Stereoselective Synthesis of C-Glycosyl α-Amino Acids

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β-D-C-Allosyl-(R)-alanine **12** and β-D-C-altrosyl-(R)-alanine lactone **15** were synthesized from the common intermediate **7** in just a few steps. The β-C-glycosyloxazolone **7** was obtained in two steps from the protected D-glucal **4** by a sequential coupling with N-benzoylalanine followed by a Claisen rearrangement.

C-Glycosyl compounds have been the subject of intensive synthetic efforts in recent years.[1] The interest in this class of carbohydrates is partly due to their use as chirons in organic synthesis.[2] Moreover, naturally occurring C-glycosides with interesting biological properties have been discovered and many natural products contain moieties structurally related to these compounds. Less attention has been paid to the synthesis of C-glycosyl α-amino acids, and synthetic approaches to such systems are limited to C-furanosyl derivatives.[3]

As a part of a program directed toward the synthesis of glycopeptide-based potential immunomodulating agents, we have become interested in developing a versatile and stereocontrolled route to C-pyranosyl α-amino acids. To our knowledge, there is only one very recent report on the synthesis of such compounds that deals with the synthesis of the β-anomers of C-glucosyl α-amino acid derivatives.[4]

The synthetic approach we devised takes advantage of the Steglich[5] technology for the synthesis of γ-dehydro α-amino acids, which is based on a Claisen rearrangement of allylic N-benzoyl α-amino acid esters. We envisaged that the use of a suitably protected glycal as the allylic counterpart of the ester **1** (Scheme I) would allow the construction of the entire backbone of the target molecule. Moreover either α- or β-C-glycosides can be obtained from the glycals of the arabino[6] or ribo[7] series, respectively.

Here, we report on the application of this methodology to the stereoselective synthesis of β-C-allosyl- and altrosylalanine derivatives **12** and **15**.

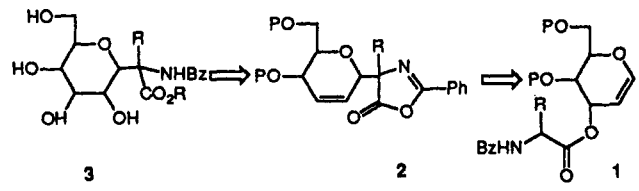
The allylic ester **5** was prepared in a straightforward manner by coupling N-benzoylalanine and the known alcohol **4**[8] using DCC and 4-(dimethylamino)pyridine. Treatment of the ester **5** with $Ph_3P/CCl_4/Et_3N$ as a dehydrating agent[5] gave, directly, the oxazolone **7** as a mixture of two diastereosiomers in a 3:1 ratio, as determined by ^1H and ^{13}C NMR. This process involves formation and rearrangement of an intermediate oxazole **6** that could not be detected.

The two diastereoisomers were shown to be the anticipated β-glycosidic compounds, epimeric at the oxazolone stereocenter, by conversion of the mixture of **7** into the amino acid **8** whose ^1H NMR spectrum showed distinct signals to the respective protons H-1′ and H-5′ of the two diastereoisomers. NOE difference spectra experiments on the mixture of **8** showed a large enhancement of the H-5′ signals by irradiation of H-1′ resonances of both isomers (Scheme II).

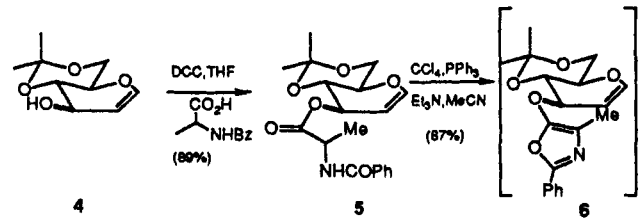
The assignment of the configuration of the amino acid stereocenter followed from NOE measurements on conformationally fixed derivatives such as iodolactones **9** and **10**, which were chromatographically separable and which were obtained from **6** by treatment with 1 N NaOH in THF and subsequent addition of 3 equiv of iodine to the resulting carboxylate.[9] The two iodolactones were produced in an improved 5.9:1 ratio by kinetic resolution. The cis ring junction of both γ-lactones was evidenced by ^1H NMR data; the 1.7 Hz coupling constant between H-1′ and H-2′ for both isomers is indicative of an equatorial disposition of the latter hydrogen atom.

