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TETRAHEDRON

An Improved Preparation of the Desmethyl Qinghao Acid Precursor of (±)-6,9-Desmethylqinghaosu

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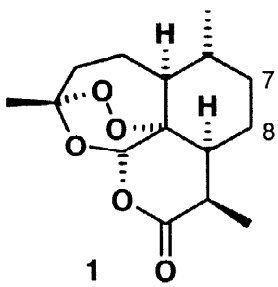
Abstract: The trimethylsilyl triflate catalysed DA reaction of the 3,5-hexadien-1-ol TMS ether with (±)-6-methylcyclohexenone efficiently gives the trans-fused adduct acetal, whose controlled hydrolysis converts it into (3a*RS*,6a*SR*,9*SR*,9a*SR*,9b*RS*)-9a-hydroxy-9-methyl-2,3,3a,6,6a,7,8,9,9a,9b-decahydro-1-oxa-1-H-phenalene. An efficient sequence involving hydrogenation, stereoselective reduction with lithium tri-*tert*-butoxyaluminohydride to the alcohol, selective protection of the primary hydroxyl group with *tert*-butyldimethylsilyl chloride, dehydration of the secondary alcohol to the alkene, deprotection and oxidation of the primary alcohol group to the carboxylic acid provides the desmethyl qinghao acid analogue which has been converted previously into (±)-6,9-desmethylqinghaosu.

INTRODUCTION

With the exception of the efficient syntheses as reported by Avery and co-workers, most total syntheses of the antimalarial drug qinghaosu (artemisinin) **1** and its derivatives are not easily amenable to scale-up.[1,2] In contrast, semisyntheses involving conversion of qinghao (artemisinic) acid, the biosynthetic precursor of artemisinin in *Artemisia annua*,[3] and artemisinic acid derivatives, represent relatively practical routes to artemisinin and its derivatives.[4-6] The key steps in the artemisinic acid - artemisinin conversion involve the photo-oxygenation of dihydroartemisinic acid methyl ester in acetonitrile to provide the corresponding tertiary allylic hydroperoxide, which upon treatment with catalytic copper(II) triflate catalyst under oxygen at low temperature furnishes artemisinin.[5,6] Several artemisinin derivatives have been prepared by using this process commencing with structurally modified artemisinic acid precursors.[7-9] These semisyntheses also represent the most effective means of obtaining artemisinin derivatives which cannot be prepared from artemisinin itself. Nevertheless, total synthesis does represent the only feasible means of obtaining epi-artemisinin derivatives,



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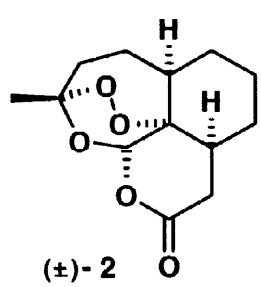

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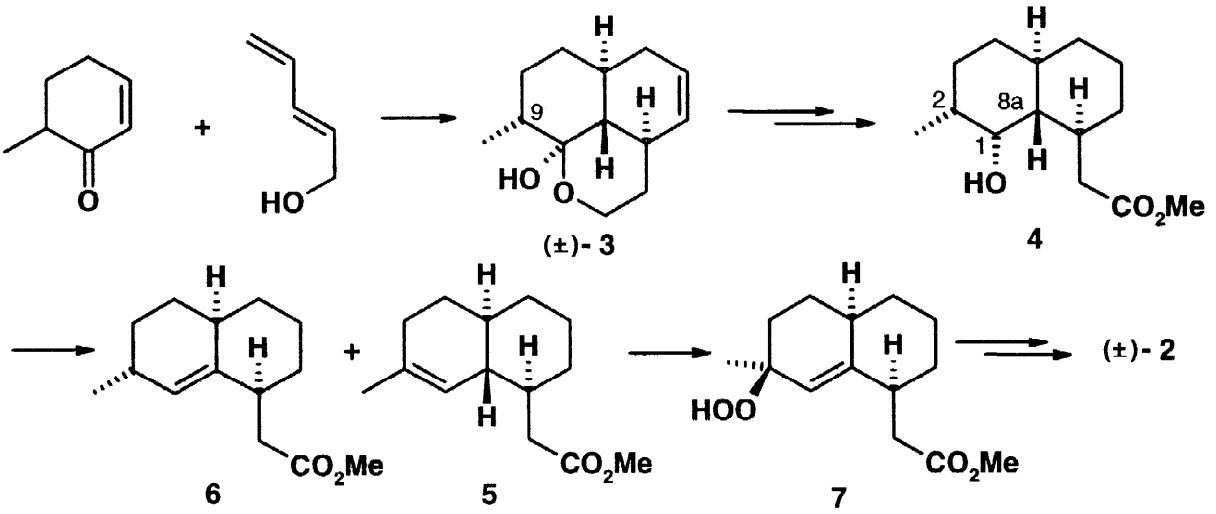
which are required for studies on structure-activity relationships of this fascinating class of antimalarial drug. The most expeditious of such syntheses would be those that proceed through epi-artemisinic acid derivatives.

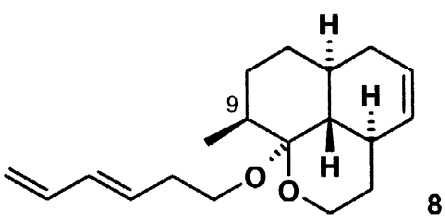
We are conducting a study which has as its ultimate aim the preparation of epi-artemisinin derivatives from epi-artemisinic acid derivatives. During the preliminary phase of this work, we uncovered a new variation of an $AlCl_3$-catalysed ionic Diels-Alder reaction between 6-methyl-2-cyclohexenone and (3*E*)-3,5-hexadien-1-ol, which provided racemic hemiacetal **3** (Scheme 1).[10-12] This was converted into hydroxy ester **4**



Scheme 1

and then *via* dehydration into the bicyclic trans-fused des-dimethyl analogue **5** of artemisinic acid ester. Photo-oxygenation of **5** provided the tertiary hydroperoxide **7**, treatment of which with a catalytic amount of $Fe(phen)_3(PF_6)_3$ and copper(II) triflate under oxygen followed by *p*-toluenesulfonic acid gave (±)-6,9-desdi-methylartemisinin **2**.[10]

Unfortunately, dehydration of alcohol **4** (Scheme 1) is not regioselective. With axial hydrogens at C-2 and C-8a in antiperiplanar relationships with the axial hydroxyl,[10] elimination at each centre is equally favoured on stereoelectronic grounds,[13] but is only partially biased towards C-2 on steric grounds, and provides alkenes **5** and **6** as a 5:2 mixture. However, the regioisomer **6** cannot be used, and thus about 28% of the material is lost. The problem has its origin in the 'incorrect' configuration of the methyl group at C-9 in **3**. This, according to an X-ray crystallographic analysis,[11,12] is equatorial, and adversely affects the stereochemical outcome of hydride reduction of an intermediate ketone leading to **4**.



