Synthesis of Polycyclic Oxanorbornanes via a Sequential Epoxyhexopyranoside Ring Contraction−Intramolecular Diels−Alder Reaction

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Ring contraction of methyl 2,3-anhydro-6-deoxy-6-(furfurylthio)-α-D-allopyranoside with LiBr/TMU in boiling toluene gave the corresponding α,*β*-unsaturated furanosidic aldehyde **1** together with a small amount of the corresponding oxanorbornene Diels−Alder adduct **2**. Pumping a mixture of heptane and Et_3N slowly through a SiO_2 column containing **1** and **2** shifted the ratio strongly toward **2**. The products were eluted from the column by EtOAc/EtOH and chromatographed to give pure **2** and **1** in 79% and 15% yield, respectively. Compound **2** was submitted to a number of oxidations and reductions, which gave the oxanorbornanes **4**−**15**. The structures were determined by 2D ^1H and ^{13}C NMR techniques and by a single-crystal X-ray investigation of compound **5**.

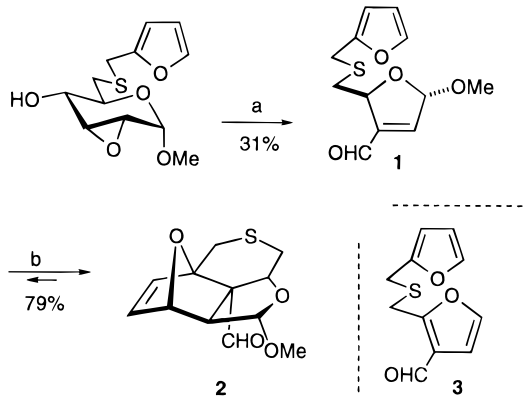
Introduction

Small and highly functionalized molecules with well-defined conformations are attractive targets in the search for *inter alia* new bioactive compounds.[1] Within a project aimed at the preparation of such small (<500 Da) molecules, we report a series of enantiomerically pure oxanorbornanes. The key synthetic sequence (Scheme 1) consists of ring contraction of a furan-linked epoxyhexopyranoside[2] followed by intramolecular Diels−Alder reaction of the resulting α,*β*-unsaturated furanosidic aldehyde. A limited number of ring systems have been constructed *via* intramolecular Diels−Alder reactions with α,*β*-unsaturated aldehydes as the dienophile;[3] only one such example with a furan moiety as the diene was found in the literature.[3f] The functional groups present in the oxanorbornanes give opportunities for structural variation on the tetracyclic framework, as exemplified below by the various reductions and oxidations of the formyl, thioether, and olefin groups.

Results and Discussion

I. The Intramolecular Diels−Alder Reaction. Ring contraction[2] of methyl 2,3-anhydro-6-deoxy-6-furfurylthio-α-D-allopyranoside[4] (Scheme 1) was performed by treatment with LiBr/TMU in toluene at reflux temperature for 10 min, to give the α,*β*-unsaturated aldehyde **1** (31%) and a small amount of its Diels−Alder adduct **2** (4%). Further investigation led to procedures that transformed **1** into **2** in good yield (60−80%; see below). The overall yield of isolated **2** from methyl α-D-glucopyranoside over seven steps was 18% (steps 1−5 gave crystalline products[4]).

Scheme 1[a]



[a] (a) LiBr, TMU, toluene, reflux, 10 min. (b) SiO_2 column; (i) heptane/Et_3N, 300:1, 20 h; (ii) EtOAc/MeOH, 20:1.

The establishment of a Diels−Alder equilibrium is generally accelerated by Lewis acids and by heat. However, aldehyde **1** suffers a 1,4-elimination of methanol in the presence of acids, thus forming the bisfuran **3**, and heating shifts the **2**/**1** equilibrium toward **1** (see below).

Monitoring of the reaction **1** → **2** by ^1H NMR ($CDCl_3$, Na_2CO_3, sealed tube) at different temperatures gave an indication about the position of the **2**/**1** equilibrium: at room temperature, the **2**/**1** ratio was 28:72 (70 h), and at 60 °C, the **2**/**1** ratio was 27:73 (1 h), 55:45 (25 h), and 56:44 (53 h). Raising the temperature to 120 °C gave a **2**/**1** ratio of 25:75 after 10 h. A sample of **2**, containing 3−5% of **1**, was stored at −20 °C for 3 years, which resulted in complete transformation of **1**; NMR analysis showed the sample to consist of pure **2**. These experiments demonstrate that the equilibrium between **1** and **2** is obtained rather slowly and that **2** is favored at low temperature. For obvious practical reasons, the low-temperature route to **2** was not considered further.

Intramolecular Diels−Alder reactions have been catalyzed by Lewis acids,[5] and silica gel (SiO_2) has been used as a mild catalyst.[6] Stirring a solution of **1** in toluene/

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(5) (a) Roush, W. R. *Adv. Cycloaddit.* **1990**, *2*, 91. (b) Oh, T.; Reilly, M. *Org. Prep. Proc. Int.* **1994**, *26*, 129. (c) Ciganek, E. *Org. React.* **1984**, *32*, 1. (d) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (e) Brieger, G.; Bennett, N. *Chem. Rev.* **1980**, *80*, 63.

