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SYNTHESIS OF THE PENTACYCLIC XESTOBERGSTEROL SKELETON

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Abstract: An approach to the synthesis of the histamine release inhibitor xestobergsterol is described. The intramolecular Pauson-Khand reaction was used to generate the D and E rings of the steroid. © 1998 Elsevier Science Ltd. All rights reserved.

Xestobergsterol-A (**1**) was isolated from the crude extracts of the Okinawan sponge *Xestspongia berquista* Fromont in 1992,[1,2] and the structure was secured by spectroscopic means. It was shown to strongly inhibit histamine release from rat peritoneal mast cells induced by IgE in a dose dependent manner.[3] We recently reported the use of the intramolecular Pauson-Khand reaction[4] in a model study for the synthesis of the C/D/E rings with the correct stereochemistry at C-14 and C-17.[5] We now report application of our model study to the synthesis of the pentacyclic framework of the xestobergsterols.

The proposed retrosynthesis of xestobergsterol-A, **1**, is outlined in Scheme 1. We envisioned beginning the synthesis with the readily available steroid, epiandrosterone-3-methoxymethyl ether, **3**. Oxidation of the D-ring to the Δ-15, 16 enone would provide a means of adjusting the C-14 stereocenter. Subsequent oxidative cleavage of the enone, removing one carbon, would leave lactol **4** which could be converted to enyne **5** via addition of a metallated alkyne. Dicobalthexacarbonyl mediated Pauson-Khand cycloaddition[4] would then be expected to provide the desired pentacyclic skeleton **6**.

With the retrosynthetic plan in mind, methoxymethyl ether **3** was oxidized to the Δ-15,16 enone **7** via the trimethylsilyl enol ether (Scheme 2). Epimerization at C-14 was carried out by enone deconjugation and reconjugation,[6] however, regardless of the conditions used, a mixture of enones **8** and **9** were obtained in a 4:1 ratio.[7] Catalytic hydrogenation[8] of the β,γ-enone **9** to **9a** with cis fused C/D rings, followed by ketone to enone oxidation[9] provided the desired tetracycle **8** with *cis* fused C/D rings. Following the precedent established in our model study,[5] oxidative opening of the D-ring using OsO_4 followed by treatment of the resulting aldehyde with $LiBH_4$ gave lactone **10**. Partial reduction of **10** using DIBAL followed by Wittig olefination and oxidation of the primary alcohol with tetrapropylammonium perruthenate gave aldehyde **11**.

Dedicated to our colleague and friend Professor Madeleine M. Joullie in celebration of forty years of distinguished teaching and research at the University of Pennsylvania.

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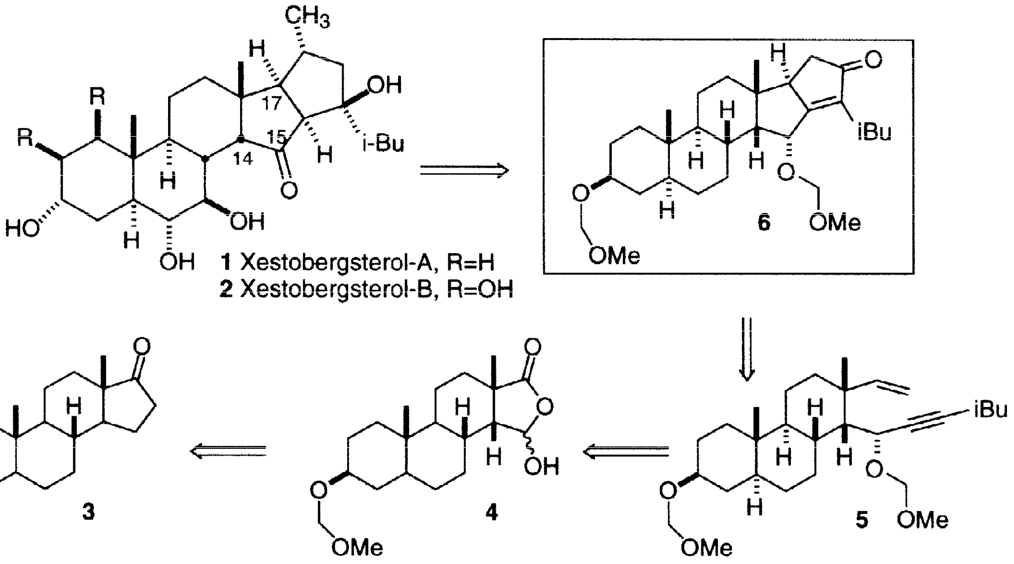
Scheme 1



Addition of 1-lithio-4-methyl-1-pentyne in THF to aldehyde **11** gave alcohol **12** as the only carbinol isomer. Based on our results from the model study, it was apparent that carbinol isomer **13** was necessary for achieving the proper configuration at C-17 from the Pauson-Khand cycloaddition. Use of 1-bromomagnesium-4-methyl-1-pentyne in THF at 0 °C or -78 °C resulted in a 3:2 ratio of alcohols **12** and **13**. Other changes in temperature and solvent and the use of additives did not significantly improve the ratio. With the desired isomer produced only as the minor isomer, we turned our attention to a more selective synthesis of **13**.

Since it was the nucleophilic addition to the C-15 aldehyde that was problematic we focussed our attention on introducing the C-15 stereocenter at an earlier stage. We reasoned that the facial selectivity could be biased by use of a metal chelate which would direct the Grignard reagent to the desired aldehyde face. Oxidative cleavage of enone **8** (Scheme 3) yielded acetal **4** which, upon reaction with 1-bromomagnesium-4-methyl-1-pentyne in THF at 0 °C, yielded lactone **14** as a single diastereomer, presumably via the chelated complex represented in Figure 1. Partial reduction of **14** using DIBAL gave a lactol which resisted all attempts at ring opening and methylenation under a variety of reaction conditions.

