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Studies toward the total synthesis of hibarimicinone. Progress on the assembly of the AB- and GH-ring systems

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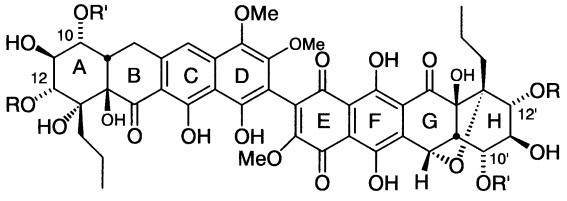
Abstract—Studies directed towards the synthesis of the AB- and GH-ring systems of hibarimicinone are described. The synthesis of tetralin **3** was accomplished in three steps (43% overall yield) from benzoquinone and resolved using a Lipase-mediated resolution to >92% ee. Key reactions developed en route to the AB/GH ring systems of hibarimicinone include a dimethyl dioxirane oxidation for stereocontrolled introduction of the C(14) and C(14′) hydroxyl groups and the stereoselective addition of a *n*-propylcerium dichloride to ketone **13** to give diol **15**. © 2002 Published by Elsevier Science Ltd.

1. Introduction

In 1998 workers in Japan described the identification of a complex of novel tyrosine kinase inhibitors produced by a rare actinomycete *Microbispora* sp. isolated from a soil sample collected at Hibari, Toyama Prefecture, Japan.[1] This complex collectively named the hibarimicins consisted of more than 10 components, the structure and biological activities of five of these substances (hibarimicins A, B, C, D and G) were described. Biological studies revealed hibarimicins A, B, C, D and G to be specific tyrosine kinase inhibitors with no affect on kinases C or A, similar to the tyrosine kinase specific inhibitor herbimycin A.[2] The structures of hibarimicins A, B, C, D and G were assigned based on extensive spectroscopic analysis and determined to share a common aglycone, we term hibarimicinone (Fig. 1), and differ in deoxyhexoses conjugated to the aglycone through the C(10)/C(10′) and C(12)/C(12′) hydroxyl groups (Fig. 1). Hibarimicin B proved to be identical to angelmicin B a microbial product previously described by Hori and co-workers.[3]

Despite extensive spectroscopic analysis some structural ambiguities of the hibarimicins remain to be resolved. First, the absolute stereochemistry of the sugar units have not been elucidated. Second, the relative stereochemistry of the C(13) stereogenic center within ring A has not been unambigously assigned as well as the collective relative stereochemistry between distal rings A and H. However, these structural uncertainties are resolved assuming a biosynthetic pathway in which hibarimicinone is produced by the dimerization of a polyketide derived tetracycle (Fig. 1).[4] Thus the absolute and relative stereochemistry of rings A and H are presumed to be identical leading to the conclusion that the structure of hibarimicinone to be nearly C-2 symmetric as shown in Fig. 1. Herein, we report on our early efforts toward the assembly of the AB- and GH-ring systems of hibarimicinone.

Several structural features of the AB- and GH-ring systems of hibarimicinone present significant synthetic challenges (Fig. 2). First, six contiguous stereogenic centers are located within rings A and H, with two of the six stereocenters [C(13)/C(14) and C(13′)/C(14′)] possessing a vicinal quarternary relationship. Thus two key stereochemical issues to be addressed in assembling the AB- and GH-ring systems are introduction of the *cis* ring fusion and the *trans* related vicinal tertiary diol (ring A) and alcohol/ether (ring H) functionality. An added level of complexity within the GH ring



Hibarimicins A, B, C, D and G (R = sug; R' = sug')
Hibarimicinone (R = R' = H)

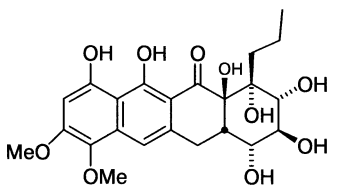


Figure 1. Structures of hibarimicinone, hibarimicins and a potential biosynthetic precursor to hibarimicinone.

Keywords: hibarimicinone; tetralin; stereoselective addition.

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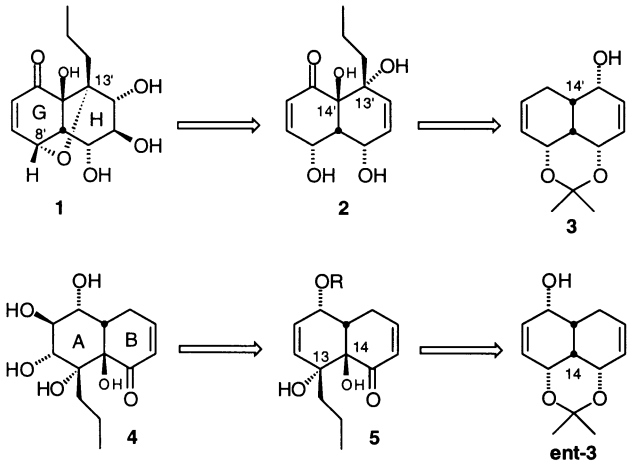
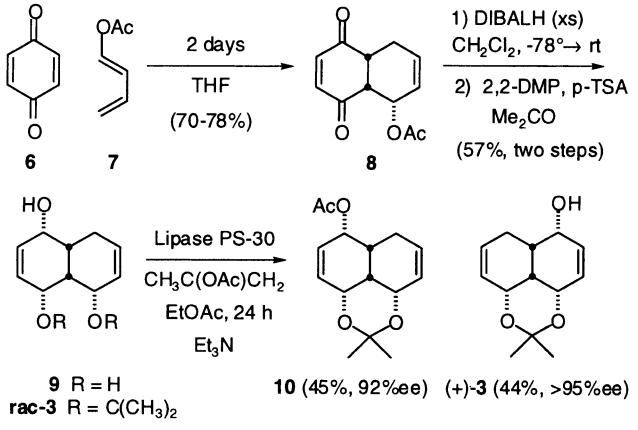


Figure 2. Retrosynthetic analysis of the AB- and GH-ring systems of hibarimicinone.

