

Synthesis of an Oxa-Norbornane Scaffold Provided with Lipid and Linker Residues

Andreas Wållberg and Göran Magnusson*

Organic Chemistry 2, Center for Chemistry and Chemical Engineering,
Lund University, P.O. Box 124, S-221 00 Lund, Sweden

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Abstract: Rigid and highly functionalized compounds with a tetracyclo [6.3.1.1^{1,4}.0^{5,12}] framework were transformed into a number of derivatives, including a lipid (**1**) and a linker (**2**) compound. The former carries a highly oxygenated polar head, and has characteristics common to glycolipids, whereas the latter carries a linker moiety suitable for coupling to a solid support for further manipulations. © 1998 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

Conformationally restricted compounds are potentially useful as scaffolds for the development of lead structures in the search for novel drugs and other biologically active compounds. Furthermore, cyclic structures have been suggested to represent the most interesting targets, and such rigid structures provide more information about the three-dimensional requirements for ligand binding than do conformationally less defined structures.¹ Of special interest are densely oxygenated compounds, due to their similarity with carbohydrates, a class of compounds that is increasingly appreciated as important ligands for protein binding in connection with e.g. bacterial and viral infection.² Another aspect of conformationally restricted structures is their usefulness as scaffolds for the synthesis of molecular libraries by combinatorial methods.

We wish to report the synthesis of some functionalized, enantiomerically pure, oxa-norbornanes and transformation into the corresponding lipid and linker derivatives **1** and **2** (Fig. 1). These compounds are potentially useful for further functionalization, both by liquid and solid phase methods.

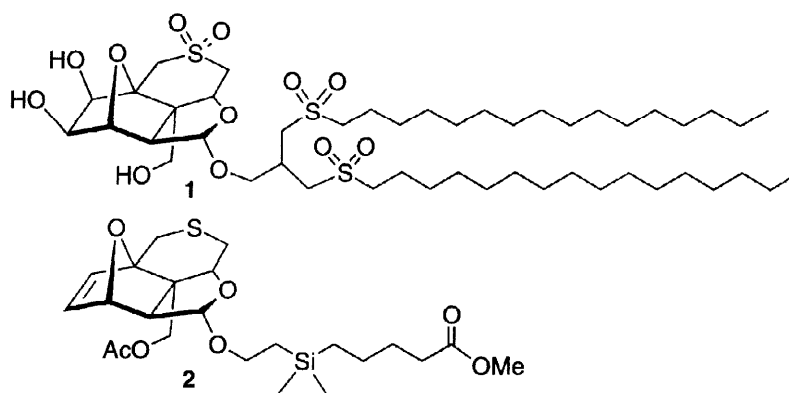
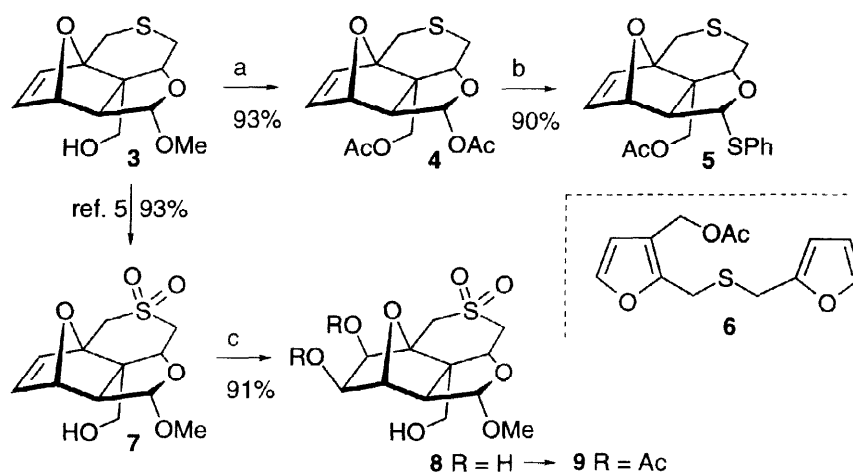


Figure 1. The oxa-norbornane scaffold conjugated to a lipid (**1**) and a linker (**2**) residue.

