Synthesis of Trihydroxylated Pyrrolizidine using 1,3-Dipolar Cycloaddition of D-Erythrose Derived Nitrone

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Abstract: A route has been developed for the synthesis of enantiomerically and diastereomerically pure trihydroxylated pyrrolizidines. A chiral sugar derived nitrone undergoes diastereoselective dipolar cycloaddition with methyl acrylate to afford *erythro-cis* isoxazolidine; a suitable cycloadduct undergoes N-O cleavage and recyclization to (1*S*,2*R*,6*R*,7a*S*)-trihydroxylated pyrrolizidine.

Key words: cycloadditions, nitrones, isoxazolidines, stereoselectivity, pyrrolizidine alkaloid

Many naturally occurring polyhydroxylated pyrrolizidine alkaloids are endowed with a wide spectrum of biological activities and therapeutic applications in diabetes, obesity and AIDS due to their action of glycosidase inhibitors because of a structural resemblance to the sugar moiety of the natural substrate.[1] The high potential of pyrrolizidine alkaloids in a range of biological applications makes them inviting targets for synthesis. In particular the preparation of other structural analogs of alexine (**1**) and australine (**2**), that are specific inhibitors of amylglycosidase, has created much interest since the biological activity of these molecules varies substantially with the number, position, and stereochemistry of the hydroxy groups in the pyrrolizidine skeleton (Figure 1).[2]

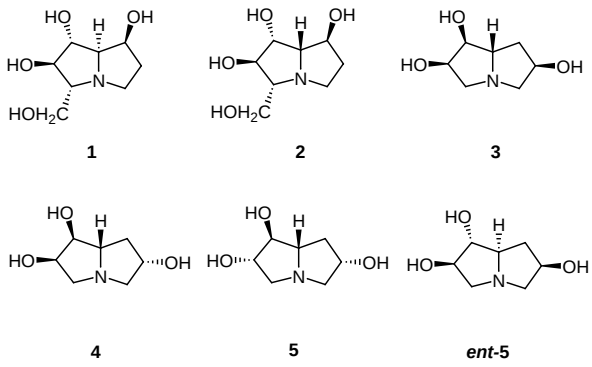

Figure 1

Pyrrolizidine syntheses involving 1,3-dipolar cycloadditions have been recently reviewed.[3] Most of these approaches make use of carbohydrates as chiral auxiliaries or chiral building blocks. In connection with our interest concerning the utilization of chiral nitrones in asymmetric cycloadditions,[4] we have designed sugar-derived nitrones[5] as templates for synthesis of polyhydroxylated derivatives of pyrrolizidines. Nitrones are 1,3-dipoles known to undergo cycloadditions to form isoxazolidines and cleavage of the N-O bond to enable recyclization to carbon-nitrogen heterocycles is a recognized synthetic strategy.[6]

As part of our program devoted to developing of a simple route to polyhydroxylated derivatives of pyrrolizidines, we describe herein a stereoselective synthesis of enantiopure (1*S*,2*R*,6*R*,7a*S*)-trihydroxylated pyrrolizidine **3**. The synthesis of diastereoisomers (±)-**4**, (+)-**5** and (−)-**5** using the cycloadditions of 3,4-disubstituted pyrroline-*N*-oxides with *O*-silyl-protected allyl alcohol has been described by Wightman[7] but, to the best of our knowledge, **3** has not been described previously.

In the foregoing paper we have shown that sugar derived nitrones react with methyl acrylate with useful stereoselectivity, particularly if hydroxy group in the nitrone is protected with the bulky *tert*-butyldimethylsilyl group.[8] We decided to exploit this knowledge of the stereochemical course of these cycloadditions in the development of a synthetic method to (1*S*,2*R*,6*R*,7a*S*)-pyrrolizidine-1,2,6-triol (**3**) from carbohydrate precursors. Our retrosynthetic strategy is outlined in Figure 2 in which we proposed to build the pyrrolizidine skeleton of general formula **3** via nitrone cycloaddition. Reaction of nitrone **6** with methyl acrylate opens a way for the novel functionalization of isoxazolidine cycloadduct **7** in which the methyl ester may be converted into a hydroxymethyl group for ring closure to the pyrrolizidine skeleton. Stereoselective cycloaddition, followed by reduction of the N-O bond, to produce both an amino and a hydroxy function, allows the synthesis of tailor-made products of possible biological interest.

