 1:4) to give the Z-protected amine (7), (7.17 g, 96%), m. p. 87.5°-89°C [lit.[9] 88°-89°C]. The benzyloxycarbonyl derivative (7) (4.14 g, 13.0 mmol) in ethanol (100 ml) and ethyl acetate (70 ml) was stirred under hydrogen in the presence of palladium black (340 mg) for 12 h; the catalyst was removed by filtration and the solvent removed. The crude residue was dissolved in dichloromethane (100 ml) and treated at 0°C with pyridine (3.1 ml, 38 mmol) and trifluoroacetic anhydride (4.1 ml, 29 mmol). The reaction mixture was stirred at 0°C for 3 h, poured into brine (50 ml) and the organic layer washed with diluted aqueous hydrochloric acid (20 ml), brine (20

ml) and the solvent removed. The residue was purified by flash chromatography (ethyl acetate:petroleum ether, 1:4) to give *3,6-imino-1,2-O-isopropylidene-3,5,6-trideoxy-N-trifluoroacetyl-α-D-glucofuranose (10)*, (3.44 g, 94%), m. p. 46°-47°C, $[\alpha]^{20}$ -108.7° (c, 1.53 in $CHCl_3$), ν_{max} (KBr): 2950, 1690 (CO), 1450 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.81 (1H, d, H-1, J 3.8 Hz), 4.92 (1H, t, H-4, J 3.7 Hz), 4.73 (1H, d, H-2, J 3.8 Hz), 4.36 (1H, d, H-3, J 3.9 Hz), 3.88 (1H, br t, H-6, J 8.8 Hz), 3.56 (1H, ddd, H-6', $J_{6,6'}$ 11.9 Hz, $J_{5,6'}$= $J_{5',6'}$= 5.9 Hz), 2.20 (1H, dd, H-5, $J_{5,6}$ 5.9 Hz, $J_{5,5'}$ 13.7 Hz), 1.95 (1H, m, H-5'), 1.49 (3H, s, CMe) and 1.28 (3H, s, CMe). ^{13}C NMR ($CDCl_3$) δ 26.56 (q, CMe), 27.09 (q, CMe), 30.93 (t, C-5), 45.93 (t, C-6), 69.14 (d, C-3), 80.35 and 83.04 (2 x d, C-2 and C-4), 106.13 (d, C-1), 112.30 (s, Me_2C), 116.22 (CF_3), and 156.24 (q, C=O, J_{C-F} 37 Hz). m/z (DCI, NH_3): 299 (100%, M+NH_4^+), 282 (10%, M+H^+). (Found C, 47.08; H, 4.98; N, 4.86. $C_{11}H_{14}NO_4F_3$ requires C, 46.98; H, 5.01; N, 4.98%).

