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Potent Antimalarial 1,2,4-Trioxanes through Perhydrolysis of Epoxides

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Abstract: Perhydrolysis of a sterically congested multifunctional epoxide was achieved in ethereal H_2O_2 with the aid of a recently developed Mo catalyst. The resulting hydroperoxide cyclized to give a 1,2,4-trioxane, which could be readily elaborated into qinghaosu and a range of novel analogues. Some of the compounds with two such trioxane moieties showed in vitro antimalarial activity comparable to or even better than that of artesunate or chloroquine.

Keywords: biological activity · cyclization · epoxides · molybdenum · peroxides · ring opening

Introduction

Qinghaosu[1] (QHS, artemisinin, **1**; Figure 1) has proven to be one of the molecules that will have a lasting influence on the health of mankind. This sesquiterpene endoperoxide

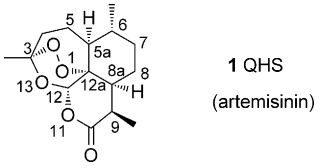

Figure 1. The structure for QHS (**1**), with the atom numbering adopted in this work indicated.

was first isolated from the Chinese herb qinghao (*Artemisia annua* L.) in the early 1970s.[2] The discovery of QHS ushered in a new era for malaria chemotherapy because of the unusual fast action of the molecule against multi-drug-resistant malaria.

The most prominent feature in QHS is the 1,2,4-trioxane structural motif incorporating the peroxy bridge that is responsible for the antimalarial activity. Total syntheses of QHS itself and of synthetic analogues have to counter the difficult problem of introducing the peroxide bridge. A range of reagents may be used, depending upon the substrate structure. These may include singlet oxygen[3] (through either an ene reaction or a [2+2] cycloaddition), hydrogen peroxide[4] (through simple alkylation or perhydrolysis of a strained small ring or ketal exchange), or ozone[5] (through ozonolysis of a C–C double bond).

However, for QHS (**1**) itself or for other closely related structures, singlet oxygen appears to be essentially the only choice.[6] This is because both terminals of the peroxy bond in **1** are attached to quaternary carbon atoms, one of which (C12a) is also further hindered by substitution in the cyclohexane ring on each side (that is, at the C5a and C8a atoms, respectively). The extent of steric crowding around the C12a carbon atom would render methods based on perhydrolysis of an epoxide rather difficult. Nevertheless, with the aid of a novel catalyst, we managed to attach a peroxy group to the C12a atom and, thereby, developed a new approach to preparing QHS and related trioxanes. Herein, we present this study in full detail.

Results and Discussion

We have previously found that phosphomolybdic acid (PMA) effectively catalyzes the conversion of ketones and ketals into *gem*-dihydroperoxy ketals.[7] Although the reactions proceed smoothly at ambient temperature, the reagent failed to discriminate between functionalities such as epoxides and ketals if these were present in the same molecule (see, for example, compound **2** in Scheme 1). However, we have developed a new catalyst from sodium molybdate and glycine, the molecular formula of which ($HO_2CCH_2NH_2{\cdot}HOMo(O_2)OMo(O_3){\cdot}H_2O$) indicates incorporation of one mole of glycine. Herein, we abbreviate the catalyst as "Na_2MoO_4-gly", and it effectively discriminates between the epoxide and ketal functionalities during the perhydrolysis of compound **2** (Scheme 1).[8]

To establish if this perhydrolysis protocol is applicable to the synthesis of QHS (**1**), a substrate with an additional sub-

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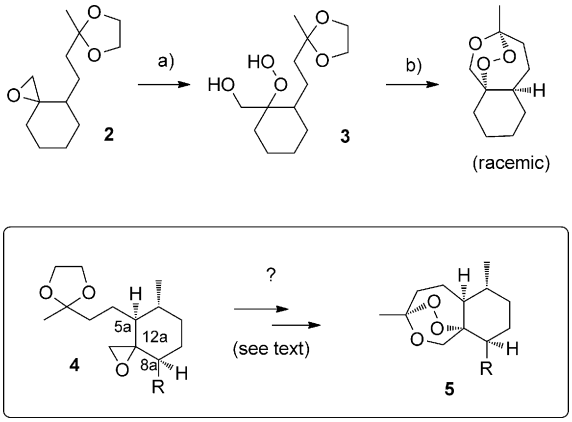
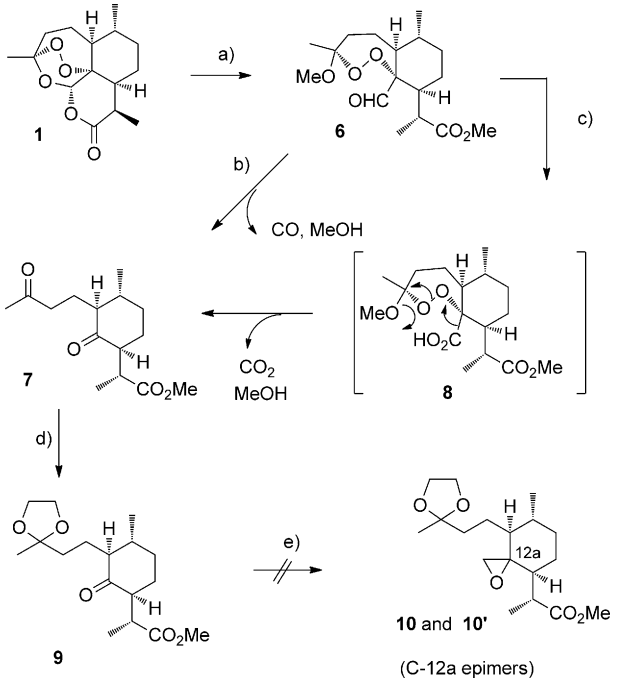


Scheme 1. a) Na_2MoO_4-gly, Et_2O, H_2O_2, RT, 61%; b) *p*TsOH, CH_2Cl_2, RT, 74%. *p*Ts = toluene-4-sulfonyl.

stituent at the C8a-position is required, preferably one with the relative configuration shown in compound **4**, to reflect that in QHS.

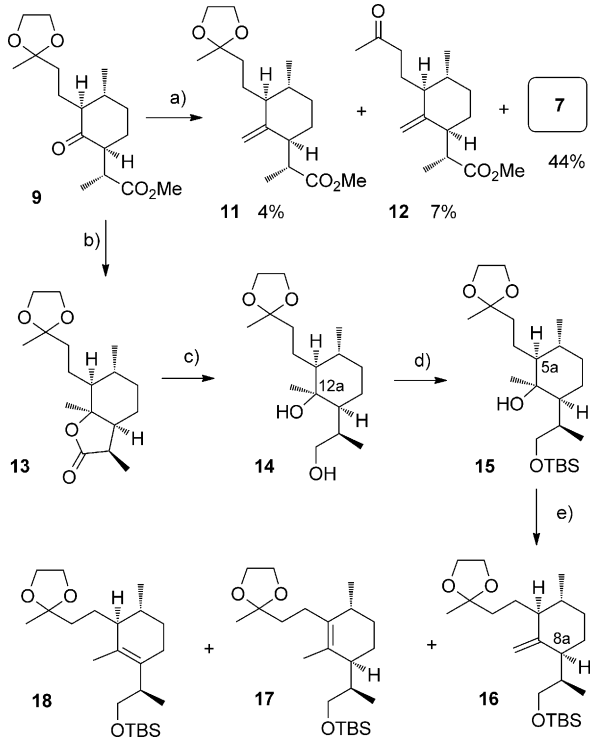
The known diketone **7**, obtained by acid-mediated degradation of QHS (Scheme 2), retains the chiral centers of QHS and has been used in previous work related to QHS.[9]



Scheme 2. a) F_3CCO_2H, MeOH, reflux, 73%; b) H_2SO_4, HOAc; c) $KMnO_4$, NaH_2PO_4, *t*BuOH/H_2O, 92%; d) $Me_3SiO(CH_2)_2OSiMe_3$, Me_3SiOTf, 99%; e) see the text. Tf = trifluromethylsulfonyl.

Acid-mediated degradation of QHS in accordance with the reported procedure by using H_2SO_4/HOAc[9a] (or HCl[9d]) turned out to be erratic, and the procedure was therefore modified as follows. Treatment of QHS with CF_3CO_2H in methanol enabled the intermediate aldehyde **6** (Scheme 2) to be isolated. This was oxidized with $KMnO_4$ in phosphate buffer to give the carboxylic acid **8**, which underwent a spontaneous decarboxylation–Grob cleavage to provide the diketone **7** in 92% yield (Scheme 2). Use of $RuCl_3$/$NaIO_4$ in acetone instead of $KMnO_4$ enabled the intermediate carboxylic acid **8** to be isolated. This decomposed gradually if left to stand or more rapidly if stirred in aqueous NaH_2PO_4/acetone,[10] to provide diketone **7**.

Next, ketone **7** was converted into epoxide **10**. The Noyori conditions with the reagent $Me_3SiO(CH_2)_2OSiMe_3$/Me_3SiOTf[11] were used to selectively protect the less-hindered side-chain carbonyl group and generate ketal **9**. However, various attempts to convert the remaining and sterically very hindered carbonyl group in the latter compound directly into epoxide **10** through the use of reagents such as Me_3SI/NaH/DMSO/THF[12] or CH_2I_2/LiBr/MeLi/THF[13] (or CH_2I_2/*n*BuLi/THF) were not successful. Therefore, an indirect approach involving conversion of the carbonyl group to form the methylene compound **11**, followed by epoxidation, was then evaluated (Scheme 3). In this case also, attempted methenylation through the use of various reagents, including the traditional Wittig conditions of Ph_3PMeI/*n*BuLi/THF, $[Ti(Cp)_2(Me)_2]$ (Cp = cyclopentadienyl)/THF/reflux, Tebbe reagent/py (py = pyridine)/THF,[14] $Mg/TiCl_4/CH_2Cl_2$/THF,[15] and Nysted reagent/THF,[16] was unsuccesssful and either re-

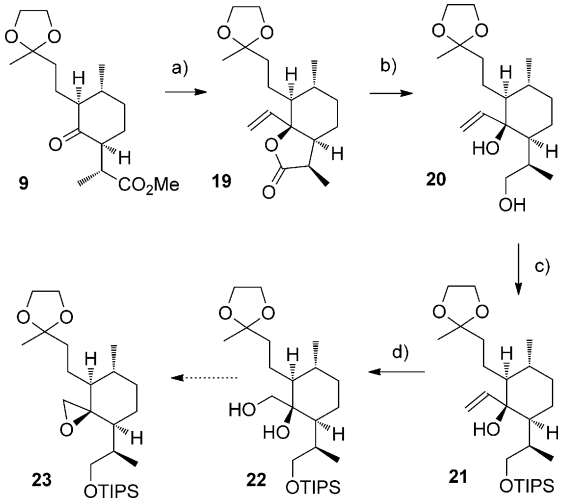


Scheme 3. a) Nysted reagent, THF; b) MeMgBr, THF, 0°C, 2 h, 100%; c) $LiAlH_4$, THF, 0°C, 4 h, 93%; d) TBSCl, imidazole, DMF, RT, 8 h, quantitative; e) MsCl, Et_3N, CH_2Cl_2; or $(COCl)_2$/DMSO, CH_2Cl_2; or DCC, CuCl, PhMe, reflux; or 4-NO_2-PhSeCN, *n*Bu_3P, pyridine; or CS_2, MeI, NaH, THF; see also the text. DCC = *N*,*N*'-dicyclohexylcarbodiimide; Ms = methanesulfonyl; TBSCl = *tert*-butyldimethylsilylchloride.

turned the diketone **7** or produced only a small amount of the desired compound **11** (Nysted reagent).

Addition of MeMgBr, $LiAlH_4$ reduction, and TBSCl protection all proceeded well (Scheme 3). However, the (formal) dehydration was unsuccessful. $MsCl/Et_3N/CH_2Cl_2$ led to a complex mixture. $SOCl_2/py/CH_2Cl_2$[17] gave an inseparable mixture of **16**–**18** in 56% yield. Burgess reagent/py/CH_2Cl_2[18] resulted in a mixture of **16**–**18** (42% altogether), along with 26% of recovered **15**. Under the $(COCl)_2$/DMSO/CH_2Cl_2,[19] DCC/CuCl/PhMe/reflux,[20] 4-NO_2-PhSeCN/nBu_3P/py,[21] or CS_2/MeI/NaH/THF[22] conditions, essentially no reactions occurred.

Addition of a vinyl group to **9** and subsequent elaboration provided **21** smoothly (Scheme 4). However, the yield for the ozonolysis of **21** and subsequent reduction (to afford diol **22**) was unacceptably low.

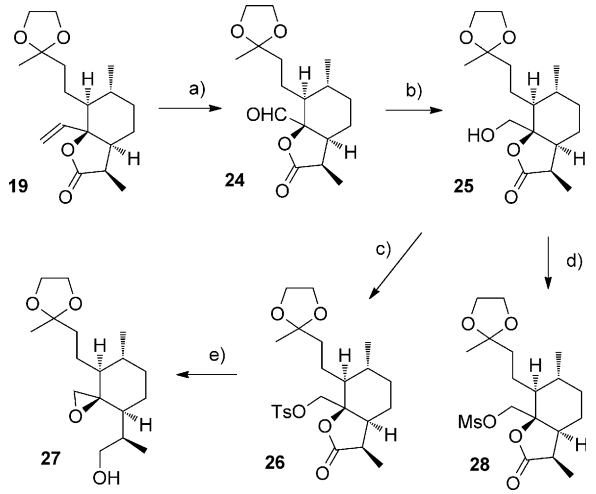


Scheme 4. a) CH_2=CHMgBr, THF, 81%; b) $LiAlH_4$, THF, 0°C, 4 h, 76%; c) TIPSCl, imidazole, DMF, 100%; d) 1. O_3, CH_2Cl_2, −78°C, 2. $NaBH_4$, MeOH, low yields. TIPS = triisopropylsilyl.

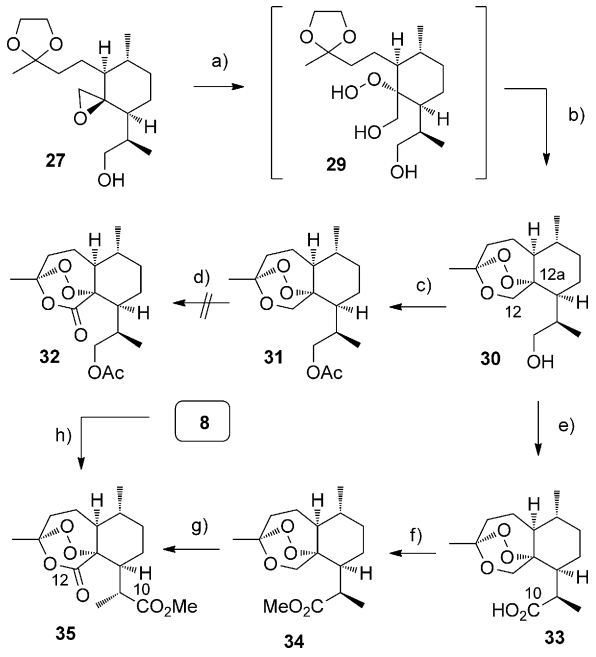
The approach in Scheme 5 was then examined. Ozonolysis of **19** gave aldehyde **24**[6k,8] in 87% yield. Reduction of **24** into **25** failed to occur under such conditions as diisobutylaluminum hydride (DIBAL-H)/CH_2Cl_2/−78°C, BH_3·Me_2S/THF/0°C, or $NaBH(OAc)_3/CH_2Cl_2$/RT. The use of $NaBH_4$/MeOH/RT led to a complex mixture. However, if the reaction was performed at −10°C, the desired compound **25** was obtained in quantitative yield.

