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Further explorations on bridged 1,2,4-trioxanes

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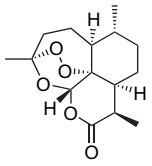
Abstract—Three new bicyclo[3.2.1]-type 1,2,4-trioxanes have been designed and synthesized. One of them demonstrates better tolerance of the intramolecular hemiketals to steric crowding in hydroperoxidation. The other represents a prototype for possible manipulation of the transient radicals generated in cleavage reactions. A new substitution pattern in the bridged system is explored through synthesis of the third molecule. The configurations of all stereogenic centers in the bridged system can be effectively controlled by the chirality of the allyl alcohol as illustrated by the enantioselective synthesis of the fourth molecule. Finally, similar bicyclo[3.3.1]-type 1,2,4-trioxanes are shown very difficult to be synthesized because of the involvement of a conformer with two substituents at axial positions at the same time.

1. Introduction

World-wide recognition of qinghaosu[1] (artemisinin) and its derivatives as effective weapons in the battle against malaria has led to a dramatically renewed interest in organic peroxides, a rather old class of organic compounds known[2a] since 1850s, and thus has greatly stimulated the studies[2b–x] on such compounds.



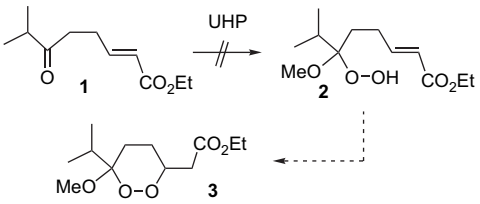
Qinghaosu
(Artemisinin)

Peroxy bonds are the central functionality of organic peroxides. Compared with other covalent bonds commonly found in organic compounds, peroxy bonds are very fragile because their average bond energy is only approximately half of that for a C–C single bond. This decides that peroxy bonds cannot survive a range of reaction conditions as well as reagents commonly employed in organic synthesis and thus makes synthesis of organic peroxides more difficult than otherwise. Besides, peroxy bonds are practically impossible to form from two alkoxyls or related species. It is therefore not surprising that the existing methods for 'making' peroxy bond(s) in an organic molecular framework are rather limited in number. Under such circumstances, making use of one of the known methods for introducing peroxy bonds in different molecular systems has become the most common practice in the synthesis of organic peroxides.

One of the practical methodologies for incorporating peroxy bond(s) into organic molecules is that introduced by Kobayashi[3] and co-workers, which utilizes UHP (urea–hydrogen peroxide complex) as the source of the peroxy functionality. By employing this protocol we have made a range of new organic peroxides, including monocyclic, fused bicyclic, spiro, and bridged ones.[4] In this paper we describe our further explorations on the bridged trioxanes.

2. Results and discussions

One of the major purposes of our studies here is to exploit the facile formation of intramolecular hemiketal in the incorporation of a hydroperoxyl group. In the previous molecular setups we already demonstrated that intramolecular hemiketals were superior to the intermolecular ones. These observations encouraged us to re-examine the possibility to include a bulky isopropyl group at ketone carbonyl group, which was shown[4b] to be impossible in an intermolecular hemiketal system (Scheme 1) with either **1** or its dimethyl ketal as the starting material.



Scheme 1.

Keywords: Antimalarials; Hemiketals; Peroxides; Cyclization; Heterocycles.
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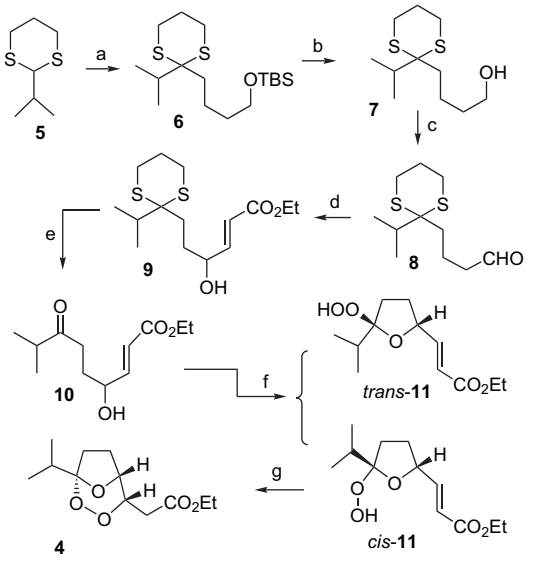
An additional thing that we wish to examine through this molecule is whether the cis/trans ratio of the hydroperoxyl intermediate could be improved by a bulkier substituent so that more desired cis isomer (with –OOH cis to the Michael acceptor) could be formed in the hydroperoxidation.

The synthesis of the first target (**4**) of this work is outlined in Scheme 2. The known dithiane **5**[5] was deprotonated with *n*-BuLi at −25 °C followed by treatment with $I(CH_2)_4OTBS$[6] to give **6** in 84% yield. The TBS protecting group was then removed with TBAF to afford alcohol **7**. A $SO_3\cdot Py$ oxidation gave the corresponding aldehyde **8**, which on treatment with $PhSOCH_2CO_2Et$ via the SPAC[7] reaction (Sulfoxide Piperidine And Carbonyl reaction) yielded alcohol **9**.

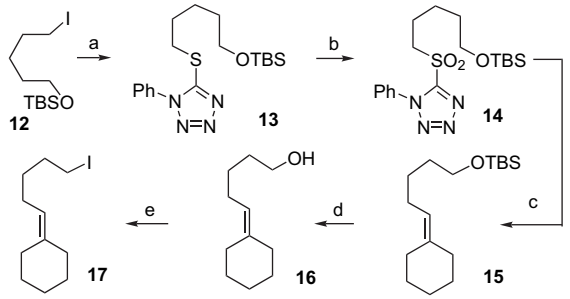


Scheme 2. (a) (i) *n*-BuLi/−25 °C/4 h; (ii) HMPA/$I(CH_2)_4OTBS$/0 °C/17 h, 84%; (b) TBAF/THF/rt/4 h, 70%; (c) $SO_3\cdot Py$/DMSO/NEt_3/CH_2Cl_2/0 °C/0.5 h, 86%; (d) $PhSOCH_2CO_2Et$/piperidine/CH_3CN/rt/17 h, 62%; (e) I_2/$NaHCO_3$/acetone–H_2O/0 °C/0.5 h, 82%; (f) UHP (ca. 7.5 equiv)/*p*-TsOH·H_2O/DME/rt/12 h, 90% (*trans*-**11**/*cis*-**11**=1.3:1); (g) cat. $HNEt_2$/CF_3CH_2OH/rt/24 h, 30%.

The sulfur protecting group was then removed to release the carbonyl group to set up a stage for incorporation of a hydroperoxyl group. To our gratification, when treating **10** with *p*-TsOH/UHP[4d] the reaction did take place as anticipated, giving **11** as a 1.3:1 mixture of the trans and cis isomers. This result proves again that with a transient intramolecular hemiketal as an immediate precursor, the driving force for the incorporation of the hydroperoxyl group is significantly increased compared with those in intermolecular cases. Thus, for the first time we are able to include an isopropyl at the carbonyl group in the ketal exchange reaction. And the content of the desired cis isomer (with the –OOH cis to the C–C double bond) in the product mixture reached an unprecedented 44%. Further treatment of *cis*-**11** with $HNEt_2$ in CF_3CH_2OH at ambient temperature for 24 h led to the desired end product **4** in 30% yield.

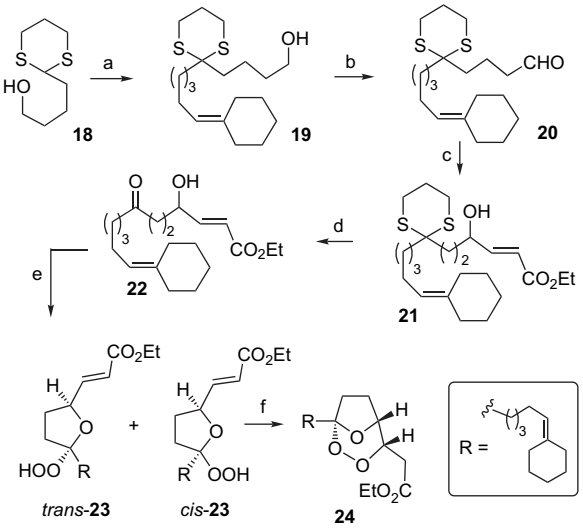
We also designed a similar trioxane that carries a different substituent in place of the isopropyl group in **4**. The side chain in this case is a substituted pentyl group with a cyclohexylidene group at the terminal, which may allow the carbon-centered radical generated in a single electron reducing species induced cleavage reaction (a likely model for in vivo antimalarial action) to evolve further into a secondary radical through an intramolecular addition[3c] and thus improve the antimalarial potency.

The synthesis is shown in Scheme 3. Reaction of the known iodide **12**[8] with 1-phenyl-1*H*-tetrazole-5-thiol followed by oxidation with *m*-CPBA led to sulfone **14**. Deprotonation of **14** with NaHMDS and reaction with cyclohexanone afforded **15**. The TBS protecting group was readily removed by treatment with TBAF. The resulting alcohol (**16**[9]) was then converted into the corresponding iodide **17**.



Scheme 3. (a) NaH/1-phenyl-1*H*-tetrazole-5-thiol/rt/overnight, 97%; (b) *m*-CPBA/$NaHCO_3$/rt/1 d, 91%; (c) NaHMDS/cyclohexanone/−78 °C/6 h, 74%; (d) TBAF/THF/0 °C/1 h, 96%; and (e) I_2/imid./PPh_3/0 °C/30 min, 85%.

With the side chain in hand, we set out to build up the framework of the second target molecule (Scheme 4). The known dithiane **18**[10] was first converted into the corresponding dianion by treatment with slightly more than 2 equiv of *n*-BuLi at −20 °C. The above mentioned iodide **17** was then introduced along with HMPA. After reaction at ambient temperature for 15 h, the desired alcohol **19** was obtained in 70% overall yield.