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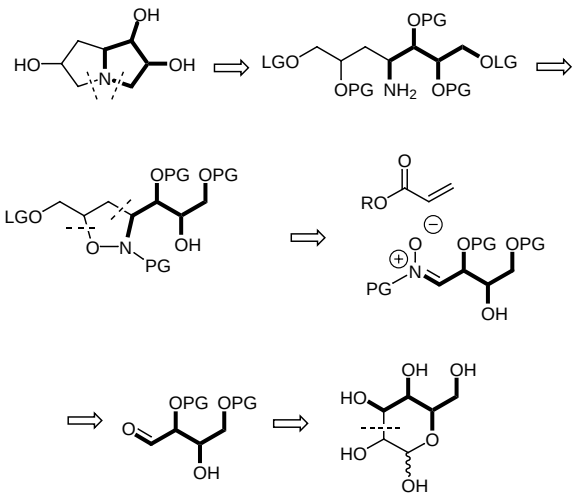
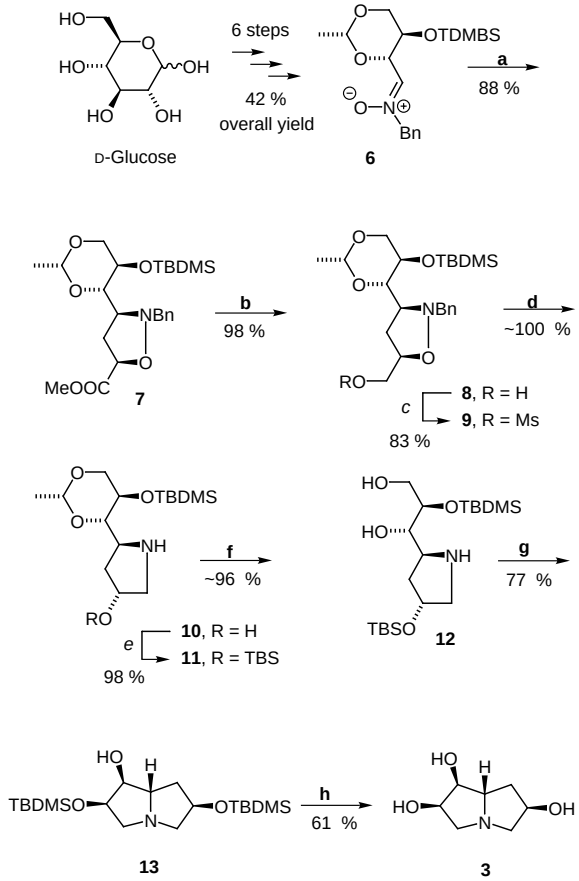


Figure 2



Scheme (a) Methyl acrylate in toluene, 4 h at 110 °C (b) DIBALH in THF, 1.5 h at –10 °C (c) MsCl, Et_3N in CH_2Cl_2, 12 h at 0 °C–r.t. (d) H_2, $Pd(OH)_2/C$ in MeOH, 72 h at r.t. (e) TBDMSCl, Et_3N in CH_2Cl_2, 23 h at r.t. (f) 80% AcOH, 6 h at 80 °C (g) MsCl, Et_3N in CH_2Cl_2, 3 h at –10 °C, then 16 h at r.t. (h) NH_4F, TBAF, in THF–water, 50 h at r.t.

