abEstablishing the Absolute Configuration of the Asbestinins: Enantioselective Total Synthesis of 11-Acetoxy-4-deoxyasbestinin D

Michael T. Crimmins* and J. Michael Ellis

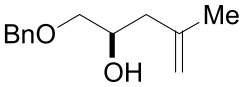
Venable and Kenan Laboratories of ChemistryThe University of North Carolina at Chapel HillChapel Hill, North Carolina 27599-3290

crimmins@email.unc.edu

Supporting Informaiton: Experimental Procedures

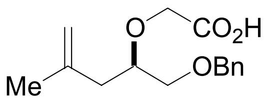
Materials and Methods: General. Infrared (IR) spectra were obtained using a Jasco 460 Plus Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on the following instruments: Bruker 400 (^{1}H at 400 MHz; ^{13}C at 100 MHz) and Bruker 500 (^{1}H at 500 MHz; ^{13}C at 125 MHz). Optical rotations were determined using a Jasco P1010 polarimeter. Thin layer chromatography (TLC) was conducted on silica gel F_{254} TLC plates purchased from Scientific Adsorbents, Inc. Flash column chromatography was carried out using silica gel (32 to 63 μm) purchased from Scientific Adsorbents, Inc. Diethyl ether (Et_2O), tetrahydrofuran (THF), and dichloromethane (CH_2Cl_2) were dried by being passed through a column of neutral alumina under nitrogen immediately prior to use. Alkylamines, benzene, and toluene were distilled from calcium hydride immediately prior to use. Chloroform was washed and distilled over phosphorous pentoxide immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled from calcium hydride under reduced pressure and stored over 4 Å molecular sieves. Anhydrous *N,N*-

dimethylformamide (DMF) was purchased from Aldrich chemical company in 1L Sure/Seal^{TM} bottles. Acetic anhydride was distilled and stored under a blanket of argon. Trifluoromethanesulfonic anhydride was distilled over phosphorous pentoxide immediately prior to use. All other reagents and solvents were used as received from the manufacturer. All air and water sensitive reactions were preformed in flasks flame dried under positive flow argon and conducted under an argon atmosphere.

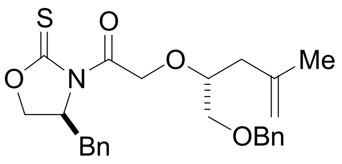


(*2R*)-1-Benzyloxy-4-methylpent-4-en-2-ol. Into a flask equipped with a reflux condenser and an addition funnel was added freshly ground magnesium (10.55 g, 434.0 mmol). The flask and its contents were flame dried. 125 mL of THF and iodine (one crystal) were added to the flask. 2-bromopropene (50.00 g, 413.3 mmol) was added in 125 mL of THF to the addition funnel. Several drops of the 2-bromopropene solution were added to the flask via addition funnel and the solution was stirred until colorless. 350 mL of THF was added to the addition funnel and the solution was added dropwise to the flask. Following addition, 125 mL of THF was added to the flask, and the solution was stirred vigorously for 2 hours.

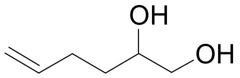
Into a flask equipped with an addition funnel and a low-temperature thermometer was added cuprous iodide (3.58 g, 18.8 mmol) in 375 mL of THF. The solution was cooled to –35 °C. The solution of 2-propenylmagnesium bromide was transferred via cannula to the addition funnel and added dropwise to yield a yellow solution. (*R*)-benzylglycidyl ether (**5**) (28.66 mL, 187.4 mmol) was added to the addition funnel in 200 mL of THF. The epoxide was added dropwise, and the solution was stirred at –35 °C for 1 hour. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and then warmed to room temperature. The resultant mixture was filtered through celite, yielding a blue solution. The layers were separated and the organic layer was washed with brine. The aqueous portions were extracted twice with a 1:1 solution of EtOAc/hexanes. The organic layers were combined, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/Hexanes) provided 38.22 g (99%) of the alcohol as a colorless oil.



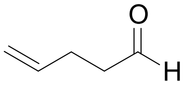
(*2R'*)-(1-Benzyloxymethyl-3-methylbut-3-enyloxy)-acetic acid. Into a flask equipped with an addition funnel was added sodium hydride (60% dispersion in mineral oil, 23.95 g, 598.6 mmol). The sodium hydride was rinsed with pentane three times, diluted in 100 mL of THF, and cooled to 0 °C. Bromoacetic acid (41.58 g, 299.3 mmol) was added to the addition funnel in 100 mL of THF and added dropwise to the flask. The solution was warmed to room temperature and stirred for 1 hour. The flask was again cooled to 0 °C, and the previous secondary alcohol (41.16 g, 199.5 mmol) was added to the addition funnel in 200 mL of DMF. The solution of alcohol was added to the flask dropwise. Following addition, the reaction was warmed to room temperature and allowed to stir overnight. The reaction was quenched by the addition of saturated aqueous NH_4Cl and diluted with diethyl ether. The solution was acidified to pH 3-4 by the addition of 10% H_2SO_4, then extracted. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (10% then 25% EtOAc/Hexanes) provided 49.71 g (95%) of the acid as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 1.75 (s, 3H), 2.13 (dd, J = 14.0, 6.0 Hz, 1H), 2.27 (dd, J = 14.0, 7.1 Hz, 1H), 3.48 (dd, J = 10.0, 8.5 Hz, 1H), 3.54 (dd, J = 10.1, 2.9 Hz, 1H), 3.71 (m, 1H), 4.10 (d, *J* = 17.3 Hz, 1H), 4.28 (d, *J* = 17.3 Hz, 1H), 4.59 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.77 (d, *J* = 0.8 Hz, 1H), 4.85 (dd, *J* = 1.6, 1.6 Hz, 1H), 7.29-7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 40.0, 68.2, 72.2, 73.6, 79.6, 114.3, 127.9, 128.1, 128.6, 136.7, 140.8, 172.2; IR (film) 3483 (br), 3201 (br), 2917, 1733 (str), 1454, 1454, 1364, 1205, 1129 cm^{-1}; $[\alpha]^{25}_D$ = -25.0 (c = 1.30, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{15}H_{21}O_4$ $[M + 1]^+$: 265.14, found: 265.2.



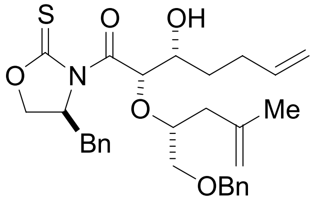
(*1R'*,*4R'*)-2-(1-Benzyloxymethyl-3-methylbut-3-enyloxy)-1-(4-benzyl-2-thioxooxazo-lidin-3-yl)-ethanone (4). A flask was charged with the glycolic acid (49.13 g, 185.9 mmol) and (*4S*)-4-benzyl-1,3-oxazolidine-2-thione (39.52 g, 204.5 mmol) in 150 mL of CH_2Cl_2. The solution was cooled to 0 °C. Dicyclohexylcarbodiimide (38.35 g, 185.9 mmol), 4-dimethylaminopyridine (1.14 g, 9.33 mmol), and 35 mL of CH_2Cl_2 were added to the solution and the mixture was warmed to room temperature. The yellow solution was stirred 4 hours, then cooled to 0 °C, and filtered. The filtrate was washed with CH_2Cl_2. The combined organic portions were washed with saturated aqueous $NaHCO_3$, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/Hexanes) provided 70.13 g (86%) of the glycolate as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (s, 3H), 2.31 (dd, *J* = 14.1, 6.7 Hz, 1H), 2.44 (dd, *J* = 14.3, 6.8 Hz, 1H), 2.64 (dd, *J* = 13.3, 10.2 Hz, 1H), 3.26 (dd, *J* = 13.3, 3.2 Hz, 1H), 3.64 (m, 2H), 3.93 (m, 1H), 4.23 (dd, *J* = 7.7, 7.7 Hz, 1H), 4.31 (dd, *J* = 9.3, 2.4 Hz, 1H), 4.54 (s, 2H), 4.79 (s, 1H), 4.83-4.90 (m, 1H), 4.83 (s, 1H), 5.23 (d, *J* = 18.3 Hz, 1H), 5.34 (d, *J* = 18.3 Hz, 1H), 7.17-7.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 37.3, 40.3, 59.8, 71.2, 71.9, 73.3, 73.5, 77.7, 113.1, 127.4, 127.5, 127.6, 128.4, 129.0, 129.4, 135.1, 138.1, 142.1, 171.4, 184.7; IR (film) 2924, 1712 (str), 1361, 1324, 1206, 1124 cm^{-1}; $[\alpha]^{22}_D$ = +93 (c = 0.26, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{25}H_{30}NO_4S$ $[M + 1]^+$: 440.18, found: 440.3.