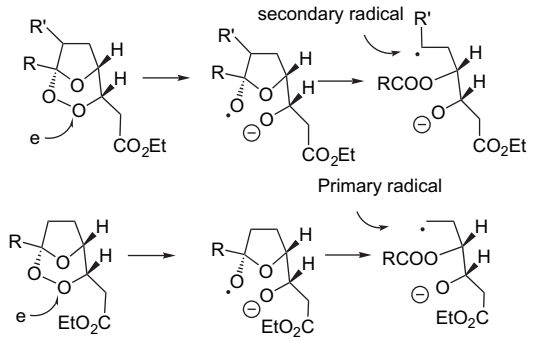


Scheme 4. (a) (i) *n*-BuLi/−20 °C/4 h, (ii) HMPA/**17**/rt/15 h, 70%; (b) $SO_3\cdot Py$/NEt_3/DMSO/0 °C, 30 min, 89%; (c) $PhSOCH_2CO_2Et$/piperidine/CH_3CN/rt/overnight, 63%; (d) I_2/$NaHCO_3$/acetone–H_2O/0 °C/0.5 h, 78%; (e) UHP/*p*-TsOH·H_2O/rt/20 h, total yield 88% (*trans*-**23**/*cis*-**23**=1.6:1); and (f) $HNEt_2$/CF_3CH_2OH/rt/15 h, 28%.

A subsequent $SO_3\cdot Py$/DMSO oxidation transformed the terminal alcohol into an aldehyde, which on exposure to

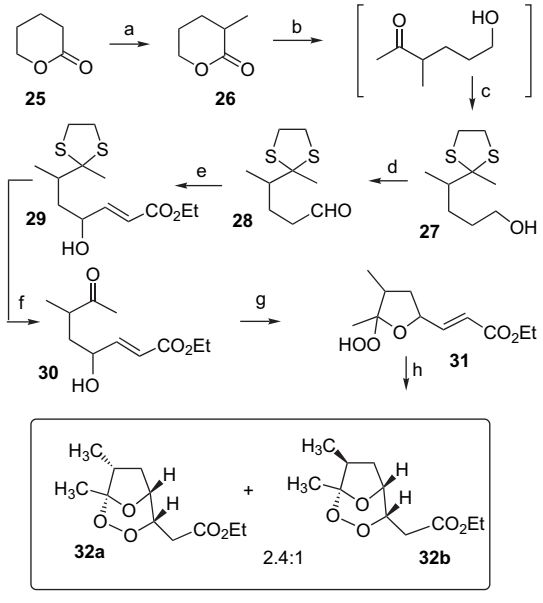
$PhSOCH_2CO_2Et$/piperidine underwent SPAC reaction smoothly yielding the ester **21**. The sulfur protecting group was then hydrolyzed with iodine to release the carbonyl group. Further reaction of **22** with UHP in the presence of *p*-TsOH·H_2O led to peroxy hemiketal **23** as a 1.6:1 mixture of the trans/cis isomers. The cis isomer was separated from the trans one on silica gel and treated with $HNEt_2$ in CF_3CH_2OH to give the end product **24** in 28% yield.

Ring substitution was also examined in this work. Introduction of a substituent in the THF ring at the position α to the ketal carbon might lead to interesting consequences in later biotesting and cleavage studies. This is because in a single electron reducing species induced cleavage,[11] a substituent at the α position would give a secondary carbon-centered radical at the position indicated in Scheme 5 instead of a primary one as might occur with other trioxanes mentioned above.



Scheme 5.

Synthesis of a target molecule of this substitution pattern is shown in Scheme 6. Starting from the commercially available lactone **25** via deprotonation with LDA and methylation with MeI in the presence of HMPA, a methyl group was introduced at the α position as reported in the literature.[12] The resultant **26** was converted into the corresponding methyl ketone by reaction with MeLi in Et_2O at −78 °C. The ketone carbonyl group was then masked with ethanedithiol before the hydroxyl group was oxidized into an aldehyde. An SPAC reaction converted **28** into **29**, completing the whole molecular framework for the target structure.



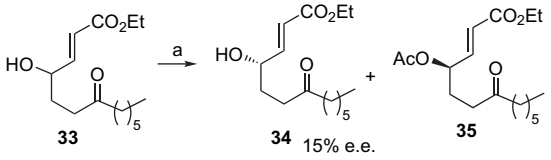
Scheme 6. (a) (i) LDA/HMPA/−15 °C, 15 min; (ii) MeI/0 °C, 6 h, 70%; (b) MeLi/Et_2O/−78 °C/30 min; (c) $HS(CH_2)_2SH/BF_3\cdot Et_2O$/rt/15 h, 64% from **26**; (d) $SO_3\cdot Py/NEt_3$/DMSO/0 °C/30 min, 91%; (e) $PhSOCH_2CO_2Et$/piperidine/CH_3CN/rt/15 h, 64%; (f) $I_2/NaHCO_3$/acetone–H_2O/0 °C/0.5 h, 78%; (g) UHP/*p*-TsOH·H_2O/rt/20 h, 90%; and (h) $HNEt_2/CF_3CH_2OH$/rt/1 d, 10% (**32a** and **32b**).

The sulfur protecting group was removed with iodine. Under the same conditions employed above for incorporating a hydroperoxyl group, **30** afforded the hydroperoxy hemiketal **31** in 90% yield as a mixture of diastereomers. These isomers are rather difficult to separate from each other. Therefore, in an initial run we directly utilized the mixture of all isomers in the subsequent ring-closure reaction. Because of larger difference in polarity, the end products **32** could be readily separated from the unreacted precursors **31** (presumably mainly the isomers with –OOH trans to the C–C double bond, which possibly cannot undergo the Michael addition).

The ^1H NMR spectrum clearly showed that **32** was a 2.4:1 mixture of two diastereomers. However, it was not possible to assign whether the major isomer is **32a** or **32b**. Fortunately, after exhaustive efforts we managed to obtain a small sample of a single diastereomer of **31** by chromatography on silica gel using 1:3 Et_2O/petroleum ether as eluant. The ring-closure product from this precursor was shown by ^1H NMR to be a single diastereomer, with the two methyl groups trans to each other as shown by the structure **32a**. And, the ^1H NMR data were consistent with the major isomer in the above mentioned 2.4:1 mixture. The minor isomer therefore must have the structure of **32b**.

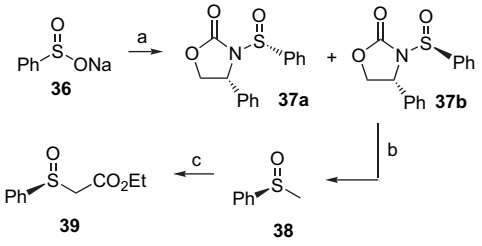
As already mentioned in a previous[4d] paper, the Michael addition (closing of the peroxy ring) proceeds in a highly stereoselective way. Consequently, the relative configuration of the whole molecule should be dictated by the first stereogenic center—the one generated in the SPAC reaction. It therefore seems possible to make optically active bridged trioxanes by employing a single enantiomer of the allyl alcohol (e.g., **9**, **21**, and **29** above).

One of the potential ways to obtain optically active alcohol is the enzymatic resolution reported by Burgess and co-workers.[13] As we still have **33**[4d] in hand, we tried that approach first. The progress of the acetylation (Scheme 7) was monitored by ^1H NMR. After 4 h of reaction about half of the starting **33** was transformed into the corresponding acetate. However, the optical rotation for the recovered alcohol (**34**) was very small ($[\alpha]_D^{20}$ −1.1), suggesting a failure in differentiating the two isomers. Chiral HPLC analysis further confirmed that the ee value of **34** was only 15%.



Scheme 7. (a) Pseudomonas AK/vinyl acetate/hexane/25 °C.

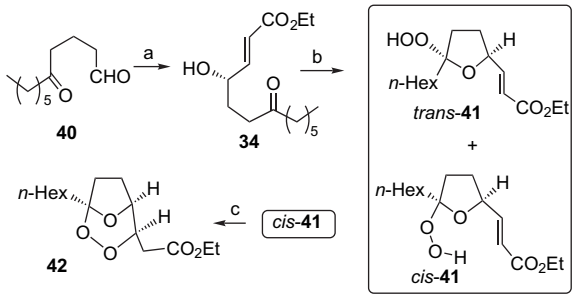
The desired enantiomerically pure allyl alcohols are also accessible from asymmetric SPAC reaction, which uses an optically active sulfoxide reagent. To obtain the desired reagent, we tried to make use of Evans auxiliary to resolve a racemic sulfoxide.[14] As shown in Scheme 8, sequential treatment of **36** with $SOCl_2$ and lithiated (*R*)-4-phenyl-oxazolidin-2-one gave an *N*-sulfinyloxazolidinone **37** as a 1.5:1 mixture separable on silica gel. At that time we were not able to assign the configurations of these two compounds. For convenience, the major component was used in the following transformations.



Scheme 8. (a) (i) $SOCl_2$/rt/2 h, (ii) (*R*)-4-phenyl-oxazolidin-2-one/*n*-BuLi/−78 °C/25 min, 87% from **36** (**37a**/**37b**=1:1.5); (b) MeMgBr/THF/−78 °C/20 min, 96%; and (c) (i) LDA/−78 °C/40 min, (ii) $ClCO_2Et$/−78 °C/5 h, 47%.

Removal of the chiral auxiliary using a Reformatsky reaction to directly obtain **39**[15] was not very successful (10–20% yields). Therefore, we next turned to an indirect way—to cut off the auxiliary with MeMgBr first to yield the desired optically active sulfoxide **38**[16] with concurrent configuration inversion as reported previously by Evans.[14] The absolute configuration of **38** was assigned by comparison with the known (*S*)-isomer[16] in the literature. Further treatment of **38** with LDA followed by $ClCO_2Et$ resulted in **39** in 47% yield.

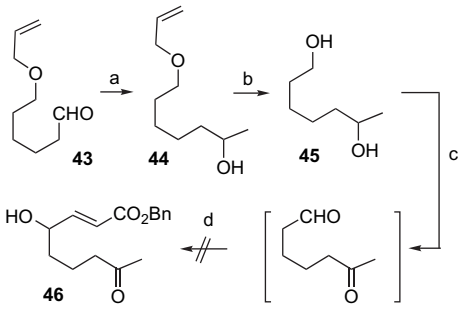
With **39** in hand, we went on with the same route used in the synthesis of racemic **42**[4d] (Scheme 9). Treatment of aldehyde **40**[4d] with the optically active reagent **39** gave **34** in 59% yield with an ee value of 95% as determined by chiral HPLC. The absolute configuration of **34** was assigned according to the rule[13] in the literature. Incorporation of hydroperoxyl group under the UHP/*p*-TsOH conditions gave *trans*-**41** and *cis*-**41** as observed before in the racemic synthesis. Finally, reaction of the isolated *cis*-**41** with $HNEt_2$ in F_3CCH_2OH gave the optically active bridged trioxane **42** as planned.