RESULTS AND DISCUSSION

The oxa-norbornane scaffold is available in eight reaction steps, starting with D-glucose. Key steps include ring-contraction of an epoxysugar and intramolecular Diels-Alder reaction of a furan aldehyde.³⁻⁵

The known⁵ methyl acetal **3** (Scheme 1) was hydrolyzed in aqueous sulfuric acid to give the corresponding hemiacetal, which was conventionally acetylated to furnish the diacetate **4** (93%) as a single epimer. Treatment of **4** with BF₃OEt₂ and thiophenol in CH₂Cl₂ yielded the "thioglycoside" **5** (90%), also as a single epimer. Treatment of **4** with 3-bromo-2-(bromomethyl)propanol⁶ under similar conditions gave (in addition to **10**; Scheme 2) substantial amounts of the bis-furan **6**, presumably via a retro Diels-Alder reaction followed by 1,4-elimination of acetic acid. The formation of single epimers of **4** and **5** reflects the propensity for a pseudoaxial positioning of the aglycons, in accord with the anomeric effect in furanosides.⁷



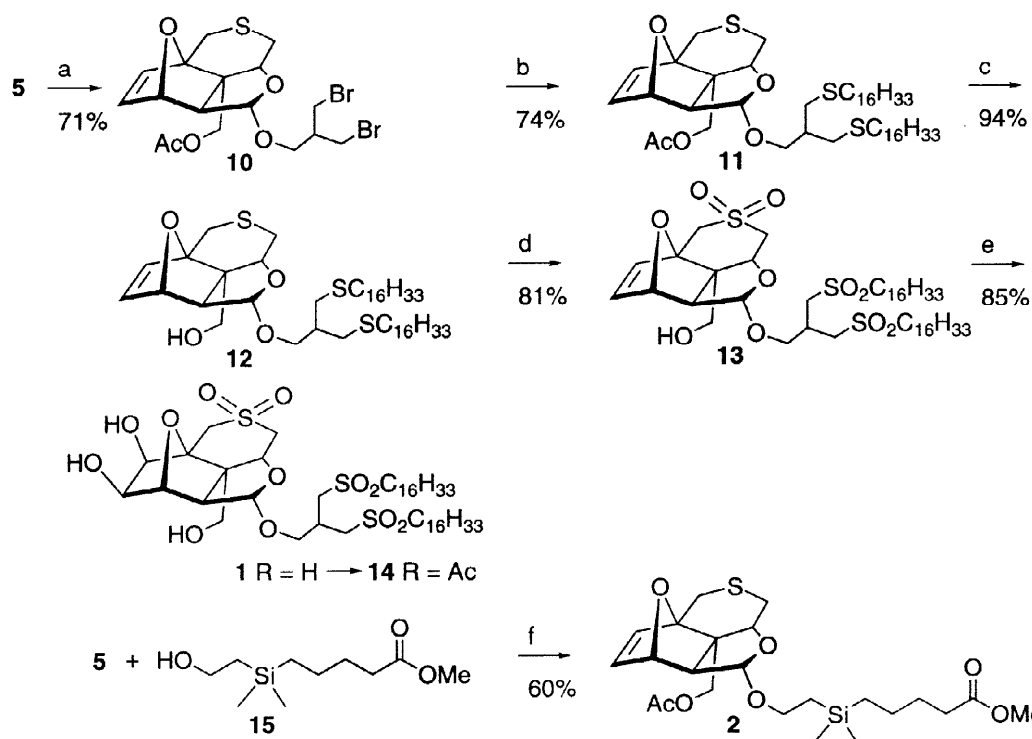
Scheme 1. (a) Aq. H₂SO₄ (pH 3), 70 °C, 48 h, then pyridine, Ac₂O, 24 h. (b) PhSH, BF₃OEt₂, CH₂Cl₂, -30 °C, 15 min. OsO₄ (cat.), N-methylmorpholine oxide, acetone, H₂O, 72 h.

In order to probe the stability of the oxa-norbornanes under various reaction conditions, we performed some oxidation reactions starting with compound **3**, as well as different functionalisations at the anomeric position. The latter reactions were designed to elucidate the possibility of solid-phase manipulations of oxa-norbornanes without risking a retro-Diels-Alder reaction in compounds retaining the double bond.

Selective oxidation of **3** gave the sulfone **7**, as previously described.⁵ Treatment of **7** with N-methylmorpholine-N-oxide and a catalytic amount of OsO₄⁸ furnished the densely oxygenated water soluble compound **8** (91%). The face selectivity in the OsO₄-oxidation of **7** (\rightarrow **8**) is expected and well in line with the corresponding epoxidation.⁵ The structure of **8** is supported by the J₃₋₄ coupling constant (0 Hz; Table 1). Conventional acetylation of **8** provided the triacetate **9** suitable for detailed ¹H NMR analysis.