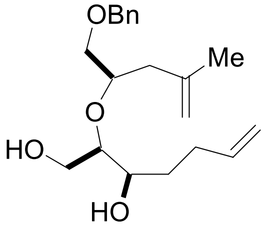
Hex-5-ene-1,2-diol. Into a flask equipped with a mechanical stirrer, an addition funnel, and a low temperature thermometer was added allylmagnesium chloride (2.0 M in THF, 800.0 mL, 1.600 mol) and 800 mL of THF. The solution was cooled to –20 °C. Glycidol (35.40 mL, 533.3 mmol) in 800 mL of THF was added dropwise via addition funnel keeping the temperature at –20 °C. The mixture was stirred 1 hour at –20 °C, then quenched by the addition of saturated aqueous NH_4Cl. The organic layer was washed with brine, and the combined aqueous extracts were washed twice with 50% EtOAc/Hexanes. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (10% then 50% EtOAc/Hexanes) provided 57.16 g (93%) of the diol as a colorless oil.



Pent-4-enal. Into a flask equipped with a mechanical stirrer was added hex-5-ene-1,2-diol (65.31 g, 562.2 mmol), 800 mL of CH_2Cl_2, and 800 mL of water. Sodium periodate (240.52 g, 1.1245 mol) was added to the biphasic solution which was stirred for one hour. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$. The organic layer was washed twice with 10% $Na_2S_2O_3$ in water, then dried over Na_2SO_4. The volume was reduced to 100 mL in vacuo at 0 °C. Purification via distillation (bp: 96 °C, 760 mm Hg) gave 29.33 g (63%) of the aldehyde as a colorless liquid.

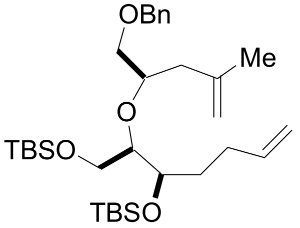


(*1R',2S',3R,4R'*)-2-(1-Benzyloxymethyl-3-methylbut-3-enyloxy)-1-(4-benzyl-2-thioxooxazolidin-3-yl)-3-hydroxyhept-6-en-1-one (6). Into a flask equipped with an addition funnel was added glycolate **4** (28.63 g, 65.13 mmol) and 435 mL of CH_2Cl_2. The solution was cooled to –78 °C and titanium tetrachloride (7.50 mL, 68.4 mmol) was added dropwise via addition funnel. The solution was stirred 10 minutes at –78 °C and *N, N*-diisopropylethylamine (26.92 mL, 162.8 mmol) was added dropwise to give a purple solution that was stirred at –78 °C for 2.5 hours. *N*-methylpyrrolidinone (6.57 mL, 68.3 mmol) was added to the solution via addition funnel and stirred for 10 minutes. 4-pentenal was added dropwise via addition funnel and stirred at –78 °C for 2 hours. The solution was warmed to –40 °C for 1 hour, then quenched by the addition of half saturated aqueous NH_4Cl and warmed to room temperature. The aqueous layer was extracted twice with CH_2Cl_2, then the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (20% then 50% EtOAc/Hexanes) provided 23.61 g (70%) of the alcohol as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67-1.78 (m, 2H), 1.80 (s, 3H), 2.01 (dd, J = 13.2, 11.1 Hz, 1H), 2.15 (ddd, J = 14.9 , 7.1, 7.1 Hz, 1H), 2.20-2.36 (m, 3H), 2.41 (dd, J = 14.0, 7.9 Hz, 1H), 3.20 (dd, J = 13.3, 2.8 Hz, 1H), 3.51 (dd, J = 10.3, 2.7 Hz, 1H), 3.68 (dd, J = 10.3, 7.6 Hz, 1H), 3.92-4.01 (m, 2H), 4.14 (dd, *J* = 9.4, 2.1 Hz, 1H), 4.19 (ddd, *J* = 9.3, 9.3, 9.3 Hz, 1H), 4.47 (d, *J* = 12.3 Hz, 1H), 4.53 (d, *J* = 12.3 Hz, 1H), 4.77 (m, 1H), 4.84 (s, 1H), 4.86 (s, 1H), 4.98 (d, *J* = 10.2 Hz, 1H), 5.05 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.83 (dddd, *J* = 17.0, 10.3, 3.6, 3.6 Hz, 1H), 6.34 (d, *J* = 2.0 Hz, 1H), 7.08-7.35 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 29.9, 33.2, 36.7, 40.7, 60.9, 70.6, 72.5, 73.1, 74.2, 78.7, 80.8, 114.0, 114.9, 127.22, 127.24, 127.5, 128.4, 128.9, 129.3, 135.6, 138.0, 138.1, 141.6, 172.2, 185.2; IR (film) 3458 (br), 2924, 1712 (str), 1446, 1361, 1324, 1206, 1128 cm^{-1}; $[\alpha]^{23}_{D}$ = +25 (c = 0.43, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{30}H_{38}NO_5S$ $[M + 1]^+$: 524.24, found: 524.3.

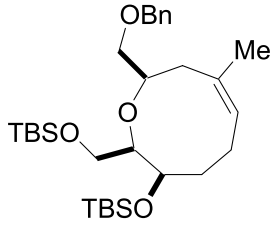


(*1R',2S,3R*)-2-(1-Benzyloxymethyl-3-methylbut-3-enyloxy)-hept-6-ene-1,3-diol. Into a flask equipped with an addtion funnel was added alcohol **6** (19.89 g, 38.01 mmol) in 380 mL of Et_2O. Methanol (3.08 mL, 76.0 mmol) was added, and the solution was cooled to 0 °C. Lithium borohydride (2.0 M in Et_2O, 38.01 mL, 76.03 mmol) was added dropwise via addition funnel, and the solution was stirred 1.5 hours at 0 °C. The reaction was quenched by the addition of aqueous NaOH (380 mL, 190 mmol) and stirred 15 minutes at room temperature. The layers were separated and the aqueous was washed three times with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (20% EtOAc/Hexanes) gave 11.96 g (95%) of the diol as a colorless oil: ^{1}H NMR (400 MHz,

$CDCl_3$) δ 1.51-1.60 (m, 2H), 1.75 (s, 3H), 2.08-2.19 (m, 2H), 2.26 (ddd, *J* = 14.4, 7.8, 7.8 Hz, 1H), 2.36 (dd, *J* = 14.0, 6.5 Hz, 1H), 2.72 (br s, 1H), 3.32 (m, 1H), 3.47 (dd, *J* = 10.0, 7.9 Hz, 1H), 3.56-3.61 (m, 3H), 3.75 (br s, 1H), 3.77 (br s, 1H), 3.90 (dddd, *J* = 7.0, 7.0, 7.0, 2.6 Hz, 1H), 4.56 (s, 2H), 4.77 (s, 1H), 4.84 (s, 1H), 4.96 (ddd, *J* = 10.2, 1.9, 0.7 Hz, 1H), 5.03 (ddd, *J* = 17.1, 3.5, 1.6, 1H), 5.82 (dddd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H), 7.29-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 29.8, 32.5, 41.2, 62.7, 71.2, 72.9, 73.6, 76.7, 83.0, 114.0, 114.8, 127.9, 128.1, 128.6, 137.1, 138.3, 141.7; IR (film) 3436 (br), 2921, 1641, 1454, 1092 cm^{-1}; $[\alpha]^{24}_D$ = -11 (c = 0.32, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{30}O_4Na$ $[M + Na]^+$: 357.20, found: 357.3.