Scheme 9. (a) Piperidine/**39**/CH_3CN/rt/10 h, 59%; (b) UHP (ca. 7.5 equiv)/*p*-TsOH·H_2O/DME/rt/overnight, 35%; and (c) cat. $HNEt_2$/F_3CCH_2OH/rt/12 h, 32%.

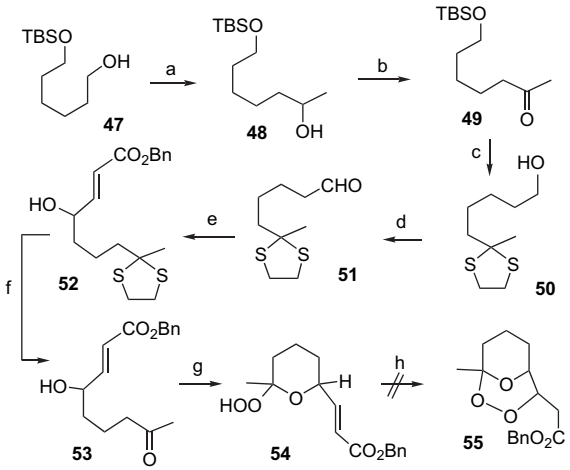
After completing several bicyclo[3.2.1]-type trioxanes, we also attempted to extend the methodology to [3.3.1] bridged system. This requires building a tetrahydropyran instead of the tetrahydrofuran in the intermediate hemiketal. In the beginning it seemed that we only needed to increase one more CH_2 unit in the carbon chain.

Thus, the known aldehyde **43**[17] was converted into alcohol **44** by reaction with MeMgBr (Scheme 10). The allyl protecting group was removed with $PdCl_2$/MeOH. The resultant diol **45**[18] was oxidized into the corresponding aldehyde–ketone and treated with $PhSOCH_2CO_2Bn$[4d]/piperidine with the hope that the SPAC reaction would take place preferentially at the aldehyde group. However, probably because of the interference of the intramolecular aldol reaction of the dicarbonyl intermediate, no expected **46** was formed at all. This result made us to adopt a slightly longer route, with the ketone group masked at the SPAC reaction.



Scheme 10. (a) MeMgBr/Et_2O/0 °C, 75%; (b) $PdCl_2$/MeOH, 62%; (c) Swern oxidation; and (d) $PhSOCH_2CO_2Bn$/piperidine/rt, 15 h.

Starting from the known alcohol **47**[19] via oxidation and MeMgBr addition, we obtained alcohol **48**[20] in 75% yield (Scheme 11). A SO_3·Py/DMSO oxidation gave the methyl ketone **49**,[20] which on treatment with $HS(CH_2)_2SH$/$F_3B\cdot OEt_2$ in CH_2Cl_2 led to carbonyl protection with



Scheme 11. (a) (i) SO_3·Py/DMSO/NEt_3/0 °C, 30 min; (ii) MeMgBr/Et_2O/0 °C, 75%; (b) SO_3·Py/DMSO/NEt_3/0 °C, 3 h, 86%; (c) $HS(CH_2)_2SH$/$F_3B\cdot OEt_2$/CH_2Cl_2/rt, 97%; (d) SO_3·Py/DMSO/NEt_3/0 °C, 30 min, 82%; (e) $PhSOCH_2CO_2Bn$/piperidine/rt/15 h, 57%; (f) I_2/$NaHCO_3$/acetone–H_2O/0 °C/15 min, 80%; (g) UHP (ca. 7.5 equiv)/*p*-TsOH·H_2O/DME/rt/12 h, 95%; and (h) cat. $HNEt_2$/F_3CCH_2OH/rt/2 d.

concurrent removal of the TBS protecting group. The newly-freed hydroxyl group was oxidized with $SO_3 \cdot Py$/DMSO, giving aldehyde **51**. Without the interference of the ketone group, the SPAC reaction occurred smoothly, affording the expected allyl alcohol **52** in 57% yield. The sulfur protecting group was then removed. The hydroxy ketone was treated with UHP/*p*-TsOH to produce hydroperoxy hemiketal **54** as a ca. 9:1 mixture of two diastereomers in an unprecedented 95% yield. However, the final ring-closure reaction did not occur as planned. Stirring with $HNEt_2$ in F_3CCH_2OH did not result in any anticipated **55**.

Prolonged reaction time (55 h) still did not make any discernible change. Raising the temperature (55 °C or reflux for 24 h), on the other hand, led to a complex mixture without organic peroxide (visualization with $Fe(SCN)_2$ on TLC). Replacing the heating with microwave (3 min) also gave a complex mixture. Using KOH, LiOH, $Me_4N^+OH^-$, DBU, DMAP, NEt_3 or pyridine to replace $HNEt_2$ did not lead to any improvement. At ambient temperature, no reaction took place. At 55 °C, all the runs led to complex mixtures but still without peroxide. We also tried to initiate the cyclization with NBS, NIS, I_2 or $Hg(OAc)_2$. Unfortunately, none of these gave useful results.

Repeated failure prompted us to look into the molecular structure to seek possible reasons. Close inspection of the stereo-model of **54** revealed that there are four possible conformations (Fig. 1) for the two sets of diastereomers of **54** (A and B for *trans*-**54**, C and D for *cis*-**54**). Among these, only conformer C of the cis isomer is able to undergo the intramolecular Michael addition to give the ring-closure product **55**. However, in this conformer, both –OOH and C–C double bond are in axial positions and thus may be of rather high energy. This seems to explain why **55** could not be formed under a variety of conditions.

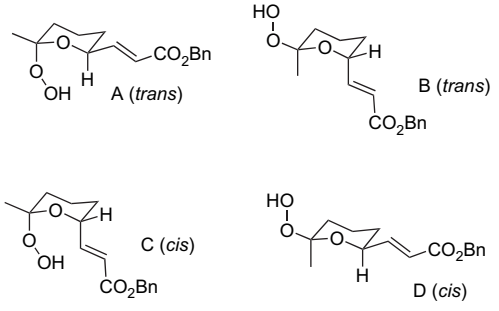


Figure 1. The four possible conformers of **54**.

3. Conclusions

Three new bicyclo[3.2.1]-type 1,2,4-trioxanes have been synthesized. One of them carries an isopropyl group at the ketal carbon, demonstrating that such intramolecular hemiketals as in the present systems are indeed more tolerable to steric crowding than those intermolecular hemiketals involved in monocyclic peroxides in the hydroperoxidation. The second trioxane reported above contains a cyclohexylidene group in the side chain and thus allows for possible evolution of the initial radical generated in a cleavage reaction. The synthesis of the third trioxane explores a new substitution pattern in the present bridged framework. To demonstrate the possibility of performing enantioselective synthesis of these trioxanes, a single enantiomer of a previously reported trioxane with an *n*-hexyl as side chain was synthesized. Finally, through exhaustive efforts it is proven that similar bicyclo[3.3.1]-type trioxanes are difficult to be synthesized probably because of the involvement of the conformation with two substituents in axial positions at the same time.

4. Experimental

4.1. General

Unless otherwise stated, the ^1H NMR and ^{13}C NMR spectra were recorded in deuterochloroform at ambient temperature using a Varian Mercury 300 or a Bruker Avance 300 instrument (operating at 300 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FTIR spectrometer. EIMS and EIHRMS were recorded with an HP 5989A and a Finnigan MAT 8430 mass spectrometer, respectively. The ESIMS and ESIHRMS were recorded with a PE Mariner API-TOF and an APEX III (7.0 T) FTMS mass spectrometer, respectively. MALDIHRMS were recorded on an IonSpec 4.7 T FTMS instrument. Elemental analyses were performed on an Elementar VarioEL III instrument. The melting point was uncorrected. Dry THF was distilled from Na/Ph_2CO under N_2. Dry HMPA, DMF, and DMSO were stirred with CaH_2 at ambient temperature under N_2 for 4 d before being distilled under reduced pressure and kept under N_2 over activated 4 Å molecular sieves. Dry CH_2Cl_2 was distilled over CaH_2 and kept over activated 4 Å molecular sieves. UHP was purchased from Acros. All other solvents and reagents were commercially available and used as received without any further purification. PE stands for petroleum ether (bp 60–90 °C).

4.1.1. Alkylation of 5 (6). *n*-BuLi (1.6 M in hexanes, 11.0 mL, 17.6 mmol) was added dropwise to a solution of **5** (2.618 g, 16.16 mmol) in dry THF (45 mL) stirred at −78 °C under N_2. After completion of the addition, the stirring was continued at −25 °C for 4 h. Dry HMPA (3.2 mL) and a solution of $I(CH_2)_4OTBS$ (5.075 g, 16.16 mmol) in dry THF (10 mL) were introduced. The mixture was stirred at 0 °C for 17 h before being diluted with Et_2O (50 mL), washed in turn with satd aq NH_4Cl, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:12 EtOAc/PE) on silica gel afforded **6** as a colorless oil (4.736 g, 13.61 mmol, 84% yield). FTIR (film) 2953, 2930, 2857, 1471, 1462, 1255, 1102, 835, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.64 (t, J=5.4 Hz, 2H), 2.92–2.84 (m, 2H), 2.77–2.69 (m, 2H), 2.15 (heptet, J=6.6 Hz, 1H), 2.02–1.87 (m, 4H), 1.59–1.49 (m, 4H), 1.18 (d, J=6.6 Hz, 6H), 0.90 (s, 9H), 0.069 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.0, 59.0, 35.6, 34.2, 33.2, 26.0, 25.7, 25.5, 20.9, 18.3, 17.7, −5.2; EIMS *m/z* (%) 348 (M^+, 2.49), 333 (M^+-CH_3, 1.72), 75 (100); EIHRMS calcd for $C_{17}H_{36}OS_2Si$ (M^+) 348.1977, found 348.1976.

