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Stereoselective Synthesis of the "Cyathin" Diterpene Skeleton *via* an Intramolecular Pyrylium Ylide-Alkene Cyclization†

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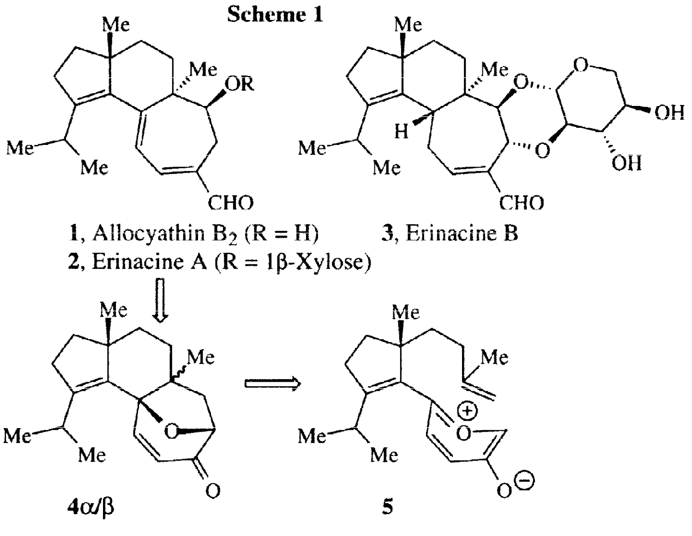
Abstract: The pyrylium ylide precursor **18**, available in eight steps from diethyl adipate, undergoes acid catalyzed cyclization to give the cyathin derivative **4α** and no detectable amount of the incorrect diastereomer **4β**.

Introduction

The diterpene metabolites isolated from *Cyathus earlei* Lloyd (bird's nest fungus) have the unusual 5,6,7-ring fused skeleton, and allocyathin B_2 **1** is a typical representative.[1] More recently, the xylose derivatives erinacine A **2** and erinacine B **3** have been isolated from the mycelia of *Hericium erinaceum*, and exhibit potent nerve growth factor synthesis stimulation.[2] Snider[3] reported the first syntheses of (±)-**1** and (+)-**2**, and recently Tori[4] has described a synthesis of (±)-**1**.[5]

Scheme 1



1, Allocyathin B_2 (R = H)
2, Erinacine A (R = 1β-Xylose)
3, Erinacine B
4α/β
5

Our recent use[6] of pyrylium ylide-alkene cyclizations[7] suggested the retrosynthetic synthetic possibility that the cyathin carbon skeleton could be assembled from the [5+2] cyclization of **5** to give **4α/β**, **Scheme 1**. While this is a very sterically demanding example, the pyrylium ylides do not appear to be too adverse to this situation and tolerate the formation of quaternary centers.[6] The key issue is the control of relative stereochemistry at the 1,4 quaternary methyl groups during the conversion of **5** into **4α/β**. MM2 calculations of the strain energy of the required *trans*-1,4-dimethyl product **4α** versus the *cis*-1,4-dimethyl diastereomer **4β**, indicated that **4α** is less strained than **4β** by approximately 10 kcal.mol^{-1}. The transition state leading to **4α** accommodates the newly forming cyclohexane ring in a chair conformation with the 1,4-dimethyl groups axially disposed. Whereas, the transition state leading to **4β** is a boat conformation, again the 1,4-dimethyl groups are in an axial conformation.

