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Note

Synthesis from lactose of new enantiomerically pure polyhydroxylated pyrrolidines with branched structures ☆

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Optically active polyhydroxylated pyrrolidines belong to a large and now well-established class of specific and powerful glycosidase inhibitors [2–5]. Such compounds, despite their well-known hepatotoxicity [6a], may also possess potential biological applications due to their antifungal [6b], antibiotic [6c] and antiviral (anti-HIV) [7] properties.

So far, mainly non-branched structures have been prepared, with very few branched compounds having been described [7]. It was thus useful to complete the series with the description of an access to polyhydroxylated pyrrolidines with branched skeletons, as a variation of the N-substitution has been demonstrated to have an effect upon biological properties [8]. Our target in this work has been 2,4-dihydroxymethyl-4-hydroxy-*N*-substituted pyrrolidines, the C-4 atom being a quaternary center.

We present in this paper routes to functionalized pyrrolidines starting from a lactone readily available from lactose and using pentitol **4** as a key intermediate.

3-Deoxy-2-*C*-hydroxymethyl-D-*erythro*-pentono-1,4-lactone, more commonly known as "α-D-isosaccharino-1,4-lactone" (**1**), was prepared according to the literature in two steps from lactose [9] in an overall yield of 17%. Treatment of lactone **1** with acetone in the presence of an acid (thermodynamic control) gave the *O*-isopropylidene derivative **2** (Scheme 1) in 62% yield [10]. The remaining hydroxymethyl group was then protected

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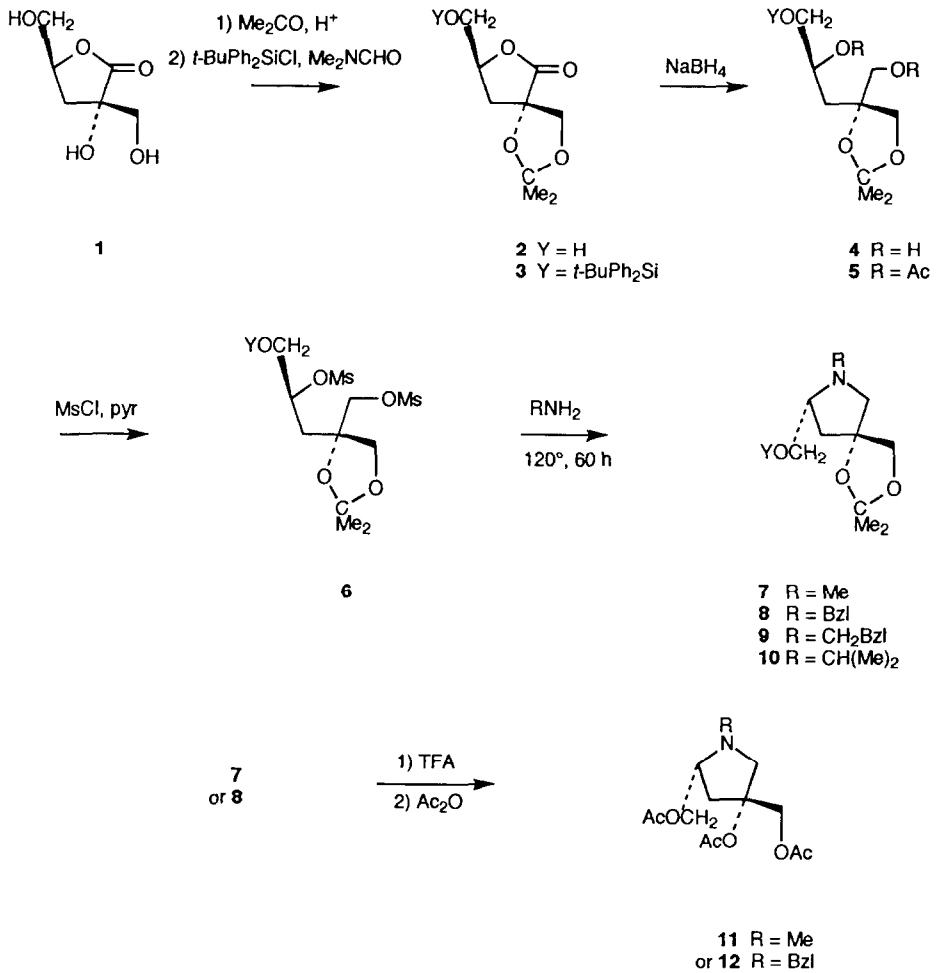

Scheme 1.

