Functionalization of *trans*-Decalin. II. A Synthesis of *dl*-Isopetasol from *trans*-5-Oxodecalin-8a,2-carbolactone

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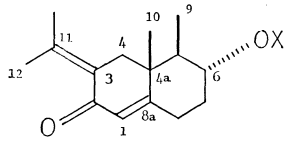
(Received September 21, 1978)

A stereocontrolled synthesis of *dl*-isopetasol (**1a**) from *trans*-5-oxodecalin-8a,2-carbolactone (**2a**) is described. The key intermediate, *trans*-5,5-ethylenedioxy-1β,8aβ-dimethyldecalin-2-one (**7b**) was prepared by reductive methylation of *trans*-5,5-ethylenedioxydecahydrocyclopropa[*d*]naphthalen-2-one (**5**) for introducing the vicinal two methyl groups at C-1 and C-8a carbon atoms. The cyclopropyl ketone **5** was obtained by reduction of the acetal of **2a** followed by (1) tosylation of the primary alcohol, (2) oxidation of the secondary alcohol with Corey's NCS–DMS reagent, and (3) cyclization with *t*-BuOK. Reduction of **5** with lithium in liquid ammonia provides initially the corresponding enolate anion, which can be trapped with methyl iodide to give *trans*-5,5-ethylenedioxy-1α,8aβ-dimethyldecalin-2-one (**7a**), smoothly. Epimerization of **7a** with MeONa in MeOH gave the desired intermediate **7b**. Reduction of **7b** with lithium in liquid ammonia gives the 2α-alcohol **8b**, stereoselectively. The conversion of **8b** into **1a** was carried out as follows: (1) deacetalization of **8b** followed with acetylation, giving *trans*-6α-acetoxy-4aβ,5β-dimethyldecalin-1-one (**9b**); (2) reduction of **9b** with $NaBH_4$ and subsequent dehydration affording the olefinic acetate **11**; (3) oxidation of **11** with CrO_3–pyridine complex, giving the enone **12**; (4) aldol condensation of **12** with acetone followed by dehydration, isomerization of double bond, and hydrolysis, providing the desired **1a**.

Previous paper from our laboratory has presented a convenient preparative method of *trans*-5-oxodecalin-8a,2-carbolactone (**2a**), provided by iodo–lactonization of *trans*-1-oxo-$\Delta^{6,7}$-octalin-4a-carboxylic acid and subsequent reduction of the carbon–iodine bond with tri-*n*-butyltin hydride.[1] As an extensible use of the intermediate **2a**, we describe here a stereocontrolled synthesis of *dl*-isopetasol (**1a**),[2] an eremophilane type sesquiterpene, isolated from *Petasites officinalis*[2a,b] and *P. japonicus* Maxim,[2c] whose carbon skeleton coincides with that of biologically active phomenone.[3]

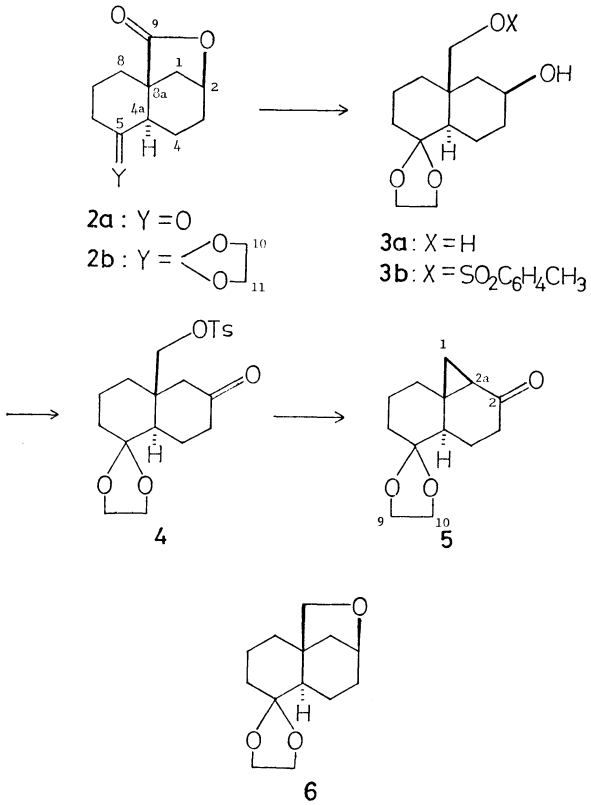


1a: X = H
1b: X = Ac
1c: X = CCH=CMe$_2$ (O)

The key starting material in our attempt is *trans*-5,5-ethylenedioxydecalin-8a,2-carbolactone (**2b**), prepared by acetalization of **2a**. The lactone function of **2b** is expected to be used for the construction of the substituents at C-4a, C-5, and C-6 carbons of **1**. In particular, the stereocontrolled formation of vicinal *cis* two methyl groups at the C-4a and C-5 carbons as well as stereoselective introduction of the α-hydroxyl group at the C-6 carbon is of interest.

Reduction of **2b** with lithium aluminum hydride (LAH) affords the acetal diol **3a** in 85% yield. Selective tosylation[4] of the primary alcohol of **3a** provides smoothly **3b** in 92% yield. The formation of cyclopropyl ketone **5** can be achieved by heating the tosylated ketone **4**, prepared from **3b** by oxidation with NCS–DMS,[5] with potassium *t*-butoxide in *t*-butyl alcohol at 78 °C. In contrast, LAH-induced reaction of either **3b** or **4** affords the corresponding etherated compound **6** as a sole product.

