Synthesis of the cyclobutanone core of solanoeclepin A via intramolecular allene butenolide photocycloaddition

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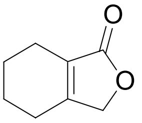
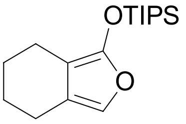
General information. All reactions involving oxygen or moisture sensitive compounds were carried out under a dry nitrogen atmosphere. THF and Et_2O were distilled from sodium and CH_2Cl_2 was distilled from CaH_2. DMF and toluene were distilled from CaH_2 and stored over 4 Å molecular sieves. Triethylamine was stored over KOH pellets, DMSO was dried and stored over 4 Å molecular sieves. Column chromatography was performed using Acros silica gel (0.030-0.075 mm). Petroleum ether (PE, 60/80) used for chromatography was distilled prior to use. TLC analyses were performed on Merck F-254 silica gel plates. IR spectra were measured using a Bruker IFS 28 FT-spectrophotometer and wavelengths (ν) are reported in cm^{-1}. ^1H NMR spectra were recorded on a Bruker AC 200 (200 MHz), a Bruker ARX 400 (400 MHz) and Varian Inova (500 MHz). The latter machines were also used for ^{13}C NMR spectra (50, 100 and 125 MHz, respectively). Unless otherwise indicated, $CDCl_3$ was used as the solvent. Chemical shifts are given in ppm (δ) relative to an internal standard of chloroform (7.26 ppm for ^1H-NMR and 77.0 for ^{13}C-NMR). Mass spectra and accurate mass determinations were performed on a JEOL JMS SX/SX102A, coupled to a JEOL MS-MP7000 data system. Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany.

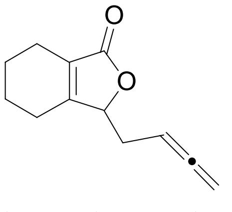


4,5,6,7-Tetrahydro-3*H*-isobenzofuran-1-one (9). To a stirred suspension of $NaBH_4$ (950 mg, 25.1 mmol) in THF (70 cm^3) at 0 °C was added dropwise over 2 h a solution of 3,4,5,6-tetrahydrophthalic anhydride (**8**, 3.8 g, 25.0 mmol) in THF (100 cm^3). The reaction mixture was stirred at 0 °C for 1 h and at rt for another 1 h. The reaction mixture was cooled to 0 °C and acidified with 2 M HCl (until pH 3). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 cm^3). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (300 cm^3) and brine (300 cm^3), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by chromatography (PE/EtOAc = 2:1) afforded 9 (2.13 g, 15.4 mmol, 60%) as a colorless solid, mp 56-57 °C (lit.[1] mp 53-54 °C). ^1H NMR δ 4.67 (br s, 2 H), 2.30 (m, 2 H), 2.22 (m, 2 H), 1.75 (m, 4 H). ^{13}C NMR δ 174.1, 160.9, 126.0, 71.8, 23.3, 21.3, 21.2, 19.7. IR ($CHCl_3$) ν 1735, 1678 cm^{-1}.

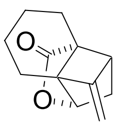


Triisopropyl-(4,5,6,7-tetrahydro-isobenzofuran-1-yloxy)-silane (10). To a stirred solution of lactone **9** (100 mg, 0.72 mmol) in CH_2Cl_2 (2 cm^3) at 0 °C was added dropwise triisopropylsilyl triflate (250 µL, 285 mg, 0.93 mmol) and diisopropylethylamine (251 µL, 186 mg, 1.44 mmol). The reaction mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with icecold saturated aqueous NH_4Cl (2 cm^3). The layers were separated and the aqueous phase was extracted with ether (3 × 10 cm^3). The combined organic layers were washed with brine (30 cm^3), dried over $MgSO_4$, and concentrated *in vacuo* to afford **10** as a colorless oil, which was used for the next step without further purification. ^{1}H NMR δ 6.55 (s, 1 H), 2.46 (m, 2 H), 2.34 (m, 2 H), 1.63 (m, 4 H), 1.21 (m, 3 H), 1.07 (m, 18 H).

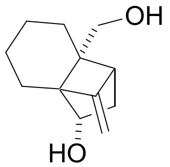
3-(Buta-2,3-dienyl)-4,5,6,7-tetrahydro-3H-isobenzofuran-1-one (11). To a solution of the crude silyloxyfuran **10** and 1-bromobuta-2,3-diene[2] (144 mg, 1.08 mmol, 1.5 equiv) in CH_2Cl_2 (25 cm^3) at –78 °C was added silver trifluoroacetate (240 mg, 1.09 mmol). The reaction mixture was stirred at –78 °C for 20 min and then at –20 °C for 3 h and at rt for overnight. The mixture was filtered through Celite® and the filtrate concentrated *in vacuo*. Purification by chromatography (PE/EtOAc 4:1) afforded **11** (85 mg, 0.45 mmol, 62% from **9**) as a slightly yellow oil (R_f = 0.17). ^{1}H NMR δ 5.00 (m, 1 H), 4.88 (m, 1 H), 4.70 (m, 2 H), 2.58 (m, 1 H), 2.31 (m, 1 H), 2.22 (m, 4 H), 1.74 (m, 4 H). ^{13}C NMR δ 209.3, 173.2, 162.7, 127.2, 83.2, 81.6, 75.2, 31.1, 23.1, 21.4 (2 C), 19.7. IR (neat) ν 2941, 2947, 1957, 1747, 1681. HRMS (FAB) calcd for $C_{12}H_{15}O_2$ (MH+) 191.1072, found 191.1076.