4.1.2. Deprotection of 6 (7). TBAF (1 M in THF, 13.61 mL, 13.61 mmol) was added dropwise to a solution of **6** (4.736 g, 13.61 mmol) in THF (27 mL) stirred at 0 °C. The stirring was then continued at ambient temperature for 17 h. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:6 EtOAc/PE) on silica gel afforded **7** as a colorless oil (2.230 g, 9.53 mmol, 70% yield). FTIR (film) 3371, 1460, 1385, 1274, 1168 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68 (t, J=6.1 Hz, 2H), 2.87 (ddd, J=3.4, 9.6, 14.0 Hz, 2H), 2.75 (ddd, J=3.6, 6.0, 10.4 Hz, 2H), 2.17 (heptet, J=6.8 Hz, 1H), 2.02–1.87 (m, 4H), 1.65–1.54 (m, 5H), 1.12 (d, J=6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.8, 58.9, 35.3, 34.0, 33.0, 25.7, 25.4, 20.9, 17.7; EIMS m/z (%) 234 (M^+, 7.19), 191 (100); EIHRMS calcd for $C_{11}H_{22}OS_2$ (M^+) 234.1112, found 234.1105.

4.1.3. Oxidation of 7 (8). A solution of $SO_3\cdot Py$ (850 mg, 5.34 mmol) in DMSO (7.5 mL) was added dropwise to a solution of **7** (500 mg, 2.13 mmol) and NEt_3 (1.47 mL, 10.65 mmol) in dry CH_2Cl_2 (10 mL) was stirred in an ice-water bath. The stirring was continued at the same temperature for 30 min. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:15 EtOAc/PE) on silica gel afforded **8** as a colorless oil (425 mg, 1.83 mmol, 86% yield). FTIR (film) 1732, 1457, 1418, 1386, 1275 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1H), 2.89 (ddd, J=3.5, 9.9, 14.0 Hz, 2H), 2.73 (ddd, J=3.8, 5.7, 14.4 Hz, 2H), 2.50 (t, J=6.5 Hz, 2H), 2.17 (heptet, J=6.7 Hz, 1H), 2.03–1.80 (m, 6H), 1.12 (d, J=6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.2, 58.6, 43.9, 35.0, 34.1, 25.7, 25.3, 17.7, 17.4; ESIMS m/z 233.2 ([M+H]$^+$); EIHRMS calcd for $C_{11}H_{20}OS_2$ (M^+) 232.0956, found 232.0957.

4.1.4. Synthesis of 9. A solution of **8** (188 mg, 0.81 mmol) in CH_3CN (3 mL) was added to a solution of $PhSOCH_2CO_2Et$ (173 mg, 0.81 mmol) and piperidine (0.081 mL, 0.81 mmol) in CH_3CN (2 mL). The mixture was stirred at ambient temperature overnight before being diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:6 EtOAc/PE) on silica gel afforded **9** as a yellowish oil (160 mg, 0.50 mmol, 62% yield). FTIR (film) 3465, 1718, 1656, 1368, 1304, 1274, 1174, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (dd, J=4.7, 15.6 Hz, 1H), 6.07 (d, J=15.6 Hz, 1H), 4.36 (br s, 1H), 4.21 (q, J=7.1 Hz, 2H), 2.89 (ddd, J=2.8, 9.7, 13.9 Hz, 2H), 2.73 (ddd, J=3.3, 5.5, 13.9 Hz, 2H), 2.21–1.68 (m, 8H), 1.30 (t, J=7.1 Hz, 3H), 1.12 (d, J=6.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 149.7, 120.6, 71.1, 60.5, 58.6, 34.2, 31.67, 31.0, 25.7, 25.23, 17.6, 14.2; EIMS m/z (%) 318 (M^+, 0.89), 300 (M^+-H_2O, 0.51), 41 (100); EIHRMS calcd for $C_{15}H_{26}O_3S_2$ (M^+) 318.1323, found 318.1329.

4.1.5. Deprotection of 9 (10). $NaHCO_3$ (409 mg, 4.87 mmol) and I_2 (498 mg, 1.96 mmol) were added to a solution of **9** (180 mg, 0.57 mmol) in CH_3COCH_3–H_2O (3 mL, 5:1 v/v) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at the same temperature for 15 min before the excess I_2 was destroyed by addition of satd aq $Na_2S_2O_3$ (2 mL). The mixture was extracted with EtOAc (3×30 mL). The combined organic phases were washed with satd aq $Na_2S_2O_3$, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:5 EtOAc/PE) on silica gel afforded **10** as a yellowish oil (105 mg, 0.46 mmol, 81% yield). FTIR (film) 3482, 1716, 1658, 1468, 1369, 1304, 1273, 1176, 1041, 982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (dd, J=4.6, 15.3 Hz, 1H), 6.07 (d, J=15.8 Hz, 1H), 4.37 (br s, 1H), 4.20 (q, J=7.2 Hz, 2H), 2.84 (d, J=4.5 Hz, 1H), 2.68–2.59 (m, 2H), 2.01–1.76 (m, 3H), 1.29 (t, J=6.9 Hz, 3H), 1.10 (d, J=7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.5, 166.5, 149.6, 120.6, 70.2, 60.4, 41.0, 35.9, 29.8, 18.3, 18.2,[21] 14.2; EIMS m/z (%) 228 (M^+, 0.11), 210 (M^+-H_2O, 3.37), 43 (100); EIHRMS calcd for $C_{12}H_{18}O_3$ ([M^+-H_2O]) 210.1256, found 210.1259.

4.1.6. Synthesis of 4. A solution of **10** (47 mg, 0.21 mmol), UHP (148 mg, 1.58 mmol), and *p*-TsOH (monohydrate, 53 mg, 0.28 mmol) in $MeO(CH_2)_2OMe$ (4 mL) was stirred at ambient temperature overnight. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:8 EtOAc/PE) on silica gel afforded *cis*-**11** (colorless oil, 20 mg, 0.082 mmol) and *trans*-**11** (colorless oil, 26 mg, 0.11 mmol). Total yield: 90%. Data for *cis*-**11** (the less polar component): ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 6.99 (dd, J=15.6, 6.1 Hz, 1H), 6.06 (d, J=15.7 Hz, 1H), 4.64–4.61 (m, 1H), 4.21 (q, J=7.1 Hz, 2H), 2.36 (heptet, J=7.0 Hz, 1H), 2.13–1.96 (m, 4H), 1.30 (t, J=7.1 Hz, 3H), 0.97 (d, J=6.7 Hz, 3H), 0.96 (d, J=7.3 Hz, 3H). Data for *trans*-**11** (the more polar component): ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 1H), 6.93 (dd, J=15.4, 5.3 Hz, 1H), 6.06 (d, J=15.9 Hz, 1H), 4.82–4.76 (m, 1H), 4.21 (q, J=7.2 Hz, 2H), 2.42 (7, J=6.9 Hz, 1H), 2.33–12.22 (m, 1H), 2.05 (ddd, J=4.1, 9.5, 13.7 Hz, 1H), 2.09–2.00 (m, 1H), 1.68–1.55 (m, 1H), 1.30 (t, J=7.2 Hz, 3H), 0.99 (d, J=6.8 Hz, 3H), 0.97 (d, J=6.8 Hz, 3H).

A solution of *cis*-**11** (37 mg, 0.15 mmol) and $HNEt_2$ (2 μL, 0.019 mmol) in CF_3CH_2OH (4 mL) was stirred at ambient temperature for 1 d. The solvent was removed by rotary evaporation. The residue was chromatographed (1:12 EtOAc/PE) on silica gel to give **4** as colorless oil (11 mg, 0.045 mmol, 30% yield). FTIR (film) 2925, 2854, 1741, 1462, 1185, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.87 (t, J=6.7 Hz, 1H), 4.34–4.33 (m, 1H), 4.16 (q, J=7.1 Hz, 2H), 2.37–2.23 (m, 3H), 1.99–1.87 (m, 4H), 1.27 (t, J=7.1 Hz, 3H), 0.99 (d, J=5.5 Hz, 3H), 0.98 (d, J=5.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 114.7, 80.2, 77.2, 61.1, 34.9, 32.6, 30.2, 23.9, 17.1, 16.8, 14.1; ESIMS m/z 267.2 ([M+Na]$^+$); MALDIHRMS calcd for $C_{12}H_{20}O_5Na$ ([M+Na]$^+$) 267.1203, found 267.1211.

4.1.7. Synthesis of 13. A solution of 1-phenyl-1*H*-tetrazole-5-thiol (PTTS, 5.764 g, 32.38 mmol) in dry THF (12 mL) was added to a mixture of NaH (60% in mineral oil, washed with hexanes before use, 1.3 g, 32.38 mmol) in dry THF (48 mL) and dry DMF (8 mL). The mixture was stirred at ambient temperature for 30 min. A solution of **12** (5.31 g, 16.19 mmol) in dry THF (12 mL) was then introduced.

The stirring was continued at ambient temperature overnight. Excess hydride was quenched by addition of satd aq NH_4Cl. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:10 EtOAc/PE) on silica gel afforded **13** as a colorless oil (5.940 g, 15.71 mmol, 97% yield). FTIR (film) 1500, 1471, 1462, 1387, 1250, 1103, 835, 776, 760 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58–7.51 (m, 5H), 3.57 (t, J=5.8 Hz, 2H), 3.37 (t, J=7.3 Hz, 2H), 1.81 (quintet, J=7.1 Hz, 2H), 1.54–1.44 (m, 4H), 0.84 (s, 9H), 0 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 133.8, 130.1, 129.8, 123.9, 62.8, 33.3, 32.1, 28.9, 26.0, 25.0, 18.4, −5.3; ESIMS m/z ($[M+H]^+$) 379.2; EIHRMS calcd for $C_{18}H_{30}N_4OSiS$ (M^+) 378.1910, found 378.1906.