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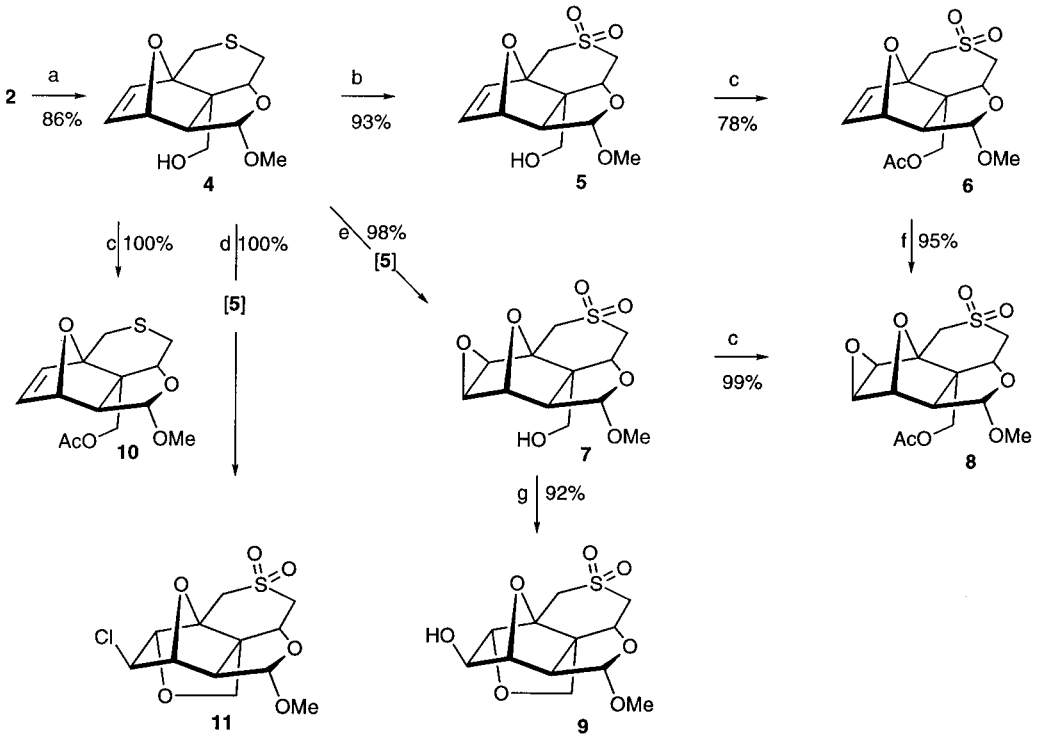
Scheme 2[a]



[a] (a) $NaBH_4$, EtOH, 22 °C, 1.5 h; (b) MCPBA, CH_2Cl_2, 22 °C, 1 h; (c) Ac_2O, pyridine, 22 °C, 2−20 h; (d) (i) MCPBA, THF, 22 °C, 1 h; (ii) LiCl, 1 min; (e) MCPBA, CH_2Cl_2, 22 °C, 24 h; (f) MCPBA, CH_2Cl_2, 22 °C, 6 d; (g) MeONa, MeOH, 22 °C, 5 d.

Et_3N at room temperature in the presence of a small amount of SiO_2 gave a mixture of **2** and **1** (1:1) within 24 h. When Et_3N was omitted, the bisfuran **3** was also formed.

When **1** was added to a column of SiO_2 and the solvent (heptane/Et_3N, 300:1) was pumped slowly through the column, the **2**/**1** ratio was shifted strongly toward **2**. Elution of the products from the column with EtOAc/EtOH, followed by chromatographic separation of **1** and **2**, gave pure **2** and unreacted **1** in 79 and 15% yield, respectively.

The conditions on the column eluted with heptane/Et_3N shifted the equilibrium toward the adduct **2**. This effect might be due to stabilisation of **2** on SiO_2, as indicated by the low R_f value [TLC, heptane/Et_3N, 300:1; $R_f = 0.0$ (**2**) and 0.1 (**1**)]; **2** might form a complex with the SiO_2 surface. It should be noted that the two hydrofuranoid oxygens of **2** are sterically well situated for complexation with cations. An additional example of cation complexation is given below in the purification of compound **11**.

II. Functional Group Manipulations of the Oxanorbornanes. Reduction of aldehyde **2** with $NaBH_4$ gave the corresponding alcohol **4** (86%), which was stable against retro-Diels−Alder reaction for 24 h at 60 °C. The same stability was found for compounds **5**, **6**, and **10** (Scheme 2).

The unsaturated sulfide alcohol **4** was selectively oxidized to the corresponding sulfone **5** (93%) by treatment with ~2.5 equiv of MCPBA for 1 h. With 6 equiv of MCPBA and prolonged reaction time (24 h), **4** was converted to the epoxy sulfone **7** (98%) in a one-pot reaction. Acetylation of **4** and **5** with Ac_2O in pyridine gave the acetates **10** (100%) and **6** (78%), respectively. Oxidation of **6** with MCPBA gave the epoxy sulfone acetate **8** (95%), which was also obtained by acetylation (99%) of the epoxy alcohol **7**.

Treatment of **7** with a catalytic amount of methanolic MeONa led to the formation of **9** (92%), having an additional hydrofuranoic ring. The reaction presumably proceeds via an intramolecular alkoxide attack on the epoxide ring. Under acidic conditions (*p*-TsOH, THF, H_2O), **9** was formed very slowly, according to TLC analysis.

The unsaturated sulfide alcohol **4** was oxidized in a one-pot reaction to afford **11** in quantitative yield. Thus, using 5.3 equiv of MCPBA and adding an excess of LiCl when all of **4** had been converted to **5** gave **11** in a rapid reaction (<1 min). A similar reaction with a norbornene derivative has been reported.[7] However, this reactions required the addition of crown ether to complexate the cation of the halide salt. Compound **5** (as well as the other sulfones presented here) carries three oxygens (one sulfone and two hydrofuranoic oxygens) in a geometric arrangement that might bind Li ion,[8] thereby accelerating the reaction with MCPBA and LiCl. As an alternative route, treatment of **5** with *N*-chlorosuccinimide also gave **11** in quantitative yield; however, removal of succinimide from the product was difficult.