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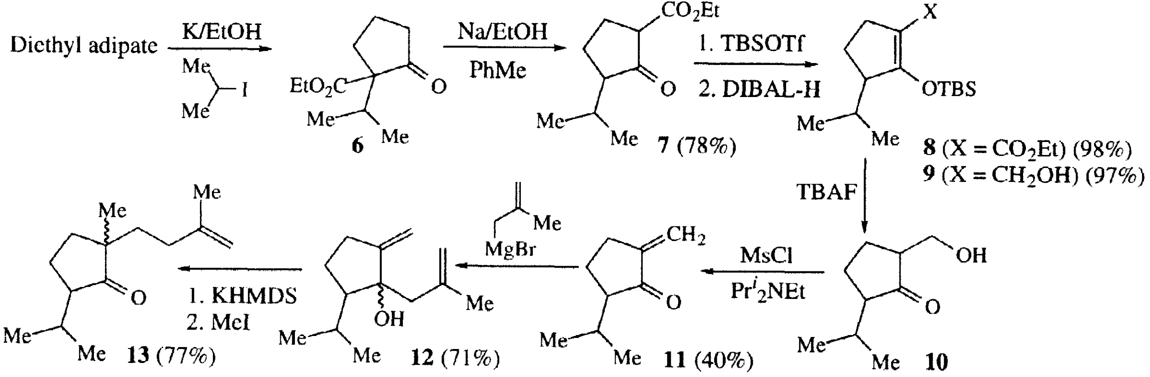
Results

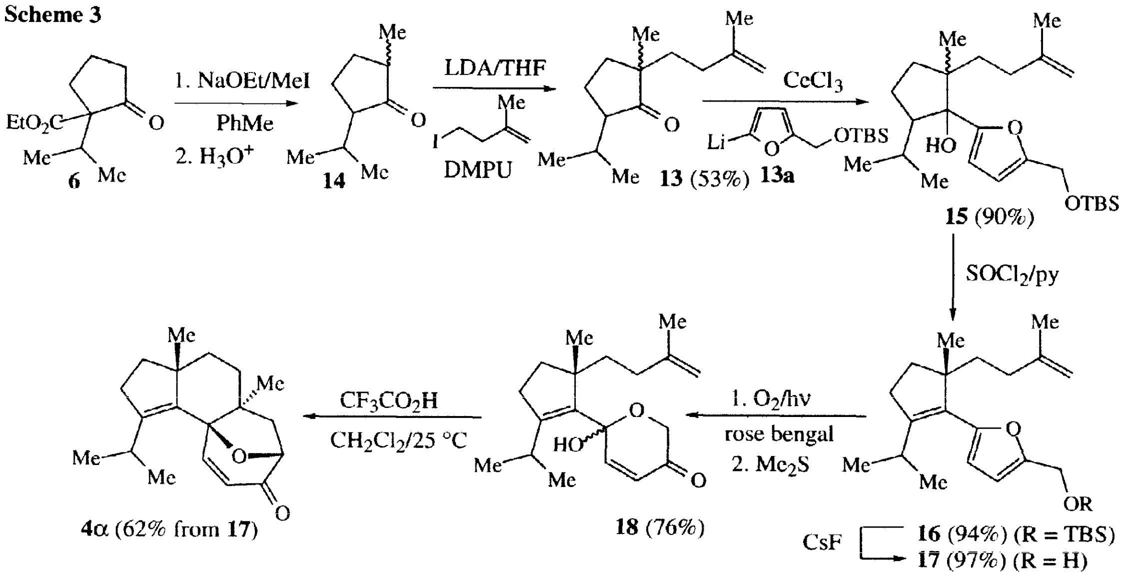
The initial synthesis of the cyclopentanone precursor **13** (**Scheme 2**) was developed to avoid direct alkylation for the introduction the butenyl side-chain, since it was felt that this might be a difficult reaction because of competing elimination (homoallylic leaving group). Diethyl adipate was converted into **6** by a standard Dieckman reaction by followed alkylation with isopropyl iodide. Treatment of **6** with NaOEt/EtOH, followed by azeotropic (toluene 110 °C) removal of the ethanol resulted in $-CO_2Et$ migration to give **7**.[8]

Scheme 2



The β-ketoester **7** was converted into **8**, and reduced with DIBAL-H to provide **9**. While **9** could not be directly β-eliminated to give **11**, deprotection gave **10**, and treatment of **10** with mesyl chloride/$Pr^i{}_2NEt$ resulted in **11** (40% from **9**). Treatment of **11** with isobutenyl magnesium bromide gave **12**, which was subjected to anionic accelerated oxy Cope rearrangement,[9] and the resulting enolate trapped with MeI to give **13**. The major drawback of this sequence of reactions is the conversion of **10** into **11**, and the instability of **11**. Consequently, it was decided to see if the direct alkylation of **14** to give **13** was indeed a viable option.

