An Easy Route to 2-Amino-β-*C*-Glycosides by Conjugate Addition to 2-Nitroglycals

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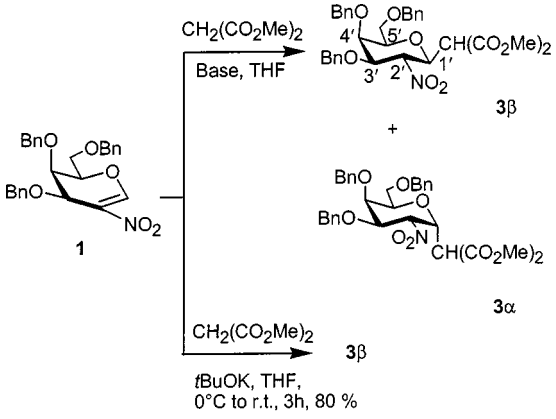
Keywords: Glycosides / Cyclization / Michael addition / Nitroglycals / Nitro group

2-Nitroglycals were found to undergo conjugate addition with a variety of stabilized soft carbanions. The Michael adducts from galactal derivatives were converted into bicyclic lactams.

Introduction

The synthesis of *C*-glycosides, which in general have conformations similar to those of the parent *O*-glycosides,[1,2] has gained wide attention owing to their biological significance[3] and their synthetic utility,[4] mainly because of their stability towards enzymes, acids or bases. 2-Amino sugars such as *N*-acetylglucosamine (GlcNAc) and *N*-acetylgalactosamine (GalNAc) are major components of a number of important compounds and are attractive targets for the design of *C*-linked mimetics.[5,6] *C*-Glycosyl derivatives of 2-amino sugars have been regarded as among the most difficult to prepare by common *C*-glycosylation strategies,[7–13] due to the incompatibility of neighbouring nitrogen-based functional groups (i.e., amides, carbamates and azides). Therefore, not many methods for the synthesis of α-linked 2-amino-*C*-glycosides are reported in the literature,[14–24] while methods for the synthesis of β-linked 2-amino-*C*-glycosides[25–34] are also limited. It is thus desirable to introduce new and stereoselective approaches for the synthesis of 2-amino-2-deoxy-*C*-glycosides.

Recently, Michael-type addition to 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal (**1**) (Scheme 1) was shown to be a convenient method for the synthesis of α- and β-*O*-glycosides[35] and β-nucleosides[36] of glactosamine, and this methodology was also extended to the synthesis of α-GalNAc-Ser and -Thr building blocks[37] for glycopeptide synthesis. Here we now report the synthesis of 2-deoxy-2-nitro-β-*C*-glycosides by Michael addition of carbon nucleophiles to 3,4,6-tri-*O*-benzyl-2-nitro-D-glycals **1** and **2**.



Scheme 1. Addition of dimethyl malonate to 2-nitrogalactal **1**

Results and Discussion

Initial experiments were carried out with 3,4,6-tri-*O*-benzyl-2-nitro-D-galactal (**1**) and dimethyl malonate in the presence of different bases such as NaH, DBU, *t*BuOK, $NaOCH_3$, KHMDS and NaHMDS, to afford **3α** and **3β** (Scheme 1, Table 1). Of the bases used, the best was found to be *t*BuOK, in terms both of yield and of anomeric selectivity. Investigations with various solvents, such as CH_3CN, CH_2Cl_2, DMF and THF, showed the best results for THF, and we therefore pursued further studies with *t*BuOK in THF as solvent. Thus, addition of dimethyl malonate to galactal derivative **1** gave only the β-*C*-glycoside **3β**, in 80% yield. In its ^1H NMR spectrum, the anomeric hydrogen signal appeared at δ = 4.4 as a dd with $J_{1',2}$ = 4.6 Hz and $J_{1',2'}$ = 10.2 Hz. Similarly, the 2′-H signal appeared as an overlapping dd (like a triplet) at δ = 5.22 with = 10.2 Hz. This clearly indicated *trans* relationships between 1′-H and 2′-H and between 2′-H and 3′-H. For the α anomer, the 1′-H signal appeared at δ = 5.09 as a dd with $J_{1',2'}$ = 4.9 Hz,