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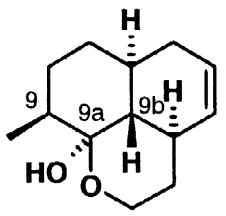

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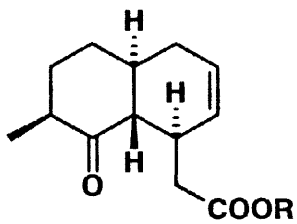
We have recently prepared the full acetal **8** via the trimethylsilyl triflate catalysed DA reaction between 6-methyl-2-cyclohexenone and the TMS ether of (3*E*)-3,5-hexadien-1-ol.[11,12] This adduct has a different stereo-

chemistry at C-9 to that in hemiacetal adduct **3** of the $AlCl_3$-catalysed reaction. This stereochemical difference in **8** offers the potential of allowing us to improve the synthetic sequence to the artemisinin analogue. With acquisition of **8**, we now also sought to prepare functionalized analogues of artemisinin (**1**) bearing hydroxyl groups at C7 and C8 (artemisinin numbering).

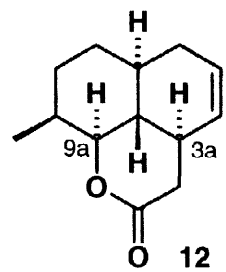
DISCUSSION

Reaction of acetal 8

Acetal **8** was hydrolysed to the hemiacetal **9**,[12] whose treatment with pyridinium dichromate in DMF directly furnished keto acid **10** (53%). The derived keto-ester **11** with sodium borohydride in methanol gave a mixture of products containing predominantly lactone **12**, with H-9a and H-3a axial, and ester **13**. The formation of **12** means that axial addition of hydride to the carbonyl in keto-ester **11** occurs from the α-face to provide an incipient equatorial β-alcohol, which lactonizes. H-1' appeared as a broad singlet at δ 3.58 in the ^{1}H NMR spectrum of hydroxy ester **13**, indicative of an equatorial proton; thus the α-hydroxyl group is axial. The proclivity of the incipient equatorial β-alcohol obtained from **11** to form the lactone **12** required us to use an approach which does not proceed via the carboxylic acid.



10 R = H
11 R = Me



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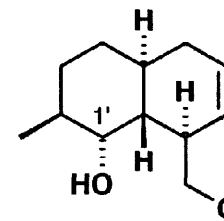

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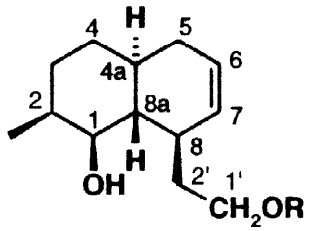
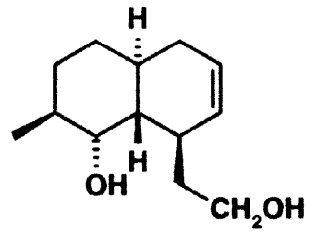
In alcohol **4** (Scheme 1), the hydroxyl group is antiperiplanar to H-2' and H-8a'. Thus both protons can be eliminated to produce the mixture of alkenes. In hemiacetal **9**, the methyl is axial, H-9 is equatorial and projects from the α-face while H-9b is axial and projects from the β-face.[12] Therefore, reduction of the hemiacetal group should provide an alcohol (*cf.* structure **14**) with a β-hydroxyl group. Nevertheless, with an anticipated trans-diequatorial arrangement of hydroxyl and H-2 in a conformationally-locked arrangement within the trans-octalin system of the putative alcohol product, it was unclear at the outset how regioselective the planned elimination would be.

Reduction of hemiacetal **9** with lithium aluminium hydride in THF gave diols **14** and **15** in a ratio of 3:1. However, use of lithium tri-*tert*-butoxyaluminium hydride at 0 °C in THF improved the ratio to ≥ 98:2 (97% overall). The ^{1}H NMR spectrum of diol **14** contained signals due to H-8a at δ 1.48 ppm with J = 9.8 and 10.3 Hz, and H1 at 3.60 with J = 4.9 and 10.3 Hz. The two couplings for H8a indicate the presence of adjacent antiperiplanar protons; H-1 is involved in one such coupling. In diol **15**, the signal due to H-1 appears at δ 3.79 as a broad singlet and contains no coupling corresponding to an adjacent antiperiplanar proton (*cf.* hydroxy acid **13** above).



14 R = - H
16 R = -Si-*t*-Bu(Me)$_2$



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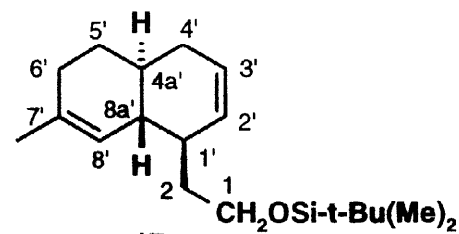
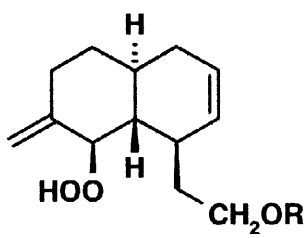


17

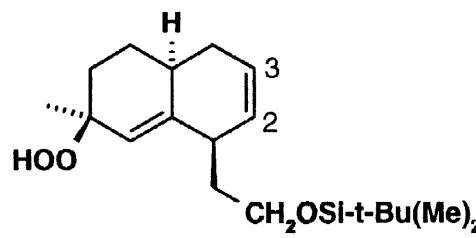
Thus, diol **14** is formed by the stereoelectronically-preferred axial attack of hydride at the carbonyl anti to the methyl group. Equatorial attack to provide diol **15** is less favoured due to steric hindrance from both the flanking axial methyl group and the side chain. Diol **14** was converted into *tert*-butyldimethylsilyl ether **16**, which upon treatment with phosphorus oxychloride in pyridine[10] gave diene **17** as the sole product (87%). Thus, elimination of H-8a to form the regioisomer was completely suppressed. However, this fortuitous outcome is not due to the trans relationship of H-2 and the hydroxyl at C-1, as opposed to the syn relationship of H-8a and the hydroxyl, but rather to the presence of the bulky *tert*-butyldimethylsiloxy group inhibiting abstraction of H-8a. This is discussed below.

Attempted reactions of diene 17 with singlet oxygen

As indicated above, an aim is to prepare artemisinin derivatives bearing hydroxyl groups at C-7 and C-8 (artemisinin numbering; structure **1**). To these end, we sought to exploit the different reactivities of the di- and trisubstituted double bonds in **17** towards singlet oxygen. After formation of the artemisinin skeleton as described above, dihydroxylation of the disubstituted double bond would then be carried out. However, photo-oxygenation of compound **17** with Rose Bengal in methanol under oxygen at -20 °C provided two highly unstable products in equal amounts, identified by their NMR spectra as secondary hydroperoxide **18** and tertiary hydroperoxide **19**, and other products derived from decomposition of the hydroperoxides. The reaction