to give the silylated lactone **3** (58%), which was reduced with sodium borohydride to the diol **4** (67%) identified by NMR spectroscopy and by its conversion into the diacetate **5**. ^{1}H NMR (300 MHz, $CDCl_3$) spectral data showed in particular two singlets at 2.07 and 2.00 ppm corresponding to the acetyl groups and AB quartet for H-1A (at 3.80 ppm) and H-1B (at 3.92 ppm) (J 9.0 Hz) as expected. Activation of the free hydroxyl groups of **4** by methanesulfonyl chloride in dry pyridine [11] led to the dimesylate **6** (62%), which could be rapidly converted into protected pyrrolidines by heating with the appropriate amine (methyl-, benzyl-, phenethyl- or isopropyl-amine) at 120°C for 60 h. So **7**, **8**, **9** and **10** were isolated with 55%, 93%, 42% and 63% yields, respectively. Their 400 MHz ^{1}H NMR spectral data ($CDCl_3$) showed in particular a doublet (or a doublet of doublets) from 3.00 to 3.35 ppm ($J_{5,5'}$ ~ 10 Hz, H-5′) and another one from 2.45 to 2.10 ppm (H-5). These chemical shifts and coupling constants were in agreement with those

expected for the protons alpha to the nitrogen atom of a five-membered ring. The mechanism of the last reaction, known to be a S_N2-type reaction [12], was in favor of the formation of the (2*R*,4*S*) diastereoisomer of compounds **7**–**10** (isomers **a**). Each compound was actually contaminated by traces of another derivative. Elemental analysis, NMR spectral data and other results [13] of each mixture let us suppose that this minor compound could be the diastereoisomeric pyrrolidines (2*S*,4*S*) (isomers **b**, see Experimental).

These protected pyrrolidines were obtained from lactone **1** with a total yield of 11 to 22% depending upon the amine used in the last step.

Finally, **7** and **8** were submitted to acid hydrolysis with a 30% solution of trifluoroacetic acid in water and then acetylation to give the expected pure **11** and **12** (Scheme 1), identified by NMR spectroscopy and elemental analysis.

In conclusion, we have illustrated a convenient route to branched, N-substituted enantiomerically pure pyrrolidines starting from sugar lactones. They are available for further structural modifications and biological evaluations.

1. Experimental

General methods.—Melting points were determined on a Büchi apparatus. Evaporations were performed under diminished pressure. Optical rotations were measured at room temperature on a Perkin–Elmer 241 polarimeter (path length 1 dm) (*c* 1). Column chromatography was carried out using Silica Gel 60 (E. Merck 70–230 mesh) or 60A (E. Merck 35–70 mesh). TLC was performed on precoated plates (E. Merck 5724), and compounds were visualised with a spray of 30% sulfuric acid in water or a solution of phosphomolybdic acid (25 g) in ethanol (500 mL), and heating. All organic solvents were dried and distilled. Pyridine was dried and distilled under diminished pressure. *N*,*N*-Dimethylformamide was stirred over CaH_2 and distilled under reduced pressure. Anhydrous Na_2SO_4 was used to dry organic extracts. ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded on a Bruker MSL 300 or AC 400 spectrometer. Chemical shift data are given in δ-units (ppm) measured downfield from internal Me_4Si, and spin–spin couplings are in Hz. Microanalyses were performed by the microanalytical services of Centre National de la Recherche Scientifique (C.N.R.S.), Service Central d'Analyse, B.P. 22, 69390 Vernaison, France.

*3-Deoxy-2-C-hydroxymethyl-*D-erythro-*pentono-1,4-lactone* (*"α-*D-*isosaccharino-1,4-lactone"*, **1**).—This lactone was prepared from lactose following the process reported by Whistler and BeMiller [9]: mp 91–92°C; $[\alpha]_D$ +62.0° (H_2O), lit. [9] mp 95–96°C; $[\alpha]_D$ +62° (*c* 1, H_2O); NMR data (Me_2SO-d_6): ^1H, δ 5.90 (s, 1 H, OH-2), 5.05 (m, 2 H, OH-2^1 and OH-5), 4.50 (m, 1 H, H-4), 3.55 (m, 2 H, $J_{2^1,2^{1'}}$ 10.4 Hz, H-2^1 and H-2$^{1'}$), 3.45 (dd, 1 H, $J_{5,5'}$ 11.4, $J_{4,5'}$ 6.0 Hz, H-5'), 3.30 (dd, 1 H, $J_{4,5}$ 4.0 Hz, H-5), 2.20 (dd, 1 H, $J_{3,3'}$ 14.0, $J_{3',4}$ 8.4 Hz, H-3'), 1.95 (dd, 1 H, $J_{3,4}$ 6.8 Hz, H-3); ^{13}C, δ 176.87 (C-1), 77.78 (C-4), 76.86 (C-2), 63.10 and 62.75 (C-2^1 and C-5), 33.56 (C-3). Anal. Calcd for $C_6H_{10}O_5$: C, 44.45; H, 6.22; O, 49.34. Found: C, 44.41; H, 6.28; O, 48.78.

