Application of the Anionic Oxy-Cope Rearrangement to Stereocontrolled Synthesis of the A/B Subunit of Cytoxic 8,9-Seco-*ent*-kaurenes

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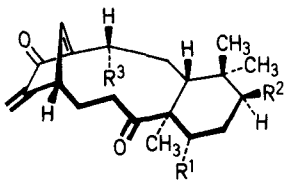
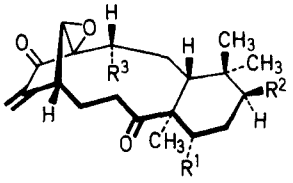
Methodology is described for expedient synthesis of the A/B framework of 8,9-seco-*ent*-kaurenes and for introduction of the 5-methylene-2-cyclopentenone moiety. In the first part of the study, a sequence of only six steps is necessary to convert 2-(hydroxymethylene)cyclohexanone to a key functionalized intermediate. Five of the transformations are 100% stereocontrolled as a direct result of complementary steric biases that operate in the desired direction. The final target is arrived at by selective protection/oxidation of the oxygenated centers. This first synthetic entry to the structural core of the titled diterpenes is expected to guide the future *de novo* acquisition of these cytotoxic agents.

Intensive investigation by several Japanese research groups of plants from the genus *Rabdosia* (Labiatae) has resulted in the isolation and identification of seven 8,9-seco-*ent*-kaurene diterpenes.[1-7] These include shikodomedin (**1a**), rabdolatifolin (**1b**), shikoccin (**1c**), *O*-methylshikoccin (**1d**), shikokiamedin (**2a**), epoxyshikoccin (**2b**), and *O*-methylepoxyshikoccin (**2c**). Subsequent screening for cytotoxic activity has shown **1a** to be a potent inhibitor of cultured FM 3A/B rat mammary cancer cells.[8] The other members of this class exhibit the same antitumor response, although to a lesser degree. As a result of its scarcity, **1a** has not been developed as an agent that might contribute to our understanding of leukemia and other types of cancer at the molecular level.



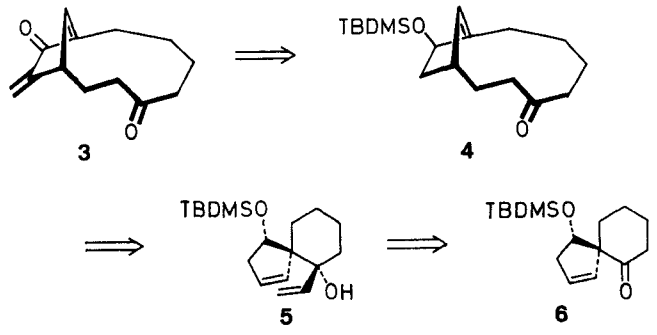
1a R^1 = OAc, R^2 = OAc, R^3 = OH
b R^1 = OH, R^2 = H, R^3 = OH
c R^1 = H, R^2 = OAc, R^3 = OH
d R^1 = H, R^2 = OAc, R^3 = OMe



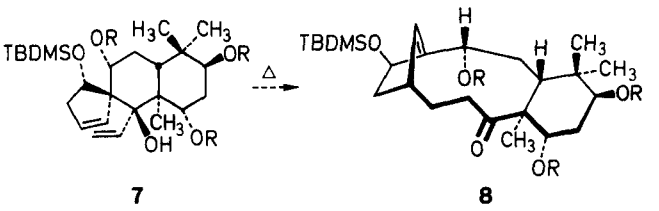
2a R^1 = OAc, R^2 = OAc, R^3 = OH
b R^1 = H, R^2 = OAc, R^3 = OH
c R^1 = H, R^2 = OAc, R^3 = OMe

The structural features of shikodomedin and its congeners, which were originally elucidated by X-ray diffraction, are sufficiently unusual that they have commanded interest in these laboratories[9] and elsewhere.[10] Of particular note is the intracyclic bridgehead double bond that forms part of a 5-methylene-2-cyclopentenone unit in **1**. Central to our development of a synthetic route to this class of compounds was the realization that the bicyclo[7.2.1]dodec-1(12)ene-6,11-dione core **3** of rings A and B is related to spirocycle **5** via an oxy-Cope rearrangement that would lead initially to **4**.

Accordingly, the present goals were to gain access to the protected aldol **6** in a fully stereocontrolled manner and to transform this intermediate into **3**. The possibility of preparing **1a** by a related protocol (*viz* **7** → **8**) would thereby be accorded reasonable precedence.



