Efficient Synthesis of Cyclic Glycolipid Analogues

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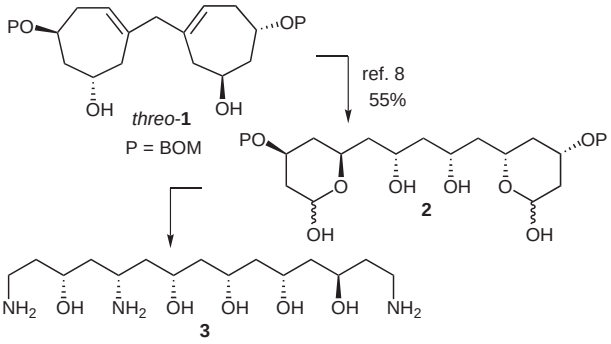
Abstract: A straightforward approach to macrocyclic structures containing deoxysugar subunits was developed through the functionalization of a bishemiketal. The choice of the length and the nature of the linkers can provide macrocycles with diverse rigidities and polarities.

Key words: cyclic glycolipid analogues, biscoupling reaction, coupling reagent, C-glycosylation, ring-closing metathesis

Carbohydrate-containing macrocycles and analogues represent highly interesting molecules in view of their diverse architectures and promising biological properties.[1] For instance, rigid cyclic glycolipids containing a phenylene-1,4-diamine subunit[2] have been prepared and may be used for modeling carbohydrate–carbohydrate interactions at interfaces relevant to cell–cell adhesion and communication. Butane-1,4-diol-linked cyclic neooligoaminodeoxysaccharides[3] have been synthesized for studying the RNA–small molecules interactions and for their ability to be superior binders for RNA than natural aminoglycosides. Carbohydrate macrocycles may also be useful as functional molecular pores.[4] It has been reported by Bundle et al.[5] that tethered analogues of trisaccharide epitopes display enhanced affinity for the binding to a monoclonal antibody. Strained cyclic glycophanes containing glucal subunits[6] also represent potential cage molecules for the complexation of cations and small molecules.[7] Recently, we disclosed[8] the synthesis of bishemiketal intermediate **2** through an ozonolysis–diastereoselective reduction sequence on diolefin *threo*-**1**.[9]

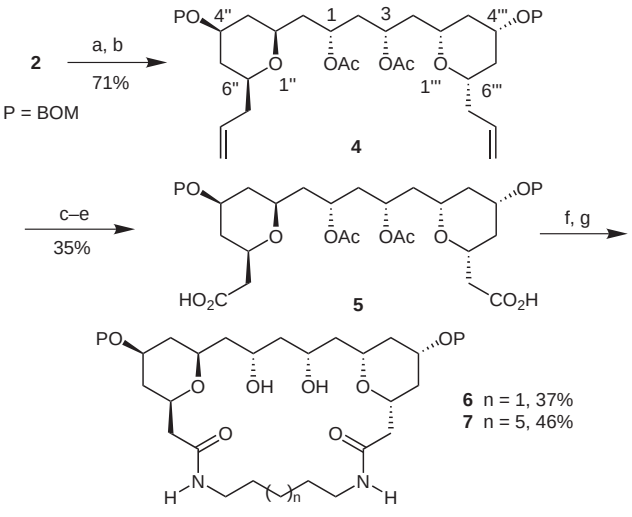
This derivative was then efficiently converted into several amino-functionalized polyketides. Polyketide-like macrolides were also efficiently prepared from diolefin **1** (Scheme 1).[10] We report here the straightforward conversion of **2** into analogues of carbohydrate-containing macrocycles.

Our strategy for the preparation of macrocyclic structures was based on the double functionalization of the hemiketal moieties of **2** through a C-glycosylation reaction followed by biscoupling with a linker to close the macrolide. Peracetylation of **2**, followed by treatment with allyltrimethylsilane and $BF_3{\cdot}OEt_2$, under diluted conditions,[11] afforded the bisallyl derivative **4** in 71% yield (two steps), as a single isomer (Scheme 2). The equatorial arrangement of the substituents at C(2″, 2‴), C(4″, 4‴) and C(6″, 6‴) was established by 2D NOESY experiment.