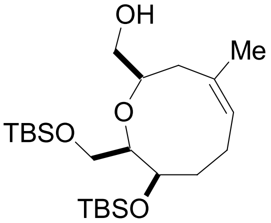


(*1S',2R,2R*)-{2-[2-(*tert*-Butyl-dimethyl-silanyloxy)-1-(*tert*-butyldimethylsilanyloxymethyl)-hex-5-enyloxy]-4-methylpent-4-enyloxymethyl}-benzene (3). A flask was charged with the 1,3-diol (11.96 g, 35.76 mmol) and 140 mL DMF. Imidazole (18.26 g, 268.2 mmol) and 4-dimethylaminopyridine (437 mg, 3.58 mmol) were added to the solution, followed by *tert*-butyldimethylsilyl chloride (13.48 g, 89.40 mmol). The solution was warmed to 50 °C and stirred overnight. The reaction was quenched by the addtion of saturated aqueous NH_4Cl, cooled to room temperature, and diluted with Et_2O. The layers were separated, and the aqueous portion was washed twice with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (1% EtOAc/Hexanes) provided 17.42 g (86%) of the diene as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.107 (s, 3H), 0.112 (s, 3H), 0.93 (s, 9H), 0.95 (s, 9H), 1.29 (dddd, *J* = 14.7, 9.9, 9.9, 5.0 Hz, 1H), 1.74-1.82 (m, 1H), 1.82 (s, 3H), 1.98 (m, 1H), 2.18-2.28 (m, 1H), 2.24 (dd, *J* = 13.8, 7.9 Hz, 1H), 2.39 (dd, *J* = 13.8, 4.6 Hz, 1H), 3.45 (dd, *J* = 9.7, 6.2 Hz, 1H), 3.45-3.50 (m, 1H), 3.61 (dd, *J* = 10.6, 7.9 Hz, 1H), 3.69 (dd, *J* = 9.8, 4.6 Hz, 1H), 3.70-3.75 (m, 1H), 3.82-3.88 (m, 1H), 3.89 (dd, *J* = 10.6, 2.2 Hz, 1H), 4.59 (s, 2H), 4.82 (s, 1H), 4.85 (m, 1H), 4.98 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.05 (ddd, *J* = 17.0, 3.3, 1.5 Hz, 1H), 5.85 (dddd, *J* = 16.9, 10.2, 6.6, 6.6 Hz, 1H), 7.27-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.5, -5.3, -4.6, -4.3, 18.0, 18.2, 23.0, 25.8, 25.86, 25.92, 25.93, 30.6, 30.9, 41.4, 62.8, 71.9, 72.7, 73.2, 77.2, 83.3, 113.0, 114.3, 127.4, 127.5, 128.2, 138.6, 138.8, 142.6; IR (film) 2929, 1463, 1255, 1095 cm^{-1}; $[\alpha]^{24}_{D}$ = +35.7 (c = 1.24, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{32}H_{58}O_4Si_2Na$ $[M + Na]^+$: 585.38, found: 585.5.

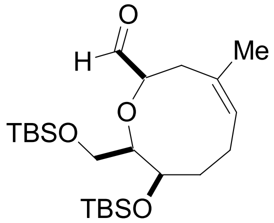


(*2S,3R,9R*)-9-Benzyloxymethyl-3-(*tert*-butyldimethylsilanyloxy)-2-(*tert*-butyldimethylsilanyloxymethyl)-7-methyl-2,3,4,5,8,9-hexahydrooxonine (7). Into a flask equipped with a reflux condenser was added diene **3** (16.56 g, 29.24 mmol) and 2.9 L CH_2Cl_2. The solution was brought to reflux for 30 minutes, followed by the addtion of Grubbs' catalyst (1.25 g, 1.47 mmol) and stirring three hours at reflux. The solution was cooled to room temperature and concentrated in vacuo. Purification by flash column chromatography (1% EtOAc/Hexanes) provided 15.53 g (99%) of the oxonene as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 9H), 0.88 (s, 9H), 0.89

(s, 9H), 1.42 (dddd, *J* = 3.9, 3.9, 13.5, 13.5 Hz, 1H), 1.73 (m, 1H), 1.79 (s, 3H), 1.86 (m, 1H), 1.98 (d, *J* = 14.02 Hz, 1H), 2.44 (dd, *J* = 14.2, 7.9 Hz, 1H), 2.81 (dddd, *J* = 13.2, 13.2, 13.2, 4.4 Hz , 1H), 3.29-3.35 (m, 2H), 3.38 (m, 1H), 3.54 (dd, *J* = 13.6, 8.9 Hz, 1H), 3.67 (dd, *J* = 11.0, 8.5 Hz, 1H), 3.92 (dd, *J* = 11.1, 2.4 Hz, 1H), 3.96 (m, 1H), 4.56 (s, 2H), 5.34 (dd, *J* = 11.4, 5.3 Hz, 1H), 7.27-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.2, -5.1, -4.8, 18.1, 18.3, 25.3, 25.8, 25.9, 26.0, 26.1, 32.2, 36.1, 61.8, 67.7, 73.0, 73.4, 77.9, 84.3, 126.1, 127.5, 127.6, 128.3, 134.7, 138.4; IR (film) 2928, 1471, 1254, 1089 cm^{-1}; $[\alpha]^{24}_{D}$ = +33.6 (c = 1.16, CH_2Cl_2); MS (electrosray ionization) calculated for $C_{30}H_{54}O_4Si_2Na$ [M + Na]$^+$: 557.35, found: 557.4.

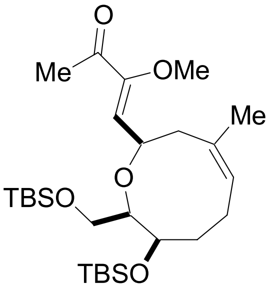


(2*R*,8*R*,9*S*)-[8-(*tert*-Butyldimethylsilanyloxy)-9-(*tert*-butyldimethylsilanyloxy-methyl)-4-methyl-2,3,6,7,8,9-hexahydrooxonin-2-yl]-methanol. Into a flask equipped with a cold finger condenser, cooled to –78 °C, and a stir bar was added oxonene **7** (4.03 g, 7.52 mmol) and 210 mL of THF. The solution was cooled to –78 °C, and 105 mL of ammonia was condensed into the flask. Freshly cut sodium metal (3.46 g, 150 mmol) was added to the solution yielding a blue color. After 15 minutes at –78 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl. The ammonia was allowed to evaporate at room temperature, and the layers were separated. The aqueous portion was washed three times with Et_2O, dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (5% EtOAc/Hexanes) gave 2.86 g (86%) of the alcohol as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.09 (s, 3H), 0.10 (s, 3H), 0.86 (s, 9H), 0.91 (s, 9H), 1.44 (m, 1H), 1.49 (d, *J* = 10.6 Hz, 1H), 1.70 (dddd, *J* = 13.8, 13.8, 5.3, 2.0 Hz, 1H), 1.78 (s, 3H), 1.90 (m, 1H), 2.39 (dd, *J* = 14.1, 9.9 Hz, 1H), 2.77 (dddd, *J* = 13.0, 13.0, 13.0, 5.4 Hz, 1H), 3.33 (m, 1H), 3.44-3.52 (m, 2H), 3.59 (m, 1H), 3.73 (dd, 10.0, 10.0 Hz, 1H), 3.88 (ddd, *J* = 6.6, 3.5, 3.5 Hz, 1H), 3.97 (ddd, *J* = 8.8, 3.2, 3.2 Hz, 1H), 4.01 (dd, *J* = 10.5, 2.1 Hz, 1H), 5.35 (dd, *J* = 11.8, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.5, -5.3, -5.0, -4.9, 18.0, 18.5, 25.6, 25.78, 25.79, 26.0, 31.6, 35.0, 62.5, 67.7, 68.0, 81.2, 85.8, 125.9, 133.9; IR (film) 3477 (br), 2929, 1463, 1255, 1089 cm^{-1}; $[\alpha]^{24}_{D}$ = +26.9 (c = 2.44, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{23}H_{48}O_4Si_2Na$ $[M + Na]^+$: 467.30, found: 467.4.

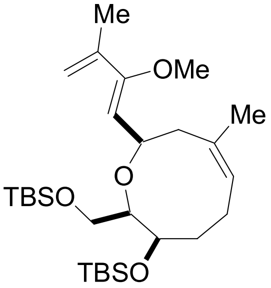


(*2R,8R,9S*)-8-(*tert*-Butyldimethylsilanyloxy)-9-(*tert*-butyldimethylsilanyloxy-methyl)-4-methyl-2,3,6,7,8,9-hexahydrooxonine-2-carbaldehyde. A flask was charged with oxalyl chloride (2.0 M in CH_2Cl_2, 3.52 mL, 7.04 mmol) and 40 mL of CH_2Cl_2 and cooled to –78 °C. Dimethylsulfoxide (1.00 mL, 14.1 mmol) in 8 mL of CH_2Cl_2 was added dropwise, and the solution was stirred 2 minutes. The primary alcohol (2.85 g, 6.40 mmol) and 16 mL CH_2Cl_2 were added dropwise to the mixture and allowed to stir 30 minutes at –78 °C. Triethylamine (4.46 mL, 32.0 mmol) was added dropwise and stirred 5 minutes at –78 °C, followed by warming to 0 °C for 1 hour. The reaction was quenched by the addition of cold water. The organic portion was washed with cold saturated aqueous $NaHCO_3$, then water. The combined aqueous portions were washed with CH_2Cl_2. The combined organic extracts were then washed with brine, dried over