Scheme 3



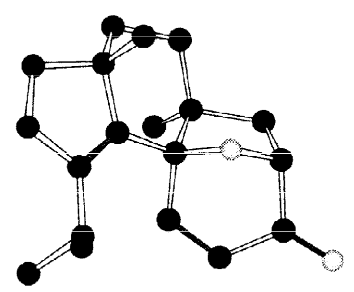


Figure 1, Chem 3D representation of 4α from the X-ray coordinates

Treatment of **6** with EtONa/EtOH/PhMe, followed by MeI and acid hydrolysis gave **14**.[10] Exposure of **14** to lithium diisopropylamide/THF/DMPU followed by 4-iodo-2-methyl-but-1-ene at 23 °C gave **13** (53%), and recovered **14**. The regioisomer resulting from alkylation at the more hindered α-position was not detected. While the furyl lithium **13a**[11] did not add to **13**, the adduct formed from **13a** and $CeCl_3$ reacted with **13** to give **15** as a mixture of diastereoisomers. Thionyl chloride in pyridine converted the diastereoisomers of **15** into **16**.[12] Deprotection of **16** gave **17**, which on oxidative rearrangement using the Williams procedure[13] gave the unstable pyranenone **18**. Attempts to form the acetate derivative of **18** and thus **5** failed. Fortunately, it was eventually found that treatment of a dilute solution of **18** in dichloromethane with trifluoroacetic acid at 23 °C gave **4α** (62% from **17**). The ^1H NMR spectrum of the crude reaction mixture did not show any signals that could be associated with other diastereomers of **4α**. The structure and relative stereochemistry of **4α** was confirmed by X-ray crystallography, and **Figure 1** shows a Chem 3D representation from the coordinates. Our experiences with pyrylium ylide cyclizations would indicate that if other diastereomers of **4α** were present (by ^1H NMR),[6] then they are to the extent of less than 3%.

The pyrylium ylide-alkene cyclization to construct the cyathin core structure **4α** is noteworthy for the mild reaction conditions and stereoselectivity.

Experimental Section

2-Carboethoxy-5-isopropylcyclopentanone 7. Potassium (10.7 g, 274 mmol) was dissolved in anhydrous ethanol (120 mL) and diethyl adipate (46.5 g, 230 mmol) was added slowly with mechanical stirring. After the mixture was refluxed for 7.5 h, ethanol was distilled off azeotropically with toluene. 2-Iodopropane (48.0 g, 282 mmol) was added and the mixture was heated at reflux for 10 h. A second portion of 2-iodopropane (12.0 g, 70.5 mmol) was added, and heating continued for a further 11 h. The mixture was cooled to room temperature, water (100 mL) was added, and the layers were separated. The aqueous phase was extracted with benzene (3x40 mL), and the combined extracts washed with brine (30 mL), dried (K_2CO_3) and evaporated *in vacuo* to give crude **6** (44.8 g).

Sodium (6.8 g, 296 mmol) was dissolved in anhydrous ethanol (100 mL), and crude **6** (44.8 g) was added dropwise. After the reddish-brown solution was heated at reflux for 14 h, ethanol was removed by azeotropical distillation with toluene until the temperature of the vapor reached 110 °C. The resulting residue was poured into 10% acetic acid (300 mL) under ice cooling. The layers were separated and the aqueous phase extracted with benzene (3x50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (30 mL), dried (K_2CO_3), and evaporated *in vacuo* . The crude product was purified by chromatography over silica gel eluting with 7% Et_2O/petrol to give **7** as a colorless oil (35.4 g, 78%).