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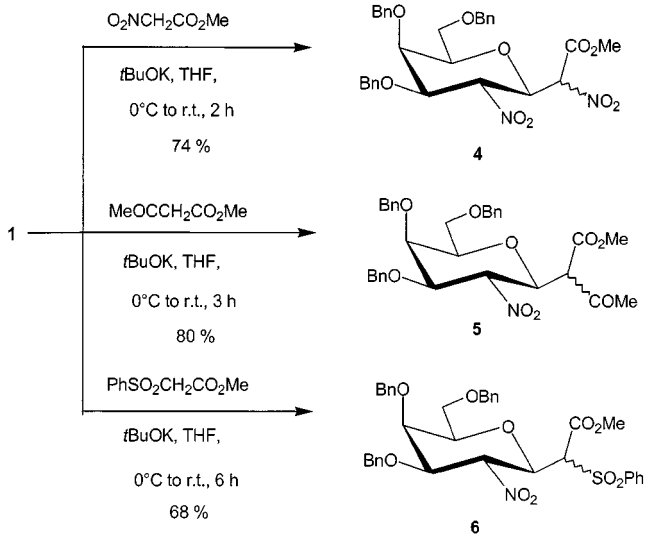
Table 1. Influence of the base on the addition of dimethyl malonate to **1**

Entry	Base	Time [h]	Temperature	Anomer (3α/3β)	Yield[a] (%)
1	NaH	1	0 °C	–	–
2	NaOMe	48	−40 °C to room temp.	1:2.8	48
3	NaHMDS	5	−40 °C to room temp.	1:1.4	52
4	*t*BuOK	3	0 °C to room temp.	β	80
5	KHMDS	3	−78 °C	1:15.2	81
6	DBU	3	0 °C to room temp.	β	62

[a] All reactions were carried out in THF.

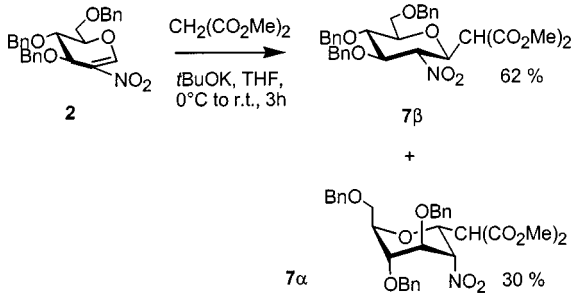
and the 2′-H signal appeared at δ = 5.27 with $J_{2',3'}$ = 8.0 Hz, thus indicating an axial-equatorial relationship between 1′-H and 2′-H and a $^4C_1$ conformation for **3α**.

The anions derived from methyl phenylsulfonylacetate, methyl acetoacetate and methyl nitroacetate also added across the conjugated nitro olefin **1** to yield only the β anomers **4**, **5** and **6** (Scheme 2), respectively, although a mixture of two diastereomers was, as would be expected, formed in each case. This was apparent in each case from the appearance of the 2′-H signal as two triplets in the ^{1}H NMR spectrum, in a ratio of approximately 35:65. Thus, for example, in compound **4**, the 2′-H signal appeared at δ = 5.07 and 5.37 with J = 11.5 Hz, while in compound **5** this proton signal appeared at δ = 4.94 and 5.19 with J = 10.4 Hz. In compound **6**, on the other hand, the 2′-H signal appeared at δ = 5.26 and 5.30 as two triplets with J = 9.3 Hz. In addition, the methoxy group signal also appeared as two singlets in each case.



Scheme 2. Addition of unsymmetrical CH-acidic compounds to 2-nitrogalactal **1**

Surprisingly, however, the 2-nitro-D-glucal derivative **2** gave a mixture of two anomers **7β** and **7α** (Scheme 3) in a 2:1 ratio when treated with dimethyl malonate in THF as solvent and in the presence of *t*BuOK as base. The structures of these glycosides were confirmed by ^{1}H NMR spectroscopic data (cf. Exp. Sect.). Compound **2** also yielded a mixture of α/β-*C*-glycosides with other bases. For the α anomer, the 1′-H signal appeared at δ = 4.99 as a dd with

