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Synthesis and in vitro antimalarial activity of spiro-analogues of peroxyplakoric acids

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ABSTRACT

Four 1,2,7-trioxa-spiro[5.5]undecanes and two 1,6,7-trioxa-spiro[4.5]decanes were synthesized using the hydrogen peroxide in UHP (urea–H_2O_2 complex) as the source of the peroxy bond. Incorporation of H_2O_2 into the organic molecular framework was facilitated by the potential to form a five- or six memberd cyclic hemiketal. Saturation of the double bond in a substituted γ-keto-butenal, a step required in all the syntheses, was achieved in one case with NaI/concd HCl at low temperature without cleaving the TBS protecting group or causing excessive side reactions as observed at ambient temperature. All these peroxides showed in vitro antimalarial activity comparable to that of natural peroxyplakoric acids and the known analogues.

1. Introduction

Qinghaosu[1] (artemisinin, **1**) derived antimalarial agents now have become the first line drugs for treatment of malaria.[2] However, the global quest for simple synthetic peroxides of comparable activity triggered off by the discovery of qinghaosu some thirty years ago still goes on,[3] partially because of the limited natural resource of qinghaosu, which is structurally too complex for total synthesis on industrial scales, and the need for a diverse of yet related compounds for revealing structure–activity relationship and understanding the antimalarial mechanism of the peroxide type antimalarials.

In previous[4] papers we reported several 1,6,7-trioxa-spiro-[4.5]decane (**2**) and 1,7,8-trioxa-spiro[5.6]do-decane (**3**) type peroxides (Fig. 1). Here in this contribution we wish to describe the synthesis and in vitro antimalarial activity of several previously unknown 1,2,7-trioxa-spiro[5.5]undecane type peroxides **4**–**7**, along with two substituted analogues of **2** (**8** and **9**). An attempted synthesis of a nitrogen-containing analogue **10** is also briefly described (Fig. 2).

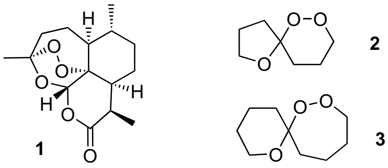

Figure 1. The structure for **1** (artemisinin), **2**, and **3**.

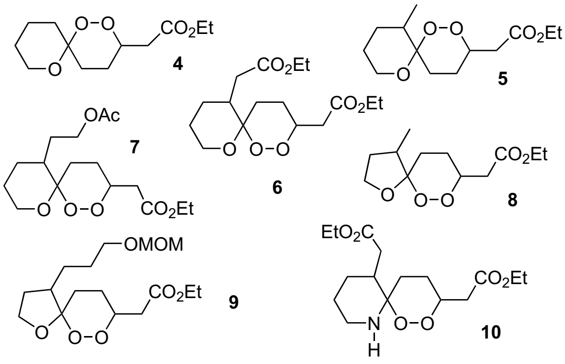

Figure 2. The targets of the present work.

2. Results and discussions

The present work began with synthesis of **4**, the simplest in the series. As shown in Scheme 1, alkylation of the known MOM protected dithiane **11**[5] with iodide **12**[6] under the standard conditions

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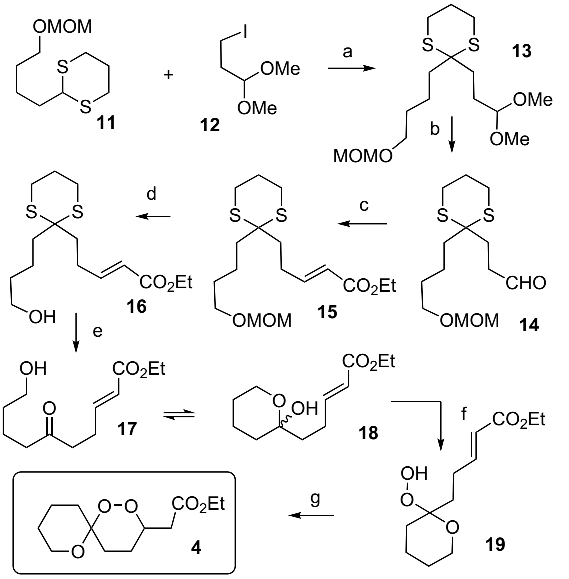


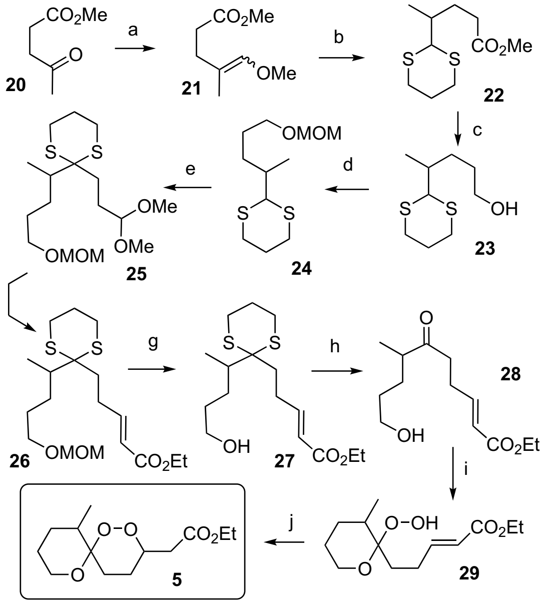
Scheme 1. (a) (i) *n*-BuLi/THF/−78 °C/30 min, then −40 °C/30 min, (ii) HMPA/**12** in THF/−40 °C/5 h, (iii) rt/12 h, 66%; (b) (i) PPTS/acetone–H_2O (10:1)/reflux/2 h, 83%; (c) $Ph_3P{=}CHCO_2Et/CH_2Cl_2$/rt/12 h, 91%; (d) 4 N HCl/THF/50 to 60 °C/6 h, 73%; (e) I_2/acetone–H_2O (20:3)/$NaHCO_3$/rt/1 h, 70%; (f) UHP/*p*-TsOH/EtOH/rt/12 h, 89%; (g) $HNEt_2/CF_3CH_2OH–CH_2Cl_2$ (4:1)/rt/24 h, 53%.

gave **13** in 66% yield. Removal of the dimethyl acetal protecting group by hydrolysis in acetone–water (10:1) with PPTS (pyridium *p*-toluenesulfonate) as the catalyst gave the aldehyde **14** (83%), which on treatment with $Ph_3P{=}CHCO_2Et$ afforded (*E*)-α,β-unsaturated ester **15** in 91% isolated yield.

Cleavage of the MOM protecting group in **15** was then realized with 4 N HCl at 50–60 °C in THF to give alcohol **16**, which on further treatment with I_2 in acetone–H_2O in the presence of $NaHCO_3$ led to hydrolysis of the thioketal. The resulting alcohol **17**, which is interchangeable with the hemiketal form **18** but in great favor of **17** as shown by ^1H NMR, was subjected to UHP (urea–H_2O_2 complex) in anhydrous EtOH in the presence of a catalytic amount of *p*-TsOH to introduce the desired hydroperoxyl group as reported[4] previously. Finally, an intramolecular Michael addition of the hydroperoxyl group to the C–C double bond yielded the end product **4**.

Synthesis of **5** was achieved using the route shown in Scheme 2. Like the majority of the targets of this work, compound **5** also carries a substituent at the carbon next to the spiroketal center. We incorporated such a feature into the target structures of this work because it might lead to a secondary carbon-centered radical once the peroxyketal functionality is cleaved by some single-electron reductants (Fig. 3) as suggested by previous studies[5] and different subsequent radical behavior might follow. Thus, treatment of the commercially available levulinate **20** with the Wittig reagent generated in situ from the known[6] phosphonium salt $Ph_3PCH_2(OMe)BF_4$ by deprotonation with LDA (lithium diisopropylamide) at −78 °C led to clean formation of the acid-sensitive enol ether **21**, which on further treatment with propane-1,3-dithiol in the presence of $BF_3{\cdot}Et_2O$ afforded dithiane **22** in 76% overall yield. It is noteworthy that although (to the best of our knowledge) unlike its halide counterparts $Ph_3PCH_2(OMe)BF_4$ has never been employed in such reactions, it does offer an apparent advantage—its preparation and isolation is much simpler than the corresponding halides.

The choice of base in the seemingly rather simple deprotonation of $Ph_3PCH_2(OMe)BF_4$ also deserves a few more words. *n*-BuLi led to extensive formation of side products, giving **21** in only 24% yield. *s*-BuLi was better, but the yield was only 65%. Replacement of a phenyl group in the phosphonium ion by an alkyl group could be the reason according to Kabalka's[7] studies on similar systems.



Scheme 2. (a) (i) $Ph_3PCH_2(OMe)BF_4$/LDA/THF/−78 °C addition then 0 °C/2 h, (ii) **20**/THF introduced at −78 °C, (iii) −78 °C to rt/6 h; (b) $HS(CH_2)_2SH/BF_3{\cdot}Et_2O/CH_2Cl_2$/rt/12 h, 76% from **20**; (c) $LiAlH_4$/THF/0 °C/1 h, 92%; (d) MOMCl/*i*-Pr_2NEt/CH_2Cl_2, 98%; (e) *n*-BuLi/HMPA/THF, then **12**, 43%; (f) (i) PPTS/acetone–H_2O (8:1), (ii) $Ph_3P{=}CHCO_2Et/CH_2Cl_2$/rt/12 h, 87% from **25**; (g) 4 N HCl/THF/60 °C/6 h, 79%; (h) $I_2/NaHCO_3$/acetone–H_2O (10:1)/rt/1 h, 68%; (i) UHP/*p*-TsOH/EtOH/rt/12 h, 70%; (j) $Et_2NH/CF_3CH_2OH–CH_2Cl_2$ (2:1)/rt/12 h, 42%.

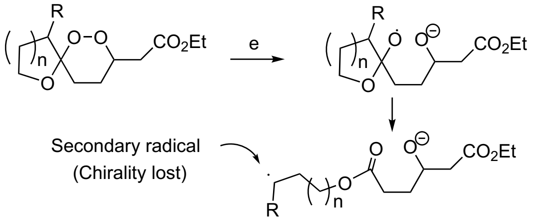
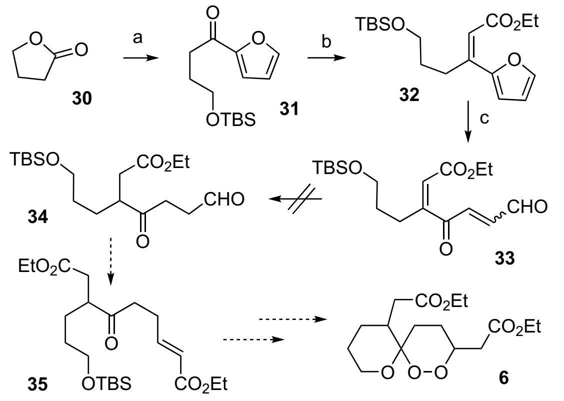


Figure 3. Substituted spiroperoxides might generate a secondary carbon-centered radical on cleavage induced by single-electron reducing species.

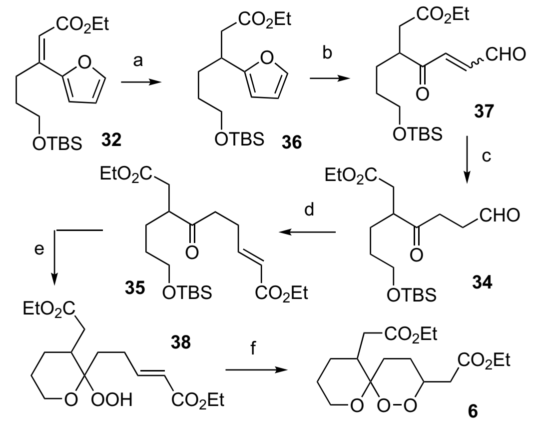
The ester group in **22** was then reduced to alcohol with $LiAlH_4$ in THF, and the newly formed hydroxyl group was masked as a MOM ether by treatment with *i*-Pr_2NEt/MOMCl in CH_2Cl_2. Subsequent three-carbon chain extension was achieved again with iodide **12** as in the synthesis of **13**. This was immediately followed by incorporation of another two-carbon unit via hydrolysis of the dimethyl acetal and a Wittig reaction with $Ph_3P{=}CHCO_2Et$.

The MOM and dithiane protecting groups in **26** was then removed by sequential treatment with 4 N HCl and $I_2/NaHCO_3$ to afford **28**. Further exposure of **28** to UHP/*p*-TsOH introduced the hydroperoxyl group in 70% yield. Finally, the hemiperketal **29** was subjected to the $Et_2NH/CF_3CH_2OH–CH_2Cl_2$ conditions to result in the desired target molecule **5**.

In the synthesis of the third target molecule (**6**), a different approach was attempted. As shown in Scheme 3, a furan-based strategy was adopted. From the known acyl furan species **31**, which could be readily prepared from the commercially available lactone **30** as reported by Ohmori[8] and co-workers, (*Z*)-α,β-unsaturated ester **32** (confirmed by NOESY data) was easily obtained via reaction with $(EtO)_2P(O)CHCO_2Et$[9]/NaH. Subsequent exposure to NBS[10] (*N*-bromo-succinimide) cleaved the furan ring smoothly, yielding aldehyde-enone **33** as expected. According to our original plan, the **33** next should be converted into **34** by saturation of the two C–C double bonds and then **35** by a selective Wittig reaction to obtain the precursor for perhydroxylation. Unfortunately, the



Scheme 3. (a) *n*-BuLi/furan/−78 °C/5 h then TBSCl, 85% for 2 steps; (b) $(EtO)_2P(O)CHCO_2Et$/NaH/THF, 80%; (c) NBS/acetone–H_2O (10:1)/$NaHCO_3$/Py, 62%.