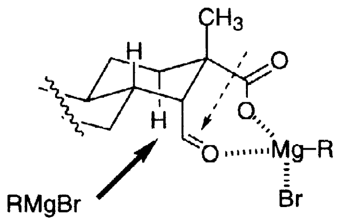
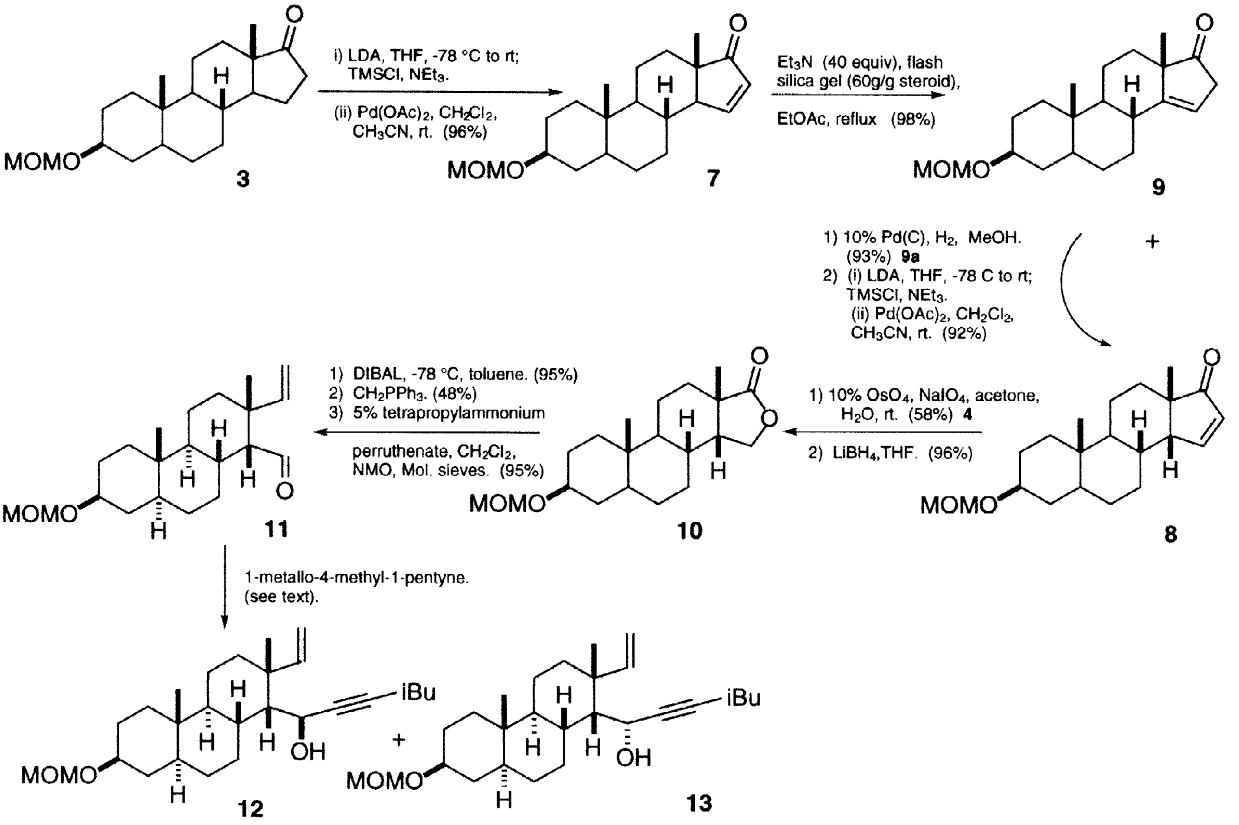


Fig 1.

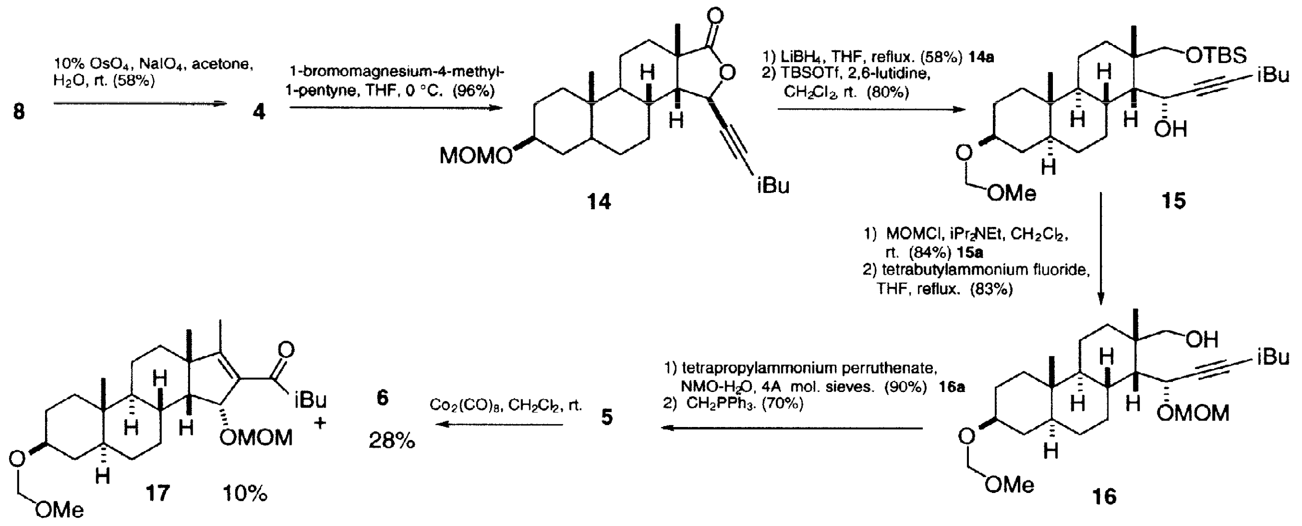
Scheme 2



Thus, an alternate route to the desired enyne **5** was followed. Reduction of **14** to the diol followed by selective protection of the primary alcohol using *tert*-butyldimethylsilyl trifluoromethanesulfonate at -78°C cleanly afforded silyl ether **15**. Protection of the secondary alcohol as the methoxymethyl ether proceeded smoothly and subsequent desilylation gave alkyne **16**. Oxidation and Wittig olefination yielded the Pauson-Khand precursor **5**. *In situ* generation of the hexacarbonyldicobalt complex of the alkyne in CH_2Cl_2 followed by stirring at ambient temperature for 20 hours yielded a 3:1 mixture of the desired pentacycle **6**, with the correct configuration at C-17, and the interrupted Pauson-Khand product **17** in 35-40% yield.[10] The tetracyclic enone presumably arises from reaction of an organometallic intermediate with oxygen, in accord with our previous observations.[11] Use of a high purity nitrogen or argon atmosphere did not completely inhibit the formation of the interrupted Pauson-Khand tetracycle as we had anticipated.