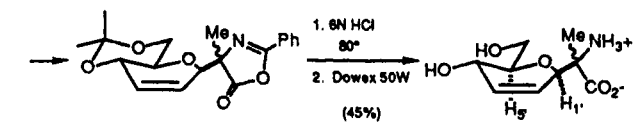
Irradiation of the methyl group in the γ-lactone ring of

Scheme I



Scheme II





(1) Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752. Kraus, A. G.; Shi, J. *J. Org. Chem.* **1990**, *55*, 4922 and references cited therein.
(2) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: New York, 1983.
(3) Garner, P.; Min Park, J. *J. Org. Chem.* **1990**, *55*, 3772. Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1990**, *55*, 3853.
(4) Simchen, G.; Pürkner, E. *Synthesis* **1990**, 525.
(5) Kübel, B.; Hofle, G.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 58. Engel, N.; Kübel, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 394. See also: Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933.
(6) Ireland, R. E.; Wilcox, C. S.; Thaisrivongs, S.; Vanier, N. R. *Can. J. Chem.* **1979**, *57*, 1743. Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205. Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854.
(7) Tulshian, D. B.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 518.
(8) Fraser-Reid, B.; Walker, D. L.; Tam, S. Y. K.; Holder, N. L. *Can. J. Chem.* **1973**, *51*, 3950.
(9) High yields were obtained only when the solvent THF was freshly distilled under nitrogen on Na/Ph_2CO.

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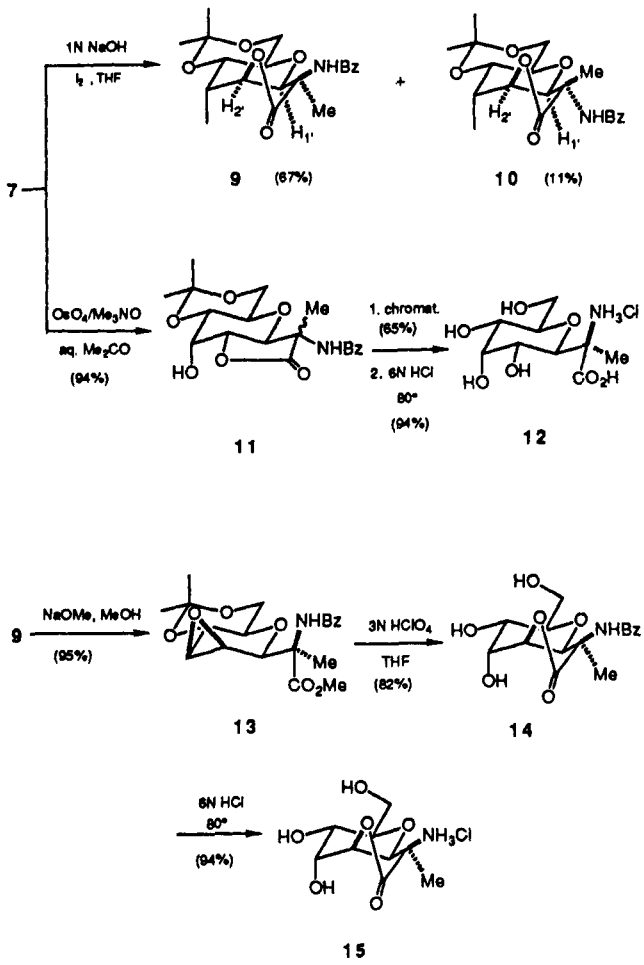
Scheme III



the major isomer **9** caused a large enhancement of the signals corresponding to both H-1′ and H-2′, while in the minor isomer **10** enhancement of only H-1′ was observed. In addition, the minor isomer showed a medium NOE effect between the NH of the amide group and both H-1′ and H-2′. This effect was not apparent in the major iodolactone. These data leave no doubt as to the *R* configuration of the quaternary carbon linked to the glycosyl moiety of iodo lactone **11**.

Isomerically pure iodo lactone **9** was converted into the epoxy ester **13** by mild methanolysis with MeONa in MeOH. Stereoselective axial opening of the epoxide **13** promoted by 3 N $HClO_4$ in THF afforded the trihydroxy lactone **14**. The stereochemical assignments on this lactone were made by examining the ^1H NMR coupling pattern of the sugar protons. The 3.5-Hz coupling constant between H-1′ and H-2′ together with a value of 2.9 Hz for the H-4′–H-3′ coupling show that both H-2′ and H-3′ have an equatorial arrangement.

The final β-*C*-altrosyl-(*R*)-alanine lactone **15** was obtained in 94% yield from **14** by hydrolysis with 6 N HCl at 80 °C (Scheme III). The lactone function was not hydrolyzed and survived the reaction conditions used for the amide hydrolysis. The presence of the lactone was evidenced by the IR absorbance of the C=O bond (1774 cm^{-1}), the low-field resonance of H-2′ (δ 4.84), and strong NOE effect between the methyl group and both H-1′ and H-2′.

The isomeric 1-β-*C*-allosyl-(*R*)-alanine was synthesized from the common intermediate oxazolone **7** in two steps. Catalytic dihydroxylation with OsO_4 gave the same 3:1 mixture of two diastereoisomeric lactones **11**, both deriving from α attack by the osmium reagent. ^1H NMR spectra show very similar coupling patterns for all protons (see Experimental Section). The trans diaxial arrangement of H-1′ and H-2′ is evidenced by a large (10-Hz) coupling constant. The major isomer was isolated by flash chromatography[10] and hydrolyzed to the target β-*C*-allosyl-(*R*)-alanine **12** in 94% yield in one step.

