Lewis Acid Catalyzed Ring-Opening Reactions of Sugar-Derived Semicyclic *N*,*O*-Acetals

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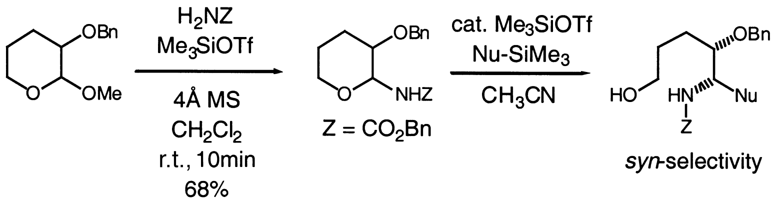
This paper is dedicated to Professor Dr. *Dieter Seebach* on the occasion of his 65th birthday

N-(Alkoxycarbonyl)-*N*-glycosides (polyoxygenated semicyclic *N*,*O*-acetals) were efficiently synthesized from regular acetyl or methyl glycosides (glucopyranoside, ribofuranoside, arabinofuranoside, and 2-deoxyribofuranoside) and a carbamate by treatment of trimethylsilyl trifluoromethanesulfonate and 4 Å molecular sieves. It was found that these *N*-glycosides underwent *Lewis* acid catalyzed ring-opening reactions with silylated nucleophiles to give ring-opened amino alcohols with good-to-high diastereoselectivity. The reactivity order, 2-deoxyribofuranoside > arabinofuranoside > ribofuranoside > glucopyranoside, was revealed. Ring-opening reductions were also investigated with silanes or diisobutylaluminium hydride. An appropriate reducing agent was found to be dependent on the *N*-glycosides used. A glycosidase inhibitor, (2*S*,3*R*,4*R*)-2-hydroxymethylpyrrolidine-3,4-diol (**7**) was synthesized by means of the reactions.

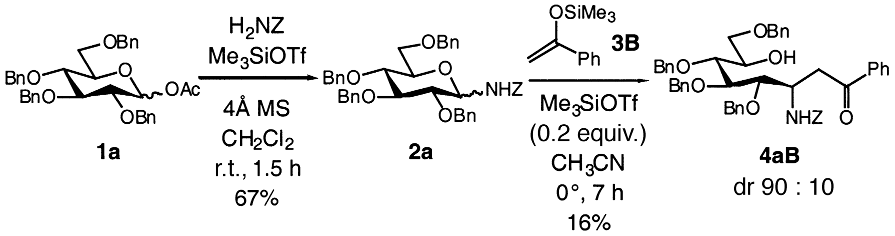
Introduction. – *N*-Glycosides (=semicyclic *N*,*O*-acetals with an exocyclic N-atom) are abundant in nature such as in nucleosides, *N*-glycopeptides, and glycolipids, and they play an important role in their biological activities [1]. Although they are often chemically synthesized *via* direct *N*-glycosylation of aza-nucleophiles (for example, azidotrimethylsilane), *N*-acylated aza-nucleophiles such as amides are less utilized due to their low nucleophilicity. *Kahne et al.* first reported that glycosyl sulfoxides serve as powerful glycosyl donors toward less reactive nucleophiles, including acetamide, in the presence of triflic anhydride [2]. However, the most common procedure for the synthesis of *N*-acylated- *N*-glycosides is acylation of glycosylamines [1c]. Meanwhile, we have recently found that direct *N*-glycosylation proceeded smoothly in the presence of trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) and 4-Å molecular sieves (4-Å MS), when simple monooxygenated glycosyl donors such as 2-methoxy-3-(benzyloxy)-tetrahydro-2*H*-pyran and carbamates as *N*-acylated aza-nucleophiles were used (*Scheme 1*) [3]. Moreover, the resulting *N*-(alkoxycarbonyl)-*N*-glycosides were found to undergo *Lewis* acid catalyzed ring-opening reactions with silylated nucleophiles (silyl enolates, allylsilanes, and trimethylsilanecarbonitrile) to afford ring-opened products (1,4- or 1,5-amino alcohols) with high stereoselectivity. Along this line, we describe herein a further extension of the reactions to that of *sugar-derived* semicyclic *N*,*O*-acetals, which can afford polyoxygenated amino alcohols as useful intermediates for the synthesis of biologically important, polyoxygenated, N-containing compounds such as alkaloids. This report is the first systematic study of *Lewis* acid catalyzed ring-opening reactions of *N*-acyl-*N*-glycosides, while ring-opening alkylation or reduction of *N*-alkyl-*N*-glycosides including nucleosides with excess *Grignard* reagents or diisobutylaluminium hydride [4]¹) and a *Lewis* acid promoted ring-opening rearrangement of *N*-homoallyl-*N*-galactoside [6] or anomeric isomerization of nucleosides [7] or *N*-acyl-*N*-glycosides [8] have been reported.

Scheme 1. *Preparation and Ring-Opening Reaction of Six-Membered Semicyclic* N,O-*Acetals*



Results and Discussion. – At first, we investigated the feasibility of a series of the reactions with a glucose derivative (*Scheme 2*). Glucose-derived *N*-[(benzyloxy)carbonyl]-*N*,*O*-acetal **2a** was obtained in good yield from 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucose (**1a**) and benzyl carbamate (H_2NZ) according to the procedure that we described previously (see *Scheme 1*). Then, **2a** was subjected to the conditions of the Me_3SiOTf-catalyzed ring-opening reaction with the silyl enol ether **3B** derived from acetophenone. However, the desired ring-opened product **4aB** was obtained in low yield even after a prolonged reaction time, though good diastereoselectivity was observed. We speculated that the six-membered pyranose structure of **2a** might be stabilized due to the equatorial substituents at the positions C(2) to C(5) (*Fig. 1*). Thus, the assumed reactive intermediate, an acyclic *N*-acyliminium salt, could not be formed in sufficient amounts during the reaction²)³).

Scheme 2. *Preparation and Ring-Opening Reaction of* N-*Glucopyranoside* **2a**



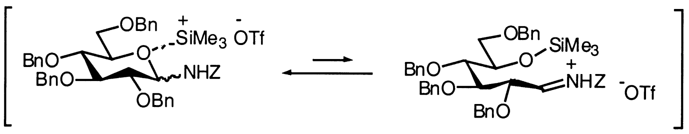


Fig. 1. *Ring-opening of* N-*glucopyranoside* **2a**

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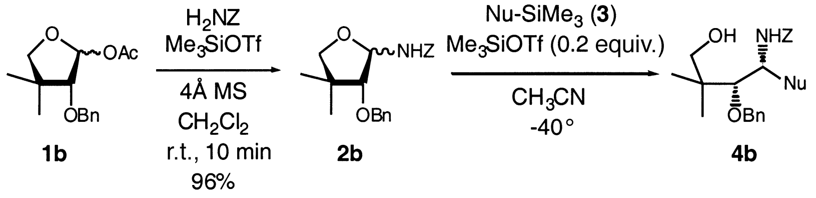
¹) For ring-opening reactions of nucleosides by *Grignard* reagents or diisobutylaluminium hydride, see [5].

²) We have proposed the formation of an acyclic *N*-acyliminium ion as a reactive intermediate for the *Lewis* acid catalyzed ring-opening reactions, see [3c].

³) For a recent review on the chemistry of *N*-acyliminium ions, see [9].

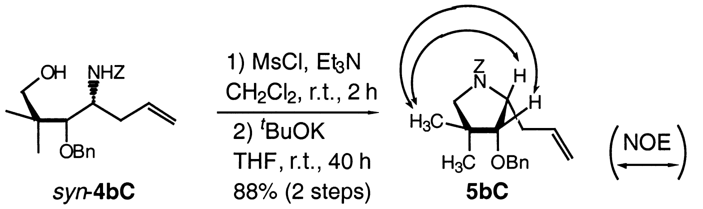
Accordingly, we anticipated that *furanose*-derived *N*,*O*-acetals would be more reactive because the relatively high ring strain could be released by ring opening. Indeed, it was found that ring-opening reactions of (*R*)-pantolactone derivative **2b**, which was prepared in high yield from the corresponding 1-(acetyloxy)tetrahydrofuran **1b**, with silylated nucleophiles **3A** – **C** proceeded smoothly to give *syn*-amino alcohols **4bA** – **C** with good diastereoselectivity (*Table 1*). The configuration assignment of the allylation product **4bC** was made after conversion to pyrrolidine derivative **5bC** (*Scheme 3*). An NOE enhancement observed by NMR analysis of **5bC** (see *Exper. Part*) supported its 2,3-*cis* configuration, thus establishing the formation of the *syn*-product **4bC** as the major diastereoisomer. The relative configurations of other products were tentatively assigned by analogy. The stereochemistry of the reaction is consistent with our previous observation in reactions of six-membered *N*,*O*-acetals [3].

Table 1. *Ring-Opening Reactions of a Pantolactone Derivative*



Nu-SiMe$_3$ (**3**)	**4b**	Time/h	Yield/%	*syn*/*anti*
Me$_2$C=C(OSiMe$_3$)(OMe) (**3A**)	**4bA** Nu = CMe$_2$CO$_2$Me	36	92	91 : 9
H$_2$C=C(OSiMe$_3$)Ph (**3B**)	**4bB** Nu = CH$_2$COPh	16	94	90 : 10
H$_2$C=CHCH$_2$SiMe$_3$ (**3C**)	**4bC** Nu = CH$_2$CH=CH$_2$	20	72	89 : 11

Scheme 3. *Configuration Assignment of Allylation Product* syn-**4bC** *by Conversion to* **5bC**



Next, we set our investigation on the reactions of D-ribose, D-arabinose, and 2-deoxy-D-ribose derivatives. Formation of the corresponding *N*,*O*-acetals **2c** – **e** proceeded in high yields from regular furanosides **1c** – **e**, respectively (*Scheme 4*)[4]). Although use of the acetyloxy group as the leaving group is a key to obtain high yields of ribose and arabinose derivatives **2c** and **2d**, the methoxy group can be utilized for the *N*-glycosylation of the more reactive 2-deoxy-D-ribofuranoside **1e**.

