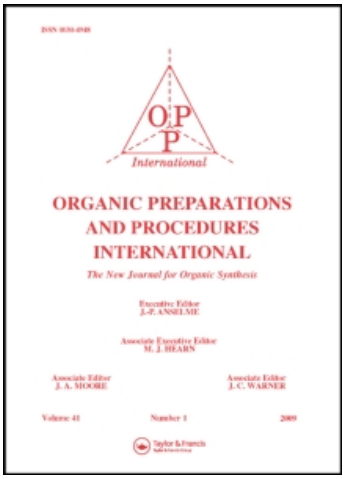

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SYNTHESIS OF 3-*O*-BENZYL-3,7-IMINO-1,3,6,7-TETRADEOXY-L-*MANNO*-HEPTITOL AND OF 3-*O*-BENZYL-3,7-IMINO-1,3,6,7-TETRADEOXY-D-*GLUCO*-HEPTITOL

Fabio Degiorgis[a]; Marco Lombardo[a]; Claudio Trombini[a]
[a] Università di Bologna Dipartimento di Chimica "G. Ciamician", Bologna, ITALY

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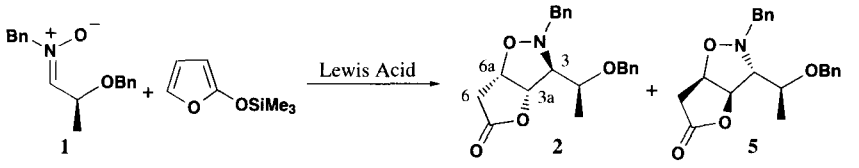
SYNTHESIS OF 3-*O*-BENZYL-3,7-IMINO-1,3,6,7-TETRADEOXY-L-*MANNO*-HEPTITOL AND OF 3-*O*-BENZYL-3,7-IMINO-1,3,6,7-TETRADEOXY-D-*GLUCO*-HEPTITOL

Submitted by (11/01/96)

Fabio Degiorgis, Marco Lombardo and Claudio Trombini*

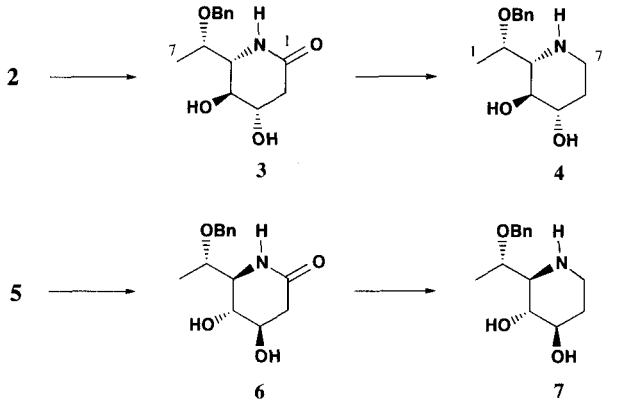
Università di Bologna
Dipartimento di Chimica "G.Ciamician"
via Selmi 2, I-40126, Bologna, ITALY

A number of naturally occurring polyhydroxylated piperidines (or azasugars) as well as a number of synthetic congeners which displayed outstanding pharmacological properties as β-glycosidases inhibitors, have been studied for the last decade.[1] We recently examined trimethylsilyl trifluoromethanesulfonate (TMSOTf)-promoted Mukaiyama-type reactions of silylated nucleophiles with nitrones.[2] The use of 2-trimethylsilyloxyfuran led to the development of a facile route to 3-substituted tetrahydrofuro[2,3-d]isoxazol-5(2H)ones;[3] with the (*S*)-lactaldehyde-derived nitrone **1**, tetrahydrofuro[2,3-d]isoxazol-5(2H)ones **2** and **5** were obtained as major products, depending on the experimental conditions (Scheme 1).[3a] We now report a short synthesis of enantiomerically pure piperidines



Scheme 1

4 and **7** *via* a simple manipulation of tetrahydrofuro[2,3-d]isoxazol-5(2H)ones **2** or **5**, as depicted in Scheme 2.



