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Total Synthesis of (±)-Hirsutene *via* Pd^{2+}-Promoted Cycloalkenylation Reaction

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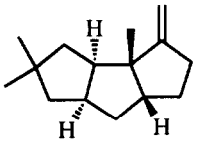
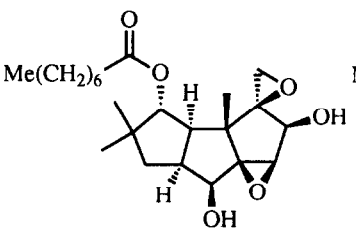
Abstract: Beginning with *trans*-2-methyl-4-cyclohexenecarboxylic acid (**9**), a total synthesis of linear triquinane sesquiterpene (±)-hirsutene (**1**) has been accomplished. An acid catalyzed intramolecular conjugate addition (**7**→**6a**) and a Pd^{2+}-promoted highly stereocontrolled cyclization (**5**→**4**) were utilized for the key step of the sequence. Interestingly, some synthetic intermediates exhibited cytotoxicity.

Introduction

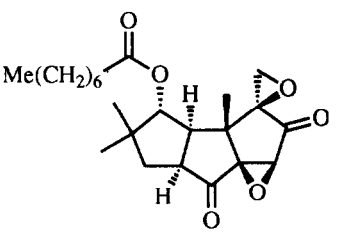
The mold metabolite hirsutene (**1**) was first isolated from the hydrocarbon extracts of fermented mycelium of *Coriolus consors*.[1] Its structure was determined through a combination of spectral analysis and original synthesis.[1] Hirsutene (**1**) is parent member of an important class of linear triquinanes and a biogenetic precursor of more oxygenated compounds such as coriolin B (**2**). Coriolin B (**2**) does not exhibit substantial biological activity whereas its derivative, diketocoriolin B (**3**), shows a pronounced cytotoxic activity.[2]



Hirsutene (**1**)



Coriolin B (**2**)



Diketocoriolin B (**3**)

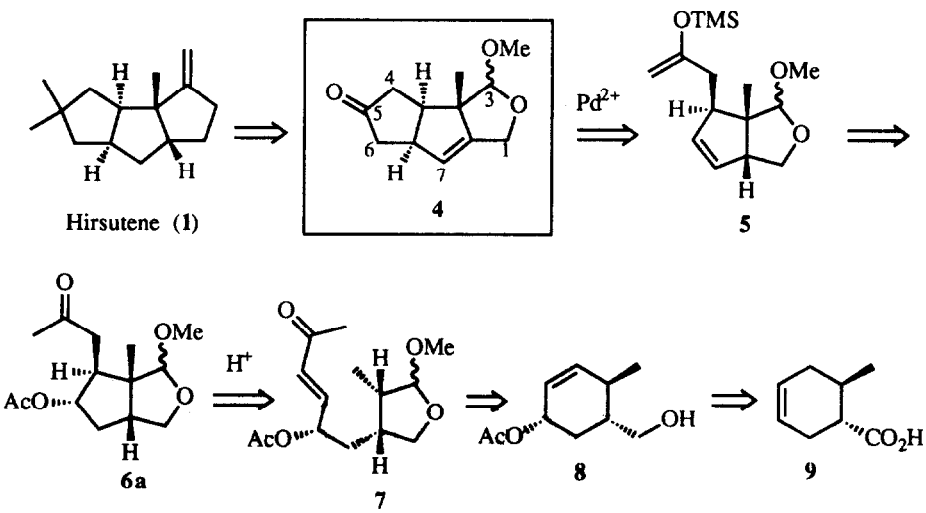
Hirsutene (**1**) has served as prototype for the synthesis of *cis, anti, cis* linear triquinanes and has frequently been used to illustrate new methods for construction of condensed cyclopentane rings.

Over the last 17 years much effort has been devoted to the synthesis of linear triquinane sesquiterpenes, however, there remains a conspicuous need of general methods to prepare both simple and complex congeners and flexible ones to prepare topographical relatives.[3] We herein embark upon a program to develop a unified strategy for the synthesis of linear condensed cyclopentanoids employing acid catalyzed intramolecular conjugate addition and a Pd^{2+}-promoted cycloalkenylation reaction as the key steps.

In addition, in order to find out novel antitumor agents which seem to rival or surpass diketocoriolin B (**3**) in terms of biological promise, the selected synthetic intermediates were screened for cytotoxicity activity against murine lymphoma L1210 cells and against the human epidermoid carcinoma KB cells.

Synthetic Strategy

We have devised a strategy for the synthesis of hirsutene (**1**) that would allow access to the various members of this family *via* a common synthetic intermediate, the tricyclic ketone **4** (Scheme I). Access to this key intermediate is provided through Pd^{2+}-promoted cycloalkenylation reaction of the olefinic silyl enol ether **5**, which is in turn available from an acid catalyzed intramolecular conjugate addition (**7**→**6a**) with undiminished diastereoselectivity. Pivot to the success of this total synthesis venture is the ready availability of the acetate **8** from *trans*-2-methyl-4-cyclohexenecarbocylic acid (**9**).[4]



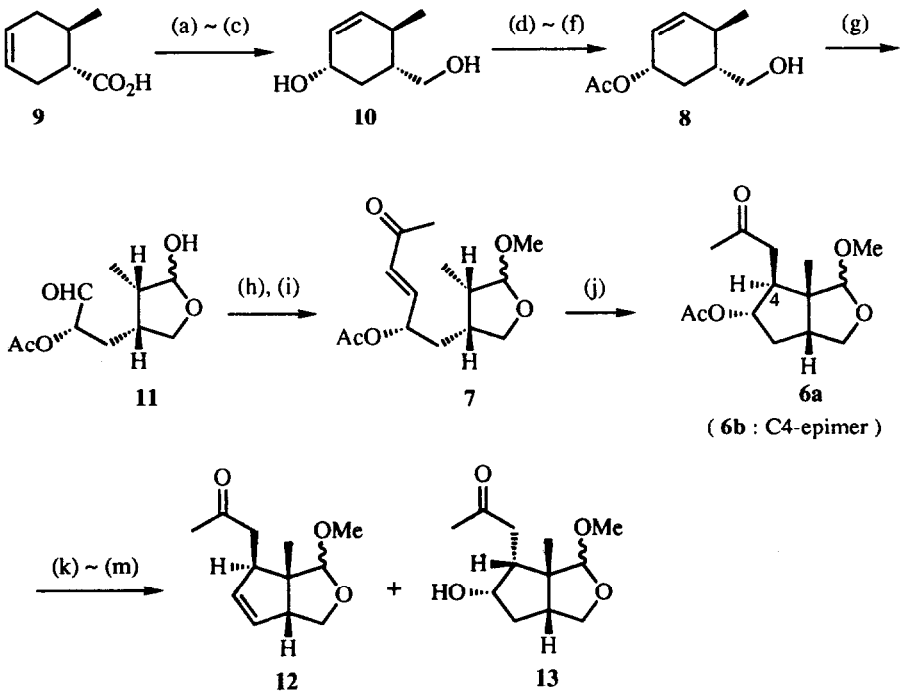
Scheme I

Results and Discussion

While we elected to commence our exploratory phase with the racemic **9**, the ready availability of its (1S, 2R)-enantiomer[5] could prove to be of great value toward the ultimate goal of synthesizing **1**.