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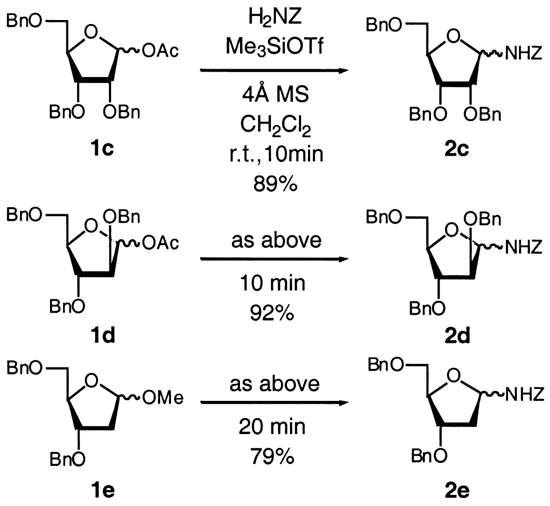
[4]) Semicyclic *N*,*O*-acetals **2** were obtained as anomeric mixtures (dr 5:5 to 8:2). We have observed that anomers can be interconverted in the presence of a *Lewis* acid, see [3c].

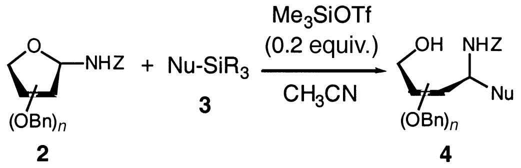
Scheme 4. *Preparation of* N-*Furanosides*

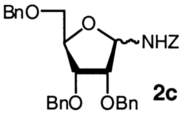
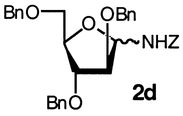
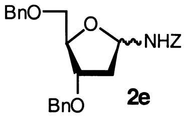
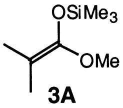
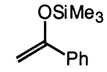
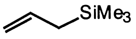


With furanose-derived *N*,*O*-acetals **2c**–**e** in hand, Me_3SiOTf-catalyzed ring-opening reactions with the silylated nucleophiles **3A**–**C** were next examined (*Table 2*). The reactions were carried out with a nucleophile (2 equiv.) and a catalytic amount of Me_3SiOTf (0.2 equiv.) in MeCN at low temperature depending on the reactivity of the nucleophile. In most reactions of ribose and arabinose derivatives **2c** and **2d**, good yields of *syn*-ring-opened products **4cA**–**B** and **4dA**–**C**, respectively, were obtained with high diastereoselectivity, while the reaction of deoxyribose derivative **2e** with acetophenone-derived silyl enol ether **3B** showed no diastereoselectivity. In contrast to the high yields obtained from the reactions of **2c** with silyl enolates **3A** and **3B**, no reaction of **2c** with allyltrimethylsilane (**3C**) was observed. The higher reactivity of arabinofuranoside **2d** than that of ribofuranoside **2c** might be attributed to the differences in ring strain or conformation caused by steric repulsion between substituents on the furan ring. The *syn*-configurations of products **4cA** and **4dC** were confirmed by ^{1}H-NMR analyses of the corresponding pyrrolidine derivatives **5cA** and **5dC** (*Scheme 5*).

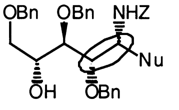
The stereochemistry can be rationalized by assuming the α- and β-(benzyloxy)-chelated transition states $\mathbf{TS}_\alpha$ and $\mathbf{TS}_\beta$, respectively, for acyclic *N*-acyliminium intermediates (*Fig. 2*). In $\mathbf{TS}_\alpha$, the diastereofaces of the iminium ion can be discriminated efficiently because of the close asymmetric environment created by the chiral C(α), and therefore, a nucleophile attacks preferentially from the side of the H-atom to give the *syn*-adduct (for the reactions of **2b**–**d**). On the other hand, in $\mathbf{TS}_\beta$, the asymmetric environment created by the chiral C(β) is far from the reaction site leading to low selectivity (for the reaction of **2e**). In reactions of α,β-bis(benzyloxy)-substituted *N*,*O*-acetals such as **2c** and **2d**, chelation by both α- and β-(benzyloxy) groups might be also possible, though clear evidence in this respect has not been obtained yet.

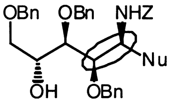
Table 2. *Ring-Opening Reactions of Furanose Derivatives*

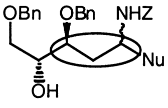


	 **2c**	 **2d**	 **2e**
 **3A**	– 40°, 12 h **4cA** (quant.)[a]) *syn*/*anti* 93 : 7	– 40°, 21 h **4dA** (62%)[a]) *syn*/*anti* 91 : 9	–
 **3B**	– 40°, 16 h **4cB** (70%)[a]) *syn*/*anti* 93 : 7	– 40°, 37 h **4dB** (77%)[a]) *syn*/*anti* 93 : 7	– 40°, 9 h **4eB** (80%)[a]) dr 50 : 50
 **3C**	0°, 23 h **4cC** (0%)[a])	– 30°, 39 h **4dC** (64%)[a]) *syn*/*anti* 94 : 6	–

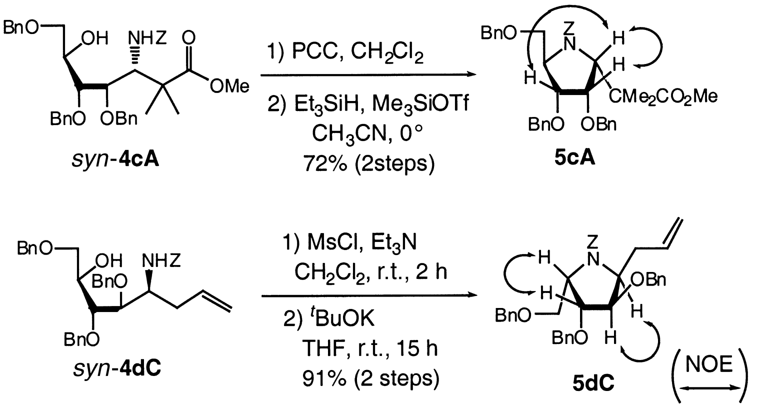
[a]) Product **4**: **A** Nu = CMe_2CO_2Me; **B** Nu = CH_2COPh; **C** Nu = $CH_2CH{=}CH_2$.


syn-**4c**


syn-**4d**


4e

Scheme 5. *Configuration Assignment of Ring-Opened Products* syn-**4cA** *and* syn-**4dC**



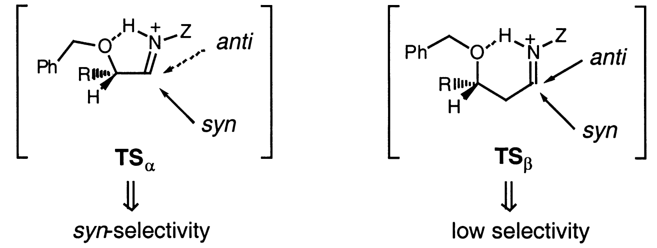
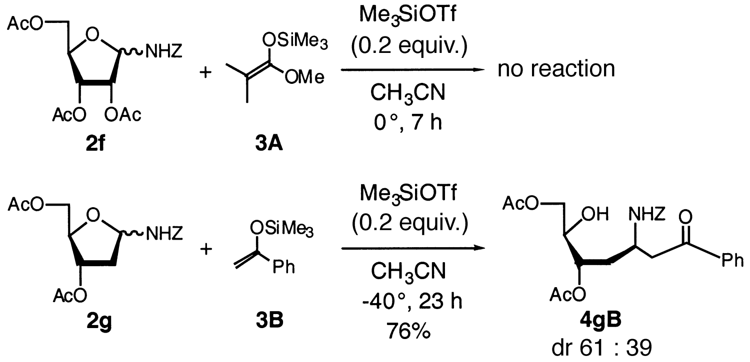


Fig. 2. *Assumed transition states for the acyclic acyliminium intermediates*

The choice of the protective groups at the OH groups of the sugars was also found to be important for the ring-opening reactions, *i.e.*, *O*-acetyl-protected ribose-derived *N*,*O*-acetal **2f** was unreactive under similar conditions, while the analogous deoxyribose derivative **2g** underwent the reaction with low selectivity (*Scheme 6*). An electron-withdrawing substituent at the α-position might retard the formation of the assumed *N*-acyliminium intermediate as proposed in glycosylation chemistry [10].

Scheme 6. *Ring-Opening Reactions of* O-*Acetyl-Protected* N-*Furanosides*



We next focused our attention on the ring-opening *reduction* of **2c** and **2d** (*Table 3*). At first, ribofuranoside **2c** was subjected to the conditions with triethylsilane as a reducing agent and Me$_3$SiOTf as a *Lewis* acid in MeCN (*Entry 1*). While **2c** remained unreacted under these conditions, use of chlorodimethylsilane improved the reaction dramatically to give amino alcohol **4cD** in good yield (*Entries 2* and *3*). Treatment of **2c** with diisobutylaluminium hydride (DIBAL) in THF [5] resulted in a low yield (*Entry 4*). On the other hand, arabinofuranoside **2d** reacted with triethylsilane to give **4dD** in moderate yield besides furan **6** (*Entry 5*). Other silanes such as chlorodimethylsilane and dimethylisopropylsilane were examined, but no remarkable improvement was observed (*Entries 6–8*). Meanwhile, treatment of **2d** with 3 equiv. of DIBAL in THF provided **4dD** in good yield (*Entry 9*).

Finally, reduction product **4dD** was successfully transformed to the glycosidase inhibitor (2*S*,3*R*,4*R*)-2-(hydroxymethyl)pyrrolidine-3,4-diol (**7**) (*Scheme 7*)[5]. That is, ring closure of **4dD** *via* mesylation followed by treatment with ^{t}BuOK gave pyrrolidine

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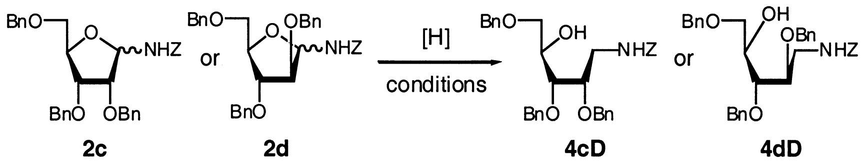
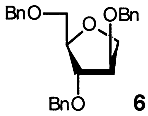
[5] For syntheses of **7**, see [11].

