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A facile access to bridged 1,2,4-trioxanes

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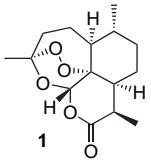
Abstract—Bicyclo[3.2.1] type 1,2,4-trioxanes are readily synthesized from precursors that may form intramolecular hemiketals using UHP (H_2O_2–urea complex) as the source of the peroxy bond and *p*-TsOH or CSA as the catalyst. The ring closure through an intramolecular Michael addition occurred in a highly stereoselective way, giving only one diasteromer as shown by the NMR spectra.

1. Introduction

Organic peroxides are currently of great interest because of the excellent antimalarial activity observed with qinghaosu[1] (artemisinin, **1**) and closely related organic peroxide. The peroxy bond in **1** constitutes a part of 1,2,4-trioxane ring system. Therefore, the 1,2,4-trioxane class of peroxides are considered to be particularly interesting among various organic peroxides over the last decades. Considerable efforts in synthesizing this class of compounds have been documented in the literature.



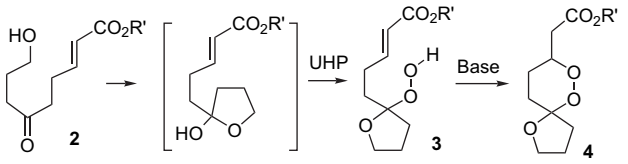
1

Organic peroxides are difficult to synthesize partly because formation of an O–O bond between two alkoxyl-related species is practically impossible unless using radical coupling strategy. As a consequence, the peroxy bonds in organic peroxides are all essentially acquired through making a C–O bond on each end of an inorganic species that contains an O–O bond. It is therefore not surprising that the existing methodologies for incorporating/introducing peroxy bonds into organic molecules are rather few. In fact those of synthetic significance are: (1) photosensitized oxygenation,[2] (2) trapping ozonides of enolates or vinylsilanes,[3] (3) ring opening of epoxides with H_2O_2,[4] and (4) transition metal ion-mediated radical trapping of O_2.[5]

Apart from the extremely limited number of means for introducing peroxy bonds, another factor also contributes to the difficulty of synthesizing organic peroxides—the peroxy bonds themselves are much more fragile than most other covalent bonds in organic compounds, with an average bond energy of only 34 kcal/mol[1e] (less than half of that for a C–C single bond). Hence, the timing of incorporating the peroxy bond into the substrate must be carefully planned to avoid involvement of reagents and conditions that would cleave the peroxy bond after their introduction. This of course adds additional difficulties to the synthesis. Consequently, cautious design of a precursor for incorporating the peroxy bond in combination of a proper choice of the peroxy bond source is of critical importance in the synthesis of novel organic peroxides. Here in this paper we wish to report an experimentally feasible entry to a bridged 1,2,4-trioxane system.

2. Results and discussions

Using Kobayashi's[6] methodology, we previously synthesized[7] some spiro 1,2-dioxanes, where the key step of incorporating a hydroperoxyl group was realized by exploiting facile formation of intramolecular hemiketals as illustrated in Scheme 1 through converting precursor **2** into hydroperoxy compound **3**. Encouraged by those results, we set out to explore the possibility of extending this methodology from the spiro systems to bridged ones.



Scheme 1.

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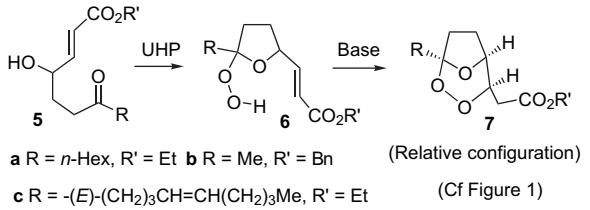
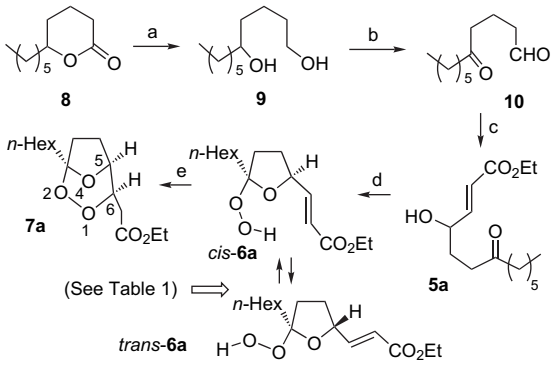
In the present work we designed (Scheme 2) a new type of substrates **5**, which were expected to form hydroperoxy intermediates **6** and eventually led to bridged 1,2,4-trioxanes **7**. Compared with the previous mono cyclic[6] or the spiro[7] systems, such a trioxane system is much closer to the core structure of qinghaosu **1** and therefore deserves investigation.



Scheme 2.

Synthesis of the first target **7a** started from the commercially available lactone **8** (Scheme 3). Reduction with $LiAlH_4$ gave diol **9**[8] in 95% yield. Both hydroxyl groups were then oxidized to the intermediate aldehyde–ketone **10** by Swern oxidation. The resulting **10** when treated with the sulfoxide reagent **11**[9] in the presence of piperidine afforded the desired hydroperoxidation precursor **5a**.

