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The Synthesis of 14-Membered Macrocyclic Ethers

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Abstract: *As part of an ongoing study of the chemistry of macrocyclic compounds, 14-membered macrocyclic ethers with a variety of methyl substitution patterns were synthesized. The preparation of these macrocyclic ethers involved either the Baeyer-Villiger ring expansion of a cyclic ketone, or the macrolactonization of a hydroxy acid to give a lactone. The lactone carbonyl was removed either by conversion to an intermediate thionolactone obtained by reaction with Lawesson's reagent and reduction, or by direct reduction using a boron trifluoride etherate mediated sodium borohydride reaction.* © 1999 Elsevier Science Ltd. All rights reserved.

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INTRODUCTION

The synthesis of macrocyclic crown ethers is well documented,[1] and recently there has been a great deal of interest in the synthesis of medium ring ethers due in part to the structure and biological activity of brevetoxin and related compounds.[2] However, the synthesis of simple macrocyclic ethers has not been extensively studied. Dale has suggested that replacing a methylene unit of a macrocyclic ring with an ether oxygen should have a minimal perturbation on the macrocyclic system.[3] Although he did predict that the oxygen should occupy a position in the conformation of such rings that leads to a reduction in transannular C-H interactions. For some time we have been interested in the synthesis, conformational analysis, and reactivity of simple macrocyclic compounds with the goal of developing a conformational model to rationalize the physical and chemical properties of these compounds. Here we report the first detailed study of the synthesis of 14-membered ring mono-ethers shown in Figure 1.

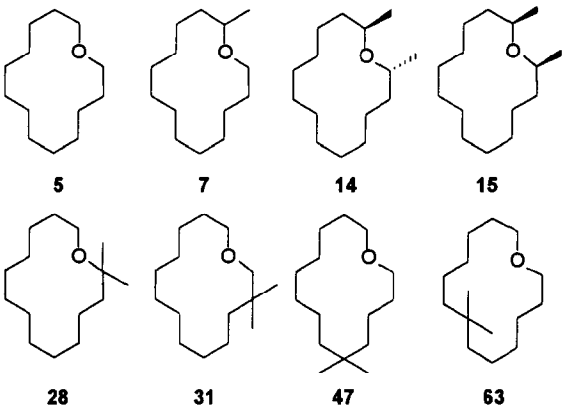

Figure 1. Macrocyclic ethers prepared in this study.

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A number of synthetic methods have been developed for the preparation of cyclic ethers, and these can be grouped into two general strategies. The first involves an intramolecular cyclization to form the cyclic ether. Such a cyclization at the ether oxygen was found to be difficult to carry out successfully in large rings. A study of the cyclization of a series of bromo alcohols using a variety of base and solvent combinations in our laboratory met with limited success in the production of the desired 14-membered macrocyclic ethers.[4] An alternative to cyclization at the ether oxygen is cyclization via a carbon-carbon bond forming process. The ring closing metathesis reaction[5] has been successfully applied to the preparation of small- and medium-sized cyclic ethers.[6] In addition, radical cyclization has been used to synthesize macrocyclic polyethers with an endocyclic or exocyclic ester.[7]

The second strategy involves the modification of an existing ring, such as a lactone, to give the cyclic ether. Macrocyclic lactones are readily available via a variety of methods,[8] and can be viewed as precursors to macrocyclic ethers where the issue of ring closure has already been solved. The problem of cyclic ether synthesis is thereby reduced to converting a lactone into the desired cyclic ether. Tsurugi and coworkers have prepared cyclic ethers from γ, δ, and ε lactones via γ or uv radiation induced trichlorosilane reduction under free radical conditions.[9] Dias and Pettit have reduced lactones to cyclic ethers directly using a mixture of sodium borohydride and boron trifluoride etherate.[10] Alkyl substituents adjacent to the ether oxygen can be introduced by reaction of a lactone with the Tebbe reagent.[11] The resultant exocyclic olefin can subsequently be reduced to give an α-methyl group, or further modified to give other substituents. For example, a hydroboration-oxidation sequence on such an exocyclic enol ether was used in the syntheses of C-2 substituted cyclic ethers from the alga *Laurencia*.[12]

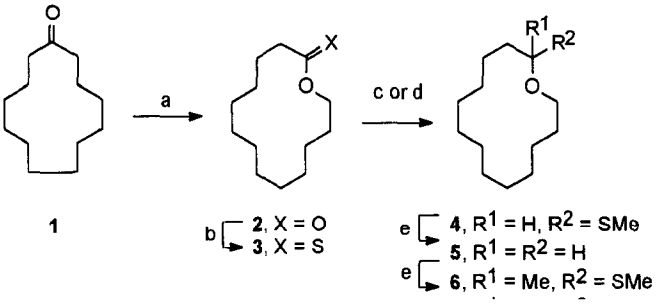
The transformation of a lactone into a thionolactone and subsequent reduction represents another approach to macrocyclic ethers. A dithiodiphosphetane disulfide, such as Lawesson's reagent, has been shown to effect thionation of most simple lactones in good yield.[13] The direct nucleophilic attack on the carbonyl of a lactone generally results in ring fission due to the instability of the initially formed tetrahedral intermediate. However, the analogous tetrahedral intermediate derived from the attack on a thionolactone, is stable at low temperature and undergoes *S*-alkylation to give a mixed thioketal. Reductive desulfurization of this mixed thioketal with tin hydride gives a cyclic ether.[14]

RESULTS AND DISCUSSION

The synthetic strategy that was first explored for the preparation of the macrocyclic ethers in this study involved the ring expansion of a cyclic ketone to the corresponding lactone. The lactone functionality would be used to introduce substituents in the vicinity of the ether oxygen, and the carbonyl would then be removed to give the macrocyclic ether. This strategy should allow for the preparation of a variety of macrocyclic ethers as the result of variations in the substitution pattern of the ketone and lactone from the alkylation reactions, and the nucleophile used.

The macrocyclic ethers **5** and **7** were prepared via the Baeyer-Villiger oxidation of cyclotridecanone (**1**) to give 13-tridecanolide (**2**) (Scheme 1). The trifluoroperoxyacetic acid was generated by the addition of either 70% H_2O_2 solution or solid urea hydrogen peroxide (UHP)[15] to a solution of trifluoroacetic anhydride (TFAA) in CH_2Cl_2. The UHP method usually gave higher yields of the desired lactone.[16] In addition the UHP reaction was easier to perform since the Na_2HPO_4 buffer tended to form a difficult to stir paste with the water present in the 70% H_2O_2 solution. Lactone **2** was converted into thionolactone **3** with Lawesson's reagent. The ^{13}C NMR spectrum of the resultant oil contained a signal at 224.66 ppm for the C-1 thionocarbonyl. Reaction of the thionocarbonyl of **3** with lithium triethylborohydride and trapping of the resultant thiolate with methyl iodide gave the mixed thioacetal **4**. Reaction of **3** with methyllithium and trapping with methyl iodide produced the mixed thioketal **6**.[14] These monothioketals were reduced immediately with tri(*n*-butyl)tin hydride to give the macrocyclic ethers **5** and **7** respectively.

The ^{1}H NMR spectrum of **5** at rt contained a four-proton triplet at 3.41 ppm for the alpha protons, and a four-proton quintet at 1.57 ppm for the beta protons. The ^{13}C NMR spectrum of **5** contained seven signals. The simplicity of these spectra indicates that **5** is undergoing rapid conformational interconversion on the NMR



Scheme 1[a]

[a]Key: (a) UHP, TFAA, Na_2HPO_4, CH_2Cl_2, 0 °C, 96%; (b) Lawesson's reagent, toluene, Δ, 73%; (c) $LiEt_3BH$, THF, -78 °C; then MeI, 91%; (d) MeLi, THF, -78 °C; then MeI, 90%; (e) *n*-Bu_3SnH, AIBN, toluene, Δ, 43% (**5**) or 63% (**7**).

timescale, giving an averaged conformation with a plane of symmetry. The ^{1}H NMR spectrum of **7** at rt contained signals at 3.61, 3.43 and 3.22 ppm for the C-2 methine and C-14 methylene protons, and a three-proton doublet at 1.09 ppm for the C-15 methyl group. The three low-field protons were assigned from ^{1}H COSY and ^{1}H NOE difference experiments. A correlation between the signals at 3.61 ppm and 3.22 ppm in the COSY led to their assignment to the C-14 methylene protons. Irradiation of the H-14 signal at 3.22 ppm showed an enhancement of the *syn* disposed H-2 proton signal at 3.43 ppm, and of the geminal H-14 signal at 3.61 ppm (Figure 2). The ^{13}C NMR spectrum of **7** contained 14 lines, two of which were at low field.

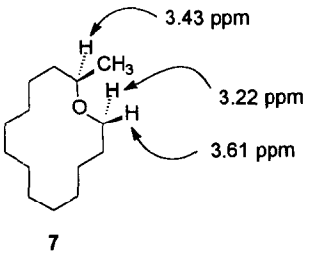
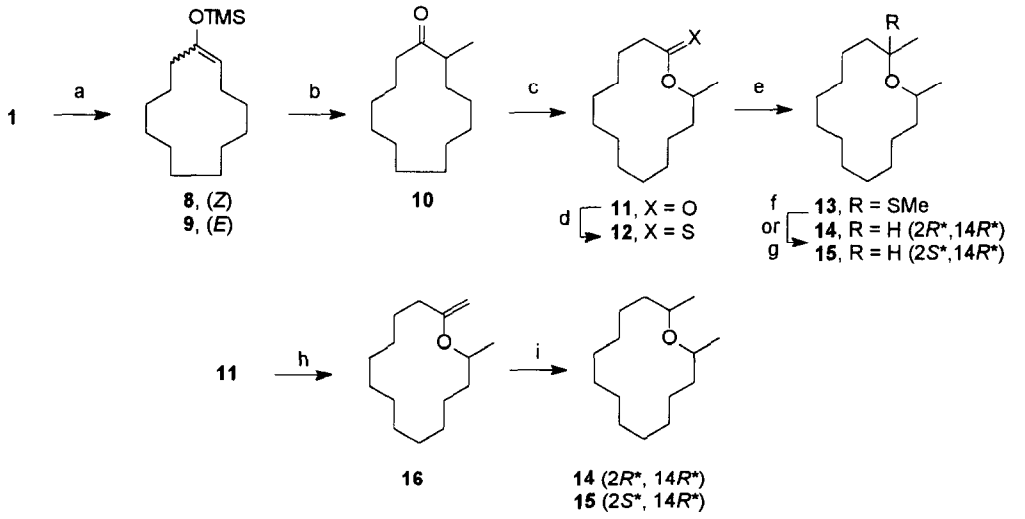


Figure 2. Selected ^{1}H NMR assignments of **7** from COSY and NOEDS experiments.

The C-2 methyl group of the diastereomeric pair of macrocyclic ethers **14** and **15** was introduced onto a macrocyclic ketone prior to the Baeyer-Villiger reaction. Thereafter, the synthetic strategy was the same as that employed for the synthesis of **5**. The preparation of 2-methylcyclotridecanone (**10**) featuring a combination ring expansion-alkylation reaction of cyclododecanone via a modification of the Yamamoto procedure[17] was abandoned due to low yields of the desired ketone. In a second route, **1** was reacted with hexamethyldisilazane and a mixture of trimethylsilyl chloride and lithium iodide[18] to give a separable mixture of the trimethylsilyl enol ethers **8** and **9**. These isomers were identified from their ^{13}C NMR spectra.[19] In general, the chemical shift for

C-1 of the *Z* isomer is shifted upfield relative to that of the *E* isomer, and the chemical shift for C-13, the allylic carbon, is shifted downfield for the *Z* isomer relative to the *E* isomer. The major enol ether **8** was assigned the *Z* configuration based on chemical shifts of 150.17 ppm and 36.11 ppm for C-1 and C-13 compared to chemical shifts of 151.70 ppm and 29.48 ppm for C-1 and C-13 of **9**, the *E* isomer. A mixture of **8** and **9** was reacted with an aliquot of a solution of methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR)[20] and subsequently alkylated with methyl triflate to give ketone **10** (Scheme 2). The ^{1}H NMR spectrum of **10** contained a signal at 2.60 ppm for the C-2 methine proton, as well as a three-proton doublet at 1.01 ppm for the C-14 methyl group, which indicated that the desired transformation had occurred.



Scheme 2[a]

[a]Key: (a) $(TMS)_2NH$, TMSCl, LiI, CH_2Cl_2; then Et_3N, 72%; (b) MABR, MeOTf, CH_2Cl_2, -40 °C, 79%; (c) UHP, TFAA, Na_2HPO_4, CH_2Cl_2, 0 °C, 97%; (d) Lawesson's reagent, toluene, Δ, 77%; (e) MeLi, THF, -78 °C; then MeI, 80%; (f) *n*-Bu_3SnH, AIBN, toluene, Δ, 21%; (g) TTMSH, AIBN, toluene, Δ, 43%; (h) Tebbe reagent, DMAP, pyridine, THF, -40 °C, 86%; (i) PtO_2, H_2, Et_2O, 26%.

Baeyer-Villiger oxidation of ketone **10** gave 13-tetradecanolide (**11**) that was converted into the thionolactone **12**. The ^{1}H NMR spectrum of **12** contained a one-proton signal at 5.62 ppm for the C-13 methine and a three-proton doublet at 1.30 ppm for the C-14 methyl group, which demonstrated that the Baeyer-Villiger reaction proceeded with the expected regioselectivity. The thionolactone **12** was reacted with methyllithium and trapping of the resultant thiolate gave the mixed thioketal **13**. This material was immediately reduced with either tri(*n*-butyl)tin hydride, or tris(trimethylsilyl)silane (TTMSH),[21] to give the desired macrocyclic ethers **14** and **15**. The four-step reaction sequence proceeded in modest yield and low diastereoselectivity (Table 1). Reaction of pure **14** and **15** with tri(*n*-butyl)tin hydride under radical conditions showed no isomerization to the other macrocyclic ether. Therefore it was concluded that the macrocyclic ethers did not equilibrate during the reduction of the mixed thioketal, and the low diastereoselectivity is ascribed to the high reactivity of the conformationally mobile radical intermediate.