Scheme 1 Preparation of amino-functionalized polyketides

Transformation of diolefin **4** into the corresponding diol, followed by coupling with biscarboxylic acids[12] failed to provide the corresponding cyclic bislactones. Alternatively, ozonolysis of **4** followed by oxidation of the resulting aldehyde moieties, in the presence of $NaClO_2$, gave diacid **5** in 35% yield (three steps). A biscoupling reaction with linear polyamines such as pentane-1,5-diamine and nonane-1,9-diamine, using PyBOP (benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate) as



Scheme 2 Synthesis of macrocyclic diamides. *Reagents and conditions*: (a) Ac_2O, pyridine, DMAP (cat.); (b) $H_2C{=}CHCH_2SiMe_3$, $BF_3{\cdot}OEt_2$, 4 A MS, MeCN, 0 °C; (c) O_3, CH_2Cl_2, –78 °C; (d) Me_2S, –78 °C; (e) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*-BuOH–H_2O; (f) $H_2N(CH_2)_5NH_2$ or $H_2N(CH_2)_9NH_2$, $(i\text{-}Pr)_2NEt$, PyBOP, DMF; (g) K_2CO_3, MeOH.

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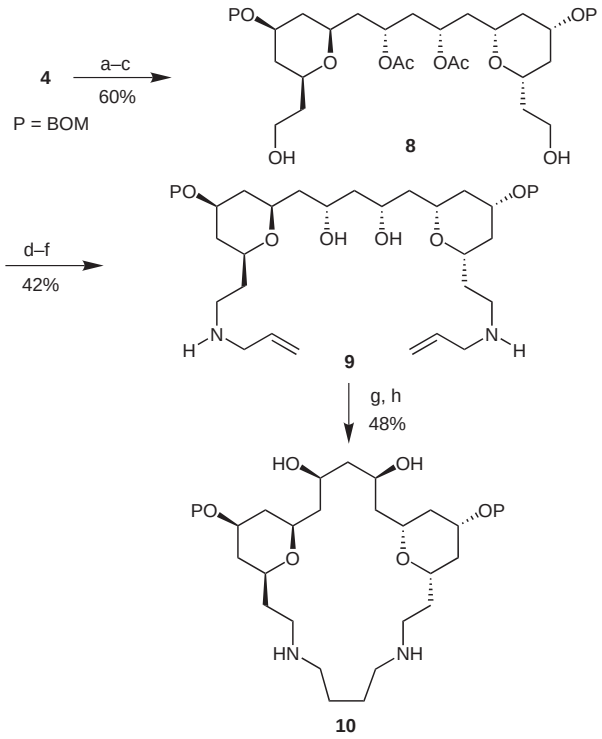
coupling reagent under diluted conditions, afforded macrocyclic bisamides **6** and **7**, in 37% and 46% yields, respectively, after methanolysis of the acetyl groups.

We also envisaged the use of ring-closing metathesis[13] for the formation of macrocycles containing deoxysugars. Esterification of diol **8**[14] with methanesulfonyl chloride, followed by displacement of the intermediate dimesylate with allylamine and cleavage of the acetyl groups, provided diamine **9** in 42% yield (three steps). Upon treatment with Grubbs' II catalyst at low concentration (0.003 M), compound **9** underwent a ring-closing metathesis reaction. Contrarily to our previous studies on the cyclization of linear polyketides[10] which led to a cross-metathesis process prior to ring closure, no traces of cross-coupling derivatives were observed with bisallyl intermediate **9**. Subsequent reduction of the double bond by catalytic hydrogenation afforded the macrocyclic diamine **10**[14] in 48% yield (two steps; Scheme 3).