1-*tert*-Butyldimethylsilyl(oxy)-2-carboethoxy-5-isopropylcyclopent-1-ene 8 (X = CO_2Et). To a solution of **7** (6.59 g, 33.2 mmol) in dichloromethane (25 mL) was added diisopropylethylamine (8.7 mL, 49.9 mmol) at 23 °C, followed by slow addition of *tert*-butyldimethylsilyl triflate (9.92 mL, 43.1 mmol). The mixture was stirred for 50 min, the solvent was evaporated *in vacuo* , and the residue was diluted with pentane (20 mL) and filtered through celite. The crude product was filtered through a short column of silica gel eluting with 10% Et_2O/petrol to give **8** as a light yellow oil (10.2 g, 98%). IR (thin film) 2986, 1711, 1627, 1472, 1371 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.14 (3H, s), 0.21 (3H, s), 0.76 (3H, d, J = 6 Hz), 0.87 (3H, d, J = 6 Hz), 0.94 (9H, s), 1.24 (3H, t, J = 6 Hz), 1.53-1.77 (2H, m), 2.04 (1H, m), 2.45 (2H, t, J = 6 Hz), 2.51 (1H, m), 4.14 (2H, m). ^{13}C NMR (75 MHz, C_6D_6) δ -4.3, -3.7, 14.6, 16.2, 19.6, 20.4, 25.4, 28.7, 28.8, 53.5, 59.0, 109.3, 166.8.

1-*tert*-Butyldimethylsilyl(oxy)-2-hydroxymethyl-5-isopropyl-cyclopent-1-ene 9 (X = CH_2OH). To a solution of **8** (10.2 g, 32.5 mmol) in dichloromethane (160 mL) was slowly added at -78 °C diisobutylaluminum hydride (150 mL, 1 M in dichloromethane). After the addition was completed, the mixture was stirred at -78 °C for 50 min, and then warmed to 0 °C for 50 min. The mixture was quenched with methanol (10 mL), and aqueous 10% sodium tartrate solution (50 mL) at -78 °C. The layers were separated and the aqueous phase extracted with dichloromethane (3x50 mL). The combined extracts were dried (K_2CO_3) and evaporated *in vacuo* to give **9** as a colorless oil (8.51g, 97%). IR (thin film) 3347, 2955, 1678, 1472 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.11 (6H, s), 0.76 (3H, d, J = 6 Hz), 0.91 (3H, d, J = 6 Hz), 0.92 (9H, s), 1.63 (1H, m), 1.77 (1H, m), 1.95 (1H, m), 2.24 (2H, t, J = 6 Hz), 2.43 (1H, m), 4.15 (2H, m).

2-Isopropyl-5-hydroxymethyl-cyclopentanone 10. To a solution of **9** (8.50 g, 31.5 mmol) in tetrahydrofuran (40 mL) was added tetra-*n*-butyl ammonium fluoride (37.8 mL, 1 M in tetrahydrofuran) at 0 °C, and the mixture was warmed to 23 °C with stirring for 4 h. The mixture was diluted with dichloromethane (100 mL), and washed with water (5x30 mL). The organic phase was dried (K_2CO_3) and evaporated *in vacuo*. Although the crude alcohol could be purified by flash chromatography, substantial decomposition occurred. Therefore, crude **10** was used without further purification. IR (thin film) 3438, 2959, 1732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.81 (3H, d, J = 6 Hz), 0.96 (3H, d, J = 6 Hz), 1.61-1.80 (1H, m), 1.94-2.26 (4H, m), 2.45 (1H, m), 2.52 (1H, m), 3.64-3.82 (2H, m).

2-Isopropyl-5-methylene-cyclopentanone 11. To a solution of crude **10** in dichloromethane (40 mL) was added methanesulfonyl chloride (3.02 mL, 37.8 mmol), and diisopropylethylamine (16.5 mL, 94.4 mmol) at 0 °C. The mixture was stirred at room temperature for 6 h, and quenched with saturated aqueous NH_4Cl (5 mL). The layers were separated, and the aqueous phase extracted with dichloromethane (3x5 mL). The combined extracts were dried (K_2CO_3) and evaporated *in vacuo*. Flash chromatography over silica gel eluting with 10 % Et_2O/petrol gave **11** as a volatile colorless oil (1.79 g, 40% from **9**). IR (thin film) 2958, 1728, 1641, 1467 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (3H, d, J = 6 Hz), 1.00 (3H, d, J = 6 Hz), 1.59-1.68 (1H, m), 1.95-2.05 (1H, m), 2.11-2.21 (2H, m), 2.41-2.54 (1H, m), 2.59-2.69 (1H, m), 5.25 (1H, s), 5.94 (1H, s).