In an alternative synthesis of ethers **14** and **15**, a solution of Tebbe reagent[22] was reacted with lactone **11** to give the unstable vinyl ether **16** (Scheme 2). The vinyl ether **16** was hydrogenated with Adams' catalyst to give the macrocyclic ethers **14** and **15** again with essentially no diastereoselectivity (Table 1). The reaction

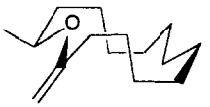
sequence proceeded in 22% yield from **11**. The vinyl ether **16** was very susceptible to hydrolysis and the choice of platinum oxide as the catalyst was important for the success of the reduction. Palladium on charcoal or rhodium on alumina gave lower yields of the desired macrocycles presumably due to hydrolysis of the starting material during the hydrogenation.

Table 1. Yield and Selectivity in the Preparation of **14** and **15**

Reagent	Starting Material	**14**:**15**[b]	Yield **14**+**15** (%)
n-Bu_3SnH, AIBN[a]	**13**	52:48	21[c]
TTMSH, AIBN	**13**	57:43	43[d]
PtO_2, H_2	**16**	49:51	26[e]

[a] A syringe pump was used to slowly add the solution of tri(*n*-butyl)tin hydride and AIBN in toluene to the reaction solution. [b] The ratio of **14**:**15** was determined by gas chromatography. [c] The diastereomers **14** and **15** were separated via radial chromatography. [d] The diastereomers **14** and **15** were purified but not separated.

Molecular modeling calculations with the MM3* force field, which is based on the MM3 force field developed by Allinger and coworkers,[23] suggested that the most stable conformation of **16** is the [3434] conformation shown below, with the exocyclic double bond close to perpendicular to the plane of the ring. The next lowest energy conformation was 1.84 kcal/mol higher in energy. As essentially no diastereoselectivity was observed in this reduction, the *exo*-face of the double bond must be blocked by the C-14 methyl group to approximately the same degree as the macrocyclic ring blocks the *endo*-face.



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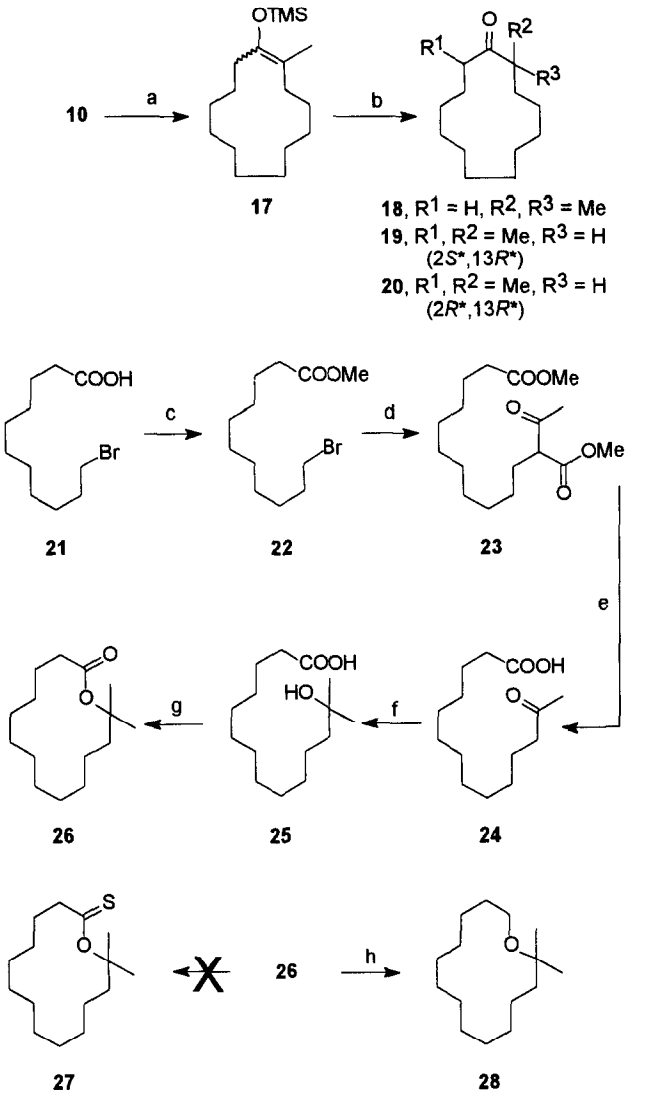
The macrocyclic ethers **14** and **15** were separable on silica chromatography, and each gave a single, distinct peak on GC analysis with a DB-210 column. The relative configuration of the C-2 and C-14 methyl substituents of **14** and **15** was determined through GC analysis with a chiral Cyclodex-B column. The macrocyclic ether **14**, which gave two peaks on the chiral GC column, was identified as the diastereomer with the methyl groups in an *anti* configuration (2*R**,14*R**) and the more polar macrocyclic ether **15** was identified as the meso compound with the methyl groups having the *syn* configuration (2*S**,14*R**).

The ^1H NMR spectrum of **14** at rt contained a two-proton sextet at 3.65 ppm for the alpha protons, a two-proton sextet at 1.63 ppm for two of the beta protons, and a six-proton doublet at 1.08 ppm for the C-15 and C-16 methyl groups. The ^{13}C NMR spectrum contained seven lines indicative of symmetry in the molecule. The ^1H NMR spectrum of **15** at rt contained a two-proton signal at 3.54 ppm for the alpha protons, and a six-proton doublet at 1.10 ppm for the C-15 and C-16 methyl groups. The ^{13}C NMR spectrum contained eight signals for this 15-carbon molecule, indicative of a symmetry-averaged plane of symmetry at rt.

Dale has shown that incorporation of a *gem*-dimethyl group restricts the conformations of macrocyclic rings and the *gem*-dimethyl group is usually located on a "corner" position.[24] Hence we were interested in synthesizing 14-membered ethers with *gem*-dimethyl substitution. Our first attempt at the synthesis of macrocyclic ether **28** involved a Baeyer-Villiger oxidation of the 2,2-dialkylated ketone. Thus ketone **18** was prepared via a two-step sequence starting with ketone **10** and proceeding through the trimethylsilyl enol ether **17** (Scheme 3).[18] Unfortunately, a mixture of regioisomers was obtained in this step. The MABR mediated alkylation[20] of this mixture of enol ethers with methyl triflate gave ketone **18**, along with ketones **19** and **20**.



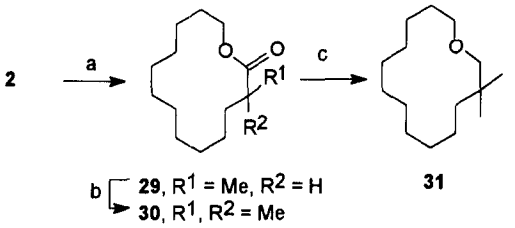
Scheme 3[a]

[a]Key: (a) $(TMS)_2NH$, TMSCl, LiI, CH_2Cl_2; then Et_3N, 94%; (b) MABR, MeOTf, CH_2Cl_2, -40 °C, 33%; (c) H_2SO_4, CH_3OH, Δ, 82%; (d) NaH, $CH_3COCH_2COOCH_3$, THF, DMF, rt; **22**, Δ; (e) HCl (conc.), CH_3OH, H_2O, Δ, 95% (2 steps); (f) CH_3MgBr, CH_2Cl_2, 0 °C, 43%; (g) Et_3N, THF, 2,4,6-trichlorobenzoyl chloride, rt; then DMAP, toluene, Δ, 54%; (h) $NaBH_4$, $BF_3{\cdot}Et_2O$, THF, rt, then triglyme, 51%.

Products **19** and **20** were identified by a GC comparison with authentic samples.[25] Based on GC analysis of the three ketones formed in the alkylation step, the ratio of enol ether regioisomers was determined to be ca. 1:1, which was less than expected. The two-step sequence gave **18** in only 31% yield. The Baeyer-Villiger oxidation

of ketone **18** was attempted under a variety of conditions. However, even with a ten-fold excess of trifluoroperoxyacetic acid, the reaction failed. The reaction also failed with *m*-CPBA in the presence of either *p*-TsOH or Li_2CO_3. As a result we were forced to find another route to **28**.

Cyclization of the acyclic hydroxy acid **25** represented such an alternative approach to lactone **26**. The preparation of **26** began with the Fischer esterification of bromo acid **21** (Scheme 3). This ester was alkylated with methyl acetoacetate to give diester **23**. The diester **23** was decarboxylated to give the keto acid **24**. The *gem*-dimethyl group was introduced using Grignard chemistry to give the hydroxy acid **25**, and hydroxy acid **25** was cyclized[26] to give the *gem*-dimethyl lactone **26**. The ^{1}H NMR spectrum of **26** contained a two-proton multiplet from 2.15-2.17 ppm for the C-2 methylene, as well as a six-proton singlet at 1.35 ppm for the C-14 and C-15 methyl groups. The IR spectrum of **26** had a band at 1727 cm^{-1} and the ^{13}C NMR spectrum contained a signal at 172.14 ppm for the C-1 carbonyl. The conversion of lactone **26** into thionolactone **27** was attempted with Lawesson's reagent, a modified Lawesson's reagent,[27] and phosphorus pentasulfide in toluene, or even refluxing xylene. However, none of these reactions produced any of the desired thionolactone **27**. Decomposition of the starting material occurred, presumably via hydrolysis caused by acidic species formed from the thionation reagents. The reaction of Lawesson's reagent in refluxing xylene with either pyridine or thiourea as a base also showed no formation of the desired thionolactone **27**, although, under these conditions the starting material was present even after two days. The reaction of the Lawesson's reagent was apparently blocked by the dimethyl substituents adjacent to the lactone functionality of **26**. As a result of our inability to prepare thionolactone **27**, we examined the direct lactone reduction with sodium borohydride in the presence of boron trifluoride etherate.[10] Application of this methodology to **26** gave the macrocyclic ether **28** in 51% yield. The ^{1}H NMR spectrum of **28** at rt contained a two-proton triplet at 3.25 ppm for the C-14 protons, a two-proton quintet at 1.57 ppm for the C-13 protons, and a six-proton singlet at 1.13 ppm for the C-2 geminal methyl groups. The ^{13}C spectrum of this compound contained 14 lines.



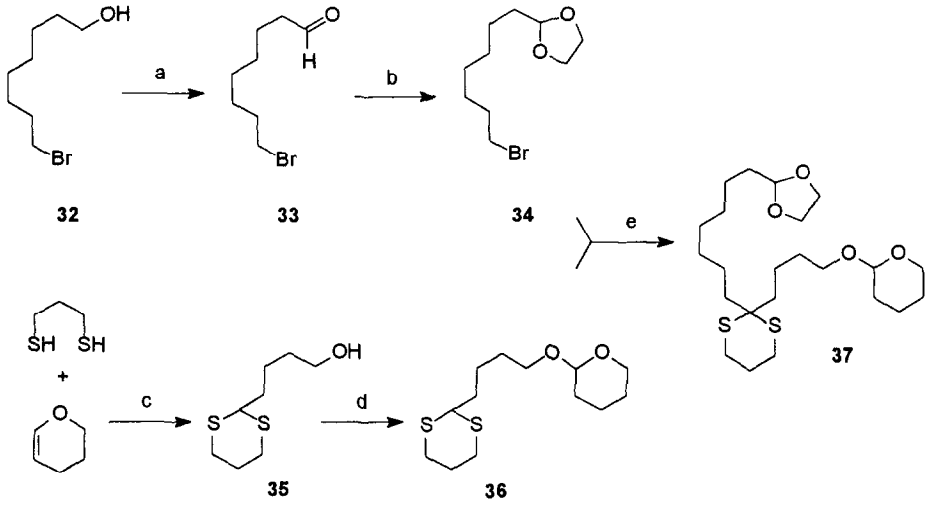
Scheme 4[a]

[a]Key: (a) LDA, THF, -78 °C; then MeI, 84%; (b) LDA, THF, -78 °C; then MeI, 86%; (c) BF_3·Et_2O, $NaBH_4$, THF, rt; then triglyme, Δ, 11%.

The *gem*-dimethyl substituents of ether **31** were introduced via alkylation of **2** to give lactone **30** (Scheme 4). Since the formation of the thionolactone from **30** with Lawesson's reagent is problematic (*vide supra*),[28] the conversion of this lactone to the macrocyclic ether **31** was also performed via the direct sodium borohydride reduction. When the reduction was performed at rt, none of the desired product was obtained. However at reflux this reaction did proceed, albeit in a low yield. The ^{1}H NMR spectrum of **31** at rt contained a two-proton triplet at 3.38 ppm for the C-14 protons, a two-proton singlet at 3.03 ppm for the C-2 protons, a two-proton quintet at 1.55 ppm for the C-13 protons, and a six-proton singlet at 0.84 ppm for the C-3 geminal methyl groups. The ^{13}C spectrum of **31** contained the expected 14 lines.

The preparation of macrocyclic ether **47** required a different approach than that used to synthesize the above ethers. The introduction of a *gem*-dimethyl group at a position remote from the ether oxygen meant that

these substituents could not be introduced through the alkylation of the intermediate lactone or ketone. Instead, the synthetic strategy involved the preparation of the molecule from two components that were coupled together using a dithiane as the central unit of the acyclic molecule. This dithiane ring was then converted into the desired *gem*-dimethyl group, and the macrocycle was formed via cyclization of a hydroxy acid. Thus the monobrominated alcohol **32**[29] was oxidized to give the bromo aldehyde **33** that was subsequently protected as the ethylene acetal **34** (Scheme 5). The ^{1}H NMR spectrum of **34** contained a diagnostic one-proton triplet at 4.78 ppm for the C-1 methine proton of the acetal. The preparation of the other fragment started with the hydroxy dithiane **35**,[30] which was protected as its tetrahydropyranyl ether. The anion of **36** was alkylated with bromo acetal **34** to give **37**. This reaction proceeded in only modest yield, even when performed with an excess of the anion from **36**. The ^{1}H NMR spectrum of **37** contained one-proton doublet of doublets with chemical shifts of 4.78 ppm and 4.53 ppm for the C-1 methine of the ethylene acetal and the C-13 methine of the tetrahydropyranyl ether respectively. The ^{13}C NMR spectrum contained two low-field signals at 104.56 and 98.74 ppm for the acetal carbons of the acetal and the tetrahydropyranyl protecting groups, indicating that the desired alkylation had taken place.