Reductive cleavage of the cyclopropyl ring of **5** with lithium metal in liquid ammonia and subsequent methylation of the carbanion *in situ*[6] gives the desired intermediate **7a** in 76% yield. Epimerization[7] of the C-1 axial methyl of **7a** provides **7b** exclusively after



2a: Y = O
2b: Y = ethylenedioxy
3a: X = H
3b: X = $SO_2C_6H_4CH_3$
4
5
6

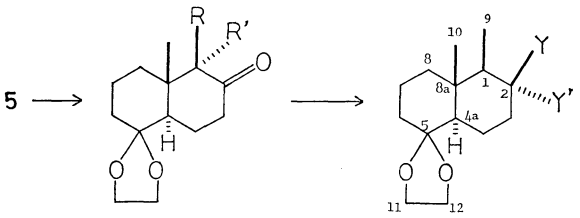
treatment with sodium methoxide at room temperature for 24 h. The reference compound **7c** can be easily obtained by the reduction of **5**.

The epimerized product **7b** is apparently homogeneous by NMR spectroscopy and is assigned the equatorial stereochemistry at the C-5 methyl group based on the comparison of ^{13}C NMR results of **7a**, **7b**, and **7c** with calculated values from Crews's substituent increment parameter[8] (Table 1). Direct evidence for the assigned structure **7b** is presented by ^{13}C NMR chemical shifts of C-1 and C-8a methyl groups appearing at 5.8 and 7.8 ppm higher fields than those of **7a**, due to steric compression effect.

Table 1. The shielding effect of ^{13}C NMR spectra of the C-8a (C-1) methyl groups of **7a**, **7b**, and **7c**

Compound	^{13}C Chemical shift, ppm		
	Obsereved		Calculated[a]
	C-8a Me	(C-1 Me)	C-8a Me
7a (*anti*-axial)	21.1	(12.9)	20.4
7b (equatorial)	13.3	(7.1)	13.1±0.5
7c	18.7		

a) Based on the Crews's substituent increment parameter as follows: the increment of the chemical shift of methyl (ax) group, being affected by the vicinal methyl groups (equatorial and *anti*-axial) is given as follows: the shielding effect of methyl (ax) with methyl (eq): +5.6±0.5 ppm; the shielding effect of methyl (ax) with *anti*-methyl (ax): −1.7 ppm.



7a: R=H, R'=Me
7b: R=Me, R'=H
7c: R=R'=H

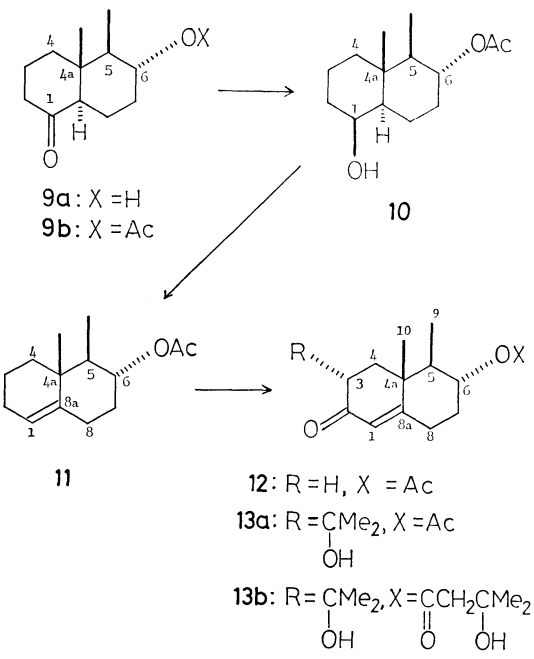
8a: Y=OH, Y'=H
8b: Y=H, Y'=OH

Stereospecific reduction of the carbonyl group of **7b** was achieved as follows. Treatment of **7b** with lithium metal in liquid ammonia with a trace of ethanol affords the thermodynamically stable equatorial alcohol **8a**[9] (92%), whereas the bulky reducing reagent such as lithium tri-*t*-butoxyaluminum hydride[10] gives the corresponding axial alcohol **8b** (98%), selectively.

The ^{13}C NMR spectra of **8** reveal that the marked downfield shifts of the C-8a methyl signals of **8a**, δ_{ax-eq} +1.4 ppm, due to 1,3-*syn*-axial interaction[11] between C-8a methyl and C-2 hydroxyl groups would account for the stereochemistry assigned to the structures of **8a** and **8b**. In addition, the structures of **8** can be rationally interpreted on the basis of 1,3-diaxial downfield shift[12] of ^1H NMR signals due to C-8a methyl protons of **8a** (δ 1.09), comparing to **8b** (δ 0.87).

The conversion of **8b** into the alcohol **10** *via* **9a** and **9b** was carried out in 91% overall yield by deacetalization with perchloric acid and subsequent reduction with sodium borohydride after treatment with acetic anhydride–pyridine. The tentative assignment of the *syn*-axial hydroxyl group of **10** is based on 1,3-diaxial downfield shift of ^1H NMR signals due to C-4a methyl protons at δ 1.01, contrasting to that of **9b** at δ 0.71.

Dehydration of the hydroxyl group of **10** attached to the C-1 carbon *via* the corresponding mesylate affords the olefin **11** in quantitative yield. Allylic oxidation of **11** with a slurry of anhydrous chromium trioxide–pyridine complex (Sarett reagent)[13] gives the promising intermediate **12** in 85% yield. Kinetically controlled aldol condensation[14] of the enone **12** with



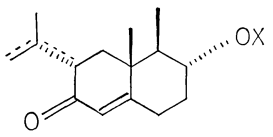
9a: X=H
9b: X=Ac

10

11

12: R=H, X=Ac
13a: R=CMe_2(OH), X=Ac
13b: R=CMe_2(OH), X=CCH_2CMe_2(=O)(OH)

acetone can lead smoothly to **13a** (38%) as well as **13b** (38%). Thermal decomposition of the mesylates of **13** giving the corresponding *exo* and *endo* double bond isomers **14** and subsequent isomerization from isopropenyl group to the corresponding isopropylidene group on treatment with rhodium(III) chloride[15] in ethanol at 110 °C and/or by passing an activated alumina column affords a mixture of **1b** and **1c**, precursors of *dl*-isopetasol, whose hydrolysis gives the desired *dl*-isopetasol (**1a**)[16] (46—51% from **13**).