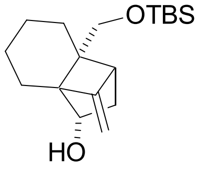
Photocycloaddition product 12. A solution of allene **11** (85 mg, 0.45 mmol) in acetonitrile/acetone (0.05 M, 9:1 v/v) was degassed by bubbling argon through for 30 min. The solution was kept under argon and irradiated (300 nm) for 5 h. The reaction was followed by TLC. When complete conversion was observed, the solvent was removed *in vacuo*. Purification by chromatography (PE/EtOAc 4:1) provided **15** (60 mg, 0.32 mmol, 70%) as colorless crystals (R_f = 0.40, mp 125-127 °C). ^{1}H NMR δ 4.76 (s, 1 H), 4.61 (d, *J* = 3.9 Hz, 1 H), 4.56 (s, 1 H), 2.94 (s, 1 H), 2.17 (br d, *J* = 13.8 Hz, 1 H), 2.10 (dd, *J* = 12.0, 4.1 Hz, 1 H), 1.87 (br d, *J* = 15 Hz, 1 H), 1.73 (dd, *J* = 12.0, 2.3 Hz, 1 H), 1.62 - 1.45 (m, 4 H), 1.35 (m, 1 H), 0.96 (m, 1 H). ^{13}C NMR δ 175.6, 150.8, 96.0, 79.6, 66.0, 53.9, 48.4, 36.6, 21.7, 21.1, 20.1, 19.3. IR ($CHCl_3$) ν 2941, 1763, 1215 cm^{-1}. Elemental analysis: calcd for $C_{12}H_{14}O_2$ C: 75.76%, H: 7.42%; found C: 75.65%, H: 7.40%. For X-ray data, vide infra..



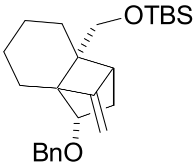
7a-Hydroxymethyl-8-methylene-octahydro-1,3a-methano-inden-3-ol (13). To a 1M solution of $LiAlH_4$ in THF (6.5 cm^3, 5 equiv) at rt was added a solution of lactone **12** (250 mg, 1.315 mmol) in THF (5 cm^3). The resulting mixture was stirred at rt for 30 min and carefully quenched with EtOAc. Saturated aqueous Na_2SO_4 (10 drops) was then added and the mixture was stirred for 1 h. After addition of more solid Na_2SO_4 the mixture was filtered through Celite® and concentrated *in vacuo.* Purification by chromatography (EtOAc) afforded diol **13** as a colorless solid (189 mg, 74%). R_f = 0.30, mp 110-114 °C. ^{1}H NMR (CD_3OD) δ 4.53 (s, 1 H), 4.35 (s, 1 H), 4.23 (dd, J = 11.9, 1.8 Hz, 1 H), 3.88 (dd, J = 7.6, 2.6 Hz, 1 H), 3.46 (d, J = 11.9 Hz, 1 H), 2.65 (s, 1 H), 2.10 (ddd, J = 11.8, 7.8, 1.7 Hz, 1 H), 2.03 (br d, J = 13.4 Hz, 1 H), 1.87 (m, 1 H), 1.67-1.50 (m, 6 H), 1.30 (m, 1 H). ^{13}C NMR (CD_3OD) δ 158.0, 94.5, 73.3, 63.5, 60.3, 51.3, 47.1, 36.6, 28.8, 23.0, 22.8, 21.6. IR (neat) ν 3397, 2934, 1690 cm^{-1}.



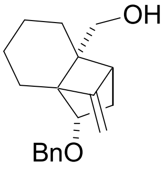
7a-(*tert*-Butyl-dimethyl-silanyloxymethyl)-8-methylene-octahydro-1,3a-methano-inden-3-ol. To a stirred solution of diol **13** (158 mg, 0.81 mmol) in DMF (5 cm^3) at rt was added *tert*-butyldimethylsilyl chloride (182 mg, 1.5 equiv) and imidazole (386 mg, 7 equiv). The reaction mixture was stirred for 5 h and diluted with EtOAc (10 cm^3). The organic phase was washed with 2% aqueous solution of citric acid (10 cm^3), water (10 cm^3), and brine (10 cm^3), dried over $MgSO_4$ and concentrated *in vacuo* to provide 273 mg (0.88 mmol) crude silyl-protected alcohol as a colorless oil. The crude silyl ether was used for the next step without further purification. ^{1}H NMR δ 4.51 (s, 1 H), 4.34 (s, 1 H), 3.94 (m, 2 H), 3.74 (d, J = 10.9 Hz, 1 H), 3.12 (d, J = 6.8 Hz, 1 H), 2.61 (s, 1 H), 2.14 (ddd, J = 12.0, 7.6, 1.6 Hz, 1 H), 1.86–1.72 (m, 3 H), 1.67 – 1.48 (m, 5 H), 1.35 (m, 1 H), 0.90 (s, 9 H), 0.07 (s, 3 H),



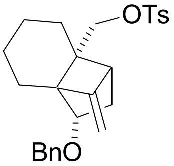
0.06 (s, 3 H). ^{13}C NMR δ 156.2, 93.7, 72.6, 63.8, 62.4, 50.4, 45.1, 36.5, 30.8, 25.7, 21.9, 21.5, 20.7, 18.0, -5.6, -5.8. IR (neat) ν 3400, 2930, 1684 (w), 1254, 1080 cm^{-1}.