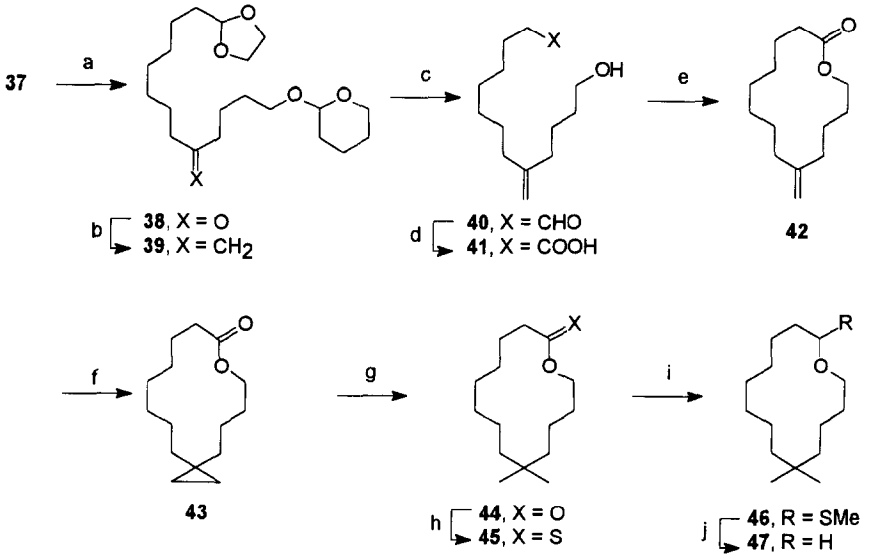


Scheme 5[a]

[a]Key: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 90%; (b) PPTS, $HOCH_2CH_2OH$, C_6H_6, Δ, 93%; (c) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C, 84%; (d) DHP, PPTS, CH_2Cl_2, rt, 96%; (e) *n*-BuLi, THF, -20 °C; then **34**, 49%.

The dithiane ring of **37** was hydrolyzed to the ketone **38** (Scheme 6). This was first attempted with NBS, but difficulty with the cleavage of the acetal protecting groups was encountered. To overcome this problem, an alternative cleavage involving the use of mercuric perchlorate with calcium carbonate was investigated.[31] This reaction proceeded rapidly and in good yield to give the ketone **38** with both acetals intact. The carbonyl of **38** was converted into the exo-methylene group of **39** using the Tebbe reagent. Removal of the protecting groups gave the hydroxy aldehyde **40**. Chemoselective oxidation of the aldehyde **40** was done using a silver oxide oxidation[32] in the absence of light. Unfortunately the reaction proceeded in only a 30% yield. The Yamaguchi procedure[26] was used to cyclize the hydroxy acid **41**. The exocyclic methylene of **42** then was converted into a cyclopropyl group via a procedure similar to that developed by Denmark and Edwards.[33] This reaction was found to be superior to the traditional Simmons-Smith procedure.[34] The cyclopropane in **43** was ring opened with hydrogen and Adams' catalyst to give the *gem*-dimethyl lactone **44**. The ^{1}H NMR spectrum

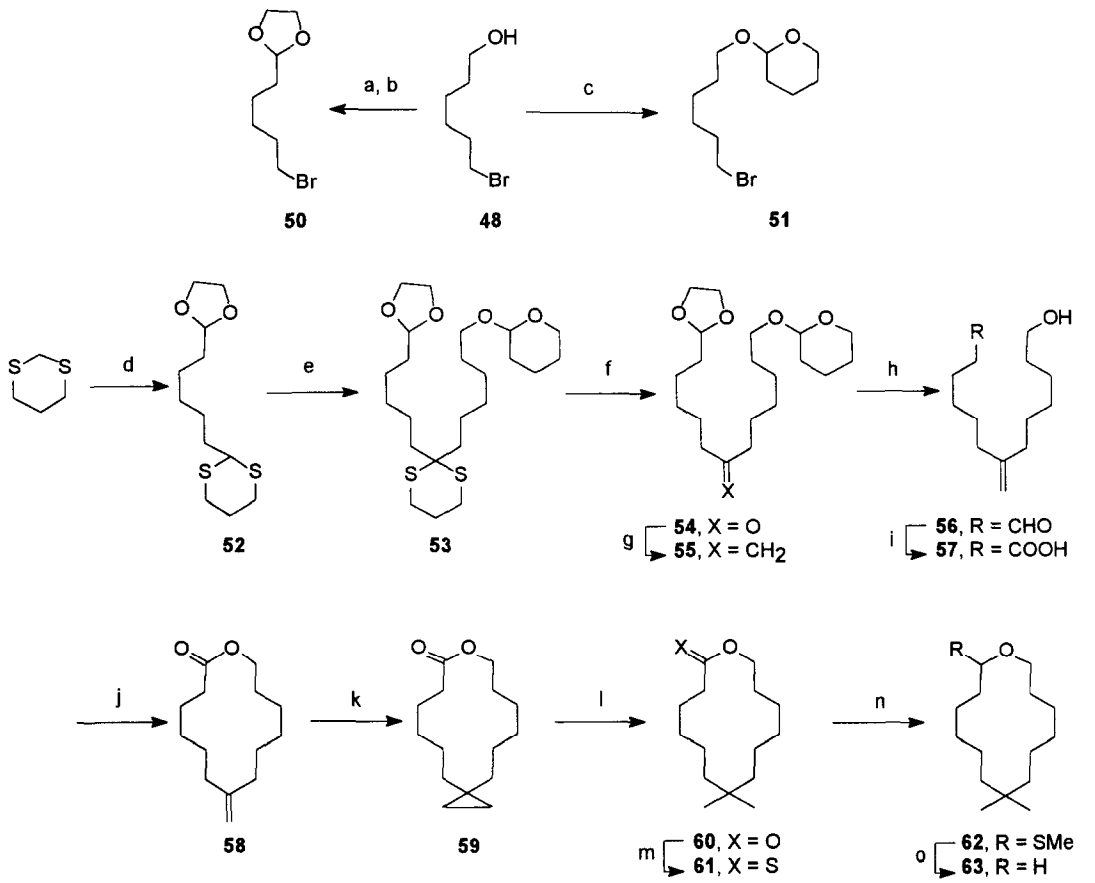
of **44** contained a six-proton singlet at 0.82 ppm for the geminal methyl groups, as well as a two-proton multiplet from 4.10-4.12 ppm for the C-13 methylene group. The ^{13}C NMR spectrum of **44** contained the expected 14 lines, with one low-field signal at 173.70 ppm for the C-1 carbonyl. Lactone **44** was reacted with Lawesson's reagent to give the thionolactone **45**. This thionolactone was reduced and alkylated to give the mixed thioacetal **46**, and **46** was reacted immediately with a solution of tri(*n*-butyl)tin hydride to cleave the thiomethyl group and yield the desired macrocyclic ether **47**. The ^1H NMR spectrum of **47** contained two-proton triplets at 3.43 and 3.42 ppm for the alpha protons, and a six-proton singlet at 0.84 ppm for the C-6 geminal methyl groups. The ^{13}C NMR spectrum contained the expected 14 lines.



Scheme 6[a]

[a]Key: (a) $Hg(ClO_4)_2$, $CaCO_3$, THF, H_2O, 80%; (b) Tebbe reagent, DMAP, pyr, THF, -40 °C, 53%; (c) PPTS, acetone, H_2O, Δ, 90%; (d) $AgNO_3$, NaOH, THF, H_2O, 30%; (e) Et_3N, THF, 2,4,6-trichlorobenzoyl chloride, rt; then DMAP, toluene, Δ, 52%; (f) Et_2Zn, $ClCH_2I$, $ClCH_2CH_2Cl$, 0 °C, 85%; (g) PtO_2, H_2, HOAc, 73%; (h) Lawesson's reagent, toluene, Δ, 47%; (i) $LiEt_3BH$, THF, -78 °C; then MeI, 94%; (j) *n*-Bu_3SnH, AIBN, toluene, Δ, 67%.

Ether **63** was synthesized via a route similar to that of ether **47**. Both the left and right fragments of **63** were prepared from 1,6-hexanediol. This diol was treated with 48% hydrobromic acid to give the monobrominated alcohol **48**[29] which was divided into two portions. One portion was oxidized to give the bromo aldehyde **49**, and then protected as the ethylene acetal **50**. The remaining portion of **48** was protected as its tetrahydropyranyl ether (Scheme 7). The anion of 1,3-dithiane was alkylated with 0.66 equivalents of bromo acetal **50** to give **52**, and **52** was reacted further with *n*-butyllithium to generate the anion of **52** which was alkylated with 1.2 equivalents of bromide **51** to give **53**. Hydrolysis of the dithiane ring gave ketone **54**. The ^1H NMR spectrum of **54** contained a one-proton triplet at 4.81 ppm for the C-1 methine of the acetal, and a one-proton doublet of doublets at 4.54 ppm for the C-13 methine of the tetrahydropyranyl ether indicating that the desired bisalkylation had occurred. The ^{13}C NMR spectrum of **54** showed a signal at 211.32 ppm and the IR spectrum showed a sharp band at 1716 cm^{-1} for the C-7 carbonyl.



Scheme 7[a]

[a]Key: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 76%; (b) PPTS, $HOCH_2CH_2OH$, C_6H_6, Δ, 90%; (c) DHP, PPTS, CH_2Cl_2, rt, 97%;(d) *n*-BuLi, THF, -20 °C; then **50**, 67%; (e) *n*-BuLi, THF, -20 °C; then **51**, 38%; (f) $Hg(ClO_4)_2$, $CaCO_3$, THF, H_2O, rt, 61%; (g) $(C_6H_5)PCH_3I$, *n*-BuLi, THF, 0 °C, 66%; (h) PPTS, acetone, H_2O, Δ, 86%; (i) $NaClO_2$, NaH_2PO_4, $(CH_3)_2CCHCH_3$, *tert*-butyl alcohol, H_2O, rt, 63%; (j) Et_3N, THF, 2,4,6-trichlorobenzoyl chloride, rt; then DMAP, toluene, Δ, 42%; (k) Zn-Cu, CH_2I_2, I_2, Et_2O, Δ, 34%; (l) PtO_2, H_2, HOAc, rt, 78%; (m) Lawesson's reagent, toluene, Δ, 54%; (n) $LiEt_3BH$, THF, -78 °C; then MeI, 98%; (o) *n*-Bu_3SnH, AIBN, tol, Δ, 40%.

Conversion of the ketone into the *gem*-dimethyl group was accomplished by two ways. The small-scale reaction of ketone **54** with Tebbe reagent proceeded to give alkene **55** in 70% yield. The crude reaction mixture was filtered directly through basic alumina which quenched the excess Tebbe reagent and removed unwanted titanium compounds from the alkene product. This filtration step was problematic, and led to low yields when performed on a larger scale. To overcome this, the methylenation of the ketone with a Wittig reagent was investigated and found to be better suited to the larger reaction scale giving the alkene **55** in 66% yield. Removal of the protecting groups under weakly acidic conditions gave the hydroxy aldehyde **56**.

Aldehyde **56** was oxidized[35] to hydroxy acid **57**. The cyclization[26] of the hydroxy acid **57** gave the lactone **58** in 42% yield. The exocyclic methylene of **58** was converted into a cyclopropyl group.[34] This reaction was sluggish and further addition of the zinc complex precursors was necessary to improve the yield. The cyclopropyl group of **59** was hydrogenolyzed to give the *gem*-dimethyl lactone **60**. The ^{1}H NMR spectrum of **60** contained a two-proton multiplet between 4.14-4.16 ppm for the C-13 methylene adjacent to the ether oxygen as well as a six-proton singlet at 0.81 ppm for the new geminal methyl groups. The ^{13}C NMR spectrum contained the expected 14 lines with a low-field signal at 173.56 ppm for the C-1 carbonyl. The IR spectrum contained a band at 1736 cm^{-1} also due to the C-1 carbonyl. These results were consistent with the desired transformations and the structure of lactone **60**. The lactone **60** was reacted with Lawesson's reagent to give the thionolactone **61**. This thionolactone was reduced and alkylated to give the mixed thioacetal **62**. This compound was immediately reduced to give the macrocyclic ether **63**. The ^{1}H NMR spectrum of **63** at rt contained a four-proton triplet at 3.40 ppm for the alpha protons, and a six-proton singlet at 0.81 ppm for the C-8 geminal methyl groups. The ^{13}C NMR spectrum contained eight lines indicating that ether **63** is undergoing site exchange that is rapid on the NMR timescale.

CONCLUSION

The syntheses of the 14-membered macrocyclic ethers **5**, **7**, **14**, and **15** were done via the Baeyer-Villiger ring expansion of the ketones **1** and **10** to give intermediate lactones **2** and **11**. Further reaction of these lactones under thionation conditions and subsequent radical reduction gave the macrocyclic ethers. The diastereomeric ethers **14** and **15** were prepared under both hydrogenation and radical reduction conditions with essentially no diastereoselectivity observed under either conditions. The relative configuration of the methyl substituents in **14** and **15** was determined by chiral GC analysis. The Baeyer-Villiger ring expansion of ketone **18** failed, and the required lactone **26** was instead prepared via the cyclization of hydroxy acid **25**. The thionation of this lactone also failed. Fortunately the direct reduction of the lactone with sodium borohydride in the presence of boron trifluoride etherate gave macrocyclic ether **28**. The macrocyclic ether **31** was prepared via the reduction of lactone **30**. However, even under refluxing conditions, the boron trifluoride mediated sodium borohydride reduction of this lactone proceeded in low yield. Macrocyclic ethers **47** and **63** were prepared from hydroxy acid intermediates **41** and **57**. The cyclization of these intermediates gave lactones **42** and **58**. Further reaction of these lactones under thionation conditions and subsequent radical reduction gave the desired macrocyclic ethers.