4.1.8. Oxidation of 13 (14). A mixture of **13** (3.218 g, 8.51 mmol), *m*-CPBA (70%, 5.25 g, 21.28 mmol), and $NaHCO_3$ (3.547 g, 42.55 mmol) in CH_2Cl_2 (42 mL) was stirred at ambient temperature for 24 h. Satd aq $Na_2S_2O_3$was added. The mixture was stirred vigorously before being extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were washed with satd aq $NaHCO_3$ and brine before being dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:10 EtOAc/PE) on silica gel afforded **14** as a colorless oil (3.175 g, 7.74 mmol, 91% yield). FTIR (film) 1596, 1498, 1471, 1463, 1342, 1256, 1154, 1103, 836, 776, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 77.67–7.54 (m, 5H), 3.73–3.67 (m, 2H), 3.53 (t, J=5.9 Hz, 2H), 1.99–1.88 (m, 2H), 1.59–1.50 (m, 4H), 0.84 (s, 9H), 0 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5, 133.1, 131.5, 129.7, 125.1, 62.4, 56.0, 32.0, 26.0, 24.7, 21.8, 18.3, −5.3; ESIMS m/z 411.2 ($[M+H]^+$); MALDIHRMS calcd for $C_{18}H_{30}N_4O_3$-SiSNa ($[M+Na]^+$) 433.1700, found 433.1705.

4.1.9. Julia coupling of 14 with cyclohexanone (15). NaHMDS (2.0 M in THF, 3 mL, 5.93 mmol) was added to a solution of **14** (2.114 g, 5.16 mmol) in dry THF (18 mL) stirred at −78 °C under N_2. After stirring for another 30 min at the same temperature, the reaction was quenched by addition of satd aq NH_4Cl (2 mL). Most of the solvent was removed on a rotary evaporator. The residue was extracted with Et_2O (3×30 mL), washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:50 EtOAc/PE) on silica gel afforded **15** as a colorless oil (1.077 g, 3.82 mmol, 74% yield). FTIR (film) 1472, 1462, 1447, 1255, 1104, 835, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.01 (t, J=7.2 Hz, 1H), 3.56 (t, J=6.5 Hz, 2H), 2.08–1.90 (m, 6H), 1.52–1.40 (m, 8H), 1.35–1.25 (m, 2H), 0.85 (s, 9H), 0 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 121.3, 63.2, 37.2, 32.5, 28.7, 27.9, 27.0, 26.8, 26.4, 26.0, 18.4, −5.2; EIMS m/z (%) 282 (M^+, 0.20), 267 (M^+-CH_3, 1.47), 67 (100); EIHRMS calcd for $C_{16}H_{31}OSi$ (M^+-CH_3) 267.2144, found 267.2137.

4.1.10. Deprotection of 15 (16). TBAF (1 M in THF, 2.9 mL, 2.86 mmol) was added dropwise to a solution of **15** (806 mg, 2.86 mmol) in THF (5 mL) stirred at 0 °C. The stirring was then continued at ambient temperature for 1 h. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:3 EtOAc/PE) on silica gel afforded **16**[9] as a colorless oil (460 mg, 2.74 mmol, 96% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (t, J=7.2 Hz, 1H), 3.64 (t, J=6.0 Hz, 2H), 2.14–1.98 (m, 6H), 1.60–1.37 (m, 11H).

4.1.11. Conversion of alcohol 16 into iodide 17. I_2 (775 mg, 3.05 mmol) was added in portions to a mixture of **16** (426 mg, 2.54 mmol), PPh_3 (799 mg, 3.05 mmol), and imidazole (207 mg, 3.05 mmol) in Et_2O–CH_3CN (5:1 v/v, 12 mL) stirred in an ice-water bath. After completion of the addition, the stirring was continued at the same temperature for 30 min. The mixture was diluted with *n*-hexane. Solids were filtered off. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed (PE) on silica gel to give **17** as a colorless oil (600 mg, 2.16 mmol, 85% yield). FTIR (film) 2925, 2852, 1446, 1218, 1197 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (t, J=7.2 Hz, 1H), 3.19 (t, J=7.2 Hz, 2H), 2.13–1.97 (m, 6H), 1.83 (quintet, J=7.4 Hz, 2H), 1.54–1.38 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 120.5, 32.2, 33.1, 31.0, 28.7, 27.9, 27.0, 25.9, 7.2; EIMS m/z (%) 278 (M^+, 5.04), 67 (100); EIHRMS calcd for $C_{11}H_{19}I$ (M^+) 278.0532, found 278.0536.

4.1.12. Alkylation of dithiane 18 with iodide 17 (19). *n*-BuLi (1.6 M in hexanes, 6.9 mL, 11 mmol) was added dropwise to a solution of **18** (960 mg, 5.00 mmol) in dry THF (20 mL) stirred at −78 °C under N_2. After completion of the addition, the stirring was continued at −25 °C for 4 h. Dry HMPA (2 mL) and a solution of **17** (1.390 g, 5.00 mmol) in dry THF (5 mL) were introduced. The mixture was stirred at 0 °C for 15 h before being diluted with Et_2O (50 mL), washed in turn with satd aq NH_4Cl, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:5 EtOAc/PE) on silica gel afforded **19** as a colorless oil (1.193 g, 3.94 mmol, 70% yield). FTIR (film) 3391, 2928, 2852, 1446, 1274, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (t, J=7.2 Hz, 1H), 3.68 (t, J=6.1 Hz, 2H), 2.83–2.79 (m, 4H), 2.13–1.83 (m, 12H), 1.72 (br s, 1H), 1.64–1.25 (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 121.0, 62.7, 53.3, 38.2, 38.0, 37.2, 32.8, 30.4, 28.7, 27.9, 27.0, 26.9, 26.0, 25.6, 23.7, 20.5; ESIMS m/z 343.2 ($[M+H]^+$); MALDIHRMS calcd for $C_{19}H_{35}OS_2$ ($[M+H]^+$) 343.2124, found 343.2128.

4.1.13. Oxidation of alcohol 19 (20). A solution of $SO_3\cdot Py$ (111 mg, 0.70 mmol) in DMSO (1 mL) was added to a solution of **19** (95 mg, 0.28 mmol) and NEt_3 (0.19 mL, 1.38 mmol) in dry CH_2Cl_2 (1.5 mL) stirred in an ice-water bath. The stirring was continued at the same temperature for 30 min. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:10 EtOAc/PE) on silica gel afforded **20** as a colorless oil (85 mg, 0.25 mmol, 89% yield). FTIR (film) 2927, 2851, 1725, 1447, 1275 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 5.06 (t, J=7.5 Hz, 1H), 2.89–2.73 (m, 4H), 2.48 (t, J=7.4 Hz, 2H), 2.13–1.73 (m, 14H), 1.52–1.26 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 139.9, 121.0, 53.1, 43.7, 38.4, 37.4, 37.2, 30.3, 28.7, 27.9, 27.0, 26.9, 26.0, 25.4, 23.6, 17.2; ESIMS m/z 341.2

([M+H]$^+$); EIHRMS calcd for $C_{19}H_{32}OS_2$ (M^+) 340.1895, found 340.1893.

4.1.14. Synthesis of 21. A solution of **20** (445 mg, 1.31 mmol) in CH_3CN (3 mL) was added to a solution of $PhSOCH_2CO_2Et$ (278 mg, 1.31 mmol) and piperidine (0.13 mL, 1.31 mmol) in CH_3CN (5 mL). The mixture was stirred at ambient temperature overnight before being diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:6 EtOAc/PE) on silica gel afforded **21** as a colorless oil (353 mg, 0.83 mmol, 63% yield). FTIR (film) 3458, 1720, 1657, 1447, 1368, 1273, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (dd, J=15.7, 5.0 Hz, 1H), 6.06 (d, J=15.5 Hz, 1H), 5.06 (t, J=7.3 Hz, 1H), 4.36–4.34 (m, 1H), 4.21 (q, J=7.1 Hz, 2H), 2.90–2.75 (m, 4H), 2.13–2.04 (m, 11H), 1.84–1.67 (m, 4H), 1.52–1.25 (m, 10H), 1.30 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 149.6, 139.9, 121.0, 120.6, 71.0, 60.5, 53.0, 38.5, 37.2, 33.4, 31.4, 30.3, 28.7, 27.9, 27.0, 26.9, 26.0, 25.4, 23.5, 14.3; ESIMS m/z 449.3 ([M+Na]$^+$); MALDIHRMS calcd for $C_{23}H_{38}O_3S_2Na$ ([M+Na]$^+$) 449.2155, found 449.2168.

4.1.15. Deprotection of 21 (22). $NaHCO_3$ (548 mg, 6.53 mmol) and I_2 (666 mg, 2.63 mmol) were added to a solution of **21** (320 mg, 0.75 mmol) in CH_3COCH_3–H_2O (7.5 mL, 5:1 v/v) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at the same temperature for 15 min before the excess I_2 was destroyed by addition of satd aq $Na_2S_2O_3$ (2 mL). The mixture was extracted with EtOAc (3×30 mL). The combined organic phases were washed with satd aq $Na_2S_2O_3$, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:5 EtOAc/PE) on silica gel afforded **22** as a yellowish oil (196 mg, 0.58 mmol, 78% yield). FTIR (film) 3481, 1718, 1658, 1447, 1386, 1303, 1271, 1175 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (dd, J=15.9, 4.4 Hz, 1H), 6.07 (d, J=16.2 Hz, 1H), 5.04 (t, J=7.8 Hz, 1H), 4.37 (br s, 1H), 4.20 (q, J=7.1 Hz, 2H), 2.80 (s, 1H), 2.59 (dt, J=3.4, 6.7 Hz, 2H), 2.43 (t, J=6.9 Hz, 2H), 2.12–1.93 (m, 7H), 1.85–1.75 (m, 2H), 1.62–1.46 (m, 7H), 1.36–1.25 (m, 2H), 1.30 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.1, 166.5, 149.6, 128.6, 120.7, 120.7, 70.2, 42.9, 38.3, 37.2, 29.7, 29.7, 28.7, 27.9, 27.9, 27.0, 28.5, 14.3; ESIMS m/z 359.3 ([M+Na]$^+$); MALDIHRMS calcd for $C_{20}H_{32}O_4Na$ ([M+Na]$^+$) 359.2193, found 359.2211.