Tosylation of **25** gave **26** in 94% yield. Treatment of **26** with $LiBH_4$/THF afforded **27**. Mesylation of **25** was also feasible, but the reduction/epoxidation step was then complicated by the formation of **14**.

Perhydrolysis of **27** occurred smoothly (Scheme 6). The resulting compound **30**[23] was then acetylated to afford **31**. However, oxidation of **31** to afford lactone **32** was unsuccessful under $RuCl_3/NaIO_4/CH_2Cl_2$,[24] $KMnO_4/FeCl_3$/acetone, or $AlCl_3/KMnO_4$/acetone[25] conditions. Oxidation of **30** to give acid **33** and subsequent esterification to form **34** all worked well, but the low yield (13%) for the conversion



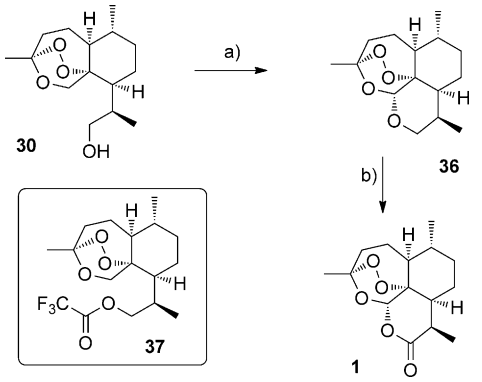
Scheme 5. a) 1. O_3, CH_2Cl_2, −78°C, 2. Me_2S, 87%; b) $NaBH_4$, MeOH, −10°C, 100%; c) *p*TsCl, Et_3N, DMAP, CH_2Cl_2, 94%; d) MsCl, Et_3N, DMAP, CH_2Cl_2, 93%; e) $LiBH_4$, THF, 74%. DMAP = 4-dimethylaminopyridine.



Scheme 6. a) ethereal H_2O_2, $NaMoO_4$-gly, RT, 11 h, 74%; b) *p*TsOH, CH_2Cl_2, RT, 1.5 h, 84%; c) Ac_2O, pyridine, DMAP, CH_2Cl_2, 100%; d) see the text; e) $RuCl_3$, $NaIO_4$, MeCN/CCl_4/H_2O (2:2:3), RT, 2 h, 94%; f) MeI, K_2CO_3, acetone, RT, 16 h, 57%; g) $KMnO_4$, $FeCl_3$, acetone, reflux, 13%; h) *p*TsOH, 73%.

of **34** into **35** (also attainable from **8**), along with difficulties at later stages, forced us to seek other approaches.

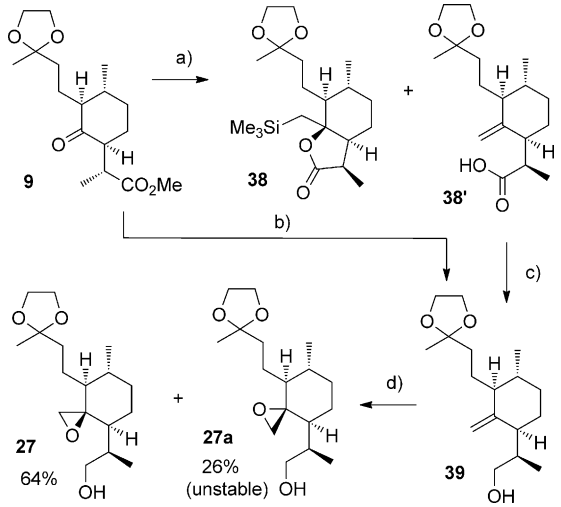
An alternative, that is, to close the lower ring in QHS (**1**) without a carbonyl group at the C10-position, was then explored (Scheme 7). Under the $Pd(OAc)_4$/benzene/reflux conditions of Yamada and co-workers,[26] the desired compound **36** was formed in 64% yield. Even better results were achieved by using the $PhI(OAc)_2/I_2$/cyclohexane/RT conditions of Suarez and co-workers.[27] If $PhI(OTFA)_2$ was used in-



Scheme 7. a) $PhI(OAc)_2$, I_2, cyclohexane, RT, 69%; or $PhI(OTFA)_2$, I_2, cyclohexane, RT, 32% of **36** and 66% of **37**; b) $RuCl_3$, $NaIO_4$, 49%. TFA = trifluoroacetyl.

stead of $PhI(OAc)_2$, the major product was **37**. Compound **36** was then converted into **1** under known conditions.[6h]

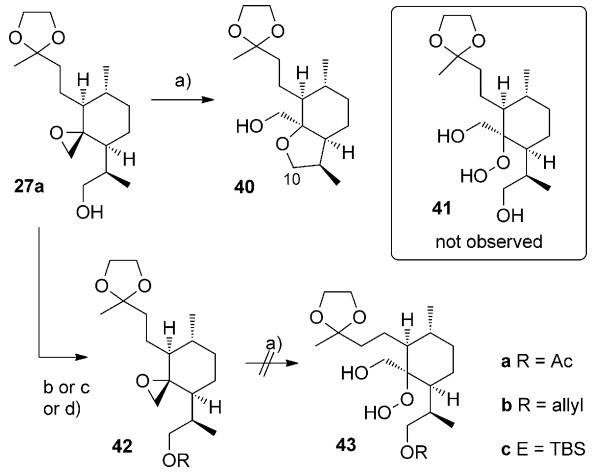
The possibility of converting **27a** (the C12a epimer of **27**) into **29** was also examined. As shown in Scheme 8, addition of Me_3SiCH_2MgCl to **9** afforded **38** (17%) and **38′** (79%).



Scheme 8. Reagents and conditions: a) Me_3SiCH_2MgCl, toluene, reflux, 2 h, 17% of **38**, 79% of **38′**; b) 1. Me_3SiCH_2MgCl, toluene, reflux, 1 h, 2. $LiAlH_4$, reflux, 2 h, 57% from **9**; c) $LiAlH_4$, THF, reflux, 92%; d) *m*CPBA, Na_2CO_3, CH_2Cl_2. *m*CPBA = *meta*-chloroperoxybenzoic acid.

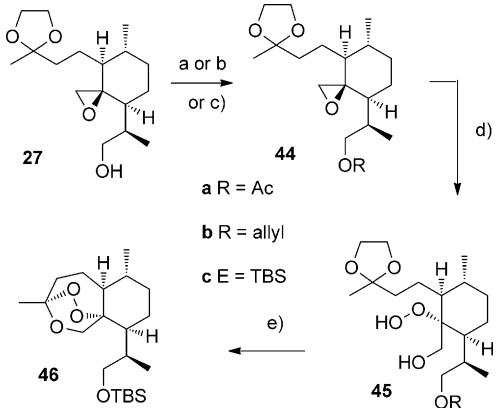
Reduction of **38′** with $LiAlH_4$ yielded **39**. The two steps could also be done in a "one-pot" manner to provide **39** in 57% overall yield. Epoxidation with *m*CPBA/Na_2CO_3/CH_2Cl_2 gave **27** and **27a** in 64 and 26% yields, respectively.

Perhydrolysis of **27a** resulted in **40** as the only product (Scheme 9). The same transformation also occurred spontaneously during storage of **27a**. To eliminate the interference of this side reaction, the OH group in **27a** was masked with acetyl, allyl, or TBS groups, respectively, and the resulting compounds **42a–c** were tested. The results clearly showed that no perhydrolysis occurred with **42a–c**. For comparison, the OH group in **27** was also protected and tested. Although



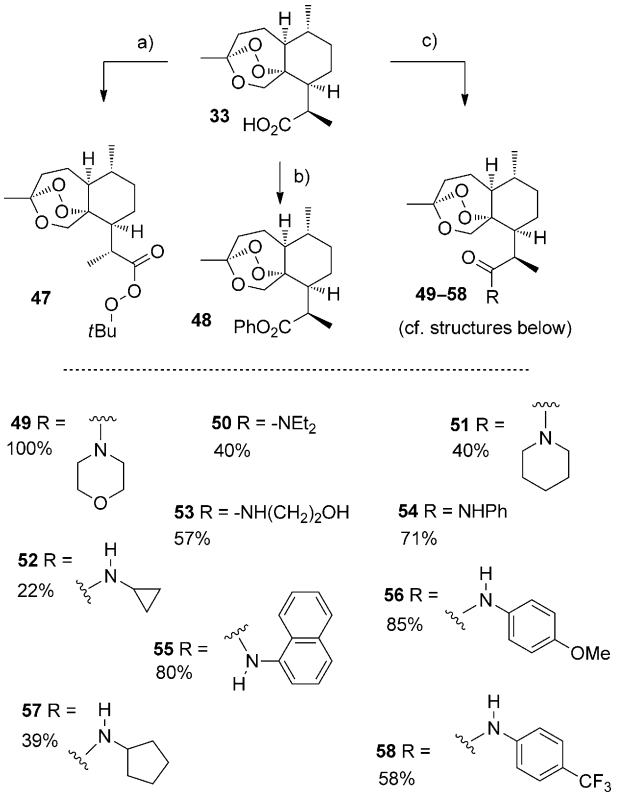
Scheme 9. a) ethereal H_2O_2, $NaMoO_4$-gly, RT, 24 h, 63%; b) Ac_2O, pyridine, DMAP, CH_2Cl_2, 68% of **42a**; c) allyl bromide, NaH, DMF, THF, 45% of **42b**; d) TBSCl, imidazole, DMF, 93% of **42c**.

the reactions were slower than that of **27**, perhydrolysis was observed with **44a–c** (Scheme 10). These results unambiguously show the importance of the epoxide ring configuration.



Scheme 10. a) Ac_2O, pyridine, DMAP, CH_2Cl_2, 86% of **44a**; b) allyl bromide, NaH, DMF, THF, 39% of **44b**; c) TBSCl, imidazole, DMF, 91% of **44c**; d) ethereal H_2O_2, $NaMoO_4$-gly, RT, 24 h, 0% of **45a** (no reaction occurred), 32% of **45b** (along with 46% of recovered **44b**), **45c** decomposed on the silica gel and was thus directly exposed to e) *p*TsOH, CH_2Cl_2, 20% of **46**.

With acid **33** as the starting material, some simple esters and amides (**47**–**58**) were also synthesized (Scheme 11), along with three more complex derivatives (**59**, **61**, and **63**; Scheme 12), which were designed in light of the discoveries by Posner, O'Neill, and their respective co-workers that tethering two QHS residues together through an appropriate linker may result in significantly increased antimalarial activity.[28] The newly accessed trioxanes were then tested in vitro for their antimalarial activity. Many of the IC_{50} values (Table 1) were at ng mL^{-1} levels, with the best ones rather



Scheme 11. a) EDCI, DMAP, CH_2Cl_2, *t*BuOOH, 69%; b) EDCI, DMAP, CH_2Cl_2, PhOH, 99%; c) EDCI, DMAP, CH_2Cl_2, RNH_2 (R is shown in each individual structure for **49**–**58**, along with the corresponding yields). EDCI = *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide.

close to or even better than that for artesunate (which is an even better antimalarial than QHS itself).[29]

Conclusion

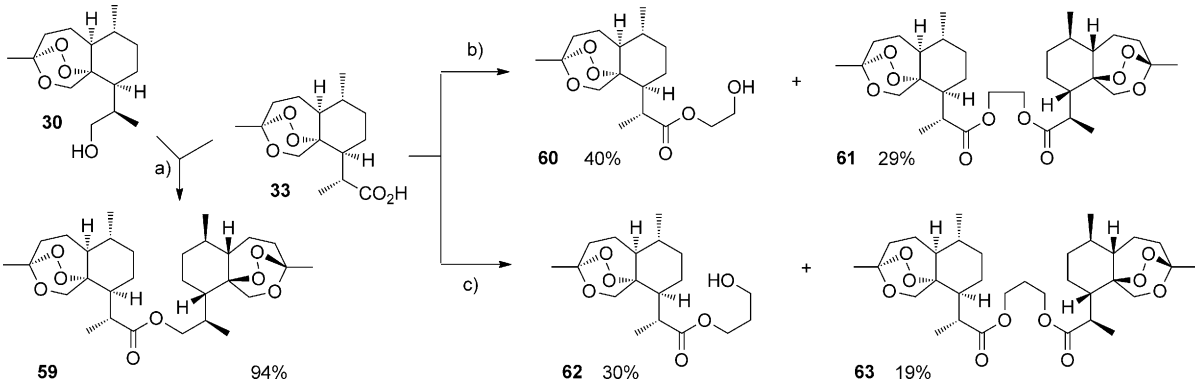
With the aid of a molybdenum catalyst recently developed in our laboratory, smooth perhydrolysis of a sterically highly congested epoxide ring was achieved at ambient temperature in ethereal H_2O_2 in a stereoselective manner, without cleavage of a ketal functionality that was present in the same substrate molecule. By varying the relative configuration and functionality of the peroxy substrate, some insights into the stereochemical requirements of the key perhydrolysis reaction were also gained. The new methods described herein have enabled the ready construction of a 1,2,4-trioxane closely related to QHS to be carried out for the first time. This compound was further elaborated into QHS through a C–H insertion followed by oxidation at the C10-position. Alternatively, C10 derivatives were generated through esterification or amidation at the C10-position. A range of new QHS analogues were thus obtained, some of which showed ng mL^{-1} level in vitro activity against *P. falciparum* (strain NF 45), with the best ones being comparable to or even better than artesunate and chloroquine. The new potent analogues and their activity data also provide valuable information about the structure–activity relationship for the trioxane-type antimalarials and may serve as useful lead compounds in searching for even better structures.

Apart from the unprecedented H_2O_2-based approach to the synthesis of QHS and the new simplified QHS analogues, the facile access to diketone **7** developed in this work is also noteworthy. By oxidation of intermediate aldehyde **6**, rather than treatment with H_2SO_4/HOAc (or HCl), the reaction enabled **7** to be easily acquired on a preparative scale. This compound may find diverse applications in synthesis because of its well-defined stereogenic centers and multifunctional nature.