In summary, we have described an efficient synthetic route toward novel macrocyclic derivatives containing deoxysugar subunits and diamino- or diamidoalkyl linkers. In particular, ring-closing metathesis and peptide coupling reactions under diluted conditions have proven to be suitable transformations for the construction of these derivatives. The methods reported so far for the preparation of glycolipids analogues often rely on the synthesis of sugar units appended with alkenyl, alkynyl and azido functionalities for further cyclization through ring-closing metathesis or Cu(I)-catalyzed 1,3-dipolar cycloadditions. The bidirectional strategy disclosed here provides an alternative pathway, using synthon **2** as a template to introduce nitrogen-containing linkers for generating macrocyclic structures. These molecules represent interesting scaffolds for the preparation of biologically active compounds.



Scheme 3 Synthesis of a macrocyclic diamine through ring-closing metathesis. *Reagents and conditions*: (a) O_3, CH_2Cl_2, –78 °C; (b) Me_2S, –78 °C; (c) $NaBH_4$, MeOH; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C; (e) allylamine–DMF (1:3), K_2CO_3, 40 °C; (f) MeOH; (g) Grubbs' II catalyst (0.2 equiv), CH_2Cl_2 (0.003 M), 50 °C; (h) H_2, Pd/C, EtOAc–MeOH.

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References and Notes

(1) (a) Furukawa, J.; Sakairi, N. *Trends Glycosci. Glycotechnol.* **2001**, *13*, 1. (b) Wessjohann, L. A.; Ruijter, E.; Garcia-Rivera, D.; Brandt, W. *Mol. Diversity* **2005**, *9*, 171.

(2) (a) Velasco-Torrijos, T.; Murphy, P. V. *Org. Lett.* **2004**, *6*, 3961. (b) Murphy, P. V.; Müller-Bunz, H.; Velasco-Torrijos, T. *Carbohydr. Res.* **2005**, *340*, 1437. (c) Velasco-Torrijos, T.; Murphy, P. V. *Tetrahedron: Asymmetry* **2005**, *16*, 261.

(3) (a) Chen, G. W.; Kirschning, A. *Chem. Eur. J.* **2002**, *8*, 2717. (b) Jaunzems, J.; Oelze, B.; Kirschning, A. *Org. Biomol. Chem.* **2004**, *2*, 3448.

(4) Bodine, K. D.; Gin, D. Y.; Gin, M. S. *Org. Lett.* **2005**, *7*, 4479.

(5) McGavin, R. S.; Gagne, R. A.; Chervenak, M. C.; Bundle, D. R. *Org. Biomol. Chem.* **2005**, *3*, 2723.

(6) Belghiti, T.; Joly, J. P.; Didierjean, C.; Dahaoui, S.; Chapleur, Y. *Tetrahedron Lett.* **2002**, *43*, 1441.

(7) Fukudome, M.; Shiratani, T.; Nogami, Y.; Yuan, D. Q.; Fujita, K. *Org. Lett.* **2006**, *8*, 5733.

(8) Coste, G.; Gerber-Lemaire, S. *Eur. J. Org. Chem.* **2006**, 3903.

(9) (a) Schwenter, M. E.; Vogel, P. *Chem. Eur. J.* **2000**, *6*, 4091. (b) Csákÿ, A. G.; Vogel, P. *Tetrahedron: Asymmetry* **2000**, *11*, 4935. (c) Schwenter, M. E.; Vogel, P. *J. Org. Chem.* **2001**, *66*, 7869. (d) Gerber-Lemaire, S.; Vogel, P. *Eur. J. Org. Chem.* **2003**, 2959. (e) Meilert, K. M.; Schwenter, M. E.; Shatz, Y.; Dubbaka, S. R.; Vogel, P. *J. Org. Chem.* **2003**, *68*, 2964. (f) Vogel, P.; Gerber-Lemaire, S.; Carmona Asenjo, A. T.; Meilert, K.; Schwenter, M. E. *Pure Appl. Chem.* **2005**, 131.

(10) Coste, G.; Gerber-Lemaire, S. *Synlett* **2006**, 685.

(11) Kagawa, N.; Ihara, M.; Toyota, M. *Org. Lett.* **2006**, *5*, 875.

(12) Muthusamy, S.; Gnanaprakasam, B.; Zurres, E. *Org. Lett.* **2006**, *5*, 1913.