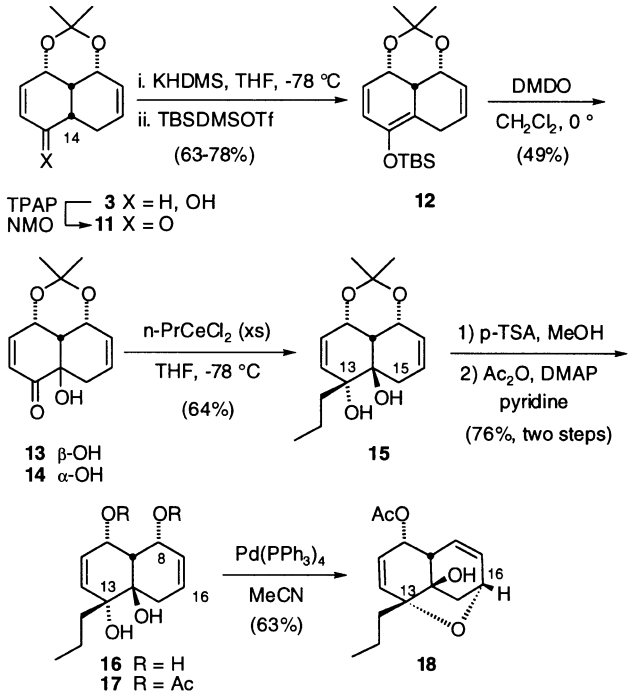
sub-structure is a bridging furan spanning C(8′) and C(13′). Our synthetic strategy required the AB- and GH-ring systems to be derived from tetralins **3** and *ent*-**3** which we planned to obtain by lipase-resolution of racemic **3**.[5] Since according to our biosynthetic proposal (Fig. 1) the A and H-rings are derived from the same intermediate (Fig. 1) our retrosynthetic analysis requires unique functionalization *ent*-**3** and **3** in order to provide AB and GH ring systems that possess identical absolute and relative stereochemistry. For example, hydroxylation of opposite ring fusion carbons (cf. C(14′) and C(14), **3** and *ent*-**3**) will be required in order to arrive at intermediates **1** and **4** that possess identical absolute stereochemistry at the six contiguous stereocenters located within the H and A rings, respectively.

2. Results and discussion

Our synthetic route to *rac*-**3** started with an endo selective Diels–Alder cycloaddition between benzoquinone (**6**) and 1-acetoxybutadiene (**7**) and afforded cycloadduct **8** in 70–78% yield (Scheme 1).[6] Exhaustive reduction (DIBALH) of **8** provides triol **9** (70% yield, one isomer as determined by ^{13}C NMR analysis) which was subject to standard acetalization conditions to give *rac*-**3** in 82% yield. The relative stereochemistry of *rac*-**3** was assigned based on a single-crystal X-ray analysis.



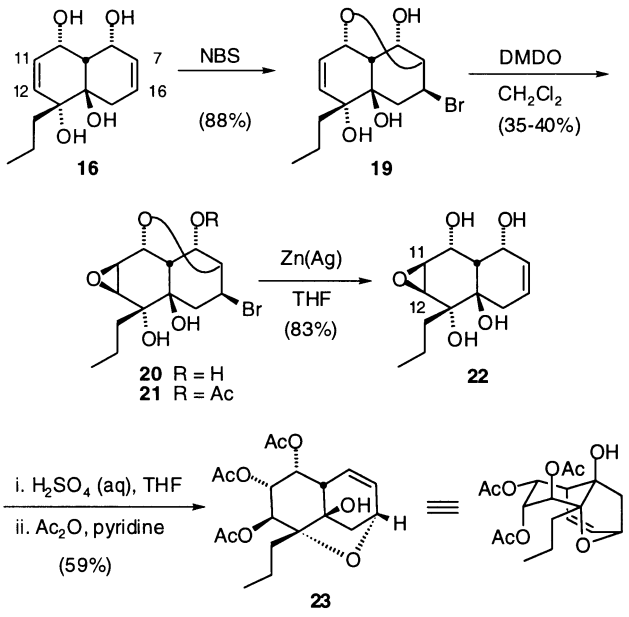
Scheme 1.



Scheme 2.

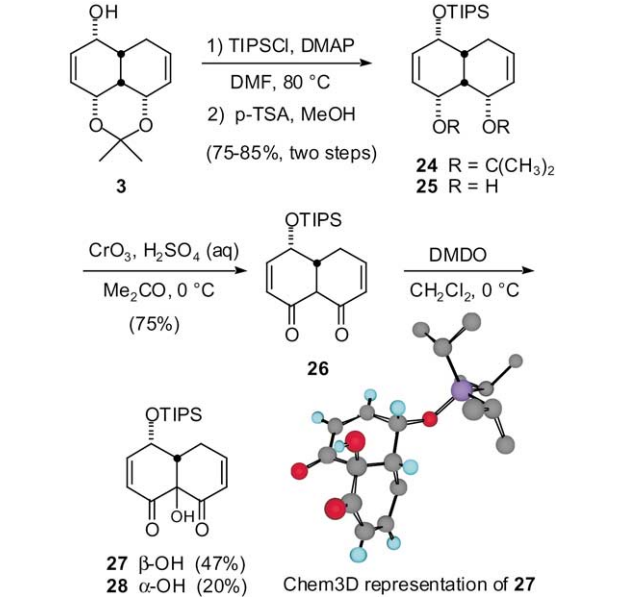
Resolution of alcohol *rac*-**3** using Amano PS-30 lipase afforded (+)-**3** and acetate **10** in 74 and >95% ee, respectively. The resolution required seven days to proceed to completion. Fortunately, modification of the Lipase resolution by the addition of 0.7 equiv of triethylamine provided (+)-**3** (44%) and acetate **10** (45%), >95 and 92% ee, respectively, and required only one day to proceed to completion.[7] The absolute stereochemistry of acetate **10** was assigned by single-crystal X-ray analysis.