Experimental Section

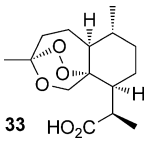
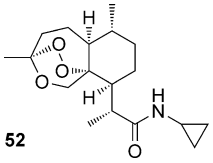
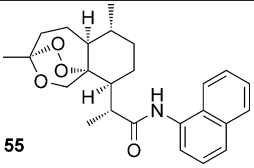
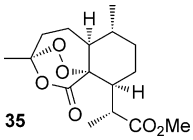
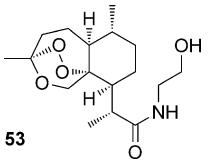
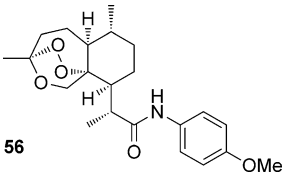
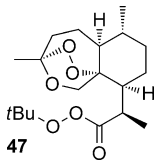
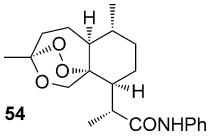
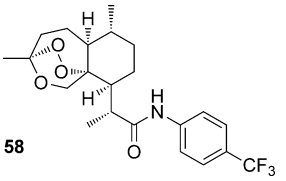
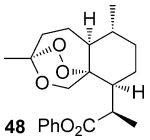
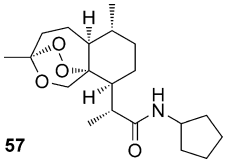
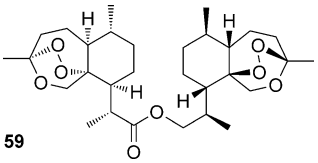
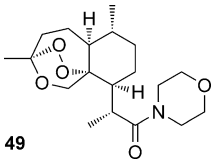
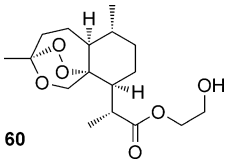
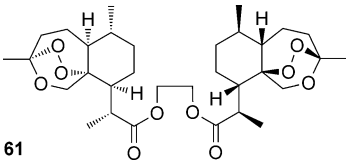
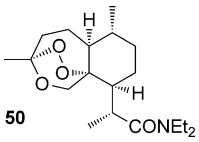
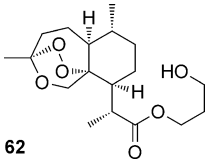
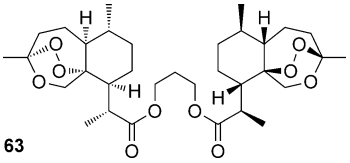
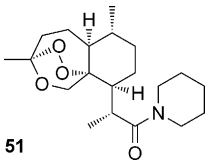
General: THF and Et_2O (the solvents for moisture-sensitive reactions) were distilled over Na/benzophenone under argon prior to use. CH_2Cl_2 and MeCN were distilled over CaH_2 prior to use. DMSO were stirred with CaH_2 at ambient temperature for several days (in a septum-sealed flask with a flat balloon to collect the H_2 gas evolved), distilled under vacuum, and kept over activated 4 Å molecular sieves under argon. The ethereal H_2O_2 and the molybdenum catalyst "Na_2MoO_4-gly" were prepared as reported previously.[8] The chromatography solvent was petroleum ether (PE; b.p. 60–90 °C).

Degradation of QHS to afford diketone 7 (via 6 and 8): A solution of QHS (**1**; 10.00 g, 35.4 mmol) in MeOH (300 mL) and CF_3CO_2H (5.5 mL)



Scheme 12. a) EDCI, DMAP, CH_2Cl_2; b) EDCI, DMAP, CH_2Cl_2, $HO(CH_2)_2OH$; c) EDCI, DMAP, CH_2Cl_2, $HO(CH_2)_3OH$.

Table 1. In vitro activity (IC_{50} values) of the newly synthesized trioxanes against *Plasmodium falciparum* (strain NF45).[a]

Trioxane	IC_{50} [ng mL^{-1}]	Trioxane	IC_{50} [ng mL^{-1}]	Trioxane	IC_{50} [ng mL^{-1}]
 **33**	2.0×10	 **52**	4.5×10	 **55**	2.9
 **35**	1.8×10^2	 **53**	6.7×10	 **56**	7.3
 **47**	5.0	 **54**	4.6	 **58**	8.6×10^2
 **48**	2.1	 **57**	9.1	 **59**	0.41
 **49**	5.3	 **60**	8.5	 **61**	0.71
 **50**	7.1	 **62**	7.9	 **63**	0.97
 **51**	2.8	chloroquine diphosphate	6.8	artesunate	1.2

[a] These data are the averages of two or three independent experiments. For further details of the procedure, see ref. [30].

was heated at reflux with stirring for 5 h. The mixture was concentrated on a rotary evaporator until a volume of about 100 mL was left in the flask. Aq. sat. $NaHCO_3$ (30 mL) was added. The mixture was extracted with Et_2O (3×100 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 30:1) on silica gel gave the intermediate aldehyde **6** as a colorless sticky oil (8.48 g, 25.8 mmol, 73% from **1**). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=9.88$ (d, $J=2.4$ Hz, 1H), 3.60 (s, 3H), 3.32 (s, 3H), 3.20–3.09 (m, 1H), 2.37–2.20 (m, 1H), 2.03 (dd, $J=14.4$, 7.7 Hz, 1H), 1.93–1.85 (m, 1H), 1.85–1.56 (m, 4H), 1.40–1.23 (m, 2H), 1.19 (d, $J=7.1$ Hz, 3H), 1.16–1.06 (m, 1H), 1.14 (s, 3H), 0.96–0.83 (m, 1H), 0.85 ppm (d, $J=6.5$ Hz, 3H); ESI-MS: *m/z*: 351.1 $[M+Na]^+$. The main portion of aldehyde **6** (7.34 g, 22.3 mmol) was dissolved in *t*BuOH/H_2O (1:1, 200 mL) at ambient temperature with stirring. NaH_2PO_4 (28.00 g, 178.8 mmol) was added, followed by $KMnO_4$ (14.00 g, 89.4 mmol). The mixture was stirred at the same temperature for 20 h (TLC analysis indicated completion of the reaction) before being extracted with Et_2O (3×150 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 6:1) on silica gel gave diketone **7** as a white solid (5.52 g, 20.5 mmol, 92% from **6**). M.p. 47–49 °C (Ref. [9a]: m.p. 51–52 °C); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.58$ (s, 3H), 2.68 (quint, $J=6.9$ Hz, 1H), 2.58–2.38 (m, 2H), 2.34–2.21 (m, 1H), 2.04 (s, 3H), 2.02–1.85 (m, 2H), 1.81–1.60 (m, 3H), 1.57–1.38 (m, 3H), 1.09 (d, $J=6.9$ Hz, 3H), 0.99 ppm (d, $J=5.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=211.3$, 208,8, 175.8, 56.5, 53.2, 51.3, 40.9, 39.9, 39.0, 34.2, 30.7, 29.7, 20.3, 19.9, 14.8 ppm; FTIR (film): $\tilde{\nu}=2952$, 2931, 2876, 1737, 1709, 1456, 1435, 1371, 1358, 1256, 1161, 619 cm^{-1}; ESI-MS: *m/z*: 269.1 $[M+H]^+$, 286.1 $[M+NH_4]^+$, 291.1 $[M+Na]^+$.

Alternatively, elaboration of **6** into **7** could also be achieved in a stepwise manner, with the intermediate acid **8** isolated. A small portion of intermediate **6** (177 mg, 0.54 mmol) was dissolved in acetone (4 mL) and H_2O (2 mL). $NaIO_4$ (461 mg, 2.16 mmol) and $RuCl_3$ (3 mg, 0.014 mmol) were

added to this solution. The mixture was stirred at ambient temperature for 5 h. H_2O (3 mL) was added. The mixture was extracted with EtOAc (3×40 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 3:4) on silica gel gave the intermediate acid **8** as a colorless oil (139 mg, 0.171 mmol, 75% from **6**). ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.65 (s, 3H), 3.34 (s, 3H), 3.08 (quint, J=7.4 Hz, 1H), 2.37–2.20 (m, 1H), 2.16–2.07 (m, 1H), 1.97–1.90 (m, 1H), 1.89–1.50 (m, 7H), 1.32 (d, J=7.3 Hz, 3H), 1.23 (s, 3H), 1.09–0.94 (m, 1H), 0.91 ppm (d, J=6.4 Hz, 3H); FTIR (film): $\tilde{\nu}$=3224, 2953, 1735, 1710, 1458, 1260, 1210, 1188, 1143, 1118, 1087, 876, 735 cm^{-1}. The intermediate acid **8** (41 mg, 0.12 mmol) was dissolved in acetone (3 mL). NaH_2PO_4 (149 mg, 0.95 mmol) was added to the solution. The mixture was stirred at ambient temperature for 10 h. Et_2O (3 mL) was added, followed by H_2O (3 mL). The mixture was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 5:1) on silica gel gave diketone **7** as a white solid (22 mg, 0.082 mmol, 68% from **8**).

Conversion of ketone 7 into ketal 9: A solution of diketone **7** (2.00 g, 7.5 mmol) in dry CH_2Cl_2 (15 mL) was added to a solution of $Me_3SiO(CH_2)_2OSiMe_3$ (7.5 mL, 29.8 mmol) and Me_3SiOTf (0.23 mL, 1.12 mmol) in dry CH_2Cl_2 (20 mL) stirred at −78 °C under N_2 (balloon). The mixture was stirred at the same temperature for 3 h (TLC analysis indicated completion of the reaction). Pyridine (1 mL) was added. The mixture was then poured into aq. sat. $NaHCO_3$ (30 mL). The mixture was extracted with CH_2Cl_2 (3×70 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 7:1) on silica gel gave **9** as a yellowish oil (2.31 g, 7.40 mmol, 99% from **7**). $[\alpha]_D^{24}$=−37.1 (c=0.90 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.99–3.87 (m, 4H), 3.66 (s, 3H), 2.77 (quint., J=7.0 Hz, 1H), 2.65–2.54 (m, 1H), 2.12–2.02 (m, 1H), 1.99–1.91 (m, 1H), 1.87–1.78 (m, 1H), 1.75–1.45 (m, 7H), 1.33 (s, 3H), 1.16 (d, J=6.9 Hz, 3H), 1.06 ppm (d, J=6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=211.3, 176.2, 110.1, 64.5, 64.4, 57.4, 53.6, 51.5, 40.4, 39.4, 36.0, 34.5, 31.4, 23.5, 20.5, 20.4, 15.3 ppm; FTIR (film): $\tilde{\nu}$=2933, 2877, 1737, 1709, 1455, 1377, 1252, 1206, 1159, 1051, 866 cm^{-1}; ESI-MS: m/z: 313.1 [M+H]$^+$, 335.1 [M+Na]$^+$; ESI-HRMS: m/z: calcd for $C_{17}H_{28}O_5Na$: 335.18290 [M+Na]$^+$; found: 335.18269.

Reaction of 9 with Nysted reagent: Nysted reagent (520 mg) was added to a solution of $TiCl_4$ (35 μL, 0.32 mmol) in dry THF (2 mL) stirred in an ice/water bath under a N_2 (balloon). The mixture was stirred at ambient temperature for 20 min. The resulting dark-brown mixture was added slowly to a solution of **9** (50 mg, 0.160 mmol) in dry THF (1 mL). The mixture was stirred at ambient temperature under the N_2 (balloon) for 5 h and heated at reflux for 12 h. The gray/white mixture was poured into aq. sat. $NaHCO_3$ (10 mL) and extracted with Et_2O (2×30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 15:1) on silica gel gave **11** (2 mg, 0.0064 mmol, 4% from **9**), **12** (3 mg, 0.011 mmol, 7% from **9**), unreacted **9** (20 mg, 0.064 mmol, 40%), and **7** (20 mg, 0.064 mmol, 44% from **9**). Compound **11** was a colorless oil and less polar than **12**. ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.73 (s, 1H), 4.65 (s, 1H), 3.91–3.81 (m, 4H), 3.60 (s, 3H), 2.69–2.59 (m, 1H), 2.09–2.00 (m, 1H), 1.77–1.58 (m, 4H), 1.57–1.41 (m, 3H), 1.38–1.27 (m, 1H), 1.25 (s, 3H), 1.23–1.07 (m, 2H), 1.10 (d, J=6.7 Hz, 3H), 0.87 ppm (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=177.2, 150.2, 110.2, 107.0, 64.6, 64.5, 51.34, 51.31, 48.0, 41.8, 38.7, 36.8, 32.3, 31.3, 24.3, 23.7, 20.2, 16.2 ppm; FTIR (film): $\tilde{\nu}$=2951, 2926, 2873, 1738, 1647, 1461, 1376, 1166, 1050 cm^{-1}; ESI-MS: m/z: 333.2 [M+Na]$^+$; ESI-HRMS: m/z: calcd for $C_{18}H_{30}NaO_4$: 333.20363 [M+Na]$^+$; found: 333.20487; compound **12** was a white solid and more polar than **11**; m.p. 29–31 °C; $[\alpha]_D^{24}$=−71.2 (c=1.10 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=4.73 (d, J=6.6 Hz, 2H), 3.68 (s, 3H), 2.75–2.65 (m, 1H), 2.57 (ddd, J=17.4, 9.7, 4.7 Hz, 1H), 2.38 (ddd, J=17.2 Hz, 9.1, 6.3 Hz, 1H), 2.13 (s, 3H), 2.12–2.07 (m, 1H), 1.99–1.88 (m, 1H), 1.80–1.54 (m, 4H), 1.45–1.33 (m, 1H), 1.24–1.15 (m, 2H), 1.18 (d, J=6.7 Hz, 3H), 0.95 ppm (d, J=6.6 Hz, 3H); FTIR (film): $\tilde{\nu}$=2931, 2872, 1737, 1716, 1641, 1456, 1434, 1355, 1254, 1191, 1165, 898 cm^{-1}; ESI-MS: m/z: 267.2 [M+H]$^+$, 289.2 [M+Na]$^+$, 305.1 [M+K]$^+$; ESI-HRMS: m/z: calcd for $C_{16}H_{26}NaO_3$: 289.17742 [M+Na]$^+$; found: 289.17717.

Reaction of 9 with MeMgBr to afford lactone 13: MeMgBr (3 M in THF, 0.15 mL, 0.45 mmol) was added to a solution of ketone **9** (110 mg, 0.35 mmol) in dry THF (3 mL) stirred in an ice–water bath under N_2 (balloon). The mixture was stirred at the same temperature for 2 h. Water was added. The mixture was extracted with Et_2O (2×30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 7:1) on silica gel gave **13** (105 mg, 0.35 mmol, 100%). $[\alpha]_D^{28}$=−60.3 (c=1.90 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.02–3.83 (m, 4H), 3.09 (quint, J=7.3 Hz, 1H), 2.15–2.03 (m, 1H), 1.95–1.78 (m, 2H), 1.72–1.58 (m, 3H), 1.57–1.44 (m, 1H), 1.42 (s, 3H), 1.40–1.33 (m, 1H), 1.31 (s, 3H), 1.12 (d, J=7.2 Hz, 3H), 1.09–0.98 (m, 2H), 0.96 (d, J=6.8 Hz, 3H), 0.94–0.89 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=179.3, 109.7, 85.8, 64.6, 64.5, 50.6, 44.7, 39.6, 39.2, 32.9, 32.4, 24.4, 24.2, 23.6, 22.9, 20.1, 9.3 ppm; FTIR (film): $\tilde{\nu}$=2978, 2932, 2877, 1767, 1451, 1379, 1210, 1165, 1054, 925 cm^{-1}; ESI-MS: m/z: 297.1 [M+H]$^+$, 319.1 [M+Na]$^+$; ESI-HRMS: m/z calcd for $C_{17}H_{28}NaO_4$: 319.18798 [M+Na]$^+$; found: 319.18757.