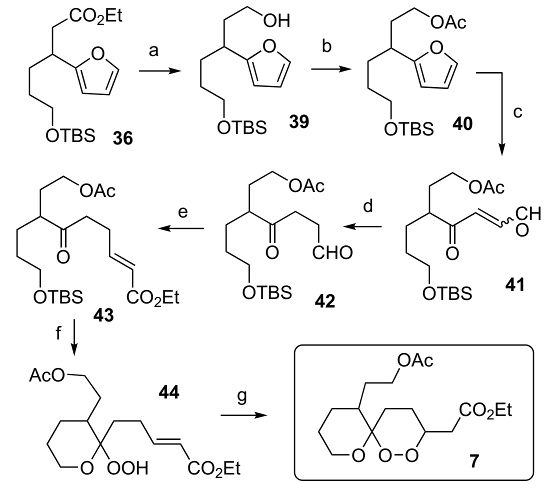
Scheme 4. (a) $NiCl_2 \cdot 6H_2O/NaBH_4$/MeOH, 88%; (b) acetone–$H_2O$ (10:1)/NBS/$NaHCO_3$/Py, 67%; (c) H_2/Pd–C/EtOAc, 51%; (d) Ph_3PCHCO_2Et/CH_2Cl_2, 92%; (e) UHP/*p*-TsOH/EtOH, 70%; (f) Et_2NH/CF_3CH_2OH, 65%.

saturation of the double bond using either H_2/Pd–C[11] or HCl/NaI[12] conditions resulted in a complicated mixture. For these reasons we adjusted the plan, switching to a stepwise strategy with only one C–C double bond saturated at a time (Scheme 4).

Thus, reduction of **32** with $NiCl_2 \cdot 6H_2O/NaBH_4$[13] in MeOH led to **36** in 88% yield. Subsequent oxidative cleavage of the furan ring gave **37** without any complication. The C–C bond was then saturated by catalytic hydrogenation over Pd–C. With one less double bond in the molecule, the hydrogenation of **37** was much less complicated than that of **33**, affording the desired **34** in 51% yield.

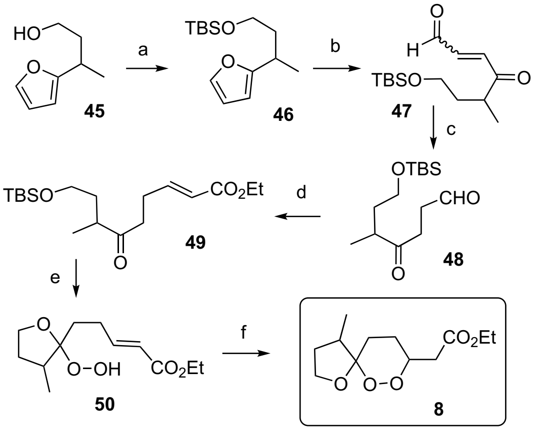
Successful acquisition of **34** made it possible for us to resume the originally planned route despite the interruption of the failure with reduction of **33**. Thus, treatment of **34** with $Ph_3P{=}CHCO_2Et$ resulted in the expected α,β-unsaturated ester **35** with very high regioselectivity. Unlike in the synthesis of **4** and **5**, where a separate step was required for the deprotection of the terminal hydroxyl group, in construction of **6** removal of the TBS group was achieved at the same time when introducing the hydroperoxyl group. The resulting **38** was then exposed to Et_2NH/CF_3CH_2OH to induce the intramolecular Michael addition leading to spiroperketal **6**.

The fourth target molecule (**7**) was synthesized as outlined in Scheme 5. Reduction of **36** with $LiAlH_4$ in THF followed by acylation with Ac_2O afforded acetate **40** in 72% overall. The remaining steps were performed in the way as employed for converting **36** into **6** depicted in Scheme 4.



Scheme 5. (a) $LiAlH_4$/THF, 80%; (b) Ac_2O/pyridine/CH_2Cl_2, 90%; (c) acetone–H_2O (10:1)/NBS/$NaHCO_3$/Py, 89%; (d) H_2/Pd–C/EtOAc, 48%; (e) $CH_2Cl_2/Ph_3P{=}CHCO_2Et$, 87%; (f) UHP/*p*-TsOH/EtOH, 93%; (g) Et_2NH/CF_3CH_2OH, 52%.

Apart from the above mentioned four 1,2,7-trioxa-spiro-[5.5]undecane type peroxides (**4**–**7**) efforts were also made in synthesis of two 1,6,7-trioxa-spiro[4.5]decanes of a similar substitution pattern (**8** and **9**). Scheme 6 summaries the synthesis of **8**. Starting from the known **45**, which could be readily prepared from 2-acetylfuran as described[14] in the literature, via a standard TBS protection and the NBS-mediated oxidative cleavage of the furan ring the desired aldehyde-enone **47** was obtained in 68% overall yield.

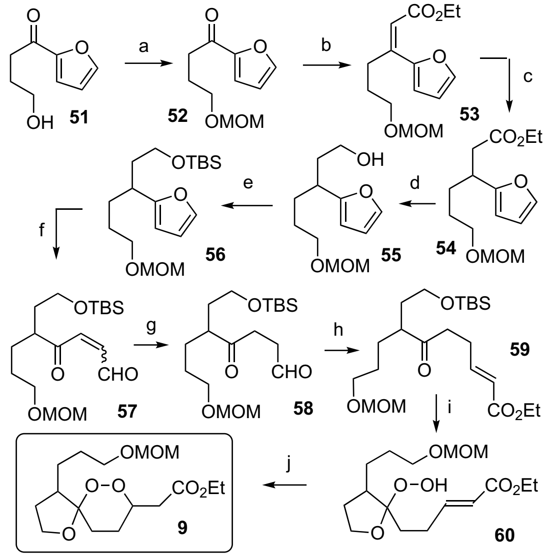


Scheme 6. (a) TBSCl/DMF/imidazole, 95%; (b) acetone–H_2O (10:1)/NBS, Py/$NaHCO_3$, 72%; (c) NaI/HCl/acetone/−50 °C, 71%; (d) Ph_3PCHCO_2Et/CH_2Cl_2, 82%; (e) UHP/*p*-TsOH/EtOH, 72%; (f) Et_2NH/CF_3CH_2OH, 40%.

Reduction of the C–C double bond in **47** initially was also attempted using the NaI/HCl[12] protocol as with **33**. Similar failure was encountered. However, when we lowered the temperature from the ambient temperature in the literature to −50 °C the product mixture became much simpler. And the **48** could be isolated in 71% yield. It appears that if performing the reduction at lower temperatures, the literature protocol would find much broader application.

The remaining three steps were then completed in the same way as in the previous cases: First, the chain was extended by two carbon units through reaction with Ph_3PCHCO_2Et. The resultant **49** was then subjected to the hydroperoxidation conditions to remove the TBS protecting group and introduce the hydroperoxyl group in a one-flask manner. Finally, the free terminal of the hydroperoxyl group was 'alkylated with the double bond' via the intramolecular Michael addition, yielding the fifth target molecule **8**.

Another substituted 1,2,7-trioxa-spiro[5.5]undecane (**9**) was synthesized with **51**[15] as the starting material (Scheme 7). MOM protection of the hydroxyl group and Wittig reaction with $(EtO)_2P(O)CHCO_2Et$ gave **53**, which on treatment with $NiCl_2\cdot 6H_2O/NaBH_4$ in MeOH to saturate the C–C double bond and $LiAlH_4$ to reduce the ester functionality afforded alcohol **55**.



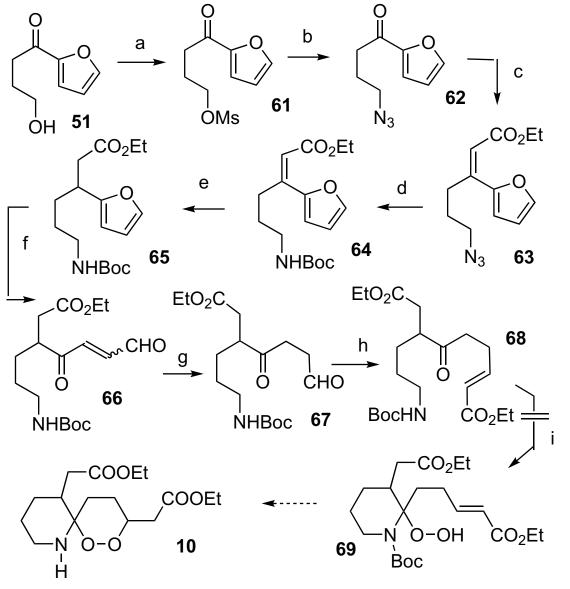
Scheme 7. (a) MOMCl/*i*-Pr_2NEt/CH_2Cl_2, 90%; (b) $(EtO)_2P(O)CHCO_2Et$/NaH/THF, 88%; (c) $NiCl_2\cdot 6H_2O/NaBH_4$/MeOH, 72%; (d) $LiAlH_4/Et_2O$, 89%; (e) DMF/TBSCl/imidazole, 99%; (f) acetone–H_2O (10:1)/NBS/$NaHCO_3$/Py, 81%; (g) H_2/Pd–C/EtOAc, 48%; (h) Ph_3PCHCO_2Et/CH_2Cl_2, 87%; (i) UHP/*p*-TsOH/EtOH, 80%; (j) Et_2NH/CF_3CH_2OH, 52%.

After masking the hydroxyl group as a TBS ether, the furan ring was cleaved to release the desired 1,4-dicarbonyl functionalities through reaction with NBS. The product (**57**) was isolated as an inseparable mixture of the cis/trans isomers as seen from the ^1H NMR as in all the similar cases (**33**, **37**, **41**, **47**, and **66**). Again, because both isomers would lead to the same compound after saturation of the double bond, the mixture was used as such in the next step to yield **58**. The subsequent chain extension, removal of the TBS protecting group, introduction of the hydroperoxyl group, and the ring-closure were then completed in the same way as before, providing the sixth target compound **9**.

We have also attempted to make a nitrogen substituted analogue (**10**). As shown in Scheme 8, activation of the hydroxyl group in **51** as a mesylate followed by a NaN_3 substitution gave azide **62**. A two-carbon unit was then introduced via a Wittig reaction with $Ph_3P{=}CHCO_2Et$ to afford **63**. Subsequent reduction of the α,β-unsaturated C–C double bond in **63** with $NiCl_2\cdot 6H_2O/NaBH_4$ in MeOH was complicated by unexpected partial reduction of the azido group. Increasing the amount of the added reducing agent did not lead to any discernible improvement. Hence, a different reduction protocol must be utilized.

We next tried Staudinger[16] reaction, which used Ph_3P as reducing agent to selectively convert the azido group into an amino group without affecting the C–C double bond. The free amino group was then protected as a Boc ester. The resulting **64** was treated with $NiCl_2\cdot 6H_2O/NaBH_4$ in MeOH to deliver **65** in 91% yield.

Oxidative cleavage of the furan ring was carried out as done in the previous cases, affording *trans*-γ-keto-butenal **66** in 56% isolated yield. Saturation of the C–C double bond was achieved by catalytic hydrogenation over Pd–C to yield aldehyde **67**, which on reaction with $Ph_3P{=}CHCO_2Et$ provided the hydroperoxidation substrate **68**. However, further exposure of **68** to the UHP/*p*-TsOH did not result in any detectable amounts of the anticipated **69**. We also tried the hydroperoxidation with a substrate without the Boc protecting group and/or using other catalyst such as $BF_3\cdot Et_2O$, $Ce(NH_4)_2(NO_3)_6$ (CAN), or $Sc(OTf)_2$ instead of *p*-TsOH. Unfortunately, all these attempts did not lead to any improvements. The synthesis of **10** was thus discontinued.



Scheme 8. (a) $MsCl/Et_3N/CH_2Cl_2$/−78 °C, 90%; (b) NaN_3/DMF, 86%; (c) NaH/THF/$(EtO)_2P(O)CHCO_2Et$, 76%; (d) (i) $PPh_3/THF/H_2O$/50 °C, (ii) $(Boc)_2O/CH_2Cl_2$, 96% over 2 steps; (e) $NiCl_2\cdot 6H_2O/NaBH_4$/MeOH, 91%; (f) acetone–H_2O (10:1)/NBS/$NaHCO_3$/Py, 56%; (g) H_2/Pd–C/EtOAc, 96%; (h) $Ph_3P{=}CHCO_2Et/CH_2Cl_2$, 80%; (i) UHP/*p*-TsOH/EtOH, no reactions.

The newly synthesized peroxides (**4**–**9**) along with five bridged peroxides synthesized earlier[17] in our group (Fig. 4) were then tested in vitro on *Plasmodium falciparum* (NF54 strain) for their antimalarial activity. The preliminary results are outlined in Table 1, which appear to be compatible with those reported[17c,18] for natural peroxyplakoric acids and the known analogues.

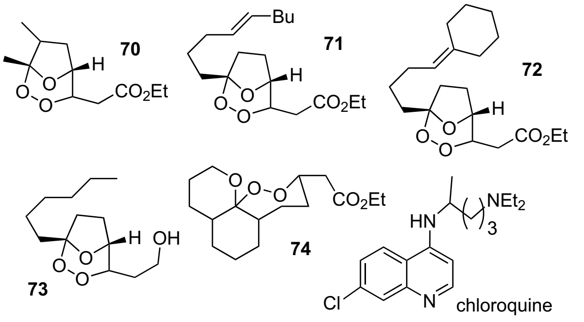


Figure 4. The structures of a few other cyclic peroxides synthesized previously (with those known partial relative configurations shown) and chloroquine. The in vitro antimalarial activity data of these compounds are given in Table 1.

