Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 2, pp. 371-374, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00016-X

Diastereoselective Synthesis of α-*C*-Arabinofuranosyl Glycine

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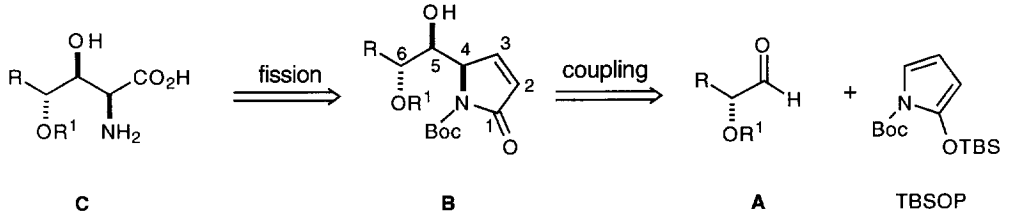
Abstract: *Exploiting N-(tert-butoxycarbonyl)-2-(tert-butyldimethylsiloxy)pyrrole (TBSOP) as a masked glycine anion equivalent, a short enantiospecific synthesis of the title C-glycosyl α-aminoacid* ***5*** *was devised and executed, via diastereospecific α-C-glycosylation of protected arabinose* ***1*** *at the anomeric carbon.*

We have recently reported[1] an approach to the synthesis of chiral non-racemic β-hydroxy-α-amino acids of the type **C** in which the crucial step is the diastereoselective coupling of *N*-(*tert*-butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP) with homochiral α-hydroxyaldehyde derivatives **A** to produce 4,5-*threo*-5,6-*erythro*-configurated α,β-unsaturated lactams **B**, followed by enantioconservative fission of the 2,3-carbon bond to create the carboxylic function (Scheme 1).

Scheme 1



C **B** **A** TBSOP

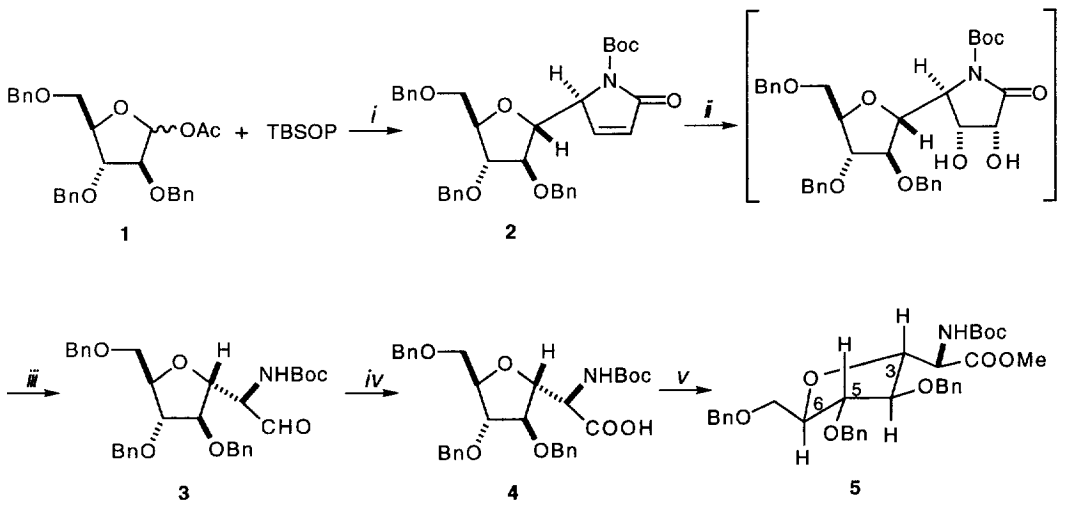
As part of a program to develop approaches to bioactive peptidyl *C*-glycosides of improved bioavailability, we required a strategy to assemble the appropriate *C*-glycosyl α-amino acid subunits in a short and enantiospecific manner.[2] Herein we present a study which has culminated in the stereocontrolled synthesis of the "anomeric" α-arabinofuranosyl glycine derivative **5** by exploiting the TBSOP-based chemistry outlined in Scheme 2.

In order to access the key lactam intermediate **2**, it would be necessary to append the pyrrolinone fragment of TBSOP to the anomeric carbon of aldofuranose **1**, taking into consideration the stereochemistry of the two newly emerging stereocentres. Trityl perchlorate-promoted addition of TBSOP to arabinose **1** (Et_2O, 0°C to rt.)[3] proceeded, as expected, with excellent diastereoselectivity, to give the 4,5-*threo*-5,6-*erythro*-configurated lactam **2** as the predominant adduct in 62% yield after flash chromatography.

