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SYNTHESIS FROM D-GLUCOSE OF ALEXINE [(1R,2R,3R,7S,8S)-3-HYDROXYMETHYL-1,2,7-TRIHYDROXYPYRROLIZIDINE], 3-EPIALEXINE AND 7-EPIALEXINE

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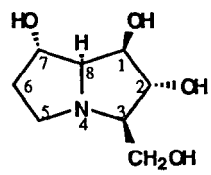
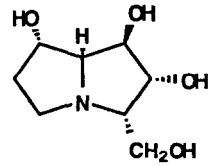
A protected 2-azido-2-deoxymannose is a key intermediate in the synthesis of alexine [(1R,2R,3R,7S,8S)-3-hydroxymethyl-1,2,7-trihydroxypyrrolizidine], 3-epialexine and 7-epialexine from D-glucose.

Although there are many pyrrolizidine alkaloids with a carbon substituent at C-1,[1] alexine (1), isolated from Alexa leiopetala, is the first example of a pyrrolizidine alkaloid with a carbon substituent at C-3.[2] This paper reports the synthesis from D-glucose of alexine [(1R,2R,3R,7S,8S)-3-hydroxymethyl-1,2,7-trihydroxy-pyrrolizidine] (1), 3-epialexine (2) and 7-epialexine (3); very recently, the isolation from Castanospermum australe of 3,8-diepialexine has been reported.[3] The alexines, which are structurally related to the alkaloidal glucosidase inhibitor 2,5-dideoxy-2,5-imino-D-mannitol,[4,5] may be of interest as glycosidase inhibitors.



(1)



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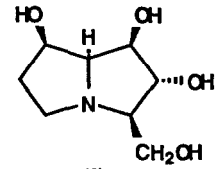

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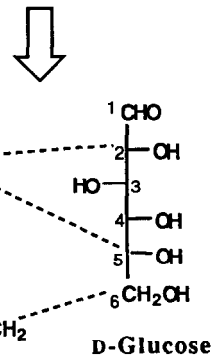
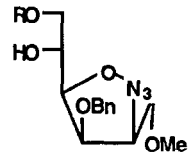
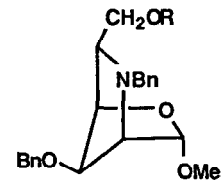


D-Glucose



(4) R=H
(5) R=[Si]



(6) R=[Si]
(7) R=H

The synthesis of alexine (1) from glucose requires the formation of a pyrrolidine ring by joining C-2 and C-5 by nitrogen (with inversion at both centres); the pyrrolizidine ring system may then be generated by the connection of the nitrogen to the terminal carbon derived from a two carbon extension from C-6 of glucose. Methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside (4), readily prepared from glucose,[6] has been used as a divergent intermediate in the

synthesis of polyhydroxylated piperidines and pyrrolidines, including 2,5-dideoxy-2,5-imino-D-mannitol;[7,8] in (4), nitrogen has been introduced with inversion at C-2 and the required stereochemistry at C-1, C-2, C-3 and C-8 in alexine may be acheived by formation of a pyrrolidine ring by displacement of a leaving group at C-5 with inversion by the nitrogen function.

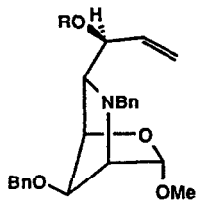
Reaction of the diol (4) with tert-butyldimethylsilyl chloride in dimethylformamide at 0°C gave the silyl ether (5),[9] syrup, $[\alpha]_D^{20}$ +40.8° (c, 1.28 in $CHCl_3$), in 95% yield. Esterification of the free hydroxyl group in (5) with trifluoromethane sulphonic anhydride in the presence of pyridine at -30°C followed by hydrogenation of the resulting triflate in ethyl acetate in the presence of palladium gave, after treatment of the crude product with benzyl bromide in dimethylformamide in the presence of sodium hydroxide, the fully protected pyrrolidine (6), syrup, $[\alpha]_D^{20}$ +86.6° (c, 1.06 in $CHCl_3$), in 77% yield. Removal of the silyl ether from (6) by reaction with tetrabutylammonium fluoride in tetrahydrofuran gave methyl N-benzyl-3-O-benzyl-2,5-dideoxy-2,5-imino-ß-L-gulofuranoside (7), syrup, $[\alpha]_D^{20}$ +93.4° (c, 1.62 in $CHCl_3$), in 88% yield [66% overall yield from (4)]; in (7), only the C-6 of the sugar is unprotected, thus allowing the two carbon extension to be made at this stage.