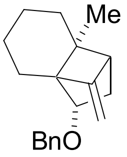
(3-Benzyloxy-8-methylene-hexahydro-1,3a-methano-inden-7a-ylmethoxy)-*tert*-butyl-dimethylsilane. To a solution of the above crude alcohol (273 mg, 0.88 mmol) in THF (5 cm^3) at rt was added benzyl bromide (0.2 cm^3, 288 mg, 1.68 mmol), and sodium hydride (60 wt.% dispersion in mineral oil, 80 mg, 2 equiv). The resulting mixture was stirred at rt for 30 min. Tetra-*n*-butylammonium iodide (cat) was added and stirring was continued overnight. The reaction was quenched with ice-water. The layers were separated and the aqueous phase extracted with ether (3 × 10 cm^3). The combined organic layers were washed with brine (30 cm^3), dried over MgSO$_4$ and concentrated *in vacuo* to afford a colourless oil after chromatographic purification (290 mg, 0.73 mmol, 90% from **13**). ^{1}H NMR δ 7.35-7.24 (m, 5 H), 4.56 (d, J = 12.2 Hz, 1 H), 4.52 (s, 1 H), 4.46 (d, J = 12.2 Hz, 1 H), 4.34 (s, 1 H), 4.23 (dd, J = 10.8, 1.7 Hz, 1 H), 3.69 (dd, J = 7.3, 2.7 Hz, 1 H), 3.47 (d, J = 10.8 Hz, 1 H), 2.68 (s, 1 H), 2.09-2.00 (m, 2 H), 1.87 (dd, J = 11.5, 1.9 Hz, 1 H), 1.64-1.46 (m, 6 H), 1.23 (m, 1 H), 0.88 (s, 9 H), 0.02 (s, 6 H). ^{13}C NMR (200 MHz) δ 156.2, 139.0, 128.2 (2 C), 127.23, 127.18 (2 C), 94.0, 79.8, 72.1, 61.4, 59.7, 49.9, 46.2, 33.7, 26.9, 26.0, 21.9, 21.7, 21.1, 18.3, -5.31, -5.33. IR (neat) ν 2929, 1684 (w), 1077 cm^{-1}.



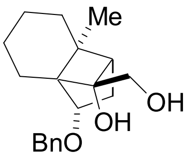
(3-Benzyloxy-8-methylene-hexahydro-1,3a-methano-inden-7a-yl)-methanol (14). To a stirred solution of the above silyl ether (312 mg, 0.78 mmol) in CH$_2$Cl$_2$/MeOH (9/1 v/v) (5 cm^3) at rt was added camphorsulphonic acid (60 mg, 0.3 equiv). The reaction mixture was stirred at rt for 3 h and quenched with saturated aqueous NaHCO$_3$ (5 cm^3). The layers were separated and the aqueous phase extracted with EtOAc (3 × 5 cm^3). The combined organic layers were washed with brine (20 cm^3), dried over MgSO$_4$, and concentrated *in vacuo* to give alcohol **14** as a slightly yellow oil (185 mg, 0.65 mmol, 84%) after chromatography (hexanes/EtOAc = 3:1). R_f= 0.26. ^{1}H NMR δ 7.34-7.26 (m, 5 H), 4.63 (d, J = 11.9 Hz, 1 H), 4.55 (s, 1 H), 4.48 (d, J = 11.9 Hz, 1 H), 4.37 (s, 1 H), 3.93 (d, J = 11.9 Hz, 1 H), 3.81-3.76 (m, 2 H), 2.66 (s, 1 H), 2.11 (br s, 1 H), 2.05 (ddd, J = 11.9, 7.1, 1.6 Hz, 1 H), 1.97 (br d, J = 11 Hz, 1 H), 1.90-1.48 (m, 8 H). ^{13}C NMR δ 155.3, 138.1, 128.2 (2 C), 127.4, 127.2 (2 C), 94.2, 79.5, 71.2, 63.7, 61.8, 49.8, 45.6, 33.6, 30.8, 21.8, 21.5, 21.2. IR (neat) ν 3370, 2930, 1687, 1452 cm^{-1}.



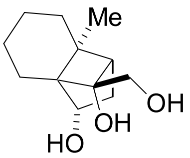
Toluene-4-sulfonic acid 3-benzyloxy-8-methylene-hexahydro-1,3a-methano-inden-7a-yl methyl ester. To a stirred solution of alcohol **14** (227 mg, 0.80 mmol) in pyridine (4 cm^3) at rt was added *p*-toluenesulfonyl chloride (306 mg, 1.60 mmol). The reaction mixture was stirred overnight and quenched with icecold 3% aqueous citric acid (10 cm^3). The layers were separated and the aqueous phase extracted with EtOAc (3 × 10 cm^3). The combined organic layers were washed with water (30 cm^3), brine (30 cm^3), dried over MgSO$_4$, and concentrated *in vacuo* to afford the crude tosylate as a colorless oil (341 mg, 0.78 mmol), that was used for the next step without further purification. ^{1}H NMR δ 7.73 (d, J = 8.3 Hz, 2 H), 7.37–7.21 (m, 7 H), 4.77 (dd, J = 10.5, 1.9 Hz, 1 H), 4.58 (s, 1 H), 4.42 (d, J = 12.0 Hz, 1 H), 4.38 (s, 1 H), 4.32 (d, J = 12.0 Hz, 1 H), 3.92 (d, J = 10.5 Hz, 1 H), 3.64 (dd, J = 7.3, 2.5 Hz, 1 H), 2.71 (s, 1 H), 2.41 (s, 3 H), 1.98–1.90 (m, 2 H), 1.67–1.41 (m, 7 H), 1.02 (m, 1 H). ^{13}C NMR δ 154.4, 144.2, 138.3, 132.8, 129.5 (2 C), 128.1 (2 C), 127.8 (2 C), 127.2, 126.9 (2 C), 95.3, 78.8, 70.7, 68.7, 62.2, 49.7, 44.0, 33.0, 26.8, 21.4, 21.3, 21.0, 20.6. IR (CHCl$_3$) ν 2939, 1696, 1598, 1452, 1356, 1175 cm^{-1}. HRMS (FAB) calcd for C$_{26}$H$_{31}$O$_4$S (MH+) 439.1943, found 439.1945.