Table 1
Results of in vitro tests against NF54 strain[a,b]

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
4	1.38	**70**	13.40
5	1.00	**71**	0.554
6	0.60	**72**	0.160
7	4.28	**73**	0.732
8	3.44	**74**	1.56
9	4.14	Chloroquine	0.013

[a] The in vitro antimalarial data were obtained as described previously.[19]
[b] Data shown are the values from n=2–3 independent experiments.

3. Conclusions

Six new cyclic peroxides (four 1,2,7-trioxa-spiro[5.5]undecanes and two 1,6,7-trioxa-spiro[4.5]decanes) were synthesized using the hydrogen peroxide in UHP (urea–H_2O_2 complex) as the source of the peroxy bond. Incorporation of H_2O_2 into the organic molecular framework was made facile by formation of a five- or six memberd cyclic hemiketal. Saturation of the double bond in the substituted γ-keto-butenal (a step required in synthesis of all the compounds) was satisfactorily effected in one case with the highly acidic NaI/concd HCl conditions at −50 °C without cleaving the TBS protecting group or causing excessive side reactions as observed at ambient temperature recommended in the literature. All these peroxides showed in vitro antimalarial activity comparable to that of natural peroxyplakoric acids and the known analogues.

4. Experimental

4.1. General

The ^{1}H 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 an 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. Alkylation of 11 with 12 leding to 13

n-BuLi (1.6 M, in hexanes, 4.4 mL, 7.03 mmol) was added via a syringe to a solution of **11** (1.46 g, 7.13 mmol) in dry THF (20 mL) stirred at −78 °C under N_2. After completion of the addition, the stirring was continued at −78 °C for 30 min. Dry HMPA (1.3 mL, 7.13 mmol) was introduced. The mixture was stirred at −40 °C for another 30 min before iodide **12** (2.22 g, 9.62 mmol, dissolved in 5 mL of dry THF) was introduced. The mixture was then stirred at ambient temperature for 12 h. Aqueous satd NH_4Cl (10 mL) was added, followed by Et_2O (50 mL). The phases were separated. The aqueous layer was back-extracted with Et_2O (3×20 mL). The combined organic layers were washed with aq satd NH_4Cl and then with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (6:1 *n*-hexane/EtOAc) on silica gel to give the **13** as a colorless oil (1.58 g, 4.70 mmol, 66%): FTIR (film) 2938, 2828, 1452, 1384, 1276, 1128 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (s, 2H), 4.38 (t, *J*=6.0 Hz, 1H), 3.53 (t, *J*=5.7 Hz, 2H), 3.37 (s, 3H), 3.33 (s, 6H), 2.92–2.71 (m, 4H), 2.01–1.70 (m, 8H), 1.48–1.67 (m, 4H); ESIMS *m*/*z* 361.3 ([M+Na]$^+$). Anal. Calcd for $C_{15}H_{30}O_4S_2$: C 53.71, H 8.58. Found: C 53.69, H 8.60.

4.3. Hydrolysis of acetal 13 leading to aldehyde 14

A solution of **13** (1.53 g, 4.54 mmol) and PPTS (295 mg, 1.18 mmol) in 10:1 (v/v) acetone–H_2O (55 mL) was refluxed for 2 h. Acetone was removed on a rotary evaporator. The residue was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (6:1 *n*-hexane/EtOAc) on silica gel to give **14** as a colorless oil (1.10 g, 3.76 mmol, 83%): FTIR (film) 2935, 2723, 1722, 1449, 1422, 1277, 1150 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 4.62 (s, 2H), 3.57 (t, *J*=6.6 Hz, 2H), 3.36 (s, 3H), 2.83–2.62 (m, 4H), 2.52 (t, *J*=7.9 Hz, 2H), 2.03–1.81 (m, 4H), 1.59–1.50 (m, 4H); ESIMS *m*/*z* 315.2 ([M+Na]$^+$). Anal. Calcd for $C_{13}H_{24}O_3S_2$: C 53.39, H 8.27. Found: C 53.69, H 8.57.

4.4. Wittig reaction of 14 leading to 15

A mixture of **14** (1.10 g, 3.78 mmol) and $Ph_3PCH{=}CO_2Et$ (2.17 g, 5.67 mmol) in CH_2Cl_2 (25 mL) was stirred at the ambient temperature overnight. The mixture was partitioned between brine and Et_2O. The phases were separated. The organic phase was washed in turn with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was purified by column chromatography (10:1 *n*-hexane/EtOAc) on silica gel to give **15** as a colorless oil (1.08 g, 2.99 mmol, 91%): FTIR (film) 2942, 1717, 1275, 1169, 1113, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (dt, *J*=6.7, 15.1 Hz, 1H), 5.86 (d, *J*=15.1 Hz, 1H), 4.61 (s, 2H), 4.19 (q, *J*=6.8 Hz, 2H), 3.54 (t, *J*=6.2 Hz, 2H), 2.93–2.72 (m, 4H), 2.24–2.41 (m, 2H), 1.82–2.01 (m, 6H), 1.62–1.45 (m, 4H), 1.24 (t, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 148.1, 121.7, 96.5, 67.5, 60.3, 55.2, 52.7, 38.5, 36.2, 29.9, 27.3, 26.0, 25.3, 20.8, 14.3; ESIMS *m*/*z* 385.1 ([M+Na]$^+$). Anal. Calcd for $C_{17}H_{30}O_4S_2$: C 56.32, H 8.34. Found: C 56.46, H 8.31.

4.5. Removal of the MOM protecting group in 15 (16)

A solution of **15** (1.08 g, 3.0 mmol) in THF (10 mL) and 4 N HCl (5 mL) was heated at 50–60 °C with stirring for 6 h. After being cooled to ambient temperature, the mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, before being dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give compound **16** as a colorless oil (790 mg, 2.2 mmol, 73%): FTIR (film) 3427, 2928, 1703, 1638, 1037 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (dt, *J*=16.1, 6.4 Hz, 1H), 5.84 (d, *J*=16.1 Hz, 1H), 4.21 (q, *J*=7.3 Hz, 2H), 3.73 (t, *J*=5.8 Hz, 2H), 2.71–2.91 (m, 4H), 2.41–2.33 (m, 2H), 2.12–1.83 (m, 2H), 1.73–1.53 (m, 4H), 1.32 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 148.1, 121.7, 62.5, 60.2, 52.8, 38.4, 36.3, 32.7, 27.4, 26.0, 25.2, 20.3, 14.3; ESIMS *m*/*z* 341.1 ([M+Na]$^+$). Anal. Calcd for $C_{15}H_{26}O_3S_2$: C 56.57, H 8.23. Found: C 56.57, H 8.29.

4.6. Hydrolysis of the dithiane protecting group in 16 (17/18)

$NaHCO_3$ (1.23 g, 12 mmol) and I_2 (1.85 g, 8.0 mmol) were added to a solution of **16** (610 mg, 2.0 mmol) in aqueous acetone (20 mL of acetone plus 4 mL of water) at 0 °C. The resulting mixture was stirred at ambient temperature for 1 h. Aqueous saturated $Na_2S_2O_3$ was added, followed by Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed in turn with aqueous saturated $Na_2S_2O_3$, water, and brine, before being dried over Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was purified by column chromatography on silica gel (2:1 *n*-hexane/EtOAc) to give **17**/**18** as a colorless oil (320 mg, 1.40 mmol, 70%): FTIR (film) 3484, 2939, 1716, 1654, 1440, 1369, 1270, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (dt, *J*=6.4, 16.1 Hz, 1H), 5.81 (d, *J*=16.1 Hz, 1H), 4.17 (q, *J*=7.0 Hz, 2H), 3.67–3.59 (m, 2H), 2.62–2.42 (m, 4H), 1.79–1.52 (m, 6H), 1.23 (t, *J*=7.0 Hz, 3H); ESIMS *m*/*z* 251.2 ([M+Na]$^+$); EIHRMS calcd for $C_{12}H_{20}O_4$ ([M−H_2O]$^+$) 210.1256, found 210.1256.

4.7. Synthesis of 19

p-TsOH (280 mg, 1.47 mmol) and UHP (1.16 g, 12.3 mmol) were added to a solution of **17** (280 mg, 1.23 mmol) in EtOH (30 mL). The resulting mixture was stirred at ambient temperature for 10 h. When TLC showed complete disappearance of **17**/**18**, the mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give compound **19** (268 mg, 1.10 mmol, 89%): FTIR (film) 3396, 2944, 1718, 1644, 1187, 1099, 1049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 6.98 (dt, *J*=6.7, 16.3 Hz, 1H), 5.84 (d, *J*=16.3 Hz, 1H), 4.02 (q, *J*=7.3 Hz, 2H), 3.90–3.72 (m, 2H), 2.51–2.20 (m, 2H), 2.10–1.92 (m, 1H), 1.83–1.73 (m, 1H), 1.63–1.52 (m, 6H), 1.32 (t, *J*=7.3 Hz, 3H); ESIMS *m*/*z* 267.1 ($[M+Na]^+$); EIHRMS calcd for $C_{12}H_{20}O_5$ (M^+) 244.1311, found 244.1320.

4.8. Synthesis of compound 4

The **19** (172 mg, 0.70 mmol) was dissolved in CF_3CH_2OH (4 mL) containing CH_2Cl_2 (1 mL) and $NHEt_2$ (6.5 μL). The mixture was stirred at the ambient temperature overnight. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (8:1 *n*-hexane/EtOAc) to give compound **4** as a colorless oil (92 mg, 0.37 mmol, 53% yield): FTIR (film) 2944, 1738, 1444, 1293 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54–4.50 (m, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 3.90 (dt, *J*=11.1, 3.2 Hz, 1H), 3.71 (d, *J*=11.1 Hz, 1H), 2.51 (dd, *J*=7.1, 16.1 Hz, 1H), 2.38 (dd, *J*=5.6, 16.1 Hz, 1H), 1.82–1.42 (m, 10H), 1.32 (t, *J*=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 98.8, 76.9, 61.2, 60.7, 38.4, 33.0, 32.8, 25.1, 24.8, 18.6, 18.4, 14.1; ESIMS *m*/*z* 267.1 ($[M+Na]^+$); MALDIHRMS calcd for $C_{12}H_{20}O_5Na$ ($[M+Na]^+$) 267.1203, found 267.1204.

4.9. Conversion of 20 into dithiane 22 via enol ether 21

n-BuLi (1.6 M, in hexanes, 10.0 mL, 16 mmol) was added via a syringe to a solution of *i*-Pr_2NH (2.4 mL, 17.2 mmol) in dry THF (14 mL) stirred at −78 °C under nitrogen (balloon). After completion of the addition, the solution was stirred at 0 °C for another 30 min. The resulting solution was then added slowly to a mixture of $Ph_3P^+CH_2OMe\ BF_4^-$ (6.5 g, 16 mmol) and in dry THF (20 mL) stirred at −78 °C under nitrogen. After completion of the addition the stirring was continued at the same temperature for 2 h before a solution of **20** (1.3 g, 10 mmol) in dry THF (12 mL) was introduced. The bath temperature was allowed to warm slowly to ambient temperature. The mixture was stirred for another 6 h before aq satd NH_4Cl (10 mL) and Et_2O (50 mL) were added. The phases were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with aq satd NH_4Cl, water and brine, before being dried over anhydrous anhydrous Na_2SO_4. Most of the solvent was distilled off under normal pressure with bath temperature kept blow 70 °C. The residue **21**, with following identifying data: FTIR (film) 2933, 2840, 1740, 1686, 1438, 1207 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.80 (s, 0.5H), 5.74 (s, 0.5H), 3.65 (s, 3H), 3.52 (s, 1.5H), 3.49 (s, 1.5H), 2.38–2.20 (m, 2H), 1.57 (s, 1.5H), 1.51 (s, 1.5H) was directly used for next step.

The above obtained crude **21** (10 mL) was dissolved in CH_2Cl_2 (15 mL). To this solution were added 1,3-propanedithiol (0.8 mL, 10 mmol) and $BF_3\cdot Et_2O$ (1.4 mL, 11 mmol). The mixture was stirred at ambient temperature for 12 h, when TLC showed completion of the reaction. Water (5 mL) was added, followed by Et_2O (50 mL). The phases were separated. The aqueous layer was back-extracted with Et_2O (3×20 mL). The combined organic layers were washed with aq satd $NaHCO_3$, water, and brine, before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (15:1 *n*-hexane/EtOAc) on silica gel to give **22** as a colorless oil (1.78 g, 7.62 mmol, 76% from **20**): FTIR (film) 2950, 2900, 1736, 1434, 1171, 909, 767 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (d, *J*=3.8 Hz, 1H), 3.69 (s, 3H), 2.94–2.83 (m, 4H), 2.42–2.32 (m, 2H), 2.13–1.67 (m, 5H), 1.42 (d, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 54.8, 51.5, 37.8, 31.8, 31.0, 30.7, 29.17, 26.2, 16.6; ESIMS *m*/*z* 257.1 ($[M+Na]^+$); ESIHRMS calcd for $C_{10}H_{18}O_2S_2Na$ ($[M+Na]^+$) 257.0640, found 257.0653.

