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Conjugation of Amines and α-Amino Acid Derivatives as Pyrroles Using Tethered 1,4-Diketones

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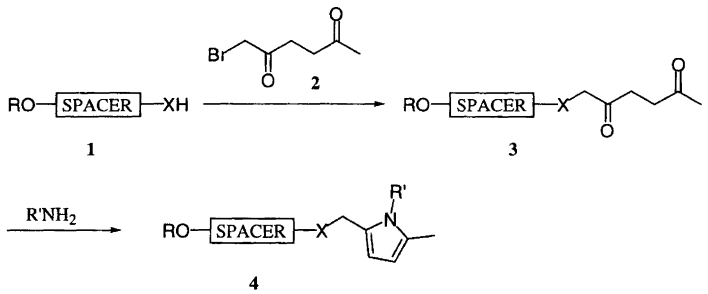
The preparation of two 1,4-diketones, and their subsequent Paal–Knorr reaction with various primary amines and amino acid derivatives to give the corresponding pyrroles, is described.

Synthesis of oligosaccharides linked through a spacer unit to lipids, proteins and synthetic polymers giving neoglycoconjugates is of interest due primarily to the variety of biological functions exhibited by these molecules.[1–3] Two important applications are the use of neoglycoconjugates as antigens in diagnostic tests and as immunogens.[4] The preparation of these neoglycoconjugates normally relies on an initial activation of one component followed by coupling to the second component and, not surprisingly, several different spacers and coupling methods have been developed over the years.[5–9] For example, conjugates have been prepared from amino functionalities by reductive amination, succinimide esters, diazo-, isothiocyanate-,[10] and acylazide-coupling[11] techniques. In this respect we required a coupling procedure that would immobilize amines and provide us with conjugates with good base- and reasonable acid-stability. As a result we have prepared a novel spacer of the general structure **3**, by coupling of **1** and **2**, which contains a 1,4-dicarbonyl functionality, and herein detail a model study elucidating its efficiency in the formation of conjugates with different amines and amino acid derivatives through a Paal–Knorr reaction to give the corresponding pyrroles **4** (Scheme 1).[12–14]

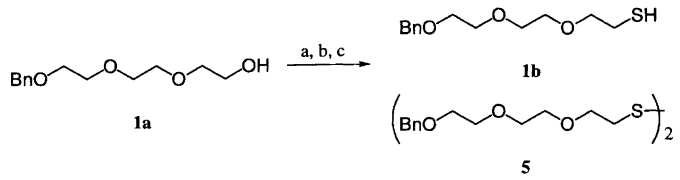
Results and discussion

It has previously been shown that spacer units derived from oligoethylene glycols often perform well in hydrophilic environments,[15–17] and since such properties were of interest to us, triethylene glycol derivatives **1a–c** were chosen for initial experiments. The known alcohol **1a** was converted into the corresponding tosylate (Scheme 2).[18,19] This material was then reacted with $Na_2S_2O_3$ in EtOH followed by treatment with cysteamine hydrochloride to give a mixture of **1b** and disulfide **5** (**1b**:**5** 4:5, 90%).[20,21] Attempts to suppress the formation of **5** were fruitless but this problem was partially circumvented by $LiAlH_4$ reduction of **5** which gave **1b** in 92% yield, thus securing a reasonable material throughput. The third precursor, thiol **1c**, was prepared from the D-glucose derivative **6** as outlined in Scheme 3.[22] Alkylation of **6** followed by acetylation, to simplify separation, gave a mixture of regioisomers from which the expected

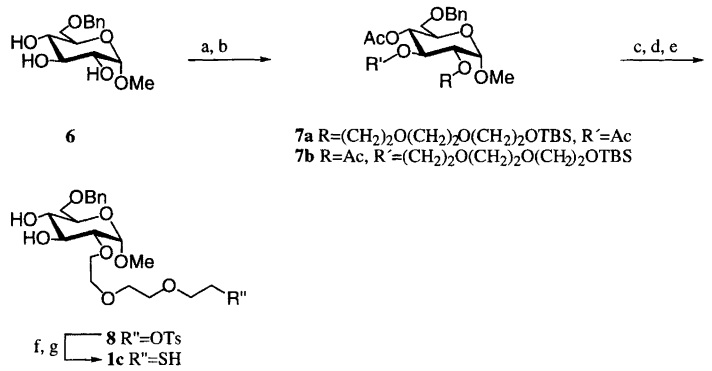


Scheme 1.

* To whom correspondence should be addressed.



Scheme 2. (a) Ref. 19; (b) $Na_2S_2O_3$, EtOH, H_2O, Δ; (c) cystemine hydrochloride, H_2O, **1b**:**5** 4:5, 90% (two steps).