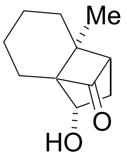
3-Benzyloxy-7a-methyl-8-methylene-octahydro-1,3a-methano-indene (15). Sodium triethylborohydride (1 M in THF, 3 cm^3, 4 equiv) was added to a solution of the above tosylate in THF (10 cm^3) at 0 °C. The reaction mixture was brought to reflux for 1 h and then cooled to 0 °C. The reaction was quenched with icewater and the layers were separated. The aqueous layer was extracted with ether (3 × 10 cm^3). The combined organic layers were washed with 3 N aqueous NaOH (10 cm^3) and 30% aqueous H_2O_2 (10 cm^3), water (30 cm^3), brine (30 cm^3), dried over $MgSO_4$, and concentrated *in vacuo* to provide **15** (142 mg, 0.53 mmol, 66% from **14**) as colorless oil after chromatography (hexanes/EtOAc = 20:1). R_f = 0.50. ^{1}H NMR δ 7.36–7.24 (m, 5 H), 4.58 (d, J = 12.3 Hz, 1 H), 4.49 (s, 1 H), 4.47 (d, J = 12.3 Hz, 1 H), 4.33 (s, 1 H), 3.69 (dd, J = 7.3, 2.8 Hz, 1 H), 2.51 (s, 1 H), 2.02 (ddd, J = 11.4, 7.3, 1.6 Hz, 1 H), 1.91–1.81 (m, 2 H), 1.66–1.42 (m, 6 H), 1.26 (m, 1 H), 1.16 (s, 3 H). ^{13}C NMR δ 157.0, 139.1, 128.0 (2 C), 127.0, 126.9 (2 C), 93.7, 79.8, 71.0, 61.0, 51.8, 41.2, 34.1, 33.8, 22.2, 21.8, 20.6, 16.4. IR (neat) ν 2931, 2857, 2860, 1686, 1455, 1355, 867 cm^{-1}. HRMS (FAB) calcd for $C_{19}H_{25}O$ (MH+) 269.1905, found 269.1908.



3-Benzyloxy-8-hydroxymethyl-7a-methyl-octahydro-1,3a-methano-inden-8-ol (16). To a stirred solution of **15** (113 mg, 0.42 mmol) in pyridine/water (1/1, v/v, 5 cm^3) at rt was added OsO_4 (161 mg, 0.63 mmol, 1.5 equiv). The reaction mixture was heated to 65 °C, stirred for 6 h at this temperature and then cooled to rt. Saturated aqueous $NaHSO_3$ (10 cm^3) and solid Na_2SO_3 (50 mg) were added and the resulting mixture was stirred for 30 min. The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 cm^3). The combined organic layers were washed with saturated aqueous $NaHSO_3$ (30 cm^3), water (30 cm^3), brine (30 cm^3), dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude product. Chromatographic purification (hexanes/EtOAc = 1:1) gave residual starting material (26.0 mg, 0.097 mmol) and diol **16** (55.6 mg, 0.18 mmol, 60% yield, based on 73% conversion) as colorless oil. R_f = 0.37. ^{1}H NMR δ 7.36–7.23 (m, 5 H), 4.62 (d, J = 12.3 Hz, 1 H), 4.50 (d, J = 12.3 Hz, 1 H), 4.38 (br d, J = 11 Hz, 1 H), 4.25 (br d, J = 11 Hz, 1 H), 4.15 (dd, J = 7.1, 2.2 Hz, 1 H), 3.15 (s, 1 H), 2.29 (s, 1 H), 2.26 (m, 1 H), 2.11 (m, 1 H), 1.90 (m, 2 H), 1.67-1.60 (m, 4 H), 1.46 – 1.32 (m, 3 H), 1.20 (s, 3 H). ^{13}C NMR δ 139.3, 128.0 (2 C), 126.9 (3 C), 81.0, 80.8, 71.5, 67.8, 58.3, 48.3, 38.7, 33.0, 32.4, 22.0, 21.7, 21.2, 20.4. IR (neat) ν 3400, 2926, 1453, 1274, 1073 cm^{-1}.

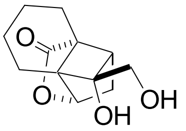


8-Hydroxymethyl-7a-methyl-octahydro-1,3a-methano-indene-3,8-diol. A mixture of benzyl ether **16** (48 mg, 0.159 mmol) and pre-equilibrated 10% Pd/C (40 mg) in ethanol (2 cm^3) was treated with hydrogen at rt and atmospheric pressure for 30 min. The mixture was filtered and the filtrate was evaporated to yield the desired triol (22 mg, 0.104 mmol, 65 %) as a colorless oil after chromatographic purification (EtOAc). R_f = 0.30. ^{1}H NMR (CD_3OD) δ 4.36 – 4.32 (m, 1 H), 4.33 (d, J = 11.5 Hz, 1 H), 4.1 (d, J = 11.5 Hz, 1 H), 2.3 – 2.27 (m, 2 H), 2.24 (s, 1 H), 1.7 (dd, J = 1 Hz, J = 11 Hz, 1 H), 1.66 – 1.4 (m, 7 H), 1.16 (s, 3 H). ^{13}C NMR δ 81.0, 73.9, 67.8, 58.0, 48.4, 38.6, 34.6, 33.2, 22.0, 21.35, 21.31, 19.9. IR (neat) ν 3400, 2932, 1058 cm^{-1}.