18 R = -Si-*t*-Bu(Me)$_2$
21 R = -H



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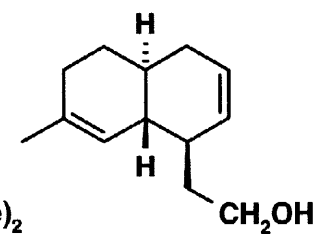
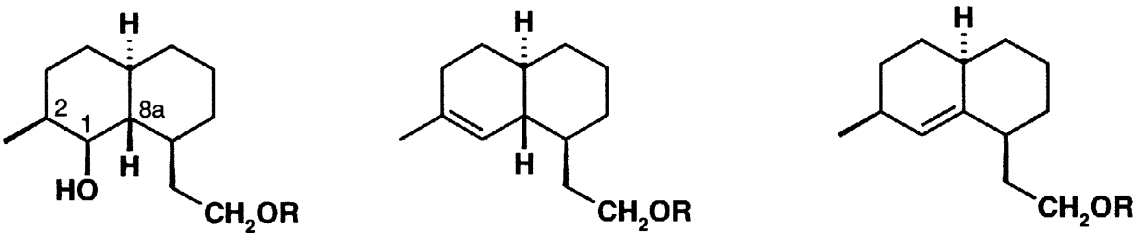


20

was very sluggish; approximately 2-3 days were needed for 10 mg of **17** to react completely. Hydroperoxides resulting from attack of singlet oxygen at the disubstituted double bond were not detected. The overall outcome, in terms of reaction rate, and regiochemistry, was very different to that of photo-oxygenation of alkene **5** (Scheme 1) to provide hydroperoxide **7**.[10]

It may be argued that the presence of the bulky *tert*-butyldimethylsiloxy group hinders abstraction of axial H8a' in the transition state of the reaction of singlet oxygen with **17** to give **19**, and instead, preferential abstraction of hydrogen from the exocyclic methyl group takes place to give secondary hydroperoxide **18**. However, removal of the silyl group and photo-oxygenation of the resulting alcohol **20** was equally sluggish in giving the unstable secondary hydroperoxide **21** as the *major* product. Thus, the failure to obtain the tertiary hydroperoxide as the major product is due to the disubstituted double bond, which affects the conformation of the molecule such that abstraction of hydrogen from the methyl group is enhanced over abstraction of H8a'. Alcohols structurally related to **20**, but without the double bond at C2-C3, have been converted successfully via hydroperoxides into various 10-deoxoartemisin derivatives.[7,9] Thus, attempts to persevere with the diene **17** as a precursor to functionalized artemisinin derivatives were abandoned.

*Conversion of diol **14** into the desdimethyldihydroartemisinic acid derivative **28** for synthesis of (±)-6,9-desdimethylartemisinin **6**.*

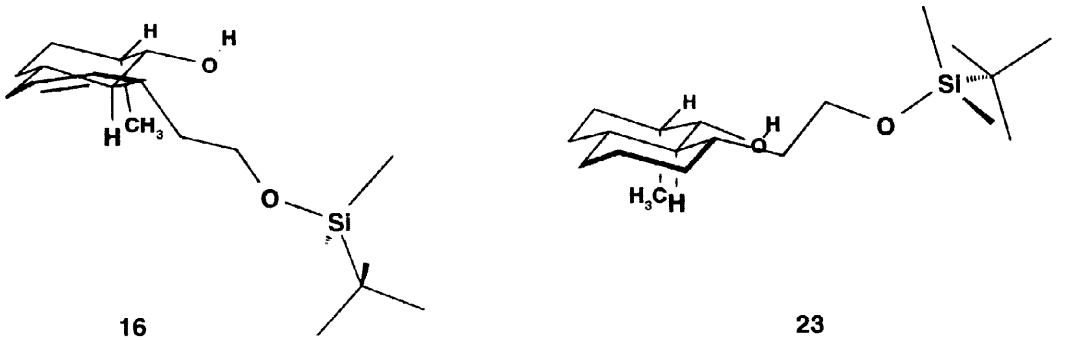


22 R = - H
23 R = - Si-t-Bu(Me)$_2$

24 R = -Si-t-Bu(Me)$_2$
26 R = -H

25 R = -Si-t-Bu(Me)$_2$
27 R = -H

Diol **14** was hydrogenated to provide saturated diol **22**, which was converted into the TBDMS ether **23**. Elimination was effected as above to give an inseparable 86:14 mixture (91% overall) of alkenes **24** and **25**. The result stands in contrast to dehydration of alcohol **16**, which gives only alkene **17** arising from elimination away from the ring junction. Thus, the syn-relationship between H8a and the hydroxyl group in **23** does not shut down elimination towards the ring junction. However, H-8a is obviously less accessible to abstraction in



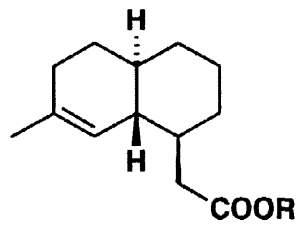
16 23

Figure 1: Minimum energy conformers (MM+, Hyperchem 5, Hypercube Inc., Gainesville FA) for compounds **16** and **23**.

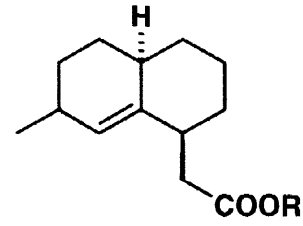
16 than in **23**, as is indicated in the minimum energy conformers of **16** and **23** (Figure 1) in which the unsaturated ring in **16** adopts a twist boat conformation. The side chain is pseudoaxial, and is thereby placed in proximity to H-8a, which is shielded to abstraction by base. On the other hand, the two rings adopt chair conformations in **23**, the bulky side chain is now equatorial, and H-8a is now accessible.

Of interest is the stereochemistry of the elimination process. Both compounds **16** and **23** represent conformationally-locked systems, and thus elimination takes place within a synclinal relationship of leaving group and participating protons, possibly via an E1 pathway.[13]

The primary hydroxyl group in alkenes **24** and **25** was deprotected, and the resulting mixture of alcohols **26** and **27** was treated with pyridinium dichromate in DMF to give the mixture of carboxylic acids **28** and **29** (92:8, 70% overall).



28 R = H
30 R = C_6H_5



29 R = H
31 R = C_6H_5

Target compound **28**, obtained in six steps from hemiacetal **8** with good to excellent yields in each step, has been converted previously via the methyl ester into **5** into (±)-6,9-desdimethylartemisinin **2**.[10] For characterization, the mixture was converted to the corresponding UV-active phenol esters **30** and **31** (72% overall) by treatment with phenol in the presence of dicyclohexylcarbodiimide. However, attempts to separate the esters by HPLC with a variety of columns, solvents, and conditions were completely unsuccessful. Resort had to be made to a chiral column (Chiralpak AS chiral column) in conjunction with hexane solvent at a flow rate of 0.8 mL/min to give a single enantiomer of the major isomer **30**.

The importance of the present work is that it now provides us with a robust route to prepare a number of artemisinin analogues suitable for structure-activity studies. As we have now been able to adapt the DA reaction used to prepare the acetal **9** to provide enantiomerically-pure adducts, the way is now open to prepare enantiomerically pure artemisinin derivatives, and in particular, epi-artemisinin, a target which has special interest from a structure-activity viewpoint, as foreshadowed in the previous paper.[12]

EXPERIMENTAL SECTION

General Experimental

Dichloromethane was dried over calcium hydride and distilled under nitrogen before use. Acetonitrile and *N,N*-dimethylformamide were dried over calcium hydride prior to distillation and stored over 4Å molecular sieves under nitrogen. Other solvents were dried and distilled according to standard techniques. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker ARX 300 and JEOL JNM-EX-400 NMR spectrometers. ^1H

NMR spectra were referenced on $CHCl_3$ (δ 7.26 ppm), and ^{13}C NMR spectra on $CDCl_3$ (δ 77.0 ppm). Mass spectra were recorded on a Finnegan TSQ-700 quadrupole mass spectrometer. Accurate mass measurements were recorded on Kratos MS-80 and Finnigan MAT 95 mass spectrometers. Infra-red spectra were recorded on a Perkin-Elmer 16PC FT-IR spectrometer. Melting points were determined in capillary tubes on an Electrothermal melting point apparatus. Merck Kieselgel 60 (230-400 mesh) was used for flash chromatography. Elemental microanalyses were performed by MEDAC Ltd. at the Department of Chemistry, Brunel University, UK.