Table 3. *Ring-Opening Reductions of* **2c** *and* **2d**



Entry	**2**	Reagent	Conditions	Yield/%
1	**2c**	Et_3SiH (2.0 equiv.), Me_3SiOTf (0.2 equiv.)	MeCN, 0°, 1.5 h → r.t., 3 h	0
2		Me_2ClSiH (2.0 equiv.), Me_3SiOTf (0.2 equiv.)	MeCN, 0°, 6 h	67
3		Me_2ClSiH (2.0 equiv.), Me_3SiOTf (1.0 equiv.)	MeCN, 0°, 6 h	76
4		DIBALH (3.0 equiv.)	THF, –23°, 4 h	37
5	**2d**	Et_3SiH (2.0 equiv.), Me_3SiOTf (0.2 equiv.)	MeCN, 0°, 1.5 h → r.t., 3 h	52[a])
6		Me_2ClSiH (2.0 equiv.), Me_3SiOTf (0.2 equiv.)	MeCN, 0°, 11 h	37
7		Me_2ClSiH (2.0 equiv.), Me_3SiOTf (1.0 equiv.)	MeCN, 0°, 9 h	59
8		$Me_2{}^iPrSiH$ (2.0 equiv.), Me_3SiOTf (0.2 equiv.)	MeCN, 0°, 15 h	43
9		DIBALH (3.0 equiv.)	THF, –23°, 4 h	75

[a]) Furan **6** was obtained in 38% yield.



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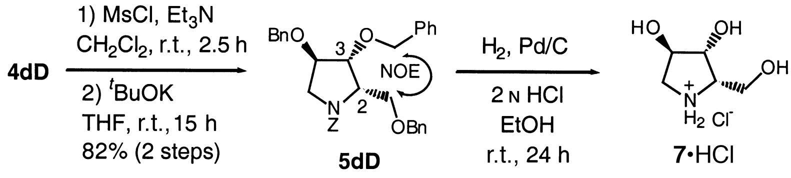
5dD in high yield, and removal of all protective groups was achieved by hydrogenolysis over Pd/C with hydrochloric acid in EtOH providing the hydrochloride of **7** in high yield. Although this synthesis is one of the simple applications of our findings, diastereoselective syntheses of *C*-glycosides of imino sugars or polyoxygenated alkaloids utilizing the reactions are possible.

Scheme 7. *Synthesis of Glycosidase Inhibitor* **7**



In summary, we revealed that *N*-(alkoxycarbonyl)-*N*-glycosides (polyoxygenated five-membered semicyclic *N*,*O*-acetals) can be directly prepared from the corresponding regular glycosides with a carbamate, and that they undergo Me_3SiOTf-catalyzed ring-opening reactions with silylated nucleophiles to give ring-opened amino alcohols with good to high diastereoselectivity. The synthetic utility of this reaction was demonstrated by the synthesis of a glycosidase inhibitor, (2*S*,3*R*,4*R*)-2-(hydroxymethyl)pyrrolidine-3,4-diol (**7**).

This work was partially supported by *CREST* and *SORST, Japan Science Technology Corporation* (*JST*), and a *Grant-in-Aid for Scientific Research* from the *Japan Society of the Promotion of Sciences* (*JSPS*).

Experimental Part

1. *General.* CH_2Cl_2 was distilled from P_2O_5, then from CaH_2, and dried over molecular sieves 4-Å. MeCN was distilled from CaH_2 and dried over molecular sieves 4-Å. All other solvents and chemical compounds were purified by standard procedures. Column chromatography (CC): silica gel *60* (*Merck*). TLC: *Wakogel B-5F.* Optical rotations: *Jasco P-1010* polarimeter; 10-cm cell. IR Spectra: *Jasco FT/IR-610* infrared spectrometer in cm^{-1}; ^{1}H- and ^{13}C-NMR Spectra: *Jeol JNM-LA300* or *JNM-LA400* spectrometer; in $CDCl_3$ unless otherwise noted; δ in ppm rel. to $SiMe_4$ as internal standard (δ(H) = 0) and $CDCl_3$ as internal standard (δ(C) = 77.0); *J* in Hz; dr = diastereoisomer ratio. MS: for high-resolution (HR) *Jeol JMX-SX-102A* spectrometer; for low-resolution (EI) *Shimazu GCMS-QP5050A* spectrometer.

2. N-*[(Benzyloxy)carbonyl]*-N-*glycosides* **2** (= semicyclic *N,O*-acetals with an exocyclic N-atom): *General Procedure:* To a suspension of a regular glycoside **1** (1.0 equiv.), benzyl carbamate (1.1 equiv.) and 4-Å-molecular-sieves powder (300 mg/1 mmol of glycoside) in CH_2Cl_2 (1.0M) was added dropwise trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf; 1.0 equiv.) at r.t. The mixture was stirred for 10 to 20 min and then quenched with sat. aq. $NaHCO_3$ soln. After filtration through a *Celite* pad and extraction of the filtrate with AcOEt (3 ×), the combined org. phase was washed with brine, dried ($MgSO_4$), and evaporated, and the residue purified by CC (silica gel): **2**.

*Benzyl (2,3,4,6-Tetra-*O*-benzyl-*D*-glucopyranosyl)carbamate* (**2a**). From 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**1a**) in 67% yield. Colorless oil: α-D/β-D 35 : 65. ^{1}H-NMR (400 MHz, $CDCl_3$): β-D-isomer: 7.35–7.21 (*m*, 23 H); 7.14–7.10 (*m*, 2 H); 5.15 (*d*, *J* = 12.2, 1 H); 5.11 (br.*d*, *J* = 10.0, 1 H); 5.06 (*d*, *J* = 12.2, 1 H); 4.90 (*dd*, *J* = 10.0, 8.6, 1 H); 4.89 (*d*, *J* = 10.9, 1 H); 4.85 (*d*, *J* = 10.9, 1 H); 4.79 (*d*, *J* = 11.0, 1 H); 4.76 (*d*, *J* = 11.3, 1 H); 4.67 (*d*, *J* = 11.3, 1 H); 4.59 (*d*, *J* = 12.2, 1 H); 4.50 (*d*, *J* = 11.0, 1 H); 4.46 (*d*, *J* = 12.2, 1 H); 3.76–3.65 (*m*, 4 H); 3.49 (br.*d*, *J* = 7.6, 1 H); 3.32 (br.*t*, *J* = 8.6, 1 H); α-D-isomer: 7.36–7.21 (*m*, 23 H); 7.14–7.09 (*m*, 2 H); 5.62 (*t*, *J* = 6.2, 1 H); 5.58 (br.*d*, *J* = 6.2, 1 H); 5.16 (*d*, *J* = 12.2, 1 H); 5.11 (*d*, *J* = 12.2, 1 H); 4.89 (*d*, *J* = 11.0, 1 H); 4.79 (*d*, *J* = 10.7, 1 H); 4.76 (*d*, *J* = 11.0, 1 H); 4.61 (*d*, *J* = 12.0, 1 H); 4.58 (*s*, 2 H); 4.50 (*d*, *J* = 10.7, 1 H); 4.45 (*d*, *J* = 12.2, 1 H); 3.82–3.56 (*m*, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$, β-D-isomer 155.5; 138.3; 138.0; 137.8; 137.7; 136.1; 128.44; 128.38; 128.33; 128.31; 128.27; 128.12; 128.06; 127.95; 127.77; 127.69; 127.66; 85.9; 81.7; 80.2; 77.5; 76.2; 75.6; 74.9; 74.7; 73.5; 68.1; 67.0.

*Benzyl [(3*R*)-3-(Benzyloxy)tetrahydro-4,4-dimethylfuran-2-yl]carbamate* (**2b**). From (3*R*)-3-(benzyloxy)-tetrahydro-4,4-dimethylfuran-2-yl acetate (**1b**)⁶) in 91% yield. Colorless oil. $[\alpha]_D^{22} = +34.8$ (*c* = 0.345, $CHCl_3$). IR (film): 3431, 3326, 3064, 3032, 2961, 2871, 1728, 1502, 1224, 1036, 736, 697. ^{1}H-NMR (300 MHz, $CDCl_3$; dr *ca.* 6 : 4): 7.37–7.22 (*m*, 10 H); 5.89 (br. *d*, *J* = 9.6, 0.6 H); 5.72 (br. *dd*, *J* = 9.6, 5.0, 0.6 H); 5.58 (br. *d*, *J* = 9.0, 0.4 H); 5.43 (br. *dd*, *J* = 9.0, 4.1, 0.4 H); 5.10 (*s*, 2 H); 4.66 (br. *d*, *J* = 11.7, 0.4 H); 4.57 (*d*, *J* = 11.5, 0.6 H); 4.53 (br. *d*, *J* = 11.7, 0.4 H); 4.51 (*d*, *J* = 11.5, 0.6 H); 3.69 (*d*, *J* = 8.1, 0.6 H); 3.64 (*d*, *J* = 8.4, 0.4 H); 3.58 (*d*, *J* = 8.4, 0.4 H); 3.50 (*d*, *J* = 5.0, 0.6 H); 3.45 (br. *d*, *J* = 4.1, 0.4 H); 3.39 (*d*, *J* = 8.1, 0.6 H); 1.11 (*s*, 1.2 H); 1.08 (*s*, 1.8 H); 1.06 (*s*, 1.8 H); 1.04 (*s*, 1.2 H). ^{13}C-NMR (100 MHz, $CDCl_3$, dr *ca.* 6 : 4): 155.7; 155.3; 137.9; 137.2; 136.2; 136.0; 128.5; 128.4; 128.3; 128.2; 128.10; 128.06; 128.01; 127.9; 127.6; 127.4; 89.1; 87.2; 84.9; 82.7; 78.1; 76.7; 74.3; 72.2; 66.9; 66.8; 42.8; 41.6; 25.2; 24.4; 19.8; 19.5. Anal. calc. for $C_{21}H_{25}NO_4$: C 70.96, H 7.09, N 3.94; found: C 71.01, H 7.13, N 3.91.