Reduction of 13 to afford diol 14: $LiAlH_4$ (307 mg, 8.10 mmol) was added to a solution of lactone **13** (1.2 g, 4.05 mmol) in dry THF (60 mL) stirred in an ice/water bath under N_2 (balloon). The mixture was stirred at the same temperature for 4 h (TLC analysis indicated completion of the reaction) before being diluted with Et_2O (15 mL). Aq. NaOH (1 N, 3 mL) was added slowly, followed by aq. sat. potassium sodium tartrate (20 mL). The cloudy mixture was stirred at ambient temperature until a clear two-phase solution resulted. The mixture was extracted with Et_2O (2×60 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 1:1) on silica gel gave **14** (1.131 g, 3.77 mmol, 93% from **13**) as a white solid; m.p. 88–90 °C. $[\alpha]_D^{24}$=−23.2 (c=1.97 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.01–3.90 (m, 4H), 3.50–3.38 (m, 1H), 3.32 (dd, J=10.7, 3.3 Hz, 1H), 2.45–2.31 (m, 1H), 1.88–1.34 (m, 7H), 1.32 (s, 3H), 1.29 (s, 3H), 1.27–1.17 (m, 2H), 1.05–0.95 (m, 1H), 0.92 (d, J=6.5 Hz, 3H), 0.84 (d, J=7.4 Hz, 3H), 0.78–0.70 ppm (dt, J=11.1, 3.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=110.1, 74.1, 64.5, 64.4, 63.7, 53.3, 53.0, 39.4, 35.8, 33.8, 33.5, 24.8, 23.5, 23.0, 20.6, 20.1, 18.3 ppm; FTIR (film): $\tilde{\nu}$=3304, 2956, 2927, 2873, 1456, 1376, 1058 cm^{-1}; ESI-MS: m/z: 323.1 [M+Na]$^+$; ESI-HRMS: m/z: calcd for $C_{17}H_{32}NaO_4$: 323.21928 [M+Na]$^+$; found: 323.21900.

TBS protection of 14 to afford 15: A solution of **14** (516 mg, 1.665 mmol), imidazole (170 mg, 2.5 mmol), and TBSCl (301 mg, 2 mmol) in dry DMF (3 mL) was stirred at ambient temperature for 8 h. Water (3 mL) was added. The mixture was extracted with Et_2O (2×40 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 25:1) on silica gel gave **15** (689 mg, 1.665 mmol, quantitative yield from **14**) as a colorless oil. $[\alpha]_D^{22}$=−3.88 (c=1.83 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.12 (d, J=1.2 Hz, 1H), 3.88–3.82 (m, 4H), 3.40 (t, J=10.4 Hz, 1H), 3.26 (dd, J=10.3, 3.3 Hz, 1H), 2.31–2.16 (m, 1H), 1.81–1.39 (m, 7H), 1.35–1.21 (m, 2H), 1.24 (s, 3H), 1.18–1.08 (m, 1H), 1.13 (s, 3H), 0.88–0.78 (m, 12H), 0.74 (d, J=7.3 Hz, 3H), 0.56–0.47 (m, 1H), 0.007 (s, 3H), 0.00 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=110.2, 72.8, 64.9, 64.4, 53.7, 53.2, 39.7, 36.1, 33.9, 33.2, 25.8 (3C), 25.2, 23.5, 23.2, 20.6, 19.9, 18.27, 18.24, −5.5, −5.6 ppm; FTIR (film): $\tilde{\nu}$=3431, 2955, 2929, 2860, 1466, 1375, 1254, 1057, 837, 778 cm^{-1}; ESI-MS: m/z: 437.2 [M+Na]$^+$; ESI-HRMS: m/z: calcd for $C_{23}H_{46}O_4Si$: 415.3238 [M+H]$^+$; found: 415.3239.

Addition of vinyl Grignard reagent to ketone 9 to afford lactone 19: Vinyl Grignard reagent (1.0 M in THF, 0.36 mL, 0.36 mmol) was added to a solution of ketone **9** (75 mg, 0.24 mmol) in dry THF (2 mL) stirred in an ice/water bath under a N_2 (balloon). Stirring was continued for 6 h and the bath was allowed to warm to ambient temperature naturally. Et_2O (5 mL) was added, followed by aq. sat. NH_4Cl (5 mL). The mixture was extracted with Et_2O (2×30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc,

5:1) on silica gel gave **19** (60 mg 0.195 mmol, 81%) as a yellowish oil. $[\alpha]_D^{28}=-52.0$ ($c=0.53$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.63$ (dd, $J=17.3$, 10.6 Hz, 1H), 5.29 (d, $J=17.3$ Hz, 1H), 5.24 (d, $J=11.4$ Hz, 1H), 3.94–3.79 (m, 4H), 2.87 (quint, $J=7.0$ Hz, 1H), 2.12–2.00 (m, 1H), 1.82–1.60 (m, 4H), 1.58–1.32 (m, 3H), 1.23 (s, 3H), 1.06–0.96 (m, 3H), 1.03 (d, $J=7.4$ Hz, 3H), 0.94 ppm (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=179.8$, 140.2, 115.4, 110.1, 87.6, 64.5, 47.9, 43.4, 39.1, 37.8, 32.8, 31.9, 24.0, 23.6, 22.0, 20.2, 9.0 ppm; FTIR (film): $\tilde{\nu}=2935$, 2879, 1774, 1452, 1378, 1178, 1053, 946, 858, 524 cm^{-1}; EI-MS: m/z (%): 87 (100), 281 (0.32), 179 (2.03), 293 $[M-CH_3]^+$ (6.65); EI-HRMS: m/z: calcd for $C_{17}H_{25}O_4$: 293.1753 $[M-CH_3]^+$; found: 293.1758.

Reduction of lactone 19 to afford diol 20: $LiAlH_4$ (76 mg, 2.0 mmol) was added to a solution of lactone **19** (308 mg, 1.00 mmol) in dry THF (5 mL) stirred in an ice–water bath under N_2 (balloon). The mixture was stirred at the same temperature for 4 h (TLC analysis indicated completion of the reaction) before being diluted with Et_2O (5 mL). Aq. NaOH (1 N, 3 mL) was added slowly, followed by aq. sat. potassium sodium tartrate (10 mL). The cloudy mixture was stirred at ambient temperature until a clear two-phase solution resulted. The mixture was extracted with Et_2O (2×60 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 3:1) on silica gel gave diol **20** (233 mg, 0.747 mmol, 75% from **19**) as white prisms. M.p. 132–135 °C; $[\alpha]_D^{27}=+1.09$ ($c=1.35$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.63$ (dd, $J=17.3$, 10.6 Hz, 1H), 5.30 (dd, $J=12.3$, 1.5 Hz, 1H), 5.25 (dd, $J=5.6$, 1.8 Hz, 1H), 4.19–3.55 (m, 6H), 3.44–3.26 (m, 2H), 2.25–2.11 (m, 1H), 1.87–1.71 (m, 2H), 1.70–1.41 (m, 5H), 1.36–1.20 (m, 2H), 1.27 (s, 3H), 1.09–0.98 (m, 1H), 0.94 (d, $J=6.8$ Hz, 3H), 0.90–0.81 (m, 1H), 0.78 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=144.5$, 114.0, 110.3, 78.2, 64.4, 64.3, 64.0, 51.1, 51.0, 38.0, 35.7, 34.3, 32.5, 23.4, 22.7, 20.5, 20.1, 18.4 ppm; FTIR (film): $\tilde{\nu}=3359$, 2950, 2929, 2872, 1707, 1692, 1459, 1378, 1222, 1066, 1045, 999, 915 cm^{-1}; ESI-MS: m/z: 335.1 $[M+Na]^+$; EI-HRMS: m/z: calcd for $C_{18}H_{32}O_4$: 312.2301 $[M^+]$; found: 312.2302.

TIPS protection of diol 20 to afford 21: A solution of diol **20** (182 mg, 0.583 mmol), imidazole (59 mg, 0.875 mmol), and TIPSCl (148 μL, 0.7 mmol) in dry DMF (3 mL) was stirred at ambient temperature for 12 h. Et_2O (5 mL) and water (3 mL) were added. The mixture was extracted with Et_2O (2×40 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 30:1) on silica gel gave **21** (273 mg, 0.583 mmol, 100% from **20**) as a colorless oil. $[\alpha]_D^{28}=-17.2$ ($c=1.70$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.59$ (dd, $J=17.3$, 10.6 Hz, 1H), 5.33 (dd, $J=17.0$, 2.3 Hz, 1H), 5.18 (dd, $J=10.3$, 2.5 Hz, 1H), 4.36 (s, 1H, OH), 3.94–3.81 (m, 4H), 3.48–3.38 (m, 1H), 3.32 (dd, $J=10.0$, 3.5 Hz, 1H), 2.22–2.08 (m, 1H), 1.83–1.33 (m, 6H), 1.33–1.21 (m, 2H), 1.26 (s, 3H), 1.18–0.93 (m, 23H), 0.90 (d, $J=7.4$ Hz, 3H), 0.75 (d, $J=7.0$ Hz, 3H), 0.72–0.63 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=145.4$, 113.8, 110.4, 77.2, 65.4, 64.3, 64.2, 51.6, 51.2, 38.5, 36.0, 34.5, 32.4, 23.3, 23.1, 20.5, 20.4, 18.5, 17.9 (5C), 17.6, 11.8 ppm (3C). Attempts to acquire MS data for **21** were unsuccessful.

Ozonolysis of 19 to afford aldehyde 24: Ozone was bubbled into a solution of alkene **19** (40 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) cooled in a −78 °C bath until a blue color developed. N_2 gas was then bubbled into the mixture while stirring was continued at ambient temperature until the blue color disappeared. Me_2S (0.1 mL, 1.36 mmol) was then introduced. The mixture was stirred at ambient temperature for 6.5 h (TLC analysis indicated completion of the reaction). The mixture was diluted with Et_2O (5 mL) and concentrated on a rotary evaporator. The residue was subjected to chromatography (PE/EtOAc, 5:1) on silica gel to give the known aldehyde **24** as a colorless oil (35 mg, 0.113 mmol, 87% from **19**). All spectroscopic data were fully consistent with those reported previously.[8]

Conversion of alcohol 25 into mesylate 28: MsCl (20 μL, 0.25 mmol) was added to a solution of alcohol **25**[8] (31 mg, 0.1 mmol), Et_3N (42 μL, 0.3 mmol), and DMAP (6 mg, 0.05 mmol) in dry CH_2Cl_2 (3 mL) stirred in an ice/water bath. The mixture was then stirred at ambient temperature for 4 h (TLC analysis indicated completion of the reaction). Et_2O (5 mL) was added, followed by aq. sat. NH_4Cl (5 mL). The mixture was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 3:1) on silica gel gave mesylate **28** (36 mg, 0.092 mmol, 92% from **25**) as a colorless oil. $[\alpha]_D^{21}=-22.8$ ($c=1.93$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.26$ (s, 2H), 3.98–3.91 (m, 4H), 3.17–3.05 (m, 4H), 2.53–2.42 (m, 1H), 1.97–1.58 (m, 4H), 1.55–1.35 (m, 2H), 1.30 (s, 3H), 1.28–1.20 (m, 2H), 1.17–1.02 (m, 2H), 1.14 (d, $J=7.0$ Hz, 3H), 0.99 ppm (d, $J=7.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=178.6$, 109.7, 84.6, 67.7, 64.66, 64.62, 44.8, 39.7, 38.6, 37.5, 32.5, 31.5, 23.8, 23.6, 22.3, 20.3, 9.5 ppm; FTIR (film): $\tilde{\nu}=2937$, 1776, 1713, 1466, 1359, 1178, 1155, 1052, 992, 966, 843, 817, 528, 515 cm^{-1}; ESI-MS: m/z: 391.2 $[M+H]^+$, 408.2 $[M+NH_4]^+$, 413.2 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{18}H_{30}O_7SNa$: 413.16045 $[M+Na]^+$; found: 413.16018.

Oxidation of alcohol 30 to afford acid 33: $NaIO_4$ (950 mg, 4.44 mmol) and $RuCl_3$ (4.6 mg, 0.022 mmol) were added in turn to a solution of alcohol **30** (400 mg, 1.48 mmol) in $MeCN/CCl_4/H_2O$ (2:2:3, 7 mL) stirred at the ambient temperature. The mixture was stirred at the same temperature for 2 h (TLC analysis indicated completion of the reaction). CH_2Cl_2 (20 mL) was added, followed by H_2O (20 mL). The phases were separated. The aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 5:1) on silica gel gave acid **33** (396 mg, 1.39 mmol, 94% from **30**). M.p 119–121 °C; $[\alpha]_D^{29}=+49.2$ ($c=0.55$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=10.4$ (brs, 1H, COOH), 4.35 (dd, $J=11.5$, 0.9 Hz, 1H), 3.99 (d, $J=11.4$ Hz, 1H), 2.94–2.83 (m, 1H), 2.39 (dt, $J=3.8$, 14.1 Hz, 1H), 2.00–1.90 (m, 1H), 1.89–1.78 (m, 1H), 1.70–1.45 (m, 4H), 1.44–1.33 (m, 1H), 1.31 (d, $J=5.0$ Hz, 3H), 1.29 (s, 3H), 1.27–1.15 (m, 2H), 1.07–0.95 (m, 1H), 0.92 ppm (d, $J=6.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=182.2$, 104.1, 86.2, 60.4, 53.5, 48.5, 40.2, 37.24, 37.21, 34.6, 26.1, 25.4, 25.3, 19.7, 18.1 ppm; FTIR (film): $\tilde{\nu}=3192$, 2934, 2873, 1736, 1705, 1455, 1375, 1207, 1143, 1088, 1047, 942, 893, 832 cm^{-1}; ESI-MS: m/z: 307.1 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{15}H_{24}O_5Na$: 307.15159 $[M+Na]^+$; found: 307.15172; elemental analysis: calcd (%) for $C_{15}H_{24}O_5$: C 63.36, H 8.51; found: C 62.94, H 8.52.

Esterification of acid 33 to afford ester 34: K_2CO_3 (37 mg, 0.27 mmol) and MeI (336 μL, 5.4 mmol) were added to a solution of acid **33** (51 mg, 0.18 mmol) in acetone (3 mL) stirred at ambient temperature. Stirring was continued at the same temperature for 16 h. Aq. sat. NH_4Cl (5 mL) was added. The mixture was extracted with Et_2O (2×15 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 20:1) on silica gel gave acid **34** as a colorless oil (29 mg, 0.097 mmol, 54% from **33**); $[\alpha]_D^{30}=+82.0$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.34$ (dd, $J=11.5$ Hz, 1H), 3.97 (d, $J=11.6$ Hz, 1H), 3.65 (s, 3H), 2.95–2.87 (m, 1H), 2.46–2.36 (m, 1H), 2.00–1.93 (m, 1H), 1.90–1.81 (m, 1H), 1.65–1.56 (m, 3H), 1.55–1.46 (m, 1H), 1.45–1.34 (m, 1H), 1.32 (s, 3H), 1.28 (d, $J=7.0$ Hz, 3H), 1.27–1.20 (m, 1H), 1.19–1.10 (m, 1H), 1.06–0.97 (m, 1H), 0.95 ppm (d, $J=6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=176.2$, 104.0, 86.2, 60.3, 53.5, 51.4, 48.7, 40.0, 37.27, 37.23, 34.6, 26.2, 25.4, 25.3, 19.7, 18.3 ppm; FTIR (film): $\tilde{\nu}=2935$, 2874, 1736, 1455, 1435, 1375, 1197, 1170, 1149, 1087, 1048, 835 cm^{-1}; ESI-MS: m/z: 321.0 $[M+Na]^+$; MALDI-HRMS: m/z: calcd for $C_{16}H_{26}NaO_5$: 321.1672 $[M+Na]^+$; found: 321.1679.