Oxidation of Hemiacetal 9

Hemiacetal **9** (984 mg, 4.73 mmol) and pyridinium dichromate (9.85 g) in dry DMF (25 mL) under nitrogen was stirred at room temperature for 3 days and then treated with water (200 mL). The mixture was extracted with diethyl ether (3 x 100 mL). The combined organic layers were extracted with 5% sodium carbonate solution (3 x 20 mL). The combined aqueous layers was acidified with hydrochloric acid (5 M) until the carboxylic acid began to precipitate out. Chloroform (3 x 30 mL) was then used to extract the carboxylic acid product out of the aqueous layer. The combined organic layers were washed with water (50 mL), brine (50 mL) and dried ($MgSO_4$). Solvent was removed under reduced pressure and the crude product crystallized from ethyl acetate to yield (2'*SR*,4a'*SR*,8'*RS*,8a'*RS*)-2-(2'-methyl-1'-oxo-1',2',3',4',4a',5',8',8a'-octahydronaphthalen-8'-yl)acetic acid **10** (692 mg, 53 %) as colourless cubes, m.p. 146.9-147.8 °C; ^1H NMR (400 MHz) δ 1.23 (3H, d, J = 7.3 Hz, Me); 1.64-1.82 (4H, m, H3', 2 x H4' and H4a'); 1.88-1.97 (2H, m, H3' and H5'); 2.13-2.18 (1H, m, H5'); 2.23 (1H, dd, J = 6.8 Hz, J = 15.6 Hz, H2); 2.45 (1H, dd, J = 10.3 Hz, J = 11.7 Hz, H8a'); 2.60 (1H, dd, J = 4.4 Hz, J = 15.6 Hz, H2); 2.61-2.65 (1H, m, H2'); 2.97 (1H, dddd, J = 2.0 Hz, J = 4.4 Hz, J = 6.4 Hz, J = 10.3 Hz, H8'); 3.64 (3H, s, OMe); 5.60 (1H, d, J = 10.3 Hz, H7'); 5.67 (1H, dddd, J = 2.0 Hz, J = 2.4 Hz, J = 4.9 Hz, J = 10.3 Hz, H6'); ^{13}C NMR (100 MHz) δ 16.45 (Me); 27.39 (C4'); 31.26 (C8'); 32.07 (C3'); 32.87 (C5'); 38.82 (C2); 40.42 (C4a'); 44.98 (C2'); 50.12 (C8a'); 125.66 (C6'); 129.30 (C7'); 178.28 (COOH); 215.48 (C=O); ν_{max} (CCl_4) 3200 br w, 3034, m, 2927 s, 2859 m, 1705 vs, 1699 vs, 1441 m, 1429 m, 1273 s, 1231 m, 1181 m cm^{-1}; *m/z* (EI) 222 (M^+, 8%); 91 (100%). Anal. calcd. for $C_{13}H_{18}O_3$ C 70.23, H 8.17; found C 70.25, H 8.13.

The acid (410 mg, 1.85 mmol) in dichloromethane (50 mL) and methanol (2 mL) was esterified with diazomethane generated from Diazald (11.94 g) in water (5 mL), ethanol (10 mL) and 50% KOH solution (35 mL). The crude product was purified by flash chromatography (15% ethyl acetate/hexanes) to yield methyl (2'*SR*,4a'*SR*,8'*RS*,8a'*RS*)-2-(2'-methyl-1'-oxo-1',2',3',4',4a',5',8',8a'-octahydronaphthalen-8'-yl)acetate **11** (438 mg, quantitative) as a colourless oil; ^1H NMR (400 MHz) δ 1.23 (3H, d, J = 7.3 Hz, Me); 1.64-1.81 (4H, m, H3', 2 x H4' and H4a'); 1.86-1.95 (2H, m, H3' and H5'); 2.11-2.16 (1H, m, H5'); 2.20 (1H, dd, J = 8.3 Hz, J = 14.7 Hz, H2); 2.45 (1H, dd, J = 10.3 Hz, J = 11.2 Hz, H8a'); 2.53 (1H, dd, J = 4.4 Hz, J = 14.7 Hz, H2); 2.59-2.63 (1H, m, H2'); 2.97 (1H, dddd, J = 2.0 Hz, J = 3.9 Hz, J = 7.8 Hz, J = 12.2 Hz, H8'); 3.64 (3H, s, OMe);

5.60 (1H, d, J = 10.3 Hz, H7'); 5.67 (1H, dddd, J = 2.0 Hz, J = 2.4 Hz, J = 4.9 Hz, J = 10.3 Hz, H6'); ^{13}C NMR (100 MHz) δ 16.41 (CH_3); 27.42 (C4'); 31.41 (C8'); 32.12 (C3'); 32.87 (C5'); 38.87 (C2); 40.48 (C4a'); 45.01 (C2'); 50.15 (C8a'); 51.36 (OMe); 125.45 (C6'); 129.60 (C7'); 172.90 (COOH); 215.20 (C=O); ν_{max} 2037 m; 2916 s; 2860 s; 1737 s; 1702 s; 1657 m; 1454 s; 1437 s; 1372 m; 1256 s; 1157 s; 1055 m cm^{-1}; *m/z* (EI) 236 (M^+, 23%); 176 (100%).

For characterization, the methyl ester (221 mg, 0.936 mmol) in dry methanol (8 mL) was treated with *p*-toluenesulfonylhydrazine (325 mg, 1.75 mmol) and concentrated hydrochloric acid (3 drops), and then stirred under nitrogen at room temperature for 2 days. Solvent was removed under reduced pressure and the crude product was submitted to chromatography (10% ethyl acetate/hexanes) to give the tosylhydrazone (327 mg, 86%) as white solid which crystallized from methanol as cubes, m.p. 159.7-161.7 °C; ^{1}H NMR (400 MHz) δ 1.07 (3H, d, J = 7.3 Hz, Me); 1.38-1.62 (5H, m, 2 x H3', 2 x H4' and H4a'); 1.76-1.83 (1H, m, H5'); 1.93 (1H, dd, J = 9.3 Hz, J = 15.1 Hz, H2); 2.03 (1H, m, H5'); 2.10 (1H, dd, J = 9.8 Hz, J = 10.7 Hz, H8a'); 2.42 (3H, s, Me); 2.63 (1H, dd, J = 3.4 Hz, J = 15.1 Hz, H2); 2.96-3.01 (2H, m, H2'and H8'); 3.69 (3H, s, OCH_3); 5.49 (1H, d, J = 10.3 Hz, H7'); 5.63 (1H, dddd, J = 2.0 Hz, J = 2.4 Hz, J = 4.9 Hz, J = 10.3 Hz, H6'); 7.29 (2H, d, J = 8.3 Hz, aromatic protons); 7.45 (1H, s, NH); 7.85 (2H, d, J = 8.30 Hz, aromatic protons); ^{13}C NMR (100 MHz) δ 15.97; 21.58; 27.55; 29.47; 30.91; 31.99; 32.80; 38.47; 39.14; 44.12; 51.25; 125.19; 128.30; 129.45; 129.63; 135.21; 143.95; 164.16; 173.32; ν_{max} (CCl_4) 3192 s, 2918 m, 2863 m, 1738 s, 1731 s, 1626 w, 1597 w, 1434 m, 1405 m, 1337 s, 1266 m, 1164 s cm^{-1}; *m/z* (EI) 404 (M, 13 %); 249 (49 %); 234 (75 %); 175 (42 %); 146 (40 %); 91 (100 %); 79 (26 %). Anal. calcd. for $C_{21}H_{28}N_2SO_4$ C 62.35, H 6.98; found C 62.33, H 6.95.