(13) For the synthesis of cyclic glycolipids using ring-closing metathesis, see: (a) Fürstner, A.; Müller, T. *J. Am. Chem. Soc.* **1999**, *121*, 7814. (b) Fürstner, A. *Eur. J. Org. Chem.* **2004**, 943. (c) Dörner, S.; Westermann, B. *Chem. Commun.* **2005**, 2852.

(14) **Preparation and Data for 4**: A solution of **2** (176 mg, 0.305 mmol) in pyridine–Ac_2O (1:1, 6 mL) was treated with DMAP (15 mg, 0.122 mmol, 0.4 equiv) at 25 °C for 3 h. After completion of the reaction, solvents were evaporated in vacuo. Purification of the residue by flash chromatography (60% EtOAc in pentane) afforded the resulting peracetylated bishemiketal as a yellow oil (205 mg, quant.). To a solution of this intermediate in MeCN (68 mL) was added 4 Å MS (1.4 g) and the mixture was stirred for 30 min. Allyltrimethylsilane (525 µL, 3.303 mmol, 12 equiv) was introduced and the solution was stirred for an additional 30

min. At 0 °C, $BF_3{\cdot}OEt_2$ (210 μL, 1.651 mmol, 6 equiv) was added. After stirring for 1 h at 0 °C the reaction mixture was poured into a sat. aq $NaHCO_3$ solution (40 mL) and filtered through a pad of celite®. The filtrate was extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with brine (70 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (30% EtOAc in pentane) afforded **4** as a colorless oil (153 mg, 71% over two steps). IR (film): 3410, 2100, 1450, 1370, 1240, 1190, 1140, 1060, 960, 830, 780 cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.25–7.35 (m, 10 H), 5.74–5.80 (m, 2 H), 4.98–5.10 (m, 6 H), 4.78 (s, 4 H), 4.60 (s, 4 H), 3.95–4.02 (m, 4 H), 3.73–3.80 (m, 2 H), 2.32–2.48, 2.13–2.24 (2 × m, 2 × 2 H), 1.96–2.07, 1.53–1.72 (2 × m, 4 H), 1.83–1.96, 1.27–1.36 (2 × m, 4 H), 1.73–1.83, 1.53–1.72 (2 × m, 6 H), 1.98 (s, 6 H). ^{13}C NMR (100 MHz, MeOD): δ = 171.5, 171.4, 142.2, 135.5, 135.4, 128.4, 128.0, 127.7, 116.4, 116.3, 92.9, 70.8, 70.7, 69.9, 69.8, 69.6, 69.5, 69.0, 66.8, 66.0, 39.9, 39.5, 38.6, 37.4, 37.3, 37.2, 37.1, 34.9, 20.4, 20.3. ESI–MS: *m*/*z* = 709.3 [M + H]. MALDI–HRMS: *m*/*z* [M + Na] calcd for $C_{41}H_{56}O_{10}$: 731.3771; found: 731.3769.

Preparation and Data for 5: O_3 was passed through a solution of **4** (200 mg, 0.282 mmol) in CH_2Cl_2 (9 mL) during 5 min at –78 °C. After persistence of a blue coloration, O_2 was passed through the solution to eliminate the excess of O_3. Dimethyl sulfide (83 μL, 1.128 mmol, 4 equiv) was added and the mixture was stirred for an additional 10 min. The solvent was evaporated in vacuo at 0 °C. The residual oil was dissolved in *t*-BuOH–H_2O (1:1, 4 mL) and treated with KH_2PO_4 (461 mg, 3.385 mmol, 12 equiv), $NaClO_2$ (383 mg, 231 mmol, 15 equiv) and 2-methylbut-2-ene (200 μL, 231 mmol, 15 equiv) at 25 °C for 12 h. The mixture was poured into brine (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (5–20% of MeOH in CH_2Cl_2) afforded **5** as a yellow oil (74 mg, 35% over three steps). IR (film): 3440, 2940, 1740, 1715, 1680, 1375, 1245, 1100, 1140, 740, 700 cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.24–7.34 (m, 10 H), 5.10–5.16 (m, 2 H), 4.78 (d, 4 H), 4.61 (s, 4 H), 4.49–4.57 (m, 2 H), 3.93–4.04 (m, 2 H), 3.83–3.91, 3.67–3.78 (2 × m, 2 × 1 H), 2.54–2.65, 2.27–2.35 (2 × m, 2 × 2 H), 2.05, 2.03 (2 × s, 6 H), 1.87–1.98, 1.61–1.86 (3 × m, 14 H). ^{13}C NMR (100 MHz, MeOD): δ = 181.7, 181.6, 174.2, 173.3, 139.4, 129.4, 128.9, 128.7, 93.8, 71.3, 70.9, 70.9, 70.6, 70.6, 70.3, 69.8, 68.2, 67.6, 42.2, 41.7, 41.6, 39.8, 39.3, 38.5, 37.8, 36.7, 36.6, 21.6, 21.5. ESI–HRMS: *m*/*z* [M + K] calcd for $C_{39}H_{52}O_{14}$: 783.2994; found: 783.3040.