Evidence supporting the sterochemical assignment was obtained after completion of the synthesis. *Threo,anti*-selective additions of pyrrole-, furan- and thiophene-based siloxydienes to *in situ*-generated

oxonium, thioxonium and iminium species are typically observed when a Lewis acid promoter is involved and can be ascribed to a preferential approach of the two reactants along the less demanding trajectory, as predicted by the transition state models depicted in the Figure.[3,4]

Scheme 2



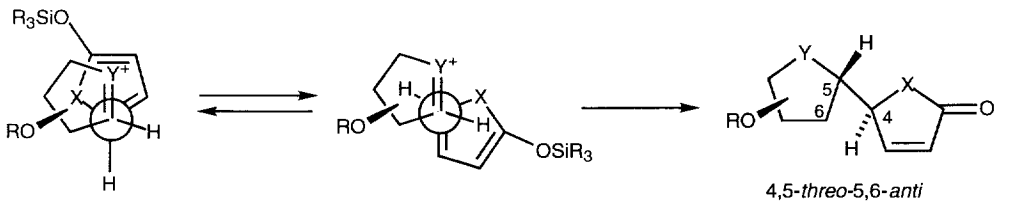
Reagents: *i*) $TrClO_4$, Et_2O, 0°C to rt., 28h; *ii*) $KMnO_4$, dicyclohexano-18-crown-6-ether, CH_2Cl_2, rt., 12h; *iii)* 1M LiOH, THF, 0°C, 15 min; then 0.65M $NaIO_4$, SiO_2, CH_2Cl_2, rt., 1h; *iv*) $NaClO_2$, $NaHPO_4$, 2-methyl-2-butene, MeCN, H_2O, Bu^tOH, 0°C, 10 min; *v*) CH_2N_2, Et_2O, rt., 10 min.

The next stage of our scheme called for unmasking of the glycine moiety embodied in the pyrrolinone ring of **2**. Thus, oxidative extrusion of the C-1 and C-2 carbon atoms in **2** was attained according to a protocol of three clean transformations. Avoiding isolation of the intermediate products, the sequence began with the dihydroxylation of the double bond ($KMnO_4$, dicyclohexano-18-crown-6 ether) followed by opening of the lactone ring (LiOH, THF) and fission of the vicinal 2,3-diol (aq. $NaIO_4$, SiO_2, CH_2Cl_2). Without purification, the crude α-amino aldehyde **3** so obtained (66% yield for the three steps) was selectively oxidized to protected amino acid **4** by treatment with sodium chlorite/2-methyl-2-butene[5] in 90% yield after flash chromatography (37% overall yield from arabinose **1**).

Evidence supporting the stereochemical assignment was obtained by converting **4** to the corresponding amino acid methyl ester **5** (CH_2N_2, Et_2O, quantitative) and analyzing its NOE difference spectral data. The observed correlation between H-3 and H-5 in *cis* orientation and the absence of any effect between *trans*-disposed H-3 and H-6 confirmed the α-location of the anomeric glycine fragment of the sugar.

This asymmetric synthesis of **5**, based upon the exploitation of TBSOP as a masked glycine anion equivalent, illustrates the viability of our approach to *C*-glycosyl α-amino acids and sets the stage for application of this protocol to syntheses of a variety of α-aminoacyl sugar subunits to be incorporated into *C*-glycosylated peptide derivatives.

Figure



X, Y = O, S, NBoc

EXPERIMENTAL SECTION

General. *N*-(*tert*-Butoxycarbonyl)-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP) was prepared on a multigram scale from pyrrole.[6] 1-*O*-Acetyl-2,3,5-tri-*O*-benzylarabinose **1** was prepared from commercially available 2,3,5-tri-*O*-benzyl-D-arabinofuranose by conventional acetylation procedure (Ac_2O, pyridine, DMAP).

^1H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Varian XL 300 instrument (δ in ppm referred to TMS, unless otherwise stated, *J* in Hz). Rotations were measured on a Perkin-Elmer 241. Flash chromatography was performed using silica gel 70-230 mesh purchased from Merck. Kieselgel 60 F_{254} (from Merck) was used for TLC. The solvents were distilled before use: THF over Na/benzophenone; Et_2O over $LiAlH_4$; CH_2Cl_2 over CaH_2. Elemental analyses were performed by the Microanalytical Laboratory of University of Sassari.