Conversion of the acid **9** into the enone **7** was achieved *via* the reaction sequence summarized in Scheme II. The starting material, *trans*-2-methyl-4-cyclohexenecarboxylic acid (**9**), upon reaction with iodine and potassium iodide in the presence of sodium hydrogen carbonate gave rise to the corresponding iodolactone, and then subjected to an elimination reaction using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). After treatment of the resulted unsaturated lactone with lithium aluminum hydride (LAH) in tetrahydrofuran (THF), the diol **10** was obtained in 58% yield from **9**. Silylation of the primary hydroxyl group with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole followed by acetylation[6] of the secondary hydroxyl group afforded the acetate, which was converted into the alcohol **8** after desilylation (tetrabutylammonium fluoride in THF) (82% yield from **10**). Subsequent conversion to the aldehyde **11** was accomplished in 93% yield through ozonolysis of **8** and reductive work-up. Wittig olefination of **11** with 1-triphenylphosphoranylidene-2-propanone provided the corresponding enone, which was allowed to react with pyridinium *p*-toluenesulfonate (PPTS) at 50 °C in methanol, giving **7** in 69% yield from **11**. In order to construct the bicyclic compound **6a** diastereoselectively, the acid catalyzed conjugate addition[7] was attempted at room temperature for 10 h, proceeding nicely to provide the ketone **6a**, together with its C4-epimer **6b** in a ratio of 10 : 1 (95%). After hydrolysis of the above mixture

with lithium hydroxide, the corresponding alcohols were on the action of *o*-nitrophenyl selenocyanate and tributylphosphine,[8] converted into the selenide, oxidation of which with 30% hydrogen peroxide afforded the olefin **12** (66% from **6**), along with the recovered **13** (Scheme II).



(a) I_2, KI, $NaHCO_3$, CH_2Cl_2-H_2O (1:1), 0 °C, (b) DBU, THF, reflux, (c) LAH, THF, (d) TBSCl, imidazole, DMF, (e) Ac_2O, pyridine, DMAP, (f) $^nBu_4N^+F^-$, THF, (g) O_3, MeOH, -78 °C ; Me_2S, (h) Ph_3P=CHCOMe, $CHCl_3$, (i) PPTS, MeOH, 50 °C, (j) TsOH, CH_2Cl_2, (k) LiOH, MeOH-H_2O (3:1), 0 °C, (l) *o*-$NO_2PhSeCN$, $^nBu_3P$, THF, (m) 30% H_2O_2, THF, 0 °C → room temperature

Scheme II

The acid catalyzed conjugate addition of the enone **7** can be explained by protonation at the methoxyl group followed by elimination of methanol to give the oxonium intermediate **15**, in which the acidic proton is abstracted to provide **16**. The unstable dihydrofuran **16** can be smoothly converted into the ketones **6** by intramolecular conjugate addition followed by addition of methanol (Figure I).

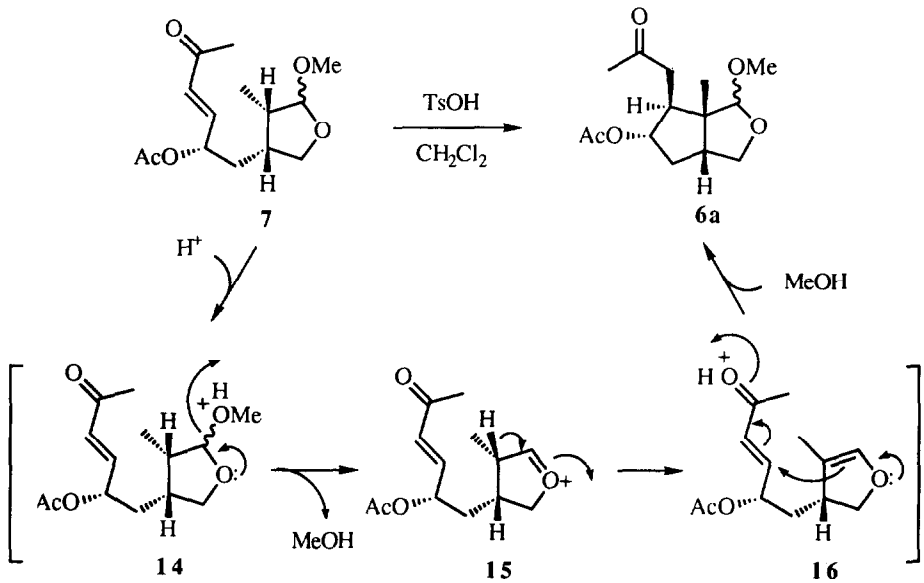


Figure I

The stereoselectivity of the above process in the intermediate **16** can be rationalized by considering the conformers **17a** and **17b**. The steric congestion between the olefinic hydrogen and the methyl group of dihydrofuran ring in the conformer **17b** makes it less favorable than the alternative conformer **17a** which gives rise to the desired product **6a** (Figure II).

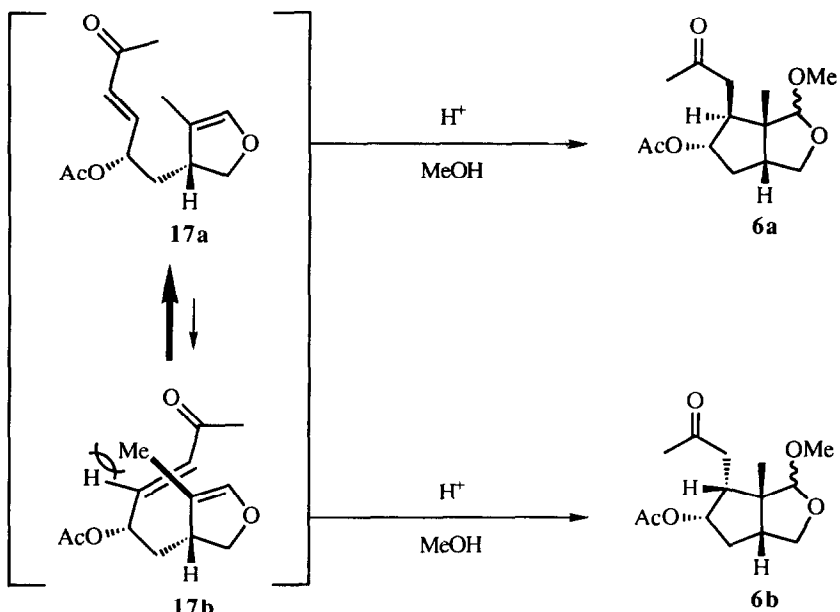
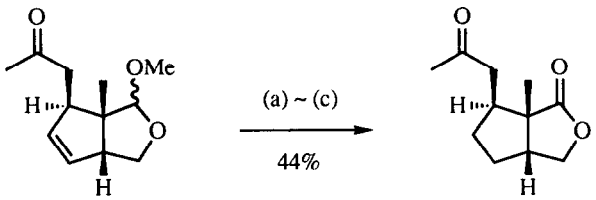


Figure II

Although the stereochemical assignment of **6a, 6b** and **12** was not possible at this moment, successful elaboration of olefin **12** to the known lactone **18**[7] definitely confirmed their stereochemistry as shown below (Scheme III).

