121. A Convenient Procedure for the Synthesis of 2,3,4,6-Tetra-*O*-benzyl-D-gluconolactam and D-Nojirilactam

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Swern oxidation of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**1**) followed by ammonolysis gave the crystalline amide **3** which was oxidized (DMSO/pyridine · SO_3) to yield the oxo-amide **4** and the hydroxy-lactams **5** and **6**. Cyclization of **4** to the very slowly equilibrating **5** and **6** was completed by treatment with AcOH in $CHCl_3$. The configuration of the hydroxy-lactams was assigned on the basis of NOEs. Reduction ($Et_3SiH/BF_3 \cdot Et_2O$) of the hydroxy-lactams either individually or as a mixture led to 2,3,4,6-tetra-*O*-benzyl-D-gluconolactam (**7**). The procedure, based upon modifications of a patent, does not require chromatography; the overall yield of **7** from **1** is 43%. Hydrogenolysis of **7** gave D-nojirilactam (**8**); benzylation led to the known pentabenzyl-D-nojirilactam (**9**) and to the unsaturated lactam **10**.

For the preparation of new inhibitors of β-glucosidases, we required a facile access to large amounts of 2,3,4,6-tetra-*O*-benzyl-D-gluconolactam (**7**; *O*-benzylated nojirilactam). Its synthesis from **2** *via* **3**–**5** according to the *Scheme* has been described in a Japanese patent [1]. Essentially the same route has been reported very recently by *Pandit et al.* [2]. The patent procedure specifies DMSO/Ac_2O for the oxidation of the amide **3**, and the same conditions were applied by *Pandit et al.* In our hands, this reaction was only half-complete after 24 h, and longer reaction times led to unidentified side-products. The reduction of the hydroxy-lactam **5** by $NaBH_4$ in the presence of $BF_3 \cdot Et_2O$, as described by the chemists of *Nippon Shinyaku* [1], gave a mixture of **7** and the corresponding L-*ido*-isomer in a ratio of *ca.* 6:1, while *Pandit et al.* obtained **7** through treatment of the oxo-amide **4** with HCO_2H and diastereoselective reduction with $NaCNBH_3$.

Considering the potential of **7** as an intermediate, we report complete experimental details for its synthesis, involving an advantageous method for the oxidation of **3**, a high-yielding and fully diastereoselective alternative for the reduction of **5**, **6**, and mixtures of both to **7**, the hydrogenolysis of **7** to **8** [3], and the *N*-benzylation of **7** to yield **9** [4] and **10**.

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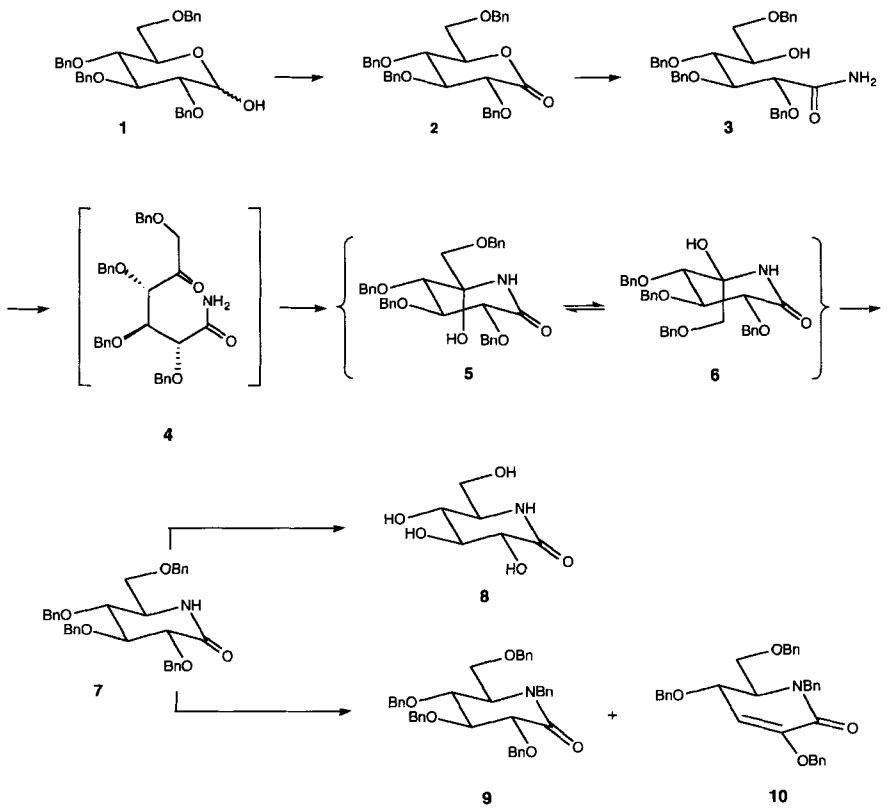
Scheme