Hydrogenation of **4**, using Pd/C as a catalyst (Scheme 3), afforded the saturated sulfide−alcohol **12** (99%), and oxidation of **12** with MCPBA gave the corresponding sulfone−alcohol **13** (86%).

The unsaturated aldehyde **2** was oxidized with pyridinium dichromate in DMF/MeOH[9] to give the unsatur-

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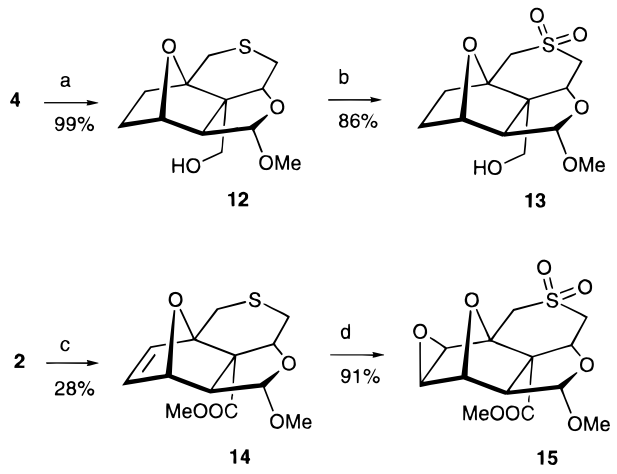
Scheme 3[a]



[a] (a) H_2, Pd/C, EtOAc, 22 °C, 2 h; (b) MCPBA, CH_2Cl_2, 22 °C, 2.5 h; (c) PDC, DMF, MeOH, 22 °C, 7 d; (d) MCPBA, CH_2Cl_2, 22 °C, 5 d.

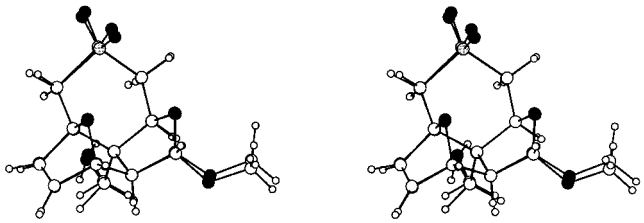


Figure 1. Stereoview of the superimposed X-ray and MM3 structures of **5**, obtained by least-squares fitting (RMS = 0.057 Å) of all ring atoms. Dark gray, oxygen; light gray, sulfur; unfilled, carbon and hydrogen. The torsional angle $H_1-C_1-C_2-H_2$ was 96° in both structures.

ated methyl ester **14** (28%) after 7 days. Residual **2** was also isolated, and several byproducts were formed, presumably by retro-Diels–Alder reactions and oxidation of the sulfur atom of **2** and the ring-opened products. Attempted oxidation of the sulfur atom of **2** with MCPBA before oxidation of the formyl group was unsuccessful. The ester **14** underwent partial retro-Diels–Alder reaction on storage at room temperature for 4 months. However, epoxidation of **14** with MCPBA gave the stable epoxy sulfone ester **15** (91%).

III. Structure and Solubility of the Oxanorbornanes. The structures of compounds **2** and **4**–**15** were determined by ^{1}H- and ^{13}C-NMR spectroscopy, including various 2D techniques, such as COSY, NOESY, and HETCOR (Tables 1 and 2). A single-crystal X-ray analysis of **5** confirmed the overall structure of the tetracyclic framework. Molecular mechanics calculation (MM3)[10] of **5** gave a minimum-energy structure very similar to the X-ray structure. An overlay of the X-ray and MM3 structures was obtained by least-squares fitting of all ring atoms, giving an RMS value of 0.057 Å (Figure 1). The good fit indicates that the structures of the remaining compounds can be calculated with high precision by the MM3 program.

All the ^{1}H NMR chemical shifts and coupling constants of compounds **2** and **4**–**15** are in good agreement with the proposed rigid structures (Figure 2 and Table 1). It can be deduced from the spectral data that simple substitutions of functional groups do not affect appreciably the over-all conformation of the molecular framework. On the other hand, introduction of the additional furanoid ring causes a slight twist of the ring system, as seen by the small J_{12} and J_{34endo} coupling constants of **9** and **11**; in all the other compounds, J_{12} and J_{34endo} equal zero (Table 1). All the compounds, except **6** and **13**, show a $J_{9eq10eq}$ coupling constant, in agreement with the *W* arrangement of the two protons.[11] The remaining J_9-J_{10} couplings are zero, except for $J_{9eq10ax}$ of **8** (1.1 Hz) and $J_{9ax10eq}$ of **15** (1.3 Hz) (not shown in Table 1). The chemical shifts of H-2 in **4**–**8**, **10**, **12**, and **13** are in the range 1.87–2.30. The larger H-2 shifts for **2**, **9**, **11**, **14**, and **15** (2.42–3.10) are in agreement with a close proximity between H-2 and the carbonyl or ring oxygens (O-11).[12] The ^{13}C NMR chemical shift signals of compounds **2**, **4**, **7**–**9**, and **11** were assigned by the HETCOR technique and found to be in good agreement with the proposed structures.

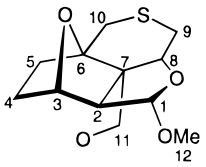


Figure 2. Atom numbering for compounds **2** and **4**–**15**.

We have previously shown that furanoid acetals, where the ring carbon atoms are fixed in one plane by a norbornane scaffold, carry the alkoxy substituent in a pseudoaxial orientation, whereas their *C*-glycosidic analogs have a pseudoequatorially positioned alkyl group. The ^{1}H NMR coupling constant J_{12} (cf. Figure 2) was ~0 and ~6 Hz, respectively. This investigation provided the first experimental evidence for an anomeric effect in furanosides.[13] The same effect is operating in the oxanorbornane furanosides presented here. The anomeric effect is important for the geometrical positioning of the furanosidic ring oxygen atom, which might be crucial for the binding of lithium ion discussed above.