Once prepared, the conformational properties of these macrocyclic ethers including the location of the ether oxygen in the conformation and the effect of alkyl substituents, especially *gem*-dimethyl substituents on the conformation of these ethers were analyzed using NMR spectroscopic techniques and molecular mechanics calculations.[36] The rt NMR spectra of these ethers indicated that they were undergoing rapid conformational equilibrium which resulted in quite simple ^{13}C- and ^{1}H-NMR spectra.

EXPERIMENTAL

Unless otherwise stated, all reactions were performed under a nitrogen atmosphere in flame- or oven-dried glassware. Anhydrous solvents were obtained by distillation. The low boiling fraction of petroleum ether (bp 35-60 °C) was used. Solvents were deoxygenated with the freeze-pump-thaw method. Otherwise the solvent was used as received from the supplier. Reagents were purified according to the procedure given in the literature.[37] Unless otherwise noted, reagents were purchased from the Aldrich Chemical Co. Adams' catalyst (PtO_2) was purchased from BDH Chemicals Ltd. Urea hydrogen peroxide (UHP),[15] tri(*n*-butyl)tin hydride,[38] Tebbe reagent,[39] pyridinium *p*-toluenesulfonate,[40] zinc-copper couple,[41] and bromo alcohols **32** and **48**[29] were prepared as described in the literature.

Analytical gas-liquid chromatography (GC) was performed with helium as the carrier gas with OV-101, DB-210 (0.22 mm x 12 m) or Cyclodex-B (0.25 mm x 30 m) (Chromatographic Specialties Inc.) capillary

columns. Thin layer chromatography (TLC) was performed on commercially available aluminum backed plates of silica gel 60 (Merck 5554, 0.2 mm thickness) and visualized with ultraviolet light (254 nm) or 1% *p*-anisaldehyde spray. Flash chromatography[42] was performed using silica gel 60, 230-400 mesh, supplied by E. Merck Co. Radial chromatography was performed using a Harrison Chromatotron model 8924 with silica gel 60, PF_{254} with gypsum binder supplied by EM Science. Melting points were performed using a Mel-Temp II apparatus (Lab Devices USA) and are uncorrected. Infrared (IR) spectra were recorded on a Bomem Michelson 100 FT-IR spectrophotometer as solutions between NaCl plates with internal calibration. Proton (^1H) and carbon (^{13}C) nuclear magnetic resonance spectra were recorded on $CDCl_3$ solutions unless otherwise noted using a Bruker AMX-500 (^1H, 500 MHz; ^{13}C, 125 MHz) spectrometer. Chemical shifts are given in parts per million (ppm) on the δ scale, referenced to chloroform (δ 7.24) or benzene (δ 7.15) for proton, and $CDCl_3$ (δ 77.0) or benzene-d_6 (δ 128.0) for carbon as internal standards. Microanalyses were performed in the Microanalytical Laboratory at the University of British Columbia.

13-Tridecanolide (2). Trifluoroacetic anhydride (1.9 mL, 14 mmol) was added via a syringe to a mixture of cyclotridecanone (**1**) (0.42 g, 2.1 mmol), urea hydrogen peroxide (1.20 g, 12.8 mmol), and Na_2HPO_4 (2.09 g, 14.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The reaction was stirred for 18 hours with slow warming to rt. The reaction was diluted with CH_2Cl_2, washed with saturated $NaHCO_3$ solution, saturated $Na_2S_2O_3$ solution, water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 2% ethyl acetate in petroleum ether as eluant gave lactone **2** (0.43 g, 96%) as a pale yellow oil: IR ($CDCl_3$): 2934, 2861, 1719, 1447, 1251, 1051 cm^{-1}; ^1H NMR: δ 4.11-4.13 (m, 2 H), 2.34-2.36 (m, 2 H), 1.60-1.66 (m, 4 H), 1.22-1.44 (m, 16 H); ^{13}C NMR: δ 173.92, 63.25, 34.36, 27.64, 26.22, 26.04, 25.86, 25.66, 24.72, 24.63, 24.03, 23.70, 22.77; HRMS (EI) *m/z* calcd for $C_{13}H_{24}O_2$: 212.1776, found: 212.1775. Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.40; H, 11.43.

2-Oxacyclotetradecanethione (3). A solution of lactone **2** (0.21 g, 0.97 mmol) in toluene (5 mL) was added via a cannula to a suspension of Lawesson's reagent (0.87 g, 2.2 mmol) in toluene (5 mL) and the reaction was heated at reflux for 4.5 days. The reaction was cooled to rt, filtered, and the solid residue was rinsed with diethyl ether. The organic layers were combined, and the solvent was removed under reduced pressure. Column chromatography of the residue with petroleum ether as eluant gave thionolactone **3** (0.16 g, 73%) as a yellow oil: IR ($CDCl_3$): 3154, 2908, 1445, 1273, 1198, 1019, 829 cm^{-1}; ^1H NMR: δ 4.46-4.48 (m, 2 H), 2.85-2.88 (m, 2 H), 1.74-1.82 (m, 2 H), 1.67-1.73 (m, 2 H), 1.43-1.48 (m, 2 H), 1.16-1.39 (m, 14 H); ^{13}C NMR: δ 224.66, 71.37, 47.14, 27.25, 27.00, 26.09, 25.97, 25.84, 25.03, 24.38 (2), 23.39, 23.19; HRMS (EI) *m/z* calcd for $C_{13}H_{24}OS$: 228.1548, found: 228.1547. Anal. Calcd for $C_{13}H_{24}OS$: C, 68.37; H, 10.59. Found: C, 68.12; H, 10.54.

2-(Methylthio)oxacyclotetradecane (4). A solution of lithium triethylborohydride in THF (1.8 mL, 1.8 mmol) was added to a solution of thionolactone **3** (81 mg, 0.36 mmol) in THF (5 mL) at -78 °C and the reaction was stirred for 30 minutes. Methyl iodide (0.14 mL, 2.2 mmol) was added, and the reaction was stirred for a further 30 minutes at -78 °C, and then allowed to slowly warm to rt. The solution was diluted with diethyl ether and cooled to -78 °C. Aqueous 3 M NaOH solution (3 mL) and 30% H_2O_2 (1.5 mL) were added sequentially. The solution was stirred for 20 minutes at -78 °C and then allowed to warm to rt. The reaction was washed with saturated $Na_2S_2O_3$ solution, water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure to give mixed thioacetal **4** (79 mg, 91%) as an oil. Thioacetal **4** was unstable and was used immediately without further purification: HRMS (EI) *m/z* calcd for $C_{14}H_{28}OS$: 244.1861, found: 244.1856.

Oxacyclotetradecane (5). A deoxygenated solution (3 mL) of tri(n-butyl)tin hydride (0.38 mL, 1.4 mmol) and AIBN (10 mg) in toluene was added over three hours via a syringe pump to a deoxygenated solution of mixed thioacetal **4** (57 mg, 0.23 mmol) and AIBN (5 mg) in toluene (15 mL) heated at reflux. After the addition of the tri(*n*-butyl)tin hydride, the solvent was removed under reduced pressure. The tin compounds

were removed by column chromatography of the residue with 2% ethyl acetate in petroleum ether. Further column chromatography using $AgNO_3$ impregnated silica with petroleum ether as eluant gave ether **5** (20 mg, 43%) as a pale yellow oil: IR ($CDCl_3$): 3932, 2860, 1442, 1351, 1266, 1119, 1038 cm^{-1}, ^1H NMR: δ 3.41 (t, J = 5.5 Hz, 4 H), 1.57 (quint, J = 5.5 Hz, 4 H), 1.29-1.43 (m, 16 H), 1.21-1.27 (m, 2 H); ^{13}C NMR: δ 68.58 (2), 28.59 (2), 26.34 (2), 25.15 (2), 24.37 (2), 23.42 (2), 23.19; HRMS (EI) *m/z* calcd for $C_{13}H_{26}O$: 198.1984, found: 198.1991. Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 79.08; H, 13.18.

2-Methyl-2-(methylthio)oxacyclotetradecane (6). Methyllithium in diethyl ether (1.7 mL, 1.7 mmol) was added to a solution of thionolactone **3** (73 mg, 0.32 mmol) in THF (5 mL) at -78 °C and the reaction was stirred for 40 minutes at -78 °C. Methyl iodide (0.12 mL, 1.9 mmol) was added, the reaction was stirred for an additional 20 minutes at -78 °C, and finally allowed to warm to rt. The reaction was diluted with diethyl ether, and washed with water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure to give the mixed thioketal **6** (74 mg, 90%) as a pale yellow oil. Thioketal **6** was unstable and was used without further purification: HRMS (EI) *m/z* calcd for $C_{15}H_{30}OS$: 258.2018, found: 258.2027.

2-Methyloxacyclotetradecane (7). A deoxygenated solution of mixed thioketal **6** (0.21 g, 0.82 mmol) was reacted with a deoxygenated solution (10 mL) of tri(*n*-butyl)tin hydride (2.2 mL, 8.2 mmol) and AIBN (10 mg) in toluene according to the procedure for **5** over 10 hours to give ether **7** (0.11 g, 63%) as a pale yellow oil: IR ($CDCl_3$): 2929, 2859, 1459, 1372, 1340, 1130, 1098, 1039 cm^{-1}; ^1H NMR: δ 3.61 (dt, J = 9.2, 4.2 Hz, 1 H), 3.43 (ddq, J = 3.1, 9.2, 6.2 Hz, 1 H), 3.22 (ddd, J = 3.0, 9.2, 10.6 Hz, 1 H), 1.65-1.73 (m, 1 H), 1.10-1.61 (m, 21 H), 1.09 (d, J = 6.2 Hz, 3 H); ^{13}C NMR: δ 73.32, 65.99, 36.42, 29.00, 26.48, 26.22, 25.46, 25.27, 24.93, 24.66, 23.84, 23.19, 22.99, 19.82; HRMS (EI) *m/z* calcd for $C_{14}H_{28}O$: 212.2140, found: 212.2140. Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 79.23; H, 13.70.

(*Z/E*)-1-(Trimethylsiloxy)cyclotridecene (8) and (9). 1,1,1,3,3,3-Hexamethyldisilazane (0.21 mL, 1.0 mmol) and trimethylsilyl chloride (0.13 mL, 1.0 mmol) were added sequentially via a syringe to a mixture of **1** (0.10 g, 0.51 mmol) and lithium iodide (0.13 g, 1.0 mmol) in CH_2Cl_2 (5 mL), and the reaction was stirred for 19 hours at rt in the dark. Triethylamine (0.14 mL, 1.0 mmol) was added to the reaction mixture, and it was stirred for an additional 30 minutes. The reaction was diluted with diethyl ether, and washed with saturated $NaHCO_3$ solution and brine and dried over anhydrous $MgSO_4$. The organic extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue (GC ratio **8**:**9**, 83:17) with petroleum ether as eluant gave **8** (86 mg, 63%) and **9** (12 mg, 9%) both as colorless oils: **8** (***Z***): IR ($CDCl_3$): 2929, 2857, 1670, 1451, 1362, 1252, 1164, 1047, 947, 850 cm^{-1}; ^1H NMR (C_6D_6): δ 4.44 (t, J = 7.3 Hz, 1 H), 2.10 (dt, J = 7.3, 6.7 Hz, 2 H), 2.01-2.03 (m, 2 H), 1.50-1.55 (m, 2 H), 1.33-1.46 (m, 16 H), 0.14 (s, 9 H); ^{13}C NMR (C_6D_6): δ 150.17, 110.67, 36.11, 28.32, 26.82, 26.70, 26.69, 26.09, 25.94, 25.91, 25.74, 25.12, 24.87, 0.63 (3); HRMS (EI) *m/z* calcd for $C_{16}H_{32}OSi$: 268.2222, found: 268.2215. Anal. Calcd for $C_{16}H_{32}OSi$: C, 71.57; H, 12.01. Found: C, 71.71; H, 11.89. **9** (***E***): IR ($CDCl_3$): 2929, 2859, 2353, 1659, 1452, 1252, 1135, 859 cm^{-1}; ^1H NMR (C_6D_6): δ 4.66 (t, J = 7.3 Hz, 1 H), 2.17 (t, J = 6.6 Hz, 2 H), 2.04 (dt, J = 7.3, 6.7 Hz, 2 H), 1.64-1.68 (m, 2 H), 1.32-1.45 (m, 16 H), 0.21 (s, 9 H); ^{13}C NMR (C_6D_6): δ 151.70, 108.47, 29.48, 29.33, 28.76 (2), 27.58, 27.22, 26.54, 25.66, 25.23, 25.21, 24.50, 0.50 (3); HRMS (EI) *m/z* calcd for $C_{16}H_{32}OSi$: 268.2222, found: 268.2222.

2-Methylcyclotridecanone (10). A solution of MABR was generated by the addition of trimethylaluminum in hexanes (6.0 mL, 12 mmol) to a solution of 4-bromo-2,6-di-*tert*-butylphenol (3.42 g, 12.0 mmol) in CH_2Cl_2 (24 mL) and the reaction was stirred for 2.5 hours at rt. An aliquot of the MABR solution (33 mL, 6.6 mmol) was added to a solution of silyl enol ethers **8** and **9** (1.27 g, 4.73 mmol) in CH_2Cl_2 (50 mL) at -40 °C and the reaction was stirred for 20 minutes. Methyl triflate (1.1 mL, 9.5 mmol) was added, and the reaction was stirred with slow warming to rt over 15 hours. The reaction was diluted with CH_2Cl_2, and washed with 1 M HCl, saturated $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue

with 2% ethyl acetate in petroleum ether as eluant gave ketone **10** (0.79 g, 79%) as a white solid: mp: 31-33 °C; IR ($CDCl_3$): 2933, 2862, 1703, 1595, 1491, 1214, 1017, 792 cm^{-1}; ^1H NMR: δ 2.60 (ddq, J = 3.6, 7.1, 6.9 Hz, 1 H), 2.57 (ddd, J = 3.8, 9.5, 16.4 Hz, 1 H), 2.30 (ddd, J = 3.8, 7.6, 16.4 Hz, 1 H), 1.72-1.79 (m, 1 H), 1.60-1.67 (m, 1 H), 1.46-1.53 (m, 1 H), 1.09-1.37 (m, 17 H), 1.01 (d, J = 6.9 Hz, 3 H); ^{13}C NMR: δ 215.52, 46.19, 40.17, 32.86, 26.55, 26.26, 26.09, 25.57, 25.24, 24.93, 24.36, 24.30, 22.61, 16.94; HRMS (EI) *m/z* calcd for $C_{14}H_{26}O$: 210.1984, found: 210.1985. Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.69; H, 12.30.