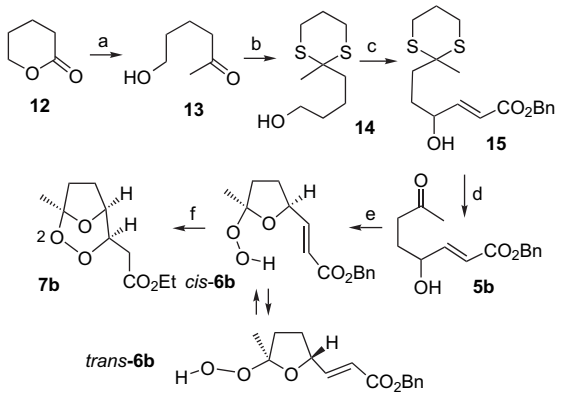


Scheme 3. (a) $LiAlH_4$/THF, 95%; (b) Swern oxidation; (c) $PhS(O)CH_2$–CO_2Et (**11**)/piperidine/rt/15 h, 41% from **10**; (d) UHP (ca. 7.5 equiv)/*p*-TsOH/DME/rt/overnight, 89% (*trans*-**6a**/*cis*-**6a**=1.6:1); and (e) cat. $HNEt_2/F_3CCH_2OH$/rt/12 h, 35%.

The hydroperoxyl group was then introduced by treatment with UHP (urea–H_2O_2 complex, a commercially available solid reagent) in the presence of *p*-TsOH in DME ($MeO(CH_2)_2OMe$) in 89% yield. It should be noted that if MeOH is used as solvent as in Kobayashi's original recipe, the yield of the hydroperoxy hemiketals *trans*-**6a** and *cis*-**6a** was <50%.

The *cis*-**6a**, which was readily separated from *trans*-**6a** on silica gel, was treated with Et_2NH/F_3CCH_2OH, giving the end product **7a** in 35% yield.

When the *n*-hexyl group was replaced by a methyl group, which is much smaller in size, the selective reaction of $PhSOCH_2CO_2Bn$ (**16**) with the aldehyde group in the presence of a ketone functionality was not possible, presumably due to the interference of the intramolecular aldol reaction. For this reason, we next turned to a slightly longer route (Scheme 4), where the ketone carbonyl group could be masked during the reaction of the aldehyde with the sulfoxide reagent **16**.



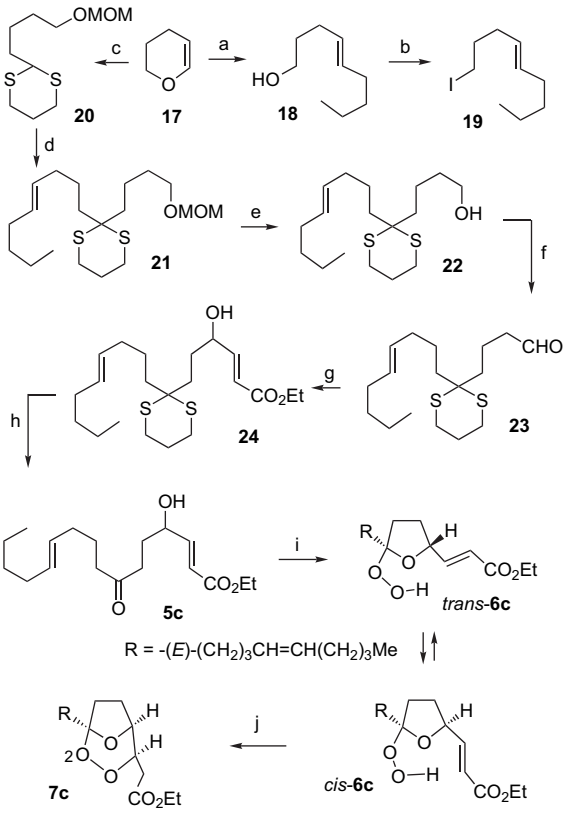
Scheme 4. (a) MeLi/Et_2O/−78 °C, 80%; (b) $HS(CH_2)_3SH/F_3B\cdot OEt_2/CH_2Cl_2$, 98%; (c) (i) $SO_3\cdot Py$/DMSO/NEt_3, 92%; (ii) $PhS(O)CH_2CO_2Bn$ (**16**)/piperidine/rt/15 h, 60%; (d) $I_2/NaHCO_3$/acetone–H_2O, 95%; (e) UHP (ca. 7.5 equiv)/*p*-TsOH/DME/rt/12 h, 88% (*trans*-**6b**/*cis*-**6b**=1.8:1); and (f) cat. $HNEt_2/F_3CCH_2OH$/rt/12 h, 29%.

The starting material in this case was, again, a lactone (**12**). Addition of methyllithium to **12** under carefully controlled conditions resulted in the methyl ketone **13**. The carbonyl group was then protected with $HS(CH_2)_2SH$ in the presence of borontrifluoride etherate and the alcohol was oxidized with $SO_3\cdot Py$ to afford the intermediate aldehyde, which on treatment with the sulfoxide reagent **16** gave the α,β-unsaturated ester **15**.

The sulfur protecting group was then removed with $I_2/NaHCO_3$ in 5:1 acetone–H_2O to give the hydroperoxidation precursor **5b** in 95% yield. The subsequent introduction of the hydroperoxyl group was performed under the same conditions as described above for the synthesis of **6a**, giving **6b** in 88% yield as a 1.8:1 mixture of *trans*-**6b** and *cis*-**6b**. The desired isomer *cis*-**6b** was separated from *trans*-**6b** by chromatography on silica gel and treated with $HNEt_2$ in F_3CCH_2OH to yield the end product **7b**.

The long-chain substrate **7c** was synthesized from dihydropyran **17** using the sequence outlined in Scheme 5. The iodide **19** was obtained by reaction of **17** with 2 equiv of *n*-BuLi to afford the alcohol **18**,[10] followed by treatment with Ph_3P/I_2/imidazole in MeCN–Et_2O. The dithiane moiety **20** was constructed by reaction of $HS(CH_2)_2SH$ with **17** and subsequent protection of the newly formed terminal hydroxyl group as a MOM ether.