The oxidation of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**1**) [5] to the lactone **2** by a number of methods is well known [6] [7]. We found the *Swern* procedure [8] to be the most convenient one on a 70-g scale. The lactone **2** is quite labile, and as much as half of it can be lost by silica gel chromatography. The crude lactone was, however, sufficiently pure. It was treated with NH_3 in dry Et_2O [1] under reflux (–33°) to yield the readily crystallizing amide **3**. Overall yields between 70 and 81% were realized for the oxidation and the ammonolysis. *Pandit et al.* [2] indicate a yield of 86% for the ammonolysis of **2**, without specifying the scale of the reaction.

Good results for the oxidation of **3** on a large scale were realized with DMSO in the presence of Et_3N and pyridine · SO_3 complex [10]. The oxo-amide **4** [1] [2] was observed by TLC. It cyclizes readily and was not obtained pure. Cyclization is catalyzed by AcOH in $CHCl_3$ [1]. Under these conditions, the process of cyclization is completed within three to four days, leading to **5** and **6** in a ratio ranging from 66:33 to 75:25. Equilibration of **5** and **6** proceeds slowly. Thus, under the conditions of the cyclization, **5** is transformed into a 84:16 mixture of **5** and **6** within two months, while **6** leads to a 72:28 mixture of the two epimers within the same time. Equilibration was interrupted at this stage due to the appearance of side products.

Treatment of **5** with Et_3SiH and $BF_3 \cdot Et_2O$ [11] [12] in $MeCN/CH_2Cl_2$ at 0° led to the rapid formation of **7**, which was isolated in 98% yield. Similarly, **6** led to the same product in the same yield, reflecting the strong stereoelectronic control [13]. Deoxygenation of a crude 2:1 mixture of **5** and **6** on a 43-g scale gave crystalline **7** (71%). The overall yield of **7** from 70.4 g of **1** was 43%. The lactam **7** was identified on the basis of its physical [1] [2] and spectral data. Hydrogenolysis of **7** [14] gave D-nojirilactam (**8**, 46%, after crystallization). *N*-Benzylation of **7** led to pentabenzyl-D-nojirilactam (**9**, 41%) [4] and to the unsaturated lactam **10** (44%), illustrating a facile β-elimination under these conditions (BnCl, DMSO, KOH) [4].

The optical rotation and the ^{1}H-NMR data of **2** match the reported ones [6] [16]. The ^{1}H-NMR data of **3** agree with those reported by *Dax et al.* [9], except that we find $J(3,4)$ = 5.5 rather than 7.2 Hz.

Correct elemental analyses were obtained for **5** and **6**. The melting point and the optical rotation of **5** are slightly lower than those reported [1]. The IR spectrum of **5** shows OH, NH, and carbonyl bands at 3560, 3380, and 1695 cm^{-1}, respectively. A comparison of the ^{13}C-NMR spectrum of **5** with the one of **3** shows an additional *s* at 81.87 ppm with concomitant loss of a *d*. The spectral data of **6** parallel those of **5**. The *d* at 3.76 ppm of **6** ((D_6)DMSO) is assigned to H–C(5); it shows a NOE of 4.5% upon irradiation at 6.09 ppm (HO–C(6)). A NOE of 2.6% is observed for the H–C(4) *t* at 4.12 ppm of **5** ((D_6)DMSO) upon irradiation at 5.73 ppm (HO–C(6)). These effects evidence the D-*gluco*-configuration of **5** and the L-*ido*-configuration of **6**.