4.10. Reduction of ester 22 leading to alcohol 23

$LiAlH_4$ (700 mg, 18 mmol) was added in small portions to a solution of **22** (4.2 g, 18 mmol) in dry THF (70 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature for 1 h before aq satd NH_4Cl and Et_2O were introduced. 4 N HCl was then added slowly until the reaction mixture became clear. The phases were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with water, brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed (4:1 *n*-hexane/EtOAc) on silica gel to give **23** as a colorless oil (3.40 g, 16.5 mmol, 92%): FTIR (film) 3368, 2930, 1455, 1422, 1379, 1276, 1185, 1055, 908, 769 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.14 (d, *J*=4.6 Hz, 1H), 3.66 (t, *J*=6.3 Hz, 2H), 2.94–2.83 (m, 4H), 2.18–2.05 (m, 1H), 1.97–1.79 (m, 2H), 1.573–1.54 (m, 2H), 1.46–1.32 (m, 2H), 1.11 (d, *J*=7.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 62.7, 55.3, 38.3, 31.0, 30.7, 30.3, 30.0, 26.3, 17.0. EIMS *m*/*z* (%) 206 (M^+, 22), 119 (100). Anal. Calcd for $C_9H_{18}OS_2$: C 52.38, H 8.79. Found: C 52.25, H 8.95.

4.11. Protection of 23 leading to 24

MOMCl (1.95 mL, 26 mmol) was added to a solution of **23** (2.74 g, 13 mmol) and *i*-Pr_2NEt (4.5 mL, 26 mmol) in CH_2Cl_2 (90 mL) stirred in an ice-water bath. After completion of the addition, the cooling bath was removed. The mixture was stirred at ambient temperature overnight. Water (5 mL) was added, followed by Et_2O (50 mL). The phases were separated. The aqueous layer was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (20:1 *n*-hexane/EtOAc) on silica gel to give **24** as a colorless oil (3.15 g, 12.7 mmol, 98%): FTIR (film) 2931, 2897, 1445, 1422, 1380, 1276, 1151, 1110, 1044, 917 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (s, 2H), 4.14 (d, *J*=4.6 Hz, 1H), 3.52 (t, *J*=6.7 Hz, 2H), 3.36 (s, 3H), 2.93–2.79 (m, 4H), 2.17–2.04 (m, 1H), 1.94–1.78 (m, 2H), 1.73–1.53 (m, 4H), 1.10 (d, *J*=7.2 Hz, 3H); ESIMS *m*/*z* 273.15 ($[M+Na]^+$). Anal. Calcd for $C_{11}H_{22}O_2S_2$: C 52.76, H 8.85. Found: C 52.43, H 9.15.

4.12. Alkylation of 24 leading to 25

n-BuLi (1.6 M, in hexanes, 1.5 mL, 2.5 mmol) was added to a solution of **24** (517 mg, 2.08 mmol) in dry THF (6 mL) stirred at −78 °C under N_2. After completion of the addition, the stirring was continued at −78 °C for 30 min. Dry HMPA (0.36 mL, 2.09 mmol) was introduced. The mixture was stirred at −40 °C for another 30 min before iodide **12** (0.37 mL, 2.5 mmol) was added. The stirring was continued at ambient temperature for 12 h. Aqueous satd NH_4Cl (10 mL) was introduced, followed by Et_2O (50 mL). The phases were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were washed with aq satd NH_4Cl, water and brine, before being dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed (6:1 *n*-hexane/EtOAc) on silica gel to give **25** as a colorless oil (314 mg, 0.89 mmol, 43%): FTIR (film) 2930, 2828, 1452, 1381, 1127, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (s, 2H), 4.39 (t, *J*=5.3 Hz, 1H), 3.60–3.44 (m, 2H), 3.37 (s, 3H), 3.33 (s, 6H), 2.98–2.64 (m, 4H), 2.15–1.66 (m, 11H), 1.11 (d, *J*=7.2 Hz, 3H); ESIMS *m*/*z* 375.2 ([M+Na]$^+$); EIHRMS calcd for $C_{16}H_{32}O_4S_2$ (M$^+$) 352.1742, found 352.1743.

4.13. Conversion of 25 into 26

A solution of **25** (175 mg, 0.50 mmol) and PPTS (32 mg, 0.13 mmol) in 10:1 (v/v) acetone–H_2O (6.6 mL) was refluxed for 6 h. Acetone was removed on a rotary evaporator. The residue was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was dissolved in CH_2Cl_2 (5 mL) containing Ph_3PCHCO_2Et (207 mg, 0.6 mmol). The mixture was stirred at ambient temperature overnight. Water (5 mL) was added, followed by Et_2O. The organic phase was washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed (8:1 *n*-hexane/EtOAc) on silica gel to give **26** as a colorless oil (165 mg, 0.44 mmol, 87% from **25**): FTIR (film) 2930, 1720, 1650, 1448, 1367, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (dt, *J*=6.7, 15.2 Hz, 1H), 5.87 (d, *J*=15.2 Hz, 1H), 4.64 (s, 2H), 4.19 (q, *J*=7.3 Hz, 2H), 3.67–3.39 (m, 2H), 3.37 (s, 3H), 2.98–2.66 (m, 4H), 2.50–2.34 (m, 2H), 2.19–1.70 (m, 8H), 1.57–1.43 (m, 1H), 1.29 (t, *J*=7.3 Hz, 3H), 1.12 (d, *J*=7.2 Hz, 3H); ESIMS *m*/*z* 399.2 ([M+Na]$^+$); EIHRMS calcd for $C_{18}H_{32}O_4S_2$ (M$^+$) 376.1742, found 376.1748.

4.14. Hydrolysis of the MOM protecting group in 26 leading to 27

A solution of **26** (150 mg, 0.398 mmol) in THF (2 mL) and 4 N HCl (1 mL) was heated at 50–60 °C with stirring for 6 h. After being cooled to ambient temperature, the mixture was diluted with Et_2O and washed with water. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (3:1 *n*-hexane/EtOAc) to give compound **27** as a colorless oil (104 mg, 0.314 mmol, 79%): FTIR (film) 3481, 2924, 2853, 1715, 1649, 1464, 1272, 1161, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (dt, *J*=15.6, 6.7 Hz, 1H), 5.87 (d, *J*=15.6 Hz, 1H), 4.20 (q, *J*=7.1 Hz, 2H), 3.68 (t, *J*=6.6 Hz, 2H), 2.48–2.32 (m, 2H), 2.19–1.70 (m, 8H), 1.25 (t, *J*=7.3 Hz, 3H), 1.12 (d, *J*=7.2 Hz, 3H); ESIMS *m*/*z* 355.2 ([M+Na]$^+$); EIHRMS calcd for $C_{16}H_{28}O_3S_2$ (M$^+$) 332.1480, found 332.1467.

4.15. Hydrolysis of the diathiane protecting group in 27 leading to 28

$NaHCO_3$ (176 mg, 1.74 mmol) and I_2 (263 mg, 1.2 mmol) were added to a solution of **27** (96 mg, 0.29 mmol) in aqueous acetone (3 mL of acetone plus 0.3 mL of water) stirred at 0 °C. The stirring was continued at ambient temperature for 1 h. Aqueous satd $Na_2S_2O_3$ was added, followed by Et_2O. The phases were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with aq satd $Na_2S_2O_3$, water, and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (2:1 *n*-hexane/EtOAc) to give **28** as a colorless oil (47 mg, 0.20 mmol, 68%): FTIR (film) 3480, 2924, 2853, 1714, 1657, 1463, 1268 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (dt, *J*=15.8, 6.3 Hz, 1H), 5.83 (d, *J*=15.8 Hz, 1H), 4.20 (q, *J*=7.3 Hz, 2H), 3.62 (t, *J*=6.2 Hz, 2H), 2.68–2.42 (m, 4H), 1.85–1.41 (m, 5H), 1.25 (t, *J*=7.3 Hz, 3H), 1.01 (d, *J*=7.2 Hz, 3H); ESIMS *m*/*z* 265.2 ([M+Na]$^+$); EIHRMS calcd for $C_{13}H_{22}O_4$ (M$^+$) 242.1518, found 242.1524.

4.16. Synthesis of 29

p-TsOH (40 mg, 0.21 mmol) and UHP (166 mg, 1.77 mmol) were added to a solution of **28** (43 mg, 0.18 mmol) in EtOH (4 mL). The resulting mixture was stirred at ambient temperature for 12 h. When TLC showed complete disappearance of **28**, the mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (5:1 *n*-hexane/EtOAc) to afford compound **29** (32 mg, 0.13 mmol, 70%): FTIR (film) 3385, 2935, 1721, 1650, 1450, 1213 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (s, 0.6H), 7.44 (s, 0.4H), 6.93 (dt, *J*=15.6, 6.7 Hz, 1H), 5.87 (d, *J*=15.6 Hz, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 3.89–3.44 (m, 2H), 2.39–2.13 (m, 2H), 1.98–1.73 (m, 2H), 1.60–1.31 (m, 3H), 1.23 (t, *J*=7.2 Hz, 3H), 1.04 (d, *J*=6.5 Hz, 1.9H), 0.94 (d, *J*=6.6 Hz, 1.1H); ESIMS *m*/*z* 281.15 ([M+Na]$^+$); EIHRMS calcd for $C_{13}H_{22}O_5$ (M$^+$) 258.1467, found 258.1465.

4.17. Synthesis of compound 5

A solution of **29** (24 mg, 0.093 mmol) and $NHEt_2$ (0.7 μL) in CF_3CH_2OH–CH_2Cl_2 (1.5 mL, 2:1 v/v) was stirred at room temperature overnight. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (8:1 *n*-hexane/EtOAc) to give compound **5** as a colorless oil (10 mg, 0.04 mmol, 42%): FTIR (film) 2929, 2855, 1739, 1466, 1288 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56–4.41 (m, 1H), 4.18 (q, *J*=7.2 Hz, 2H), 3.96–3.82 (m, 1H), 3.75–3.59 (m, 1H), 2.51 (dd, *J*=7.4, 14.7 Hz, 1H), 2.37 (dd, *J*=6.0, 14.7 Hz, 1H), 2.12–1.76 (m, 3H), 1.71–1.45 (m, 6H), 1.23 (t, *J*=7.2 Hz, 3H), 1.07–0.83 (m, 3H); ESIMS *m*/*z* 281.15 ([M+Na]$^+$); MALDIHRMS calcd for $C_{13}H_{22}O_5Na$ ([M+Na]$^+$) 281.13595, found 281.1369.

4.18. Conversion of 30 into 31

A solution of BuLi (1.6 M, 27 mL, 44 mmol) was added dropwise to a stirred solution of furan (2.9 mL, 40 mmol) in dry THF (40 mL) at 0 °C under a N_2 atmosphere (balloon). After 2 h, the resulting solution of lithiated furan was added dropwise to a solution of **30** (4.6 mL, 60 mmol, dissolved in 40 mL of dry THF) stirred at −78 °C. After the completion of the addition, stirring was continued at the same temperature for 1 h. The bath was warmed naturally and the stirring was continued at ambient temperature overnight. TBSCl (6.03 g, 40 mmol) was added. The mixture was stirred for another 3 h before aq satd NH_4Cl (20 mL) and Et_2O (80 mL) were introduced. The phases were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with aq satd NH_4Cl, water, and brine before being dried over Na_2SO_4. Concentration on a rotary evaporator and purification by column chromatography on silica gel (20:1 *n*-hexane/EtOAc) afforded the known **31**[8] as a colorless oil (9.3 g, 34 mmol, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 6.29–6.24 (m, 1H), 6.20–6.18 (m, 1H), 3.60 (t, *J*=5.9 Hz, 2H), 2.35 (t, *J*=6.8 Hz, 2H), 1.23–1.17 (m, 2H), 0.85 (s, 9H), 0.05 (s, 6H).

4.19. Wittig of reaction of 31 leading to 32

A solution of $(EtO)_3P(O)CH_2CO_2Et$ (3.5 g, 15.6 mmol in dry THF 10 mL) was slowly added to a mixture of NaH (624 mg, 15.6 mmol, pre-washed with hexanes and dry THF) and dissolved in THF (15 mL) stirred at 0 °C. After the addition, the stirring was continued at the same temperature for an additional 30 min before **31** (2.14 g, 7.8 mmol) was introduced. The cooling bath was then removed. The mixture was heated to reflux with stirring for 6 h. After the mixture was cooled to ambient temperature aq satd NH_4Cl

(10 mL) and Et_2O (50 mL) were added. The phases were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with aq satd NH_4Cl, water, and brine before being dried over Na_2SO_4. Concentration on a rotary evaporator and purification by column chromatography on silica gel (50:1 *n*-hexane/EtOAc) gave **32** as a colorless oil (2.7 g, 6.24 mmol, 80%): FTIR (film) 2955, 2857, 1717, 1612, 1473, 1371, 1256, 1175 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, *J*=1.8 Hz, 1H), 7.13 (d, *J*=3.5 Hz, 1H), 6.40 (dd, *J*=1.8, 3.5 Hz, 1H), 5.71 (s, 1H), 4.20 (q, *J*=7.0 Hz, 2H), 3.59 (t, *J*=6.4 Hz, 2H), 2.54 (t, *J*=7.9 Hz, 2H), 1.76–1.61 (m, 2H), 1.23 (t, *J*=7.0 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 151.0, 142.8, 142.7, 115.1, 114.1, 111.5, 62.0, 59.9, 32.8, 32.1, 25.8, 18.2, 14.2, −5.4; ESIMS *m*/*z* 361.2 ([M+Na]$^+$); MALDIHRMS calcd for $C_{18}H_{30}O_4SiNa$ ([M+Na]$^+$) 361.18056, found 361.1815.

