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Model Studies Related to CP-225,917: Stereocontrolled Generation of the Quaternary Center

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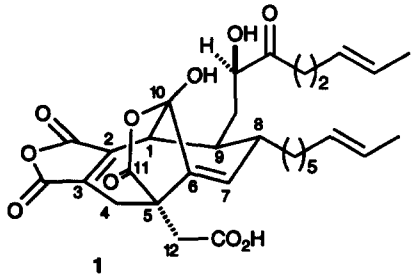
Abstract The enolate derived from ester **15** reacts with diketone **10** stereoselectively (10:1), and the major isomer can be converted into lactone **21**. This rearranges in boiling 1,2-dichlorobenzene to afford the tricyclic lactone **22**, a model compound which shares with CP-225,917 (**1**) the bridgehead double bond, the C(5) quaternary center, a C(5) side chain of correct length, and the γ-lactone subunit.

Keywords: Aldols; bridgehead chemistry; lactones; oxy-Cope rearrangements

The complex natural product CP-225,917 (**1**),[1,2] which is an inhibitor of Ras farnesyl transferase,[3] has attracted much attention as a synthetic target, and several model studies have been reported,[4] as well as one total synthesis[5] of the racemic compound. Our own approach[4d,m] is based on oxy-Cope rearrangement, and was



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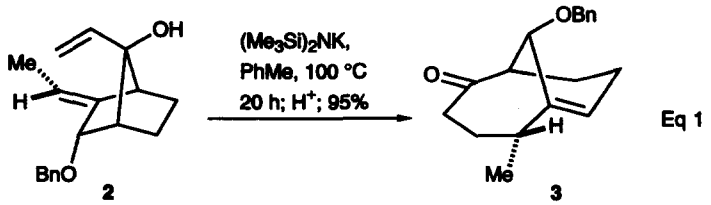
initially illustrated[4d] by the anionic version **2** → **3**. This process turned out not to be general, and did not work when the ethylidene unit of **2** was modified by chain extension. We found, however, that corresponding



2 **3** Eq 1

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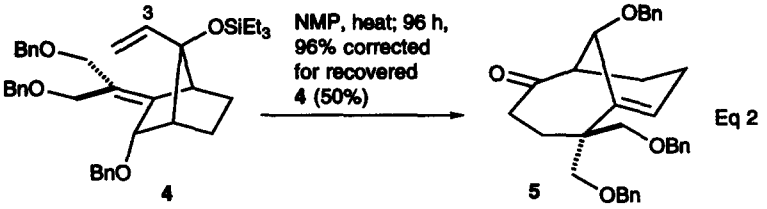
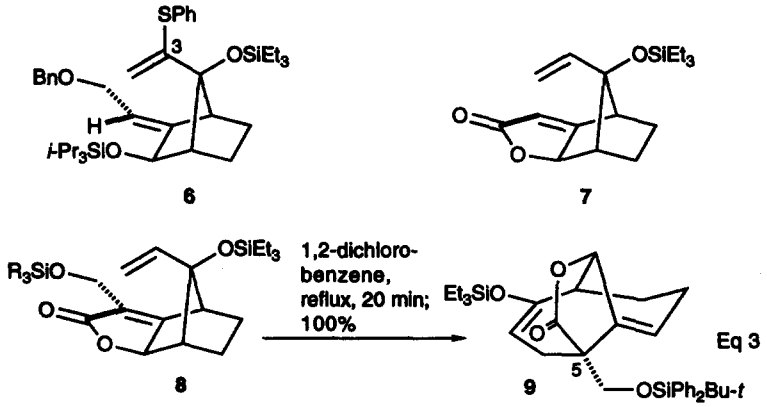
siloxy-Cope rearrangements could be accomplished thermally, provided *N*-methylpyrrolidone was used as the solvent and, under these conditions, even substituted compounds such as **4** rearranged (**4** → **5**),[4m] the presumed intermediate being hydrolyzed *in situ* so as to afford the ketone directly, as shown in Eq 2. We also found[4m] that conformational effects engendered by substitution at C(3), as in **6**, could speed up the rearrange-