Treatment of the thioglycoside **5** (Scheme 2) with N-iodosuccinimide and trifluoromethanesulfonic acid¹⁰ (conventional glycosylation conditions) in the presence of 3-bromo-2-(bromomethyl)propanol⁶ (DIBOL) furnished the DIB glycoside **10** (71%). Displacement of the bromine atoms in **10** by hexadecylmercaptan provided the bis-sulfide lipid **11** (74%), which was deacetylated with MeONa-MeOH to give **12** (94%). The three sulfur atoms of **12** were oxidized by MCPBA to yield the tris-sulfone **13** (81%). Compound **13** was dihydroxylated with N-methylmorpholine-N-oxide and a catalytic amount of OsO₄ to furnish the densely oxygenated lipid **1** (85%), which was conventionally acetylated to give the triacetate **14** (>95%). The water solubility of **8** indicated that the corresponding lipid **1** would have physical properties similar to glycolipids.

Thus, it was found that **1** migrates on a TLC plate similar to the corresponding glucose lipid.⁹ Furthermore, the polar head of **1** might contain epitopes suitable for binding of various carbohydrate-recognizing proteins, such as plant lectins, antibodies, and bacterial and viral adhesins.²



Scheme 2. (a) 3-bromo-2-bromomethylpropan-1-ol, *N*-iodosuccinimide, TfOH (cat.), CH₂Cl₂, -40 °C, 35 min. (b) C₁₆H₃₃SH, Cs₂CO₃, DMF, 96 h at 22 °C, 24 h at 60 °C. (c) MeONa, MeOH, CH₂Cl₂, 11 h. (d) MCPBA, CH₂Cl₂, 3 h. (e) OsO₄ (cat.), *N*-methylmorpholine oxide, acetone, H₂O, 144 h. (f) *N*-iodosuccinimide, TfOTMS (cat.), CH₂Cl₂, -40 °C, 1 h.

Treatment of **5** with *N*-iodosuccinimide and trimethylsilyl trifluoromethanesulfonate in the presence of the 2-silylethanol linker **15**¹¹ gave the linker conjugate **2** (60%), suitable for coupling to a solid support, as described for the galactose analog.¹¹ Structural variations of **2** on solid support, as indicated in Fig. 2, should lead to molecular libraries of interest for drug development. It is envisioned that Lewis acid-carboxylic anhydride-mediated release of the structurally modified oxa-norbornanes from the solid support will proceed by simultaneous introduction of acyl groups on the anomeric oxygen, as has been amply demonstrated for 2-(trimethylsilyl)ethyl glycosides.¹² Such structural variation during the release step would greatly expand the size of a molecular library.

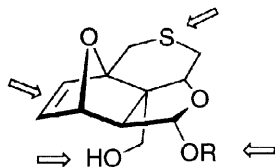


Figure 2. The oxa-norbornane scaffold; arrows indicate positions suitable for structural manipulations.

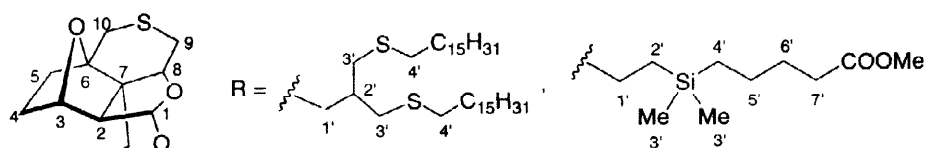


Figure 3. Atom numbering for Table 1.

Table 1. ¹H NMRⁱ chemical shiftsⁱⁱ, signal multiplicities and coupling constantsⁱⁱⁱ.