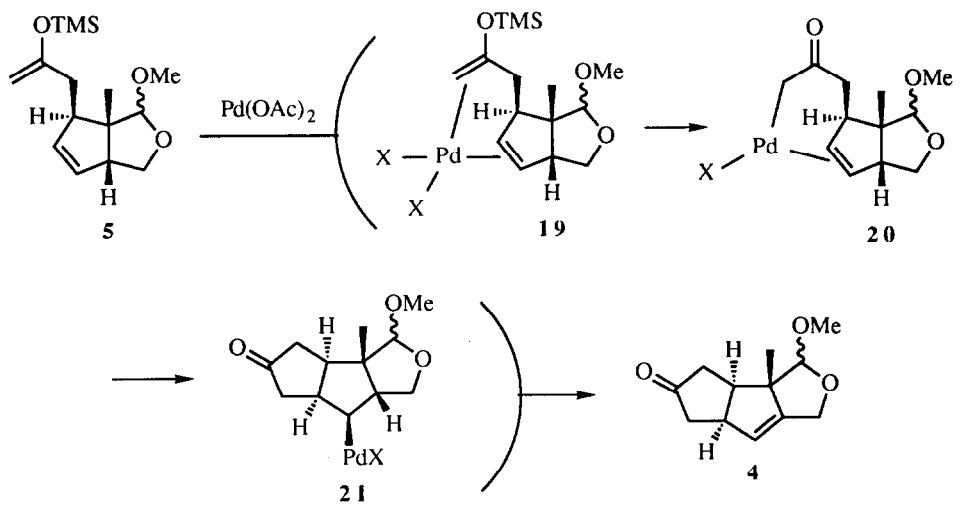


12 **18**

(a) 10% $HClO_4$, Me_2CO, 0 °C, (b) H_2, 10% Pd-C, EtOAc,
(c) PCC, NaOAc, CH_2Cl_2

Scheme III

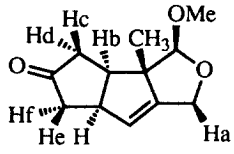
With convenient access to **12** secure, we then examined on the stereoselective Pd^{2+}-promoted cycloalkenylation[9] for the construction of the third ring. Upon treatment of the silyl enol ether **5** with palladium(II) acetate in acetonitrile-dichloromethane (1 : 1), the desired ketone **4** was produced in 99% yield. Mechanistically, we believe this reaction proceeds as shown in Figure III. The first step can be rationalized in term of coordination of the both double bonds of **5** to palladium. The resulting intermediate **19** forms the alkylpalladium complex **20** which rapidly cyclizes to give rise to the tricyclic intermediate **21**. This species then undergoes *syn* palladium β-hydride elimination.



5 **19** **20** **21** **4**

Figure III

Flash column chromatography of **4** on silica gel (4 : 1 hexane-EtOAc) provided two fractions. The first fraction gave **4a** (minor epimer), on the other hand the second one afforded **4b** (major epimer). Results of nuclear Overhauser experiments of **4b** confirm the assigned structure for the ketone **4**.



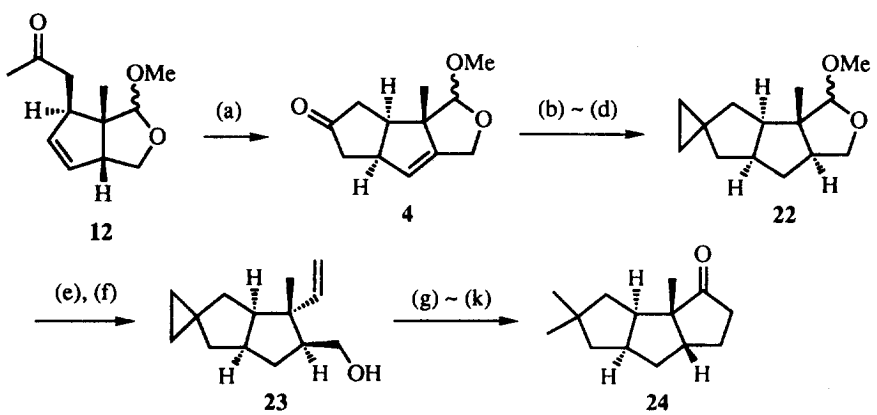
4b

NOE enhancements	
CH_3, Hc	10.0 %
CH_3, He	4.5 %
CH_3, Ha	5.4 %
Hf, Hd	23.0 %
Hf, Hb	6.9 %

The overall conversion of **9** into **4** was highly stereoselective and produced a functionalized tricycle in which the three contiguous stereogenic centers required for the eventual synthesis of (±)-**1** had been installed cleanly and efficiently.

With the efficient synthesis of the highly functionalized tricyclic ketone **4** realized, the stage was now set for the completion of the synthesis. Catalytic hydrogenation of **4** in the presence of 10% palladium-charcoal led quantitatively to the corresponding ketone, which was subjected to Wittig olefination ($Ph_3P^+MeBr^-$, ^nBuLi, 1,2-dimethoxyethane, reflux) followed by cyclopropanation[10] of the resulting olefin with diiodomethane and diethylzinc to furnish **22** in 50% yield from **4**. The ring opening of the tetracyclic compound **22** was next accomplished by sequential hydrolysis with 10% perchloric acid and Wittig olefination to give rise to the alcohol **23** (61% yield from **22**).

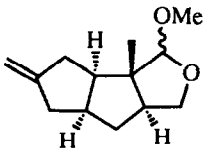
Finally, successive PCC oxidation in the presence of sodium acetate, Wacker oxidation,[11] aldol condensation[12] with epimerization, hydrogenation (84% yield from **23**)[13] and PCC oxidation provided a 74% yield[14] of the ketone **24**, which displayed spectrum properties identical with those reported[15] in a total synthesis of hirsutene (**1**), thus completing a formal synthesis of the latter (Scheme IV).[16]



(a) LDA, THF, -78 °C ; TMSCl ; $Pd(OAc)_2$, MeCN-CH_2Cl_2 (1:1), (b) H_2, 10% Pd-C, EtOAc, (c) $Ph_3P^+MeBr^-$, ^nBuLi, DME, reflux, (d) CH_2I_2, Et_2Zn, C_6H_6, (e) aq. $HClO_4$, Me_2CO, (f) $Ph_3P^+MeBr^-$, ^nBuLi, DME, reflux, (g) PCC, NaOAc, CH_2Cl_2, (h) $PdCl_2$, CuCl, O_2, DMF-H_2O (1:1), (i) $^nBu_4N^+OH^-$, THF-Et_2O-5% KOH (8:8:11), reflux, (j) H_2, PtO_2, NaOAc, AcOH, (k) PCC, NaOAc, CH_2Cl_2

Scheme IV

Our interest in exploiting this chemistry further was heightened upon finding that the following synthetic intermediates such as **22**, **25**, **26**, and **27** exhibit potent *in vitro* cytotoxic activity. As a result of testing of all the synthetic intermediates for cytotoxic properties, **22**, **25**, **26**, and **27** exhibited cytotoxicities against L1210 murine leukemia cells with IC_{50} values of 0.38, 6.6, 0.69, and 0.13 μg/mL and KB human epidermoid carcinoma cells with those of 5.6, 9.6, 5.1 and 5.8 μg/mL *in vitro*, respectively.



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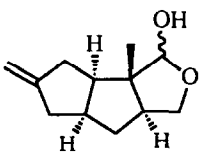

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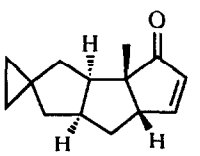


27

In conclusion, new and highly diastereocontrolled approach for the synthesis of hirsutene (**1**) has been developed. Our methodology based upon acid catalyzed conjugate addition and Pd^{2+}-promoted cycloalkenylation showed is believed to be an efficient tool in the synthesis of other complex linear triquinane sesquiterpene systems, such as coriolin B (**2**) and diketocoriolin B (**3**).

EXPERIMENTAL SECTION

General: Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled under argon from sodium benzophenone immediately prior to use. Dichloromethane (CH_2Cl_2), pyridine, acetonitrile (MeCN), and diisopropylamine were distilled under argon from CaH_2 and used immediately. Dimethylformamide (DMF) was distilled from 4 Å molecular sieves. The concentration of commercially available solution of n-butyllithium in hexanes was checked by titration using diphenylacetic acid.[17] All reactions involving organometallic reagents or strong bases (e.g., DL) were conducted under an argon atmosphere in dry flasks. Unless otherwise noted, reagents and solvents were added by syringe, and organic extracts were dried by being stirred over anhydrous $MgSO_4$, filtered through Celite, and concentrated under reduced pressure (aspirator) with the aid of a rotary evaporator. Chromatography was carried out using Merck 60 (230-400 mesh) silica gel according to the procedure described by Still.[18] Reactions and chromatography fractions were analyzed using precoated silica gel 60 F_{254} plates (Merck). Infrared spectra were recorded as films on NaCl plates unless otherwise noted. ^1H NMR spectra were measured as $CDCl_3$ solutions at 500 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane or relative to internal $CHCl_3$. *J* values are in hertz. Since all synthetic products were sufficiently pure by 500 MHz ^1H NMR spectral analyses, they were directly subjected to *in vitro* cytotoxicity assay.