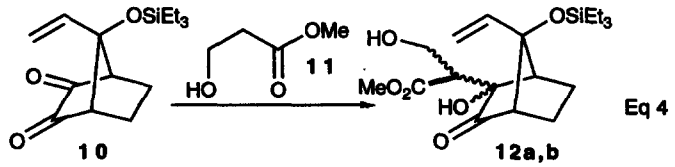
Eq 2

ment, and very significant rate enhancements were obtained with lactones such as **7**. In the latter case the presence of the lactone ring imposes some strain on the starting structure.[4k,m]



Eq 3

Our most advanced model was **8** (Eq 3); it led[4m] to a rearranged product **9** having a quaternary C(5), which is a feature of the natural product. Unfortunately, the route to **8** was not stereocontrolled, since a key step — reaction of **10** with the dianion derived from **11** (see Eq 4) — gave two isomers (**12a,b**) of undetermined stereochemistry, and only the major one (39% yield) could be taken further, the minor isomer

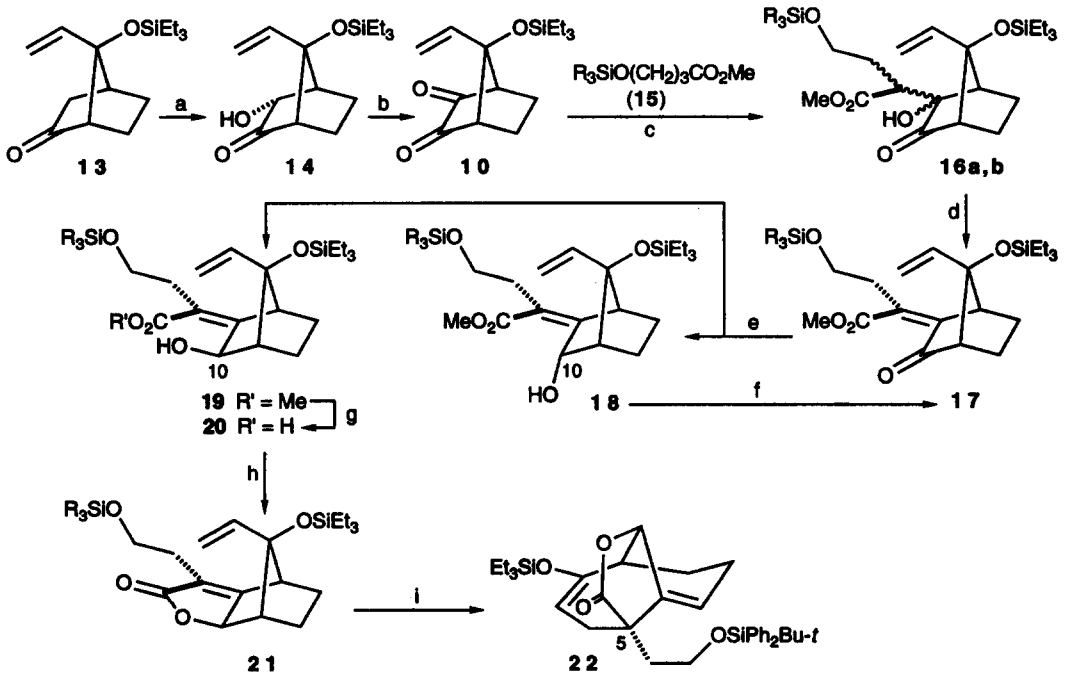


Eq 4

(29% yield) being discarded. Here we report a modified approach (Scheme 1) that overcomes this problem, and gives, in the corresponding condensation (see **10** → **16a,b** Scheme 1), a much improved isomer ratio (10:1). Our modified route also has the advantage of providing a side chain of correct length (*cf.* **22** and **1**) at C(5).

Diketone **10**, which is readily available[4m] from **13**[4d] (Scheme 1) by α-hydroxylation (**13** → **14**, LDA, THF, -23 °C; MoO_5.py.HMPA[6]; 85%, or 91% after correction of recovered **13**) and oxidation (Dess-Martin

reagent;[7] CH_2Cl_2, 95%), was added to the enolate derived (LDA, THF, -78 °C) from the protected ester **15**. Reaction occurred smoothly and with much greater stereoselectivity than in the case of the related process **10** → **12a,b**. Two hydroxy ketones corresponding to **16a,b** (major, 80%; minor 8%) were isolated. The stereochemistry of the isomers was not established, and it is not clear why the selectivity is so much higher than that observed with **11**, although several contributing factors can be identified. The reagent from **11** is a dianion, while that from **15** is a monoanion and is also bulkier; hence differences in size, in polarity, or in the state of aggregation — each of which could influence the direction of approach to the carbonyl — may play a role. The major hydroxy ketone (**16a**)[8] was dehydrated ($SOCl_2$, pyridine, room temperature) to afford the (*Z*) keto ester **17** (90%). Reduction[9] ($NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C to room temperature) gave *exo* alcohol