*Benzyl (2,3,5-Tri-*O*-benzyl-*D*-ribofuranosyl)carbamate* (**2c**). From 2,3,5-tri-*O*-benzyl-D-ribofuranose 1-acetate (**1c**)⁷) in 89% yield. Colorless oil; dr *ca.* 7 : 3. $[\alpha]_D^{25} = +61.2$ (*c* = 2.295, $CHCl_3$). IR (film): 3417, 3063, 3031, 2925, 2866, 1732, 1505, 1455, 1353, 1239, 1027, 737, 698. ^{1}H-NMR (400 MHz, $CDCl_3$): major isomer: 7.32–7.12 (*m*, 20 H); 6.27 (br. *d*, *J* = 9.5, 1 H); 5.64 (*dd*, *J* = 9.5, 5.6, 1 H); 5.04 (*s*, 2 H); 4.58 (*d*, *J* = 12.2, 1 H); 4.50 (*d*, *J* = 12.2, 1 H); 4.48 (*s*, 2 H); 4.46 (*d*, *J* = 11.9, 1 H); 4.36 (*d*, *J* = 11.9, 1 H); 4.16 (*ddd*, *J* = 4.2, 3.5, 2.2, 1 H); 3.96 (*t*, *J* = 5.1, 1 H); 3.89 (*dd*, *J* = 5.1, 2.3, 1 H); 3.38 (*dd*, *J* = 10.5, 3.4, 1 H); 3.34 (*dd*, *J* = 10.5, 4.6, 1 H); minor isomer (selected signals): 5.47 (*dd*, *J* = 8.9, 5.2, 1 H); 5.03 (*s*, 2 H); 4.12 (*m*, 1 H); 3.76 (*t*, *J* = 11.1, 1 H); 3.54 (*dd*,

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⁶) Acetate **1b** was prepared from (*R*)-pantolactone in 3 steps including benzylation of the OH group by benzyl trichloroacetoimidate, reduction by diisobutylaluminium hydride, and acetylation by Ac_2O and a catalytic amount of *N,N* dimethylpyridine-4-amine in Et_3N.

⁷) Regular glycosides were prepared from the corresponding sugars according to conventional methods including *a*) methyl glycoside formation by treatment with a catalytic amount of acetyl chloride in MeOH, *b*) benzylation of OH groups by NaH and benzyl bromide in DMF, *c*) hydrolysis of the methyl glycoside with 1N HCl in refluxing dioxane, and *d*) acetylation of the anomeric OH group by Ac_2O and a catalytic amount of *N,N*-dimethylpyridin-4-amine in Et_3N, see [12].

$J = 11.1, 4.6$, 1 H). ^{13}C-NMR (75 MHz, CDCl$_3$; major isomer: 155.9; 137.8; 137.6; 137.3; 136.3; 128.41; 128.38; 128.35; 128.1; 128.0; 127.9; 127.82; 128.78; 127.7; 127.6; 127.5; 127.4; 81.2; 81.1; 77.8; 76.5; 73.5; 72.48; 72.45; 70.0; 66.7. Anal. calc. for $C_{34}H_{35}NO_6$: C 73.76, H 6.37, N 2.53; found: C 73.44, H 6.34, N 2.51.

*Benzyl (2,3,5-Tri-*O*-benzyl-*D*-arabinofuranosyl)carbamate* (**2d**). From 2,3,5-tri-*O*-benzyl-D-arabinofuranose 1-acetate (**1d**)[7]) in 92% yield. Colorless oil. $[\alpha]_D^{26} = +2.2$ ($c = 0.825$, CHCl$_3$). IR (film): 3411, 3339, 3087, 3062, 3031, 2922, 2864, 1728, 1509, 1498, 1454, 1215, 1091, 1048, 1028, 738, 697, 459. H-NMR (400 MHz, CDCl$_3$, dr *ca.* 1:1): 7.38–7.18 (*m*, 20 H); 5.92 (br. *d*, $J = 10.2$, 0.5 H); 5.87 (br. *d*, $J = 10.2$, 0.5 H); 5.75 (br. *d*, $J = 10.2$, 0.5 H); 5.71 (br. *dd*, $J = 9.9, 5.5$, 0.5 H); 5.13 (*d*, $J = 12.2$, 0.5 H); 5.10 (*s*, 1 H); 5.08 (*d*, $J = 12.2$, 0.5 H); 4.57–4.39 (*m*, 6 H); 4.34 (*ddd*, $J = 7.6, 5.4, 1.7$, 0.5 H); 4.07–3.93 (*m*, 2 H); 3.89 (*s*, 0.5 H); 3.59 (*dd*, $J = 9.8, 5.4$, 0.5 H); 3.53 (*d*, $J = 3.9$, 1 H); 3.48 (*dd*, $J = 9.8, 8.3$, 0.5 H). ^{13}C-NMR (75 MHz, CDCl$_3$, dr *ca.* 1:1): 155.3; 155.0; 137.9; 137.7; 137.5; 137.0; 136.9; 136.05; 136.02; 136.00; 135.97; 128.38; 128.36; 128.32; 128.30; 128.22; 128.19; 128.08; 128.04; 127.99; 127.93; 127.84; 127.81; 127.74; 127.71; 127.63; 127.58; 127.54; 127.51; 85.5; 84.9; 82.5; 82.2; 81.93; 81.85; 81.2; 80.1; 73.2; 73.1; 72.0; 71.6; 71.5; 71.3; 69.9; 69.7; 66.8. Anal. calc. for $C_{34}H_{35}NO_6$: C 73.76, H 6.37, N 2.53; found: C 73.67, H 6.36, N 2.50.

*Benzyl (3,5-di-*O*-benzyl-2-deoxy-*D*-ribofuranosyl)carbamate* (**2e**). From methyl 3,5-di-*O*-benzyl-2-deoxy-D-ribofuranoside (**1e**)[7]) in 79% yield. Colorless oil. $[\alpha]_D^{25} = +21.1$ (c = 0.435, CHCl$_3$). IR (film): 3409, 3328, 3060, 3032, 2920, 2863, 1727, 1504, 1452, 1357, 1247, 1212, 1078, 741, 697. ^{1}H-NMR (300 MHz, CDCl$_3$; dr *ca.* 8:2): 7.40–7.20 (*m*, 15 H); 6.11 (br. *d*, $J = 10.1$, 0.8 H); 5.95 (br, 0.2 H); 5.81 (br. *dd*, $J = 9.8, 7.1$, 0.8 H); 5.65 (br, 0.2 H); 5.12 (*d*, $J = 12.2$, 0.8 H); 5.08 (*s*, 0.4 H); 5.06 (*d*, $J = 12.2$, 0.8 H); 4.54 (*d*, $J = 12.1$, 0.8 H); 4.48–4.43 (*m*, 3.2 H); 4.35 (*dd*, $J = 5.5, 4.5$, 0.8 H); 4.28–4.20 (*m*, 0.4 H); 4.07 (*d*, $J = 5.5$, 0.8 H); 3.56 (*dd*, $J = 10.1, 3.1$, 0.2 H); 3.45 (*dd*, $J = 10.1, 3.8$, 1.0 H); 3.32 (*dd*, $J = 10.1, 6.0$, 0.8 H); 2.27 (*ddd*, $J = 13.6, 6.2, 2.7$, 0.2 H); 2.18 (apparent *dt*, $J = 13.7, 6.5$, 0.8 H); 1.95 (*d*, $J = 13.7$, 0.8 H); 1.89 (*m*, 0.2 H). ^{13}C-NMR (75 MHz, CDCl$_3$; dr *ca.* 8:2): 155.3; 137.8; 137.7; 137.4; 136.19; 136.14; 128.36; 128.32; 128.28; 128.24; 128.06; 128.01; 127.9; 127.7; 127.59; 127.53; 127.48; 127.42; 83.0; 82.9; 82.5; 82.4; 80.2; 79.7; 73.5; 73.3; 70.95; 70.91; 70.3; 66.6; 66.5; 38.5; 37.0. Anal. calc. for $C_{27}H_{29}NO_5$: C 72.46, H 6.53, N 3.13; found: C 72.23, H 6.61, N 3.08.

3. *Me_3SiOTf-Catalyzed Ring-Opening Reactions of* N-*Glycosides* **2**: *General Procedure.* To a soln. of an *N*-glyoside **2** (1 equiv.) and a nucleophile **3** (2 equiv.) in MeCN (0.1M) was added dropwise Me$_3$SiOTf (0.2 equiv.) at the appropriate temp. After being stirred at that temp. for the time indicated in the schemes or tables, the mixture was quenched with sat. aq. NaHCO$_3$ soln. and extracted with AcOEt (2 ×). The combined org. phase was washed with brine, dried (MgSO$_4$), and evaporated and the residue purified by prep. TLC to give a ring-opened product **4**. The dr of **4** were determined by ^{1}H-NMR analyses.

*Benzyl [(2*S*,3*R*,4*R*,5*R*)-2,3,4,6-Tetrakis(benzyloxy)-5-hydroxy-1-(2-oxo-2-phenylethyl)hexyl]carbamate (***4aB**). Yield 16%. Colorless oil; dr 90:10. ^{1}H-NMR (300 MHz, CDCl$_3$): major isomer: 7.72 (*d*, $J = 7.5$, 2 H); 7.52 (*t*, $J = 7.5$, 2 H); 7.46–7.10 (*m*, 26 H); 5.30 (br. *d*, $J = 9.7$, 1 H); 5.09 (*s*, 2 H); 4.82 (*d*, $J = 11.5$, 1 H); 4.74 (*d*, $J = 11.2$, 1 H); 4.68–4.42 (*m*, 6 H); 4.35 (*m*, 1 H); 4.05 (*m*, 1 H); 3.91 (*s*, 2 H); 3.81 (*m*, 1 H); 3.70–3.57 (*m*, 2 H); 3.08 (*dd*, $J = 17.0, 5.1$, 1 H); 2.82 (br. *s*, 1 H); 2.78 (*dd*, $J = 17.0, 7.9$, 1 H); minor isomer (selected signal): 5.83 (*d*, $J = 7.1$, 1 H). ^{13}C-NMR (100 MHz, CDCl$_{3,}$ major isomer): 197.5; 156.0; 138.3; 138.1; 136.53; 136.46; 133.1; 128.5; 128.44; 128.40; 128.37; 128.30; 128.29; 128.26; 128.16; 128.05; 127.9; 127.74; 127.67; 127.63; 127.56; 79.4; 78.8; 77.5; 77.2; 74.9; 73.4; 71.2; 70.4; 66.9; 48.7; 41.3; 29.7.