Chemical shifts ⁱⁱ	1	2	4	5	8	9	10	11	12	13	14
Proton ^{iv}	1	2	4	5	8	9	10	11	12	13	14
1	4.90	5.11	6.28	5.81	5.00	5.03	5.10	5.10	5.06	5.12	5.17
s	s	s	s	d	s	s	s	s	s	s	s
2	1.87	1.95	2.12	2.12	2.18	2.34	2.00	1.98	1.88	2.01	2.33
s	s	s	s	d	s	s	s	s	s	s	s
3	4.18	4.98	5.08	5.03	4.45	4.56	4.98	4.98	4.92	5.03	4.56
s	d	d	d	s	m	d	d	d	d	d	s
4	4.05	6.54	6.57	6.66	4.13	5.39	6.54	6.54	6.52	6.57	5.45
d	dd	dd	dd	dd	d	d	dd	dd	dd	dd	d
5	3.74	6.28	6.31	6.32	4.12	4.93	6.28	6.28	6.31	6.37	4.92
d	d	d	d	d	d	d	d	d	d	d	d
8	4.40	4.33	4.48	4.62	4.69	4.56	4.31	4.32	4.42	4.73	4.61
t	t	t	t	t	t	m	t	t	t	t	t
9eq		2.92	2.96	2.95		3.62	2.91	2.92	2.89	3.56	3.62
m	m	ddd	ddd	ddd		ddd	m	m	dd	ddd	dd
9ax		3.21	3.18	3.25		3.47	3.20	3.21	3.24		3.46
dd	dd	dd	dd	dd		dd	dd	dd	dd		dd
10eq		2.96	3.01	3.00		3.67	2.96	2.96	3.02		3.69
m	dd	dd	dd	dd		dd	m	m	d		m
10ax		3.32	3.31	3.33		3.39	3.31	3.32	3.39	3.80	3.39
d	d	d	d	d		d	d	d	d	d	d
9,10	3.57-3.35 m				3.79-3.72 m					3.73-3.63 m	
11	3.64	4.18	4.20	4.16	3.83	4.50	4.12	4.12	3.71	3.94	4.45
d	m	d	d	s	d	d	d	d	dd	m	d
11	3.57	4.00	4.02	4.06		4.29	3.99	4.01	3.60	3.73-	4.37
d	d	d	d				d	d	dd	3.63 m	d
1'	3.77	3.75					3.78	3.78	3.78	3.92	3.97
dd	m						dd	dd	dd	m	dd
1'	3.45	3.46					3.55-3.43 m	3.48	3.49	3.73-	3.69
m	m						2.28	1.96	1.98	2.98	3.06
2'	2.78	0.88					3.55-3.43 m	2.59	2.60	3.41-	3.40-
m	m						m	m	m	3.37 m	3.33 m
3'	3.22	-0.01								3.23-	3.19-
m	s									3.10 m	3.09 m
3'	3.03	-0.03								3.01	3.06-
m	s									m	2.99 m
4'	2.89	0.51						2.48	2.48		
m	m							m	m		
5'	1.66	1.30						1.60-	1.56	1.89-	1.88-
m	m							1.51 m	m	1.76 m	1.78 m
6'-18'	1.32-1.03 m							1.39-	1.40-	1.47-	1.48-
								1.21 m	1.20 m	1.21 m	1.22 m
19'	0.70							0.87	0.88	0.87	0.89
m								m	m	m	m
Other		1.62	2.13	7.47	3.33	3.34	2.11	2.12	1.89		2.15
		m 6'	s Ac	m Ar	s OMe	s OMe	s Ac	s Ac	m OH		s Ac
		2.30	2.05	7.25		2.14					2.12
		m 7'	s Ac	m Ar		s Ac					s Ac
		3.66		2.15		2.11					2.09
		s OMe		s Ac		s Ac					s Ac
		2.12				2.08					
		s Ac				s Ac					
Coupling constants ⁱⁱⁱ											
J ₁₋₂	0	0	0	0.81	0	0	0	0	0	0	0
J ₂₋₃	0	0	0	0	0	0	0	0	0	0	0
J ₃₋₄	0	1.8	1.8	1.8	0	0	1.8	1.8	1.6	1.8	0
J ₄₋₅	6.0	5.7	5.7	5.7	6.0	6.1	5.7	5.7	5.7	5.7	6.0
J ₈₋₉	4.1	3.0	3.4	3.1	3.5	5.4	3.0	3.0	4.3	5.2	5.9
J _{9eq-9ax}		14.7	14.9	14.8		14.7	14.8	14.7	14.3	14.8	14.8
J _{9eq-10eq}			1.7	1.6		2.0			0	2.0	0
J _{10eq-10ax}		14.1	14.2	14.2		15.1	14.2	14.0	14.0	10.6	14.0
J ₁₁₋₁₁	11.1	11.5	11.5	11.5		12.4	11.5	11.5	10.4		12.4
J _{11-OH}									5.3,2.9		
J _{1'-1'}	10.0						9.9	9.7	9.7		10.0
J _{1'-2'}	4.6						6.1	5.4	5.4		4.8
J _{2'-3'}							5.9,5.7				

ⁱSolvents: CDCl₃ (2, 4, 5, 9-14), CDCl₃-CD₃OD 3:1 (1) and D₂O (8). ⁱⁱppm. ⁱⁱⁱHz.^{iv}for numbering of protons see Fig. 3.

