exo-Glycals: Intermediates in the Synthesis of 1,1-Disubstituted *C*-Glycosides

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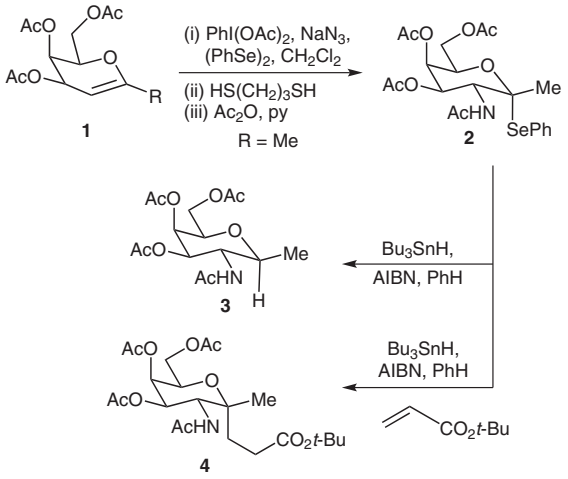
Abstract: The synthesis of 1,1-disubstituted *C*-glycosides containing amino and ester containing moieties at what is formally the anomeric site is described. Petasis olefination of pyranosyl lactones provided *exo*-glycals which underwent regioselective azidoselenation and subsequent radical-mediated *C*-glycoside formation.

Key words: *C*-glycosides, azidoselenation, Petasis olefination

The synthesis of *C*-glycosides as carbohydrate mimetics has been the subject of considerable interest due to the improved stability of this class of carbohydrate derivative towards acidic and enzymatic hydrolysis while still retaining in many cases the desirable biological profile of the 'parent' *O*-glycoside.[1] Consequently, a number of methods have been developed for the preparation of *C*-glycoside analogues of complex carbohydrates.[2] Our contributions[3] in this area have been focused on defining methods for generating α-*C*-glycosides based on gluco, galacto, and manno 2-acetamido sugars, given the biological importance of amino sugars associated in particular with O-linked glycopeptides. We have also extended this chemistry to a wider range of *C*-glycosides and this is illustrated in Scheme 1 for a C1-methylated galacto variant **1** (R = Me). Azidoselenation[4] of *endo*-glycal **1** (R = Me) provided anomeric selenide **2** and C–Se homolysis (and the associated anomeric radical reactivity) was harnessed to provide the β-*C*-glycoside series **3** (by reduction) and by trapping the anomeric radical derived from **2** with a reactive alkene, the 1,1-disubstituted *C*-glycoside **4**.[3c]

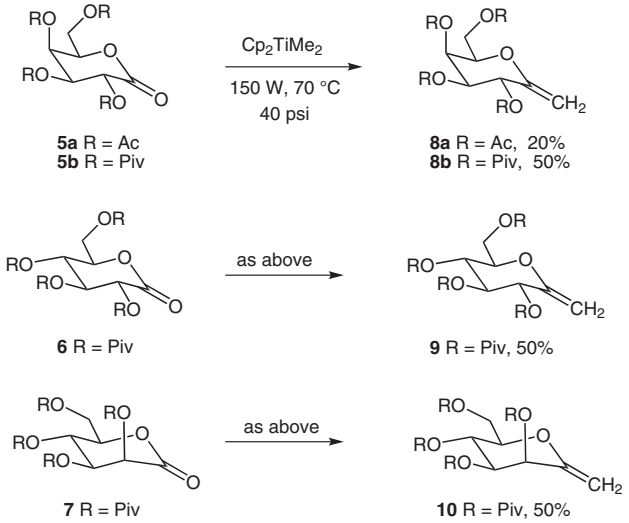


Scheme 1 β-*C*-Glycosides and 1,1-disubstituted *C*-glycosides

However, this chemistry was limited to the use of the C1-unsubstituted or C1-methyl variants (i.e., **1**, R = H or Me) and attempts to extend this chemistry to include other C1 substituents (**1**, R = alkyl or aryl) were unsuccessful. The issue here was that the azidoselenation step (i.e., **1** → **2**) failed when R ≠ H or Me.[5] In order to solve this issue and extend this methodology to a wider range of C1 substitution patterns, we have explored the use of *exo*-cyclic glycals (e.g., **8**–**10**) as a more general starting point for *C*-glycoside synthesis.