In summary, we have developed a versatile, flexible, and high-yielding approach to the synthesis of *C*-glycosyl α-amino acids. Biological trials are in progress to test the potential therapeutical properties of compounds **12** and **15**.

Experimental Section

General Procedures. ^1H NMR and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer. Chemical shifts are given in ppm downfield from Me_4Si (δ) for spectra in $CDCl_3$ and with reference to internal HDO (δ 4.63) or CHD_2SOCD_3 (δ 2.52) for spectra recorded respectively in D_2O or $(CD_3)_2SO$. Infrared spectra were recorded on a Bruker IFS 66 FT spectrometer. Peaks yielding structural information are reported. Optical rotation were measured with a Perkin-Elmer 141 polarimeter. Melting points are uncorrected.

1,5-Anhydro-4,6-*O*-isopropylidene-2-deoxy-3-*O*-(2-benzamidopropionyl)-D-*arabino*-hex-1-enitol (5). To a solution of the protected glucal **4** (4.666 g, 25.06 mmol) in 84 mL of dry THF were added sequentially *N*-benzoylalanine (60% ee; 13,554 g, 70.16 mmol), DCC (7.754 g, 37.60 mmol), and a catalytic amount of DMAP (200 mg) under an argon atmosphere. The reaction mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with 100 mL of Et_2O, filtered, and washed three times with 50-mL portions of Et_2O. Concentration of the filtrate gave an oil that was purified by flash chromatography, eluting with hexane/ethyl acetate (7:3) to afford pure **5** (8.090 g, 89.3%): IR ($CHCl_3$) 3435, 3155, 1741, 1650, 1517, 1384, 1304, 1109 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$; major diastereomer) δ 1.43 (s, 3 H, Me), 1.52 (s, 3 H, Me), 1.54 (s, 3 H, Me), 3.77–3.90 (m, 3 H, H-5, H-6_{ax}, H-6_{eq}), 4.08 (dd, 1 H, H-4, J_{4-5} = 10.0, J_{4-3} = 7.9), 4.72 (dd, 1 H, H-2, J_{2-3} = 1.7, J_{2-1} = 6.3), 4.88 (quintet, 1 H, J_{H-Me} = J_{H-NH} = 7.4), 5.44 (dt, 1 H, H-3, J_{3-2} = 1.7, J_{4-3} = 7.9), 6.38 (dd, 1 H, H-1, J_{1-2} = 6.3, J_{1-3} = 1.7), 6.90 (d, 1 H, NH, *J* = 7.4), 7.38–7.62 (m, 3 H, *m*,*p*-ArH), 7.77–7.84 (m, 2 H, *o*-ArH); (Minor diastereomer) 1.40 (s, 3 H, Me), 1.50 (s, 3 H, Me), 1.52 (s, 3 H, Me), 3.92–4.01 (m, 3 H, H-5, H-6_{ax}, H-6_{eq}), 4.06 (dd, 1 H, H-4, J_{4-5} = 10.0, J_{4-3} = 7.9), 4.76 (dd, 1 H, H-2, J_{2-3} = 1.7, J_{2-1} = 6.2), 5.48 (dt, 1 H, H-3, J_{3-2} = 1.7 J_{4-3} = 7.9); ^{13}C NMR (75.4 MHz, $CDCl_3$) (major diastereomer) quaternary carbons δ 173.03, 166.71, 133.80, 99.85, DEPT sequence CH 145.87, 131.65, 128.45, 126.97, 99.92, 70.50, 69.69, 69.49, 48.33, CH_2 61.36, CH_3 28.73, 18.80, 18.59; (minor diastereomer) quaternary carbons 173.07, 166.81, 133.73, 99.73, DEPT sequence CH 145.69, 131.63, 128.44, 126.95, 100.10, 70.27, 69.81, 69.61, 48.56, CH_2 61.46, CH_3 28.73, 18.89, 18.46. Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15, H, 6.41; N, 3.88. Found: C, 63.31, H, 6.52; N, 3.76.