2-Isopropyl-5-methylenyl-1-(2-methyl-2-propenyl)-cyclopentan-1-ol 12. To a suspension of magnesium (184 mg, 7.57 mmol) in Et_2O (7 mL) was added 3-bromo-2-methylpropene (0.575 mL, 5.70 mmol) and catalytic amount of I_2. The mixture was heated at reflux for 30 min, and a solution of **11** (656 mg, 4.75 mmol) in Et_2O (5 mL) was added at -78 °C. The mixture was stirred at -78 °C for 15 min and warmed to 23 °C for 100 min. The mixture was cooled to 0 °C, and quenched with saturated aqueous NH_4Cl (2 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3x3 mL). The combined extracts were dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography over silica gel eluting with 10% Et_2O/pentane gave **12** as a colorless oil (652 mg, 71%). IR (thin film) 3502, 2955, 1486 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (3H, d, J = 6 Hz), 0.97 (3H, d, J = 6 Hz), 1.45 (1H, m), 1.73 (3H, s), 1.87 (2H, m), 2.11-

2.23 (2H, m), 2.33 (1H, m), 2.39 (2H, d, J = 3 Hz), 4.71 (1H, s), 4.75 (1H, s), 4.94 (1H, s), 5.05 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.1, 23.1, 24.5, 24.7, 27.3, 30.9, 49.0, 51.8, 80.7, 106.2, 114.9, 142.7, 159.6.

5-Isopropyl-2-(3-methyl-but-3-enyl)-2-methyl-cyclopentanone 13. To a solution of **12** (122 mg, 0.629 mmol) in tetrahydrofuran (5 mL) was added potassium bis(trimethylsilyl)amide (1.58 mL, 0.5 M in toluene), followed by a catalytic amount of 18-crown-6 ether. After stirring the mixture at 23 °C for 21 h, iodomethane (0.40 mL, 6.42 mmol) was added and the mixture was allowed to stir at 23 °C for 12 h. The mixture was quenched with saturated aqueous NH_4Cl (2 mL). The layers were separated and the aqueous phase extracted with dichloromethane (3x3 mL). The combined extracts were dried (K_2CO_3) and evaporated *in vacuo*. Flash chromatography over silica gel eluting with 5% Et_2O/hexane gave recovered **12** (29 mg), and **13** (77.2 mg, 77%). IR (thin film) 2959, 1733, 1456 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76, 0.78 (3H, s), 0.91 (3H, d, J = 12 Hz), 0.98 (3H, d, J = 12 Hz), 1.37-1.43 (1H, m), 1.51-1.57 (2H, m), 1.59-1.65 (1H, m), 1.67 (3H, s), 1.84-1.94 (4H, m), 2.11-2.15 (2H, m), 4.61, 4.63 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 18.6, 20.4, 20.7, 21.1, 21.2, 22.3, 22.5, 27.1, 27.6, 32.0, 32.4, 33.1, 33.5, 34.1, 35.7, 48.3, 48.6, 54.6, 55.8, 109.5, 109.7, 145.8, 223.4, 223.6. HRMS (CI) calcd for $C_{14}H_{24}O$ (M^+ + 1) 209.1905. Found 209.1896.

2-Isopropyl-5-methylcyclopentanone 14. Sodium (7.0 g, 304 mmol) was dissolved in anhydrous ethanol (105 mL), and a mixture of diethyl adipate and **6** (52.3 g, 9:91) was added slowly. The mixture was heated at reflux with rapid stirring for 12 h, after which ethanol was removed azotropically with toluene (210 mL). Methyl iodide (37.3 g, 263 mmol) was added to the mixture and heating continued for 10 h. A second portion of methyl iodide (5.60 g, 39.4 mmol) was added and heating was continued for a further 12 h. The mixture was cooled to room temperature, water (50 mL) was added, the layers were separated, and the aqueous phase was extracted with benzene (15 mL). The extract was washed with brine and evaporated *in vacuo*. The resulting residue was mixed with concentrated sulfuric acid (85 mL) and water (170 mL), and heated at reflux with vigorous stirring for 24 h. The solution was cooled to room temperature, and the layers were separated. The aqueous layer was extracted with benzene (3x15 mL) and the combined extracts were washed with water (15 mL), saturated aqueous $NaHCO_3$ (20 mL) and water (10 mL), dried (K_2CO_3), evaporated *in vacuo*, and distilled to give **14** (30.0 g, 64%) as a colorless oil, bp 55-56 °C (1.2 mm) [Lit.[10] bp 181-186 °C (740 mm)].