Oxidation of alcohol **3** under Ley conditions (TPAP, NMO) provided crystalline ketone **11** in 84% yield.[8] Next, we turned our attention to the installation of the C(14) ring fusion hydroxyl group. Attempted α-hydroxylation of ketone **11** using Davis' oxaziridine failed to give any oxidized product, but instead resulted in epimerization of the C(14) stereocenter leading to the corresponding *trans* isomer of tetralin **11**.[9] As an alternative we investigated the Rubottom oxidation protocol.[10] To this end, ketone **11** was converted to silyl enol ether **12** (63–78%) by deprotonation (KHDMS) and quenching with TBDMSOTf (Scheme 2). Initially, oxidation of **12** employing peracids (*m*-CPBA or MMPP) provided only the undesired *trans* ring fused tetralin, alcohol **14** (68% yield for MMPP).[11] Gratifyingly, oxidation of **12** with dimethyl dioxirane gave exclusively the desired *cis* fused isomer, enone **13** in 49% yield.[12] Having introduced the C(14) stereocenter, we next faced the significant challenge of introducing the C(13) tertiary alcohol which required the stereoselective addition of an *n*-propyl group to hydroxy ketone **13**. As well as the issue of facial stereoselectivity, we were also cognizant of the potential for competing 1,4-addition to **13**. We determined protection of the C(14) hydroxyl group as a TES ether led to



Scheme 3.

a completely unreactive derivative of ketone **13**. In contrast, addition of 10 equiv. of in situ generated *n*-propylcerium dichloride to the free alcohol (**13**) provided a 5:1 mixture of **15** and the corresponding C(13) stereoisomer in 64% yield.[13] The success of this stereoselective alkylation may rest on a hydroxyl-directing effect of the neighboring tertiary alcohol. Having achieved introduction of the vicinal related C(13) and C(14) tertiary alchols we turned our attention to formation of the bridging furan ring common to the GH ring system of hibarimicinone (Fig. 2). This required ether formation across C(8) and C(13) carbons. We envisioned a chemo- and regioselective palladium(0) mediated cyloetherification of diacetate **17**. To this end, *p*-TSA assisted methanolysis of **15** was followed by acetylation to give diacetate **17** in 76% overall yield. Unfortunately, treatment of a refluxing acetonitrile solution of



Scheme 4.

17 with palladium tetrakis(triphenylphosphine) led to exclusive cyclization of the C(13) hydroxyl group at the undesired C(16) carbon resulting in the formation of furan **18**, bridging across the C(13) and C(16) carbons. Attempts to redirect the cyclization to C(8) using other catalysts[14] and reaction conditions as well as attempts to effect allylic oxidation at C(15) prior to the cycloetherification failed.[15] At this point we reasoned installation of the *trans* C(11) and C(12) diol may have a beneficial effect on the course of furan formation and redirect ring closure to C(8). We therefore turned our attention to the introduction of the *trans* diol at C(11) and C(12) (Scheme 3). This required first protection of the C(7)–C(16) alkene which was accomplished by a chemoselective bromoetherification of tetraol **16** to give crystalline furan **19** in 88% yield. The remaining C(11)–C(12) alkene was then oxidized using dimethyldioxirane to afford epoxide **20** (35–40%). The stereochemistry of **20** was assigned based on a single-crystal X-ray analysis of acetate derivative **21**. Exposure of **20** to zinc–silver couple gave tetraol **22** in 83% yield. Aqueous acid solvolysis of **22** followed by acetylation of the crude product gave, unexpectedly, furan **23**. The structure of **23** was assigned based on NMR analysis and spectral comparison to furan **18** (Scheme 2). We presume the sequence of events leading to triacetate **23** were initiated by acid-catalyzed epoxide opening at C(11) by water followed by cyclodehydration and finally peracetylation to give **23** in 59% yield. In this case not only did furan formation occur in the undesired sense but opening of epoxide **22** at C(11) provided the incorrect relative stereochemistry between the C(11) and C(12) stereocenters.

As outlined in the retrosynthetic analysis shown in Fig. 2 an alternative approach to either the AB or GH ring system is to oxidize the masked 1,3-diol of decalin **3** to the corresponding diketone.[16] To this end, protection of alcohol **3** as a TIPS ether followed by removal of the acetonide group afforded 1,3-diol **25** as a light yellow solid in 75–85% yield for two steps (Scheme 4). Oxidation with an excess of Jones reagent then provided diketone **26** (75%). We were now faced with the task of introducing the ring fusion hydroxyl group with the desired *cis* stereoselectivity and again observed divergent stereoselectivity for peracid and dioxirane oxidations. First, oxidation of **26** with peracids afforded the undesired *trans* ring fusion product (**28**) as the major product. In contrast, dimethyldioxirane oxidation of **26** provided the *cis* alcohol **27** (47%) as the major isomer and **28** (20%) as the minor. The stereochemistry of **27** and **28** were assigned based on a single-crystal X-ray analysis of the *cis* isomer **27**. To date, all attempts to effect a chemoselective alkylation of 1,3-diketone **27** to give **5** (Fig. 2) have failed.

3. Conclusion

In conclusion, we have examined two approaches to the AB and GH ring system of hibarimicinone starting from tetralin **3** available in three steps and 43% overall yield starting from benzoquinone. Lipase-mediated resolution of **3** provided (−)-**3** and its acetylated enantiomer in >95% and 92% ee. Key aspects of our synthetic studies include stereoselective oxidation of the ring fusion carbon to deliver tetralins **13** and **27** as well as stereoselective *n*-propyl

addition to ketone **13** to afford diol **15**. We encountered difficulty in introduction of the bridging furan unit of the GH ring system and stereoselective diol formation at C(11) and C(12). Synthetic strategies currently under investigation in our lab directed toward a total synthesis of hibarimicinone take advantage of these finding.