Conversion of 8 into 35: A solution of acid **8** (50 mg, 0.145 mmol) and *p*TsOH (3 mg, 0.015 mmol) in CH_2Cl_2 (5 mL) was stirred at ambient temperature overnight. Once TLC analysis indicated completion of the reaction, water (3 mL) was added. The mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 20:1) on silica gel gave **35** as a yellowish oil (33 mg, 0.105 mmol, 73%); $[\alpha]_D^{28}=+42.57$ ($c=1.00$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.65$ (s, 3H), 2.94 (quint., $J=7.3$ Hz, 1H), 2.48–2.36 (m, 1H), 2.23–2.14 (m, 1H), 2.09–1.90 (m, 2H), 1.84–1.73 (m, 1H), 1.73–1.60 (m, 1H), 1.58 (s, 3H), 1.46–1.23 (m, 2H), 1.30–1.24 (m, 1H), 1.26 (d, $J=7.1$ Hz, 3H), 1.23–0.95 (m, 1H), 0.91 ppm

(d, $J=6.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=176.5$, 165.0, 108.9, 89.1, 51.48, 51.41, 46.9, 41.6, 34.6, 34.4, 33.6, 28.1, 24.8, 24.2, 19.3, 16.6 ppm; FTIR (film): $\tilde{\nu}=2954$, 2925, 2853, 1752, 1738, 1456, 1379, 1293, 1238, 1194, 1149, 1073, 1042, 904 cm^{-1}; ESI-MS: m/z: 313.0 $[M+H]^+$, 334.9 $[M+Na]^+$; elemental analysis: calcd for $C_{16}H_{24}O_6$: C 61.52, H 7.74; found: C 61.54, H 7.97.

Oxidation of 30 with PhI(OTFA)$_2$ to afford 36 and 37: A solution of **30** (50 mg, 0.185 mmol), $PhI(OTFA)_2$ (88 mg, 0.204 mmol), and I_2 (24 mg, 0.093 mmol) in cyclohexane (5 mL) was stirred at ambient temperature for 19 h. An additional portion of $PhI(OTFA)_2$ (88 mg, 0.204 mmol) was introduced. The mixture was stirred at the same temperature for another 16 h, after which time, TLC analysis showed complete disappearance of **30**. Et_2O (5 mL) was added, followed by water (5 mL) and the phases were separated. The aqueous layer was back-extracted with Et_2O (2× 30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration. The filtrate was concentrated on a rotary evaporator to give an oily residue, which was subjected to chromatography (PE/EtOAc, 15:1) on silica gel to afford first **37** (45 mg, 0.123 mmol, 66% from **30**) as a colorless oil and then **36** (16 mg, 0.060 mmol, 32% from **30**) as a white solid. The data for **36** were identical with those reported previously.[8] Compound **37** was less polar than **36**. $[\alpha]_D^{22}=+26.6$ ($c=0.70$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.34$–4.26 (m, 2H), 4.12–3.98 (m, 2H), 2.60–2.47 (m, 1H), 2.40 (dt, $J=3.8$, 14.4 Hz, 1H), 2.02–1.92 (m, 1H), 1.90–1.79 (m, 1H), 1.73–1.63 (m, 2H), 1.63–1.50 (m, 1H), 1.47–1.34 (m, 2H), 1.32 (s, 3H), 1.18–1.10 (m, 1H), 1.08 (d, $J=6.4$ Hz, 3H), 1.05–0.99 (m, 1H), 0.95 ppm (d, $J=6.4$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=157.7$ (q, $J_{CF}=42.5$ Hz, 1C), 114.5 (q, $J_{CF}=285.4$ Hz, 1C), 104.2, 86.7, 71.2, 60.4, 53.7, 49.1, 37.27, 37.24, 34.9, 30.9, 25.5, 25.4, 24.1, 19.7, 18.6 ppm; ^{19}F NMR (282.3 MHz, $CDCl_3$): $\delta=-75.3$ ppm; FTIR (film): $\tilde{\nu}=2927$, 2874, 1785, 1461, 1376, 1353, 1222, 1167, 1049, 1029, 948, 893, 859, 844, 775, 731 cm^{-1}; ESI-MS: m/z: 389.3 $[M+Na]^+$; EI-HRMS: m/z: calcd for $C_{17}H_{25}O_5F_3$: 366.1654 $[M^+]$; found: 366.1655.

Reaction of ketone 9 with Me$_3$SiCH$_2$MgCl to afford 38 and 38′: Me_3SiCH_2MgCl (1 M in Et_2O, 0.48 mL, 0.48 mmol) was added to a solution of ketone **9** (60 mg, 0.192 mmol) in dry toluene (2 mL) stirred at ambient temperature under a N_2 (balloon). The mixture was then heated at reflux for 2 h (TLC analysis indicated completion of the reaction). Et_2O (5 mL) was added, followed by aq. sat. NH_4Cl (5 mL). The mixture was extracted with Et_2O (2×30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration. The filtrate was concentrated on a rotary evaporator to give an oily residue, which was subjected to chromatography (PE/EtOAc, 5:1) on silica gel to deliver first **38** (12 mg, 0.032 mmol, 17% from **9**) and then **38′** (45 mg, 0.152 mmol, 79% from **9**). Compound **38** was a yellowish oil and less polar than acid **38′**. $[\alpha]_D^{24}=-39.7$ ($c=2.53$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.90$–3.70 (m, 4H), 2.89 (quint., $J=7.0$ Hz, 1H), 2.14–2.03 (m, 1H), 1.87–1.69 (m, 2H), 1.61–1.40 (m, 5H), 1.34–1.18 (m, 1H), 1.20 (s, 3H), 1.12–0.86 (m, 4H), 1.01 (d, $J=7.4$ Hz, 3H), 0.85 (d, $J=6.5$ Hz, 3H), 0.00 ppm (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=179.3$, 109.9, 89.7, 64.6, 64.5, 49.3, 44.4, 40.2, 38.3, 32.9, 32.4, 26.5, 24.5, 23.7, 23.1, 20.5, 9.4, 0.24 ppm; FTIR (film): $\tilde{\nu}=2950$, 1765, 1453, 1378, 1251, 1165, 1052, 924, 860, 840 cm^{-1}; ESI-MS: m/z: 391.4 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{20}H_{36}O_4NaSi$: 391.2275 $[M+Na]^+$; found: 319.2280. Compound **38′** was a colorless oil and more polar than **38**. $[\alpha]_D^{28}=-27.2$ ($c=0.73$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.82$ (s, 1H), 4.74 (s, 1H), 3.99–3.89 (m, 4H), 2.76–2.66 (m, 1H), 2.17–2.08 (m, 1H), 1.88–1.47 (m, 7H), 1.45–1.36 (m, 1H), 1.33 (s, 3H), 1.30–1.19 (m, 2H), 1.23 (d, $J=6.7$ Hz, 3H), 0.95 ppm (d, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=182.6$, 150.0, 110.3, 107.1, 64.6, 51.1, 47.4, 41.3, 38.4, 36.2, 32.3, 31.3, 24.1, 23.6, 19.6, 16.2 ppm; FTIR (film): $\tilde{\nu}=3181$, 2932, 2874, 1736, 1705, 1641, 1459, 1376, 1220, 1059, 897, 860 cm^{-1}; ESI-MS: m/z: 297.2 $[M+H]^+$, 319.1 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{17}H_{28}O_4Na$ $[M+Na]^+$: 319.18798; found: 319.18867.

Reduction of acid 38′ to afford alcohol 39: $LiAlH_4$ (110 mg, 2.90 mmol) was added to a solution of acid **38′** (429 mg, 1.45 mmol) in dry THF (20 mL) stirred in an ice/water bath under a N_2 (balloon). The mixture was heated at reflux with stirring for 4.5 h (TLC indicated completion of the reaction) before being diluted with Et_2O (10 mL). Aq. NaOH (1 N) was added slowly until no gas evolved, followed by aq. sat. potassium sodium tartrate (10 mL). The cloudy mixture was stirred at ambient temperature until a clear two-phase solution resulted. The mixture was extracted with Et_2O (3×40 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 3:1) on silica gel gave alcohol **39** (378 mg, 1.34 mmol, 92%) as a colorless oil. $[\alpha]_D^{28}=-8.79$ ($c=0.40$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.74$ (s, 1H), 4.71 (s, 1H), 3.94–3.82 (m, 4H), 3.70 (dd, $J=10.5$, 3.8 Hz, 1H), 3.46 (dd, $J=10.5$, 7.5 Hz, 1H), 1.92–1.63 (m, 7H), 1.55–1.38 (m, 4H), 1.27 (s, 3H), 1.15–1.06 (m, 2H), 0.97 (d, $J=6.8$ Hz, 3H), 0.89 ppm (d, $J=6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=152.1$, 110.3, 105.6, 65.9, 64.6, 64.5, 51.3, 47.8, 38.9, 36.5, 35.8, 33.7, 29.7, 23.9, 23.7, 20.5, 16.5 ppm; FTIR (film): $\tilde{\nu}=3431$, 2926, 2874, 1638, 1454, 1376, 1250, 1221, 1056, 894, 862, 524 cm^{-1}; ESI-MS: m/z: 283.2 $[M+H]^+$, 305.0 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{17}H_{30}O_3Na$: 305.2087 $[M+Na]^+$; found: 305.2085.

Alternatively, alcohol **39** could be obtained from **9** in a one-pot manner: Me_3SiCH_2MgCl (1 M in Et_2O, 1.92 mL, 1.92 mmol) was added to a solution of ketone **9** (180 mg, 0.577 mmol) in dry toluene (4 mL) stirred at ambient temperature under a N_2 (balloon). The mixture was then heated at reflux for 1 h (TLC analysis indicated completion of the reaction). The mixture was cooled to ambient temperature. $LiAlH_4$ (49 mg, 1.28 mmol) was added. The mixture was heated at reflux for 3 h (TLC analysis indicated completion of the reaction) before being cooled to ambient temperature and diluted with Et_2O (15 mL). Aq. NaOH (1 N) was added slowly until no gas evolved, followed by aq. sat. potassium sodium tartrate (10 mL). The cloudy mixture was stirred at ambient temperature until a clear two-phase solution resulted. The mixture was extracted with Et_2O (2×50 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 2:1) on silica gel gave alcohol **39** (92 mg, 0.326 mmol, 57% from **9**) as a colorless oil.

Epoxidation of alkene 39 to afford epoxides 27 and 27a: Na_2CO_3 (124 mg, 1.17 mmol) and *m*CPBA (480 mg, 2.34 mmol) were added to a solution of **39** (300 mg, 1.064 mmol) in dry CH_2Cl_2 (20 mL) stirred at ambient temperature. Stirring was continued at the same temperature for 2 h, at which time TLC analysis indicated completion of the reaction. The reaction mixture was poured into a mixture of aq. sat. Na_2SO_3 (25 mL) and aq. sat. Na_2CO_3 (25 mL) and extracted with Et_2O (3× 60 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 5:1) on silica gel gave **27** (203 mg, 0.681 mmol, 64% from **39**), **27a** (unstable, 81 mg, 0.272 mmol, 26% from **39**), and unreacted **39** (16 mg, 0.057 mmol, 6%). The data for **27** were identical to those reported before.[8] Compound **27a** was more polar than **27**. $[\alpha]_D^{25}=-21.6$ ($c=0.27$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.95$–5.83 (m, 1H), 5.25 (dd, $J=17.0$, 1.2 Hz, 1H), 5.15 (d, $J=9.5$ Hz, 1H), 3.98–3.84 (m, 6H), 3.34 (dd, $J=9.3$, 4.6 Hz, 1H), 3.16 (dd, $J=9.0$, 6.8 Hz, 1H), 2.68 (d, $J=4.0$ Hz, 1H), 2.56 (d, $J=4.2$ Hz, 1H), 1.93–1.85 (m, 1H), 1.80–1.71 (m, 2H), 1.70–1.63 (m, 2H), 1.62–1.32 (m, 5H), 1.29 (s, 3H), 1.22–1.14 (m, 2H), 1.03 (d, $J=6.5$ Hz, 3H), 1.01 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=110.1$, 66.4, 64.60, 64.59, 61.9, 49.1, 47.4, 45.6, 39.0, 36.8, 33.9, 29.7, 26.0, 23.7, 21.7, 20.6, 17.3 ppm; ESI-MS: m/z: 321.2 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{17}H_{30}O_4Na$: 321.20363 $[M+Na]^+$; found: 321.20475.

Conversion of epoxide 27a into alcohol 40 under the perhydrolysis conditions: A mixture of epoxide **27a** (8 mg, 0.027 mmol) and the catalyst Na_2MoO_4-gly (1 mg) in ethereal H_2O_2 (1 mL) was stirred at ambient temperature for 5 h. Et_2O (5 mL) was added, followed by H_2O (5 mL). The mixture was extracted with Et_2O (2×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 3:1) on silica gel gave alcohol **40** (5 mg, 0.017 mmol, 63% from **27a**) as a colorless oil. $[\alpha]_D^{24}=-12.8$ ($c=0.67$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.00$–3.91 (m, 4H), 3.87 (t, $J=8.3$ Hz, 1H), 3.50–3.35 (m, 3H), 2.77–2.60 (m, 1H), 2.24 (brs, 1H; OH), 1.97–1.66 (m, 4H), 1.65–1.49 (m, 2H), 1.46–1.32 (m, 2H), 1.30 (s, 3H), 1.23–1.13 (m, 2H),

1.12–0.96 (m, 1H), 0.94 (d, $J=6.2$ Hz, 3H), 0.90 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=110.5$, 87.3, 72.1, 64.8, 64.6, 64.4, 46.1, 42.2, 39.0, 35.1, 33.7, 23.6, 23.3, 22.5, 20.7, 11.5 ppm; FTIR (film): $\tilde{\nu}=$ 3455, 2927, 2874, 1466, 1377, 1221, 1139, 1057, 949, 856 cm^{-1}; ESI-MS: m/z: 321.0 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{17}H_{30}O_4Na$: 321.20363 $[M+Na]^+$; found: 321.20401.

Acetylation of 27a to afford 42a: A mixture of **27a** (28 mg, 0.094 mmol), DMAP (1 mg, 0.009 mmol), pyridine (30 μL, 0.376 mmol), and Ac_2O (36 μL, 0.376 mmol) in CH_2Cl_2 (2 mL) was stirred at ambient temperature for 13 h. Et_2O (5 mL) was added, followed by H_2O (2 mL). The mixture was extracted with Et_2O (2×15 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 5:1) on silica gel gave **42a** (21 mg, 0.064 mmol, 68%) as a colorless oil. $[\alpha]_D^{25}=-24.9$ ($c=0.90$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=4.07$ (dd, $J=11.1$, 4.0 Hz, 1H), 3.97–3.86 (m, 4H), 3.77 (dd, $J=10.8$, 7.5 Hz, 1H), 2.67 (d, $J=3.8$ Hz, 1H), 2.60 (d, $J=3.7$ Hz, 1H), 2.04 (s, 3H), 1.93–1.85 (m, 1H), 1.82–1.73 (m, 1H), 1.71–1.63 (m, 3H), 1.55–1.44 (m, 2H), 1.42–1.32 (m, 2H), 1.29 (s, 3H), 1.23–1.11 (m, 2H), 1.03 (d, $J=$ 6.8 Hz, 3H), 1.01 ppm (d, $J=7.0$ Hz, 3H); FTIR (film): $\tilde{\nu}=2927$, 2874, 1739, 1463, 1375, 1236, 1038, 856 cm^{-1}; ESI-MS: m/z: 341.4 $[M+H]^+$, 363.4 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{19}H_{32}O_5Na$: 363.2142 $[M+Na]^+$; found: 363.2143.