The melting point and the optical rotation of **7** were almost identical to the reported values [1] [2]. The IR spectrum is characterized by an NH band at 3205 and a carbonyl band at 1685 cm^{-1} corresponding to a broad NH *s* at 5.91 ppm in the ^{1}H-NMR spectrum, and a carbonyl *s* at 170.50 ppm in the ^{13}C-NMR spectrum. CI-MS (C_4H_{10}) shows the $[M + H]^+$ base peak at *m/z* 539. The ^{13}C-NMR data of **8** match the reported values [14], as do the melting point and the optical rotation [2] [3] [14]. The ^{1}H-NMR spectrum ($CDCl_3$) of **9** shows strongly overlapping signals, and is in keeping with the reported data [4]. Complete resolution was observed when using C_6D_6 as solvent. The two *d* at 4.06 and 5.36 ppm (J =14.9 Hz) and the absence of the NH *s* evidence the *N*-benzylation. The ^{13}C-NMR spectrum shows a *t* at 77.07 rather than at 60.3 ppm [4]. We also observed a *d* at 74.50 ppm rather than a *t* [4]. All other ^{13}C-NMR resonances match the reported values. The same is true for the MS and the optical rotation. The IR spectrum of **10** shows an olefin band at 1670 cm^{-1} and a carbonyl band at 1635 cm^{-1}, in keeping with an α,β-unsaturated carbonyl function. The MS and the elemental analysis of **10** agree with the structure given in the *Scheme*. Accordingly, the ^{1}H-NMR spectrum shows signals of four $PhCH_2$ groups, but none for H–C(3), and a signal for H–C(4) which is shifted downfield, as compared to **9**. The ^{13}C-NMR spectrum confirms the presence of four $PhCH_2$ groups, and shows two olefinic signals at 149.16 and 101.76 ppm for C(3) and C(4), respectively.

Experimental Part

General. Solvents, except for DMSO, were distilled before use. DMSO was obtained from freshly opened bottles and stored over 4-Å molecular sieves. Reactions were run under Ar. TLC: *Merck* silica gel *60* F_{254} plates; detection by heating with 1:1 I_2 soln./20% H_2SO_4 (I_2 soln.: 10 g of I_2, 100 g of KI, 1000 ml H_2O) or with mostain [15]. Flash chromatography (FC): silica gel (*Merck 60*; 0.040–0.063 mm). M.p.: uncorrected. Except where specifically noted, ^{1}H-NMR spectra were recorded at 300 MHz, and ^{13}C-NMR spectra at 50 MHz. Chemical shifts δ in ppm and coupling constants J in Hz.

*2,3,4,6-Tetra-*O*-benzyl-*D*-gluconolactone* (**2**). Freshly distilled oxalyl chloride (25.0 ml, 291 mmol) in dry CH_2Cl_2 (1.10 l) was treated at –60° with dry DMSO (44.4 ml, 625 mmol) in CH_2Cl_2 (800 ml; *ca.* 30 min), and then with a soln. of *2,3,4,6-tetra-*O*-benzyl-*D*-glucopyranose* (**1**; 70.4 g, 130.3 mmol) in CH_2Cl_2 (700 ml) and DMSO (10 ml), keeping the temp. below –50° (*ca.* 90 min). The mixture was warmed to –40° within 15 min, to –10° within 20 min, stirred for 10 min at –10°, and cooled to –60°. Et_3N (109 ml, 780 mmol) was added over 10 min. The mixture was warmed to r. t. (1 h), and washed with H_2O (2 × 1 l) and brine (1 l). The org. layer was dried ($MgSO_4$), and evaporated. The residue (76.4 g) was used for the next step. A small portion of **2**, resulting from a parallel experiment, was purified by FC (hexane/Et_2O 2:1). Clear oil. R_f (hexane/Et_2O 1:1) 0.54. $[\alpha]_D^{25}$ = +76.7 (*c* = 1.35, $CHCl_3$; [6]: $[\alpha]_D^{20}$ = +79.9 ($CHCl_3$), [16]: $[\alpha]_D$ = +73.2 ($CHCl_3$)). IR ($CHCl_3$): 3090*w*, 3070*w*, 3035*w*, 3000*w*, 2920*m*, 2875*m*, 1755*s*, 1495*w*, 1450*m*, 1360*m*, 1160*m* (sh), 1120*s* (sh), 1100*s*, 1070*s*, 1030*m*, 1000*m* (sh), 915*w*, 865*w*, 690*m*, 665*w* (sh). ^{1}H-NMR ($CDCl_3$, 400 MHz): 3.68 (*dd*, *J* = 11.0, 3.3, H–C(6)); 3.74 (*dd*, *J* = 11.0, 2.4, H'–C(6)); 3.92 (*t*, *J* = 6.4, H–C(3)); 3.97 (*t*, *J* = 6.8, H–C(4)); 4.13 (*d*, *J* = 6.5, H–C(2)); 4.45 (br. *dt*, *J* ≈ 8.2, 2.7, H–C(5)); 4.49 (*d*, *J* = 11.9), 4.58 (*d*, *J* = 11.9, PhCH_2); 4.53 (*d*, *J* = 11.3), 4.61 (*d*, *J* = 11.3, PhCH_2); 4.72 (*d*, *J* = 11.1), 4.74 (*d*, *J* = 11.1, PhCH_2); 4.65 (*d*, *J* = 11.4), 5.16 (*d*, *J* = 11.4, PhCH_2); 7.18–7.21 (*m*, 2 arom. H); 7.25–7.41 (*m*, 18 arom. H). CI-MS (NH_3): 558 (6), 557 (29), 556 (100, $[M + NH_4]^+$), 539 (9, $[M + H]^+$).