6α-Hydroxy-4α-hydroxymethyl-3β-methylcyclohex-1-ene (10)

To a stirred mixture of the acid **9** (20.5 g, 146 mmol) and H_2O (150 mL) in CH_2Cl_2 (150 mL) were added I_2 (66.8 g, 263 mmol), KI (43.7 g, 263 mmol) and $NaHCO_3$ (43.7g, 520 mmol) at 0 °C. After being stirred at the same temperature for 0.5 h, to the mixture was added saturated $Na_2S_2O_3$ solution (300 mL) at 0 °C, then the resulting mixture was extracted with CH_2Cl_2 (300 mL). After the addition of pyridine (1 mL) to the

above extract, the organic layer was washed with brine, dried and evaporated to give the crude iodolactone (27.3 g) as needles, which was used directly in the next step without purification. IR: 1782 cm^{-1}. ^1H NMR: δ 1.14 (3H, d, *J*=7.2), 2.39 (1H, ddq, *J*=7.2, 6.8 and 2.0), 2.53 (1H, dd, *J*=5.8 and 2.0), 4.40 (1H, dd, *J*=4.5 and 3.7), 4.89 (1H, dd, *J*=5.8 and 3.7).

To a stirred solution of the crude iodolactone (27.3 g) in THF (100 mL) was added DBU (34 mL) at ambient temperature, and the mixture was refluxed for 0.5 h. After filtration, the filtrate was diluted with Et_2O (100 mL), then the ethereal layer was washed with brine. The organic layer was dried and evaporated to give a crude oil, which was distilled to afford the unsaturated lactone (12.0 g, 60% from **9**) as a colorless oil, bp 112 °C, 4 mmHg. IR: 1766 cm^{-1}. ^1H NMR: δ 1.19(3H, d, *J*=7.2), 4.73 (1H, d, *J*=5.5), 5.69-5.73 (1H, m), 6.15-6.19(1H, m). MS m/z: 138 (M^+). Anal. Calcd for $C_8H_{10}O_2$: C, 69.53; H, 7.30. Found: C, 69.34; H, 7.23.

To a stirred suspension of LAH (0.73 g, 19.2 mmol) in THF (20 mL) was added dropwise a THF solution (10 mL) of the above lactone (1.33 g, 9.60 mmol) at ambient temperature, and the mixture was stirred at room temperature for 0.5 h. After successive addition of H_2O (0.7 mL), 15% NaOH solution (0.7 mL), and H_2O (2.2 mL), followed by stirring for 0.5 h, the mixture was filtered through Celite and washed with Et_2O. Evaporation of the combined filtrate and washings gave a residue which was recrystallized from Et_2O to afford the diol **10** (1.3 g, 96%) as needles, mp 66-67 °C. IR: 3620 and 3433 cm^{-1}. ^1H NMR: δ 1.04 (3H, d, *J*=7.2), 2.18 (1H, ddq, *J*=7.2, 3.0 and 1.0), 3.61 (1H, dd, *J*=11.0 and 5.6), 3.75 (1H, dd, *J*=11.0 and 3.3), 4.34 (1H, br s), 5.61 (1H, ddd, *J*=10.0, 2.0 and 1.0), 5.68 (1H, d, *J*=10.0). MS m/z: 142 (M^+). Anal Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.59; H,10.06.

6α-Acetoxy-4α-hydroxymethyl-3β-methylcyclohex-1-ene (8)

To a stirred solution of the diol **10** (33.0 g, 232 mmol) in DMF (500 mL) were added successively imidazole (15.8 g, 232 mmol) and *tert*-butyldimethylsilyl chloride (34.9 g, 232 mmol). The mixture was stirred at room temperature for 0.7 h, diluted with brine (500 mL), and extracted with Et_2O (3×500 mL). The extracts were washed with brine, dried, and concentrated. Gravity column chromatography on silica gel provided two fractions. The first fraction (10:1 hexane-EtOAc) gave disilyl ether (15.0 g 18%), and the second fraction (4:1 hexane-EtOAc) gave the desired compound (41.3 g, 88%) as an oil. IR: 3601 and 3210 cm^{-1}. ^1H NMR: δ 0.02 (6H, s), 0.87 (9H, s), 3.53 (1H, dd, *J*=10.0 and 5.8), 3.65 (1H, dd, *J*=10.0 and 3.0), 5.49 (1H, dd, *J*=10.0 and 1.5), 5.59 (1H, d, *J*=10.0). MS m/z: 256 (M^+). Anal. Calcd for $C_{14}H_{28}O_2Si$: C, 65.57; H, 11.00. Found: C, 65.32; H, 11.00.

A mixture of the alcohol (2.10 g, 8.20 mmol), acetic anhydride (20 mL, 212 mmol), DMAP (*ca.* 5 mg), and pyridine (20 mL, 247 mmol) was stirred at room temperature for 1 h. The reaction mixture was diluted with saturated $KHSO_4$ solution (200 mL), then the resulting mixture was extracted with Et_2O (3×100 mL). The combined ethereal layers were washed with saturated $NaHCO_3$ solution, brine, dried, and evaporated to leave an oil. Purification by column chromatography on silica gel with 100:5 hexane-EtOAc gave the acetate (2.3 g, 93%) as a colorless oil. IR: 1738 cm^{-1}. ^1H NMR: δ 0.02 (6H, s), 0.87 (9H, s), 2.04 (3H, s), 3.56 (1H, dd, *J*=10.0 and 5.8), 3.63 (1H, dd, *J*=10.0 and 3.2), 5.35-5.36 (1H, m), 5.52 (1H, dd, *J*=10.0 and 1.8), 5.61 (1H, dt, *J*=10.0 and 1.8). MS m/z: 298 (M^+). Anal. Calcd for $C_{16}H_{30}O_3Si$: C, 64.39; H, 10.14. Found: C, 64.56; H, 10.22.

To a stirred solution of the above acetate (1.00 g, 3.20 mmol) in THF (20 mL) was added dropwise $^nBu_4N^+F^-$ (4.8 mL, 4.80 mmol) at 0 °C, then the mixture was continued to stir at room temperature for 1 h. To the mixture was added brine (50 mL), and the resulting mixture was extracted with Et_2O (2×30 mL). The

combined ethereal layers were dried and evaporated to give rise to a crude product, which was subjected to column chromatography on silica gel with 2:1 hexane-EtOAc to afford the alcohol **8** (600 mg, 100%) as a colorless oil. IR: 3424 and 1732 cm^{-1}. ^1H NMR: δ 1.05 (3H, d, *J*=7.2), 2.06 (3H, s), 3.61 (1H, dd, *J*=10.8 and 5.5), 3.74 (1H, dd, *J*=10.8 and 3.1), 5.37-5.39 (1H, m), 5.58 (1H, d, *J*=10.0), 5.66 (1H, dd, *J*=10.0 and 1.9). MS m/z: 184 (M^+). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.18; H, 8.76. Found: C, 65.07; H, 8.99.

***4α-(2α-Acetoxy-5-oxohex-3-enyl)-3α-methyl-2-methoxy-2,3,4,5-tetrahydrofuran* (7)**

The olefin **8** (550 mg, 3.00 mmol) was treated with ozone in MeOH (15 mL) at -78 °C until a blue color persisted. The reaction mixture was purged with nitrogen. Dimethyl sulfide (0.65 mL, 8.90 mmol) was added at -78 °C and the reaction mixture allowed to warm to room temperature. Following removal of the volatiles *in vacuo*, the residue was purified by flash column chromatography (3:10 hexane-EtOAc) to give rise to the aldehyde **11** (600 mg, 93%) as a *ca.* 4:1 mixture of C3-epimers. IR: 3410 and 1731 cm^{-1}. ^1H NMR: δ 0.89 (2.4 H, d, *J*=7.0), 0.99 (0.6H, d, *J*=7.0), 2.12 (2.4H, s), 2.16 (0.6H, s), 3.83 (1H, dd, *J*=11.0 and 11.0), 3.84 (1H, dd, *J*=11.0 and 11.0), 4.93-4.98 (1H, m), 4.98 (0.2H, s), 5.03 (0.8H, s), 9.66 (0.2H, d, *J*=1.8), 9.67 (0.8H, d, *J*=1.8).