The coupling of **19**[11] with **20** (prepared from the corresponding alcohol following the literature[12]) was then realized under action of *n*-BuLi. The MOM protecting group was then cleaved with MeOH and the resulting alcohol was oxidized with $SO_3\cdot Py$ to afford the aldehyde **23**. Further treatment of the aldehyde with sulfoxide reagent **11** led to α,β-unsaturated ester **24**, which on deprotection of the thioketal gave the hydroperoxidation precursor **5c**. Conversion of **5c** to **7c** was performed in a similar fashion as described above for **7a** and **7b**.



Scheme 5. (a) *n*-BuLi (2 equiv)/reflux/3 h, 80%; (b) I_2/imidazole/Ph_3P/MeCN–Et_2O (1:4)/15 min, 82%; (c) (i) $HS(CH_2)_3SH/BF_3\cdot Et_2O$, 90%; (ii) MOMCl/*i*-$Pr_2NEt/CH_2Cl_2$/rt, 85%; (d) (i) *n*-BuLi/THF/−78 to −20 °C/4 h, (ii) HMPA/**19**/0 °C/12 h, 68% from **20**; (e) *p*-TsOH/MeOH/40–50 °C/3 h, 90%; (f) $SO_3\cdot Py$/DMSO/NEt_3, 86%; (g) $PhS(O)CH_2CO_2Et$ (**11**)/piperidine/rt/15 h, 63%; (h) $I_2/NaHCO_3$/acetone–H_2O, 87%; (i) UHP (ca. 7.5 equiv)/*p*-TsOH/DME/rt/12 h, 86% (*trans*-**6c**/*cis*-**6c**=2.3:1); and (j) cat. $HNEt_2/F_3CCH_2OH$/rt/12 h, 32%.

The *trans*-**6**a–c isomers, which were unable to undergo the Michael addition, could be partially transformed into the corresponding cis ones by acid catalyzed equilibration. The conversion ratio varied depending on the catalyst (exemplified with the re-equilibrium of **6a** in Table 1). In DME with CSA ((±)-camphor-10-sulfonic acid) as the catalyst (entry 1), the trans/cis ratio at the end of the equilibration was 2.3:1 (calculated from the isolated yields). Using TFA (trifluoroacetic acid) as the catalyst, however, did not result in any conversion at all under the otherwise same conditions (entry 2).

p-TsOH gave more or less the same conversion ratio as CSA. The recovery rate was usually excellent in DME, but not so good in MeOH (entry 5). Presence of a small amount of MeOH apparently facilitated the conversion. Thus, in 9:1 DME–MeOH, the trans/cis ratio could reach 1.8:1.

It is noteworthy that unlike in the monocyclic or spirocyclic cases encountered in our previous work, where both diastereomers were formed in rather close amounts, in the present system the Michael addition proceeded in a highly stereoselective manner, leading to only one diastereomer.

With assistance of 2D NMR experiments including COSY, NOESY, and HMQC, the structure of the bridged product was firmly established. The relative configuration at C-6 was assigned as follows: As the coupling between H-5 and H-6 was essentially 0 Hz (Fig. 1), the dihedral angle between these two hydrogens must be near 90°. From molecular model it can be seen that only the relative configuration as depicted in Figure 1 could satisfy this requirement.

Table 1. Acid catalyzed re-equilibrium between *trans*-**6a** and *cis*-**6a**[a]

Entry	Acid	Solvent[b]	*trans*/*cis*	Recovery[c] (%)
1	CSA	DME	2.3:1	100
2	F_3CCO_2H	DME	NC[d]	100
3	$BF_3\cdot OEt_2$	DME	5.6:1	96
4	*p*-TsOH	DME	2.1:1	94
5	*p*-TsOH	MeOH	2.1:1	84
6	*p*-TsOH	PEG 400	7.8:1	76
7	*p*-TsOH	9:1 DME–MeOH	1.8:1	100
8	CSA	9:1 DME–MeOH	1.8:1	100

[a] The re-equilibrium of the *trans*-**6a** was performed by stirring a 0.025 M solution of *trans*-**6a** in the indicated solvent in the presence of 7.5 equiv of UHP and 1.2 equiv of the indicated acid at ambient temperature overnight.
[b] PEG 400=polyethylene glycol (molecular weight=400).
[c] The total yield of *trans*-**6a** and *cis*-**6a**.
[d] No changes were observed.

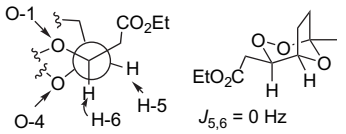


Figure 1. The dihedral angle between H-5 and H-6 is close to 90°.

3. Conclusions

A convenient approach to a 1,2,4-trioxane system has been developed, which utilized the commercially available and easy-handling solid UHP as the source of the peroxy bond and complements the existing protocols that do not involve excited state chemistry.

4. Experimental

4.1. General

The ^1H NMR and ^{13}C NMR spectra were recorded in deuterochloroform at ambient temperature using a Varian Mercury 300 or a Bruke Avance 300 instrument (operating at 300 MHz for proton). The FTIR spectra were scanned with a Nicolet Avatar 360 FT-IR. 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 a APEX III (7.0 Tesla) FTMS mass spectrometer, respectively. 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 CH_2Cl_2 was distilled over CaH_2 and kept over 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.

4.2. Reduction of lactone 8 (9)

$LiAlH_4$ (1.143 g, 30.08 mmol) was added in portions to a solution of **8** (3.738 g, 20.30 mmol) in anhydrous THF (95 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature for 40 min before the excess hydride was destroyed by addition of 2 N HCl with cooling in an ice-water bath. The mixture was extracted with EtOAc (4×100 mL). The combined organic layers were washed with water, satd aq $NaHCO_3$, and brine, and dried over anhydrous Na_2SO_4. The residue after removal of the solvent and drying agent was chromatographed (3:2 *n*-hexane/EtOAc) on silica gel to give diol **9**[8] as a colorless wax (3.625 g, 95% yield). ^{1}H NMR δ 3.67–3.63 (m, 3H), 1.97 (s, 2H), 1.60–1.25 (m, 16H), 0.89 (t, J=7.2 Hz, 3H).