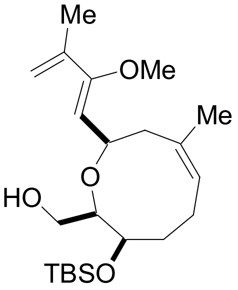
Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/Hexanes) provided 2.64 g (94%) of the aldehyde as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.06 (m, 6H), 0.86 (s, 9H), 0.89 (s, 9H), 1.46 (dddd, *J* = 13.6, 13.6, 4.2, 4.2 Hz , 1H), 1.74-1.85 (m, 1H), 1.79 (s, 3H), 1.89 (m, 1H), 2.06 (d, *J* = 14.3 Hz, 1H), 2.50 (dd, *J* = 14.1, 10.2 Hz, 1H), 2.76 (dddd, *J* = 13.1, 13.1, 13.1, 4.1 Hz, 1H), 3.49 (d, *J* = 10.0 Hz, 1H), 3.49-3.53 (m, 1H), 3.78 (dd, *J* = 10.9, 8.7 Hz, 1H), 3.89 (ddd, *J* = 10.3, 3.7, 3.7 Hz, 1H), 3.95 (dd, *J* = 16.5, 1.6 Hz, 1H), 5.39 (dd, *J* = 11.3, 5.3 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.3, -5.1, -4.9, -4.7, 18.1, 18.3, 24.9, 25.8, 25.9, 32.5, 34.0, 62.3, 67.6, 83.6, 85.6, 127.5, 132.8, 204.5; IR (film) 2929, 1737 (str), 1473, 1254, 1086 cm^{-1}; $[\alpha]^{24}_D$ = +84 (c = 0.48, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{23}H_{46}O_4Si_2Na$ $[M + Na]^+$: 443.28, found: 443.4.



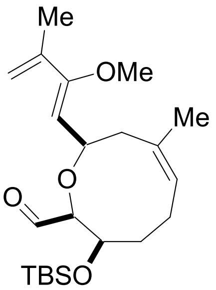
(*2R,8R,9S*)-4-[8-(*tert*-Butyldimethylsilanyloxy)-9-(*tert*-butyldimethylsilanyloxymethyl)-4-methyl-2,3,6,7,8,9-hexahydrooxonin-2-yl]-3-methoxybut-3-en-2-one. Into a flask equipped with a reflux condenser was added the aldehyde (2.70 g, 6.10 mmol), 60 mL of toluene, and 1-Methoxy-1-(triphenyl-l5-phosphanylidene)-propan-2-one (**8**) (6.37 g, 18.3 mmol). The solution was brought to reflux overnight, then cooled to room temperature. The mixture was concentrated in vacuo, then purified by flash column chromatography (5% EtOAc/Hexanes) to provide 2.59 g (84%) of the enone as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.02 (s, 6H), 0.85 (s, 18H), 1.42 (dddd, *J* = 13.4, 13.4, 3.8, 3.8 Hz, 1H), 1.69 (d, *J* = 14.0 Hz, 1H), 1.70-1.78 (m, 1H), 1.79 (s, 3H), 1.85 (m, 1H), 2.42 (s, 3H), 2.71 (dd, *J* = 13.8, 9.1 Hz, 1H), 2.77 (dddd, *J* = 13.1, 13.1, 13.1, 4.5 Hz , 1H), 3.34 (dd, *J* = 5.9, 5.9 Hz, 1H), 3.62-3.68 (m, 1H), 3.64 (s, 3H), 3.91 (dd, *J* = 11.4, 2.2 Hz, 1H), 3.96 (ddd, *J* = 11.4, 3.7, 3.7 Hz, 1H), 4.21 (dd, *J* = 8.7, 8.7 Hz, 1H), 5.34 (dd, *J* = 11.5, 5.4 Hz, 1H), 6.20 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.2, -5.04, -5.01, -4.97, 18.1, 18.2, 25.4, 25.79, 25.81, 25.86, 26.0, 32.2, 39.4, 59.7, 61.6, 74.2, 84.0, 126.3, 131.7, 134.1, 151.5, 195.0; IR (film) 2929, 1687 (str), 1471, 1253, 1086 cm^{-1}; $[\alpha]^{24}_D$ = -48.6 (c = 1.46, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{27}H_{52}O_5Si_2Na$ $[M + Na]^+$: 535.32, found: 535.5.



(*2S,3R,9R*)-3-(*tert*-Butyldimethylsilanyloxy)-2-(*tert*-butyldimethylsilanyloxymethyl)-9-(2-methoxy-3-methylbuta-1,3-dienyl)-7-methyl-2,3,4,5,8,9-hexahydrooxonine (9). A flask was charged with methylenetriphenylphosphine bromide (6.59 g, 18.5 mmol) and 15 mL of THF and cooled to 0 °C. Potassium *tert*-butoxide (1.0 M in THF, 14.8 mL, 14.8 mmol) was added to the heterogeneous mixture to give a yellow homogeneous solution. After stirring 30 minutes at 0 °C, the enone (1.89 g, 3.69 mmol) in 20 mL of THF was added dropwise and stirred 30 minutes at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, warmed to room temperature, and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (5% EtOAc/Hexanes) gave 1.63 g (87%) of the diene as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.038 (s, 3H), 0.045 (s, 3H), 0.06 (s, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.43 (m, 1H), 1.72 (d, J = 14.1 Hz, 1H), 1.74 (m, 1H), 1.82 (s, 6H), 1.85 (m, 1H), 2.72 (dd, J = 14.1, 9.7 Hz, 1H), 2.84 (dddd, J = 13.0, 13.0, 13.0, 4.6 Hz, 1H), 3.39 (dd, J = 6.5, 4.7 Hz, 1H), 3.57 (s, 3H), 3.67 (dd, J = 11.2, 8.9 Hz, 1H), 3.95 (dd, J = 11.2, 2.1 Hz, 1H), 4.02 (ddd, J = 11.5, 3.6, 3.6 Hz, 1H), 4.19 (dd, J = 8.9, 8.9 Hz, 1H), 5.00 (s, 1H), 5.24 (d, J = 1.5 Hz, 1H), 5.30 (d, J = 8.6 Hz, 1H), 5.34 (dd, J = 11.4, 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.1, -4.97, -4.96, -4.9, 18.2, 18.3, 19.6, 25.5, 25.9, 26.0, 26.3, 32.3, 40.3, 59.9, 61.8, 67.8, 74.5, 83.6, 113.4, 118.7, 125.9, 134.8, 137.2, 154.6; IR (film) 2928, 1463, 1253, 1086 cm^{-1}; $[\alpha]^{24}_D$ = -31 (c = 0.38, CH_2Cl_2)**;** MS (electrospray ionization) calculated for $C_{28}H_{54}O_4Si_2Na$ $[M + Na]^+$: 533.35, found: 533.5.

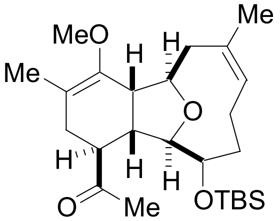


***(2S,3R,9R)*-[3-(*tert*-Butyldimethylsilanyloxy)-9-(2-methoxy-3-methylbuta-1,3-dienyl)-7-methyl-2,3,4,5,8,9-hexahydrooxonin-2-yl]-methanol.** A flask was charged with diene **9** (1.55 g, 3.03 mmol) and 30 mL of methanol. Ammonium fluoride (2.25 g, 60.6 mmol) was added to the solution and stirred overnight. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/Hexanes) provided 940 mg (79%) of the alcohol as a colorless oil, as well as 240 mg (16%) of recovered starting diene: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.07 (s, 3H), 0.88 (m, 9H), 1.49 (dddd, *J* = 14.5, 14.5, 6.0, 6.0 Hz, 1H), 1.72 (d, *J* = 14.2 Hz, 1H), 1.82 (s, 3H), 1.83 (s, 3H), 1.85-1.94 (m, 2H), 2.38 (dd, *J* = 7.8, 4.2 Hz, 1H), 2.65 (dd, *J* = 15.0, 10.5 Hz, 1H), 2.73 (m, 1H), 3.52-3.59 (m, 1H), 3.58 (s, 3H), 3.65 (m, 1H), 3.83 (ddd, 11.1, 7.9, 4.6 Hz, 1H), 4.10 (ddd, *J* = 11.5, 3.9, 3.9 Hz, 1H), 4.21 (dd, *J* = 9.1, 9.1 Hz, 1H), 5.04 (d, *J* = 0.5 Hz, 1H), 5.17 (d, *J* = 8.6 Hz, 1H), 5.27 (m, 1H), 5.37 (dd, *J* = 11.5, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.1, -4.9, 18.1, 19.8, 25.4, 25.8, 26.2, 31.8, 40.2, 59.9, 61.2, 68.7, 75.1, 81.4, 114.4, 117.2, 125.9, 134.6, 137.1, 155.7; IR (film) 3435 (br), 2928, 1644, 1444, 1247, 1085 cm^{-1}; $[\alpha]^{22}_D$ = -13 (c = 0.31, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{22}H_{40}O_4SiNa$ $[M + Na]^+$: 419.26, found: 419.3.