Reduction of Methyl Ester 11

Excess of sodium borohydride (28.9 mg) was added portionwise with cooling to a stirred solution of methyl ester **11** (59.9 mg, 0.254 mmol) in methanol (6 mL) under nitrogen during 15 min. The reaction was quenched by the dropwise addition of dilute acetic acid. The volume of the reaction mixture was reduced to about one third and was poured onto water (20 mL). The products were extracted with diethyl ether (3 x 10 mL). The combined ether extracts were washed with water (2 x 10 mL), sodium carbonate solution (15%, 10 mL), brine (10 mL), and then dried ($MgSO_4$). After removal of solvent, the crude mixture was purified by chromatography (10% ethyl acetate/hexanes). The first portion (33 mg) was an inseparable mixture of products dominant in lactone **12**. ^{1}H NMR (400 MHz) δ 1.00 (3H, d, J = 7.32 Hz, methyl); 1.20-1.29 (1H, m, H7); 1.33 (1H, dd, J = 10.7 Hz, J = 10.7 Hz, H9b); 1.44-1.60 (2H, m, H6a and H7); 1.62-1.72 (1H, m, H2'); 1.90-2.01 (3H, m, 2 x H5 and H2'); 2.03-2.08 (1H, m, H2); 2.27-2.30 (2H, m, 2 x H8); 1.77-1.86 (1H, m, H6); 2.16 (1H, dd, J = 13.19 Hz, J = 17.6 Hz, H3β); 2.20-2.34 (3H, m, H3a, H6 and H9); 2.79 (1H, dd, J = 4.9 Hz, J = 17.6 Hz, H1); 4.18 (1H, dd, J = 4.9 Hz, J = 10.7 Hz, H9a); 5.45 (1H, dd, J = 1.5 Hz, J = 9.8 Hz, H4); 5.71 (1H, dddd, J = 2.4 Hz, J = 2.4 Hz, J = 4.9 Hz, J = 9.8 Hz, H5); ^{13}C NMR (100 MHz) δ 11.31, CH3; 26.32, C7;

29.41, C8; 31.74, C3a; 31.99, C6; 34.61, C9; 35.18, C6a; 37.10, C3; 38.96, C9b; 85.50, C9a; 127.46, C4; 127.68, C5; 170.75, C1.

The second fraction isolated was also a mixture containing predominantly alcohol **13** (10.1 mg, ~17%); ^{1}H NMR (400 MHz) δ 0.97 (3H, d, *J* = 7.3 Hz, methyl); 1.18-1.26 (2H, m); 1.32 (1H, dd, *J* = 2.0 Hz, *J* = 13.7 Hz); 1.50 (1H, dddd, *J* = 3.4 Hz, *J* = 3.4 Hz, *J* = 3.4 Hz, *J* = 13.7 Hz); 1.63-1.81 (2H, m, H4a' and H5'); 1.94 (1H, dddd, *J* = 4.4 Hz, *J* = 4.4 Hz, *J* = 13.7 Hz, *J* = 13.7 Hz, H3'β); 2.04-2.12 (2H, m, H2' and H5'); 2.27 (1H, dd, *J* = 6.4 Hz, *J* = 12.7 Hz, H2); 2.47 (1H, dd, *J* = 6.4 Hz, *J* = 16.1 Hz, H2); 2.74-2.83 (1H, m, H8'); 3.58 (1H, br s, H1'); 3.70 (3H, s, OMe) 5.50 (1H, d, *J* = 10.3 Hz, H7'); 5.65 (1H, dddd, *J* = 2.4 Hz, *J* = 2.4 Hz, *J* = 4.9 Hz, *J* = 9.8 Hz, H6'); ^{13}C NMR (100 MHz) δ 15.74; 24.68; 27.24; 30.73; 32.34; 32.78; 34.72; 38.01; 42.05; 51.45; 70.05; 126.29; 130.33; 174.07.

Reduction of Hemiacetal 9

A solution of hemiacetal **9** (708 mg, 3.40 mmol) in dry THF (80 mL) at 0 °C was treated dropwise with lithium tri-*tert*-butoxyaluminium hydride (1M in THF, 8.5 mL) under nitrogen, and the resulting mixture was stirred for 18 h. Excess hydride was decomposed by cautious addition of water followed by dilute hydrochloric acid. The mixture was extracted with diethyl ether (3 x 150 mL), and the combined organic extracts were washed with water (2 x 100 mL), brine (100 mL) and then dried ($MgSO_4$). After evaporation of solvent, the crude product was purified by chromatography (20% ethyl acetate/hexanes) to yield diol **14** (688 mg, 96%) as white solid, which crystallized from ethyl acetate as cubes, m.p. 96-97 °C. ^{1}H NMR (400 MHz) δ 0.99 (3H, d, *J* = 7.3 Hz, methyl); 1.22-1.30 (2H, m, H4β and H4a); 1.38-1.42 (1H, m, H4); 1.48 (1H, dd, *J* = 9.8 Hz, *J* = 10.3 Hz, H8a); 1.56-1.62 (2H, m, 2 x H3); 1.69-1.75 (1H, m, H2'); 1.90-2.01 (3H, m, 2 x H5 and H2'); 2.03-2.08 (1H, m, H2); 2.27-2.30 (1H, m, H8); 2.44 (1H, br. s, OH); 3.60 (1H, dd, *J* = 4.9 Hz, *J* = 10.3 Hz, H1); 3.68-3.78 (2H, m, 2 x H1'); 5.45 (1H, ddd, *J* = 2.4 Hz, *J* = 2.4 Hz, *J* = 9.8 Hz, H7); 5.69 (1H, dddd, *J* = 2.0 Hz, *J* = 2.0 Hz, *J* = 5.9 Hz, *J* = 9.8 Hz, H6); ^{13}C NMR (100 MHz) δ 11.73 (Me); 27.24 (C4); 30.31 (C3); 32.25 (C2'); 35.56 (C2); 38.03 (C8); 38.16 (C4a); 38.45 (C5); 42.55 (C8a); 60.76 (C1'); 79.67 (C1); 125.77 (C6); 132.49 (C7); ν_{max} (CCl_4) 3365 br s, 315 br s, 168 m, 2915 s, 2855 m, 1653 w, 1457 m, 1441 m, 1374 m, 1175 w, 1089 m, 1057 s, 1020 m cm^{-1}; *m/z* (EI) 210 (M^+, 1%); 148 (100%). Anal. calcd. for $C_{13}H_{22}O_2$ C, 74.23, H 10.55; found C 74.10, H 10.50.