4.3. Synthesis of 5a

DMSO (5.16 mL, 72.27 mmol) was added dropwise to a solution of $(COCl)_2$ (2.84 mL, 32.85 mmol) in dry CH_2Cl_2 (36 mL) stirred at −60 °C under N_2. After completion of the addition, the mixture was stirred at the same temperature for 30 min. A solution of **9** (1.235 g, 6.57 mmol) in dry CH_2Cl_2 (14 mL) was added slowly. After another 30 min stirring at −60 °C, NEt_3 (8.20 mL, 59.13 mmol) was introduced dropwise. The stirring was continued at −60 °C. When TLC showed completion of the oxidation, HCl (2.4 N, 11 mL) was added. The mixture was extracted with Et_2O (3×50 mL). The combined ethereal phases were washed with diluted HCl until pH 7, then with water and brine before being dried over anhydrous Na_2SO_4. The residue (**10**) after removing drying agent and the solvent was added slowly to a solution of $PhSOCH_2CO_2Et$ (1.393 g, 6.57 mmol) and piperidine (0.67 mL, 6.57 mmol) in MeCN (11 mL) stirred at rt. The stirring was continued at rt until TLC showed completion of the reaction. The mixture was partitioned between water (25 mL) and Et_2O (25 mL). The phases were separated and the aqueous layer was back extracted with Et_2O (3×50 mL). The combined ethereal phases were washed with diluted HCl until *p*H 7, then with water and brine before being dried over anhydrous Na_2SO_4. The residue after removal of solvent was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **5a** as a yellowish oil (727 mg, 41% from **9**). FTIR (film) 3447, 1720, 1661, 1466, 1272, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.91 (dd, J=15.7, 4.5 Hz, 1H), 6.06 (d, J=15.4 Hz, 1H), 4.37 (s, 1H), 4.20 (q, J=6.8 Hz, 2H), 3.02 (d, J=5.2 Hz, 1H), 2.60 (t, J=5.9 Hz, 2H), 2.43 (t, J=7.5 Hz, 2H), 1.96–1.80 (m, 2H), 1.58–1.54 (m, 2H), 1.35–1.28 (m, 9H), 0.88 (t, J=6.7 Hz, 3H); ESIMS *m*/*z* 271.2 ([M+H]$^+$); ESIHRMS calcd for $C_{15}H_{26}O_4Na$ ([M+Na]$^+$) 293.1729; found 293.1720.

4.4. Hydroperoxidation of 5a (*cis*-6a and *trans*-6a)

A mixture of **5a** (285 mg, 1.05 mmol), UHP (748 mg, 8.0 mmol), and *p*-TsOH·H_2O (248 mg, 1.30 mmol) in DME (42 mL) was stirred at rt overnight. The solvent was removed by rotary evaporation and the residue was chromatographed (10:1 *n*-hexane/EtOAc) on silica gel to afford *cis*-**6a** (103 mg, 0.360 mmol, 34% yield) and *trans*-**6a** (165 mg, 0.576 mmol, 55% yield) as colorless oils. Data for compound *cis*-**6a** (the less polar component): FTIR (film): 3386, 1718, 1659, 1463, 1304, 1271, 1179, 1041 cm^{-1}; ^{1}H NMR 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). Data for compound *trans*-**6a** (the more polar component): FTIR (film) 3390, 1722, 1660, 1465, 1304, 1267, 1041 cm^{-1}; ^{1}H NMR δ 8.07 (s, 1H), 6.91 (dd, J=5.2, 15.8 Hz, 1H), 6.05 (d, J=15.8 Hz, 1H), 4.80–4.78 (m, 1H), 4.21 (q, J=7.0 Hz, 2H), 2.33–1.96 (m, 4H), 1.75–1.22 (m, 13H), 0.87 (t, J=10.5 Hz, 3H). Because these hydroperoxides are not very stable, they should be used as soon as possible.

4.5. Synthesis of 7a

A mixture of *cis*-**6a** (83 mg, 0.29 mmol) and $HNEt_2$ (4 μL) in CF_3CH_2OH (1.5 mL) was stirred at rt for ca. 14 h, when TLC showed disappearance of the starting material. The solvent was removed by rotary evaporation and the residue was chromatographed (20:1 *n*-hexane/EtOAc) on silica gel to yield **7a** as a colorless oil (29 mg, 0.101 mmol, 35% yield). FTIR (film) 2956, 2925, 2854, 1741, 1426, 1185, 1026 cm^{-1}; ^{1}H NMR 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); MALDIHRMS *m*/*z* calcd for $C_{15}H_{26}O_5Na$ ([M+Na]$^+$) 309.16725; found 309.1679.

4.6. Addition of methyllithium to lactone 12 (13)

MeLi (2.2 M in Et_2O, 2.35 mL, 5.16 mmol) was added to a solution of **12** (516 mg, 5.16 mmol) in anhydrous Et_2O (13 mL) stirred at −78 °C under N_2. The mixture was stirred at the same temperature for 15 min and aq satd NH_4Cl (10 mL) was added. The mixture was extracted with Et_2O (3×30 mL) and the combined organic layers were washed with water and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (2:1 *n*-hexane/EtOAc) on silica gel to give **13**[13] as a colorless oil (479 mg, 4.12 mmol, 80% yield). ^{1}H NMR δ 3.62 (t, J=6.0 Hz, 2H), 2.49 (t, J=6.9 Hz, 2H), 2.19 (s, 1H), 2.18 (s, 3H), 1.72–1.51 (m, 4H).