To a stirred solution of this aldehyde **11** (187 mg, 0.900 mmol) dissolved in ethanol-free $CHCl_3$ (freshly distilled from $CaCl_2$, 3 mL) at ambient temperature was added 1-triphenylphosphoranylidene-2-propanone (1.40 g, 4.30 mmol). The resulting mixture was stirred at room temperature for 10 h. After removal of the solvent, the residue was diluted with Et_2O (30 mL) and the resulting precipitate was filtrated through Celite. The filtrate was concentrated to give an oil, which was chromatographed on SiO_2 with 10:3 benzene-acetone to afford the desired enone (204 mg) as a *ca.* 4:1 mixture of C3-epimers, together with a slight amount of triphenylphosphine oxide, which was used in the next step without further purification. IR: 3602, 3348, 1740 and 1682 cm^{-1}. ^1H NMR: δ 0.89 (2.4H, d, *J*=7.2), 0.97 (0.6H, d, *J*=7.2), 2.11(0.6H, s), 2.12 (2.4H, s), 2.26 (0.6H, s), 2.28 (2.4H, s), 3.57 (1H, dd, *J*=9.5 and 8.0), 4.12 (1H, dd, *J*=8.0 and 8.0), 5.08 (0.2H, s), 5. 13 (0.8H, s), 5.35-5.43 (1H, m), 6.19 (1H, dd, *J*=16.0 and 1.0), 6.65 (1H, dd, *J*=16.0 and 5.5).

To a solution of the crude enone (204 mg) in freshly distilled MeOH (30 mL) at room temperature was added pyridinium *p*-toluenesulfonate (*ca.* 10 mg). After being stirred at 50 °C for 4 h, the solvent was removed under reduced pressure. The residual oil was purified by flash chromatography (10:1 benzene-acetone) to afford the enone **7** (161 mg, 69% from **11**) as a *ca.* 4:1 mixture of C3-pimers. IR: 1743 and 1683 cm^{-1}. ^1H NMR: δ 0.90 (2.4H, d, *J*=7.2), 0.94 (0.6H, d, *J*=7.2), 2.04 (0.6H, s), 3.32 (2.4H, s), 3.42 (0.6H, s), 3.59 (1H, dd, *J*=9.5 and 8.3), 4.03 (1H, t, *J*=8.3), 4.32 (0.2H, d, *J*=1.0), 4.61 (0.8H, s), 5.34-5.38 (1H, m), 6.18 (1H, dd, *J*=16.0 and 1.0), 6.64 (1H, dd, *J*=16.0 and 5.5). MS m/z: 270 (M^+). HRMS Calcd for $C_{14}H_{22}O_5$: 270.1467. Found: 270.1468.

***5α-Acetoxy-3,3a,4,5,6,6aβ-hexahydro-3-methoxy-3aβ-methyl-4-(2-oxopropyl)-1H-cyclopenta[c]furan* (6)**

To a stirred solution of the enone **7** (606 mg, 2.24 mmol) in CH_2Cl_2 (35 mL) was added *p*-toluenesulfonic acid monohydrate (*ca.* 15 mg) at room temperature, then the mixture was continued to stir at the same temperature for 10 h. Saturated $NaHCO_3$ solution (50 mL) was added to the above mixture, and the resulting mixture was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with brine, dried, and evaporated to yield a crude **6**, which was chromatographed with 10:1 benzene-acetone to give rise to the bicyclic ketone **6** (575 mg, 95%) as a *ca.* 4:1 mixture of C3-epimers. IR: 1733 and 1712 cm^{-1}. ^1H NMR: δ

0.94 (2.4H, d, *J*=7.2), 1.00 (0.6H, d, *J*=7.2), 2.01 (2.4H, s), 2.02 (0.6H, s), 2.19 (0.6H, s), 2.27 (2.4H, s), 3.33 (2.4H, s), 3.42 (0.6H, s), 3.57 (0.8H, dd, *J*=9.0 and 2.7), 3.59 (0.2H, dd, *J*=9.0 and 7.0), 3.98 (0.8H, dd, *J*=9.0 and 7.0), 4.03 (0.2H, dd, *J*=9.0 and 9.0), 4.44 (0.2H, s), 4.74 (0.8H dt, *J*=9.8 and 6.7), 4.80 (0.8H, s), 4.82 (0.2H, dt, *J*=9.8 and 6.5). MS m/z: 270 (M^+). HRMS Calcd for $C_{14}H_{22}O_5$: 270. 1467 (M^+). Found: 270.1467.

***3-Methoxy-3aβ-methyl-4β-(2-oxopropyl)-3,3a,4,6aβ-tetrahydro-1H-cyclopenta[a]furan* (12)**

To a stirred solution of the ketone **6** (31.3 mg, 0.100 mmol) in MeOH-H_2O (2.4 mL, 3:1) was added lithium hydroxide monohydrate (42.0 mg, 1.00 mmol) at 0 °C. After 10 min of stirring at the same temperature, the mixture was diluted with brine (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried and evaporated to give an oil. The residual oil was purified by flash chromatography (10:3 benzene-acetone) to give the alcohol (29.3 mg, 96%) as a *ca.* 4:1 mixture of C3-epimers.

IR: 3450 and 1712 cm^{-1}. ^1H NMR: δ 0.94 (2.4H, s), 1.01 (0.6H, s), 2.23 (0.6H, s), 2.25 (2.4H, s), 2.60 (1H, dd, *J*=17.1 and 9.0), 2.70 (1H, dd, *J*=17.1 and 4.6), 3.33 (2.4H, s), 3.42 (0.6H, s), 3.63 (1H, dd, *J*=9.0 and 3.1), 3.80-3.92 (1H, m), 4.01 (1H, dd, *J*=9.0 and 7.5), 4.42 (0.2H, s), 4.64 (0.8H, s). MS m/z: 228 (M^+). HRMS Calcd for $C_{12}H_{20}O_4$: 228.1362 (M^+). Found: 228.1362.

To a solution of the above alcohol (1.09 g, 4.79 mol) and *o*-nitrophenyl selenocyanate (1.80 g, 7.89 mmol) dissolved in THF (48 mL) at room temperature was added dropwise tri-n-butylphosphine (from a fresh bottle of reagent-grade solvent, 2.5 mL, 10.0 mmol). The reaction mixture was stirred at the same temperature for 4.5 h and the solvent was removed under reduced pressure. The residual oil was purified by flash chromatography (3:1 hexane-EtOAc) to give the selenide (2.34 g) together with a small amount of inseparable compound.