14a: X=Ac
14b: X=CCH=CMe(=O)

Experimental

Melting points and boiling points are uncorrected. Column chromatography was carried out using silica gel (100—200 mesh) unless otherwise noted. IR spectra were determined with a JASCO IRA-1 grating spectrometer. ^1H NMR spectra were determined at 60 MHz with a Hitachi Model R-24 or at 100 MHz with a JEOL Model MH-100, and ^{13}C NMR spectra were measured at 25.05 MHz with a JEOL Fourier transform spectrometer, Model FX-100. Samples were dissolved in $CDCl_3$ containing TMS as an internal standard and signals are reported in parts per million (δ) downfield from the internal standard. Elemental analyses were performed in our laboratory.

*trans-5,5-Ethylenedioxydecalin-8a,2-carbolactone (**2b**).* A solution of **2a** (388 mg, 2.0 mmol), ethylene glycol (1.2 g, 19 mmol) and *p*-toluenesulfonic acid (50 mg) in benzene (40 ml) was refluxed for 12 h using a Dean-Stark apparatus

and most of water was removed azeotropically. The mixture was washed with aqueous 5% $NaHCO_3$, dried (Na_2SO_4), and concentrated to give 369 mg (77%) of **2b** as a white solid : mp 128.5 °C (benzene); IR (Nujol) 1777 cm^{-1} (lactone) ; ^1H NMR (60 MHz) δ 0.90—2.55 (m, 13, CH_2, CH), 3.85—3.91 (m, 4, CH_2O), 4.60 (t, 1, J=5 Hz, CH-O) ; ^{13}C NMR δ 17.6 (t), 19.3 (t), 27.9 (t), 30.9 (t, C-8), 35.0 (t, C-6), 45.0 (s, C-8a), 45.6 (t, C-1), 48.2 (d, C-4a), 64.6, 66.1 (t, C-10, C-11), 74.8 (d, C-2), 108.6 (s, C-5), 178.2 (s, C-9). Found : C, 65.71; H, 7.78%. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61%.

trans-*5,5-Ethylenedioxy-8aβ-(hydroxymethyl)decalin-2β-ol* (**3a**). To a stirred suspension of $LiAlH_4$ (230 mg, 6.1 mmol) in dry ether (10 ml) was added dropwise a solution of **2b** (720 mg, 3.0 mmol) in THF (5 ml) with cooling. After being stirred for 1 h at room temperature, the mixture was quenched with AcOEt. After workup in the usual manner, there was obtained 620 mg (85%) of **3a** as a white solid : mp 112.5—114.0 °C (hexane–benzene, 1:1); IR (Nujol) 3300 cm^{-1} (OH); ^1H NMR (60 MHz) δ 0.80—2.15 (m, 13, CH_2, CH), 3.12 (s, 2, OH), 3.87 (AB_q, 2, J=10 Hz, CH_2O), 3.65—4.07 (m, 5, CH_2O, CH-O); ^{13}C NMR δ 15.1 (t), 19.2 (t), 33.5 (t), 35.7 (t), 36.0 (t), 39.0 (s, C-8a), 43.5 (t, C-1), 51.8 (d, C-4a), 64.4, 64.7, 65.7 (t, C-9, C-10, C-11), 66.1 (d, C-2), 109.9 (s, C-5). Found: C, 64.40; H, 9.33%. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15%.

trans-*5,5-Ethylenedioxy-8aβ-(*p*-tolylsulfonyloxymethyl)decalin-2β-ol* (**3b**). To a cold solution of **3a** (242 mg, 1.0 mmol) in pyridine (13 ml) was added *p*-toluenesulfonyl chloride (250 mg, 1.3 mmol) with stirring. The mixture was stirred for 36 h at 5 °C, taken up in AcOEt, and washed with cold aqueous 5% $NaHCO_3$. The organic phase was washed with aqueous 2% $NaHCO_3$, dried (Na_2SO_4), and rotoevaporated at 30 °C. The residue was chromatographed (hexane–AcOEt, 3 : 1) to give 364 mg (92%) of **3b** as an oil, slowly crystallized on standing: mp 97.0—98.0 °C (dec, benzene–hexane, 1 : 1); IR (Nujol) 3550 (OH), 1598 cm^{-1} (C=C); ^1H NMR (60 MHz) δ 0.85—2.35 (m, 13, CH_2, CH), 1.68 (s, 1, OH), 2.43 (s, 3, CH_3), 3.84 (broad complex 4, CH_2O), 4.06 (br s, 1, CH-O), 4.67 (AB_q, 2, J=10 Hz, CH_2O), 7.26 (d, 2, J=8 Hz, HC=C), 7.75 (d, 2, J=8 Hz, HC=C); ^{13}C NMR δ 14.4 (t), 18.1 (t), 21.6 (q, aromatic C-Me), 32.6 (t), 34.5(t, C-8), 35.6 (t, C-6), 38.4 (s, C-8a), 41.0 (t, C-1), 52.1 (d, C-4a), 64.6, 65.5 (t, C-10, C-11), 66.4 (d, C-2), 71.7 (t, C-9), 109.2 (s, C-5), 127.7 (d, 2C), 129.6 (d, 2C), 133.3 (s), 144.3 (s). Found: C, 60.58; H, 7.22%. Calcd for $C_{20}H_{28}O_6S$: C, 60.59; H, 7.12%.