4.7. Protection of 13 with propane-1,3-dithiol (14)

A solution of **13** (479 mg, 4.12 mmol), $HS(CH_2)_2SH$ (0.42 mL, 4.12 mmol), and $BF_3\cdot Et_2O$ (0.22 mL) in CH_2Cl_2 (20 mL) was stirred at rt for 3 h, when TLC showed completion of the reaction. Acetone was added (to remove excess thiol) and the stirring was continued for 1 h and the mixture was extracted with Et_2O (3×25 mL). The combined organic layers were washed in turn with aq $NaHCO_3$, water, and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (8:1 *n*-hexane/EtOAc) on silica gel to give **14**[14] as a colorless oil (832 mg, 4.04 mmol, 98% yield). ^{1}H NMR δ 3.68 (t, J=6.0 Hz, 2H), 2.87–2.83 (m, 4H), 1.98–1.92 (m, 4H), 1.63 (s, 3H), 1.60–1.58 (m, 4H).

4.8. Synthesis of 15

A solution of $SO_3\cdot Py$ (446 mg, 2.81 mmol) in DMSO (4 mL) was added slowly to a solution of **14** (165 mg,

0.80 mmol) and NEt_3 (0.55 mL, 4.0 mmol) in dry CH_2Cl_2 (2 mL) and stirred at 0 °C. After completion of the addition, the bath was removed and the mixture was stirred at rt until TLC showed (ca. 3 h) full disappearance of the starting alcohol. Water (10 mL) was added to quench the reaction and the mixture was extracted with Et_2O (3×25 mL). The combined organic layers were washed with aq satd $CuSO_4$ (until no more floccule formed), water, and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (40:1 *n*-hexane/EtOAc) on silica gel to give the known intermediate aldehyde[15] as a colorless oil (150 mg, 0.74 mmol, 92% yield). ^{1}H NMR δ 9.80 (s, 1H), 2.88–2.82 (m, 4H), 2.51 (t, J=6.7 Hz, 2H), 1.99–1.80 (m, 6H), 1.61 (s, 3H).

A solution of the above prepared aldehyde (3.046 g, 14.93 mmol) in MeCN (25 mL) was added dropwise to a solution of $PhSOCH_2CO_2Bn$ (**16**, 4.091 g, 14.93 mmol) and piperidine (1.48 mL, 14.93 mmol) in MeCN (50 mL) and stirred at rt. The stirring was continued at rt until TLC showed completion of the reaction. Water was added to quench the reaction and the mixture was extracted with Et_2O (3×25 mL). The combined organic layers were washed first with diluted HCl until pH 7 and then with water and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (6:1 *n*-hexane/EtOAc) on silica gel to give **15** as a yellowish oil (3.144 g, 8.93 mmol, 60% yield). FTIR (film) 3447, 2923, 1717, 1655, 1455, 1274, 1162, 979, 908, 738, 697 cm^{-1}; ^{1}H NMR δ 7.39–7.33 (m, 5H), 7.00 (dd, J=4.7, 15.5 Hz, 1H), 6.12 (d, J=15.6 Hz, 1H), 5.20 (s, 2H), 4.39–4.35 (m, 1H), 2.86–2.76 (m, 4H), 2.13–1.73 (m, 7H), 1.58 (s, 3H); ESIMS *m*/*z* 370.2 ([M+NH_4]$^+$); ESIHRMS calcd. for $C_{18}H_{24}O_3S_2Na$ ([M+Na]$^+$) 375.1065; found 375.1060.

4.9. Deprotection of 15 (5b)

Powdered $NaHCO_3$ (300 mg, 3.57 mmol) and I_2 (369 mg, 1.44 mmol) were added in turn to a solution of **15** (146 mg, 0.41 mmol) in acetone (4 mL) and water (1 mL) and stirred in an ice-water bath. The mixture was stirred for 15 min when TLC showed disappearance of the starting material. Aq satd $Na_2S_2O_3$ (2 mL) was added to quench the reaction. The mixture was extracted with Et_2O (3×30 mL). The combined organic layers were washed in turn with aq satd $NaHCO_3$, water, and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **5b** as a yellowish oil (103 mg, 0.39 mmol, 96% yield). FTIR (film) 3448, 1716, 1658, 1455, 1271, 1164, 1112, 984, 699 cm^{-1}; ^{1}H NMR δ 7.38–7.32 (m, 5H), 6.95 (dd, J=15.5, 4.3 Hz, 1H), 6.12 (d, J=15.7 Hz, 1H), 5.19 (s, 2H), 4.38–4.35 (m, 1H), 2.70 (d, J=4.8 Hz, 1H), 2.61 (t, J=6.5 Hz, 2H), 2.17 (s, 3H), 2.02–1.92 (m, 1H), 1.81–1.74 (m, 1H); ESIMS *m*/*z* 263 ([M+H]$^+$); ESIHRMS calcd for $C_{15}H_{18}O_4Na$ ([M+Na]$^+$) 285.1103; found 285.1098.