The compounds **4**–**15** are all soluble in rather polar solvents or solvent combinations. For example, the sulfide **4** and the sulfone **5** are soluble in H_2O at a concentration of 10 and 20 mM, respectively. The sulfone **8** is insoluble in H_2O and in MeOH, but soluble in $CHCl_3$/MeOH/H_2O or acetone/H_2O. Most of the compounds are soluble enough in $CDCl_3$ or acetone, for determination of optical rotations (see the Experimental Section). Such promiscous solubility characteristics would probably be useful in assays during the search for potential bioactivity of these compounds.

Experimental Section

^{1}H-NMR spectra were recorded at 300, 400, or 500 MHz proton frequency, using $CDCl_3$ or acetone-d_6 as solvent and $CHCl_3$ (δ 7.26 ppm) or acetone-d_5 (δ 2.05 ppm) as internal

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Table 1. ^{1}H NMR[a] Chemical Shifts,[b] Signal Multiplicities, and Coupling Constants[c] for Compounds 2 and 4−15

proton[d]	2	4	5	6	7	8	9	10	11	12	13	14	15
						Chemical Shifts							
1	5.10 s	4.99 s	4.89 s	5.03 s	4.88 s	4.97 s	4.92 d	5.01 s	5.11 d	4.93 s	4.96 s	5.06 s	5.10 s
2	2.66 s	1.89 s	1.87 s	2.13 s	2.17 s	2.30 s	2.42 d	1.97 s	2.53 d	1.95 s	2.02 s	2.91 s	3.10 s
3	5.09 d	4.95 d	4.98 d	5.07 d	4.48 s	4.56 s	4.43 d	4.98 d	4.69 d	4.48 d	4.60 d	5.04 d	4.67 s
4	6.59 dd	6.54 dd	6.52 dd	6.62 dd				6.55 dd				6.58 dd	
4_{exo}										1.97 m	1.95 m		
4_{endo}					3.57 d	3.55 AB q	3.73 d		4.12 d	1.52 ddd	1.50 m		3.33 d
5	6.35 d	6.33 d	6.69 d	6.32 d				6.29 d				6.19 d	
5_{exo}							3.75 s		3.83 s	1.42 dt	1.50 m		
5_{endo}					3.68 d	3.54 AB q				2.05 ddd	2.22 m		3.51 d
8	4.49 dd	4.43 dd	4.69 dd	4.69 t	4.48 dd	4.51 t	4.64 t	4.32 t	4.66 t	4.31 t	4.61 t	4.37 t	4.64 t
9_{eq}	2.95 ddd	2.93 ddd	3.44 dt	3.65 dd	3.45 ddd	3.57 ddt	3.39 dt	2.93 ddd	3.61 dt	2.95 ddd	3.59 d	2.88 ddd	3.58 dd
9_{ax}	3.11 dd	3.27 dd	3.79 dd	3.52 dd	3.58 dd	3.44 dd	3.56 dd	3.22 dd	3.28 dd	3.13 dd	3.59 d	3.29 dd	3.58 dd
10_{eq}	3.02 dd	3.04 dd	3.45 dd	3.73 s	3.41 dd	3.64 brs	3.58 dd	2.97 dd	3.82 dd	2.89 dd	3.70 d	2.94 dd	3.67 dt
10_{ax}	3.36 d	3.42 d	3.99 d	3.73 s	3.86 d	3.64 brs	3.72 d	3.33 d	3.53 d	3.12 d	3.50 d	3.74 d	3.94 d
11	9.55 s	3.74 d	3.70 dd	4.35 d	4.05 d	4.39 d	4.24 d	4.19 d	4.17 d	3.91 dd	4.00 dd		
11		3.63 d	3.59 dd	4.08 d	3.78 d	4.37 d	4.03 d	4.00 d	4.02 d	3.81 dd	3.90 dd		
12	3.37 s	3.36 s	3.26 s	3.35 s	3.24 s	3.29 s	3.29 s	3.34 s	3.39 s	3.34 s	3.34 s	3.39 s	3.36 s
CH_3				2.13 s		2.12 s		2.12 s				3.69 s	3.85 s
						Coupling Constants[c]							
J_{12}	0	0	0	0	0	0	1.2	0	1.0	0	0	0	0
J_{23}	0	0	0	0	0	0	0	0	0	0	0	0	0
J_{34}	1.8	1.7	1.8	1.8				1.8				1.8	
J_{34exo}										5.6	5.6		
J_{34endo}					0	0	1.3		0.7	0	0		0
$J_{4exo4endo}$										12.1			
J_{45}	5.7	5.7	5.6	5.7				5.6				5.7	
$J_{4exo5exo}$										12.3			
$J_{4exo5endo}$										3.5			
$J_{4endo5exo}$							0		0	5.6			
$J_{4endo5endo}$					3.2	3.1				8.8			3.2
$J_{5exo5endo}$										12.2			
J_{89eq}	3.6	4.5	3.1	4.8	3.6	4.8	3.3	3.2	3.6	4.6	5.3	2.8	3.9
J_{89ax}	3.2	4.0	4.7	4.8	4.7	4.8	3.6	3.2	3.6	4.6	5.3	2.8	3.9
J_{9eq9ax}	15.0	14.3	14.7	15.2	14.6	14.9	15.5	14.9	15.3	14.1	0	14.9	0
$J_{9eq10eq}$	1.8	1.3	3.1	0	3.0	1.1	3.4	1.8	3.3	1.6	0	1.9	1.3
$J_{10eq10ax}$	14.4	14.1	14.6	0	14.4	0	15.1	14.1	15.3	13.9	14.8	14.3	14.8
$J_{11,11}$		10.3	11.1	11.7	11.2	12.2	9.3	11.6	9.6	10.6	10.7		