13-Tetradecanolide (11). Ketone **10** (0.55 g, 2.6 mmol) was reacted according to the procedure for **2** to give lactone **11** (0.57 g, 97%) as a pale yellow oil with spectral data in agreement with that reported in the literature.[43]

3-Methyl-2-oxacyclotetradecanethione (12). Lactone **11** (0.41 g, 1.8 mmol) was reacted according to the procedure for **3** to give thionolactone **12** (0.34 g, 77%) as a yellow oil: IR ($CDCl_3$): 2930, 2860, 1455, 1357, 1289, 1181, 1094, 773 cm^{-1}; ^1H NMR: δ 5.62 (ddq, J = 7.4, 3.7, 6.3 Hz, 1 H), 2.86 (ddd, J = 5.1, 8.0, 13.0 Hz, 1 H), 2.73 (ddd, J = 4.6, 7.4, 13.0 Hz, 1 H), 1.67-1.75 (m, 4 H), 1.17-1.42 (m, 16 H), 1.30 (d, J = 6.3 Hz, 3 H); ^{13}C NMR: δ 224.35, 78.27, 47.50, 34.83, 27.70, 26.16, 26.01, 25.80, 25.76, 25.22, 24.08, 23.77, 22.27, 19.06; HRMS (EI) *m/z* calcd for $C_{14}H_{26}OS$: 242.1704, found: 242.1704. Anal. Calcd for $C_{14}H_{26}OS$: C, 69.36; H, 10.81. Found: C, 69.23; H, 10.67.

2-Methyl-2-(methylthio)-14-methyloxacyclotetradecane (13). Thionolactone **12** (44 mg, 0.18 mmol) was reacted according to the procedure for **6** to give the mixed thioketal **13** (39 mg, 80%) as a pale yellow oil. Thioketal **13** was unstable and was used without further purification: HRMS (EI) *m/z* calcd for $C_{16}H_{32}OS$: 272.2174, found: 272.2169.

2-Methylene-14-methyloxacyclotetradecane (16). A solution of Tebbe reagent in toluene (0.22 mL, 0.22 mmol) was added to a solution of lactone **11** (25 mg, 0.11 mmol), DMAP (20 mg, 0.13 mmol), and pyridine (10 μL, 1.3 μmol) stirred in THF (2 mL) at -40 °C and the reaction was warmed slowly to rt overnight. The reaction mixture was filtered through basic alumina with petroleum ether as eluant, and the solvent was removed under reduced pressure to give alkene **16** (21 mg, 86%) as a pale yellow oil. Enol ether **16** was unstable and was used without further purification: IR ($CDCl_3$): 2930, 2859, 1647, 1455, 1375, 1274, 1132 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{15}H_{28}O$: 224.2140, found: 224.2138.

(2*R,14*R**) and (2*S**,14*R**)-Dimethyloxacyclotetradecane (14) and (15).**

(a) Reduction of **16**. Adams' catalyst was added to a solution of alkene **16** (62 mg, 0.28 mmol) in diethyl ether (5 mL) and the mixture was stirred under H_2 at rt overnight. The reaction was filtered through silica with diethyl ether as eluant, and the solvent was removed under reduced pressure. Radial chromatography of the residue (GC ratio **14**:**15**, 49:51) with petroleum ether as eluant gave **14** (8.0 mg, 13%) and **15** (7.7 mg, 13%) both as oils: **14 (2*R**,14*R**)**; IR ($CDCl_3$): 2928, 2859, 1457, 1374, 1135, 1059 cm^{-1}; ^1H NMR: δ 3.65 (sext, J = 6.2 Hz, 2 H), 1.63 (sext, J = 6.2 Hz, 2 H), 1.18-1.43 (m, 20 H), 1.08 (d, J = 6.2 Hz, 6 H); ^{13}C NMR: δ 69.02 (2), 33.64 (2), 26.56 (2), 25.34 (2), 25.15 (3), 23.13 (2), 19.63 (2); HRMS (EI) *m/z* calcd for $C_{15}H_{30}O$: 226.2297, found: 226.2294. Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.42; H, 13.37. **15 (2*S**,14*R**)**; IR ($CDCl_3$): 2928, 2860, 1458, 1371, 1330, 1123, 1051 cm^{-1}; ^1H NMR: δ 3.54 (ddq, J = 4.2, 5.7, 6.2 Hz, 2 H), 1.18-1.49 (m, 22 H), 1.10 (d, J = 6.2 Hz, 6 H); ^{13}C NMR: δ 71.77 (2), 36.10 (2), 26.41 (2), 26.17 (2), 25.55 (2), 24.86, 22.95 (2), 21.18 (2); HRMS (EI) *m/z* calcd for $C_{15}H_{30}O$: 226.2297, found: 226.2294.

(b) Reduction of **13** with Tri(*n*-butyl)tin Hydride. A deoxygenated solution of the mixed thioketal **13** (0.15 g, 0.55 mmol) was reacted with a deoxygenated solution (10 mL) of tri(*n*-butyl)tin hydride (1.5 mL, 5.5 mmol) and AIBN (cat.) in toluene according to the procedure for **5** over 10 hours to give ethers **14** and **15** (GC ratio **14**:**15**, 52:48). Radial chromatography with petroleum ether as eluant gave **14** (13.0 mg, 10%) and **15** (13.3 mg, 11%) both as pale yellow oils with spectral data in agreement with that reported above.

(c) Reduction of **13** with Tris(trimethylsilyl)silane (TTMSH). AIBN (cat.) and TTMSH (0.54 mL, 0.17 mmol) were added to a deoxygenated solution of mixed thioketal **13** (47 mg, 0.17 mmol) in toluene (20 mL) and the reaction was heated at reflux for 24 hours. The solvent was removed under reduced pressure. Column chromatography of the residue with petroleum ether as eluant followed by 1% ethyl acetate in petroleum ether as eluant gave ethers **14** and **15** (17 mg, 43%; GC ratio **14**:**15**, 57:43) as a pale yellow oil with spectral data in agreement with that reported above.

***(Z/E)*-1-(Trimethylsiloxy)-2-methylcyclotridecene (17)**. Ketone **10** was reacted according to the procedure for **8** and **9** to give a mixture of silyl enol ethers (0.43 g, 94%) as a pale yellow oil. This mixture was used without purification: HRMS (EI) *m/z* calcd for $C_{17}H_{34}OSi$: 282.2379, found: 282.2376.

2,2-Dimethylcyclotridecanone (18). Silyl enol ethers **17** (0.43 g, 1.5 mmol) were reacted according to the method for **10** to give, after radial chromatography with petroleum ether as eluant, ketone **18** (0.11 g, 33%) as a pale yellow oil: ^{1}H NMR: δ 2.48-2.51 (m, 2 H), 1.61-1.66 (m, 2 H), 1.47-1.51 (m, 2 H), 1.20-1.34 (m, 16 H), 1.09 (s, 6 H); ^{13}C NMR: δ 216.09, 47.77, 40.75, 35.63, 26.83, 26.61, 26.52, 25.30, 25.12, 24.62 (2), 24.38, 24.33, 22.14, 21.76; HRMS (EI) *m/z* calcd for $C_{15}H_{28}O$: 224.2140, found: 224.2142.

Methyl 11-bromoundecanoate (22). Concentrated sulfuric acid (3 mL) was added to a solution of 11-bromoundecanoic acid (**21**) (19.27 g, 76.72 mmol) in methanol (100 mL) and the solution was heated at reflux for nine hours. The solvent was removed under reduced pressure, and the resultant oil was diluted with diethyl ether. The ether solution was washed with saturated $NaHCO_3$ solution, water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with diethyl ether as eluant gave ester **22** (25.98 g, 82%) as a pale yellow oil. This material was used in subsequent reactions without further purification. Column chromatography of a sample of **22** (ca. 100 mg) with 2% ethyl acetate in petroleum ether as eluant gave pure **22** with spectral data in agreement with that reported in the literature.[44]

Methyl 12-carbomethoxy-13-oxotetradecanoate (23). Methyl acetoacetate (20.1 mL, 186 mmol) was added dropwise to a suspension of sodium hydride (7.44 g, 186 mmol) in a mixture of THF and DMF (3:1, 400 mL) at rt. After the effervescence had subsided, ester **22** (25.98 g, 93.04 mmol) was added to the reaction over three hours, and the mixture was heated at reflux for two days. The resultant solution was concentrated under reduced pressure, diluted with CH_2Cl_2, and washed with 1 M HCl, water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure to give crude diester **23** (32 g). This material was used in subsequent reactions without further purification. Column chromatography of a sample of **23** (ca. 100 mg) with 5% ethyl acetate in petroleum ether as eluant gave pure **23** as a white solid: mp: 42-43 °C; IR (CCl_4): 2932, 2857, 1743, 1721, 1436, 1357, 1273, 1171 cm^{-1}; ^{1}H NMR: δ 3.68 (s, 3 H), 3.61 (s, 3 H), 3.37 (t, J = 7.3 Hz, 1 H), 2.25 (t, J = 7.5 Hz, 2 H), 2.17 (s, 3 H), 1.78 (quint, J = 7.3 Hz, 2 H), 1.56 (quint, J = 7.5 Hz, 2 H), 1.11-1.29 (m, 14 H); ^{13}C NMR: δ 203.15, 174.20, 170.34, 59.66, 52.22, 51.32, 34.01, 29.32, 29.27, 29.21, 29.17, 29.12, 29.04, 28.67; HRMS (EI) *m/z* calcd for $C_{17}H_{30}O_5$: 314.2093, found: 314.2090. Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 64.82; H, 9.66.

13-Oxotetradecanoic acid (24). A solution of diester **23** (10.06 g, 32.00 mmol) in a mixture of concentrated HCl, methanol, and water (3:1:1, 112 mL) was heated at reflux for nine hours. The reaction was cooled, diluted with water, and extracted with diethyl ether. The organics were combined, washed with brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure to give keto acid **24** (6.71 g, 87%) as a white solid. This material was used in subsequent reactions without further purification. Column chromatography of a sample of **24** (ca. 100 mg) with 4% methanol in CH_2Cl_2 gave pure **24** with spectral data in agreement with that reported in the literature.[43]

13-Hydroxy-13-methyltetradecanoic acid (25). A solution of methylmagnesium bromide in diethyl ether (5.2 mL, 16 mmol) was added to a solution of keto acid **24** (1.27 g, 5.24 mmol) in diethyl ether (20 mL) at 0 °C and the reaction was stirred with slow warming to rt overnight. The reaction mixture was diluted with

diethyl ether, and acidified with 1 M HCl. The organic layer was washed with water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 20% ethyl acetate in petroleum ether as eluant gave hydroxy acid **25** (0.58 g, 43%) as a white solid: mp: 50-52 °C; IR ($CDCl_3$): 3607, 2930, 2856, 1709, 1195, cm^{-1}; ^1H NMR: δ 2.31 (t, J = 7.5 Hz, 2 H), 1.61 (quint, J = 7.5 Hz, 2 H), 1.44 (t, J = 6.1 Hz, 2 H), 1.23-1.34 (m, 16 H), 1.19 (s, 6 H); ^{13}C NMR: δ 179.16, 71.31, 43.92, 34.02, 30.10, 29.45 (3), 29.32, 29.13 (2), 28.99, 24.69, 24.27; HRMS [CI(+), isobutane] *m/z* calcd for $C_{15}H_{31}O_3$ (M^++1) 259.2273, found: 259.2272. Anal. Calcd for $C_{15}H_{30}O_3$: C, 69.72; H, 11.70. Found: C, 69.58; H, 11.58.

13-Methyl-13-tetradecanolide (26). Triethylamine (0.28 mL, 2.0 mmol) was added to a solution of hydroxy acid **25** (0.46 g, 1.8 mmol) in THF (20 mL) at rt and the reaction was stirred for 15 minutes. 2,4,6-Trichlorobenzoyl chloride (0.28 mL, 1.8 mmol) was added and the reaction was stirred for a further two hours. The reaction mixture was filtered and concentrated under reduced pressure. Trace amounts of solvent were removed under high vacuum over one hour. A solution of the resultant mixed anhydride in toluene (100 mL) was divided into two portions and simultaneously added via a syringe pump to two solutions of DMAP (0.88 g, 7.2 mmol) in toluene (600 mL) at reflux over 40 hours. The reaction was concentrated under reduced pressure, diluted with diethyl ether, and washed with water, 1 M HCl, saturated $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 1% ethyl acetate in petroleum ether gave lactone **26** (0.16 g, 54%) as a colorless oil: IR (CCl_4): 2932, 2861, 1727, 1462, 1385, 1368, 1200, 1174, 1150, 1082 cm^{-1}; ^1H NMR (C_6D_6): δ 2.15-2.17 (m, 2 H), 1.76-1.79 (m, 2 H), 1.48-1.53 (m, 2 H), 1.21-1.40 (m, 16 H), 1.35 (s, 6 H); ^{13}C NMR (C_6D_6): δ 172.14, 81.89, 38.56, 34.55, 27.16 (2), 26.98, 26.72, 26.64, 26.07, 25.55, 24.86, 24.03, 23.65; HRMS (EI) *m/z* calcd for $C_{15}H_{28}O_2$: 240.2089, found: 240.2084. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.13; H, 11.74.