Preparation and Data for 6: To a solution of **5** (25 mg, 0.033 mmol) in DMF (1.4 mL) were added (*i*-Pr)$_2$NEt (15 μL, 0.081 mmol, 2.4 equiv), and PyBOP (40 mg, 0.081 mmol, 2.4 equiv). Pentane-1,5-diamine (3 μL, 0.033 mmol, 1 equiv) solution in DMF (1 mL) was added dropwise, at 0 °C, over 6 h. The mixture was stirred at 25 °C for 6 h. After completion of the reaction, the solvent was evaporated in vacuo. The crude oil was taken up in MeOH (1.5 mL) and treated with K_2CO_3 (20 mg, 0.145 mmol, 4 equiv) at 25 °C for 4 h. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (2–4% MeOH in CH_2Cl_2) afforded **6** (7 mg, 37% over two steps). IR (film): 3440, 2930, 1740, 1715, 1410, 1355, 1245, 1180, 1100, 1140, 740, 700 cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.25–7.50 (m, 10 H), 4.86 (br s, 4 H), 4.60 (br s, 4 H), 4.53–4.59, 4.44–4.49 (2 × m, 2 H), 3.92–4.07 (m, 6 H), 2.97–3.12, 2.78–2.87 (2 × m, 2 × 2 H), 1.94–2.20 (m, 4 H), 1.66–1.78 (m, 4 H), 1.52–1.65 (m, 6 H), 1.20–1.50 (m, 10 H). ^{13}C NMR (100 MHz, MeOD): δ = 176.4, 175.7, 142.0, 131.9, 131.5, 131.2, 96.2, 75.7, 73.3, 73.2, 72.7, 71.7, 68.9, 73.1, 73.7, 73.5, 47.8, 47.1, 46.9, 42.7, 42.5, 42.2, 42.1, 42.0, 39.8, 39.1, 32.5, 32.2, 27.2. ESI–HRMS: *m*/*z* [M + Na] calcd for $C_{40}H_{58}N_2O_{10}$: 749.3989; found: 749.3995.

Data for 7: IR (film): 3365, 2960, 1610, 1570, 1410, 1335, 1070, 740, 700 cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.28–7.37 (m, 10 H), 4.84 (br s, 4 H), 4.64 (s, 4 H), 4.40–4.59 (m, 2 H), 3.85–4.07 (m, 6 H), 2.97–3.15, 2.75–2.85 (2 × m, 2 × 2 H), 1.97–2.21 (m, 4 H), 1.66–1.82 (m, 4 H), 1.46–1.64 (m, 10 H), 1.23–1.43 (m, 14 H). ^{13}C NMR (100 MHz, MeOD): δ = 176.3, 176.0, 142.0, 131.9, 131.5, 131.2, 96.4, 73.8, 73.2, 72.0, 71.7, 70.1, 69.6, 73.4, 73.1, 48.0, 46.8, 46.7, 42.9, 42.5, 42.4, 41.9, 41.4, 39.6, 39.4, 32.8, 32.7, 32.6, 30.2, 29.9. ESI–HRMS: *m*/*z* [M + Na] calcd for $C_{44}H_{66}N_2O_{10}$: 805.4615; found: 805.4620.