Scheme 1

R_3SiO = *t*-$BuPh_2Si$. (a) LDA, THF, -78 °C, 1h; MoO_5.py.HMPA, -23 °C, 30 min; 85% or 91% after correction for recovered **13**. (b) Dess-Martin reagent, CH_2Cl_2, 30 min; 95%. (c) LDA, THF, -78 °C, compound **15**, 1 h; add diketone **10**, 15 min; 80% yield of **16a**, 8% yield of **16b**. (d) $SOCl_2$, pyridine, 3 h; 90%. (e) $NaBH_4$, MeOH, $CeCl_3.7H_2O$; 22% yield of **18**, 65% yield of **19**. (f) Dess-Martin reagent, CH_2Cl_2, 30 min; 98%. (g) PrSLi, HMPA, 2 h; 81%. (h) Et_3N, 2-chloro-1-methylpyridinium iodide, reflux, 36 h; 85%. (i) 1,2-dichlorobenzene, reflux, 20 min; 100%.

19 (65%) and the *endo* isomer **18** (22%). The latter could be oxidized (Dess-Martin reagent, 98%) back to ketone **17**. Demethylation (PrSLi,[10] HMPA, room temperature, 2 h; 81%) of ester **19** afforded the corresponding hydroxy acid **20**, which was correctly set up for lactonization (**20** → **21**). This was accomplished by warming with 2-chloro-1-methylpyridinium iodide[11] (CH_2Cl_2, reflux, 36 h; 85%). Finally,

rearrangement was induced by heating the lactone in degassed, refluxing *o*-dichlorobenzene for 20 min. Under these conditions the desired rearrangement product **22** was obtained in quantitative yield.

These experiments illustrate a route, based on siloxy-Cope rearrangement, that affords a tricyclic model that shares with CP-225,917 the bridgehead double bond, the C(5) quaternary center, a C(5) side chain of correct length, and the γ-lactone subunit.

Experimental section

General Procedures.

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[12] and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,[13] followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles. Dry THF was distilled from sodium benzophenone ketyl. Dry Et_3N, *i*-Pr_2NH, CH_2Cl_2, and pyridine were distilled from CaH_2. HMPA was distilled from CaH_2 under reduced pressure (oil pump), and kept under an Ar atmosphere over molecular sieves. All other solvents were used as purchased. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were assumed to have the stated molarity.

FT-IR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent using potassium bromide plates.

The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on the APT experiment.

Compounds isolated by flash chromatography were homogeneous by TLC and, unless otherwise stated, were pure as judged by high field ^1H NMR spectra.

(1α,3β,4α,7*R)-7-Ethenyl-3-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-one (14).** A solution of ketone **13**[4d] (500.8 mg, 1.880 mmol) in THF (10 mL, plus 2 x 0.6 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) solution of LDA [prepared by addition of *n*-BuLi (2.5 M in hexane, 1.0 mL, 2.5 mmol) to a stirred and cooled (0 °C) solution of (*i*-Pr)$_2$NH (330 μL, 2.52 mmol) in THF