[a] Solvents: $CDCl_3$ (**2**, **4**, **6**, **10**−**15**), acetone-d_6 (**5**, **9**), acetone-d_6/D_2O (**7**), $CDCl_3$/CD_3OD (**8**). [b] ppm; relative to $CHCl_3$ (δ 7.26 ppm) or acetone-d_5 (δ 2.05 ppm); assignments were made by 2D techniques (COSY, NOESY, HETCOR). [c] Hz. [d] For numbering of protons, see Figure 2.

standards. ^{13}C-NMR spectra were recorded at 75, 100, or 125 MHz carbon frequency, using the same solvents as above as internal standards (δ 77.0 and 29.8 ppm, respectively). *m*-Chloroperbenzoic acid (MCPBA) was dried at room temperature under reduced pressure (1 mmHg) for 1 h before use. TLC analyses were performed with Merck SiO_2 60 F_{256} precoated aluminum sheets with visualization by UV light, I_2, charring with H_2SO_4 (10% in water), or charring with anisaldehyde in ethanolic sulfuric acid.[14] Preparative column chromatography was performed with Matrex SiO_2 60 (35−70 μm). The naming of compounds was based on the computer program ACD/Name 1.0; a demo of the program is available on the Internet (http://www.acdlabs.com/).

Molecular Mechanics. MM3 calculations were performed with the MacMimic/MM3(92) package.[10] The MM3(92) program was the unadulterated version developed by Allinger and co-workers and customized for use on Macintosh computers. The standard force field includes treatment of the O−C−O anomeric effect.[15]

(+)-(2*S*,5*S*)-2-[(2′-Furfurylthio)methyl]-5-methoxy-2,5-dihydrofuran-3-carbaldehyde (1). A mixture of methyl 2,3-anhydro-6-deoxy-6-(furfurylthio)-α-D-allopyranoside[4] (926 mg, 3.40 mmol), toluene (30 mL), LiBr (510 mg, 5.87 mmol), and TMU (0.980 mL, 8.17 mmol) was refluxed for 10 min and then cooled to room temperature. TLC analysis showed UV-active **1** with an R_f value 2−3 times greater than the R_f value of the

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Table 2. ^{13}C NMR[a] Chemical Shifts[b] for Compounds 2, 4, 7−9, and 11

carbon[c]	2	4	7	8	9	11
1	107.4	107.0	107.4	106.8	109.0	107.8
2	58.4	57.9	57.5	58.7	60.7	61.9
3	81.3	81.1	77.4	77.8	84.5	83.9
4	139.0	138.4	49.8	52.4	92.0	92.0
5	139.9	139.4	52.6	50.1	80.2	63.2
6	84.9	86.4	83.8	83.7	89.5	89.8
7	66.2	55.3	56.3	55.0	54.3	53.6
8	70.8	76.9	80.9	79.3	74.5	73.4
9	28.1	28.9	52.1	51.5	49.6	49.4
10	28.7	29.2	51.5	51.2	50.2	49.8
11	201.2	69.0	64.2	65.7	71.6	71.2
12	55.1	54.9	54.2	55.2	55.1	55.9

[a] Solvents: $CDCl_3$ (**2**, **4**, **11**), acetone-d_6 (**7**, **9**), $CDCl_3$/CD_3OD (**8**). [b] ppm; relative to $CHCl_3$ (δ 77.0 ppm) or acetone-d_5 (δ 29.8 ppm); assignments were made by 2D HETCOR. [c] For numbering of carbons, see Figure 2.

byproducts (developed by the anisaldehyde/H_2SO_4 reagent[14]). The mixture was chromatographed (heptane/EtOAc, 6:1) to give **1** (271 mg, 31%) and a small amount of **2** (33 mg, 0.13 mmol, 4%). Compound **1**: $[\alpha]^{23}_D$ +13 (*c* 0.2, EtOAc); ^{1}H NMR data ($CDCl_3$) δ 9.88 (s, 1 H), 7.37 (dd, 1 H, *J* 0.8, 1.9 Hz), 6.77 (t, 1 H, *J* 1.5 Hz), 6.32 (dd, 1 H, *J* 1.9, 3.2 Hz), 6.21 (dd, 1 H, *J* 0.7, 3.2 Hz), 5.95 (dd, 1 H, *J* 1.3, 4.2 Hz), 5.38 (m, 1 H), 3.79, 3.76 (AB q, 2 H, *J* 14.7 Hz), 3.46 (s, 3 H), 3.14 (dd, 1 H, *J* 3.2, 14.2 Hz), 2.87 (dd, 1 H, *J* 4.9, 14.2 Hz); ^{13}C NMR data ($CDCl_3$) δ 187.5, 151.8, 146.5, 143.2, 142.6, 110.8, 108.33, 108.27, 83.8, 55.5, 35.2, 29.9; HRMS calcd for $C_{12}H_{14}O_4S$ (M^+) 254.0613, found 254.0609.

(+)-(1*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-7,13-dioxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{5,12}]tridec-2-ene-12-carbaldehyde (2). (a) Compound **1** (185 mg, 0.727 mmol) was dissolved in toluene/Et_3N (5 mL, 300:1), and the solution was added to a SiO_2 column (200 g SiO_2, d = 30 mm, l = 600 mm; washed with 200 mL of heptane/Et_3N, 100:1). Heptane/Et_3N (50 mL, 300:1) was circulated (2.5−3.0 mL/min) through the column for 20 h, using a medium-pressure LC pump. The material on the column was eluted (EtOAc/EtOH, 20:1, 1200 mL), and the eluate was concentrated to give a mixture of **1** and **2**. The residue was chromatographed (heptane/EtOAc, 2:1) to give **2** as an oil (147 mg, 79%) and **1** (27 mg, 15%). Crystallization from heptane/EtOAc gave pure **2**: mp 98−102 °C (the heating caused a retro-Diels−Alder reaction, as evidenced by TLC of the melted material); $[\alpha]^{23}_D$ +105 (*c* 1.0, $CHCl_3$); for ^{1}H and ^{13}C NMR data, see Table 1 and 2. Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.7; H, 5.5. Found: C, 56.8; H, 5.5.