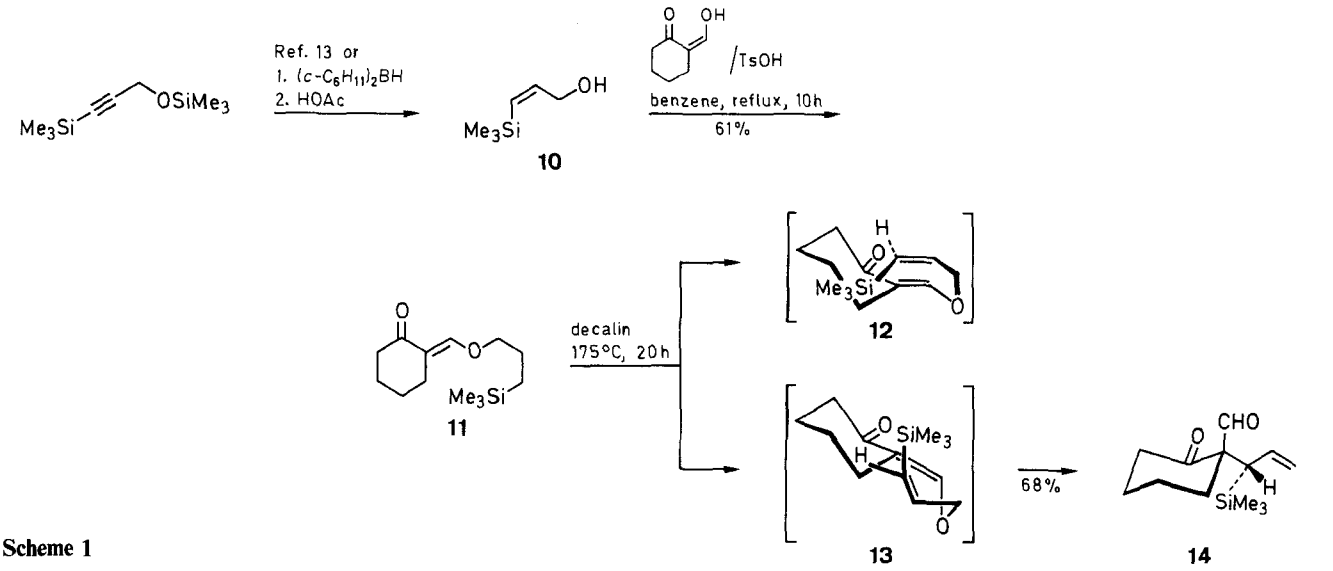
TBDMS = *t*-BuMe$_2$Si



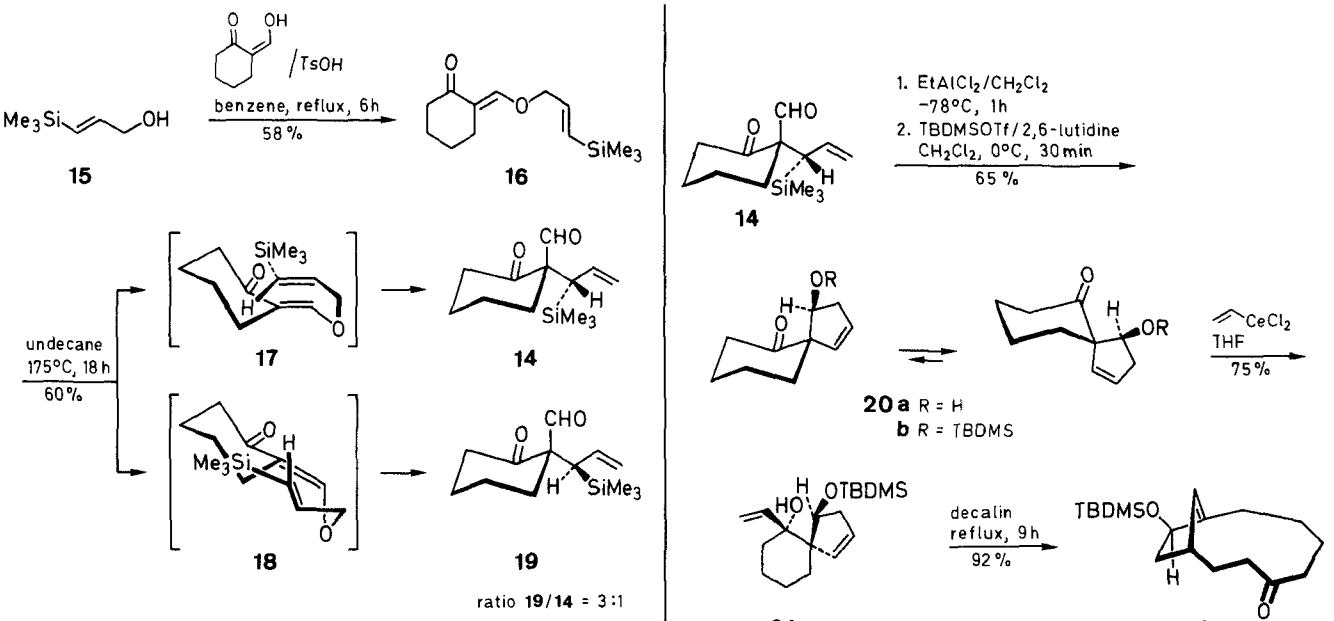
Results and Discussion

The extent to which the aliphatic Claisen rearrangement can be relied upon to control stereoselectivity[11] prompted its utilization at the outset. For the sake of completeness, 2-(hydroxymethylene)cyclohexanone was condensed[12] with both isomers of 3-(trimethylsilyl)-2-propen-1-ol (Schemes 1 and 2). Althougth *Z*-alcohol **10** had been earlier produced by semihydrogenation of the corresponding alkyne,[13] we chose to utilize a two-step procedure involving hydroboration with dicyclohexylborane followed by protonolysis with acetic acid so as to skirt possible overreduction. The pure *E* isomer **15** was prepared by dilithiation of propargyl alcohol, silylation with Me_3SiCl, and Red-Al reduction of the hyrolysis product according to precedent.[14]

Once the enol ethers **11** and **16** were available, they were independently heated in decalin or undecane at 175 °C for 18–20 hours. The *Z* isomer **11** isomerized smoothly to afford **14** exclusively (Scheme 1). Thus, the [3,3] sigmatropic shift in this case proceeds strictly via chair transition state **13**. The steric congestion present in boat conformation **12** is particularly adverse to its involvement on a competitive basis. This is not so for **16** where chair option **18** is now more crowded than the boat alternative **17**. These steric control elements act to force approximately 25% of the aldehydic product to be formed via **17**. For the present purposes, it is particularly relevant that the olefinic geometry localized in the double bonds of **11** is transformed into two unequivocally defined stereogenic centers in **14**.