EXPERIMENTAL SECTION

^1H NMR-spectra were recorded at 400 MHz proton frequency, using CDCl_3 , $\text{CDCl}_3\text{-CD}_3\text{OD}$ 3:1, or D_2O as solvent and CHCl_3 (δ 7.26) and H_2O (δ 4.80) as internal standards. ^1H NMR spectra for all novel oxanorbornanes are presented in Table 1; a key for atom numbering is depicted in Fig. 3. ^{13}C NMR-spectra were recorded at 100 MHz carbon frequency, using CDCl_3 or $\text{D}_2\text{O-CD}_3\text{OD}$ as solvent and CHCl_3 (δ 77.0) and MeOH (δ 49.9) as internal standards. TLC analyses were performed with Merck SiO_2 60 F_{256} precoated aluminium sheets with visualisation by UV light, charring with H_2SO_4 (10% in water) or charring with anisaldehyde in ethanolic sulfuric acid. Column chromatography was performed with Matrex SiO_2 60 (35–70 μm).

(+)-(1R,2R,3S,4S,5R,6S,8S,12S)-6-{3-(Hexadecylsulfonyl)-2-[(hexadecylsulfonyl)-methyl]propyloxy}-2,3-dihydroxy-7,10,10,13-tetraoxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{8,12}]-tridecan-12-ylmethanol (1). Compound **13** (23.2 mg, 0.0256 mmol) was dissolved in a mixture of H_2O (0.6 mL) and acetone (1.3 mL), and *N*-methylmorpholine-*N*-oxide (3.8 mg, 0.0324 mmol) and OsO_4 (0.011 mL of a 2.5% *t*BuOH solution, 55×10^{-6} mmol) were added under Ar. The mixture was stirred at -22°C for 72 h, OsO_4 solution (0.025 mL, 125×10^{-6} mmol) was added and the stirring was continued for another 72 h. $\text{Na}_2\text{S}_2\text{O}_5$ (32 mg) was dissolved in H_2O (0.1 mL) and added to the reaction mixture. The solvent was removed and the residue was chromatographed (20:1 EtOAc-EtOH) to give **1** (20.5 mg, 85%); $[\alpha]^{25}_{\text{D}} +5.0$ (*c* 1.0, CHCl_3). ^1H NMR in $\text{CDCl}_3\text{-CD}_3\text{OD}$: see Table 1; with pure CDCl_3 , severe line-broadening was observed. ^{13}C NMR (CDCl_3): δ 106.8, 88.9, 85.4, 82.2, 72.9, 72.5, 67.9, 65.2, 64.5, 55.2, 53.9, 53.8, 52.1, 51.8, 51.4, 50.4, 31.9, 29.7, 29.6, 29.5, 29.4, 29.2, 28.5, 22.7, 21.7, 21.6, 14.1. HRMS calcd for $\text{C}_{47}\text{H}_{88}\text{O}_{12}\text{S}_3\text{Na}$ ($\text{M}+\text{Na}$) 963.5336, found 963.5358. An analytical sample of **14** (quantitative yield) was obtained by conventional acetylation in Ac_2O -pyridine; ^1H NMR: see Table 1.