*2,3,4,6-Tetra-*O*-benzyl-*D*-gluconamide* (**3**). A soln. of **2** (76.4 g, crude) in dry Et_2O (1.5 l) was added within 20 min to condensed ammonia (100 ml) at –60°. The cooling bath was removed, the reaction flask fitted with a cold finger cooling trap, and the soln. kept at reflux for 45 min. After removal of the cooling trap, NH_3 and Et_2O were evaporated. The residue was treated with Et_2O (800 ml), and the supernatant was cooled to 5°, leading to a yellowish precipitate. Filtration and recrystallization at 5° gave white **3** (39.4 g). Evaporation and filtration through silica gel (hexane/Et_2O 1:8) of the combined mother liquors afforded an additional crop of **3** (11.1 g) as a colorless oil. Total yield: 70% from **1**. M.p. 89–90°. R_f (hexane/AcOEt 2:3) 0.16. $[\alpha]_D^{21}$ = +24.5 (*c* = 0.79, $CHCl_3$; [9]: $[\alpha]_D^{20}$ = +18.7 ($CHCl_3$)). IR (KBr): 3560*s*, 3390*s*, 3200*m*, 3060*w*, 3030*w*, 2920*w* (sh), 2880*w* (sh), 2830*w*, 1640*s* (sh), 1560*w*, 1540*w*, 1500*m*, 1475*w*, 1450*m* (sh), 1410*w*, 1400*w*, 1390*w*, 1360*m*, 1340*w*, 1320*w*, 1280*m*, 1270*w*, 1250*w*, 1210*m* (sh), 1180*w*, 1120*s* (sh), 1100*m*, 1070*m* (sh), 1050*s*, 1030*m*, 1000*m*, 940*w*, 900*w* (sh), 850*w*, 780*w*, 750*m*, 730*s*, 700*s*, 650*w*, 620*w* (sh), 610*w*. CI-MS (NH_3): 557 (8), 556 (23, $[M + H]^+$), 450 (7), 449 (23), 448 (100, $[M - BnOH + H]^+$). Anal. calc. for $C_{34}H_{37}NO_6$ (555.67): C 73.49, H 6.71, N 2.52; found: C 73.57, H 6.54, N 2.54.

*(3*R*,4*S*,5*S*,6*S*)-6-Hydroxy-3,4,5-tris(benzyloxy)-6-[(benzyloxy)methyl]piperidin-2-one* (**5**) *and (3*R*,4*S*,5*S*,6*R*)-6-Hydroxy-3,4,5-tris(benzyloxy)-6-[(benzyloxy)methyl]piperidin-2-one* (**6**). *a*) A stirred soln. of **3** (684.3 mg, 1.23 mmol) and Et_3N (1.37 ml, 9.83 mmol) in DMSO (6 ml) was treated with a soln. of pyridine · SO_3 (1.176 g, 7.39 mmol) in DMSO (6 ml; kept for 15 min at r. t.) at ≤ 25° for 4 h. The soln. was poured into C_6H_6/H_2O 20:3 (230 ml). Separation of the org. layer, extraction of the aq. layer with C_6H_6, drying ($MgSO_4$) of the combined org. layers, filtration, and evaporation gave a thick oil which was dried *i. v.* for 3 h. The stirred soln. of the residue in $CHCl_3$ (6.8 ml) was treated with AcOH (0.34 ml, 5.9 mmol) for 3 d at r. t. Sat. aq. $NaHCO_3$ soln. (2 ml) was added, followed by $CHCl_3$ (5 ml). The org. layer was separated and dried ($MgSO_4$). Filtration, evaporation, and FC (hexane/AcOEt 3:2) gave **5** (345 mg, 51%) and **6** (191 mg, 28%). Compound **5** was crystallized from Et_2O/hexane.

b) Similarly, a soln. of pyridine · SO_3 (80.0 g, 502 mmol) in DMSO (350 ml) was added dropwise within 45 min to a soln. of **3** (47.0 g, 84.6 mmol) and Et_3N (95.0 ml, 682 mmol) in DMSO (350 ml). Toluene was used for the extraction. The crude 2:1 mixture (^{1}H-NMR) of **5/6** (44.0 g) was used for the next step.