Our strategy has involved use of O-protected *exo*-glycals **8**–**10**, which were readily available via Petasis olefination[6] (using Cp_2TiMe_2 under microwave-mediated conditions[7]) from the corresponding galacto, gluco and manno lactones **5**–**7**, respectively (Scheme 2).[8] The olefination process showed only modest levels of selectivity for the lactone carbonyl in the presence of competing *O*-acetate residues (e.g., **5a**) but a higher and synthetically useful level of discrimination was observed when the corresponding *O*-pivaloyl (Piv)-protected carbohydrates (e.g., **5b**) were employed.

Our objective was to evaluate *exo*-glycals **8**–**10** as substrates for a series of addition processes, and these included use of organometallic nucleophiles as well as



Scheme 2 Petasis olefination of galacto, gluco, and manno carbohydrate lactones

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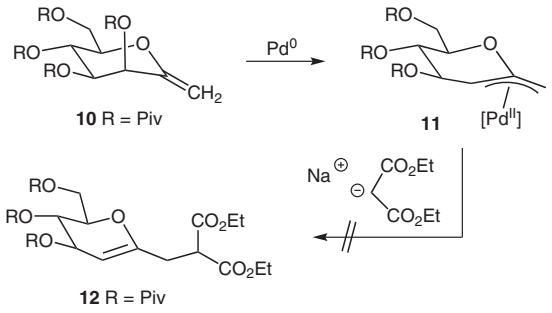
azidoselenation to provide a more general entry to C1-substituted glycals.

While a variety of methods were examined, we were unable to achieve Pd(0)-mediated allylic displacements involving **8**–**10**. Substrates **8b** and **9** were unreactive towards Pd(0) under a variety of conditions, and this was demonstrated using a series of control experiments.[9] In the case of the manno derivative **10**, in which the allylic leaving group is positioned in a stereoelectronically more favorable arrangement for displacement,[10] evidence for the intermediacy of the π-allyl Pd(II) species **11** was obtained. However, this species was unreactive towards a malonate nucleophile, and the desired adduct **12** was not observed (Scheme 3).[9,11]



Scheme 3

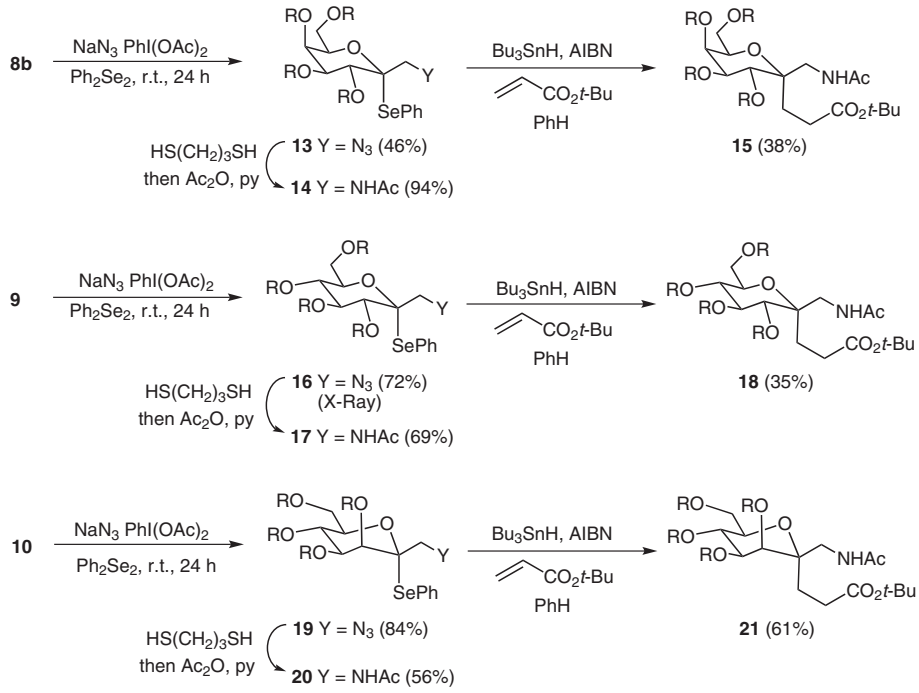
Azidoselenation does, however, provide an alternative means of functionalizing *exo*-glycals **8b**, **9**, and **10**. In the case of the galacto derivative **8b**, azidoselenation gave the selenoglycoside adduct **13** in 46% yield.[12]