trans-*5,5-Ethylenedioxy-8a-(*p*-tolylsulfonyloxymethyl)decalin-2-one* (**4**). To a stirred suspension of *N*-chlorosuccinimide (843 mg, 6.3 mmol) and Me_2S (429 mg, 1.26 mmol) in toluene (10 ml) was added a solution of **3b** (500 mg, 1.26 mmol) in CH_2Cl_2 (7 ml) in a 15 min at −25 °C. After being stirred for 12 h at −25 °C and for 1.5 h at 5 °C, the mixture was treated with Et_3N (708 mg, 7.0 mmol), then taken up in CH_2Cl_2, washed with water, dried (Na_2SO_4), and rotoevaporated. The residue was chromatographed (hexane–AcOEt, 3 : 1) to give 415 mg (84%) of **4** as an oil, slowly crystallized on standing : mp 132.0—133.0 °C (hexane–benzene); IR (Nujol) 1708 (C=O), 1595 cm^{-1} (C=C); ^1H NMR (60 MHz) δ 1.30—2.70 (m, 13, CH_2, CH), 2.45 (s, 3, CH_3), 3.88 (br s, 4, CH_2O), 4.15 (AB_q, 2, J=10 Hz, CH_2O), 7.28 (d, 2, J=8 Hz, HC=C), 7.72 (d, 2, J=8 Hz, HC=C); ^{13}C NMR δ 18.8 (t), 19.8 (t), 21.7 (q, aromatic C-Me), 34.5 (t, C-8), 35.4 (t, C-6), 40.4 (t, C-3), 42.2 (s, C-8a), 49.9 (d, C-4a), 51.0 (t, C-1), 64.6, 65.6 (t, C-10, C-11), 69.5 (t, C-9), 109.0 (s, C-5), 127.9 (d, 2C), 129.8 (d, 2C), 132.8 (s), 144.6 (s), 208.8 (s, C-2). Found: C, 61.01; H, 6.90%. Calcd for $C_{20}H_{26}O_6S$: C, 60.90; H, 6.64%.

trans-*5,5-Ethylenedioxydecahydrocyclopropa*[d]*naphthalen-2-one* (**5**). To a suspension of **4** (86 mg, 0.22 mmol) in *t*-BuOH (3 ml) was added a solution of *t*-BuOK (286.7 mg, 2.56 mmol) in *t*-BuOH (7 ml). The stirred mixture was heated at 75—78 °C for 20 min and then allowed to cool to room temperature. The mixture was poured into cold water (*ca.* 100 ml) and extracted with benzene–ether. The extracts were worked up in the usual manner to give 38 mg (79%) of **5** : bp 99.0—102.0 °C/0.003 Torr (Kugelrohr); IR (neat) 1690 (shoulder), 1682 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.74—1.04 (m, 2, CH_2), 1.25—2.35 (m, 12, CH_2, CH), 3.92 (br s, 4, CH_2O), ^{13}C NMR δ 15.9 (t), 16.0 (t), 22.3 (t), 28.7 (s, C-8a), 32.1 (d, C-2a), 35.4 (t), 35.6 (t), 36.0 (t), 42.9 (d, C-4a), 64.9, 65.3 (t, C-9, C-10), 109.7 (s, C-5), 208.4 (s, C-2). Found: C, 70.19; H, 8.12%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%.

4,4-Ethylenedioxy-9-oxatricyclo[*8.2.1.0*^{5,11}]*dodecane* (**6**). To a refluxing suspension of $LiAlH_4$ (50 mg, 1.32 mmol) in THF (3 ml) was added a solution of **3b** (32 mg, 0.08 mmol) in THF (1 ml) and stirring was continued for 3 h. After being cooled, the mixture was quenched with AcOEt and aqueous 5% $NaHCO_3$ and the organic layer was decanted. Removal of the solvent and following chromatography (hexane–AcOEt, 4 : 1) gave 14 mg (77%) of **6** as a white solid : mp 86.5—87.5 °C; IR (Nujol) 1143, 1090, 1041, 1005, 886 cm^{-1}; ^1H NMR (100 MHz) δ 1.12—1.90 (m, 13, CH_2, CH), 3.86 (AB_q, 2, J=8 Hz, CH_2O), 3.76—4.02 (m, 4, CH_2O), 4.24 (t, 1, J=5 Hz, CH-O). Found: C, 69.71; H, 9.21%. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99%.

Similarly, **6** was obtained in 71% yield by the reaction of **4** (37 mg, 0.094 mmol) and $LiAlH_4$ (70 mg, 1.84 mmol) in THF (3 ml) at reflux for 5 h.

trans-*5,5-Ethylenedioxy-1α,8aβ-dimethyldecalin-2-one* (**7a**). A solution of **5** (265 mg, 1.19 mmol) and *t*-BuOH (88 mg, 1.19 mmol) in DME (5 ml) was added to a blue solution of lithium (40 mg, 5.7 mmol) in liquid NH_3 (*ca.* 40 ml). After being stirred for 30 min at −70 °C and for 10 min at −33 °C, the blue solution was quenched with an excess amount of MeI (0.75 ml, 12.1 mmol) and allowed to stand at room temperature in order to dispel most of liquid NH_3. To the residue, DME (5 ml) and HMPA (1 ml) was added and the mixture was stirred for 1 h, washed with a cold aqueous NH_4Cl, and taken up in ether–benzene. The organic phase was washed with aqueous 5% $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was chromatographed (hexane–ether, 4 : 1) to give 216 mg (76%) of **7a** as a white solid: mp 47.5—48.5 °C; IR (Nujol) 1698 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.98 (s, 3, CH_3), 1.09 (d, 3, J=7.5 Hz, CH_3), 0.80—2.55 (m, 12, CH_2, CH), 3.80—3.96 (m, 4, CH_2O); ^{13}C NMR δ 12.9 (q, C-9), 19.1 (t, C-7), 20.6 (t, C-6), 21.1 (q, C-10), 35.1 (t, C-4), 35.7 (t, C-8), 36.9 (t, C-3), 39.6 (s, C-8a), 42.9 (d, C-4a), 57.1 (d, C-1), 64.1, 65.5 (t, C-11, C-12), 110.3 (s, C-5), 215.8 (s, C-2). Found : C, 70.56; H, 9.35%. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30%.