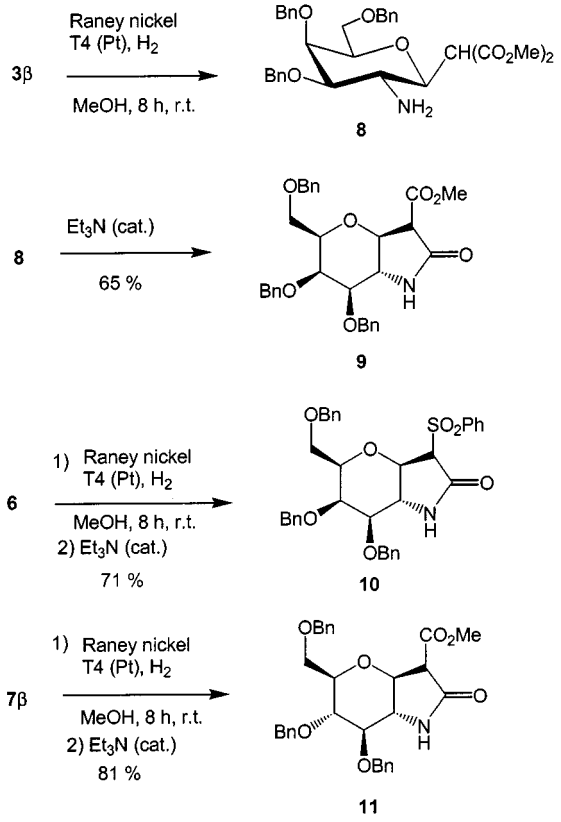


Scheme 3. Addition of dimethyl malonate to 2-nitroglucal **2**

$J_{1',2'}$ = 7.0 Hz, indicating an axial/equatorial arrangement for 1′-H and 2′-H, while the 2′-H signal appeared at δ = 5.18 with $J_{2',3'}$ = 4.9 Hz, indicating diequatorial arrangements for 2′-H and 3′-H as well as for all the other ring protons and thus supporting a preferential $^1C_4$ conformation for **7α**.[17,38] This structural assignment was also supported by NOE experiments, which indicated strong interaction between 1′-H/2′-H and 1′-H/6′-H but no interaction between 2′-H/3′-H, thus also ruling out formation of *manno*-configured products.

The presence of a nitro group at *C*-2′ has several advantages, especially since the *C*-glycosides formed are β at the anomeric centre. For example, radical-mediated[39] reduction of the nitro group could result in 2-deoxy-β-*C*-glycosides. Similarly, it might also be expected that use of the Nef[40] reaction should result in the formation of a carbonyl group at C-2′, which could be reduced to form either an axial or an equatorial hydroxy group, depending on the reaction conditions. This would provide flexibility in obtaining different β-*C*-glycosides. In this study, our efforts were concentrated on the formation of 2-amino-2-deoxy-*C*-glycosides.

In some cases (**3β**, **6** and **7β**) the nitro group was reduced with Raney nickel T4/H_2,[41] followed by treatment with Et_3N, resulting in immediate cyclization to the corresponding lactams **9**, **10** and **11** (Scheme 4), respectively, in good yields; amine **8** was only obtained as a crude intermediate. Formation of the lactam was also found to occur even without treatment with Et_3N, albeit in lower yields. Furthermore, if the reaction mixture was filtered to remove Raney nickel and the solvent was evaporated at higher temperature (ca. 55−60 °C), the amount of cyclized products increased. This indicated that the lactam formation was also dependent on the temperature. However, treatment with Et_3N gave

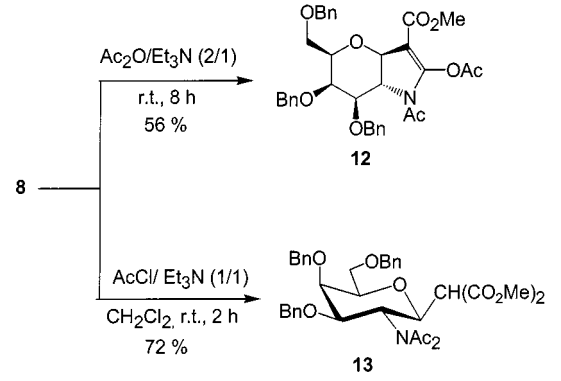


Scheme 4. Synthesis of bicyclic lactams **9**−**11**

the best yield of the cyclized products. The *trans* fusion of bicyclic lactams **9**−**11** could be deduced from the ^{1}H NMR spectroscopic data ($J_{2,3} \approx 9$ Hz). Surprisingly, treatment of **9** with strong base (for instance, DBU) resulted in decomposition rather than anomerisation to the *cis*-fused lactam.

Moreover, it was also found that ethyl esters invariably underwent transformation into the cyclized products more readily than the corresponding methyl esters did.