Using the intramolecular Pauson-Khand reaction we have achieved a synthesis of the pentacyclic skeleton of xestobergsterol-A with the key stereocenters at carbons 13, 14 and 17 established. Further work to improve the efficiency of the route is in progress.[12]

Scheme 3



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EXPERIMENTAL:

General. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from potassium prior to each use. Methylene chloride (CH_2Cl_2) and pyridine were distilled from calcium hydride. Hexane, chloroform ($CHCl_3$), methanol (MeOH), and ethyl acetate (EtOAc) were distilled prior to use. Toluene was distilled from sodium metal prior to use. All reactions were performed under an atmosphere of nitrogen. Infrared spectra (IR) were obtained on a Perkin-Elmer #1320 Infrared Spectrophotometer in $CHCl_3$ solutions. ^1H NMR spectra were obtained at 300 MHz on a Varian Gemini spectrometer or at 500 MHz on a Varian VXR500 spectrometer in $CDCl_3$ solutions unless otherwise noted. Carbon spectra were obtained at 75 MHz on a Varian Gemini 300 spectrometer in $CDCl_3$ solutions. Chemical shifts are reported in parts per million downfield relative to tetramethylsilane (δ 0.00); coupling constants are reported in Hz. Low resolution mass spectra were obtained on a Finnigan 4510 GC/MS instrument. Mass spectral data is reported as m/e (relative intensity). Melting points were taken on a Meltemp melting point apparatus and are uncorrected. Elemental Analyses were performed by Atlantic Microlab Inc, Norcross, GA.

Synthesis of 3: To a solution of 3β-hydroxy-5α-androstan-17-one (20 g, 66.8 mmol) and diisopropylethyl amine (23.2 mL, 133.6 mmol) in dichloromethane (330 mL) cooled to 0°C was added methoxymethyl chloride (7.6 mL, 100.2 mmol). The solution was kept at 0°C and stirred for 1 hour. It was then allowed to warm to room temperature and stirred overnight. The mixture was then diluted with methylene chloride and washed with water, 10% HCl, saturated sodium bicarbonate and brine. The organic layer was then dried over anhydrous magnesium sulfate and condensed to give a white solid. Purification by flash chromatography on silica gel (3/1 hexane/ethyl acetate) gave methoxymethyl ether **3** as white needles (22.1g, 99%). 500-MHz ^1H NMR: δ 0.69 (dt, *J*=3.9, 11.4, 1H), 0.84 (s, 3H), 0.86 (s, 3H), 0.94-1.03 (m, 2H), 1.12 (m, 1H), 1.20-1.38 (m, 6H), 1.42-1.58 (m, 3H), 1.62-1.70 (m, 2H), 1.74 (dt, *J*=13.3, 3.4, 1H), 1.78-1.98 (m, 4H), 2.05 (ddd, *J*=9.1, 9.1, 19.1, 1H), 2.43 (ddd, *J*=1, 9.1, 19.1, 1H), 3.50 (dddd, *J*=4.9, 4.9, 11.1, 11.1, 1H), 3.36 (s, 3H), 4.67 (bs, 2H). 75-MHz ^{13}C NMR: δ 12.00, 13.60, 20.29, 21.58, 28.33, 28.51, 30.77, 31.46, 34.98, 35.13, 35.68, 36.87, 44.86, 47.66, 51.41, 54.49, 55.02, 76.21, 94.68, 221.50. IR(cm^{-1}): 2925, 1721, 1031. Mass spectrum *m/e* (PCI: isobutane): 335 (M^++1), 303 (M^+-31), 273 (M^+-61, 100). Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.25, H, 10.15. mp: 95-96 °C. $[\alpha]_D^{25}$ +46 (c = 29.4, $CHCl_3$).

Synthesis of 7: To a solution of diisopropylamine (5 mL, 36 mmol) in THF (84 mL) cooled to -78°C was added a solution of BuLi in hexanes (22.8 mL, 36 mmol). The mixture was stirred at -78°C for 15 minutes. A solution of **3** (6 g, 18 mmol) in THF (18 mL) was added dropwise over a 30-minute period and the reaction mixture was stirred at -78°C for 15 more minutes. Then, trimethylsilyl chloride (3.4 mL, 24.3 mmol) and triethylamine (7.5 mL, 54 mmol) were added. The mixture was warmed to room temperature and stirred for an additional 25 minutes. It was then quenched with saturated sodium bicarbonate. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were dried over magnesium sulfate and condensed under vacuum. The crude enol ether was then dissolved in dichloromethane (15 mL) and acetonitrile (75 mL). Palladium acetate (4.40 g, 19 mmol) was added in one portion. The reaction mixture was stirred for 2 hours at room temperature It was filtered twice through silica gel pads (3/1 hexane ethyl acetate). Purification of the residue by flash chromatography on silica gel (3/1 hexane ethyl acetate) gave enone **7** as white needles (5.72 g, 96%). 500-MHz ^1H NMR: δ 0.80 (m, 1H), 0.89 (s, 3H), 1.00 (dt, *J*=3.9, 13.8, 1H), 1.06 (m, 3H), 1.06-1.20 (m, 2H), 1.30-1.58 (m, 6H), 1.65 (m, 1H), 1.69-1.82 (m, 3H), 1.84-1.91 (m, 2H), 1.99 (dq, *J*=12.8, 3.9, 1H), 2.27 (dt, *J*=11.4, 2.3, 1H), 3.37 (s, 3H), 3.51 (dddd, *J*=5, 5, 11.2, 11.2, 1H), 4.67 (bs, 2H), 6.01 (dd, *J*=3, 6, 1H), 7.50 (ddd,*J*=1, 3, 6, 1H). 75-MHz ^{13}C NMR: δ 12.06, 20.03, 20.45, 28.18, 28.48, 29.09, 30.67, 32.31, 35.11, 35.92, 36.63, 45.10, 51.03, 55.01, 55.80, 56.92, 76.15, 94.70, 131.95, 158.61, 213.46. IR (cm^{-1}): 2909, 2830, 1696, 1444, 1323, 1140. Mass spectrum *m/e* (PCI:isobutane): 333 (M^++1, 100). Anal. Calcd for $C_{21}H_{32}O_3 \cdot 0.4\ H_2O$: C, 74.26; H, 9.61. Found: C, 74.27; H, 9.58. mp: 56-58 °C. $[\alpha]_D^{25}$ -52 (c = 17.4, $CHCl_3$).

