Intramolecular Ketalization of Functionalized 7-Norbornenols

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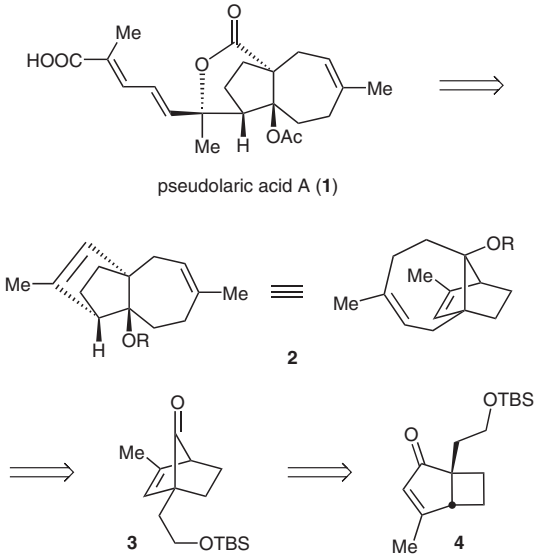
Abstract: Convenient access to polycondensed heterocyclic networks has been realized through exposure of bridged hydroxy acetonides to appropriate reagents.

Key words, photochemistry, heterocycles, acetals, sulfones, sulfoxides

We envisioned the synthesis of the oxygenated diterpene pseudolaric acid A (**1**),[1] which was isolated from the root bark of *Pseudolarix kaempferi Gordon* (pinaceae),[2] to originate via the properly substituted norbornenol **3** (Scheme 1). The structural features inherent to **3** were expected to be obtained by photo-1,3-rearrangement of the bicyclic enone **4**.[3] Herein we report the synthesis of **3** and the subsequent formation of polycondensed heterocyclic networks encountered during attempts to form **2**.



Scheme 1 Retrosynthetic analysis of pseudolaric acid A (**1**)

The synthetic approach commenced with the lithiation of vinylic bromide **5**[4] in diethyl ether at low temperature, followed by 1,2-addition of this organometallic reagent to aldehyde **6**[5] (Scheme 2). The resulting 1:1 diastereomeric mixture of allylic carbinols **7** and **8** was directly irradiated in the presence of the copper(I) triflate–benzene complex (5 mol% in Et_2O) as catalyst.[6] A salient feature of the photocyclization that operates is the anticipated adoption of the thermodynamically more favored conformers **9** and **10** en route to the bicyclic products **11** and **12**, respectively. The modest levels of competitive silyl deprotection that gave rise to **11b** and **12b** proved ideally suited to chromatographic separation and to the assignment of relative configuration to the diols by means of NOE correlations (see formulas in Scheme 2). Once this information was made known, separation of diastereomers at this stage was no longer warranted since sequential exposure to *tert*-butyldimethylsilyl triflate and 2,6-lutidine in advance of oxidation with 2-iodoxybenzoic acid (IBX)[7] allowed for matched conversion to **13** in high yield. The required desaturation of **13** as in **4** proved to be highly problematic. After the evaluation of many varied reaction conditions, including α-halogenation/elimination, α-selenation/elimination, and 2-iodoxybenzoic acid oxidation,[8] the use of stoichiometric levels of palladium(II) acetate in dimethyl sulfoxide[9] at room temperature for two days emerged as the most workable option.

Upon ultraviolet irradiation, **4** was converted into the synthetically useful β,γ-unsaturated ketone **3** (25%, Scheme 3), which proved readily separable from the polymer inevitably formed under the best circumstances. The main strength of this transformation is that it results in the direct generation of a nonsymmetric 7-ketonorbornene, nucleophilic attack on which was expected to favor approach *syn* to the double bond to avoid the *exo*-hydrogens encountered via an *anti* approach. The first construct for the formation of **2** to be examined originated in the addition of the Grignard reagent derived from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[10] to the ketone **3**. Installation of the new C–C bond arose from nucleophilic attack very predominantly from that direction *syn* to the olefinic functionality to deliver **16**.[11] The silyl ether so formed was cleaved efficiently with tetrabutylammonium fluoride to liberate diol **17**. Treatment of **17** with pyridinium *p*-toluenesulfonate in acetone at room temperature, in order to afford a dicarbonyl compound for ring closure via a McMurry reaction,[12] resulted in a dramatic increase in structural complexity as a direct result of alternative ketal formation with the loss of ethylene glycol. The new bonding arrangement resident in **18** holds interest when one considers that full retention of configuration is maintained at the original tertiary carbinol site. It is, of course, possible that ionization does not operate during the course of this transformation. However, should the incipient carbocation be generated, the powerful anchimeric assistance earlier recognized in simpler *anti*-7-norbornenyl