4-Methyl-4-(4′,6′-*O*-isopropylidene-2′,3′-dideoxy-β-D-*erythro*-2′-hexenopyranosyl)-2-phenyl-5(4*H*)-oxazolone (7). To a solution of **5** (3.901 g, 10.87 mmol), triethylamine (4.0 mL, 29.10 mmol), and CCl_4 (2.3 mL, 24.23 mmol) in 36 mL of dry acetonitrile was added triphenylphosphine (5.700 g, 21.54 mmol). The resulting mixture was stirred at room temperature for 14 h, becoming dark brown and giving a heavy precipitate. After concentration at reduced pressure, the mixture was treated with diethyl ether, filtered on a Celite pad, and washed abundantly with diethyl ether. The filtrate was evaporated at reduced pressure and flash chromatographed (hexane–ethyl acetate (7:3)) to afford a white solid (3.250 g, 87.7%): IR (KBr disk) 2990, 1823, 1652, 1491, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) (major diastereomer) δ 1.41 (s, 3 H, Me), 1.50 (s, 3 H, Me), 1.57 (s, 3 H, Me), 3.40 (ddd, 1 H, H-5′, $J_{5'-6'eq}$ = 5.2, $J_{5'-6'ax}$ = 10.4, $J_{5'-4'}$ = 8.4), 3.70 (t, 1 H, H-6′ax, $J_{6'ax-6'eq}$ = $J_{6'ax-5'}$ = 10.4), 3.85 (dd, 1 H, H-6′eq, $J_{6'eq-6'ax}$ = 10.4, $J_{6'eq-5'}$ = 5.2), 4.10–4.25 (m, 1 H, H-4′), 4.60 (m, 1 H, H-1′), 5.79 (dt, 1 H, H-2′, $J_{2'-3'}$ = 10.4, $J_{2'-1'}$ = $J_{2'-4'}$ = 2.3),

(10) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

6.10 (b d, 1 H, H-3′, $J_{3'-2'}$ = 10.4,$J_{3'-4'}$ = 1.5), 7.45–7.65 (m, 3 H, *m,p*-ArH), 8.00–8.10 (m, 2 H, *o*-ArH); (minor diastereomer) 3.61 (t, 1 H, H-6′ax, $J_{6'ax-6'eq} = J_{6'ax-5'}$ = 10.4), 3.87 (dd, 1 H, H-6′eq, $J_{6'eq-6'ax}$ = 10.4, $J_{6'eq-5'}$ = 5.2); ^{13}C NMR (75.4 MHz, $CDCl_3$) (major diastereomer) quaternary carbons δ 176.74, 160.03, 124.72, 98.69, 71.03, DEPT sequence CH 131.80, 130.88, 127.74, 127.03, 122.53, 77.57, 70.92, 65.84, CH_2 61.86, CH_3 28.14, 18.83, 18.07; (minor diastereomer) quaternary carbons 177.50, 160.30, 124.70, 98.64, 71.61, DEPT sequence CH 131.84, 130.98, 127.78, 127.03, 122.61, 77.15, 70.50, 66.06, CH_2 61.93, CH_3 28.12, 18.50, 17.88. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.16; N, 4.08. Found: C, 66.71, H, 6.25; N, 4.10.

2-(2′-3′-Dideoxy-β-D-*erythro*-hex-2′-enopyranosyl)-2-aminopropionic Acid (8). A suspension of the oxazolone 7 (221.5 mg) in 6 N HCl (3 mL) in a sealed vial was manually shaken at room temperature to complete dissolution. The vial was then heated in an oil bath at 80 °C for 3 h. The solution was cooled to room temperature (benzoic acid precipitated) and extracted with two 5-mL portions of methylene chloride. The aqueous solution was evaporated and the residue, dissolved in the minimum amount of water, purified by ionic exchange chromatography (DOWEX 50W, H^+ form, 6.6 mL of wet resin), eluting with water to neutral pH and then with 1 N NH_3. Fractions containing the amino acid were evaporated, giving 63.6 mg of a pale yellow solid (45.5%): IR (KBr disk) 3381, 1629, 1602, 1508, 1397, 1126 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) (major diastereomer) δ 1.49 (s, 3 H, Me), 3.40 (ddd, 1 H, H-5′, $J_{4'-5'}$ = 8.9, $J_{5'-6'}$ = 2.4 and 5.6), 3.69 (dd, 1 H, one of H-6′, J_{gem} = 12.7, $J_{6'-5'}$ = 5.6), 3.84 (dd, one of H-6′, J_{gem} = 12.7, $J_{6'-5'}$ = 2.4), 4.05 (d, 1 H, H-4′, $J_{4'-5'}$ = 8.9), 4.42 (m, 1 H, H-1′), 5.66 (d, 1 H, H-2′, $J_{2'-3'}$ = 10.4), 5.98 (m, 1 H, H-3′); (minor diastereomer) 1.27 (s, 3 H, Me), 3.35 (m, 1 H, H-5′) 4.54 (m, 1 H, H-1′), 5.90 (d, 1 H, H-2′, $J_{2'-3'}$ = 10.4), 6.04 (m, 1 H, H-3′); ^{13}C NMR (75.4 MHz, D_2O) (major diastereomer) quaternary carbons δ 175.61, 65.38, DEPT sequence CH 135.26, 126.45, 80.48, 77.75, 63.54, CH_2 62.63, CH_3 20.89; (minor diastereomer) DEPT sequence CH 135.77, 125.10, 80.33, 77.97, 63.54, CH_2 62.54, CH_3 19.35. Anal. Calcd for $C_9H_{15}NO_5$: C, 49.76; H, 6.96; N, 6.45. Found: C, 49.81, H, 6.95; N, 6.38.