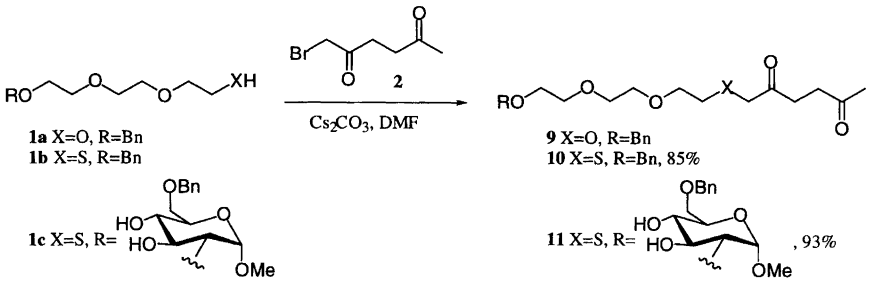


Scheme 3. (a) $TsO(CH_2)_2O(CH_2)_2O(CH_2)_2OTBS$ (**20**), NaH, **7a**:**7b** 4.3:1, 30%; (b) Ac_2O, pyridine 88%; (c) Bu_4NF, THF, 90%; (d) *p*-TsCl, pyridine, 77%; (e) NaOMe, MeOH, 83%; (f) $Na_2S_2O_3$, EtOH, H_2O, Δ; (g) cysteamine hydrochloride, H_2O, 81% (two steps).

2-alkylated derivative **7a** could be isolated as the major product (**7a**:**7b** 4.3:1).[23] Removal of the silyl group in **7a** followed by tosylation and deacetylation then afforded **8**. Conversion of this material into thiol **1c** using the procedure described above proceeded in good yield and this time without concomitant formation of the corresponding disulfide.

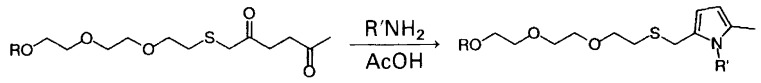
Attempts to alkylate **1a** with bromide **2**[24] under a variety of conditions gave none of the expected ether **9** (Scheme 4). In all these experiments, rapid consumption of **2** was observed and it is reasonable to assume that the 1,4-diketone moiety is too sensitive to withstand the basic reaction conditions. To circumvent these problems **1b** was selected as a more suitable substrate and it was gratifying to find that this material was smoothly converted into sulfide **10** in good yields.[25] It should be noted that the solvent must be thoroughly deoxygenated to avoid formation of the corresponding disulfide with a resultant decrease in the yield of **10** and that the base must be removed from the crude reaction mixture before the solvent to minimize an apparently facile intramolecular aldol condensation. Using identical reaction conditions thiol **1c** was converted into sulfide **11** (93%).

The results from the Paal–Knorr reaction of 1,4-diketones **10** and **11** with various amines are collected in Table 1. In general the condensation was quite insensitive to the choice of solvent, although it appeared to be somewhat faster in apolar solvents, and this parameter was decided upon based only on solubility considerations. Also, the progress of the cyclization was readily followed by monitoring the UV-absorption of the forming pyrrole chromophore. As can be seen, primary amines like benzylamine, *n*-$BuNH_2$, tyramine, cyclohexylamine and triethylenetetramine worked well in their condensations with **10** and **11** affording the corresponding pyrrole derivatives **12**, **13**, **16**–**18**, respectively, in good yields (entries 1, 2, 5–7). Having established the feasibility of this protocol we were of course interested in proceeding with more relevant amines, such as amino acid and peptide derivatives. Thus, it was gratifying to find that glycinamide and Bz-glycinyl-L-lysine performed equally well in the Paal–Knorr reaction to give the corresponding

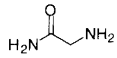
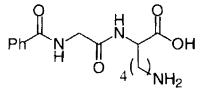
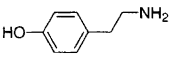
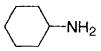
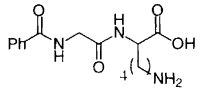


Scheme 4.

Table 1. The Paal–Knorr reaction of diketones **10** and **11** with various amines.[a]



10, 11 **12–19**

Entry	Diketone	Amine ($R'NH_2$)	Product	Solvent	Yield[b] (%)
1	**10**	$BnNH_2$	**12**	PhMe	69
2	**10**	n-$BuNH_2$	**13**	PhMe	94
3	**10**		**14**	MeOH	91[c]
4	**10**		**15**	MeOH	82
5	**11**		**16**	H_2O–i-PrOH	73
6	**11**		**17**	i-PrOH	75
7	**11**		**18**	i-PrOH	65
8	**11**		**19**	MeOH	84

[a]All reactions were carried out in the solvents indicated at room temperature with 5–10 mol% AcOH and terminated when complete as indicated by TLC analysis. [b]Isolated yields. [c]Based on recovered starting material.

pyrroles (entries 3, 4 and 8). The conjugates **14**, **15** and **19** so obtained were readily isolated and could be purified by standard flash chromatography.

In summary, we have prepared 1,4-diketones **10** and **11** and used them as model substrates in the Paal–Knorr reaction with various amines, affording the corresponding pyrroles. The condensation works equally well in both protic and aprotic solvents, the former conditions indicating that hydroxy moieties in the substrates need not be protected. The sequence proceeds in good overall yield and should offer an interesting alternative for the conjugate formation of substrates containing a primary amine functionality.