*3-Deoxy-2-*C*-hydroxymethyl-2,2'-*O*-isopropylidene-*D*-erythro-pentono-1,4-lactone* (**2**).—To 2.5 g (15 mmol) of **1** in acetone (130 mL) was added 5 drops of concd H_2SO_4 and 2 g of copper(II) sulfate. The reaction mixture was stirred at room temperature for 3 h (checking by TLC in 5:1 EtOAc–methanol) and then neutralized (sodium carbonate) and filtered. After removing the solvent, the residue was recrystallized from 6:1 ether–hexane, to give **2** (1.9 g, 62%): mp 52°C; $[\alpha]_D$ +43.7° ($CHCl_3$), lit. [10] mp 56°C; $[\alpha]_D$ +43° (*c* 1, $CHCl_3$); NMR data ($CDCl_3$): ^{1}H, δ 4.70 (m, 1 H, H-4), 4.30 (d, 1 H, $J_{2',2''}$ 9.0 Hz, H-2''), 4.10 (d, 1 H, H-2'), 3.95 (dd, 1 H, $J_{5,5'}$ 12.0, $J_{4,5'}$ 1.5 Hz, H-5'), 3.60 (dd, 1 H, $J_{4,5}$ 3.0 Hz, H-5), 2.60 (wide signal, 1 H, OH-5), 2.45 (dd, 1 H, $J_{3,3'}$ 13.5, $J_{3',4}$ 7.5 Hz, H-3'), 2.35 (dd, 1 H, $J_{3,4}$ 6.0 Hz, H-3), 1.50 (s, 3 H, Me), 1.45 (s, 3 H, Me); ^{13}C, δ 175.98 (C-1), 112.39 (CMe$_2$), 81.02 (C-2), 77.85 (C-4), 71.76 (C-2'), 63.15 (C-5), 35.86 (C-3), 26.52 and 25.70 (C*Me*$_2$). Anal. Calcd for $C_9H_{14}O_5$: C, 53.46; H, 6.98; O, 39.56. Found: C, 53.49; H, 6.93; O, 39.11.

*5-*O*-tert-Butyldiphenylsilyl-3-deoxy-2-*C*-hydroxymethyl-2,2'-*O*-isopropylidene-*D*-erythro-pentono-1,4-lactone* (**3**).—A solution of imidazole (2.2 g, 2.6 equiv) in dry *N*,*N*-dimethylformamide (30 mL) was added to 2.5 g (12 mmol) of **2** under argon. After addition of *tert*-butylchlorodiphenylsilane (3.8 mL, 1.2 equiv), the solution was stirred at room temperature. After 15 h, the reaction mixture was diluted with water (60 mL) and extracted with CH_2Cl_2. The organic layer was washed with brine (60 mL), dried, and the solvent was removed. The resulting oil was chromatographed (1:4 EtOAc–cyclohexane) to give **3** (3.2 g, 58%). An analytical sample was obtained by recrystallization from EtOH: mp 87°C; $[\alpha]_D$ +22.0° ($CHCl_3$); NMR data ($CDCl_3$): ^{1}H, δ 7.75–7.45 (m, 10 H, Ar), 4.70 (m, 1 H, H-4), 4.35 (d, 1 H, $J_{2',2''}$ 8.9 Hz, H-2''), 4.05 (d, 1 H, H-2'), 3.90 (dd, 1 H, $J_{5,5'}$ 11.6, $J_{4,5'}$ 6.0 Hz, H-5'), 3.72 (dd, 1 H, $J_{4,5}$ 3.5 Hz, H-5), 2.45 (dd, 1 H, $J_{3,3'}$ 13.8, $J_{3',4}$ 8.8 Hz, H-3'), 2.35 (dd, 1 H, $J_{3,4}$ 8.8 Hz, H-3), 1.50 (s, 3 H, Me), 1.45 (s, 3 H, Me), 1.10 (s, 9 H, *t*-Bu); ^{13}C, δ 175.38 (C-1), 135.67, 135.56, 134.85, 132.80, 132.50, 130.05, 129.67, 127.94, 127.75 (Ar), 112.39 (CMe$_2$), 80.77 (C-2), 77.36 (C-4), 71.65 (C-2'), 64.44 (C-5), 36.03 (C-3), 26.85, 26.62, 25.66 (C*Me*$_2$, C*Me*$_3$), 19.29 (CMe$_3$). Anal. Calcd for $C_{25}H_{32}O_5Si$: C, 68.15; H, 7.32. Found: C, 68.12; H, 7.50.

