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HIGH PRESSURE APPROACH TO THE TOTAL SYNTHESIS OF 6-*EPI*-D-PURPUROSAMINE B

ADAM GOŁĘBIOWSKI,[a] ULLA JACOBSSON,[b] AND JANUSZ JURCZAK*[a]

[a] Institute of Organic Chemistry, Polish Academy of Sciences, 01-224 Warszawa, Poland; [b] Department of Organic Chemistry, Royal Institute of Technology, S-100 44 Stockholm, Sweden

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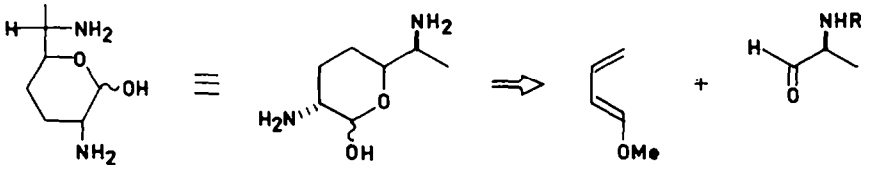
Abstract - Methyl 2,6-di-N-acetyl-6-*epi*-α-D-purpurosaminide B (11) was synthesized from L-alanine by an eleven-step reaction sequence. Eu(fod)$_3$-mediated high-pressure [4+2]cycloaddition of 1-methoxybuta-1,3-diene (2) to α-amino aldehyde 3, easily available from L-alanine (4), is the key step in the synthetic sequence.

2,6-Diamino-2,3,4,6,7-pentadeoxy-L-*lyxo*-heptopyranose, commonly named 6-*epi*-D-purpurosamine B (1), is apart from aminocyclitol fortamine, a component of an aminoglycosidic antibiotic fortimicin.[1,2] The N-protected derivatives of 1 have recently been synthesized by two Japanese groups: Suami et al.[3] and Yasuda et al.[4] In both methods, 2-amino-2-deoxy-D-glucose served as starting material, and - as typical of such transformations - both require multistep synthetic sequences. Our approach, according to simple retro-synthetic analysis (Scheme 1), is based on [4+2]cycloaddition of 1-methoxybuta-1,3-diene (2) to chiral aldehyde 3, easily available from L-alanine (4).



1 2 3

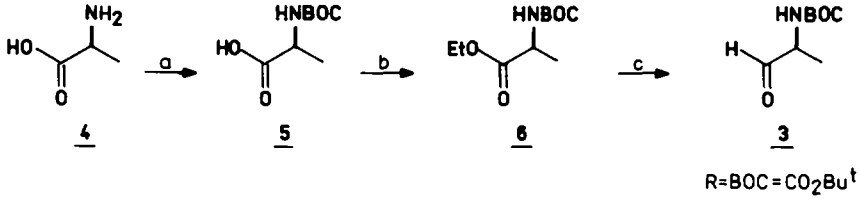
Scheme 1

[4+2]Cycloaddition of diene 2 to α-amino aldehydes offers an easy access to the chiral 5,6-dihydro-2H-pyran system with the amino functionality attached to the C-6 carbon atom. Consequent stereoselective functionalization of the C-2 carbon atom of the respective [4+2]cycloadduct should give a direct route to the corresponding purpurosamine. We have recently applied this strategy for the total synthesis of D,L-purpurosamine C.[5]

In this paper we describe the total synthesis of optically pure methyl 2,6-di-N-acetyl-6-*epi*-D-purpurosaminide B (11), based on Eu(fod)$_3$-mediated high-pressure [4+2]cycloaddition of 1-methoxybuta-1,3-diene (2) to N-*tert*-butoxycarbonyl-L-alaninal (3).