Allyl protection of 27a to afford 42b: Allyl bromide (44 μL, 0.533 mmol) was added to a solution of **27a** (53 mg, 0.179 mmol) and NaH (60% w/w in mineral oil, 16 mg, 0.533 mmol) in dry DMF/THF (1:1, 4 mL) stirred at ambient temperature under a N_2 (balloon). Stirring was continued at the same temperature for 12 h. Et_2O (3 mL) was added, followed by H_2O (2 mL). The mixture was extracted with Et_2O (3×10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 3:1) on silica gel gave **42b** (27 mg, 0.080 mmol, 45%) as a colorless oil along with recovered **27a** (16 mg, 0.302 mmol, 30%). Compound **42b** was less polar than **27a**. $[\alpha]_D^{25}=-23.0$ ($c=0.95$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=5.95$–5.83 (m, 1H), 5.25 (dd, $J=17.0$, 1.2 Hz, 1H), 5.15 (d, $J=9.5$ Hz, 1H), 3.98–3.84 (m, 6H), 3.34 (dd, $J=9.3$, 4.6 Hz, 1H), 3.16 (dd, $J=9.0$, 6.8 Hz, 1H), 2.68 (d, $J=4.0$ Hz, 1H), 2.56 (d, $J=4.2$ Hz, 1H), 1.93–1.85 (m, 1H), 1.80–1.71 (m, 2H), 1.70–1.63 (m, 2H), 1.62–1.32 (m, 5H), 1.29 (s, 3H), 1.22–1.14 (m, 2H), 1.03 (d, $J=6.5$ Hz, 3H), 1.01 ppm (d, $J=7.0$ Hz, 3H); FTIR (film): $\tilde{\nu}=$ 2927, 2872, 1459, 1376, 1252, 1220, 1141, 1096, 1057, 946, 923, 856 cm^{-1}; ESI-MS: m/z: 339.4 $[M+H]^+$, 361.4 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{20}H_{34}O_4Na$: 361.23493 $[M+Na]^+$; found: 361.23477.

TBS protection of 27a to afford 42c: A solution of **27a** (20 mg, 0.067 mmol), imidazole (7 mg, 0.101 mmol), and TBSCl (12 mg, 0.080 mmol) in dry DMF (1 mL) was stirred at ambient temperature for 13 h. Et_2O (3 mL) was added, followed by H_2O (3 mL). The mixture was extracted with Et_2O (2×10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 30:1) on silica gel gave **42c** (26 mg, 0.062 mmol, 93% from **27a**) as a colorless oil. $[\alpha]_D^{27}=-18.6$ ($c=0.60$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.97$–3.85 (m, 4H), 3.47 (dd, $J=9.7$, 4.4 Hz, 1H), 3.36 (dd, $J=10.0$, 6.2 Hz, 1H), 2.69 (d, $J=4.4$ Hz, 1H), 2.54 (d, $J=4.2$ Hz, 1H), 1.94–1.83 (m, 1H), 1.80–1.69 (m, 1H), 1.57–1.31 (m, 5H), 1.28 (s, 3H), 1.21–1.09 (m, 3H), 1.03 (d, $J=6.7$ Hz, 3H), 0.94 (d, $J=6.7$ Hz, 3H), 0.89–0.82 (m, 11H), 0.00 ppm (s, 6H); FTIR (film): $\tilde{\nu}=2954$, 2928, 2858, 1463, 1377, 1253, 1086, 1060, 837, 775 cm^{-1}; ESI-MS: m/z: 435.4 $[M+Na]^+$; ESI-HRMS: m/z calcd for $C_{23}H_{44}O_4SiNa$: 435.29011 $[M+Na]^+$; found: 435.29158.

Acetylation of 27 to afford 44a: A mixture of **27** (43 mg, 0.144 mmol), DMAP (3.5 mg, 0.03 mmol), pyridine (46 μL, 0.577 mmol), and Ac_2O (55 μL, 0.577 mmol) in CH_2Cl_2 (2 mL) was stirred at ambient temperature for 9 h. Et_2O (5 mL) was added, followed by H_2O (2 mL). The mixture was extracted with Et_2O (3×15 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 5:1) on silica gel gave **44a** (42 mg, 0.124 mmol, 86%) as a colorless oil. $[\alpha]_D^{28}=-29.5$ ($c=0.73$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.16$ (dd, $J=11.2$, 3.8 Hz, 1H), 4.00–3.87 (m, 4H), 3.75 (dd, $J=10.8$, 8.2 Hz, 1H), 2.89 (d, $J=3.8$ Hz, 1H), 2.87 (d, $J=3.8$ Hz, 1H), 2.04 (s, 3H), 1.89–1.31 (m, 9H), 1.29 (s, 3H), 1.26–1.05 (m, 3H), 0.98 (d, $J=$ 6.2 Hz, 3H), 0.96 ppm (d, $J=5.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=171.1$, 109.9, 66.9, 64.6, 62.4, 49.8, 47.6, 45.2, 37.3, 34.0, 33.8, 31.2, 24.7, 23.8, 20.9, 20.4, 20.3, 17.7 ppm; FTIR (film): $\tilde{\nu}=2933$, 2878, 1738, 1455, 1375, 1241, 1047, 853, 829 cm^{-1}; ESI-MS: m/z: 341.2 $[M+H]^+$, 363.2 $[M+Na]^+$; EI-HRMS: m/z: calcd for $C_{19}H_{32}O_5Na$: 363.21420 $[M+Na]^+$; found: 363.21483.

Allyl protection of 27 to afford 44b: A solution of **27** (63 mg, 0.211 mmol) in dry DMF (1 mL) was added to a mixture of NaH (60% w/w in mineral oil, 13 mg, 0.423 mmol) in dry DMF (1 mL) stirred at ambient temperature under a N_2 (balloon). Five minutes later, allyl bromide (36 μL, 0.423 mmol) was added. Stirring was continued at the same temperature for 10 h. Et_2O (5 mL) was added, followed by H_2O (3 mL). The mixture was extracted with Et_2O (3×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 3:1) on silica gel gave **44b** (28 mg, 0.083 mmol, 39%) as a colorless oil, along with recovered **27** (28 mg, 0.094 mmol, 44%). Compound **44b** was less polar than **27**. $[\alpha]_D^{25}=-23.5$ ($c=0.73$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.96$–5.82 (m, 1H), 5.25 (dd, $J=17.3$, 1.8 Hz, 1H), 5.15 (dd, $J=10.6$, 1.5 Hz, 1H), 3.99–3.83 (m, 6H), 3.44 (dd, $J=9.1$, 3.5 Hz, 1H), 3.11 (t, $J=8.5$ Hz, 1H), 2.86 (d, $J=3.9$ Hz, 1H), 2.83 (d, $J=3.8$ Hz, 1H), 1.88–1.32 (m, 9H), 1.27–1.05 (m, 3H), 1.28 (s, 3H), 1.01 (d, $J=6.7$ Hz, 3H), 0.95 ppm (d, $J=6.5$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=135.2$, 116.5, 110.1, 72.8, 71.9, 64.7, 62.6, 49.9, 47.8, 45.4, 37.5, 34.3, 34.0, 32.3, 29.7, 25.0, 23.9, 20.5, 20.4, 18.3 ppm; FTIR (film): $\tilde{\nu}=2954$, 2925, 2872, 1458, 1376, 1254, 1220, 1097, 1058, 922, 772 cm^{-1}; EI-MS: m/z (%): 87 (100), 267 (2), 163 (10), 323 $[M-CH_3]^+$ (2); EI-HRMS: m/z: calcd for $C_{20}H_{34}O_4$: 338.2457 $[M^+]$; found: 338.2454.

TBS protection of 27 to afford 44c: A solution of **27** (58 mg, 0.195 mmol), imidazole (20 mg, 0.292 mmol), and TBSCl (35 mg, 0.234 mmol) in dry DMF (2 mL) was stirred at ambient temperature for 10 h. H_2O (3 mL) was added. The mixture was extracted with Et_2O (3× 10 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 30:1) on silica gel gave **44c** (73 mg, 0.177 mmol, 91%) as a colorless oil. $[\alpha]_D^{27}=-25.5$ ($c=0.50$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.98$–3.86 (m, 4H), 3.56 (dd, $J=9.7$, 2.7 Hz, 1H), 3.31 (dd, $J=9.6$, 6.3 Hz, 1H), 2.84 (d, $J=3.6$ Hz, 1H), 2.79 (d, $J=4.1$ Hz, 1H), 1.86–1.68 (m, 2H), 1.67–1.54 (m, 3H), 1.53–1.30 (m, 4H), 1.27 (s, 3H), 1.26–1.03 (m, 3H), 0.98–0.90 (m, 6H), 0.86 (s, 9H), 0.00 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=110.0$, 65.0, 64.6, 62.4, 50.3, 47.8, 45.1, 37.5, 34.06, 33.99, 33.97, 25.8, 23.8, 20.5, 20.4, 18.2, 17.8, −5.46, −5.48 ppm; FTIR (film): $\tilde{\nu}=2954$, 2929, 2858, 1471, 1463, 1376, 1252, 1222, 1083, 1057, 837, 775, 515, 505 cm^{-1}; ESI-MS: m/z: 435.5 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{23}H_{44}O_4SiNa$: 435.2901 $[M+Na]^+$; found: 435.2904.

Perhydrolysis of epoxide 44b to afford 45b: Na_2MoO_4-gly (2 mg) was added to a solution of epoxide **44b** (28 mg, 0.083 mmol) in ethereal H_2O_2 (1 mL) stirred at ambient temperature. The mixture was stirred at the same temperature for 24 h, at which time TLC analysis showed complete disappearance of **44b**. Et_2O (5 mL) was added, followed by H_2O (3 mL). The mixture was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and column chromatography (PE/EtOAc, 2:1) on silica gel gave **45b** as a colorless oil (10 mg, 0.027 mmol, 32%) along with recovered **44b** (13 mg, 0.038 mmol, 46%). Compound **45b** was more polar than **44b**. $[\alpha]_D^{25}=-15.9$ ($c=0.47$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=9.38$ (br s, 1H; OOH), 5.97–5.81 (m, 1H), 5.26 (dd, $J=17.2$, 1.4 Hz, 1H), 5.20 (dd, $J=10.2$, 0.6 Hz, 1H), 4.12–3.92 (m, 6H), 3.86–3.72 (m, 1H), 3.50 (d, $J=12.9$ Hz, 1H), 3.37 (dd, $J=20.0$, 9.7 Hz, 1H), 3.30 (dd, $J=9.1$, 4.7 Hz, 1H), 2.79–2.64 (m, 1H), 2.12–1.88 (m, 3H), 1.78–1.56 (m, 5H), 1.52–1.36 (m, 2H), 1.34 (s, 3H), 1.23–0.98 (m, 2H), 0.95 (d, $J=7.0$ Hz, 3H), 0.91 ppm (d, $J=$ 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=133.8$, 117.9, 111.0, 87.5,

74.1, 72.2, 64.48, 64.46, 60.5, 51.9, 45.6, 39.8, 35.9, 35.8, 29.9, 23.56, 23.55, 21.2, 21.1, 19.3 ppm; FTIR (film): $\tilde{\nu}$ = 3357, 2925, 2872, 1463, 1375, 1266, 1079, 738 cm^{-1}; ESI-MS: *m/z*: 395.1 $[M+Na]^+$; ESI-HRMS: *m/z*: calcd for $C_{20}H_{36}O_6Na$: 395.2404 $[M+Na]^+$; found: 395.2410.

Perhydrolysis of epoxide 44c and subsequent ring closure to afford 46: Na_2MoO_4-gly (3 mg) was added to a solution of epoxide **44c** (43 mg, 0.104 mmol) in ethereal H_2O_2 (1 mL) stirred at ambient temperature. The mixture was stirred at the same temperature for 9 h, at which time TLC analysis showed complete disappearance of **44c**. Et_2O (5 mL) was added to the reaction mixture, followed by H_2O (3 mL). The mixture was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration. The filtrate was concentrated on a rotary evaporator to afford the unstable intermediate **45c**, which gave the following data after purification (from a parallel run). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.43 (s, 1H), 4.16–3.97 (m, 5H), 3.82 (dd, *J* = 12.9, 5.6 Hz, 1H), 3.64–3.44 (m, 3H), 2.71–2.57 (m, 1H), 2.10–1.86 (m, 3H), 1.78–1.56 (m, 6H), 1.45–1.35 (m, 2H), 1.33 (s, 3H), 0.94–0.86 (m, 15H), 0.09 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.0, 87.7, 67.5, 64.5, 60.5, 51.8, 45.4, 39.9, 36.0, 35.9, 32.1, 25.9, 23.9, 23.6, 21.2, 21.1, 19.1, 18.4, −5.5, −5.6 ppm; FTIR (film): $\tilde{\nu}$ = 3347, 2954, 2926, 2855, 1465, 1376, 1255, 1055, 837, 777 cm^{-1}; ESI-MS: *m/z*: 469.5 $[M+Na]^+$; ESI-HRMS: *m/z*: calcd for $C_{23}H_{46}O_6SiNa$: 469.2955 $[M+Na]^+$; found: 469.2969.

The above-mentioned residue (crude **45c**, 55 mg) was dissolved in CH_2Cl_2 (1.5 mL). *p*TsOH (monohydrate, 2 mg) was added to this solution. The mixture was stirred at ambient temperature for 16 h. Et_2O (5 mL) was added, followed by H_2O (3 mL). The mixture was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Removal of the solvent by rotary evaporation and chromatography (PE/EtOAc, 8:1) on silica gel gave trioxane **46** as yellowish prisms (8 mg, 0.021 mmol, 20%) along with the desilylated alcohol **30** (11 mg, 0.041 mmol, 39%). Compound **46** was less polar than **30**. M.p. 46–48 °C; $[\alpha]_D^{27}$ = +68.8 (*c* = 2.07 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.33 (dd, *J* = 11.3, 1.4 Hz, 1H), 3.93 (d, *J* = 11.3 Hz, 1H), 3.45 (dd, *J* = 10.1, 5.6 Hz, 1H), 3.31 (dd, *J* = 10.0, 7.1 Hz, 1H), 2.38 (dt, *J* = 4.1, 13.9 Hz, 1H), 2.23–2.11 (m, 1H), 1.96–1.88 (m, 1H), 1.85–1.75 (m, 1H), 1.70–1.47 (m, 3H), 1.40–1.29 (m, 1H), 1.27 (s, 3H), 1.26–1.04 (m, 4H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.85 (s, 9H), 0.001 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 103.9, 86.9, 66.2, 61.1, 53.8, 49.3, 37.3 (2C), 35.2, 33.8, 25.9 (3C), 25.5, 25.4, 24.0, 19.8, 19.1, 18.2, −5.44, −5.49 ppm; FTIR (film): $\tilde{\nu}$ = 2954, 2928, 2858, 1471, 1462, 1389, 1373, 1361, 1255, 1206, 1146, 1087, 1048, 1006, 939, 893, 837, 799, 775, 669 cm^{-1}; EI-MS: *m/z* (%): 75 (100), 73 (78), 84 (75), 327 $[M-C_4H_9]^+$ (12), 297 $[M-C_4H_9-2Me]^+$ (7.94); EI-HRMS: *m/z*: calcd for $C_{17}H_{31}O_4Si$: 327.1992 $[M-C_4H_9]^+$; found: 327.1995.