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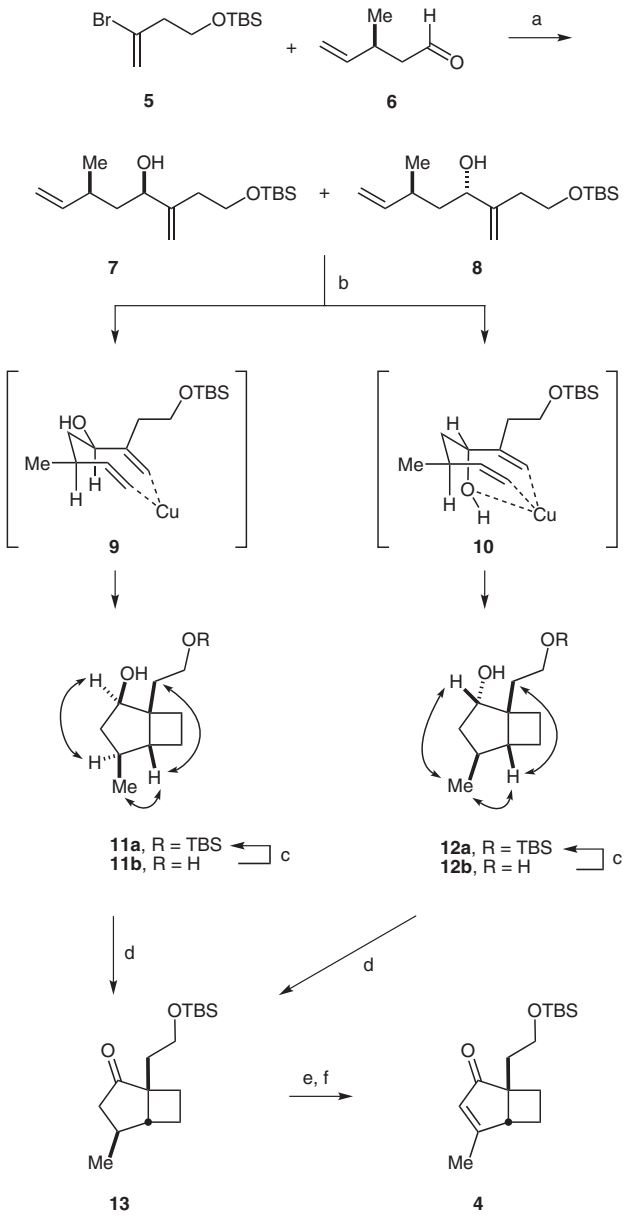
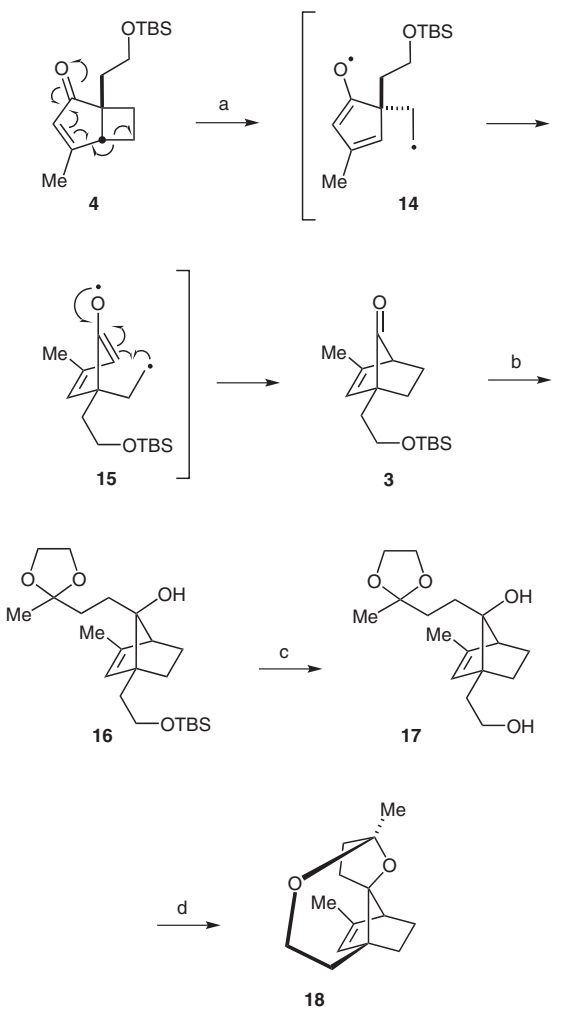