trans-*5,5-Ethylenedioxy-1β,8aβ-dimethyldecalin-2-one* (**7b**). A solution of **7a** (280 mg, 0.85 mmol) and MeONa (658.8 mg, 12.2 mmol) in MeOH (12 ml) was stirred for 24 h at room temperature. The mixture was poured into cold water and extracted with ether–benzene. The organic phase was worked up to give 269 mg (96%) of **7b** as a white solid : mp 41.0—42.0 °C; IR (Nujol) 1708 cm^{-1}; ^1H NMR (60 MHz) δ 0.81 (s, 3, CH_3), 0.89 (d, 3, J=7.0 Hz, CH_3), 0.90—2.50 (m, 12, CH_2, CH), 3.87—4.07 (m, 4, CH_2O); ^{13}C NMR δ 7.1

(q, C-9), 13.3 (q, C-10), 19.6 (t, C-7), 21.1 (t, C-6), 35.3 (t, C-4), 38.0 (t, C-3), 40.9 (t, C-8), 42.2 (s, C-8a), 51.7 (d, C-4a), 56.7 (d, C-1), 64.1, 65.5 (t, C-11, C-12), 109.8 (s, C-5), 212.3 (s, C-2). Found : C, 70.37; H, 9.38%. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30%.

trans-*5,5-Ethylenedioxy-8a-methyldecalin-2-one (**7c**)*. To a stirred solution of **5** (30 mg, 0.135 mmol) in *t*-BuOH (10 mg, 0.135 mmol), ether (4 ml), and liquid NH_3 was added a piece of lithium (14 mg, 2.0 mmol). After being stirred for 30 min at −33 °C, the solution was cooled to −70 °C and quenched all at once with NH_4Cl (500 mg). The mixture was worked up in the usual manner to give 28 mg (92%) of **7c** as a white solid : mp 66.0—67.5 °C; IR (Nujol) 1715 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 1.00 (s, 3, CH_3), 1.10—2.50 (m, 13, CH_2, CH), 3.78—3.93 (m, 4, CH_2O); ^{13}C NMR δ 18.7 (q, C-9), 19.5 (t, C-7), 20.7 (t, C-6), 35.7 (t, C-4), 39.0 (s, C-8a), 40.6 (t, C-8), 41.1 (t, C-3), 50.1 (d, C-4a), 57.5 (t, C-1), 64.2, 65.5 (t, C-10, C-11), 109.7 (s, C-5), 211.2 (s, C-2). Found : C, 69.53 ; H, 9.03%. Calcd for $C_{13}H_{20}O_3$: C, 69.61 ; H, 8.99%.

trans-*5,5-Ethylenedioxy-1β,8aβ-dimethyldecalin-2β-ol (**8a**)*. To a stirred slurry of $LiAl(t\text{-}BuO)_3H$ (610 mg, 2.4 mmol) in THF (3 ml) was added a solution of **7b** (115 mg, 0.48 mmol) in THF (7 ml) at 0—5 °C under N_2. After being stirred for 12 h at room temperature, the mixture was quenched with cold aqueous 5% $NaHCO_3$ and worked up in the usual manner to give 113 mg (98%) of **8a** as a white solid : mp 82.5—83.5 °C; IR (Nujol) 3340 cm^{-1} (OH); ^1H NMR (60 MHz) δ 0.98 (d, 3, J=7 Hz, CH_3), 1.09 (s, 3, CH_3), 0.80—2.10 (m, 13, CH_2, CH, OH), 3.73 (m, 1, CH-O), 3.75—4.00 (m, 4, CH_2O); ^{13}C NMR δ 11.7 (q, C-9), 14.3 (q, C-10), 15.0 (t), 18.9 (t), 34.2 (t), 35.6 (t), 38.3 (s, C-8a), 38.3 (t, C-8), 47.3 (d, C-4a), 53.6 (d, C-1), 64.0, 65.4 (t, C-11, C-12), 72.2 (d, C-2), 110.2 (s, C-5). Found: C, 70.02; H, 10.10%. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07%.

trans-*5,5-Ethylenedioxy-1β,8aβ-dimethyldecalin-2α-ol (**8b**)*. To a blue solution of lithium (8.9 mg, 1.27 mmol) in liquid NH_3 (6 ml) was added a solution of **7b** (30 mg, 0.126 mmol) in EtOH (7.2 μl), ether (3 ml), and dioxane (1 ml). After being stirred for 10 min at −70 °C and for 1 h at −33 °C, the solution was quenched with aqueous saturated NH_4Cl and worked up to give 28 mg (93%) of **8b** as an oil : bp 139.0—142.0 °C/0.1 Torr (Kugelrohr); IR (neat) 3360 cm^{-1} (OH); ^1H NMR (60 MHz) δ 0.87 (s, 3, CH_3), 0.95(d, 3, J=2 Hz, CH_3), 0.90—2.30 (m, 12, CH_2, CH), 2.25 (br, s, 1, OH), 3.38 (m, 1, CH-O), 3.75—3.98 (m, 4, CH_2O); ^{13}C NMR δ 10.3 (q, C-9), 12.9 (q, C-10), 18.8 (t), 19.2(t), 35.4(t), 35.7 (t), 38.1 (t, C-8), 38.8 (s, C-8a), 51.3 (d, C-4a), 52.5 (d, C-1), 64.0, 65.4 (t, C-11, C-12), 72.0 (d, C-2), 110.3 (s, C-5). Found : C, 70.12 ; H, 10.13%. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07%.