In an attempt to acetylate the amino compound **8** with acetic anhydride in the presence of Et_3N and DMAP (cat.), formation of the bicyclic compound **12** (Scheme 5) was observed. However, treatment of **8** with acetyl chloride in dichloromethane gave *N*,*N*-diacetylated product **13**, and no cyclized product was obtained under the reaction condition.



Scheme 5. Acetylation of 2-amino-2-deoxy-*C*-glucopyranoside **8**

Conclusion

CH-acidic compounds can readily be added to 2-nitroglycals. In the case of 2-nitrogalactal only the β-product could be obtained, and this was readily transformed into the corresponding galactosamine derivatives.

Experimental Section

General: Infrared spectra were recorded with Bruker FT/IR Vector 22 spectrometers. ^{1}H and ^{13}C NMR spectra were recorded withn a Jeol LA-400 NMR spectrometer in $CDCl_3$ solutions with tetramethylsilane as the internal standard. FAB mass spectra were obtained with a Jeol SX 102/DA-6000 spectrometer. Elemental analyses were carried out in a Coleman automatic CHN analyser. 2-Nitroglucal **1** and 2-nitrogalactal **2** were prepared according to literature procedures.[35]

Dimethyl (3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-β-D-galactopyranosyl)malonate (3β): *t*BuOK (112 mg, 1 mmol) was added at 0 °C to a stirred solution of 2-nitrogalactal **1** (461 mg, 1 mmol) and dimethyl malonate (132 mg, 1 mmol) in THF (4 mL). The reaction mixture was then brought to room temperature and stirred for 3 h. It was quenched with saturated NH_4Cl solution and extracted with ethyl acetate, washed with water and brine, and dried with Na_2SO_4. Evaporation of the solvent and purification by column chromatography yielded the pure compound. Yield 474 mg, 80%. R_f = 0.5 (hexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = +7 (*c* = 0.85, CH_2Cl_2). IR (CH_2Cl_2): $\tilde{\nu}$ = 1557, 1749 cm^{-1}. ^{1}H NMR: δ = 3.55 (br. d, *J* = 6.7 Hz, 2 H, 6-H, 6′-H), 3.62 (s, 3 H, −OCH_3), 3.64 (d, *J* = 4.7 Hz, 1 H, 2-H), 3.69 (s, 3 H, OCH_3), 3.7−3.74 (m, 1 H, 5′-H), 4.04 (d, *J* = 2.1 Hz, 1 H, 4′-H), 4.16 (dd, *J* = 10.2, 2.4 Hz, 1 H, 3′-H), 4.40 (dd, *J* = 10.0, 4.6 Hz, 1 H, 1′-H), 4.39−4.84 (m, 6 H, 3 × OCH_2Ph), 5.22 (t, *J* = 10.1 Hz, 1 H, 2′-H), 7.23−7.36 (m, 15 H). ^{13}C NMR: δ = 52.6, 52.8, 53.7, 67.8, 71.8, 72.4, 73.4, 74.6, 74.7, 77.3, 80.0, 85.5, 127.7−138 (18 C), 165.7, 166.3. MS (FAB): *m*/*z* (%) = 594 (50) [M$^+$ + 1], 593 (100) [M$^+$]. $C_{32}H_{35}NO_{10}$ (593.62): calcd. C 64.75, H 5.94, N 2.36; found C 64.80, H 6.12, N 2.15.

Dimethyl (3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-α-D-galactopyranosyl)-malonate (3α): The same procedure was applied as for compound **3β**, but NaOMe was used instead of *t*BuOK and the reaction took 48 h for completion. Under these reaction condition, two anomers (**3α** and **3β**) were formed and were separated by column chromatography. R_f = 0.6 (hexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = +38 (*c* = 1, CH_2Cl_2). IR (CH_2Cl_2): $\tilde{\nu}$ = 1557, 1749 cm^{-1}. ^{1}H NMR: δ = 3.55−3.62 (m, 2 H, 6′-H, 6′′-H), 3.65, 3.72 (2 s, 6 H, 2 × OCH_3), 3.78 (d, *J* = 11.2 Hz, 1 H, 2-H), 4.08−4.13 (m, 2 H, 5′-H, 4′-H), 4.34 (dd, *J* = 7.8, 2.4 Hz, 1 H, 3′-H), 4.4−4.82 (m, 6 H, 3 × OCH_2Ph), 5.09 (dd, *J* = 11.0, 4.9 Hz, 1 H, 1′-H), 5.27 (dd, *J* = 8.0, 4.9 Hz, 1 H, 2′-H), 7.24−7.37 (m, 15 H, aromatic). ^{13}C NMR: δ = 52.9, 53, 53.2, 67.1, 69.6, 72.3, 72.7, 73.4, 74.4, 75.1, 86.3, 95.7, 127.8−137.7(18 C), 166.1, 166.5. MS (FAB): *m*/*z* (%) = 594 (55) [M$^+$ + 1], 593 (100) [M$^+$]. $C_{32}H_{35}NO_{10}$ (593.62): calcd. C 64.75, H 5.94, N 2.36; found C 64.85, H 6.22, N 2.10. The same experimental procedure as for compound **3β** was applied, but methyl nitroacetate, methyl (phenylsulfonyl)acetate and methyl acetoacetate were employed instead of dimethyl malonate to obtain **4**, **5** and **6**, respectively.