2-(4′,6′-*O*-Isopropylidene-3′-deoxy-3′-iodo-β-D-allopyranosyl)-2-benzamido-(2*R*)-propionic Acid 1′,2′-Lactone and 2*S* Epimer (9 and 10). To a solution of the oxazolone 7 (2.036 g, 5.93 mmol) in 30 mL of distilled THF was added an aqueous solution of 1 M NaOH. After 30 min, 4.520 g of sublimed iodine were added in one portion and the solution was stirred for 24 h under an inert atmosphere at room temperature. The reaction mixture was diluted with ethyl acetate (50 mL) and saturated brine (50 mL). An aqueous 20% $Na_2S_2O_3$ solution was added to complete disappearance of the brown color and the organic phase separated. The aqueous layer was extracted with ethyl acetate (4 × 50 mL), and the organic extracts were combined, dried ($MgSO_4$), and evaporated. The crude mixture was purified by flash chromatography (hexane–ethyl acetate (7:3)) to give 1.953 g of the pure major diastereomer **9** (67.6%) and 0.318 g of the minor one **10** (11.0%).

Major diastereomer: IR (KBr disk) 3432, 3333, 1790, 1660, 1520, 1379, 1375, 1163, 1109 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 3 H, Me), 1.48 (s, 3 H, Me), 1.72 (s, 3 H, Me), 2.96 (dd, 1 H, H-4′, $J_{4'-3'}$ = 3.8, $J_{4'-5'}$ = 8.2), 3.64 (t, 1 H, H-6′ax, $J_{6'ax-6'eq} = J_{6'ax-5'}$ = 9.1), 3.69–3.77 (m, 1 H, H-5′), 3.80 (dd, 1 H, H-6′eq, $J_{6'ax-6'eq}$ = 9.1, $J_{6'eq-5'}$ = 4.5), 4.76 (dd, 1 H, H-3′, $J_{3'-4'}$ = 3.8, $J_{3'-2'}$ = 2.4), 5.06 (t, 1 H, H-2′, $J_{2'-3'}$ = 2.4), 5.11 (d, 1 H, H-1′, $J_{1'-2'}$ = 1.7), 6.54 (s, 1 H, NH), 7.45–7.58 (m, 3 H, *m,p*-ArH), 7.77–7.82 (m, 2 H, *o*-ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) quaternary carbons δ 176.39, 166.87, 133.60, 100.07, 31.90, DEPT sequence CH 131.97, 128.66, 126.94, 81.63, 74.57, 67.81, 65.70, 28.65, CH_2 61.23, CH_3 28.20, 19.86, 18.33; $[\alpha]_D$ −1.5° (*c* 3,35, $CHCl_3$); mp 159–160 °C (hexane–diethyl ether). Anal. Calcd for $C_{19}H_{22}INO_6$: C, 46.83; H, 4.55; N, 2.87. Found: C, 47.03, H, 4.73; N, 2.76.

Minor diastereomer: IR (KBr disk) 3328, 3062, 1766, 1654, 1539, 1386, 1379, 1165, 1106 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$, 300 MHz) δ 1.32 (s, 3 H, Me), 1.44 (s, 3 H, Me), 1.49 (s, 3 H, Me), 3.01 (dd, 1 H, H-4′, $J_{4'-3'}$ = 3.9, $J_{4'-5'}$ = 8.8), 3.62 (ddd, 1 H, H-5′, $J_{5'-6'ax}$ = 10.0, $J_{5'-6'eq}$ = 5.8, $J_{5'-4}$ = 8.8), 3.78 (t, 1 H, H-6′ax, $J_{6'ax-6'eq} = J_{6'ax-5'}$ = 10.0), 3.90 (dd, 1 H, H-6′eq, $J_{6'ax-6'eq}$ = 10, $J_{6'eq-5'}$ = 5.8), 4.55 (d, 1 H, H-1′, $J_{1'-2'}$ = 1.7) 4.95 (dd, 1 H, H-3′, $J_{3'-4'}$ = 3.9, $J_{3'-2'}$ = 2.6), 5.01 (t, 1 H, H-2′, $J_{2'-3'}$ = 2.6, $J_{2'-1'}$ = 1.7), 7.41–7.62 (m, 3 H, *m,p*-ArH), 7.78–7.85 (m, 2 H, *o*-ArH), 8.81 (s, 1 H, NH); ^{13}C NMR ($(CD_3)_2SO$, 75.4 MHz) quaternary carbons δ 173.94, 166.07, 132.94, 99.37, 60.85, DEPT sequence CH 131.80, 128.25, 127.55, 80.56, 76.29, 67.71, 65.23, 28.98, CH_2 60.49, CH_3 28.62, 19.69, 17.18; $[\alpha]_D$ −22.8° (*c* 0.84, MeOH); mp 202–204 °C ($CDCl_3$). Anal. Calcd for $C_{19}H_{22}INO_6$: C, 46.83; H, 4.55; N, 2.87. Found: C, 46.93, H, 4.33; N, 2.57.