4. Experimental

4.1. General

All reactions were carried out under a nitrogen or argon atmosphere using dry glassware which had been flame-dried under a stream of nitrogen, unless otherwise noted. All necessary solvents were purified prior to use. Tetrahydrofuran and ethyl ether were distilled from sodium/benzophenone; dichloromethane and benzene were distilled from calcium hydride. Pyridine and triethylamine were distilled from calcium hydride and stored over sodium hydroxide. Toluene was distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) using 0.25-mm E. Merck precoated silica gel plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution or anisaldehyde stain followed by charring on a hot-plate. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 0.040–0.063 mm). Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points are uncorrected unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a Varian-300 MHz spectrometer at ambient temperature. ^{1}H and ^{13}C NMR data are reported as δ values relative to tetramethylsilane. Infrared spectra were recorded on Mattson Galaxy Series FT-IR 5000 or FT-IR 6021 spectrometers. Optical rotations were measured on a Jasco DIP-181 digital polarimeter at ambient temperature. High-resolution mass spectra were obtained at Texas A&M University Mass Spectrometry Service Center on a VG Analytical 70S high resolution, double focusing, sectored (EB) mass spectrometer.

4.1.1. Acetate 8. Benzoquinone (15.0 g, 139 mmol) was dissolved in THF (80 mL), and 1-acetoxybutadiene (18.6 g, 166.5 mmol) was added slowly. The reaction mixture was then stirred at room temperature for 2 days. The reaction mixture was concentrated and chromatographed (3:1→2:1 hexanes–EtOAc) to give 21.4 g (70%) of **8** as a crystalline orange solid: mp 66–68°C; IR ($CHCl_3$) 3022, 2976, 1742, 1690, 1214 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (s, 3H), 2.08–2.17 (m, 1H), 2.98–3.07 (m, 1H), 3.29–3.31 (m, 2H), 5.27–5.30 (m, 1H), 5.86–5.99 (m, 2H), 6.66–6.70 (m, 1H), 6.84 (d, J=10.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1, 196.9, 141.8, 140.2, 131.2, 122.9, 116.0, 66.2, 49.6, 42.2, 21.3, 20.6; HRMS (FAB) m/z 219.0659 [$(M+H)^+$, calcd for $C_{12}H_{11}O_4$ 219.0657].

4.1.2. Triol 9. To a solution of **8** (21.0 g, 95.4 mmol) in CH_2Cl_2 (500 mL) at −78°C a solution of DIBALH (480 mL, 1 M solution in hexane, 480 mmol) was added dropwise. The reaction mixture was stirred at −78°C for 3 h, and then 7 h at room temperature. The reaction mixture was cooled to 0°C and quenched with 1:1 CH_3OH–H_2O (180 mL) followed by saturated Rochelle salt solution (380 mL). The resulting mixture was then stirred vigorously overnight. The aqueous layer was extracted with EtOAc (6×500 mL). The combined organic extracts were dried ($MgSO_4$), concentrated and chromatographed (1:2 hexanes–EtOAc) to give 12.2 g (70%) of triol **9** as a white solid: mp 119–120°C; IR ($CDCl_3$) 3355, 3022, 2966 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13–2.21 (m, 2H), 2.30–2.42 (m, 2H), 3.42 (brs, 3OH), 4.00 (d, J=3.9 Hz, 1H), 4.42 (t, J=4.5 Hz, 1H), 4.50 (d, J=7.8 Hz, 1H), 5.77–5.94 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8, 130.1, 130.0, 127.7, 67.4, 67.0, 63.3, 38.9, 32.6, 27.6; HRMS (FAB) m/z 183.2237 [$(M+H)^+$, calcd for $C_{10}H_{14}O_3$ 183.2288].

4.1.3. Allylic alcohol 3. Triol **9** (12 g, 65.9 mmol) was dissolved in acetone (80 mL). 2,2-dimethoxypropane (30 mL, 244 mmol) and a catalytic amount of *p*-toluenesulphonic acid (ca. 25 mg) were added to the solution. The reaction mixture was stirred for 30 min, concentrated and chromatographed (3:1→2:1 hexanes–EtOAc) to give 12.0 g (82%) of allylic alcohol **3** as a crystalline white solid: mp 62–63°C; IR ($CHCl_3$) 3442, 3017, 2909, 1378 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, J=0.9 Hz, 3H), 1.47 (d, J=0.6 Hz, 3H), 2.15–2.21 (m, 3H), 2.44–2.59 (m, 1H, 1OH), 4.09 (brs, 1H), 4.42–4.53 (m, 2H), 5.72–5.77 (m, 1H), 5.80–5.85 (m, 1H), 5.91–5.96 (m, 1H), 6.00–6.06 (m, 1H); ^{13}C NMR, (75 MHz, $CDCl_3$) δ 132.8, 131.3, 129.3, 127.5, 101.9, 68.7, 65.5, 64.0, 35.1, 29.5, 25.5, 24.2; HRMS (FAB) m/z 2451149 [$(M+H)^+$, calcd for $C_{13}H_{18}O_3$ 245.1154)].

4.2. Lipase-resolution of allylic alcohol 3

To a solution of allylic alcohol **3** (1 g, 4.5 mmol) in isopropenyl acetate (20 mL) was added triethylamine (0.44 mL, 3.15 mmol) Amano Lipase PS-30 (1 g). The reaction mixture was stirred for 24 h, and the lipase was removed by gravity filtration. The filtrate was concentrated and chromatographed (3:1 hexanes–EtOAc) to give acetate 543.2 mg (45%) of **10** as a white solid and 439 mg (44%) of alcohol **3** as a colorless oil.