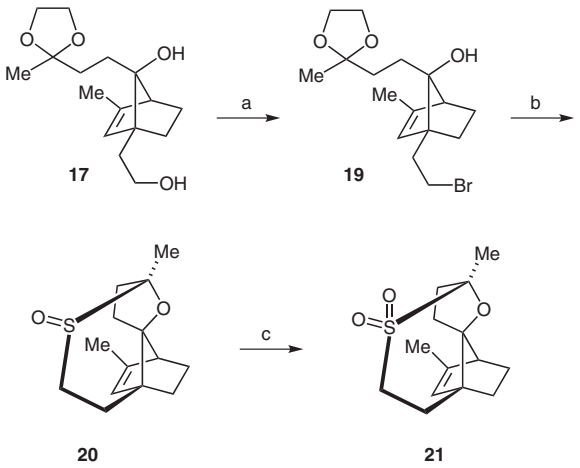
Scheme 2 *Reagents and conditions*: (a) *t*-BuLi, Et_2O, –78 °C to 0 °C, then **7**, 0 °C, 89%; (b) $(CuOTf)_2{\cdot}C_6H_6$ (5 mol%), Et_2O, *hν* (254 nm), quartz tube, r.t., 35% **11a**, 13% **11b**, 30% **12a**, 16% **12b**; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 91%; (d) IBX, MeCN, 65 °C, 96%; (e) TMSOTf, Et_3N, CH_2Cl_2, 0 °C, 99%; (f) $Pd(OAc)_2$, DMSO, r.t., 88%.

derivatives[13] would be anticipated and lead comparably to **18**. Although a mechanistic distinction was not pursued, the ultimate involvement of the primary hydroxy group led to incorporation of a fourth ring. The bonding arrangement held together in **18** can be considered to constitute a heterocyclic analogue of **2**. Various attempts to open the acetal were unsuccessful.

An apparent strength of this chemistry is its generality. Thus, we have also achieved the conversion of **17** into bromide **19** as a prelude to admixture with an equivalent of thiourea (Scheme 4). Direct alkaline saponification of the isothiouronium salt so formed led to cyclization with



Scheme 3 *Reagents and conditions*: (a) CH_2Cl_2, *hν* (254 nm), Pyrex, r.t., 25%; (b) 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, Mg, $BrCH_2CH_2Br$, THF, r.t. then ketone **3**, THF, reflux, 85%, 10:1 *anti*/*syn*; (c) TBAF, THF, 0 °C to r.t., 94%; (d) PPTS, acetone, r.t., 70%.



Scheme 4 *Reagents and conditions*: (a) CBr_4, 2,6-lutidine, Ph_3P, THF, r.t., 70%; (b) thiourea, EtOH, reflux then NaOH, H_2O, reflux, 50%; (c) MCPBA, Et_2O, 0 °C to r.t., 94%.

concomitant unexpected in situ oxidation to give the sulfoxide **20** in 50% overall yield. Although **20** proved to be a single diastereomer, no effort was made to decipher its configuration. Rather, **20** was oxidized with *m*-chloroperoxybenzoic acid in diethyl ether to generate sulfone **21**, whose heightened crystallinity allowed the corroboration of structure by X-ray crystallography. Conversion of **21** into the corresponding thioacetal and subsequent oxidation in order to perform a Ramberg–Bäcklund ring contraction to install the desired seven-membered ring was unsuccessful.[14]

In summary, we have uncovered the capability of 7-norbornenols of type **17** that carry a functionalized side chain linked to one of the bridgehead centers to undergo intramolecular ketalization with generation of highly condensed frameworks. The ready accessibility of substances such as **18**, **20**, and **21** is illustrative of a potentially general route for the production of related structures. Alternative methods for the construction of the seven-membered ring required for the preparation of pseudolaric acid A (**1**) are currently being investigated and will be reported in due course.

All reactions were performed under an atmosphere of dry N_2 in oven- or flame-dried glassware. All other solvents and reagents were purified by standard techniques or used as supplied.[15] Silica gel column chromatography (flash chromatography) was carried out using silica gel 60 (230–400 mesh).[16] Brine refers to sat. aq NaCl soln. Melting points were measured on a capillary melting point apparatus and are uncorrected. IR spectra were recorded as evaporated films. All ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz (operating frequencies: ^{1}H, 400.13 MHz; ^{13}C, 100.63 MHz) and 500 MHz (operating frequencies: ^{1}H, 500.02 MHz; ^{13}C, 125.73 MHz) FT spectrometers at r.t. using the NMR solvent as an internal reference. The reference values used for $CDCl_3$ were δ = 7.26 and 77.00 for ^{1}H and ^{13}C NMR spectra, respectively. The mode of ionization for LR-MS and for HRMS was electrospray.