*Methyl (4*R*)-4-(Benzyloxy)-3-{[(benzyloxy)carbonyl]amino}-6-hydroxy-2,2,5,5-tetramethylhexanoate* (**4bA**). Yield 92%. Colorless oil; *syn*/*anti* 91:9. $[\alpha]_D^{25} = +54.0$ ($c = 0.455$, CHCl$_3$). IR (film) 3447, 3089, 3064, 3032, 2952, 2878, 1725, 1507, 1456, 1319, 1265, 1219, 1146, 1056, 735, 697. ^{1}H-NMR (300 MHz, CDCl$_3$): *syn*-isomer: 7.36–7.25 (*m*, 10 H); 5.63 (*d*, $J = 9.0$, 1 H); 5.11 (*s*, 2 H); 4.77 (*d*, $J = 11.3$, 1 H); 4.54 (*d*, $J = 11.3$, 1 H); 4.12 (*d*, $J = 9.9$, 1 H); 3.59 (*s*, 3 H); 3.51 (*s*, 1 H); 3.51 (*d*, $J = 11.3$, 1 H); 3.36 (*d*, $J = 11.3$, 1 H); 2.04 (br. *s*, 1 H); 1.25 (*s*, 3 H); 1.20 (*s*, 3 H); 0.98 (*s*, 3 H); 0.911 (*s*, 3 H); (*anti*-isomer (selected signals): 5.41 (*d*, $J = 10.3$, 1 H); 5.21 (*d*, $J = 12.5$, 1 H); 5.14 (*d*, $J = 12.5$, 1 H); 4.08 (*d*, $J = 11.0$, 1 H); 3.44 (*d*, $J = 11.4$, 1 H); 3.30 (*d*, $J = 11.4$, 1 H). ^{13}C-NMR (75 MHz, CDCl$_{3;}$ *syn*-isomer): 177.2; 156.4; 138.1; 136.7; 128.44; 128.41; 128.2; 127.6; 127.0; 81.3; 74.4; 69.6; 66.8; 55.9; 52.0; 47.4; 41.4; 24.3; 21.8; 21.6; 21.3. Anal. calc. for $C_{26}H_{35}NO_6 \cdot 0.15\ H_2O$: C 67.84, H 7.73, N 3.04; found: C 67.81, H 7.56, N 3.04.

*Benzyl [(2*R*)-2-(Benzyloxy)-4-hydroxy-3,3-dimethyl-1-(2-oxo-2-phenylethyl)butyl]carbamate* (**4bB**). Yield 94%. Colorless oil; *syn*/*anti* 90:10. $[\alpha]_D^{22} = +4.3$ ($c = 0.645$, CHCl$_3$). IR (film): 393, 2923, 2878, 1712, 1598, 1497, 1450, 1294, 1216, 1057, 914, 736, 698. ^{1}H-NMR (400 MHz, CDCl$_3$; *syn*-isomer): 7.83 (*d*, $J = 7.6$, 2 H); 7.56 (*t*, $J = 7.6$, 1 H); 7.42 (*t*, $J = 7.6$, 2 H); 7.40–7.15 (*m*, 10 H); 5.56 (*d*, $J = 8.3$, 1 H); 5.08 (*s*, 2 H); 4.76 (*d*, $J = 11.7$, 1 H); 4.49 (*d*, $J = 11.7$, 1 H); 4.47 (*m*, 1 H); 3.60 (*s*, 2 H); 3.43 (*dd*, $J = 11.2, 8.3$, 1 H); 3.21 (*dd*, $J = 17.6, 3.2$, 1 H); 3.14 (*m*, 1 H); 2.90 (*dd*, $J = 17.6, 10.5$, 1 H); 1.05 (*s*, 3 H); 0.92 (*s*, 3 H). ^{13}C-NMR (100 MHz, CDCl$_3$; *syn*-

isomer): 199.3; 155.3; 138.0; 136.4; 136.1; 133.5; 128.5; 128.4; 128.1; 128.04; 128.00; 82.7; 76.4; 70.2; 66.7; 46.7; 43.4; 41.1; 22.2; 20.6. Anal. calc. for $C_{29}H_{33}NO_5$: C 73.24, H 6.99, N 2.95; found: C 73.00, H 7.11, N 2.83.

*Benzyl [1-[(1*R*)-1-(Benzyloxy)-3-hydroxy-2,2-dimethylpropyl]but-3-enyl]carbamate* (**4bC**). Yield 72%. Colorless oil; *syn*/*anti* 89:11. $[\alpha]_D^{25} = +21.3$ ($c = 0.200$, $CHCl_3$). IR (film): 3439, 3065, 3032, 2962, 2875, 1702, 1499, 1331, 1214, 1053, 1027, 914, 736, 697. ^{1}H-NMR (400 MHz, $CDCl_3$): *syn*-isomer: 7.37–7.24 (*m*, 10 H); 5.78 (*m*, 1 H); 5.34 (*d*, *J* = 9.0, 1 H); 5.18–5.00 (*m*, 4 H); 4.73 (*d*, *J* = 11.0, 1 H); 4.64 (*d*, *J* = 11.0, 1 H); 3.98 (apparent q, *J* = 8.0, 1 H); 3.56 (*d*, *J* = 10.4, 1 H); 3.49 (*s*, 1 H); 3.29 (*d*, *J* = 10.4, 1 H); 2.38 (*m*, 1 H); 2.26 (*m*, 1 H); 2.16 (br, 1 H); 1.00 (*s*, 3 H); 0.88 (*s*, 3 H); *anti*-isomer (selected signal): 3.88 (*m*, 1 H). ^{13}C-NMR (100 MHz; $CDCl_3$, *syn*-isomer): 155.7; 138.0; 136.6; 134.7; 128.5; 128.4; 128.0; 127.9; 127.6; 118.0; 83.7; 76.2; 69.9; 66.6; 50.4; 40.4; 40.2; 22.6; 20.8. Anal. calc. for $C_{24}H_{31}NO_4$: C 72.52, H 7.86, N 3.52; found: C 72.26, H 7.88, N 3.47.

*Methyl (4*S*,5*R*,6*R*)-4,5,7-Tris(benzyloxy)-3-{[(benzyloxy)carbonyl]amino}-6-hydroxy-2,2-dimethylheptanoate* (**4cA**). Yield quant. Colorless oil; *syn*/*anti* 93:7. $[\alpha]_D^{24} = +40.5$ ($c = 0.135$, $CHCl_3$). IR (film): 3447, 3063, 3031, 1725, 1507, 1454, 1218, 1067, 1028, 736, 697. ^{1}H-NMR (400 MHz, $CDCl_3$): *syn*-isomer: 7.38–7.12 (*m*, 20 H); 5.65 (*d*, *J* = 9.9, 1 H); 5.03 (*d*, *J* = 12.2, 1 H); 4.73 (*d*, *J* = 11.8, 1 H); 4.68 (*d*, *J* = 11.1, 1 H); 4.57 (*d*, *J* = 12.2, 1 H); 4.51 (*d*, *J* = 12.0, 1 H); 4.45 (*d*, *J* = 12.0, 1 H); 4.45 (*d*, *J* = 11.8, 1 H); 4.38 (*d*, *J* = 11.1, 1 H); 4.29 (*d*, *J* = 9.9, 1 H); 3.96 (*dddd*, *J* = 8.3, 5.5, 5.4, 3.0, 1 H); 3.91 (*d*, *J* = 2.2, 1 H); 3.81 (*dd*, *J* = 8.3, 2.2,1 H); 3.68 (*dd*, *J* = 9.6, 3.0, 1 H); 3.58 (*dd*, *J* = 9.6, 5.5, 1 H); 3.49 (*s*, 3 H); 2.75 (*d*, *J* = 5.4, 1 H); 1.25 (*s*, 3 H); 1.20 (*s*, 3 H); *anti*-isomer (selected signals): 5.51 (*d*, *J* = 10.2, 1 H); 2.60 (*d*, *J* = 5.4, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 177.1; 156.4; 138.5; 137.8; 137.5; 136.5; 128.37; 128.33; 128.2; 128.1; 128.0; 127.9; 127.74; 127.72; 127.4; 127.3; 78.3; 77.8; 74.0; 73.3; 71.7; 71.1; 69.6; 66.6; 55.8; 51.9; 46.6; 23.9; 21.4. Anal. calc. for $C_{39}H_{45}NO_8 \cdot 0.23\ H_2O$: C 70.98, H 6.94, N 2.12; found: C 70.98, H 7.07, N 2.12.