trans-*6α-Hydroxy-4aβ,5β-dimethyldecalin-1-one (**9a**)*. A cold solution (0—5 °C) of **8b** (24 mg, 0.1 mmol) and 3 drops of 70% $HClO_4$ in THF (2 ml) and water (1 ml) was stirred for 12 h. The organic layer was taken up in benzene and washed with brine, dried (Na_2SO_4), and concentrated to give 18 mg (92%) of **9a** as an oil : bp 77.0—78.0 °C/0.007 Torr (Kugelrohr); IR (neat) 3360 (OH), 1700 cm^{-1} (C=O) ; ^1H NMR (60 MHz) δ 0.66 (s, 3, CH_3), 0.97 (d, 3, J=6 Hz, CH_3), 0.90—2.45 (m, 12, CH_2, CH), 2.05 (s, 1, OH), 3.36 (d, d, d, 1, J=10, 5, 5 Hz, CH-O); ^{13}C NMR δ 11.0 (q, C-9), 13.3 (q, C-10), 19.6 (t), 22.1 (t), 34.5 (t), 37.5 (t, C-4), 41.0 (t, C-2), 43.4 (s, C-4a), 50.1 (d, C-5), 58.1 (d, C-8a), 71.5 (d, C-6), 212.6 (s, C-1). Found : C, 73.65 ; H, 10.25%. Calcd for $C_{12}H_{20}O_2$: C, 73.43 ; H, 10.27%.

trans-*6α-Acetoxy-4aβ,5β-dimethyldecalin-1-one (**9b**)*. A cold solution (5 °C) of **9a** (70 mg, 0.357 mmol) in pyridine (1.2 ml) and Ac_2O (0.5 ml, 5.29 mmol) was stirred for 12 h at room temperature. The mixture was poured into cold water and extracted with ether–benzene. The extracts were worked up to give 85 mg (100%) of **9b** as a white solid : mp 88.0—89.5 °C; IR (Nujol) 1724 (ester C=O), 1709 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.71 (s, 3, CH_3), 0.85 (d, 3, J=7 Hz, CH_3), 1.00—2.45 (m, 12, CH_2, CH), 2.02 (s, 3, $COCH_3$), 4.63 (d, d, d, 1, J=10, 5, 5 Hz, CH-O); ^{13}C NMR δ 10.9 (q, C-9), 13.3 (q, C-10), 19.4 (t), 21.3 (q, acetyl CH_3), 22.1 (t), 30.7 (t), 37.5 (t, C-4), 40.9 (t, C-2), 43.4 (s, C-4a), 47.0 (d, C-5), 57.8 (d, C-8a), 74.2 (d, C-6), 170.6 (s, acetyl C=O), 211.9 (s, C-1). Found: C, 70.56; H, 9.28%. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30%.

trans-*6α-Acetoxy-4aβ,5β-dimethyldecalin-1β-ol (**10**)*. A solution of **9b** (37 mg, 0.155 mmol) in MeOH (1.5 ml) was treated with a solution of $NaBH_4$ (19 mg, 0.5 mmol) in water (0.3 ml) at 0—5 °C for 30 min. The mixture was quenched with cold AcOH (0.15 ml) and water (1.35 ml), and extracted with ether–benzene. The extracts were worked up to give 37 mg (99%) of **10** as a white solid : mp 87.5—89.0 °C; IR (Nujol) 3540 (OH), 1715 cm^{-1} (ester C=O); ^1H NMR (60 MHz) δ 0.75 (d, 3, J=6 Hz, CH_3), 1.01 (s, 3, CH_3), 0.80—2.42 (m, 12, CH_2, CH), 1.69 (s, 1, OH), 2.02 (s, 3, $COCH_3$), 3.88 (br s, 1, CH-O), 3.75 (d, d, d, 1, J=10, 5, 5 Hz, CHO); ^{13}C NMR δ 9.7 (q, C-9), 14.0 (q, C-10), 16.3 (t), 21.3 (q, acetyl CH_3), 24.6 (t), 32.3 (t), 33.8 (t), 37.0 (s, C-4a), 38.5 (t, C-4), 48.4, 48.8 (d, C-5, C-8a), 71.5 (d, C-1), 75.1 (d, C-6), 170.8 (s, acetyl C=O). Found: C, 70.02; H, 10.07%. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07%.

*6α-Acetoxy-4aβ,5β-dimethyl-$\Delta^{1,8a}$-octalin (**11**)*. To a stirred, cold solution (0—5 °C) of **10** (28 mg, 0.117 mmol) in pyridine (0.5 ml) was added methanesulfonyl chloride (148 mg, 1.29 mmol). After being stirred for 30 min at 0—5 °C and for 30 min at 40—50 °C, the mixture was quenched with water and extracted with ether–benzene. The organic phase was washed with cold aqueous 5% tartaric acid, aqueous 5% $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (hexane–ether, 5 : 1) to give 26 mg (100%) of **11** as an oil : bp 99.0—101.0 °C/0.1 Torr (Kugelrohr); IR (neat) 1735 cm^{-1} (ester C=O); ^1H NMR (60 MHz) δ 0.86 (d, 3, J= 6 Hz, CH_3), 0.99 (s, 3, CH_3), 1.06—2.45 (m, 11, CH_2, CH), 2.03 (s, 3, $COCH_3$), 4.80 (d, d, d, 1, J=10, 5, 5 Hz, CH-O), 5.39 (t, 1, J=3 Hz, HC=C); ^{13}C NMR δ 10.8 (q, C-9), 18.7 (t), 19.2 (q, C-10), 21.3 (q, acetyl CH_3), 25.6 (t), 30.7 (t), 33.1 (t), 37.5 (t, C-4), 37.8 (s, C-4a), 47.3 (d, C-5), 75.1 (d, C-6), 120.6 (d, C-1), 142.1 (s, C-8a), 170.8 (s, acetyl C=O). Found: C, 75.69; H, 10.01%. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97%.