As shown in Scheme, 1,3-dipolar cycloaddition of sugar derived *O*-silylated nitrone **6** prepared from D-glucose with methyl acrylate gave the diastereoisomerically pure isoxazolidine **7** in 88% yield.[8–10] NO-heterocycles are prone to hydrogenolysis since the relatively weak N-O bond is easily cleaved.[6]

Therefore, the C-COOMe functionalized isoxazolidine **7** represents a sub-unit with potential for cleavage and recyclization to form the pyrrolizidine **3.** This opens a new route to the stereocontrolled formation of polyhydroxysubtituted pyrrolizidines. To demonstrate this, the diastereoisomerically pure isoxazolidine **7** was reduced with DIBALH to yield the primary alcohol **8**.[11] Treatment of the crude **8** with excess mesyl chloride in the presence of triethylamine furnished the spectroscopically pure mesylate **9** in 83% yield (Scheme).

Direct hydrogenolysis of **9** in the presence of catalyst palladium hydroxide on carbon in methanol resulted in a cascade reaction sequence involving isoxazolidine N–O bond cleavage, *N*-debenzylation and spontaneous cyclization affording pyrrolidine **10**, pure enough for the next step, although pyrrolidine **10** was converted to its mesylate for characterization purposes. The hydroxy group of **10** was protected as its *tert*-butyldimethylsilyl ether in 82% yield (purified by flash chromatography) before liberation of the 1,3-diol functionality. Hydrolysis of ethylidene acetal in **11** was achieved using 80% acetic acid at 80 °C yielded crude diol **12**. Cyclization of this product **12** with mesyl chloride/triethylamine afforded the expected pyrrolizidine derivative **13** (77% overall yield from **11**, after column chromatography). Finally, removal of the protecting groups in **13** with NH_4F with TBAF in aqueous THF gave an oily triol **3** in 61% yield (Scheme).

Product identification was carried out by NMR spectroscopy.[12] A detailed NMR study using 2D COSY and NOE experiments was undertaken in order to decide the stereochemistry of **13**. NOE experiments revealed the *cis* location of 1-H and 6-H in the **13** and confirmed the 3,4'-*erythro* stereochemistry in adduct **7**.[8]

In summary an efficient synthetic pathway to pyrrolizidine **3** has been established from D-glucose via enantiomerically pure isoxazolidine intermediate in 14 steps with an overall yield of 12%. This process will be widely applicable to the synthesis of other pyrrolizidine alkaloids.

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(9) The alternative access to the cycloadduct **7** via the cycloaddition of the unprotected nitrone **6** with methyl acrylate with the subsequent silylation (90% yield) has also been performed. The cycloaddition was less selective and gave a 48:29:18:5 diastereomeric mixture of cycloadducts.[8]

(10) In addition, allyl alcohol and its mesyl derivative were used for the cycloaddition, but the cycloaddition with nitrone **6** gave a 62:17:11:10 and 73:18:7:2 diastereomeric mixture of cycloadducts in low yield (43% and 37%), respectively.

(11) The use of $LiAlH_4$ instead of DIBALH lowers the yield from 98% to 75%.