2,2-Dimethyloxacyclotetradecane (28). Boron trifluoride etherate (0.88 mL, 7.0 mmol) and sodium borohydride (0.06 g, 1.6 mmol) were added to a solution of lactone **26** (56.1 mg, 0.233 mmol) in THF (2 mL) at rt and the reaction was stirred for 45 minutes. Triglyme (1.0 mL) was added and the reaction was stirred for 16 hours at rt. The reaction was quenched with saturated $NaHCO_3$ solution, and diluted with diethyl ether. The ether layer was separated and was washed with saturated $NaHCO_3$ solution, water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure to give crude ether **28** (37.1 mg, 70%). This material was combined with additional crude **28** (29.2 mg, 64%) obtained from lactone **26** (48.7 mg, 0.203 mmol) in a second reaction done under similar conditions. Radial chromatography of the combined residue with 0.5% ethyl acetate as eluant gave ether **28** (50.6 mg, 51%) as a colorless oil: IR (CCl_4): 2928, 2860, 1462, 1381, 1363, 1276, 1202, 1179, 1088, 1031 cm^{-1}; ^1H NMR: δ 3.25 (t, J = 6.4 Hz, 2 H), 1.57 (quint, J = 6.4 Hz, 2 H), 1.23-1.43 (m, 20 H), 1.13 (s, 6 H); ^{13}C NMR: δ 73.88, 58.88, 37.97, 28.34, 26.69, 26.66 (2), 26.39, 26.15, 25.15, 24.56, 24.50, 23.52, 23.38, 20.33; HRMS (EI) *m/z* calcd for $C_{15}H_{30}O$: 226.2297, found: 226.2295.

2-Methyl-13-tridecanolide (29). A solution of *n*-butyllithium in hexanes (8.0 mL, 20 mmol) was added to a solution of diisopropylamine (3.0 mL, 23 mmol) in THF (9.0 mL) at -78 °C and the reaction was stirred for 15 minutes, warmed to 0 °C, and stirred for an additional 15 minutes. An aliquot of this LDA solution (2.6 mL, 2.6 mmol) was added to a solution of lactone **2** (0.43 g, 2.0 mmol) in THF (5 mL) and the reaction was stirred for four hours at -78 °C. Methyl iodide (0.25 mL, 3.0 mmol) was added, the reaction was stirred for 15 minutes at -78 °C, warmed to rt, and stirred for an additional 15 minutes at rt. The reaction was diluted with diethyl ether, and washed with water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 2% ethyl acetate in petroleum ether gave lactone **29** (0.38 g, 84%) as a pale yellow oil: IR (CCl_4): 2934, 2860, 1732, 1461, 1349, 1170, 1088 cm^{-1}; ^1H NMR: δ 4.24 (dt, J = 11.0, 5.5 Hz, 1 H), 3.97 (dt, J = 11.0, 5.3 Hz, 1 H), 2.51 (ddq, J = 3.2, 9.8, 7.0 Hz, 1 H), 1.55-1.65 (m, 4 H), 1.15-1.48 (m, 16 H), 1.12 (d, J = 7.0 Hz, 3 H); ^{13}C

NMR: δ 176.87, 63.16, 39.70, 33.79, 27.73, 26.17, 26.05, 26.04, 24.65, 24.47, 24.00, 23.59, 22.82, 17.61; HRMS (EI) *m/z* calcd for $C_{14}H_{26}O_2$: 226.1933, found: 226.1930.

2,2-Dimethyl-13-tridecanolide (30). Lactone **29** (0.34 g, 1.5 mmol) was reacted according to the procedure for **29** with an aliquot of an LDA solution (3.0 mL, 3.0 mmol) and methyl iodide (0.28 mL, 4.5 mmol) for nine hours to give lactone **30** (0.31 g, 86%) as a pale yellow oil: IR (CCl_4): 2934, 2861, 1728, 1464, 1390, 1321, 1162, 1136 cm^{-1}; ^1H NMR: δ 4.04-4.07 (m, 2 H), 1.62-1.66 (m, 2 H), 1.45-1.48 (m, 2 H), 1.26-1.41 (m, 12 H), 1.13-1.22 (m, 4 H), 1.15 (s, 6 H); ^{13}C NMR: δ 178.21, 63.20, 42.72, 40.68, 28.03, 26.53, 26.18, 25.92, 25.68 (2), 24.32, 23.69, 22.71, 22.62, 22.47; HRMS (EI) *m/z* calcd for $C_{15}H_{28}O_2$: 240.2089, found: 240.2086. Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.93; H, 11.92.

3,3-Dimethyloxacyclotetradecane (31). Lactone **30** (125 mg, 0.520 mmol) was reacted according to the procedure for **28** and heated at reflux for three hours to give, after column chromatography, ether **31** (25 mg, 11%) as a pale yellow oil: IR (CCl_4): 2935, 2859, 1463, 1382, 1118 cm^{-1}; ^1H NMR: δ 3.38 (t, J = 5.4 Hz, 2 H), 3.03 (s, 2 H), 1.55 (quint, J = 5.4 Hz, 2 H), 1.18-1.42 (m, 18 H), 0.84 (s, 6 H); ^{13}C NMR: δ 77.38, 68.81, 37.43, 34.09, 28.81, 26.79, 26.61, 26.12 (2), 25.79, 24.17, 24.07, 22.84, 22.81, 20.39; HRMS [CI(+), isobutane] *m/z* calcd for $C_{15}H_{31}O$ (M^++1): 227.2375, found: 227.2374. Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.51; H, 13.39.

8-Bromooctanal (33). A solution of dimethylsulfoxide (3.0 mL, 42 mmol) in CH_2Cl_2 (10 mL) was added via a cannula to a solution of oxalyl chloride (1.8 mL, 21 mmol) in CH_2Cl_2 (50 mL) at -78 °C. The resulting solution was stirred for two minutes and alcohol **32** (2.21 g, 10.6 mmol) in CH_2Cl_2 (10 mL) was added via a cannula and the mixture was stirred for 40 minutes. Triethylamine (7.4 mL, 53 mmol) was added and the mixture was stirred for an additional 10 minutes then warmed to rt. The reaction was quenched with water, and the organic layer was collected. The aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 10% ethyl acetate in petroleum ether as eluant gave aldehyde **33** (1.98 g, 90%) as a pale yellow oil: IR (CCl_4): 2934, 2859, 1711, 1436, 1288, 937 cm^{-1}; ^1H NMR: δ 9.72 (t, J = 1.7 Hz, 1 H), 3.36 (t, J = 6.8 Hz, 2 H), 2.38 (dt, J = 1.7, 7.4 Hz, 2 H), 1.81 (quint, J = 6.8 Hz, 2 H), 1.56-1.62 (m, 2 H), 1.37-1.42 (m, 2 H), 1.28-1.31 (m, 4 H); ^{13}C NMR: δ 202.57, 43.72, 33.76, 32.58, 28.84, 28.39, 27.83, 21.83; HRMS [CI(+), isobutane] *m/z* calcd for $C_8H_{16}O^{81}Br$ (M^++1): 209.0364, found: 209.0373; calcd for $C_8H_{16}O^{79}Br$ (M^++1): 207.0385, found: 207.0377. Anal. Calcd for $C_8H_{15}OBr$: C, 46.39; H, 7.30. Found: C, 46.64; H, 7.25.

8-Bromooctanal ethylene acetal (34). A solution of aldehyde **33** (1.82 g, 8.79 mmol), ethylene glycol (2.5 mL, 44 mmol), and PPTS (0.45 g, 1.8 mmol) in benzene (100 mL) was heated at reflux under Dean-Stark conditions for 12 hours. The solvent was removed under reduced pressure, and the resultant oil was diluted with diethyl ether, washed with saturated $NaHCO_3$ solution, water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 10% ethyl acetate in petroleum ether as eluant gave acetal **34** (2.06 g, 93%) as a pale yellow oil with spectral data in agreement with that reported in the literature.[45]

5-(1′,3′-Dithian-2′-yl)-1-pentanol (35). Boron trifluoride etherate (10.0 mL, 81.3 mmol) was added dropwise to a solution of 1,3-propanedithiol (5.4 mL, 54 mmol) and dihydropyran (6.0 mL, 66 mmol) in CH_2Cl_2 (100 mL) at 0 °C, and the reaction was stirred for 19.5 hours with slow warming to rt. The reaction was quenched with water, and washed with 3 M NaOH solution, water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 30% ethyl acetate in petroleum ether as eluant gave alcohol **35** (8.74 g, 84%) as a pale yellow oil with spectral data in agreement with that reported in the literature.[30]

5-(1′,3′-Dithian-2′-yl)-1-(2″-tetrahydropyranyloxy)pentane (36). A solution of alcohol **35** (8.73 g, 45.4 mmol), dihydropyran (5.0 mL, 55 mmol), and PPTS (2.28 g, 9.08 mmol) in CH_2Cl_2 (100 mL) was stirred

at rt for 23 hours. The resultant solution was washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 10% ethyl acetate in petroleum ether as eluant gave dithiane **36** (12.02 g, 96%) as a pale yellow oil with spectral data in agreement with that reported in the literature.[30]

9-(1′,3′-Dithian-2′-yl)-13-(2″-tetrahydropyranyloxy)-tridecanal ethylene acetal (37). A solution of *n*-butyllithium in hexanes (31 mL, 31 mmol) was added to a solution of dithiane **36** (8.64 g, 31.3 mmol) in THF (50 mL) at -20 °C and the reaction was stirred at -20 °C for five hours. A solution of bromide **34** (3.13 g, 12.5 mmol) in THF (10 mL) was added via a cannula. This reaction was stirred for one hour at -20 °C, warmed to rt, and stirred for an additional hour at rt. The reaction was quenched with saturated NH_4Cl solution and diluted with diethyl ether. The ether layer was washed with water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 10% ethyl acetate in petroleum ether as eluant gave dithiane **37** (2.75 g, 49%) as a pale yellow oil: IR (CCl_4): 2917, 2863, 1458, 1354, 1276, 1132, 1077, 1034, 945, 908 cm^{-1}; ^1H NMR: δ 4.78 (dd, J = 4.8, 5.0 Hz, 1 H), 4.53 (dd, J = 3.1, 2.7 Hz, 1 H), 3.77-3.92 (m, 5 H), 3.70 (dt, J = 9.7, 6.6 Hz, 1 H), 3.42-3.47 (m, 1 H), 3.35 (dt, J = 9.7, 6.7 Hz, 1 H), 2.73-2.76 (m, 4 H), 1.76-1.91 (m, 6 H), 1.23-1.68 (m, 22 H); ^{13}C NMR: δ 104.56, 98.74, 67.14, 64.71 (2), 62.20, 53.22, 38.12, 37.90, 33.77, 30.67, 29.74, 29.60, 29.39, 29.28, 25.91 (2), 25.47, 25.41, 23.92, 23.83, 20.79, 19.54; HRMS (EI) *m/z* calcd for $C_{23}H_{42}O_4S_2$: 446.2524, found: 446.2523. Anal. Calcd for $C_{23}H_{42}O_4S_2$: C, 61.84; H, 9.48. Found: C, 62.12; H, 9.60.

9-Oxo-13-(2′-tetrahydropyranyloxy)-tridecanal ethylene acetal (38). Mercuric perchlorate (2.96 g, 6.52 mmol) in water (2 mL) was added to a mixture of dithiane **37** (2.65 g, 5.93 mmol) and calcium carbonate (0.71 g, 7.1 mmol) in THF (40 mL) and the reaction was stirred for 20 minutes at rt. The reaction was diluted with diethyl ether and filtered. The filtrate was washed with brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 15% ethyl acetate in petroleum ether as eluant gave ketone **38** (1.70 g, 80%) as a pale yellow oil: IR (CCl_4): 2939, 2866, 1716, 1458, 1410, 1358, 1130, 1078, 1035 cm^{-1}; ^1H NMR: δ 4.78 (t, J = 4.8 Hz, 1 H), 4.51 (dd, J = 2.7, 4.0 Hz, 1 H), 3.77-3.92 (m, 5 H), 3.69 (dt, J = 9.7, 6.4 Hz, 1 H), 3.42-3.47 (m, 1 H), 3.33 (dt, J = 9.7, 6.3 Hz, 1 H), 2.38 (t, J = 7.2 Hz, 2 H), 2.33 (t, J = 7.5 Hz, 2 H), 1.21-1.80 (m, 22 H); ^{13}C NMR: δ 211.11, 104.57, 98.78, 67.09, 64.74 (2), 62.23, 42.70, 42.38, 33.78, 30.66, 29.25, 29.20, 29.18, 29.03, 25.40, 23.90, 23.74, 20.61, 19.56; HRMS (EI) *m/z* calcd for $C_{20}H_{35}O_5$: 355.2484, found: 355.2488.

9-Methylene-13-(2′-tetrahydropyranyloxy)-tridecanal ethylene acetal (39). Ketone **38** (1.66 g, 4.66 mmol) was reacted according to the procedure for **16** to give, after column chromatography with 5% ethyl acetate in petroleum ether as eluant, alkene **39** (0.88 g, 53%) as a pale yellow oil: IR (CCl_4): 2909, 1644, 1451, 1354, 1323, 1132, 1132, 1035, 945, 892 cm^{-1}; ^1H NMR: δ 4.81 (t, J = 4.8 Hz, 1 H), 4.66 (s, 2 H), 4.55 (dd, J = 2.9, 4.0 Hz, 1 H), 3.80-3.94 (m, 5 H), 3.71 (dt, J = 9.5, 6.7 Hz, 1 H), 3.45-3.49 (m, 1 H), 3.36 (dt, J = 9.5, 6.5 Hz, 1 H), 2.00 (t, J = 7.6 Hz, 2 H), 1.95 (t, J = 7.5 Hz, 2 H), 1.22-1.83 (m, 22 H); ^{13}C NMR: δ 149.85, 108.68, 104.66, 98.76, 67.41, 64.78 (2), 62.23, 35.94, 35.76, 33.87, 30.73, 29.47, 29.42, 29.40, 29.26, 27.73, 25.48, 24.37, 24.03, 19.61; HRMS (EI) *m/z* calcd for $C_{21}H_{38}O_4$: 354.2770, found: 354.2768. Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.15; H, 10.80. Found: C, 71.42; H, 10.89.