Methyl 2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-β-*O*-galactopyranosyl)-2-nitroacetate (4): Yield 429 mg, 74%. R_f = 0.2 (hexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = +7.2 (*c* = 1.25, CH_2Cl_2). IR (CH_2Cl_2): $\tilde{\nu}$ =

1563, 1762 cm^{-1}. ^1H NMR: δ = 3.49−3.81 (m, 3 H, 5′-H, 6′-H, 6′′-H), 3.63, 3.75 (2 s, 3 H, OCH_3), 4.05 (dd, 11.5, 2.8 Hz, 1 H, 3′-H), 4.13, 4.17 (2 dd, *J* = 10.2, 2.8 Hz, 1 H, 4′-H), 4.39−4.85 (m, 7 H, 1′-H, 3 × OCH_2Ph), 5.07, 5.37 (2 t, *J* = 11.5 Hz, 1 H, 2′-H), 5.18 (2d, *J* = 6.0 Hz, 1 H, 2-H), 7.21−7.34 (m, 15 H, aromatic). ^{13}C NMR: δ = 53.6, 67.4, 71.5, 72.4, 73.6, 74.1, 74.7, 79.7, 83.8, 85.7, 87.6, 127.9−137.9 (18 C), 161.3. MS (FAB): *m*/*z* (%) = 581 (38) [M^+ + 1], 580 (100) [M^+]. $C_{30}H_{32}N_2O_{10}$ (580.58): calcd. C 62.06, H 5.56, N 4.83; found C 61.91, H 5.62, N 5.01.

Methyl 2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-β-D-galactopyranosyl)-2-acetylacetate (5): Yield 462 mg, 80%. R_f = 0.3 (hexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = +6.0 (*c* = 1.25, CH_2Cl_2). IR (CH_2Cl_2): 1555, 1731, 1743 cm^{-1}. ^1H NMR: δ = 2.21, 2.23, (2 s, 3 H, $COCH_3$), 3.49−3.73 (m, 4 H, H-2, 6′-H, 6′′-H, 5′-H), 3.61, 3.68 (2 s, 3 H, $-OCH_3$), 4.02−4.18 (m, 2 H, 4′-H, 3′-H), 4.35−4.84 (m, 7 H, 1′-H, 3 × OCH_2Ph), 4.94, 5.19, (2 t, *J* = 10.4 Hz, 1 H, 2′-H), 7.22−7.33 (m, 15 H, aromatic). ^{13}C NMR: δ = 29.4, 60.4, 61.4, 67.8, 72.0, 72.4, 73.4, 74.1, 74.6, 75.4, 79.8, 80.5, 127.4−138.3 (18 C), 166.3, 198.9. MS (FAB): *m*/*z* (%) = 578 (40) [M^+ + 1], 577 (100) [M^+]. $C_{32}H_{35}NO_9$ (577.62): calcd. C 66.54, H 6.11, N 2.43; found C 66.58, H 6.02, N 2.48.