Data of **5**: M.p. 103–104.5° ([1]: 108.5–109°). R_f (hexane/AcOEt 1:1) 0.20. $[\alpha]_D^{25}$ = +74.2 (*c* = 1.03, EtOH; [1]: $[\alpha]_D^{24}$ = +75.6 (EtOH)). IR ($CHCl_3$): 3560*w*, 3520*w*, 3380*w*, 3100*w*, 3080*w*, 3040*w*, 3010*w*, 2950*m*, 2875*m*, 1695*s*, 1610*w*, 1570*w*, 1500*w*, 1455*m*, 1360*m*, 1330*m*, 1290*w*, 1230*m* (sh), 1180*s*, 1100*s* (sh), 1070*s*, 1030*m*, 915*w*, 865*w*, 695*m*. ^{1}H-NMR ($CDCl_3$): 3.20 (*d*, *J* = 9.5), 3.28 (*d*, *J* = 9.5, CH_2–C(6)); 3.30 (*s*, OH); 3.69 (*d*, *J* =

9.5, H–C(5)); 3.96 (*d*, *J* = 8.5, H–C(3)); 4.17 (*dd*, *J* = 9.4, 8.4, H–C(4)); 4.38–4.45 (*m*, PhC*H*$_2$); 4.70 (*d*, *J* = 10.9), 4.82 (*d*, *J* = 10.9, PhC*H*$_2$); 4.73 (*d*, *J* = 11.1), 4.85 (*d*, *J* = 11.1, PhC*H*$_2$); 4.49 (*d*, *J* = 11.1), 5.12 (*d*, *J* = 11.1, PhC*H*$_2$); 6.41 (*s*, NH); 7.18–7.45 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$): 72.56 (*t*); 73.55 (*t*); 74.68 (*t*); 75.17 (*t*); 75.33 (*t*); 77.31 (*d*); 79.38 (*d*, 2 C); 81.87 (*s*); 127.70–128.53 (several *d*); 136.95 (*s*); 137.27 (*s*); 137.77 (*s*); 138.15 (*s*); 171.29 (*s*). CI-MS (NH_3): 571 (5, [*M* + NH_4]$^+$), 554 (33, [*M* + H]$^+$), 537 (14), 536 (39), 486 (5), 446 (9), 430 (9), 428 (100), 420 (9), 338 (7), 320 (7), 265 (14), 262 (30), 230 (21), 108 (26). Anal. calc. for $C_{34}H_{35}NO_6$ (553.65): C 73.76, H 6.37, N 2.53; found: C 73.79, H 6.52, N 2.55.

Data of **6**: Oil. R_f (hexane/AcOEt 1:1) 0.08. $[\alpha]_D^{25}$ = +8.1 (*c* = 0.54, EtOH; [1]: $[\alpha]_D^{24}$ = +13.8 (EtOH)). IR ($CHCl_3$): 3550*m*, 3400*m*, 3380*m* (sh), 3080*w*, 3060*w*, 3030*w*, 3005*m*, 2920*m*, 2870*m*, 2000*w*, 1950*w*, 1870*w*, 1810*w*, 1690*s*, 1610*w*, 1590*w*, 1540*w*, 1500*m*, 1455*s*, 1400*m* (sh), 1355*m*, 1315*m*, 1255*w*, 1160*m* (sh), 1100*s*, 1075*s* (sh), 1030*m*, 1010*m*, 965*w*, 910*m*, 860*w*, 820*w*, 700*s*. ^{1}H-NMR ($CDCl_3$): 3.51 (*d*, *J* = 9.2), 3.63 (*d*, *J* = 9.2, CH_2–C(6)); 3.71 (*s*, OH); 4.16 (*d*, *J* = 4.2, H–C(5)); 3.90 (*dd*, *J* = 7.1, 4.1, H–C(4)); 4.34 (*d*, *J* = 6.7, H–C(3)); 4.39 (*d*, *J* = 11.6), 4.62 (*d*, *J* = 11.6, PhC*H*$_2$); 4.55 (*d*, *J* = 11.5), 4.73 (*d*, *J* = 11.5, PhC*H*$_2$); 4.55 (*s*, PhC*H*$_2$); 4.72 (*d*, *J* = 11.3), 5.12 (*d*, *J* = 11.3, PhC*H*$_2$); 6.40 (*s*, NH); 7.12–7.44 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$): 72.65 (*t*); 73.01 (*t*); 73.59 (*t*, 2 C); 74.11 (*t*); 78.50 (*d*); 79.76 (*d*); 80.54 (*d*); 83.41 (*s*); 127.38–128.48 (several *d*); 137.07 (*s*); 137.38 (*s*); 137.80 (*s*); 137.92 (*s*); 170.94 (*s*). CI-MS (NH_3): 571 (5, [*M* + NH_4]$^+$), 555 (17), 554 (48, [*M* + H]$^+$), 537 (13), 536 (38), 446 (14), 430 (6), 429 (28), 428 (100), 355 (7), 338 (10), 320 (7), 265 (12), 248 (6), 230 (26), 198 (12), 140 (7), 108 (36), 91 (8). Anal. calc. for $C_{34}H_{35}NO_6$ (553.65): C 73.76, H 6.37, N 2.53; found: C 73.46, H 6.41, N 2.50.