13-Hydroxy-9-methylenetridecanal (40). A solution of alkene **39** (0.84 g, 2.4 mmol) and PPTS (0.12 g, 0.47 mmol) in acetone and water (10:1, 50 mL) was heated at reflux for 20 hours. The acetone was removed under reduced pressure, and the reaction mixture was diluted with diethyl ether. The organic layer was washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 30% ethyl acetate in petroleum ether as eluant gave hydroxy aldehyde **40** (0.48 g, 90%) as a colorless oil: IR (CCl_4): 3635, 3437, 3076, 2932, 2859, 2716, 1729, 1644, 1427, 1052, 891 cm^{-1}; ^1H NMR: δ 9.73 (t, J = 1.7 Hz, 1 H), 4.68 (s, 2 H), 3.64 (t, J = 6.4 Hz, 2 H), 2.40 (dt, J = 1.7, 7.4 Hz, 2 H), 2.01 (dt, J = 1.0, 7.5 Hz, 2 H), 1.97 (dt, J = 1.0, 7.6 Hz, 2 H), 1.52-1.64 (m, 4 H), 1.25-1.51 (m, 10 H); ^{13}C NMR: δ 202.90, 149.64, 108.87, 62.90,

43.88, 35.90, 35.72, 32.48, 29.21, 29.13, 29.09, 27.65, 23.87, 22.04; HRMS [CI(+), isobutane] *m/z* calcd for $C_{14}H_{27}O_2$ (M^++1): 227.2011, found: 227.2012.

13-Hydroxy-9-methylenetridecanoic acid (41). Silver nitrate (3.50 g, 20.3 mmol) and sodium hydroxide (1.64 g, 41.0 mmol) were added to a solution of hydroxy aldehyde **40** (0.46 g, 2.03 mmol) in THF and water (1:1, 50 mL) and the mixture was stirred at rt for six hours in the dark. The reaction mixture was filtered and the solid residue was washed with ethyl acetate. The aqueous layer was acidified with 1 M HCl and extracted with ethyl acetate. The organic layers were combined, washed with brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 4% methanol in CH_2Cl_2 gave hydroxy acid **41** (0.15 g, 30%) as a colorless oil: IR (CCl_4): 3639, 2933, 2858, 1712, 1644, 1434, 1054, 891 cm^{-1}; ^1H NMR: δ 4.68 (s, 2 H), 3.64 (t, J = 6.3 Hz, 2 H), 2.32 (t, J = 7.4 Hz, 2 H), 2.01 (t, J = 7.5 Hz, 2 H), 1.97 (t, J = 7.6 Hz, 2 H), 1.61 (quint, J = 7.4 Hz, 2 H), 1.45-1.57 (m, 4 H), 1.23-1.41 (m, 8 H); ^{13}C NMR: δ 179.13, 149.67, 108.89, 62.84, 35.84, 35.71, 32.34, 29.03, 28.96 (2), 28.87, 27.56, 24.65, 23.88; HRMS [CI(+), isobutane] *m/z* calcd for $C_{14}H_{27}O_3$ (M^++1): 243.1960, found: 243.1961. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.52; H, 11.00.

9-Methylene-13-tridecanolide (42). Hydroxy acid **41** (76 mg, 0.31 mmol) was reacted according to the procedure for **26**. A solution of the resultant mixed anhydride in toluene (150 mL) was added via a syringe pump to a solution of DMAP (0.23 g, 1.9 mmol) in toluene (31 mL) heated at reflux over six hours. Radial chromatography of the residue with 1% ethyl acetate in petroleum ether as eluant gave lactone **42** (37 mg, 52%) as a pale yellow oil: IR (CCl_4): 2935, 2862, 1734, 1643, 1452, 1243, 1138, 1084, 892 cm^{-1}; ^1H NMR: δ 4.67 (s, 2 H), 4.11-4.13 (m, 2 H), 2.32-2.35 (m, 2 H), 2.05 (br t, J = 7.6 Hz, 2 H), 1.96 (br t, J = 7.8 Hz, 2 H), 1.58-1.64 (m, 6 H), 1.26-1.56 (m, 8 H); ^{13}C NMR: δ 173.63, 149.28, 110.37, 63.09, 34.81, 34.25, 33.14, 27.62, 26.18, 25.73, 25.56, 24.66, 24.40, 23.51; HRMS (EI) *m/z* calcd for $C_{14}H_{24}O_2$: 224.1776, found: 224.1776.

9-Cyclopropyl-13-tridecanolide (43). Chloroiodomethane (80 μL, 1.1 mmol) was added to a solution of diethylzinc (54 μL, 0.53 mmol) in deoxygenated $ClCH_2CH_2Cl$ (2 mL) at 0 °C and the reaction was stirred for seven minutes. A solution of lactone **42** (59 mg, 0.26 mmol) in deoxygenated $ClCH_2CH_2Cl$ (1 mL) was added via a cannula and the reaction was stirred for an additional ten minutes at 0 °C. The reaction was quenched with a 1:1 mixture of saturated $Na_2S_2O_3$ solution and saturated NH_4Cl solution, slowly warmed to rt, and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, the organic layers were combined, washed with water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 1% ethyl acetate in petroleum ether as eluant gave lactone **43** (54 mg, 85%) as a pale yellow oil: IR (CCl_4): 3069, 2933, 2860, 1733, 1458, 1247, 1171, 1137, 1086 cm^{-1}; ^1H NMR: δ 4.09-4.14 (m, 2 H), 2.34-2.37 (m, 2 H), 1.60-1.67 (m, 4 H), 1.46-1.52 (m, 2 H), 1.10-1.37 (m, 12 H), 0.16 (dd, J = 1.9, 7.4 Hz, 2 H), 0.13 (dd, J = 1.9, 7.4 Hz, 2 H); ^{13}C NMR: δ 173.87, 63.03, 34.69, 34.37, 33.73, 27.91, 26.31, 25.75, 25.70, 24.63, 21.92, 21.73, 18.24, 12.26 (2); HRMS (EI) *m/z* calcd for $C_{15}H_{26}O_2$: 238.1933, found: 238.1927.

9,9-Dimethyl-13-tridecanolide (44). Adams' catalyst was added to a solution of lactone **43** (51 mg, 0.21 mmol) in acetic acid (2 mL) and the mixture was stirred under H_2 for 22 hours at rt. The reaction was diluted with diethyl ether and filtered. The solid residue was rinsed with diethyl ether and the organic layers were combined. The organic solution was washed with saturated $NaHCO_3$ solution, water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 2% ethyl acetate in petroleum ether as eluant gave lactone **44** (37 mg, 73%) as a pale yellow oil: IR (CCl_4): 2941, 2861, 1733, 1464, 1364, 1250, 1145, 1086 cm^{-1}; ^1H NMR: δ 4.10-4.12 (m, 2 H), 2.33-2.35 (m, 2 H), 1.56-1.65 (m, 4 H), 1.05-1.38 (m, 14 H), 0.82 (s, 6 H); ^{13}C NMR: δ 173.70, 62.99, 37.87, 37.84, 35.11, 32.37, 29.16 (2), 28.82, 26.65, 25.96, 25.82, 24.30, 19.66, 19.22; HRMS (EI) *m/z* calcd for $C_{15}H_{28}O_2$: 240.2089, found: 240.2087.

7,7-Dimethyl-2-oxacyclotetradecanethione (45). Lactone **43** (36 mg, 0.15 mmol) was reacted according to the procedure for **3** to give thionolactone **45** (18 mg, 47%) as a yellow oil: IR (CCl_4): 2942, 2861, 1463, 1383, 1362, 1293, 1262, 1199, 1139, 1119, 1085 cm^{-1}; ^1H NMR: δ 4.46-4.50 (m, 2 H), 2.87-2.91 (m, 2 H), 1.75-1.80 (m, 2 H), 1.60-1.66 (m, 2 H), 1.27-1.39 (m, 8 H), 1.02-1.16 (m, 6 H), 0.83 (s, 6 H); ^{13}C NMR: δ 224.28, 70.86, 47.85, 38.23, 37.45, 32.34, 29.17 (2), 28.14, 26.56, 25.96 (2), 24.79, 19.64, 19.13; HRMS (EI) *m/z* calcd for $C_{15}H_{28}OS$: 256.1861, found: 256.1856.

2-(Methylthio)-10,10-dimethyloxacyclotetradecane (46). Thionolactone **45** (14 mg, 0.056 mmol) was reacted according to the procedure for **4** to give mixed thioacetal **46** (14 mg, 94%) as an oil. Thioacetal **46** was unstable and was used without further purification: HRMS [CI(+), isobutane] *m/z* calculated for $C_{16}H_{33}OS$ (M^++1): 273.2252, found: 273.2252.

6,6-Dimethyloxacyclotetradecane (47). Mixed thioacetal **46** (14 mg, 0.052 mmol) was reacted according to the procedure for **5** with a deoxygenated solution (10 mL) of tri(*n*-butyl)tin hydride (0.14 mL, 0.52 mmol) and AIBN (cat.) in toluene over 10 hours to give ether **47** (7.9 mg, 67%) as an oil: IR ($CDCl_3$): 2937, 2861, 1451, 1357, 1116 cm^{-1}; ^1H NMR: δ 3.43 (t, J = 5.3 Hz, 2 H), 3.42 (t, J = 5.4 Hz, 2 H), 1.60 (quint, J = 5.3 Hz, 2 H), 1.54 (quint, J = 5.4 Hz, 2 H), 1.29-1.42 (m, 10 H), 1.11-1.17 (m, 6 H), 0.84 (s, 6 H); ^{13}C NMR: δ 68.17, 67.70, 38.88, 37.76, 32.39, 29.32 (2), 29.19, 28.74, 26.48, 26.22, 23.54, 22.47, 19.84, 18.46; HRMS (EI) *m/z* calcd for $C_{15}H_{30}O$: 226.2297, found: 226.2296.

6-Bromohexanal (49). Bromo alcohol **48** (7.20 g, 39.8 mmol) was reacted according to the procedure for **33** to give aldehyde **49** (5.41 g, 76%) as a pale yellow oil with spectral data in agreement with that reported in the literature.[46]

6-Bromohexanal ethylene acetal (50). Aldehyde **49** (4.95 g, 27.6 mmol) was reacted according to the procedure for **34** to give crude acetal **50** (5.50 g, 90%) as a pale yellow oil. This material was used in subsequent reactions without further purification. Column chromatography of a small sample of **50** (ca. 100 mg) with 5% ethyl acetate in petroleum ether as eluant gave pure **50**: IR ($CDCl_3$): 2947, 2875, 1460, 1435, 1407, 1360, 1237, 1136, 1041, 946 cm^{-1}; ^1H NMR: δ 4.83 (t, J = 5.0 Hz, 1 H), 3.90-3.97 (m, 2 H), 3.79-3.86 (m, 2 H), 3.38 (t, J = 6.8 Hz, 2 H), 1.82-1.88 (m, 2 H), 1.61-1.67 (m, 2 H), 1.41-1.49 (m, 4 H); ^{13}C NMR: δ 104.39, 64.84 (2), 33.67, 33.63, 32.68, 28.04, 23.13; HRMS (EI) *m/z* calcd for $C_8H_{14}O_2{}^{81}Br$ (M^+-1): 223.0157, found: 223.0156; calcd for $C_8H_{14}O_2{}^{79}Br$ (M^+-1): 221.0177, found: 221.0183.

6-Bromo-1-(2′-tetrahydropyranyloxy)-hexane (51). Alcohol **48** (5.00 g, 27.6 mmol) was reacted according to the procedure for **36** to give crude bromide **51** (7.08 g, 97%) as a pale yellow oil. This material was used in subsequent reactions without further purification. Column chromatography of a small sample of **51** (ca. 100 mg) with 5% ethyl acetate in petroleum ether as eluant gave pure **51** with spectral data in agreement with that reported in the literature.[47]

7-(1′,3′-Dithian-2′-yl)-heptanal ethylene acetal (52). The anion of 1,3-dithiane (4.06 g, 33.8 mmol) was reacted according to the procedure for **37** with a solution of bromo acetal **50** (5.00 g, 22.5 mmol) in THF (50 mL) to give, after column chromatography, dithiane **52** (3.95 g, 67%) as a pale yellow oil: IR (CCl_4): 2912, 1457, 1423, 1276, 1137, 1038, 942, 909 cm^{-1}; ^1H NMR: δ 4.79 (t, J = 5.4 Hz, 1 H), 3.99 (t, J = 7.1 Hz, 1 H), 3.87-3.92 (m, 2 H), 3.78-3.82 (m, 2 H), 2.75-2.85 (m, 4 H), 1.29-2.08 (m, 12 H); ^{13}C NMR: δ 104.46, 64.73 (2), 47.47, 35.23, 33.67, 30.37 (2), 29.02, 26.42, 25.96, 23.68; HRMS (EI) *m/z* calcd for $C_{12}H_{22}O_2S_2$: 262.1061, found: 262.1065. Anal. Calcd for $C_{12}H_{22}O_2S_2$: C, 54.92; H, 8.45. Found: C, 54.99; H, 8.60.

7-(1′,3′-Dithian-2′-yl)-13-(2″-tetrahydropyranyloxy)-tridecanal ethylene acetal (53). Dithiane **52** (3.59 g, 13.7 mmol) was reacted according to the procedure for **37** with a solution of bromide **51** (4.51 g, 17.0 mmol) in THF (10 mL) to give, after column chromatography, dithiane **53** (1.38 g, 38%) as a pale yellow oil: IR (CCl_4): 2940, 2865, 1459, 1353, 1275, 1133, 1078, 1033, 907 cm^{-1}; ^1H NMR: δ 4.80 (t, J = 4.8 Hz, 1 H), 4.53 (dd, J = 2.9, 4.2 Hz, 1 H), 3.88-3.94 (m, 2 H), 3.78-3.84 (m, 3 H), 3.68 (dt, J = 9.7, 6.9 Hz, 1 H), 3.45

(ddd, J = 3.8, 5.0, 10.9, 1 H), 3.33 (dt, J = 9.7, 6.7 Hz, 1 H), 2.73-2.76 (m, 4 H), 1.77-1.92 (m, 6 H), 1.27-1.69 (m, 22 H); ^{13}C NMR: δ 104.50, 98.73, 67.46, 64.75 (2), 62.20, 53.24, 38.12, 38.00, 33.78, 30.69, 29.66, 29.64, 29.61, 26.07, 25.92 (2), 25.49, 25.43, 23.96, 23.93, 23.82, 19.59; HRMS (EI) *m/z* calcd for $C_{23}H_{42}O_4S_2$: 446.2524, found: 446.2518. Anal. Calcd for $C_{23}H_{42}O_4S_2$: C, 61.48; H, 9.48. Found: C, 61.62; H, 9.62.