Coupling of acid 33 with *t*BuOOH to afford ester 47: A solution of *t*BuOOH (2.5 M in CH_2Cl_2, 0.7 mL, 1.75 mmol) was added to a solution of acid **33** (100 mg, 0.352 mmol), DMAP (8.5 mg, 0.070 mmol), and EDCI (135 mg, 0.704 mmol) in dry CH_2Cl_2 (6 mL) stirred at ambient temperature. The mixture was then stirred at the same temperature for 10 h, at which time TLC analysis showed completion of the reaction. Et_2O (5 mL) was added, followed by H_2O (2 mL). The mixture was then extracted with Et_2O (2×40 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was subjected to chromatography (PE/EtOAc, 30:1) on silica gel to give ester **47** (87 mg, 0.244 mmol, 69% from **33**) as a white solid. M.p. 74–75 °C; $[\alpha]_D^{29}$ = +47.06 (*c* = 0.80 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.24 (d, *J* = 11.5 Hz, 1H), 3.97 (d, *J* = 11.4 Hz, 1H), 2.86 (quint., *J* = 7.0 Hz, 1H), 2.37 (dt, *J* = 14.1, 3.8 Hz, 1H), 1.98–1.88 (m, 1H), 1.87–1.77 (m, 1H), 1.72–1.46 (m, 4H), 1.33 (d, *J* = 5.6 Hz, 3H), 1.30–1.15 (m, 15H), 1.03–0.93 (m, 1H), 0.91 ppm (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 104.1, 86.0, 83.3, 60.1, 53.4, 48.5, 38.1, 37.2, 37.1, 34.5, 26.2, 26.1, 25.4, 25.3, 19.7, 18.3 ppm; FTIR (film): $\tilde{\nu}$ = 2979, 2937, 2875, 1774, 1455, 1367, 1281, 1207, 1195, 1046, 943, 913, 894, 858, 842, 830, 800, 734, 649, 599, 563, 536, 521 cm^{-1}; ESI-MS: *m/z*: 374.3 $[M+NH_4]^+$, 379.2 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{19}H_{32}O_6$: C 64.02, H 9.05; found: C 64.26, H 9.32.

Conversion of acid 33 into phenyl ester 48: A solution of acid **33** (100 mg, 0.352 mmol), DMAP (8.6 mg, 0.0704 mmol), and EDCI (135 mg, 0.704 mmol) in dry CH_2Cl_2 (3 mL) was stirred at ambient temperature for 30 min before phenol (66 mg, 0.704 mmol) was added. The mixture was then stirred at the same temperature for 17 h, at which time TLC analysis showed completion of the reaction. EtOAc (3 mL) was added, followed by H_2O (2 mL). The mixture was then extracted with Et_2O (2×30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was subjected to chromatography (PE/EtOAc, 30:1) on silica gel to give ester **48** as a white solid (126 mg, 0.350 mmol, 99%). The product was 99.11% pure (t_r (major) = 13.67 min) as determined by HPLC analysis on a Kromasil C18 column (150×4.5 mm) eluted with MeOH/H_2O (80:20, containing 0.1% TFA) at a flow rate of 1.0 mL min^{-1} with a UV detector set to 214 nm; M.p. 63–65 °C; $[\alpha]_D^{28}$ = +54.02 (*c* = 2.55 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 2H), 7.25–7.18 (m, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 4.47 (dd, *J* = 11.4, 1.2 Hz, 1H), 4.07 (d, *J* = 11.4 Hz, 1H), 3.20–3.10 (m, 1H), 2.44 (dt, *J* = 14.0, 3.8 Hz, 1H), 2.04–1.94 (m, 1H), 1.93–1.73 (m, 2H), 1.73–1.49 (m, 3H), 1.44 (d, *J* = 7.3 Hz, 3H), 1.40–1.22 (m, 6H), 1.07 (dt, *J* = 12.6, 3.2 Hz, 1H), 0.96 ppm (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.2, 150.5, 129.3 (2C), 125.7, 121.4 (2C), 104.1, 86.3, 60.4, 53.6, 48.9, 40.3, 37.3, 37.2, 34.7, 26.3, 25.4, 25.3, 19.7, 18.3 ppm; FTIR (film): $\tilde{\nu}$ = 2929, 2873, 1756, 1494, 1455, 1193, 1162, 1144, 1120, 1087, 689 cm^{-1}; ESI-MS: *m/z*: 361.1 $[M+H]^+$, 378.3 $[M+NH_4]^+$, 383.1 $[M+Na]^+$; ESI-HRMS: *m/z*: calcd for $C_{21}H_{28}Na_1O_5$: 383.18128 $[M+Na]^+$; found: 383.18214.

General procedure for the preparation of amides 49–58 from acid 33: A solution of acid **33** (50 mg, 0.176 mmol), DMAP (4 mg, 0.035 mmol), and EDCI (67 mg, 0.352 mmol) in dry CH_2Cl_2 (2 mL) was stirred at ambient temperature for 1 h before the appropriate amine (0.352 mmol) was added. The mixture was then stirred at the same temperature for 24 h. EtOAc (3 mL) was added, followed by H_2O (2 mL). The mixture was then extracted with Et_2O (2×30 mL). The combined organic layers were washed in turn with aq. HCl (0.5 N), water, and brine before being dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was subjected to chromatography on silica gel to give amides **49**–**58**.

Compound 49: A white solid; m.p. 143–144 °C; $[\alpha]_D^{28}$ = +75.32 (*c* = 0.80 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.15 (dd, *J* = 11.5, 1.5 Hz, 1H), 4.02 (d, *J* = 11.4 Hz, 1H), 3.78–3.64 (m, 6H), 3.63–3.49 (m, 2H), 3.16 (quint, *J* = 6.7 Hz, 1H), 2.42 (dt, *J* = 14.4, 3.9 Hz, 1H), 2.02–1.49 (m, 6H), 1.47–1.20 (m, 3H), 1.31 (s, 3H), 1.27 (d, *J* = 7.0 Hz, 3H), 1.08–0.98 (m, 1H), 0.95 ppm (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.0, 104.1, 86.2, 66.9, 66.6, 60.2, 53.5, 48.9, 46.3, 41.9, 37.5, 37.1, 35.0, 34.3, 26.2, 25.5, 25.3, 19.8, 17.9 ppm; FTIR (film): $\tilde{\nu}$ = 2923, 2857, 1641, 1458, 1432, 1227, 1185, 1116, 1064, 1046, 1032 cm^{-1}; ESI-MS: *m/z*: 354.3 $[M+H]^+$, 376.2 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{19}H_{31}O_5$: C 64.56, H 8.84, N 3.96; found: C 64.08, H 8.50, N 3.83.

Compound 50: A colorless oil; 97.23% pure (t_r (major) = 20.64 min) as determined by HPLC analysis on a Kromasil C18 column (150×4.5 mm) eluted with MeOH/H_2O (10:90) at a flow rate of 1.0 mL min^{-1} with a UV detector set to 220 nm; $[\alpha]_D^{28}$ = +62.73 (*c* = 0.13 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (d, *J* = 11.2 Hz, 1H), 4.01 (d, *J* = 11.3 Hz, 1H), 3.52–3.25 (m, 4H), 2.99 (quint, *J* = 6.7 Hz, 1H), 2.41 (dt, *J* = 14.0, 3.7 Hz, 1H), 1.99–1.91 (m, 1H), 1.91–1.80 (m, 1H), 1.76–1.65 (m, 2H), 1.63–1.50 (m, 2H), 1.45–1.23 (m, 9H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.09 (t, *J* = 7.1 Hz, 3H), 1.05–0.95 (m, 1H), 0.93 ppm (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.5, 104.0, 86.3, 60.3, 53.6, 48.7, 42.0, 40.5, 37.5, 37.2, 35.6, 35.0, 26.6, 25.5, 25.3, 19.8, 18.1, 14.6, 12.7 ppm; FTIR (film): $\tilde{\nu}$ = 2953, 2925, 2871, 1642, 1458, 1376, 1144, 1089 cm^{-1}; ESI-MS: *m/z*: 340.3 $[M+H]^+$, 362.2 $[M+Na]^+$; MALDI-HRMS: *m/z* calcd for $C_{19}H_{34}NO_4$: 340.24824 $[M+H]^+$; found: 340.2497.

Compound 51: A colorless oil; $[\alpha]_D^{28}$ = +69.49 (*c* = 0.70 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.17 (dd, *J* = 11.3, 1.6 Hz, 1H), 4.02 (d, *J* = 11.2 Hz, 1H), 3.71–3.55 (m, 2H), 3.52–3.40 (m, 2H), 3.12 (quint, *J* = 7.1 Hz, 1H), 2.43 (dt, *J* = 4.2, 14.2 Hz, 1H), 2.00–1.92 (m, 1H), 1.91–1.83 (m, 1H), 1.76–1.69 (m, 2H), 1.69–1.47 (m, 4H), 1.44–1.32 (m, 2H), 1.31

(s, 3H), 1.30–1.17 (m, 8H), 1.06–0.97 (m, 1H), 0.94 ppm (d, J=6.3 Hz, 3H); FTIR (film): $\tilde{\nu}$=2927, 2855, 1639, 1442, 1187, 1143, 1010 cm^{-1}; ESI-MS: m/z: 352.3 $[M+H]^+$, 374.2 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{20}H_{33}NO_4$: C 68.34, H 9.46, N 3.99; found: C 68.50, H 9.41, N 3.54.

Compound 52: Amorphous; m.p. >185 °C (decomposed); 99.81% pure (t_r (major)=15.51 min) as determined by HPLC analysis on a Diamonsil C18 column (250×4.5 mm) eluted with MeOH (containing 0.1% aq. TFA) at a flow rate of 1.0 mL min^{-1} and with detection by an evaporative light-scattering detector (ELSD); $[\alpha]_D^{28}$=+54.72 (c=0.73 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.68 (br s, 1H; NH), 4.20 (d, J=11.7 Hz, 1H), 3.98 (d, J=11.1 Hz, 1H), 2.72–2.61 (m, 1H), 2.48–2.32 (m, 2H), 2.00–1.78 (m, 2H), 1.68–1.47 (m, 4H), 1.40–1.32 (m, 1H), 1.32–1.11 (m, 8H), 1.05–0.89 (m, 1H), 0.92 (d, J=6.2 Hz, 3H), 0.78–0.70 (m, 2H), 0.49–0.41 ppm (m, 2H); FTIR (film): $\tilde{\nu}$=3267, 2950, 2930, 1638, 1542, 1375, 1189 cm^{-1}; ESI-MS: m/z: 324.2 $[M+H]^+$, 346.2 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{18}H_{29}NNaO_4$: 346.19888 $[M+Na]^+$; found: 346.19906.

Compound 53: A colorless oil; 99.66% pure (t_r (major)=14.29 min) as determined by HPLC analysis on a Diamonsil C18 column (250× 4.5 mm) eluted with MeOH (containing 0.1% aq. TFA) at a flow rate of 1.0 mL min^{-1} and with detection by an ELSD; $[\alpha]_D^{28}$=+79.54 (c=0.26 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=5.96 (br s, 1H; NH), 4.19 (dd, J=11.6, 1.8 Hz, 1H), 3.95 (d, J=11.3, 1H), 3.65 (t, J=5.0 Hz, 1H), 3.41–3.27 (m, 2H), 2.54 (br s, 1H; OH), 2.49 (quint., J=7.0 Hz, 1H), 2.36 (dt, J=14.4, 3.8 Hz, 1H), 1.94–1.86 (m, 1H), 1.84–1.76 (m, 1H), 1.69–1.61 (m, 1H), 1.59–1.45 (m, 4H), 1.39–1.30 (m, 1H), 1.28 (d, J=7.0 Hz, 3H), 1.25 (s, 3H), 1.24–1.10 (m, 2H), 0.95 (dt, J=3.7, 13.1 Hz, 1H), 0.88 ppm (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=177.3, 104.2, 86.3, 62.6, 60.2, 53.6, 48.4, 42.5, 42.3, 37.4, 37.2, 34.8, 26.5, 25.6, 25.4, 19.8, 18.5 ppm; FTIR (film): $\tilde{\nu}$=3505, 2925, 2873, 1648, 1545, 1455, 1375, 1207, 1189, 1064, 1033, 829 cm^{-1}; ESI-MS: m/z: 328.2 $[M+H]^+$, 350.2 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{17}H_{29}NO_5$: C 62.36, H 8.93, N 4.28; found C 62.80, H 9.40, N 4.48.

Compound 54: A colorless oil; 98.64% pure (t_r (major)=21.30 min) as determined by HPLC analysis on a Kromasil C18 column (150×4.5 mm) eluted with MeOH/H_2O (10:90 to 100:0) at a flow rate of 1.0 mL min^{-1} with a UV detector set to 243 nm; $[\alpha]_D^{28}$=+64.30 (c=1.10 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.51 (d, J=8.2 Hz, 2H), 7.47 (br s, 1H), 7.30 (t, J=7.6 Hz, 2H), 7.09 (t, J=7.4 Hz, 1H), 4.26 (d, J=10.9 Hz, 1H), 4.03 (d, J=11.4 Hz, 1H), 2.66 (quint., J=7.0 Hz, 1H), 2.43 (dt, J=3.8, 14.0 Hz, 1H), 2.01–1.75 (m, 4H), 1.70–1.50 (m, 3H), 1.43 (d, J=7.1 Hz, 3H), 1.36–1.27 (m, 2H), 1.31 (s, 3H), 1.07–0.96 (m, 1H), 0.94 ppm (d, J= 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=174.4, 137.8, 128.9, 124.2, 119.9, 104.2, 86.2, 60.2, 53.5, 48.4, 43.7, 37.4, 37.2, 34.7, 26.6, 25.5, 25.3, 19.8, 18.4 ppm; FTIR (film): $\tilde{\nu}$=3301, 2927, 2873, 1659, 1598, 1543, 1500, 1441, 1375, 1178, 943, 755, 692 cm^{-1}; ESI-MS: m/z: 360.3 $[M+H]^+$, 382.3 $[M+Na]^+$; EI-HRMS: m/z: calcd for $C_{21}H_{30}NO_4$: 360.21693 $[M+H]^+$; found: 360.21817.

Compound 55: A pale-yellow solid; 97.68% pure (t_r (major)=21.08 min) as determined by HPLC analysis on a Kromasil C18 column (150× 4.5 mm) eluted with MeOH/H_2O (10:90 to 100:0) at a flow rate of 1.0 mL min^{-1} with a UV detector set to 291 nm; m.p. 171–173 °C; $[\alpha]_D^{29}$= +72.83 (c=0.65 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.92–7.83 (m, 3H), 7.76–7.66 (m, 2H), 7.57–7.42 (m, 3H), 4.40 (d, J=11.3 Hz, 1H), 4.07 (d, J=11.6 Hz, 1H), 2.93 (quint, J=7.2 Hz, 1H), 2.46 (dt, J=14.3, 3.5 Hz, 1H), 2.04–1.83 (m, 3H), 1.74–1.57 (m, 2H), 1.54 (d, J=7.1 Hz, 3H), 1.47–1.24 (m, 7H), 1.08–0.98 (m, 1H), 0.95 ppm (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=175.1, 134.0, 132.0, 128.5, 127.5, 126.1, 125.86, 125.83, 125.4, 121.5, 120.8, 104.1, 86.2, 60.2, 53.4, 48.4, 37.3, 37.2, 34.7, 26.4, 25.5, 25.3, 19.7, 18.5 ppm; FTIR (film): $\tilde{\nu}$=3245, 2929, 2875, 1655, 1536, 1504, 1376, 1345, 1280, 1252, 1206, 1184, 1171, 1142, 1090, 1046, 944, 911, 830, 798, 774, 734 cm^{-1}; ESI-MS: m/z: 410.3 $[M+H]^+$, 432.2 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{25}H_{31}NNaO_4$: 432.21453 $[M+Na]^+$; found: 432.21408.

