and concentrated by rotary evaporation. Radial chromatography (1 mm silica gel plate, eluting with a 3:1 hexane/ethyl acetate to ethyl acetate gradient), gave 205 mg (63%) of product: $[\alpha]_D$ +45.0° (*c* 1.43, $CHCl_3$).

Determination of Enantiomeric Purities Using a Chiral NMR Shift Reagent. Racemic β-lactam (±)-**22** (10.8 mg, 0.0358 mmol) and Eu(hfc)$_3$ (12.7 mg, 0.0106 mmol) were dissolved in 0.7 mL of $CDCl_3$/TMS. Baseline resolution was obtained for the *tert*-butyl (δ 1.34, 1.45 ppm) and methyl ester (δ 3.75, 3.77 ppm) peaks in a 300-MHz ^{1}H NMR spectrum.

(+)-(*SSR*)-**22** (23.4 mg, 0.0776 mmol) and Eu(hfc)$_3$ (25.7 mg, 0.0215 mmol) were dissolved in 0.7 mL of $CDCl_3$/TMS. Exclusively one peak was observed each for the *tert*-butyl (δ 1.26 ppm) and methyl ester (δ 3.73 ppm) peaks in the 300-MHz ^{1}H NMR spectrum.

Authentic (+)-(*SSR*)-**22** (18.3 mg, 0.0607 mmol) and Eu(hfc)$_3$ (20.9 mg, 0.0175 mmol) were dissolved in 0.7 mL of $CDCl_3$/TMS. Exclusively one peak was observed each for the *tert*-butyl (δ 1.40 ppm) and methyl ester (δ 3.75 ppm) in the 300-MHz ^{1}H NMR spectrum.

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Synthesis of Medium-Sized Ring Ethers from Thionolactones. Applications to Polyether Synthesis†

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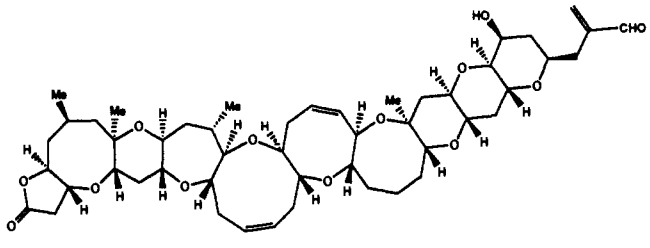
Abstract: A variety of medium-sized thionolactones have been prepared and condensed with nucleophiles giving alkylated thioacetals upon quenching with methyl iodide. Reductive desulfurization using triphenyltin hydride under radical conditions afforded the corresponding cyclic ethers rapidly and efficiently and, in most cases, with complete stereocontrol. This methodology has been proven through the construction of model systems of rings B and D of brevetoxin A (**1**) and a synthesis of (±)-lauthisan (**44**).

Introduction

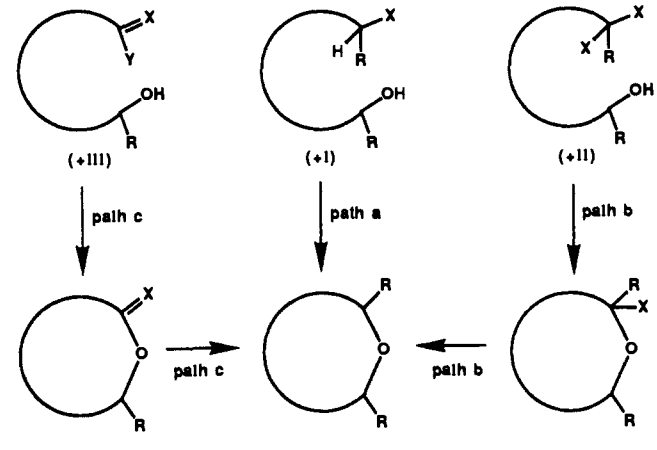
Medium-sized ring ethers occur widely in nature, particularly in marine natural products[1] such as brevetoxins A (**1**)[2a,b] and B,[2c]



1: Brevetoxin A

laurencin,[3] isolaurallene,[4] and ciguatoxin.[5] The construction of such systems is complicated by the difficulties in effecting ring closure due to unfavorable entropy factors[6] as well as nonbonding interactions inherent in the medium ring structures themselves.[7] A number of elegant approaches to these problems have recently been reported that utilize both carbon–carbon and carbon–oxygen bond-forming processes to effect cyclization.[8] In connection with the total synthesis of brevetoxins A (**1**) and B, currently in progress in these laboratories, we have sought general methods for the synthesis of seven-, eight-, and nine-membered ring ethers. Clearly, ring closure by carbon–oxygen bond formation provides the most flexible approach to these systems, allowing, in principle, the use of a variety of carbon-centered electrophilic groups at either the I, II, or III oxidation states (Scheme I). This would lead to either

Scheme I



the cyclic ether directly (path a) or, in the case of the aldehyde or carboxylic acid oxidation states, to cyclic intermediates, which

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† This work was partially carried out at the University of Pennsylvania.

(1) Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251.
(2) (a) Shimizu, Y.; Chou, H. N.; Bando, H.; Van Duyne, G.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514. (b) Pawlak, M.; Tempesta, M. S.; Golik, J.; Zagorski, M. G.; Lee, M. S.; Nakanishi, K.; Iwashita, T.; Gross, M. L.; Tomer, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1144. (c) Lin, Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.
(3) Irie, T.; Suzuki, M.; Masamune, T. *Tetrahedron* **1968**, *24*, 4193.
(4) Kurata, K.; Furusaki, A.; Suehiro, K.; Katayama, C.; Suzuki, T. *Chem. Lett.* **1982**, 1031.
(5) Murata, M.; Legrand, A. M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc.* **1989**, *111*, 8929.
(6) Winnik, M. L. *Chem. Rev.* **1981**, *81*, 491.

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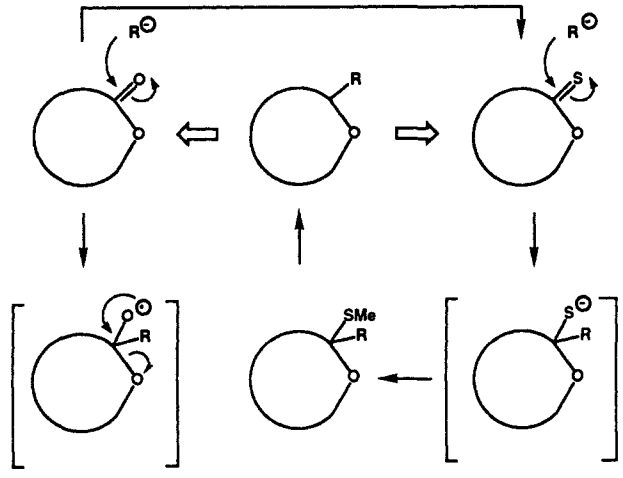
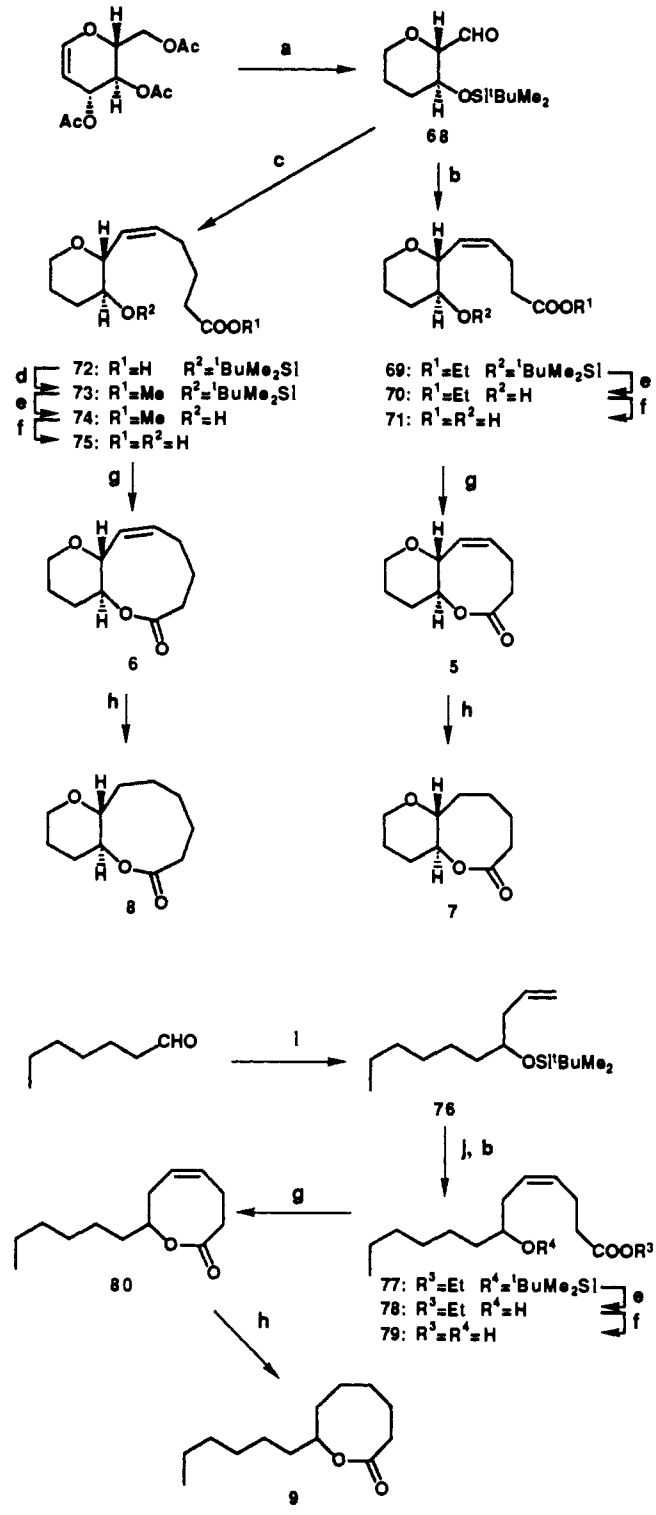
Scheme II



could potentially be subjected to a stereocontrolled reduction sequence to provide the desired ether functionality (paths b and c, respectively, Scheme I). Methods involving the I and II oxidation states of the electrophilic carbon have recently been described in detail from these laboratories.[9,10] In this paper we describe the details of a method for the conversion of medium and large ring lactones to the corresponding ethers in a stereocontrolled manner[11] (use of oxidation state III, path c, Scheme I). In addition, we illustrate the use of this methodology in the construction of model systems for rings B and D of brevetoxin A (**1**).

Medium and large ring lactones are readily available via a number of independent routes[12] and thus represent excellent potential precursors to the corresponding ethers, since the difficult issue of ring closure has already been resolved for these systems. The problem of cyclic ether synthesis is thereby reduced to that of converting a lactone to an ether. Scheme II outlines our proposed solution to this problem for the case of medium size rings.[11] Nucleophilic attack on the carbonyl of a medium ring lactone generally results in ring fission due to the instability of the initially formed tetrahedral intermediate. However, it has been shown that the analogous tetrahedral intermediate, formally derived from attack on the carbon of a thionolactone, is stable at low temperature and undergoes S-alkylation cleanly to afford the stable mixed thioketal compound. This intermediate can, in turn, be converted to the desired ether stereoselectively.[8b,i,13]

Scheme III[a]



[a] Reagents and conditions: (a) Reference 9; (b) 1.3 equiv of $Ph_3P^+(CH_2)_3CO_2EtBr^-$, 1.2 equiv of $NaN(SiMe_3)_2$, 4.0 equiv of HMPA, THF, −78 to 25 °C, 2 h, 83–90%; (c) 1.3 equiv of $Ph_3P^+(CH_2)_4CO_2HBr^-$, 2.4 equiv of $NaN(SiMe_3)_2$, 4.0 equiv of HMPA, THF, 0–20 °C, 2 h, 73%; (d) 2.25 equiv of MeI, 2.15 equiv of K_2CO_3, DMF, 20 °C, 4 h, 76%; (e) 1.5 equiv of Bu_4NF, THF, 20 °C, 2 h, 85–92%; (f) 2.5 equiv of LiOH, $THF/CH_3OH/H_2O$ 4:1:1, 20 °C, 90 min, 88–97%; (g) 1.1 equiv of Ph_3P, 1.1 equiv of PySSPy, CH_2Cl_2, 20 °C, 2 h, then 0.02 equiv of $AgClO_4$, 0.001 M toluene, 110 °C, 18 h, 65–75%; (h) H_2, 0.1 equiv of $(Ph_3P)_3RhCl$, benzene, 25 °C, 24 h, 82–92%; (i) 1.1 equiv of allylmagnesium bromide, THF, 0 °C, 2 h, then 1.1 equiv of $^tBuMe_2SiOTf$, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 85%; (j) O_3, CH_2Cl_2, −78 °C then excess Me_2S, 81%.

(7) (a) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981 and references cited therein. (b) Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312.

(8) (a) Jackson, W. P.; Ley, S. V.; Morton, J. A. *Tetrahedron Lett.* **1981**, 2601. (b) Corey, E. J.; Shimoji, K. *J. Am. Chem. Soc.* **1983**, *105*, 1662. (c) Schreiber, S.; Kelly, S. E. *Tetrahedron Lett.* **1984**, 1757. (d) Overman, L. E.; Blumenkopf, T. A.; Castañeda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516. (e) Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093. (f) Nicolaou, K. C.; Duggan, M. E.; Hwang, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 2468. (g) Heslin, J. C.; Moody, C. J.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1986**, 1403. (h) Carling, R. W.; Holmes, A. B. *J. Chem. Soc., Chem. Commun.* **1986**, 565. (i) Nicolaou, K. C.; Hwang, C. K.; Duggan, M. E.; Reddy, K. B.; Marron, B. E.; McGarry, D. *J. Am. Chem. Soc.* **1986**, *108*, 6800. (j) Bartlett, P. A.; Ting, P. C. *J. Org. Chem.* **1986**, *51*, 2230. (k) Carling, R. W.; Curtis, N. R.; Holmes, A. B. *Tetrahedron Lett.* **1989**, *30*, 6081. (l) Castañeda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5707. (m) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153.

(9) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(10) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 5321.

(11) Nicolaou, K. C.; McGarry, D.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504.

(12) (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (b) Back, T. G. *Tetrahedron* **1977**, *33*, 3041. (c) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (d) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

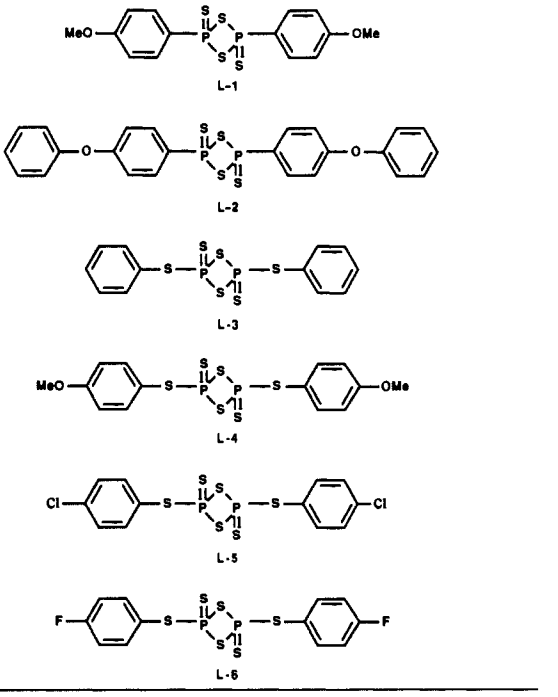
(13) The idea of preparing ethers from their corresponding lactones has been successfully exploited by a number of groups. For examples, see: Kraus, G. A.; Molina, M. T. *J. Org. Chem.* **1988**, *53*, 752 and references cited therein. Reference 8h above.

Table I. Synthesis of Thionolactones

Entry	Lactone	Reagent	Thionolactone	Yield (%)
1	2: n = 1	L-1	2a: n = 1	80
2	3: n = 2	L-1	3a: n = 2	40
3	4: n = 3	L-1	4a: n = 3	62
4	5: n = 1	L-1	5a: n = 1	28
5	6: n = 2		6a: n = 2	72
6	7: n = 1	L-1	7a: n = 1	56
7	8: n = 2	L-1	8a: n = 2	80
8	9: R = n-C_6H_{13}	L-1	9a: R = n-C_6H_{13}	32
9	10a	L-1	10c	60
10	11	L-1	11a	80
11	12	L-1	12a	61
12	13	L-1	13a	68
13	14	L-1	14a	60
14		L-2		67
15		L-3		57
16		L-4		50
17		L-5		67
18		L-6		63

Furthermore, Swenton[14] has demonstrated that acyclic thionoesters do indeed undergo nucleophilic attack at the thiocarbonyl carbon[15] and that the resulting tetrahedral intermediates can be trapped at low temperature by using methyl iodide. On the basis of the above precedent, we reasoned that the sequence described in Scheme II would constitute a general route to medium size ring ethers. In practice these ideas proved quite viable, providing an efficient and versatile method for the synthesis of a wide range of cyclic ether structures.