Methyl 3,6-imino-3,5,6-trideoxy-N-trifluoroacetyl-α-D-glucofuranoside (11α) and Methyl 3,6-imino-3,5,6-trideoxy-N-trifluoroacetyl-β-D-glucofuranoside (11β). A solution of (10) (1.06 g, 3.77 mmol), in methanolic hydrogen chloride [prepared by the addition of acetyl chloride (210 µl) to methanol (30 ml)] was heated at 50°C for 3 h. The reaction mixture was then neutralised by aqueous ammonium hydroxide (SG 0.88) and the solvent removed. The residue was dissolved in chloroform and the organic solution was washed with brine (20 ml), dried (sodium sulphate); the solvent was removed and the resulting oil purified by flash chromatography (ethyl acetate:petroleum ether, 2:3) to give as the major product, the less polar β anomer (11β), (781 mg, 81%) together with a small amount of the more polar α anomer (11α) (62 mg, 6%) [combined yield of the two anomers, 87%].
Methyl 3,6-imino-3,5,6-trideoxy-N-trifluoroacetyl-α-D-glucofuranoside (11α),, oil, $[\alpha]^{20}$ -17.5° (c, 1.13 in $CHCl_3$), ν_{max} (KBr): 3490, 2950, 1690 (CO), 1450 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.02 (1H, d, H-1, J 4.6 Hz), 4.83 (1H, t, H-4, J 5.1 Hz), 4.41 (1H, m, H-2), 4.12 (1H, m, H-3), 3.93 (1H, br t, H-6, J 9.9 Hz), 3.63 (1H, dt, H-6', $J_{5',6'}$ 6.5 Hz, $J_{5,6'}$= $J_{6,6'}$ 11.2 Hz), 3.49 (3H, s, OMe) and 2.20 (1H, dd, H-5', $J_{5,5'}$ 13.9 Hz, $J_{5',6'}$ 6.5 Hz), 2.06 (1H, m, H-5). ^{13}C NMR ($CDCl_3$) δ 30.75 (t, C-5), 45.45 (t, C-6), 55.38 (q, OMe), 70.68 (d, C-3), 78.15 and 79.03 (2 x d, C-2 and C-4), 103.92 (d, C-1), 116.13 (CF_3), and 157.22 (q, C=O). m/z (DCI, NH_3): 273 (100%, M+NH_4^+), 256 (11%, M+H^+). (Found C, 42.66; H, 4.94; N, 5.65. $C_9H_{12}NO_4F_3$ requires C, 42.35; H, 4.74; N, 5.49%).
Methyl 3,6-imino-3,5,6-trideoxy-N-trifluoroacetyl-β-D-glucofuranoside (11β), m. p. 22°-24°C, $[\alpha]^{20}$ -220.3° (c, 1.55 in $CHCl_3$), ν_{max} (KBr): 3450, 2950, 1690 (CO), 1450 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.05 (1H, t, H-4, J 5.1 Hz), 4.89 (1H, s, H-1), 4.34 (1H, d, H-3, $J_{3,4}$ 5.4 Hz), 4.31 (1H, s, H-2), 3.84 (1H, br t, H-6, J 9.8 Hz), 3.68 (1H, dt, H-6', $J_{5',6'}$ 6.4 Hz, $J_{5,6'}$= $J_{6,6'}$= 11.7 Hz), 3.32 (3H, s, OMe), 2.20 (1H, dd, H-5', $J_{5,5'}$ 14.0 Hz, $J_{5',6'}$ 6.3 Hz) and 2.04 (1H, m, H-5). ^{13}C NMR ($CDCl_3$) δ 32.50 (t, C-5), 45.97 and 45.92 (t, C-6), 55.16 (q, OMe), 69.52 (d, C-3), 77.97 and 81.67 (2 x d, C-2 and C-4), 109.84 (d, C-1), 116.24 (CF_3), and 156.07 (q, C=O, J_{C-F} 37 Hz). m/z (DCI, NH_3): 273 (100%, M+NH_4^+), 256 (14%, M+H^+). (Found C, 42.28; H, 4.80; N, 5.40. $C_9H_{12}NO_4F_3$ requires C, 42.35; H, 4.74; N, 5.49%).

Methyl 3,6-imino-2-oxo-3,5,6-trideoxy-N-trifluoroacetyl-β-D-threo-hexofuranoside (12). Molecular sieve (2.94 g) and pyridinium chlorochromate (2.54 g, 11.8 mmol) were added to a solution of alcohol (11β) (1.51 g, 5.9 mmol) in dry dichloromethane (50 ml), and the resulting reaction mixture was stirred under nitrogen overnight. Ether (50 ml) was then added, causing the precipitation of chromium salts, and the reaction mixture was filtered through silica; the silica filter was washed with ether and the combined filtrates were evaporated and the residue purified by flash chromatography (ethyl acetate:petroleum ether, 2:3) to give unreacted starting material (11ß) (316 mg) and *methyl 3,6-imino-2-oxo-3,5,6-trideoxy-N-trifluoroacetyl-β-D-threo-hexofuranoside (12).*, (1.14

g, 78%) an unstable oil, ν_{max} (film): 2980, 1750 and 1690 (CO) cm^{-1}. m/z (DCI, NH_3): 271 (100%, $M+NH_4^+$), which was used immediately in the next step.

Methyl 2-(E,Z)-C-(carbomethoxymethylene)-3,6-imino-2,3,5,6-tetradeoxy-N-trifluoroacetyl-β-D-threo-hexofuranoside (13). Carbomethoxymethylenetriphenylphosphorane (2.19 g, 6.55 mmol) was added to a solution of the ketone (12) (830 mg, 3.28 mmol) in benzene (50 ml) and the reaction mixture was then gently refluxed for 3 h. The solvent was removed and the residue purified by flash chromatography (ether:petroleum ether, 2:3) to give *methyl 2-(E,Z)-C-(carbomethoxymethylene)-3,6-imino-2,3,5,6-tetradeoxy-N-trifluoroacetyl-β-D-threo-hexofuranoside (13),* (871 mg, 86%), an oil, $[\alpha]^{20}$ -216.5° (c, 2.73 in $CHCl_3$), ν_{max} (KBr): 2950, 1720 and 1690 (CO), 1450 cm^{-1}. ^1H NMR ($CDCl_3$) δ 6.50 (1H, CH=C), 5.93 (1H, s, H-1), 5.06 (1H, d, H-3, $J_{3,4}$ 5.8 Hz), 4.83 (1H, t, H-4, $J_{4,3}$= $J_{4,5'}$ 5.6 Hz), 3.83 (2H, m, H-6), 3.73 (3H, s, COOMe), 3.47 (3H, s, OMe), 2.23 (1H, ddd, H-5', $J_{5,5'}$ 14.2 Hz, $J_{5',6}$ 5.3 Hz, $J_{5',6'}$ 2.3 Hz) and 2.11 (1H, m, H-5). ^{13}C NMR ($CDCl_3$) δ 33.24 (t, C-5), 45.22 and 45.27 (t, C-6), 51.72 (q, OMe), 55.98 (q, OMe), 63.73 (d, C-3), 79.76 (d, C-4), 101.82 (d, C-1), 116.04 (CF_3), 121.17 (d, CH=C), 152.25 (s, C-2), 155.52 (q, C=O) and 165.22 (s, C=O). m/z (DCI, NH_3): 327 (31%, $M+NH_4^+$), 310 (29%, $M+H^+$). (Found C, 47.07; H, 4.60; N, 4.65. $C_{12}H_{14}NO_5F_3$ requires C, 46.61; H, 4.56; N, 4.53%).