(+)-(1R,4S,5R,6S,8S,12S)-6-(methyl 6,6-dimethyl-6-sila-8-oxyoctanoate)-7,13-dioxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{5,12}]tridec-2-en-12-ylmethyl acetate (2). A solution of **15** (86.6 mg, 0.396 mmol) was dissolved in dry CH_2Cl_2 . The solution was added to a mixture of **5** (99.4 mg, 0.264 mmol), *N*-Iodosuccinimid (73.2 mg, 0.325 mmol), and activated molecular sieves (AW-300). The mixture was cooled to -40°C and $\text{CF}_3\text{SO}_3\text{SiMe}_3$ (0.01 mL, 0.055 mmol) was added. The reaction mixture was stirred at -40°C for 1 h, Et_3N (0.10 mL) was added, and the temperature was raised to -22°C . The reaction mixture was filtered (Celite) and concentrated and the residue was chromatographed (2:1 heptane-EtOAc) to give **2** (76.4 mg, 60 %) and the corresponding equatorial isomer (~25 %). Compound **2** had $[\alpha]^{22}_{\text{D}} +68$ (*c* 1.0, CHCl_3). ^1H NMR: see Table 1. ^{13}C NMR (CDCl_3): δ 174.1, 170.0, 138.5, 138.1, 105.2, 85.1, 80.6, 75.5, 70.0, 64.3, 57.4, 52.1, 51.3, 33.6, 28.7, 28.6, 28.5, 23.3, 20.8, 16.4, 15.0, -3.2. HRMS calcd for $\text{C}_{23}\text{H}_{36}\text{O}_7\text{SSiNa}$ ($\text{M}+\text{Na}$) 507.1849, found 507.1845.

(+)-(1R,4S,5R,6R,8S,12S)-6-acetoxy-7,13-dioxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{5,12}]-tridec-2-en-12-ylmethyl acetate (4). Compound **3⁵** (337.2 mg, 1.32 mmol) was dissolved in H_2O (50 mL) and pH was adjusted to 3 with 3 M H_2SO_4 . The mixture was stirred at 70°C for 48 h, then neutralized with aq NaOH (1 M) and co-concentrated with toluene. The resulting crude hemiacetal was dissolved in pyridine (25 mL) and acetic anhydride (25 mL) and the mixture was stirred at -22°C for 24 h. The mixture was co-concentrated with toluene and the residue was chromatographed (1:1→1:2 heptane-EtOAc) to give crystalline **4** (402.1 mg,

93%); mp 168–169 °C; $[\alpha]^{20}_{\text{D}} +35$ (*c* 1.1, CHCl_3). ^1H NMR: see Table 1. ^{13}C NMR (CDCl_3): δ 170.0, 169.8, 138.6, 138.1, 100.9, 85.4, 80.4, 76.7, 69.2, 57.5, 52.4, 28.3, 27.9, 21.1, 20.8. HRMS calcd for $\text{C}_{15}\text{H}_{18}\text{O}_6\text{S}$ (M^+) 326.0824, found 326.0826.

(+)-(1R,4S,5R,6R,8S,12S)-6-phenylsulfanyl-7,13-dioxo-10-thiatetracyclo-[6.3.1.1^{1.4}.0^{5.12}]tridec-2-en-12-ylmethyl acetate (5). Compound **4** (518.9 mg, 1.59 mmol) and thiophenol (0.650 ml, 6.36 mmol) were dissolved in CH_2Cl_2 (45 mL) and cooled to -30 °C under Ar. $\text{BF}_3\cdot\text{OEt}_2$ (0.85 mL, 3.25 mmol) was added and the mixture was stirred for 15 min. Sat aq NaHCO_3 (10 mL) was added and the mixture was allowed to reach ~22 °C. The aqueous layer was extracted with CH_2Cl_2 (4x10 mL) and the collected organic layers were washed with H_2O (10 mL), dried (Na_2SO_4), and concentrated. The residue was chromatographed (3:1→1:1 heptane-EtOAc) to give amorphous **5** (538.2 mg, 90 %); mp 161–163 °C; $[\alpha]^{22}_{\text{D}} +252$ (*c* 1.3, CHCl_3). ^1H NMR: see Table 1. ^{13}C NMR (CDCl_3): δ 170.1, 138.2, 138.0, 134.9, 130.4, 128.8, 126.8, 89.9, 85.3, 82.9, 74.9, 68.9, 57.5, 52.7, 28.5, 27.9, 20.9. HRMS calcd for $\text{C}_{19}\text{H}_{21}\text{O}_4\text{S}_2$ ($\text{M}+\text{H}$) 377.0881, found 377.0882.