The second product eluted as a white gum was diol **15** (8 mg, 1%). ^{1}H NMR (400 MHz) δ 0.99 (3H, d, *J* = 7.8 Hz, methyl); 1.15-1.28 (2H, m, H4β and H8a); 1.32-1.35 (1H, m, H3α); 1.43-1.51 (2H, m, H4α and H2'); 1.63-1.74 (2H, m, H4a and H5); 1.79-1.85 (1H, m, H2'); 1.91 (1H, dddd, *J* = 4.4 Hz, *J* = 4.4 Hz, *J* = 13.7 Hz, *J* = 13.7 Hz, H3α); 2.01-2.08 (2H, m, H2 and H5); 2.39-2.42 (1H, m, H8); 3.68-3.78 (2H, m, 2 x H1'); 3.79 (1H, br. s, H1); 5.62 (2H, br. s, H6 and H7); ^{13}C NMR (100 MHz) δ 16.06 (Me); 25.03 (C3); 27.53 (C4); 31.32 (C4a); 32.51 (C8); 33.16 (C5); 34.97 (C2'); 35.32 (C2); 41.25 (C8a); 60.87 (C1'); 70.47 (C1); 125.68 (C6); 131.22 (C7).

A mixture of *tert*-butyldimethylsilyl chloride (519 mg, 3.44 mmol), diol **14** (101.3 mg, 0.482 mmol) and imidazole (173 mg, 2.54 mmol) in dry THF (18 mL) was stirred overnight under nitrogen at 0 °C, and then quenched by addition of water (30 mL). The mixture was extracted with diethyl ether (3 x 15 mL), and the combined organic layer was washed with water (2 x 20 mL), brine (20 mL) and then dried ($MgSO_4$). Solvent was evaporated under reduced pressure and the residue was submitted to chromatography (3% ethyl acetate/ hexanes) to give TBDMS ether **16** (140.5 mg, 90%) as a colourless liquid. ^{1}H NMR (400 MHz) δ 0.08 (3H, s, SiMe); 0.09 (3H, s, SiMe); 0.91 (9H, s, *t*-Bu); 0.97 (3H, d, *J* = 7.3 Hz, Me); 1.20-1.29 (2H, m); 1.35-1.43 (2H, m); 1.53-1.61 (2H, m); 1.67-1.77 (2H, m); 1.92-1.96 (1H, m); 2.06-2.22 (3H, m); 3.45 (1H, d, *J* = 3.9 Hz, OH); 3.53 (1H, ddd, *J* = 4.9 Hz, *J* = 4.9 Hz, *J* = 9.8 Hz, H1); 3.65 (1H, ddd, *J* = 2.9 Hz, *J* = 9.8 Hz, *J* = 9.8 Hz, H1'); 3.75 (1H, ddd, *J* = 3.9 Hz, *J* = 5.4 Hz, *J* = 9.8 Hz, H1'); 5.43 (1H, dd, *J* = 2.4 Hz, *J* = 8.3 Hz, H7); 5.66 (1H, dddd, *J* = 2.0 Hz, *J* = 2.4 Hz, *J* = 5.4 Hz, *J* = 9.8 Hz, H6); ^{13}C NMR (100 MHz) δ -5.41; 12.04; 18.46; 26.03; 27.31; 30.46; 32.30; 34.81; 37.77; 37.97; 38.28; 43.37; 61.84; 79.52; 125.28; 132.27; ν_{max} (film) 3346 br s; 160 m; 2955 s; 2858 s; 1658 w; 1471 s; 1464 s; 1389 m; 1362 m; 1074 s; 1039 m; 1006 s; 938 m; 867 s; 837 s cm^{-1}; *m/z* (CI, NH_3) 325 (M^++1, 45%); 175 (100%); HRMS (EI): M^+, found 324.2478. $C_{19}H_{36}O_2Si$ requires 324.2485. Anal. calcd. for $C_{19}H_{36}O_2Si$ C 70.31, H 11.18; found C 70.18, H 11.06.

Dehydration of Alcohol 16

Phosphorus oxychloride (83 μl) was added dropwise to a stirred solution of the alcohol **16** (60.9 mg, 0.188 mmol) in dry pyridine (4.5 mL) under nitrogen. The resulting mixture was stirred at room temperature for 10 h. A small amount of water was added cautiously to quench the reaction, and the resulting mixture was then poured onto water (50 mL). The aqueous mixture was extracted with diethyl ether (3 x 15 mL), and the combined organic extracts were washed with water (40 mL), hydrochloric acid (3M, 50 mL), brine (2 x 20 mL) and then dried ($MgSO_4$). After evaporation of solvent, the residual oil was submitted to chromatography with 1% ethyl acetate/hexanes to give diene **17** (50.9 mg, 88%) as a colourless unstable liquid. ^{1}H NMR (400 MHz) δ 0.06 (6H, s, $SiMe_2$); 0.90 (9H, s, *t*-Bu); 1.25-1.50 (3H, m); 1.55-1.75 (6H, m); 1.82-1.93 (3H, m); 2.01-2.04 (2H, m); 3.63-3.76 (2H, m, 2 x H1); 5.47 (1H, br.s, H8'); 5.60 (1H, d, *J* = 10.3 Hz, H2'); 5.68 (1H, dddd, *J* = 2.0 Hz, *J* = 2.4 Hz, *J* = 4.9 Hz, *J* = 10.3 Hz, H3'); ^{13}C NMR (100 MHz) δ -5.57; 18.00; 23.49; 25.65; 29.60; 30.04; 32.40; 35.29; 35.54; 38.14; 41.92; 60.69; 122.81; 126.12; 131.04; 134.32; ν_{max} (film) 161 w; 2960 s; 2929 vs; 2858 s; 1648 w; 1472 m; 1431 w; 1386 w; 1361 w; 1259 m; 1095 s; 832 s cm^{-1}; *m/z* (CI, NH_3) 19 (M^++1, 18%); 160 (100%); HRMS (EI): M^+, found 306.2388. $C_{19}H_{34}OSi$ requires M^+ 306.2379. Anal. calcd. for $C_{19}H_{34}OSi$ C 74.44, H 11.18; found C 74.14, H 10.70.