*6α-Acetoxy-4aβ,5β-dimethyl-$\Delta^{1,8a}$-octalin-2-one (**12**)*. To a solution of **11** (22 mg, 0.1 mmol) in dry CH_2Cl_2 (5 ml) was added in one portion a slurry of anhydrous CrO_3-(pyridine)$_2$ complex (800 mg, 31 mmol) in CH_2Cl_2 (5 ml) under argon. After being stirred for 24 h at room temperature, the mixture was filtered off and the solid in the flask was washed with ether. The combined filtrate and washings were washed with aqueous 5% $NaHCO_3$, cold aqueous 5% HCl, and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (hexane–ether, 4 : 1) to give 20 mg (85%) of **12** as a solid : mp 69.0—70.5 °C; IR (Nujol) 1731 (ester C=O), 1676 (C=O), 1618 cm^{-1} (C=C); ^1H NMR (60 MHz) δ 0.82 (d, 3, J=6.5 Hz, CH_3), 1.15 (s, 3, CH_3), 1.00—2.65 (m, 9, CH_2, CH), 2.04 (s, 3, $COCH_3$), 4.71 (d, d, d, 1, J=10, 5, 5 Hz, CH-O), 5.72 (br s, 1, HC=C);

^{13}C NMR δ 10.5 (q, C-9), 17.1 (q, C-10), 21.2 (q, acetyl CH_3), 30.9 (t, C-8), 31.5 (t, C-7), 33.3 (t, C-4), 35.7 (t, C-3), 39.3 (s, C-4a), 46.7 (d, C-5), 73.4 (d, C-6), 124.6 (d, C-1), 167.6 (s, C-8a), 170.6 (s, acetyl C=O), 198.9 (s, C-2). Found: C, 71.06; H, 8.60%. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53%.

6α-Acetoxy-3α-(1-hydroxy-1-methylethyl)-4aβ,5β-dimethyl-$\Delta^{1,8a}$*-octalin-2-one* (**13a**) and *3α-(1-Hydroxy-1-methylethyl)-6α-(3-hydroxy-3-methylbutyryloxy)-4aβ,5β-dimethyl-*$\Delta^{1,8a}$*-octalin-2-one* (**13b**). To a stirred solution of *i*-Pr_2NLi (246.1 mg, 2.3 mmol) in THF (4 ml) was added dropwise a solution of **12** (115 mg, 0.49 mmol) in THF (4 ml) at −78 °C under argon. After being stirred for 1 h at −78 °C, $ZnCl_2$[17] (133 mg, 0.98 mmol) in ether (5 ml) was added and stirred for 10 min and to this mixture acetone (300 mg, 5.2 mmol) was added. The mixture was quenched with cold aqueous 5% tartaric acid and extracted with ether–benzene. The organic phase was worked up in the usual manner and the crude product was chromatographed (hexane–AcOEt, 4 : 1) to give 55 mg (38%) of **13a** and 65 mg (38%) of **13b** as an oil. Physical constants along with elemental analyses of **13a** and **13b** are as follows : **13a**; IR (neat) 3440 (OH), 3020, 1735 (ester C=O), 1650 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.94 (d, 3, J=7 Hz, CH_3), 1.19 (s, 3, CH_3), 1.22 (s, 6, CH_3), 1.10—2.70 (m, 8, CH_2, CH), 4.83 (d, d, d, 1, J=10, 5, 5 Hz, CH-O), 5.01 (br s, 1, OH), 5.73 (br s, 1, HC=C); ^{13}C NMR δ 10.5 (q, C-9), 17.1 (q, C-10), 21.2 (q, acetyl CH_3), 24.6 (q, C-13), 28.3 (q, C-12), 30.5 (t, C-8), 31.3 (t, C-7), 38.7 (t, C-4), 40.0 (s, C-4a), 47.1 (d, C-5), 50.6 (d, C-3), 72.4 (s, C-11), 73.1 (d, C-6), 125.1 (d, C-1), 168.2 (s, C-8a), 170.6 (s, acetyl C=O), 202.8 (s, C-2). Found: C, 69.44; H, 8.92%. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90%.

13b: IR (neat) 3440 (OH), 3020, 1720 (ester C=O), 1660 cm^{-1} (C=O); ^1H NMR (60 MHz) δ 0.85 (d, 3, J= 7 Hz, CH_3), 1.00 (s, 3, CH_3), 1.21 (s, 6, CH_3), 1.20—2.75 (m, 8, CH_2, CH), 1.29 (s, 6, CH_3), 2.02 (s, 2, CH_2), 4.93 (d, d, d, 1, J=10, 5, 5 Hz, CH-O), 4.96 (br s, 1, OH), 5.31 (br s, 1, OH), 5.73 (br s, 1, HC=C). Found: C, 68.31; H, 9.11%. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15%.

Independently, the compound **13a** was prepared as follows: To a stirred solution of lithium *N*-isopropylcyclohexylamide (73.6 mg, 0.5 mmol) in THF (3 ml) was added dropwise a solution of **12** (24 mg, 0.1 mmol) in THF (3 ml) at −78 °C. After being stirred for 2.5 h at −78 °C, $ZnCl_2$ (13.6 mg, 0.1 mmol) in ether (3 ml) was added and stirred for 10 min and to this mixture acetone (0.1 ml, 13.6 mmol) was added. The mixture was quenched with cold aqueous 5% tartaric acid and worked up to give 20 mg (68%) of **13a**.

