2 h. The product 96% (28.4 g) of theory, was isolated as in entry 1. VPC indicated 99% one component: bp 109–111 °C (0.03 mm); IR (neat, cm^{-1}) 2838, 2868, 1470, 1452, 1354, 1100 (C–O–C); ^{13}C NMR (ppm, $CDCl_3$) 76.90 (α-ring carbon), 68.64 (α-chain carbon), 31.81, 30.31, 29.06, 26.00, 24.78, 24.31, 23.29, 22.71, 20.78, 14.10; MS m/z (relative intensity) 268 (M^+, 1.1), 225 (0.03), 211 (0.2), 197 (1.0), 183 (0.4), 138 (2.4), 124 (3.6), 111 (4.5), 110 (6.4), 97 (2.0), 96 (19.9), 83 (15.4), 82 (46.5), 69 (16.1), 68 (17.1), 55 (34.2), 54 (6.2), 43 (100.0), 41 (40.3), 39 (14.8). Anal. Calcd for $C_{18}H_{36}O$: C, 80.53; H, 13.52. Found: C, 80.77; H, 13.33.

***n*-Propoxycyclotridecane (Entry 6).** Cyclotridecanol (900.0 mg, 4.54 mmol), sodium hydride (320.0 mg of 50% in mineral oil, 6.67 mmol), and 1-bromopropane were strongly refluxed for 3 h. A 770.0-mg sample (71%) was isolated as in entry 1. VPC indicated 98% one component: bp 82–84 °C (0.05 mm); IR (neat, cm^{-1}) 2930, 2850, 1460, 1350, 1100 (C–O–C), 1025. Anal. Calcd for $C_{16}H_{32}O$: C, 79.93; H, 13.42. Found: C, 79.90; H, 13.43.

***n*-Propoxycyclotetradecane (Entry 10).** Cyclododecanol (89 g, 0.42 mol), sodium hydride (55.0 g of 60% in mineral oil, 1.38 mol), and 1-iodopropane (340.0 g, 2.0 mol) were refluxed for 4 h. A 105.8-g sample (99%) was isolated as in entry 1. VPC indicated 99% one component: bp 99–101 °C (0.03 mm); IR (neat, cm^{-1}) 2930, 2860, 1460, 1380, 1360, 1350, 1105 (C–O–C), 1020. Anal. Calcd for $C_{17}H_{34}O$: C, 80.24; H, 13.47. Found: C, 80.42; H, 13.33.

Ethoxycyclopentadecane (Entry 11). Cyclododecane (3.8 g, 16.79 mmol), sodium hydride (3.8 g of 60% in mineral oil, 94.98 mmol), and iodoethane were refluxed for 18 h. A 4.1-g sample (95%) was collected as in entry 1. VPC indicated 99% one component: bp 105–106 °C (0.05 mm); IR (neat, cm^{-1}) 2930, 2850, 1460, 1350, 1100 (C–O–C), 1025. Anal. Calcd for $C_{17}H_{34}O$: C, 80.24; H, 13.47. Found: C, 80.31; H, 13.44.

***n*-Propoxycyclopentadecane (Entry 12).** Cyclopentadecanol (25.0 g, 0.11 mol), sodium hydride (22.5 g of 60% in mineral oil, 0.56 mol), and 1-iodopropane (186.9 g, 1.10 mol) were reacted at reflux for 4 h. A 28.3-g sample (96%) was isolated as in entry 1. VPC indicated 99% one component: bp 114–115 °C (0.09 mm); IR (neat, cm^{-1}) 2925, 2850, 1460, 1362, 1092 (C–O–C), 1030; ^{13}C NMR (ppm, $CDCl_3$) 78.62 (α-ring carbon), 70.30 (α-chain carbon), 32.17, 31.19, 29.75, 28.91, 28.54, 28.35, 27.45, 26.94, 26.75, 23.37; MS m/z (relative intensity) 268 (M^+, 4.5), 239 (0.3), 225 (1.0), 211 (0.6), 197 (0.5), 183 (0.4), 138 (3.1), 124 (5.5), 111 (4.0), 110 (7.4), 97 (13.6), 96 (26.8), 83 (19.5), 82 (86.0), 69 (20.4), 68 (20.1), 55 (100.0), 54 (9.4), 43 (94.3), 41 (93.4). Anal. Calcd for $C_{18}H_{36}O$: C, 80.52; H, 13.52. Found: C, 80.70; H, 13.50.