Experimental

^1H and ^{13}C NMR spectra were obtained on a Varian XL 300 MHz or a Bruker DRX 400 MHz spectrometer using $CDCl_3$ ($CHCl_3$ δ 7.26) as the solvent. *J* values are given in Hz. IR spectra were run on a Perkin–Elmer 298 spectrophotometer and only the strongest/structurally most important peaks are listed. Flash chromatography was conducted on Grace Amicon silica gel 60 (0.035–0.070 mm). All non-aqueous reactions were run in septum-capped, oven-dried flasks under atmospheric pressure of nitrogen, solvents, reactant solutions and liquid reagent being transferred via oven-dried syringes unless otherwise stated.

8-Benzyloxy-3,6-dioxaoctane-1-thiol **1b** *and bis-(8-benzyl-3,6-dioxaoctyl) disulfide* **5**. Alcohol **1a**[18] was converted into the corresponding tosylate as described previously.[19]

A solution of $Na_2S_2O_3 \cdot 3H_2O$ (45.8 mg, 0.185 mmol) in water (240 µl) was added in one portion to a stirred solution of the above tosylate (56 mg, 0.142 mmol) in ethanol (620 µl). The mixture was heated under reflux for 18 h, and then additional $Na_2S_2O_3$ (7.0 mg, 0.028 mmol, 0.2 equiv.) in water (50 µl) was added. The mixture was heated under reflux for another 6 h, after which the ethanol and most of the water were evaporated off under reduced pressure to leave a white precipitate. To the precipitate a solution of cysteamine hydrochloride (400 mg) in water (0.88 ml), adjusted to pH 8 with 10% aq. HCl, was added and the mixture was stirred at room temperature for 14 h, after which it was acidified to pH 3–4 with 10% HCl. The solvent was evaporated off under reduced pressure which gave a white slurry. The slurry was extracted with EtOAc–MeOH (3:1). The combined organic phases were concentrated and flash chromatographed (heptane–EtOAc, 3:2) to give thiol **1b** (14.5 mg, 40%) and disulfide **5** (18.2 mg, 50%).

Thiol **1b**: ^1H NMR ($CDCl_3$, 300 MHz): δ 1.57 (1 H, t, J=8.2), 2.71 (2 H, dd, J=7.1, 6.4), 3.55–3.71 (10 H, m), 4.58 (2 H, s), 7.27–7.39 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.3, 69.5, 70.3, 70.6, 70.7, 72.9, 73.3, 127.6, 127.8, 128.4, 138.3. IR (neat): 3030, 2860 cm^{-1}. (Found: M^+, 257.1204. Calc. for $C_{13}H_{21}O_3S$: $M^+ + H$, 257.1211).

Disulfide **5**: ^1H NMR ($CDCl_3$, 300 MHz): δ 2.87 (4 H, t, J=6.7), 3.64–3.74 (20 H, m), 4.61 (4 H, s), 7.26–7.34 (10 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 38.2, 69.3, 70.5, 70.6, 73.2, 76.5, 127.8, 128.0, 128.6, 138.5. IR (neat): 3030, 2860 cm^{-1}.

Reduction of disulfide **5** *to* **1b**. To disulfide **5** (131 mg, 0.257 mmol) in THF (6 ml) at 0 °C was added $LiAlH_4$ (49 mg, 1.28 mmol) in one portion and the resultant mixture was warmed to room temperature. After 20 h the reaction was quenched by careful addition of EtOAc, acidified with 10% HCl and then extracted with Et_2O (3 × 4 ml). The combined organic layers were dried ($MgSO_4$) and evaporated under reduced pressure to give thiol **1b** (122 mg, 92%) as an oil.

*Methyl 3,4-di-*O*-acetyl-6-*O*-benzyl-2-*O*-[8-(*tert*-butyldimethylsilyloxy)-3,6-dioxaoctyl]-*α*-*D*-glucopyranoside* **7a** *and methyl 2,4-di-*O*-acetyl-6-*O*-benzyl-3-*O*-[8-(tert-butyldimethylsilyloxy)-3,6-dioxaoctyl]-*α*-*D*-glucopyranoside* **7b**. A mixture of methyl 6-*O*-benzyl-α-D-glucopyranoside **6**[22] (3.03 g, 10.7 mmol) in DMF (10 ml) was added to NaH (0.426 g, 10.7 mmol, 60%) in DMF (10 ml) at 0 °C. The reaction was stirred for 45 min after which **20** (4.46 g, 10.7 mmol) in DMF (10 ml) was added. The resultant solution was stirred for 14 h at 45 °C and then for 1.5 h at 95 °C. The reaction was quenched with pH 7 buffer (4 ml). The solvents were evaporated off under reduced pressure and the residue was flash chromatographed (toluene–CH_2Cl_2, 1:1, 1% MeOH) to give a mixture of the corresponding 2- and 3-alkylated isomers (1.69 g, 30%, ratio 4.3:1), which was used directly in the next step.