To a stirred solution of the above selenide in THF (57 mL) was added 30% hydrogen peroxid (5.9 mL, 57.8 mmol) at 0 °C. The resulting solution was stirred at the same temperature for 1 h then allowed to come to room temperature. After 3 h of stirring, the mixture was diluted with H_2O (30 mL) and extracted with Et_2O (2×30 mL). The combined ethereal layers were washed with saturated Na_2CO_3 solution, brine, dried and evaporated to yield an oil, which was subjected to column chromatography with 10:3 hexane-EtOAc to provide the olefin **12** (660 mg, 66% from the above alcohol) as a *ca.* 4:1 mixture of C3-epimers and the alcohol **13** (99 mg, 9%). Each epimers was easily separated by careful flash column chromatography.

major epimer ; IR: 1715 cm^{-1}. ^1H NMR: δ 0.98 (3H, s), 2.17 (3H, s), 2.47 (1H, dd, *J*=17.5 and 7.0), 2.65 (1H, dd, *J*=17.5 and 8.0), 2.80 (1H, dddd, *J*=8.0, 2.5, 2.0 and 1.0), 3.13 (1H, dddd, *J*=8.0, 7.0, 2.0 and 2.0), 3.36 (3H, s), 3.57 (1H, dd, *J*=8.5 and 2.5), 3.97 (1H, dd, *J*=8.5 and 7.5), 4.83 (1H, s), 5.47 (1H, ddd, *J*=6.0, 2.0 and 1.0), 5.63 (1H, ddd, *J*=6.0, 3.0 and 2.0). MS m/z: 178 (M^+ -32). HRMS Calcd for $C_{11}H_{14}O$: 178.0994 (M^+ -32). Found: 178.0997.

minor epimer ; IR: 1715 cm^{-1}. ^1H NMR: δ 0.98 (3H, s), 2.17 (3H, s), 2.32 (1H, dd, *J*=16.5 and 8.5), 2.59 (1H, dd, *J*=16.5 and 6.0), 2.89 (1H, dddd, *J*=8.5, 6.0, 2.0 and 2.0), 3.37 (3H, s), 3.51 (1H, dddd, *J*=8.0, 5.5, 2.0 and 2.0), 3.64 (1H, dd, *J*=8.5 and 5.5), 4.07 (1H, dd, *J*=8.5 and 8.0), 4.52 (1H, s), 5.54 (1H, ddd, *J*=6.0, 2.0 and 1.5), 5.64 (1H, ddd, *J*=6.0, 2.0 and 1.5).

13: ^1H NMR: δ 0.93 (3H, s), 2.22 (3H, s), 3.32 (3H, s), 4.63 (1H, s).

12 → 18

To a stirred solution of the acetal **12** (51.0 mg, 0.243 mmol) in acetone (6 mL) was added 10% perchloric acid (2 mL) at 0 °C, whereupon the mixture was continued to stir for 1 h. The reaction mixture was extracted with EtOAc, and then the organic layer was washed with brine, dried and evaporated to give an oil, which was chromatographed. Elution with 10 : 3 mixture of C_6H_6-acetone afforded the olefin (22.0 mg, 46%) as a colorless oil.

IR: 3400 and 1720 cm^{-1}. ^1H NMR: δ 1.00 (3H, s), 2.20 (3H, s), 5.40-5.70 (2H, m). MS m/z: 178 (M^+-18). HRMS Calcd for $C_{11}H_{14}O_2$: 178.0994. Found: 178.0993.

A mixture of the above olefin (22.0 mg, 0.112 mmol) and 10% palladium-charcoal (5.0 mg) in EtOAc (2 mL) was stirred under hydrogen until the absorption has been ceased. After filtration, the filtrate was evaporated and the residue was chromatographed. Elution with 3 : 4 hexane-EtOAc furnished the hemiacetal (22.0 mg, 99%) as a colorless oil.

IR: 3400 and 1710 cm^{-1}. ^1H NMR: δ 1.00 (3H, s), 2.10 (3H, s). MS m/z: 180 (M^+-18). HRMS Calcd for $C_{11}H_{16}O_2$: 180.1150. Found: 180.1132.

A mixture of the above hemiacetal (17.0 mg, 0.0859 mmol), PCC (35.0 mg, 0.162 mmol) and NaOAc (18.0 mg, 0.220 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 1.5 h. After dilution with Et_2O, the resulting mixture was filtered and the filtrate was evaporated. The crude product was chromatographed. Elution with 3:4 hexane-EtOAc gave rise to the lactone **17** (16.4 mg, 44% yield from **12**) as a colorless oil.

IR: 1760 and 1710 cm^{-1}. ^1H NMR: δ 1.18 (3H, s), 2.17 (3H, s), 1.30-1.56 (4H, m), 2.17 (3H, s), 2.30 (1H, dd, *J*=16.5 and 10.5), 2.52-2.66 (2H, m), 2.76 (1H, dd, *J*=16.5 and 3.3), 4.00 (1H, dd, *J*=9.3 and 5.4), 4.42 (1H, dd, *J*=9.3 and 8.4). MS m/z: 196 (M^+). HRMS Calcd for $C_{11}H_{16}O_3$: 196.1099. Found: 196.1104.

***1,3bα,4,5,6,6aα-Hexahydro-3-methoxy-3aβ-methyl-5-oxopentaleno[1,2-c]furan* (4)**

To a stirred solution of LDA, prepared from diisopropylamine (0.14 mL, 0.74 mmol) and n-butyllithium (10% solution in hexane, 0.48 mL, 0.74 mmol) in THF (5 mL), at -78 °C was added dropwise a solution of the olefin **12** (104 mg, 0.495 mmol) in THF (3 mL), and the mixtrure was then stirred for 1 h. After addition of chlorotrimethylsilane (freshly distilled from CaH_2, 0.18 mL, 0.743 mmol) at -78 °C, the mixture was allowed to warm to room temperature over a period of 1 h. A solution of this silyl enol ether dissolved in CH_2Cl_2-MeCN (6 mL, 1:1) was added dropwise to a stirred solution of $Pd(OAc)_2$ (167 mg, 0.743 mmol) dissolved in MeCN (4 mL). The mixture was continued to stir at room temperature for 19 h. The reaction mixture was filtrated through Celite, then the filtrate was concentrated to give an oil, which was subjected to column chromatography with 4:1 hexane-EtOAc to give rise to the ketone **4** (84.0 mg, 99%) as a *ca.* 4:1 mixture of C3-epimers. Each epimers was separated by flash column chromatography.

minior epimer ; IR: 1730 cm^{-1}. ^1H NMR: δ 1.02 (3H, s), 2.07 (1H, ddd, *J*=19.5, 9.3 and 1.5), 2.35 (1H, ddd, *J*=19.5, 9.8 and 1.5), 2.45 (1H, br d, *J*=19.0), 2.54 (1H, br dd, *J*=19.0 and 9.8), 3.29-3.37 (1H, m), 3.61-3.70 (1H, m), 4.26-4.34 (2H, m), 5.66-5.69 (1H, m).

major epimer ; IR: 1730 cm^{-1}. ^1H NMR: δ 0.98 (3H, s), 2.08 (1H, ddd, *J*=19.2, 8.9 and 1.0), 2.37 (1H, ddd, *J*=19.2, 9.8 and 1.0), 2.49 (1H, br d, *J*=19.2), 2.53 (1H, br dd, *J*=19.2 and 10.0), 2.89 (1H, ddd, *J*=10.0, 8.9 and 1.0), 3.57-3.65 (1H, m), 4.28 (1H, br d, *J*=12.0), 4.46 (1H, ddd, *J*=12.0, 1.8 and 1.2), 5.63-5.66 (1H, m). MS m/z: 280 (M^+). HRMS Calcd for $C_{12}H_{16}O_3$: 208.1100. Found: 208.1123.