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Total Synthesis of Purpurosamine B from D-Alanine

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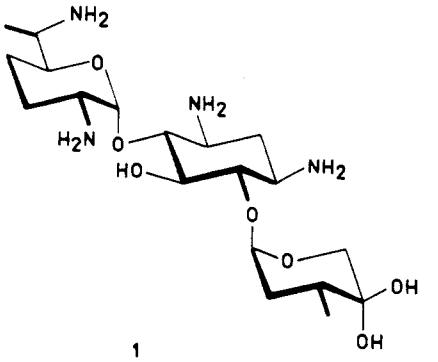
Purpurosamine B (**2**) is one of the two sugar components of the aminoglycosidic antibiotic gentamycin C_2 (**1**).[2]

The N-protected derivatives of purpurosamine B have been prepared in both racemic[3] and optically active[4,5] forms. The latter syntheses were based on multistep



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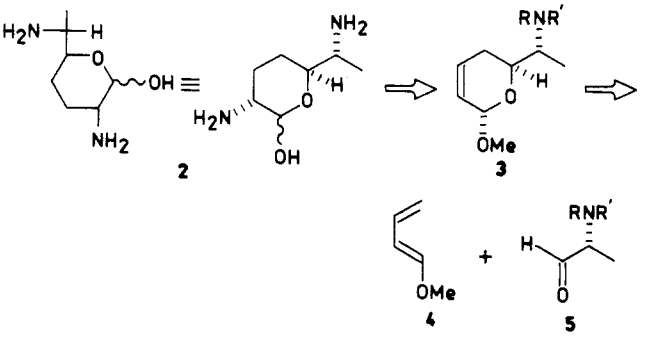
transformations of naturally occurring sugars. The key step, in our approach, is the high-pressure Diels–Alder reaction of 1-methoxybuta-1,3-diene (**4**) with the N-protected α-amino aldehyde **5**.[6]



2 **3**

4 **5**

It is obviously most important in this strategy that the major product obtained in the cycloaddition step has the correct configuration.[7] We have selected *N*-benzyl-*N*-(*tert*-butoxycarbonyl)-D-alaninal (**5a**) as an efficient heterodienophile on the basis of our recent results.[7,8]

The Eu(fod)$_3$-mediated[9] high-pressure reaction of **4** with **5a** was carried out in the presence of 2% catalyst in ethyl ether at 15 kbar and 50 °C to afford, after acidic isomerization, a mixture of diasteroisomers **3a** and **3b** in a 16:1 ratio (80% yield).

A mixture of adducts **3a** and **3b** was subjected to hydroboration with thexylborane.[10] After oxidative workup, we obtained alcohol **6** as a major product, which was debenzylated with sodium in liquid ammonia[11] to produce alcohol **7** in a 70% overall yield after chromatographic separation. Functionalization of alcohol **7** was carried out as in our total syntheses of purpurosamine C,[10] and 6-epi B,[12] to afford methyl 2,6-di-*N*-acetyl-α-D-purpurosaminide B (**8**) in a 6% overall yield based on D-alanine (Scheme I).

This total synthesis is a practical alternative to known procedures based on monosaccharides as starting materials.[4,5] Moreover, it exemplifies the usefulness of N-protected α-amino aldehydes in the synthesis of natural products.

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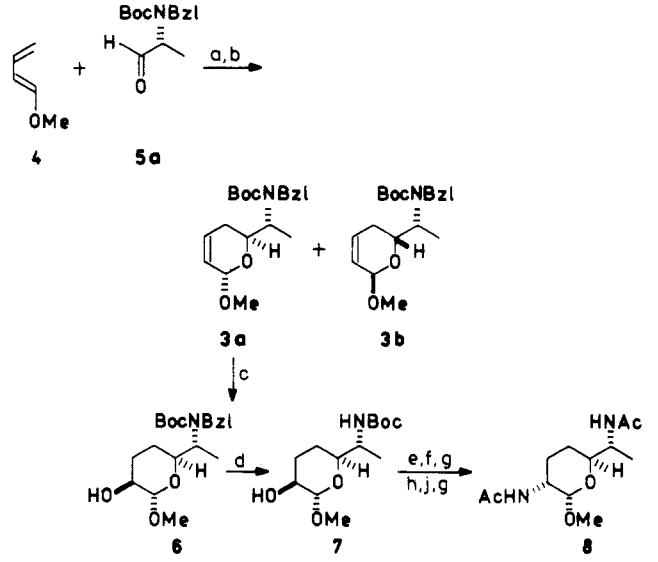
Scheme I[a]