*(3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-6-[(benzyloxy)methyl]piperidin-2-one* (**7**). a) *From Crude* **5**/**6**: $BF_3 \cdot Et_2O$ (49.5 ml, 394 mmol) was added at 0° to a soln. of Et_3SiH (62.8 ml, 394 mmol) in 1.5 l of dry MeCN. Stirring was continued for 5 min. A soln. of a crude 2:1 mixture **5**/**6** (43.57 g, 78.69 mmol) in cooled CH_2Cl_2 (1.5 l) was added over a period of 1.3 h, while the temp. was kept below 3°. The mixture was stirred for 10 min, quenched by addn. of 300 ml sat. aq. $NaHCO_3$ soln., diluted with. CH_2Cl_2 (500 ml), and extracted. The aq. phase was further extracted with 500 ml of CH_2Cl_2. The combined org. phases were dried ($MgSO_4$), filtered, and taken to dryness. The solid residue was recrystallized in boiling MeOH to yield colorless needles (29.0 g; m.p. 103–104.5°). A second less pure crop was obtained from the mother liquor (1.2 g, m.p. 102–104°). Recrystallization led to a sample with only slightly higher m.p. Total yield: 30.2 g (71%).

b) *From Pure* **5**: Similarly, a pure sample of **5** (136.2 mg, 0.246 mmol) gave 130.0 mg **7** (98%).

c) *From Pure* **6**: Similarly, a pure sample of **6** (61.9 mg, 0.112 mmol) gave 59.0 mg **7** (98%). Mixed m.p. of the samples obtained according to *b* and *c* was undepressed.

Data of **7**: M.p. 104.2–104.6° ([1]: 100.5–102°; [2]: 100–102°). R_f (hexane/Et_2O 1: 3) 0.36. $[\alpha]_D^{25}$ = +102.8 (*c* = 0.67, $CHCl_3$; [2]: $[\alpha]_D$ = +105.5 ($CHCl_3$)). IR (KBr): 3205*m*, 3120*w*, 3060*w*, 3020*w*, 2940*w*, 2905*w*, 2870*w*, 1685*s*, 1560*w*, 1540*w*, 1500*w*, 1455*m*, 1410*w*, 1385*w*, 1365*w*, 1350*w*, 1320*m*, 1280*w*, 1260*w*, 1235*w*, 1210*w*, 1175*w*, 1130*m*, 1105*m*, 1070*m*, 1030*w*, 1015*w*, 990*w*, 940*w*, 910*w*, 805*w*. ^{1}H-NMR (400 MHz, $CDCl_3$) 3.26 (*td*, *J* = 8.1, 1.5, H–C(5)); 3.50–3.62 (*m*, 3 H, H–C(6), CH_2–C(6)); 3.91 (*t*, *J* = 8.1, H–C(4)); 4.00 (*d*, *J* = 8.0, H–C(3)); 4.42 (*d*, *J* = 12.0), 4.49 (*d*, *J* = 12.0, PhC*H*$_2$); 4.77 (*d*, *J* = 11.2), 4.84 (*d*, *J* = 11.2, PhC*H*$_2$); 4.73 (*d*, *J* = 11.1), 4.86 (*d*, *J* = 11.1, PhC*H*$_2$); 4.49 (*d*, *J* = 11.2), 5.18 (*d*, *J* = 11.2, PhC*H*$_2$); 5.91 (*s*, NH); 7.18–7.20 (*m*, 2 arom. H); 7.27–7.43 (*m*, 18 arom. H). ^{13}C-NMR ($CDCl_3$): 53.79 (*d*); 69.79 (*t*); 73.23 (*t*); 74.46 (*t*, 2 C); 74.57 (*t*); 77.00 (*d*); 78.72 (*d*); 82.24 (*d*); 127.66–128.42 (several *d*); 137.25 (*s*); 137.54 (*s*); 137.78 (*s*); 137.97 (*s*); 170.50 (*s*). CI-MS (C_4H_{10}); 541 (7), 540 (37), 539 (100, [*M* + H]$^+$), 181 (12), 140 (7), 91 (35). Anal. calc. for $C_{34}H_{35}NO_5$ (537.66): C 75.95, H 6.56, N 2.61; found: C 75.71, H 6.73, N 2.71.