Scheme 2

When **2** and **5** were hydrogenated in the presence of 10% $Pd(OH)_2/C$ (Pearlman's catalyst) at 45 p.s.i. for 12 h at room temperature, a nice reaction cascade occurred involving *i*) reductive cleavage of the N-O bond, *ii*) chemoselective *N*-debenzylation, and, *iii*) spontaneous cyclization of the

intermediate amino-lactone to give lactams **3** or **6**.[4] It is interesting to note that Pearlman's catalyst which is the catalyst of choice for the hydrogenolysis of *N*-benzyl groups did not cleave *O*-benzyl groups. As a result, the protected hydroxyl group on the side-chain were preserved, and this may allow an orthogonal protection of the ring hydroxy groups and further selective manipulations on the side-chain. Conversion of lactams **3** or **6** to piperidines **4** and **7** can be achieved by standard methods; among others, we tested the use of BH_3•THF at room temperature and obtained the final products in acceptable yields.

We believe that the present synthetic sequence can be applied to a variety of starting nitrones thus affording an easy entry to 2-substituted 3,4-dihydroxypiperidines.

EXPERIMENTAL SECTION

^1H NMR and ^{13}C NMR spectra in deuterated solvents were recorded at 300 and 75 MHz, respectively, using a Varian Gemini 300 spectrometer. Chemical shifts are reported in ppm relative to internal standard Me_4Si (δ). IR spectra were recorded on a NICOLET 205 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Water contents of anhydrous solvents used were measured with Karl-Fisher titrator Mettler DL18. Reactions were performed in oven-dried glassware in atmosphere of dry argon. Hydrogenations were performed on a Parr apparatus. Melting points are uncorrected. [3S[3α(R*),3aβ,6aβ]]-Tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)one (**2**) and [3R[3α(S*),3aβ,6aβ]]-tetrahydro-2-benzyl-3-(1-benzyloxyethyl)-furo[2,3-d]isoxazol-5(2H)one (**5**) were synthesized according to ref.3a.

5-Amino-6-*O*-benzyl-2,5,7-trideoxy-L-*manno*-heptonic Acid Amide (3).- To a solution of lactone **2** (562 mg, 1.59 mmol) in anhydrous methanol, 10% $Pd(OH)_2$ on carbon (170 mg) was added and the mixture was subjected to hydrogenation at 45 p.s.i. for 12 h. Silica was added to the heterogeneous solution, the solvent was removed under vacuum and the solid was chromatographed on silica gel. Elution with ethyl acetate followed by ethyl acetate/methanol (9:1) afforded 241 mg (57%) of pure **3** as a colorless oil: R_f: 0.21 (ethyl acetate/methanol, 9:1); $[\alpha]_D^{20}$: +1.2 (c = 0.24, methanol); IR (neat): 3388, 2988, 2924, 2868, 1652, 1448, 1413, 1349, 1068, 738, 702 cm^{-1}; ^1H NMR (CD_3OD): δ 1.21 (d, *J* = 6.4 Hz, 3H, H-7), 2.27 (dd, *J* = 17.3/10.2 Hz, 1H, H-2), 2.64 (dd, *J* = 17.3/5.8 Hz, 1H, H-2), 3.45 (t, *J* = 8.3 Hz, 1H, H-4), 3.50 (dd, *J* = 8.3/2.8 Hz, 1H, H-5), 3.80 (ddd, *J* = 10.2/8.3/5.8 Hz, 1H, H-3), 3.93 (dq, *J* = 6.4/2.8 Hz, 1H, H-6), 4.54 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 4.61 (d, *J* = 11.6 Hz, 1H, OCH_2Ph), 7.32-7.50 (m, 5H, Ar-H); ^{13}C NMR (CD_3OD, HETCOR): δ 13.9 (C-7), 38.8 (C-2), 60.0 (C-5), 69.8 (C-3 or C-6), 71.7 (C-4), 71.9 (OCH_2Ph), 75.3 (C-3 or C-6), 128.7, 128.9, 129.4, 139.7 (Cquat.), 173.6 (C-1).