Swern oxidation of (7) [oxalyl chloride/ dimethyl sulphoxide, followed by triethylamine] gave the corresponding aldehyde which on subsequent treatment with vinyl magnesium bromide in tetrahydrofuran gave a mixture of the epimeric allylic alcohols (8), syrup, $[\alpha]_D^{20}$ +88.6° (c, 0.82 in $CHCl_3$), in 38% yield and (13), syrup, $[\alpha]_D^{20}$ +85.7° (c, 0.90 in $CHCl_3$), in 37% yield; the alcohols are readily separated by flash chromatography [hexane:ethyl acetate, 3:1], with the more polar (8) being eluted after (13). Oxidation of either pure (8) or (13) by manganese dioxide gave a ketone which on reduction with sodium borohydride gave a mixture of (8) and (13) in the same ratio.

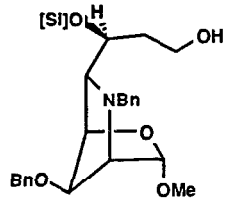
The more polar alcohol (8) was converted into alexine (1) and 3-epialexine (2). Reaction of allylic alcohol (8) with tert-butyldimethylsilyl chloride gave the silyl ether (9) [89% yield] which with borane:dimethylsulphide in tetrahydrofuran, followed by alkaline hydrogen peroxide, gave the primary alcohol (10), syrup, $[\alpha]_D^{20}$ +84.1° (c, 1.67 in $CHCl_3$) [67% yield]. Esterification of (10) with p-toluenesulphonyl chloride in dichloromethane in the presence of pyridine gave a tosylate which spontaneously cyclised to the salt (11), syrup, $[\alpha]_D^{20}$ +31.1° (c, 0.76 in $CHCl_3$) in 77% yield. Hydrogenolysis of the benzyl groups in (11) in aqueous acetic acid in the presence of 10% palladium on charcoal gave the silyl ether (12), m.p. 125°-127°C, $[\alpha]_D^{20}$ +109.5° (c, 0.54 in $CHCl_3$) [72% yield].

Treatment of (12) with aqueous trifluoroacetic acid over 36 h resulted in removal of the silyl protecting group and slow hydrolysis of the furanoside; the resulting lactol was then reduced with sodium borohydride in ethanol to give, after purification by ion exchange chromatography (Amberlite CG120 - NH_4^+ form), alexine (1), 54% yield, m.p. 159°-162°C, [lit.[2] m.p. 162°-163°C, $[\alpha]_D^{20}$ +40.0° (c, 0.25 in H_2O)] identical to an authetic sample; since the structure of alexine has been established by X-ray crystallography, this work establishes the

structure of allylic alcohol (8). A small amount (about 7%) of 3-epialexine (2), m.p. 190°-192°C, was also isolated and presumably arises from epimerisation of the open chain form of the intermediate lactol.



(8) R=H
(9) R=[Si]



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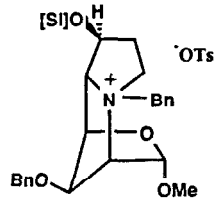

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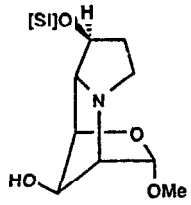

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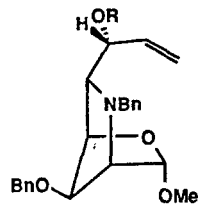
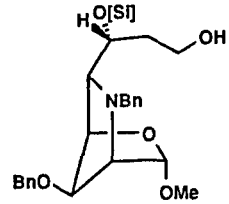


(13) R=H
(14) R=[Si]



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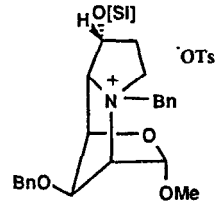

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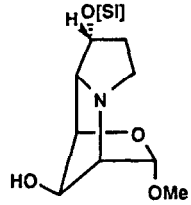
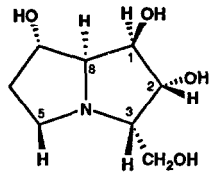


(17)