The optical purity of allylic alcohol **3** was determined to be >95% ee, by chiral phase HPLC using a Daicel AD column, 2.5% *i*-PrOH in hexanes as eluent at a flow rate of 1.0 mL/min, detection at 215 nm with elution times t_{major}=5.9 min, t_{minor}=6.6 min. For acetate **10** the optical purity was determined to be 92% ee by chiral phase HPLC using Daicel AD column, 2.5% *i*-PrOH in hexanes as eluent at a flow rate of 1 mL/min, detection at 215 nm with elution times t_{minor}=14.2 min, t_{major}=15.3 min.

4.2.1. Ketone 11. To a solution of allylic alcohol **3** (5 g, 22.5 mmol) in CH_2Cl_2 (60 mL) was added *N*-methyl morpholine oxide (3.96 g, 33.8 mmol) and 4 Å molecular sieve (11.3 g). Tetrapropyl ammonium peruthenate (TPAP) (2×120 mg, 0.68 mmol) was then added in two portions 10 min apart. The reaction mixture was stirred at room temperature for 1 h, filtered through a short pad of silica, filtered, concentrated and chromatographed (5:1 hexanes–EtOAc with 1% Et_3N) to give 4.18 g (84%) of

enone **11** as a yellow solid: mp 75–77°C; IR ($CHCl_3$) 3022, 2986, 2945, 2909, 1680, 1434, 1383, 1322, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, 0.6 Hz, 3H), 1.43 (d, J=0.9 Hz, 3H), 1.80–1.88 (m, 1H), 2.65–2.70 (m, 1H), 2.77–2.86 (m, 1H), 3.14 (q, J=7.5 Hz, 1H), 4.35–4.38 (m, 1H), 4.82–4.87 (m, 1H), 5.62–5.66 (m, 1H), 5.97–6.06 (m, 2H), 6.89–6.94 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4, 149.6, 130.1, 129.3, 126.1, 102.0, 66.8, 61.6, 41.4, 39.9, 30.0, 24.6, 23.6; HRMS (FAB) m/z 221.1185 [$(M+H)^+$, calcd for $C_{13}H_{16}O_3$ 221.1178].

4.2.2. Silyl enol ether 12. To a solution of KHMDS (68.2 mL, 0.5 M solution in toluene, 34.1 mmol) in THF (70 mL) cooled to −78°C was added a solution of enone **11** (5 g, 22.7 mmol) in THF (20 mL) dropwise. After stirring for 30 min, neat TBSOTf (8 mL) was added slowly and the reaction mixture continued to stir for 5 h at −78°C. The reaction was then quenched with saturated $NaHCO_3$ (50 mL) and the aqueous layer extracted with CH_2Cl_2 (3×80 mL). The combined extracts were dried (Na_2SO_4), concentrated and chromatographed (30:1 hexanes–EtOAc) to give 5.7 g (75%) of enolether **12** as a light yellow solid: mp 61–63°C; IR ($CHCl_3$) 3022, 2955, 1655, 1516 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.95 (s, 9H), 1.34 (s, 3H), 1.52 (s, 3H), 2.33 (brs, 1H), 2.88–3.21 (m, 2H), 4.39 (t, J=5.7 Hz, 1H), 4.52 (dd, J=6.3, 3.6 Hz, 1H), 5.77–5.82 (m, 1H), 5.90–5.96 (m, 1H), 6.03–6.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 131.9, 130.7, 124.6, 121.8, 111.0, 96.3, 62.4, 61.9, 35.8, 30.2, 25.8, 25.1, 19.0, 18.1, −3.8, −4.2; HRMS (FAB) m/z 334.1954 [$(M+H)^+$, calcd for $C_{19}H_{29}O_3Si$ 334.1964].

4.2.3. Alcohol 13. To a solution of enol ether **12** (4.8 g, 14.3 mmol) in CH_2Cl_2 (100 mL) was added dimethyl dioxirane solution (ca. 0.05 M, 320 mL). Stirring was continued at 0°C until all the starting material was consumed by TLC analysis. The reaction mixture was then dried ($MgSO_4$), concentrated and chromatographed (4:1 hexanes–EtOAc) to give 1.63 g (49%) of α-hydroxyenone **13** as a light yellow solid: mp 77–79°C; IR ($CHCl_3$) 3503, 3017, 2930, 1214 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (s, 3H), 1.51 (s, 3H), 1.88–1.95 (m, 1H), 2.53–2.62 (m, 1H), 2.72–2.78 (m, 1H), 4.62–4.66 (m, 1H), 4.75–4.78 (m, 1H), 5.84–5.98 (m, 2H), 6.20 (dd, J=9.9, 1.5 Hz, 1H), 6.85 (dd, J=9.9, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 147.1, 129.8, 127.2, 126.2, 102.5, 74.7, 66.4, 63.1, 40.3, 34.3, 29.5, 25.3; HRMS (FAB) m/z 259.0952 [$(M+Na)^+$, calcd for $C_{13}H_{16}O_4$ 259.0946].

4.2.4. Alcohol 14. To a solution of enol ether **12** (100 mg, 0.30 mmol) in isopropanol (3 mL) was added a solution of magnesium monoperoxyphthalate (203.4 mg, 0.33 mmol) in water (2 mL). The reaction mixture was stirred for 20 min, and CH_2Cl_2 (20 mL) and saturated solution of $NaHCO_3$ (20 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined extracts were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrate. The residue was purified by chromatography (4:1 hexanes–EtOAc) to give 48 mg (68%) of α-hydroxyl enone **14** as a light brown solid; mp 161–163°C; IR ($CHCl_3$) 3519, 3017, 2940, 2904, 2873, 1701, 1660, 1424 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 3H), 1.64 (s, 3H), 1.92 (t, J=3.9 Hz, 1H), 2.25 (d, J=18.9 Hz, 1H), 2.58 (dd, J=18.6, 5.4, 1H), 4.06 (brs, OH), 4.64 (t, J=3.6 Hz, 1H), 4.71 (t, J=4.2 Hz, 1H), 5.85–5.90 (m, 1H), 6.04–6.10 (m, 1H), 6.23 (d, J=10.5 Hz, 1H), 6.83 (dd, J=10.2 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3, 142.6, 126.0, 129.5, 124.0, 123.1, 70.4, 64.0, 62.7, 35.9, 31.5, 30.0, 18.5.