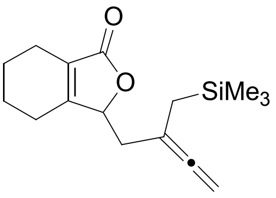


3-Hydroxy-7a-methyl-octahydro-1,3a-methano-inden-8-one (17). To a stirred solution of the above triol (22 mg, 0.104 mmol) in acetone/water (1:1 v/v, 2 cm^3) at 0 °C was added $NaIO_4$ (45 mg, 2 equiv). The resulting mixture was allowed to warm up to rt and stirred for 30 min. Most of the acetone was evaporated *in vacuo*. The residue was dissolved in EtOAc (5 cm^3) and the organic phase washed with brine (5 cm^3) and concentrated *in vacuo* to provide cyclobutanone **17** as colorless solid after chromatography purification (hexanes/EtOAc = 4:1). R_f = 0.10. Recrystallization (diisopropyl ether) gave colorless crystals (12 mg, 0.067 mmol, 64%), mp 103-106 °C. ^{1}H NMR δ 4.08 (dd, J = 7.8, 2.8 Hz, 1 H), 2.63 (s, 1 H), 2.28 (ddd, J = 12.7, 7.8, 1.5 Hz, 1 H), 2.00 (ddd, J = 12.7, 3.0, 1.6 Hz, 1 H), 1.87 (br s, 1 H), 1.8–1.2 (m, 8 H), 1.31 (s, 3 H). ^{13}C NMR δ 202.8, 70.0, 67.9, 61.0, 36.1, 35.3, 32.4, 22.2, 21.3, 18.8, 14.2. IR (neat) ν 3430, 2938, 1798, 1766 cm^{-1}. For X-ray data, vide infra.

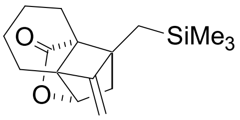
Synthesis of 18 by dihydroxylation of methylenelactone 12. To a stirred solution of lactone **12** (116 mg, 0.61 mmol) in *n*-butanol/water/acetone (5 cm^3, 5.0/1.5/1.0 v/v/v) was added *N*-methylmorpholine-*N*-oxide (142 mg, 2 equiv) and OsO_4 (1.55 mg, 1 mol %) at rt. The reaction mixture was stirred for overnight and quenched with saturated aqueous $Na_2S_2O_3$ (10 cm^3). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 10 cm^3). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ (30 cm^3), water (30 cm^3), brine (30 cm^3), dried over $MgSO_4$, and concentrated *in vacuo* to afford diol **18** (81 mg, 0.36 mmol, 59%) as an oil after chromatography (EtOAc). R_f = 0.34. ^{1}H NMR δ 4.67 (dd, J = 4.2, 1.2 Hz, 1 H), 4.32 (d, J = 10.8 Hz, 1 H), 4.20 (d, J = 10.8 Hz, 1 H), 3.37 (br s, 1 H), 2.81 (s, 1 H), 2.76 (dd, J = 11.9, 4.3 Hz, 1 H), 2.35 (dd, J = 14.6, 3.7 Hz, 1 H), 2.07 (br s, 1 H), 1.90-1.76 (m, 2 H), 1.70 (m, 1 H), 1.59 (m, 1 H), 1.48-1.39 (m, 2 H), 1.20 (m, 1 H), 1.02 (m, 1 H). ^{13}C NMR δ 178.0, 82.0, 79.6, 64.7, 62.5, 49.7, 47.1, 34.0, 22.6, 21.3, 20.5, 18.5. IR (neat) ν 3450, 2936, 1749 cm^{-1}.



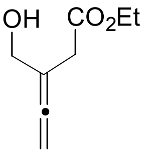
3-[2-(Trimethyl-silanylmethyl)-buta-2,3-dienyl]-4,5,6,7-tetrahydro-3*H*-isobenzofuran-1-one (22a). To a mixture of silver trifluoroacetate (116 mg, 0.525 mmol) and powdered molecular sieves (4 Å, 116 mg) was added at –78 °C a solution of allenyl bromide **20a** (105 mg, 0.48 mmol)^3 in 1.5 cm^3 of dichloromethane. After being stirred at –78 °C for 10 min a solution of the freshly prepared dienol silyl ether **10** (141 mg, 0.48 mmol) in CH_2Cl_2 (1.5 cm^3) was added. The resulting mixture was stirred for 4 h, while it was allowed to slowly warm up to rt. The mixture was then filtered through Celite and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (eluant first pentane/dichloromethane 7:3, then pure dichloromethane) giving **22a** as a colorless oil (38 mg, 0.14 mmol, 29%). ^{1}H NMR δ 4.94 (t, J = 5.8 Hz, 1 H), 4.69 (m, 2 H), 2.36 - 2.20 (m, 6 H), 1.72 (m, 4 H), 1.36 (m, 2 H), 0.04 (s, 9 H).