The above mixture of isomers (1.69 g, 3.18 mmol) in pyridine (20 ml) was added to Ac_2O (1.17 ml, 12.4 mmol) in pyridine (20 ml) at 0 °C. 4-Dimethylaminopyridine (cat.) was added and the resultant solution was stirred at room temperature overnight. The mixture was then poured into Et_2O–H_2O and the organic phase was washed with 1% HCl (aq.) and evaporated off under reduced pressure. Drying ($MgSO_4$) and flash chromatography (CH_2Cl_2–EtOAc, 19:1, 1% MeOH) gave **7a** (1.34 g, 68%), **7b** (0.31 g, 18%) and a mixture of the isomers (68 mg). Total yield: 1.71g (88%).

7a: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.05 (6 H, s), 0.88 (9 H, s), 1.89 (3 H, s), 2.03 (3 H, s), 3.43 (3 H, s), 3.45–3.68 (12 H, m), 3.73 (3 H, m), 3.83 (1 H, m), 4.42 (1 H, A portion of AB system, J=12.0), 4.56 (1 H, B portion of AB system, J=12.0), 4.91 (1 H, d, J=3.4), 5.06 (1 H, t, J=10.0), 5.36 (1 H, t, J=9.5), 7.27–7.33 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −4.8, 18.8, 21.1, 21.3, 26.4, 55.8, 63.1, 68.6, 68.7, 69.7, 71.1, 71.4, 72.7, 73.1, 73.9, 78.8, 98.3, 128.1, 128.3, 128.8, 138.1, 170.3, 170.6. IR (neat): 3030, 2880, 1780 cm^{-1}. (Found: M^+, 637.3022. Calc. for $C_{30}H_{50}NaO_{11}Si$: M^+ + Na, 637.3020).

7b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.05 (6 H, s), 0.88 (9 H, s), 2.06 (6 H, s), 3.37 (3 H, s), 3.40–3.81 (16 H, m), 4.57 (1 H, A portion of AB system, J=12.0), 4.65 (1 H, B portion of AB system, J=12.0), 4.80–4.90 (2 H, m), 5.47 (1 H, t, J=9.3), 7.30–7.36 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −5.3, 20.8, 21.0, 25.9, 55.1, 62.7, 68.2, 69.9, 70.4, 70.6, 70.7, 71.4, 71.4, 71.9, 72.1, 72.6, 73.5, 96.9, 127.7, 127.8, 128.3, 138.0, 169.8, 170.4. IR (neat): 3030, 2880, 1780 cm^{-1}.

*Methyl 6-*O*-benzyl-2-*O*-(8-*p*-tolylsulfonyl-3,6-dioxaoctyl)-α-*D*-glucopyranoside* **8**. $Bu_4NF \cdot 3H_2O$ (0.884 g, 2.80 mmol) was added to a solution of **7a** (1.18 g, 1.92 mmol) in THF (30 ml) at 0 °C and the mixture was stirred at 0 °C for 3 h. The solvent was then evaporated off under reduced pressure. Flash chromatography of the residue (EtOAc, 1% MeOH) gave the corresponding alcohol (0.86 g, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.89 (3 H, s), 2.03 (3 H, s), 3.43 (3 H, s), 3.45–3.68 (12 H, m), 3.73 (3 H, m), 3.83 (1 H, m), 4.43 (1 H, A portion of AB system, J=12.0), 4.57 (1 H, B portion of AB system, J=12.0), 4.91 (1 H, d, J=3.4), 5.06 (1 H, t, J=10.0), 5.36 (1 H, t, J=9.5), 7.27–7.33 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7, 20.9, 55.4, 61.8, 68.2, 68.2, 69.3, 70.4, 70.7, 71.0, 71.0, 72.4, 72.7, 78.4, 98.0, 127.7, 127.9, 128.3, 137.7, 169.8, 170.3. IR (neat): 3480, 3030, 2880, 1780 cm^{-1}. (Found, M^+, 523.2178. Calc. for $C_{24}H_{36}NaO_{11}$: M^+ + Na, 523.2155).

A solution of *p*-TsCl (24 mg, 0.125 mmol) and 4-dimethylaminopyridine (cat.) in pyridine (1.5 ml) was added to a solution of the above alcohol (54 mg, 0.108 mmol) in pyridine (1.5 ml) at 0 °C and the resultant mixture was placed in a refrigerator. After 18 h additional *p*-TsCl (10.4 mg, 0.054 mmol, 0.5 equiv.) was added and the mixture was placed in the refrigerator for another 18 h. The mixture was then poured into Et_2O–$CuSO_4$ (aq.). The organic phase was washed with $CuSO_4$ (aq.) (5 × 4 ml). The combined aqueous phases were extracted with Et_2O (3 × 3 ml). Drying ($MgSO_4$), evaporation and flash chromatography (heptane–EtOAc, 1:4 → 0:1) gave the corresponding tosylate (54 mg, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.90 (3 H, s), 2.02 (3 H, s), 2.44 (3 H, s) 3.43 (3 H, s), 3.45–3.72 (13 H, m), 3.83 (1 H, m), 4.15 (2 H, t, J=4.6), 4.43 (1 H, A portion of AB system, J=12.1), 4.57 (1 H, B portion of AB system, J=12.1), 4.90 (1 H, d, J=3.4), 5.06 (1 H, t, J=10.0), 5.32 (1 H, t, J=9.5), 7.27–7.33 (7 H, m), 7.80 (2 H, d, J=8.3). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7, 20.8, 21.0, 55.4, 68.2, 68.2, 68.7, 69.3, 70.6, 70.7, 70.8, 70.9, 72.3, 73.5, 78.3, 97.9, 127.7, 127.9, 128.0, 128.4, 129.8, 137.7, 142.7, 144.8, 169.8, 170.2. IR (neat): 3030, 2880, 1780, 1600, 1360 cm^{-1}. (Found: M^+, 677.2213. Calc. for $C_{31}H_{42}NaO_{13}S$: M^+ + Na, 677.2244).