(5 mL), followed by stirring at 0 °C for 15 min]. The mixture was stirred at -78 °C for 1 h and then transferred to a dry ice/CCl_4 bath at -23 °C. Freshly prepared solid MoO_5.py.HMPA (1.464 g, 3.370 mmol) was added in one portion with vigorous stirring. Stirring at -23 °C was continued for 0.5 h, and the mixture was quenched with saturated aqueous Na_2SO_3 solution (10 mL). The coldbath was removed and, after ca. 10 min, the mixture was diluted with brine (20 mL), and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with aqueous 5% HCl (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 10% EtOAc-hexane, gave **14** [453.4 mg, 85% or 91% after correction for recovered starting material (35 mg)] as a colorless oil: FTIR (CH_2Cl_2 cast) 3428, 1758 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.58-0.65 (m, 6 H), 0.95 (t, *J* = 7.9 Hz, 9 H), 1.43-1.51 (m, 1 H), 1.89-2.02 (m, 2 H), 2.22-2.32 (m, 1 H), 2.42-2.48 (m, 1 H), 2.66 (d, *J* = 5.1 Hz, 1 H), 3.23 (br s, 1 H), 4.00 (dd, *J* = 4.8, 0.9 Hz, 1 H), 5.20 (dd, *J* = 17.7, 0.5 Hz, 1 H), 5.24 (dd, *J* = 10.7, 0.5 Hz, 1 H), 6.14 (dd, *J* = 17.7, 10.7 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 7.0 (q'), 18.6 (t'), 25.8 (t'), 50.1 (d'), 56.8 (d'), 75.4 (d'), 82.5 (s'), 118.7 (t'), 138.6 (d'), 217.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{15}H_{26}NaO_3Si$ (M + Na) 305.1549, found 305.1543. The stereochemistry was assigned by analogy to reference compounds having *exo* or *endo* hydroxyl groups.[14]

(*Anti*)-7-Ethenyl-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2,3-dione (10). A solution of **14** (360.0 mg, 1.277 mmol) in CH_2Cl_2 (7 mL, plus 3 x 0.5 mL as a rinse) was added dropwise to a stirred solution of Dess-Martin reagent[7] (700.0 mg, 1.660 mmol) in CH_2Cl_2 (8 mL). Stirring was continued for 0.5 h, and Et_2O (40 mL) was added, followed by saturated aqueous $NaHCO_3$ (20 mL) containing $Na_2S_2O_3$ (2.520 g). The mixture was stirred for 5 min, and extracted with Et_2O (100 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (10 mL), water (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 26 cm), using 5% EtOAc-hexane, gave **10** (339.6 mg, 95%) as a yellow solid: mp 38-41 °C; FTIR (CH_2Cl_2 cast) 1782, 1758 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.60-0.67 (m, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.68-1.75 (m, 2 H), 2.35-2.44 (m, 2 H), 3.01 (dd, *J* = 3.2, 2.5 Hz, 2 H), 5.24 (d, *J* = 17.7 Hz, 1 H), 5.32 (d, *J* = 10.8 Hz, 1 H), 6.13 (dd, *J* = 17.7, 10.8 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.0 (q'), 23.5 (t'), 58.7 (d'), 81.3 (s'), 120.7 (t'), 138.4 (d'), 200.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{15}H_{24}NaO_3Si$ (M + Na) 303.1392, found 303.1397.

Methyl 4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]butanoate (15). MeI (3.3 mL, 52 mmol) in dry DMF (6 mL) was added to a stirred solution of sodium 4-hydroxy-butanoate[15] (1.01 g, 8.01 mmol) in DMF (22 mL). Stirring was continued for 24 h, and then imidazole (1.201 g, 17.62 mmol) was added, followed by *t*-$BuPh_2SiCl$ (2.5 mL, 9.6 mmol). Stirring was continued for 12 h, and the mixture was diluted with EtOAc (70 mL), washed with water (5 x 35 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.2 x 28 cm), using 5% EtOAc-hexane, gave **15** (2.601 g, 91%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1740 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.06 (s, 9 H), 1.85-1.93 (m, 2 H), 2.47 (t, *J* = 7.4 Hz, 2 H), 3.64 (s, 3 H), 3.71 (t, *J* = 6.1 Hz, 2 H), 7.37-7.47 (m, 6 H), 7.65-7.70 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 19.6 (s'), 27.2 (q'), 28.3 (t'), 30.9 (t'), 51.7 (q'), 63.4 (t'), 128.2 (d'), 130.1 (d'), 134.3 (s'), 136.0 (d'), 174.1 (s'); exact mass (electrospray) *m/z* calcd for $C_{21}H_{28}NaO_3Si$ (M + Na) 379.1705, found 379.1702.