Scheme 1



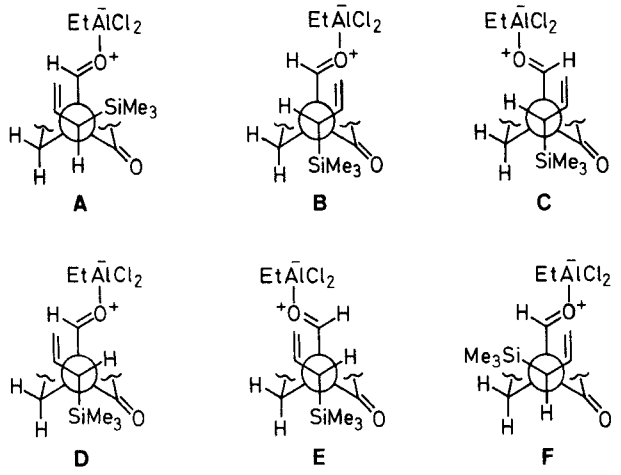
Scheme 2

Scheme 3

While aldehydes **14** and **19** can easily be dinstinguished by means of their respective -CHO singlets (δ = 9.48 and 9.23 in $CDCl_3$), their relative configurations at this stage were deduced solely on the basis of mechanistic reasoning. The correctness of these assignments and the strategic importance of the clean conversion to **11** and **14** shall become very apparent in the sequel.

Of the catalysts examined for promoting intramolecular 5-*exo,trig* cyclization within **14** and **19**,[15] ethylaluminum dichloride emerged as the most efficacious. Both reactions were fully stereocontrolled, with **14** giving rise cleanly to anti aldol **20a** and **19** leading to syn diastereomer **23a** (Scheme 3). These sensitive β-hydroxy ketones were silylated prior to further handling.

The excellent stereoselectivity associated with these ring closure reactions is indicative that several stererochemical determinants are operating in the same direction. The need to position the terminal carbon of the allylsilane moiety in close proximity to the aldehyde center limits **14** to conformations such as those depicted by Newman projections **A**–**C**.



For **19**, the corresponding structural alignments are **D–F**. Once Lewis acid complexation occurs at oxygen from that direction anti to the R group of the aldehyde,[16] two product-related steric biases gain importance. The first involves those nonbonded interactions operating between the collective substituents. Thus, **A** and **B** are clearly more sterically congested than **C**; likewise, the spatial dispositions of the groups in **E** and **F** are more encumbered than that present in **D**. Facial selectivity associated with bonding to the carbonyl carbon must also be considered. In both **C** and **D**, the bulky cationic oxygen center is oriented in the direction of a hydrogen atom rather than toward vinyl. Therefore, the combined energetic advantages enjoyed by these rotamers are responsible for their involvement of the antiperiplanar transition states of choice for clean conversion to **20a** and **23a**, respectively.

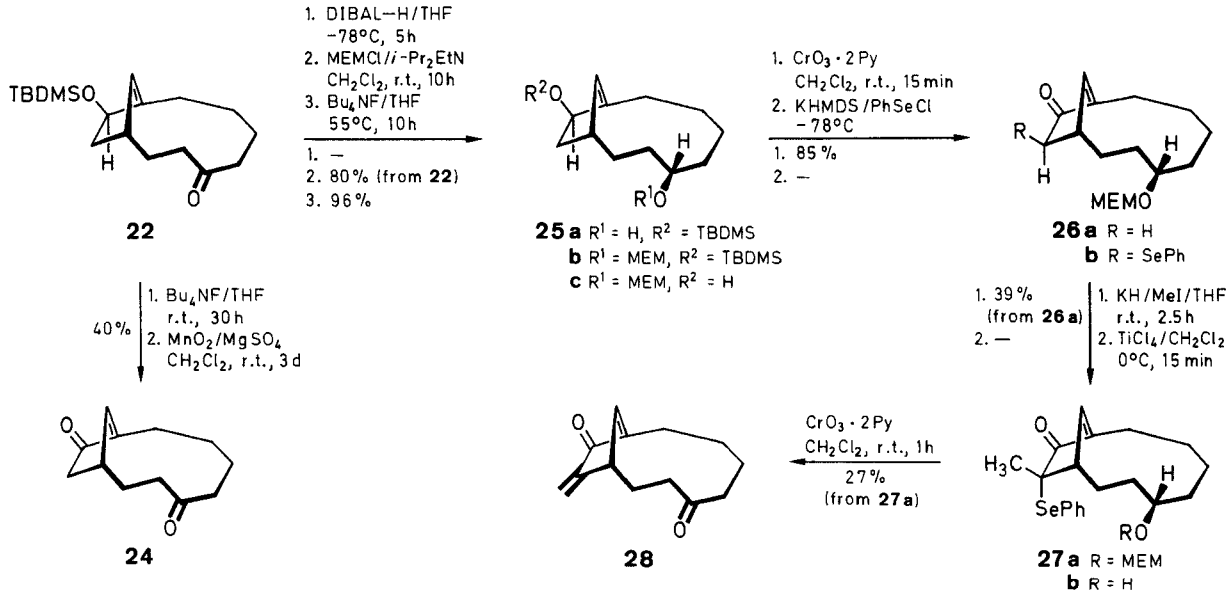
Proper distinction between **20b** and **23b** could now be made on the basis of chemical reactivity. Thus, **20b** condensed smoothly with vinylcerium dichloride,[17] while **23b** was totally unreactive. The syn orientation of the OTBDMS group so blockades the ketone functionality in **23b** that condensation reactions with organometallic reagents are kinetically deterred.