4.2.5. Alcohol 15. Cerium chloride heptahydrate (34.7 g, 93.2 mmol) was dried under 0.1 mm Hg at 135–140°C for 3 h. The anhydrous cerium chloride was suspended in THF (200 mL), stirred at room temperature for 30 min and then cooled to −78°C. Propylmagnesium chloride (42.4 mL, 2 M solution in Et_2O, 84.8 mmol) was added and the reaction mixture was stirred for 3 h. A solution of α-hydroxyenone **13** (2 g, 8.47 mmol) in THF (15 mL) was added dropwise. After stirring for 5 h, the reaction mixture was quenched with 0.1N HCl (150 mL) and H_2O (150 mL). The aqueous layer was extracted with EtOAc (3×200 mL). The combined extracts were dried ($MgSO_4$), concentrated and chromatographed (2:1 hexanes–EtOAc) to give 1.70 g (74%) of diol **15** as a yellow solid: mp 95–97°C; IR ($CHCl_3$) 3590, 3467, 3017, 2960, 1521 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (t, J=7.2 Hz, 3H), 1.26–1.61 (m, 10H), 1.26 (s, 3H), 1.41 (s, 3H), 1.74–1.86 (m, 3H), 2.19 (dd, J=18, 5.4 Hz, 1H), 2.48 (d, J=17.7 Hz, 1H), 2.64–2.70 (m, 1H), 4.40 (d, J=6.6 Hz, 1H), 4.66 (d, J=9 Hz, 1H), 5.61 (dd, J=10.5, 3 Hz, 1H), 5.77–5.96 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 130.2, 126.2, 125.7, 101.3, 76.2, 67.5, 63.4, 39.4, 30.9, 29.7, 24.8, 16.7, 14.8 (2C); HRMS (FAB) m/z 303.1564 [$(M+H)^+$, calcd for $C_{16}H_{23}O_4$ 303.1572].

4.2.6. Tetraol 16. Diol **15** (1.2 g, 4.29 mmol) was dissolved in methanol (40 mL) and a catalytic amount of *p*-toluenesulphonic acid (ca. 15 mg) was added. The reaction mixture was stirred at room temperature for 1.5 h and concentrated to give a white solid. The white solid was washed with CH_2Cl_2 (100 mL) to give 804 mg (78%) of tetraol **16** as a white powder: mp 203–205°C; IR (KBr) 3529, 3457, 3401, 3355, 3027, 2960, 2925, 1240 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.93 (t, J=7.2 Hz, 3H), 1.32–1.77 (m, 4H), 2.08 (d, J=18.9 Hz, 1H), 2.36 (t, J=6.6 Hz, 1H), 3.30 (s, 1H), 4.47 (s, 1H), 4.66 (s, 1H), 5.63–5.73 (m, 4H); HRMS (FAB) m/z 263.1264 [$(M+Na)^+$, calcd for $C_{13}H_{20}O_4$ 263.1259].

4.2.7. Diacetate 17. To a solution of tetraol **16** (569 mg, 2.37 mmol) in pyridine (8 mL) was added acetic anhydride (1.1 mL, 11.6 mmol) and a catalytic amount of DMAP (ca. 5 mg). The reaction mixture was then heated to 50°C and stirred for 2 h. The mixture was concentrated and chromatographed (30:1 $CHCl_3$–CH_3OH) to give 650 mg (97%) of diacetate **16** as a white solid: mp 153–155°C; IR ($CHCl_3$) 3391, 3022, 2971, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J=6.6 Hz, 3H), 1.24–1.46 (m, 1H), 1.50–1.63 (m, 2H), 1.96 (s, 3H), 2.02 (s, 3H), 2.22 (d, J=21 Hz, 1H), 2.52 (d, J=15.3 Hz, 1H), 2.82 (t, J=5.7 Hz, 1H), 5.46–5.83 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.1, 135.8, 127.2, 126.0, 123.0, 75.6, 69.7, 65.4, 39.9, 39.2, 32.1, 21.3, 20.9, 16.7, 14.8; HRMS (FAB) m/z 347.1479 [$(M+Na)^+$, calcd for $C_{17}H_{24}O_6$ 347.1471].

4.2.8. Furan 18. To a solution of diacetate **17** (25 mg, 0.09 mmol) in CH_3CN (2 mL) was added $Pd(PPh_3)_4$

(5.1 mg, 0.018 mmol, 20 mol%). The reaction mixture was refluxed for 12 h, concentrated and chromatographed (4:1 hexanes–EtOAc) to give 12.5 mg (63%) of furan **18** as an orange solid: mp 78–80°C; IR ($CHCl_3$) 3022, 2966, 2397, 1737, 1373, 1250, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90–0.94 (m, 3H), 1.44–1.50 (m, 4H), 1.93–1.97 (m, 1H), 2.11 (s, 3H, 1OH), 2.34 (dd, J=10.5, 5.4 Hz, 1H), 3.21–3.24 (m, 1H), 4.25–4.29 (m, 1H), 5.43–5.47 (m, 1H), 5.66–5.76 (m, 1H), 5.75–5.76 (m, 1H), 5.84 (dd, J=10.2, 2.1 Hz, 1H), 6.05–6.11 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 131.5, 131.4, 128.2, 124.6, 78.9, 78.4, 70.4, 69.2, 48.5, 42.7, 40.1, 21.2, 16.5, 14.9.