Methyl 2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-β-D-galactopyranosyl)-2-phenylsulfonylacetate (6): Yield 460 mg, 68%. R_f = 0.3 (hexane/ethyl acetate, 6:4). $[\alpha]_D^{25}$ = +5.0 (*c* = 0.8, CH_2Cl_2). IR (CH_2Cl_2): $\tilde{\nu}$ = 1554, 1752 cm^{-1}. ^1H NMR: δ = 2.9 (dd, *J* = 9.0, 5.9 Hz, 1 H, 5′-H), 3.29 (dd, *J* = 15.1, 5.9 Hz, 2 H, 6′-H, 6′′-H), 3.51, 3.65 (2 s, 3 H, OCH_3), 3.90−4.85 (m, 10 H, 2-H, 1′-H, 3′-H, 4′-H, 3 × OCH_2Ph) 5.26, 5.30 (2 t, *J* = 9.3 Hz, 1 H, 2′-H), 7.15−7.97 (m, 20 H, aromatic). ^{13}C NMR: δ = 66.5, 69.8, 71.4, 71.9, 72.3, 73.3, 73.9, 74.6, 74.9, 79.7, 84.8, 127.6−137.9 (24 C), 162.4. MS (FAB): *m*/*z* (%) = 676 (23) [M^+ + 1], 677 (52) [M^+]. $C_{36}H_{37}NO_{10}S$ (675.75): calcd. C 63.99, H 5.52, N 2.07; found C 64.12, H 5.48, N 2.20.

Dimethyl 2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-β-D-glucopyranosyl)-malonate (7β): The same procedure was adopted as for preparation of compound **3**, but 2-nitroglucal was employed instead of 2-nitrogalactal. Yield 368 mg, 62%. R_f = 0.5 (hexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = −0.63 (*c* = 3.15, CH_2Cl_2). IR (CH_2Cl_2): $\tilde{\nu}$ = 1557, 1749 cm^{-1}. ^1H NMR: δ = 3.55−3.78 (m, 5 H, 6′-H, 6′′-H, 2-H, 4′-H, 5′-H), 3.70, 3.71 (2 s, 6 H, 2 × OCH_3), 4.33 (t, *J* = 9.8 Hz, 1 H, 3′-H), 4.42 (dd, *J* = 9.8, 4.4 Hz, 1 H, 1′-H), 4.46−4.82 (m, 6 H, 3 × OCH_2Ph), 4.94 (t, *J* = 9.8 Hz, 1 H, 2′-H), 7.19−7.34 (m, 15 H, aromatic). ^{13}C NMR: δ = 52.8, 52.8, 53.3, 67.9, 73.3, 74.5, 75.0, 75.8, 77.5, 79.8, 82.1, 87.6, 127.5−138.0 (18 C), 165.6, 166.3. MS (FAB): *m*/*z* (%) = 594 (25) [M^+ + 1], 593 (65) [M^+]. $C_{32}H_{35}NO_{10}$ (593.62): calcd. C 64.75, H 5.94, N 2.36; found C 64.70, H 6.01, N 2.25.

Dimethyl 2-(3,4,6-Tri-*O*-benzyl-2-deoxy-2-nitro-α-D-glucopyranosyl)-malonate (7α): Yield 178 mg, 30%. R_f = 0.4 (hexane/ethyl acetate, 8:2). $[\alpha]_D^{25}$ = +3 (*c* = 1, CH_2Cl_2). IR (CH_2Cl_2): $\tilde{\nu}$ = 1557, 1750 cm^{-1}. ^1H NMR: δ = 3.62−3.70 (m, 2 H, 6′-H, 6′′-H), 3.64, 3.67 (2 s, 6 H, 2 × OCH_3), 3.77 (d, *J* = 6.7 Hz, 1 H, 2-H), 3.90 (t, *J* = 4.9 Hz, 1 H, 4′-H), 3.95 (dd, *J* = 10.2, 4.9 Hz, 1 H, 5′-H), 4.14 (dd, *J* = 4.9 Hz, 1 H, 3′-H), 4.40−4.53 (m, 6 H, OCH_2Ph), 4.99 (dd, *J* = 7.0, 7.0 Hz, 1 H, 1′-H), 5.18 (dd, *J* = 7.0, 4.9 Hz, 1 H, 2′-H), 7.09−7.27 (m, 15 H, aromatic). ^{13}C NMR: δ = 52.8, 52.8, 53.1, 67.8, 67.9, 72.1, 72.8, 73.2, 73.3, 74.5, 76.2, 82.0, 127.6−138.0 (18 C), 166.4, 166.9. MS (FAB): *m*/*z* (%) = 594 (20) [M^+ + 1], 593 (72) [M^+]. $C_{32}H_{35}NO_{10}$ (593.62): calcd. C 64.75, H 5.94, N 2.36; found C 64.50, H 5.81, N 2.45.