(b) Compound **1** (17 mg, 0.067 mmol) was dissolved in $CDCl_3$ (1.0 mL), the solution was filtered into an NMR tube, a few grains of Na_2CO_3 were added, and the sample was heated at 60 °C. ^{1}H NMR spectra were recorded at intervals. The aldehyde hydrogen signals of **2** (9.55 ppm) and **1** (9.88 ppm) were integrated, which gave the ratio of the two compounds. The initial ratio **2**/**1** at room temperature was 1:50. The ratios **2**/**1** at 60 °C were 27:73 (80 min), 55:45 (25 h), and 56:44 (53 h). After 53 h at 60 °C, the sample was transferred to a pressure-proof tube and heated at 120 °C for 10 h; the **2**/**1** ratio was 25:75.

(c) Compound **1** (271 mg, 1.06 mmol) was dissolved in a mixture of toluene and CH_2Cl_2 (1.5 mL, 10:1) and submitted to centrifugal chromatography[16] (SiO_2, 30 g, 2 mm layer, Merck F_{256}, containing $CaSO_4$, conditionated with heptane/Et_3N, 100:1). The solvent (heptane/Et_3N, 100:1) flow rate was kept at 1−2 mL/min, circulated with a medium-pressure LC pump. After 24 h, two broad bands of different intensity were visualized on the plate (UV detection). The flow rate was increased to 8 mL/min, and the plate was eluted with EtOAc (40 mL), followed by MeOH (200 mL), and the collected eluents were concentrated. The residue was submitted to centrifugal chromatography[16] (1 mm SiO_2 layer, Merck F_{256}, heptane/EtOAc 3:1) to give **2** (164 mg, 60%) and **1** (32 mg, 12%) as oils.

2-[2-(2-Thiapropyl)furyl]furan-3-carbaldehyde (3). Isolated as a byproduct during initial Diels−Alder experiments with **1**. Compound **3**: ^{1}H NMR data ($CDCl_3$) δ 9.93 (s, 1 H, CHO), 7.40 (dd, 1 H, *J* 0.5, 2.0 Hz, H-5), 7.38 (dd, 1 H, *J* 0.8, 1.8 Hz, H-5′), 6.74 (d, 1 H, *J* 2.0 Hz, H-4), 6.33 (dd, 1 H, *J* 1.8, 3.2 Hz, H-4′), 6.24 (dd, 1 H, *J* 0.7, 3.7 Hz, H-3′), 4.01 (s, 2 H, CH_2S), 3.76 (s, 2 H, CH_2S); ^{13}C NMR data ($CDCl_3$) δ 185.0 (CHO), 160.7, 151.1, 143.5, 142.9, 123.7 (C-3), 111.0 (C-4′), 109.0 (C-4), 108.6 (C-3′), 28.7, 26.5; HRMS calcd for $C_{11}H_{10}O_3S$ (M + H) 223.0429, found 223.0419.

[(+)-(1*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-7,13-dioxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{5,12}]tridec-2-en-12-yl]methanol (4). Compound **2** (77 mg, 0.30 mmol) was dissolved in ethanol (6 mL, 99,5%), $NaBH_4$ (13 mg, 0.34 mmol) was added, and the reaction mixture was sonicated (1 min) and stirred for 40 min. Acetone (5 mL) was added, and after 10 min, the mixture was concentrated, and water (10 mL) and CH_2Cl_2 (5 mL) were added to the residue. The water phase was extracted with CH_2Cl_2 (4 × 5 mL), and the extract was dried ($MgSO_4$) and concentrated. The residue was chromatographed (SiO_2, heptane/EtOAc, 1:2) to give **4** (69 mg, 86%): mp 130−132 °C; $[\alpha]^{23}_D$ +119 (*c* 1.3, $CHCl_3$); for ^{1}H and ^{13}C NMR data, see Tables 1 and 2. Anal. Calcd for $C_{12}H_{16}O_4S$; C 56.2%, H 6.3%; found C 56.2%, H 6.3%.

[(+)-(1*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-7,10,10,13-tetraoxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{5,12}]tridec-2-en-12-yl]methanol (5). Compound **4** (45 mg, 0.17 mmol) was dissolved in CH_2Cl_2 (15 mL), and dry MCPBA (141 mg, 0.45 mmol, 55%) was added. After 75 min, the reaction mixture was passed through a short column of grade III Al_2O_3 (CH_2Cl_2 → CH_2Cl_2/EtOH, 10:1). The eluent was concentrated to give **5** (46 mg, 93%). An analytical sample was obtained by recrystallization from acetone: mp 204−206 °C; $[\alpha]^{23}_D$ +73 (*c* 0.6, MeOH); $[\alpha]^{23}_D$ +67 (*c* 0.6, water); for ^{1}H NMR data, see Table 1; ^{13}C NMR data (acetone-d_6) δ 139.8, 137.0, 107.2, 89.0, 81.6, 79.6, 67.7, 56.9, 55.2, 54.1, 52.8, 52.7; HRMS calcd for $C_{12}H_{16}O_6SNa$ (M + Na) 311.0566, found 311.0565. Material for single-crystal X-ray crystallographic analysis of **5** was obtained by crystallization from acetone. The crystal structure is presented in Figure 1 as an overlayed comparison with the structure obtained by molecular mechanics calculation (MM3).[10]