Compound 56: A yellow/brown solid; 96.88% pure (t_r (major)= 5.81 min) as determined by HPLC analysis on a Kromasil C18 column (150×4.5 mm) eluted with MeOH/H_2O (80:20, containing 0.1% TFA) at a flow rate of 1.0 mL min^{-1} with a UV detector set to 214 nm; m.p. >180 °C (decomp.). $[\alpha]_D^{28}$=+42.21 (c=1.70 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.33 (d, J=8.8 Hz, 2H), 7.30 (br s, 1H), 6.77 (d, J=8.8 Hz, 2H), 4.20 (d, J=11.3 Hz, 1H), 3.96 (d, J=11.3 Hz, 1H), 3.71 (s, 3H), 2.57 (quint., J=7.1 Hz, 1H), 2.36 (dt, J=14.0, 3.7 Hz, 1H), 1.94–1.86 (m, 1H), 1.85–1.76 (m, 1H), 1.76–1.68 (m, 1H), 1.63–1.45 (m, 3H), 1.36 (d, J=7.0 Hz, 3H), 1.28–1.13 (m, 6H), 0.97–0.90 (m, 1H), 0.87 ppm (d, J=6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.2, 156.4, 130.8, 121.8 (2C), 114.0 (2C), 104.2, 86.2, 60.2, 55.4, 53.5, 48.5, 43.4, 37.4, 37.2, 34.8, 26.6, 25.5, 25.3, 19.8, 18.4 ppm; FTIR (film): $\tilde{\nu}$=3504, 2949, 2833, 1655, 1451, 1413, 1116, 1033, 1016 cm^{-1}; ESI-MS: m/z: 390.2 $[M+H]^+$, 412.2 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{22}H_{31}NaO_5$: 412.20944 $[M+Na]^+$; found: 412.20898.

Compound 57: A white powder; m.p. 155 °C (decomp.); $[\alpha]_D^{28}$=+83.70 (c=0.27, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=5.47 (d, J=7.3 Hz, 1H), 4.26 (d, J=11.4 Hz, 1H), 4.22–4.11 (m, 1H), 4.01 (d, J=11.1 Hz, 1H), 2.51–2.36 (m, 2H), 2.04–1.83 (m, 4H), 1.77–1.49 (m, 8H), 1.45–0.99 (m, 12H), 0.95 ppm (d, J=6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 175.4, 104.1, 86.3, 60.2, 53.5, 50.9, 48.4, 42.6, 37.4, 37.2, 34.8, 33.00, 32.99, 26.4, 25.6, 25.4, 23.7, 23.6, 19.8, 18.4 ppm; FTIR (film): $\tilde{\nu}$=3292, 2954, 2925, 2870, 1638, 1552, 1454, 1374, 1208, 1190, 1141, 1090, 1066, 1046, 940, 893, 830 cm^{-1}; ESI-MS: m/z: 352.2 $[M+H]^+$, 374.2 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{20}H_{33}N_1Na_1O_4$: 374.23018 $[M+Na]^+$; found: 374.23046; elemental analysis: calcd (%) for $C_{20}H_{33}NO_4$: C 68.34, H 9.46, N 3.99; found: C 68.75, H 9.76, N 4.50.

Compound 58: A white solid; 96.79% pure (t_r (major)=22.00 min) as determined by HPLC analysis on a Kromasil C18 column (150×4.5 mm) eluted with MeOH/H_2O (10:90 to 100:0) at a flow rate of 1.0 mL min^{-1} with a UV detector set to 243 nm; m.p. 180–182 °C; $[\alpha]_D^{26}$=+46.37 (c= 1.00 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.72–7.64 (m, 3H), 7.56 (d, J=8.9 Hz, 2H), 4.24 (dd, J=11.3, 1.6 Hz, 1H), 4.04 (d, J=11.3 Hz, 1H), 2.74 (quint., J=7.0 Hz, 1H), 2.44 (dt, J=14.1, 3.8 Hz, 1H), 2.02–1.95 (m, 1H), 1.93–1.76 (m, 3H), 1.63–1.54 (m, 3H), 1.44 (d, J=7.1 Hz, 3H), 1.42–1.33 (m, 1H), 1.32 (s, 3H), 1.31–1.25 (m, 1H), 1.02 (dt, J= 12.8, 3.7 Hz, 1H), 0.95 ppm (d, J=6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=174.7, 140.9, 126.6, 126.2 (q, J_{C-F}=3.7 Hz), 125.9, 125.6, 124.0 (q, J_{C-F}=271 Hz), 119.5, 104.3, 86.2, 60.2, 53.6, 48.8, 43.4, 37.4, 37.2, 34.8, 26.3, 25.5, 25.3, 19.8, 18.5 ppm; ^{19}F NMR (282 MHz, $CDCl_3$): δ= −62.5 ppm (s, 3F); FTIR (film): $\tilde{\nu}$=3301, 2932, 2876, 1666, 1605, 1535, 1410, 1325, 1253, 1166, 1123, 1091, 1068, 1017, 943, 844, 829, 739, 593, 512 cm^{-1}; ESI-MS: m/z: 428.2 $[M+H]^+$, 450.3 $[M+Na]^+$; ESI-HRMS: m/z: calcd for $C_{22}H_{28}F_3NNaO_4$: 450.18386 $[M+Na]^+$; found: 450.18465.

Coupling of acid 33 with alcohol 30 to afford ester 59: A solution of acid **33** (100 mg, 0.352 mmol), DMAP (8.6 mg, 0.0704 mmol), and EDCI (135 mg, 0.704 mmol) in dry CH_2Cl_2 (3 mL) was stirred at ambient temperature for 30 min before alcohol **30** (190 mg, 0.704 mmol) was added. The mixture was then stirred at the same temperature for 17 h, at which time TLC analysis indicated completion of the reaction. EtOAc (3 mL) was added, followed by H_2O (2 mL). The mixture was then extracted with Et_2O (2×30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was subjected to chromatography (PE/EtOAc, 20:1) on silica gel to give ester **59** as a white solid (172 mg, 0.329 mmol, 94% from **33**). M.p. 110–111 °C; $[\alpha]_D^{28}$=+88.72 (c=2.00 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ=4.31 (dd, J=6.2, 1.5 Hz, 1H), 4.27 (dd, J=5.8, 1.4 Hz, 1H), 4.02–3.92 (m, 3H), 3.76–3.66 (m, 1H), 2.90–2.79 (m, 1H), 2.45–2.29 (m, 3H), 1.99–1.88 (m, 2H), 1.88–1.76 (m, 2H), 1.71–1.45 (m, 7H), 1.44–1.32 (m, 2H), 1.32–1.06 (m, 14H), 1.04 (d, J=6.7 Hz, 3H), 1.05–0.94 (m, 2H), 0.92 ppm (d, J=6.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=175.9, 104.09, 104.06, 86.8, 86.1, 67.6, 60.5, 60.3, 53.6, 53.4, 49.1, 48.5, 40.7, 37.2, 37.1, 34.9, 34.6, 30.6, 26.4, 25.4, 25.39, 25.34, 23.9, 19.78, 19.75, 19.2, 18.1 ppm; FTIR (film): $\tilde{\nu}$=2933, 2873, 1731, 1455, 1374, 1207, 1196, 1170, 1146, 1088, 1048, 830 cm^{-1}; ESI-MS: m/z: 537.4 $[M+H]^+$, 554.4 $[M+NH_4]^+$, 559.4 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{32}H_{50}O_{10}\cdot H_2O$: C 64.96, H 9.09; found: C 65.07, H 8.65.

Coupling of acid 33 with ethylene glycol to afford esters 60 and 61: A solution of acid **33** (100 mg, 0.352 mmol), DMAP (8.6 mg, 0.0704 mmol), and EDCI (135 mg, 0.704 mmol) in dry CH_2Cl_2 (3 mL) was stirred at am-

bient temperature for 30 min before ethylene glycol (10 μL, 0.179 mmol) was added. The mixture was then stirred at the same temperature for 11 h, at which time TLC analysis indicated completion of the reaction. Et_2O (3 mL) was added, followed by H_2O (2 mL). The mixture was then extracted with Et_2O (2×30 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was subjected to chromatography (PE/EtOAc, 1:1) on silica gel to give ester **61** (30 mg, 0.0507 mmol, 29% from **33**) and **60** (46 mg, 0.140 mmol, 40% from **33**). Compound **61** was less polar than **60**. $[\alpha]_D^{28} = +78.94$ ($c = 1.95$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.32$ (dd, $J = 11.5$, 1.1 Hz, 2H), 4.29–4.20 (m, 4H), 3.96 (d, $J = 11.5$ Hz, 2H), 2.93–2.82 (m, 2H), 2.40 (dt, $J = 14.0$, 3.8 Hz, 2H), 2.00–1.90 (m, 2H), 1.90–1.78 (m, 2H), 1.66–1.32 (m, 10H), 1.32–1.26 (m, 13H), 1.26–0.96 (m, 5H), 0.93 ppm (d, $J = 7.0$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 175.51$, 104.1, 86.2, 61.9, 60.3, 53.5, 48.5, 40.4, 37.28, 37.24, 34.6, 26.3, 25.4, 25.3, 19.7, 18.1 ppm; FTIR (film): $\tilde{\nu} =$ 2930, 2874, 1733, 1455, 1375, 1196, 1170, 1147, 1088, 1060, 1048 cm^{-1}; ESI-MS: m/z: 612.5 $[M+NH_4]^+$, 717.5 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{32}H_{50}O_{10}\cdot 0.5\,H_2O$: C 63.66, H 8.51; found: C 63.66, H 8.60. Compound **60** was more polar than **61**. $[\alpha]_D^{28} = +57.97$ ($c = 2.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.36$ (dd, $J = 11.6$, 1.5 Hz, 1H), 4.27–4.15 (m, 2H), 4.00 (d, $J = 11.5$ Hz, 1H), 3.88–3.80 (m, 2H), 2.98–2.89 (m, 1H), 2.42 (dt, $J = 3.8$, 14.3 Hz, 1H), 2.20–2.14 (m, 1H), 2.01–1.93 (m, 1H), 1.91–1.82 (m, 1H), 1.68–1.53 (m, 4H), 1.48–1.35 (m, 1H), 1.35–1.16 (m, 8H), 1.07–0.98 (m, 1H), 0.95 ppm (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 176.1$, 104.1, 86.4, 65.8, 60.9, 60.3, 53.5, 48.6, 40.1, 37.2, 37.1, 34.6, 26.2, 25.4, 25.3, 19.7, 17.9 ppm; FTIR (film): $\tilde{\nu} = 3452$, 2934, 2875, 1732, 1455, 1376, 1172, 1149, 1087, 1048, 829 cm^{-1}; ESI-MS: m/z: 329.2 $[M+H]^+$, 351.2 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{17}H_{28}O_6\cdot 0.5\,H_2O$: C 60.51, H 8.66; found: C 60.38, H 8.65.

Coupling of acid 33 with propane-1,3-diol to afford esters 62 and 63: A solution of acid **33** (200 mg, 0.704 mmol), DMAP (17 mg, 0.141 mmol), and EDCI (270 mg, 1.41 mmol) in dry CH_2Cl_2 (6 mL) was stirred at ambient temperature for 30 min, before propane-1,3-diol (23 μL, 0.317 mmol) was added. The mixture was then stirred at the same temperature for 11 h, at which time TLC analysis indicated completion of the reaction. Et_2O (5 mL) was added, followed by H_2O (2 mL). The mixture was then extracted with Et_2O (2×40 mL). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation and the residue was subjected to chromatography (PE/EtOAc, 1:1) on silica gel to give **63** (a white solid, 41 mg, 0.067 mmol, 19% from **33**) and **62** (a colorless oil, 73 mg, 0.213 mmol, 30% from **33**). Compound **63** was the less polar component. M.p. 118–120 °C; $[\alpha]_D^{29} = +78.28$ ($c = 1.45$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.29$ (d, $J = 11.5$ Hz, 2H), 4.10 (t, $J = 6.5$ Hz, 4H), 3.95 (d, $J =$ 11.4 Hz, 2H), 2.84 (quint., $J = 6.5$ Hz, 2H), 2.38 (dt, $J = 13.8$, 3.5 Hz, 2H), 1.98–1.88 (m, 4H), 1.88–1.76 (m, 2H), 1.64–1.44 (m, 8H), 1.42–1.31 (m, 2H), 1.30–1.24 (m, 13H), 1.20–1.10 (m, 3H), 1.04–0.94 (m, 2H), 0.91 ppm (d, $J = 6.1$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 175.7$, 104.1, 86.2, 60.7, 60.3, 53.4, 48.5, 40.5, 37.3, 37.2, 34.6, 27.8, 26.4, 25.4, 25.3, 19.7, 18.1 ppm; FTIR (film): $\tilde{\nu} = 2934$, 2874, 1732, 1456, 1374, 1196, 1169, 1146, 1087, 1047, 988, 941, 829, 800 cm^{-1}; ESI-MS: m/z: 626.6 $[M+NH_4]^+$, 631.6 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{33}H_{52}O_{10}$: C 65.11, H 8.61; found: C 64.96, H 8.59. Compound **62** was the more polar component. $[\alpha]_D^{29} = +73.69$ ($c = 0.85$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.34$ (dd, $J = 11.5$, 1.4 Hz, 1H), 4.22 (t, $J = 6.1$ Hz, 2H), 3.98 (d, $J =$ 11.5 Hz, 1H), 3.70 (t, $J = 6.0$ Hz, 2H), 2.90–2.85 (m, 1H), 2.42 (dt, $J =$ 14.2, 3.8 Hz, 1H), 2.07–1.93 (m, 2H), 1.91–1.81 (m, 3H), 1.68–1.49 (m, 4H), 1.48–1.35 (m, 1H), 1.33 (s, 3H), 1.30 (d, $J = 7.0$ Hz, 3H), 1.27–0.98 (m, 3H), 0.95 ppm (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 176.3, 104.1, 86.3, 61.1, 60.3, 59.0, 53.5, 48.6, 40.3, 37.3, 37.2, 34.6, 31.5, 26.2, 25.4, 25.3, 19.7, 18.2 ppm; FTIR (film): $\tilde{\nu} = 3445$, 2935, 2876, 1731, 1456, 1375, 1281, 1253, 1224, 1197, 1172, 1149, 1087, 1049, 941, 894, 829 cm^{-1}; ESI-MS: m/z: 343.2 $[M+H]^+$, 365.2 $[M+Na]^+$; elemental analysis: calcd (%) for $C_{18}H_{30}O_5\cdot 0.5\,H_2O$: C 61.52, H 8.89; found: C 61.64, H 8.93.

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