2-(4′,6′-*O*-Isopropylidene-β-D-allopyranosyl)-2-benzamido-(2*R*)-propionic Acid 1′,2′-Lactone and 2*S* Epimer (11). To a solution of the oxazolone 7 (2.073 g, 6.04 mmol) in 5% aqueous acetone (30 mL) was added trimethylamine *N*-oxide dihydrate (1.00 g, 9.00 mmol) and 3.1 mL of a 0.098 M solution of OsO_4 in *tert*-butyl alcohol (0.30 mmol). The reaction mixture was stirred at room temperature under an argon atmosphere for 12 h, at which time 0.500 g of trimethylamine *N*-oxide dihydrate and 1.0 mL of the OsO_4 solution were added. Stirring was continued for a further 12 h. The reaction mixture was evaporated at reduced pressure and directly purified by flash chromatography (diethyl ether–chloroform–isopropyl alcohol (60:40:5)) to afford 1.289 g of the major diastereomer (white solid, 56.5%) and 0.872 g of a mixture of the two diastereomers (38.3%). This mixture was chromatographed as in the previous text to give 0.202 mg of the pure major diastereomer (8.9%).

Major diastereomer: IR (KBr disk) 3550, 3490, 1779, 1650, 1535, 1378, 1054, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 3 H, Me), 1.47 (s, 3 H, Me), 1.67 (s, 3 H, Me), 2.77 (d, 1 H, OH, $J_{OH-3'H}$ = 1.9), 3.69 (dd, 1 H, H-4′, $J_{4'-3'}$ = 2.4, $J_{4'-5'}$ = 9.3) 3.74 (t, 1 H, H-6′ax, $J_{6'ax-6'eq} - J_{6'ax-5'}$ = 11.8), 3.92–4.00 (m, 2 H, H-5′ and H-6′eq), 4.15 (d, 1 H, H-1′, $J_{1'-2'}$ = 10.0), 4.39 (dd, 1 H, H-2′, $J_{1'-2'}$ = 10.0, $J_{2'-3'}$ = 2.2), 4.59 (m, 1 H, H-3′), 6.14 (s, 1 H, NH), 7.41–7.58 (m, 3 H, *m,p*-ArH), 7.78–7.83 (m, 2 H, *o*-ArH); The splitting pattern of H-5′ was deduced from a NOE difference spectrum irradiating H-1′ δ 3.96 (ddd, H-5′, $J_{5'-4'}$ = 9.3, $J_{5'-6'ax}$ = 11.8, $J_{5'-6'eq}$ = 4.8); ^{13}C NMR ($CDCl_3$, 75.4 MHz); quaternary carbons δ 172.09, 166.51, 132.67, 100.14, 56.35, DEPT sequence CH 132.24, 128.68, 127.22, 78.29, 76.58, 71.59, 70.29, 65.59, CH_2 62.17, CH_3 28.78, 23.35, 19.20; $[\alpha]_D$ +80.2° (*c* 0.75, $CHCl_3$); mp 215–217 °C (CH_2Cl_2–hexane). Anal. Calcd for $C_{19}H_{23}NO_7$: C, 60.47; H, 6.14; N, 3.71. Found: C, 60.53, H, 6.12; N, 3.70.

Minor diastereomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (s, 3 H, Me), 1.50 (s, 3 H, Me), 1.54 (s, 3 H, Me), 2.82 (s, 1 H, OH), 3.70 (dd, 1 H, H-4′, $J_{4'-5'}$ = 9.5, $J_{4'-3'}$ = 2.3), 3.76 (t, 1 H, H-6′ax, $J_{6'ax-5'} = J_{6'ax-6'eq}$ = 9.0), 3.87–3.98 (m, 2 H, H-5′, H-6′eq), 4.00 (dd, 1 H, H-2′, $J_{2'-1'}$ = 10.1, $J_{2'-3'}$ = 2.0), 4.64 (t, 1 H, H-3′, $J_{3'-2'}$ = 2.0, $J_{3'-4'}$ = 2.3), 5.26 (d, 1 H, H-1, $J_{1'-2'}$ = 10.1) 6.51 (s, 1 H, NH), 7.38–7.56 (m, 3 H, *m,p*-ArH), 7.78–7.82 (m, 2 H, *o*-ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) quaternary carbons δ 172.87, 166.68, 132.84, 100.01, 59.27, DEPT sequence CH 132.13, 128.57, 127.21, 76.57, 73.85, 71.91, 70.25, 65.89, CH_2 62.26, CH_3 28.79, 19.19, 14.71.