Preparation and Data for 9: To a solution of **8** (70 mg, 0.097 mmol) dissolved in CH_2Cl_2 (1 mL) were added Et_3N (122 μL, 0.879 mmol, 9 equiv) and methanesulfonyl chloride (28 μL, 0.293 mmol, 3 equiv) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was poured into a sat. aq $NaHCO_3$ solution (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$ and concentrated in vacuo. The residual oil was dissolved in a mixture of DMF–allylamine (3:1, 4 mL) and treated, at 40 °C, with K_2CO_3 (120 mg, 0.879 mmol, 9 equiv) for 12 h. The solvents were evaporated in vacuo. The residual oil was taken up in MeOH (3 mL) and the solution was stirred for 3 h. The reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with brine (40 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by flash chromatography (4% NH_4OH in MeCN) afforded **9** (28 mg, 42% over three steps) as a colorless oil. IR (film): 3440, 2950, 1740, 1715, 1455, 1370, 1240, 1165, 1100, 1040, 740, 700 cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.26–7.34 (m, 10 H), 5.85–5.99 (m, 2 H), 4.31, 5.28 (2 × d, 4 H), 4.82 (s, 4 H), 4.61 (s, 4 H), 3.87–4.15 (m, 8 H), 3.37, 3.35 (2 × d, 4 H), 2.74–2.92 (m, 4 H), 2.13–2.50 (3 × m, 14 H), 1.22–1.50 (m, 4 H). ^{13}C NMR (100 MHz, MeOD): δ = 139.4, 134.3, 134.2, 129.4, 128.9, 128.7, 119.9, 119.8, 93.9, 93.8, 71.4, 70.9, 70.8, 70.7, 70.0, 69.4, 67.7, 66.6, 70.6, 52.4, 52.3, 47.0, 46.8, 45.7, 44.3, 43.8, 39.3, 38.3, 37.1, 37.0, 31.8, 31.3. ESI–HRMS: *m*/*z* [M + H] calcd for $C_{41}H_{62}N_2O_8$: 711.4584; found: 711.4588.

Preparation and Data for 10: To a solution of **9** (25 mg, 0.035 mmol) dissolved in CH_2Cl_2 (15 mL) was added Grubbs' II catalyst (6 mg, 0.007 mmol, 0.2 equiv) and the mixture was stirred at 50 °C for 9 h. The solvent was evaporated in vacuo. The crude oil was dissolved in MeOH–EtOAc (1:3, 3 mL) and was treated at 25 °C for 4 h with a catalytic amount of $Pd(OH)_2$ on activated charcoal under 1 atm of H_2. The reaction mixture was filtered through a pad of celite®. The filtrate was concentrated in vacuo. Purification of the residue by flash chromatography (5% NH_4OH in MeCN) afforded **10** as a pale yellow oil (18 mg, 48%). IR (film): 3405, 2955, 1730, 1605, 1510, 1450, 1370, 1250, 1170, 1110, 1030, 850, 775 cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.27–7.35 (m, 10 H), 4.82 (s, 4 H), 4.62 (s, 4 H), 3.85–4.15 (m, 8 H), 3.21–3.83 (2 × m, 8 H), 1.91–2.12, 1.50–1.90 (2 × m, 18 H), 1.23–1.52 (m, 4 H). ^{13}C NMR (100 MHz, MeOD): δ = 130.0, 128.4, 127.9, 126.9, 93.0, 92.9, 69.7, 69.6, 70.0, 69.9, 69.6, 69.5, 69.2, 68.5, 66.3, 65.6, 49.8, 49.7, 46.3, 45.8, 45.3, 42.9, 42.2, 38.0, 36.3, 35.9, 26.6, 26.5, 26.3. ESI–HRMS: *m*/*z* [M + Na] calcd for $C_{39}H_{60}N_2O_8$: 707.4247; found: 707.4234.