The complete stereocontrol achieved in the formation of **21** likely stems from the fact that the β-siloxy substituted carbon is projected equatorially such that axial attack is favored. Unfortunately, we were unable to corroborate the relative configurations of **21** by NOE studies at 500 MHz.

With arrival at **21**, the stage was set for the pivotal [3,3] sigmatropic rearrangement. However, attempts to capitalize on the kinetic acceleration associated with the anionic oxy-Cope reaction proved disappointing. Exposure of **21** to KH, $KN(SiMe_3)_2$, and other potassium bases with or without added 18-crown-6 resulted in no reaction at room temperature; when heated, rapid conversion to a black tarry material took place. This turn of events was ultimately traced to the sensitivity of the anticipated ketonic product to strong bases. As a result, this complication could easily be skirted by simply heating **21** in decalin at 190 °C for 9 h. These purely thermal conditions provided for the efficient formation of **22** (92 %). The 300 MHz ^1H NMR spectrum of **22** (in $CDCl_3$) shows two very distinctive signals due to the unique olefinic (s at δ = 5.17) and carbinol protons (d, J = 8.6 Hz at δ = 4.63). Further, its carbonyl infrared absorption appears at 1670 cm^{-1}.

As shown in Scheme 4, the lability of **22** under strongly alkaline conditions could be skirted to achieve its conversion to **28**. Initially, a second carbonyl group was directly introduced to provide **24**. This macrocyclic diketone proved to be a more sensitive compound than expected, being prone to decomposition simply on standing in neat condition at room temperature. Our apprehensiveness regarding a comparable level of instability of **28** proved, however, to be unfounded.

Several routes from **22** to **28** were briefly examined. The illustrated sequence was determined to be serviceable, although the yields of the individual steps have not been maximized. A number of points are noteworthy. The DIBAL-H reduction of **22** proved to be 100 % stereose-



Scheme 4

lective. Product stereochemistry has been arbitrarily assigned. Since the final step was to involve reoxidation of this center, more definitive stereochemical proof was not sought. The virtually complete stereocontrol achieved in the methylation and selenylation of enolates derived from **26** conforms to expectations associated with kinetically favored exo capture of electrophiles by related bicyclic systems. Trigonalization of the α-carbonyl site was realized by exposure of **27b** to the chromium trioxide–dipyridine complex.[18] Under these conditions, selenoxide elimination[19] and oxidation to the ketone were accomplished concurrently. Diene dione **28** exhibited spectral properties fully commensurate with its structural assignment.

In summary, this study describes successful application of the oxy-Cope rearrangement to the synthesis of 10-methylenebicyclo[7.2.1]dodec-1(12)-ene-6,11-dione **(28)**, an appropriately functionalized model for the A/B ring system of the 8,9-seco-*ent*-kaurene diterpenes. The process that regulates access to **22** involves six steps, five of which are fully stereocontrolled. Only the protective silylation maneuver falls outside of this boundary claim. On the practical side, this sequence leading directly to the structural core is impressively short. As this strategy applies to ultimate arrival at shikodomedin, proper allowance has been made for those operations required to develop the 5-methylene-2-cyclopentenone part structure. Further synthetic studies involving those tricyclic intermediates necessary to achieve this objective will be reported in due course.

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. ^{1}H NMR spectra were recorded at 300 or 250 MHz and the ^{13}C NMR data obtained at 75 or 20 MHz as iondicated. Mass spectra were measured on a Kratos MS-30 instrument at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All flash chromatographic separations were carried out on Merck silica gel 60 (60–200 mesh) and reactions were routinely performed under an inert atmosphere (nitrogen or argon) unless otherwise indicated. Solvents were reagent grade and dried prior to use.

2-[(*E*)-[(*Z*)-3-(Trimethylsilyl)allyl]oxy]methylene]cyclohexanone (11):

A solution of 2-(hydroxymethylene)cyclohexanone (12.0 g, 95 mmol) in dry benzene (350 mL) was treated with **10**[13] (14.0 g, 108 mmol) and TsOH (350 mg) and heated at reflux under a Dean–Stark trap for 10 h. The cooled mixture was concentrated, filtered through a short column of silica gel (elution with 1:1 petroleum ether/EtOAc), and evaported. Chromatography (elution with 95:5 petroleum ether/EtOAc) followed by Kugelrohr distillation (160 °C/0.3 Torr) gave **11** (13.7 g, 61 %) as a faint yellow oil.

IR (neat): ν = 1670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (t, J = 2.0 Hz, 1 H), 6.32 (m, 1 H), 5.80 (td, J = 14.5, 1.3 Hz, 1 H), 4.49 (dd, J = 6.5, 1.3 Hz, 2 H), 2.38 (td, J = 6.4, 2.0 Hz, 2 H), 2.28 (t, J = 6.6 Hz, 2 H), 1.70 (m, 4 H), 0.09 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.1, 155.3, 141.2, 135.3, 115.7, 73.6, 39.4, 23.1, 22.9, 22.6, −0.18.

MS: m/z ($M^+ - Me_3S$) calcd 133.0973; found 133.1033.