General Procedure for the Preparation of Bicyclic Lactams 9, 10 and 11: The nitro compound **3β**, **6** or **7β** (1 mmol) was added to a stirred solution of freshly prepared Raney nickel T4 (Pt)[13] catalyst (1 g) in EtOH, and the reaction mixture was stirred under hydrogen for 8 h at room temperature. After the completion of reaction (TLC monitoring), the reaction mixture was filtered and the solvent was evaporated under vacuum to give the crude amine **8**. This amine was dissolved in CH_2Cl_2 (2 mL), and Et_3N (0.15 mmol) was added. After 3 h of stirring at room temperature, the solvent was evaporated and the crude product was purified by column chromatography.

Bicyclic Lactam 9: Yield 345 mg, 65%. R_f = 0.5 (hexane/ethyl acetate, 3:7). $[\alpha]_D^{25}$ = +42 (*c* = 1.55, CH_2Cl_2). IR (CH_2Cl_2): $\tilde{\nu}$ = 1730, 1750 cm^{-1}. ^1H NMR: δ = 3.57 (d, *J* = 11.2 Hz, 1 H, 2-H), 3.60−3.71 (m, 3 H, 3′-H, 6′-H, 6′′-H), 3.74 (s, 3 H, OCH_3), 3.80−3.86 (m, 2 H, 2′′-H, 5′-H), 3.95 (dd, *J* = 11, 8.8 Hz, 1 H, 1′-H), 4.1 (br. s, 1 H, 4′-H), 4.43−4.9 (m, 6 H, 3 × OCH_2Ph), 6.54 (s, 1 H, NH), 7.23−7.37 (m, 15 H, aromatic). ^{13}C NMR: δ = 52.7, 53.8, 55.1, 69.0, 71.3, 73.0, 73.6, 75.4, 79.8, 80.1, 81.4, 127.7−138.1 (18 C), 168.3, 169.7. MS (FAB): *m*/*z* (%) = 532 (12) [M^+ + 1], 531 (100) [M^+]. $C_{31}H_{33}NO_7$ (531.60): calcd. C 70.05, H 6.26, N 2.63; found C 69.01, H 6.32, N 2.82.

Bicyclic Lactam 10: Yield 435 mg, 71%. R_f = 0.4 (hexane/ethyl acetate, 3:7). ^1H NMR: δ = 3.22 (dd, *J* = 9.0, 5.1 Hz, 1 H, 5′-H), 3.46 (t, *J* = 8.8 Hz, 1 H, 6′-H), 3.52 (dd, *J* = 10.2, 2.4 Hz, 1 H, 3′-H), 3.62−3.64 (m, 1 H, 6′′-H), 3.7 (t, *J* = 10.5 Hz, 1 H, 2′-H), 3.90 (dd, *J* = 10.5, 8.8 Hz, 1 H, 1′-H), 3.99 (br. s, 1 H, 4′-H), 4.12 (d, *J* = 11.0 Hz, 1 H, 2-H), 4.33−4.78 (m, 6 H, 3 × OCH_2Ph), 5.9 (s, 1 H, NH), 7.17−7.88 (m, 20 H, aromatic). ^{13}C NMR: δ = 54.3, 67.3, 68.0, 71.4, 72.7, 73.4, 75.5, 77.6, 80.2, 81.2, 127.7−138.4 (24C), 165.2. MS (FAB): *m*/*z* (%) = 614 (40) [M^+ + 1], 613 (100) [M^+]. $C_{35}H_{35}NO_7S$ (613.72): calcd. C 72.27, H 6.06, N 2.41; found C 72.21, H 6.20, N 2.62.

Bicyclic Lactam 11: Yield 430 mg, 81%. $[\alpha]_D^{25}$ = +22.8 (*c* = 1.05, CH_2Cl_2). IR (CH_2Cl_2): $\tilde{\nu}$ = 1730, 1750 cm^{-1}. ^1H NMR: δ = 3.20 (t, *J* = 9.5 Hz, 1 H, 2′-H), 3.58 (d, *J* = 11.2 Hz, 1 H, 2-H), 3.63−3.81 (m, 5 H, 3′-H, 4′-H, 5′-H, 6′-H, 6′′-H), 3.73 (s, 3 H, OCH_3), 4.01 (dd, *J* = 11.2, 9.5 Hz, 1 H, 1′-H), 4.45−4.85 (m, 6 H, 3 × OCH_2Ph), 6.23 (s, 1 H, NH), 7.16−7.36 (m, 15 H, aromatic). ^{13}C NMR: δ = 52.8, 53.6, 58.6, 68.2, 73.6, 74.3, 75.4, 78.2, 78.8, 81.3, 83.9, 127.8−137.9 (18 C), 168.2, 169.8. MS (FAB): *m*/*z* (%) = 532 (10) [M^+ + 1], 531 (100) [M^+]. $C_{31}H_{33}NO_7$ (531.60): calcd. C 70.05, H 6.26, N 2.63; found C 70.21, H 6.42, N 2.72.