*Benzyl [(2*S*,3*R*,4*R*)-2,3,5-Tris(benzyloxy)-4-hydroxy-1-(2-oxo-2-phenylethyl)pentyl]carbamate* (**4cB**). Yield 70%. Colorless oil; *syn*/*anti* 93:7. $[\alpha]_D^{24} = +12.1$ ($c = 0.105$, $CHCl_3$). IR (film): 3430, 3063, 3031, 2918, 2870, 1717, 1684, 1507, 1497, 1454, 1215, 1090, 1071, 1027, 738, 697. ^{1}H-NMR (400 MHz, $CDCl_3$): *syn*-isomer: 7.84 (*d*, *J* = 7.3, 2 H); 7.54 (*tt*, *J* = 7.3, 1.2, 1 H); 7.41 (*t*, *J* = 7.3, 2 H); 7.36–7.14 (*m*, 20 H); 5.62 (br. *d*, *J* = 8.6, 1 H); 5.04 (*d*, *J* = 12.2, 1 H); 4.88 (*d*, *J* = 12.2,1 H); 4.70 (*d*, *J* = 11.1, 1 H); 4.66 (*d*, *J* = 11.5, 1 H); 4.72–4.59 (*m*, 1 H, overlapped), 4.56 (*d*, *J* = 11.1, 1 H); 4.55 (*d*, *J* = 12.0, 1 H); 4.50 (*d*, *J* = 12.0, 1 H); 4.47 (*d*, *J* = 11.5, 1 H); 4.12 (*m*, 1 H); 3.89 (*dd*, *J* = 4.6, 1.8, 1 H); 3.84 (*dd*, *J* = 6.3, 4.6, 1 H); 3.67 (*dd*, *J* = 9.8, 3.4, 1 H); 3.63 (*dd*, *J* = 9.8, 5.4, 1 H); 3.26 (*dd*, *J* = 16.5, 4.6, 1 H); 3.10 (br. s, 1 H); 3.06 (*dd*, *J* = 16.5, 9.0, 1 H); *anti*-isomer (selected signals): 7.78 (*d*, *J* = 8.0, 1 H); 6.03 (br. *d*, *J* = 9.0, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 198.8; 155.8; 138.1; 138.0; 137.4; 136.52; 136.42; 133.3; 128.5; 128.44; 128.42; 128.40; 128.38; 128.29; 128.26; 128.22; 128.12; 128.03; 128.00; 127.95; 127.88; 127.78; 127.69; 127.56; 79.2; 78.3; 74.0; 73.4; 73.1; 71.1; 70.8; 66.6; 47.9; 41.6. Anal. calc. for $C_{42}H_{43}NO_7 \cdot 0.2\ H_2O$: C 74.47, H 6.46, N 2.07; found: C 74.46, H 6.49, N 2.12.

*Benzyl [(2*S*,3*R*,4*R*)-2,3,5-Tris(benzyloxy)-4-hydroxypentyl]carbamate* (**4cD**). Yield 76%. Colorless oil. ^{1}H-NMR (300 MHz, (D_6)DMSO, 80°): 7.36–7.21 (*m*, 20 H); 6.74 (br. *s*, 1 H); 5.03 (*s*, 2 H); 4.66 (*d*, *J* = 11.3, 1 H); 4.58 (*d*, *J* = 11.7, 1 H); 4.57 (*d*, *J* = 11.3, 1 H); 4.53 (*d*, *J* = 11.7, 1 H); 4.50 (*d*, *J* = 12.4, 1 H); 4.46 (*d*, *J* = 12.4, 1 H); 3.91–3.81 (*m*, 2 H); 3.69 (*dd*, *J* = 6.2, 3.6, 1 H); 3.61 (*dd*, *J* = 10.1, 3.6, 1 H); 3.52 (*dd*, *J* = 10.1, 6.0, 1 H); 3.46 (*ddd*, *J* = 14.1, 5.5, 4.2, 1 H); 3.33 (*ddd*, *J* = 14.1, 6.4, 6.4, 1 H). ^{13}C-NMR (75 MHz, (D_6)DMSO, 80°): 155.8; 138.43; 138.36; 138.28; 137.0; 127.8; 127.66; 127.63; 127.61; 127.17; 127.13; 127.08; 127.05; 127.01; 126.80; 126.75; 79.9; 78.0; 72.5; 72.1; 71.8; 71.0; 69.3; 64.9; 40.8 Anal. calc. for $C_{34}H_{37}NO_6 \cdot 0.28\ H_2O$: C 72.83, H 6.75, N 2.49; found: C 72.83, H 6.67, N 2.45.

*Methyl (4*R*,5*R*,6*R*)-4,5,7-Tris(benzyloxy)-3-{[(benzyloxy)carbonyl]amino}-6-hydroxy-2,2-dimethylheptanoate* (**4dA**). Yield 62%. Colorless oil; *syn*/*anti* 91:9. $[\alpha]_D^{25} = -33.4$ ($c = 0.050$, $CHCl_3$). IR (film): 3443, 3063, 3031, 2950, 2869, 1719, 1507, 1454, 1250, 1217, 1148, 1100, 1052, 1028, 735, 697. ^{1}H-NMR (400 MHz, $CDCl_3$); *syn*-isomer: 7.38–7.10 (*m*, 20 H); 5.86 (*d*, *J* = 10.5, 1 H); 5.14 (*d*, *J* = 12.4, 1 H); 5.10 (*d*, *J* = 12.4, 1 H); 4.90 (*d*, *J* = 10.7,1 H); 4.65 (*d*, *J* = 11.0, 1 H); 4.56 (*d*, *J* = 12.0, 1 H); 4.50 (*d*, *J* = 12.0, 1 H); 4.45 (*d*, *J* = 11.0, 1 H); 4.34 (*d*, *J* = 10.7, 1 H); 4.04 (*d*, *J* = 10.7, 1 H); 3.93 (*m*, 1 H); 3.89 (*d*, *J* = 7.0, 1 H); 3.72–3.56 (*m*, 3 H); 3.30 (*s*, 3 H); 2.82 (*d*, *J* = 5.4, 1 H); 1.23 (*s*, 3 H); 1.21 (*s*, 3 H); *anti*-isomer (selected signals): 5.54 (*d*, *J* = 11.0, 1 H); 2.41 (*d*, *J* = 4.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$, *syn*-isomer): 176.4; 156.8; 138.10; 138.05; 137.99; 137.8; 136.5; 128.5; 128.3; 128.23; 128.17; 128.11; 128.07; 127.9; 127.8; 127.61; 127.58; 127.4; 78.7; 77.8; 74.5; 73.9; 72.2; 70.9; 70.8; 66.9; 59.1; 51.7; 45.2; 23.7; 23.4. Anal. calc. for $C_{39}H_{45}NO_8$: C 71.43, H 6.92, N 2.14; found: C 71.16, H 7.03, N 2.09.

*Benzyl [(2*R*,3*R*,4*R*)-2,3,5-Tris(benzyloxy)-4-hydroxy-1-(2-oxo-2-phenylethyl)pentyl]carbamate* (**4dB**). Yield 77%. Colorless oil; *syn*/*anti* 93:7. $[\alpha]_D^{25} = +7.6$ ($c = 0.880$, $CHCl_3$). IR (film): 3437, 3063, 3031, 2909, 2868, 1716, 1683, 1597, 1497, 1454, 1215, 1071, 1027, 737, 698. ^{1}H-NMR (400 MHz, $CDCl_3$); *syn*-isomer: 7.81 (*d*, *J* = 7.3, 2 H); 7.53 (*tt*, *J* = 7.3, 1.2, 1 H); 7.40 (*t*, *J* = 7.3, 2 H); 7.36–7.13 (*m*, 20 H); 5.50 (br. *d*, *J* = 9.0, 1 H); 5.09

(*d*, $J = 12.2$, 1 H); 5.02 (*d*, $J = 12.2$, 1 H); 4.79 (*d*, $J = 11.2$, 1 H); 4.66 (*d*, $J = 11.2$, 1 H); 4.57 (*d*, $J = 11.2$, 1 H); 4.56 (*d*, $J = 11.9$, 1 H); 4.51 (*d*, $J = 11.2$, 1 H); 4.50 (*d*, $J = 11.9$, 1 H); 4.56 – 4.46 (*m*, 1 H, overlapped), 4.05 (*m*, 1 H); 3.92 (*dd*, $J = 6.3, 2.3$, 1 H); 3.75 (*t*, $J = 6.3$, 1 H); 3.72 (*dd*, $J = 9.6, 3.6$, 1 H); 3.67 (*dd*, $J = 9.6, 6.0$, 1 H); 3.23 (*dd*, $J = 16.9, 4.5$, 1 H); 3.01 (*dd*, $J = 16.9, 8.6$, 1 H); 2.86 (br. *d*, $J = 5.1$, 1 H); *anti*-isomer (selected signals): 6.00 (br. *d*, $J = 8.3$, 1 H); 3.60 (*dd*, $J = 9.6, 5.4$, 1 H); 3.57 (*dd*, $J = 9.6, 4.6$, 1 H); 3.41 (*dd*, $J = 17.5, 5.1$, 1 H); 2.97 (*dd*, $J = 17.5, 6.8$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$; *syn*-isomer): 198.2; 155.9; 138.2; 138.0; 137.8; 136.45; 136.37; 133.2; 128.5; 128.41; 128.36; 128.35; 128.30; 128.12; 128.08; 127.92; 127.87; 127.84; 127.65; 127.60; 80.2; 78.8; 75.0; 74.4; 73.3; 71.1; 70.7; 66.8; 49.2; 41.3. Anal. calc. for $C_{42}H_{43}NO_7$: C 74.87, H 6.43, N 2.08; found: C 74.58, H 6.53, N 2.11.

*Benzyl {1-[(1*R*,2*R*,3*R*)-1,2,4-Tris(benzyloxy)-3-hydroxybutyl]but-3-enyl}carbamate* (**4dC**). Yield 64%. Colorless oil; *syn*/*anti* 94 : 6. $[\alpha]_D^{26} = +10.2$ ($c = 0.275$, $CHCl_3$). IR (film): 3438, 3064, 3031, 2916, 2865, 1718, 1497, 1454, 1213, 1092, 1028, 736, 698. ^{1}H-NMR (300 MHz, $CDCl_3$): *syn*-isomer: 7.36 – 7.19 (*m*, 20 H); 5.66 (*ddt*, $J = 17.1, 10.1, 7.1$, 1 H); 5.23 (*d*, $J = 9.5$, 1 H); 5.10 (*d*, $J = 12.2$, 1 H); 5.02 (*d*, $J = 12.2$, 1 H); 4.99 (br. *d*, $J = 10.1$, 1 H); 4.95 (br. *d*, $J = 17.1$, 1 H); 4.82 (*d*, $J = 11.0$, 1 H); 4.68 (*d*, $J = 11.2$, 1 H); 4.56 (*d*, $J = 12.1$, 1 H); 4.54 (*d*, $J = 11.0$, 1 H); 4.51 (*d*, $J = 12.1$, 1 H); 4.49 (*d*, $J = 11.2$, 1 H); 4.07 – 4.01 (*m*, 2 H); 3.70 – 3.58 (*m*, 4 H); 2.73 (*d*, $J = 5.9$, 1 H); 2.39 – 2.15 (*m*, 2 H); *anti*-isomer (selected signals): 5.92 (*d*, $J = 9.7$, 1 H); 3.10 (*d*, $J = 6.8$, 1 H). ^{13}C-NMR 75 MHz, $CDCl_3$; *syn*-isomer): 156.2; 138.3; 138.04; 137.97; 136.5; 134.6; 128.5; 128.4; 128.3; 128.1; 127.9; 127.8; 127.7; 127.6; 117.7; 80.0; 79.7; 74.9; 74.6; 73.3; 71.3. 70.7; 66.7; 51.9; 38.0. Anal. calc. for $C_{37}H_{41}NO_6$: C 74.60, H 6.94, N 2.35; found: C 74.30, H 6.95, N 2.35.