One-pot azide reduction (using a dithiol) and protection provided the N-acetylated amine **14** in 94% yield. The regiochemistry of the azidoselenation step was confirmed by ^{1}H NMR: acetamide **14** clearly showed CH*H*NHAc as a doublet of doublets (J = 14.5, 3.5 Hz) where coupling (J = 3.5 Hz) to the amide NH was apparent. *C*-Glycoside formation was achieved by homolysis of the C–Se bond in **14** and trapping of the resulting anomeric (and tertiary) radical species with *tert*-butyl acrylate to give the 1,1-disubstituted *C*-glycoside **15** as a single isomer (see below). Similar sequences were achieved in the gluco series (**9** → **16** → **17**) and in the manno series (**10** → **19** → **20**) to provide 1,1-disubstituted *C*-glycosides **18** and **21**, respectively.

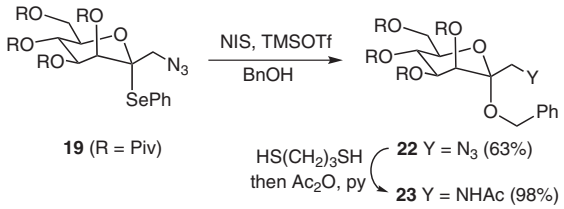
Regiochemical assignments of **15**, **18**, and **21** were based on ^{1}H NMR analysis (following from the assignment of the acetamide **14**) but it was not possible to assign 'anomeric' stereochemistry unambiguously. For this reason, the structure of azidoselenide **16**[13] was determined by X-ray crystallography, which demonstrated the expected preference of the anomeric radical to undergo axial attack, with the trapping agent being Ph_2Se_2. We have assumed that the galacto and manno adducts and the corresponding *C*-glycosides **15**, **18**, and **21** display the same stereochemical preference, and this is indicated as the outcomes shown in Scheme 4.

It is also pertinent to note that selenoglycosides function as glycosyl donors in more conventional O-glycosylation processes.[14] Using the manno adduct **19**, activation using NIS/TMSOTf and employing benzyl alcohol as the acceptor, gave *O*-glycoside **22** which underwent dithiol-mediated azide reduction and in situ acetylation to give *O*-glycoside **23** in 60% overall yield (Scheme 5).[15]

The α-stereochemistry of *O*-glycosides **22** and **23** is assumed (based on an expected preference for an α-manno-



Scheme 4 Generation of 1,1-disubstituted *C*-glycosides via C1-substituted selenide intermediates; R = Piv throughout



Scheme 5

side) as ^{1}H NMR did not allow for an unambiguous assignment of anomeric stereochemistry.

In summary, radical-mediated azidoselenation, which is well established for conventional endocyclic glycals, is also effective with *exo*-glycals. The resulting adducts function as intermediates for the synthesis of 1,1-disubstituted *C*-glycosides which constitute an unusual class of carbohydrate-based amino acids derivatives **15**, **18**, and **21**, and also *O*-glycosides, such as **22** and **23**.

Acknowledgment

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(5) Using C1-metalated *endo*-glycals we have prepared a series of C1-substituted alkyl and aryl glycals (i.e., **1** R = Alk, Ar) and evaluated these as substrates for azidoselenation. Even under forcing conditions, no azidoselenation was observed and this is attributed to the known (and facile) reversible nature of the azidoselenation process. We assume that trapping with Ph_2Se_2 of the intermediate (a tertiary or benzylic anomeric radical) resulting from initial N_3·addition is slow and expulsion of N_3·(and its subsequent decomposition) is too efficient. When the C1 substituent carried a pendent alkenyl residue (e.g., allyl), only addition to this less electron-rich alkene was observed (Gallagher, T.; Wang, J.-W. *unpublished work*).