(±)-(*R)-2-Oxo-1-[(*R**)-1-(trimethylsilyl)allyl]cyclohexanecarboxaldehyde (14):**

A solution of **11** (3.1 g, 13 mmol) in anhydr. decalin (100 mL) was heated at 175 °C under an argon atmosphere for 20 h, cooled to r.t., and poured onto a column of silica gel. The decalin was removed by elution with petroleum ether. An increase in polarity to 96:4 petroleum ether/EtOAc afforded **14** (2.1 g, 68 %) as a colorless crystalline solid; mp 49 °C.

IR (KBr) ν = 1710, 1690 cm^{-1}.

^{1}H MNR (250 MHz, $CDCl_3$): δ = 9.48 (s, 1 H), 5.65 (m, 1 H), 4.90 (m, 2 H), 2.6–1.5 (series of m, 8 H), 0.04 (m, 10 H).

^{13}C NMR (20 MHz): δ = 210.0, 201.2, 135.5, 115.8, 66.5, 41.2, 39.4, 33.0, 26.4, 21.4, −0.36.

MS: m/z (M^+) calcd 238.1389, found 238.1366.

Anal. Calcd for $C_{13}H_{22}O_2Si$ C 65.49 H 9.30. Found: C, 65.52; H, 9.31.

2-[(*E*)-[[(*E*)-3-(Trimethylsilyl)allyl]oxy]methylene]cyclohexanone (16):

To a solution of 2-(hydroxymethylene)cyclohexanone (1.0 g, 7.9 mmol) in dry benzene (20 mL) was added **15** (1.4 g, 1.1 mmol) and TsOH (30 mg). This mixture was refluxed for 6 h under a Dean–Stark trap while being blanketed with argon. The predescribed workup afforded 1.1 g (58 %) of **16** as a pale yellow oil.

IR (neat): ν = 1670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (s, 1 H), 6.1–5.9 (m, 2 H), 4.5 (d, J = 4.4 Hz, 2 H), 2.47 (t, J = 6.5 Hz, 2 H), 2.35 (t, J = 6.4 Hz, 3 H), 1.9–1.6 (m, 4 H), 0.08 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 220.0, 177.9, 163.1, 155.5, 138.1, 98.7, 62.3, 46.2, 45.8, 45.3, 21.0.

MS: m/z ($M^+ - Me_3Si$) calcd 133.0973, found 133.1025.

(±)-(*R)-2-Oxo-1-[(*S**)-(trimethylsilyl)allyl]cyclohexanecarboxaldehyde (19):**

Heating a 1.0 g (4.2 mmol) sample of **16** in dry undecane (20 mL) at 175 °C under argon for 18 h and workup as before gave 600 mg (60 %) of a 3:1 mixture of **19** and **14**.

For **19**:

IR (neat): ν = 1720, 1680 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.23 (s, 1 H), 6.0–5.45 (m, 1 H), 5.0–4.8 (m, 2 H), 2.6–1.6 (series of m, 9 H), 0.0–0.01 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0, 203.0, 134.1, 116.1, 67.5, 41.4, 38.6, 30.3, 25.3, 21.7, −0.3, −0.6, −1.5.

MS: m/z ($M^+ - CO$) calcd 210.1440, found 210.1407.

(±)-(4*R,5*R**)-4-(*tert*-Butyldimethylsiloxy)spiro[4.5]dec-1-en-6-one (20b):**

(±)-(4R,5R*)-4-Hydroxyspiro[4.5]dec-1-en-6-one* **(20a)**:

A solution of **14** (5.1 g, 21.5 mmol) in CH_2Cl_2 (125 mL) was cooled to −78 °C under argon, treated with $EtAlCl_2$ (43 mL of 1 M in hexanes, 0.43 mmol), and stirred at this temperature for 1 h. Sat. NH_4Cl solution (50 mL) was introduced and the mixture was allowed to warm to r.t., poured into water (50 mL), and extracted with $CHCl_3$ (2 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give **20a** as a pale yellow oil that was immediately silylated.

(±)-(4R,5R*)-4-(tert-Butyldimethylsiloxy)spiro[4.5]dec-1-en-6-one* **(20b)**:

The above material **20a** (ca. 5 g) was dissolved in cold (0 °C) CH_2Cl_2 (100 mL) and treated sequentially with 2,6-lutidine (5.5 mL, 44 mmol) and *tert*-butyldimethylsilyl triflate (3.4 mL, 14.4 mmol). After 30 min of stirring at 0 °C, the mixture was poured into water (100 mL) and extracted with Et_2O (3 × 150 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to leave a residue that was purified by chromatography (elution with 2 % EtOAc in petroleum ether). There was isolated 3.9 g (65 %) of **20b** as a colorless oil.

IR (neat): ν = 1695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.75–5.65 (m, 2 H), 4.49 (dd, J = 2.6, 5.8 Hz, 1 H), 2.7–1.55 (series of m, 10 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.7, 134.4, 128.3, 78.1, 67.2, 42.1, 41.8, 36.8, 27.0, 25.7, 22.5, 17.8, −3.8, −4.8.

MS: *m/z* (M^+) calcd 280.1858, found 280.1836.

Anal. Calcd for $C_{16}H_{28}O_2Si$: C, 68.52; H, 10.06. Found: C, 68.46; H, 10.01.