4.1.16. Synthesis of 24. A solution of **22** (175 mg, 0.52 mmol), UHP (367 mg, 3.90 mmol), and p-TsOH (monohydrate, 119 mg, 0.64 mmol) in $MeO(CH_2)_2OMe$ (10 mL) was stirred at ambient temperature overnight. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:10 EtOAc/PE) on silica gel afforded *cis*-**23** (colorless oil, 62 mg, 0.18 mmol) and *trans*-**23** (colorless oil, 100 mg, 0.28 mmol). Total yield: 88%. Data for compound *cis*-**23** (the less polar component): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 6.98 (dd, J=16.3, 6.1 Hz, 1H), 6.05 (d, J=16.0 Hz, 1H), 5.06 (t, J=7.1 Hz, 1H), 4.68–4.66 (m, 1H), 4.20 (q, J=7.1 Hz, 2H), 2.18–1.92 (m, 11H), 1.72–1.62 (m, 1H), 1.57–1.19 (m, 10H), 1.29 (t, J=7.2 Hz, 3H). Data for compound *trans*-**23** (the more polar component): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 6.91 (dd, J=15.8, 5.1 Hz, 1H), 6.05 (d, J=15.6 Hz, 1H), 5.06 (t, J=7.3 Hz, 1H), 4.79–4.77 (m, 1H), 4.21 (q, J=7.1 Hz, 2H), 2.32–2.26 (m, 1H), 2.13–1.91 (m, 10H), 1.74–1.63 (m, 2H), 1.51–1.25 (m, 9H), 1.30 (t, J=7.1 Hz, 3H).

A solution of *cis*-**23** (60 mg, 0.17 mmol) and $HNEt_2$ (6 μL, 0.055 mmol) in CF_3CH_2OH (10 mL) was stirred at ambient temperature for 15 h. The solvent was removed by rotary evaporation. The residue was chromatographed (1:20 EtOAc/PE) on silica gel to give **24** as colorless oil (17 mg, 0.048 mmol, 28% yield). FTIR (film) 1740, 1460, 1378, 1331, 1278, 1184, 1025, 969, 913 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.04 (t, J=7.2 Hz, 1H), 4.87 (t, J=6.9 Hz, 1H), 4.38 (d, J=5.1 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 2.37–2.22 (m, 3H), 2.11–2.04 (m, 4H), 2.00–1.87 (m, 5H), 1.76–1.69 (m, 2H), 1.52–1.38 (m, 8H), 1.36–1.30 (m, 2H), 1.26 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 139.8, 121.0, 112.5, 80.1, 77.0, 61.1, 37.2, 34.9, 34.1, 32.6, 30.3, 28.7, 27.8, 27.0, 26.8, 24.1, 23.1, 14.1; ESIMS m/z ([M+Na]$^+$) 375.3; MALDIHRMS calcd for $C_{20}H_{32}O_5Na$ ([M+Na]$^+$) 375.2142, found 375.2155.

4.1.17. Synthesis of 27. MeLi·LiBr (1.6 M in Et_2O, 3.12 mL, 5 mmol) was added dropwise to a solution of **26** (570 mg, 5.0 mmol) in dry Et_2O (25 mL) stirred at −78 °C under N_2. After completion of the addition, the stirring was continued at the same temperature for 15 min before the mixture was diluted with Et_2O, washed with satd aq NH_4Cl, water, and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was dissolved in CH_2Cl_2 (25 mL). To this solution were added in turn $HS(CH_2)_2SH$ (0.49 mL, 5.0 mmol) and $BF_3\cdot Et_2O$ (0.12 mL, 1.0 mmol) with cooling (ice-water bath) and stirring. The mixture was then stirred at ambient temperature. When TLC showed completion of the reaction, acetone was added. The mixture was stirred at ambient temperature overnight before being diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:6 EtOAc/PE) on silica gel afforded **27** as a yellowish oil (660 mg, 3.2 mmol, 64% yield from **26**). FTIR (film) 3361, 1444, 1371, 1277, 1094, 1055 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.66 (t, J=6.3 Hz, 2H), 3.35–3.25 (m, 4H), 1.97–1.68 (m, 4H), 1.71 (s, 3H), 1.57–1.44 (m, 1H), 1.31–1.19 (m, 1H), 1.12 (d, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.9, 62.7, 45.9, 39.5, 39.5, 31.2, 30.8, 28.9, 17.4; EIMS m/z (%) 206 (M^+, 0.41), 119 (100); EIHRMS calcd for $C_9H_{18}OS_2$ (M^+) 206.0799, found 206.0806.

4.1.18. Oxidation of 27 (28). A solution of $SO_3\cdot Py$ (1.50 g, 9.38 mmol) in DMSO (13 mL) was added to a solution of **27** (735 mg, 3.57 mmol) and NEt_3 (2.5 mL, 17.85 mmol) in dry CH_2Cl_2 (12 mL) stirred in an ice-water bath. The stirring was continued at the same temperature for 30 min. The mixture was diluted with Et_2O, washed with satd aq $CuSO_4$, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:15 EtOAc/PE) on silica gel afforded **28** as

a colorless oil (665 mg, 3.26 mmol, 91% yield). FTIR (film) 2965, 2922, 1742, 1372, 1277 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.79 (s, 1H), 3.35–3.25 (m, 4H), 2.56–2.44 (m, 2H), 2.22–2.17 (m, 1H), 1.94–1.85 (m, 1H), 1.73 (s, 3H), 1.54–1.47 (m, 1H), 1.10 (d, J=6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 72.5, 45.9, 42.7, 39.8, 39.7, 29.3, 26.9, 17.1; ESIMS m/z ($[M+H]^+$) 205.1; EIHRMS calcd for $C_9H_{16}OS_2$ (M^+) 204.0643, found 204.0641.

4.1.19. Synthesis of 29. A solution of **28** (612 mg, 3.0 mmol) in CH_3CN (3 mL) was added to a solution of $PhSOCH_2CO_2Et$ (636 mg, 3.0 mmol) and piperidine (0.3 mL, 3.0 mmol) in CH_3CN (10 mL). The mixture was stirred at ambient temperature for 15 h before being diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:4 EtOAc/PE) on silica gel afforded **29** as a yellowish oil (1:1 mixture of two diastereomers, 557 mg, 1.92 mmol, 64% yield). FTIR (film) 3443, 1717, 1656, 1446, 1370, 1302, 1276, 1177, 1038, 982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00–6.91 (m, 1H), 6.11–6.03 (m, 1H), 4.49–4.29 (m, 1H), 4.21 (q, J=7.0 Hz, 2H), 3.35–3.26 (m, 4H), 2.33–2.23 (m, 0.5H), 2.13–1.89 (m, 2.5H), 1.72 (s, 3H), 1.63–1.50 (m, 1H), 1.30 (t, J=7.7 Hz, 3H), 1.18–1.15 (m, 3H); ESIMS m/z 313.1 ($[M+Na]^+$); Anal. calcd for $C_{13}H_{22}O_3S_2$ C 53.76, H 7.63, found C 53.82, H 7.54.

4.1.20. Deprotection of 29 (30). $NaHCO_3$ (2.54 g, 30.28 mmol) and I_2 (3.094 g, 12.18 mmol) were added to a solution of **29** (1:1 mixture of the two diastereomers, 1.010 g, 3.48 mmol) in CH_3COCH_3–H_2O (20 mL, 5:1 v/v) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at the same temperature for 15 min before the excess I_2 was destroyed by addition of satd aq $Na_2S_2O_3$ (5 mL). The mixture was extracted with EtOAc (3×30 mL). The combined organic phases were washed with satd aq $Na_2S_2O_3$, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:4 EtOAc/PE) on silica gel afforded **30** as a colorless oil (580 mg, 2.71 mmol, 78% yield). FTIR (film) 3420, 1720, 1656, 1461, 1369, 1305, 1273, 1181, 1036, 981, 864 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.00–6.85 (m, 1H), 6.11–5.95 (m, 1H), 4.75–4.33 (m, 1H), 4.32–4.11 (m, 2H), 2.80–1.88 (m, 5H), 1.76–1.00 (m, 8H); ESIMS m/z 237.2 ($[M+Na]^+$); Anal. calcd for $C_{11}H_{18}O_4$ C 61.66, H 8.47, found C 61.27, H 8.80.

4.1.21. Synthesis of 32 (mixture). A solution of **30** (1:1 mixture of the two diastereomers, 546 mg, 2.55 mmol), UHP (1.798 g, 19.13 mmol), and p-TsOH (monohydrate, 582 mg, 3.06 mmol) in $MeO(CH_2)_2OMe$ (50 mL) was stirred at ambient temperature for 20 h. The mixture was diluted with Et_2O (100 mL), washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:6 EtOAc/PE) on silica gel afforded **31** as a colorless oil (a 1:1.9:2.3:3.4 mixture of four diastereomers, 530 mg, 2.30 mmol, 90% yield in total). This mixture was used in the next step.

Further chromatography (1:3 Et_2O/PE) on silica gel led to a single diastereomer (*a priori*, *cis*-**31**), which gave the following data: ^1H NMR (300 MHz, $CDCl_3$) δ 7.81 (s, 1H), 6.95 (dd, J=5.9, 15.4 Hz, 1H), 6.05 (d, J=15.8 Hz, 1H), 4.68–4.64 (m, 1H), 4.21 (q, J=7.4 Hz, 2H), 2.26–2.18 (m, 2H), 1.84–1.75 (m, 1H), 1.49 (s, 3H), 1.13 (t, J=7.4 Hz, 3H), 1.11 (d, J=6.2 Hz, 3H).

A solution of **31** (the mixture of four diastereomers, 390 mg, 1.70 mmol) and $HNEt_2$ (22 μL, 0.21 mmol) in CF_3CH_2OH (53 mL) was stirred at ambient temperature for 1 d. The solvent was removed by rotary evaporation. The residue was chromatographed (1:10 EtOAc/PE) on silica gel to give **32a** and **32b** as colorless oil (1:2.4 mixture of two diastereomers, 39 mg, 0.17 mmol, 10% yield). FTIR (film) 2983, 2879, 1738, 1455, 1381, 1183, 997, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.88–4.81 (m, 1H), 4.32–4.27 (m, 1H), 4.16 (q, J=7.1 Hz, 2H), 2.35–2.19 (m, 4H), 1.56–1.51 (m, 1H), 1.33 (s, 2.13H), 1.32 (s, 0.87H), 1.29–1.21 (m, 5.13H), 0.87 (d, J=7.2 Hz, 0.87H); ESIMS m/z 231.2 ($[M+H]^+$); Anal. calcd for $C_{11}H_{18}O_5$ C 57.38, H 7.88; found C 57.29, H 7.89.