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(8) **Data for *exo*-Glycals**
Conventional carbohydrate numbering (cf. sialic acids) is used.
Compound **8b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13, 1.20, 1.23, 1.28 [36 H, 4 × s, 4 × $COC(CH_3)_3$], 3.99–4.10 (2 H, m, H7a + H7b), 4.25 (1 H, m, H6), 4.50 (1 H, t, *J* = 1.5 Hz, =CH*H*, H1a), 4.77 (1 H, t, *J* = 1.5 Hz, =C*H*H, H1b), 5.15 (1 H, dd, *J* = 10.5, 3.0 Hz, H4), 5.53 (1 H, dd, *J* = 3.0, 1.0 Hz, H5), 5.76 (1 H, dt, *J* = 10.5, 1.5 Hz, H3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0, 27.1, 38.7, 38.8, 61.2, 66.6, 67.2, 71.5, 75.8, 95.3, 154.6, 176.7, 176.8, 177.8. ESI-HRMS: *m/z* calcd for $C_{27}H_{44}0_9$ [M + Na]$^+$: 535.2878; found: 535.2868. Compound **9**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14–1.24 [36 H, m, 4 × $COC(CH_3)_3$], 3.77–3.78 (1 H, m, H6), 4.06–4.26 (2 H, m, H7a + H7b), 4.49 (1 H, t, *J* = 1.5 Hz, H1a), 4.80 (1 H, t, *J* = 1.5 Hz, H1b), 5.26 (2 H, dd, *J* = 7.0, 2.5 Hz, H4 + H5), 5.47 (1 H, m, H3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.1, 27.2, 38.8, 38.9, 61.7, 67.6, 69.0, 72.8, 76.6, 96.2, 154.0, 176.4, 176.5, 177.1, 178.1. ESI-HRMS: *m/z* calcd for $C_{27}H_{44}0_9$ [M + Na]$^+$: 535.2878; found: 535.2902. Compound **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13–1.25 [36 H, m, 4 × $COC(CH_3)_3$], 3.87 (1 H, m, H6), 4.23–4.25 (2 H, m, H7a + H7b), 4.71 (1 H, d, *J* = 1.0 Hz, H1a), 4.83 (1 H, d, *J* = 1.0 Hz, H1b), 5.15 (1 H, dd, *J* = 10.0, 3.5 Hz, H4), 5.62 (1 H, app t, *J* = 10.0 Hz, H5), 5.69 (1 H, d, *J* = 3.5 Hz, H3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0, 27.1, 27.1, 38.7, 38.8, 38.9, 61.4, 64.5, 68.9, 71.0, 77.0, 101.4, 152.9, 176.6, 176.9, 177.3, 178.1. ESI-HRMS: *m/z* calcd for $C_{27}H_{44}O_9$ [M + Na]$^+$: 535.2877; found: 535.2890.

(9) To determine whether the carbohydrate substrates were reactive towards Pd(0), a series of control experiments were carried using cinnamyl acetate as a standard. Exposure of cinnamyl acetate and *exo*-glycal **8b** (or **9** or **10**) to sodio-diethyl malonate in the presence of a catalytic quantity of Pd(0) (Pd_2dba_3/dppe) led to the expected substituted cinnamyl adduct as the only product observed and galacto **8b** was recovered unchanged. With the gluco substrates **9** essentially the same outcome was observed: cinnamyl acetate reacted but *exo*-glycal **9** did not. In the case of the manno variant **10**, and under the same reaction conditions, none of the cinnamyl substitution product was detected, suggesting that coordination of Pd(0) to **10** occurred [to sequester Pd(0)] but any resulting complex (e.g., **11**) was then unreactive towards the external malonate nucleophile.

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(11) Extensive attempts (varying ligands, reaction temperatures, solvents and catalysts, including use of palladium and nickel) to carry out the allylic displacement chemistry using manno substrate **10** were all unsuccessful.

(12) Spectroscopic data are provided for the galacto series shown in Scheme 4.
Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.28 [36 H, m, 4 × $COC(CH_3)_3$], 3.12 (1 H, d, *J* = 13.5 Hz, 1 × CH_2N_3), 3.62 (1 H, d, *J* = 13.5 Hz, 1 × CH_2N_3), 3.94 (1

H, dd, J = 11.0, 9.0 Hz, H6a), 4.03 (1 H, dd, J = 11.0, 6.0 Hz, H6b), 4.71 (1 H, m, H5), 5.48 (1 H, dd, J = 10.5, 3.0 Hz, H3), 5.59 (1 H, dd, J = 3.0, 1.0 Hz, H4), 5.87 (1 H, d, J = 10.5 Hz, H2), 7.35–7.44 (3 H, m, ArCH), 7.58–7.61 (2 H, m, ArCH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.9, 27.0, 27.1, 38.7, 38.8, 38.9, 39.0, 56.1, 60.3, 66.5, 66.7, 70.5, 70.5, 91.9, 124.5, 129.3, 137.6, 176.3, 177.9, 180.4, 180.5. ESI-HRMS: *m/z* calcd for $C_{33}H_{49}N_3O_9Se$ $[M + Na]^+$: 734.2526; found: 734.2556.