Table II. Lawesson-Type Reagents Prepared and Used in this Study



Results and Discussion

Preparation of Thionolactones. The lactones employed in this study are shown in Table I. Compounds **2** and **14** were obtained from commercial sources. Compounds **3** and **4** were prepared by Baeyer–Villiger oxidation of the corresponding, commercially available ketones. The synthesis of lactones **5–9** is outlined in Scheme III and detailed in the Supplementary Material, whereas compounds **10–13** were prepared according to procedures to be described below.

A crucial step in the proposition described above (Scheme II) involves the conversion of a lactone to a thionolactone.[16] This process is most commonly carried out by a dithiodiphosphetane disulfide such as Lawesson's reagent[16c] (**L-1**, Table II). This reagent (**L-1**) effects thionation of most simple lactones in good yield. However, the efficacy of this reagent is highly dependent on the nature of the substrate and the reaction conditions. In particular, strict control of temperature is required in order to obtain optimum yields. To address these problems a number of other reagents have been introduced (e.g., **L-2**,[17] **L-3**,[18] **L-4**[18]). In accordance with a recent mechanistic proposal[19] for the thionation reaction (nucleophilic attack by the carbonyl oxygen at phosphones), the reagents **L-5** and **L-6** were expected to show higher reactivity. We therefore synthesized these compounds and carried out a complete study of the thionation reaction utilizing the 17-membered ring lactone as a substrate and the reagents of Table II. Reagents **L-3**, **L-4**, **L-5**, and **L-6** exhibit slightly enhanced reactivity relative to reagents **L-1** and **L-2** as expected from mechanistic considerations. However, these reagents are also much more potentially acidic (generating phosphoric acid-type species

(14) Narashimhau, L.; Sanitra, R.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1978**, 719.

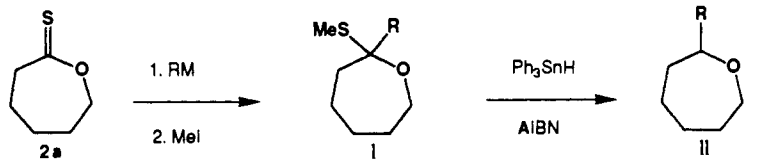
(15) This is in contrast to the behavior of dithioesters and thioketones, which give products of thiophilic attack on reaction with organolithium reagents. For examples, see: (a) Bertz, S. H.; Dabbagh, G.; Williams, L. M. *J. Org. Chem.* **1985**, *50*, 4414. (b) Beak, P.; Yamamoto, J.; Upton, C. J. *J. Org. Chem.* **1975**, *40*, 3052.

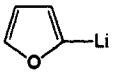
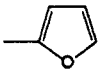
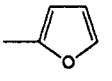
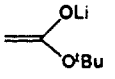
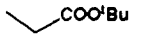
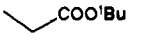
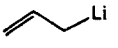
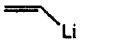
(16) For reviews on the preparation of thionolactones and thionoesters, see: (a) Jones, B. A.; Bradshaw, J. S. *Chem. Rev.* **1984**, *84*, 17. (b) Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061. For the most commonly used reagent, see: Sheibye, S.; Pederson, E. S.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229.

(17) Lajoie, G.; LëPine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, 3815.

(18) Yokoyama, M.; Hasegawa, Y.; Hatanaka, H.; Kawazoe, Y.; Imamoto, T. *Synthesis* **1984**, 827.

Table III. Addition of Various Nucleophiles to Caprothionolactone (2a) and Synthesis of Oxepanes of Varying Substitution



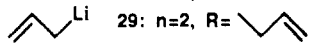
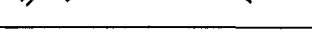
Entry	Nucleophile (RM)	Addition Product (I)	Yield (%)	Reduction Product (II)	Yield (%)
1	MeLi	**15**: R = Me	83	**23**: R = Me	85
2	PhLi	**16**: R = Ph	86	**24**: R = Ph	97
3	$LiEt_3BH$	**17**: R = H	75	—	—
4	Bu_3SnLi	**18**: R = $SnBu_3$	79	—	—
5		**19**: R = 	92	**25**: R = 	90
6		**20**: R = 	95	**26**: R = 	88
7		**21**: R =	86	**27**: R =	85
8		**22**: R =	80	—	—
9		**21**: R =	89	—	—
10		**22**: R =	89	—	—
11		**22**: R =	trace	—	—
12	MeMgBr	**15**: R = Me	trace	—	—
13	PhMgBr	**16**: R = Ph	23	—	—

with moisture at elevated temperatures) and generally require the presence of a buffering agent such as 1,1,3,3-tetramethylthiourea to moderate the inevitable buildup of strong acid during long reaction periods at elevated temperatures. In fact, these reagents do not result in significantly improved yields in comparison to Lawesson's reagent (Table I, entries 13–18). In addition, the following are apparent. α,β-Unsaturated lactones react more readily than their saturated counterparts (cf. entries 6, 10, 11, and 12, Table I, see also ref 16b), a result which is in line with mechanistic considerations.[19] Acid-sensitive groups such as the MEM or SEM groups undergo decomposition (unpublished results in these laboratories), although silyl groups (e.g., Si^tBuPh_2, Si^tBuMe_2) may be compatible depending on the conditions used (e.g., entry 9, Table I). The presence of Lewis basic functional groups such as ethers retard the thionation reaction and allow only moderate yields of thionated products.[16b]

Nucleophilic Additions to Thionolactones. A variety of organometallic reagents were examined as nucleophiles toward thionolactones. As shown in Table III, nucleophilic addition of a range of organolithium reagents to thionocaprolactone proceeds smoothly at −78 °C to provide, upon S-alkylation with methyl iodide, the corresponding mixed thioketals in good to excellent yields. The use of Grignard reagents was less successful, however. From those examined, only allylmagnesium bromide added cleanly (Table III, entry 9), whereas reaction of methyl- or phenylmagnesium bromides (Table III, entries 12 and 13) resulted in

(19) Rauchfuss, T. B.; Zank, G. A. *Tetrahedron Lett.* **1986**, 3445.

Table IV. Synthesis of Cyclic Ethers of Various Sizes and Substitutions from Thionolactones

Entry	Thionolactone	Reagent	Addition Product	Yield(%)	Reagent	Reduction Product	Yield(%)
1	3a: n=1	n-BuLi	28: n=1, R=nBu	96	Ph_3SnH/ AIBN Toluene, 110 °C	38: n=1, R=nBu	84
2	4a: n=2		29: n=2, R=	94	"	39: n=2, R=	85
3	6a: n=2	MeLi	30: n=2, R=Me	91	"	40: n=2, R=Me	0[a]
4	6a: n=2	PhLi	31: n=2, R=Ph	85	"	41: n=2, R=Ph	—
5	7a: n=1	MeLi	32: n=1, R=Me	89	"	42: n=1, R=Me	90
6	7a: n=1	$LiEt_3BH$	33: n=1, R=H	74	mCPBA, $AlMe_3$[71]	42: n=1, R=Me	82
7	8a: n=2	MeLi	34: n=2, R=Me	96	Ph_3SnH/ AIBN Toluene, 110 °C	43: n=2, R=Me	84
8	9a: R'=n-C_6H_{13}	EtLi	35: R=Et ,R'=n-C_6H_{13}	84	"	44: R=Et, R'=n-C_6H_{13}	92
9	14a	MeLi	36: R=Me	78	"	45: R=Me	90
10	14a		37: R=	81	"	46: R=	85

[a] See Scheme 4.

sluggish reactions and mainly recovered starting material. Interestingly, while reaction of vinylmagnesium bromide produced only traces of the desired product, addition of catalytic amounts of cuprous iodide resulted in rapid reaction yielding the expected mixed thioketal in 89% yield (Table III, entries 10 and 11). These results can be understood in terms of a single electron transfer mechanism involving formation of a radical anion by oxidation of the organometallic species, followed by facile organic radical transfer. Table IV illustrates that this sequence can be applied equally well to 8-, 9-, and 16-membered thionolactones. Notably, where applicable, only one diastereoisomer is obtained with addition occurring most often from the less sterically hindered face. The X-ray crystallographic analysis of mixed thioketal **31** (see Figure 1 for ORTEP structure) confirmed this notion, at least for the case of entry 4, Table IV.

Reductive desulfurization of the thioethers so obtained can be accomplished with triphenyltin hydride, in most cases with complete stereocontrol. Thus, the thiomethyl group attached to an eight-membered ring framework can be reduced stereospecifically (Table IV, entries 5, 6, and 8) leading to 2,8-cis-disubstituted oxocanes. This result can be rationalized on the basis of hydride attack from the least hindered face of the most stable ring conformation in which the radical is electronically stabilized further by the oxygen lone pairs of electrons.[20] The chemistry of entry

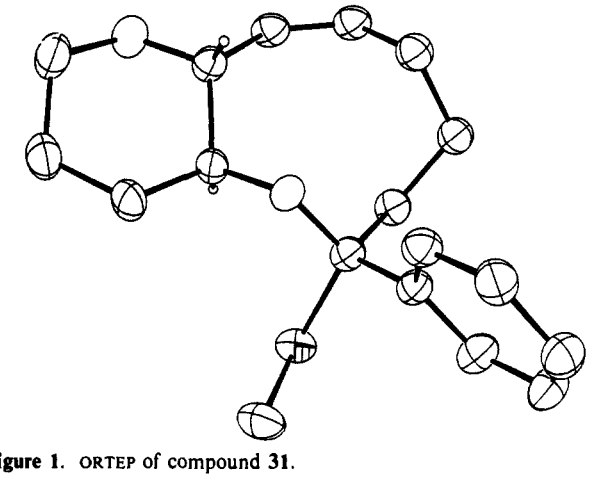
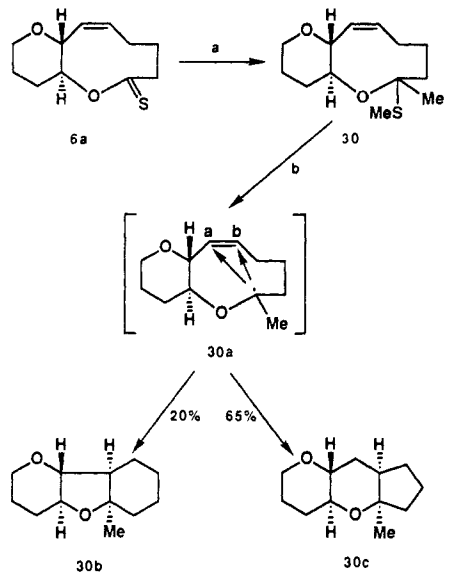


Figure 1. ORTEP of compound **31**.

8, Table IV, led to (±)-lauthisan[21] **44**, identical with a naturally derived sample. A similar pattern of selectivity is found in the

(20) (a) Giese, B.; Dupuis, J. *Tetrahedron Lett.* **1984**, *25*, 1349. (b) Korth, H. G.; Sustmann, R.; Dupuis, J.; Giese, B. *J. Chem. Soc., Perkin Trans. II* **1986**, 1453.

Scheme IV[a]



[a] Reagents and conditions: (a) 1.5 equiv of MeLi, THF, −78 °C, 5 min, then 1.9 equiv of MeI, 91%; (b) 2.0 equiv of Ph_3SnH, AIBN, toluene, 110 °C, 30 min, 85%.

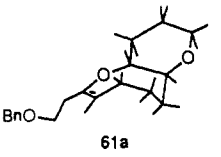
case of the nine-membered ring (Table IV, entry 7). However, in this instance the degree of selectivity is not as high, presumably due to the greater number of low-energy conformations accessible to this system. Desulfurization of the nine-membered ring system containing unsaturation was not successful (Table IV, entry 3) leading instead to the formation of ring-contracted products **30b** and **30c**, respectively (Scheme IV).[11] This contraction occurs via transient species **30a** (Scheme IV).

Finally we have applied this methodology to the construction of model systems of rings B and D of brevetoxin A. The requisite bicyclic lactones **11** and **13** were prepared in racemic form as shown in Scheme V. Starting from dihydropyran, oxidation with mCPBA in methanol[22] followed by benzylation and Ferrier-type allylation[23] afforded a 1:1 mixture of *cis*- and *trans*-2-allyl-substituted pyrans **48a** and **48b** in 81% yield which were readily separated by flash chromatography. Hydroboration of the trans isomer **48b** followed by oxidative workup[24] gave primary alcohol **49**, which upon oxidation under Swern conditions[25] provided the aldehyde **50** in 64% overall yield. Mukaiyama aldol[26] reaction of **50** with [(benzyloxy)ethenyl]oxy-*tert*-butyldimethylsilane in ether at −78 °C using $ZnBr_2$ as Lewis acid afforded the β-siloxy ester (**51ab**) as a 1:1 mixture of diastereoisomers in 78% yield. Debenzylation of the mixture **51ab**, followed by cyclization[27] of the resulting hydroxy acid, furnished lactones **52ab** in 70% overall yield. Removal of the *tert*-butyldimethylsilyl group with HF-pyridine complex,[28] followed by regiospecific dehydration, then afforded the α,β-unsaturated lactone **13** in 75% yield for the two steps.

trans-2-Allyl-3-(benzyloxy)pyran (**48b**) was also converted to bicyclic lactone **11** as follows. Oxymercuration of the terminal olefin[29] and then Swern oxidation of the resulting mixture of secondary alcohols afforded ketone **55**. Further elaboration of ketone **55** to the unsaturated lactone **11** was accomplished by using the same procedures described above for ketone **13** as indicated in Scheme V.

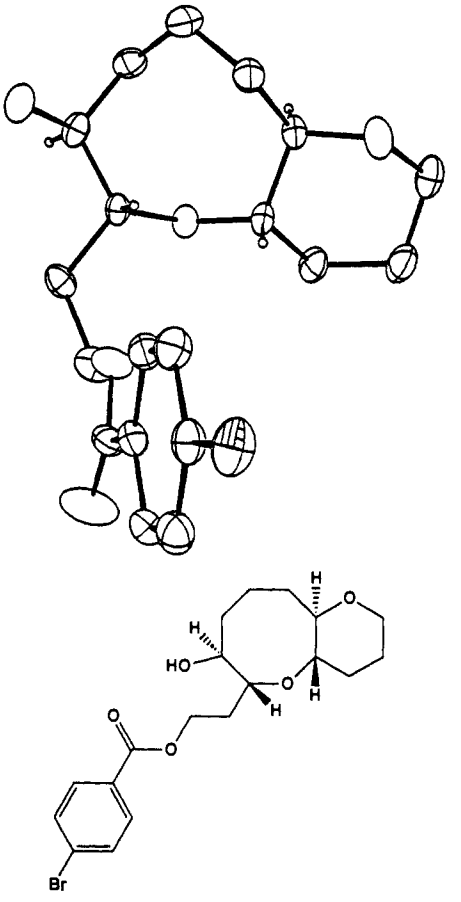
Conversion of lactone **13** to the appropriately substituted oxocane corresponding to ring B of brevetoxin A (**1**) is shown in Scheme VI. Thus, thionation of **13** proceeded rapidly at 110 °C in toluene to furnish the corresponding thionolactone **13a** in 68% yield. Addition of the lithium enolate of *tert*-butyl acetate occurred regio- and stereospecifically to provide, after quenching with methyl iodide, the mixed thioketal **58** in 77% yield.[30] Subsequent reductive desulfurization using Ph_3SnH afforded enol ether **59** in high yield with only traces of the alternative regioisomeric allylic ether. Low-temperature reduction of the ether group using lithium triethylborohydride and benzylation of the resulting primary alcohol then afforded compound **61** in 65% yield for the two steps.

Quantitative conformational analysis of **61**, incorporating the restriction that the enol ether lone pair should be delocalized through the olefin n orbital, suggested that conformer **61a** shown in Figure 2 would represent the preferred configuration of the molecule in solution. This conformation exposes the β face of the



61a

Figure 2.



62-p-Br-Bz

Figure 3. ORTEP of *p*-bromobenzoate derivative of compound **62**.