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.36; H, 7.22. Found: C, 63.40; H, 7.11

5-Amino-6-*O*-benzyl-2,5,7-trideoxy-L-*gulo*-heptonic Acid Amide (6).- According to the same procedure described for **3**, lactone **5** (710 mg, 2.0 mmol) was hydrogenated in the presence of 10% $Pd(OH)_2$ on carbon (215 mg). Purification by flash-chromatography (ethyl acetate followed by ethyl acetate/methanol, 9:1) afforded **6** (441 mg, 85%) as a colorless oil: R_f: 0.27 (ethyl acetate/methanol,

9:1); $[\alpha]_D^{20}$: +21.4(c = 0.39, methanol); IR (neat): 3388, 3346, 2981, 2924, 2875, 1652, 1455, 1406, 1349, 1286, 1082, 752, 695 cm^{-1}; ^1H NMR (CD_3OD): δ 1.30 (d, *J* = 6.4 Hz, 3H, H-7), 2.27 (dd, *J* = 17.0/8.8 Hz, 1H, H-2), 2.63 (dd, *J* = 17.0/5.3 Hz, 1H, H-2), 3.14 (dd, *J* = 6.5/5.2 Hz, 1H, H-5), 3.66 (dd, *J* = 8.0/6.5 Hz, 1H, H-4), 3.75-3.89 (m, 2H, H-3 + H-6), 4.47 (d, *J* = 11.5 Hz, 1H, OCH_2Ph), 4.65 (d, *J* = 11.5 Hz, 1H, OCH_2Ph), 7.21-7.40 (m, 5H, ArH); ^{13}C NMR (CD_3OD, HETCOR): δ 16.5 (C-7), 38.1 (C-2), 62.6 (C-5), 69.5 (C-3 or C-6), 71.1 (C-4), 72.2 (OCH_2Ph), 75.9 (C-3 or C-6), 128.8, 129.0, 129.4, 139.7 (Cquat.), 173.2 (C-1).

Anal. Calcd. for $C_{14}H_{19}NO_4$: C, 63.36; H, 7.22. Found: C, 63.24; H, 7.21

3-*O*-Benzyl-3,7-imino-3,6,7-trideoxy-L-*manno*-heptitol (4).- To a solution of **3** (230 mg, 0.87 mmol) in dry THF (5 mL), 4.35 mL of BH_3•THF (1M solution, 4.35 mmol) were added dropwise at room temperature and the reaction mixture was stirred for 6 h. The reaction was quenched with methanol, silica was added and the solvent was removed *in vacuo*. Residue was chromatographed on silica eluting with ethyl acetate/methanol (9:1) affording pure **4** (75 mg, 34%) as a white solid: mp. 80-82° (ethyl acetate); R_f: 0.29 (ethyl acetate/methanol, 7:3); $[\alpha]_D^{20}$: +2.3 (c = 0.58, methanol); IR (neat): 3395, 3297, 2995, 2938, 2846, 1455, 1420, 1321, 1061, 934, 900, 835, 716 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32 (d, *J* = 6.2 Hz, 3H, H-1), 1.50 (dq, *J* = 12.6/4.6 Hz, 1H, H-6), 1.95 (ddt, *J* = 12.6/4.9/2.4 Hz, 1H, H-6), 2.60 (dd, *J* = 9.2/5.7 Hz, 1H, H-3), 2.63 (dt, *J* = 12.6/2.4 Hz, 1H, H-7), 3.05 (ddd, *J* = 12.6/4.6/2.4, 1H, H-7), 3.26 (t, *J* = 9.2 Hz, 1H, H-4), 3.49 (ddd, *J* = 12.6/9.2/4.9 Hz, 1H, H-5), 3.79 (quintet, *J* = 5.7, 1H, H-2), 4.47 (d, *J* = 11.5, 1H, OCH_2Ph), 4.68 (d, *J* = 11.5, 1H, OCH_2Ph), 7.28-7.40 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$): δ 15.1 (C-1), 33.1 (C-6), 43.9 (C-7), 63.0 (C-3), 70.8 (OCH_2Ph), 74.6, 76.4, 76.5 (C-4, C-5, C-2), 127.7, 127.8, 128.5, 138.0 (Cquat.).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.89; H, 8.43. Found: C, 66.97; H, 8.33