Compound **14**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.27 [36 H, m, 4 × $COC(CH_3)_3$], 2.09 (3 H, s, $NHCOCH_3$), 3.36 (1 H, dd, J = 14.5, 3.5 Hz, 1 × $CH_2NHCOCH_3$), 3.97 (1 H, m, H6a), 4.06–4.15 (2 H, m, H6b + 1 × $CH_2NHCOCH_3$), 4.85 (1 H, m, H5), 5.50–5.53 (2 H, m, H2 + H4), 5.61 (1 H, m, H3), 6.03 (1 H, m, NH), 7.31–7.38 (3 H, m, ArCH), 7.59–7.64 (2 H, m, ArCH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7, 26.9, 27.0, 27.1, 27.2, 27.2, 38.7, 38.8, 39.0, 45.0, 60.4, 66.4, 67.1, 70.2, 71.1, 91.6, 124.7, 129.1, 129.2, 129.2, 137.4, 169.3, 176.4, 177.2, 177.9, 178.1. ESI-HRMS: *m/z* calcd for $C_{35}H_{53}NO_{10}Se$ $[M + Ma]^+$: 750.2727; found: 750.2712.

Compound **15**: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11–1.30 [36 H, m, 4 × $COC(CH_3)_3$], 1.40–1.55 [2 H, m, $CH_2CH_2CO_2C(CH_3)_3$], 2.06 (3 H, s, $NHCOCH_3$), 2.17–2.32 [2 H, m, $CH_2CH_2CO_2C(CH_3)_3$], 3.38–3.44 (2 H, m, $CH_2NHCOCH_3$), 3.62 (1 H, m, H5), 3.97–4.04 (2 H, m, H6a + H6b), 5.08 (1 H, dd, J = 10.5, 3.0 Hz, H4), 5.20 (1 H, d, J = 10.0 Hz, H2), 5.48 (1 H, dd, J = 10.0, 3.0 Hz, H3), 6.05 (1 H, d, J = 5.0 Hz, NH). ^{13}C NMR (100 MHz, acetone-d_6): δ = 20.2, 23.5, 26.5, 26.6, 26.7, 26.8, 27.1, 27.5, 27.5, 27.6, 27.6, 38.4, 38.8, 39.5, 42.5, 61.3, 66.5, 67.8, 72.5, 77.0, 106.9, 172.1, 172.9. ESI-HRMS: *m/z* calcd for $C_{36}H_{61}NO_{12}$ $[M + Na]^+$: 722.4086; found: 722.4098.

Compound **18**: ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.09–1.22 [36 H, m, 4 × $COC(CH_3)_3$], 1.44–1.49 [2 H, m, $CH_2CH_2CO_2C(CH_3)_3$], 2.01 (3 H, s, $NHCOCH_3$), 2.40-2.42 (2 H, m, $CH_2CH_2CO_2C(CH_3)_3$), 3.26 (1 H, dd, J = 14.5, 4.5, 1 × $CH_2NHCOCH_3$), 3.43 (1 H, dd, J = 14.5, 7.5, 1 × $CH_2NHCOCH_3$), 4.02 (1 H, m, H5), 4.09–4.11 (2 H, m, H6a + H6b), 5.00 (1 H, app t, J = 10.0 Hz, H4), 5.17 (1 H, d, J = 10.0 Hz, H2), 5.49 (1 H, app t, J = 10.0 Hz, H3), 6.42 (1 H, br s, NH). ^{13}C NMR (100 MHz, acetone-d_6): δ = 20.2, 23.3, 26.5, 26.6, 26.7, 27.5, 27.0, 27.6, 29.5, 29.3, 42.4, 62.7, 68.6, 70.1, 71.2, 104.1, 169.2, 172.0, 176.8, 177.3, 177.3. ESI-HRMS: *m/z* calcd for $C_{36}H_{61}NO_{12}$ $[M + Na]^+$: 722.4086; found: 722.4109.