(21) For the naming of this skeleton, see: Blunt, J. M.; Lake, R. J.; Munro, M. H. G.; Yorke, S. C. *Aust. J. Chem.* **1981**, *34*, 2393. For preparation from laurencin, see: Fukuzawa, A.; Masamune, T. *Tetrahedron Lett.* **1981**, *22*, 4081. For recent total syntheses, see ref 8h,m.

(22) Cox, P.; Mahon, M. F.; Molloy, K. C.; Lister, S.; Gallagher, T. *Tetrahedron Lett.* **1988**, 1993.

(23) Hosomi, A.; Yasuyuki, S.; Sakurai, H. *Tetrahedron Lett.* **1984**, 2383.

(24) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 5281.

(25) Swern, D. *Synthesis* **1981**, 501.

(26) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. Ketene acetal preparation: Rathke, M. N.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67.

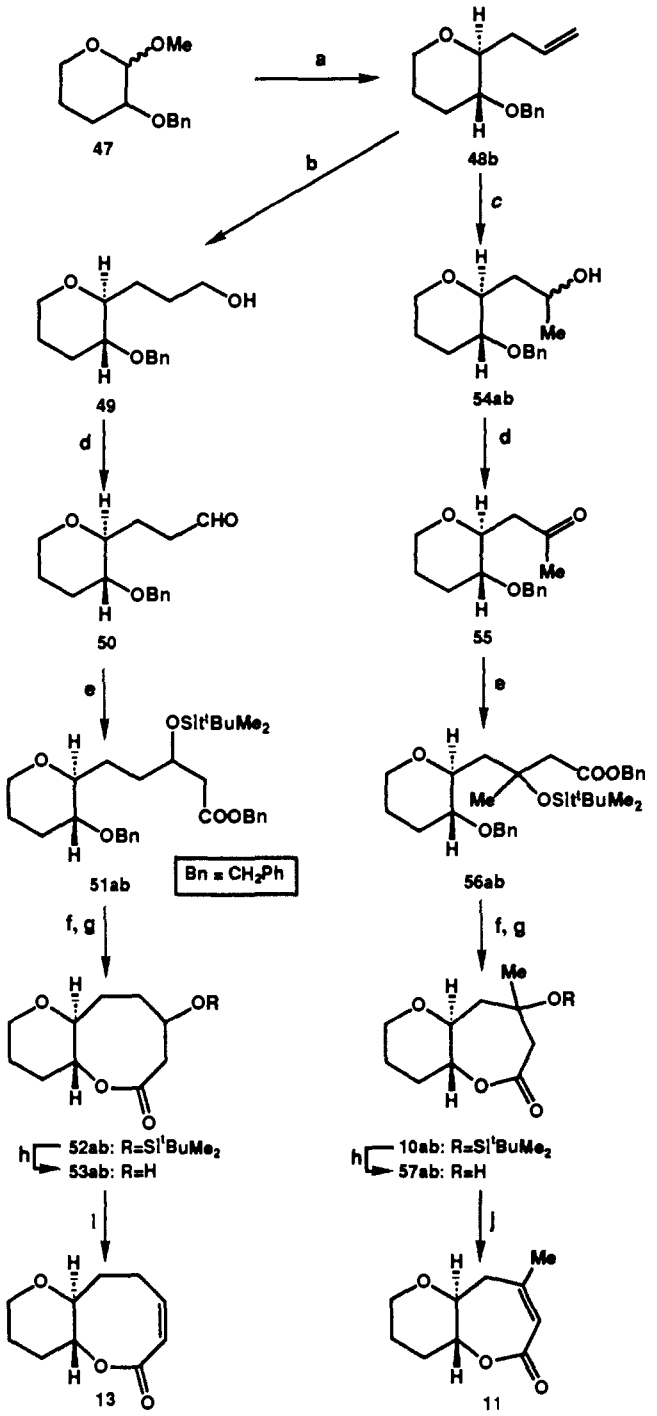
(27) (a) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. (b) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661.

(28) (a) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1222. (b) Nicolaou, K. C.; Webber, S. E. *Synthesis* **1986**, 453.

(29) Brown, H. C.; Geoghegan, P. J., Jr. *J. Org. Chem.* **1970**, *35*, 1844.

(30) Lithium ester enolates have been reported to undergo Claisen-type condensation with thionoesters. See: Duus, F. *Synthesis* **1985**, 672 and references cited therein.

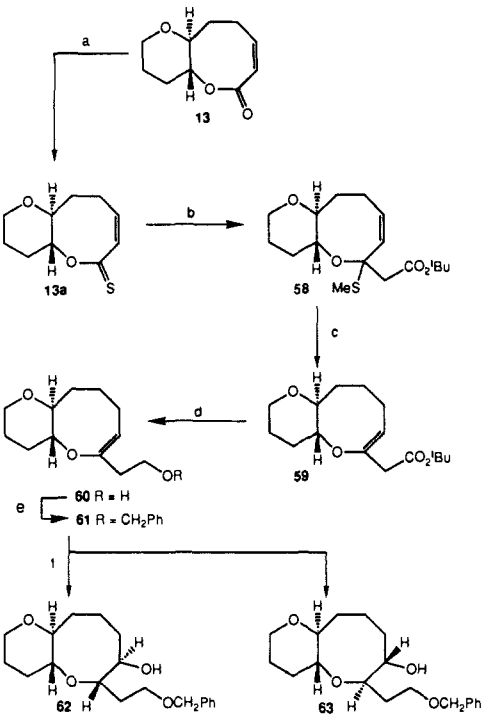
Scheme V[a]



[a] Reagents and conditions: (a) 2.0 equiv of allyltrimethylsilane, 0.2 equiv of TMSOTf, CH_3CN, 25 °C, 15 min, then chromatography, 41%; (b) 1.1 equiv of 9-BBN, THF, 0 °C, 1 h, then excess H_2O_2, excess NaOH, 90%; (c) 1.1 equiv of $Hg(OAc)_2$, THF, H_2O, 25 °C, 30 min, then $NaBH_4$, NaOH, 0 °C, 30 min; (d) 1.5 equiv of $(COCl)_2$, 2.0 equiv of DMSO, CH_2Cl_2, −78 °C, 30 min, 71% (**50**), 74% (**48b** to **55**); (e) 1.5 equiv of [(1-(benzyloxy)ethenyl)oxy]-*tert*-butyldimethylsilane, 1.0 equiv of $ZnBr_2$, ether, −78 °C, 20 min, 78–88%; (f) H_2, $Pd(OH)_2$, MeOH, 25 °C, 3 h, 100%; (g) 1.5 equiv of Ph_3P, 1.5 equiv of pySSpy, THF, 25 °C, 30 min, then 1.1 equiv of $AgClO_4$, benzene, 80 °C, 4 h, 63% (1:1 **10a**:**10b**), 70% (1:1 **52a**:**52b**); (h) 1.3 equiv of HF·py, THF, 20 °C, 2 h; (i) 1.5 equiv of CH_3SO_2Cl, 2.0 equiv of Et_3N, toluene, 20 °C, 30 min, then 3.0 equiv of DBU, 105 °C, 3 h, 75% from **52ab**; (j) 1.5 equiv of CH_3SO_2Cl, 2.0 equiv of Et_3N, benzene/CH_2Cl_2, 5:1, 20 °C, 30 min, then 3.0 equiv of DBU, 45 °C, 1 h, 66% from **10ab**.

enol ether to external attack. We then reasoned that hydroboration of **61** would occur selectively from the upper face, thereby ultimately setting the hydroxyl group and the side chain in the correct relative configuration for ring B of brevetoxin A (**1**). In practice,

Scheme VI[a]



[a] Reagents and conditions: (a) 1.5 equiv of Lawesson's reagent, toluene, 110 °C, 3.5 h, 68%; (b) 1.4 equiv of LDA, 1.4 equiv of *tert*-butyl acetate, THF, −78 °C, 15 min, then 2.0 equiv of MeI, 77%; (c) 2.0 equiv of Ph_3SnH, AIBN, toluene, 110 °C, 84%; (d) 3.5 equiv of $LiEt_3BH$, THF, 25 °C, 1 h, 71%; (e) 3.0 equiv of KH, THF, 0 to 25 °C, 1.5 h, then 3.0 equiv of $PhCH_2Br$, 55 °C, 3 h, 92%; (f) 1.0 equiv of BH_3·THF, 0 °C, 30 min, then excess H_2O_2, excess NaOH, 87%.

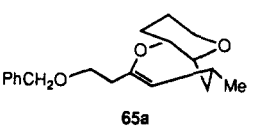


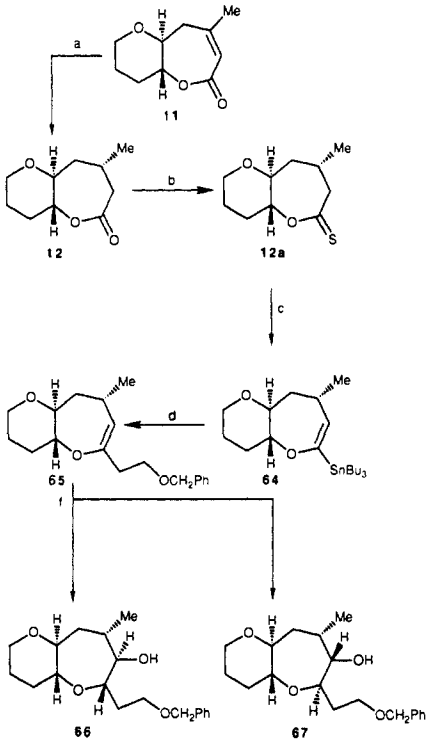
Figure 4.

treatment of **61** with borane in THF at 0 °C afforded a 5:1 mixture of facial isomers **62** and **63** in 87% total yield.[31] X-ray crystallographic analysis of the *p*-bromobenzoate derivative of the major isomer (**62-p-Br-Bz**) confirmed that this compound was indeed the product of initial attack of borane on the β-face of **61** (see ORTEP drawing, Figure 3).

A conceptually different approach to the medium-sized rings of brevetoxin A (**1**) is illustrated in Scheme VII for the case of ring D. Examination of molecular models of lactone **11** once again revealed an exposed β-face. Thus, hydrogenation of **11** over palladium catalyst provided the β-methyl lactone **12** stereospecifically and in near quantitative yield. Thionation of **12** under forcing conditions then afforded thionolactone **12a** in 61% yield. Addition of lithium tributylstannane[32] to **12a**, trapping of the resulting thiolate anion with diiodobutane, followed by in situ elimination of tetrahydrothiophene using 2,6-lutidine provided the vinylstannane **64** in 75% overall yield from the thionolactone. Introduction of the 2-(benzyloxy)ethyl side chain was effected by transmetalation[33] of the vinylstannane **64** with *n*-butyllithium in THF at −78 °C, followed by alkylation of the vinyllithium

(31) Greatly improved facial selectivity has been observed on a closely related system employing thexylborane in THF. See: Somers, P. K. Ph.D. Dissertation, University of Pennsylvania, 1989.
(32) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.
(33) For a previous example of this type of metal exchange see: Hanessian, S.; Martin, M.; Desai, R. C. *J. Chem. Soc., Chem. Commun.* **1986**, 926. For a review on transmetalation of α-heterosubstituted organotin compounds, see: Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987; pp 165–177.

Scheme VII[a]



[a] Reagents and conditions: (a) H_2, 10% Pd on C, THF, 25 °C, 30 min, 95%; (b) 4.0 equiv of Lawesson's reagent, toluene, 110 °C, 4 h, 61%; (c) 1.5 equiv of Bu_3SnLi, THF, −78 °C, 10 min, then 10 equiv of $I(CH_2)_4I$, 2.0 equiv of 2,6-lutidine, −78 to 25 °C, 2 h, 75%; (d) 1.5 equiv of nBuLi, HMPA, THF, −78 °C, then 2.0 equiv of $BnOCH_2CH_2OTf$, 30 min, 60%; (e) 2.0 equiv of BH_3·THF, THF, 0 °C, 30 min, then excess H_2O_2, excess NaOH, 85%.

species with 2-(benzyloxy)ethyltrifluoromethane sulfonate in the presence of HMPA (60% yield). Similar conformational analysis of **65** to that described above again predicted a low-energy conformation with a convex β-face for the oxepane ring as illustrated in Figure 4. In addition, the presence of the α-allylic methyl group was expected to augment the ring conformational effect. Not surprisingly then, treatment of **65** with borane, as described above,[34] provided a 13:1 mixture of **66** and **67**. The structure of **66** was again confirmed by single-crystal X-ray diffraction analysis of a related substance to **66**, compound **66a** (see ORTEP drawing, Figure 5). Compound **66a**, which has the same relative stereochemistry at the ring fusion but the opposite relative stereochemistry at the remaining centers, was chemically and spectroscopically correlated with **66**.

Conclusion

The chemistry presented herein provides new inroads to the problem of mono- and polycyclic ether construction, especially medium-sized systems. The method involves alkylation of thionolactones, which are readily prepared from simple lactones, followed by trapping with methyl iodide. The mixed methyl thioketals produced are convenient precursors to free radicals and are thus potentially important intermediates in the construction of complex polycyclic frameworks. A number of model studies for brevetoxin A (**1**) have been successfully performed by using this new technology. Further applications of the present method are currently under investigation in these laboratories.

(34) Hydroboration–oxidation has been successfully employed for the functionalization of the analogous, six-membered cyclic enol ethers. See: (a) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1985**, *50*, 3017. (b) Brown, H. C.; Ramachandran, P. V.; Vara Prasad, J. V. N. *J. Org. Chem.* **1985**, *50*, 5583.

(35) Paquette, L. A.; Begland, R. W.; Storm, P. C. *J. Am. Chem. Soc.* **1970**, *92*, 1971.

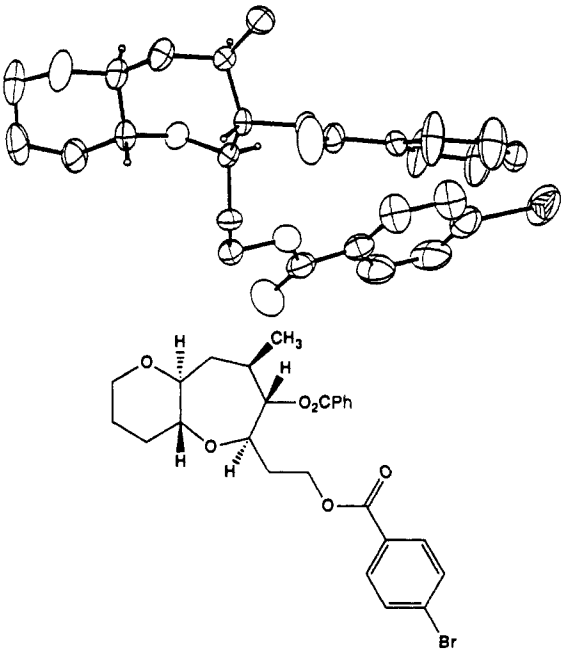


Figure 5. ORTEP of *p*-bromobenzoate derivative of **66a**.

Experimental Section

General Methods. NMR spectra were recorded on one of the following instruments: IBM WP-200, Bruker WM-250, IBM AF-250, or Bruker AM-500. IR spectra were recorded on a Perkin-Elmer Model 781 infrared spectrophotometer. UV and visible spectra were recorded on a Perkin-Elmer Model 553 ultraviolet–visible spectrophotometer.

High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VC ZAB E instrument under FAB conditions.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) with UV light and 7% ethanolic phosphomolybdic acid-heat as developing agent. Preparative-layer chromatography was performed on 0.5 or 0.25 mm × 20 cm × 20 cm E. Merck Silica plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.63 mm) was used for flash column chromatography.

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials unless otherwise stated.

2-Oxepanethione (2a). A mixture of caprolactone **2** (2.16 g, 19 mmol) and Lawesson's reagent (7.27 g, 19 mmol) in toluene (63 mL) was stirred at reflux for 1 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (50% ether in petroleum ether) without concentration to give thionocaprolactone **2a** (1.99 g, 80%): oil; R_f 0.33 (50% ether in petroleum ether); IR (neat) ν_{max} 2980, 2930, 2855, 1470, 1433, 1389, 1360, 1322, 1295, 1240, 1199, 1168, 1145, 1091, 1062, 1023, 981, 922, 881, 839 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.50 (t, J = 4.6 Hz, 2 H), 3.20 (m, 2 H), 1.90–1.77 (m, 6 H); HRMS calcd for $C_6H_{11}OS$ $(M + H)^+$ 131.141, found 131.139.