Synthesis of 8 and 9: To a mixture of flash silica gel (placed in the oven for 2 days at 120°C) (350 g), triethylamine (87 mL, 624 mmol) and ethyl acetate (1.1 L) was added enone **7** (5.72 g, 7.2 mmol). The mixture was then brought to reflux and stirred (using a mechanical stirrer) for 22 hours. It was then filtered through a celite pad and rinsed several times with ethyl acetate. Evaporation of the solvent gave a mixture of 2 compounds which was subjected to flash chromatography (silica gel) to give the deconjugated enone **9** (4.48 g, 78%) and the C-14 epimerized enone **8** (1.12 g, 20%) as white needles. **9:** 500-MHz ^1H NMR: δ 0.71 (dt, *J*=3.9, 11.4, 1H), 0.88 (s, 3H), 0.96 (dt, *J*=3.9, 13.5, 1H), 1.12 (s, 3H), 1.12 (s, 3H), 1.12 (m, 1H), 1.23 (dt, *J*=3.6, 13, 1H), 1.32-1.52 (m, 6H), 1.64-1.74 (m, 2H), 1.84-1.92 (m, 2H), 2.17 (m, 1H), 2.81 (dt, *J*=22.9, 1.8, 1H), 2.98 (ddd, *J*=1.8, 3.9, 22.9, 1H), 3.37 (s, 3H), 3.49 (dddd, *J*=4.9, 4.9, 11.2, 11.2, 1H), 4.67 (bs, 2H), 5.50 (q, *J*=1.8, 1H). 75-MHz ^{13}C NMR: δ 11.76, 19.65, 20.52, 27.98, 28.38, 28.65, 33.04, 34.98, 35.31, 35.90, 36.68, 41.20, 44.45, 50.79, 54.78, 54.99, 76.07, 94.62, 113.02, 153.85, 222.87. IR (cm^{-1}): 2923, 1736, 1626, 1441, 1140, 1040. Mass spectrum *m/e* (PCI: isobutane): 332 (M$^+$, 100). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.87; H, 9.70. Found: C, 75.80; H, 9.76. mp (°C) : 53-54. $[\alpha]_D^{25}$ +85 (c = 13.5, $CHCl_3$). **8:** 500-MHz ^{1}H NMR: δ 0.73 (dt, *J*=12.5, 7.4, 1H), 0.79 (s, 3H), 0.83 (dt, *J*=3.9, 13.5, 1H), 1.06 (m, 1H), 1.09 (s, 3H), 1.24-1.34 (m, 3H), 1.36-1.50 (m, 5H), 1.62-1.69 (m, 3H), 1.76 (dq, *J*=15.8, 3.6, 1H), 1.82 (m, 1H), 1.92 (tt, *J*=4.9, 12.2, 1H), 2.57 (dt *J*=4.9, 2.3, 1H), 3.36 (s, 3H), 3.47 (dddd, *J*=4.7, 4.7, 11.2, 11.2, 1H), 4.67 (bs, 2H), 6.19 (dd, *J*=2.3, 6, 1H), 7.68 (dd, *J*=2.3, 6, 1H). 75-MHz ^{13}C NMR: δ 10.88, 19.67, 21.79, 27.97, 28.47, 30.62, 32.60, 33.86, 34.87, 36.04, 36.45, 44.43, 45.43, 47.24, 54.54, 54.87, 76.06, 94.56, 133.18, 164.20, 215.75. IR (cm^{-1}): 2918, 1693, 1442, 1141, 1102, 1041. Mass spectrum *m/e* (PCI: isobutane): 333 (M$^+$+1, 100). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.87; H, 9.70. Found: C, 75.90; H, 9.76. mp: 73-75 °C. $[\alpha]_D^{25}$ +211 (c = 32, $CHCl_3$).

Synthesis of 9a: A solution of ketone **9** (5 g, 15.1 mmol) in MeOH (1.07 L) was added to 10% Pd/C (5 g). The reaction vessel was then fitted with a balloon filled with hydrogen and the mixture was stirred for 2 hours at room temperature. It was then filtered through a pad of celite. After concentration in vacuo, the residue was subjected to column chromatography (silica gel) using a 3/1 mixture of hexane/ethyl acetate as the eluent to give ketone **9a** as white needles (4.6 g, 93%). 500-MHz ^{1}H NMR: δ 0.82 (s, 3H), 0.92-1.00 (m, 2H), 1.11 (m, 1H), 1.08 (s, 3H), 1.15-1.22 (m, 2H), 1.26-1.40 (m, 5H), 1.42-1.54 (m, 2H), 1.56-1.68 (m, 2H), 1.72-1.88 (m, 6H), 2.10 (ddd, *J*=8.7, 8.7, 18.8, 1H), 2.45 (ddd, *J*=1.2, 8.7, 18.8, 1H), 3.36 (s, 3H), 3.50 (dddd, *J*=5, 5, 11.1, 11.1, 1H), 4.68 (bs, 2H). 75-MHz ^{13}C NMR: δ 11.77, 18.28, 19.35, 20.14, 28.17, 28.26, 28.51, 30.71, 33.16, 35.01, 35.45, 36.69, 44.54, 46.42, 47.70, 48.17, 54.90, 76.17, 94.59, 223.01. IR (cm^{-1}): 2913, 1727, 1440, 1244, 1197, 1036. Mass spectrum *m/e* (PCI: isobutane): 333 (M$^+$+1). Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.32; H, 10.26. Mp = 50-51°C. $[\alpha]^{25}_D$ +72 (c = 10, $CHCl_3$).

Synthesis of 8: To a solution of diisopropylamine (3.6 mL, 25.8 mmol) in THF (60 mL) cooled to -78°C was added a solution of BuLi in hexanes (16.4 mL, 25.8 mmol). The mixture was stirred at -78°C for 15 minutes. A solution of **9a** (4.39 g, 13.1 mmol) in THF (13 mL) was added dropwise over a 30-minute period and the reaction mixture was stirred at -78°C for 15 more minutes. Then, triethylamine (5.5 mL, 39.4 mmol) and trimethylsilyl chloride (2.5 mL, 19.7 mmol) were added. The mixture was warmed to room temperature and stirred for an additional 25 minutes. It was quenched with saturated sodium bicarbonate. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were dried over magnesium sulfate and condensed under vacuum. The crude enol ether was then dissolved in dichloromethane (15 mL) and acetonitrile (75 mL). Palladium acetate (2.96 g, 13.2 mmol) was added in one portion. The reaction mixture was stirred for 2 hours. It was filtered twice through silica gel pads (3/1 hexane/ethyl acetate). Purification of the residue by flash chromatography on silica gel (3/1 hexane/ethyl acetate) gave **8** enone as white needles (4 g, 92%).