Bicyclic Enolacetate 12: Et_3N (1 mL) was added to a stirred solution of crude amine **8** (563 mg, 1 mmol) in acetic anhydride (1 mL), and stirring was continued for 6 h at room temperature. After completion of the reaction, the excess acetic anhydride and Et_3N were evaporated to give a crude product, which was purified by column chromatography. Yield 345 mg, 56%. R_f = 0.4 (hexane/ethyl acetate, 1:1). IR (CH_2Cl_2): $\tilde{\nu}$ = 1720, 1600 cm^{-1}. ^1H NMR: δ = 2.26, 2.48 (2 s, 6 H, 2 × $OCOCH_3$), 3.56−3.65 (m, 2 H, 6′-H, 6′′-H), 3.75−3.76 (m, 1 H, 2′-H), 3.84 (br. t, *J* = 5.4 Hz, 1 H, 5′-H), 3.89 (s, 3 H, OCH_3), 4.03 (br. s, 1 H, 4′-H), 4.19−4.26 (m, 2 H, 1′-H, 3′-H), 4.4−5.0 (m, 6 H, 2 × OCH_2Ph), 7.24−7.36 (m, 15 H, aromatic). ^{13}C NMR: δ = 26.7, 30.4, 53.7, 56.6, 68.1, 71.8, 72.6, 73.5, 73.7, 75.3, 77.8, 80.6, 82.7, 127.5−138.3 (18 C), 165.8, 167.1, 170.8, 198.3. MS (FAB): *m*/*z* (%) = 617 (40) [M^+ + 1], 616 (100) [M^+]. $C_{35}H_{37}NO_9$ (615.67): calcd. C 68.28, H 6.06, N 2.28; found C 68.32, H 6.26, N 2.49.

Dimethyl 2-[3,4,6-Tri-*O*-benzyl-2-deoxy-2-(*N*,*N*-diacetylamino)-β-D-galactopyranosyl]malonate (13): Acetyl chloride (195 mg, 2.5 mmol) and Et_3N (252 mg, 2.5 mmol) were added to a stirred solution of crude amine **8** (563 mg, 1 mmol) in dichloromethane, and stirring

was continued at room temperature for 3 h. The reaction mixture was extracted with ethyl acetate, washed with water and dried with Na_2SO_4. The solvent was evaporated under reduced pressure to yield a crude product, which was purified by column chromatography. Yield 466 mg, 72%. IR (CH_2Cl_2): $\tilde{\nu}$ = 1720, 1710 cm^{-1}. ^1H NMR: δ = 2.27, 2.41 (2 s, 6 H, 2 × $OCOCH_3$), 3.53−3.61 (m, 3 H, 2-H, 6′-H, 6′′-H), 3.65, 3.68 (2 s, 6 H, 2 × OCH_3), 3.75 (t, *J* = 6.6 Hz, 1 H, 5′-H), 4.07 (d, *J* = 2.2 Hz, 1 H, 4′-H), 4.36−4.85 (m, 8 H, 3′-H, 2′-H, 3 × OCH_2Ph), 4.98 (dd, *J* = 9.3, 4.9 Hz, 1 H, 1′-H), 7.15−7.34 (m, 15 H, aromatic). ^{13}C NMR: δ = 25.1, 27.9, 52.5, 52.6, 53.6, 57.6, 68.3, 71.9, 73.3, 73.3, 74.3, 74.5, 77.2, 77.5, 127.4−138.6 (18 C), 166.6, 167.0, 175.0, 175.8. MS (FAB): *m*/*z* (%) = 648 (35) [M^+ + 1], 647 (100) [M^+]. $C_{36}H_{41}NO_{10}$ (647.71): calcd. C 66.76, H 6.38, N 2.16; found C 66.82, H 6.45, N 2.01.

Acknowledgments

We thank the Department of Science & Technology, New Delhi, for financial assistance through a project (DST/SP/S1/G-07/1997). K. P thanks the Council of Scientific and Industrial Research, New Delhi, for senior research fellowship. Financial support from the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged. J. D. thanks the Alexander von Humboldt Foundation for a Fellowship.

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Received September 24, 2001
[O01456]