NaOMe (25 μl, 1 M) was added to a solution of the above tosylate (46 mg, 0.070 mmol) in methanol (1.5 ml) and the mixture was stirred at room temperature for 6 h. The reaction was quenched by addition of Amberlyst (15 H^+) until neutral pH. The resin was filtered off and the filtrate was evaporated under reduced pressure. Flash chromatography of the residue (EtOAc–MeOH, 99:1 → 19:1) gave **8** (33 mg, 83%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.45 (3 H, s), 2.79 (1 H, s), 3.35 (1 H, dd, J=3.6 and 5.9), 3.43 (3 H, s), 3.58–3.77 (12 H, m), 3.88 (1 H, t, J=9.3), 3.99 (2 H, m), 4.19 (2 H, t, J=4.7), 4.62 (2 H, A portion of AB system, J=12.2,

B portion of AB system, $J=5.6$), 4.89 (1 H, d, $J=3.6$), 7.33–7.37 (7 H, m), 7.82 (2 H, d, $J=8.4$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.7, 55.2, 68.7, 69.2, 69.5, 70.0, 70.3, 70.6, 70.9, 70.9, 71.0, 73.2, 73.5, 81.5, 98.1, 127.6, 128.0, 128.4, 129.8, 138.2, 144.8. IR (neat): 3420, 3030, 2880, 1600, 1360 cm^{-1}. (Found: M^+, 593.2033. Calc. for $C_{27}H_{38}NaO_{11}S$: $M^+ + Na$, 593.2059).

Methyl 6-O-benzyl-2-O-(8-sulfanyl-3,6-dioxaoctyl)-α-D-glucopyranoside **1c**. A solution of $Na_2S_2O_3 \cdot 3H_2O$ (101 mg, 0.41 mmol) in H_2O (0.52 ml) was added to a solution of **8** (184 mg, 0.322 mmol) in ethanol (2.1 ml) and the mixture was stirred at 85 °C for 8 h after which the solvent was evaporated off under reduced pressure. To the resulting precipitate a solution of cysteamine hydrochloride (0.94 g) in water (2.1 ml), adjusted to pH 8 with 10% aq. HCl, was added and the mixture was stirred at room temperature for 14 h. The solvent was then removed under reduced pressure and the resulting slurry was extracted with EtOAc–MeOH (3:1). The combined organic phases were concentrated and the residue was flash chromatographed (EtOAc–MeOH, 99:1 → 9:1) to give **1c** (113 mg, 81%). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.69 (1 H, t, $J=4.5$), 2.71 (2 H, dd, $J=6.5$, 6.8), 3.35 (1 H, dd, $J=3.6$, 5.9), 3.43 (3 H, s) 3.55–3.69 (13 H, m), 3.87 (1 H, t, $J=8.8$), 3.97 (1 H, dd, $J=4.2$, 4.0), 4.58 (1 H, A portion of AB system, $J=12.2$), 4.63 (1 H, B portion of AB system, $J=12.2$), 4.82 (1 H, d, $J=3.6$), 7.25–7.37 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.2, 55.2, 69.5, 69.9, 70.0, 70.4, 71.0, 71.0, 72.9, 73.2, 73.6, 81.4, 98.2, 127.6, 128.4, 138.1. IR (neat): 3420, 3030, 2880 cm^{-1}. (Found: M^+, 455.1714. Calc. for $C_{20}H_{32}NaO_8S$: $M^+ + Na$, 455.1716).

15-Benzyloxy-7-thia-10,13-dioxapentadecane-2,5-dione **10**. A solution of thiol **1b** (85 mg, 0.33 mmol) in deoxygenized DMF (1.5 ml) was added to a stirred solution of 1-bromohexane-2,5-dione (**2**)[21] (66 mg, 0.34 mmol) in deoxygenized DMF (1.5 ml). To the mixture was added Cs_2CO_3 (111 mg, 0.34 mmol) and the resultant solution was stirred at room temperature for 40 min after which it was poured into Et_2O–H_2O. The aqueous phase was extracted with Et_2O (3 × 4 ml) and the combined organic layers were washed with water (2 × 3 ml). Drying ($MgSO_4$), evaporation and flash chromatography (heptane–EtOAc, 3:1 → 2:3) gave **10** (104 mg, 85%). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.18 (3 H, s), 2.68–2.77 (4 H, m), 2.84–2.88 (2 H, m), 3.35 (2 H, s), 3.58–3.70 (10 H, m), 4.57 (2 H, s), 7.25–7.39 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.9, 31.6, 34.02, 37.3, 41.4, 69.5, 70.3, 70.4, 70.6, 70.7, 73.2, 127.6, 127.7, 128.4, 138.3, 204.8, 206.9. IR (neat): 3030, 2860, 1710 cm^{-1}. (Found: M^+, 369.1734. Calc. for $C_{19}H_{29}O_5S$: $M^+ + H$, 369.1736).