Photocycloaddition of 22a to 23a. This reaction was carried out as described for the synthesis of **12**. The starting material **22a** (29 mg, 0.105 mmol) was gone after 35 min. The product was purified by chromatography (hexanes/dichloromethane 1:1) to give a colorless crystalline product (0.18 mg, 0.065 mmol). Mp 70-72 °C. ^{1}H NMR δ 4.68 (d, J = 0.6 Hz, 1 H), 4.60 (d, J = 4.1 Hz, 1 H), 4.52 (d, J = 0.6 Hz), 2.03 (dd, J = 11.8, 4.2 Hz, 1 H), 2.02 (m, 1 H), 1.88 (m, 1 H), 1.68 (d, J = 11.8 Hz, 1 H), 1.64-1.24 (m, 5 H), 1.00 (m, 1 H), 0.99 (d, J = 15.1 Hz, 1 H), 0.88 (d, J = 15.1 Hz, 1 H), 0.03 (s, 9 H). ^{13}C NMR δ 175.7, 155.9, 93.5, 80.4, 64.1, 58.1, 56.5, 41.1, 21.5, 20.1, 19.4, 19.3, 14.5, -0.1 (3C), IR ($CHCl_3$) ν 1760, 1693, 1324, 1251 cm^{-1}. HRMS (FAB) calcd for $C_{16}H_{24}O_2Si$ (MH^+) 277.1624, found 277.1615.

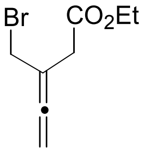


Ethyl 3-(hydroxymethyl)penta-3,4-dienoate (21). Triethyl orthoacetate (47.1, 290 mmol), 1,4-butynediol (5.0 g, 58.1 mmol) and propionic acid (1.0 cm^3) were heated at 110 °C for 2 h and then the temperature raised to 125 °C while the ethanol liberated was allowed to distill out of the reaction mixture over 4 h. The mixture was kept at 125 °C for 18 h under positive nitrogen pressure and cooled to room temperature. The mixture was cooled in an ice bath and a mixture of THF (22 cm^3) and aqueous 2 N HCl was added dropwise over 30 min. After coming to room temperature over 30 min volatiles were removed *in vacuo* keeping the bath temperature at 40 ^{o}C. The residue was taken up in dichloromethane (50 cm^3), washed with water, saturated sodium bicarbonate and dried over anhydrous sodium sulfate. Concentration afforded a brown oil consisting primarily of diethyl 3,4-bismethylene

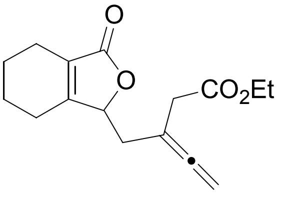


adipate and the desired hydroxyallenic ester in a ratio of 2:3. Flash chromatography (EtOAc/hexanes 1:1) afforded pure ethyl 3-(hydroxymethyl)penta-3,4-dienoate (2.54 g, 28% yield). ^{1}H NMR ($CDCl_3$) δ 4.88 (quintet, J = 2.4 Hz, 2 H), 4.20-4.14 (m, 4 H), 3.12 (t, J = 2.3 Hz, 2 H), 2.17 (t, J = 6.1 Hz, 1 H), 1.27 (t, J = 7.1 Hz, 3 H). IR (neat) ν 3420, 1960, 1737 cm^{-1}, consistent with the spectra previously described for this compound.[4] ^{13}C NMR δ 206.8, 171.8, 97.3, 77.2, 63.3, 61.1, 35.9, 14.2.

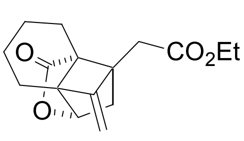
Ethyl 3-(bromomethyl)penta-3,4-dienoate (20b). A mixture of ethyl 3-(hydroxymethyl)penta-3,4-dienoate (**21**) (700 mg, 4.48 mmol) and Et_3N (680 mg, 6.72 mmol), dissolved in CH_2Cl_2 (12 cm^3), was added to a solution of methanesulfonyl chloride (770 mg, 6.72 mmol) in CH_2Cl_2 (2 cm^3) at 0 °C. The stirred mixture was allowed to warm up to room temperature over 1 h. Then more CH_2Cl_2 was added to the mixture, which was then washed with water and saturated aqueous $NaHCO_3$, and dried with Na_2SO_4. A crude oil was obtained upon concentration (960 mg, 4.10 mmol, 91%). LiBr (1.42 g, 16.4 mmol) in acetone (10 cm^3) was added to this crude mesylate dissolved in acetone (5 cm^3) at 0 °C. The mixture was allowed to come to room temperature and stirred for 45 min. It was was concentrated, diluted with CH_2Cl_2, and washed with water, 2 N HCl, and $NaHCO_3$. It was then dried over Na_2SO_4 and concentrated to afford a brown oil (607 mg, 68%); ^{1}H NMR δ 4.88 (m, 2 H), 4.20-4.15 (m, 4 H), 3.19 (t, J = 2.3 Hz, 2 H), 1.28 (t, J = 7.1 Hz, 3 H). ^{13}C NMR δ 208.4, 170.5, 95.6, 77.1, 60.9, 35.6, 34.6, 14.2. IR (neat) ν 2983, 1956, 1736 cm^{-1}.