2-Oxocanethione (3a). A mixture of 2-oxooxocane (**3**) (500 mg, 3.9 mmol) and Lawesson's reagent (1.57 g, 3.9 mmol) was stirred in toluene (13 mL) at reflux for 1 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (10% ether in petroleum ether) without concentration to give thionolactone **3a** (224 mg, 40%): oil; R_f 0.40 (10% ether in petroleum ether); IR (thin film) ν_{max} 2940, 2870, 1490, 1450, 1390, 1378, 1345, 1318, 1310, 1300, 1279, 1238, 1200, 1179, 1142, 1135, 1091, 1000, 972 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.59 (t, J = 5.5 Hz, 2 H), 3.07 (t, J = 6.3 Hz, 2 H), 1.94–1.62 (m, 4 H), 1.59–1.51 (m, 4 H); HRMS calcd for $C_7H_{13}OS$ $(M + H)^+$ 145.157, found 145.159.

2-Oxonanethione (4a). A mixture of lactone **4** (221 mg, 1.15 mmol) and Lawesson's reagent (464 mg, 1.15 mmol) in toluene (5 mL) was stirred at reflux for 1 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (5% ether in petroleum ether) without concentration to give thionolactone **4a** (113 mg, 62%): oil, R_f 0.70 (5% ether in petroleum ether); IR (thin film) ν_{max} 2920, 2850, 1450, 1370, 1280, 1195, 1122, 1100, 1088, 1051, 1043, 1028, 1008, 953, 910, 725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.71 (t, J = 5.6 Hz, 2 H), 2.72 (t, J = 6.0 Hz, 2 H), 1.60 (m, 2 H), 1.52 (m, 4 H), 1.32 (m, 4 H); HRMS calcd for $C_8H_{15}OS$ $(M + H)^+$ 159.173, found 159.176.

2,3,4,4a,7,8-Hexahydro-(4a*S*,9*Z*,10a*R*)-pyrano[3,2-*b*]oxocine-6-thione (5a). A mixture of lactone **5** (268 mg, 1.47 mmol) and Lawesson's reagent (595 mg, 1.47 mmol) in toluene (6 mL) was stirred at reflux for 1 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (50% ether in petroleum ether) without concentration to give thionolactone **5a** (81 mg, 28%) as a clear oil: R_f 0.63 (50% ether in petroleum ether); IR (neat) ν_{max} 3020, 2940, 2844, 1454, 1342, 1253, 1230, 1190, 1122, 1030 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.71 (m, 1 H, olefin), 5.35 (m, 1 H, olefin), 4.89 (m, 1 H, C*H*-O-CS), 3.85 (m, 1 H, CH_2-O), 3.56 (m, 1 H, C*H*-O), 2.88 (m, 1 H, CH_2-O), 2.88 (m, 1 H, CH_2-CS), 2.50 (m, 1 H, CH_2-CS), 2.50 (m, 1 H, CH_2-CH=CH), 2.05 (m, 1 H, CH_2-CH=CH), 1.41 (m, 3 H, CH_2), 1.04 (m, 1 H, CH_2); HRMS calcd for $C_{10}H_{15}O_2S$ (M + H)$^+$ 199.079, found 199.078.

2,3,4,4a,7,8,9,11a-Octahydro-(4a*S*,10*Z*,11a*R*)-pyrano[3,2-*b*]-oxonine-6-thione (6a). A mixture of lactone **6** (434 mg, 2.21 mmol) and Lawesson's reagent (895 mg, 2.21 mmol) in toluene (6 mL) was stirred at reflux for 1 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (50% ether in petroleum ether) without concentration to give thionolactone **6a** (337 mg, 72%) as a clear oil: R_f 0.55 (50% ether in petroleum ether); IR (neat) ν_{max} 2944, 2852, 1442, 1352, 1309, 1292, 1192, 1155, 1082, 1031 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 5.49 (ddd, J = 10.7, 9.4, 4.8 Hz, 1 H, *H*C-COS), 5.42 (ddd, J = 11.6, 6.6, 1.5 Hz, 1 H, olefin), 5.23 (ddt, J = 11.6, 5.3, 1.6 Hz, 1 H, olefin), 3.90 (m, 1 H, C*H*-CH=CH), 3.63 (m, 1 H, CH_2-O), 2.99 (m, 1 H, CH_2-O), 2.85 (m, 1 H), 2.33 (m, 1 H), 2.10 (m, 1 H), 1.95 (m, 1 H), 1.74 (m, 1 H), 1.61 (m, 1 H), 1.41 (m, 3 H), 1.10 (m, 1 H); HRMS calcd for $C_{11}H_{17}O_2S$ (M + H)$^+$ 213.095, found 213.096.

Octahydro-(4a*S*,10a*R*)-pyrano[3,2-*b*]oxocine-6(2*H*)-thione (7a). A mixture of lactone **7** (191 mg, 1.03 mmol) and Lawesson's reagent (419 mg, 1.03 mmol) in toluene (4 mL) was stirred at reflux for 14 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (30% ether in petroleum ether) without concentration to give thionolactone **7a** (115 mg, 56%) as an orange solid: mp 92–93 °C (ether–petroleum ether); R_f 0.70 (60% ether in petroleum ether); IR (CCl_4) ν_{max} 2945, 2860, 1450, 1352, 1323, 1301, 1277, 1264, 1233, 1212, 1200, 1192, 1179, 1167, 1145, 1128, 1110, 1090, 1052, 1040, 1010, 971, 942, 933, 912, 850 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.60 (ddd, J = 9.9, 9.7, 4.3 Hz, 1 H), 3.93 (m, 1 H), 3.42 (m, 2 H), 3.02 (ddd, J = 11.3, 11.7, 4.0 Hz, 1 H), 2.25 (m, 1 H), 2.1–1.6 (m, 10 H); HRMS calcd for $C_{10}H_{17}O_2S$ (M + H)$^+$ 201.095, found 201.097.

Decahydro-(4a*S*,11a*R*)-pyrano[3,2-*b*]oxonine-6(2*H*)-thione (8a). A mixture of lactone **8** (127 mg, 0.64 mmol) and Lawesson's reagent (270 mg, 0.64 mmol) in toluene (6 mL) was stirred at reflux for 1 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (5% ether in petroleum ether) without concentration to give thionolactone **8a** (109 mg, 80%) as an oil: R_f 0.63 (50% petroleum ether); IR (neat) ν_{max} 2943, 2840, 1312, 1303, 1288, 1082, 786 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.19 (ddd, J = 10.3, 9.45, 5.1 Hz, 1 H), 3.93–3.87 (m, 1 H, CH_2), 3.41–3.2 (m, 2 H), 3.01–2.95 (m, 1 H), 2.60–2.50 (m, 1 H), 2.31–2.26 (m, 1 H), 1.94–1.22 (m, 11 H); HRMS calcd for $C_{11}H_{19}O_2S$ (M + H)$^+$ 215.110, found 215.111.

(±)-8-Hexyl-2-oxocanethione (9a). A mixture of lactone **9** (367 mg, 1.73 mmol) and Lawesson's reagent (700 mg, 1.73 mmol) in toluene (6 mL) was stirred together at reflux for 1 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (5% ether in petroleum ether) without concentration to give thionolactone **9a** (126 mg, 32%) as a clear oil: R_f 0.65 (5% ether in petroleum ether); IR (neat) ν_{max} 2930, 2863, 1485, 1460, 1365, 1341, 1309, 1235, 1208, 1182, 1147, 1120, 1085, 1000, 940, 728, 680 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.81 (m, 1 H), 3.12 (m, 1 H), 2.90 (ddd, J = 10.7, 10.7, 4.4 Hz, 1 H), 1.9–1.2 (m, 18 H), 0.85 (t, J = 5.2 Hz, 3 H); HRMS calcd for $C_{13}H_{25}OS$ (M + H)$^+$ 229.163, found 229.163.

8-Methyl-8-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,4,4a,7,8,9,9a-octahydro-(4a*S*,9a*R*)-pyrano[3,2-*b*]oxepane-6-thione (10c). A mixture of lactone **10a** (202 mg, 0.64 mmol), Lawesson's reagent (520 mg, 1.28 mmol), and 1,1,3,3-tetramethylthiourea (170 mg, 1.28 mmol) in xylene (6 mL) was heated in a sealed tube at 170 °C for 2 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (20% ether in petroleum ether) without concentration to give thionolactone **10c** (127 mg, 60%): oil, R_f 0.32 (20% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2956, 2932, 1330, 1303, 1254, 1133, 1089, 1071, 1029 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.31–4.23 (m, 1 H), 3.88–3.81 (m, 1 H), 3.57–3.50 (m, 1 H), 3.34–3.17 (m, 3 H), 2.33–2.22 (m, 2 H), 1.89–1.64 (m, 4 H), 1.36 (s, 3 H), 0.81 (s, 9 H), 0.09 (s, 6 H); HRMS calcd for $C_{16}H_{31}O_3SSi$ (M + H)$^+$ 331.176, found 331.177.

8-Methyl-2,3,4,4a,9,9a-hexahydro-(4a*S*,7*Z*,9a*R*)-pyrano[3,2-*b*]oxepane-6-thione (11a). A mixture of lactone **11** (275 mg, 1.51 mmol) and Lawesson's reagent (610 mg, 1.51 mmol) in toluene (6 mL) was stirred at reflux for 1 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (50% ether in petroleum ether) without concentration to give thionolactone **11a** (239 mg, 80%) as a clear oil: R_f 0.51 (50% ether in petroleum ether); IR (neat) ν_{max} 2960, 2865, 1620, 1450, 1390, 1319, 1283, 1191, 1132, 1090, 1017, 978, 920, 850, 790, 740, 620 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.58–6.56 (t, J = 1.5 Hz, 1 H), 4.38–4.28 (ddd, J = 9.7, 9.2, 4.7 Hz, 1 H), 3.94–3.87 (m, 1 H), 3.72–3.64 (ddd, J = 8.1, 8.1, 3.5 Hz, 1 H), 3.44–3.33 (ddd, J = 11.4, 11.4, 3.4 Hz, 1 H), 2.94–2.83 (m, 1 H), 2.36–2.21 (m, 2 H), 1.94 (s, 3 H), 1.9–1.66 (m, 3 H); HRMS calcd for $C_{10}H_{15}O_2S$ (M + H)$^+$ 199.079, found 199.081.

8-Methyl-2,3,4,4a,7,8,9,9a-octahydro-(4a*S*,9a*R*)-pyrano[3,2-*b*]oxepane-6-thione (12a). A mixture of lactone **12** (450 mg, 2.45 mmol) and Lawesson's reagent (500 mg, 1.22 mmol) in toluene (8.2 mL) was heated to reflux. An additional 500 mg of Lawesson's reagent was added every 4 h for a total reaction time of 12 h. The reaction was then cooled to room temperature and flash chromatographed directly (gradient elution 20%–70% ether in petroleum ether) to give recovered starting lactone **12** (60 mg, 14%) and the desired thionolactone **12a** (300 mg, 61%): solid; mp = 83 °C; (ether–petroleum ether) R_f 0.51 (50% ether in petroleum ether); IR (CCl_4) ν_{max} 2980, 2955, 2878, 1472, 1369, 1352, 1333, 1312, 1278, 1265, 1209, 1182, 1168, 1101, 1060, 999, 959 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.33–4.23 (m, 1 H), 3.93–3.85 (m, 1 H), 3.52–3.29 (m, 3 H), 3.12–3.05 (dd, J = 13.3, 2.6 Hz, 1 H), 2.36–2.31 (m, 1 H), 2.30–2.21 (m, 1 H), 2.19–2.0 (m, 1 H), 1.94–1.66 (m, 4 H), 1.13 (d, J = 7.3 Hz, 3 H); HRMS calcd for $C_{10}H_{17}O_2S$ (M + H)$^+$ 201.095, found 201.095.

2,3,4,4a,9,10-Hexahydro-(4a*S*,7*Z*,10a*R*)-pyrano[3,2-*b*]oxocine-6-thione (13a). A mixture of α,β-unsaturated lactone **13** (645 mg, 3.5 mmol) and recrystallized Lawesson's reagent (2.1 g, 5.25 mmol) in toluene (17.5 mL) was heated together at reflux for 3.5 h. After cooling to room temperature, the reaction mixture was flash chromatographed directly (20% ether + 2% triethylamine in petroleum ether and then 60% ether in petroleum ether) to give thionolactone **13a** (471 mg, 68%) as a bright yellow oil: R_f 0.33 (30% ether in petroleum ether); IR (neat) ν_{max} 2950, 2858, 1612, 1485, 1469, 1448, 1422, 1409, 1370, 1358, 1340, 1290, 1200, 1130, 1090, 1030, 1009, 950, 910, 870, 827, 789, 738, 685 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.26–6.19 (ddd, J = 12.8, 1.3, 1.2 Hz, 1 H), 5.25–5.18 (ddd, J = 12.8, 4.3, 3.7 Hz, 1 H), 4.39–4.29 (ddd, J = 9.9, 9.9, 4.5 Hz, 1 H), 3.51–3.44 (m, 1 H), 3.06–2.99 (ddd, J = 11.5, 11.5, 3.2 Hz, 1 H), 2.18–2.06 (m, 1 H), 1.91–1.82 (m, 1 H), 1.78 (m, 2 H), 1.49–1.32 (m, 2 H), 1.16–1.03 (m, 3 H); HRMS calcd for $C_{10}H_{14}O_2S$ (M)$^+$ 198.071, found 198.072.

2-Oxacycloheptadecanethione (14a). A mixture of lactone **14** (91 mg, 0.36 mmol) and Lawesson's reagent (146 mg, 0.36 mmol) in toluene (4 mL) was stirred together at reflux for 14 h. The reaction mixture was cooled to room temperature and subjected to silica gel chromatography (50% ether in petroleum ether) without concentration to give thionolactone **14a** (58 mg, 60%) as an oil: R_f 0.57 (petroleum ether); IR (neat) ν_{max} 2938, 2860, 1465, 1384, 1290, 1204, 1110, 1075 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.34 (m, 2 H, C*H*-CSO), 2.70 (t, J = 7.0 Hz, 2 H, CH_2-O), 1.65 (m, 2 H, CH_2), 1.20 (m, 24 H, CH_2); HRMS calcd for $C_{16}H_{31}OS$ (M + H)$^+$ 271.209, found 271.209.

(±)-2-Methyl-2-(methylthio)oxepane (15). To a stirred solution of thionolactone **2a** (121 mg, 0.93 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon a 1.8 M MeLi solution (77 μL), and the resulting mixture was stirred for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash chromatography gave **15** (124 mg, 83%): oil; R_f 0.50 (5% ether in petroleum ether); IR (neat) ν_{max} 2940, 1479, 1478, 1378, 1280, 1260, 1205, 1081 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.76 (m, 1 H, CH_2-O), 3.55 (m, 1 H, CH_2-O), 1.99 (s, 3 H, S-CH_3), 1.90–1.41 (m, 7 H, CH_2), 1.48 (s, 3 H, C-CH_3), 1.22 (m, 1 H, CH_2); HRMS calcd for $C_8H_{17}OS$ (M + H)$^+$ 161.100, found 161.100.

(±)-2-(Methylthio)-2-phenyloxepane (16). To a stirred solution of thionolactone **2a** (260 mg, 2 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon a 2.0 M solution of PhLi in THF (1.1 mL). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash chromatography gave **16** (380 mg, 86%): oil; R_f 0.72 (10% ether in petroleum ether); IR (CCl_4) ν_{max} 2930, 2864, 1495, 1480, 1450, 1280, 1126, 1100, 1054 cm^{-1}; ^{1}H NMR (250 MHz, C_6D_6) δ 7.85 (m, 2 H, aromatic), 7.22 (m, 2 H, aromatic), 7.07 (m, 1 H, aromatic), 4.03 (m, 1 H, CH_2-O), 3.64 (m, 1 H, CH_2-O), 2.38 (m, 1 H, CH_2), 2.00 (m, 1 H, CH_2), 1.65 (s, 3 H, S-CH_3), 1.60–1.12 (m, 5 H, CH_2), 0.97 (m, 1 H,

CH_2); HRMS calcd for $C_{13}H_{19}OS$ $(M + H)^+$ 223.115, found 223.116.

(±)-2-(Methylthio)oxepane (17). To a stirred solution of thionolactone **2a** (210 mg, 1.61 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon a solution of $LiEt_3BH$ in THF (1.8 mL). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash chromatography gave **17** (176 mg, 75%): oil; R_f 0.40 (2% ether in petroleum ether); IR (neat) ν_{max} 2930, 2856, 1470, 1445, 1352, 1291, 1232, 1200, 1182, 1096, 1022, 970 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.83 (dd, J = 10.4, 5.3 Hz, 1 H, HC-SMe), 3.76 (m, 1 H, CH_2-O), 3.46 (m, 1 H, CH_2-O), 2.08 (m, 1 H, CH_2), 2.05 (s, 3 H, S-CH_3), 1.55 (m, 6 H, CH_2), 1.22 (m, 1 H, CH_2); HRMS calcd for $C_7H_{15}OS$ $(M + H)^+$ 147.085, found 147.085.