Methyl 6-O-benzyl-2-O-(11,14-dioxo-3,6-dioxa-9-thiapentadecyl)-α-D-glucopyranoside **11**. A solution of 1-bromohexane-2,5-dione (**2**)[21] (62 mg, 0.32 mmol) in deoxygenized DMF (3.5 ml) was added to a stirred solution of **1c** (125 mg, 0.289 mmol) in deoxygenized DMF (3.5 ml). To the mixture was added Cs_2CO_3 (96 mg, 0.30 mmol) and the resultant mixture was stirred at room temperature for 20 min and was then poured into CH_2Cl_2–brine. The aqueous phase was extracted with CH_2Cl_2 (4 × 6 ml) and the combined organic layers were dried ($MgSO_4$) and evaporated off under reduced pressure. Flash chromatography of the residue (EtOAc–MeOH, 1:0 → 19:1) gave **11** (146 mg, 93%). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.17 (3 H, s), 2.71 (4 H, m), 2.87 (2 H, m), 3.35–3.41 (6 H, m), 3.55–3.69 (13 H, m), 3.87 (1 H, t, $J=8.8$), 3.97 (1 H, dd, $J=4.2$, 4.0), 4.57 (1 H, A portion of AB system, $J=12.2$), 4.63 (1 H, B portion of AB system, $J=12.2$), 4.82 (1 H, d, $J=3.6$), 7.25–7.37 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 29.9, 31.3, 34.0, 37.3, 41.4, 55.1, 69.5, 70.0, 70.1, 70.4, 70.9, 71.1, 73.2, 73.5, 81.5, 98.2, 127.6, 128.3, 138.2, 205.1, 207.1. IR (neat): 3420, 3030, 2880, 1710 cm^{-1}. (Found: M^+, 567.2231. Calc. for $C_{26}H_{40}NaO_{10}S$: $M^+ + Na$, 567.2240).

1-Benzyl-2-(10-benzyloxy-2-thia-5,8-dioxadecyl)-5-methylpyrrole **12**. To **10** (15 mg, 0.041 mmol) in toluene (1 ml) was added benzylamine (5.0 μl, 0.046 mmol) and acetic acid (cat.) and the resultant mixture was stirred at room temperature. After 6 h the solvent was evaporated off and the residue flash chromatographed (heptane–EtOAc, 4:1) to give **12** (12.4 mg, 69%). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.13 (3 H, s), 2.62 (2 H, t, $J=6.8$), 3.52–3.69 (12 H, m), 4.57 (2 H, s), 5.19 (2 H, s), 5.85 (1 H, d, $J=3.4$), 6.01 (1 H, d, $J=3.3$), 6.87 (2 H, d, $J=6.8$), 7.22–7.35 (8 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.5, 28.4, 30.2, 46.7, 69.5, 70.3, 70.6, 70.7, 70.8, 73.3, 105.8, 108.8, 125.6, 126.4, 127.1, 127.6, 127.7, 128.4, 128.7, 130.2, 138.3, 138.5. IR (neat): 3030, 2860 cm^{-1}. (Found: M^+, 439.2185. Calc. for $C_{26}H_{33}NO_3S$: M^+, 439.2181).

1-Butyl-2-(10-benzyloxy-2-thia-5,8-dioxadecyl)-5-methylpyrrole **13**. To **10** (20 mg, 0.054 mmol) in toluene (1 ml) was added *N*-butylamine (5.7 μl, 0.057 mmol) and acetic acid (cat.) and the resultant mixture was stirred at room temperature. After 18 h the solvent was evaporated off and the residue flash chromatographed (heptane–EtOAc, 3:1) to give **13** (20.7 mg, 94%).^1H NMR ($CDCl_3$, 300 MHz): δ 0.96 (3 H, t, $J=7.3$), 1.36 (2 H, m), 1.66 (2 H, m), 2.22 (3 H, s), 2.64 (2 H, t, $J=6.8$), 3.52–3.71 (12 H, m), 3.85 (2 H, t, $J=7.8$), 4.58 (2 H, s), 5.76 (1 H, d, $J=3.3$), 5.92 (1 H, d, $J=3.4$), 7.28–7.36 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.5, 13.9, 20.3, 28.4, 30.3, 33.3, 43.5, 69.5, 70.3, 70.7, 70.7, 70.9, 73.3, 105.4, 108.3, 125.8, 127.6, 127.8, 128.4, 129.4, 142.7. IR (neat): 3030, 2860 cm^{-1}. (Found: M^+, 405.2339. Calc. for $C_{23}H_{35}NO_3S$: M^+, 405.2338).