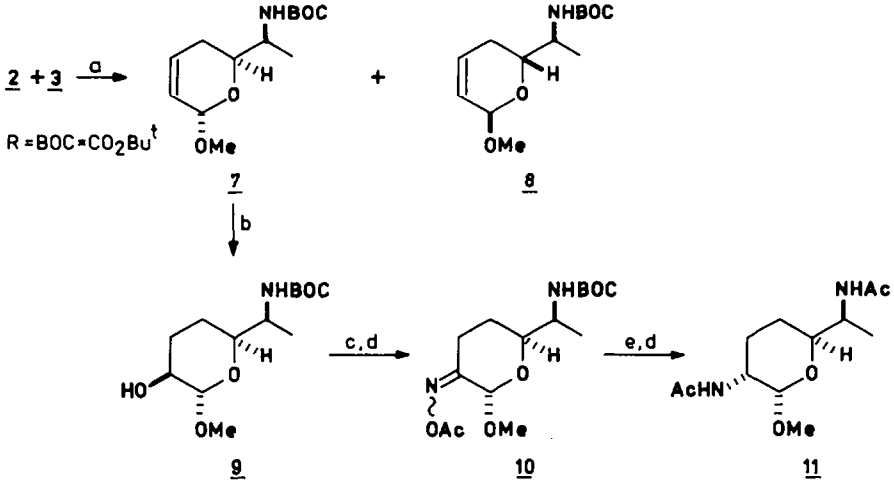
RESULTS

Efficient transformation of L-alanine (4) to N-*tert*-butoxycarbonyl-L-alaninal (3) comprises protection of the amino group with di-*tert*-butyl dicarbonate ($(BOC)_2O$),[6] followed by esterification of the carboxy group in N-protected α-amino acid 5, according to the Kim et al.[7] procedure. Finally, ester 6 was reduced with diisobutylaluminum hydride (DIBAL)[8] to afford the desired α-amino aldehyde 3 in 75% overall yield (Scheme 2).



Scheme 2. Reagents and reaction conditions: (a) $(BOC)_2O$, Bu^tOH, H_2O, pH 8-9, RT, 16 h; (b) $ClCO_2Et$, Et_3N, DMAP, 0°C→RT, 0.5 h; (c) DIBAL, Et_2O, -78°C, 0.5 h.

High sensitivity of diene 2 to Lewis acids and low reactivity of aldehyde 3 under thermal conditions call for application of the high-pressure approach for performing the (4+2)cycloaddition.[9] The $Eu(fod)_3$-mediated[10] high-pressure reaction of 2 with 3 was carried out in ethyl ether as solvent under 20 kbar at 50°C, to afford in 70% yield a mixture of four possible diastereoisomers: two *cis*-adducts by *endo* addition and two *trans*-adducts by *exo* addition.[11] Acidic isomerization[12] of the mixture, followed by chromatographic separation, led to thermodynamically more stable *trans* adducts 7 and 8 in a ratio of 2:1 (Scheme 3).



Scheme 3. Reagents and reaction conditions: (a) *i*. 20 kbar, 2% $Eu(fod)_3$, Et_2O, 50°C, 20 h; *ii*. PPTS, MeOH, RT, 24 h; (b) *i*. $ThxBH_2$·DMS, Et_2O, -20°C, 1.5 h; *ii*. 30% H_2O_2, 30% NaOH aq; (c) *i*. PCC, molecular sieves 4Å, CH_2Cl_2, RT, 2 h; *ii*. NH_2OH·HCl, K_2CO_3, MeOH, RT, 3 h; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 0.5 h; (e) *i*. BH_3·THF, THF, -78°C→RT, 12 h; *ii*. TFA, RT, 1 h.

Hydroboration of cycloadduct 7 using thexyl borane,[5] followed by oxidative work-up, afforded alcohol 9 in 80% yield. Pyridinium chlorochromate (PCC) oxidation of compound 9, carried out in the presence of molecular sieves 4Å,[13] led to the corresponding ketone which was then treated with hydroxylamine to give the oxime; acetylation of the oxime afforded a 1:1 *syn-anti* mixture of oxime acetates 10. The next step of the synthesis consisted of reduction of 10 with BH_3·THF complex,

followed by hydrolysis of the resulting product with trifluoroacetic acid (TFA) and acetylation, affording methyl 2,6-di-N-acetyl-6-*epi*-α-D-purpurosaminide B (11) and its 2-epimer in a 6:1 ratio.