1,4-Anhydro-3-C-(carbomethoxymethyl)-3,6-imino-2,3,5,6-tetradeoxy-N-trifluoroacetyl-D-lyxo-hexitol (14) A solution of (13) (265 mg, 0.85 mmol) in ethanol (10 ml) was stirred in a hydrogen atmosphere in the presence of palladium black (50 mg) for 12 h; the catalyst was removed by filtration and the solvent removed to give an oil which was purified by flash chromatography (ethyl acetate: petroleum ether, 1:4) to give *1,4-anhydro-3-C-(carbomethoxymethyl)-3,6-imino-2,3,5,6-tetradeoxy-N-trifluoroacetyl-D-lyxo-hexitol (14)* (221 mg, 92%), oil, $[\alpha]^{20}$ -173.0° (c, 2.56 in $CHCl_3$), ν_{max} (film): 2950, 1740 and 1690 (CO), 1450 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.79 (1H, t, H-3, J 6.1 Hz), 4.62 (1H, t, H-4, J 5 Hz), 3.99 (2H, m, H-1 and H-6), 3.66 (3H, s, COOMe), 3.52 (1H, dd, H-1', $J_{1,1'}$ 8.9 Hz, $J_{1',2}$ 7.6 Hz), 3.41 (1H, dt, H-6', $J_{5',6'}$ 6.1 Hz, J $_{5,6'}$= $J_{6,6'}$= 12 Hz), 2.98 (1H, m, H-2), 2.55 (1H, dd, H-2a, $J_{2,2a'}$ 5.1 Hz, $J_{2a,2a'}$ 16.5 Hz), 2.16 (2H, m, H-2a' and H-5) and 1.93 (1H, m, H-5'). ^{13}C NMR ($CDCl_3$) δ 32.04 and 33.03 (2 x t, C-5 and CH_2COOMe), 40.91 (d, C-2), 47.15 (t, C-6), 51.73 (q, OMe), 65.23 (d, C-3), 73.23 (t, C-1), 81.47 (d, C-4), 116.22 (CF_3), 156.67 (q, C=O) and 172.19 (s, C=O). m/z (DCI, NH_3): 299 (15%, $M+NH_4^+$), 298 (100%) and 281 (71%, $M+H^+$). (Found C, 46.89; H, 4.76; N, 5.03. $C_{11}H_{14}NO_4F_3$ requires C, 46.98; H, 5.02; N, 4.98%).

Methyl 3-C-(carbomethoxymethyl)-3,6-imino-2,3,5,6-tetradeoxy-N-trifluoroacetyl-β-D-lyxo-hexofuranoside (15) A solution of (13) (368 mg, 1.17 mmol) in ethyl acetate (15 ml) was stirred in a hydrogen atmosphere in the presence of 10% palladium on charcoal (33 mg) for 12 h; the catalyst was removed by filtration and the solvent evaporated to give the crude product which was purified by flash chromatography (ethyl acetate:petroleum ether, 1:4) to give *methyl 3-C-(carbomethoxymethyl)-3,6-imino-2,3,5,6-tetradeoxy-N-trifluoroacetyl-β-D-lyxo-hexofuranoside (15),* (364 mg, 99%), oil, $[\alpha]^{20}$ -255.2° (c, 0.46 in $CHCl_3$), ν_{max} (film): 2950, 1740 and 1690 (CO), 1450 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.00 (1H, d, H-1, J 4.9 Hz), 4.85 (2H, m, H-3 and H-4), 3.84 (1H, m, H-6), 3.75 (1H, dd, H-6', $J_{5,6'}$ 6 Hz, $J_{6,6'}$ 8 Hz), 3.69 (3H, s, OMe), 3.32 (3H, s, OMe), 2.83 (1H, m, H-2), 2.74 (1H, dd, H-2a, $J_{2a,2a'}$ 17.3 Hz, $J_{2,2a}$ 5.6 Hz), 2.45 (1H, dd, H-2a', $J_{2,2a'}$ 9.7 Hz, $J_{2a,2a'}$ 17.3 Hz), 2.09 (1H, dd, H-5, $J_{5,6}$ 6 Hz, $J_{5,5'}$ 14 Hz) and 1.96 (1H, m, H-5'). ^{13}C NMR ($CDCl_3$) δ 28.98 and 33.25 (2 x t, C-5 and CH_2COOMe), 44.78 (d, C-2), 45.10 (t, C-6), 51.50 (q, OMe), 55.03 (q, OMe), 63.12 (d, C-3), 81.37 (d, C-4), 104.51 (d, C-1), 116.19 (CF_3), 156.00 (q, C=O) and 172.47 (s, C=O).