1-(Carbonnoylmethyl)-2-(10-benzyloxy-2-thia-5,8-dioxadecyl)-5-methylpyrrole **14**. A solution of glycinamide hydrochloride (4.6 mg, 0.042 mmol) in methanol was

treated with ion-exchange resin (Amberlite IR-45, OH^-), and the solvent was evaporated off. The residue was dissolved in methanol (300 µl) and the resultant mixture and acetic acid (cat.) were then added to **10** (12.8 mg, 0.035 mmol). The mixture so obtained was stirred at room temperature until the reaction was complete. Removal of the solvent and flash chromatography (heptane–EtOAc 1:2 → 0:1) gave **14** (8.0 mg, 57%) as a white precipitate and **10** (4.1 mg, 34%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.18 (3 H, s), 2.64 (2 H, t, J=6.3), 3.47–3.68 (10 H, m), 3.73 (2 H, s), 4.57 (4 H, s), 5.46 (1 H, s), 5.60 (1 H, s), 5.84 (1 H, d, J=3.4), 6.00 (1 H, d, J=3.4), 7.28–7.36 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.3, 28.3, 30.7, 47.2, 69.4, 70.3, 70.6, 70.7, 73.2, 107.0, 109.8, 126.6, 127.6, 127.8, 128.4, 130.2, 142.7, 171.3. IR (neat): 3300, 3030, 2860 cm^{-1}. (Found: M^+, 406.1908. Calc. for $C_{21}H_{30}NO_4S_2$: M^+, 406.1926).

Pyrrole **15**. To **10** (11 mg, 0.0300 mmol) in methanol (350 µl) was added Bz-glycinyl-L-lysine (11 mg, 0.0358 mmol) and acetic acid (cat.) and the resultant mixture was stirred at room temperature until the reaction was complete. The solvent was evaporated off and the residue flash chromatographed (EtOAc–MeOH, 2:1) to give **15** (15.8 mg, 82%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.36 (2 H, m), 1.64 (3 H, m), 1.81 (1 H, m), 2.08 (3 H, s), 2.61 (2 H, t, J=6.9), 3.53 (2 H, t, J=7.0), 3.60–3.69 (10 H, m), 3.75 (2 H, t, J=7.8), 4.10 (1 H, A portion of AB system, J=17.0), 4.22 (1 H, B portion of AB system, J=17.0), 4.45 (1 H, s), 4.55 (2 H, s), 5.72 (1 H, d, J=3.3), 5.88 (1 H, d, J=3.3), 7.30–7.39 (8 H, m), 7.46 (1 H, t, J=7.4), 7.62 (1 H, s), 7.81 (2 H, d, J=7.3). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.9, 23.3, 28.9, 30.9, 31.0, 32.0, 43.8, 44.0, 52.8, 69.7, 70.5, 71.0, 71.2, 73.6, 73.7, 106.0, 108.8. 126.2, 127.7, 128.1, 128.2, 128.2, 128.3, 128.3, 128.8, 128.8, 128.8, 129.0, 129.8, 129.9, 132.5, 133.7, 138.4, 168.7, 170.0, 174.9. IR (neat): 3300, 3030, 2860, 1640 cm^{-1}. (Found: M^+, 684.2680. Calc. for Na-salt of **15**, $C_{34}H_{45}N_3Na_2O_7S$: M^+ + Na, 684.2695).

Pyrrole **16**. A solution of tyramine (4.0 mg, 0.029 mmol) in water (0.38 µl) and acetic acid (cat.) were added to a solution of **11** (15.4 mg, 0.028 mmol) in isopropyl alcohol (0.38 µl) and the mixture was stirred at room temperature until the reaction was complete. The solvent was evaporated off under reduced pressure and the residue was flash chromatographed (EtOAc, 2% MeOH) to give **16** (13.3 mg, 73%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.23 (3 H, s), 2.58 (2 H, t, J=7.0), 2.88 (2 H, t, J=6.8), 3.32 (2 H, d, J=5.8), 3.36 (1 H, m), 3.42 (3 H, s), 3.50 (2 H, t, J=7.0), 3.58–3.76 (11 H, m), 3.95 (2 H, m), 4.03 (2 H, t, J=7.0), 4.59 (1 H, A portion of AB system, J=12.2), 4.64 (1 H, B portion of AB system, J=12.2), 4.84 (1 H, d, J=3.6), 5.80 (1 H, d, J=3.3), 5.90 (1 H, d, J=3.3), 6.77 (2 H, d, J=8.5), 6.90 (2 H, d, J=8.5), 7.29–7.37 (5 H, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.5, 28.5, 30.8, 36.6, 45.7, 55.2, 69.4, 69.9, 70.4, 70.8, 73.3, 73.6, 81.3, 98.0, 105.8, 107.8, 115.7, 126.7, 127.7, 128.4, 129.2, 130.1, 130.4, 138.0, 154.9. IR (neat): 3420, 3030, 2880 cm^{-1}. (Found: M^+, 668.2879. Calc. for $C_{34}H_{47}NNaO_9S$: M^+ + Na, 668.2869).