[(+)-(1*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-7,10,10,13-tetraoxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{5,12}]tridec-2-en-12-yl]methyl Acetate (6). Compound **5** (63 mg, 0.22 mmol) was dissolved in pyridine (5.0 mL), and acetic anhydride (0.50 mL, 5.29 mmol) was added. After 2 h, the reaction mixture was co-concentrated with toluene (3 × 10 mL). The residue was crystallised from EtOH/ether to give **6** (56 mg, 78%): mp 208−209 °C; $[\alpha]^{23}_D$ +106 (*c* 0.2, MeCN); for ^{1}H NMR data, see Table 1; ^{13}C NMR data ($CDCl_3$) δ 170.5, 138.9, 138.2, 106.7, 88.6, 81.8, 78.6, 69.5, 58.4, 55.4, 53.8, 52.7, 52.2, 21.3; HRMS calcd for $C_{14}H_{18}O_7SNa$ (M + Na) 353.0671, found 353.0671.

[(+)-(1*S*,5*S*,7*S*,8*R*,9*R*,10*R*,12*R*,13*S*)-7-Methoxy-3,3,6,11,14-pentaoxa-3-thiapentacyclo[6.4.1.1^{1,9}.0^{5,13}.0^{10,12}]tetradec-13-yl]methanol (7). Compound **4** (48 mg, 0.19 mmol) was dissolved in CH_2Cl_2 (5 mL), and dry MCPBA (294 mg, 1.28 mmol, 75%) was added. After 20 h, the reaction mixture was passed through a short column of grade III Al_2O_3 (CH_2Cl_2). The eluent was concentrated to give **7** (57 mg, 98%): mp 190−194 °C; $[\alpha]^{23}_D$ +69 (*c* 0.4, acetone); for ^{1}H and ^{13}C NMR data, see Tables 1 and 2; HRMS calcd for $C_{12}H_{16}O_7SNa$ (M + Na) 327.0515, found 327.0511.

[(1*S*,5*S*,7*S*,8*R*,9*R*,10*R*,12*R*,13*S*)-7-Methoxy-3,3,6,11,14-pentaoxa-3-thiapentacyclo[6.4.1.1^{1,9}.0^{5,13}.0^{10,12}]tetradec-13-yl]methyl Acetate (8). (a) Compound **7** (9 mg, 0.029 mmol) was dissolved in pyridine (0.5 mL), and acetic anhydride (0.25 mL, 2.64 mmol) was added. After 20 h, the reaction mixture was co-concentrated with toluene (3 × 1 mL) to give **8** (10 mg, 99%): mp 261−265 °C; $[\alpha]^{23}_D$ +58 (*c* 0.2, $CHCl_3$/MeOH/H_2O, 65:30:5).

(b) Compound **6** (5.5 mg, 0.017 mmol) was dissolved in CH_2Cl_2, and dry MCPBA (75%, 11 mg, 0.048 mmol) was added. After 6 days, the reaction mixture was passed through a short column of grade III Al_2O_3 (CH_2Cl_2 → CH_2Cl_2/MeOH, 9:1). The

(16) (a) Hostettmann, K.; Hostettmann-Kaldas, M; Sticher, O. *J. Chromatogr.* **1980**, *202*, 154. (b) Stahl, E.; Müller, J. *J. Chromatogr.* **1982**, *15*, 493.

eluent was concentrated to give **8** (5.5 mg, 95%); for ^{1}H and ^{13}C NMR data, see Tables 1 and 2. HRMS calcd for $C_{14}H_{18}O_8SNa$ (M + Na) 369.0620, found 369.0625.

[(+)-(1*S*,2*R*,3*S*,5*S*,9*S*,11*R*,12*R*,13*S*)-12-Hydroxy-3-methoxy-4,7,7,10,14-pentaoxa-7-thiapentacyclo[7.6.0.0^{1,5}.0^{2,11}.0^{9,13}]pentadecane (9). Compound **7** (9.3 mg, 0.031 mmol) was dissolved in MeOH/CH_2Cl_2 (1.5 mL, 2:1), and methanolic NaOMe (0.010 mL, 0.5 M) was added. After 5 days, SiO_2 (ca 0.5 g) was added, and the mixture was filtered (Celite) and concentrated. The residue was chromatographed (CH_2Cl_2/EtOH, 25:1) to give **9** (8.6 mg, 92%): mp 126−129 °C; $[\alpha]^{23}_D$ +42 (*c* 0.6, acetone); for ^{1}H and ^{13}C NMR data, see Tables 1 and 2; HRMS calcd for $C_{12}H_{16}O_7SNa$ (M + Na) 327.0515, found 327.0512.

[(+)-(1*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-7,13-dioxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{5,12}]tridec-2-en-12-yl]methyl Acetate (10). Compound **4** (10 mg, 0.041 mmol) was dissolved in pyridine (0.5 mL), and acetic anhydride (0.010 mL, 0.10 mmol) was added. After 18 h, the reaction mixture was coconcentrated with toluene (3 × 1 mL). The residue was chromatographed (heptane/EtOAc, 1:1) to give **10** (12 mg, 100%): mp 134−137 °C; $[\alpha]^{23}_D$ +104 (*c* 1.05, $CDCl_3$); for ^{1}H NMR data, see Table 1; ^{13}C NMR data ($CDCl_3$) δ 170.2, 138.6, 138.2, 106.9, 85.2, 80.6, 75.5, 70.0, 57.5, 54.5, 52.2, 28.7, 28.5, 20.9. Anal. Calcd for $C_{14}H_{18}O_5S$: C, 56.3; H, 6.1. Found: C, 56.5; H, 5.9.