5-Isopropyl-2-(3-methyl-but-3-enyl)-2-methyl cyclopentanone 13. To a solution of **14** (3.01 g, 21.5 mmol) in tetrahydrofuran (97 mL) was added at -74 °C slowly a freshly prepared tetrahydrofuran solution of lithium diisopropylamide (32.3 mL, 32.3 mmol), and followed by addition of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) (2.60 mL, 21.5 mmol). The mixture was stirred at -74 °C for 1 h, and 4-iodo-2-methyl-but-1-ene (4.45 g, 22.7 mmol) in tetrahydrofuran (22 mL) was added. After stirring at 23 °C for 15 h, the mixture was quenched with saturated aqueous NH_4Cl (30 mL). The phases were separated, and the aqueous layer was extracted with Et_2O (3x20 mL). The combined extracts were dried (K_2CO_3) and evaporated *in vacuo*. Distillation of the residue afforded two fractions: recovered **14** (406 mg) and **13** (2.04 g, 53%), bp 90-91 °C (0.45 mm). IR (thin film) 2959, 1733, 1456 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.76, 0.78 (3H, s), 0.91 (3H, d, J = 12 Hz), 0.98 (3H, d, J = 12 Hz), 1.37-1.43 (1H, m), 1.51-1.57 (2H, m), 1.59-1.65 (1H, m), 1.67 (3H, s), 1.84-1.94 (4H, m), 2.11-2.15 (2H, m), 4.61, 4.63 (2H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.3, 18.6, 20.4, 20.7, 21.1, 21.2, 22.3, 22.5, 27.1, 27.6, 32.0, 32.4, 33.1, 33.5, 34.1, 35.7, 48.3, 48.6, 54.6, 55.8, 109.5, 109.7, 145.8, 223.4, 223.6. HRMS (CI) calcd for $C_{14}H_{24}O$(M^+ + 1) 209.1905. Found 209.1896.

5-Isopropyl-2-(3-methyl-but-3-enyl)-2-methyl-1-[4-methylene-*tert*-butyldimethylsilyl(oxy)furyl]-cyclopentan-1-ol 15. Cerium (III) chloride heptahydrate (3.60 g, 9.66 mmol) was dried *in vacuo* at 80 °C for 4 h, 100 °C for 3 h and 150 °C for 10 h. The powder was cooled to room temperature, tetrahydrofuran (36 mL) was added, and the mixture was stirred vigorously for 1 day to form a fine suspension.

To a solution of **13a** (1.62 g, 7.66 mmol) in tetrahydrofuran (18 mL) at -80 °C was added a hexane solution of *n*-butyl lithium (4.0 mL, 8.43 mmol), the mixture was stirred at -80 °C for 15 min and then at 0 °C for 1 h. The light yellow solution was transferred to the stirring cerium chloride suspension and the white suspension was changed to a bright yellow transparent solution. After stirring the mixture at -80 °C for 6 h, **13** (422 mg, 2.03 mmol) in tetrahydrofuran (2.8 mL) was added. The mixture was stirred at -80 °C for 1 h, and quenched with saturated aqueous $NaHCO_3$ (12 mL). The mixture was filtered through celite and washed with Et_2O (10 mL). The organic phase was dried (K_2CO_3) and evaporated *in vacuo*. Chromatography over silica gel eluting with 10% Et_2O/hexane gave **15** as a pale green-yellow oil (770 mg, 90%). IR (thin film) 3468, 2956, 1472 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.06 (6H, s), 0.68 (3H, d, J = 6 Hz), 0.87 (3H, s), 0.93 (3H, d, J = 6 Hz), 0.96 (9H, s), 1.41-1.59 (5H, m), 1.69 (3H, s), 1.86-2.04 (4H, m), 2.50 (1H, m), 4.45 (2H, s), 4.80 (1H, s), 4.86 (1H, s), 6.01 (1H, d, J = 3 Hz), 6.07 (1H, d, J = 3 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ -5.0, 18.4, 21.6, 22.6, 22.8, 26.0, 26.6, 30.0, 32.9, 33.5, 35.1, 51.0, 51.5, 58.1, 84.6, 106.8, 108.5, 109.9, 146.9, 152.9, 158.1. HRMS (CI) calcd for $C_{25}H_{44}O_3Si$ (M^+ + 1) 420.3060. Found 420.3058.