Methyl 2-(4′,6′-*O*-Isopropylidene-2′,3′-epoxy-β-D-mannopyranosyl)-2-benzamido-(2*R*)-propionate (13). The iodo lactone **9** (1.821 mg, 3.73 mmol) was treated with a 0.2 M solution of MeONa in MeOH (20.5 mL) at 0 °C. The reaction mixture was allowed to reach room temperature and stirred for additional 30 min. The clear solution was poured rapidly into 200 mL of a saturated aqueous NH_4Cl solution and extracted three times with 100-mL portions of ethyl acetate. The organic extracts were combined, dried ($MgSO_4$), and evaporated at reduced pressure to give pure epoxide **13** as a white solid (1.392 g, 95.3%): IR (KBr disk) 3425, 1738, 1664, 1521, 1250, 1374 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.44 (s, 3 H, Me), 1.53 (s, 3 H, Me), 1.84 (s, 3 H, Me), 3.14 (ddd, 1 H, H-5′, $J_{5'-6'ax} = J_{5'-4'}$ = 10.0, $J_{5'-6'eq}$ = 4.9), 3.31 (d, 1 H, H-2′, $J_{2'-3'}$ = 3.9), 3.34 (d, 1 H, H-3′, $J_{3'-2'}$ = 3.9), 3.71 (d, 1 H, H-4′, $J_{4'-5'}$ = 10.0), 3.74 (t, 1 H, H-6′ax, $J_{6'ax-6'eq} = J_{6'ax-5'}$ = 10.5), 3.79 (s, 3 H, OMe), 3.90 (dd, 1 H, H-6′eq, $J_{6'eq-5'}$ = 4.9, $J_{6'eq-6'ax}$ = 10.5), 4.17 (d, 1 H, H-1′, $J_{1'-2'}$ = 0.6), 7.31 (s, 1 H, NH), 7.38–7.56 (m, 3 H, *m,p*-ArH), 7.78–7.84 (m, 2 H, *o*-ArH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) quaternary carbons δ 171.46, 166.88, 134.03, 100.24, 63.07, DEPT sequence CH 131.37, 128.33, 126.86, 76.37, 71.69, 64.45, 53.64, 50.21, CH_2 62.69, CH_3 52.77, 28.74, 20.17, 18.83; mp 83–85 °C (hexane–isopropyl alcohol); $[\alpha]_D$ +41.6° (*c* 2.09, CH_2Cl_2). Anal. Calcd for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.53, H, 6.26; N, 3.51.

2-(β-D-Altropyranosyl)-2-benzamido-(2*R*)-propionic Acid 1′,2′-Lactone (14). A solution of the epoxide **13** (323 mg, 0.83 mmol) in THF (4.2 mL) was treated with aqueous 3 M $HClO_4$

(275 μL) and the reaction mixture stirred for 3 h at 60 °C. The clear colorless solution was cooled to room temperature, diluted with saturated brine (20 mL), and extracted five times with 20-mL portions of ethyl acetate. The organic extracts were combined, dried ($MgSO_4$) and evaporated to give a white solid that was purified by flash chromatography (ethyl acetate–methanol (9:1)), affording 230 mg of the pure lactone 14 (82.1%): IR (KBr disk) 3413, 1781, 1652 cm^{-1}; ^1H NMR ($(CD_3)_2SO$, 300 MHz) δ 1.58 (s, 1 H, Me), 3.28–3.44 (m, 2 H, 2 H-6′), 3.44–3.53 (m, 1 H, H-5′), 3.64 (m, 1 H, H-4′, after D_2O exchange dd, $J_{4'-5'}$ = 7.1, $J_{4'-3'}$ = 2.9), 3.96 (m, 1 H, H-3′, after exchange with D_2O dd, $J_{3'-4'}$ = 2.9, $J_{2'-3'}$ = 3.5), 4.09 (dd, 1 H, C_6′-OH, $J_{OH-H-6'}$ = 4.4 and 7.8, exchanges with D_2O), 4.32 (d, 1 H, H-1′, $J_{1'-2'}$ = 3.5), 4.63 (t, 1 H, H-2′, $J_{2'-1'}$ = $J_{2'-3'}$ = 3.5), 5.01 (d, 1 H, C_4′-OH, $J_{OH-H-4'}$ = 5.9, exchanges with D_2O), 5.42 (d, 1 H, C_3′-OH, $J_{OH-H-3'}$ = 4.6, exchanges with D_2O), 7.38–7.56 (m, 3 H, *m,p*-ArH), 7.78–7.82 (m, 2 H, *o*-ArH), 8.18 (s, 1 H, NH); ^{13}C NMR ($(CD_3)_2SO$, 75.4 MHz) quaternary carbons δ 175.33, 167.34, 134.34, 60.69, DEPT sequence CH 131.35, 128.19, 127.48, 79.35, 75.48, 74.78, 66.84, 64.97, CH_2 60.81, CH_3 19.32; $[\alpha]_D$ −58.3° (*c* 1.03, MeOH); mp 129–132 °C. Anal. Calcd for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15. Found: C, 57.12, H, 5.91; N, 4.12.