(12) Selected data:
(3*S*,5*R*,2'*R*,4'*S*,5'*R*)-2-*N*-benzyl-3-(5-*tert*-butyldimethylsilyloxy-2-methyl-1,3-dioxan-4-yl)-5-hydroxymethylisoxazolidine (**8**): Colourless oil, yield 98%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42-7.28 (m, 5 H), 4.65 (q, 1 H, *J* = 5.1 Hz), 4.30-4.21 (m, 1 H), 4.01 (s, 2 H), 4.00 (dd, 1 H, *J* = 10.8 and 4.9 Hz), 3.81 (dd, 1 H, *J* = 12.0 and 2.9 Hz), 3.58 (dd, 1 H, *J* = 12.0 and 4.4 Hz), 3.50 (ddd, 1 H, *J* = 9.6, 9.4 and 4.9 Hz), 3.44-3.42 (m, 1 H), 3.39-3.35 (m, 1 H), 3.31 (dd, 1 H, *J* = 10.8 and 9.6 Hz), 2.50 (ddd, 1 H, *J* = 12.0, 7.4 and 5.7 Hz), 2.12 (ddd, 1 H, *J* = 12.0, 8.6 and 8.2 Hz), 1.79 (s, 1 H), 1.35 (d, 3 H, *J* = 5.1 Hz), 0.85 (s, 9 H), 0.05 and 0.03 (2 × s, 2 × 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.7, 129.2, 128.3, 126.9 (NCH_2Ph), 98.8 (C-2'), 81.1 (C-4'), 78.6 (C-5), 71.2 (C-6'), 64.3 (C-3), 64.1 (C-5'), 63.4 (CH_2OH), 62.4 (NCH_2Ph), 29.8 (C-4), 25.6 ($OSiC(CH_3)_3$), 20.5 (2'-CH_3), 17.7 ($OSiC(CH_3)_3$), −4.3 and −4.9 ($OSi(CH_3)_2$).
(3*S*,5*R*,2'*R*,4'*S*,5'*R*)-2-*N*-benzyl-3-(5-*tert*-butyldimethylsilyloxy-2-methyl-1,3-dioxan-4-yl)-5-(-*O*-methanesulfonyl)hydroxymethylisoxazolidine (**9**): Colourless solid, mp 71-74 °C; yield 83%; $[\alpha]_D$ = –29.6 (CH_2Cl_2, *c* 0.21); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34-7.19 (m, 5 H), 4.60 (q, 1 H, *J* = 5.1 Hz), 4.37-4.32 (m, 1 H), 4.26-4.25 (m, 2 H), 3.99 (s, 2 H), 3.94 (dd, 1 H, *J* = 10.8 and 4.6 Hz), 3.41 (ddd, 1 H, *J* = 9.5, 9.0 and 4.6 Hz), 3.40-3.38 (m, 1 H), 3.35 (dd, 1 H, *J* = 9.0 and 4.7 Hz), 3.25 (dd, 1 H, *J* = 10.8 and 9.5 Hz), 2.92 (s, 3 H), 2.52 (ddd, 1 H, *J* = 12.1, 7.4 and 4.7 Hz), 1.99 (ddd, 1 H, *J* = 12.1, 8.7 and 8.7 Hz), 1.28 (d, 3 H, *J* = 5.1 Hz), 0.78 (s, 9 H), 0.02 and –0.01 (2 × s, 2 × 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 136.7, 129.2, 128.3, 127.5 (NCH_2Ph), 98.8 (C-2'), 81.3 (C-4'), 75.9(C-5), 71.1 (C-6'), 70.1 (CH_2OMs), 64.1 (C-3), 63.9 (C-5'), 62.5 (NCH_2Ph), 37.7 (OSO_2CH_3), 30.4 (C-4), 25.6 ($OSiC(CH_3)_3$), 20.5 (2'-CH_3), 17.7 ($OSiC(CH_3)_3$), -4.3 and -4.8 ($OSi(CH_3)_2$); $C_{23}H_{39}NO_7SSi$ (501.71) calcd C 55.06, H 7.83, N 2.79, S 6.39; found: C 54.88, H 7.76, N 2.93, S 6.04.
(2*R*,4*S*,5*R*,1'*S*,4'*R*)-5-*O*-*tert*-butyldimethylsilyloxy-4-(4-hydroxypyrrolidine-2-yl)-2-methyl-1,3-dioxane methanesulfonate (**10**): Colourless oil, yield 99%; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.52 and 8.54 (2 × s, 2 × 1 H), 4.81 (q, 1 H, *J* = 5.0 Hz), 4.48-4.42 (m, 1 H), 4.06 (s, 1 H), 3.97 (dd, 1 H, *J* = 10.2 and 4.5 Hz), 3.89 (dd, 1 H, *J* = 9.0 and 2.3 Hz), 3.48-3.20 (m, 4 H), 2.66 (s, 3 H), 2.25 (ddd, 1 H, *J* = 13.9, 9.7 and 6.2 Hz), 2.11-2.02 (m, 2 H), 1.31 (d, 3 H, *J* = 5.0 Hz), 0.81 (s, 9 H), −0.02 and −0.03 (2 × s, 2 × 3 H).