4.1.22. Synthesis of 32a. A solution of *cis*-**31** (the isolated diastereomer mentioned above, 51 mg, 0.22 mmol) and $HNEt_2$ (6 μL, 0.07 mmol) in CF_3CH_2OH (6 mL) was stirred at ambient temperature overnight. The solvent was removed by rotary evaporation. The residue was chromatographed (1:10 EtOAc/PE) on silica gel to give **32a** as a colorless oil (16 mg, 0.07 mmol, 32% yield). FTIR (film) 1738, 1455, 1381, 1183, 997, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.85 (t, J=6.9 Hz, 1H), 4.30 (d, J=7.2 Hz, 1H), 4.16 (q, J=7.1 Hz, 2H), 3.11–2.91 (m, 4H), 1.55–1.51 (m, 1H), 1.33 (s, 3H), 1.28–1.21 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 111.3, 79.5, 76.3, 61.1, 40.9, 34.7, 31.8, 18.9, 14.1, 12.5; ESIMS m/z 231.15 ($[M+H]^+$); EIHRMS calcd for $C_{11}H_{18}O_5$ (M^+) 230.1154, found 230.1160.

4.1.23. Synthesis of 37a and 37b. Sodium benzenesulfinate (10 g, 50 mmol) was added in portions to $SOCl_2$ (10.9 mL, 150 mmol) stirred at ambient temperature. After completion of the addition, the stirring was continued for 2.5 h. Excess $SOCl_2$ was removed by rotary evaporation. The residue was diluted with Et_2O and re-evaporated to dryness. The residue (crude PhSOCl) was dissolved in dry THF to form a solution (25 mL) for the subsequent reaction.

n-BuLi (1.6 M, 3.13 mL, 5 mmol) was added to a solution of (*R*)-4-phenyl-oxazolidin-2-one (815 mg, 5 mmol) in dry THF (10 mL) stirred in an ice-water bath under N_2. After stirring for 5 min, the cooling bath was replaced with an acetone-dry ice bath (−78 °C). The above prepared PhSOCl solution (5.5 mL from the 25 mL stock solution) was added quickly. The stirring was continued at −78 °C for 25 min before satd aq NH_4Cl was introduced. The mixture was diluted with EtOAc, washed first with satd aq $NaHCO_3$ to pH=7, then with brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:3.3 EtOAc/PE) on silica gel afforded **37a** (500 mg, 1.74 mmol) and **37b** (749 mg, 2.61 mmol). Total yield: 87%. Data for compound **37a**: $[\alpha]_D^{20}$ −362.8 (c 1.12, $CHCl_3$); mp 119–121 °C. FTIR (film) 1738, 1455, 1381, 1183, 997, 861 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63–7.48 (m, 5H), 7.36–7.32 (m, 3H), 7.15–7.11 (m, 2H), 4.56–4.49 (m, 2H), 4.14 (t, J=10.5 Hz, 1H); ESIMS

288.2 ([M+H]$^+$), 310.1 ([M+Na]$^+$); Anal. calcd for $C_{15}H_{13}NO_3S$ C 62.70, H 4.56, N 4.87, found C 62.84, H 4.66, N 4.65. Data for compound **37b**: $[\alpha]_D^{20}$ −92.6 (*c* 0.78, $CHCl_3$); mp 117–118 °C. FTIR (film) 2983, 2879, 1738, 1455, 1381, 1183, 997, 861 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–6.86 (m, 10H), 5.29 (t, *J*=7.8 Hz, 1H), 4.71 (t, *J*=9.8 Hz, 1H), 4.21 (t, *J*=8.2 Hz, 1H); ESIMS *m/z* 288.2 ([M+H]$^+$), 310.1 ([M+Na]$^+$); Anal. calcd for $C_{15}H_{13}NO_3S$ C 62.70, H 4.56, N 4.87, found C 62.75, H 4.56, N 4.67.

4.1.24. Synthesis of 38. MeMgBr (1.7 M in Et_2O, 1.4 mL, 2.31 mmol) was added dropwise to a solution of **37b** (311 mg, 1.08 mmol) in dry THF (8 mL) stirred at −78 °C under N_2. The mixture was stirred at the same temperature for 20 min. Satd aq NH_4Cl (5 mL) was added, followed by Et_2O (60 mL). The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (2.5:1 EtOAc/PE) on silica gel afforded **38**[16] as a colorless oil (146 mg, 1.04 mmol, 96% yield). $[\alpha]_D^{20}$ −136.2 (*c* 1.49, acetone), (lit.[16] $[\alpha]_D^{20}$ −143 (*c* 1.0, acetone)); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63–7.68 (m, 2H), 7.50–7.57 (m, 3H), 2.73 (s, 3H).

4.1.25. Synthesis of 39. *n*-BuLi (1.6 M in hexanes, 0.81 mL, 1.3 mmol) was added dropwise to a solution of *i*-Pr_2NH (0.17 mL, 1.3 mmol) in dry THF (4.5 mL) stirred at 0 °C under N_2. The mixture was stirred at the same temperature for 30 min before the bath was cooled to −78 °C. A solution of **38** (138 mg, 0.99 mmol) in THF (4 mL) was then added slowly. After completion of the addition, the mixture was stirred at the same temperature for 40 min. $ClCO_2Et$ (0.12 mL, 1.1 mmol) was then introduced while the bath temperature remained at −78 °C. The stirring was continued at the same temperature for 5 h. Satd aq NH_4Cl (5 mL) was added, followed by Et_2O (60 mL). The phases were separated. The aqueous layer was back-extracted with EtOAc (20 mL×3). The combined organic layers were washed first with 1 N HCl to pH 7, then with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:2 EtOAc/PE) on silica gel afforded **39**[15] as a colorless oil (100 mg, 0.47 mmol, 47% yield). $[\alpha]_D^{20}$ −132.7 (*c* 0.95, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.54 (m, 5H), 4.16 (q, *J*=6.8 Hz, 2H), 3.86 (d, *J*=13.6 Hz, 1H), 3.67 (d, *J*=13.6 Hz, 1H), 1.22 (t, *J*=7.4 Hz, 3H).

4.1.26. Synthesis of 34. A solution of **40**[4d] (51 mg, 0.27 mmol) in CH_3CN (1 mL) was added to a solution of optically active sulfoxide **39** (58 mg, 0.27 mmol) and piperidine (27 μL, 0.27 mmol) in CH_3CN (10 mL). The mixture was stirred at ambient temperature for 10 h before being diluted with Et_2O, washed first withaq NH_4Cl then with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:4.5 EtOAc/PE) on silica gel afforded **34** as a colorless oil (43 mg, 0.16 mmol, 59% yield). This sample was of 95% ee as shown by chiral HPLC analysis (performed on a Chiralpak OD column (4.6×250 mm), eluting 9:1 *n*-hexane/isopropanol (v/v) at a flow rate of 0.7 mL/min with the detector set to 214 nm). $[\alpha]_D^{20}$ −122.4 (*c* 1.20, $CHCl_3$). FTIR (film) 3447, 2925, 2855, 1720, 1661, 1466, 1272 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (dd, *J*=15.5, 4.3 Hz, 1H), 6.07 (d, *J*=15.4 Hz, 1H), 4.37 (s, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 2.71 (d, *J*=4.1 Hz, 1H), 2.60 (t, *J*=5.9 Hz, 2H), 2.43 (t, *J*=7.5 Hz, 2H), 2.03–1.95 (m, 2H), 1.35–1.28 (m, 11H), 0.86 (t, *J*=9.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 166.5, 149.6, 120.6, 70.0, 60.4, 42.9, 38.1, 31.5, 29.8, 28.8, 23.8, 22.4, 14.2, 13.9; ESIMS *m/z* 271.2 ([M+H]$^+$); ESIHRMS calcd for $C_{15}H_{26}O_4Na$ ([M+Na]$^+$) 293.1729, found 293.1720.

4.1.27. Synthesis of 42. A solution of *ent*-**34** (50 mg, 0.19 mmol), UHP (130 mg, 1.35 mmol), and *p*-TsOH (monohydrate, 43 mg, 0.22 mmol) in $MeO(CH_2)_2OMe$ (2 mL) was stirred at ambient temperature overnight. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:8 EtOAc/PE) on silica gel afforded *cis*-**41** as a colorless oil (19 mg, 0.066 mmol, 35% yield). $[\alpha]_D^{20}$ −22.1 (*c* 1.05, $CHCl_3$). FTIR (film) 3386, 2979, 2940, 1718, 1659, 1304, 1271 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 6.78 (dd, *J*=6.1, 15.3 Hz, 1H), 6.05 (d, *J*=15.4 Hz, 1H), 4.69–4.66 (m, 1H), 4.21 (q, *J*=6.9 Hz, 2H), 2.15–2.11 (m, 4H), 1.70–1.25 (m, 13H), 0.86 (t, *J*=9.3 Hz, 3H).

A solution of *cis*-**41** (19 mg, 0.066 mmol) and $HNEt_2$ (2 μL, 0.021 mmol) in CF_3CH_2OH (2 mL) was stirred at ambient temperature for 12 h. The solvent was removed by rotary evaporation. The residue was chromatographed (1:20 EtOAc/PE) on silica gel to give **42** as colorless oil (6 mg, 0.02 mmol, 32% yield). $[\alpha]_D^{20}$ −40.0 (*c* 0.31, $CHCl_3$). FTIR (film) 2925, 2854, 1741, 1462, 1185, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (t, *J*=7.2 Hz, 1H), 4.34 (d, *J*=4.3 Hz, 1H), 4.16 (q, *J*=7.1 Hz, 2H), 2.33–2.27 (m, 3H), 1.99–1.87 (m, 3H), 1.77–1.68 (m, 2H), 1.16–1.09 (m, 2H), 1.04–0.98 (m, 9H), 0.70 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 112.6, 80.2, 77.1, 61.2, 35.0, 34.3, 32.7, 31.7, 29.8, 24.13, 23.5, 22.6, 14.2, 14.1; EIMS *m/z* (%) 286 (M$^+$, 2.8), 113 (100); MALDIHRMS calcd for $C_{15}H_{26}O_5Na$ ([M+Na]$^+$) 309.1674, found 309.1666.