(4*R,6*S**)-1-(*tert*-Butyldimethylsiloxy)-6-methyl-3-methyleneoct-7-en-4-ol (7) and (4*R**,6*R**)-1-(*tert*-Butyldimethylsiloxy)-6-methyl-3-methyleneoct-7-en-4-ol (8)**

To a soln of **5** (19.50 g, 73.58 mmol) in Et_2O (400 mL) at –78 °C was added 1.6 M *t*-BuLi in hexanes (105 mL, 168 mmol) and the resultant soln was allowed to warm to 0 °C over 1 h. A soln of **6** (9.50 g, 9.69 mmol) in Et_2O (150 mL) was then added. After 4 h at 0 °C, H_2O (150 mL) was added. The mixture was extracted with Et_2O (3 × 100 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (hexanes–Et_2O, 4:1) afforded an inseparable mixture (1:1) of **7** and **8** as a colorless oil; yield: 18.53 g (89%); R_f = 0.29 (hexanes–Et_2O, 4:1).

IR (film): 3434 (br), 1646, 1472, 1256 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.07 (s, 12 H), 0.90 (s, 18 H), 1.02 (dd, *J* = 6.7, 1.0 Hz, 6 H), 1.53 (m, 4 H), 2.30 (m, 6 H), 2.94 (d, *J* = 4.7 Hz, 1 H, OH),[17] 3.14 (d, *J* = 4.4 Hz, 1 H, OH),[17] 3.69 (m, 2 H), 3.80 (m, 2 H), 4.11 (m, 2 H), 4.97 (m, 8 H), 5.72 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.52, –5.49, –5.46, 18.3, 20.1, 20.8, 25.9, 34.36, 34.42, 34.8, 42.6, 42.9, 63.9, 64.0, 72.8, 73.2, 112.0, 112.6, 112.8, 113.2, 144.1, 144.6, 149.4, 150.0.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{32}NaO_2Si$: 307.2069; found: 307.2068.

(1*R,2*S**,4*R**,5*S**)-1-[2-(*tert*-Butyldimethylsiloxy)ethyl]-4-methylbicyclo[3.2.0]heptan-2-ol (11a), (1*R**,2*R**,4*R**,5*S**)-1-[2-(*tert*-Butyldimethylsiloxy)ethyl]-4-methylbicyclo[3.2.0]heptan-2-ol (12a), (1*R**,2*S**,4*R**,5*S**)-1-(2-Hydroxyethyl)-4-methylbicyclo[3.2.0]heptan-2-ol (11b), and (1*R**,2*R**,4*R**,5*S**)-1-(2-Hydroxyethyl)-4-methylbicyclo[3.2.0]heptan-2-ol (12b)**

A soln of **7** and **8** (1:1, 1.31 g, 4.61 mmol) and $(CuOTf)_2$·benzene (119 mg, 0.237 mmol) in Et_2O (600 mL) in a quartz reaction vessel was deoxygenated by bubbling N_2 through it for 10 min. The resultant mixture was irradiated with 254 nm light for 28 h after which the soln was poured onto a mixture of ice (50 g) and sat. NH_4OH soln (50 mL). The mixture was extracted with Et_2O (3 × 100 mL) and the combined organic layers were washed with brine (3 × 100 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (hexanes–Et_2O, 4:1 then Et_2O) afforded **11a**, **12a**, **11b**, and **12b**.

11a

Yellow oil; yield: 459 mg (35%); R_f = 0.55 (hexanes–Et_2O, 4:1).

IR (film): 3500 (br), 1470, 1329, 1257 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.069, (s, 3 H), 0.073 (s, 3 H), 0.90 (s, 9 H), 1.06 (d, *J* = 7.3 Hz, 3 H), 1.39 (m, 1 H), 1.52 (m, 1 H), 1.76 (m, 4 H), 2.01 (m, 1 H), 2.13 (m, 2 H), 2.41 (m, 1 H), 3.60 (td, *J* = 10.0, 1.5 Hz, 1 H), 3.71 (dt, *J* = 10.0, 3.5 Hz, 1 H), 3.78 (s, 1 H), 3.84 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.7, 18.2, 20.70, 20.72, 25.9, 26.3, 37.3, 40.5, 40.6, 51.8, 53.0, 60.2, 80.0.

12a

Yellow oil; yield: 393 mg (30%); R_f = 0.38 (hexanes–Et_2O, 4:1).

IR (film): 3478 (br), 1470, 1255 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.05, (s, 3 H), 0.06 (s, 3 H), 0.87 (m, 12 H), 1.41 (m, 2 H), 1.64 (m, 1 H), 1.72 (m, 1 H), 1.80 (m, 1 H), 1.91 (m, 2 H), 2.14 (m, 3 H), 3.69 (m, 3 H), 4.05 (dd, *J* = 11.0, 6.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6, –5.5, 18.2, 19.0, 21.5, 22.4, 25.8, 37.4, 39.0, 42.8, 49.2, 50.9, 60.4, 77.1.