(±)-(4*R,5*R**,6*S**)-4-(*tert*-Butyldimethylsiloxy)-6-vinylspiro[4.5]-dec-1-en-6-ol (21):**

A cold (−78 °C), magnetically stirred slurry of anhydr. $CeCl_3$ (4.0 g, 16.3 mmol) in dry THF (150 mL) was treated with vinylmagnesium bromide (18 mL of 1.0 M in THF, 10 mmol) and the mixture was stirred at this temperature for 30 min. A solution of **20b** (3.9 g, 13.9 mmol) in dry THF (50 mL) was quickly introduced and the mixture was allowed to warm to r.t. After 30 min, the mixture was returned to −78 °C for a second addition of the Grignard reagent (10 mL). After a return to r.t. and 30 min of added stirring, sat. NH_4Cl solution (5 mL) was introduced and the mixture was poured into water (150 mL). The aqueous phase was extracted with EtOAc (3 × 400 mL) and the combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered, and evaporated. Chromatography of the residue (2% EtOAc in petroleum ether) afforded 3.2 g (75%) of **21** as a colorless oil.

IR (neat): ν = 3465 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.21 (dd, *J* = 10.8, 17.2 Hz, 1 H), 5.88 (td, *J* = 6.5, 1.9 Hz, 1 H), 5.73 (td, *J* = 6.5, 2.4 Hz, 1 H), 5.30 (dd, *J* = 17.2, 1.0 Hz, 1 H), 4.95 (dd, *J* = 10.7, 2.0 Hz, 1 H), 4.88 (s, 1 H), 4.03 (t, *J* = 8.4 Hz, 1 H), 2.5–1.0 (series of m, 10 H), 0.93 (s, 9 H), 0.12 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.3, 134.1, 129.2, 111.5, 85.4, 76.0, 54.9, 40.8, 35.5, 34.1, 25.8, 22.8, 20.7, 17.8, −4.5, −5.3.

MS: *m/z* (M^+) calcd 308.2172, found 308.2152.

Anal. Calcd for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.46. Found: C, 69.86; H, 10.47.

(±)-(1*R,10*R**)-10-(*tert*-Butyldimethylsiloxy)bicyclo[7.2.1]dodec-9-(12)-en-4-one (22):**

A solution of **21** (62 mg, 0.2 mmol) in dry decalin (6 mL) was heated at gentle reflux under argon for 9 h. The cooled mixture was poured onto a column of silica gel and flushed with petroleum ether to remove the decalin. Subsequent elution with 5% EtOAc in petroleum ether gave pure **22** (57 mg, 92%) as a white solid; mp 66–67 °C.

IR: ($CHCl_3$): ν = 1670 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.17 (s, 1 H), 4.63 (d, *J* = 8.6 Hz, 1 H), 3.29 (ddd, *J* = 16.5, 11.3, 3.0 Hz, 1 H), 2.8–1.1 (series of m, 14 H), 0.96 (s, 9 H), 0.12 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 215.3, 143.3, 135.0, 78.9, 42.3, 42.1, 37.7, 37.4, 33.6, 25.9, 25.6, 24.7, 22.1, 18.0, −4.5, −4.9.

MS: *m/z* (M^+) calcd 308.2172, found 308.2169.

Anal. Calcd for $C_{18}H_{32}O_2Si$: C, 70.07; H, 10.46. Found: C, 70.01; H, 10.49.

(±)-(4*R,5*S**)-4-(*tert*-Butyldimethylsiloxy)spiro[4.5]dec-1-en-6-one (23b):**

(±)-(4R,5S*)-4-Hydroxyspiro[4.5]dec-1-en-6-one* **(23a)**:

A solution of **19** (800 mg, 3.36 mmol) in CH_2Cl_2 (25 mL) was cooled to −78 °C under argon, treated with $EtAlCl_2$ (13.4 mL of 1 M in hexanes, 0.13 mmol), and stirred at this temperature for 1 h. Workup in the manner predescribed for **20a** furnished 410 mg (4%) of **23a**, which was immediately silylated.

(±)-(4R,5S*)-4-(tert-Butyldimethylsiloxy)spiro[4.5]dec-1-en-6-one* **(23b)**:

The above material **23a** (400 mg) was dissolved in cold (0 °C) CH_2Cl_2 (12 mL) and treated sequentially with 2,6-lutidine (0.60 mL, 4.8 mmol) and *tert*-butyldimethylsilyl triflate (0.68 mL, 2.9 mmol). After 15 min of stirring at 0 °C, the usual workup followed to give 484 mg (72%) of **23b** as a colorless oil.

IR (neat): ν = 1695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.70–5.30 (m, 2 H), 4.84 (dd, *J* = 5.0, 6.3 Hz, 1 H), 2.67–1.61 (series of m, 10 H), 0.88 (s, 9 H), 0.07 (s, 3 H), 0.06 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.6, 132.4, 130.0, 73.6, 66.3, 40.9, 40.4, 32.5. 27.1, 25.9, 22.3, 18.1, −4.6, −4.8.

MS: *m/z* (M^+) calcd 280.1859, found 280.1836.

(±)-Bicyclo[7.2.1]dodec-9(12)-ene-4,10-dione (24):

(±)-(1R,10R*)-10-Hydroxybicyclo[7.2.1]dodec-9(12)-en-4-one:*

A solution of **22** (40 mg, 0.13 mmol) in dry THF (4 mL) was treated with Bu_4NF (0.3 mL of 1 M in THF, 0.3 mmol) and stirred at r.t. for 30 h. The mixture was partitioned between Et_2O (40 mL) and water (10 mL) and the aqueous phase was extracted with Et_2O (300 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and evaporated to leave 40 mg of unpurified alcohol.