*(3*R*,4*S*,5*R*,6*R*)-3,4,5-Trihydroxy-6-(hydroxymethyl)piperidin-2-one* (**8**; D-*Nojirilactam*). Pd-black (*ca.* 150 mg) was suspended in degassed EtOH (70 ml), and treated with H_2 (5 bar) for 5 h. Then, **7** (1.0 g, 1.86 mmol) was added and hydrogenated at 5 bar for 40 h. Filtration of the mixture, washing with MeOH (10 ml), and evaporation gave only traces of **8**. Washing the mixture with H_2O, however, afforded, after evaporation, 310 mg of crude **8** as a crystalline solid which was recrystallized from H_2O/EtOH to yield 150 mg of **8** (46%). M.p. 206–207° (dec.; [3]: 203–205° (dec.); [2]: 197–199°; [14]: 204–205°). R_f (AcOEt/MeOH/H_2O 7:2:1) 0.14. $[\alpha]_D^{22}$ = +64.2 (*c* = 1.09, H_2O; [3]: $[\alpha]_D^{22}$ = +63 (H_2O); [2]: $[\alpha]_D$ = +63; [14]: $[\alpha]_D^{20}$ = 57 (*c* = 0.63, H_2O)). IR (KBr): 3420*s* (br.), 3360*s* (br.), 3250*s* (br.), 3180*s* (br.), 3040*w* (sh), 2940*w*, 2880*w*, 1660*s*, 1645*s*, 1560*w*, 1540*w*, 1490*m*, 1470*m*, 1450*m*, 1410*m*, 1385*s*, 1350*s*, 1335*m*, 1320*s*, 1290*w*, 1260*m*, 1240*w*, 1210*w*, 1160*s*, 1130*s*, 1080*s*, 1070*s*, 1050*s*, 1035*s*, 990*m*, 950*m*, 885*m*, 860*m*, 710*m*, 680*w*. ^{1}H-NMR ((D$_6$)DMSO): 2.98–3.02 (*m*, H–C(6)); 3.33–3.44 (*m*, H–C(4), H–C(5), CH–C(6)); 3.52 (*dd*, *J* = 9.1, 4.2, H–C(3)); 3.57 (*ddd*, *J* = 11.1, 5.5, 2.8, CH–C(6)); 4.68 (*t*, *J* = 5.7, OH); 5.01 (*d*, *J* = 4.3, OH); 5.13 (*d*, *J* = 4.8, OH); 5.18 (*d*, *J* = 4.1, HO–C(3)); 7.20 (*s*,

NH). CI-MS (NH_3): 196 (8), 195 (100, $[M + NH_4]^+$), 178 (25, $[M + H]^+$). Anal. calc. for $C_6H_{11}NO_5$ (177.15): C 40.68, H 6.26, N 7.91; found: C 40.81, H 6.10, N 7.64.

(3R,4S,5R,6R)-N-Benzyl-3,4,5-tris(benzyloxy)-6-[(benzyloxy)methyl]piperidin-2-one (**9**; *Pentabenzyl-D-nojirilactam) and (5R,6R)-N-Benzyl-3,5-bis(benzyloxy)-6-[(benzyloxy)methyl]-1,2,5,6-tetrahydropyridin-2-one* (**10**). The lactam **7** (105.0 mg, 0.195 mmol) was added to a stirred suspension of freshly pulverized KOH (21.9 mg, 0.39 mmol) in dry DMSO (3.9 ml) at r. t., treated with BnCl (90 ml, 0.781 mmol) for 5 min, and poured into a mixture of sat. aq. $NaHCO_3$ soln. (2 ml) and Et_2O (20 ml). The org. layer was separated, and the aq. layer was extracted with Et_2O (2 × 10 ml) and AcOEt (10 ml). The combined org. layers were dried ($MgSO_4$), filtered and evaporated. FC of the residue yielded **9** (50.6 mg, 41%) and **10** (44.9 mg, 44%).