11b

Orange solid; yield: 102 mg (13%); mp 62–64 °C; R_f = 0.49 (Et_2O).

IR (film): 3355 (br), 1684, 1654, 1458 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 7.3 Hz, 3 H, Me), 1.40 (m, 1 H, H6$_\alpha$), 1.55 (m, 1 H, H7$_\alpha$), 1.71 (m, 2 H, H7$_\beta$ and H3$_\alpha$), 1.87 (m, 2 H, C*H*HCH$_2$OH and H4$_\alpha$), 2.02 (m, 1 H, H5$_\beta$), 2.13 (m, 2 H, CH*H*CH$_2$OH and H6$_\beta$), 2.45 (m, 1 H, H3$_\beta$), 2.98 (br s, 2 H, OH), 3.66 (td, *J* = 10.4, 2.3 Hz, 1 H, CH$_2$C*H*HOH), 3.75 (m, 1 H, CH$_2$CH*H*OH), 3.91 (d, *J* = 5.2 Hz, 1 H, H2$_\alpha$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 22.7, 27.0, 37.1, 40.4, 41.5, 51.5, 52.9, 59.3, 80.2.

HRMS: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{18}NaO_2$: 193.1204; found: 193.1204.

12b

Yellow oil; yield: 125 mg (16%); R_f = 0.36 (Et_2O).

IR (film): 3318 (br), 1684, 1654, 1543, 1508 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.89 (d, *J* = 7.4 Hz, 3 H, Me), 1.47 (m, 1 H, H6$_\alpha$), 1.52 (m, 1 H, H7$_\alpha$), 1.76 (m, 2 H, H4$_\alpha$ and C*H*HCH$_2$OH), 1.85 (dd, *J* = 12.3, 6.2 Hz, 1 H, H3$_\beta$), 1.97 (m, 2 H, CH*H*CH$_2$OH and H5$_\beta$), 2.09 (m, 1 H, H7$_\beta$), 2.20 (m, 2 H, H3$_\beta$ and H6$_\beta$), 2.71 (br s, 1 H, OH), 3.06 (br s, 1 H, OH), 3.69 (td, *J* = 10.7, 2.6 Hz, 1 H, CH$_2$C*H*HOH), 3.75 (m, 1 H, CH$_2$CH*H*OH), 4.15 (dd, *J* = 11.1, 6.4 Hz, 1 H, H2$_\beta$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 21.5, 22.3, 37.3, 42.6, 48.9, 50.8, 59.5, 77.6.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{10}H_{18}NaO_2$: 193.1204; found: 193.1204.

(1*R,2*S**,4*R**,5*S**)-1-[2-(*tert*-Butyldimethylsiloxy)ethyl]-4-methylbicyclo[3.2.0]heptan-2-ol (11a) and (1*R**,2*R**,4*R**,5*S**)-1-[2-(*tert*-Butyldimethylsiloxy)ethyl]-4-methylbicyclo[3.2.0]heptan-2-ol (12a)**

To a soln of **11b** and **12b** (~1:1, 522 mg, 3.07 mmol) and 2,6-lutidine (0.55 mL, 4.7 mmol) in CH_2Cl_2 (50 mL) at –78 °C was added TBSOTf (0.78 mL, 3.5 mmol). After 4 h, the mixture was poured into sat. $NaHCO_3$ soln (50 mL). The resultant mixture was extracted with CH_2Cl_2 (3 × 50 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (hexanes–Et_2O, 4:1) afforded **11a** and **12a** as an orange oil; yield: 790 mg (91%).

(1*R,4*R**,5*S**)-1-[2-(*tert*-Butyldimethylsiloxy)ethyl]-4-methylbicyclo[3.2.0]heptan-2-one (13)**

To a soln **11a** and **12a** (~1:1, 4.02 g, 14.2 mmol) in MeCN (300 mL) was added IBX (7.94 g, 28.4 mmol) and the resultant mixture was heated at 65 °C for 3.25 h. The mixture was cooled to r.t., filtered through a pad of Celite with Et_2O (3 × 150 mL), and concentrated in vacuo. Purification by flash chromatography (hexanes–Et_2O, 4:1) afforded **13** as a yellow oil; yield: 3.83 g (96%); R_f = 0.46 (hexanes–Et_2O, 4:1).