4.20. Oxidative cleavage of the furan ring in 32 leading to 33

A solution of **32** (745 mg, 2.2 mmol) in acetone–H_2O (3 mL, 10:1 v/v) was added to a mixture of NBS (429 mg, 2.42 mmol) and $NaHCO_3$ (370 mg, 4.4 mmol) in acetone–H_2O (10 mL, 10:1 v/v) stirred at −15 °C. The mixture was stirred at the same temperature for 1 h. Pyridine (0.6 mL) was introduced. The stirring was continued at ambient temperature for 1 h. When TLC showed completion of the reaction, 1 N HCl (2 mL) was added, followed by EtOAc (50 mL). The phases were separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with aq satd NH_4Cl, water, and brine, before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **33** as a yellowish oil (482 mg, 1.36 mmol, 62%): FTIR (film) 2928, 2857, 1725, 1699, 1471, 1254, 1184, 1107 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.61 (d, *J*=7.6 Hz, 1H), 7.41 (d, *J*=15.5 Hz, 1H), 6.87 (dd, *J*=7.6, 15.5 Hz, 1H), 4.20 (q, *J*=7.0 Hz, 2H), 3.59 (t, *J*=5.9 Hz, 2H), 2.91 (t, *J*=8.1 Hz, 2H), 1.71–1.60 (m, 2H), 1.23 (t, *J*=7.0 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ESIMS *m*/*z* 377.20 ([M+Na]$^+$); MALDIHRMS calcd for $C_{18}H_{30}O_5SiNa$ ([M+Na]$^+$) 377.17547, found 377.1760.

4.21. Saturation of the double bond in 32 leading to 36

$NaBH_4$ (29 mg, 0.75 mmol) was added to a solution of **32** (85 mg, 0.25 mmol) and $NiCl_2\cdot6H_2O$ (10 mg, 0.04 mmol) in MeOH (3 mL) stirred at 0 °C. After the completion of the addition the mixture wad stirred at ambient temperature for an additional 2 h. When TLC showed completion of the reaction Et_2O (30 mL) was added, followed by water (10 mL). The phases were separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water, brine, before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (50:1 *n*-hexane/EtOAc) on silica gel to give **36** as a colorless oil (75 mg, 0.22 mmol, 88%): FTIR (film) 2925, 2855, 1712, 1622, 1460, 1172 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 1H), 6.23 (s, 1H), 6.20 (d, *J*=2.5 Hz, 1H), 4.07 (q, *J*=6.6 Hz, 2H), 3.53 (t, *J*=6.3 Hz, 2H), 3.22 (q, *J*=7.2 Hz, 1H), 1.72–1.61 (m, 2H), 1.49–1.36 (m, 2H), 1.23 (t, *J*=6.0 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 156.9, 141.1, 109.9, 105.2, 62.9, 60.3, 39.2, 35.4, 30.2, 30.1, 25.9, 18.3, 14.1, −5.4. EIMS *m*/*z* (%) 340 (M$^+$, 0.71), 324 (3.9), 295 (10.7), 283 (77.2), 195 (26.4), 165 (18.6), 121 (100); EIHRMS calcd for $C_{18}H_{32}O_4$ Si(M$^+$) 340.2070, found 340.2073.

4.22. Conversion of 36 into 34 via 37

A solution of **36** (1.0 g, 2.94 mmol) in acetone–H_2O (5 mL, 10:1 v/v) was added to a mixture of NBS (572 mg, 3.23 mmol) and $NaHCO_3$ (494 mg, 5.88 mmol) in acetone–H_2O (13 mL, 10:1 v/v) stirred at −15 °C. The reaction was stirred at the same temperature for 1 h. Pyridine (0.8 mL) was added. The mixture was stirred at ambient temperature for 1 h, when TLC showed completion of the reaction. 1 N HCl (3 mL) was added, followed by EtOAc (50 mL). The phases were separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with aq satd NH_4Cl, water, and brine before being dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **37** as a colorless oil (700 mg, 1.97 mmol, 67%): FTIR (film) 2953, 2930, 1733, 1698, 1472, 1103 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (d, *J*=7.5 Hz, 1H), 7.00 (d, *J*=17.7 Hz, 1H), 6.84 (dd, *J*=7.5, 17.7 Hz, 1H), 4.06 (q, *J*=6.8 Hz, 2H), 3.57 (t, *J*=5.7 Hz, 2H), 2.83 (dd, *J*=9.8, 17.3 Hz, 1H), 2.46 (dd, *J*=3.8, 17.2 Hz, 1H), 1.79–1.64 (m, 1H), 1.58–1.40 (m, 3H), 1.20 (t, *J*=6.8 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ESIMS *m*/*z* 357.10 ([M+Na]$^+$).

A mixture of the above obtained **37** (164 mg, 0.64 mmol) and 10% palladium on charcoal (10 mg) in EtOAc (15 mL) was stirred at ambient temperature under H_2 (1 atm) until TLC showed complete disappearance of **37** (ca. 5 h). The catalyst was filtered off. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to give compound **34** as a colorless oil (80 mg, 0.33 mmol, 51%): FTIR (film) 2954, 2929, 2857, 2721, 1733, 1715, 1427, 1255 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (s, 1H), 4.06 (q, *J*=6.8 Hz, 2H), 3.57 (t, *J*=6.2 Hz, 2H), 3.10–2.98 (m, 1H), 2.91–2.70 (m, 5H), 2.42 (dd, *J*=4.6, 7.0 Hz, 1H), 1.52–1.48 (m, 4H), 1.23 (t, *J*=7.2 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ESIMS *m*/*z* 381.2 ([M+Na]$^+$); MALDIHRMS calcd for $C_{18}H_{34}O_5SiNa$ ([M+Na]$^+$) 381.20677, found 381.2071.

4.23. Wittig reaction of 34 leading to 35

A mixture of **34** (80 mg, 0.22 mmol) and $Ph_3PCH{=}CO_2Et$ (85 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) was stirred at ambient temperature overnight. When TLC showed completion of the reaction, the mixture was partitioned between brine and Et_2O. The phases were separated. The organic one was washed with water and brine before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (10:1 *n*-hexane/EtOAc) on silica gel to give **35** as a colorless oil (87 mg, 0.20 mmol, 92%): FTIR (film) 2954, 2929, 1720, 1655, 1472, 1257, 1099 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (dt, *J*=7.9, 16.6 Hz, 1H), 5.80 (d, *J*=16.6 Hz, 1H), 4.14 (q, *J*=7.4 Hz, 2H), 4.06 (q, *J*=7.6 Hz, 2H), 3.57 (t, *J*=5.7 Hz, 2H), 3.01–2.80 (m, 1H), 2.81–2.61 (m, 3H), 2.53–2.29 (m, 3H), 1.79–1.64 (m, 1H), 1.58–1.40 (m, 3H), 1.23 (t, *J*=7.4 Hz, 3H), 1.20 (t, *J*=7.6 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ESIMS *m*/*z* 451.2 ([M+Na]$^+$); MALDIHRMS calcd for $C_{22}H_{40}O_6SiNa$ ([M+Na]$^+$) 451.24864, found 451.2483.

4.24. Conversion of 35 into 38

A mixture of **35** (75 mg, 0.20 mmol), *p*-TsOH (76 mg, 0.40 mmol) and UHP (188 mg, 2.0 mmol) in EtOH (5 mL) was stirred at ambient temperature for 10 h, when TLC showed complete disappearance of **35**. Et_2O was added, followed by water. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration on a rotary evaporator and purification by chromatography on silica gel (6:1 *n*-hexane/EtOAc) gave compound **38** as a colorless oil (46 mg, 0.14 mmol, 70%): FTIR (film) 3394, 2926, 2854, 1719, 1655, 1370, 1279 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 0.23H), 7.38 (s, 0.77H), 6.90 (dt, *J*=7.9, 16.6 Hz, 1H), 5.80 (d, *J*=16.6 Hz, 1H), 4.18–4.10 (m, 4H), 3.80–3.71 (m, 1H), 3.56–3.42 (m, 1H), 2.36–2.18 (m, 4H), 1.64–1.43 (m, 9H), 1.23 (m, 6H); ESIMS *m*/*z* 353.1 ([M+Na]$^+$); MALDIHRMS calcd for $C_{16}H_{26}O_7Na$ ([M+Na]$^+$) 353.15708, found 353.1583.

4.25. Synthesis of 6

A solution of **38** (40 mg, 0.12 mmol) and $NHEt_2$ (0.9 μL) in CF_3CH_2OH–CH_2Cl_2 (1.5 mL, 2:1 v/v) was stirred at ambient temperature overnight. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (8:1 *n*-hexane/EtOAc) to give compound **6** as a colorless oil (26 mg, 0.078 mmol, 65% yield): FTIR (film) 2938, 1736, 1448, 1374, 1290, 1176, 1091, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.61–4.40 (m, 1H), 4.15 (q, *J*=7.2 Hz, 2H), 4.10 (q, *J*=7.6 Hz, 2H), 3.897–3.80 (m, 1H), 3.75–3.63 (m, 1H), 2.51–2.39 (m, 3H), 2.23–2.19 (m, 2H), 1.93–1.76 (m, 1H), 1.74–1.51 (m, 6H), 1.48–1.33 (m, 1H), 1.26 (t, *J*=7.2 Hz, 3H), 1.23 (t, *J*=7.4 Hz, 3H); ESIMS *m/z* 353.1 ($[M+Na]^+$); MALDIHRMS calcd for $C_{16}H_{26}O_7Na$ ($[M+Na]^+$) 353.15708, found 353.1580.

4.26. $LiAlH_4$ Reduction of 36 leading to 39

$LiAlH_4$ (81 mg, 2.12 mmol) was added in portions to a solution of **36** (722 mg, 2.12 mmol) in anhydrous THF (40 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature for 1 h before the excess hydride was destroyed by addition of 2 N HCl with cooling (ice-water bath). The mixture was extracted with EtOAc (3×50 mL). The combined organic layers were washed with water, aq satd $NaHCO_3$, and brine before being dried over anhydrous Na_2SO_4. The residue after removal of the solvent and drying agent was chromatographed (3:1 *n*-hexane/EtOAc) on silica gel to give **39** as a colorless oil (577 mg, 1.70 mmol, 80%): FTIR (film) 3367, 2930, 2858, 1507, 1472, 1255, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J*=1.8 Hz, 1H), 6.28 (dd, *J*=1.8, 2.6 Hz, 1H), 6.03 (d, *J*=2.6 Hz, 1H), 3.67–3.48 (m, 4H), 2.88 (q, *J*=7.0 Hz, 1H), 1.86 (q, *J*=6.0 Hz, 2H), 1.66 (q, *J*=7.2 Hz, 2H), 1.50–1.38 (m, 2H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 140.9, 109.9, 105.2, 63.0, 60.9, 37.3, 35.4, 30.5, 30.4, 26.0, 18.3, −5.3; ESIMS *m/z* 321.2 ($[M+Na]^+$); MALDIHRMS calcd for $C_{16}H_{30}O_3SiNa$ ($[M+Na]^+$) 321.18564, found 321.1866.

4.27. Acetylation of 39 leading to 40

A solution of **39** (435 mg, 1.45 mmol), Ac_2O (0.51 mL, 5.43 mmol) and pyridine (0.44 mL, 5.43 mmol) in CH_2Cl_2 (10 mL) was stirred at ambient temperature overnight. 10% Aqueous citric acid (5 mL) was added, followed by Et_2O. The phases were separated. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with aq satd $CuSO_4$, water and brine, before being dried over Na_2SO_4. Concentrated on a rotary evaporator and chromatography on silica gel (50:1 *n*-hexane/EtOAc) afforded compound **40** as a colorless oil (443 mg, 1.30 mmol, 90%): FTIR (film) 2953, 2857, 1743, 1471, 1387, 1365, 1238, 1098, 1036, 836, 776, 730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 1H), 6.24 (s, 1H), 5.98 (s, 1H), 4.01–3.84 (m, 2H), 3.53 (t, *J*=7.2 Hz, 2H), 2.80 (q, *J*=7.2 Hz, 1H), 1.99 (s, 3H), 1.90 (q, *J*=6.9 Hz, 2H), 1.70–1.57 (m, 2H), 1.48–1.34 (m, 2H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 157.3, 141.0, 109.9, 105.5, 62.9, 62.7, 35.6, 33.0, 30.4, 30.3, 25.9, 25.9, 20.9, 18.3, −5.3; ESIMS *m/z* 363.2 ($[M+Na]^+$); MALDIHRMS calcd for $C_{18}H_{32}O_4SiNa$ ($[M+Na]^+$) 363.19621, found 363.1966.

4.28. Oxidative cleavage of 40 leading to 41

A solution of **40** (420 mg, 1.23 mmol) in acetone–H_2O (2 mL, 10:1 v/v) was added to a mixture of NBS (241 mg, 1.36 mmol) and $NaHCO_3$ (207 mg, 2.46 mmol) in acetone–H_2O (6 mL, 10:1 v/v) stirred at −15 °C. The stirring was continued at the same temperature for 1 h before pyridine (0.35 mL, 4.4 mmol) was introduced. The mixture was stirred at ambient temperature for 1 h, when TLC showed completion of the reaction. 1 N HCl (3 mL) was added, followed by EtOAc (50 mL). The phases were separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with aq satd NH_4Cl, water, and brine, before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **41** as a colorless oil (390 mg, 1.01 mmol, 89%): FTIR (film) 2928, 2858, 2738, 1738, 1695, 1472, 1388, 1255, 1100 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.76 (d, *J*=7.2 Hz, 1H), 6.96 (d, *J*=16.1 Hz, 1H), 6.80 (dd, *J*=7.2, 16.1 Hz, 1H), 4.02 (t, *J*=6.3 Hz, 2H), 3.56 (t, *J*=6.1 Hz, 2H), 3.01–2.88 (m, 1H), 2.15–2.01 (m, 1H), 1.99 (s, 3H), 1.85–1.66 (m, 2H), 1.65–1.52 (m, 1H), 1.52–1.37 (m, 2H), 0.85 (s, 9H), 0.05 (s, 6H); ESIMS *m/z* 379.2 ($[M+Na]^+$); MALDIHRMS calcd for $C_{18}H_{32}O_5SiNa$ ($[M+Na]^+$) 379.19112, found 379.1913.