In conclusion, the use of $Eu(fod)_3$-mediated high-pressure [4+2]cycloaddition of diene 2 to aldehyde 3 provides a direct route to optically pure 6-*epi*-D-purpurosamine B (1). Transformation of L-alanine (4) to methyl 2,6-di-N-acetyl-6-*epi*-α-D-purpurosaminide B (11) requires eleven reaction steps (5% overall yield). The presented total synthesis proves to be a practical alternative to known procedures[3,4] using monosaccharides as starting materials.

EXPERIMENTAL

The ^1H (200 MHz) and ^{13}C (50.288 MHz) NMR spectra were recorded with a Bruker AM 200 spectrometer for $CDCl_3$ solutions (δ scale, TMS=0). The IR spectra were measured with a Beckman IR-4240 spectrophotometer.

Column chromatography was performed on Merck Kieselgel 60 (230–400 mesh), according to Still's procedure.[14] All chromatographic separations were monitored by TLC carried out on Merck DC Alufolien Kieselgel 60F-254. The reported yields refer to chromatographically pure compounds.

High-pressure reactions were carried out in a piston-cylinder type apparatus, with working volume of about 90 mL. Construction details have been reported previously.[15] The pressure inside the working volume was measured with a calibrated coil exact to ± 0.1 kbar. The accuracy of temperature measurements using a calibrated thermocouple was ± 1°C.

trans-1-Methoxybuta-1,3-diene (2) was prepared according to the literature.[16]

N-*tert*-Butoxycarbonyl-L-alanine (5). L-Alanine (8.9 g, 0.1 mol) and sodium hydroxide (4.4 g, 0.11 mol) were dissolved in 75 mL of a *tert*-butanol - water mixture (1:1 v/v). To this solution (pH 8-9), di-*tert*-butyl dicarbonate (24.0 g, 0.11 mol) was added in one portion. The reaction mixture was stirred at room temperature for 16 h. The excess of di-*tert*-butyl dicarbonate was then removed by ethyl acetate extraction (2×50 mL). The aqueous layer was treated with potassium hydrosulfate (22.4 g in 150 mL of water) and then was extracted with ethyl acetate (4×50 mL). The combined extracts were washed with water (2×50 mL), dried ($MgSO_4$), and finally the solvent was evaporated under reduced pressure. The residue was crystallized from a mixture of ethyl acetate and hexane, to afford 16.0 g (87% yield) of pure compound 5: mp 79–81°C, $[\alpha]_{589}^{20}$ -25° (c 2, AcOH). [Lit.[6] mp 79–81°C, $[\alpha]_{589}^{20}$ -25° (c 2, AcOH)].

Ethyl ester of N-*tert*-butoxycarbonyl-L-alanine (6). To a solution of compound 5 (1.89 g, 10 mmol) in methylene chloride (30 mL), triethylamine (1.53 mL, 11 mmol) was added at 0°C, followed by ethyl chloroformate (0.8 mL, 10.5 mmol). After 10 min stirring, 4-dimethylaminopyridine (125 mg, 1 mmol) was added in one portion and stirring was continued for additional 20 min. A reaction mixture was diluted with ethyl ether (100 mL) and extracted with 1 N hydrochloric acid. The organic layer was washed with saturated aqueous sodium bicarbonate (2×30 mL), dried ($MgSO_4$) and concentrated under reduced pressure, to give 1.95 g (90% yield) of crude compound 6 as a colourless oil, which was subsequently used in the next reaction.