4.1.28. Synthesis of 44. MeMgBr (2.4 M, 4.0 mL, 9.64 mmol) was added dropwise to a solution of **43** (1.504 g, 9.64 mmol) in dry Et_2O (44 mL) stirred at 0 °C under argon. After completion of the addition, the stirring was continued at the same temperature until TLC showed completion of the reaction. Satd aq NH_4Cl was added. The mixture was extracted with Et_2O (50 mL×3), washed with satd aq NH_4Cl, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:5 EtOAc/PE) on silica gel afforded **44** as a colorless oil (1.245 g, 7.24 mmol, 75% yield). FTIR (film) 3407, 2931, 2857, 1460, 1101 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92 (ddt, *J*=7.1, 10.1, 1.6 Hz, 1H), 5.26 (br d, *J*=7.1 Hz, 1H), 5.17 (br d, *J*=10.1 Hz, 1H), 3.97 (t, *J*=1.6 Hz, 1H), 3.96 (t, *J*=1.6 Hz, 1H), 3.82–3.76 (m, 1H), 3.43 (t, *J*=6.6 Hz, 2H), 1.64–1.31 (m, 9H), 1.18 (d, *J*=6.4 Hz, 3H); ESIMS *m/z* 173.3 ([M+H]$^+$); ESIHRMS calcd for $C_{10}H_{20}O_2Na$ ([M+Na]$^+$) 195.1356, found 195.13586.

4.1.29. Deprotection of 44 (45). $PdCl_2$ (155 mg, 0.87 mmol) was added to a solution of **44** (617 mg, 3.59 mmol) in anhydrous MeOH (20 mL). The mixture was stirred at ambient temperature overnight. Most of the solvent was removed by rotary evaporation. The residue was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:1 EtOAc/PE) on silica gel afforded **45**[18] as a colorless oil (294 mg, 2.23 mmol, 62% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86–3.75 (m, 1H), 3.65 (t, J=6.3 Hz, 2H), 1.61–1.33 (m, 10H), 1.19 (d, J=8.7 Hz, 3H).

4.1.30. Synthesis of 48. A solution of $SO_3\cdot Py$ (5.15 g, 32.4 mmol) in DMSO (46 mL) was added to a solution of **47**[19] (2.504 g, 10.8 mmol) and NEt_3 (7.47 mL, 54 mmol) in CH_2Cl_2 (30 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature for 1 h before being diluted with Et_2O (150 mL), washed first with satd aq $CuSO_4$, then with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was dissolved in dry Et_2O (30 mL) and stirred in an ice-water bath under argon. MeMgBr (2.4 M, 4.5 mL, 10.8 mmol) was introduced dropwise. The stirring was continued in an ice-water bath until TLC showed completion of the reaction. Satd aq NH_4Cl was added. The mixture was extracted with Et_2O (50 mL×3). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:9 EtOAc/PE) on silica gel afforded **48**[20] as a colorless oil (1.992 g, 8.1 mmol, 75% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77–3.75 (m, 1H), 3.57 (t, J=5.8 Hz, 2H), 1.49–1.13 (m, 12H), 0.85 (s, 9H), 0.00 (s, 6H).

4.1.31. Oxidation of 48 (49). A solution of $SO_3\cdot Py$ (1.148 g, 7.22 mmol) in DMSO (10 mL) was added to a solution of **48** (587 mg, 2.39 mmol) and NEt_3 (1.67 mL, 12.1 mmol) in CH_2Cl_2 (6 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature for 3 h before being diluted with Et_2O (200 mL), washed first with satd aq $CuSO_4$, then with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:50 EtOAc/PE) on silica gel afforded **49**[20] as a colorless oil (503 mg, 2.06 mmol, 86% yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.56 (t, J=6.2 Hz, 2H), 2.39 (t, J=7.2 Hz, 2H), 2.10 (s, 3H), 1.62–1.20 (m, 6H), 0.83 (s, 9H), 0.00 (s, 6H).

4.1.32. Synthesis of 50. A solution of $HS(CH_2)_2SH$ (0.11 mL, 1.12 mmol), $BF_3\cdot Et_2O$ (0.03 mL, 0.25 mmol), and **49** (169 mg, 0.69 mmol) was stirred at ambient temperature for 5 h. Acetone was added to eliminate the excess thiol. The stirring was continued at ambient temperature overnight. The mixture was diluted with CH_2Cl_2, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:6 EtOAc/PE) on silica gel afforded **50** as a colorless oil (138 mg, 0.67 mmol, 97% yield). FTIR (film) 3376, 2925, 1460, 1375, 1275, 1052 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (t, J=6.5 Hz, 2H), 3.36–3.29 (m, 4H), 1.98–1.92 (m, 2H), 1.76 (s, 3H), 1.45–1.35 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.8, 62.9, 45.7, 39.7, 32.6, 32.3, 27.1, 25.8; ESIMS m/z 224.1 ([M+NH_4]$^+$); ESIHRMS calcd for $C_9H_{18}ONa$ ([M+Na]$^+$) 229.0688, found 229.0691.

4.1.33. Synthesis of 51. A solution of $SO_3\cdot Py$ (1.769 g, 11.1 mmol) in DMSO (16 mL) was added to a solution of **50** (746 mg, 3.62 mmol) and NEt_3 (2.57 mL, 18.6 mmol) in CH_2Cl_2 (10 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature for 0.5 h before being diluted with Et_2O (200 mL), washed first with satd aq $CuSO_4$, then with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:17 EtOAc/PE) on silica gel afforded **51** as a colorless oil (606 mg, 2.97 mmol, 82% yield). FTIR (film) 3392, 2922, 1734, 1447, 1041, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1H), 3.27–3.18 (m, 4H), 2.45 (t, J=4.9 Hz, 2H), 1.88–1.81 (m, 2H), 1.75 (s, 3H), 1.54–1.43 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 66.5, 45.4, 43.7, 39.8, 32.4, 26.8, 22.1; ESIMS m/z 205.1 ([M+H]$^+$); EIHRMS calcd for $C_9H_{16}OS_2$ (M^+) 204.0636, found 204.0635.

4.1.34. Synthesis of 52. A solution of **51** (518 mg, 2.54 mmol) in CH_3CN (4 mL) was added to a solution of $PhSOCH_2CO_2Bn$[4d] (704 mg, 2.57 mmol) and piperidine (0.25 mL, 2.57 mmol) in CH_3CN (6 mL). The mixture was stirred at ambient temperature for 15 h before being diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:5 EtOAc/PE) on silica gel afforded **52** as a colorless oil (510 mg, 1.45 mmol, 57% yield). FTIR (film) 3446, 1715, 1656, 1456, 1271, 1160, 982, 752, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.23 (m, 5H), 6.93 (dd, J=5.1, 15.8 Hz, 1H), 6.04 (d, J=15.5 Hz, 1H), 5.13 (s, 2H), 4.28 (br s, 1H), 3.32–3.21 (m, 4H), 1.95–1.43 (m, 7H), 1.69 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 150.6, 135.8, 128.5, 128.2, 128.2, 119.9, 70.8, 66.6, 66.3, 45.4, 39.9, 36.4, 32.3, 23.0; ESIMS m/z 370.1 ([M+NH_4]$^+$); ESIHRMS calcd for $C_{18}H_{24}O_3S_2Na$ ([M+Na]$^+$) 375.1059071, found 375.1053470.

4.1.35. Deprotection of 52 (53). $NaHCO_3$ (935 mg, 11.13 mmol) and I_2 (1.139 g, 4.48 mmol) were added to a solution of **52** (450 mg, 1.28 mmol) in CH_3COCH_3 (13 mL) and H_2O (2.6 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at the same temperature for 30 min before the excess I_2 was destroyed by addition of satd aq $Na_2S_2O_3$ (10 mL). The mixture was extracted with EtOAc (3×30 mL). The combined organic phases were washed with satd aq $Na_2S_2O_3$, water, and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:3 EtOAc/PE) on silica gel afforded **53** as a colorless oil (238 mg, 1.03 mmol, 80% yield). FTIR (film) 3446, 1718, 1656, 1455, 1275, 1163, 980, 697, 666 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (br s, 5H), 6.79 (dd, J=4.4, 15.9 Hz, 1H), 6.04 (d, J=15.7 Hz, 1H), 5.19 (s, 2H), 4.57 (br s, 1H), 4.33–4.29 (m, 1H), 2.50 (t, J=8.0 Hz, 2H), 2.21 (s, 3H), 1.75–1.65 (m, 4H); ESIMS m/z 294.2

($[M+NH_4]^+$); MALDIHRMS calcd for $C_{16}H_{20}O_4Na$ ($[M+Na]^+$) 299.1254, found 299.1270.

4.1.36. Hydroperoxidation of 53 (54). A solution of **53** (265 mg, 0.96 mmol), UHP (683 mg, 6.79 mmol), and *p*-TsOH (monohydrate, 224 mg, 1.18 mmol) in MeO-$(CH_2)_2$OMe (15 mL) was stirred at ambient temperature overnight. The mixture was diluted with Et_2O, washed with water and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (1:5 EtOAc/PE) on silica gel afforded **54** as a colorless oil (a 9:1 mixture, 265 mg, 0.91 mmol, 95% yield). FTIR (film) 3400, 1717, 1660, 1456, 1379, 1219, 1174, 976, 739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.37–7.32 (m, 5H), 6.96 (dd, J=15.7, 4.4 Hz, 0.9H), 6.89 (dd, J=15.7, 4.5 Hz, 0.1H), 6.14 (d, J=15.7 Hz, 0.9H), 6.09 (d, J=15.7 Hz, 0.1H), 5.19 (s, 2H), 4.44 (dt, J=11.7, 2.2 Hz, 1H), 1.84–1.54 (m, 6H), 1.47 (s, 3H). (Because of its unstable/reactive nature, it was not possible to obtain HRMS or elemental analysis data for **54**).

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