*5-*O*-tert-Butyldiphenylsilyl-3-deoxy-2,2'-*O*-isopropylidene-(2*R*,4*S*)-pentitol* (**4**).—To a solution of **3** (8.0 g, 18 mmol) in absolute methanol (80 mL) was added by small portions 1.4 g (2.0 equiv) of sodium borohydride. After 2 h at room temperature, the solvent was evaporated, the residue dissolved in water and extracted continuously with CH_2Cl_2 (24–48 h). The organic layer was dried and removed to give, after purification by chromatography (1:1 EtOAc–cyclohexane), **4** (5.2 g, 65%): $[\alpha]_D$ −4.9° ($CHCl_3$); NMR data (C_6D_6): ^{1}H, δ 7.95–7.45 (m, 10 H, Ar), 4.40 (m, 1 H, H-4), 4.23 (d, 1 H, $J_{2',2''}$ 8.7 Hz, H-2''), 3.97 (d, 1 H, $J_{1,1'}$ 11.3 Hz, H-1'), 3.87 (d, 1 H, H-1), 3.82 (d, 1 H, H-2'), 3.75 (dd, 1 H, $J_{5,5'}$ 10.0, $J_{4,5'}$ 4.8 Hz, H-5'), 3.70 (dd, 1 H, $J_{4,5}$ 7.4 Hz, H-5), 3.33, 3.22 (2 broad signals, 2 H, OH-1 and OH-4), 1.86 (dd, 1 H, $J_{3,3'}$ 14.7, $J_{3',4}$ 9.3 Hz, H-3'), 1.76 (dd, 1 H, $J_{3,4}$ 2.0 Hz, H-3), 1.58 (s, 3 H, Me), 1.49 (s, 3 H, Me), 1.35 (s, 9 H, *t*-Bu); ^{13}C, δ 136.63, 135.99, 134.32, 134.26, 130.83, 130.41, 129.24, 128.95, 128.85, 128.71, 128.46 (Ar), 110.07 (CMe$_2$), 83.52 (C-2), 73.21 (C-2'), 69.50 (C-1), 69.43 (C-4), 66.55 (C-5), 39.41 (C-3), 28.40, 27.71, 27.53 (C*Me*$_2$, C*Me*$_3$), 20.10 (CMe$_3$).

*1,4-Di-O-acetyl-5-O-*tert*-butyldiphenylsilyl-3-deoxy-2,2′-O-isopropylidene-(2R,4S)-pentitol* (**5**).—Following a classical procedure, 2.0 equiv/OH of acetic anhydride were added to 5.0 g (11 mmol) of **4** dissolved in dry pyridine, giving the diacetate **5**: $[\alpha]_D$ −26.1° ($CHCl_3$); NMR data ($CDCl_3$): ^{1}H, δ 7.70–7.30 (m, 10 H, Ar), 5.15 (m, 1 H, H-4), 4.14 (d, 1 H, $J_{2',2''}$ 11.4 Hz, H-2′′), 3.99 (d, 1 H, H-2′), 3.92 (d, 1 H, $J_{1,1'}$ 9.0 Hz, H-1′), 3.80 (d, 1 H, H-1), 3.72 (dd, 1 H, $J_{5,5'}$ 10.8, $J_{4,5'}$ 5.0 Hz, H-5′), 3.68 (dd, 1 H, $J_{4,5}$ 4.8 Hz, H-5), 2.10 (dd, 1 H, $J_{3,3'}$ 14.8, $J_{3',4}$ 3.8 Hz, H-3′), 2.07 (s, 3 H, OAc), 2.02 (dd, 1 H, $J_{3,4}$ 8.8 Hz, H-3), 2.00 (s, 3 H, OAc), 1.40 (s, 3 H, Me), 1.35 (s, 3 H, Me), 1,05 (s, 9 H, *t*-Bu); ^{13}C, δ 170.69, 170.28 (C=O), 135.71, 135.65, 133.34, 129.90, 127.83 (Ar), 110.02 (CMe_2), 80.30 (C-2), 71.69 (C-2′), 71.13 (C-4), 66.00, 65.40 (C-1 and C-5), 36.82 (C-3), 27.10, 26.87, 26.78 (CMe_3, CMe_2), 21.29, 20.93 (CO*Me*), 19.36 (CMe_3). Anal. Calcd for $C_{29}H_{40}O_7Si$: C, 65.88; H, 7.63. Found: C, 65.81; H, 7.39.