Synthesis of 4: To a solution of enone **8** (2.36 g, 7.1 mmol) in acetone (110 mL) was added osmium tetraoxide (176 mg, 0.71 mmol) at room temperature. The solution was stirred for 30 minutes. A solution of sodium periodate (14.7g, 69 mmol) in water (110 mL) was then added dropwise, and the resulting mixture was stirred for 18 hours. After concentration in vacuo to half volume, the reaction mixture was extracted with ethyl acetate. The organic layer was then dried over anhydrous magnesium sulfate and condensed. Purification of the residue by flash chromatography on silica gel (1/1 hexane/ethyl acetate) afforded 2 C-15 hydroxylactones **4** as white needles (2.95 g, 58%). 500-MHz ^{1}H NMR: (Major diastereomer) δ 0.81 (s, 3H), 0.89 (dt, *J*=2, 11.6, 1H), 0.98 (dt, *J*=3.8, 13.5, 1H), 1.17-1.50 (m, 13H), 1.52-1.77 (m, 3H), 1.79 (dt, *J*=12.8, 3.6, 1H), 1.87 (m, 1H), 1.93 (t, *J*=6, 1H), 3.36 (s, 3H), 3.50 (dddd, *J*=4.9, 4.9, 11.4, 11.4, 1H), 4.67 (s, 2H), 5.74 (bs, 1H). Mixture of C-15-epimers. IR (cm^{-1}): 3382, 2928, 1755, 1140, 1034. Mass spectrum *m/e* (PCI: isobutane): 353 (M$^+$+1, 100). Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.16; H, 9.15. Found C, 68.03; H, 9.22.

Synthesis of 10: To a solution of hydroxylactone **10a** (0.65 g, 1.83 mmol) in THF (18 mL) cooled to 0°C was added in one portion lithium borohydride (60 mg, 2.74 mmol). The solution was stirred at 0°C for 15 minutes and then an additional 30 minutes at room temperature. It was diluted with ethyl acetate and carefully quenched with 10% HCl. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate and dried over magnesium sulfate and condensed under vacuum. Purification of the residue by flash chromatography gave lactone **10** (592 mg, 96%). 500-MHz ^{1}H NMR: δ 0.81 (s, 3H), 0.90-1.20 (m, 5H), 1.25 (s, 3H), 1.26-1.36 (m, 3H), 1.42-1.56 (m, 2H), 1.58-1.68 (m, 4H), 1.74 (tt, *J*=4, 12, 1H), 1.79 (dt, *J*=13.5, 3.5, 1H), 1.87 (m, 1H), 2.26 (ddd, *J*=5, 8, 12, 1H), 3.36 (s, 3H), 3.50 (dddd, *J*=5, 5, 11.5, 11.5, 1H), 4.10 (dd, *J*=8, 12, 1H), 4.16 (t, *J*=8, 1H), 4.67 (s, 2H). 75-MHz ^{13}C NMR: δ 11.64, 19.35, 19.86, 28.15, 28.24, 29.92, 30.40, 32.38, 34.81, 35.40, 36.53, 40.70, 44.25, 46.71, 47.10, 54.95, 66.48, 75.91, 94.47, 182.29. IR (cm^{-1}): 2927, 1756, 1444, 1368, 1142, 1039. Mass spectrum *m/e* (PCI: isobutane): 337 (M$^+$+1, 100). Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.30; H, 9.64. mp (°C) = 105-106. $[\alpha]_D^{25}$ +60 (c = 17, $CHCl_3$).

Synthesis of 11a: To a solution of lactone **10** (1.67 g, 4.96 mmol) in toluene (50 mL) cooled to -78°C was added dropwise a solution of Dibal in toluene (6.6 mL, 9.94 mmol). The solution was stirred at this temperature for 3 hours. The mixture was then diluted with ethyl acetate and washed with 10% HCl and saturated sodium bicarbonate. The combined organic layers were dried over magnesium sulfate and condensed under vacuum. Purification of the residue by flash chromatography gave a mixture of lactols **11a** (1.57 g, 95%).

Synthesis of 11b: To a solution of Ph_3PCH_3Br (7.9 g, 22.15 mmol) in toluene (140 mL) cooled to 0°C was added dropwise a solution of BuLi in hexanes (13.8 mL, 22.15 mmol). The mixture was stirred at 0°C for 30 minutes and was then warmed to room temperature. A solution of hydroxylactones **11a** (1.5 g, 4.43 mmol) in toluene (6 mL) was added dropwise at room temperature and the mixture was then refluxed over night. After cooling to room temperature, it was quenched with acetone. After evaporation of toluene under reduced pressure, the residue was purified by flash chromatography to give **11b** as a white solid (0.66 g, 48%). 500-MHz ^{1}H NMR: δ 0.77 (dt, *J*=4, 12, 1H), 0.83 (s, 3H), 0.94 (dt, *J*=4, 13.5, 1H), 1.07 (s, 3H), 1.08 (m, 1H), 1.24-1.62 (m, 11H), 1.65 (dtt, *J*=12.5, 2.5, 3, 1H), 1.76 (dt, *J*=13.5, 3.5, 1H), 1.85 (m, 1H), 1.92 (tt, *J*=4.5, 12, 1H), 3.36 (s, 3H), 3.49 (dddd, *J*=4.5, 4.5, 11.5, 11.5, 1H), 3.62-3.70 (m, 2H), 4.67 (s, 2H), 4.98 (dd, *J*=1, 17.5, 1H), 5.02 (dd, *J*=1, 11, 1H), 6.00 (dd, *J*=11, 17.5, 1H). 75-MHz ^{13}C NMR: δ 12.03, 20.27, 24.54, 28.24, 28.56, 29.73, 31.11, 33.43, 35.01, 35.61, 36.80, 39.18, 44.40, 47.15, 52.00, 54.83, 60.70, 76.06, 94.33, 110.32, 149.63. IR (cm^{-1}): 3425, 2924, 1625, 1445, 1142, 1037. Mass spectrum *m/e* (PCI: isobutane): 337 (M^{+}+1), 275 (M^{+}-61, 100). Anal. calcd for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 74.83; H, 10.74. mp: = 57-58 °C. $[\alpha]_D^{25}$ -5 (c = 10, $CHCl_3$).

Synthesis of 11: To a solution of **11b** (195 mg, 0.58 mmol) and 4-methylmorpholine N-oxide monohydrate (94 mg, 0.69 mmol) in dichloromethane (5.8 mL) was added molecular sieves. The mixture was stirred for 15 minutes at room temperature. Tetrapropylammonium perruthenate (11 mg, 0.03 mmol) was then added to the mixture and it was stirred for 1 hour. The mixture was then diluted with dichloromethane and filtered through a pad of celite. Evaporation of the solvent gave the crude aldehyde **11** as a colorless viscous oil (0.184 g, 95%) which was used with further purification.