4.10. Synthesis of 7b

A mixture of **5b** (43 mg, 0.16 mmol), UHP (100 mg, 1.06 mmol), and *p*-TsOH·H_2O (37 mg, 0.19 mmol) in DME (4.6 mL) was stirred at rt overnight. The solvent was removed by rotary evaporation and the residue was chromatographed (8:1 *n*-hexane/EtOAc) on silica gel to afford *cis*-**6b** (14 mg, 0.050 mmol, 32%) and *trans*-**6b** (25 mg, 0.090 mmol, 56%) as colorless oils. Data for compound *cis*-**6b** (the less polar component): FTIR (film) 3389, 1719, 1659, 1456, 1379, 1301, 1227, 1171, 1030 cm^{-1}; ^{1}H NMR δ 8.18 (s, 1H), 7.36–7.32 (m, 5H), 7.02 (dd, J=6.0, 15.6 Hz, 1H), 6.11 (d, J=15.5 Hz, 1H), 5.19 (s, 2H), 4.74–4.76 (m, 1H), 2.26–1.60 (m, 4H), 1.55 (s, 3H). Data for compound *trans*-**6a** (the more polar component): FTIR (film): 3394, 1720, 1659, 1456, 1380, 1300, 1270, 1170, 1028 cm^{-1}; ^{1}H NMR δ 8.14 (s, 1H), 7.37–7.35 (m, 5H), 6.96 (dd, J=4.8, 15.7 Hz, 1H), 6.10 (d, J=15.7 Hz, 1H), 5.19 (s, 2H), 4.80–4.78 (m, 1H), 2.33–2.26 (m, 1H), 2.17–2.08 (m, 1H), 1.98–1.88 (m, 1H), 1.75–1.71 (m, 1H), 1.57 (s, 3H). Because these hydroperoxides are not very stable, they should be used as soon as possible.

A mixture of *cis*-**6b** (175 mg, 0.63 mmol) and $HNEt_2$ (6 μL) in CF_3CH_2OH (37 mL) was stirred at rt until TLC showed disappearance of the starting material. The solvent was removed by rotary evaporation and the residue was chromatographed (10:1 *n*-hexane/EtOAc) on silica gel to yield **7b** as a colorless oil (51 mg, 0.18 mmol, 29% yield). FTIR (film) 2993, 2956, 1736, 1457, 1170, 1032, 983, 877, 752, 699 cm^{-1}; ^{1}H NMR δ 7.38–7.36 (m, 5H), 5.14 (s, 2H), 4.91 (t, J=7.1 Hz, 1H), 4.91 (br s, 1H), 2.44–2.26 (m, 3H), 2.00–1.82 (m, 3H), 1.46 (s, 3H); EIHRMS *m*/*z* calcd for $C_{15}H_{18}O_5$ (M^+) 278.1267; found 278.1142.

4.11. Synthesis of the benzyl ester sulfoxide reagent 16

PhSH (3.46 mL, 33.78 mmol) was added dropwise to EtONa solution (freshly prepared by dissolving 388 mg of Na metal in 12.5 mL of anhydrous EtOH). The mixture was stirred at rt for 1 h before a solution of $BrCH_2CO_2Bn$ (3.867 g, 16.89 mmol) in anhydrous EtOH (5 mL) was introduced. The mixture was heated to reflux with stirring for 2 h and re-cooled to rt. Water (10 mL) was added and the mixture was extracted with $CHCl_3$ (3×30 mL). The combined organic layers were washed with water and brine, and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the residue (the sulfide) was used directly in the next step.

$NaIO_4$ (9.037 g, 42.22 mmol) was added to a solution of the above prepared sulfide (4.358 g, 16.89 mmol) in MeOH (32 mL) and water (17 mL). The mixture was stirred at rt overnight before being diluted with Et_2O (40 mL). The solids were filtered off (washed with Et_2O) and the filtrate was washed with water. The aqueous layer was back extracted with Et_2O (3×40 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. The residue after removal of solvent was chromatographed (3:1 *n*-hexane/EtOAc) on silica gel to give **16** as a colorless oil (4.078 g, 14.88 mmol, 88% yield). FTIR (film) 1732, 1658, 1444, 1270, 1050 cm^{-1}; ^{1}H NMR δ 7.65–7.25 (m, 10H), 5.12 (s, 2H), 3.91 (d, J=13.5 Hz, 1H), 3.71 (d, J=13.8 Hz, 1H); ESIMS *m*/z 275 ([M+H]$^+$); EIHRMS calcd for $C_{15}H_{14}O_3S$ (M^+) 274.0664; found 274.0673.

4.12. Synthesis of iodide 19

Solid I_2 (2.54 g, 10 mmol) was added in portions to a solution of alcohol **18**[10] (1.42 g, 10 mmol), Ph_3P (2.62 g, 10 mmol),

and imidazole (680 mg, 10 mmol) in 4:1 (v/v) Et_2O–CH_3CN (50 mL) stirred in an ice-water bath. After completion of the addition, the stirring was continued for 30 min. *n*-Hexane (100 mL) was added. The solids were filtered off and the filtrate was concentrated on a rotary evaporator. The residue was chromatographed (*n*-hexane) on silica gel to give iodide **19** as a colorless oil (2.06 g, 8.17 mmol, 82% yield). FTIR (film) 2956, 2925, 1459, 1219, 1167 cm^{-1}; ^1H NMR δ 5.51–5.29 (m, 2H), 3.18 (t, J=6.5 Hz, 2H), 2.12–1.84 (m, 6H), 1.32–1.25 (m, 4H), 0.89 (t, J=6.1 Hz, 3H); EIMS *m*/*z* (%) 252 (M, 15.8), 210 (M−$CH_3CH{=}CH_2$, 0.8); EIHRMS calcd for $C_9H_{17}I$ (M^+) 252.0375; found 252.0386.

4.13. Synthesis of 20

Dihydropyran **17** (2.42 mL, 26 mmol) was added dropwise to a solution of $HS(CH_2)_2SH$ (2.6 mL, 25.8 mmol) and $BF_3{\cdot}Et_2O$ (0.5 mL) in CH_2Cl_2 (25 mL) and stirred at −78 °C. After completion of the addition, the cooling bath was removed and the mixture was stirred at rt for 5 h, when TLC showed completion of the reaction. Water (5 mL) was added to quench the reaction. Et_2O (50 mL) was added and the phases were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with aq satd $NaHCO_3$, water, and brine, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed (3:1 *n*-hexane/EtOAc) on silica gel to give the intermediate alcohol[12] as a colorless oil (4.50 g, 23.4 mmol, 90% yield).