4.2.9. Furan 19. To a solution of tetraol **16** (320 mg, 1.33 mmol) in DMF (10 mL) was added *N*-bromosuccinimide (237 mg, 1.33 mmol). The reaction mixture was stirred for 30 min and diluted with EtOAc (30 mL). The solution was then washed with 10% aqueous $NaHCO_3$ (30 mL) and the aqueous layer extracted with EtOAc (3×50 mL). The extracts were dried ($MgSO_4$), concentrated and chromatographed (1:1 hexanes–EtOAc) to give 424 mg (99%) of furan **19** as a colorless crystalline solid: mp 160–162°C; IR (KBr) 3376, 3165, 3078, 2960 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.93 (t, J=7.2 Hz, 3H), 1.21–1.66 (m, 3H), 1.71–1.80 (m, 1H), 1.99–2.05 (m, 1H), 2.42–2.44 (m, 1H), 2.58 (dd, J=17.4, 7.2, 1H), 4.14 (d, J=4.8 Hz, 1H), 4.23–4.27 (m, 1H), 4.62 (t, J=3.9 Hz, 1H), 5.11 (s, 1H), 5.79–5.80 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 139.0, 124.6, 84.8, 79.4, 78.9, 76.2, 72.4, 50.7, 39.1, 38.4, 30.7, 18.0, 15.4; LRMS (FAB) m/z 319 [$(M+H)^+$, calcd for $C_{13}H_{19}O_4$ 319].

4.2.10. Epoxide 20. To a solution of bromoether **19** (200 mg, 0.63 mmol) in CH_2Cl_2 (10 mL) was added a solution of dimethyl dioxirane (ca. 0.05 M, 50 mL). The reaction mixture was sealed, stirred for 6 h, dried ($MgSO_4$), concentrated and chromatographed (2:1 hexanes–EtOAc) to give 64.8 mg (31%) of epoxide **20** as a white solid: mp 201–202°C; IR (KBr) 3406, 2966, 2930, 1245 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.95 (t, J=7.2 Hz, 3H), 1.40–1.66 (m, 5H), 2.00–2.08 (m, 2H), 2.44 (dd, J=17.4, 6.6 Hz, 1H), 3.03 (dd, J=3.3, 1.2 Hz, 1H), 3.33–3.37 (m, 1H), 4.17 (d, J=4.8 Hz, 1H), 4.29 (dd, J=6.3, 4.8 Hz, 1H), 4.58 (d, J=3.9 Hz, 1H), 5.03 (s, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 85.6, 78.8, 77.5, 76.8, 72.2, 61.6, 54.0, 48.1, 47.8, 36.8, 35.2, 17.5, 15.3.

4.2.11. Tetraol 22. To a solution of epoxide **20** (90 mg, 0.27 mmol) in THF (5 mL) was added Zn/Ag couple (500 mg) prepared from refluxing Zn and AgOAc in acetic acid. The reaction mixture was refluxed for 12 h, and filtered through a pad of celite. The filtrate was concentrated and chromatographed (1:3 hexanes–EtOAc) to give 57.4 mg (83%) of alcohol **22** as a white solid: mp 125–126°C; IR ($CHCl_3$) 3401, 3032, 2960, 1061, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92–0.99 (m, 3H), 1.40–1.52 (m, 3H), 1.84–2.02 (m, 2H), 2.19, (3, J=3.3 Hz, 1H), 2.67–2.74 (m, 1H), 3.38 (s, 1H), 3.81 (d, J=5.4 Hz, 1H), 4.20 (d, J=5.7 Hz, 1H), 4.72 (t, J=4.2 Hz, 1H), 5.83–5.88 (m, 1H), 6.10–6.16 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 137.8, 123.4, 87.2, 79.0, 75.6, 77.0, 76.2, 70.7, 53.7, 38.8, 35.2, 17.0, 15.4; HRMS (FAB) m/z 257.1386 [$(M+H)^+$, calcd for $C_{13}H_{19}O_5$ 257.1387].

4.2.12. Triacetate 23. Epoxy alcohol **22** (17 mg, 0.07 mmol) was dissolved in 1:1 THF–0.1N H_2SO_4 (1 mL) and was stirred for 7 days. The solution was then treated with Amberlyst A21 ion exchange resin and was shaked for 12 h. The resin was then filtered off and the filtrate was concentrated. The residue was dissolved pyridine (1 mL) followed by the addition of acetic anhydride (0.5 mL) and DMAP (ca. 2 mg). The reaction mixture was stirred for 24 h, concentrated. and chromatograped (10:1 $CHCl_3$–CH_3OH) to give 10 mg (59%) of furan **23** as a yellow oil: IR ($CHCl_3$) 3411, 3027, 2966, 1742, 1373, 1224 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.91 (t, J=7.2 Hz, 3H), 1.44–1.54 (m, 3H), 1.91 (d, J=10.8 Hz, 1H), 2.00–2.10 (m, 9H), 2.60 (dd, J=10.8, J=5.7 Hz, 1H), 3.00–3.04 (m, 1H), 4.27–4.31 (m, 1H), 5.11 (d, J=3.9 Hz, 1H), 5.18 (t, J=3.3 Hz, 1H), 5.52–5.56 (m, 1H), 5.94–5.99 (m, 1H), 6.14–6.19 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 170.4, 170.0, 169.1, 132.5, 131.0, 82.0, 79.7, 71.6, 71.0, 68.6, 67.9, 48.7, 42.5, 36.2, 21.2, 21.2, 16.4, 15.6, 15.1.