Bn=$PhCH_2$ [Si]=TBDMS Ts=pMe-C_6H_4-SO_3^-

The less polar alcohol (13) was transformed into 7-epialexine by a similar sequence of reactions to those use for the conversion of (8) into alexine. Thus hydroboration of the silyl ether (14), followed by alkaline hydrogen peroxide oxidation of the intemediate borane, gave the primary alcohol (15), syrup, $[\alpha]_D^{20}$ +78.9° (c, 0.62 in $CHCl_3$) [54% yield from (13)]. Esterification of (14) with p-toluenesulphonyl chloride in dichloromethane in the presence of pyridine gave a tosylate which spontaneously cyclised to the salt (16), m.p. 154°-158°C, $[\alpha]_D^{20}$ +18.1° (c, 0.74 in $CHCl_3$) in 65% yield. Hydrogenolysis of the benzyl groups in (16) in aqueous acetic acid in the presence of 10% palladium on charcoal gave the silyl ether (17), m.p. 138°-142°C, $[\alpha]_D^{20}$ +133.3° (c, 1.12 in $CHCl_3$) [82% yield]. Hydrolysis of (17) by aqueous trifluoroacetic acid was complete in 16 h; reduction of the resulting lactol with sodium borohydride in ethanol gave, after purification by ion exchange chromatography (Amberlite CG120 - NH_4^+ form), 7-epialexine (3), syrup, in 70% yield.

The structure of alexine (1) has been established by X-ray crystallography;[2] the structures of the epimers (2) and (3) are assigned on the basis of the synthetic work in this paper and on the basis of carbon-13 and proton NMR spectra, including equilibrium nOe measurements. The ^1H NMR spectra [500 MHz in D_2O] of (2) and (3) as the free bases were assigned on the basis of homonuclear shift correlation (COSY) experiments; the assignments of the ^{13}C NMR spectra [125 MHz in D_2O] of (2) and (3) followed from heteronuclear shift



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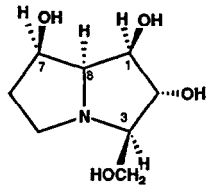

(3)

correlation experiments. In 3-epialexine (2), nOe's were observed between H8 and H1 (irradiation of H8 generated a 15% enhancement of H1 and irradiation of H1 generated a 21% enhancement of H8), between H2 and H3 (irradiation of H2 generated a 12% enhancement of H3 and irradiation of H3 generated a 18% enhancement of H2), and between H3 and H5β). In 7-epialexine (3), nOe's were observed between H7 and H8 (irradiation of H8 generated a 11% enhancement of H7), between H1 and H8 (irradiation of H8 generated a 13% enhancement of H1), and between H1 and H3 (irradiation of H3 generated a 10% enhancement of H1).

^{13}C NMR Spectra of alexines (1,4-dioxan [δ 67.3] internal standard)

multiplicity	C1(d)	C2(d)	C3(d)	C5(t)	C6(t)	C7(d)	C8(d)	CH2(t)
alexine (1)	77.0	77.1	65.0	46.2	34.8	70.7	70.9	59.9
3-epialexine (2)	75.4	78.8	69.5	52.9	35.5	70.6	74.9	60.1
7-epialexine (3)	77.5	75.2	64.2	46.9	34.2	72.4	67.1	59.2

Specific rotation (°) $[\alpha]^{20}$ in water for alexines

wavelength	589	578	546	436	365
alexine (1) (c, 0.16)	+37.0	+39.4	+44.2	+72.7	+109.7
3-epialexine (2) (c, 0.11)	+63.8	+66.7	+75.2	+117.1	+173.3
7-epialexine (3) (c, 0.56)	-10.6	-11.5	-12.9	-19.3	-22.5

In summary, this paper reports the synthesis of alexine (1), 3-epialexine (2) and 7-epialexine (3) and further illustrates the value of methyl 2-azido-3-O-benzyl-2-deoxy-α-D-mannofuranoside (4) as a divergent intermediate for the synthesis of polyhydroxylated alkaloids; the carbon-13 NMR data and the specific rotations of the alexines are tabulated. The properties of the alexines as glycosidase inhibitors will be reported elsewhere.[10]

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9. All new compounds have spectral data consistent with the structures proposed; correct CHN microanalyses have been obtained for (5) - (16) inclusive.
10.We thank Dr. A. E. Derome for his help in interpretation of NOE experiments; support for this work has been provided by the Medical Research Council (RJN) and an ICI Research Fellowship in commemoration of Alfred Nobel (MH).

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