Methyl (1α,4α,7*R)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-3-hydroxy-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-yl]butanoate (16a and 16b).** A solution of **15** (158.2 mg, 0.4437 mmol) in THF (0.2 mL, plus 2 x 0.1 mL as a rinse) was added dropwise to a stirred and cooled (-78 °C) solution of LDA in THF (0.5 mL) [prepared by addition of *n*-BuLi (2.5 M in hexane, 178 μL, 0.445 mmol) to a stirred and cooled (0 °C) solution of (*i*-Pr)$_2$NH (58 μL, 0.44 mmol) in THF (0.5 mL), followed by stirring at 0 °C for 15 min]. Stirring at -78°C was continued for 1 h, and then diketone **10** (113.0 mg, 0.4040 mmol) in THF (0.4 mL, plus 2 x 0.2 mL as a rinse) was added dropwise. Stirring at -78°C was continued for 15 min, the mixture was quenched with saturated aqueous NH_4Cl (0.5 mL) and allowed to warm to room temperature over ca. 15 min. Water (0.5 mL) was added and the mixture was extracted with Et_2O (40 mL). The organic extract was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 5% EtOAc-hexane, gave **16a** (206.9 mg, 80%) and **16b** (20.0 mg, 8%) as colorless oils. Compound **16a** had: FTIR (CH_2Cl_2 cast) 3458, 1756, 1716 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 0.59-0.66 (m, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.06 (s, 9 H), 1.48-1.71 (m, 2 H), 1.80-1.88 (m, 1 H), 1.92-2.02 (m, 1 H), 2.15-2.34 (m, 3 H), 2.74-2.78 (m, 1 H), 2.86 (dd, *J* = 11.5, 2.8 Hz, 1 H), 3.50 (td, *J* = 10.2, 3.9 Hz, 1 H), 3.66 (s, 3 H), 3.70-3.76 (m, 1 H), 4.35 (s, 1 H), 5.16 (dd, *J* = 10.7, 0.7 Hz, 1 H), 5.18 (dd, *J* = 17.7, 0.7 Hz, 1 H), 6.33 (dd, *J* = 17.7, 10.7 Hz, 1 H), 7.37-7.48 (m, 6 H), 7.64-7.69 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.8 (t'), 7.1 (q'), 19.4 (s'), 21.6 (t'), 23.3 (t'), 27.0 (q'), 31.3 (t'), 43.9 (d'), 52.3 (d') or (q'), 54.6 (d') or (q'), 56.7 (d') or (q'), 61.6 (t'), 80.4 (s'), 84.7 (s'), 116.9 (t'), 128.1 (d'), 130.1 (d'), 133.8 (s'), 133.9 (s'), 135.9 (d'), 136.0 (d'), 140.2 (d'), 176.9 (s'), 214.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{36}H_{52}NaO_6Si_2$ (M + Na) 659.3200, found 659.3189.

Compound **16b** had: FTIR (CH_2Cl_2 cast) 3495, 1755 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 0.56-0.63 (m, 6 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 1.02 (s, 9 H), 1.48-1.56 (m, 1 H), 1.80-1.95 (m, 2 H), 2.08-2.28 (m, 3 H), 2.57-2.65 (m, 1 H), 2.73-2.77 (m, 1 H), 3.01-3.07 (m, 2 H), 3.52-3.60 (m, 1 H), 3.63 (s, 3 H), 3.66-3.72 (m, 1 H), 5.20-5.26 (m, 2 H), 6.31 (dd, *J* = 17.7, 10.8 Hz, 1 H), 7.35-7.45 (m, 6 H), 7.61-7.67 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 7.0 (q'), 19.4 (s'), 22.5 (t'), 22.6 (t'), 26.9 (q'), 29.6 (t'), 45.7 (d'), 52.1 (d') or (q'), 57.3 (d') or (q') 57.5 (d') or (q'), 62.2 (t'), 79.6 (s'), 84.2 (s'), 117.8 (t'), 128.0 (d'), 130.0 (d'), 134.08 (s'), 134.12 (s'), 135.9 (d'), 140.3 (d'), 174.9 (s'), 212.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{36}H_{52}NaO_6Si_2$ (M + Na) 659.3200, found 659.3209.