Pyrrole **17**. To **11** (12 mg, 0.022 mmol) in isopropyl alcohol (200 µl) was added cyclohexylamine (22.9 µl, 0.0257 mmol) and acetic acid (cat.) and the resultant mixture was stirred at room temperature until the reaction was complete. The solvent was evaporated off and the residue flash chromatographed (EtOAc–MeOH, 19:1 → 9:1) to give **18** (10 mg, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.22 (1 H, m), 1.39 (2 H, m), 1.74 (1 H, m), 1.88–1.97 (6 H, m), 2.35 (3 H, s), 2.64 (2 H, t, J=6.9), 3.36 (1 H, dd, J=3.6, 5.9), 3.43 (3 H, s), 3.53 (2 H, t, J=6.9), 3.58–3.77 (13 H, m), 3.88 (1 H, t, J=9.2), 3.98 (1 H, m), 4.05 (1 H, m), 4.60 (1 H, A portion of AB system, J=12.2), 4.65 (1 H, B portion of AB system, J=12.2), 4.84 (1 H, d, J=3.6), 5.74 (1 H, d, J=3.6), 5.89 (1 H, d, J=3.3), 7.28–7.37 (5 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.6, 26.0, 27.0, 29.7, 30.5, 32.8, 55.6, 56.9, 69.9, 70.3, 70.4, 70.8, 71.3, 71.4, 71.5, 73.6, 74.0, 81.9, 98.6, 107.7, 108.9, 127.0, 128.0, 128.8, 130.1, 138.6. IR (neat): 3420, 3030, 2880 cm^{-1}. (Found: M^+, 630.3085. Calc. for $C_{32}H_{49}NNaO_8S$: M^+ + Na, 630.3077).

Pyrrole **18**. A solution of tris(2-aminoethyl)amine (0.97 µl, 0.0066 mmol) in isopropyl alcohol (43 µl) and acetic acid (cat.) was added to a solution of **11** (10.5 mg, 0.019 mmol) in isopropyl alcohol (200 µl) and the mixture was stirred at room temperature until the reaction was complete. The solvent was evaporated off under reduced pressure and the residue was flash chromatographed (EtOAc, 10% MeOH) to give **18** (7.2 mg, 65%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.24 (9 H, s), 2.62 (6 H, t, J=6.8), 2.88 (6 H, t, J=6.7), 3.35 (3 H, m), 3.42 (9 H, s), 3.50–3.76 (48 H, m), 3.87 (6 H, m), 3.95 (3 H, dd, J=4.6, 4.0), 4.59 (3 H, A portion of AB system, J=12.2), 4.63 (3 H, B portion of AB system, J=12.2), 4.84 (3 H, d, J=3.8), 5.82 (3 H, d, J=3.4), 5.92 (3 H, d, J=3.3), 7.29–7.37 (15 H, m). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.1, 28.2, 30.3, 42.9, 55.6, 56.0, 69.9, 70.4, 70.4, 70.8, 71.1, 71.3, 71.4, 73.6, 74.0, 81.8, 98.5, 106.4, 109.4, 126.4, 128.0, 128.8, 128.9, 138.6. IR (neat): 3400, 3030, 2880 cm^{-1}. (Found: M^+, 1693.7827. Calc. for $C_{84}H_{126}N_4NaO_{24}S_3$: M^+ + Na, 1693.7822).

Pyrrole **19**. To **11** (12 mg, 0.022 mmol) in methanol (300 µl) was added Bz-glycinyl-L-lysine (8.4 mg, 0.027 mmol) and acetic acid (cat.) and the resultant mixture was stirred at room temperature until the reaction was complete. The solvent was evaporated off and the residue flash chromatographed (EtOAc–MeOH, 2:1) to give **19** (15.0 mg, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.44 (2 H, m), 1.70 (3 H, m), 1.91 (1 H, m), 2.17 (3 H, s), 2.65 (2 H, t, J=6.5), 3.35–3.39 (4 H, m). 3.54–3.75 (17 H, m), 3.93 (2 H, m), 4.13 (1 H, A portion of AB system, J=13.1), 4.29 (1 H, B portion of AB system,

$J=13.1$), 4.58 (3 H, m), 4.83 (1 H, d, $J=3.5$), 5.74 (1 H, d, $J=3.1$), 5.90 (1 H, d, $J=3.2$), 7.30–7.42 (9 H, m), 7.49 (1 H, t, $J=7.1$), 7.83 (2 H, d, $J=7.53$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 12.9, 23.2, 29.0, 30.9, 31.1, 32.0, 43.8, 55.5, 55.6, 69.7, 70.1, 70.7, 70.8, 71.0, 73.9, 81.4, 98.2, 106.0, 108.6, 126.2, 127.7, 128.0, 128.7, 128.8, 129.0, 129.5, 129.8, 132.3, 133.9, 138.6, 168.5. IR (neat): 3300, 3030, 2860, 1640 cm^{-1}. (Found: M^+, 860.3393. Calc. for Na-salt of **19**, M^+ $C_{41}H_{56}N_3Na_2O_{12}S$: $M^+ + Na$, 860.3380).

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