Synthesis of 12 : To a solution of 4-methyl-1-pentyne (55μL, 0.46 mmol) in THF (4 mL) at 0°C was added dropwise a solution of n-BuLi in hexanes (0.29 mL, 0.46 mmol). The resulting solution was stirred for 30 minutes at 0°C and aldehyde **11** (80 mg, 0.24 mmol) in THF (1 mL) was then added. After being stirred at 0°C for 2 hours, the reaction was quenched by addition of water. The reaction mixture was then diluted with ethyl acetate and washed with brine. The combined organic portions were dried over $MgSO_4$, filtered and concentrated to give **12** (87 mg, 90%). 300 MHz ^{1}H NMR: δ 0.80 (s, 3H), 0.97 (d, *J*=6.5, 6H), 1.05(s, 3 H), 0.8-1.69(m, 13 H), 1.71-1.88 (m, 3H), 1.98 (m, 1H), 2.10 (dd, *J*=2.2, 6, 2H), 2.33 (d, *J*=8.8, 1H), 2.45 (dt, *J*=3.9, 14.5, 1H), 3.36(s, 3H), 3.50 (dddd, *J*=4.5, 4.5, 11.5, 11.5, 1H), 4.68 (s, 2H), 4.71(dd, *J*=8.8, 2.2, 1H), 5.10 (dd, *J*=17.5, 11, 2H), 6.17 (dd,*J*=11, 17.5, 1H). 75-MHz^{13}C NMR: δ 12.06, 20.56, 22.32, 26.33, 28.18, 28.45, 28.76, 29.56, 29.99, 32.70, 34.36, 35.51, 36.54, 37.29, 40.09, 45.03, 46.41, 53.91, 55.38, 62.92, 84.14, 87.28, 95.03, 111.95, 150.61. IR(cm^{-1}):2925; 2862; 1460; 1378; 1142; 1099; 1035; 1007. Mass spectrum *m/e* (PCI: isobutane): 416(M^+), 398(M^+-18), 337(M^+-79, 100). Anal. calcd for $C_{27}H_{44}O_3{\cdot}H_2O$: C, 77.62; H, 10.66. Found: C, 77.64; H, 10.46.

Synthesis of 14: To a solution of 4-methyl-1-pentyne (1.13 mL, 9.59 mmol) in THF (5.25 mL) cooled to 0°C was added dropwise EtMgBr (9.59 mL, 9.59 mmol). The solution was kept at 0°C and stirred for 15 minutes. It was then allowed to warm to room temperature and stirred for 20 minutes. This solution was then added dropwise via syringe to a solution of hydroxylactones **4** (1.35 g, 3.83 mmol) in THF (22 mL) cooled to 0°C. After being stirred for 15 minutes at 0°C, it was warmed to RT and stirred for 15 minutes. The mixture was then quenched with ammonium chloride. The aqueous layer was extracted with ethyl acetate. The combined organic layers were then washed with saturated sodium bicarbonate and dried over magnesium sulfate and concentrated. Purification of the residue by flash chromatography gave the lactone **14** as a viscous oil (1.5 g, 96%). 500-MHz ^{1}H NMR: δ 0.81 (s, 3H), 0.92 (m, 1H), 0.97 (d, *J*=6.5, 6H), 1.08-1.20 (m, 2H), 1.25-1.50 (m, 7H), 1.26 (s, 3H), 1.58-1.69 (m, 3H), 1.71-1.90 (m, 5H), 2.13 (dd, *J*=2, 6.5, 2H), 2.24 (dd, *J*=2, 6.5, 1H), 3.36 (s, 3H), 3.50 (dddd, *J*=5, 5, 11, 11, 1H), 4.68 (s, 2H), 4.92 (dt, *J*=2, 10.5, 1H). 75-MHz ^{13}C NMR: δ 11.71, 19.13, 19.73, 21.61, 27.53, 27.63, 28.12, 28.45, 30.62, 31.76, 32.79, 34.86, 35.58, 36.63, 42.03, 44.14, 47.54, 53.89, 54.87, 68.18, 75.97, 78.37, 87.87, 94.59, 180.41. IR (cm^{-1}): 2917, 1766, 1433, 1041. Mass spectrum *m/e* (PCI: isobutane): 417 (M^++1, 100), 335 (M^+-80). Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 74.79; H, 9.63. $[\alpha]_D^{25}$ -7 (c = 10, $CHCl_3$).

Synthesis of 14a: To a solution of lactone **14** (0.2 g, 0.48 mmol) in THF (4.8 mL) cooled to 0 °C was added lithium borohydride (22 mg, 0.96 mmol). The solution was warmed to room temperature and refluxed for 4.5 hours. It was then cooled to room temperature, diluted with ethyl acetate and carefully quenched with 10% HCl. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated sodium bicarbonate and dried over magnesium sulfate and condensed under vacuum. Purification of the residue by flash chromatography (silica gel 2/1 hexane/ethyl acetate) gave 2 lactols (55 mg, 27%) and diol **14a** as a white solid (110 mg, 55%). **14a:** 500-MHz ^1H NMR: δ 0.80 (s, 3H), 0.90-1.15 (m, 3H), 0.97 (d, *J*=6.5, 6H), 1.03 (s, 3H), 1.25-1.93 (m, 16H), 2.13 (dd, *J*=2.5, 7, 2H), 3.37 (s, 3H), 3.48 (dddd, *J*=4.5, 4.5, 11.5, 11.5, 1H), 3.55 (d, *J*=12, 1H), 3.75 (d, *J*=12, 1H), 4.68 (s, 2H), 4.95 (d, *J*=2, 1H). 75-MHz ^{13}C NMR: δ 12.02, 20.11, 21.91, 23.72, 27.85, 27.92, 28.41, 28.97, 30.40, 31.97, 34.73, 35.22, 36.16, 36.97, 38.91, 44.45, 46.62, 50.59, 55.01, 61.23, 71.31, 76.47, 84.80, 94.72. IR (cm^{-1}): 3403, 2921, 1457, 1377, 1141, 1035. Mass spectrum *m/e* (PCI: isobutane): 403 (M^+-17), 341 (M^+-79, 100). Anal. Calcd for $C_{26}H_{44}O_4$: C, 71.20; H, 10.56. Found: C, 71.52; H, 10.24. $[\alpha]_D^{25}$ -4 (c = 10, $CHCl_3$).