(±)-Bicyclo[7.2.1]dodec-9(12)-ene-4,10-dione **(24)**:

This crude alcohol (40 mg) was taken up in dry CH_2Cl_2 (5 mL) to which activated MnO_2 (110 mg) and anhydr. $MgSO_4$ (10 mg) were added. The mixture was stirred at r.t. for 1 d, treated with additional MnO_2 (70 mg), and agitated for an additional 2 d. Following direct filtration of the mixture over silica gel (elution with Et_2O), the filtrate was evaporated and the residue was subjected to flash chromatography (elution with 20% Et_2O in petroleum ether). There was isolated 10 mg (40%) of **24** as an unstable colorless oil.

IR (neat): ν = 1680 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.05 (s, 1 H), 3.11 (br s, 1 H), 2.62–2.46 (m, 2 H), 2.37–1.67 (series of m, 11 H), 1.51–1.41 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 213.0, 209.4, 165.8, 143.9, 43.8, 39.8, 37.6, 36.4, 31.0, 25.0, 23.0, 22.0.

MS: *m/z* (M^+) calcd 192.1150, found 192.1158.

(±)-(1*R,4*S**,10*R**)-10-(*tert*-Butyldimethylsiloxy)bicyclo[7.2.1]dodec-9(12)-en-4-ol (25a):**

A solution of **22** (1.4 g, 4.5 mmol) in dry THF (60 mL) was treated at −78 °C under argon with DIBAL-H (20 mL of 1 M in hexanes), stirred at this temperature for 5 h, and quenched dropwise with sat. NH_4Cl solution (5 mL). The mixture was allowed to warm to r.t., poured into sat. potassium sodium tartrate solution (300 mL), and extracted with Et_2O (4 × 300 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$), filtered, and evaporated. The resultant alcohol was routinely protected directly. For characterization, a small sample was chromatographed (elution with 10% EtOAc in petroleum ether) to produce **25a** as a colorless oil

IR ($CHCl_3$): ν = 3600 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.36 (s, 1 H), 4.66 (d, *J* = 8.8 Hz, 1 H), 4.1–3.9 (m, 1 H), 2.9–2.75 (m, 1 H), 2.53 (dt, *J* = 14.3, 8.9 Hz, 8.9 Hz, 1 H), 2.2–1.0 (m, 2 H), 1.85–1.11 (series of m, 12 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.0, 131.6, 79.4, 69.0, 40.7, 40.5, 38.4, 29.6, 28.5, 27.8, 26.6, 25.8, 21.9, 17.9, −4.5, −4.9.

MS: *m/z* (M^+) calcd 310.2338, found 310.2378.

Anal. Calcd for $C_{18}H_{34}O_2Si$: C, 69.62; H, 11.04. Found: C, 69.31; H, 11.09.

(±)-*tert*-Butyl[(1*R,4*S**,10*R**)-4-[(2-methoxyethoxy)methoxy]bicyclo[7.2.1]dodec-9(12)-en-10-yl]oxydimethylsilane (25b):**

A solution of unpurified **25a** (1.4 g) in CH_2Cl_2 (25 mL) was treated at r.t. with *i*-Pr_2EtN (1.2 mL, 6.9 mmol) followed by MEMCl (0.8 mL, 7.0 mmol). The mixture was stirred under argon for 10 h, evaporated, and chromatographed (elution with 10% EtOAc in petroleum ether) to give 1.44 g (80%) of **25b** as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.39 (s, 1 H), 4.8–4.55 (m, 1 H), 4.69 (s, 2 H), 3.75–3.50 (m, 4 H), 3.37 (s, 3 H), 2.9–2.75 (m, 1 H), 2.44 (dt, *J* = 14.2, 8.7 Hz, 1 H), 2.25–2.0 (m, 2 H), 1.8–1.2 (m, 13 H), 0.90 (s, 9 H), 0.07 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.7, 132.1, 93.9, 79.2, 75.9, 71.9, 66.7, 58.9, 41.0, 39.4, 34.8, 27.6, 27.2, 26.4, 25.9, 25.4, 21.2, 181., −4.5, −4.9.

MS: *m/z* (M^+-MEM) calcd 310.2328, found 310.2344.

Anal. Calcd for $C_{22}H_{42}O_4Si$: C, 66.28; H, 10.62. Found: C, 66.36; H, 10.62.

(±)-(1*R,4*S**,10*R**)-4-[(2-Methoxyethoxy)methoxy]bicyclo[7.2.1]-dodec-9(12)-en-10-ol (25c):**
A solution of **25b** (1.44 g, 3.62 mmol) in dry THF (100 mL) was treated with a solution of Bu_4NF in THF (15 mL of 1 M) and heated at 55 °C for 10 h. Following solvent evaporation, the residue was chromatographed (elution with 30% EtOAc in petroleum ether) to give 990 mg (96%) of **25c** as a colorless oil.

IR (neat): ν = 3600–3300 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.36 (s, 1 H), 4.8–4.6 (m, 3 H), 3.95–3.50 (m, 5 H), 3.39 (s, 3 H), 3.0–2.65 (m, 1 H), 2.3 (m, 1 H), 2.3 (m, 1 H), 2.1 (m, 1 H), 2.0–1.2 (series of m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 142.5, 130.4, 93.0, 79.4, 73.1, 71.7, 67.0, 58.9, 41.0, 39.9, 35.5, 29.4, 29.3, 29.1, 26.6, 22.0.

MS: *m/z* (M^+) calcd 284.1987, found 284.1992.