(±)-2-(Methylthio)-2-(tributylstannyl)oxepane (18). To a stirred solution of thionolactone **2a** (118 mg, 0.91 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon a solution of $LiSnBu_3$ in THF (1.5 equivs). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash chromatography gave **18** (301 mg, 79%): oil; R_f 0.60 (10% ether in petroleum ether); IR (CCl_4) ν_{max} 2960, 2930, 2880, 2860, 1470, 1380, 1080, 1020, 970 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 4.00 (m, 1 H, CH_2-O), 3.36 (m, 1 H, CH_2-O), 2.38 (m, 1 H, CH_2), 2.06 (s, 3 H, S-CH_3), 2.00 (m, 1 H, CH_2), 1.8–1.02 (m, 24 H, CH_2), 0.96 (t, J = 7.3 Hz, 9 H, CH_2-CH_3); HRMS calcd for $C_{18}H_{37}OSSn$ $(M - CH_3)^+$ 421.159, found 421.158.

(±)-2-(2-Furanyl)-2-(methylthio)oxepane (19). To a stirred solution of thionolactone **2a** (130 mg, 1 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon a solution of furanyllithium in THF (1.6 equivs). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash chromatography gave **19** (195 mg, 92%): oil; R_f 0.65 (10% ether in petroleum ether); IR (CCl_4) ν_{max} 2930, 2880, 2860, 1508, 1475, 1450, 1299, 1280, 1249, 1158, 1122, 1100, 1082, 1051, 1011, 1000, 982, 960, 933, 901, 889, 836 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.07 (dd, J = 1.8, 1.1 Hz, 1 H), 6.5 (dd, J = 3.2, 1.1 Hz, 1 H), 6.06 (dd, J = 3.2, 1.8 Hz, 1 H), 3.91 (ddd, J = 11.4, 11.4, 1.2 Hz, 1 H), 3.53 (ddd, J = 12.9, 3.3, 1.6 Hz, 1 H), 2.85 (m, 1 H), 1.86 (m, 1 H), 1.74 (s, 3 H), 1.72–1.20 (m, 5 H), 0.92 (m, 1 H); HRMS calcd for $C_{11}H_{17}O_2S$ $(M + H)^+$ 213.097, found 213.097.

(±)-*tert*-Butyl [2-(Methylthio)oxepan-2-yl]ethanoate (20). To a stirred solution of thionolactone **2a** (183 mg, 1.41 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon a solution of [(1-*tert*-butoxyethenyl)oxy]lithium in THF (1.5 equivs). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash chromatography gave **20** (283 mg, 95%) as a yellow solid, mp 50–51 °C (from ether–petroleum ether): R_f 0.49 (20% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2990, 2938, 1720, 1450, 1372, 1334, 1260, 1165, 1095, 1068 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.82 (dt, J = 12.7, 1.3 Hz, 1 H, CH_2-O), 3.40 (ddt, J = 12.7, 3.2, 1.6 Hz, 1 H, CH_2-O), 2.95 (m, 1 H, CH_2), 2.76 (d, J = 13.3 Hz, 1 H, CH_2-$CO_2{}^tBu$), 2.69 (d, J = 13.3, Hz, 1 H, CH_2-$CO_2{}^tBu$), 2.03 (s, 3 H, S-CH_3), 1.45 (m, 6 H, CH_2), 1.42 (s, 9 H, ^tBu), 0.94 (m, 1 H, CH_2); HRMS calcd for $C_{12}H_{21}O_3$ $(M - SMe)^+$ 213.149, found 213.148.

(±)-2-Allyl-2-(methylthio)oxepane (21). To a stirred solution of thionolactone **2a** (260 mg, 2 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon a solution of allyllithium (1.5 equivs) in ether. The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash chromatography gave **21** (320 mg, 86%): oil; R_f 0.44 (50% ether in petroleum ether); IR (CCl_4) ν_{max} 2910, 2820, 1575, 1440, 1279, 1086, 1060 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 6.00 (m, 1 H, olefin), 5.05 (m, 2 H, olefin), 3.90 (m, 1 H, CH_2-O), 3.48 (m, 1 H, CH_2-O), 2.5 (m, 2 H, CH_2-CH=CH_2), 2.1 (m, 1 H, CH_2), 1.83 (s, 3 H, SCH_3), 1.45 (m, 6 H, CH_2), 0.98 (m, 1 H, CH_2); HRMS calcd for $C_{10}H_{19}OS$ $(M + H)^+$ 187.116, found 187.117.

(±)-2-(Methylthio)-2-vinyloxepane (22). To a stirred solution of thionolactone **2a** (254 mg, 1.95 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon a 1.0 M solution of vinyllithium in THF (2.9 mL). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash chromatography gave **22** (265 mg, 80%): oil; R_f 0.29 (petroleum ether); IR ($CHCl_3$) ν_{max} 2920, 2895, 1640, 1470, 1452, 1410, 1160, 1102, 1090, 1070 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.60 (dd, J = 16.9, 10.4 Hz, 1 H, CH=CH_2), 5.43 (dd, J = 16.9, 2.3 Hz, 1 H, —CH=CH_2), 5.09 (dd, J = 10.4, 2.3 Hz, 1 H, —CH=CH_2), 3.85 (dt, J = 12.7, 1.3 Hz, 1 H, CH_2-O), 3.49 (m, 1 H, CH_2-O), 1.69–0.95 (m, 8 H), 1.85 (s, 3 H); HRMS calcd for $C_9H_{17}OS$ $(M + H)^+$ 173.101, found 173.096.

(±)-2-Methyloxepane (23). Thiomethyl adduct **15** (60 mg, 0.37 mmol) was stirred together with triphenyltin hydride (0.20 mL, 0.75 mmol) and AIBN (5 mg) in toluene (9 mL) at reflux for 25 min. Concentration and silica gel chromatography gave the known[35] ether **23** (12 mg, 85%).

(±)-2-Phenyloxepane (24). Thiomethyl adduct **16** (222 mg, 1.0 mmol) was stirred together with triphenyltin hydride (0.51 mL, 2.0 mmol) and AIBN (5 mg) in toluene (9 mL) at reflux temperature for 25 min. Concentration and silica gel chromatography gave ether **24** (170 mg, 97%): oil; R_f 0.18 (2% ether in petroleum ether); IR (neat) ν_{max} 3030, 2940, 2860, 1605, 1496, 1452, 1360, 1284, 1127, 1028 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.25 (m, 5 H, aromatic), 4.57 (dd, J = 9.1, 3.9 Hz, 1 H, CH-aromatic), 3.95 (m, 1 H, CH_2), 3.72 (m, 1 H, CH_2-O), 2.06 (m, 1 H, CH_2), 1.75 (m, 7 H, CH_2); HRMS calcd for $C_{12}H_{17}O$ $(M + H)^+$ 176.120, found 176.119.

(±)-2-(2-Furanyl)oxepane (25). Thiomethyl adduct **19** (195 mg, 0.92 mmol) was stirred together with triphenyltin hydride (0.47 mL, 1.84 mmol) and AIBN (5 mg) in toluene (9 mL) at reflux temperature for 25 min. Concentration and silica gel chromatography gave ether **25** (137 mg, 90%): oil; R_f 0.68 (10% ether in petroleum ether); IR (neat) ν_{max} 2930, 2858, 1600, 1502, 1470, 1452, 1445, 1353, 1342, 1301, 1288, 1270, 1248, 1177, 1149, 1125, 1102, 1020, 1013, 1003, 970, 887, 730 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.34 (dd, J = 1.8, 0.9 Hz, 1 H), 6.29 (dd, J = 3.2, 1.8 Hz, 1 H), 6.2 (dd, J = 3.2, 0.9 Hz, 1 H), 4.60 (dd, J = 9.7, 4.7 Hz, 1 H), 3.85 (m, 1 H), 3.65 (m, 1 H), 2.15–1.53 (m, 8 H); HRMS calcd for $C_{10}H_{15}O_2$ $(M + H)^+$ 167.107, found 167.104.

(±)-*tert*-Butyl [2-Oxepanyl]ethanoate (26). Thiomethyl adduct **20** (70 mg, 0.27 mmol) was stirred together with triphenyltin hydride (0.07 mL, 1.84 mmol) and AIBN (5 mg) in toluene (9 mL) at reflux temperature for 25 min. Concentration and silica gel chromatography gave ether **26** (50 mg, 88%): oil; R_f 0.32 (20% ether in petroleum ether); IR (neat) ν_{max} 2938, 2860, 1743, 1460, 1375, 1110, 1040 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 3.92 (m, 1 H, CH_2-O), 3.71 (m, 1 H, CH-O), 3.43 (m, 1 H, CH_2-O), 2.49 (dd, J = 14.8, 8.5 Hz, 1 H, CH_2-$CO_2{}^tBu$), 2.16 (dd, J = 14.8, 4.9 Hz, 1 H, CH_2-$CO_2{}^tBu$), 1.51 (m, 3 H, CH_2), 1.38 (s, 9 H, ^tBu), 1.33 (m, 4 H, CH_2), 0.90 (m, 1 H, CH_2); HRMS calcd for $C_{12}H_{23}O_3$ $(M + H)^+$ 215.165, found 215.163.

(±)-2-Allyloxepane (27). Thiomethyl adduct **21** (93 mg, 0.34 mmol) was stirred together with triphenyltin hydride (0.09 mL, 0.68 mmol) and AIBN (5 mg) in toluene (9 mL) at reflux temperature for 25 min. Concentration and silica gel chromatography gave ether **27** (59 mg, 85%): oil; R_f 0.28 (5% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3007, 2934, 2858, 1430, 1104, 1073, 997 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.79 (m, 1 H, olefin), 4.97–4.89 (m, 2 H, olefin), 3.77–3.69 (m, 1 H, CH-O), 3.44–3.34 (m, 2 H, CH_2O), 2.10–1.08 (m, 10 H); HRMS calcd for $C_9H_{17}O$ $(M + H)^+$ 141.128, found 141.125.

(±)-2-*n*-Butyl-2-(methylthio)oxocane (28). To a stirred solution of thionolactone **3a** (115 mg, 0.80 mmol) in anhydrous THF (2.0 mL) at −78 °C was added under argon 1.6 M BuLi solution in hexane (0.65 mL, 1.04 mmol). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (0.11 mL, 1.6 mmol). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash column chromatography (10% ether in petroleum ether) gave thiomethyl adduct **28** (163 mg, 96%): oil; R_f 0.82 (10% ether in petroleum ether); IR (CCl_4) ν_{max} 2930, 2840, 1475, 1448, 1372, 1278, 1250, 1201, 1132, 1075, 1029, 983, 948, 910, 880, 830, 819, 648 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 3.90 (ddd, J = 12.5, 12.5, 2.3 Hz, 1 H), 3.46 (m, 1 H), 1.80 (s, 3 H), 1.9–1.1 (m, 16 H), 0.89 (t, J = 6.8 Hz, 3 H); HRMS calcd for $C_{12}H_{25}O_5$ $(M + H)^+$ 216.163, found 217.166.

(±)-2-Allyl-2-(methylthio)oxonane (29). To a stirred solution of thionolactone **4a** (113 mg, 0.71 mmol) in anhydrous THF (2.0 mL) at −78 °C was added under argon 1.4 M allyllithium solution in ether (0.76 mL, 1.07 mmol). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (0.11 mL, 1.6 mmol). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash column chromatography (3% ether in petroleum ether) gave thiomethyl adduct **29** (142 mg, 94%): oil; R_f 0.41 (3% ether in petroleum ether); IR (CCl_4) ν_{max} 2905, 2855, 1430, 1365, 1272, 1227,

1099, 1068, 1010, 947, 910, 718 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 6.04 (m, 1 H), 5.96 (m, 2 H), 3.91 (ddd, J = 12.0, 12.0, 2.2 Hz, 1 H), 3.42 (ddd, J = 12.2, 3.4, 3.4 Hz, 1 H), 2.57 (d, J = 6.6 Hz, 2 H), 1.75 (s, 3 H), 1.83–1.20 (m, 12 H); HRMS calcd for $C_{12}H_{23}OS$ $(M + H)^+$ 215.147, found 215.148.

2,3,4,4a,7,8,9,11a-Octahydro-(4a*S*,6*S*,10*Z*,11a*R*)-6-methyl-6-(methylthio)pyrano[3,2-*b*]oxonine (30). To a stirred solution of thionolactone **6a** (360 mg, 1.69 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon 1.4 M MeLi solution in ether (1.82 mL, 2.55 mmol). The reaction mxture was stirred at −78 °C for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach amient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash column chromatography (20% ether in petroleum ether) gave thiomethyl adduct **30** (374 mg, 91%): oil; R_f = 0.51 (50% ether in petroleum ether); IR (neat) ν_{max} 2992, 2920, 2852, 1438, 1374, 1096, 1042 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 5.88 (dd, J = 11.6, 4.6 Hz, 1 H, olefin), 5.21 (ddt, J = 11.6, 5.6, 1.8 Hz, 1 H, olefin), 4.03 (dd, J = 9.5, 4.6 Hz, 1 H, C*H*-CH=CH), 3.77 (dt, J = 9.5, 5.7 Hz, 1 H, C*H*-OCSMe), 3.45 (m, 1 H, CH_2), 3.04 (m, 1 H, C*H*O), 2.60 (m, 1 H, CH=CH-CH_2), 2.04 (m, 2 H), 1.81 (s, 3 H, SCH_3), 1.67 (m, 1 H, CH_2), 1.50 (m, 1 H, CH_2), 1.39 (s, 3 H, CH_3), 1.35 (m, 3 H, CH_2), 1.20 (m, 1 H, CH_2), 0.88 (m, 1 H, CH_2); HRMS calcd for $C_{13}H_{23}O_2S$ $(M + H)^+$ 243.142, found 243.144.

2,3,4,4a,7,8,9,11a-Octahydro-(4a*S*,6*S*,10*Z*,11a*R*)-6(2*H*)-(methylthio)-6-phenylpyrano[3,2-*b*]oxonine (31). To a stirred solution of thionolactone **6a** (105 mg, 0.5 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon 2.0 M PhLi solution in THF (0.5 mL, 1.0 mmol). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (65 μL, 1.0 mmol). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash column chromatography (20% ether in petroleum ether) gave thiomethyl adduct **31** (98 mg, 85%): white solid, mp = 145–146 °C (ether–petroleum ether); R_f 0.52 (20% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3010, 2944, 2857, 1447, 1118, 1094, 1072, 1060, 1024, 963 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 7.61–7.16 (m, 5 H), 5.18 (dd, J = 5.3, 11.2 Hz, 1 H, olefin), 5.38–5.29 (m, 1 H, olefin), 4.13–4.08 (m, 1 H, C*H*-OCSMe), 4.01–3.87 (m, 2 H, CH_2-O), 3.41–3.34 (m, 1 H, C*H*-CH=CH), 2.48–1.07 (m, 10 H), 1.54 (s, 3 H); HRMS calcd for $C_{18}H_{25}O_2S$ $(M + H)^+$ 305.158, found 305.158.

Octahydro-(4a*S*,6*S*,10a*R*)-6(2*H*)-methyl-6-(methylthio)pyrano[3,2-*b*]oxocine (32). To a stirred solution of thionolactone **7a** (115 mg, 0.57 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon 1.4 M MeLi solution in Et_2O (0.59 mL, 0.83 mmol). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (0.07 mL, 1.1 mmol). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash column chromatography (20% ether in petroleum ether) gave thiomethyl adduct **32** (117 mg, 89%): oil; R_f 0.46 (20% ether in petroleum ether); IR (CCl_4) ν_{max} 2940, 2830, 1463, 1380, 1351, 1294, 1230, 1220, 1182, 1100, 1087, 1050, 1029, 993, 981, 950, 938, 891, 869, 870, 815 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.80 (m, 1 H), 3.30 (m, 2 H), 3.02 (ddd, J = 10.2, 9.2, 4.0 Hz, 1 H), 2.11 (s, 3 H), 2.2–1.3 (m, 15 H); HRMS calcd for $C_{12}H_{23}O_2S$ $(M + H)^+$ 231.142, found 231.145.