4.2.13. Diol 25. To a solution of allylic alcohol **3** (3 g, 14.2 mmol) in DMF (20 mL) was added imidazole (2.4 g, 35.4 mmol), triisoproplysilyl chloride (4.5 mL, 21.2 mmol) and a catalytic amount of DMAP (ca. 20 mg). The reaction mixture was heated to 80°C and stirred for 12 h. Water (100 mL) was added and the aqueous solution was extracted with Et_2O (3×100 mL). The combined extracts were dried ($MgSO_4$) and concentrated to give crude **24** as a colorless oil. The residue was dissolved in CH_3OH (125 mL) and a catalytic amount of *p*-toluenesulphonic acid (ca. 50 mg) added. The reaction mixture was stirred for 45 min, concentrated and chromatographed (4:1 hexanes–EtOAc) to give 3.7 g (81%) of triisoproplysilyether **25** as a light yellow solid: mp 75–76°C; IR ($CHCl_3$) 3534, 3411, 3027, 2945, 1404 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 0.93–1.11 (m, 21H), 2.02–2.09 (m, 4H), 4.23 (s, 1H), 4.30–4.34 (m, 2H), 5.56–5.70 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1, 130.3, 129.0, 127.9, 70.6, 67.8, 64.0, 40.1, 36.3, 23.0, 17.4, 12.4; HRMS (FAB) m/z 361.2164 [$(M+Na)^+$, calcd for $C_{19}H_{34}O_3Si$ 361.2175].

4.2.14. Diketone 26. To a solution of diol **25** (7.48 g, 22.0 mmol) in acetone (100 mL) at 0°C was added Jones reagent (20 mL, 7.3 mmol) dropwise. The reaction mixture was stirred for 2 h, and CH_3OH (50 mL) was added and stirring continued for 5 min. The solid residue was removed by filtration through a pad of celite and washed with (2×100 mL) acetone. The filtrate was concentrated and partitioned between Et_2O (150 mL) and water (150 mL). The aqueous layer was extracted with Et_2O (3×100 mL) and the combined extracts were dried ($MgSO_4$), filtered, concentrated and chromatographed (6:1 hexanes–EtOAc) to give 5.53 g (75%) of diketone **25** as a yellow solid: mp 53–55°C; IR ($CHCl_3$) 3022, 2945, 1644, 1578, 1465, 1429 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.96–1.1 (m, 21H), 2.26–2.36 (m, 1H), 2.82–3.05 (m, 2H), 4.27 (dd, J=5.7 and 4.8 Hz, 1H), 6.05 (dd, J=9.9 and 2.1 Hz, 1H), 6.18 (d, J=10.2 Hz, 1H), 6.62 (dd, J=10.2 Hz, 1H), 6.70–6.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.5, 174.9, 144.9, 139.9, 127.7, 126.9, 102.6, 63.9, 36.3, 24.9, 18.1, 18.0, 12.8; HRMS (FAB) m/z 335.2034 [$(M+H)^+$, calcd for $C_{19}H_{30}O_3Si$ 335.2042].

4.2.15. Alcohols 26 and 27. To a solution of diketone **25** (245 mg, 0.73 mmol) in CH_2Cl_2 (5 mL) at 0°C was added a solution of dimethyl dioxirane solution (30 mL, 0.05 M, 1.5 mmol). The reaction mixture was stirred for 45 min, dried ($MgSO_4$), concentrated and chromatographed (9:1→2:1 hexanes–EtOAc) to give 121 mg (47%) of α-hydroxy enone **26** and 52 mg (20%) of α-hydroxy enone **27** (51.2 mg, 20%).

26: mp 133–135°C; IR ($CHCl_3$) 3473, 3027, 2966, 2402, 1696, 1675, 1527, 1470, 1419, 1224, 1209 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.06–1.27 (m, 21H), 2.42–2.52 (m, 1H), 2.72–2.83 (m, 1H), 2.94–2.99 (m, 1H), 4.46 (bs, 1H), 5.17–5.18 (m, 1H), 6.07 (dd, J=12.9 Hz, 1H), 6.17–6.20 (m, 1H), 6.79–6.84 (m, 1H), 7.01–7.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7, 152.8, 151.0, 127.3, 126.8, 78.3, 66.5, 48.1, 25.1, 18.0, 12.1; HRMS (FAB) m/z 351.1995 [$(M+H)^+$, calcd for $C_{19}H_{30}O_4Si$ 351.1992].

27: mp 104–105°C; IR ($CHCl_3$) 3467, 3027, 2945, 2868, 2361, 1716, 1460, 1383, 1255, 1066 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04–1.16 (m, 21H), 2.30–2.39 (m, 1H), 2.63–2.69 (m, 1H), 3.05–3.17 (m, 1H), 4.51 (dd, J=5.7 and 2.7 Hz, 1H), 4.69 (bs, 1H), 6.06 (dd, J=10.2 and 2.1 Hz, 1H), 6.17 (d, J=10.2 Hz, 1H), 6.96–7.04 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.4, 190.8, 147.4, 144.5, 130.2, 128.4, 73.8, 67.4, 44.7, 25.3, 18.0, 17.9, 12.4; HRMS (FAB) m/z 351.2000 [$(M+H)^+$, calcd for $C_{19}H_{30}O_4Si$ 351.1992].

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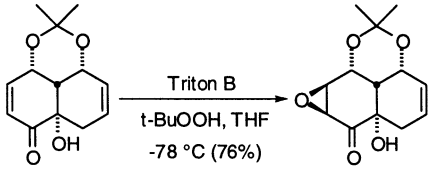
11. The stereochemistry of **14** was assigned based on a single-crystal X-ray analysis of the epoxide **i** derived from **14**.



14 **i** (X-ray)

12. Interestingly oxidation using conditions that presumably generates dimethyldioxirane led to formation of the *trans* isomer (**14**) suggesting the actual oxidant in under these conditions is not dimethyldioxirane. Cf. Ferraz, H. M. C.; Muzzi, R. M.; Vieira, T. D.; Viertler, H. *Tetrahedron Lett.* **2000**, *41*, 5021–5023.
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