IR (film): 1732, 1471, 1411, 1388 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.040, (s, 3 H), 0.044 (s, 3 H), 0.88 (s, 9 H), 0.96 (d, *J* = 7.1 Hz, 3 H), 1.82 (m, 4 H), 2.06 (m, 3 H), 2.31 (m, 1 H), 2.48 (m, 1 H), 2.92 (dd, *J* = 10.1, 7.7 Hz, 1 H), 3.68 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.4, 18.2, 21.3, 21.9, 25.9, 27.3, 34.6, 36.8, 45.4, 46.1, 51.3, 59.9, 223.0.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{16}H_{30}NaO_2Si$: 305.1913; found: 305.1912.

(1*R,5*S**)-1-[2-(*tert*-Butyldimethylsiloxy)ethyl]-4-methylbicyclo[3.2.0]hept-3-en-2-one (4)**

To a soln of **13** (5.00 g, 17.7 mmol) and Et_3N (20 mL, 140 mmol) in CH_2Cl_2 (350 mL) at 0 °C was added TMSOTf (13 mL, 71 mmol). After 3.5 h, sat. $NaHCO_3$ soln (350 mL) was added. The resultant mixture was extracted with CH_2Cl_2 (2 × 150 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. The silyl enol ether was obtained as a yellow oil and it was used without further purification; yield: 6.12 g (99%); R_f = 0.74, (hexanes–Et_2O, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.06, (s, 6 H), 0.21 (s, 9 H), 0.90 (m, 12 H), 1.59 (m, 1 H), 1.76 (m, 2 H), 1.91 (dd, *J* = 8.9, 5.5 Hz, 1 H), 2.10 (m, 2 H), 2.23 (m, 1 H), 3.55 (m, 1 H), 3.64 (m, 1 H), 4.59 (d, *J* = 2.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.2, –0.5, 18.4, 22.8, 23.9, 26.0, 30.0, 39.4, 42.6, 46.2, 51.4, 60.8, 107.1, 157.4.

To a soln of the enol ether in DMSO (400 mL) at r.t. was added $Pd(OAc)_2$ (3.98 g, 17.7 mmol). After 2 d, the resultant mixture was diluted with Et_2O (400 mL) and washed with H_2O (3 × 250 mL). The combined aqueous layers were extracted with Et_2O (5 × 200 mL) and the resultant organic layers were dried (anhyd Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (hexanes–Et_2O, 1:1) afforded **4** as a yellow oil; yield: 4.37 g (88%); R_f = 0.38 (hexanes–Et_2O, 1:1).

IR (film): 1699, 1614, 1472, 1436 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.02, (s, 3 H), 0.00 (s, 3 H), 0.85 (s, 9 H), 1.58 (m, 1 H), 1.83–2.12 (m, 4 H), 2.09 (s, 3 H), 2.45 (m, 1 H), 3.15 (dd, *J* = 9.9, 3.3 Hz, 1 H), 3.59 (m, 2 H), 6.07 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6, 17.0, 18.0, 21.1, 25.8, 26.9, 35.3, 47.9, 52.3, 60.0, 131.51, 179.6, 213.0.

(±)-1-[2-(*tert*-Butyldimethylsiloxy)ethyl]-3-methylbicyclo[2.2.1]hept-2-en-7-one (3)

A soln of **4** (1.08 g, 3.86 mmol) in CH_2Cl_2 (600 mL) in a Pyrex reaction vessel was deoxygenated by bubbling N_2 through it for 15 min. The resultant mixture was irradiated with 350 nm light for 8 h after which the soln was concentrated in vacuo. Purification by flash chromatography (hexanes–Et_2O, 9:1) afforded **3** as a colorless oil; yield: 270 mg (25%); R_f = 0.43 (hexanes–Et_2O, 9:1).

IR (film): 1777, 1472, 1255, 1097 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.06 (s, 6 H), 0.90 (s, 9 H), 1.24 (qd, *J* = 11.6, 4.8 Hz, 1 H), 1.39 (td, *J* = 13.4, 6.6 Hz, 1 H), 1.69–1.98 (m, 4 H), 1.86 (s, 3 H), 2.62 (d, *J* = 3.6 Hz, 1 H), 3.77 (m, 2 H), 6.08 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = –5.3, 16.9, 18.2, 21.9, 25.9, 28.2, 30.4, 50.4, 52.1, 60.4, 129.4, 142.6, 206.1.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{16}H_{28}NaO_2Si$: 303.1756; found: 303.1754.

(±)-1-[2-(*tert*-Butyldimethylsiloxy)ethyl]-3-methyl-7-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]bicyclo[2.2.1]hept-2-en-7-*anti*-ol (16)

To a suspension of Mg (300 mg, 12.5 mmol) in THF (30 mL) was added 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (976 mg, 5.00 mmol) and 1,2-dibromoethane (5 drops). After a brief initiation of the reaction with a heat gun, the resultant mixture was allowed to stir at r.t. for 2 h. A soln of **3** (269 mg, 0.961 mmol) in THF (25 mL) was added and the resultant mixture was heated at reflux for 1 h and then cooled to 0 °C. A sat NH_4Cl soln (50 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 60 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (gradient, CH_2Cl_2 to CH_2Cl_2–Et_2O, 17:3) afforded **16**[11] as a colorless oil; yield: 323 mg (85%); R_f = 0.54 (CH_2Cl_2–Et_2O, 3:1).