(+)-(1*S*,2*R*,3*S*,5*S*,9*S*,11*R*,12*R*,13*R*)-12-Chloro-3-methoxy-4,7,7,10,14-pentaoxa-7-thiapentacyclo[7.6.0.0^{1,5}.0^{2,11}.0^{9,13}]pentadecane (11). Compound **4** (16 mg, 0.062 mmol) was dissolved in THF (4 mL), and the solution was added to a solution of MCPBA (105 mg, 0.33 mmol, 55%) in THF (5 mL). After 1 h, compound **4** had been transformed into the sulfone **5** (TLC, EtOAc), and LiCl (37 mg, 0.87 mmol) was added. A TLC (SiO_2, EtOAc) sample, taken within 1 min from the addition of LiCl, showed complete conversion of the intermediate sulfone **5**. The reaction mixture was passed through a short column of grade III Al_2O_3 (CH_2Cl_2 → CH_2Cl_2/EtOH, 10:1). The solvent was removed to give **11** (22 mg, 109%; **11** was contaminated with ∼1 equiv of LiCl): mp 182−185 °C; $[\alpha]^{23}_D$ +65 (*c* 0.03, $CHCl_3$); for ^{1}H and ^{13}C NMR data, see Tables 1 and 2; HRMS calcd for $C_{12}H_{15}ClO_6SNa$ (M + Na) 345.0176, found 345.0184.

[(+)-(1*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-7,13-dioxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{5,12}]tridec-12-yl]methanol (12). Compound **4** (20 mg, 0.078 mmol) was dissolved in toluene/EtOAc (2 mL, 1:1), and the mixture was hydrogenated (H_2, Pd/C, 12 mg) for 2 h. The catalyst was filtered off (Celite), and the solvent was removed. The residue was chromatographed (SiO_2, heptane/EtOAc, 1:2 → 0:1) to give **12** (20 mg, 99%) as an oil: $[\alpha]^{23}_D$ +85 (*c* 0.4, $CDCl_3$); for ^{1}H NMR data, see Table 1; ^{13}C NMR data ($CDCl_3$) δ 107.7, 84.2, 78.8, 78.7, 67.4, 61.6, 54.5, 54.3, 32.6, 30.8, 30.4, 28.8. Anal. Calcd for $C_{12}H_{18}O_4S$: C, 55.8: H, 7.0. Found: C, 55.7; H, 7.1.

[(+)-(1*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-7,10,10,13-tetraoxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{5,12}]tridec-12-yl]methanol (13). Compound **12** (35 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (5 mL), and dry MCPBA (131 mg, 0.42 mmol, 55%) was added. After 2.5 h, the reaction mixture was passed through a short column of grade III Al_2O_3 (CH_2Cl_2 → CH_2Cl_2/EtOH, 10:1). The eluent was concentrated, and the residue was chromatographed (EtOAc) to give **13** (34 mg, 86%): mp 218−222 °C; $[\alpha]^{23}_D$ +84 (*c* 0.7, MeOH); for ^{1}H NMR data, see Table 1; ^{13}C NMR data ($CDCl_3$) δ 108.2, 86.8, 81.2, 79.7, 67.7, 61.7, 55.27, 55.25, 54.8, 51.9, 33.6, 29.6; HRMS calcd for $C_{12}H_{18}O_6SNa$ (M + Na) 313.0722, found 313.0731.

(+)-Methyl (1*R*,4*S*,5*R*,6*S*,8*S*,12*S*)-6-Methoxy-7,13-dioxa-10-thiatetracyclo[6.3.1.1^{1,4}.0^{5,12}]tridec-2-ene-12-carboxylate (14). Compound **2** (181 mg, 0.71 mmol) was dissolved in a mixture of dry DMF (3.6 mL) and dry MeOH (0.17 mL). Pyridinium dichromate (PDC, 1.60 g, 4.25 mmol) was added under N_2. After 7 days, the reaction mixture was poured into a layer of EtOAc (∼5 cm), which was placed on top of an SiO_2 column (12 g of SiO_2). Elution with EtOAc and concentration of the eluate gave a residue that was chromatographed (heptane/EtOAc, 1:1) to give **14** (57 mg, 28%): mp 136−138 °C; $[\alpha]^{23}_D$ +156 (*c* 0.8, $CHCl_3$); for ^{1}H NMR data, see Table 1; ^{13}C NMR data ($CDCl_3$) δ 172.1, 139.9, 139.1, 108.1, 83.9, 81.5, 73.0, 60.9, 58.7, 55.4, 53.0, 28.0, 27.6; HRMS calcd for $C_{13}H_{16}O_5SNa$ (M + Na) 307.0616, found 307.0607.

(+)-Methyl (1*S*,5*S*,7*S*,8*R*,9*R*,10*R*,12*R*,13*S*)-7-Methoxy-3,3,6,11,14-pentaoxa-3-thiapentacyclo[6.4.1.1^{1,9}.0^{5,13}.0^{10,12}]tetradecene-13-carboxylate (15). Compound **14** (15 mg, 0.053 mmol) was dissolved in CH_2Cl_2 (2 mL), and dry MCPBA (75%, 158 mg, 0.69 mmol) was added. After 5 days, the reaction mixture was passed through a short column of grade III Al_2O_3 (CH_2Cl_2 → CH_2Cl_2/EtOH, 25:1), and the eluent was concentrated to give **15** (16 mg, 91%): mp 215−217 °C; $[\alpha]^{23}_D$ +86 (*c* 0.8, $CHCl_3$); for ^{1}H NMR data, see Table 1; HRMS calcd for $C_{13}H_{16}O_8SNa$ (M + Na) 355.0464, found 355.0468.

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Supporting Information Available: ^{1}H NMR spectra for all title compounds described in the Experimental Section and atomic coordinates for the crystalline compound **5** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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