3-*O*-Benzyl-3,7-imino-3,6,7-trideoxy-D-*gluco*-heptitol (7).- According to the same procedure described for the synthesis of **4**, lactam **6** (160 mg, 0.6 mmol) was treated with BH_3•THF (1M solution, 2.4 mL). Flash-chromatography eluting with acetate:methanol (9:1) as eluent afforded pure **7** (110 mg, 34%) as a white solid: mp. 92-94° (ethyl acetate); R_f: 0.22 (ethyl acetate/methanol, 7:3); $[\alpha]_D^{20}$: +28.6 (c = 0.41, methanol); IR (neat): 3392, 3301, 2989, 2927, 2845, 1447, 1356, 1286, 1054, 976, 829, 752 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (d, *J* = 6.3 Hz, 3H, H-1), 1.43 (dq, *J* = 12.6/4.4 Hz, 1H, H-6), 1.97 (ddt, *J* = 12.6/4.4/2.2 Hz, 1H, H-6), 2.48 (dd, *J* = 9.1/2.8 Hz, 1H, H-3), 2.62 (dt, *J* = 12.6/2.2 Hz, 1H, H-7), 3.08 (ddd, *J* = 12.6/4.4/2.2, 1H, H-7), 3.38 (t, *J* = 9.1 Hz, 1H, H-4), 3.51 (ddd, *J* = 12.6/9.1/4.4 Hz, 1H, H-5), 3.87 (dq, *J* = 6.3/2.8, 1H, H-2), 4.46 (d, *J* = 11.8, 1H, OCH_2Ph), 4.67 (d, *J* = 11.8, 1H, OCH_2Ph), 7.30-7.52 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$): δ 15.6 (C-1), 34.0 (C-6), 43.8 (C-7), 63.1 (C-3), 71.0 (OCH_2Ph), 73.3, 74.3, 74.5 (C-4, C-5, C-2), 127.8, 127.9, 128.4, 138.1 (Cquat.).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.89; H, 8.43. Found: C, 66.75; H, 8.37

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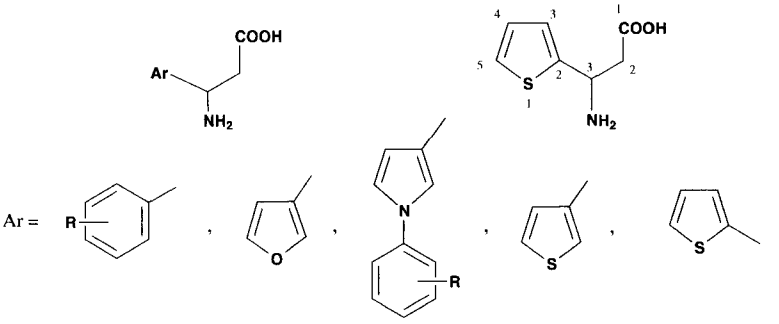
A CONVENIENT SYNTHESIS OF NEW HALOTHIENYL β-AMINOACIDS AS VERSATILE BUILDING BLOCKS

Submitted by (10/21/96)

Olivier Renault, Patrick Dallemagne and Sylvain Rault*

Centre d'Etudes et de Recherche sur le Médicament de Normandie
Laboratoire de Chimie Thérapeutique, U.F.R. des Sciences Pharmaceutiques
1, rue Vaubénard, 14032 Caen Cedex, FRANCE

During the course of our work on the synthesis of new thiophene derivatives with therapeutic interest,[1,2] we needed reasonable quantities of new β-aminoacids which are versatile building-blocks in heterocyclic chemistry and in the synthesis of peptidomimetics.[3-5] We previously reported the preparation and the chemical reactivity of several β-amino-β-arylpropionic acid derivatives (Scheme 1).[6-10] The present work describes the multigram scale preparation of new 3-amino-3-(thien-2-yl)propionic acids bearing one or two bromine or chlorine atoms at the 4 and/or 5 position of the thiophene ring.



Scheme 1