Octahydro-(4a*S*,6*S*,10a*R*)-6(2*H*)-(methylthio)pyrano[3,2-*b*]oxocine (33). To a stirred solution of thionolactone **7a** (115 mg, 0.57 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon 1.0 M $LiEt_3BH$ solution in THF (0.83 mL, 0.83 mmol). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (0.07 mL, 1.1 mmol). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash column chromatography (20% ether in petroleum ether) gave thiomethyl adduct **33** (91 mg, 74%): R_f 0.30 (20% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2960, 2880, 1475, 1462, 1450, 1343, 1305, 1279, 1250, 1100, 1070, 1038, 1000, 983, 968, 920, 842 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.80 (dd, J = 8.9, 2.9 Hz, 1 H), 3.85 (m, 1 H), 3.31 (m, 1 H), 3.1 (m, 2 H), 2.18 (s, 3 H), 2.1–1.46 (m, 12 H); HRMS calcd for $C_{11}H_{21}O_2S$ $(M + H)^+$ 217.126, found 217.124.

Decahydro-(4a*S*,6*S*,11a*R*)-6(2*H*)-methyl-6-(methylthio)pyrano[3,2-*b*]oxonine (34). To a stirred solution of thionolactone **8a** (91 mg, 0.42 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon 1.0 M $LiEt_3BH$ solution in THF (0.45 mL, 0.64 mmol). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (0.04 mL, 0.60 mmol). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash column chromatography (20% ether in petroleum ether) gave thiomethyl adduct **34** (98 mg, 96%): oil; R_f 0.51 (50% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2943, 2857, 1312, 1303, 1289, 1149, 1121, 1082, 786 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 3.91–3.78 (m, 1 H), 3.34–3.18 (m, 2 H), 3.07–2.89 (m, 1 H), 2.18–1.23 (m, 14 H), 2.17 (s, 3 H), 1.46 (s, 3 H); HRMS calcd for $C_{13}H_{25}O_2S$ $(M + H)^+$ 245.148, found 245.156.

(±)-2-Ethyl-2-(methylthio)-8-hexyloxacycloheptadecane (35). To a stirred solution of thionolactone **9a** (126 mg, 0.55 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon 1.4 M ethyllithium solution in THF (0.59 mL, 0.83 mmol). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (0.07 mL, 1.1 mmol). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash column chromatography (3% ether in petroleum ether) gave thiomethyl adduct **35** (125 mg, 84%): oil; R_f 0.8 (5% ether in petroleum ether); IR (neat) ν_{max} 2910, 2840, 1450, 1372, 1255, 1200, 1159, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.60 (m, 1 H), 2.08 (s, 3 H), 1.9–1.2 (m, 22 H), 1.01 (t, J = 10 Hz, 3 H), 0.9 (t, J = 5.2 Hz, 3 H); HRMS calcd for $C_{16}H_{32}OS$ (M^+) 272.217, found 272.217.

(±)-2-Methyl-2-(methylthio)oxacycloheptadecane (36). To a stirred solution of thionolactone **14a** (325 mg, 1.20 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon of 1.4 M MeLi in ether (1.29 mL). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash column chromatography gave **36** (282 mg, 78%): oil; R_f 0.19 (petroleum ether); IR (neat) ν_{max} 2924, 2834, 1460, 1372, 1080, 910 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 3.45 (m, 2 H, CH_2-O), 1.96 (s, 3 H, S-CH_3), 1.96 (s, 1 H, CH_2), 1.65–1.20 (m, 27 H, CH_2), 1.46 (s, 3 H, C-CH_3); HRMS calcd for $C_{18}H_{37}OS$ $(M + H)^+$ 301.257, found 301.256.

(±)-2-Allyl-2-(methylthio)oxacycloheptadecane (37). To a stirred solution of thionolactone **14a** (240 mg, 0.89 mmol) in anhydrous THF (6 mL) at −78 °C was added under argon allyllithium in ether (1.5 equivs). The reaction mixture was stirred at −78 °C for 5 min before quenching with MeI (1.9 equivs). The reaction was then allowed to reach ambient temperature with stirring. Dilution with ether (50 mL) followed by washing with H_2O (2 × 10 mL), drying ($MgSO_4$), concentration, and flash chromatography gave **37** (234 mg, 81%): oil; R_f 0.61 (2% ether in petroleum ether); IR (neat) ν_{max} 2930, 2900, 1470, 1440, 1060 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 5.95–5.79 (m, 1 H), 5.19–5.08 (m, 2 H), 3.64–3.36 (m, 2 H), 1.53–1.45 (m, 2 H), 1.93 (s, 3 H), 1.83–1.22 (m, 28 H); HRMS calcd for $C_{20}H_{39}OS$ (M^+) 327.272, found 327.275.

(±)-2-*n*-Butyloxocane (38). Thiomethyl adduct **28** (172 mg, 0.80 mmol) was stirred together with triphenyltin hydride (0.41 mL, 1.64 mmol) and AIBN (5 mg) in toluene (8 mL) at reflux temperature for 20 min. Concentration and silica gel chromatography gave ether **38** (114 mg, 84%): oil; R_f 0.70 (10% ether in petroleum ether); IR (CCl_4) ν_{max} 2910, 2840, 1448, 1370, 1355, 1342, 1280, 1190, 1100, 960, 668 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.79 (m, 1 H), 3.34 (m, 1 H), 3.24 (m, 1 H), 1.78–1.22 (m, 16 H), 0.91 (t, J = 6.7 Hz, 3 H); HRMS calcd for $C_{11}H_{23}O$ $(M + H)^+$ 171.175, found 171.174.

(±)-2-Allyloxonane (39). Thiomethyl adduct **29** (142 mg, 0.67 mmol) was stirred together with tripheyltin hydride (0.35 mL, 1.4 mmol) and AIBN (3 mg) in toluene (6 mL) at reflux temperature for 30 min. Concentration and silica gel chromatography (3% ether in petroleum ether) gave ether **39** (99 mg, 85%): oil; R_f 0.4 (3% ether in petroleum ether); IR (neat) ν_{max} 2930, 2870, 1649, 1448, 1355, 1290, 1220, 1190, 1110, 1003, 917 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.8 (m, 1 H), 5.04 (m, 2 H), 3.85 (m, 1 H), 3.41 (m, 2 H), 2.2 (m, 2 H), 1.8–1.2 (m, 12 H); HRMS calcd for $C_{11}H_{21}O$ $(M + H)^+$ 169.159, found 169.157.

Decahydro-5a-methyl-(4aα,5aα,9aα,9bβ)-2*H*-pyrano[3,2-*b*]benzofuran (30b) and Decahydro-5a-methyl-(4aα,5aα,8aα,9aβ)-2*H*-cyclopenta[*b*]-pyrano[3,2-*e*]pyran (30c). Thiomethyl adduct **30** (242 mg, 1.14 mmol) was stirred together with triphenyltin hydride (0.58 mL, 2.28 mmol) and AIBN (5 mg) in toluene (9 mL) at reflux temperature for 25 min. Concentration and silica gel chromatography gave ether **30b** (45 mg, 20%) and **30c** (146 mg, 65%). **30b**: oil; R_f 0.38 (10% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 3020, 2957, 2930, 1220, 1218, 1109 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.97 (ddd, J = 11.0, 5.5, 2.1 Hz, 1 H, CH_2-C*H*-O), 3.47–3.31 (m, 2 H, CH_2-O), 3.16 (dd, J = 11.0, 8.5 Hz, 1 H, CH-C*H*-O), 1.84–0.86 (m, 13 H), 1.56 (s, 3 H); HRMS calcd for $C_{12}H_{21}O_2$ $(M + H)^+$ 197.154, found 197.155. **30c**: oil; R_f 0.18 (10% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2998, 2967, 2945, 1463, 1376, 1121 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.89–3.84 (m, 1 H, CH_2-C*H*-O), 3.36 (ddd, J = 11.3, 11.3, 3.6 Hz, 1 H, CH_2-C*H*-O), 3.25–3.10 (m, 2 H, CH_2-O), 1.87–1.23 (m, 13 H), 1.31 (s, 3 H); HRMS calcd for $C_{12}H_{21}O_2$ $(M + H)^+$ 197.154, found 197.156.

Octahydro-(4a*S*,6*R*,10a*R*)-6(2*H*)-methylpyrano[3,2-*b*]oxocine (42). Method A. Thiomethyl adduct **33** (105 mg, 0.46 mmol) was stirred

together with triphenyltin hydride (0.29 mL, 1.15 mmol) and AIBN (5 mg) in toluene (6 mL) at reflux temperature for 45 min. Concentration and silica gel chromatography (20% ether in petroleum ether) gave ether **42** (76 mg, 90%): oil; R_f 0.42 (20% ether in petroleum ether); IR (neat) ν_{max} 2940, 2860, 1470, 1457, 1395, 1373, 1340, 1300, 1276, 1219, 1182, 1169, 1100, 1029, 990, 968, 951, 930, 912, 892, 879, 809, 735, 701, 683 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.0–3.7 (m, 2 H), 2.9–3.6 (m, 3 H), 2.1–1.3 (m, 10 H), 1.15 (d, J = 7.2 Hz, 3 H); HRMS calcd for $C_{11}H_{19}O_2$ (M + H)$^+$ 183.138, found 183.138.

Method B. A mixture of monothioacetal **33** (124 mg, 0.57 mmol), $NaHCO_3$ (96 mg, 1.14 mmol), and mCPBA (307 mg, 1.42 mmol) was stirred together in CH_2Cl_2 (3 mL) at 0 °C for 1 h. After cooling the reaction mixture to −78 °C, a 2 M solution of Me_3Al in toluene (1.43 mL, 2.85 mmol) was added. After an additional 20 min, the reaction was quenched with MeOH (0.5 mL), warmed to room temperature, and diluted with EtOAc (30 mL). The organic solution was washed successively with a standard solution of sodium–potassium tartrate (4 × 10 mL), H_2O (10 mL), and brine (10 mL) and dried ($MgSO_4$). Flash chromatography gave oxocane **42** (90 mg, 82%).

Decahydro-(4a*S*,6*R*,11a*R*)-6-(2*H*)-methylpyrano[3,2-*b*]oxonine (43). Thiomethyl adduct **34** (178 mg, 0.15 mmol) was stirred together with triphenyltin hydride (0.08 mL, 0.30 mmol) and AIBN (5 mg) in toluene (8 mL) at reflux temperature for 20 min. Concentration and silica gel chromatography gave ether **43** (148 mg, 84%) as a mixture of isomers. **43a**: oil; R_f 0.60 (20% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2963, 2930, 2855, 1088, 786 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.85–3.79 (m, 1 H, C*H*-O), 3.65–3.56 (m, 1 H, C*H*-CH_3), 3.31–3.22 (m, 1 H, CH_2-O), 3.13–2.97 (m, 2 H, CH_2-O, C*H*-O), 1.79–1.11 (m, 14 H), 1.11 (d, J = 6.25 Hz, 3 H); HRMS calcd for $C_{12}H_{23}O_2$ (M + H)$^+$ 199.166, found 199.170. **43b**: oil; R_f 0.50 (20% ether in petroleum ether); IR ($CHCl_3$) ν_{max} 2980, 2910, 2850, 1070 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.85–3.81 (m, 2 H), 3.33–3.18 (m, 3 H), 1.67–1.07 (m, 14 H), 1.13 (d, J = 6.56 Hz, 3 H); HRMS calcd for $C_{12}H_{23}O_2$ (M + H)$^+$ 197.166, found 197.168.

(±)-*cis*-2-Ethyl-8-hexyloxocane (44). Thiomethyl adduct **35** (125 mg, 0.46 mmol) was stirred together with triphenyltin hydride (0.29 mL, 1.15 mmol) and AIBN (5 mg) in toluene (8 mL) at reflux temperature for 20 min. Concentration and silica gel chromatography (2% ether in petroleum ether) gave ether **44** (95.6 mg, 92%): oil; R_f 0.61 (2% ether in petroleum ether); IR (neat) ν_{max} 2940, 2869, 1465, 1385, 1350, 1095, 903, 731, 702, 680 cm^{-1}; ^{1}H NMR (250 MHz, C_6D_6) δ 3.35 (m, 1 H), 3.22 (m, 1 H), 1.9–1.2 (m, 20 H), 0.98 (t, J = 7.4 Hz, 3 H), 0.90 (t, J = 6.3 Hz, 3 H); HRMS calcd for $C_{15}H_{29}O$ (M + H)$^+$ 225.225, found 225.223.

(±)-2-Methyloxacyclohexadecane (45). Thiomethyl adduct **36** (236 mg, 0.78 mmol) was stirred together with triphenyltin hydride (0.41 mL, 1.6 mmol) and AIBN (5 mg) in toluene (8 mL) at reflux temperature for 20 min. Concentration and silica gel chromatography gave **48** (180 mg, 90%): oil; R_f 0.40 (petroleum ether); IR (neat) ν_{max} 2946, 2870, 1420, 1381, 1348, 1106 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.60 (m, 1 H, C*H*-O), 3.30 (m, 2 H, CH_2O), 1.70–1.17 (m, 28 H, CH_2), 1.11 (d, J = 6.1 Hz, 3 H, CH_3); HRMS calcd for $C_{17}H_{38}NO$ (M + NH_4)$^+$ 272.294, found 272.296.

(±)-2-Allyloxacycloheptadecane (46). Thiomethyl adduct **37** (49 mg, 0.15 mmol) was stirred together with triphenyltin hydride (0.41 mL, 1.6 mmol) and AIBN (5 mg) in toluene (8 mL) at reflux temperature for 20 min. Concentration and silica gel chromatography gave **47** (36 mg, 85%): oil; R_f 0.14 (petroleum ether); IR ($CHCl_3$) ν_{max} 3067, 2994, 2930, 2857, 1480, 1430, 1214, 1093 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.67–5.58 (m, 1 H, olefin), 4.91–4.83 (m, 2 H, olefin), 3.47–3.40 (m, 1 H), 3.16–3.06 (m, 2 H), 1.40–1.13 (m, 30 H); HRMS calcd for $C_{19}H_{37}O$ (M + H)$^+$ 281.284, found 281.281.

[2,3,4,5-Tetrahydro-3-*O*-(benzyloxy)-(2*S*,3*R*)-pyran-2-yl]propanol (49). A solution of allyl pyranoside **48b** (22.5 g, 100 mmol) in THF (300 mL) was treated with 0.5 M 9-BBN (220 mL, 110 mmol) at 0 °C. After removal of the cooling bath and stirring at room temperature for 30 min, the reaction was again cooled to 0 °C and treated with a 3 N NaOH (128 mL, 385 mmol) solution. After 1 h at room temperature the reaction mixture was diluted with ether (500 mL), the aqueous phase was removed, and the organic layer was dried over $MgSO_4$. Silica gel chromatography (60% ether in petroleum ether) afforded primary alcohol **49** (22.5 g, 90%): oil; R_f 0.61 (ether); IR (neat) ν_{max} 3420, 2940, 2859, 1481, 1420, 1392, 1328, 1250, 1163, 1115, 1100, 1052, 977, 958, 769, cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.25 (m, 5 H), 4.65–4.43 (AB, J_{AB} = 11.5 Hz. 2 H), 3.94–3.86 (m, 1 H), 3.06 (br s, 2 H), 3.40–3.30 (ddd, J = 11.2, 11.2, 3.3 Hz, 1 H), 3.22–3.07 (m, 1 H), 2.69 (br s, 1 H), 2.31–2.25 (m, 1 H), 2.13–1.90 (m, 2 H), 1.73–1.17 (m, 6 H); HRMS calcd $C_{15}H_{23}O_3$ (M + H)$^+$ 251.165, found 251.165.

[2,3,4,5-Tetrahydro-3-*O*-(benzyloxy)-(2*S*,3*R*)-pyran-2-yl]propanal (50). To a solution of oxalyl chloride (7.2 mL, 82.0 mmol) in methylene chloride (273 mL) at −78 °C was added dropwise DMSO (7.8 mL, 109.4 mmol). After 10 min, primary alcohol **49** (13.2 g, 54.7 mmol) in methylene chloride (40 mL) was added dropwise and stirring continued at −78 °C for 30 min. After addition of triethylamine (38 mL, 273 mmol), the reaction was warmed to 25 °C, diluted with ether (500 mL), washed with water (2 × 100 mL) and brine (1 × 100 mL), and dried over $MgSO_4$. Silica gel chromatography (30% ether in petroleum ether) afforded aldehyde **51** (8.65 g, 71%): oil; R_f 0.33 (30% ether in petroleum ether); IR (neat) ν_{max} 2940, 2855, 2725, 1728, 1458, 1392, 1359, 1280, 1210, 1140, 1100, 1030, 951, 908, 742, 703 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.43 (t, J = 1.7 Hz, 1 H), 7.28–7.07 (m, 5 H), 4.4–4.13 (AB, J_{AB} = 11.7 Hz, 2 H), 3.65–3.58 (m, 1 H), 3.06–2.83 (m, 3 H), 2.25–2.11 (m, 3 H), 1.94–1.88 (m, 1 H), 1.72–1.64 (m, 1 H), 1.32–1.02 (m, 3 H); HRMS calcd for $C_{15}H_{21}O_3$ (M + H)$^+$ 249.149, found 249.149.