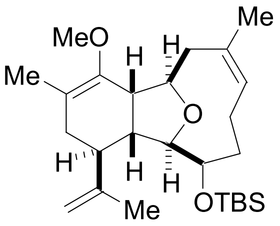
(*2S,3R,9R*)-3-(*tert*-Butyldimethylsilanyloxy)-9-(2-methoxy-3-methylbuta-1,3-dienyl)-7-methyl-2,3,4,5,8,9-hexahydrooxonine-2-carbaldehyde. A flask was charged with oxalyl chloride (2.0 M in CH_2Cl_2, 1.20 mL, 2.40 mmol) and 15 mL of CH_2Cl_2 and cooled to –78 °C. Dimethylsulfoxide (341 μL, 4.80 mmol) in 3 mL of CH_2Cl_2 was added dropwise, and the solution was stirred 2 minutes. The primary alcohol (865 mg, 2.18

mmol) and 6 mL of CH_2Cl_2 were added dropwise to the mixture and allowed to stir 30 minutes at –78 °C. Triethylamine (1.52 mL, 10.9 mmol) was added dropwise and stirred 5 minutes at –78 °C followed by warming to 0 °C for 1 hour. The reaction was quenched by the addition of cold water. The organic portion was washed with cold saturated aqueous $NaHCO_3$, then water. The combined aqueous portions were washed with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (5% EtOAc/Hexanes) provided 797 mg (93%) of the aldehyde as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (m, 6H), 0.89 (m, 9H), 1.57-1.77 (m, 3H), 1.81 (s, 3H), 1.82 (s, 3H), 1.87 (m, 1H), 2.69-2.81 (m, 2H), 3.54 (s, 3H), 4.09 (d, *J* = 4.8 Hz, 1H), 4.21-4.27 (m, 1H), 4.23 (d, *J* = 9.0 Hz, 1H), 5.03 (d, *J* = 0.5 Hz, 1H), 5.24 (m, 1H), 5.30 (d, *J* = 8.6 Hz, 1H), 5.35 (dd, *J* = 11.3, 5.6 Hz, 1H), 9.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ –5.1, -4.8, 18.1, 19.7, 24.6, 25.7, 26.2, 33.9, 39.6, 59.8, 69.4, 74.8, 85.9, 114.3, 117.1, 126.0, 134.3, 137.0, 155.5, 202.5; IR (film) 2925, 1735 (str), 1462, 1255, 1083 cm^{-1}; $[\alpha]^{22}_D$ = -11 (c = 0.33, CH_2Cl_2).

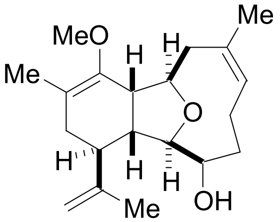


(*3S,7S,8R,14R,15R,16R*)-1-[14-(*tert*-Butyldimethylsilanyloxy)-6-methoxy-5,10-dimethyl-15-oxatricyclo[6.6.1.02,7]pentadeca-5,10-dien-3-yl]-ethanone (11). Into a flask equipped with a reflux condenser was added the previous aldehyde (664 mg, 1.68 mmol), 17 mL of toluene, and 1-(Triphenyl-l5-phosphanylidene)-propan-2-one (**10**)

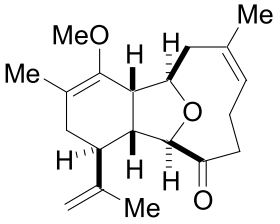
(1.61 g, 5.05 mmol). The solution was brought to reflux overnight, then cooled to room temperature. The mixture was concentrated in vacuo, then purified by flash column chromatography (5% then 10% EtOAc/Hexanes) provided 583 g (80%) of the ketone as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 0.007 (s, 3H), 0.011 (s, 3H), 0.89 (s, 9H), 1.56-1.65 (m, 1H), 1.62 (s, 3H), 1.84 (s, 3H), 1.86 (s, 3H), 1.87-2.02 (m, 3H), 2.12 (m, 1H), 2.29 (dd, J = 17.2, 6.5 Hz, 1H), 2.67 (m, 1H), 2.70 (d, J = 14.4 Hz, 1H), 2.89 (ddd, J = 6.9, 3.6, 3.6 Hz, 1H), 3.10 (m, 1H), 3.22 (m, 1H), 3.26 (s, 3H), 4.02 (dd, J = 8.4, 3.7 Hz, 1H), 4.20 (ddd, J = 10.4, 4.5, 4.5 Hz, 1H), 4.45 (ddd, J = 4.9, 2.5, 2.5 Hz, 1H), 5.49 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ –4.8, -4.7, 16.2, 18.2, 23.0, 26.1, 27.6, 28.2, 28.5, 33.1, 39.0, 40.1, 41.2, 46.7, 56.7, 73.3, 80.4, 84.3, 113.3, 130.0, 131.2, 149.1, 207.4; IR (film) 2927, 1712 (str), 1445, 1360, 1251, 1088 cm^{-1}; $[\alpha]^{22}_D$ = +40.8 (c = 1.10, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{25}H_{43}O_4Si$ $[M + 1]^+$: 435.29, found: 435.3.



(*1R,2S,6S,7R,8R,9R*)-*tert*-Butyl-(6-isopropenyl-3-methoxy-4,13-dimethyl-15-oxatricyclo[6.6.1.02,7]pentadeca-3,12-dien-9-yloxy)-dimethylsilane. A flask was charged with methylenetriphenylphosphine bromide (2.30 g, 6.43 mmol) and 10 mL of THF. Potassium *tert*-butoxide (1.0 M in THF, 5.14 mL, 5.14 mmol) was added to the heterogeneous mixture to give a yellow homogeneous solution. After stirring 30 minutes, ketoone **11** (559 mg, 1.29 mmol) in 15 mL of THF was added dropwise and stirred 3 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O, dried over Na_2SO_4,, and concentrated in vacuo. Purification via flash column chromatography (5% EtOAc/Hexanes) gave 468 mg (85%) of the alkene as a colorless oil: ^1H NMR (400 MHz, C_6D_6, 60 °C) δ 0.016 (s, 3H), 0.022 (s, 3H), 0.93 (s, 9H), 1.58-1.68 (m, 1H), 1.65 (s, 3H), 1.75 (s, 3H), 1.81 (s, 3H), 1.90 (m, 1H), 2.04 (dd, *J* = 17.2, 5.6 Hz, 1H), 2.05-2.17 (m, 2H), 2.24 (dd, *J* = 7.1, 5.5 Hz, 1H), 2.60 (dd, *J* = 12.0, 6.1 Hz, 1H), 2.60-2.71 (m, 1H), 2.72 (d, *J* = 14.2 Hz, 1H), 2.82 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.97 (m, 1H), 3.32 (s, 3H), 4.07-4.16 (m, 2H), 4.44 (m, 1H), 4.83 (m, 1H), 4.85 (m, 1H), 5.56 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ –4.8, -4.6, 16.1, 18.3, 21.3, 23.2, 26.2, 27.6, 33.0, 38.9, 40.7, 42.1, 43.0, 57.0, 73.7, 80.3, 84.6, 110.6, 114.8, 129.5, 131.7, 148.6, 149.0; IR (film) 2928, 1706, 1644, 1452, 1254, 1086 cm^{-1}; $[\alpha]^{25}_D = +22.3$ (c = 1.32, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{26}H_{45}O_3Si$ $[M + 1]^+$: 433.31, found: 433.4.

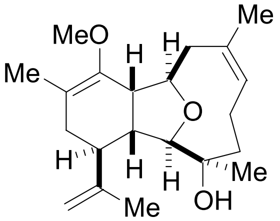


(*1R,2S,6S,7R,8R,9R*)-6-Isopropenyl-3-methoxy-4,13-dimethyl-15-oxatricyclo-[6.6.1.02,7]pentadeca-3,12-dien-9-ol. A flask was charged with the previous alkene (410 mg, 0.948 mmol) and 10 mL of THF. Tetrabutylammonium fluoride (1.0 M in THF, 1.90 mL, 1.90 mmol) was added to the solution and stirred 4 hours. Saturated aqueous NH_4Cl was added and the solution was diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (10% EtOAc/Hexanes) provided 283 mg (95%) of the alcohol as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 1.60 (s, 3H), 1.61 (s, 3H), 1.71-1.85 (m, 2H), 1.79 (s, 3H), 1.90-2.08 (m, 4H), 2.11 (dd, J = 14.5, 3.9 Hz, 1H), 2.40 (ddd, J = 9.5, 9.5, 5.7 Hz, 1H), 2.69 (ddd, J = 10.2, 7.2, 2.6 Hz, 1H), 2.85-2.92 (m, 2H), 3.07 (m, 1H), 3.30 (s, 3H), 3.70 (m, 1H), 4.16 (dd, J = 4.4, 2.7 Hz, 1H), 4.31 (ddd, J = 7.1, 3.5, 3.5 Hz, 1H), 4.78-4.82 (m, 2H), 5.67 (m, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 16.1, 19.9, 25.7, 28.2, 32.5, 35.4, 37.8, 42.6, 42.8, 44.3, 57.9, 73.4, 82.3, 85.9, 111.7, 115.7, 129.6, 134.3, 148.2, 150.0; IR (film) 3445 (br), 2918, 1695, 1638, 1448, 1221, 1053 cm^{-1}; $[\alpha]^{25}_D$ = +100 (c = 0.67, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{30}O_3Na$ $[M + Na]^+$: 341.21, found: 341.4.