IR (film): 3444 (br), 1634, 1472, 1445 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.08 (s, 6 H), 0.87 (m, 1 H), 0.90 (s, 9 H), 0.95 (m, 1 H) 1.28 (s, 3 H), 1.48–2.08 (m, 8 H), 1.69 (d, *J* = 1.4 Hz, 3 H), 2.29 (d, *J* = 3.2 Hz, 1 H), 3.70 (br s, 1 H), 3.74 (m, 1 H), 3.80 (td, *J* = 10.4, 3.5 Hz, 1 H), 3.90 (m, 4 H), 5.29 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.6, –5.4, 15.9, 18.4, 23.66, 23.72, 25.5, 26.0, 28.0, 31.1, 34.8, 52.4, 57.4, 60.4, 64.4, 64.6, 89.8, 110.3, 132.5, 143.3.

(±)-1-(2-Hydroxyethyl)-3-methyl-7-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]bicyclo[2.2.1]hept-2-en-7-*anti*-ol (17)

To a soln of **16** (142 mg, 0.356 mmol) in THF (5 mL) at 0 °C was added a soln of 1 M TBAF (1.0 mL, 1.0 mmol) and the resultant mixture was allowed to warm to r.t. over 20 min. Sat. NH_4Cl soln (5 mL) was added and the resultant mixture was extracted with Et_2O (3 × 10 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (Et_2O–MeOH, 19:1) afforded **17** as a colorless oil; yield: 94 mg (94%); R_f = 0.39 (Et_2O–MeOH, 19:1).

IR (film): 3401 (br), 1634, 1446 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (m, 2 H), 1.30 (s, 3 H), 1.45 (m, 1 H), 1.67 (m, 2 H), 1.69 (d, *J* = 1.3 Hz, 3 H), 1.80 (m, 1 H), 1.96 (m, 3 H), 2.09 (m, 1 H), 2.30 (d, *J* = 3.3 Hz, 1 H), 3.39 (br s, 1 H), 3.69 (m, 1 H), 3.78 (td, *J* = 10.7, 3.4 Hz, 1 H), 3.94 (m, 4 H), 4.00 (br s, 1 H), 5.28 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 23.5, 23.6, 24.6, 28.0, 31.1, 34.9, 52.9, 57.1, 59.3, 64.5, 64.6, 90.2, 110.3, 132.6, 143.3.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{16}H_{26}NaO_4$: 305.1729; found: 305.1723.

(1*R,5*S**)-5,10-Dimethyl-4,14-dioxatetracyclo[7.2.2.1^{5,8}0^{1,8}]tetradec-10-ene (18)**

To a soln of **17** (11 mg, 0.041 mmol) in acetone (2 mL) at r.t. was added PPTS (~1 mg) and the resultant mixture was stirred for 23 h. Sat. $NaHCO_3$ soln (5 mL) was added and the resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo. Purification of the residue by flash chromatography (hexanes–Et_2O, 4:1) afforded **18** as a colorless oil; yield: 7 mg (70%); R_f = 0.49 (hexanes–Et_2O, 4:1).

IR (film): 1654, 1458, 1438, 1379 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95 (td, *J* = 10.8, 3.6 Hz, 1 H), 1.03 (td, *J* = 11.2, 3.30 Hz, 1 H), 1.36 (s, 3 H), 1.52–1.76 (m, 3 H), 1.71 (d, *J* = 1.3 Hz, 3 H), 1.85 (m, 3 H), 2.01 (m, 2 H), 2.30 (d, *J* = 3.6 Hz, 1 H), 3.50 (dt, *J* = 12.5, 3.0 Hz, 1 H), 3.90 (t, *J* = 11.8 Hz, 1 H), 5.39 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3, 23.05, 23.08, 26.7, 30.7, 31.0, 38.9, 54.4, 54.8, 58.0, 100.0, 107.5, 130.3, 144.7.

HRMS: *m/z* [M – OH]$^+$ calcd for $C_{14}H_{19}O$: 203.1436; found: 203.1430.