*5-O-*tert*-Butyldiphenylsilyl-3-deoxy-2,2′-O-isopropylidene-1,4-di-O-(methylsulfonyl)-(2R,4S)-pentitol* (**6**).—Methanesulfonyl chloride (2 mL, 26 mmol) was added to a stirred solution of the diol **4** (2.4 g, 5 mmol) in pyridine (20 mL), and the reaction mixture stirred overnight at 0°C. Then, water (50 mL) was added, and the mixture was extracted with CH_2Cl_2 (100 mL). The organic layer was dried and evaporated, with successive additions of toluene, to give a crude product which was purified by flash chromatography (1:2 EtOAc–cyclohexane) to afford **6**. It was found preferable to immediately use this dimesylate in the next step (2.0 g, 62%): $[\alpha]_D$ −11.6° ($CHCl_3$); NMR data ($CDCl_3$): ^{1}H, δ 7.70–7.30 (m, 10 H, Ar), 4.95 (m, 1 H, H-4), 4.25 (d, 1 H, $J_{2',2''}$ 10.3 Hz, H-2′′), 4.17 (d, 1 H, H-2′), 4.09 (d, 1 H, $J_{1,1'}$ 9.4 Hz, H-1′), 3.90 (dd, 1 H, $J_{5,5'}$ 11.6, $J_{4,5'}$ 3.8 Hz, H-5′), 3.82 (dd, 1 H, $J_{4,5}$ 5.7 Hz, H-5), 3.75 (d, 1 H, H-1), 3.09 (s, 3 H, SO_2Me), 3.00 (s, 3 H, SO_2Me), 2.16 (dd, 1 H, $J_{3,3'}$ 15.1, $J_{3',4}$ 7.4 Hz, H-3′), 2.02 (dd, 1 H, $J_{3,4}$ 5.1 Hz, H-3), 1.40 (s, 3 H, Me), 1.28 (s, 3 H, Me), 1,09 (s, 9 H, *t*-Bu); ^{13}C, δ 135.66, 135.54, 132.73, 132.60, 130.13, 130.08, 127.97 (Ar), 110.66 (CMe_2), 79.74 (C-4), 79.25 (C-2), 71.82 (C-2′), 69.26 (C-1), 65.97 (C-5), 38.85 (SO_2Me), 37.51 (SO_2Me), 37.09 (C-3), 26.95, 26.89, 26.43 (CMe_3, CMe_2), 19.26 (CMe_3).

Preparation of pyrrolidines **7**, **8**, **9** *and* **10**.—The dimesylate **6** (3.0 g, 5 mmol) was warmed at 120°C for 60 h with 6 mL of a primary amine:methylamine (33% in abs ethanol), benzylamine, phenethylamine or isopropylamine. The reaction mixture was then partitioned between brine (50 mL) and CH_2Cl_2 (100 mL). The organic layer was dried and the solvent removed to give, after purification by chromatography (respectively 1:1; 1:9; 1:2 and 1:1 EtOAc–cyclohexane for each pyrrolidine), two unseparable compounds respectively **7a/b**, **8a/b**, **9a/b** and **10a/b**. It is noted that the trace quantities of isomers **b** in the mixtures did not allow the detection of each signal and their assignment by NMR spectroscopy.

*2′-O-*tert*-Butyldiphenylsilyl-4,4′-O-isopropylidene-(2R,4S)-N-methylpyrrolidine* (**7a**) *and* **7b** *(isomer 2S,4S)*.—Mixture of **a** and **b**: (1.2 g, 55%); $[\alpha]_D$ +19.0° ($CHCl_3$). NMR data for **7a** (C_6D_6): ^{1}H, δ 7.60–7.20 (m, 10 H, Ar), 3.93 (dd, 1 H, $J_{2',2''}$ 10.0, $J_{2,2''}$ 5.5 Hz, H-2′′), 3.77 (dd, 1 H, $J_{2,2'}$ 5.7 Hz, H-2′), 3.66 (s-like, 2 H, H-4′ and H-4′′), 3.20 (d, 1 H, $J_{5,5'}$ 10.1 Hz, H-5′), 2.38 (m, 1 H, H-2), 2.26 (s, 3 H, NMe), 2.07 (d, 1 H, H-5), 2.05 (deformed dd, 1 H, $J_{3,3'}$ 13.4, $J_{2,3'}$ 8.1 Hz, H-3′), 1.92 (dd, 1 H, $J_{2,3}$ 7.8 Hz, H-3), 1.43 (s, 3 H, Me), 1.40 (s, 3 H, Me), 1.22 (s, 9 H, *t*-Bu);

^{13}C, δ 134.80, 134.74, 132.93, 132.82, 128.67, 126.98, 126.78, 126.72, 126.50 (Ar), 108.14 (CMe_2), 84.17 (C-4), 72.06 (C-4^1), 66.21, 66.05 (C-2^1 and C-5), 65.63 (C-2), 41.17 (C-3), 40.33 (NMe), 25.96, 25.85, 25.60 (CMe_2, CMe_3), 18.22 (CMe_3). NMR data for **7b** (C_6D_6): ^{1}H, δ 7.60–7.20 (m, 10 H, Ar), 4.05 (d, 1 H), 3.75 (dd), 3.60 (m), 3.02 (d, 1 H), 2.48 (dd), 2.20 (s, 3 H), 1.77 (dd), 1.40 (s), 1.20 (s, 9 H); ^{13}C, δ 74.62, 66.64, 65.37, 64.50, 40.07, 38.04, 26.27, 25.26. Anal. Calcd for $C_{26}H_{37}O_3NSi$: C, 71.02; H, 8.48. Found: C, 70.60; H, 8.48.