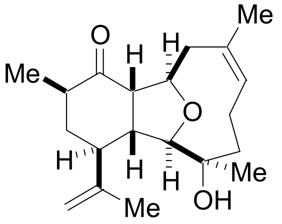


(*1R,2S,6S,7R,8R*)-6-Isopropenyl-3-methoxy-4,13-dimethyl-15-oxatricyclo-[6.6.1.02,7]pentadeca-3,12-dien-9-one. A flask was charged with the secondary alcohol (300 mg, 0.866 mmol) and 17 mL of CH_2Cl_2. Pyridine (351 μL, 4.33 mmol) followed by Dess-Martin periodinane (735 mg, 1.73 mmol) were added to the solution and stirred 15 minutes. The reaction was quenched by the addition of $Na_2S_2O_3$/$NaHCO_3$ (5:1 v:v) and the layers were separated. The aqueous portion was washed twice with CH_2Cl_2 and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo.

Purification via flash column chromatography (10% EtOAc/Hexanes) gave 290 mg (98%) of the ketone as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.64 (s, 6H), 1.78 (s, 3H), 1.93 (dd, *J* = 16.3, 4.6 Hz, 1H), 2.02 (dd, *J* = 14.4, 5.4 Hz, 1H), 2.05-2.18 (m, 2H), 2.24 (ddd, *J* = 11.2, 11.2, 4.7 Hz, 1H), 2.35 (ddd, *J* = 12.1, 12.1, 5.6 Hz, 1H), 2.51 (dd, *J* = 7.3, 7.3 Hz, 1H), 2.73 (d, *J* = 14.1 Hz, 1H), 2.82 (ddd, *J* = 12.4, 4.6, 4.6 Hz, 1H), 2.89 (dd, *J* = 11.8, 7.1 Hz, 1H), 3.10 (dddd, *J* = 12.2, 12.2, 12.2, 5.5 Hz, 1H), 3.49 (s, 3H), 4.06 (s, 1H), 4.30 (ddd, *J* = 8.0, 5.4, 3.3 Hz, 1H), 4.77 (s, 2H), 5.53 (dd, *J* = 10.8, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 19.0, 26.0, 26.4, 35.1, 37.3, 41.3, 42.0, 42.1, 42.6, 58.6, 85.1, 87.7, 112.7, 117.2, 126.9, 134.3, 146.7, 148.6, 214.0; IR (film) 3070, 1705 (str), 1448, 1202, 1119, 1032 cm^{-1}; $[\alpha]^{25}_{D}$ = -10.3 (c = 1.44, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{28}O_3Na$ $[M + Na]^+$: 339.19, found: 339.3.

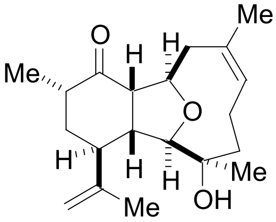


(*1R,2S,6S,7R,8R,9R*)-6-Isopropenyl-3-methoxy-4,9,13-trimethyl-15-oxatricyclo[6.6.1.02,7]pentadeca-3,12-dien-9-ol (12). A flask was charged with methylmagnesium chloride (3.0 M in THF, 3.47 mL, 10.4 mmol) and 70 mL of THF. The solution was cooled to 0 °C and the ketone (659 mg, 2.08 mmol) was added in 35 mL of THF dropwise. The solution was stirred 30 minutes, then quenched with saturated aqueous NH_4Cl, warmed to room temperature, and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (10% EtOAc/ Hexanes) provided 678 mg (98%) of the alcohol as a colorless oil: ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.95 (s, 3H), 1.66 (s, 3H), 1.69 (s, 3H), 1.69-1.79 (m, 1H), 1.85-1.96 (m, 2H), 1.90 (s, 3H), 2.00 (m, 1H), 2.17 (m, 2H), 2.28 (ddd, *J* = 11.2, 11.2, 4.5 Hz, 1H), 2.43 (dd, *J* = 11.7, 6.9 Hz, 1H), 2.75 (dd, *J* = 7.1, 7.1 Hz, 1H), 2.95 (d, *J* = 14.7 Hz, 1H), 3.07-3.24 (m, 2H), 3.52 (s, 3H), 3.87 (s, 1H), 4.18 (ddd, *J* = 8.6, 3.3, 3.3 Hz, 1H), 4.82 (s, 1H), 4.83 (m, 1H), 5.84 (dd, *J* = 10.9, 6.0 Hz, 1H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ 15.8, 19.0, 27.1, 28.3, 28.9, 35.2, 36.7, 38.8, 41.8, 42.9, 45.0, 58.6, 75.3, 83.4, 89.4, 113.0, 116.7, 128.7, 136.5, 147.0, 149.1; IR (film) 3511 (br), 2914, 1447, 1119, 1058 cm^{-1}; $[\alpha]^{24}_D$ = +74 (c = 0.42, CH$_2$Cl$_2$); MS (electrospray ionization) calculated for C$_{21}$H$_{32}$O$_3$Na [M + Na]$^+$: 355.23, found: 355.3.

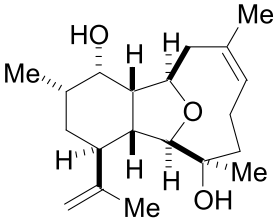


(*1R,2S,4R,6S,7R,8R,9R*)-9-Hydroxy-6-isopropenyl-4,9,13-trimethyl-15-oxatricyclo[6.6.1.02,7]pentadec-12-en-3-one. A flask was charged with alcohol **12** (678 mg, 0.255 mmol), 20 mL of CHCl$_3$, and 2.5 mL of water. Hydrochloric acid (12 M, 2.50 mL, 30.0 mmol) was added to the biphasic solution and stirred for 2 hours. The reaction was quenched by the slow addition of saturated aqueous NaHCO$_3$. The layers were separated and the aqueous portion was washed twice with CH$_2$Cl$_2$. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by flash column chromatography (10% then 25% EtOAc/Hexanes) gave 562 mg (87%) of the ketone as a white solid and 58 mg (9%) of the (*4S*)-product (#) as a colorless oil: ^{1}H NMR (400

MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.07 (d, *J* = 6.6 Hz, 3H), 1.59 (dd, *J* = 25.8, 13.0 Hz, 1H), 1.69 (s, 3H), 1.71-1.78 (m, 1H), 1.85-2.03 (m, 4H), 1.93 (s, 3H), 2.48 (ddd, *J* = 12.3, 12.3, 2.8 Hz, 1H), 2.59 (dddd, *J* = 11.7, 11.7, 6.5, 6.5 Hz, 1H), 2.69 (dd, *J* = 12.0, 7.0 Hz, 1H), 2.91-2.97 (m, 2H), 3.07 (m, 1H), 3.13 (ddd, *J* = 11.9, 11.9, 6.4 Hz, 1H), 3.94 (s, 1H), 4.36 (ddd, *J* = 9.9, 3.1, 3.1 Hz, 1H), 4.86 (m, 2H), 5.83 (dd, *J* = 11.5, 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 18.5, 27.2, 28.4, 28.7, 35.2, 38.5, 39.0, 41.8, 46.0, 48.7, 54.1, 74.8, 80.5, 91.3, 113.4, 128.3, 136.6, 146.2, 211.7; IR (film) 3514 (br), 2928, 1702 (str), 1453, 1377, 1184, 1076 cm^{-1}; $[\alpha]^{24}_D$ = +40 (c = 0.18, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{30}O_3Na$ $[M + Na]^+$: 341.21, found: 341.3.