[a] (a) 15 kbar, 50 °C, 2% $Eu(fod)_3$, Et_2O; (b) PPTS, room temperature; MeOH; (c) (i) $ThxBH_2$, −25 °C, Et_2O; (ii) 30% H_2O_2, 30% NaOH aqueous, room temperature; (d) Na, NH_3 liquid, −33 °C; (e) PCC, molecular sieves 4 Å, room temperature, CH_2Cl_2; (f) NH_2OH·HCl, room temperature, MeOH; (g) Ac_2O, Et_3N, room temperature, CH_2Cl_2; (h) BH_3 THF, −78 °C → room temperature; (j) TFA, room temperature, CH_2Cl_2.

Experimental Section

^1H NMR spectra were recorded at 400 MHz with a Bruker AM 400 spectrometer and 60 MHz with a Varian EM 360 spectrometer. ^{13}C NMR spectra were recorded at 100 MHz with a Bruker AM 400 spectrometer. Infrared spectra were recorded on a Beckman IR-4240 spectrophotometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter.

Column chromatography was carried out with Merck Kieselgel 60 (230–400 mesh), according to Still's procedure.[13] All chromatographic separations were monitored by TLC analyses, performed on Merck DC Alufolien Kieselgel 60F-254. The yields are reported for chromatographically pure compounds.

High-pressure reactions were carried out in a piston–cylinder type apparatus with a working volume of about 90 mL. Construction details have been reported previously.[14] The pressure was measured with a manganin coil calibrated to ±0.1 kbar. The temperature was measured with a thermocouple calibrated to ±1 °C.

trans-1-Methoxybuta-1,3-diene (**4**)[15] and the methyl ester of *N*-benzyl-D-alanine[16] were prepared according to literature procedures.

***N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-D-alanine Methyl Ester.** A solution of the methyl ester of *N*-benzyl-D-alanine (1.93 g, 10 mmol) in acetonitrile (15 mL) was treated with di-*tert*-butyl dicarbonate (4.36 g, 20 mmol) and 0.122 g (1 mmol) of DMAP in one portion. The mixture was stirred at room temperature for 1 h and at reflux for an additional hour. Evaporation of the solvent afforded a crude product, which was purified by flash chromatography (hexane–ethyl acetate, 9:1) to give 2.04 g (75% yield) of the desired ester as a colorless oil: $[\alpha]^{20}_D$ +4.9° (*c* 1.3, $CHCl_3$); IR (neat) ν 1750, 1705 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 7.20 (br s, 5 H), 4.40 (br s, 2 H), 4.35 (q, J = 6.2 Hz, 1 H), 3.50 (s, 3 H), 1.40 (s, 9 H), 1.35 (d, J = 6.2 Hz, 3 H). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.51; H, 8.09; N, 4.75.

***N*-Benzyl-*N*-(*tert*-butoxycarbonyl)-D-alaninal (5a).** A solution of the above ester (1.37 g, 5 mmol) in ethyl ether (30 mL) was treated with diisobutylaluminum hydride (1.5 M solution in toluene, 7 mL, 10.5 mmol) at −78 °C. After 30 min of stirring, methanol (1 mL) was added, and the mixture was poured into saturated aqueous Rochelle salt (100 mL) and stirred until all the precipitated solid had dissolved (about 1 h). The layers were separated, and the aqueous one was extracted with ethyl ether (2 × 30 mL). The extracts were combined and dried ($MgSO_4$). The solvent was evaporated, and the oil residue purified by flash chromatography (hexane–ethyl acetate, 9:1) to give 0.97 g (80% yields) of aldehyde **5a** as a colorless oil:[17] IR (CCl_4) ν 3000, 1750, 1700 cm^{-1}; ^1H NMR (60 MHz, $CDCl_3$) δ 9.35 (s, 1 H), 7.30 (br s, 5 H), 4.40 (m, 3 H), 1.40 (s, 9 H), 1.35 (d, J = 6.0 Hz, 3 H).