4.29. Hydrogenation of 41 giving 42

A mixture of **41** (366 mg, 1.03 mmol) and 10% palladium on charcoal (10 mg) in EtOAc (15 mL) was stirred at the ambient temperature under H_2 (1 atm) until TLC showed complete disappearance of **41** (ca. 5 h). The catalyst was filtered off. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to give compound **42** as a colorless oil (175 mg, 0.49 mmol, 48%): FTIR (film) 2928, 2858, 2725, 1743, 1711, 1471, 1387, 1365, 1253, 1103, 1040, 835, 755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (dt, *J*=3.6, 15.6 Hz, 1H), 6.45 (d, *J*=15.6 Hz, 1H), 4.36 (s, 2H), 4.08–3.91 (m, 2H), 3.58 (t, *J*=6.0 Hz, 2H), 2.01 (s, 3H), 2.08–1.97 (m, 1H), 1.78–1.60 (m, 3H), 1.58–1.39 (m, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ESIMS *m/z* 381.2 ($[M+Na]^+$), MALDIHRMS calcd for $C_{18}H_{34}O_5SiNa$ ($[M+Na]^+$) 381.20677, found 381.2064.

4.30. Wittig reaction of 42 leading to 43

A mixture of **42** (120 mg, 0.33 mmol) and $Ph_3PCH{=}CO_2Et$ (128 mg, 0.36 mmol) in CH_2Cl_2 (5 mL) was stirred at ambient temperature overnight. The mixture was then partitioned between brine and Et_2O. The phases were separated. The organic one was washed with water and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed (8:1 *n*-hexane/EtOAc) on silica gel to give **43** as a colorless oil (122 mg, 0.29 mmol, 87%): FTIR (film) 2934, 2858, 1744, 1722, 1449, 1379, 1234, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.95 (dt, *J*=6.8, 15.8 Hz, 0.6H), 6.25 (dt, *J*=7.5, 15.4 Hz, 0.4H), 5.85 (d, *J*=15.4 Hz, 0.6H), 5.80 (d, *J*=15.8 Hz, 0.4H), 4.27–4.13 (m, 2H), 4.04 (t, *J*=6.3 Hz, 2H), 3.59 (t, *J*=5.3 Hz, 2H), 2.96–2.82 (m, 1H), 2.69–2.57 (m, 2H), 2.55–2.42 (m, 1H), 2.04 (s, 3H), 2.07–1.96 (m, 1H), 1.78–1.63 (m, 2H), 1.59–1.38 (m, 4H), 1.29 (t, *J*=7.9 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ESIMS *m/z* 451.2 ($[M+Na]^+$); MALDIHRMS calcd for $C_{22}H_{40}O_6SiNa$ ($[M+Na]^+$) 451.24864, found 451.2485.

4.31. Conversion of 43 into 44

p-TsOH (99 mg, 0.52 mmol) and UHP (244 mg, 2.6 mmol) were added to a solution of **43** (110 mg, 0.26 mmol) in EtOH (6 mL). The resulting mixture was stirred at ambient temperature for 10 h. When TLC showed complete disappearance of **43**, the mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (6:1 *n*-hexane/EtOAc) to give compound **44** as a colorless oil (78 mg, 0.24 mmol, 93%): FTIR (film) 3396, 2950, 1722, 1653, 1449, 1370, 1241, 1043 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (s, 1H), 6.49 (dt, *J*=6.6, 15.7 Hz, 1H), 5.84 (d, *J*=15.7 Hz, 1H), 4.19 (q, *J*=7.2 Hz, 2H), 4.16–4.10 (m, 1H), 4.03–3.96 (m, 1H), 3.82–3.71 (m, 2H), 2.39–2.21 (m, 3H), 2.05 (s, 3H), 1.90–1.75 (m, 3H), 1.74–1.67 (m, 1H), 1.65–1.58 (m, 2H), 1.52–1.43 (m, 2H), 1.28 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 171.0, 166.6, 148.5, 121.5, 105.6, 62.1, 61.5, 60.2, 36.8, 31.9, 29.2, 26.8, 25.4, 24.0, 21.0, 14.3; ESIMS *m/z* 353.1 ($[M+Na]^+$); EIHRMS calcd for $C_{16}H_{26}O_7$ (M^+) 330.1679, found 330.1686.

4.32. Synthesis of 7

$NHEt_2$ (1.6 μL) was added to a solution of **44** (70 mg, 0.21 mmol) in $CF_3CH_2OH–CH_2Cl_2$ (3.5 mL, 2:1 v/v) stirred at ambient temperature. The stirring was continued at the same temperature overnight. Solvents were removed on a rotary evaporator. The residue was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to give compound **7** as a colorless oil (40 mg, 0.11 mmol, 52%): FTIR (film) 2955, 2926, 1735, 1460, 1373, 1233, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.59–4.42 (m, 1H), 4.15 (q, *J*=7.1 Hz, 2H), 4.12–4.01 (m, 2H), 3.97–3.85 (m, 1H), 3.71–3.64 (m, 1H), 2.50 (dd, *J*=7.5, 16.1 Hz, 1H), 2.39 (dd, *J*=5.6, 16.1 Hz, 1H), 2.18 (s, 3H), 2.01–1.81 (m, 3H), 1.80–1.52 (m, 6H), 1.51–1.20 (m, 2H), 1.28 (t, *J*=7.1 Hz, 3H); ESIMS *m/z* 353.2 ($[M+Na]^+$); ESIHRMS calcd for $C_{16}H_{26}O_7Na$ ($[M+Na]^+$) 353.15707, found 353.15771.

4.33. TBS protection of 45 giving 46

A solution of **45** (1.47 g, 10.4 mmol), TBSCl (1.9 g, 12.5 mmol) and imidazole (850 mg, 12.5 mmol) in DMF (10 mL) was stirred at ambient temperature overnight. The mixture was partitioned between brine and Et_2O. The phases were separated. The organic layer was washed with water and brine, before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (15:1 *n*-hexane/EtOAc) on silica gel to give **46** as a colorless oil (2.50 g, 9.9 mmol, 95%): FTIR (film) 2956, 2929, 2857, 1508, 1472, 1256, 1150, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J*=1.1 Hz, 1H), 6.24 (dd, *J*=1.1, 2.9 Hz, 1H), 5.92 (d, *J*=2.9 Hz, 1H), 3.62–3.56 (m, 2H), 2.94 (sextet, *J*=7.1 Hz, 1H), 2.94–2.80 (m, 1H), 2.78–2.60 (m, 1H), 1.23 (d, *J*=7.4 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3, 140.6, 109.8, 103.5, 60.9, 38.6, 29.6, 25.9, 19.3, 18.3, −5.4; ESIMS *m/z* 255.3 ($[M+H]^+$); EIHRMS calcd for $C_{14}H_{26}O_2Si$ (M^+) 254.1702, found 254.1708.

4.34. Oxidative cleavage of 46 leading to 47

A solution of **46** (1.35 g, 5.6 mmol) in acetone–H_2O (6 mL, 10:1 v/v) was added to a mixture of NBS (1.2 g, 6.8 mmol) and $NaHCO_3$ (941 mg, 11.2 mmol) in acetone–H_2O (11 mL, 10:1 v/v) stirred at −15 °C. The reaction was stirred at the same temperature for 1 h before pyridine (1.62 mL, 20 mmol) was introduced. The mixture was then stirred at ambient temperature for 1 h. When TLC showed completion of the reaction, 1 N HCl (5 mL) was added, followed by EtOAc (50 mL). The phases were separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with aq satd NH_4Cl, water, and brine, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **47** as a colorless oil (1.07 g, 4.0 mmol, 72%): FTIR(film) 2955, 2857, 1700, 1472, 1388, 1256, 1101, 980, 836, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.32 (d, *J*=7.1 Hz, 0.4H), 9.75 (d, *J*=7.1 Hz, 0.6H), 7.01 (d, *J*=12.3 Hz, 0.4H), 6.93 (d, *J*=18.6 Hz, 0.6H), 6.82 (dd, *J*=7.1, 18.6 Hz, 0.6H), 6.21 (dd, *J*=7.1, 12.3 Hz, 0.4H), 3.60 (t, *J*=5.6 Hz, 2H), 3.10 (q, *J*=6.7 Hz, 0.6H), 2.91 (q, *J*=6.7 Hz, 0.4H), 2.01–1.87 (m, 1H), 1.64–1.53 (m, 1H), 1.24 (d, *J*=8.2 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); EIMS *m/z* 213 ($[M-C_4H_9]^+$); EIHRMS calcd for $C_{10}H_{17}O_3Si$ ($[M-C_4H_9]^+$) 213.0947, found 213.0949.

4.35. Reduction of 47 to 48 with NaI/HCl

Commercially available concentrated HCl (38%, 55 μL, 0.66 mmol) was added to a solution of **47** (81 mg, 0.3 mmol) and NaI (100 mg, 0.66 mmol) in acetone (10 mL) stirred at −50 °C. After completion of the addition, the mixture was stirred at that temperature for 25 min. Aqueous satd $NaHCO_3$ (5 mL) was introduced, followed by Et_2O. The phases were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (5:1 *n*-hexane/EtOAc) to give **48** as a colorless oil (57 mg, 0.21 mmol, 71%): FTIR(film) 2955, 2857, 2721, 1712, 1482, 1388, 1256, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 3.58 (t, *J*=6.5 Hz, 2H), 2.81–2.59 (m, 4H), 1.81 (sextet, *J*=7.1 Hz, 1H), 1.53–1.42 (m, 2H), 1.23 (d, *J*=8.3 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.1, 200.5, 60.5, 42.6, 37.3, 35.6, 33.1, 25.7, 18.1, 16.3, −5.61, −5.59; ESIMS *m/z* 215 ($[M-C_4H_9]^+$). Anal. Calcd for $C_{14}H_{28}SiO_3$: C 61.72, H 10.36. Found: C 61.86, H 10.47.

4.36. Wittig reaction of 48 leading to 49

A mixture of **48** (162 mg, 0.59 mmol) and $Ph_3PCH{=}CO_2Et$ (228 mg, 0.65 mmol) in CH_2Cl_2 (6 mL) was stirred at ambient temperature overnight. When TLC showed completion of the reaction, the mixture was partitioned between brine and Et_2O. The phases were separated. The organic one was washed with water and brine before being dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed (50:1 *n*-hexane/EtOAc) on silica gel to give **49** as a colorless oil (165 mg, 0.48 mmol, 82%): FTIR (film) 2955, 2857, 1803, 1717, 1656, 1258, 1101 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (dt, *J*=6.7, 15.7 Hz, 1H), 5.80 (d, *J*=15.7 Hz, 1H), 4.13 (q, *J*=7.1 Hz, 2H), 3.63–3.55 (m, 2H), 2.80–2.40 (m, 5H), 1.94–1.76 (m, 1H), 1.58–1.42 (m, 1H), 1.23 (t, *J*=7.1 Hz, 3H), 1.10 (d, *J*=7.1 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4, 166.4, 147.4, 121.9, 60.6, 60.1, 42.8, 39.0, 35.6, 26.0, 25.8, 18.2, 16.3, 14.17, −5.5; ESIMS *m/z* 365.1 ($[M+Na]^+$); MALDIHRMS calcd for $C_{18}H_{34}O_4NaSi$ ($[M+Na]^+$) 365.21186, found 365.2128.

4.37. Conversion of 49 into 50

p-TsOH (87 mg, 0.46 mmol) and UHP (216 mg, 2.3 mmol) were added to a solution of **49** (77 mg, 0.23 mmol) in EtOH (3 mL). The resulting mixture was stirred at ambient temperature for 10 h. When TLC showed complete disappearance of **49**, the mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (4:1 *n*-hexane/EtOAc) to give compound **50** as a colorless oil (40 mg, 0.17 mmol, 72%): FTIR (film) 3388, 2978, 2936, 1720, 1655, 1459, 1272 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 6.97 (dt, *J*=6.4, 15.2 Hz, 1H), 5.83 (d, *J*=15.2 Hz, 1H), 4.18 (q, *J*=7.1 Hz, 2H), 4.09 (dt, *J*=8.3, 9.2 Hz, 1H), 3.85 (dt, *J*=7.5, 8.3 Hz, 1H), 2.32 (dt, *J*=7.5, 6.8 Hz, 1H), 2.23–2.12 (m, 1H), 2.12–1.82 (m, 4H), 1.28 (t, *J*=7.1 Hz, 3H), 1.11 (d, *J*=6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 148.5, 121.4, 112.9, 67.6, 60.2, 40.7, 33.0, 31.8, 26.9, 14.3, 12.9; ESIMS *m/z* 267.1 ($[M+Na]^+$); ESIHRMS calcd for $C_{12}H_{20}O_5Na$ ($[M+Na]^+$) 267.12029, found 267.12051.