2^1-O-tert-Butyldiphenylsilyl-4,4^1-O-isopropylidene-(2R,4S)-N-benzylpyrrolidine (**8a**) *and* **8b** *(isomer 2S,4S).*—Mixture of **a** and **b**: (2.4 g, 93%); $[\alpha]_D$ +35.5° ($CHCl_3$). NMR data for **8a** ($CDCl_3$): ^{1}H, δ 7.85–7.20 (m, 15 H, Ar), 4.15 (d, 1 H, $J_{H,H'}$ 13.4 Hz, NCH_2Ph), 3.93 (dd, 1 H, $J_{2^1,2^{1'}}$ 10.1, $J_{2,2^{1'}}$ 5.3 Hz, H-2$^{1'}$), 3.90 (d, 1 H, $J_{4^1,4^{1'}}$ 8.4 Hz, H-4$^{1'}$), 3.83 (d, 1 H, H-4^1), 3.73 (dd, 1 H, $J_{2,2^1}$ 6.5 Hz, H-2^1), 3.36 (d, 1 H, NCH_2Ph), 3.10 (d, 1 H, $J_{5,5'}$ 10.3 Hz, H-5′), 2.82 (m, 1 H, H-2), 2.34 (d, 1 H, H-5), 2.21 (dd, 1 H, $J_{3,3'}$ 13.7 Hz, $J_{2,3'}$ 7.8 Hz, H-3′), 2.03 (dd, 1 H, $J_{2,3}$ 7.9 Hz, H-3), 1.43 (s, 3 H, Me), 1.35 (s, 3 H, Me), 1.10 (s, 9 H, *t*-Bu); ^{13}C, δ 138.82, 135.64, 133.71, 133.63, 129.66, 128.83, 128.51, 128.16, 127.70, 126.86 (Ar), 109.53 (CMe_2), 85.00 (C-4), 73.10 (C-4^1), 64.59 (C-2), 67.23, 63.90 (C-2^1 and C-5), 59.06 (NCH_2Ph), 42.09 (C-3), 26.96, 26.92, 26.54 (CMe_2, CMe_3), 19.27 (CMe_3). NMR data for **8b** ($CDCl_3$): ^{1}H, δ 7.85–7.20 (m, 15 H, Ar), 4.10 (d, 1 H), 3.97 (m, 1 H), 3.50 (m), 3.30 (d, 1 H), 2.95 (d), 2.40 (d), 1.30 (s, 3 H), 1.25 (s, 3 H), 1.05 (s, 9 H); ^{13}C, δ 134.85, 130.78, 129.32, 128.83, 128.62, 128.30, 127.99, 127.99 (Ar), 75.29, 66.43, 65.08, 63.22, 58.89, 38.99, 27.15, 26.63, 26.29. Anal. Calcd for $C_{32}H_{41}O_3NSi$: C, 74.52; H, 8.01; N, 2.72. Found: C, 74.44; H, 7.92; N, 3.04.

2^1-O-tert-Butyldiphenylsilyl-4,4^1-O-isopropylidene-(2R,4S)-N-phenethylpyrrolidine (**9a**) *and* **9b** *(isomer 2S,4S).*—Mixture of **a** and **b**: (1.1 g, 42%); $[\alpha]_D$ +32.6° ($CHCl_3$). NMR data for **9a** ($CDCl_3$): ^{1}H, δ 7.70–7.10 (m, 15 H, Ar), 3.95 (t, 2 H, H-4$^{1'}$ and H-4^1), 3.88 (dd, 1 H, $J_{2^1,2^{1'}}$ 10.0, $J_{2,2^{1'}}$ 5.3 Hz, H-2$^{1'}$), 3.68 (dd, 1 H, $J_{2,2^1}$ 7.1 Hz, H-2^1), 3.35 (dd, 1 H, $J_{5,5'}$ 10.0 Hz, $J_{3,5'}$ < 1 Hz, H-5′), 3.10 [m, 1 H, $N(CH_2)_2Ph$], 2.75 [m, 3 H, H-2 and $N(CH_2)_2Ph$], 2.45 [m, 2 H, H-5 and $N(CH_2)_2Ph$], 2.18 (dd, 1 H, $J_{3,3'}$ 13.8, $J_{2,3'}$ 8.2 Hz, H-3′), 2.02 (ddd, 1 H, $J_{2,3}$ 7.0 Hz, H-3), 1.40 (s, 6 H, 2 Me), 1.05 (s, 9 H, *t*-Bu); ^{13}C, δ 140.34, 135.62, 133.77, 133.65, 129.65, 128.66, 128.31, 127.68, 125.97 (Ar), 109.71 (CMe_2), 85.28 (C-4), 72.57 (C-4^1), 67.38, 64.26 (C-2^1 and C-5), 65.25 (C-2), 57.35 (CH_2Ph), 41.67 (C-3), 35.24 (NCH_2), 26.90, 26.65 (CMe_2, CMe_3), 19.27 (CMe_3). NMR data for **9b** ($CDCl_3$): ^{1}H, δ 7.70–7.10 (m, 15 H, Ar), 4.15 (dd, 1 H), 4.02 (d, 1 H), 3.73 (m, 2 H), 3.49 (dd, 1 H), 3.28 (d), 2.81 (d), 2.27 (dd, 1 H), 1.78 (dd, 1 H), 1.40 (s, 6 H), 1.05 (s, 9 H); ^{13}C, δ 83.98, 74.97, 66.51, 63.78, 56.40, 38.93, 34.83, 27.46, 26.10. Anal. Calcd for $C_{33}H_{43}O_3NSi$: C, 74.81; H, 8.18. Found: C, 74.90; H, 7.99.