Diene **17** (70.5 mg, 0.230 mmol) in dry THF (2 mL) was stirred with tetrabutylammonium fluoride (460 μl, 1M solution in THF) under nitrogen. After 1.5 h, the mixture was diluted with diethyl ether (15 mL). The mixture was then washed with water (2 x 5 mL), brine (5 mL), and then dried ($MgSO_4$). After filtration, the solvent was evaporated under reduced pressure and the crude product was purified by chromatography

(20% ethyl acetate/hexanes) to yield diene alcohol **20** (42.1 mg, 95%) as an unstable colourless oil. ^{1}H NMR (400 MHz) δ 1.26-1.42 (3H, m); 1.51-1.78 (7H, m); 1.87-2.09 (4H, m); 3.71-3.75 (2H, m, 2 x H1); 5.46 (1H, br. s, H8'); 5.61 (1H, d, J = 9.8 Hz, H2'); 5.71 (1H, dddd, J = 2.0 Hz, J = 2.4 Hz, J = 4.9 Hz, J = 9.8 Hz, H3'); ^{13}C NMR (100 MHz) δ 23.84; 29.84; 30.33; 32.69; 35.21; 35.82; 38.49; 41.96; 60.69; 122.68; 127.04; 131.02; 135.08; ν_{max} (film) 3332 br s; 3018 m; 2908 vs; 2830 s; 1650 w; 1450 m; 1376 w; 1130 w; 1040 m; 786 w; 758 w; 692 m; *m/z* (EI) 192 (M^+, 34%); 94 (100%); HRMS (EI): M^+ found 192.1523. $C_{13}H_{20}O$ requires M^+ 192.1514. Anal. calcd. for $C_{13}H_{20}O$ C 81.20, H 10.40; found C 81.10, H 10.68.

Hydrogenation of Diol 14

Diol **14** (498 mg, 2.37 mmol) in ethyl acetate (20 mL) containing palladium on charcoal (10%, 22 mg) was stirred under an atmosphere of hydrogen at room temperature and atmospheric pressure for 5 h. The catalyst was removed by filtering through Celite, and washed with ethyl acetate. The filtrate were combined, and then evaporated under reduced pressure. The residual yellow oil was submitted to chromatography (25-40% ethyl acetate/hexanes) to give diol **22** (456 mg, 91%) as colourless cubes, m.p. 81-82 °C. ^{1}H NMR (400 MHz) δ 0.92-1.08 (5H, m); 1.18-1.35 (5H, m); 1.52-1.61 (4H, m); 1.64-1.71 (1H, m, H8); 1.84-1.92 (1H, m, H2'); 1.97-2.09 (2H, m, H2 & H2'); 3.59 (1H, dd, J = 4.9 Hz, J = 9.8 Hz, H1); 3.69 (1H, ddd, J = 3.9 Hz, J = 7.3 Hz, J = 10.3 Hz, H1'); 3.83 (1H, ddd, J = 7.8 Hz, J = 10.3 Hz, H1'); ^{13}C NMR (100 MHz) δ 12.22, Me; 26.16, CH_2; 28.08, CH2; 30.20, CH2; 33.79, CH2; 34.39, CH2; 36.02, C2; 37.28, C2'; 39.93, C8; 42.40, C4a; 46.00, C8a; 60.67, C1'; 78.24, C1; ν_{max} (CCl_4) 3338 br s; 2926 vs; 2863 s; 1471 m; 1455 s; 1381 m; 1339 m; 1207 w; 1140 s; 1090 s; 1041 vs cm^{-1}; *m/z* (CI, NH_3) 213 (M^++1, 12%); 195 (90%); 177 (100%). Anal. calcd. for $C_{13}H_{24}O_2$ C 73.54, H 11.39; found C 73.64, H 10.99.

A mixture of *tert*-butyldimethylsilyl chloride (1.21 g, 8.03 mmol), diol **22** (211 mg, 0.995 mmol) and imidazole (354 mg, 5.20 mmol) in dry THF (30 mL) was stirred for 10 h under nitrogen at 0 °C. The reaction mixture was then quenched by addition of water (50 mL), and extracted with diethyl ether (3 x 25 mL). The combined organic layers were washed with water (2 x 20 mL), brine (20 mL), and then dried ($MgSO_4$). Solvent was removed under reduced pressure and the crude product was submitted to chromatography (3% ethyl acetate/hexanes) to give the TBDMS ether **23** as a colourless liquid (280 mg, 86%). ^{1}H NMR (400 MHz) δ 0.09 (3H, s, Me); 0.10 (3H, s, Me); 0.91-1.08 (14H, m); 1.14-1.34 (6H, m); 1.49-1.60 (3H, m); 1.62-1.69 (2H, m); 1.72-1.80 (1H, m, H2'); 2.01-2.14 (2H, m, H2 and H2'); 3.48 (1H, ddd, J = 4.9 Hz, J = 4.9 Hz, J = 9.8 Hz, H1); 3.63 (1H, ddd, J = 3.4 Hz, J = 8.8 Hz, J = 9.8 Hz, H1'); 3.81 (1H, ddd, J = 3.4 Hz, J = 6.4 Hz, J = 9.8 Hz, H1'); 4.01 (1H, d, J = 5.4 Hz, OH); ^{13}C NMR (100 MHz) δ -5.41, $SiMe_2$; 12.57, Me; 18.52, CMe_3; 26.05, CMe_3; 26.34, CH_2; 28.28, CH_2; 30.55, CH_2; 33.86, CH_2; 35.40 CH and CH_2; 37.26, C2'; 39.82, CH; 42.67, CH; 46.86, CH; 62.42, C1'; 78.00, C1; ν_{max} (film) 3433 br s, 2920 s, 2850 s, 1465 m, 1446 m, 1265 s, 1085 s, 1062 s, 1009 m, 835 s cm^{-1}; *m/z* (CI, NH_3) 327 (M^++1, 25%); 22 (38%); 177 (100%); HRMS (EI): M^+ found 326.2643. $C_{19}H_{38}O_2Si$ requires 326.2641.

Dehydration of Alcohol 23

Phosphorus oxychloride (1.4 ml , 15.25 mmol) was added dropwise with cooling to a stirred solution of alcohol **23** (937 mg, 2.87 mmol) in dry pyridine (55 mL) under nitrogen. Stirring was continued for 14 h at room temperature. Water was added cautiously to quench the reaction mixture; this mixture was then poured onto water (50 mL). The aqueous solution was extracted with diethyl ether (3 x 100 mL). The organic extracts were washed with water (150 mL), hydrochloric acid (6M, 125 mL), brine (2 x 100 mL) and then dried ($MgSO_4$). Evaporation of solvent left a liquid which was submitted to chromatography (1% ethyl acetate/hexanes) to give an 86:14 mixture of alkenes **24** and **25** (808 mg, 91% overall) as a pale yellow liquid. ^{1}H NMR (400MHz) (major isomer) δ 0.06 (6H, s, $SiMe_2$); 0.90 (9H, s, *t*-Bu); 0.94-1.16 (4H, m); 1.22-1.35 (4H, m); 3.58-3.64 (1H, m, H1); 3.70 (1H, ddd, J = 5.4 Hz, J = 9.3 Hz, J = 9.3 Hz, H1); 5.53 (1H, br. s, H1'); ^{13}C NMR (100 MHz) δ -5.65; 18.37; 23.84; 26.01; 26.29; 30.70; 30.79; 33.24; 33.51; 36.13; 38.43; 40.44; 46.40; 61.58; 123.14; 134.53; ν_{max} 150 w, 2951 vs, 2856 s, 1475 m, 1462 m, 1379 w, 1359 w, 1256 m, 1094 s, 835 s cm^{-1}; *m/z* (EI) m/z 20 (M^+, 2%); 251 (100%); HRMS (EI): M^+ found 308.2533. $C_{19}H_{36}OSi$ requires M^+ 308.2536. Anal. calcd. for $C_{19}H_{36}OSi$ C 73.95 H 11.76; found C 73.25 H 11.80.