N-*tert*-Butoxycarbonyl-L-alaninal (3). To a solution of compound 6 (1.95 g, 9 mmol) in ethyl ether (30 mL), diisobutylaluminum hydride (30 mL of 1.5 mol toluene solution, 45 mmol) was added at -78°C. After 45 min stirring, methanol (2 mL) was added and a post-reaction mixture was poured into a saturated aqueous solution of Rochelle salt (200 mL). The layers were separated and the aqueous phase was extracted with ethyl ether (2×50 mL). The combined extracts were dried ($MgSO_4$) and the solvent was evaporated to dryness. The oily residue was chromatographed on a silica gel column (hexane - ethyl acetate 85:15 v/v) to afford 1.17 g (75% yield) of crystalline compound 3: mp 88–89°C, $[\alpha]_{589}^{20}$ +36° (c 1, CH_2Cl_2). [Lit.[17] mp 88–89°C, $[\alpha]_{589}^{20}$ +36.7° (c 1, CH_2Cl_2)].

Methyl 6-N-*tert*-butoxycarbonylamino-2,3,4,6,7-pentadeoxy-β-D-*threo*-hept-2-enopyranoside (7). A solution of 3 (1.73 g, 10 mmol), 2 (1.66 g, 20 mmol), and $Eu(fod)_3$ (0.104 g, 0.1 mmol), in ethyl ether (6 mL) was charged into a Teflon ampoule which was placed in a high-pressure vessel filled with pentane as a transmission medium. The pressure was slowly elevated to 20 kbar at 50°C. After stabilization of pressure, the reaction mixture was kept under these conditions for 20 h. After cooling and decompression, the solvent was evaporated and the residue was filtered through a short silica gel pad using a mixture of hexane and ethyl acetate (8:2 v/v) as an eluent. The filtrate was evaporated to dryness and the residue was dissolved in methanol (20 mL) and to this solution pyridinium *p*-toluenesulfonate (0.25 g, 1 mmol) was added. The *cis-trans* isomerization[12] was carried out at room temperature during 20 h, and then solid sodium bicarbonate (92 mg, 1.1 mmol) was added and the mixture was stirred for 1 h. The solvent was evaporated and the residue was treated with ethyl ether (10 mL). The precipitated inorganic salts were filtered off and the crude product was purified by column chromatography using a mixture of hexane and acetone (95:5 → 9:1 v/v) as an eluent. Analytically pure compounds 7 (1.25 g) and 8 (0.62 g) were obtained in 70% overall yield.
Compound 7: an oil, $[\alpha]_{589}^{20}$ -28.5° (c 3, $CHCl_3$), IR (film), ν, 3340, 1710, 1190, 1040 cm^{-1}; ^1H NMR ($CDCl_3$), δ, 6.00 (m, 1 H), 5.70 (m, 1 H), 4.85 (m, 1 H), 4.85 (d, J=1.5 Hz, 1 H), 3.82 (m, 1 H), 3.77 (m, 1 H), 3.41 (s, 3 H), 2.05 (m, 2 H), 1.45 (s, 9 H), 1.24 (d, J=6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$), δ, 127.96, 124.59, 95.38, 68.85, 54.00, 48.97, 28.28, 26.94, 15.88. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.93; H, 9.06; N, 5.68.
Compound 8: an oil, $[\alpha]_{589}^{20}$ -46.2° (c 1.5, $CHCl_3$), IR (film), ν, 3350, 1710, 1170, 1050 cm^{-1}; ^1H NMR ($CDCl_3$), δ, 6.01 (m, 1 H), 5.72 (m, 1 H), 4.86 (s, 1 H), 4.85 (m, 1 H), 3.82 (m, 1 H), 3.73 (m, 1 H), 3.41 (s, 3 H), 2.01 (m, 2 H), 1.45 (s, 9 H), 1.17 (d, J=6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$), δ, 128.26, 124.33, 95.38, 68.63, 54.77, 48.63, 28.28, 27.15, 18.56. Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.68; H, 9.16; N, 5.39.