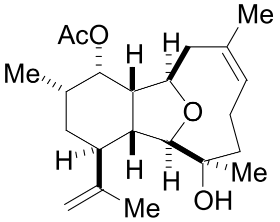


(*1R,2S,4S,6S,7R,8R,9R*)-9-Hydroxy-6-isopropenyl-4,9,13-trimethyl-15-oxatricyclo[6.6.1.02,7]pentadec-12-en-3-one. Into a flask containing the previous ketone (551 mg, 1.73 mmol) and 17 mL of methanol was added catalytic sodium hydride. After stirring 15 minutes, the reaction was quenched by the slow addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (10% then 25% EtOAc/Hexanes) gave 246 mg (45%) of the ketone as a colorless oil and 303 mg (55%) of the (*4R*)-product (#) as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.8Hz, 3H), 1.14 (s, 3H), 1.59-1.71 (m, 2H), 1.77 (s, 3H), 1.80-1.87 (m, 1H), 1.88 (s, 3H), 1.92-1.99 (m, 1H), 2.01 (dd, *J* = 14.8, 3.7 Hz, 1H), 2.11 (ddd, *J* = 13.9, 8.6, 7.1 Hz, 1H), 2.34 (s, 1H), 2.47 (ddd, *J* = 8.6, 8.6, 5.5 Hz, 1H), 2.58 (ddq, *J* = 21.7, 7.0, 7.0 Hz, 1H), 2.83 (ddd, *J* = 7.8, 7.8, 7.8 Hz, 1H), 2.84-2.93 (m, 2H), 3.02 (ddd, *J* = 8.1, 8.1, 4.6 Hz, 1H), 3.72 (d, *J* = 4.6 Hz, 1H), 4.58 (ddd, *J* = 6.3, 3.3, 3.3 Hz, 1H), 4.89 (d, *J* = 0.7 Hz, 1H), 4.92 (d, *J* = 1.3 Hz, 1H), 5.71 (dd, *J* = 11.3, 5.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 20.0, 25.3, 28.5, 28.9, 34.7, 36.5, 38.4, 40.7, 40.9, 45.9, 53.3, 74.7, 77.7, 89.1, 112.7, 129.2, 134.2, 146.9, 212.9; IR (film) 3443 (br), 2928, 1710 (str), 1642, 1446, 1376, 1081 cm^{-1}; $[\alpha]^{24}_D$ = +92 (c = 0.19, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{30}O_3Na$ $[M + Na]^+$: 341.21, found: 341.4.



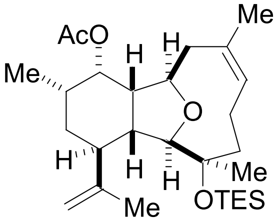
(*1R,2S,3S,4S,6S,7R,8R,9R*)-6-Isopropenyl-4,9,13-trimethyl-15-oxatricyclo-[6.6.1.02,7]pentadec-12-ene-3,9-diol. Into a flask charged with the ketone (523 mg, 1.64 mmol) was added 16 mL of THF. The solution was cooled to –78 °C and L-Selectride® (1.0 M in THF, 1.97 mL, 1.97 mmol) dropwise. The reaction was stirred 10 minutes, then quenched by the addition of sodium hydroxide (3 M, 1.0 mL, 3.0 mmol) and hydrogen peroxide (30%, 2.0 mL, 18 mmol). The mixture was stirred three hours at room temperature, then diluted with Et_2O. The layers were separated and the aqueous portions were washed twice with Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (25% EtOAc/Hexanes) gave 493 mg (94%) of the alcohol as a white solid: ^{1}H NMR (400

MHz, C_6D_6, 60 °C) δ 0.95 (d, *J* = 7.0 Hz, 3H), 1.19 (m, 1H), 1.28 (s, 3H), 1.33 (m, 2H), 1.56 (m, 1H), 1.64-1.73 (m, 2H), 1.70 (s, 3H), 1.75 (s, 3H), 1.77-1.94 (m, 2H), 1.89 (m, 1H), 2.19 (ddd, *J* = 7.8, 4.2, 4.2 Hz, 1H), 2.69-2.92 (m, 4H), 3.42 (s, 1H), 3.91 (d, *J* = 7.5 Hz, 1H), 4.24 (dd, *J* = 6.7, 3.8 Hz, 1H), 4.86 (s, 1H), 4.88 (d, *J* = 1.3 Hz, 1H), 5.52 (dd, *J* = 11.0, 6.1 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 17.2, 22.0, 24.6, 28.4, 28.8, 29.7, 31.8, 38.5, 38.6, 39.8, 42.6, 45.9, 72.2, 74.7, 80.0, 89.5, 110.6, 130.0, 132.3, 149.8; IR (film) 3329 (br), 2921, 1439, 1373, 1088 cm^{-1}; $[\alpha]^{25}_D$ = +5.7 (c = 0.46, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{20}H_{32}O_3Na$ $[M + Na]^+$: 343.23, found: 343.3.



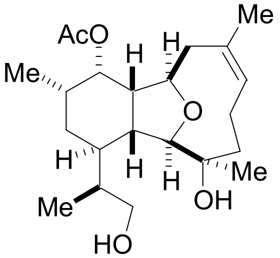
(*1R,2S,3S,4S,6S,7R,8R,9R*)-Acetic acid 9-hydroxy-6-isopropenyl-4,9,13-trimethyl-15-oxa-tricyclo[6.6.1.02,7]pentadec-12-en-3-yl ester (13). Into a flask containing the secondary alcohol (406 mg, 1.27 mmol) in 26 mL of CH_2Cl_2 was added triethylamine (707 µL, 5.07 mmol) and 4-dimethylaminopyridine (16.0 mg, 0.127 mmol). Acetic anhydride (240 µL, 2.53 mmol) was added to the solution and stirred overnight. The reaction was quenched using saturated aqueous NH_4Cl and the layers were separated. The aqueous portions were washed twice with CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (25% EtOAc/Hexanes) gave 453 mg (99%) of the ester as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 0.87 (d, *J* = 7.0 Hz, 3H), 1.25 (s, 3H), 1.37 (ddd, *J* = 13.7, 6.2, 4.1 Hz, 1H), 1.50-1.69 (m, 4H), 1.66 (s, 3H), 1.67 (s, 3H), 1.74 (dd, *J* = 14.6, 3.9 Hz, 1H), 1.77-

1.92 (m, 2H), 1.81 (s, 3H), 2.32 (ddd, *J* = 4.9, 4.9, 4.9 Hz, 1H), 2.66-2.78 (m, 3H), 2.89 (m, 1H), 3.88 (d, *J* = 6.6 Hz, 1H), 4.25 (dd, *J* = 7.0, 3.8 Hz, 1H), 4.83 (s, 1H), 4.85 (d, *J* = 1.3 Hz, 1H), 5.22 (dd, *J* = 5.1, 3.7 Hz, 1H), 5.51 (dd, *J* = 11.1, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 16.8, 20.7, 21.5, 24.9, 28.4, 29.7, 30.1, 30.2, 38.1, 38.8, 39.7, 43.0, 44.2, 73.8, 74.7, 79.7, 89.3, 111.1, 130.0, 132.6, 149.2, 170.0; IR (film) 3465(br), 2924, 1737 (str), 1450, 1374, 1237, 1039 cm^{-1}; $[\alpha]^{25}_D = +42.2$ (c = 1.32, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{22}H_{35}O_4$ $[M + 1]^+$: 363.25, found: 363.4.



(*1R,2S,3S,4S,6S,7R,8R,9R*)-Acetic acid 6-isopropenyl-4,9,13-trimethyl-9-triethylsilanyloxy-15-oxatricyclo[6.6.1.02,7]pentadec-12-en-3-yl ester (14). A flask was charged with ester **13** (64.0 mg, 0.176 mmol) in 2 mL of CH_2Cl_2 and cooled to 0 °C. 2,6-lutidine (62 μL, 0.53 mmol) and triethylsilyl trifluoromethanesulfonate (60 μL, 0.27 mmol) were added sequentially and stirred for 1 hour at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, warmed to room temperature and the layers were separated. The aqueous portions were washed twice with CH_2Cl_2, dried over Na_2SO_4 and concentrated in vacuo. Purification via flash column chromatography (5% EtOAc/Hexanes) gave 67 mg (80%) of the alkene as a colorless oil: ^{1}H NMR (400 MHz, C_6D_6, 60 °C) δ 0.62 (q, *J* = 7.8 Hz, 6H), 0.83 (d, *J* = 5.8 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 1.38 (ddd, *J* = 13.9, 3.1, 3.1 Hz, 1H), 1.55-1.65 (m, 2H), 1.57 (s, 3H), 1.71 (s, 3H), 1.73-1.89 (m, 4H), 1.79 (s, 3H), 1.86 (s, 3H), 2.20 (dd, *J* = 7.1, 4.6 Hz, 1H), 2.63 (d, *J* = 13.9