(±)-1-(2-Bromoethyl)-3-methyl-7-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]bicyclo[2.2.1]hept-2-en-7-*anti*-ol (19)

To a soln of **17** (35 mg, 0.12 mmol), Ph_3P (140 mg, 0.53 mmol), and 2,6-lutidine (14 μL, 0.14 mmol) in THF (3 mL) at r.t. was added CBr_4 (186 mg, 0.56 mmol) and the resultant mixture was stirred for 30 min. Hexanes (10 mL) were added and the resultant mixture was filtered through Celite with hexanes–Et_2O (1:1, 2 × 6 mL) and concentrated in vacuo. Purification of the residue by flash chromatography (hexanes–Et_2O, 1:2) afforded **19** as a colorless oil; yield: 30 mg (70%); R_f = 0.26 (hexanes–Et_2O, 1:2).

IR (film): 3462 (br), 1631, 1446, 1376 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (m, 1 H), 1.09 (td, *J* = 10.5, 3.2 Hz, 1 H), 1.27 (s, 3 H), 1.61–2.11 (m, 8 H), 1.67 (d, *J* = 1.2 Hz, 3 H), 2.23 (d, *J* = 3.1 Hz, 1 H), 2.72 (br s, 1 H), 3.45 (m, 2 H), 3.92 (m, 4 H), 5.45 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 23.4, 23.6, 24.2, 29.7, 30.5, 32.4, 34.7, 52.3, 57.6, 64.5, 91.5, 110.0, 128.6, 143.7.

(1*R,5*R**)-5,10-Dimethyl-14-oxa-4λ^4-thiatetracyclo[7.2.2.1^{5,8}.0^{1,8}]tetradec-10-en-4-one (20)**

To a soln of **19** (30 mg, 0.09 mmol) in EtOH (95%, 2 mL) was added thiourea (24 mg, 0.32 mmol) and the resultant mixture was heated at reflux for 23 h. After cooling to r.t., solid NaOH (49 mg, 1.2 mmol) and H_2O (3 mL) were added and the resultant mixture was heated at reflux for 2 h. The mixture was freed of EtOH in vacuo and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried (anhyd Na_2SO_4) and concentrated in vacuo. Purification of the residue by flash chromatography (hexanes–Et_2O, 19:1) afforded **20** as a white solid; yield: 11 mg (50%); mp 50–51 °C; R_f = 0.50 (hexanes–Et_2O, 19:1).

IR (film): 1456, 1439, 1374 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (m, 1 H), 1.03 (m, 1 H), 1.63 (s, 3 H), 1.70 (d, *J* = 1.2 Hz, 3 H), 1.74–2.38 (m, 9 H), 2.25 (d, *J* = 3.7 Hz, 1 H), 3.04 (ddd, *J* = 14.6, 12.1, 1.0 Hz, 1 H), 5.34 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 23.1, 25.4, 27.0, 30.2, 30.3, 32.9, 43.3, 55.2, 55.9, 91.3, 101.3, 130.8, 144.6.

LR-MS: *m/z* [M]$^+$ calcd for $C_{14}H_{20}O_2S$: 252.1; found: 252.2.

(1*R,5*R**)-5,10-Dimethyl-14-oxa-4λ^6-thiatetracyclo[7.2.2.1^{5,8}.0^{1,8}]tetradec-10-ene-4,4-dione (21)**

To a soln of **20** (55 mg, 0.20 mmol) in Et_2O (15 mL) at 0 °C was added MCPBA (53 mg, 0.31 mmol) and the resultant soln was allowed to warm to r.t. over 16 h. The mixture was washed with sat. $NaHCO_3$ soln (3 × 10 mL), dried (anhyd Na_2SO_4), and concentrated in vacuo to afford **21** as a white solid; yield: 52 mg (94%); mp 109–111 °C; R_f = 0.50 (hexanes–Et_2O, 19:1). A portion of this material was recrystallized (Et_2O) for X-ray crystal structure analysis.

IR (film): 1632, 1440, 1305, 1276 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (td, *J* = 10.8, 3.5 Hz, 1 H), 1.11 (td, *J* = 11.5, 3.0 Hz, 1 H), 1.58 (s, 3 H), 1.71 (d, *J* = 1.4 Hz, 3 H), 1.75 (m, 1 H), 1.87–2.27 (m, 6 H), 2.39 (d, *J* = 3.6 Hz, 1 H), 2.67 (dd, *J* = 13.5, 1.5 Hz, 1 H), 2.93 (dd, *J* = 14.5, 1.6 Hz, 1 H), 3.57 (dd, *J* = 14.5, 1.8 Hz, 1 H), 5.37 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.1, 21.7, 21.8, 22.8, 26.6, 29.2, 35.2, 50.3, 55.3, 55.6, 102.7, 105.8, 129.9, 144.8.

HRMS: *m/z* [M + Na]$^+$ calcd for $C_{14}H_{20}NaO_3S$: 291.1031; found: 291.1032.

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