Compound **21**: ^{1}H NMR (400 MHz, acetone-d_6): δ = 1.10–1.29 [36 H, m, 4 × $COC(CH_3)_3$], 1.44–1.50 [2 H, m, $CH_2CH_2CO_2C(CH_3)_3$], 2.12 (3 H, s, $NHCOCH_3$), 2.29–2.32 [2 H, m, $CH_2CH_2CO_2C(CH_3)_3$], 3.22 (1 H, m, 1 × $CH_2NHCOCH_3$), 3.40 (1 H, m, 1 × $CH_2NHCOCH_3$), 3.90 (1 H, m, H5), 4.12 (1 H, dd, J = 12.0, 4.5 Hz, H6a), 4.24 (1 H, d, J = 12.0, 2.0 Hz, H6b), 5.14 (1 H, dd, J = 10.0, 3.5 Hz, H3), 5.36 (1 H, d, J = 10.0 Hz, H2), 5.41 (1 H, dd, J = 3.5, 1.0 Hz, H4). ^{13}C NMR (100 MHz, acetone-d_6): δ = 20.0, 26.4, 26.5, 26.6, 26.7, 27.0, 27.5, 27.6, 27.7, 38.3, 38.5, 39.0, 42.0, 42.3, 61.9, 65.6, 68.1, 72.4, 76.2, 100.0, 173.2, 176.9, 177.1, 179.8. ESI-HRMS: *m/z* calcd for $C_{36}H_{61}NO_{12}$ $[M + Na]^+$: 722.4086; found: 722.4087.

(13) (a) An X-ray diffraction experiment on **16** was carried out at 100 K on a Bruker APEX II diffractometer using MoKα radiation (λ = 0.71073 Å). The data collection was performed using a CCD area detector from a single crystal mounted on a glass fibre. Intensities were integrated (Bruker-AXS SAINT V7.60A) from several series of exposures measuring 0.5° in ω or φ. Absorption corrections were based on equivalent reflections using SADABS (Sheldrick, G. M. SADABS V2008/1, University of Göttingen, Germany), and structures were refined against all F_o^2 data with hydrogen atoms riding in calculated positions using SHELXL Bruker-AXS SAINT V7.60A.[13b] The Cambridge Crystallographic Data Centre deposition number for **16** is CCDC 763564. (b) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112.

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(15) Compound **22**: ^{1}H NMR (400 MHz, acetone-d_6): δ = 1.06, 1.10, 1.16, 1.26 [36 H, 4 × s, 4 × $COC(CH_3)_3$], 1.97 ($NHCOCH_3$), 3.53 (1 H, dd, J = 15.0, 5.0 Hz, 1 × $CH_2NHCOCH_3$), 3.74 (1 H, dd, J = 15.0, 8.0 Hz, 1 × $CH_2NHCOCH_3$), 4.09 (1 H, m, H5), 4.16 (1 H, dd, J = 12.0, 4.5 Hz, H6a), 4.32 (1 H, dd, J = 12.0, 2.0 Hz, H6b), 4.67 (1 H, d, J = 12.0 Hz, 1 × CH_2Ph), 4.90 (1 H, d, J = 12.0 Hz, 1 × CH_2Ph), 5.37 (1 H, app t, J = 2.0 Hz, H2), 5.44–5.46 (2 H, m, H3 + H4), 6.16 (1 H, app t, J = 6.0 Hz, NH), 7.35 (1 H, m, ArCH), 7.40–7.48 (4 H, m, ArCH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 26.5, 26.5, 26.6, 26.8, 37.7, 38.3, 38.5, 38.6, 38.7, 59.7, 61.6, 62.7, 65.0, 68.1, 70.1, 101.4, 127.7, 127.8, 128.7, 138.0, 170.0, 176.3, 176.6, 177.1, 177.3. ESI-HRMS: *m/z* calcd for $C_{36}H_{55}NO_{11}$ $[M + Na]^+$: 700.3667; found: 700.3679

Compound **23**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12, 1.14, 1.25, 1.30 [36 H, 4 × s, 4 × $COC(CH_3)_3$], 3.26 (1 H, d, J = 13.5 Hz, 1 × CH_2N_3), 3.70 (1 H, d, J = 13.5 Hz, 1 × CH_2N_3), 3.92 (1 H, app dq, J = 10.0, 2.0 Hz, H5), 4.12 (1 H, app d, J = 3.5 Hz, H6a), 4.14 (1 H, app d, J = 3.5 Hz, H6b), 4.62 (2 H, ABq, J = 12.0 Hz, CH_2Ph), 5.41–5.52 (2 H, m, H3 + H4), 5.58 (1 H, d, J = 3.0 Hz, H2), 7.35–7.45 (5 H, m, ArCH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0, 27.1, 38.3, 38.8, 49.5, 61.8, 63.3, 64.7, 68.4, 70.1, 70.6, 100.8, 127.2, 128.7, 131.5, 136.4, 176.7, 177.1, 178.0. ESI-HRMS: *m/z* calcd for $C_{34}H_{51}N_3O_{11}$ $[M + Na]^+$: 684.3467; found: 684.3478.