6,7,9-Tri-*O*-benzyl-4-*N*-*tert*-butoxycarbonylamino-5,8-anhydro-2,3,4-trideoxy-D-*glycero*-D-*galacto*-non-2-enono-1,4-lactone (2). To a solution of arabinose **1** (1.0 g, 2.16 mmol) in anhydrous Et_2O (10 mL) were added TBSOP (770 mg, 2.59 mmol) and anhydrous trityl perchlorate (370 mg, 1.08 mmol) under stirring at 0°C. After 4 h, the temperature was allowed to rise to 20°C and, after additional 24 h the reaction was quenched by a saturated aqueous solution of $NaHCO_3$ (15 mL). The mixture was extracted with diethyl ether (3x20 mL), and the organic layer washed with H_2O, dried ($MgSO_4$) and concentrated in vacuo. Compound **2** was obtained in a pure state by flash chromatography on SiO_2 eluting with a hexanes/ethyl acetate 7:3 solvent mixture; 784 mg (62%), an oil; $[\alpha]_D^{22}$ = -58.9 (*c* 1.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (m, 16H, ArH and H-3), 5.99 (dd, 1H, *J* = 6.0, 1.8 Hz, H-2), 4.89 (m, 1H, H-4), 4.5-4.6 (m, 6H), 4.4-4.5 (m, 2H), 4.12 (m, 1H), 4.0 (m, 1H), 3.55 (dd, 1H, *J* = 10.2, 5.4 Hz, H-9a), 3.47 (dd, 1H, *J* = 10.2, 6.0 Hz, H-9b), 1.52 (s, 9H, Bu^t); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 169.0, 149.9, 149.3, 138.0, 137.5, 137.2, 127-128 (15 ArC), 126.3, 84.2, 82.9, 82.7, 82.5, 79.5, 73.2, 71.6, 71.5, 69.7, 62.2, 28.0 (3C); Anal. calcd. for $C_{35}H_{39}NO_7$: C, 71.78; H, 6.71; N, 2.39. Found: C, 71.70; H, 6.80; N, 2.44.

4,5,7-Tri-*O*-benzyl-2-*N*-*tert*-butoxycarbonylamino-3,6-anhydro-2-deoxy-D-*glycero*-D-*galacto*-*aldehydo*-heptose (3). To a stirred solution of lactam **2** (700 mg, 1.19 mmol) in anhydrous CH_2Cl_2 (10 mL) were added dicyclohexano-18-crown-6-ether (57 mg, 0.15 mmol) and powdered $KMnO_4$ (221 mg, 1.39 mmol) at room temperature. After 12 h, the slurry mixture was quenched by a saturated aqueous solution of Na_2SO_3 and neutralized with 5% aq. citric acid. After extraction with EtOAc (2 x 10 mL), the organic layer was dried ($MgSO_4$) and evaporated under vacuo to give a crude diol which was directly dissolved in THF (17 mL). 1M aq. LiOH (3 mL) was added to the stirred solution at 0°C. After 15 min the solvent was removed and the residue was dissolved in CH_2Cl_2 (10 mL). SiO_2 (70-230 mesh, 3g) was added and the resulting, vigorously stirred slurry was treated with 0.65 M aq. $NaIO_4$ (2 mL) at room temperature. After 1h the slurry was filtered under suction and the silica was washed with CH_2Cl_2. The filtrates were evaporated to leave aldehyde **3** which was judged pure enough to be employed in the next reaction; 525 mg (66%), an oil; $[\alpha]_D^{22}$ = -20.0 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 1H, H-1), 7.2-7.4 (m, 15H, ArH), 5.60 (bd, 1H, *J* = 7.8 Hz, NH), 4.70 (m, 1H, H-2), 4.4-4.6 (m, 7H, CH_2-Ph and H-3), 4.16 (bd, 1H, *J* = 3.6 Hz, H-4), 4.07 (ddd, 1H, *J* = 6.6, 5.4, 3.6 Hz, H-6), 4.00 (bd, 1H, *J* = 2.0 Hz, H-5), 3.59 (dd, 1H, *J* =10.2, 5.4 Hz, H-7a), 3.50 (dd, 1H, *J* = 10.2, 6.2 Hz, H-7b), 1.42 (s, 9H, Bu^t); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 199.9, 160.0, 141.4, 137.9,

137.4, 127-129 (15 ArC), 83.7, 83.0, 82.7, 81.4, 79.9, 73.4, 71.9, 71.6, 69.9, 59.4, 28.3 (3C); Anal. calcd. for $C_{33}H_{39}NO_7$: C, 70.57; H, 7.00; N, 2.49. Found: C, 70.35; H, 6.89; N, 2.42.