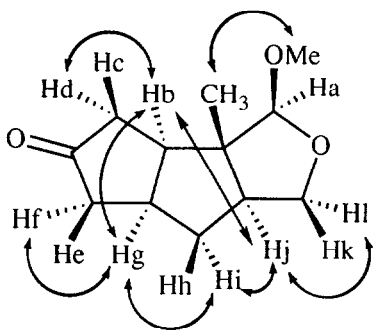
***3-Methoxy-3aβ-methyl-5-methylidene-1,3bα,4,5,6,6aα,7,7aα-octahydropentaleno[1,2-c]-furan* (25)**

A mixture of the ketone **4** (552 mg, 2.51 mmol) and 10% palladium-charcoal (*ca.* 10 mg) in EtOAc (25 mL) was stirred under an atmosphere of hydrogen until absorption of hydrogen had ceased. After filtration, the filtrate was evaporated and the residue was chromatographed. Elution with 4:1 hexane-EtOAc yielded the ketone (525 mg, 100%) as a *ca.* 4:1 mixture of C3-epimers. By flash column chromatography each epimers was separated.

minor epimer ; IR: 1730 cm^{-1}. ^1H NMR: δ 1.13 (3H, s), 1.55 (1H, ddd, *J*=13.5, 9.0 and 8.0), 1.73 (1H, ddd, *J*=13.5, 8.0 and 2.3), 2.08-2.17 (2H, m), 2.21-2.29 (1H, m), 2.35-2.43 (1H, m), 2.82-2.89 (1H, m), 2.98-3.06 (1H, m), 3.35 (3H, s), 3.54 (1H, dd, *J*=8.8 and 7.5), 4.13 (1H, dd, *J*=8.8 and 8.8), 4.52 (1H, s).

major epimer ; IR: 1730 cm^{-1}. ^1H NMR: δ 1.08 (3H, s, CH_3), 1.68 (1H, ddd, *J*=13.5, 10.5 and 7.5, Hi), 1.86 (1H, ddd, *J*=13.5, 7.5 and 1.5, Hh), 2.15 (1H, br d, *J*=19.0, He), 2.21 (1H, dd, *J*=19.0 and 9.0, Hc), 2.30 (1H, dd, *J*=19.0 and 9.0, Hd), 2.36 (1H, dddd, *J*=7.5, 7.5, 3.0 and, 1.5Hj), 2.40 (1H, ddd, *J*=19.0, 8.5 and 1.0, Hf), 2.56 (1H, ddd, *J*=9.0, 9.0 and 9.0, Hb), 2.91 (1H, dddd, *J*=19.0, 9.0, 9.0 and 2.1, Hg), 3.35 (3H, s, OMe), 3.57 (1H, dd, *J*=8.5 and 3.0, Hk), 4.08 (1H, dd, *J*=8.5 and 7.5, Hl). 4.60 (1H, s, Ha). MS m/z: 209 (M^+-1). HRMS Calcd for $C_{12}H_{17}O_3$ (M^+-1): 209.1178. Found: 209.1180.

An equivocal answer to the stereochemistry of major epimer of the above ketone was available from ^1H NMR spectral analysis



NOESY correlations of major epimer of the above ketone

A stirring suspension of methyltriphenylphosphonium bromide (735 mg, 2.06 mmol) in DME (freshly distilled from CaH_2, 6 mL) was treated dropwise with n-butyllithium (10% hexane solution, 1.3 mL, 2.06 mmol) at ambient temperature. After 1 h of reflux, the mixture was cooled to room temperature. This orange-brown ylide solution was treated dropwise with a DME solution (3 mL) of the above ketone (54 mg, 0.257 mmol). The mixture was refluxed for 3 h, at which time the mixture was diluted with Et_2O-hexane (10 mL, 10:1) to give a slurry, which was triturated with hexane (20 mL). The solid was removed though Celite, then the organic layers were concentrated to leave an oil. Column chromatography (30:1 hexane-EtOAc) yielded the olefin **25** (28.0 mg, 57%) as a *ca.* 7:3 mixture of C3-epimers, together with the starting material (4.0 mg, 5%). ^1H NMR: δ 1.06 (2.1H, s), 1.10 (0.9H, s), 1.46-1.64 (2H, m), 1.71 (1H, ddd, *J*=14.5, 8.0 and 2.0), 2.08-2.14 (1H, m), 2.24-2.34 (4H, m), 2.64-2.79 (1H, m), 3.33 (0.9H, s), 3.34 (2.1H, s), 3.50-3.54 (1H, m), 4.04

(1H, ddd, *J*=14.0, 8.5 and 8.5), 4.46 (0.29H, s), 4,54 (0.71H, s), 4.76-4.79 (1H, m), 4.82-4.85(1H, m). MS m/z: 177 (M^+-31). HRMS Calcd for $C_{12}H_{17}O$ (M^+-31): 177.1279. Found: 177.1286.

***3-Methoxy-3aβ-methyl-1,3bα,4,5,6,6aα,7,7aα-octahydro-5-spirocyclopropylpentaleno[1,2-c]furan* (22)**

To a stirred solution of the olefin **25** (59.0 mg, 0.284 mmol) and diiodomethane (0.030 mL, 0.372 mmol) in freshly distilled benzene (6 mL) was added slowly diethylzinc (0.30 mL, 0.351 mmol), then the mixture was stirred at the same temperature for 0.5 h. To the mixture was added 10% HCl solution (6 mL), then the resulting mixture was extracted with benzene (6 mL). The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried and evaporated to give an oil, which was chromatographed. Elution with 50:1 benzene-acetone afforded the compound **22** (55 mg, 87%) as an oil. ^{1}H NMR: δ 0.29-0.37 (2H, m), 0.42-0.52 (2H, m), 1.06 (2.25H, s), 1.07 (0.75H, s), 1.28-1.43 (6H, m), 1.60-1.75 (4H, m), 2.25-2.38 (1H, m), 2.65-2.80 (1H, m), 3.34 (3H, s), 3.53 (0.75H, dd, *J*=8.3 and 4.0), 3.60 (0.25H, dd, *J*=8.3 and 5.6), 4.04 (1H, dd, *J*=8.3 and 8.3), 4.46 (0.25H, s) and 4.55 (0.75H, s). MS m/z: 221 (M^+-1). HRMS Calcd for $C_{14}H_{21}O_2$ (M^+-1): 221.1542. Found: 221.1506.

***1α-Ethenyl-2β-hydroxymethyl-1β-methyl-5-spirocyclopropyl-3aα,6aα-bicyclo[3.3.0]octane* (23)**

To a stirred solution of **22** (95.0 mg, 0.428 mmol) in acetone (4 mL) were added H_2O (6 mL) and 10% perchloric acid (4 mL) at 0 °C, then the mixture was continued to stir at the same temperature for 1 h. After 1.5 h of stirring at room temperature, the mixture was extracted with EtOAc (2×10 mL). The organic layers were washed with brine (10 mL), dried and evaporated to give an oil, which was subjected to column chromatography with 20:1 benzene-acetone to give rise to the hemiacetal (54.0 mg, 79%, based on recovered starting material) as a *ca.* 2:1 mixture of C3-epimers, together with **22** (22 mg). IR ($CHCl_3$): 3400 cm^{-1}. ^{1}H NMR: δ 0.29-0.37 (2H, m), 0.43-0.51 (2H, m), 1.06 (1H, s), 1.08 (2H, s), 1.27 (0.33H, dd, *J*=12.8 and 7.9), 1.33 (0.67H, dd, *J*=12.8 and 8.6), 1.41 (0.67H, dd, *J*=12.8 and 3.7), 1.45 (0.33H, dd, *J*=12.8 and 4.3), 1.63-1.80 (3H, m), 2.32-2.48 (2H, m), 2.71-2.85 (2H, m), 2.95 (1H, br d, *J*=3.7), 3.55 (0.67H, dd, *J*=8.6 and 4.3), 3.76 (0.33H, dd, *J*=8.5 and 4.9), 4.02 (0.33H, dd, *J*=8.5 and 7.3), 4.18 (0.67H, dd, *J*=7.9 and 7.9), 4.97 (0.33H, d, *J*=3.7), 5.06 (0.67H, d, *J*=3.7). MS m/z: (M^+-1). HRMS Calcd for $C_{13}H_{19}O$ (M^+-1): 207.1385. Found: 207.1365.