Synthesis of 22b by Jefford coupling. To a stirred mixture of silver trifluoroacetate (243 mg, 1.10 mmol) and powdered molecular sieves (243 mg) in CH_2Cl_2 (2 cm^3) at -78 °C was added bromide **20b** (241 mg,1.10 mmol) in CH_2Cl_2 (2 cm^3). After being stirred at –78 °C for 10 min a solution of the freshly prepared (from 1 mmol (138 mg) of butenolide **9**) dienol silyl ether **10** in CH_2Cl_2 (2 cm^3) was added. The reaction mixture was allowed to warm up to -5 °C in 3 h and then filtered over Celite. The filter was rinsed with excess CH_2Cl_2. The filtrates were concentrated *in vacuo* and purified by flash column chromatography (hexanes/EtOAc 2:1, with 1% of Et_3N) affording 133 mg of allene **22b** (0.48 mmol, 48%) as a colorless oil (not completely pure) along with 50 mg (36%) of starting material. ^{1}H NMR δ 4.95 (br s, 1 H), 4.81 (m, 2 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 3.08 (br d, *J* = 16.1 Hz, 1 H), 3.04 (br d, *J* =16.1 Hz, 1 H), 2.60 (tdd, *J* = 3.1, 4.1, 15.4 Hz, 1 H), 1.60 – 2.33 (m, 9 H), 1.26 (t, J = 7.1 Hz, 3 H).



Photocycloaddition of 22b to 23b. This reaction was carried out as described for the synthesis of **12**. The starting material **22b** (133 mg, 0.48 mmol) was gone after 4.5 h. The usual work-up led to 53 mg (40% yield) of a colorless oil after chromatography (hexanes/EtOAc 1:2). R_f = 0.40. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.72 (d, J = 0.8 Hz, 1 H), 4.63 (d, J = 4.1 Hz, 1 H), 4.60 (d, J = 0.8 Hz, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 2.68-2.59 (AB-quartet, J = 15.7 Hz, 2 H), 2.13 (dd, J = 11.9, 4.1 Hz, 1 H), 2.09 (m, 1 H), 1.90 (m, 1 H), 1.85 (d, J = 11.9 Hz, 1 H), 1.65-1.25 (m, 5 H), 1.25 (t, J = 7.1 Hz, 3 H), 1.02 (m, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.7, 169.7, 152.5, 94.6, 79.8, 64.5, 60.8, 55.4, 54.9, 39.8, 31.4, 21.3, 20.1, 19.3, 19.2, 13.9. IR ($CHCl_3$) ν 1772, 1731, 1329, 978 cm^{-1}. HRMS (FAB) calcd for $C_{16}H_{20}O_4$ (MH+) 277.1440, found 277.1443.



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Crystallographic data for 12 (see Fig. 1). $C_{12}H_{14}O_2$, M = 190.24, triclinic, *P* $\bar{1}$, a = 6.6969(4), b = 7.0489(6), c = 10.9328(7) Å, α = 77.964(6), β = 75.679(9), γ = 80.977(8)°, V = 486.04(6) $Å^3$, Z = 2, D_{calc} = 1.30 gcm^{-3}, $\lambda(CuK_\alpha)$ = 1.5418 Å, $\mu(CuK_\alpha)$ = 0.70 mm^{-1}, F(000) = 204, -25 °C, Final R = 0.079 for 1806 observed reflections.