Benzyl [2,3,4,5-Tetrahydro-3-*O*-(benzyloxy)-(2*S*,3*R*)-pyran-2-yl]-3-methyl-3-[(1,1-dimethylethyl)dimethylsiloxy]pentanoate (51a,b). To a cooled (−78 °C) solution of $ZnBr_2$ (2.25 g, 10.0 mmol) in ether (150 mL) was added aldehyde **50** (4.9 g, 20.0 mmol) in ether (50 mL), followed 5 min later by [(benzyloxyethenyl)oxy]-*tert*-butyldimethylsilane (7.9 g, 30 mmol) in ether (50 mL). After 20 min the reaction was quenched with saturated $NaHCO_3$ (50 mL) and warmed to room temperature. The organic layer was separated, washed with H_2O (2 × 50 mL) and brine (1 × 50 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (20% ether in petroleum ether) provided a mixture of benzyl esters **51ab** (4.0 g, 78%): oil; R_f 0.4 (20% ether in petroleum ether); IR (neat) ν_{max} 2960, 2930, 2840, 1740, 1468, 1390, 1362, 1269, 1208, 1165, 1140, 1101, 840, 782, 738, 702 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34–7.2 (m, 10 H), 5.07 (s, 2 H), 4.61–4.40 (AB, J_{AB} = 11.4 Hz, 2 H), 4.15–4.10 (dt, J = 12.3, 6.1 Hz, 1 H), 3.87–3.81 (m, 1 H), 3.32–3.22 (ddd, J = 11.2, 11.2, 3.2 Hz, 1 H), 3.08–3.04 (m, 2 H), 2.47 (d, J = 6.1, 2 H), 2.25–2.21 (m, 1 H), 2.0–1.94 (m, 1 H), 1.74–1.27 (m, 6 H), 0.83 (s, 9 H), 0.03 (s, 3 H), 0.0 (s, 3 H); HRMS calcd for $C_{30}H_{45}O_5Si$ (M + H)$^+$ 513.304, found 513.310.

8-Methyl-2,3,4,4a,7,8,9,10-octahydro-(4a*S*,10a*R*)-pyrano[3,2-*b*]-oxocin-6-one (52a,b). A mixture of compounds **51ab** (13.2 g, 25.8 mmol) and $Pd(OH)_2$ (2.6 g) was stirred together in a solution of EtOAc (65 mL) and MeOH (65 mL) under an atmosphere of H_2 for 3 h. Subsequent to filtration through a pad of Celite, the hydroxy carboxylic acid was concentrated, and residual MeOH was removed by azeotropic distillation with benzene. The resulting viscous oil was stirred with a mixture of dipyridyl disulfide (8.5 g, 38.7 mmol) and triphenylphosphine (10.2 g, 38.7 mmol) in methylene chloride (130 mL) for 30 min. The yellow reaction mixture was concentrated, taken up in toluene (75 mL), and added over a period of 2 h to $AgClO_4$ (5.34 g, 25.8 mmol) in refluxing toluene (2.5 L). After an additional 1.5 h the reaction was concentrated and flash chromatographed (40–60% ether in petroleum ether) to afford **51a** (2.6 g, 32%) and **52b** (3.27 g, 37%). **52a**: R_f 0.5 (40% ether in petroleum ether); IR (neat) ν_{max} 2960, 2865, 1745, 1470, 1378, 1302, 1265, 1229, 1213, 1137, 1125, 1090, 1007, 982, 921, 840, 782 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.23–4.19 (m, 1 H), 3.97–3.95 (m, 1 H), 3.87–3.82 (m, 1 H), 3.31–3.27 (m, 1 H), 3.21–3.15 (m, 1 H), 2.81 (t, J = 11.6 Hz, 1 H), 2.62–2.55 (dd, J = 11.8, 4.9 Hz, 1 H), 2.12–2.08 (m, 1 H), 1.8–1.52 (m, 7 H), 0.80 (s, 9 H), 0.01 (s, 3 H), 0.0 (s, 3 H); HRMS calcd for $C_{16}H_{31}O_4Si$ (M + H)$^+$ 315.199, found 315.195. **52b**: oil; R_f 0.32 (40% ether in petroleum ether); IR (CCl_4) ν_{max} 2940, 2919, 2865, 1742, 1460, 1369, 1351, 1252, 1228, 1131, 1000, 982, 961, 830 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.17–4.10 (m, 2 H), 3.93–3.88 (m, 1 H), 3.39–3.23 (m, 2 H), 2.80–2.57 (ABX, J_{AB} = 12.4 Hz, J_{AX} = 6.4 Hz, J_{BX} = 2.3 Hz, 2 H), 2.15–2.08 (m, 2 H), 1.93–1.49 (m, 6 H), 0.89 (s, 9 H), 0.11 (s, 3 H), 0.06 (s, 3 H); HRMS calcd for $C_{16}H_{31}O_4Si$ (M + H)$^+$ 315.199, found 315.197.

2,3,4,4a,9,10-Hexahydro-(4a*S*,7*Z*,10a*R*)-pyrano[3,2-*b*]oxocin-6-one (13). To solution of lactone **52ab** (1.5 g, 4.7 mmol) in THF (23 mL) contained in a polypropylene reaction vessel at 0 °C was added HF·pyridine (4.7 mL, 1 mL/mmol of substrate). The reaction was warmed to room temperature and stirred 2 h. The HF-py was quenched by dilution with EtOAc (20 mL) and carefully transferred to a separatory funnel containing saturated Na_2CO_3 solution (66.7 mL, 14.2 mL/1 mL of HF-py) and EtOAc (150 mL). Gentle swirling of the separatory funnel was followed by more vigorous agitation. After removal of the aqueous layer the organic layer was washed with aqueous $NaHCO_3$ until the organic solution had a pH of 7. The aqueous washings were back extracted with EtOAc, and the combined organic solutions were dried ($MgSO_4$), filtered, and stripped in vacuo. The resultant alcohols were stirred with a mixture of NEt_3 (13 mL, 9.4 mmol) and methanesulfonyl chloride (0.55 mL, 7.05 mmol) in toluene (0.5 mL) for 30 min. DBU (2 mL, 14 mmol) was then added, and the reaction mixture was heated at 105 °C for 3 h. Subsequent to cooling to room temperature the reaction mixture was diluted with ether (20 mL), washed with H_2O (2 × 5 mL) and brine (5 mL), and dried ($MgSO_4$). Silica gel chromatog-

raphy (60% ether in petroleum ether) provided the α,β-saturated lactone **13** (650 mg, 76%): oil; R_f 0.34 (50% ether in petroleum ether); IR (neat) ν_{max} 2960, 2860, 1730, 1718, 1640, 1448, 1419, 1400, 1280, 1228, 1198, 1150, 1090, 1051, 1027, 958, 931, 912, 831, 800, 777, 625 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.35–6.30 (ddd, J = 12.9, 3.5, 3.4 Hz, 1 H), 5.83–5.76 (ddd, J = 12.9, 1.6, 1.4 Hz, 1 H), 4.38–4.34 (m, 1 H), 3.96–3.90 (m, 1 H), 3.47–3.37 (m, 2 H), 2.54–2.33 (m, 1 H), 2.17–1.6 (m, 7 H); HRMS calcd for $C_{10}H_{15}O_3$ $(M + H)^+$ 183.102, found 183.102.

2,3,4,5-Tetrahydro-2-(2-oxopropyl)-3-*O*-(benzyloxy)-(2*S*,3*R*)-pyran (55). Allyl pyranoside **48** (7.7 g, 33 mmol) was dissolved in a mixture of THF (35 mL) and H_2O (35 mL) to which $Hg(OAc)_2$ (11.2 g, 35 mmol) was added portionwise (3 × 3.73 g) over a 15-min period. After an additional 15 min the reaction was cooled to 0 °C, a 3 M NaOH solution (35 mL) was added followed by a solution of 0.5 M $NaBH_4$ (35 mL) in 3 M NaOH, and stirring was continued for 30 min. NaCl (2 g) was added, the mixture was extracted with ether (3 × 100 mL), and the organic portion was dried ($MgSO_4$), concentrated, and purified by silica gel chromatography (70% ether in petroleum ether) to give a mixture of secondary alcohols **54ab**. To a solution of oxalyl chloride (4.3 mL, 49.5 mmol) in methylene chloride (165 mL) at −78 °C was added DMSO (4.68 mL, 66 mmol) in a dropwise fashion. After 10 min the secondary alcohols **54ab** in CH_2Cl_2 (20 mL) were added dropwise with stirring at −78 °C for 45 min. After the addition of triethylamine (23 mL, 165 mmol), the reaction was warmed to 25 °C, diluted with ether (300 mL), washed with water (2 × 50 mL) and brine (1 × 50 mL), and dried over $MgSO_4$. Filtration, concentration, and flash chromatography gave ketone **55** (6.16 g, 74% for 2 steps): oil; R_f 0.40 (50% ether in petroleum ether); IR (neat) ν_{max} 2955, 2870, 1720, 1505, 1461, 1365, 1320, 1280, 1241, 1220, 1178, 1105, 1037, 1010, 948, 880, 738, 709, 690 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.73–7.26 (m, 5 H), 4.64–4.38 (AB, J_{AB} = 11.5 Hz, 2 H), 3.88–3.82 (m, 1 H), 3.71–3.62 (ddd, J = 8.5, 8.5, 3.6 Hz, 1 H), 3.42–3.31 (ddd, J = 15.5, 11.3 Hz, J_{AX} = 3.6 Hz, 1 H), 3.18–3.08 (ddd, J = 11.6, 9.1, 4.4 Hz, 1 H), 2.93–2.85 (ABX, J_{AB} = 15.5 Hz, J_{AX} = 3.6 Hz, 1 H), 2.54–2.45 (ABX, J_{AB} = 15.5 Hz, J_{AX} = 8.9 Hz, 1 H), 2.32–2.15 (m, 1 H), 2.15 (s, 3 H), 1.69–1.65 (m, 2 H), 1.49–1.40 (m, 1 H); HRMS calcd for $C_{16}H_{21}O_3$ $(M + H)^+$ 249.149, found 249.146.

Benzyl [2,3,4,5-Tetrahydro-3-*O*-(benzyloxy)-(2*S*,3*R*)-pyran-2-yl]-3-methyl-3-*O*-[[(1,1-dimethylethyl)dimethylsilyl]oxy]butanoate (56a,b). To a cooled (−78 °C) solution of $ZnBr_2$ (3.93 g, 17.5 mmol) in ether (350 mL) was added ketone **55** (8.75 g, 35 mmol) in ether (20 mL), followed 5 min later by [(benzyloxyethenyl)oxy]-*tert*-butyldimethylsilane (13.9 g, 52.5 mmol) in ether (20 mL). After 20 min the reaction was quenched with aqueous $NaHCO_3$ (100 mL) and warmed to room temperature. The organic layer was separated, washed with H_2O (2 × 75 mL) and brine (1 × 75 mL), then dried ($MgSO_4$), filtered, and concentrated. Purification by silica gel chromatography (50% ether in petroleum ether) gave the desired aldol products **56ab** (15.7 g, 88%): R_f 0.45 and 0.50 (80% ether in petroleum ether); IR (neat) ν_{max} 2940, 2855, 1790, 1500, 1459, 1382, 1364, 1230, 1130, 1100, 1030, 839, 780, 750, 700, 682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.3–7.19 (m, 10 H), 5.09–4.93 (m, 2 H), 4.58–4.34 (m, 1 H), 3.71–3.65 (m, 1 H), 3.4–3.14 (m, 2 H), 3.02–2.94 (m, 1 H), 2.66–2.51 (m, 2 H), 2.25–2.11 (m, 2 H), 1.77–1.50 (m, 5 H), 1.39 (s, 3 H), 0.78 (s, 9 H), 0.01 (s, 6 H); HRMS calcd for $C_{30}H_{45}O_5Si$ $(M + H)^+$ 513.304, found 513.300.

8-Methyl-8-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-2,3,4,4a,7,8,9,9a-octahydro-(4a*S*,9a*R*)-pyrano[3,2-*b*]oxepan-6-one (10). A mixture of compounds **56a** and **56b** (15.4 g, 30 mmol) and $Pd(OH)_2$ (2.7 g) in MeOH (150 mL) was stirred under an atmosphere of H_2 for 2 h. Subsequent to filtration through a pad of Celite the hydroxy carboxylic acid was concentrated and subjected to azeotropic distillation with benzene to remove residual MeOH. The resulting viscous oil was stirred with a mixture of dipyridyl disulfide (9.9 g, 40.1 mmol) and PPh_3 (11.8 g, 45 mmol) in THF (150 mL) for 30 min. The yellow reaction mixture was concentrated, taken up in benzene (50 mL), and added over a period of 2 h to $AgClO_4$ (8.0 g, 39 mmol) in refluxing benzene (300 mL). After an additional 1 h the reaction was concentrated and flash chromatographed (30% followed by 50% ether in petroleum ether) to yield **10a** (3.1 g, 33%) and **10b** (2.8 g, 30%). **10a**: solid, mp = 97 °C; R_f = 0.59 (50% ether in petroleum ether); IR (CCl_4) ν_{max} 2975, 2943, 2878, 1754, 1478, 1397, 1320, 1260, 1145, 1100, 1065, 1030, 942, 888, 848, 702 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 3.97–3.94 (m, 1 H), 3.79–3.74 (m, 1 H), 3.20–3.10 (m, 2 H), 2.93–2.56 (ABX, J_{AB} = 13.5 Hz, J_{AX} = 2.6 Hz, J_{BX} = 0.0 Hz, 2 H), 2.19–2.11 (m, 2 H), 1.82–1.73 (m, 1 H), 1.62–1.51 (m, 3 H), 1.24 (s, 3 H), 0.72 (s, 9 H), 0.0 (s, 6 H); HRMS calcd for $C_{16}H_{31}O_4Si$ $(M + H)^+$ 315.199, found 315.201. **10b**: solid, mp = 121 °C; R_f 0.24 (50% ether in petroleum ether); IR (CCl_4) ν_{max} 2960, 2940, 2865, 1754, 1380, 1312, 1287, 1261, 1242, 1227, 1178, 1139, 1118, 1090, 1068, 1032, 919, 849 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.01–3.89 (m, 1 H), 3.8–3.74 (m, 1 H), 3.52–3.38 (m, 1 H), 3.27–3.15 (m, 1 H), 2.82–2.62 (ABX, J_{AB} = 13.5 Hz, J_{AX} = 5.4 Hz, J_{BX} = 0.0 Hz, 2 H), 2.18–2.10 (m, 2 H), 1.7–1.5 (m, 4 H), 1.32 (s, 3 H), 0.81 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H); HRMS calcd for $C_{16}H_{31}O_4Si$ $(M + H)^+$ 315.199, found 315.201.