(±)-(1*R,4*S**)-4-[(-2-Methoxyethoxy)methoxy]bicyclo[7.2.1]dodec-9(12)-en-10-one (26a):**
A suspension of CrO_3 (156 mg, 1.56 mmol) in CH_2Cl_2 (3 mL) was treated with pyridine (0.25 mL, 3.13 mmol). After 30 min, **25c** (74 mg, 0.26 mol) dissolved in CH_2Cl_2 (1 mL) was introduced and the mixture was rapidly stirred for 15 min prior to filtration over silica gel (Et_2O elution) to remove the chromium salts. After evaporation, the residue was chromatographed (elution with 30% EtOAc in petroleum ether) to give **26a** (62 mg, 85%) as a colorless oil.

IR (neat): ν = 1685 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.22 (s, 1 H), 4.7–4.5 (m, 2 H), 3.70–3.45 (m, 4 H), 3.34 (s, 3 H), 3.2–3.0 (m, 2 H), 2.60–2.45 (m, 2 H), 2.30 (d, J = 8.8 Hz, 1 H), 2.05–1.60 (m, 5 H), 1.5–1.05 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.8, 162.0, 143.4, 93.8, 74.0, 71.7, 66.9, 58.9, 42.0, 36.1, 34.4, 26.9, 25.6, 24.8, 24.1, 22.0.

MS: *m/z* (M^+) calcd 282.1831, found 282.1856.
Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.05; H, 9.28. Found: C, 68.11, H, 9.32.

(±)-(1*R,4*R**,11*R**)-4-[(2-Methoxyethoxy)methoxy]-11-methyl-11-(phenylselenyl)bicyclo[7.2.1]dodec-9(12)-en-10-one (27a):**
(±)-(1R,4R*,11S*)-4-[(2-Methoxyethoxy)methoxy-11-(phenylselenyl)bicyclo[7.2.1]dodec-9(12)-en-10-one* **(26b):**

A solution of **26a** (27 mg, 0.096 mmol) in dry THF (2 mL) was treated at – 78 °C with a solution of potassium hexamethyldisilazide (0.23 mL of 0.5 M in hexanes, 0.11 mmol) and stirred at this temperature for 30 min. A solution of PhSeCl (21 mg, 0.11 mmol) in THF (0.5 mL) was quickly introduced and stirring at – 78 °C was maintained for an additional 30 min. Sat. NH_4Cl (5 drops) was added, the mixture was allowed to warm to r.t., at which point it was poured into water (10 mL) and extracted with $CHCl_3$ (3 × 15 mL). The usual workup (see above) provided **26b** (44 mg) as a yellow oil.

(±)-(1R,4R*,11R*)-4-[(2-Methoxyethoxy)methoxy]-11-methyl-11-(phenylselenyl)bicyclo[7.2.1]dodec-9(12)-en-10-one* **(27a):**
This material was taken up in dry THF (1 mL) and added to a suspension of KH (10 mg, 0.25 mmol) in the same solvent (2 mL). After 1 h of stirring, MeI (20 µL, 0.32 mmol) was introduced and the mixture was stirred at r.t. for 2.5 h. Excess base was destroyed by the addition of water (1 drop). The solvent was evaporated after a quick filtration through a silica gel plug and the residue was chromatographed (elution with 30% Et_2O in petroleum ether) to give **27a** as a yellowish oil (17 mg, 39%).

IR (neat): ν = 1690 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.85 (m, 2 H), 7.3 (m, 4 H), 4.73 (dd, J = 13.5, 6.9 Hz, 2 H), 3.75–3.50 (m, 4 H), 3.37 (s, 3 H), 3.35 (m, 1 H), 3.0 (m, 1 H), 2.6–1.0 (series of m, 12 H), 1.38 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.2, 159.9, 139.7, 137.7, 128.6, 128.4, 127.1, 94.3, 75.5, 71.8, 66.9, 59.0, 57.1, 51.4, 33.7, 30.0, 25.3, 24.6, 24.4, 24.0, 22.0.

MS: *m/z* (M^+) calcd 452.1465, found 452.1453.

(±)-11-Methylenebicyclo[7.2.1]dodec-9(12)-ene-4,10-dione (28):
(±)-(1R,4R*,11R*)-4-Hydroxy-11-methyl-11-(phenylselenyl)bicyclo[7.2.1]dodec-9(12)-en-10-one* **(27b):**

A solution of **27a** (25 mg, 0.055 mmol) in CH_2Cl_2 (3 mL) was treated at 0 °C with $TiCl_4$ (55 µL of 1 M in CH_2Cl_2, 0.055 mmol) and stirred for 15 min. NH_4OH solution (5 drops) was added and the mixture was poured into water (10 mL) and extracted with $CHCl_3$ (3 × 30 mL). The usual workup (see above) gave **27b** as a yellowish oil (25 mg) that was directly oxidized.

(±)-11-Methylenebicyclo[7.2.1]dodec-9(12)-ene-4.10-dione **(28):**
A suspension of CrO_3 (50 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was treated with pyridine (79 µL, 1 mmol) and 45 min later with a solution of the unpurified **27b**. The mixture was stirred at r.t. for 1 h, filtered over silica gel (elution with $CHCl_3/Et_2O$ 1:1), and evaporated. The residue was chromatographe (elution with 20% EtOAc in petroleum ether) to give **28** as a colorless oil (3 mg, 27%).

IR ($CHCl_3$): ν = 1685, 1640 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.95 (s, 1 H), 6.20 (s, 1 H), 5.42 (s, 1 H), 3.51 (s, 1 H), 2.7–2.4 (m, 2 H), 2.3–1.3 (series of m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 216.6, 213.3, 160.0, 145.9, 145.3, 116.5, 44.5, 2.3, 36.9, 31.4, 25.2, 24.1, 21.9.

MS: *m/z* (M^+) calcd 204.1150, found 204.1145.
Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.56; H, 7.69.

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