For the regioisomer **25**, the signal due to H1' is at δ 5.34. Other proton signals merged with the signals from the major isomer.

The mixture (807.7 mg, 2.62 mmol) in dry THF (30 mL) was treated with tetrabutylammonium fluoride (5.4 mL, 1M solution in THF) under nitrogen. After 16 h , the mixture was diluted with diethyl ether (180 mL). The mixture was then washed with water (2 x 60 mL), brine (60 mL), and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude product was purified by chromatography (20% ethyl acetate/hexanes) to yield an 87:13 mixture of alcohols **26** and **27** (501 mg, 98% overall) as a colorless liquid. ^{1}H NMR (400MHz) (major isomer **26**) δ 0.95-1.18 (4H, m); 1.25-1.38 (4H, m); 1.61-1.66 (5H, m); 1.69-1.76 (1H, m); 1.81-1.90 (2H, m); 1.97-2.06 (2H, m); 3.63-3.77 (2H, m, 2 x H1); 5.52 (1H, br. s, H1'); ^{13}C NMR (100 MHz) δ 23.85; 26.20; 30.70; 33.05; 33.44; 36.11; 38.30; 40.39; 46.40; 61.13; 122.74; 134.92; ν_{max} (film) 3422 br s; 3006 w; 2922 s; 2856 m; 2254 s; 1646 m; 1446 w; 1378 w; 1096 w; 1044 w; 994 w; 912 vs; 720 vs; 850 vs; *m/z* (CI, NH_3) 195 (M^++1, 18%); 177 (100%); HRMS (EI): M^+ found 194.1671. $C_{13}H_{22}O$ requires M^+ 194.1671.

For the minor isomer **27**, the signal due to H1' is at δ 5.35. Other proton signals merge with the signals from the major isomer; ^{13}C NMR (100 MHz) δ 23.62; 25.74; 32.10; 33.79; 35.69; 36.11; 37.83; 40.30; 42.89; 61.02; 120.45; 133.27.

Oxidation of Alcohols 26 and 27

A solution of the alcohol mixture (500.8 mg, 2.58 mmol) in DMF (28 mL) was treated with pyridinium dichromate (5.22 g, ~5.4 equiv.). The reaction mixture was stirred for 19 h at room temperature. It was then diluted with water (50 mL) and was extracted with diethyl ether (3 x 50 mL). The combined organic extracts

were washed with water (2 x 50 mL), brine (50 mL), and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude mixture was purified by chromatography (20% ethyl acetate/hexanes) to give a 92:8 mixture of the acids **28** and **29** (377 mg, 70% overall) as a pale yellow waxy solid. The yellow solids were recrystallized with pure hexanes to form white chunky crystals. ^{1}H NMR (400 MHz) (major isomer **28**) δ 1.02-1.18 (4H, m); 1.22-1.42 (4H, m); 1.48-1.77 (5H, m); 1.85-2.10 (4H, m); 2.75 (1H, dd, J = 3.9 Hz, J = 15.1 Hz, H2); 5.40 (1H, br s, H1'); ^{13}C NMR (100 MHz) δ 23.84; 25.92; 30.57; 30.68; 33.27; 33.35; 38.34; 38.69; 40.22; 46.04; 122.03; 135.45; 179.29; ν_{max} (film) 3026.8 br s; 2910.0 s; 2852.0 s; 2687.9 w; 2578.2 w; 1694.0 vs; 1432.0 m; 1410.0 m; 1330.0 w; 1300.0 m; 1252.0 w; 1236.0 w; 1198.0 w; 1154.0 w; 944.0 w; 864.0 w; 786.0 w; 630.0 w; *m/z* (EI, NH_3) 208 (M^+, 10%); 148 (100%); HRMS (EI): M^+ found 208.1459. $C_{13}H_{20}O_2$ requires M^+ 208.1463. Anal. calcd. for $C_{13}H_{20}O_2$ C 74.96, H 9.68; found C 74.70, H 9.53.

The mixture of acids (49.4 mg, 0.238 mmol) in dichloromethane (3.6 mL) was treated with phenol (69 mg, 0.73 mmol), 1,3-dicyclohexylcarbodiimide (149.7 mg, 0.726 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (few crystals). The reaction mixture was stirred under nitrogen at room temperature for 5 h. It was then quenched with water (10 mL) and was extracted with diethyl ether (7 x 5 mL). The combined organic extracts were washed with water (2 x 10 mL), brine (10 mL), and then dried ($MgSO_4$). After removal of the solvent under reduced pressure, the crude mixture was purified by chromatography (7% ethyl acetate/hexanes) to give the esters **30** and **31** (92:8; 49 mg, 72% overall) as a pale yellow liquid. ^{1}H NMR (300 MHz) (major isomer **30**) δ 1.00-1.95 (16H, m); 2.24-2.36 (1H, m, H2); 2.93 (1H, dd, H2); 5.48 (1H, br, s, H1'); 7.06-7.41 (5H, m, phenyl); ^{13}C NMR (100 MHz) δ 23.86; 25.98; 30.55; 30.68; 33.29; 33.40; 38.85; 39.07; 40.22; 46.29; 121.60; 122.03; 125.68; 129.36; 135.49; 150.77; 172.06.

For the minor isomer **31**, the signals due to H2 and H1' are at δ 2.81 and δ 5.37 respectively. Other protons signals merge with the signals from the major isomer.

The ester mixture was then submitted to semi-preparative HPLC. However, the regioisomers **30** and **31** could not be separated using a variety of columns, solvents, and conditions. Resort had to be made to use of a Chiralpak AS 0.46cm x 25cm chiral column in conjunction with hexane solvent at a flow rate of 0.8 mL/min. Under these conditions, one enantiomer of the major isomer **30** was able to be obtained pure as a colourless oil. ^{1}H NMR (300 MHz) δ 0.83-2.17 (16H, m); 2.24-2.32 (1H, m, H2); 2.94 (1H, dd, H2); 5.48 (1H, br, s, H1'); 7.07-7.40 (5H, m, phenyl); ^{13}C NMR (100MHz) δ 23.86 (CH_3); 25.98 (CH_2); 30.55 (CH_2); 30.68 (CH_2); 33.29 (CH_2); 33.40 (CH_2); 38.85 (C2); 39.07 (CH); 40.22 (CH); 46.29 (CH); 121.60 (phenyl); 122.03 (C8'); 125.68 (phenyl); 129.36 (phenyl); 135.49 (C); 150.77 (C); 172.06 (C); ν_{max} (film) 2934 vs; 2854 vs; 2116 vs; 1758 vs; 1640 m; 1694 m; 1492 s; 1450 s; 1360 s; 1346 m; 1398 s; 1198 s; 1162 s; 1126 s; 1094 m; 1046 s; 1024 m; 954 w; 892 s; 864 w; 836 w; 738 s; 688 s; *m/z* (EI) (Finnigan MAT 95) 284 (M^+, 1%); 191 (25), 173 (10), 148 (100), 107 (10), 91 (15), 81 (16); HRMS (EI): M^+ found 284.1762. $C_{19}H_{24}O_2$ requires M^+ 284.1776.

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