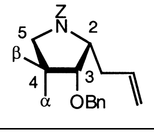
*Benzyl [(2*R*,3*R*,4*R*)-2,3,5-Tris(benzyloxy)-4-hydroxypentyl]carbamate* (**4dD**). Yield 75%. Colorless oil. $[\alpha]_D^{25} = -2.4$ ($c = 0.655$, $CHCl_3$). IR (film): 3426, 3350, 3063, 3031, 2925, 2868, 1718, 1514, 1497, 1454, 1399, 1337, 1253, 1069, 1028, 737, 698. ^{1}H-NMR (300 MHz, $CDCl_3$: 7.38 – 7.25 (*m*, 20 H); 5.05 (*s*, 2 H); 4.85 (br. *t*, $J = 5.8$, 1 H); 4.60 (*d*, $J = 11.4$, 1 H); 4.58 (*d*, $J = 11.4$, 1 H); 4.54 (*d*, $J = 11.4$, 1 H); 4.53 (*d*, $J = 11.4$, 1 H); 4.52 (*s*, 2 H); 3.99 (*ddt*, $J = 7.1, 6.0, 4.6$, 1 H); 3.78 (*ddd*, $J = 5.5, 5.3, 3.5$, 1 H); 3.63 (*d*, $J = 4.6$, 2 H); 3.61 (*dd*, $J = 7.1, 3.5$, 1 H); 3.50 (*ddd*, $J = 14.3, 5.8, .5.5$, 1 H); 3.31 (*ddd*, $J = 14.3, 5.8, 5.3$, 1 H); 2.83 (*d*, $J = 6.0$, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 156.4; 137.8; 137.6; 136.6; 128.5; 128.4; 128.3; 128.00; 127.96; 127.82; 127.8; 78.0; 77.1; 73.5; 73.4; 72.6; 70.9. 70.3; 66.5; 40.9. Anal. calc. for $C_{34}H_{37}NO_6 \cdot 0.28\ H_2O$: C 72.83, H 6.75, N 2.49; found: C 72.83, H 6.67, N 2.45.

*Benzyl [(3*S*,4*R*)-3,5bis(benzyloxy)-4-hydroxy-1-(2-oxo-2-phenylethyl)pentyl]carbamate* (**4eB**). Yield 80%. Colorless oil; dr 50 : 50. $[\alpha]^{25}{}_D = +0.6$ ($c = 0.785$, $CHCl_3$). IR (film): 3416, 3063, 3031, 2915, 2867, 1716, 1678, 1597, 1580, 1497, 1453, 1253, 1216, 1094, 1071, 1027, 752, 698. ^{1}H-NMR (400 MHz, $CDCl_3$, dr 50 : 50): 7.90 (*d*, $J = 7.3$, 1 H); 7.88 (*d*, $J = 7.3$, 1 H); 7.54 (*tt*, $J = 7.3, 1.2$, 0.5 H); 7.53 (*tt*, $J = 7.3, 1.2$, 0.5 H); 7.42 (*t*, $J = 7.3$, 1 H); 7.40 (*t*, $J = 7.3$, 1 H); 7.36 – 7.18 (*m*, 15 H); 5.80 (br. *d*, $J = 8.0$, 0.5 H); 5.64 (br. *d*, $J = 8.3$, 0.5 H); 5.05 (*s*, 2 H); 4.57 (*d*, $J = 11.0$, 0.5 H); 4.53 (*d*, $J = 11.0$, 0.5 H); 4.51 (*s*, 1 H); 4.50 (*s*, 1 H); 4.46 (*s*, 1 H); 4.42 – 4.26 (*m*, 1 H); 3.99 – 3.89 (*m*, 1 H); 3.65 (*ddd*, $J = 9.5, 4.6, 2.4$, 0.5 H); 3.62 – 3.52 (*m*, 2.5 H); 3.40 (br. *d*, $J = 17.0$, 1 H); 3.09 (*dd*, $J = 17.1, 6.6$, 0.5 H); 3.01 (*dd*, $J = 17.1, 6.6$, 0.5 H); 2.89 (*m*, 0.5 H); 2.62 (*m*, 0.5 H); 2.07 – 1.85 (*m*, 1.5 H); 1.76 (*ddd*, $J = 14.9, 9.6, 3.3$, 0.5 H). ^{13}C-NMR (100 MHz, $CDCl_3$, dr 50 : 50): 198.90; 198.85; 155.9; 155.8; 137.9; 137.81; 137.77; 137.72; 136.67; 136.66; 136.5; 136.4; 133.2; 128.55; 128.54; 128.40; 128.38; 128.35; 128.31; 128.09; 128.05; 128.03; 127.95; 127.93; 127.87; 127.80; 127.78; 127.75; 127.73; 127.70; 127.68; 77.2; 76.8; 73.4; 73.3; 72.6; 71.6; 71.5; 70.9; 70.8; 66.5; 66.4; 46.1; 46.6; 42.9; 42.5; 34.4; 33.8. Anal. calc. for $C_{35}H_{37}NO_6$: C 74.05, H 6.57, N 2.47; found: C 73.84, H 6.80, N 2.42.

4. *Cyclization* via *the Mesylation/^{t}BuOK-Treatment Sequence. General Procedure* [13]. To a soln. of **4** (1.0 equiv.) and Et_3N (2.2 equiv.) in CH_2Cl_2 (0.1M) was added dropwise methanesulfonyl chloride (2.0 equiv.) at r.t. The mixture was stirred at r.t. for 2 – 2.5 h. After dilution with AcOEt, the org. layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was diluted with dry THF (0.1M) and treated with ^{t}BuOK (2.0 equiv.) at r.t. The mixture was stirred at r.t. for 15 h, quenched with sat. aq. NH_4Cl soln., and extracted with AcOEt (3 ×). The combined org. phase was dried ($MgSO_4$) and evaporated and the residue purified by prep. TLC (hexane/AcOEt 2 : 1): **5**.

*(2*R*,3*R*)-2-Allyl-3-(benzyloxy)-1-[(benzyloxy)carbonyl]-4,4-dimethylpyrrolidine* (**5bC**). From **4bC** in 88% yield. Colorless oil; single isomer. ^{1}H-NMR (300 MHz, (D_6)DMSO, 50°): 7.35 – 7.24 (*m*, 2 Ph); 5.78 (br. *m*, C*H*=CH$_2$); 5.09 (*d*, $J = 12.8$, 1 H, PhC*H*$_2$OCO); 5.03 (*d*, $J = 12.8$, 1 H; PhC*H*$_2$OCO); 4.95 (br. *d*, $J = 9.7$, CH=C*H*$_2$); 4.58 (*d*, $J = 11.5$, 1 H, PhC*H*$_2$O–C(3)); 4.51 (*d*, $J = 11.5$, 1 H, PhC*H*$_2$O–C(3)); 3.99 (br. *dt*, $J = 5.7, 6.8$ 1 H; H–C(2)); 3.62 (*d*, $J = 5.7$, H–C(3)); 3.24 (br. *d*, $J = 10.2$, H_β–C(5)); 3.07 (*d*, $J = 10.2$, H_α–C(5)); 2.67 – 2.40 (*m*, C*H*$_2$CH=CH$_2$); 1.07 (*s*, Me_α–C(4)); 0.93 (*s*, Me_β–C(4)). NOE: see *Table 4*. ^{13}C-NMR (75 MHz, (D_6)DMSO, 50°): 154.5; 138.1; 136.9; 135.9; 128.1; 128.0; 127.5; 127.24; 127.21; 115.9; 85.1; 73.4; 65.7; 60.3; 56.7; 54.6; 30.4; 25.0; 20.1.

Table 4. *^{1}H-NOE Enhancements of* **5bC**

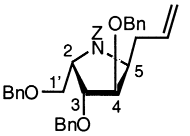


5bC

Irradiated H	Enhancements/%
H–C(2)	H–C(3) (7.9), Me$_\beta$ (3.6)
H–C(3)	H–C(2) (7.8), Me$_\alpha$ (3.4), Me$_\beta$ (3.2), PhC*H*$_2$O–C(3) (6.9)
Me$_\alpha$	H–C(3) (1.0), H$_\alpha$–C(5) (1.6), PhC*H*$_2$O–C(3) (1.1), Me$_\beta$ (2.5)
Me$_\beta$	H–C(2) (1.4), H–C(3) (2.4), H$_\beta$–C(5) (2.6), Me$_\alpha$ (2.0)
H$_\alpha$–C(5)	Me$_\alpha$ (3.2)
H$_\beta$–C(5)	Me$_\beta$ (1.9)

*(2*S*,3*R*,4*R*,5*S*)-5-Allyl-3,4-bis(benzyloxy)-1-[(benzyloxy)carbonyl]-2-[(benzyloxy)methyl]pyrrolidine* (**5dC**). From **4dC** in 91% yield. Colorless oil; single isomer. ^{1}H-NMR (300 MHz, (D$_6$)DMSO, 80°): 7.36–7.16 (*m*, 20 H, 4 Ph); 5.77 (*m*, C*H*=CH$_2$); 5.07 (*s*, PhC*H*$_2$OCO); 4.96–4.82 (*m*, CH=C*H*$_2$), 4.66 (*d*, *J* = 11.9, 1 H, PhC*H*$_2$O–C(4)); 4.60 (*d*, *J* = 11.9, 1 H, PhC*H*$_2$O–C(4)); 4.60 (*s*, 2 H, PhC*H*$_2$OCH$_2$); 4.40–4.32 (*m*, H–C(3), PhC*H*$_2$O–C(3)); 4.18 (*dd*, *J* = 8.8, 7.9, H–C(4)); 4.07–3.96 (*m*, H–C(2), H–C(5)); 3.76 (br. *s*, 1 H; PhCH$_2$OC*H*$_2$); 3.52 (br. *d*, *J* = 9.2, 1 H; PhCH$_2$OC*H*$_2$); 2.54 (*m*, 1 H; PhCH$_2$OC*H*$_2$); 2.25 (*m*, 1 H; C*H*$_2$CH=CH$_2$). NOE: see *Table 5*. ^{13}C-NMR (75 MHz, (D$_6$)DMSO, 80°): 153.4; 138.2; 138.1; 136.4; 135.4; 127.9; 127.77; 127.72; 127.44; 127.37; 127.04; 126.99; 126.94; 126.79; 126.70; 116.6; 80.25; 80.11; 72.2; 71.99; 71.96; 65.7; 55.8; 55.7; 30.1.