Methyl (1α,3*Z*,4α,7*R)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-ylidene]butanoate (17).** $SOCl_2$ (118 μL, 1.62 mmol) was added dropwise to a stirred solution of **16a** (206.0 mg, 0.3240 mmol) in pyridine (2 mL). Stirring was continued for 3 h. The mixture was cooled (0 °C), water (1 mL) was added dropwise, and the mixture was extracted with Et_2O (100 mL). The organic extract was washed with 5% hydrochloric acid (10 mL), saturated aqueous $NaHCO_3$ (10 mL), water (5 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 27 cm), using 5% EtOAc-hexane, gave **17** (180.3 mg, 90%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1736, 1658 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 0.57-0.65 (m, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.05 (s, 9 H), 1.36-1.52 (m, 2 H), 2.11-2.28 (m, 2 H), 2.45-2.58 (m, 2 H), 2.61 (dd, *J* = 4.5, 1.3 Hz, 1 H), 2.77-2.78 (m, 1 H), 3.66 (s 3 H), 3.72 (t, *J* = 7.1 Hz, 2 H), 5.14-5.20 (m, 2

H), 5.93 (dd, J = 17.8, 10.7 Hz, 1 H), 7.38-7.48 (m, 6 H) 7.64-7.69 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.7 (t'), 7.1 (q'), 19.4 (s'), 23.2 (t'), 27.00 (q'), 27.04 (t'), 35.3 (t'), 49.3 (d') or (q'), 52.4 (d') or (q'), 57.7 (d') or (q'), 62.0 (t'), 84.5 (s'), 119.1 (t'), 128.1 (d'), 130.2 (d'), 132.6 (s'), 133.9 (s'), 136.0 (d'), 138.3 (d'), 141.8 (s'), 170.0 (s'), 200.8 (s'); exact mass *m/z* calcd for $C_{36}H_{50}O_5Si_2$ 618.3197, found 618.3190.

Methyl (1α,2β,3*Z*,4α,7*S)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-ylidene]butanoate (18) and Methyl (1α,2α,3*Z*,4α,7*S**)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-ylidene]butanoate (19).** $NaBH_4$ (14.8 mg, 0.391 mmol) was added in three portions to a stirred and cooled (0 °C) mixture of **17** (80.0 mg, 0.130 mmol) and $CeCl_3.7H_2O$ (72.8 mg, 0.195 mmol) in dry MeOH (2 mL). Stirring was continued for 0.5 h, the cooling bath was removed, and stirring was continued for 1.5 h. The mixture was diluted with EtOAc (5 mL) and water (1 mL), and extracted with EtOAc (30 mL). The organic extract was washed with brine (5 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 5% EtOAc-hexane, gave **18** (18.0 mg, 22%) and **19** (52.2 mg, 65%) as colorless oils. Compound **18** had: FTIR (CH_2Cl_2 cast) 3472, 1694, 1634 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 0.56-0.64 (m, 6 H), 0.95 (t, J = 7.8 Hz, 9 H), 1.05 (s, 9 H), 1.19-1.28 (m, 1 H), 1.76-1.86 (m, 1 H), 1.95-2.03 (m, 1 H), 2.06-2.16 (m, 1 H), 2.28 (t, J = 3.9 Hz, 1 H), 2.56-2.72 (m, 3 H), 3.63-3.71 [m, including s (3 H) at δ 3.64, 5 H in all], 4.50 (br s, 1 H), 4.92 (d, J = 2.4 Hz, 1 H), 5.07 (dd, J = 10.8, 1.2 Hz, 1 H), 5.09 (dd, J = 17.7, 1.2 Hz, 1 H), 5.89 (dd, J = 17.7, 10.8 Hz, 1 H), 7.37-7.47 (m, 6 H), 7.65-7.71 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.8 (t'), 7.1 (q'), 19.3 (t'), 19.4 (s'), 27.0 (q'), 27.7 (t'), 33.5 (t'), 49.5 (d') or (q'), 52.2 (d') or (q'), 52.6 (d') or (q'), 63.6 (t'), 70.8 (d'), 84.3 (s'), 118.2 (t'), 120.5 (s'), 128.0 (d'), 130.0 (d'), 134.2 (s'), 135.9 (d'), 138.2 (d'), 167.7 (s'), 169.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{36}H_{52}NaO_5Si_2$ (M + Na) 643.3251, found 643.3255.