2-Isopropyl-5-(3-methyl-but-3-enyl)-5-methyl-1-[4-methylene-*tert*-butyldimethylsilyl(oxy)furyl]-cyclopent-1-ene 16. To a mixture of **15** (1.65 g, 3.94 mmol) in dichloromethane (39 mL) and pyridine (3.2 mL, 39.4 mmol) was added at 0 °C thionyl chloride (0.345 mL, 4.73 mmol), and after stirring for 10 min, the mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3x5 mL). The combined extracts were dried (K_2CO_3), and evaporated *in vacuo*. The crude product was purified by flash chromatography over silica gel eluting with 5% Et_2O/hexane to give **16** as a pale yellow oil (1.49 g, 94%). IR (thin film) 2929, 1463 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.06 (6H, s), 0.96 (9H, s), 0.98 (3H, d, J = 6.9 Hz), 1.01 (3H, d, J = 6.9 Hz), 1.32 (3H, s), 1.51-1.60 (2H, m), 1.69 (3H, s), 1.72-1.98 (2H, m), 2.05 (2H, m), 2.30 (2H, m), 3.15 (1H, m), 4.50 (2H, s), 4.80 (1H, s), 4.85 (1H, s), 6.12 (2H, s). ^{13}C NMR (75 MHz, C_6D_6) δ -5.1, 18.4, 21.2, 21.6, 22.8, 26.0, 27.1, 28.4, 29.2, 33.7, 36.2, 39.0, 51.0, 58.4, 108.6, 108.9, 109.9, 131.9, 146.6, 148.5, 151.6, 153.2. HRMS (CI) calcd for $C_{25}H_{42}O_2Si$ (M^+ + 1) 402.2954. Found 402.2953.

2-Isopropyl-5-(3-methyl-but-3-enyl)-5-methyl-1-(4-hydroxymethylfuryl)-cyclopent-1-ene 17. To a solution of **16** (1.09 g, 2.07 mmol) in acetonitrile (5.5 mL) was added cesium fluoride (2.11 g, 13.5 mmol), and tetra-*n*-butylammonium chloride (1.90 g, 6.70 mmol) at 23 °C. The mixture was stirred for 14 h, and quenched with saturated aqueous $NaHCO_3$ (8 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3x5 mL). The combined extracts were dried (K_2CO_3) and evaporated *in vacuo*. Flash chromatography over silica gel eluting with 20% to 50% Et_2O/hexane gave **17** as a pale yellow oil (774 mg, 99%). IR (thin film) 3307, 2959, 1645, 1464 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.96 (3H, d, J = 9 Hz), 0.99 (3H, d, J = 6 Hz), 1.29 (3H, s), 1.50-1.60 (2H, m), 1.66 (3H, s), 1.70-1.95 (2H, m), 2.03 (2H, m), 2.27 (2H, m), 3.09 (1H, m), 4.22 (2H, s), 4.78 (1H, s), 4.83 (1H, s), 6.01 (1H, d, J = 3 Hz), 6.08 (1H, d, J = 3 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 21.1, 21.5, 22.7, 27.2, 28.4, 29.3, 33.7, 36.2, 39.1, 51.1, 57.6, 108.4, 108.9, 109.8, 131.8, 146.8, 148.6, 151.7, 153.5. HRMS (CI) calcd for $C_{19}H_{28}O_2$ (M+ + 1) 288.2089. Found 288.2083.