m/z (DCI, NH_3): 329 (16%, M+NH_4^+), 312 (13%, M+H^+) and 280 (100%). (Found C, 46.51; H, 5.46; N, 4.52. $C_{12}H_{16}NO_5F_3$ requires C, 46.30; H, 5.18; N, 4.50%).

6R-Methoxy-1-aza-5-oxa-9-oxo-tricyclo[5.2.1.0^{4,10}]decane (16). Sodium methoxide (64 mg, 1.18 mmol) was added to a solution of (15) (183 mg, 0.59 mmol) in methanol (2 ml) and the solution gently refluxed for 24 h under nitrogen; a further amount of sodium methoxide (30 mg) was added. After 24 h, the solvent was removed and the resulting oil was purified by flash chromatography (ethyl acetate:isopropanol, 9:1) to give *6(R)-methoxy-1-aza-5-oxa-9-oxo-tricyclo[5.2.1.0^{4,10}]decane (16)* (57 mg, 52%), m. p. 82°-84.5°C (ether/hexane), $[\alpha]^{20}$ - 137.3° (c, 0.65 in $CHCl_3$), ν_{max} (film): 2970, 1700 (CO) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.97 (1H, d, H-6, $J_{6,7}$ 5.8 Hz), 4.66 (1H, ddd, H-4, $J_{4,10}$ 5.2 Hz, $J_{4,3}$ 1.5 Hz, $J_{4,3'}$ 8.2 Hz), 4.32 (1H, dd, H-10, $J_{10,4}$ 5.2 Hz, $J_{10,7}$ 6.6 Hz), 3.99 (1H, ddd, H-2, J 12.5 Hz, J 9.2 Hz, J 3.9 Hz), 3.38 (3H, s, OMe), 2.95 (2H, m, H-7 and H-2), 2.63 (2H, m, H-8 and H-8'), 2.24 (1H, m, H-3) and 2.09 (1H, m, H-3'). ^{13}C NMR ($CDCl_3$) δ 33.88 and 34.27 (2 x t, C-8 and C-3), 42.89 (d, C-7), 43.64 (t, C-2), 56.47 (q, OMe), 70.05 (d, C-10), 81.65 (d, C-4), 107.04 (d, C-6), 178.16 (s, C=O). m/z (DCI, NH_3): 184 (100%, M+H^+). (Found C, 58.94; H, 7.33; N, 7.53. $C_9H_{13}NO_3$ requires C, 59.00; H, 7.15; N, 7.64%).

(-)-Platynecine (3). A solution of the tricyclic amide (16) (77.3 mg, 0.42 mmol) in aqueous trifluoroacetic acid (60%, 5 ml) was allowed to stand at room temperature for 4 h. The solvent was removed *in vacuo* and the crude product was dissolved in tetrahydrofuran (10 ml) and treated with lithium aluminum hydride (128 mg, 3.45 mmol). The reaction mixture was refluxed under nitrogen for 3.5 h, treated with water (0.25 ml), aqueous sodium hydroxide (0.5 ml), water (0.25 ml) and then dried (sodium sulphate). The solvent was removed and the residue was purified by flash chromatography (chloroform:methanol:aqueous ammonia (SG 0.88), 5:5:1) to give platynecine, (52 mg, 78%), m.p. 147.5°-149°C, $[\alpha]^{20}$ -65.5° (c, 0.75 in $CHCl_3$) [lit.[13] m.p.148°-149°C, $[\alpha]^{20}$ - 60.9° (c, 1 in $CHCl_3$)]. ^{13}C NMR (CD_3OD) δ 28.85 and 37.27 (2 x t, C-2 and C-6), 44.94 (d, C-1), 54.81 and 56.56 (2 x t, C-3 and C-5), 61.61 (t, C-9), 72.90 and 73.05 (2 x d, C-7 and C-8). The proton NMR spectrum of this synthetic playnecine was superimposable on the proton NMR spectrum of an authentic sample.

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