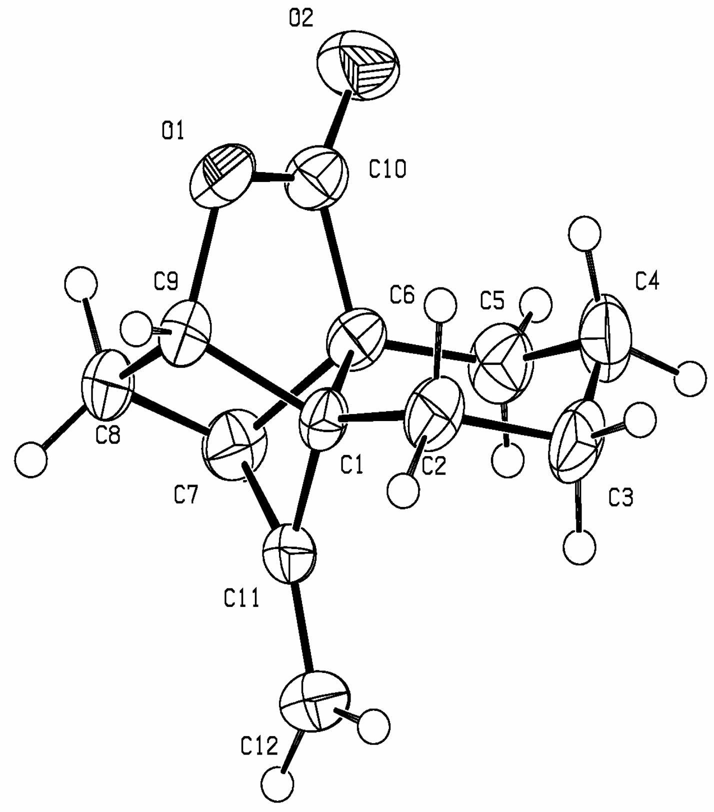

Figure 1. Ortep representation of the crystal structure of lactone 12

Experimental. A crystal with dimensions 0.20 × 0.25 × 0.50 mm approximately was used for data collection on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated CuK_α radiation and ω-2θ scan. A total of 1999 unique reflections was measured within the range $-7 \leq h \leq 8$, $-8 \leq k \leq 8$, $0 \leq l \leq 13$. Of these, 1806 were above the significance level of $2.5\sigma(I_{obs})$ and were treated as observed. The range of (sin θ)/λ was 0.048-0.626 Å ($4.2 \leq \theta \leq 74.7°$). Two reference reflections [(1 0 0),(0 1 2)] were measured hourly and showed 13% decrease during the 24 h collecting time, which was corrected for. Unit-cell parameters were refined by a least-squares fitting procedure using 23 reflections with $40.43 \leq \theta \leq 42.88°$ Corrections for Lorentz and polarisation effects were applied. The structure was solved by the program package CRUNCH (de Gelder et al., 1993). The hydrogen atoms were calculated. Full-matrix least-squares refinement on F, anisotropic for the non-hydrogen atoms and isotropic for the hydrogen atoms, restraining the latter in such a way that the distance to their carrier remained constant at approximately 1.0 Å, converged to R = 0.079, R_w = 0.099, $(\Delta/\sigma)_{max}$ = 0.13, S = 1.00. A weighting scheme $w = [0.6 + 0.01*(\sigma(Fobs))^2 + 0.001/(\sigma(Fobs))]^{-1}$ was used. The secondary isotropic extinction coefficient (Zachariasen 1967 ; Larson 1969) refined to g = 1470(151). A final difference Fourier map revealed a residual electron density between –0.35 and 0.35 $eÅ^{-3}$. Scattering factors were taken from Cromer and Mann (1968); International Tables for X-ray Crystallography (1974). All calculations were performed with XTAL (Hall, du Boulay and Olthof-Hazekamp, 2000), unless stated otherwise. Supplementary tables and molecular picture were made with PLATON (Spek, 1990).

Crystallographic data for 17 (see Fig. 2). $C_{11}H_{16}O_2$, M = 180.2, monoclinic, $P2_1/n$, a = 7.0166(3), b = 10.5703(6), c = 13.7222(13) Å, β =102.880(5)°, V = 992.13(12) $Å^3$, Z = 4, D_x = 1.21 gcm^{-3}, $\lambda(CuK_\alpha)$ = 1.5418 Å, $\mu(CuK_\alpha)$ = 0.65 mm^{-1}, F(000) = 392, room temperature, final R = 0.071 for 1743 observed reflections.

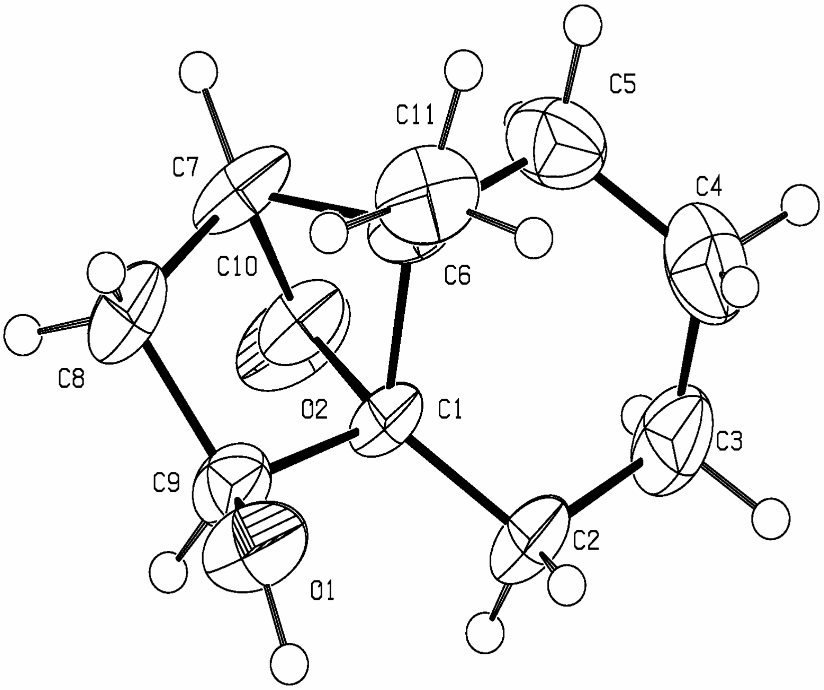

Figure 2. Ortep representation of the crystal structure of cyclobutanone 17

Experimental. A crystal with dimensions 0.20 × 0.60 × 0.60 mm approximately was used for data collection on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated CuK_α radiation and ω-2θ scan. A total of 2030 unique reflections was measured within the range $-8 \leq h \leq 8$, $0 \leq k \leq 13$, $0 \leq l \leq 17$. Of these, 1743 were above the significance level of 2.5σ (I_{obs}) and were treated as observed. The range of (sin θ)/λ was 0.060-0.626 Å ($5.3 \leq \theta \leq 74.9°$). Two reference reflections [(1 3 1),(0 0 4)] were measured hourly and showed 8% decrease during the 33 h collecting time, which was corrected for. Unit-cell parameters were refined by a least-squares fitting procedure using 23 reflections with $38.91 \leq \theta \leq 45.08°$ Corrections for Lorentz and polarisation effects were applied. The structure was solved by the program package CRUNCH (de Gelder et al., 1993). The hydrogen atoms were calculated. Full-matrix least-squares refinement on F, anisotropic for the non-hydrogen atoms and isotropic for the hydrogen atoms, restraining the latter in such a way that the distance to their carrier remained constant at approximately 1.0 Å (0.96 Å for the O-H), converged to $R = 0.071$, $R_w = 0.064$, $(\Delta/\sigma)_{max} = 0.04$, $S = 1.09$. A weighting scheme $w = [0.4 + 0.01*(\sigma\ (Fobs))^2 + 0.001/(\sigma\ (Fobs))]^{-1}$ was used. The secondary isotropic extinction coefficient (Zachariasen 1967; Larson 1969) refined to g = 1931(138). A final difference Fourier map revealed a residual electron density between –0.29 and 0.32 $eÅ^{-3}$. Scattering factors were taken from Cromer and Mann (1968); International Tables for X-ray Crystallography (1974). All calculations were performed with XTAL3.7 (Hall, du Boulay and Olthof-Hazekamp, 2000), unless stated otherwise. Supplementary tables and molecular pictures were made with PLATON (Spek, 1990).

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