1-[6-(6-Hydroxy-4-pyranen-3-one)]-2-isopropyl-5-(3-methyl-but-3-enyl)-5-methyl-cyclopent-1-ene 18. To a solution of **17** (406 mg, 1.41 mmol) in dichloromethane (9.0 mL) and anhydrous methanol (4.5 mL) was added rose bengal (1.5 mg, 0.001 mg/mmol of substrate). The pink solution was stirred at -78 °C and dry air was bubbled through the mixture. The mixture was irradiated with a 400 w tungsten lamp for 5 h, the mixture was quenched by addition of dimethyl sulfide (1.0 mL, 14.1 mmol) and allowed to warm to 0 °C for 30 min. The solvent was promptly evaporated *in vacuo*, and the residue was purified by a quick flash chromatography over silica gel eluting with 20% to 50% Et_2O/hexane to give **18** as an orange oil (327 mg, 76%). In most cases, **18** was carried through next stage without purification due to its extreme instability at room temperature. IR (thin film) 3397, 2964, 1707, 1648, 1450, 1389 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.79 (3H, d, J = 6 Hz), 0.82 (3H, d, J = 6 Hz), 1.28 (3H, s), 1.35 (1H, m), 1.71 (3H, s), 1.61-2.10 (6H, m), 2.94 (2H, m), 4.01 (2H, d, J = 6 Hz), 4.80 (1H, s), 4.86 (1H, s), 5.42 (1H, d, J = 12 Hz), 6.06 (1H, d, J = 12 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 20.9, 21.2, 22.1, 23.9, 29.2, 29.4, 33.9, 35.7, 38.0, 51.0, 68.1, 110.1, 131.8, 138.1, 141.7, 146.4, 161.9, 195.8, 201.5.

3-Isopropyl-15a,16b-dimethyl-13b,5b-oxido-tricyclo[7.5.0^{4,9}]tetradec-10-ene-12-one 4α. To a solution of **17** (469 mg, 1.63 mmol) in dichloromethane (11 mL) and anhydrous methanol (5.5 mL) was added rose bengal (1.6 mg). Dry air was bubbled through the pink solution at -78 °C, and after the mixture was irradiated with a 400 w tungsten lamp for 4 h, dimethyl sulfide (1.8 mL) was added to quench the reaction. The mixture was allowed to stir at 0 °C for 30 min, and the solvent was evaporated *in vacuo*. The resulting residue was dissolved in dichloromethane (5 mL) and added to a solution of trifluoroacetic acid (0.075 mL, 0.974 mmol) in dichloromethane (160 mL) at 23 °C. The light yellow mixture was stirred at room temperature for 14 h, and quenched with saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3x5 mL). The combined extracts were dried (K_2CO_3) and evaporated *in vacuo*. The crude product was purified by flash chromatography over florisil® eluting with 10% Et_2O/hexane to give **19** as a white solid (288 mg, 62%), m.p. 162-163 °C. IR (CH_2Cl_2) 2945, 1692, 1462, 1378 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ 0.76 (3H, s), 0.84 (3H, d, J = 6 Hz), 0.87 (3H, d, J = 9 Hz), 1.13 (3H, s), 1.31-1.61 (3H, m), 1.58 (1H, dd, J = 6, 12 Hz), 1.72-1.82 (2H, m), 2.03 (1H, dd, J = 9, 15 Hz), 2.22-2.31 (1H, m), 2.98 (1H, m), 4.38 (1H, d, J = 9 Hz), 5.88 (1H, d, J = 9 Hz), 6.83 (1H, d, J = 9 Hz). ^{13}C NMR (75 MHz, C_6D_6) δ 20.8, 21.6, 22.2, 24.2, 28.3, 28.4, 35.8, 40.4, 42.4, 45.8, 46.1, 79.6, 83.1, 124.8, 134.7, 150.1, 155.8, 195.6. HRMS(CI) calcd for $C_{19}H_{26}O_2$ (M^+ + 1) 287.2011. Found 287.2006.

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References and Footnotes

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[12] Compounds **4-18** are racemic, and where appropriate, only one enantiomer is drawn with the same absolute stereochemistry as in **1**.

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