Synthesis of 15: To a solution of diol **14a** (0.89 g, 2.12 mmol) in dichloromethane (16 mL) and 2,6-lutidine (0.5 mL, 4.3 mmol) cooled to 78°C was added dropwise a solution of t-butyldimethylsilyl trifluoromethanesulfonate (0.49 mL, 2.12 mmol) in dichloromethane (7.4 mL). The reaction mixture was stirred at -78°C for 1 hour. It was quenched at -78°C with a solution of saturated ammonium chloride. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with saturated sodium bicarbonate. The organic layer was dried over magnesium sulfate and condensed under vacuum. Purification of the residue by flash chromatography on silica gel (6/1 hexane/ethyl acetate) gave the monoprotected alcohol **15** as a colorless viscous oil (0.90 g, 80%). 500-MHz ^1H NMR: δ 0.03 (s, 3H), 0.04 (s, 3H), 0.79 (s, 3H), 0.85-1.20 (m, 3H), 0.93 (s, 9H), 0.97 (s, 3H), 0.99 (d, *J*=6.5, 6H), 1.22-1.68 (m, 9H), 1.74-1.94 (m, 7H), 2.09 (dd, *J*=2.5, 6.5, 2H), 3.37 (s, 3H), 3.41 (d, *J*=10.5, 1H), 3.48 (dddd, *J*=5, 5, 11, 11, 1H), 3.74 (d, *J*=10.5, 1H), 4.68 (s, 2H), 4.88 (d, *J*=2, 1H). 75-MHz ^{13}C NMR: δ -5.91, -5.72, -3.77, 11.99, 18.12, 20.29, 22.08, 24.26, 25.52, 25.70, 27.91, 28.22, 28.42, 29.12, 30.18, 32.09, 35.07, 35.20, 36.07, 36.89, 38.79, 44.28, 45.92, 51.95, 54.95, 61.17, 71.61, 76.41, 84.62, 94.54. IR (cm^{-1}): 3358, 2922, 2248, 1456, 1253, 1035. Mass spectrum *m/e* (PCI: isobutane): 517 (M^+-17, 100). Anal. Calcd for $C_{32}H_{58}O_4Si$: C, 71.86; H, 10.84. Found: C, 71.57; H, 10.84. mp = 58-59 °C. $[\alpha]_D^{25}$ +2 (c = 17.5, $CHCl_3$).

Synthesis of 15a: To a solution of **15** (0,75 g, 1.4 mmol) and diisopropylethylamine (1.42 mL) in dichloromethane (7.5 mL) cooled to 0°C was added methoxymethyl chloride (0.46 mL, 6.05 mmol). The solution was kept at 0 °C and stirred for 1 hour. It was then allowed to warm to room temperature and stirred for 48 hours. The mixture was then diluted with methylene chloride and washed with water, 10% HCl, saturated sodium bicarbonate and brine. The organic layer was then dried over anhydrous magnesium sulfate and condensed to give a white solid. Purification by flash chromatography on silica gel (9/1 hexane/ethyl acetate) gave **15a** as a colorless viscous oil (0.67g, 84%). 500-MHz ^1H NMR: δ 0.04 (s, 6H), 0.78 (s, 3H), 0.89 (m, 1H), 0.90 (s, 9H), 0.98 (s ,3H), 0.99 (s, 6H), 1.05-1.48 (m, 7H), 1.50-1.70 (m, 5H), 1.73-1.86 (m, 4H), 1.88-1.93 (m, 2H), 2.10 (dd, *J*=2, 6.5, 2H), 3.36 (s, 3H), 3.36 (d, *J*=10, 1H), 3.37 (s, 3H), 3.48 (dddd, *J*=5, 5, 11, 11, 1H), 3.54 (d, *J*=10, 1H), 4.55 (d, *J*=6.5, 1H), 4.68 (s, 2H), 4.70 (bs, 1H), 4.85 (d,*J*=6.5, 1H). 75-MHz ^{13}C NMR: δ -5.68, 11.70, 18.25, 19.97, 22.17, 22.20, 23.38, 25.86, 27.87, 28.26, 28.51, 29.53, 32.35, 34.67, 35.27, 36.25, 37.16, 38.42, 44.60, 46.06, 48.76, 48.79, 55.02, 55.63. IR (cm^{-1}): 2923, 1436, 1376, 1230, 1039. Mass spectrum *m/e* (PCI: isobutane): 517 (M^+-61, 100). Anal. Calcd for $C_{34}H_{62}O_5Si$: C, 70.54; H, 10.79. Found: C, 70.27; H, 10.72. $[\alpha]_D^{25}$ + 34 (c = 20, $CHCl_3$).

Synthesis of 16: To a solution of **15a** (0.67 g, 1.16 mmol) in THF (11.6 mL) was added a solution of tetrabutylammonium fluoride in THF (2.32 mL, 2.32). It was then brought to reflux and stirred for 5 hours. The reaction mixture was cooled to room temperature and quenched with water. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate and condensed under vacuum. Purification of the residue by flash chromatography on silica gel (3/1 hexane ethyl acetate) gave alcohol **16** as a colorless viscous oil (0.45 g, 83%). 500-MHz ^1H NMR: δ 0.80 (s, 3H), 0.86-1.00 (m, 2H), 0.97 (d, *J*=6.5, 6H), 1.06 (m, 1H), 1.08 (s, 3H), 1.26-1.50 (m, 7H), 1.52-1.68 (m, 4H), 1.72-1.90 (m, 5H), 2.14 (dd, *J*=1, 7, 2H), 2.56 (dd, *J*=5, 9.5, 1H), 3.18 (dd, *J*=9.5, 12, 1H), 3.37 (s, 3H), 3.43 (s, 3H), 3.47 (dddd, *J*=5, 5, 11, 11, 1H), 3.98 (dd,*J*=5, 12, 1H), 4.55 (d, *J*=7, 1H), 4.68 (s, 2H), 4.89 (bs, 1H), 4.98 (d, *J*=7, 1H). 75-MHz ^{13}C NMR: δ 12.00, 19.97, 21.99, 23.44, 27.87, 28.35, 28.99, 30.44, 32.02, 34.25, 35.11, 36.20, 37.12, 38.83, 44.78, 46.77, 48.53, 55.06, 56.51, 64.21, 71.04, 76.17, 81.37, 86.97, 93.92, 94.47. IR (cm^{-1}): 3461, 2933, 1444, 1364, 1143, 1037. Mass spectrum *m/e* (PCI: isobutane): 403 (M^+-61, 100). Anal. Calcd for $C_{28}H_{48}O_5 \cdot H_2O$: C, 69.67; H, 10.44. Found: C, 69.54; H, 10.04. $[\alpha]_D^{25}$ +62 (c = 13.7, $CHCl_3$).

Synthesis of 16a: To a solution of **16** (0.16, g, 0.35 mmol) and 4-methylmorpholine N-oxide monohydrate (70 mg, 0.52 mmol) in dichloromethane (3.5 mL) was added molecular sieves. The mixture was stirred for 15 minutes at room temperature. Tetrapropylammonium perruthenate (7 mg, 0.02 mmol) was then added to the mixture and it was stirred for 1 hour. The mixture was then diluted with dichloromethane and filtered through a pad of celite. Evaporation of the solvent gave the crude aldehyde **16a** as a colorless viscous oil (0.152 g) which was used without further purification.