A solution of the above prepared alcohol (480 mg, 2.5 mmol), *i*-Pr_2NEt (0.87 mL, 5 mmol), and MOMCl (0.38 mL, 5 mmol) in CH_2Cl_2 (25 mL) was stirred at rt for 15 h. Water (10 mL) and Et_2O (50 mL) were added and the phases were separated. The aqueous phases were extracted with Et_2O (3×20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was chromatographed (10:1 *n*-hexane/EtOAc) on silica gel to afford **20** as a yellowish oil (502 mg, 2.13 mmol, 85% yield). FTIR (film) 1413, 1269, 1146, 1111, 1043, 916 cm^{-1}; ^1H NMR δ 4.62 (s, 2H), 4.05 (t, J=6.9 Hz, 1H), 3.53 (t, J=5.5 Hz, 2H), 3.36 (s, 3H), 2.93–2.80 (m, 4H), 2.16–2.04 (m, 1H), 1.92–1.75 (m, 3H), 1.66–1.59 (m, 4H); ESRMS *m*/*z* 236 ([M+Na]$^+$); MALDIHRMS calcd for $C_{10}H_{20}O_2S_2Na$ ([M+Na]$^+$) 259.0797; found 259.0802.

4.14. Coupling of 19 with 20 (21)

n-BuLi (1.6 M, 4.0 mL, 6.54 mmol) was added to a solution of **20** (1.14 g, 5.94 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 (1.04 mL, 5.94 mmol) was introduced, followed by iodide **19** (1.496 g, 5.94 mmol, dissolved in 5 mL of dry THF). The mixture was then stirred at 0 °C for 17 h. The reaction was quenched by addition of aq satd NH_4Cl (10 mL). The mixture was diluted with Et_2O (50 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed first with 1 N HCl and then with water and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed (12:1 *n*-hexane/EtOAc) on silica gel to give **21** as a colorless oil (1.454 g, 4.04 mmol, 68% yield). FTIR (film) 1456, 1274, 1151, 1111, 1044, 968, 919 cm^{-1}; ^1H NMR δ 5.47–5.35 (m, 2H), 4.63 (s, 2H), 3.54 (t, J=6.6 Hz, 2H), 3.37 (s, 3H), 2.82–2.78 (m, 4H), 2.04–1.84 (m, 9H), 1.64–1.30 (m, 11H), 0.89 (t, J=7.1 Hz, 3H); ESRMS *m*/*z* 383 ([M+Na]$^+$); MALDIHRMS calcd for $C_{19}H_{36}O_2S_2Na$ ([M+Na]$^+$) 383.2049; found 383.2060.

4.15. Removal of the MOM protecting group in 21 (22)

A solution of **21** (2.02 g, 5.6 mmol) and *p*-$TsOH{\cdot}H_2O$ (106 mg, 0.56 mmol) in THF (40 mL) was stirred at 40 °C for 3 h. Water (10 mL) and Et_2O (50 mL) were added and the phases were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed first with aq satd $NaHCO_3$ to neutral and then with water and brine before being dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **22** as a yellowish oil (1.59 g, 5.03 mmol, 90% yield). FTIR (film) 3392, 2930, 2860, 1456, 1274, 1070, 967 cm^{-1}; ^1H NMR δ 5.47–5.35 (m, 2H), 3.68 (t, J=6.0 Hz, 2H), 2.83–2.79 (m, 4H), 2.04–1.85 (m, 9H), 1.65–1.26 (m, 11H), 0.89 (t, J=6.6 Hz, 3H); ESRMS *m*/*z* 355 ([M+K]$^+$); MALDIHRMS calcd for $C_{17}H_{32}OS_2Na$ ([M+Na]$^+$) 339.1787; found 339.1797.

4.16. Oxidation of 22 (23)

A solution of $SO_3{\cdot}Py$ (1.040 g, 6.54 mmol) in DMSO (9.2 mL) was added dropwise to a solution of **22** (690 mg, 2.18 mmol) in CH_2Cl_2 (7.3 mL) and stirred in an ice-water bath. The stirring was continued for 30 min. Water (5 mL) and Et_2O (200 mL) were added and the phases were separated. The organic layer was washed in turn with aq satd $CuSO_4$ (3×5 mL), water (3×5 mL), and brine (10 mL) before being dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed (15:1 *n*-hexane/EtOAc) on silica gel to afford the aldehyde **23** as a colorless oil (589 mg, 1.87 mmol, 86% yield). FTIR (film) 1724, 1455, 1238, 1083, 968 cm^{-1}; ^1H NMR δ 9.79 (s, 1H), 5.49–5.33 (m, 2H), 2.83–2.78 (m, 4H), 2.48 (t, J=7.6 Hz, 2H), 2.04–1.75 (m, 12H), 1.52–1.44 (m, 2H), 1.37–1.25 (m, 4H), 0.89 (t, J=7.3 Hz, 3H); ESRMS *m*/*z* 315 ([M+H]$^+$); MALDIHRMS calcd for $C_{17}H_{31}OS_2$ ([M+H]$^+$) 315.1811; found 315.1815.