A stirring suspension of methyltriphenylphosphonium bromide (398 mg, 1.12 mmol) in DME (freshly distilled from CaH_2, 10 mL) was treated dropwise with n-buthyllithium (10% hexane solution, 0.71 mL, 1.12 mmol) at ambient temperature. After 1 h of reflux, the mixture was cooled to room temperature. This orange-brown ylide solution was treated dropwise with a DME solution (2 mL) of the above hemiacetal (29.0 mg, 0.139 mmol). After 1 h of stirring at room temperature, the mixture was heated under reflux for 1.5 h. The mixture was diluted with Et_2O-hexane (10 mL, 10:1) to give a slurry, which was triturated with hexane (20 mL). The solid was removed through Celite, then the organic layers were concentrated to leave an oil. Flash chromatography (20:1 benzene-acetone) yielded the olefin **23** (22 mg, 77%) as an oil. IR ($CHCl_3$): 3400 cm^{-1}. ^{1}H NMR: δ 0.26-0.33 (2H, m), 0.43-0.50 (2H, m), 1.10 (3H, s), 1.21 (1H, ddd, *J*=12.8, 8.6 and 1.2), 1.49 (1H, dd, *J*=12.8 and 6.7), 1.54-1.60 (1H, m), 1.61-1.81 (3H, m), 2.03-2.10 (1H, m), 2.40-2.47 (1H, m), 2.68-2.77 (1H, m), 3.49 (1H, dd, *J*=11.0 and 7.9), 3.66 (1H, dd, *J*=11.0 and 5.5), 4.98 (1H, dd, *J*=11.6 and 1.2), 4.99 (1H, dd, *J*=17.1 and 1.2), 5.91 (1H, dd, *J*=17.1 and 11.6). MS m/z: 206 (M^+). HRMS Calcd for $C_{14}H_{22}O$: 206.1671. Found: 206.1652.

***1,2,3,3bα,4,5,6,6aα,7,7aβ-Decahydro-3a-hydroxy-3aβ,5,5-trimethyl-3H-cyclopenta[a]-pentalene*(29)**

To a stirred mixture of the alcohol **23** (83.0 mg, 0.403 mmol), Florisil® (180 mg), and NaOAc (66 mg, 0.806 mmol) in CH_2Cl_2 (4 mL) was added PCC (174 mg, 0.806 mmol) at ambient temperature. The resulting mixture was continued to stir at room temperature for 6 h. Filtration, followed by evaporation of the filtrate, gave a residue, which was used in the next step without purification. IR ($CHCl_3$): 1715 cm^{-1}. ^1H NMR (300 MHz): δ 0.30-0.35 (2H, m), 0.45-0.50 (2H, m), 1.23 (3H, s), 1.26-1.33 (1H, m), 1.43-1.50 (2H, m), 1.62-1.70 (2H, m), 2.31 (1H, ddd, *J*=15.3, 11.0 and 10.2), 2.50 (1H, dd, *J*=7.9 and 7.9), 2.66 (1H, ddd, *J*=17.3, 7.9 and 2.9), 2.77-2.92 (1H, m), 5.92 (1H, ddd, *J*=17.3, 11.1 and 1.3), 5.04 (1H, dd, *J*=17.3 and 1.3), 5.05 (1H, dd, *J*=11.1 and 1.3), 9.61 (1H, d, *J*=3.0). MS m/z: 204 (M^+). HRMS Calcd for $C_{14}H_{20}O$: 204.1514. Found: 204.1549.

The reactor was charged with $PdCl_2$ (71.0 mg, 0.403 mmol), CuI (160 mg, 1.61 mmol), DMF (2.5 mL) and H_2O (2.5 mL). Oxygen was passed into the solution for 2 h, then a DMF solution (1 mL) of the above aldehyde was dropwise.The resulting mixture was stirred at room temperature for 18 h with oxygen being bubbled through the mixture. The mixture was diluted with H_2O (4 mL) and extracted with Et_2O (2×10 mL). The ethereal layers were washed with brine (10 mL), dried and evaporated to give rise to the crude keto aldehyde, which without further purification was used in the following reaction.

To a stirred solution of the above keto aldehyde, Et_2O (8 mL), THF (8 mL) and 5% KOH solution (11 mL) was added 40% $^nBu_4NOH$ solution (9 drops) at room temperature. After 25 h of reflux, the mixture was diluted with H_2O (11 mL) and extracted with Et_2O (2×20 mL). The ethereal layers were washed with brine, dried and evaporated to leave an oil, which was chromatographed with Et_2O to afford the enone **27**. This material was immediately used in the next step. IR ($CHCl_3$): 1680 cm^{-1}. ^1H NMR (300 MHz): δ 0.27-0.54 (4H, m), 1,11 (3H, s), 1.21-1.36 (2H, m), 1.63-1.95 (4H, m), 2.20-2.36 (1H, m), 2.51-2.60 (1H, m), 2.96-3.33 (1H, m), 6.12 (1H, dd, *J*=5.5 and 1.8), 7.50 (1H, dd, *J*=5.5 and 2.9).

A mixture of the enone, NaOAc (3.3 mg, 0.403 mmol), PtO_2 (*ca.* 5 mg) in AcOH (0.3 mL) was stirred for 2 days at room temperature under hydrogen. H_2O (0.3 mL) was added to the above mixture, and then the resulting mixture was basified to pH 8 with saturated K_2CO_3 solution at 0 °C. The basic solution was extracted with Et_2O (2×10 mL). The ethereal layers were washed with brine, dried and evaporated to yield an oil, which was purified by flash column chromatography with 3:1 n-pentane-Et_2O to give the alcohol **29** (70 mg, 84% from **23**) as an oil. IR($CHCl_3$): 3350 cm^{-1}. ^1H NMR: δ 0.96 (3H, s), 0.97 (3H, s), 1.06 (3H, s), 1.29-1.52 (6H, m), 1.59-1.77 (4H, m), 1.92-2.01 (1H, m), 2.05-2.11 (1H, m), 2.53-2.66 (2H, m), 3.78 (1H, dd, J=6.7 and 6.7). MS m/z: 206 (M^+). HRMS Calcd for $C_{14}H_{24}O$: 208.1827. Found 208.1837.

***1,2,3,3bα,4,5,6,6aα7,7aβ-Decahydro-3aβ,5,5-trimethyl-3H-cyclopenta[a]pentalen-3-one* (24)**

To a stirred mixture of the alcohol **29** (30.0 mg, 0.144 mmol), Florisil®(120 mg) and NaOAc (46.0 mg, 0.561 mmol) in CH_2Cl_2 (2 mL) was added PCC (120 mg, 0.556 mmol) at ambient temperature.The resulting mixture was continued to stir at room temperature for 3 h. Filtration, followed by evaporation of the filtrate, the residual oil was purified by flash column chromatography with 10:1 n-pentane-Et_2O to give the ketone **24** (22.0 mg, 74%). IR ($CHCl_3$): 1725 cm^{-1}. ^1H NMR: δ 0.91 (3H, s), 0.94 (3H, s), 0.96-1.01 (1H, m), 1.04 (3H, s), 1.18 (1H, dd, *J*=11.1 and 11.1), 1.36-1.49 (2H, m), 1.56-1.76 (3H, m), 1.94-2.05 (1H, m), 2.23-2.42 (3H,

m), 2.51 (1H, dddd, J=17.9, 9.1, 9.1 and 3.8), 2.80 (1H, ddd, J=9.4, 9.1 and 9.1). MS m/z: 206 (M^+). HRMS Calcd for $C_{14}H_{22}O$ (M^+): 206.1671. Found: 206.1670.

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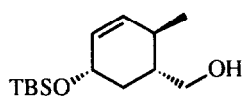

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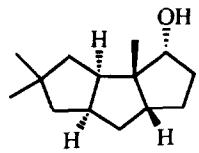
As expected, the over-reduction occurred diastereoselectively at this stage, giving the alcohol **29** as a single product. The stereochemistry of **29** was established by comparison of its ^{1}H NMR (500 MHz) spectrum with that reported in the literature.[19]



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