2^1-O-tert-Butyldiphenylsilyl-4,4^1-O-isopropylidene-(2R,4S)-N-isopropylpyrrolidine (**10a**) *and* **10b** *(isomer 2S,4S).*—Mixture of **a** and **b**: (1.5 g, 63%); $[\alpha]_D$ +20.3° ($CHCl_3$). NMR data for **10a** (C_6D_6): ^{1}H, δ 7.60–6.90 (m, 10 H, Ar), 3.61 (dd, 1 H, $J_{2^1,2^{1'}}$ 9.8, $J_{2,2^{1'}}$ 7.9 Hz, H-2$^{1'}$), 3.56 (dd, 1 H, $J_{2,2^1}$ 5.1 Hz, H-2^1), 3.40 (d, 1 H, $J_{4^1,4^{1'}}$ 8.4 Hz, H-4$^{1'}$), 3.36 (d, 1 H, H-4^1), 2.72 (dd, 1 H, $J_{5,5'}$ 9.8, $J_{3',5'}$ < 1 Hz, H-5′), 2.70 (m, 1 H, H-2), 2.48 (m, 1 H, NCH), 2.17 (d, 1 H, H-5), 1.95 (ddd, 1 H, $J_{3,3'}$ 13.3, $J_{2,3'}$ 4.5 Hz, H-3′), 1.52 (dd, 1 H, $J_{2,3}$ 8.3 Hz, H-3), 1.10 (s, 3 H, Me), 1.04 (s, 3 H, Me), 0.90

(s, 9 H, *t*-Bu), 0.62 (d, 3 H, $J_{H\text{-}Me}$ 6.6 Hz, NH*Me*), 0.46 (d, 3 H, $J_{H\text{-}Me}$ 6.3 Hz, NH*Me*); ^{13}C, δ 136.73, 135.15, 134.97, 130.59, 128.95, 128.71, 128.47 (Ar), 110.24 (CMe_2), 86.72 (C-4), 73.39 (C-4^1), 68.20 (C-2^1), 62.07 (C-2), 58.77 (C-5), 51.06 (NCH), 41.22 (C-3), 27.89, 27.84, 27.78, 27.75 (CMe_2, CMe_3), 22.93 (NH*Me*), 20.19 (NH*Me*), 17.67 (CMe_3). NMR data for **10b** (C_6D_6): ^1H, δ 7.60–6.90 (m, 10 H, Ar), 3.67 (d, 1 H), 3.12 (dd, 1 H), 2.59 (dd, 1 H), 2.53 (m), 2.42 (dd, 1 H), 2.02 (dd, 1 H), 1.13 (s, 3 H), 1.07 (s, 3 H), 0.88 (s, 9 H), 0.62 (d, 3 H), 0.46 (d, 3 H); ^{13}C, δ 134.81, 130.70, 128.78, 128.59 (Ar), 109.20, 85.32, 75.92, 60.40, 57.28, 49.90, 39.85, 28.23, 27.26, 23.12, 20.10, 15.54. Anal. Calcd for $C_{28}H_{41}O_3NSi$: C, 70.90; H, 8.84. Found: C, 71.17; H, 8.78.

2,4-Diacetoxymethyl-4-O-acetyl-(2R,4S)-N-methylpyrrolidine (**11**). A mixture of **7a/b** (0.70 g) in 30% aq TFA (15 mL) was stirred at room temperature for 4 h (checked by TLC 1:1 EtOAc–cyclohexane). The water was eliminated under diminished pressure, and the resulting oil, containing the free pyrrolidine, was then dissolved in dry pyridine (15 mL) at 0°C, and 3.5 g (3.0 equiv/OH) of Ac_2O were added. The crude product was chromatographed (5:1 EtOAc–cyclohexane) to give pure **11** (0.22 g, 48%): $[\alpha]_D$ +16.7° ($CHCl_3$); NMR data ($CDCl_3$): ^1H, δ 4.55 (d, 1 H, $J_{4^1,4^{1'}}$ 11.8 Hz, H-4$^{1'}$), 4.27 (d, 1 H, H-4^1), 4.07 (dd, 1 H, $J_{2^1,2^{1'}}$ 11.5, $J_{2,2^{1'}}$ 4.9 Hz, H-2$^{1'}$), 4.03 (dd, 1 H, $J_{2,2^1}$ 5.0 Hz, H-2^1), 3.44 (d, 1 H, $J_{5,5'}$ 11.4 Hz, H-5'), 2.46 (m, 1 H, H-2), 2.35 (d, 1 H, H-5), 2.32 (s, 3 H, NMe), 2.25 (dd, 1 H, $J_{3,3'}$ 14.5, $J_{2,3'}$ 7.4 Hz, H-3'), 2.07 (dd, 1 H, $J_{2,3}$ 9.0 Hz, H-3), 2.03, 2.01, 1.98 (3 s, 9 H, 3 OAc); ^{13}C, δ 170.80, 170.65, 170.45 (C=O), 84.88 (C-4), 65.27, 65.17, 64.90 (C-2^1, C-4^1 and C-5), 63.35 (C-2), 40.54 (NMe), 38.98 (C-3), 21.88, 20.83, 20.68 (CO*Me*). Anal. Calcd for $C_{13}H_{21}O_6N$: C, 54.35; H, 7.37. Found: C, 55.63; H, 7.32.