Compound **19** had: FTIR (CH_2Cl_2 cast) 3489, 1696, 1637 cm^{-1}; ^1H NMR (CD_2Cl_2, 360 MHz) δ 0.58-0.65 (m, 6 H), 0.96 (t, J = 7.9 Hz, 9 H), 1.00-1.18 [m, including s (9 H) at δ 1.06, 11 H in all], 1.96-2.13 (m, 3 H), 2.58-2.72 (m, 2 H), 2.75-2.79 (m, 1 H), 3.63-3.75 [m, including s (3 H) at δ 3.65, 5 H in all], 4.24 (d, J = 3.0 Hz, 1 H), 4.28 (d, J = 3.0 Hz, 1 H), 5.01 (dd, J = 10.8, 1.4 Hz, 1 H), 5.07 (dd, J = 17.6, 1.4 Hz, 1 H), 6.30 (dd, J = 17.6, 10.8 Hz, 1 H), 7.37-7.48 (m, 6 H), 7.67-7.71 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.9 (t'), 7.2 (q'), 19.4 (s'), 25.0 (t'), 27.0 (q'), 27.2 (t'), 33.7 (t'), 50.8 (d') or (q'), 51.8 (d') or (q'), 52.2 (d') or (q'), 63.3 (t'), 75.8 (d'), 86.9 (s'), 116.3 (t'), 121.5 (s'), 128.1 (d'), 130.1 (d'), 134.18 (s'), 134.22 (s'), 135.9 (d'), 140.7 (d'), 167.2 (s'), 169.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{36}H_{52}NaO_5Si_2$ (M + Na) 643.3251, found 643.3252.

Methyl (1α,3*Z*,4α,7*R)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-oxo-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-ylidene]butanoate (17) from 18.** A solution of **18** (50.0 mg, 0.081 mmol) in CH_2Cl_2 (0.5 mL plus 2 x 0.2 mL as a rinse) was added dropwise over 5-10 min to a stirred solution of the Dess-Martin reagent[7](51.3 mg, 0.121 mmol) in CH_2Cl_2 (0.6 mL). Stirring was continued for 0.5 h and Et_2O (5 mL) was added, followed by saturated aqueous $NaHCO_3$ (1 mL) containing

$Na_2S_2O_3$ (186.0 mg). The mixture was stirred for 5 min and extracted with Et_2O (10 mL). The organic extract was washed with saturated aqueous $NaHCO_3$ (2 mL), water (2 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 5% EtOAc-hexane, gave **17** (49.0 mg, 98%) as a colorless oil, spectroscopically identical to material obtained from **16a**.

(1α,2α,3*Z*,4α,7*S)-4-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-2-[7-ethenyl-2-hydroxy-7-[(triethylsilyl)oxy]bicyclo[2.2.1]hept-3-ylidene]butanoic acid (20).** *n*-PrSLi[10] (2.5 M in HMPA, 226 μL, 0.565 mmol) was added dropwise to a stirred solution of **19** (50.0 mg, 0.081 mmol) in degassed (by passage of a stream of Ar for 0.5 h) HMPA (3 mL). Stirring was continued for 2 h (TLC indicated complete reaction), the mixture was poured into ice water (50 mL) containing 10% hydrochloric acid (2 mL), and extracted the with Et_2O (4 x 30 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.6 x 28 cm), using 40% EtOAc-hexane, gave **20** (39.6 mg, 81%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2750-3400 (br), 1684, 1637 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.60 (q, *J* = 7.9 Hz, 6 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.98-1.22 [m, including s (9 H) at δ 1.06, 11 H in all], 1.88-2.09 (m, 2 H), 2.14-2.18 (m, 1 H), 2.58-2.72 (m, 2 H), 2.78 (d, *J* = 2.3 Hz, 1 H), 3.69-3.78 (m, 2 H), 4.26 (s, 1 H), 5.04-5.14 (m, 2 H), 6.29 (dd, *J* = 17.7, 10.8 Hz, 1 H), 7.35-7.47 (m, 6 H), 7.63-7.69 (m, 4 H), the OH signals were not observed; ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.8 (t'), 7.1 (q'), 19.3 (s'), 24.8 (t'), 27.0 (q'), 27.1 (t'), 33.9 (t'), 50.4 (d'), 51.8 (d'), 63.7 (t'), 75.6 (d'), 86.8 (s'), 117.3 (t'), 123.2 (s'), 128.14 (d'), 130.2 (d'), 133.4 (s'), 133.5 (s'), 135.9 (d'), 140.6 (d'), 165.8 (s'), 171.1 (s'); exact mass (electrospray) *m/z* calcd for $C_{35}H_{50}NaO_5Si_2$ (M + Na) 629.3095, found 629.3105.