(2*R*,4*S*,5*R*,2'*S*,4'*R*)-5-*tert*-butyldimethylsilyloxy-4-(4'-*tert*-butyldimethylsilyloxy-pyrrolidine-2-yl)-2-methyl-1,3-dioxolane (**11**): Colorless oil; yield 82%; $[\alpha]_D$ = –48.2 (CH_2Cl_2, *c* 0.25); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.70 (q, 1 H, *J* = 5.1 Hz), 4.34-4.26 (m, 1 H), 3.95 (dd, 1 H, *J* = 11.1 and 4.8 Hz), 3.84-3.68 (m, 1 H), 3.64-3.25 (m, 5 H), 1.98 (dddd, 1 H, *J* = 13.7, 6.2, 1.5 and 1.5 Hz), 1.76 (ddd, 1 H, *J* = 13.7, 11.7 and 4.4 Hz), 1.27 (d, 3 H, *J* = 5.1 Hz), 0.85 and 0.81 (2 × s, 2 × 9 H), 0.03, 0.02, 0.00 and −0.01 (4 × s, 4 × 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 98.5 ($CHCH_3$), 79.7 (C-5), 71.4 (C-2), 70.9 (C-7), 64.2 (C-6), 56.5 (C-4), 55.6 (C-1), 34.2 (C-3), 25.6 and 25.4 ($OSiC(CH_3)_3$), 20.2 ($CHCH_3$), 17.9 and 17.6 ($OSiC(CH_3)_3$), -4.3, -4.5, -4.9 and -5.0 ($OSi(CH_3)_2$).
(1*S*,2*R*,6*R*,7a*S*)-2,6-*O*-di-*tert*-butyldimethylsilyl-pyrrolizidine-1,2,6-triol (**13**) Slightly yellow viscous syrup; yield 77%; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.83 (dd, 1 H, *J* = 9.8 and 6.9 Hz), 4.54 (ddd, 2 H, *J* = 9.8, 8.4 and 1.5 Hz), 4.48-4.44 (m, 1 H), 4.21 (ddd, 1 H, *J* = 10.0, 6.9 and 6.2 Hz), 3.45 (dd, 1 H, *J* = 12.8 and 4.1 Hz), 3.28 (dd, 1 H, *J* = 9.8 and 1.5 Hz), 3.21 (dd, 1 H, *J* = 12.8 and 1.7 Hz), 2.88 (dd, 1 H, *J* = 9.8 and 8.4 Hz), 2.21 (ddd, 1 H, *J* = 13.8, 6.2 and 2.1 Hz), 1.82 (ddd, 1 H, *J* = 13.8, 10.0 and 4.7 Hz), 0.79 and 0.77 (2 × s, 2 × 9 H), 0.02, 0.01, −0.01 and −0.02 (4 × s, 4 × 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 83.4 (C-1), 82.7 (C-2), 72.0 (C-6), 67.3 (C-7a), 57.4 (C-3), 55.7 (C-5), 34.5 (C-7), 25.5 and 25.4 ($OSiC(CH_3)_3$), 17.8 and 17.7 ($OSiC(CH_3)_3$), −4.6, −4.7, −5.0 and -5.1 ($OSi(CH_3)_2$).
(1*S*,2*R*,6*R*,7a*S*)-pyrrolizidine-1,2,6-triol (**3**): Colourless oil; yield 61%; $[\alpha]_D$ = +49.1 (MeOH, *c* 0.30); ^{1}H NMR (300 MHz, CD_3OD): δ = 4.83-4.73 (m, 3 H), 4.18 (ddd, 1 H, *J* = 10.1, 6.8 and 6.2 Hz), 3.57-3.28 (m, 3 H), 3.01 (dd, 1 H, *J* = 10.0 and 7.8 Hz), 2.34 (ddd, 1 H, *J* = 13.5, 6.2 and 2.6 Hz), 2.05-1.97 (m, 1 H); ^{13}C NMR (125 MHz, CD_3OD): δ = 84.9 (C-1), 84.6 (C-2), 74.1 (C-6), 69.9 (C-7a), 58.4 (C-3), 56.9 (C-5), 35.1 (C-7).