Data of **9**: Syrup. R_f (hexane/Et_2O 1:2) 0.63. $[\alpha]_D^{25}$ = +67.6 (*c* = 0.58, $CHCl_3$; [4]: $[\alpha]_D^{20}$ = +62.0 ($CHCl_3$)). IR (film): 3060*m*, 3030*m*, 2920*m*, 2860*m*, 1950*w*, 1875*w*, 1810*w*, 1725*w*, 1670*s*, 1605*w*, 1590*w*, 1500*m*, 1455*s*, 1390*w*, 1360*m*, 1350w (sh), 1310*w*, 1250*w*, 1210*m*, 1180*w*, 1095*s*, 1075*s* (sh), 1030*m*, 1005*w*, 910*w*, 845*w*, 820*w*, 740*s*, 700*s*. ^{1}H-NMR (400 MHz, C_6D_6): 3.17 (*dd*, *J* = 9.9, 4.3, CH–C(6)); 3.28 (*dd*, *J* = 9.9, 5.4, CH–C(6)); 3.48–3.52 (*m*, H–C(6)); 3.87 (*dd*, *J* = 9.9, 5.4, H–C(5)); 3.98 (*dd*, *J* = 8.3, 5.4, H–C(4)); 4.04 (*d*, *J* ≈ 14.9), 5.36 (*d*, *J* = 14.9, PhCH_2); 4.06 (*s*, PhCH_2)); 4.26 (*d*, *J* = 8.3, H–C(3)); 4.15 (*d*, *J* = 11.9), 4.34 (*d*, *J* = 11.9, PhCH_2)); 4.52 (*d*, *J* = 11.5), 4.78 (*d*, *J* = 11.5, PhCH_2)); 4.83 (*d*, *J* = 11.4), 5.50 (*d*, *J* = 11.4, PhCH_2)); 7.01–7.18 (*m*, 19 arom. H); 7.24–7.27 (*m*, 4 arom. H); 7.54 (*d*, *J* = 7.0, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 48.13 (*t*); 58.90 (*d*); 67.64 (*t*); 72.39 (*t*); 73.18 (*t*); 74.00 (*t*); 74.50 (*t*); 77.07 (*d*); 78.48 (*d*); 81.94 (*d*); 127.39–128.52 (several *d*); 136.69 (*s*); 137.43 (*s*); 137.68 (*s*); 138.17 (*s*, 2 C); 169.93 (*s*). CI-MS (NH_3): 630 (9), 629 (42), 628 (100, $[M + H]^+$), 538 (6), 102 (9). Anal. calc. for $C_{41}H_{41}NO_5$ (627.78): C 78.44, H 6.58, N 2.23; found: C 78.37, H 6.55, N 2.08.

Data of **10**: Syrup. R_f (hexane/Et_2O 1:2) 0.37. $[\alpha]_D^{25}$ = +62.4 (*c* = 2.30, $CHCl_3$). IR ($CHCl_3$): 3060*w*, 3000*w*, 2920*w*, 2860*w*, 2110*w*, 1900*w*, 1750*w*, 1670*m*, 1635*s*, 1610*w* (sh), 1530*w*, 1500*w*, 1470*w*, 1455*m*, 1360*w*, 1320*w*, 1310*w*, 1255*m*, 1235*m*, 1200*w*, 1180*w*, 1085*m*, 1055*m*, 1030*m*, 985*w*, 905*w*, 815*w*, 695*m*. ^{1}H-NMR ($CDCl_3$): 3.33 (*t*, *J* ≈ 8.9, CH–C(6)); 3.43 (*dd*, *J* = 9.6, 5.1, CH–C(6)); 3.79 (*ddt*, *J* = 8.7, 5.7, 1.2, H–C(6)); 4.08 (*d*, *J* = 15.0), 5.33 (*d*, *J* = 15.0, PhCH_2N); 4.11 (*dd*, *J* = 6.8, 1.4, H–C(5)); 4.19 (*s*, PhCH_2); 4.35 (*d*, *J* = 12.0), 4.41 (*d*, *J* = 12.0, PhCH_2); 4.86 (*d*, *J* = 12.2), 4.92 (*d*, *J* = 12.2, PhCH_2); 5.34 (*dd*, *J* = 6.8, 1.1, H–C(4)); 7.10–7.44 (*m*, 20 arom. H). ^{13}C-NMR ($CDCl_3$): 48.73 (*t*); 57.47 (*d*); 68.43 (*t*); 68.91 (*d*); 69.26 (*t*); 69.98 (*t*); 73.19 (*t*); 101.76 (*d*); 127.24–128.4 (several *d*); 135.75 (*s*); 136.75 (*s*); 137.43 (*s*); 137.79 (*s*); 149.16 (*s*); 159.42 (*s*). CI-MS (NH_3): 537 (7, $[M + NH_4]^+$), 521 (33), 520 (89, $[M + H]^+$), 447 (6), 445 (6), 430 (13), 414 (6), 413 (10), 412 (33, $[M - BnOH + H]^+$), 380 (17), 339 (19), 322 (100), 292 (14). Anal. calc. for $C_{34}H_{33}NO_4$ (519.64): C 78.59, H 6.40, N 2.70; found C 78.32, H 6.67, N 2.45.

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