2-(β-D-Altropyranosyl)-2-amino-(2*R*)-propionic Acid 1′,2′-Lactone Hydrochloride (15). A solution of the lactone 14 (190 mg, 0.56 mmol) in 6 N HCl (4 mL) was heated in an oil bath at 80 °C for 5 h. The solution was cooled to room temperature (benzoic acid precipitated) and extracted with two 5-mL portions of methylene chloride. The aqueous solution was evaporated and maintained under vacuum in a dessicator (P_2O_5) until constant weight to give 142 mg of 15 (94.0%): IR (KBr disk) 3369, 1774; ^1H NMR (D_2O, 300 MHz) δ 1.61 (s, 3 H, Me), 3.66–3.84 (m, 4 H, H-4′, H-5′, 2H-6′), 4.32 (t, 1 H, H-3′, $J_{3'-4'}$ = $J_{3'-2'}$ = 3.1), 4.48 (d, 1 H, H-1 $J_{1'-2'}$ = 2.2), 4.84 (dd, 1 H, H-2′, $J_{2'-1'}$ = 2.2, $J_{2'-3'}$ = 3.1); ^{13}C NMR (D_2O, 75.4 MHz) quaternary carbons δ 176.59, 61.98, DEPT sequence CH 80.78, 75.82, 74.94, 67.03, 65.32, CH_2 62.22, CH_3 18.30; $[\alpha]_D$ −10.1° (*c* 1.40, MeOH); mp 196–198 °C. Anal. Calcd for $C_9H_{16}NO_6Cl\cdot H_2O$: C, 37.57, H, 6.31; N, 4.87. Found: C, 37.71, H, 6.22; N, 4.83.

2-(β-D-Allopyranosyl)-(*R*)-alanine Hydrochloride (12). A solution of the 2*R* lactone 11 (530 mg, 1.40 mmol) in 6 N HCl (10 mL) was heated in an oil bath at 80 °C for 5 h. The solution was cooled to room temperature (benzoic acid precipitated) and extracted with two 10-mL portions of methylene chloride. The aqueous solution was evaporated and maintained under vacuum in a dessicator (P_2O_5) until constant weight to give 382 mg of 12 (94.5%): IR (KBr disk) 3421, 2925, 1729, 1629 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 1.64 (s, 3 H, Me), 3.47 (dd, 1 H, H-4′, $J_{4'-3'}$ = 2.4, $J_{4'-5'}$ = 10.0), 3.53–3.59 (m, 2 H, H-5′ and one of the H-6′), 3.62 (dd, 1 H, H-2′, $J_{2'-1'}$ = 10.3, $J_{2'-3'}$ = 2.4), 3.80 (dd, 1 H, one of the H-6′, J_{gem} = 15.5, $J_{6'-5'}$ = 10.3), 3.82 (d, 1 H, H-1′, $J_{1'-2'}$ = 10.3), 4.09 (t, 1 H, H-3′, $J_{3'-2'}$ = $J_{3'-4'}$ = 2.4); ^{13}C NMR (D_2O, 75.4 MHz) quaternary carbons δ 173.83, 63.10, DEPT sequence CH 76.89, 76.70, 72.57, 68.75, 67.75, CH_2 62.39, CH_3 21.49; $[\alpha]_D$ −10.4° (*c* 1.06 MeOH); mp 206–210 °C. Anal. Calcd for $C_9H_{18}NO_7Cl\cdot H_2O$: C, 37.36; H, 6.59; N, 4.58. Found: C, 35.26, H, 6.76; N, 4.32.

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Synthesis of α-Benzyl γ-Lactam, α-Benzyl δ-Lactam, and α-Benzylproline Derivatives as Conformationally Restricted Analogues of Phenylalaninamide

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The ready availability of *N*-(trifluoroacetyl)-α-allylphenylalaninamide (4) via a dehydration/hetero-Cope rearrangement/ammonolysis sequence starting with *N*-(trifluoroacetyl)phenylalanine allyl ester made it an attractive intermediate for elaboration into C-α to N- or C-α to N′-bridged products as conformationally restricted phenylalaninamide analogues. Oxidative one-carbon degradation of the side-chain olefin followed by acid-catalyzed silane reduction afforded C-α to N′-bridged γ-lactam. Hydroboration/oxidation of the side-chain olefin provided an intermediate that could be cyclized selectively either to a δ-lactam or a proline analogue depending on choice of dehydrating conditions. For preparation of a target dipeptide containing the α-substituted proline moiety, a preferred route involved N-deprotection of 4 and coupling to Boc-Asp(OBn)-OH to give a dipeptide intermediate, which similarly could be elaborated selectively to either the α-benzyl δ-lactam analogue or the α-benzylproline analogue.

Introduction

The incorporation of conformationally restricted residues constitutes an important approach to studying the bioactive conformation of peptides and also offers the potential to discover analogues with improved stability, bioselectivity, and bioavailability. *N*-Methyl amino acids,[1-3] α,α-disubstituted amino acids,[4-8] proline residues[4,9,10] and, more recently, dipeptide lactam derivatives[11-17] and β- and γ-bend mimics[18-24] are common ex-

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