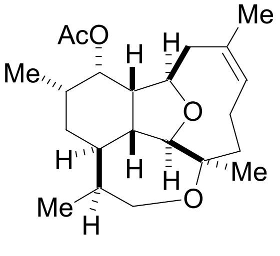
Hz, 1H), 2.68 (m, 1H), 2.96 (dd, *J* = 8.8, 8.8 Hz, 1H), 3.03 (d, *J* = 5.3 Hz, 1H), 3.97 (d, *J* = 10.4 Hz, 1H), 4.08 (d, *J* = 1.63 Hz, 1H), 4.88 (s, 1H), 4.94 (m, 1H), 5.19 (m, 1H), 5.44 (dd, *J* = 10.6, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6, 60 °C) δ 7.3, 7.5, 18.2, 20.7, 23.1, 23.5, 26.7, 28.5, 28.9, 29.5, 38.5, 39.2, 39.5, 41.4, 44.8, 74.1, 78.4, 79.4, 88.3, 110.1, 130.5, 130.9, 149.4, 170.5; IR (film) 2957, 1739 (str), 1462, 1373, 1235, 1116, 1048 cm^{-1}; $[\alpha]^{23}_{D}$ = -33 (c = 0.43, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{28}H_{48}O_4SiNa$ $[M + Na]^+$: 499.32, found: 499.4.



(*1R,1S',2S,3S,4S,6S,7R,8R,9R*)-Acetic acid 9-hydroxy-6-(2-hydroxy-1-methyl-ethyl)-4,9,13-trimethyl-15-oxatricyclo[6.6.1.02,7]pentadec-12-en-3-yl ester (16). A flask was charged with alkene **14** (10.4 mg, 21.8 μmol) in 500 μL of THF. (+)-Diisopinocampheylborane (24.0 mg, 83.2 μmol) was added to the solution and allowed to stir 30 minutes. The reaction was quenched by the addition of sodium hydroxide (3 M, 130 μL, 0.390 mmol), then hydrogen peroxide (30%, 260 μL, 2.29 mmol). The biphasic solution was stirred three hours, then diluted with brine and Et_2O. The layers were separated and the aqueous portion was washed twice with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. For purification purposes, the product and isopinocampheol were carried on to the next reaction as a mixture. In a separate experiment, purification via flash column chromatography (10% EtOAc/Hexanes) gave the alcohol as a colorless oil:

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.59 (q, *J* = 7.8 Hz, 6H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9 H), 1.01 (d, *J* = 6.7 Hz, 3H), 1.22 (d, *J* = 15.3 Hz, 1H), 1.47 (s, 3H), 1.59-1.94 (m, 9H), 1.77 (s, 3H), 2.08-2.18 (m, 2H), 2.10 (s, 3H), 2.52 (ddd, *J* = 12.2, 12.2, 8.3 Hz, 1H), 2.66 (m, 2H), 3.41 (dd, *J* = 10.9, 5.3 Hz, 1H), 3.63 (m, 1H), 3.78 (d, *J* = 10.7 Hz, 1H), 3.93 (s, 1H), 5.14 (m, 1H), 5.48 (dd, *J* = 11.2, 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.8, 6.9, 7.0, 15.8, 18.3, 21.2, 22.9, 26.7, 28.3, 28.5, 29.8, 32.9, 38.1, 38.7, 38.9, 44.4, 66.5, 73.9, 78.2, 78.8, 87.3, 130.0, 130.7, 171.4; IR (film) 3446 (br), 2957, 1737 (str), 1457, 1374, 1237, 1137, 1117, 1043 cm^{-1}; $[\alpha]^{26}_D$ = +2.3 (c = 0.68, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{28}H_{50}O_5SiNa$ $[M + Na]^+$: 517.33, found: 517.5.

Into a flask containing the alcohol **15** in 500 μL of THF was added tetrabutylammonium fluoride (1.0 M in THF, 63 μL, 63 μmol). The solution was stirred 1 hour, then quenched by the addition of saturated aqueous NH_4Cl and diluted with Et_2O. The layers were separated and the aqueous portion was washed three times with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (30% EtOAc/Hexanes) gave 5.1 mg (64% over two steps) of the diol as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.82 (d, *J* = 6.0 Hz, 3H), 0.86-0.99 (m, 1H), 0.88 (d, *J* = 6.9 Hz, 3H), 1.17 (d, *J* = 9.8 Hz, 1H), 1.42 (s, 3H), 1.64 (dd, *J* = 13.9, 8.4 Hz, 1H), 1.75-1.85 (m, 6H), 1.79 (s, 3H), 1.93 (m, 1H), 2.09-2.13 (m, 1H), 2.10 (s, 3H), 2.34 (br s, 1H), 2.49 (dd, *J* = 8.7, 8.7 Hz, 1H), 2.60 (dd, *J* = 21.1, 11.0 Hz, 1H), 2.69 (d, *J* = 14.4 Hz, 1H), 3.46 (dd, *J* = 11.6, 5.5 Hz, 1H), 3.53 (dd, *J* = 11.5, 11.5 Hz, 1H), 3.78 (d, *J* = 10.2 Hz, 1H), 4.04 (s, 1H), 5.18 (d, *J* = 3.7 Hz, 1H), 5.52 (dd, *J* = 10.7, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 1.0, 14.1, 18.4, 21.2, 23.0, 28.4, 29.4, 29.7, 29.8, 30.9, 37.9, 38.1, 42.2, 45.7, 65.4, 74.0, 75.1, 79.9, 89.1, 130.1, 171.4; IR (film) 3355 (br), 2925, 1736 (str), 1455, 1381, 1237, 1017 cm^{-1}; $[\alpha]^{26}_{D}$ = +33 (c = 0.39, CH_2Cl_2); MS (electrospray ionization) calculated for $C_{22}H_{36}O_5K$ $[M + K]^+$: 419.36, found: 419.4.



11-acetoxy-4-deoxyasbestinin D (1). A flask charged with diol **15** (8.9 mg, 24 μmol) in 1.1 mL of THF was cooled to 0 °C. 2,6 lutidine (13.6 μL, 0.117 mmol) followed by trifluoromethanesulfonic anhydride (5.8 μL, 34 μmol) were added to the solution and allowed to stir 45 minutes at 0 °C. The solution was warmed to room temperature for 4 hours, then quenched via the addition of saturated aqueous NH_4Cl. The mixture was diluted with Et_2O and the layers were separated. The aqueous portion was washed three times with Et_2O, dried over Na_2SO_4, and concentrated in vacuo. Purification via flash column chromatography (10% EtOAc/Hexanes) gave 5.5 mg (66%) of 11-acetoxy-4-deoxyasbestinin D as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 1.01 (m, 1H), 1.35 (s, 3H), 1.52 (ddd, *J* = 13.5, 13.5, 9.7 Hz, 1H), 1.61 (m, 1H), 1.75 (s, 3H), 1.75 (m, 2H), 1.84-2.08 (m, 5H), 2.10 (s, 3H), 2.34 (ddd, *J* = 10.4, 10.4, 10.4 Hz, 1H), 2.50 (br d, *J* = 14.8 Hz, 1H), 2.55 (ddd, *J* = 14.5, 10.3, 4.8 Hz, 1H), 3.48 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.86 (d, *J* = 15.2 Hz, 1H), 3.87 (d, *J* = 8.7 Hz, 1H), 4.10 (ddd, *J* = 5.5, 2.9, 2.9 Hz, 1H), 5.31 (dd, *J* = 5.1, 2.8 Hz, 1H), 5.47 (dd, *J* = 8.1, 8.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.0, 17.9, 21.3, 23.4, 26.1, 28.9, 31.3, 31.5, 37.3, 37.5, 38.0, 38.5, 40.5, 45.8, 67.9, 73.5, 76.4, 81.0, 92.2, 128.7, 130.8, 171.3; IR (film) 2926, 1737 (str), 1459, 1377, 1231, 1088 cm^{-1}; $[\alpha]^{26}_{D}$ = -15 (c = 0.17, $CHCl_3$); MS (electrospray ionization) calculated for $C_{22}H_{35}O_4$ $[M + 1]^+$: 363.25, found: 363.2.

An authentic sample of 11-acetoxy-4-deoxyasbestinin D was provided by Dr. Abimael D. Rodríguez (University of Puerto Rico, Río Piedras),[3] purified in the same manner as described above, and an optical rotation was obtained under identical conditions: $[\alpha]^{25}_{D}$ = -15 (c = 0.10, $CHCl_3$). The ^1H NMR (500 MHz, $CDCl_3$) spectrum of the authentic sample also mirrored the synthetic material.