(4α,7α,7aβ,8*R)-3-[2-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]ethyl]-8-ethenyl-5,6,7,7a-tetrahydro-4,7-methano-8-[(triethylsilyl)oxy]benzofuran-2(4*H*)-one (21).** A solution of **20** (21.0 mg, 0.035 mmol) and Et_3N (39 μL, 0.28 mmol) in dry CH_2Cl_2 (0.4 mL, plus 2 x 0.2 mL as a rinse), was added dropwise to a stirred solution of 2-chloro-1-methylpyridinium iodide [36.5 mg (97%), 0.139 mmol] in CH_2Cl_2 (1.5 mL). The mixture was refluxed for 36 h, cooled to room temperature, diluted with Et_2O (5 mL), and filtered through a pad (1 cm x 2 mm) of silica gel with Et_2O. Evaporation of the filtrate, and flash chromatography of the residue over silica gel (1.3 x 24 cm), using 5% EtOAc-hexane, gave **21** (17.3 mg, 85%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1783, 1759 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.56 (q, *J* = 7.9 Hz, 6 H), 0.92 (t, *J* = 7.9 Hz, 9 H), 1.05 (s, 9 H), 1.38-1.45 (m, 1 H), 1.61-1.69 (m, 1 H), 2.05-2.15 (m, 1 H), 2.23-2.52 (m, 3 H), 2.71 (d, *J* = 4.5 Hz, 1 H), 2.85 (d, *J* = 4.5 Hz, 1 H), 3.73-3.86 (m, 2 H), 4.48 (s, 1 H), 5.05 (dd, *J* = 10.8, 0.9 Hz, 1 H), 5.12 (dd, *J* = 17.7, 0.9 Hz, 1 H), 5.73 (dd, *J* = 17.7, 10.8 Hz, 1 H), 7.36-7.46 (m, 6 H), 7.62-7.68 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 6.6 (t'), 7.0 (q'), 19.4 (s'), 22.9 (t'), 27.0 (q'), 28.2 (t'), 28.8 (t'), 46.9 (d'), 51.8 (d'), 62.2 (t'), 86.5 (d'), 89.4 (s'), 118.9 (t'), 124.4 (s'), 128.0 (d'), 130.0 (d'), 134.1 (s'), 135.9 (d'), 137.2 (d'), 170.5 (s'), 174.4 (s'); exact mass (electrospray) *m/z* calcd for $C_{35}H_{48}NaO_4Si_2$ (M + Na) 611.2989, found 611.2980.

(3*R,7*R**,8*R**)-3,7,8-[3]Buten[1]yl[4]ylidene-3-[2-[[(1,1-dimethylethyl)diphenylsilyl]oxy]ethyl]-3,4,7,8-tetrahydro-6-[(triethylsilyl)oxy]-2*H*-oxocin-2-one (22).** A solution of

21 (12.7 mg, 0.022 mmol) in degassed (by bubbling Ar for 0.5 h) 1,2-dichlorobenzene (7 mL) was refluxed for 20 min. The solution was cooled and evaporated, and the residue was kept under oil-pump vacuum for 4 h, to give **22** (12.7 mg, 100%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 1784 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 0.60-0.68 (m, 6 H), 0.95 (t, J = 7.9 Hz 9 H), 0.99 (s, 9 H), 1.55-1.63 (m, 1 H), 1.82-1.89 (m, 1 H), 1.92-2.13 (m, 2 H), 2.15-2.22 (m, 1 H), 2.29-2.41 (m, 3 H), 2.91-2.98 (m, 1 H), 3.61-3.68 (m, 1 H), 3.70-3.78 (m, 1 H), 4.53 (q, J = 2.9 Hz, 1 H), 4.65-4.70 (m, 1 H), 5.60-5.65 (m, 1 H), 7.34-7.45 (m, 6 H), 7.60-7.68 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 5.4 (t'), 6.8 (q'), 19.2 (s'), 21.8 (t'), 23.6 (t'), 26.7 (q'), 35.3 (t'), 44.2 (t'), 45.6 (d'), 49.0 (s'), 60.6 (t'), 78.6 (d'), 102.5 (d'), 117.7 (d'), 128.0 (d'), 129.9 (d'), 130.0 (d'), 133.8 (s'), 134.0 (s'), 135.9 (d'), 136.0 (d'), 142.1 (s'), 151.7 (s'), 180.8 (s'); exact mass (electrospray) m/z calcd for $C_{35}H_{48}NaO_4Si_2$ (M + Na) 611.2989, found 611.2987.

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