Table 5. *^{1}H-NOE Enhancements of* **5dC**

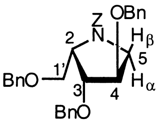


5dC

Irradiated H	Enhancements/%
H–C(2), H–C(5)	H–C(3) and/or PhC*H*$_2$O–C(3) (2.8), H–C(4) (1.7), H$_b$–C(1′) (1.9)
H–C(3), PhC*H*$_2$O–C(3)	H–C(2) (4.1), H–C(4) (1.3), H$_a$–C(1′) (0.9), PhC*H*$_2$OCH$_2$ (1.7)
H–C(4)	H–C(3) (2.1), H–C(5) (7.0), PhC*H*$_2$O–C(4) (4.8)
H$_a$–C(1′)	H–C(3) and/or PhC*H*$_2$O–C(3) (9.0), H$_b$–C(1′) (10.3)
H$_b$–C(1′)	H–C(3) and/or PhC*H*$_2$O–C(3) (6.0)
PhC*H*$_2$O–C(4), PhC*H*$_2$OCH$_2$	H–C(2) or H–C(5) (1.2), H–C(3) and/or PhC*H*$_2$O–C(3) (4.0), H–C(4) (0.7)

*(2*S*,3*R*,4*R*)-3,4-Bis(benzyloxy)-1-[(benzyloxy)carbonyl]-2-[(benzyloxy)methyl]pyrrolidine* (**5dD**). From **4dD** in 82% yield. Colorless oil. $[\alpha]_D^{25} = -7.7$ ($c = 0.430$, CHCl$_3$). IR (film): 3063, 3031, 2931, 2867, 1702, 1496, 1454, 1414, 1356, 1207, 1095, 1027, 913, 735, 697. ^{1}H-NMR (300 MHz, (D$_6$)DMSO, 50°): 7.37–7.19 (*m*, 4 Ph); 5.08 (*d*, *J* = 12.9, 1 H, PhC*H*$_2$OCO); 5.03 (*d*, *J* = 12.9, 1 H, PhC*H*$_2$OCO); 4.61 (*s*, PhC*H*$_2$O–C(3)); 4.56 (*d*, *J* = 12.2, 1 H, PhC*H*$_2$O–C(4)); 4.51 (*d*, *J* = 12.2, 1 H, PhC*H*$_2$O–C(4)); 4.42 (*s*, PhC*H*$_2$OCH$_2$); 4.23 (*ddd*, *J* = 6.4, 6.4, 4.5, H–C(4)); 4.18–4.09 (*m*, H–C(2), H–C(3)); 3.72–3.63 (*m*, PhCH$_2$OC*H*$_2$); 3.56 (*dd*, *J* = 11.3, 6.4, H$_\alpha$–C(5)); 3.34 (*dd*, *J* = 11.3, 4.5, H$_\beta$–C(5)). NOE: see *Table 6*. ^{13}C-NMR (125 MHz, (D$_6$)DMSO, 80°): 154.0; 138.1; 137.92; 137.86; 136.5; 127.9; 127.77; 127.71; 127.3; 127.11; 127.09; 127.04; 127.02; 126.99; 126.81; 126.76; 81.2; 79.0; 72.2; 71.7; 70.6; 66.3; 65.7; 57.4; 49.1. Anal. calc. for $C_{34}H_{35}NO_5$: C 75.95, H 6.56, N 2.61; found: C 76.04, H 6.74, N 2.53.

Table 6. *^{1}H-NOE Enhancements of* **5dD**

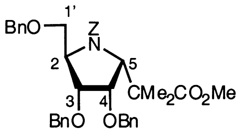


5dD

Irradiated H	Enhancements/%
H–C(2), H–C(3)	CH_2(1′) (5.2), PhCH_2O–C(3) (3.2)
H–C(4)	H_α–C(5) (8.1), PhCH_2O–C(4) (4.6), PhCH_2O–C(3) (4.6)
H_α–C(5)	H_β–C(5) (24.7), H–C(4) (7.8)
H_β–C(5)	H_α–C(5) (18.0), H–C(4) (1.8), PhCH_2O–C(4) (1.2)
CH_2(1′)	H–C(2) (5.3), PhCH_2O–C(3) (1.8), PhCH_2OCH_2 (3.9)
PhCH_2O–C(3)	H–C(3) (4.0), H–C(4) (0.9)
PhCH_2O–C(4)	H–C(3) (1.2), H–C(4) (4.0)
PhCH_2OCH_2	CH_2(1′) (2.0)

5. *(2*R*,3*R*,4*S*,5*R*)-3,4-Bis(benzyloxy)-1-[(benzyloxy)carbonyl]-2-[(benzyloxy)methyl]-5-[(1-methoxycarbonyl)-1-methylethyl]pyrrolidine* (**5cA**). To a suspension of **4cA** (21.9 mg, 0.033 mmol) and 4-Å molecular sieves powder (activated in a domestic microwave oven; 43 mg) in CH_2Cl_2 (0.66 ml) was added pyridinium chlorochromate (21.3 mg, 3 equiv.) at r.t. After being stirred at r.t. for 2 h, *Celite* and AcOEt were added to the mixture. The resulting suspension was filtered through a short column (silica gel, washing with AcOEt), and the filtrate evaporated. The residue was dissolved in dry MeCN (2 ml) and treated with Et_3SiH (19 µl, 3 equiv.) and Me_3SiOTf (18 µl, 3 equiv.) at 0°. After 20 min, the mixture was quenched with sat. aq. $NaHCO_3$ soln. and extracted with AcOEt (3 ×). The combined org. phase was washed with brine, dried ($MgSO_4$), and evaporated, and the residue purified by prep. TLC (hexane/AcOEt 3 :1) to give **5cA** (15.8 mg, 72%). Colorless oil; single isomer. ^{1}H-NMR (300 MHz, (D_6)DMSO, 80°): 7.36–7.17 (*m*, 20 H, 4 Ph); 5.11 (*d*, *J* = 12.5, 1 H, PhCH_2OCO); 4.87 (*d*, *J* = 12.5, 1 H, PhCH_2OCO); 4.66 (*d*, *J* = 11.5, 1 H, PhCH_2O–C(4)); 4.64 (*d*, *J* = 6.7, H–C(5)); 4.60 (*d*, *J* = 11.8, 1 H, PhCH_2O–C(3)); 4.55 (*d*, *J* = 11.8, 1 H, PhCH_2O–C(3)); 4.45 (*d*, *J* = 11.5, 1 H, PhCH_2O–C(4)); 4.32 (*dd*, *J* = 6.7, 5.1, H–C(4)); 4.29 (*s*, PhCH_2OCH_2); 4.07 (*dd*, *J* = 5.1, 4.2, H–C(3)); 3.93–3.83 (*m*, H–C(2), H_a–C(1′)); 3.46 (*dd*, *J* = 9.2, 1.2, H_b–C(1′)); 3.41 (*s*, MeO); 1.21 (*s*, Me_a of CMe_2CO_2Me); 1.13 (*s*, Me_b of CMe_2CO_2Me). NOE: see *Table 7.* ^{13}C-NMR (75 MHz, (D_6)DMSO, 80°): 176.3; 154.5; 137.9; 137.8; 136.2; 127.9; 127.8; 127.75; 127.68; 127.5; 127.4; 127.2; 127.04; 126.99; 126.95; 126.88; 79.0; 76.6; 71.99; 71.93; 71.6; 67.1; 65.6; 63.4; 62.2; 50.7; 44.9; 24.1; 22.5.

Table 7. *^{1}H-NOE Enhancements of* **5cA**



5cA

Irradiated	Enhancements/%
H–C(3)	H–C(4) (7.2), H–C(5) (3.9), PhCH_2O–C(3) (5.8)
H–C(2), H_a–C(1′)	H_b–C(1′) (14.2), PhCH_2OCH_2 (2.3)
H–C(4)	H–C(3) (6.6), H–C(5) (9.8)
H–C(5)	H–C(4) (5.2)
H_b–C(1′)	H–C(2) and/or H_a–C(1′) (21.0), PhCH_2OCH_2 (3.0)
Me_a of CMe_2CO_2Me	H–C(4) (1.1), H–C(5) (1.1), PhCH_2O–C(4) (1.3)
Me_b of CMe_2CO_2Me	H–C(5) (1.7)

6. *(2*S*,3*R*,4*R*)-2-(Hydroxymethyl)pyrrolidine-3,4-diol Hydrochloride* (**7** · HCl). A suspension of **5dD** (36.8 mg), 10% Pd/C (20 mg), and 2N HCl (0.5 ml) in EtOH (1.5 ml) was stirred under 1 atm of H_2 at r.t. for

24 h. After removal of H_2, the mixture was filtered through a *Celite* pad with EtOH. Evaporation of the filtrate gave almost pure **7** · HCl (13.8 mg). $[\alpha]_D^{25} = -3.4$ ($c = 0.070$, H_2O). ^{1}H-NMR (300 MHz, D_2O; dioxane (δ 3.70) as internal standard): 4.29 (br. *d*, $J = 4.4$, 1 H); 4.23 (br. *s*, 1 H); 3.98 – 3.76 (*m*, 3 H); 3.57 (*dd*, $J = 13.0, 4.7$, 1 H); 3.21 (*d*, $J = 13.0$, 1 H). ^{13}C-NMR (75 MHz, D_2O; dioxane (δ 67.40) as internal standard): 75.15; 63.84; 58.08; 51.35.

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