2,4-Diacetoxymethyl-4-O-acetyl-(2R,4S)-N-benzylpyrrolidine (**12**).—Treatment of a mixture **8a/b** (conducted as for the synthesis of **11**) gave after chromatographic purification (1:1 EtOAc–cyclohexane), 0.20 g (41%) of **12**: $[\alpha]_D$ +30.0° (*c* 0.7, $CHCl_3$); NMR data ($CDCl_3$): ^1H, δ 7.40–7.20 (m, 5 H, Ar), 4.47 (d, 1 H, $J_{4^1,4^{1'}}$ 11.8 Hz, H-4$^{1'}$), 4.34 (d, 1 H, H-4^1), 4.20 (m, 3 H), 3.50, 3.35, 3.00, 2.55 (4 wide signals, 1 H each), 2.35 (dd, 1 H, $J_{3,3'}$ 14.2 Hz $J_{2,3'}$ 7.4 Hz, H-3'), 2.17 (wrong dd, 1 H, H-3), 2.07 (s, 3 H, OAc), 2.02 (s, 3 H, OAc), 2.00 (s, 3 H, OAc); ^{13}C, δ 170.85, 170.65, 170.55 (C=O), 128.98, 128.53, 127.58 (Ar), 84.12 (C-4), 65.19, 61.39, 57.91 (NCH_2, C-2^1, C-4^1, C-5), 60.99 (C-2), 38.61 (C-3), 21.90, 20.97, 20.78 (CO*Me*); Anal. Calcd for $C_{19}H_{25}O_6N$: C, 62.80; H, 6.93; O, 26.42. Found: C, 61.58; H, 6.93; O, 26.40.

References

[1] K. Bennis, J. Gelas, L. Martin, and C. Thomassigny, Abstr. Papers XVèmes Journées de la chimie et biochimie des glucides, Le Croisic, France, 1994, p 8.
[2] G.W.J. Fleet and D.R. Witty, *Tetrahedron Asymm.*, 1 (1990) 119–136.
[3] G.W.J. Fleet, *Tetrahedron Lett.*, 26 (1985) 5073–5076.
[4] A.J. Fairbanks, N.C. Carpenter, G.W.J. Fleet, N.G. Ramsden, I.C. de Bello, B.G. Winchester, S.S. Al-Daher, and G. Nagahashi, *Tetrahedron*, 48 (1992) 3365–3376.
[5] P.M. Myerscough, A.J. Fairbanks, A.H. Jones, I. Bruce, S.S. Choi, G.W.J. Fleet, S.S. Al-Daher, I.C. di Bello, and B. Winchester, *Tetrahedron*, 48 (1992) 10177–10190.

[6] (a) J.G. Buchanan, V.B. Jigajinni, G. Singh, and R.H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, (1987) 2377–2384; (b) C.S. Pak and G.H. Lee, *J. Org. Chem.*, 56 (1991) 1128–1133; (c) J.G. Buchanan, K.A. MacLean, and R.H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, (1985) 1463–1470.
[7] (a) Y.H. Lee, H.K. Kim, I.K. Youn, and Y.B. Chae, *Bioorg. Med. Chem. Lett.*, 1 (1991) 287–290; (b) M.R. Harnden and R.L. Jarvest, *Tetrahedron Lett.*, 32 (1991) 3863–3866.
[8] N. Asano, E. Tomioka, H. Kizu, and K. Matsui, *Carbohydr. Res.*, 253 (1994) 235–245.
[9] R.L. Whistler and J.N. BeMiller, *Methods Carbohydr. Chem.*, 2 (1963) 477–479, and references cited therein.
[10] F. Bennani, J.C. Florent, M. Koch, and C. Monneret, *Tetrahedron*, 40 (1984) 4669–4676.
[11] G.W.J. Fleet and J.C. Son, *Tetrahedron*, 44 (1988) 2637–2647.
[12] A.C. Richardson, *Carbohydr. Res.*, 10 (1969) 395–402.
[13] K. Bennis, J. Gelas, and C. Thomassigny, unpublished results.