4.38. Synthesis of 8

$NHEt_2$ (0.9 μL) was added to a solution of **50** (29 mg, 0.12 mmol) in $CF_3CH_2OH–CH_2Cl_2$ (2.5 mL, 2:1 v/v) stirred at ambient temperature. The stirring was continued at that temperature overnight. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to give compound **8** as a colorless oil (12 mg, 0.05 mmol, 40%): FTIR (film) 2968, 2930, 1736, 1459, 1307, 1050, 1025 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 4.62–4.43 (m, 1H), 4.14 (q, J=7.5 Hz, 2H), 4.10–3.88 (m, 2H), 2.56 (dd, J=7.5, 15.8 Hz, 1H), 2.40 (dd, J=6.4, 15.8 Hz, 1H), 2.23–2.19 (m, 1H), 2.13–1.92 (m, 2H), 1.92–1.73 (m, 3H), 1.59–1.541 (m, 1H), 1.26 (t, J=7.5 Hz, 3H), 1.03 (d, J=6.8 Hz, 1H), 0.98 (d, J=6.8 Hz, 2H); ESIMS *m/z* 267.1 ([M+Na]$^+$); MALDIHRMS calcd for $C_{12}H_{20}O_5Na$ ([M+Na]$^+$) 267.12030, found 267.1204.

4.39. MOM protection of 51 giving 52

MOMCl (1.5 mL, 20 mmol) was added to a solution of **51** (1.54 g, 10 mmol) and *i*-Pr_2NEt (3.5 mL, 20 mmol) in CH_2Cl_2 (60 mL) stirred at 0 °C. After completion of the addition, the cooling bath was removed. The stirring was continued at ambient temperature overnight. Water (5 mL) was added, followed by Et_2O (50 mL). The phases were separated. The aqueous layer was extracted with Et_2O. The combined organic phases were dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (6:1 *n*-hexane/EtOAc) on silica gel to give **52** as a colorless oil (1.78 g, 9.0 mmol, 90%): FTIR (film) 2933, 2855, 1679, 1569, 1469, 1394, 1148, 1112, 1039 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.21 (d, J=3.6 Hz, 1H), 6.58–6.51 (m, 1H), 4.62 (s, 2H), 3.61 (t, J=6.2 Hz, 2H), 3.36 (s, 3H), 2.03 (quintet, J=7.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.9, 152.6, 146.1, 116.8, 112.0, 96.2, 66.6, 55.0, 34.9, 24.0; ESIMS *m/z* 221.2 ([M+Na]$^+$); EIHRMS calcd for $C_{10}H_{14}O_4$ (M$^+$) 198.0892, found 198.0893.

4.40. Wittig reaction of 52 giving 53

A solution of $(EtO)_3P(O)CH_2CO_2Et$ (2.68 g, 12 mmol) in THF (7 mL) was added slowly to a suspension of NaH (480 mg, 12 mmol, pre-washed with hexanes and dry THF) in THF (13 mL) stirred at 0 °C. After completion of the addition, the stirring was continued for an additional 30 min bfore **52** (1.2 g, 6.0 mmol) was introduced. The cooling bath was removed and the mixture was heated to reflux with stirring for 6 h. The mixture was cooled to ambient temperature. Aqueous NH_4Cl (10 mL) was added, followed by Et_2O (50 mL). The phases were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with aq satd NH_4Cl, water, and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (20:1 *n*-hexane/EtOAc) to give **53** as a colorless oil (1.41 g, 5.3 mmol, 88%): FTIR (film) 2929, 1711, 1621, 1479, 1178, 1111, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.20 (d, J=3.8 Hz, 0.5H), 6.72 (d, J=3.8 Hz, 0.5H), 6.46 (s, 1H), 6.36 (s, 0.5H), 5.77 (s, 0.5H), 4.63 (s, 2H), 4.19 (q, J=7.2 Hz, 2H), 3.58 (t, J=6.0 Hz, 2H), 3.37 (s, 3H), 3.00 (t, J=8.1 Hz, 1H), 2.62 (t, J=7.4 Hz, 1H), 1.94–1.73 (m, 2H), 1.28 (t, J=6.0 Hz, 3H); ESIMS *m/z* 291.2 ([M+Na]$^+$); ESIHRMS calcd for $C_{14}H_{20}O_5Na$ ([M+Na]$^+$) 291.1202948, found 291.1206220.

4.41. Reduction of 53 with $NiCl_2 \cdot 6H_2O/NaBH_4$ giving 54

$NaBH_4$ (28 mg, 0.75 mmol) was added to a mixture of **53** (67 mg, 0.25 mmol) and $NiCl_2 \cdot 6H_2O$ (10 mg, 0.04 mmol) in MeOH (3 mL) stirred at 0 °C. After the completion of the addition, the mixture was stirred at ambient temperature for 2 h. When TLC showed completion of the reaction, Et_2O (30 mL) was added, followed by water (10 mL). The phases were separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water, brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (50:1 *n*-hexane/EtOAc) on silica gel to give **54** as a colorless oil (49 mg, 0.18 mmol, 72%): FTIR (film) 2934, 2823, 1736, 1507, 1449, 1372, 1041 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.24 (s, 1H), 6.03 (d, J=3.2 Hz, 1H), 4.58 (s, 2H), 4.04 (q, J=7.2 Hz, 2H), 3.47 (t, J=6.4 Hz, 2H), 3.36 (s, 3H), 3.28 (quintet, J=7.2 Hz, 1H), 2.70–2.51 (m, 2H), 1.80–1.64 (m, 2H), 1.60–1.47 (m, 2H), 1.21 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 156.7, 141.1, 109.9, 105.3, 96.3, 67.3, 60.3, 55.0, 39.1, 35.3, 30.4, 27.2, 14.1; ESIMS *m/z* 293.3 ([M+Na]$^+$); ESIHRMS calcd for $C_{14}H_{22}O_5Na$ ([M+Na]$^+$) 293.13594, found 293.13593.

4.42. Reduction of 54 with $LiAlH_4$ giving 55

$LiAlH_4$ (140 mg, 3.7 mmol) was added in portions to a solution of **54** (722 mg, 2.12 mmol) in anhydrous Et_2O (40 mL) stirred in an ice-water bath. After completion of the addition, the mixture was stirred at ambient temperature for 1 h. 1 N NaOH (2 mL) was introduced. The stirring was continued for 1 h. The precipitates were filtrated off. The filtrate was dried over anhydrous Na_2SO_4. The residue after removal of the solvent and drying agent was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **55** as a colorless oil (750 mg, 3.3 mmol, 89%): FTIR (film) 3446, 2953, 2882, 1592, 1453, 1148, 1112, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 6.28 (m, 1H), 6.02 (d, J=3.0 Hz, 1H), 4.60 (s, 2H), 3.57–3.68 (m, 2H), 3.50 (t, J=6.6 Hz, 2H), 3.34 (s, 3H), 2.91 (quintet, J=7.2 Hz, 1H), 2.86 (q, J=6.5 Hz, 2H), 2.74–2.62 (m, 2H), 2.53–2.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 140.9, 109.8, 105.3, 96.2, 67.5, 60.6, 55.0, 37.1, 35.3, 30.8, 27.4; ESIMS *m/z* 251.2 ([M+Na]$^+$); MALDIHRMS calcd for $C_{12}H_{20}O_4Na$ ([M+Na]$^+$) 251.12538, found 251.1266.

4.43. TBS protection of 55 giving 56

A solution of **55** (700 mg, 3.07 mmol), TBSCl (510 mg, 3.3 mmol) and imidazole (224 mg, 3.3 mmol) in DMF (5 mL) was stirred at ambient temperature overnight. Et_2O was added, followed by brine. The phases were separated. The organic layer was washed with water and brine, before being dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator. The residue was chromatographed (15:1 *n*-hexane/EtOAc) on silica gel to give **56** as a colorless oil (1.06 g, 3.03 mmol, 99%): FTIR (film) 2928, 2858, 1471, 1387, 1255, 1150, 1111, 1046 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 6.24 (s, 1H), 6.01 (s, 1H), 4.60 (s, 2H), 3.68–3.57 (m, 2H), 3.50 (t, J=6.1 Hz, 2H), 2.91(quintet, J=7.4 Hz, 1H), 2.86 (q, J=6.9 Hz, 2H), 2.74–2.62 (m, 2H), 2.58–2.43 (m, 2H), 0.85 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 140.8, 109.8, 105.3, 96.3, 67.6, 60.9, 55.1, 37.1, 35.1, 30.9, 27.5, 25.9, 18.3, −5.4; ESIMS *m/z* 365.3 ([M+Na]$^+$); MALDIHRMS calcd for $C_{18}H_{34}SiO_4Na$ ([M+Na]$^+$) 365.21186, found 365.2119.

4.44. Oxidative cleavage of 56 giving 57

A solution of **56** (800 mg, 2.34 mmol) in acetone–H_2O (4 mL, 10:1 v/v) was added to a mixture of NBS (455 mg, 2.57 mmol) and $NaHCO_3$ (477 mg, 5.68 mmol) in acetone–H_2O (11 mL, 10:1 v/v) stirred at −15 °C. After stirring at the same temperature for 1 h, pyridine (0.68 mL, 8.43 mmol) was added. The resultant mixture was then stirred at ambient temperature for 1 h. When TLC showed completion of the reaction, 1 N HCl (3 mL) was added, followed by EtOAc (50 mL). The phases were separated. The aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with aq satd NH_4Cl, water, and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to afford **57** as a yellowish oil (670 mg, 1.87 mmol, 81%): FTIR (film) 2930, 2867, 1801, 1698, 1471, 1388, 1257, 1109, 1043, 837, 778 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.24 (d, J=7.2 Hz, 0.4H), 9.77 (d, J=6.0 Hz, 0.6H), 7.04 (d, J=10.1 Hz, 0.4H), 6.98 (d, J=14.3 Hz, 0.6H), 6.82 (dd, J=6.0 Hz, J=14.3 Hz, 0.6H), 6.17 (dd, J=7.2, 10.1 Hz, 0.4H), 4.58 (s, 2H), 3.70–3.55 (m, 2H), 3.54–3.44 (m, 2H), 3.34 (s, 3H), 3.10–2,79 (m, 1H), 2.04–1.47 (m, 6H), 0.85 (s, 9H), 0.05 (s, 6H);

ESIMS *m*/*z* 381.2 ([M+Na]$^+$); ESIHRMS calcd for $C_{18}H_{34}SiO_5Na$ ([M+Na]$^+$) 381.2068, found 381.2064.

4.45. Conversion of 57 into 59 via 58

A mixture of **57** (340 mg, 0.95 mmol) and 10% palladium on charcoal (60 mg) in EtOAc (30 mL) was stirred at ambient temperature under H_2 (1 atm) until TLC showed complete disappearance of **57** (5 h). The catalyst was filtered off. The filtrate was concentrated on a rotary evaporator. The residue was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to give compound **58** as a colorless oil (164 mg, 0.46 mmol, 48%): FTIR (film) 2930, 2857, 2770, 1801, 1698, 1471, 1388, 1257 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (s, 1H), 4.60 (s, 2H), 3.61 (t, *J*=7.2 Hz, 2H), 3.51 (t, *J*=6.8 Hz, 2H), 3.34 (s, 3H), 2.82–2.61 (m, 4H), 1.84–1.75 (m, 1H), 1.71–1.48 (m, 6H), 0.85 (s, 9H), 0.05 (s, 6H); ESIMS *m*/*z* 383.2 ([M+Na]$^+$).

A mixture of **58** (250 mg, 0.70 mmol) and $Ph_3PCH{=}CO_2Et$ (243 mg, 0.7 mmol) in CH_2Cl_2 (10 mL) was stirred at ambient temperature overnight. The mixture was then partitioned between brine and Et_2O. The phases were separated. The organic one was washed with water and brine, before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (8:1 *n*-hexane/EtOAc) on silica gel to give **59** as a colorless oil (262 mg, 0.61 mmol, 87%): FTIR (film) 2929, 2857, 1720, 1650, 1471, 1367, 1257, 1103 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.91 (dt, *J*=15.3 Hz, *J*=6.7 Hz, 1H), 5.81 (d, *J*=16.1 Hz, 1H), 4.58 (s, 2H), 4.16 (q, *J*=7.0 Hz, 2H), 3.55 (q, *J*=6.0 Hz, 2H), 3.47 (t, *J*=5.4 Hz, 2H), 2.56–2.73 (m, 3H), 2.44 (q, *J*=7.0 Hz, 2H), 1.95–1.75 (m, 2H), 1.71–1.42 (m, 4H), 1.26 (t, *J*=7.2 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 166.4, 147.4, 122.0, 96.4, 67.4, 60.9, 60.2, 55.1, 48.4, 40.3, 34.5, 28.4, 27.5, 25.9, 18.2, 14.2, −5.5; ESIMS *m*/*z* 453.3 ([M+Na]$^+$); ESIHRMS calcd for $C_{22}H_{42}SiO_6Na$ ([M+Na]$^+$) 453.2643, found 453.2644.

4.46. Conversion of 59 into 60

p-TsOH (133 mg, 0.70 mmol) and UHP (320 mg, 3.4 mmol) were added to a solution of **59** (150 mg, 0.34 mmol) in EtOH (6 mL). The resulting mixture was stirred at ambient temperature for 10 h. When TLC showed complete disappearance of **59**, the mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (4:1 *n*-hexane/EtOAc) to give **60** as a colorless oil (95 mg, 0.27 mmol, 80%): FTIR (film) 3362, 2938, 1720, 1653, 1450, 1369, 1036 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (s, 0.4H), 7.92 (s, 0.6H), 6.97 (dt, *J*=6.4, 15.0 Hz, 1H), 5.84 (d, *J*=15.0 Hz, 1H), 4.63 (s, 3H), 4.18 (q, *J*=7.9 Hz, 2H), 4.13–3.80 (m, 2H), 3.60–3.49 (m, 2H), 3.36 (s, 3H), 2.44–2.19 (m, 2H), 2.18–1.98 (m, 2H), 1.97–1.78 (m, 1H), 1.75–1.49 (m, 5H), 1.29 (t, *J*=7.9 Hz, 3H); ESIMS *m*/*z* 355.1 ([M+Na]$^+$); MALDIHRMS calcd for $C_{16}H_{28}O_7Na$ ([M+Na]$^+$) 355.17273, found 355.1747.