4.17. Synthesis of 24

A solution of aldehyde **23** (288 mg, 0.91 mmol) in CH_3CN (5 mL) was added to a solution of the sulfoxide reagent **11** (193 mg, 0.91 mmol) in CH_3CN (5 mL). The stirring was continued at rt overnight. Water (5 mL) and Et_2O (30 mL) were added and the phases were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with water and brine before being dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed (6:1 *n*-hexane/EtOAc) on silica gel to afford the aldehyde **24** as a colorless oil (229 mg, 0.57 mmol, 63% yield). FTIR (film) 3465,

2930, 2860, 1719, 1656, 1454, 1271, 1173, 1039, 970 cm^{-1}; ^1H NMR δ 6.95 (dd, J=16.0, 4.1 Hz, 1H), 6.06 (d, J=16.0 Hz, 1H), 5.47–5.35 (m, 2H), 4.35 (s, 1H), 4.21 (q, J=6.8 Hz, 2H), 2.81–2.79 (m, 4H), 2.09–1.27 (m, 22H), 0.89 (t, J=6.6 Hz, 3H); ESRMS m/z 423 ($[M+Na]^+$); MALDIHRMS calcd for $C_{21}H_{36}O_3S_2Na$ ($[M+Na]^+$) 423.1998; found 423.2003.

4.18. Deprotection of 24 (5c)

Powdered $NaHCO_3$ (548 mg, 6.53 mmol) and I_2 (666 mg, 2.63 mmol) were added in turn to a solution of **24** (300 mg, 0.75 mmol) in 5:1 (v/v) acetone–water (7.5 mL) stirred in an ice-water bath. The mixture was stirred for 15 min when TLC showed disappearance of the starting material. Aq satd $Na_2S_2O_3$ (10 mL) was added to quench the reaction. The mixture was extracted with Et_2O (3×30 mL). The combined organic layers were washed in turn with aq satd $NaHCO_3$, water, and brine and dried over anhydrous Na_2SO_4. The residue after removal of the solvent was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **5c** as a yellowish oil (285 mg, 0.92 mmol, 87% yield). FTIR (film) 3463, 1716, 1658, 1464, 1368, 1304, 1270, 1176, 1039, 970 cm^{-1}; ^1H NMR δ 6.90 (dd, J=15.8, 4.5 Hz, 1H), 6.06 (d, J=15.6 Hz, 1H), 5.41–5.33 (m, 2H), 4.38–4.34 (m, 1H), 4.20 (q, J=7.8 Hz, 2H), 2.66 (d, J=4.8 Hz, 1H), 2.58 (t, J=8.1 Hz, 2H), 2.42 (t, J=7.6 Hz, 2H) 2.01–1.97 (m, 5H), 2.02–1.95 (m, 1H), 1.67–1.26 (m, 2H), 1.39–1.27 (m, 7H), 0.89 (t, J=7.1 Hz, 3H); ESRMS m/z 333 ($[M+Na]^+$); MALDIHRMS calcd for $C_{18}H_{30}O_4Na$ ($[M+Na]^+$) 333.2036; found 333.2040.

4.19. Synthesis of 7c

A mixture of **5c** (233 mg, 0.75 mmol), UHP (529 mg, 5.63 mmol), and *p*-TsOH·H_2O (171 mg, 0.90 mmol) in DME (15 mL) was stirred at rt overnight. The solvent was removed by rotary evaporation and the residue was chromatographed (10:1 *n*-hexane/EtOAc) on silica gel to afford *cis*-**6c** (63 mg, 0.19 mmol, 26% yield) and *trans*-**6c** (146 mg, 0.45 mmol, 60% yield) as colorless oils. Data for compound *cis*-**6c** (the less polar component): FTIR (film) 3387, 1722, 1660, 1447, 1304, 1268, 1177, 1039 cm^{-1}; ^1H NMR δ 8.21 (s, 1H), 6.97 (dd, J=16.0, 6.0 Hz, 1H), 6.04 (d, J=16.0 Hz, 1H), 5.47–5.38 (m, 2H), 4.82–4.75 (m, 1H), 4.21 (q, J=7.1 Hz, 2H), 2.17–1.96 (m, 9H), 1.71–1.23 (m, 10H), 0.88 (t, J=6.4 Hz, 3H). Data for compound *trans*-**6c** (the more polar component): FTIR (film) 3393, 1722, 1660, 1460, 1370, 1304, 1268, 1178, 1042 cm^{-1}; ^1H NMR δ 8.16 (s, 1H), 6.91 (dd J=15.6, 5.0 Hz, 1H), 6.04 (d, J=15.5 Hz, 1H), 5.47–5.32 (m, 2H), 4.70–4.65 (m, 1H), 4.20 (q, J=7.2 Hz, 2H), 2.32–2.23 (m, 1H), 2.09–2.02 (m, 7H), 1.75–1.26 (m, 11H), 0.89 (t, J=7.1 Hz, 3H). Because these hydroperoxides are not very stable, they should be used as soon as possible.

A mixture of *cis*-**6c** (51 mg, 0.156 mmol) and $HNEt_2$ (1 μL, 0.00975 mmoL) in CF_3CH_2OH (10 mL) was stirred at rt for one day until TLC showed disappearance of the starting material. The solvent was removed by rotary evaporation and the residue was chromatographed (20:1 *n*-hexane/EtOAc) on silica gel to yield **7c** as a colorless oil (16 mg, 0.0491 mmol, 32% yield). FTIR (film) 2956, 2925, 2850, 1739, 1462, 1377, 1278, 971, 911 cm^{-1}; ^1H NMR δ 5.46–5.29 (m, 2H), 4.88 (t, J=6.6 Hz, 1H), 4.33 (d, J=4.6 Hz, 1H), 4.16 (q, J=7.2 Hz, 2H), 2.38–2.21 (m, 3H), 2.02–1.82 (m, 7H), 1.79–1.64 (m, 2H), 1.53–1.43 (m, 2H), 1.33–1.24 (m, 7H), 0.88 (t, J=6.5 Hz, 3H); MALDIHRMS m/z calcd for $C_{18}H_{30}O_5Na$ ($[M+Na]^+$) 349.1986; found 349.1985.

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