Methyl 6-[*N*-(*tert*-Butoxycarbonyl)amino]-3,4,6,7-tetradeoxy-α-D-*erythro*-heptopyranoside (7). A Teflon ampoule containing a solution of **5a** (0.97 g, 4 mmol), **4** (0.67 g, 8 mmol), and $Eu(fod)_3$ (83.2 mg, 0.08 mmol) in ethyl ether (5 mL) was placed in a high-pressure vessel filled with pentane. The pressure was slowly (10 min) elevated to 15 kbar at 50 °C. After 20 h, the reaction mixture was cooled and decompressed; the solvent was evaporated, and the residue was filtered through a short silica gel pad with hexane–ethyl acetate (85:15). Solvents were evaporated, the residue was dissolved in methanol (10 mL), and pyridinium *p*-toluenesulfonate (0.125 g, 0.5 mmol) was added. The cis–trans isomerization[18] was carried out at room temperature during 24 h, ethyl ether (50 mL) was added, and the reaction mixture was extracted with aqueous sodium bicarbonate (2 × 30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated to dryness. The oily residue was chromatographed with hexane–ethyl acetate (95:5 → 9:1) to afford 1.11 g (80% yield) of trans adduct **3a** and a small amount of the second diastereoisomer **3b** (diastereoisomeric ratio 16:1). This mixture was dissolved in ethyl ether (5 mL), added to a solution of previously prepared thexylborane[12,19] (6 mmol) and 2,3-dimethyl-2-butene (0.504 g, 6 mmol) in ethyl ether (5 mL). After 3 h at −25 °C, methanol (10 mL) and a mixture of 30% H_2O_2 and 30% NaOH aqueous (2 mL, 1:1 v/v) were added to the reaction mixture in that order; the temperature was raised to 20 °C, and stirring was continued for 1 h. The mixture was partioned between ethyl ether and water (50 mL, 1:1 v/v); the organic layer was washed with brine (2 × 10 mL) and dried ($MgSO_4$), and the solvent was evaporated. The oily residue was dissolved in tetrahydrofuran (3 mL) and added to a previously prepared solution of sodium (0.23 g, 10 mmol) in liquid ammonia (30 mL). After 30 min, an excess of NH_4Cl was added (disappearance of the blue color), and ammonia was evaporated. The semisolid residue was partioned between ethyl ether and brine. The organic layer was separated, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on a silica gel column with hexane–acetone (8:2 → 7:3) to afford 0.616 g (70% yield) of alcohol **7** as an oil: $[\alpha]^{20}_D$ −73.4° (*c* 1.5, $CHCl_3$). Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.70; H, 9.15; N, 5.09. Found: C, 56.69; H, 9.41; N, 4.94. Compound **7** was then acetylated to give the corresponding acetate as an oil: IR (neat) ν 3460, 1680, 1060, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.80 (m, 1 H), 4.58 (br s, 1 H), 3.73–3.60 (m, 2 H), 3.35 (s, 3 H), 2.09 (s, 3 H), 2.00–1.55 (m, 4 H), 1.44 (s, 9 H) 1.16 (d, J = 6.5 Hz, 3 H).

Methyl 2,6-Diacetamido-2,3,4,6,7-pentadeoxy-α-D-*ribo*-heptopyranoside (8). Alcohol **7** (0.275 g, 1 mmol) gave 0.148 g (58% overall yield) of compound **8**, and 0.015 mg of its 2-epimer, via our previously described procedure.[12] Recrystallization from acetone provided an analytically pure sample of **8**: mp 262–263 °C; $[\alpha]^{20}_D$ +186.0° (*c* 0.5, MeOH) [lit.[5] mp 261–262 °C; $[\alpha]^{20}_D$ +186.5° (*c* 0.7, MeOH)]. The IR and ^1H and ^{13}C NMR spectra of **8** were superimposable on those of an authentic sample.

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