2-[2-(2-Thia-propyl)furan]-furan-3-ylmethyl acetate (6). Obtained as a byproduct in an attempt to prepare **10** by treatment of **4** with BF_3OEt_2 and 3-bromo-2-(bromomethyl)propanol⁶ in CH_2Cl_2 , essentially as described in the preparation of **5**. ^1H NMR (CDCl_3): δ 7.37 (d, 1 H, *J* 1.4 Hz), 7.34 (d, 1 H, *J* 1.8 Hz), 6.38 (d, 1 H, *J* 1.8 Hz), 6.32 (m, 1 H), 6.22 (d, 1 H, *J* 3.1 Hz), 4.92 (s, 2 H), 3.77 (s, 2 H), 3.70 (s, 2 H), 2.04 (s, 3 H). ^{13}C NMR (CDCl_3): δ 142.3, 142.0, 111.8, 110.4, 107.7, 57.4, 28.0, 25.9, 20.9. HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{O}_4\text{S}$ (M^+) 266.0613, found 266.0601.

(+)-(1R,2R,3S,4S,5R,6S,8S,12S)-6-Methoxy-2,3-dihydroxy-7,10,10,13-tetraoxa-10-thiatetracyclo[6.3.1.1^{1.4}.0^{5.12}]tridecan-12-ylmethanol (8). Compound **7** (28.9 mg, 0.100 mmol) was dissolved in a mixture of H_2O (0.5 mL) and acetone (1.5 mL), and *N*-methylmorpholine-*N*-oxide (17.5 mg, 0.149 mmol) and OsO_4 (0.030 mL of a 2.5% *t*BuOH solution, 0.15×10^{-3} mmol) were added under Ar. The mixture was stirred at ~22 °C for 72 h, $\text{Na}_2\text{S}_2\text{O}_5$ (50 mg) was dissolved in H_2O (0.5 mL) and added to the reaction mixture. The solvent was removed and the residue was chromatographed (3:1 CH_2Cl_2 -MeOH) to give **8** (29.2 mg, 91%); $[\alpha]^{26}_{\text{D}} +1.9$ (*c* 0.8, H_2O). ^1H NMR: see Table 1. ^{13}C NMR (D_2O , CD_3OD): δ 109.5, 90.8, 87.4, 83.4, 74.2, 74.1, 65.7, 56.8, 56.2, 53.3, 52.5, 51.4. HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{O}_8\text{S}$ ($\text{M}+\text{H}$) 323.0801, found 323.0807. An analytical sample of **9** (quantitative yield) was obtained by conventional acetylation in Ac_2O -pyridine; ^1H NMR: see Table 1.

(+)-(1R,4S,5R,6S,8S,12S)-6-(3-Bromo-2-(bromomethyl)-propyloxy)-7,13-dioxo-10-thiatetracyclo[6.3.1.1^{1.4}.0^{5.12}]tridec-2-en-12-ylmethyl acetate (10). Compound **5** (49.8 mg, 0.132 mmol) and *N*-Iodosuccinimide (40.0 mg, 0.178 mmol) were dissolved in dry CH_2Cl_2 (3 mL) under Ar. The mixture was cooled to -40 °C and 3-bromo-2-(bromomethyl)propanol⁶ (59.0 mg, 0.254 mmol) and a solution of trifluoromethanesulfonic acid in CH_2Cl_2 (0.1 mL, 0.137 M, 0.014 mmol) were added. The mixture was stirred at -40 °C for 35 min, Et_3N (0.200 mL) was added, and the temperature was raised to ~22 °C. The reaction mixture was filtered (Celite) and concentrated, and the residue was chromatographed (1:1 heptane-EtOAc) to give **10** (55.9 mg, 85%), contaminated by approx. 20% of the equatorial anomer. Rechromatography (2:1 heptane-

EtOAc) gave pure **10** (46.5 mg, 71%); $[\alpha]^{23}_{\text{D}} +61$ (*c* 1.0, CHCl_3). ^1H NMR: see Table 1. ^{13}C NMR (CDCl_3): δ 170.2, 138.6, 138.1, 105.8, 85.1, 80.5, 75.7, 69.7, 66.2, 57.2, 52.2, 42.5, 32.7, 28.6, 28.3, 20.9. HRMS calcd for $\text{C}_{17}\text{H}_{22}\text{O}_5\text{SBr}_2$ ($\text{M}+\text{C}_2\text{H}_5$) 525.9946, found 525.9938.