7-Oxo-13-(2′-tetrahydropyranyloxy)-tridecanal ethylene acetal (54). Dithiane **53** (3.06 g, 6.85 mmol) was reacted according to the procedure for **38** to give ketone **54** (1.50 g, 61%) as a colorless oil: IR (CCl_4): 2940, 2866, 1716, 1454, 1409, 1358, 1133, 1078, 1033 cm^{-1}; ^{1}H NMR: δ 4.81 (t, J = 4.8 Hz, 1 H), 4.54 (dd, J = 2.7, 4.2 Hz, 1 H), 3.89-3.94 (m, 2 H), 3.80-3.85 (m, 2 H), 3.69 (dt, J = 9.5, 6.8 Hz, 1 H), 3.42-3.49 (m, 1 H), 3.34 (dt, J = 9.5, 6.6 Hz, 1 H), 2.36 (t, J = 7.4 Hz, 2 H), 2.35 (t, J = 7.4 Hz, 2 H), 1.47-1.82 (m, 15 H), 1.26-1.42 (m, 8 H); ^{13}C NMR: δ 211.32, 104.51, 98.84, 67.49, 64.80 (2), 62.32, 42.69, 42.58, 33.67, 30.75, 29.55, 29.10, 29.06, 26.04, 25.47, 23.77 (2), 23.70, 19.66; HRMS (EI) *m/z* calcd for $C_{20}H_{36}O_5$: 356.2563, found: 356.2559. Anal. Calcd for $C_{20}H_{36}O_5$: C, 67.38; H, 10.18. Found: C, 67.67; H, 10.03.

7-Methylene-13-(2′-tetrahydropyranyloxy)-tridecanal ethylene acetal (55).

(a) Reaction of Ketone **54** with Tebbe Reagent. Ketone **54** (1.50 g, 4.21 mmol) was reacted according to the procedure for **39** to give alkene **55** (1.05 g, 70%) as a pale yellow oil: IR (CCl_4): 2936, 2862, 1643, 1459, 1354, 1132, 1078, 1033, 892 cm^{-1}; ^{1}H NMR: δ 4.81 (t, J = 4.9 Hz, 1 H), 4.64 (s, 2 H), 4.54 (dd, J = 3.2, 4.2 Hz, 1 H), 3.89-3.94 (m, 2 H), 3.79-3.85 (m, 3 H), 3.69 (dt, J = 9.5, 6.9 Hz, 1 H), 3.44-3.48 (m, 1 H), 3.35 (dt, J = 9.5, 6.7 Hz, 1 H), 1.96 (t, J = 7.6 Hz, 2 H), 1.95 (t, J = 7.6 Hz, 2 H), 1.26-1.83 (m, 22 H); ^{13}C NMR: δ 150.01, 108.48, 104.60, 98.78, 67.58, 64.77 (2), 62.26, 35.93, 35.85, 33.82, 30.73, 29.67, 29.26, 29.20, 27.68, 27.63, 26.10, 25.46, 23.92, 19.64; HRMS (EI) *m/z* calcd for $C_{21}H_{38}O_4$: 354.2770, found: 354.2764. Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.15; H, 10.80. Found: C, 71.35; H, 11.00.

(b) Reaction of Ketone **54** with Wittig Reagent. A solution of *n*-butyllithium in hexanes (100 mL, 160 mmol) was added to a suspension of triphenylphosphonium iodide (65.26 g, 161.4 mmol) in THF (350 mL) at 0 °C and the reaction was stirred for one hour at 0 °C. A solution of ketone **54** (14.39 g, 40.36 mmol) in THF (100 mL) was added via a cannula and the reaction was stirred for 16 hours at 0 °C. The reaction was concentrated under reduced pressure and diluted with diethyl ether. The ether solution was washed with water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 10% ethyl acetate as eluant gave alkene **55** (9.41 g, 66%) as a pale yellow oil with spectral data in agreement with that reported above.

13-Hydroxy-7-methylenetridecanal (56). Alkene **55** (0.95 g, 2.7 mmol) was reacted according to the procedure for **40** to give hydroxy aldehyde **56** (0.52 g, 86%) as a colorless oil: IR (CCl_4): 3635, 2933, 2859, 2715, 1730, 1643, 1455, 1048, 892 cm^{-1}; ^{1}H NMR: δ 9.73 (t, J = 1.7 Hz, 1 H), 4.66 (br d, J = 3.4 Hz, 2 H), 3.61 (t, J = 6.6 Hz, 2 H), 2.40 (dt, J = 1.7, 7.4 Hz, 2 H), 1.95-1.99 (m, 4 H), 1.62 (quint, J = 7.4, 2 H), 1.54 (quint, J = 6.6 Hz, 2 H), 1.27-1.44 (m, 10 H); ^{13}C NMR: δ 202.81, 149.66, 108.76, 62.95, 43.82, 35.85, 35.70, 32.70, 29.11, 28.82, 27.67, 27.41, 25.59, 21.92; HRMS [CI(+), isobutane] *m/z* calcd for $C_{14}H_{27}O_2$ (M^++1): 227.2011, found: 227.2011.

13-Hydroxy-7-methylenetridecanoic acid (57). A solution of $NaClO_2$ (21.26 g, 235.1 mmol) and NaH_2PO_4 (21.51 g, 179.3 mmol) in water (100 mL) was added over four hours to a solution of hydroxy aldehyde **56** (5.06 g, 22.4 mmol) and 2-methyl-2-butene (60 mL) in *tert*-butyl alcohol (250 mL), and the reaction was stirred at rt overnight. The reaction was concentrated under reduced pressure, diluted with water, and extracted with diethyl ether. The organic layer was washed with water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Column chromatography of the residue with 4% methanol in CH_2Cl_2 as eluant gave hydroxy acid **57** (3.41 g, 63%) as a colorless oil: IR (CCl_4): 3637, 3373, 2977, 2933, 2862, 1712, 1644, 1382, 1350, 1120, 891 cm^{-1}; ^{1}H NMR: δ 6.14 (br s, 1 H), 4.65 (s, 2 H), 3.60 (t, J = 6.7 Hz, 2 H), 2.30 (t, J = 7.5 Hz, 2 H), 1.94-1.98 (m, 4 H), 1.61

(quint, J = 7.5 Hz, 2 H), 1.53 (quint, J = 6.7 Hz, 2 H), 1.25-1.43 (m, 10 H); ^{13}C NMR: δ 178.81, 149.64, 108.66, 62.76, 35.75, 35.65, 33.90, 32.42, 28.99, 28.66, 27.56, 27.23, 25.47, 24.51; HRMS [CI(+), ammonia/methane] *m/z* calcd for $C_{14}H_{27}O_3$ (M^++1): 243.1960, found: 243.1954. Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.63; H, 10.87.

7-Methylene-13-tridecanolide (58). Hydroxy acid **57** (0.50 g, 2.1 mmol) was reacted according to the procedure for **26** to give lactone **58** (0.20 g, 42%) as a colorless oil: IR (CCl_4): 2935, 2861, 1734, 1643, 1453, 1252, 1149, 1074, 892 cm^{-1}; ^{1}H NMR: δ 4.72-4.73 (m, 1 H), 4.70-4.71 (m, 1 H), 4.06-4.08 (m, 2 H), 2.30-2.33 (m, 2 H), 2.03 (br t, J = 6.4 Hz, 2 H), 1.98 (br t, J = 6.6 Hz, 2 H), 1.51-1.66 (m, 6 H), 1.18-1.46 (m, 8 H); ^{13}C NMR: δ 173.80, 147.36, 109.83, 63.22, 36.50, 34.16, 31.59, 27.50, 27.09, 26.36, 25.24, 25.22, 25.06, 24.13; HRMS (EI) *m/z* calcd for $C_{14}H_{24}O_2$: 224.1776, found: 224.1778. Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.12; H, 10.83.

7-Cyclopropyl-13-tridecanolide (59). A catalytic amount of iodine was added to a suspension of zinc-copper couple (0.44 g, 6.7 mmol) in diethyl ether (50 mL) and the mixture was stirred at rt for 15 minutes. Diiodomethane (0.54 mL, 6.7 mmol) was added and the mixture was stirred for an additional 15 minutes. A solution of lactone **58** (0.30 g, 1.3 mmol) in diethyl ether (2 mL) was added, and the mixture was heated at reflux for 19 hours. Additional zinc-copper couple (0.44 g, 6.7 mmol), iodine (cat.) and diiodomethane (0.54 mL, 6.7 mmol) were added and the reaction was heated at reflux for a further 14 hours. The reaction was quenched with saturated NH_4Cl solution and filtered. The solid residue was rinsed with diethyl ether. The organic layers were combined, and washed with saturated $NaHCO_3$ solution, water and brine, and dried over anhydrous $MgSO_4$. The extracts were filtered and the solvent was removed under reduced pressure. Radial chromatography of the residue with 0.5% ethyl acetate in petroleum ether as eluant gave lactone **59** (0.11 g, 34%) as a pale yellow oil: IR (CCl_4): 3070, 2934, 2859, 1724, 1580, 1550, 1448, 1347, 1276, 1206, 1159, 1062, 1011, 822 cm^{-1}; ^{1}H NMR: δ 4.13-4.15 (m, 2 H), 2.35-2.37 (m, 2 H), 1.46-1.72 (m, 6 H), 1.14-1.37 (m, 12 H), 0.16 (dd, J = 2.9, 6.6 Hz, 2 H), 0.12 (dd, J = 2.9, 6.6 Hz, 2 H); ^{13}C NMR: δ 173.80, 63.77, 36.20, 33.28, 32.87, 27.86, 27.67, 26.90, 24.59, 24.35, 23.85, 23.27, 18.87, 12.22 (2); HRMS (EI) *m/z* calcd for $C_{15}H_{26}O_2$: 238.1933, found: 238.1927.

7,7-Dimethyl-13-tridecanolide (60). Cyclopropyl lactone **59** (0.11 g, 0.46 mmol) was reacted according to the procedure for **44** to give lactone **60** (87 mg, 78%) as a pale yellow oil: IR (CCl_4): 2940, 2860, 1736, 1459, 1383, 1277, 1191, 1162, 1124 cm^{-1}; ^{1}H NMR: δ 4.14-4.16 (m, 2 H), 2.34-2.37 (m, 2 H), 1.68-1.73 (m, 2 H), 1.28-1.56 (m, 4 H), 1.27-1.35 (m, 4 H), 1.11-1.18 (m, 8 H), 0.81 (s, 6 H); ^{13}C NMR: δ 173.56, 64.15, 39.23, 37.70, 32.68, 32.21, 29.07 (2), 28.09, 27.88, 27.59, 24.47, 24.24, 21.73, 20.88; HRMS (EI) *m/z* calcd for $C_{15}H_{28}O_2$: 240.2089, found: 240.2088.

9,9-Dimethyl-2-oxacyclotetradecanethione (61). Lactone **60** (87 mg, 0.36 mmol) was reacted according to the procedure for **3** to give thionolactone **61** (50 mg, 54%) as a yellow oil: IR (CCl_4): 2941, 2859, 1461, 1366, 1293, 1192, 1134, 1054 cm^{-1}; ^{1}H NMR: δ 4.51-4.53 (m, 2 H), 2.77-2.80 (m, 2 H), 1.80-1.85 (m, 2 H), 1.66-1.71 (m, 2 H), 1.51-1.57 (m, 2 H), 1.23-1.36 (m, 4 H), 1.09-1.21 (m, 8 H), 0.80 (s, 6 H); ^{13}C NMR: δ 224.77, 72.23, 44.72, 38.80, 37.41, 32.71, 29.03 (2), 28.08, 27.62, 27.10, 26.99, 24.84, 21.50, 21.09; HRMS (EI) *m/z* calcd for $C_{15}H_{28}OS$: 256.1861, found: 256.1853.

2-(Methylthio)-8,8-dimethyloxacyclotetradecane (62). Thionolactone **61** (45 mg, 0.18 mmol) was reacted according to the procedure for **4** to give mixed thioacetal **62** (47 mg, 98%) as an oil. Thioacetal **62** was unstable and was used without further purification: HRMS [CI(+), ammonia/methane] *m/z* calcd for $C_{16}H_{33}OS$ (M^++1): 273.2252, found: 273.2255.

8,8-Dimethyloxacyclotetradecane (63). A deoxygenated solution of mixed thioacetal **62** (47 mg, 0.17 mmol) was reacted according to the procedure for **5** with a deoxygenated solution (10 mL) of tri(*n*-butyl)tin hydride (0.47 mL, 1.7 mmol) and AIBN (cat.) in toluene over ten hours to give, after radial chromatography with 0.5% ethyl acetate in petroleum ether as eluant, ether **63** (16 mg, 40%) as an oil: IR ($CDCl_3$): 2936, 2859,

1457, 1361, 1115 cm^{-1}; ^1H NMR: δ 3.40 (t, J = 5.7 Hz, 4 H), 1.53-1.58 (m, 4 H), 1.41-1.47 (m, 4 H), 1.28-1.35 (m, 4 H), 1.14-1.24 (m, 8 H), 0.81 (s, 6 H); ^{13}C NMR: δ 69.27 (2), 38.61 (2), 32.80, 29.09 (2), 27.90 (2), 27.31 (2), 24.80 (2), 21.56 (2); HRMS (EI) *m/z* calcd for $C_{15}H_{30}O$: 226.2297, found: 226.2294.

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