4,5,7-Tri-*O*-benzyl-2-deoxy-2-*N*-*tert*-butoxycarbonylamino-3,6-anhydro-D-*glycero*-D-*galacto*-heptonic Acid (4). A 0°C solution of aldehyde **3** (400 mg, 0.71 mmol) in 1:1:0.25 acetonitrile/ *tert*-butylalcohol/2-methyl-2-butene (16 mL) was treated with a solution of $NaClO_2$ (595 mg, 6.58 mmol, 80 wt %) and $NaHPO_4$ (753 mg, 4.73 mmol) in 4 mL of H_2O over 5 min and then stirred for an additional 5 min. The aqueous layer was separated and extracted with 2x10 mL of EtOAc and the combined organic extracts were washed with 30 mL of 1M $Na_2S_2O_4$ and 15 mL of brine, dried and evaporated to an oil which was flash chromatographed on silica eluting with a EtOAc/MeOH 9:1 solution. Evaporation of the collected fractions afforded 369 mg of acid **4** (90%), $[\alpha]_D^{22}$ = -30.0 (*c* 1.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$, 50°C) δ 7.2-7.4 (m, 15H, ArH), 6.6 (bs, 1H, COOH), 5.71 (bs, 1H, NH), 4.69 (bs, 1H, H-2), 4.4-4.6 (m, 6H, CH_2-Ph), 4.39 (bd, 1H, *J* = 4.5 Hz, H-3), 4.18 (m, 1H, H-4), 4.08 (m, 1H, H-6), 3.93 (m, 1H, H-5), 3.60 (dd, 1H, *J* = 10.2, 5.4 Hz, H-7a), 3.49 (dd, 1H, *J* = 10.2, 5.7 Hz, H-7b), 1.39 (s, 9H, Bu^t); ^{13}C NMR (75.4 MHz, $CDCl_3$, 50°C) δ 172.7, 156.1, 137.9, 137.4, 136.5, 127–129 (15 ArC), 83.8, 83.1, 82.8, 80.4, 79.9, 73.4, 72.3, 71.5, 69.8, 53.7, 28.3 (3C); Anal. calcd. for $C_{33}H_{39}NO_8$: C, 68.61; H, 6.80; N, 2.42. Found: C, 68.55; H, 6.85; N, 2.40.

Methyl 4,5,7-Tri-*O*-benzyl-2-deoxy-2-*N*-*tert*-butoxycarbonylamino-3,6-anhydro-D-*glycero*-D-*galacto*-heptonate (5). Amino acid **4** (350 mg, 0.6 mmol) was treated with 20 mL of a 0.4M etheral solution of CH_2N_2 (8 mmol) at room temperature. After 20 min, the solvent was evaporated and the residue subjected to flash chromatography on silica eluting with a hexanes/ethyl acetate 8:2 solvent mixture to afford 340 mg (96%) of methyl ester **5** as an oil; $[\alpha]_D^{22}$ = -16.0 (*c* 0.8, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.2-7.4 (m, 15H, ArH), 5.58 (d, 1H, *J* = 9.0 Hz, NH), 4.88 (dd, 1H, *J* = 9.0, 6.2 Hz, H-2), 4.3-4.6 (m, 6H, CH_2-Ph), 4.48 (dd, 1H, *J* = 6.2, 4.5 Hz, H-3), 4.14 (ddd, 1H, *J* = 6.9, 5.4, 3.0 Hz, H-6), 4.03 (bd, 1H, *J* = 4.5 Hz, H-4), 3.98 (bs, 1H, H-5), 3.64 (s, 3H, CH_3), 3.63 (dd, 1H, *J* = 10.2, 5.4 Hz, H-7a), 3.53 (dd, 1H, *J* = 10.2, 6.9 Hz, H-7b), 1.39 (s, 9H, Bu^t); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 171.1, 155.8, 138.1, 137.6, 136.8, 127-129 (15 ArC), 83.9, 82.9, 82.8, 79.5, 79.1, 73.5, 71.9, 71.5, 70.0, 53.5, 52.2, 28.3 (3C); Anal. calcd. for $C_{34}H_{41}NO_8$: C, 69.02; H, 6.98; N, 2.37. Found: C, 68.98; H, 6.93; N, 2.35.

Acknowledgement : Support of this work was provided by Consiglio Nazionale delle Ricerche, Roma, Italy.

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(*Received in UK 6 December* 1994)