4.47. Synthesis of 9

$NHEt_2$ (1.6 μL) was added to a solution of **60** (70 mg, 0.21 mmol) in CF_3CH_2OH–CH_2Cl_2 (3.5 mL, 2:1 v/v) stirred at ambient temperature. The stirring was continued at that temperature overnight. The solvent was removed on a rotary evaporator. The residue was chromatographed on silica gel (10:1 *n*-hexane/EtOAc) to give **9** as a colorless oil (36 mg, 0.11 mmol, 52%): FTIR (film) 2935, 1738, 1446, 1370, 1290, 1028 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.62 (s, 2H), 4.60–4.43 (m, 1H), 4.20–4.12 (m, 2H), 4.08–3.91 (m, 2H), 3.54 (t, *J*=7.5 Hz, 2H), 3.34 (s, 3H), 2.54 (dd, *J*=7.6, 15.8 Hz, 1H), 2.40 (dd, *J*=5.9, 15.8 Hz, 1H), 2.23–2.01 (m, 2H), 1.98–1.74 (m, 4H), 1.70–1.51 (m, 5H), 1.24 (t, *J*=7.2 Hz, 3H); ESIMS *m*/*z* 355.1 ([M+Na]$^+$); MALDIHRMS calcd for $C_{16}H_{28}O_7Na$ ([M+Na]$^+$) 355.17273, found 355.1744.

4.48. Mesylation of 51 leading to 61

MsCl (0.74 mL, 9.36 mmol) was added to a solution of **51** (1.2 g, 7.8 mmol), Et_3N (4.3 mL, 31 mmol) and DMAP (78 mg, 0.64 mmol) in CH_2Cl_2 (30 mL) stirred at −78 °C. After the completion of the addition, the stirring was continued at ambient temperature for 1 h. The mixture was diluted with Et_2O and washed with water. The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was chromatographed on silica gel (6:1 *n*-hexane/EtOAc) to give **61** as a yellowish oil (1.63 g, 7.0 mmol, 90%): FTIR (film) 3135, 3032, 1670, 1469, 1411, 1347, 1330, 1173, 918 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.20 (s, 1H), 6.56 (s, 1H), 4.35 (t, *J*=6.1 Hz, 2H), 3.10 (s, 3H), 3.12 (t, *J*=6.4 Hz, 2H), 2.23–2.16 (m, 2H); ESIMS *m*/*z* 255.0 ([M+Na]$^+$); MALDIHRMS calcd for $C_9H_{12}O_5SNa$ ([M+Na]$^+$) 255.02977, found 255.0307.

4.49. Conversion of mesylate 61 into azide 62

A solution of **61** (231 mg, 1.0 mmol) and NaN_3 (195 mg, 3.0 mmol) in DMF (10 mL) was stirred at ambient temperature overnight. The mixture was diluted with Et_2O (20 mL) and washed with water (5 mL). The aqueous layer was back-extracted with Et_2O. The combined organic layers were washed with water and brine three times before being dried over Na_2SO_4. Concentration on a rotary evaporator and purification by chromatography on silica gel (6:1 *n*-hexane/EtOAc) gave **62** as a colorless oil (160 mg, 0.86 mmol, 86%): FTIR (film) 2936, 2099, 1677, 1569, 1469, 1252, 1016 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J*=1.1 Hz, 1H), 7.20 (d, *J*=3.6 Hz, 1H), 6.64 (dd, *J*=1.1, 3.6 Hz, 1H), 3.40 (t, *J*=7.2 Hz, 2H), 2.01 (quintet, *J*=6.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.1, 152.5, 146.4, 117.1, 112.3, 50.7, 35.0, 23.1; ESIMS *m*/*z* 180.0 ([M+H]$^+$); EIHRMS calcd for $C_8H_9N_3O_2$ (M$^+$) 179.0695, found 179.0710.

4.50. Wittig reaction of 62 giving 63

A solution of $(EtO)_3P(O)CH_2CO_2Et$ (350 mg, 1.56 mmol) in dry THF (1 mL) was slowly introduced to a suspension of NaH (62 mg, 1.56 mmol, pre-washed with hexanes and dry THF) in dry THF (3 mL) stirred at 0 °C. After completion of the addition, the stirring was continued at that temperature for an additional 30 min before **62** (140 mg, 0.78 mmol) was introduced. The cooling bath was then removed. The mixture was heated at reflux with stirring for 6 h. The mixture was cooled to ambient temperature. Aqueous NH_4Cl (5 mL) was added, followed by Et_2O (50 mL). The phases were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with aq satd NH_4Cl, water, and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (50:1 *n*-hexane/EtOAc) to give **63** as a colorless oil (147 mg, 0.59 mmol, 76%): FTIR (film) 2981, 2935, 2098, 1719, 1612, 1479, 1241, 1178, 769 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.27 (s, 1H), 6.48 (s, 1H), 5.77 (s, 1H), 4.20 (q, *J*=7.2 Hz, 2H), 3.36 (t, *J*=6.4 Hz, 2H), 2.64 (t, *J*=7.7 Hz, 2H), 1.82–1.96 (m, 2H), 1.25 (t, *J*=7.2 Hz, 3H); ESIMS *m*/*z* 272.1 ([M+Na]$^+$). Anal. Calcd for $C_{12}H_{15}N_3O_3$: C 57.82, H 6.07, N 16.86. Found: C 57.79, H 6.06, N 16.76.

4.51. Reduction and protection of 63 giving 64

A mixture of **63** (320 mg, 1.28 mmol) and Ph_3P (1.0 g, 3.85 mmol) in H_2O (0.23 mL, 12.8 mmol) and THF (6 mL) was stirred at 55 °C for 3 h. The solvent was removed by rotary evaporation.

The residue was dissolved in CH_2Cl_2 (6 mL), to which $(Boc)_2O$ (0.3 mL, 1.40 mmol) was then added. The resulting solution was stirred at ambient temperature for 6 h before being partitioned between water (5 mL) and Et_2O (30 mL). The phases were separated. The aqueous layer was extracted with Et_2O. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The residue was purified by column chromatography on silica gel (8:1 *n*-hexane/EtOAc) to give **64** as a colorless oil (400 mg, 1.24 mmol, 96% from **63**): FTIR (film) 3385, 2978, 2934, 1710, 1620, 1519, 1367, 1250, 1174, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 6.65 (d, *J*=3.2 Hz, 1H), 6.46 (d, *J*=3.2 Hz, 1H), 2.38 (s, 1H), 5.11 (br, s, 1H), 4.21 (q, *J*=7.2 Hz, 2H), 3.18 (q, *J*=6.4 Hz, 2H), 2.92 (t, *J*=7.4 Hz, 2H), 2.78 (quintet, *J*=7.0 Hz, 2H), 1.52 (s, 9H), 1.23 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 156.1, 153.4, 146.3, 144.0, 112.5, 112.0, 11.3, 78.8, 59.9, 39.8, 29.8, 28.4, 25.6, 14.3; ESIMS *m*/*z* 346.1 ($[M+Na]^+$); EIHRMS calcd for $C_{17}H_{25}NO_5$ (M^+) 323.1733, found 323.1733.

4.52. Reduction of 64 with $NiCl_2 \cdot 6H_2O/NaBH_4$ giving 65

$NaBH_4$ (252 mg, 6.64 mmol) was added to a solution of **64** (536 mg, 1.66 mmol) and $NiCl_2 \cdot 6H_2O$ (65 mg, 0.28 mmol) in MeOH (20 mL) stirred at 0 °C. After the completion of the addition, the stirring was continued at ambient temperature for 2 h. When TLC showed completion of the reaction, Et_2O (80 mL) was added, followed by water (10 mL). 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. The solvent was removed by rotary evaporation to give **65** as a colorless oil (490 mg, 1.51 mmol, 91%): FTIR (film) 3387, 2978, 2931, 1734, 1715, 1508, 1366, 1250, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.28 (s, 1H), 6.23 (s, 1H), 6.01 (s, 1H), 4.46 (br, 1H), 4.09 (q, *J*=7.0 Hz, 2H), 3.24 (quintet, *J*=7.1 Hz, 1H), 3.15–3.00 (m, 2H), 2.71–2.51 (m, 2H), 2.74–2.60 (m, 2H), 1.14 (s, 9H), 1.23 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 156.5, 155.9, 141.2, 109.9, 105.4, 79.0, 60.4, 40.2, 39.1, 35.2, 30.8, 28.4, 27.5, 14.1; ESIMS *m*/*z* 348.1 ($[M+Na]^+$); MALDIHRMS calcd for $C_{17}H_{28}O_5N$ ($[M+H]^+$) 326.1962, found 326.1949.

4.53. Oxidative cleavage of the furan ring in 65 giving 66

A solution of **65** (40 mg, 0.12 mmol) in acetone–H_2O (1.5 mL, 10:1 v/v) was added to a mixture of NBS (23 mg, 0.13 mmol) and $NaHCO_3$ (20 mg, 0.24 mmol) in acetone–H_2O (1.0 mL, 10:1 v/v) stirred at −15 °C. The stirring was continued at the same temperature for 1 h before pyridine (35 μL, 0.43 mmol) was introduced. The mixture was then stirred at ambient temperature 1 h. When TLC showed completion of the reaction, 1 N HCl (5 mL) was added, followed by EtOAc (20 mL). The phases were separated. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with aq satd NH_4Cl, water, and brine, and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (5:1 *n*-hexane/EtOAc) on silica gel to give **66** as a colorless oil (25 mg, 0.07 mmol, 56%): FTIR (film) 3392, 2978, 2928, 1697, 1518, 1250, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.72 (d, *J*=7.4 Hz, 1H), 7.14 (d, *J*=16.2 Hz, 1H), 6.82 (dd, *J*=7.4, 16.2 Hz, 1H), 4.46 (br, 1H), 4.09 (q, *J*=6.7 Hz, 2H), 3.45–3.38 (m, 1H), 3.28–3.03 (m, 2H), 2.86 (dd, *J*=9.8 Hz, *J*=16.7 Hz, 1H), 2.50 (dd, *J*=3.7, 16.7 Hz, 1H), 1.58–1.48 (m, 4H), 1.46 (s, 9H), 1.23 (t, *J*=6.7 Hz, 3H); ESIMS *m*/*z* 364.1 ($[M+Na]^+$); MALDIHRMS calcd for $C_{17}H_{27}NO_6Na$ ($[M+Na]^+$) 364.17306, found 364.1736.

4.54. Hydrogenation of 66 giving 67

A mixture of **66** (18 mg, 0.052 mmol) and 10% palladium on charcoal (3 mg) in EtOAc (2 mL) was stirred at ambient temperature under H_2 (1 atm) until TLC showed complete disappearance of **57** (5 h). The catalyst was filtered off. The filtrate was concentrated on a rotary evaporator to give rather pure **67** as a colorless oil (17 mg, 0.05 mmol, 96%): FTIR (film) 3385, 2925, 2854, 1708, 1521, 1259, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.82 (s, 1H), 4.57 (br s, 1H), 4.08 (q, *J*=7.1 Hz, 2H), 3.31–2.83 (m, 4H), 2.80–2.62 (m, 4H), 2.47–2.25 (m, 1H), 1.58–1.48 (m, 4H), 1.47 (s, 9H), 1.23 (t, *J*=7.2 Hz, 3H); ESIMS *m*/*z* 366.1 ($[M+Na]^+$); MALDIHRMS calcd for $C_{17}H_{29}NO_6Na$ ($[M+Na]^+$) 366.18871, found 366.1891.

4.55. Wittig reaction of 67 giving 68

A mixture of **67** (18 mg, 0.051 mmol) and $Ph_3PCH{=}CO_2Et$ (19 mg, 0.055 mmol) in CH_2Cl_2 (2 mL) was stirred at ambient temperature overnight. The mixture was partitioned between brine and Et_2O. The phases were separated. The organic layer was washed with water and brine before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was chromatographed (3:1 *n*-hexane/EtOAc) on silica gel to give the **68** as a colorless oil (16 mg, 0.04 mmol, 80%): FTIR (film) 3391, 2978, 2930, 1714, 1520, 1367, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (dt, *J*=6.1, 15.8 Hz, 1H), 5.83 (d, *J*=15.8 Hz, 1H), 4.57 (br, 1H), 4.19 (q, *J*=7.1 Hz, 2H), 4.03 (q, *J*=7.2 Hz, 2H), 3.18–3.02 (m, 2H), 3.00–2.93 (m, 1H), 2.81–2.67 (m, 3H), 2.53–2.31 (m, 3H), 1.71–1.50 (m, 2H), 1.47–1.21 (m, 2H), 1.42 (s, 9H), 1.24 (t, *J*=7.1 Hz, 3H), 1.26 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0, 172.1, 166.4, 155.9, 147.2, 122.0, 60.7, 60.2, 46.6, 40.5, 40.1, 35.4, 28.4, 28.3, 27.5, 25.8, 14.2, 14.1; ESIMS *m*/*z* 436.2 ($[M+Na]^+$); EIHRMS calcd for $C_{17}H_{29}NO_6$ (M^+) 413.2414, found 413.2404.

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