Synthesis of 5: To a solution of methytriphenylphosphonium bromide (1.43 g, 4 mmol) in THF (10 mL) cooled to 0 °C was added a solution of butyllithium in hexanes (2.5 mL, 4 mmol). The mixture was kept at 0°C and stirred for 15 minutes. It was then allowed to warm to room temperature and thereafter stirring was stopped to allow lithium bromide to settle at the bottom of the flask. The salt free ylide solution was then added dropwise via syringe to a solution of aldehyde **16a** (0.39 g, 0.84 mmol) in THF (4 mL) cooled to 0 °C. The mixture was stirred for 10 minutes at 0 °C and quenched with acetone. Evaporation of the solvent and purification of the residue by flash chromatography on silica gel (9/1 hexane ethyl acetate) gave alkenyne **5** as a colorless viscous oil (0.27 g, 70%). 500-MHz ^1H NMR: δ 0.82 (s, 3H), 0.94 (dt, *J*=3.9, 13, 1H), 1.00 (d, *J*=6.5, 6H), 1.08 (s, 3H), 1.14-1.50 (m, 7H), 1.58-1.66 (m, 4H), 1.76-2.10 (m, 7H), 2.11 (dd, =2.5, 7, 2H), 3.34 (s, 3H), 3.37 (s, 3H), 3.48 (dddd, *J*=5, 5, 11, 11, 1H), 4.48 (d, *J*=6, 5, 1H), 4.68 (s, 2H), 4.70 (m, 1H), 4.87 (d, *J*=6, 5, 1H), 4.96 (dd, *J*=1.5, 17.5, 1H), 4.99 (dd, *J*=1.5, 10.5, 1H), 5.92 (dd, *J*=10.5, 17.5, 1H). 75-MHz ^{13}C NMR: δ 11.44, 20.12, 22.14, 25.87, 27.81, 28.25, 28.48, 29.41, 29.54, 31.78, 33.79, 35.25, 36.15, 37.09, 39.59, 44.54, 45.11, 52.17, 55.04, 55.36, 66.03, 76.44, 80.26, 89.11, 93.06, 94.53, 110.61, 149.18. IR (cm^{-1}): 2921, 1444, 1140, 1100, 1030. Mass spectrum *m/e* (PCI: isobutane): 461 (M$^+$+1, 100), 399 (M$^+$-61, 100). Anal. Calcd for $C_{29}H_{48}O_4\cdot 0.9\ H_2O$: C, 73.03; H, 10.52. Found: C, 72.74; H, 10.14. $[\alpha]_D^{25}$ +56 (c = 4, CHCl$_3$).

Synthesis of 6 and 17: To a solution of alkenyne **5** (20 mg, 0.43 mmol) in dichloromethane (0.4 mL) cooled to -78 °C was added dicobaltoctacarbonyl (16 mg, 48 mmol). The reaction vessel was purged and flushed with ultra high purity grade nitrogen three times and warmed to room temperature. The mixture was then stirred for 20 hours. It was diluted with dichloromethane and filtered through a pad of celite, and then silica gel. Purification of the residue by flash chromatography on silica gel (6/1 hexane/ethyl acetate) gave the Pauson-Khand adduct **6** as a viscous oil (7 mg, 28%) and tetracyclic enone **17** (2 mg, 10%). **6:** 500-MHz ^{1}H NMR: δ 0.74 (d, *J*=7, 3H), 0.76 (s, 3H), 0.82-1.05 (m, 2H), 0.89 (d, *J*=7, 3H), 0.94 (s, 3H), 1.10-1.20 (m, 2H), 1.25-1.50 (m, 6H), 1.53-1.90 (m, 9H), 2.00 (dd, *J*=9, 13, 1H), 2.20 (ddd, =2, 9, 13, 1H), 2.31 (dd, =4, 17, 1H), 2.52 (dd, =7, 17, 1H), 2.91 (bs, 1H), 3.37 (s, 3H), 3.40 (s, 3H), 3.51 (dddd, *J*=5, 5, 11, 11, 1H), 4.55 (AB q, *J*=6.5, Δv=10.7, 2H), 4.67 (dd, *J*=9, 13, 1H), 4.68 (s, 2H). 75-MHz ^{13}C NMR: δ 11.26, 21.67, 22.03, 22.76, 22.81, 26.96, 28.42, 28.94, 31.21, 32.87, 34.45, 35.16, 35.83, 37.00, 38.61, 39.30, 41.00, 44.63, 48.63, 52.17, 55.04, 55.66, 56.10, 74.38, 76.36, 94.66, 95.53, 136.26, 177.96, 211.35. IR (cm^{-1}): 2925, 1692, 1652, 1144, 1043. Mass spectrum *m/e* (PCI: isobutane): 489 (M$^+$+1), 427 (M$^+$-61). Anal. Calcd for $C_{30}H_{48}O_5\cdot H_2O$: C, 71.11; H, 9.94. Found: C, 71.28; H, 9.68. $[\alpha]_D^{25}$ + 12 (c = 0.4, CHCl$_3$. **17:** 500-MHz ^{1}H NMR: δ 0.78 (s, 3H), 0.88-1.06 (m, 2H), 0.91 (d, *J*=7, 6H), 1.04 (m, 3H), 1.08-1.20 (m, 2H), 1.24-1.38 (m, 3H), 1.40-1.52 (m, 2H), 1.54-1.67 (m, 6H), 1.73-1.86 (m, 3H), 1.94 (s, 3H), 2.09 (septuplet, *J*=7, 1H), 2.44 (dd, *J*=7, 16, 1H), 2.52 (dd, *J*=7, 16, 1H), 3.23 (s, 3H), 3.36 (s, 3H), 3.50 (dddd, *J*=5, 5, 11, 11, 1H), 4.60 (s, 2H), 4.61 (s, 1H), 4.68 (s, 2H). 75 - MHz NMR: δ 11.18, 11.94, 21.22, 21.37, 22.38, 22.77, 24.61, 28.40, 28.93, 29.61, 33.97, 34.99, 35.18, 35.62, 37.09, 44.44, 48.26, 48.93, 50.80, 53.60, 55.05, 55.51, 76.26, 83.70, 94.52, 96.57, 137.30, 164.40, 201.75. IR (cm^{-1}) 2936, 1672, 1613, 1143, 1099, 1037. Mass spectrum *m/e* (PCI: isobutane): 415 (M$^+$-61, 100). $[\alpha]_D^{25}$ + 102 (c = 0.5, CHCl$_3$).

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