8-Methyl-2,3,4,4a,9,9a-hexahydro-(4a*S*,7*Z*,9a*R*)-pyrano[3,2-*b*]oxepan-6-one (11). To a solution of lactone **10a** (or **10b**) (7.5 g, 23 mmol) in THF (30 mL) contained in a polypropylene reaction vessel at 0 °C was added HF·pyridine (30 mL, 1 mL/1 mmol of substrate). The reaction mixture was warmed to room temperature and stirred for 2 h. The HF-py was quenched by dilution with EtOAc (50 mL) and careful transfer into a separatory funnel containing saturated Na_2CO_3 (146 mL, 14.2 mL/1 mL of HF·py) and EtOAc (300 mL). Gentle swirling of the separatory funnel was followed by more vigorous agitation. After removal of the aqueous layer the organic layer was washed with additional aqueous $NaHCO_3$ until the organic solution had a pH of 7. The aqueous washings were back extracted with EtOAc, and the combined organic solutions were dried ($MgSO_4$) and stripped in vacuo. The resultant alcohols were taken up in a 5:1 benzene/methylene chloride (120 mL) solution and cooled to 0 °C. Triethylamine (9.6 mL, 969 mmol) was added to the reaction followed by methanesulfonyl chloride (3.6 mL, 46 mmol). Stirring was continued at 0 °C for 20 min and then at 25 °C for an additional 30 min. DBU (9.7 mL, 69 mmol) was then added, and the reaction was warmed to 45 °C for 1 h. The reaction mixture was diluted with ether (400 mL) and then washed with H_2O (2 × 100 mL) and brine (1 × 100 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated, and the resulting oil was stirred with a mixture of NEt_3 (3.2 mL, 23 mmmol) and $ZnCl_2$ (3.1 g, 23 mmol) in CH_2Cl_2 (50 mL) for 2 h. The reaction mixture was concentrated and subjected to silica gel chromatography (60% ether in petroleum ether) providing α,β-unsaturated lactone **11** (2.76 g, 66%): oil; R_f 0.42 (80% ether in petroleum ether); IR (neat) ν_{max} 2960, 2865, 1730, 1650, 1449, 1387, 1320, 1275, 1200, 1132, 1073, 1050, 980, 940, 875, 858, 795, 730, 708 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.87–5.85 (q, J = 1.4 Hz, 1 H), 4.17–4.13 (m, 1 H), 3.93–3.87 (m, 1 H), 3.65–3.56 (dd, J = 7.8, 7.8, 4.0, 1 H), 3.42–3.36 (m, 1 H), 2.93–2.89 (m, 1 H), 2.33–2.24 (m, 1 H), 1.98 (s, 3 H), 1.79–1.70 (m, 4 H); HRMS calcd for $C_{10}H_{15}O_3$ $(M + H)^+$ 183.102, found 183.101.

***tert*-Butyl [6-(Methylthio)-2,3,4,4a,9,10-hexahydro-(4a*S*,7*Z*,10a*R*)-pyrano[3,2-*b*]oxocin-6-yl]ethanoate (58).** A 0.67 M solution of [(*tert*-butoxyethenyl)oxy]lithium was prepared by adding ^{t}BuOAc (1.4 mL, 10.0 mmol) to a 0.73 M solution of LDA (13.6 mL, 10.0 mmol) in THF at −78 °C and stirring for 15 min. To thiolactone **13a** (200 mg, 1.0 mmol) in THF (10 mL) cooled to −78 °C was added dropwise the enolate solution (2.1 mL, 1.4 mmol) described above. After 15 min, MeI (0.12 mL, 2.0 mmol) was added, and stirring was continued for an additional 15 min. The reaction mixture was then diluted with ether (50 mL), washed with brine (1 × 10 mL), and dried over Na_2SO_4. Silica gel chromatography (10% ether in petroleum ether) gave monothioketal **58** (246 mg, 77%): oil; R_f 0.37 (20% ether in petroleum ether); IR (neat) ν_{max} 2980, 2935, 1731, 1655, 1487, 1460, 1399, 1370, 1323, 1279, 1255, 1218, 1165, 1129, 1100, 1032, 958, 940, 921, 860, 801, 770, 682 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.2–6.15 (m, 1 H), 5.69–5.64 (m, 1 H), 3.65–3.61 (m, 1 H), 3.41–3.34 (m, 1 H), 3.14–2.93 (m, 2 H), 2.59 (s, 2 H), 2.1 (s, 3 H), 2.0–1.93 (m, 1 H), 1.72–1.11 (m, 7 H), 1.41 (s, 9 H); HRMS calcd for $C_{17}H_{29}O_4S$ $(M + H)^+$ 329.179, found 329.184.

***tert*-Butyl [2,3,4,4a,9,10-Hexahydro-(4a*S*,6*Z*,10a*R*)-pyrano[3,2-*b*]-oxocin-6-yl]ethanoate (59).** A mixture of monothioketal **58** (1.1 g, 3.35 mmol), Ph_3SnH (1.7 mL, 6.70 mmol), and AIBN (20 mg) in toluene (33.5 mL) was heated at reflux for 0.5 h. The reaction mixture was then concentrated and subjected to silica gel chromatography (10% ether in benzene) to afford vinyl ether **59** (793 mg, 84%): oil; R_f 0.37 (10% ether in benzene); IR (neat) ν_{max} 2940, 2860, 1730, 1683, 1451, 1398, 1370, 1340, 1257, 1150, 1092, 1070, 1050, 1027, 990, 960, 949, 921, 850, 739, 651 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.85–4.79 (dd, J = 8.6, 6.6 Hz, 1 H), 3.84–3.79 (m, 1 H), 3.5–3.4 (m, 1 H), 3.29–3.22 (m, 1 H), 3.14–3.07 (m, 1 H), 3.04–2.86 (AB, J_{AB} = 15.1 Hz, 2 H), 2.37–2.33 (m, 1 H), 2.04–1.94 (m, 2 H), 1.79–1.46 (m, 7 H), 1.41 (s, 9 H); HRMS calcd for $C_{16}H_{27}O_4$ $(M + H)^+$ 283.191, found 283.188.

[2,3,4,4a,9,10-Hexahydro-(4a*S*,6*Z*,10a*R*)-pyrano[3,2-*b*]oxocin-6-yl]ethanol (60). To *tert*-butyl ester **59** (950 mg, 3.3 mmol) in THF (16.5 mL) at 25 °C was added a 1 M solution of $LiEt_3BH$ in THF (11.5 mL, 11.5 mmol), and stirring was continued at that temperature for 1 h. The excess hydride was quenched with water (3 mL), the reaction mixture was diluted with ether (60 mL), and the organic layer was separated and dried over $MgSO_4$. Silica gel chromatography (70% ether in petroleum ether) provided primary alcohol **60** (500 mg, 71%): oil; R_f 0.25 (60% ether in petroleum ether); IR (neat) ν_{max} 3450, 2940, 2860, 1678, 1660, 1450, 1410, 1340, 1291, 1221, 1158, 1132, 1095, 1070, 1050, 1030, 989, 949, 800, 688 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.89–4.83 (dd, J = 8.5, 6.6 Hz, 1 H), 4.0–3.3 (m, 3 H), 3.5–3.1 (m, 3 H), 2.5–2.2 (m, 3 H),

2.2–1.9 (m, 3 H), 1.8–1.5 (m, 7 H); HRMS calcd for $C_{12}H_{21}O_3$ (M + H)$^+$ 213.149, found 213.145.

2-*O*-Benzyl-[2,3,4,4a,9,10-hexahydro-(4a*S*,6*Z*,10a*R*)-pyrano[3,2-*b*]-oxocin-6-yl]ethanol (61). A solution of compound **60** (500 mg, 2.0 mmol) in THF (1.5 mL) was added dropwise to a suspension of 35% KH in oil (340 mg, 3.0 mmol) in THF (10 mL). The ice bath was removed, and the reaction mixture was stirred at room temperature for 1.5 h before the addition of benzyl bromide (0.36 mL, 3.0 mmol) and subsequent heating to 55 °C for 3 h. After cooling to room temperature the reaction was quenched with MeOH (1.5 mL), diluted with ether (50 mL), washed with H_2O (10 mL), and dried with $MgSO_4$. Silica gel chromatography (15% ether in petroleum ether) afforded benzyl ether **61** (556 mg, 92%): oil; R_f 0.44 (20% ether in petroleum ether); IR (neat) ν_{max} 2942, 2860, 1683, 1661, 1459, 1364, 1320, 1290, 1215, 1158, 1097, 1030, 989, 913, 800, 737, 701 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5 H), 4.84–4.78 (dd, J = 7.6, 7.6 Hz, 1 H), 4.53 (s, 2 H), 3.89–3.85 (m, 1 H), 3.63–3.57 (td, J = 7.5, 1.5 Hz, 2 H), 3.4–3.14 (m, 3 H), 2.44–2.38 (m, 2 H), 2.18–1.52 (m, 10 H); HRMS calcd for $C_{19}H_{27}O_3$ (M + H)$^+$ 303.196, found 303.192.

2-*O*-Benzyl-[7-hydroxy-2,3,4,4a,7,8,9,10-octahydro-(4a*S*,10a*R*)-pyrano[3,2-*b*]oxocin-6-yl]ethanol (62, 63). A solution of vinyl ether **61** (600 mg, 2.0 mmol) in THF (6.6 mL) was subjected a 1 M BH_3–THF solution (2 mL, 2.0 mmol) at 0 °C for 30 min. To this was added an aqueous 3 N NaOH solution (3 mL, 9 mmol), followed immediately by an aqueous 30% solution of H_2O_2 (1 mL, 9 mmol). The ice bath was removed, and stirring was continued for 1 h prior to diluting with ether (60 mL), washing with H_2O (2 × 15 mL) and brine (15 mL), and drying ($MgSO_4$). Silica gel chromatography (80% ether in petroleum ether) afforded a 4:1 mixture of alcohols **62** and **63** (557 mg, 87%): IR (neat) ν_{max} 3450, 2935, 2833, 1458, 1370, 1277, 1212, 1100, 1032, 989, 913, 738, 702, 782, 750 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.43–7.31 (m, 5 H), 4.61–4.45 (AB, J_{AB} = 15.2 Hz, 2 H), 3.89–3.77 (m, 1 H), 3.70–3.46 (m, 4 H), 3.42–3.0 (m, 3 H), 2.78 (br s, 1 H), 2.1–1.2 (m, 12 H); HRMS calcd for $C_{19}H_{29}O_4$ (M + H)$^+$ 321.207, found 321.205.

8-Methyl-2,3,4,4a,7,8,9,9a-octahydro-(4a*S*,9a*R*)-pyrano[3,2-*b*]oxepan-6-one (12). A mixture of unsaturated lactone **11** (446 mg, 2.45 mmol) and 10% Pd/C (90 mg, 20% by wt) was stirred together in THF (10 mL) under an atmosphere of H_2 for 30 min. Subsequent to purging with argon the reaction mixture was filtered through a pad of Celite yielding after concentration lactone **12** (428 mg, 95%) homogeneous by spectroscopic analysis: solid; mp 84 °C; R_f 0.51 (50% ether in petroleum ether); IR (CCl_4) ν_{max} 2980, 2940, 2870, 1750, 1470, 1448, 1390, 1357, 1268, 1210, 1179, 1126, 1108, 1092, 1068, 1030, 957 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.09–3.9 (m, 1 H), 3.88–3.85 (m, 1 H), 3.47–3.27 (m, 2 H), 2.87–2.80 (dd, J = 14.0, 2.6 Hz, 1 H), 2.71–2.56 (ddd, J = 14.0, 6.3, 1.6 Hz, 1 H), 2.3 (m, 2 H), 2.11–2.02 (m, 1 H), 1.8–1.62 (m, 4 H), 1.1 (d, J = 7.3 Hz, 3 H); HRMS calcd for $C_{10}H_{17}O_3$ (M + H)$^+$ 185.118, found 185.117.

8-Methyl-6-(tributylstannyl)-2,3,4,4a,8,9-hexahydro-(4a*S*,6*Z*,8*S*,9a*R*)-pyrano[3,2-*b*]oxepane (64). To a solution of diisopropylamine (88 μL, 0.63 mmol) in THF (1.4 mL) at −10 °C was added *n*-BuLi (71 μL, 0.57 mmol) in hexane followed 15 min later by the addition of tributyltin hydride (153 μL, 0.63 mmol). After stirring for 10 min at −10 °C, the solution of tributyltin lithium was cooled to −78 °C, and thionolactone **12a** (76 mg, 0.38 mmol) in THF (0.5 mL) was added. After an additional 10 min, diiodobutane (0.5 mL, 3.8 mmol) was added followed immediately by the addition of 2,6-lutidine (88 μL, 0.76 mmol). The cold bath was removed, and the reaction was stirred at room temperature for 2 h. The reaction mixture was then diluted with ether (60 mL), washed with H_2O (3 × 10 mL) and brine (1 × 10 mL), and dried ($MgSO_4$). Silica gel chromatography (5% ether in petroleum ether) afforded **64** (129 mg, 75%): oil; R_f 0.66 (10% ether in petroleum ether); IR (neat) ν_{max} 2970, 2930, 2880, 2860, 1605, 1470, 1382, 1345, 1328, 1300, 1291, 1232, 1152, 1130, 1095, 1079, 1060, 1021, 1010, 973, 870, 853, 788, 699, 670 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.50 (q, J = 1.1 Hz, 1 H), 3.92–3.74 (m, 3 H), 3.41–3.29 (m, 3 H), 2.83–2.72 (m, 1 H), 2.06–1.95 (m, 2 H), 1.68–1.24 (m, 16 H), 1.06–0.75 (m, 16 H); elemental anal. calcd for $C_{22}H_{42}O_2Sn$: C, 57.41; H, 9.24. Found: C, 57.80; H, 9.26.

2-*O*-Benzyl-[8-methyl-2,3,4,4a,8,9-hexahydro-(4a*S*,6*Z*,8*S*,9a*R*)-pyrano[3,2-*b*]oxepan-6-yl]ethanol (65). To a cooled (−78 °C) solution of vinylstannane **64** (127 mg, 0.28 mmol) in THF (5 mL) was added a 1.6 M solution of *n*-BuLi in hexane (0.26 mL, 0.42 mmol). After 5 min, HMPA (0.6 mL) was added, followed immediately by the addition of benzyloxyethyl triflate (159 mg, 0.56 mmol) in hexane 2.5 mL (2:1 THF/hex). After an additional 30 min triethylamine (0.2 mL) was added, the reaction was brought to room temperature, and stirring was continued for another 30 min to ensure that the excess triflate had been consumed by the triethylamine. Dilution with ether (60 mL) was followed by washing with water (5 × 10 mL) and brine (1 × 10 mL) and drying ($MgSO_4$). Silica gel chromatography (10% ether in petroleum ether) afforded vinyl ether **65** (51 mg, 60%): oil; R_f 0.51 (20% ether in petroleum ether); IR (neat) ν_{max} 2960, 2940, 2840, 1671, 1459, 1370, 1372, 1341, 1319, 1308, 1291, 1278, 1225, 1200, 1178, 1095, 1035, 1021, 973, 920, 878, 788, 730, 703 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5 H), 4.57–4.45 (AB, J_{AB} = 12.2 Hz, 2 H), 4.45 (d, J = 2.3 Hz, 1 H), 3.91–3.86 (m, 1 H), 3.83–3.73 (m, 2 H), 3.65–3.51 (m, 2 H), 3.40–3.31 (m, 2 H), 2.8–2.6 (m, 1 H), 2.30–2.25 (t, J = 6.4 Hz, 2 H), 2.1–1.89 (m, 2 H), 1.73–1.5 (m, 3 H), 0.98 (d, J = 7.2 Hz, 3 H); HRMS calcd for $C_{19}H_{27}O_3$ (M + H)$^+$ 303.196, found 303.200.

2-*O*-Benzyl-[7-hydroxy-8-methyl-2,3,4,4a,8,9-hexahydro-(4a*S*,8*S*,9a*R*)-pyrano[3,2-*b*]oxepan-6-yl]ethanol (66). A solution of vinyl ether **64** (42 mg, 0.14 mmol) in THF (1.4 mL) was treated with a 1 M solution of BH_3–THF in THF (0.28 mL, 0.28 mmol) at 0 °C for 30 min. To this was then added aqueous 3 N NaOH (0.32 mL, 1 mmol), followed immediately by a 30% aqueous H_2O_2 solution (0.07 mL, 1 mmol). The ice bath was removed, and stirring was continued for 1 h prior to diluting with ether (30 mL), washing with water (3 × 5 mL) and brine (1 × 5 mL), drying over $MgSO_4$. Silica gel chromatography (70% ether in petroleum ether) provided a 13:1 ratio (determined by isolation of respective benzoates) of two diastereomers (38 mg, 85%), the major product being benzyl ether **66**: oil; R_f 0.37 (80% ether in petroleum ether); IR (neat) ν_{max} 3450, 2939, 2875, 1460, 1370, 1278, 1219, 1155, 1100, 1032, 970, 958, 922, 740, 705 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5 H), 4.58–4.43 (AB, J_{AB} = 11.9 Hz, 2 H), 3.88–3.83 (m, 1 H), 3.65–3.60 (m, 2 H), 3.51–3.44 (ddd, J = 8.0, 8.0, 3.6 Hz, 1 H), 3.43–3.23 (m, 3 H), 2.7 (br s, 1 H), 2.08–1.16 (m, 10 H), 1.12 (d, J = 7.0 Hz, 3 H); HRMS calcd for $C_{19}H_{29}O_4$ (M + H)$^+$ 321.207, found 321.210.

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Supplementary Material Available: Experimental procedures and selected physical properties for compounds **5–9** and **69–80** and X-ray crystallographic data for compounds **31** and **62-p-Br-Bz** and **66a** (31 pages). Ordering information is given on any current masthead page.