Methyl 6-N-*tert*-butoxycarbonylamino-3,4,6,7-tetradeoxy-β-L-*xylo*-heptopyranoside (9). To a solution of 2,3-dimethyl-2-butene (420 mg, 5 mmol) in ethyl ether (20 mL), borane - dimethyl sulfide complex (0.35 mL, 3.5 mmol) was added at -5°C. The mixture was stirred at 0°C and then it was cooled to -25°C. Adduct 7 (514 mg, 2 mmol) dissolved in ethyl ether (1.5 mL) was added and the reaction mixture was kept at -25°C for 3 h. The excess of borane was decomposed with methanol (10 mL), followed by a mixture of 30% H_2O_2 and 30% NaOH aq (2 mL, 1:1 v/v); temperature was raised to 20°C and stirring was continued for additional 1 h. The post-reaction mixture was extracted with ethyl acetate (3×20 mL), the combined extracts were washed with water, dried with $MgSO_4$ and the solvent was evaporated. The residue was chromatographed on a silica gel column using a mixture of hexane and acetone (8:2 → 7:3 v/v) as an eluent, to afford 440 mg (80% yield) of compound 9 as an oil: $[\alpha]_{589}^{20}$ +42.3° (c 1, $CHCl_3$). Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.70; H, 9.15; N, 5.09. Found: C, 56.50; H, 9.50; N, 5.02. Compound 9 was then acetylated to give the respective acetate as an oil: IR (film), ν, 3460, 1680, 1060 cm^{-1}; ^1H NMR ($CDCl_3$), δ, 4.80 (m, 1 H), 4.69 (bs, 1 H), 4.58 (s, 1 H), 3.68 (m, 2 H), 3.36 (s, 3 H), 2.10 (s, 3 H), 1.65-1.10 (m, 4 H), 1.45 (s, 9 H), 1.21 (d, J=6.8 Hz, 3 H).

Methyl 2,6-diacetamido-2,3,4,6,7-pentadeoxy-β-L-*lyxo*-heptopyranoside (11). To a solution of alcohol 9 (275 mg, 1 mmol) in methylene chloride (5 mL) were added well grounded pyridinium chlorochromate (647 mg, 3 mmol) and freshly dried molecular sieves 4Å (1 g). The heterogeneous mixture was stirred at room temperature for 1.5 h; then ethyl ether (30 mL) was added and the post-reaction mixture was filtered through a short silica gel pad. The filtrate was evaporated and the residue was dissolved in dry methanol (5 mL); solid hydroxylamine hydrochloride (139 mg, 2 mmol) and solid potassium carbonate (276 mg, 2 mmol) were added in one portion and the whole mixture was stirred at room temperature for 16 h. Then methanol was evaporated and the residue was dissolved in methylene chloride (5 mL); triethylamine (202 mg, 2 mmol), acetic anhydride (153 mg, 1.5 mmol) and a crystal of DMAP were added and the reaction mixture was stirred at room temperature for 15 min. After evaporation of solvents, the oily residue was dissolved in tetrahydrofuran (5 mL) and the solution was cooled to -50°C. The BH_3·THF complex (2 mL of 1 mol solution) was added and the reaction mixture was stirred at -50°C for 8 h, and then at room temperature for additional 16 h. An excess of borane was decomposed with methanol (2 mL), solvents were evaporated and the residue was dissolved in trifluoroacetic acid (1 mL). The solution was stirred at room temperature for 1 h; then TFA was evaporated and to the residue, dissolved in CH_2Cl_2 (2 mL), were added Et_3N (151 mg, 1.5 mmol) and Ac_2O (112 mg, 1.1 mmol). The reaction mixture was stirred at room temperature for 1 h, and after evaporation of solvents, a crude product was chromatographed on a silica gel column using a mixture of chloroform and methanol (99:1 v/v) as an eluent, to give 102 mg (40% overall yield) of compound 11, and 17 mg of its 2-epimer. Analytically pure compound 11 was obtained by recrystallization from acetone: mp 213-214°C, $[\alpha]_{589}^{20}$ +64° (c 0.3, MeOH). (Lit.[3] mp 212-213°C, $[\alpha]_{589}^{20}$ +62.9° (c 1, MeOH)). The ^1H NMR and IR spectra of 11 were superimposable on those of an authentic sample.

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