(+)-(1R,4S,5R,6S,8S,12S)-6-{3-(Hexadecylthio)-2-[(hexadecylthio)methyl]propyloxy}-7,13-dioxo-10-thiatetracyclo[6.3.1.1^{1.4}.0^{5.12}]tridec-2-en-12-ylmethyl acetate (11). Compound **10** (103 mg, 0.207 mmol) and Cs_2CO_3 (202 mg, 0.620 mmol) were added to degassed DMF (1.1 mL) under Ar. Hexadecanethiol (0.110 mL, 0.620 mmol) was added and the mixture was stirred for 72 h at $\sim 22^\circ\text{C}$. A second aliquot of hexadecanethiol (0.110 mL, 0.620 mmol) was added and the stirring was continued for 24 h at $\sim 22^\circ\text{C}$ and for 24 h at 60°C . The mixture was diluted with CH_2Cl_2 (20 mL), washed with H_2O (3x5 mL), dried (MgSO_4), and concentrated. The residue was chromatographed (5:1 heptane-EtOAc) to give **11** (130 mg, 74%); $[\alpha]^{22}_{\text{D}} +33$ (*c* 1.0, CHCl_3). ^1H NMR: see Table 1. ^{13}C NMR (CDCl_3): δ 170.2, 138.6, 138.2, 105.8, 85.2, 80.6, 75.6, 70.1, 67.6, 57.3, 52.0, 39.2, 33.4, 33.3, 32.9, 32.8, 31.9, 29.7, 29.4, 29.3, 28.9, 28.7, 28.5, 22.7, 20.9, 14.1. HRMS calcd for $\text{C}_{49}\text{H}_{88}\text{O}_5\text{S}_3$ (M^+) 852.5794, found 852.5790.

(+)-(1R,4S,5R,6S,8S,12S)-6-{3-(Hexadecylthio)-2-[(hexadecylthio)methyl]propyloxy}-7,13-dioxo-10-thiatetracyclo[6.3.1.1^{1.4}.0^{5.12}]tridec-2-en-12-ylmethanol (12). Compound **11** (130 mg, 0.152 mmol) was dissolved in a mixture of dry MeOH (15 mL) and dry CH_2Cl_2 (10 mL). Methanolic MeONa (0.12 mL, 0.5 M, 0.06 mmol) was added and the reaction mixture was stirred for 11 h. SiO_2 (2 g) was added, and the mixture was stirred for 30 min, filtered (Celite), and concentrated, which gave crude **12** (116 mg, 94%); $[\alpha]^{25}_{\text{D}} +29$ (*c* 1.0, CHCl_3). ^1H NMR: see Table 1. ^{13}C NMR (CDCl_3): δ 138.9, 138.0, 105.4, 86.4, 80.5, 68.6, 67.5, 57.5, 54.9, 39.2, 33.4, 32.9, 31.9, 29.7, 29.6, 29.4, 29.3, 28.9, 28.7, 28.5, 22.7, 14.1. HRMS calcd for $\text{C}_{47}\text{H}_{86}\text{O}_4\text{S}_3$ (M^+) 810.5688, found 810.5675.

(+)-(1R,4S,5R,6S,8S,12S)-6-{3-(Hexadecylsulfonyl)-2-[(hexadecylsulfonyl)methyl]propyloxy}-7,10,10,13-tetraoxo-10-thiatetracyclo[6.3.1.1^{1.4}.0^{5.12}]tridec-2-en-12-ylmethanol (13). Compound **12** (96.3 mg, 0.119 mmol) was dissolved in CH_2Cl_2 (15 mL) and MCPBA (55%, 228 mg, 0.727 mmol) was added. The mixture was stirred for 3 h at $\sim 22^\circ\text{C}$, filtered through Al_2O_3 (grade III), and concentrated. The residue was chromatographed (1:4 heptane-EtOAc) to give **13** (86.8 mg, 81%); $[\alpha]^{27}_{\text{D}} +14$ (*c* 1.0, CHCl_3). ^1H NMR: see Table 1. ^{13}C NMR (CDCl_3): δ 138.2, 137.9, 105.3, 88.4, 81.2, 79.0, 68.4, 68.0, 57.7, 55.4, 54.1, 52.6, 52.1, 51.9, 51.8, 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.4, 22.7, 21.8, 14.1. HRMS calcd for $\text{C}_{47}\text{H}_{86}\text{O}_{10}\text{S}_3\text{Na}$ ($\text{M}+\text{Na}$) 929.5281, found 929.5287.

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