6α-Acetoxy-3-isopropylidene-4aβ,5β-dimethyl-$\Delta^{1,8a}$*-octalin-2-one* (**1b**). To a solution of **13a** (21 mg, 0.071 mmol) in pyridine (1.5 ml) was added MsCl (29.6 mg, 0.26 mmol) at 0 °C under N_2. After being stirred for 1 h at 20 °C and 2 h at 40—42 °C, the mixture was quenched with cold water and taken up in ether–benzene. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed (hexane–AcOEt, 4 : 1) to give 3 mg of **12** and 13 mg (66%) of an *exo* and *endo* double bond mixture **14a**: IR (neat) 3070, 1735 (ester C=O), 1675 (C=O), 1630 cm^{-1} (C=C); ^1H NMR (60 MHz) δ 4.80, 4.96 (br s, H_2C=C). Without further purification, **14a** was passed through an activated alumina 300 (Nakarai Chemicals) column (hexane–AcOEt, 3 : 1) to give **1b** in a quantitative yield as a white solid : mp 78.0—79.0 °C (lit,[18] 86.0—87.0 °C); IR (Nujol) 1735 (ester C=O), 1665 (C=O), 1635 (C=C), 1242, 1030 cm^{-1}; ^1H NMR (100 MHz) δ 0.99 (d, 3, J=6 Hz, CH_3), 1.04 (s, 3, CH_3), 1.10—2.60 (m, 6, CH_2, CH), 1.85 (s, 3, CH_3), 2.07 (s, 3, $COCH_3$), 2.09 (s, 3, CH_3), 2.94 (d, 1, J=14 Hz, C=CCH), 4.88 (d, d, d, 1, J=10, 5, 5 Hz, CH-O), 5.82 (br s, 1, HC=C); ^{13}C NMR δ 10.7 (q, C-9), 17.1 (q, C-10), 21.2 (q, acetyl CH_3), 22.1 (q, C-12), 22.6 (q, C-13), 30.1 (t, C-8), 31.5 (t, C-7), 41.1 (t, C-4), 42.2 (s, C-4a), 46.0 (d, C-5), 73.6 (d, C-6), 126.7 (d, C-1), 127.0 (s, C-3), 143.4 (s, C-11), 165.0 (s, C-8a), 170.7 (s, acetyl C=O), 191.6 (s, C-2).

6α-(3,3-Dimethylacryloyloxy)-3-isopropylidene-4aβ,5β-dimethyl-$\Delta^{1,8a}$*-octalin-2-one* (**1c**) was obtained in 72% yield by dehydration with MsCl and isomerization with activated alumina 300 column of **13b** : bp 129.0—131.0 °C/0.01 Torr (Kugelrohr); IR (neat) 3020, 1712 (ester C=O), 1665 (C=O), 1630 (C=C), 1620 cm^{-1} (C=C); ^1H NMR (100 MHz) δ 0.98 (d, 3, J=7 Hz, CH_3), 1.04 (s, 3, CH_3), 1.10—2.59 (m, 6, CH_2, CH), 1.85, 1.91, 2.10, 2.18 (s, 12, CH_3), 2.92 (d, 1, J=13 Hz, C=CCH), 4.86 (d, d, d, 1, J=10, 5, 5 Hz, CH-O), 5.65 (complex s, 1, HC=C), 5.75 (d, 1, J=1 Hz, HC=C); ^{13}C NMR δ 10.7 (q, C-9), 17.2 (q, C-10), 20.3 (q, 3,3-dimethylacryl γ-CH_3), 22.1 (q, C-13), 22.6 (q, C-12), 27.5 (q, 3,3-dimethylacryl γ-CH_3), 30.2 (t, C-8), 31.8 (t, C-7), 41.2 (t, C-4), 42.2 (s, C-4a), 46.2 (d, C-5), 72.4 (d, C-6), 116.0 (d, acryl α-CH), 126.6 (d, C-1), 127.1 (s, C-3), 143.2 (s, C-11), 157.2 (s, acryl β-C), 165.3 (s, C-8a), 166.3 (s, acryl C=O), 191.6 (s, C-2). Found: C, 75.93; H, 8.97%. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%.

Conversion of **14a** *into* **1b** *with* $RhCl_3 \cdot 2H_2O$. A solution of **14a** (19 mg, 0.069 mmol) and $RhCl_3 \cdot 2H_2O$ (2 mg, 0.008 mmol) in EtOH (2 ml) was heated for 12 h at 110 °C in a sealed tube. After being cooled, the mixture was filtered and the filtrate was concentrated. The residue was chromatographed (hexane–AcOEt, 4 : 1) to give 14 mg (84%) of **1b** as a white solid.

Similarly, **1c** was obtained by the reaction of **14b** and $RhCl_3 \cdot 2H_2O$ in EtOH at 110 °C for 12 h in 82% yield.

dl-*Isopetasol* (**1a**). To a solution of **1b** (21 mg, 0.076 mmol) in MeOH (2 ml) was added a solution of KOH (95 mg, 17 mmol) in H_2O (0.3 ml) at 5 °C. The mixture was stirred for 2 h at 10 °C and taken up in ether–benzene. The extract was worked up in the usual manner to give 13 mg (73%) of **1a** as white solid : mp 104.0—105.5 °C (lit,[2c] 124.0—125.0 °C, lit,[2d] 105.0—106.0 °C); IR (Nujol) 3390 (OH), 1652 (C=O), 1628 (C=C), 1608 (C=C), 1380, 1298, 1230, 1217, 1048, 890, 858 cm^{-1}; ^1H NMR (100 MHz) δ 0.99 (s, 3, CH_3), 1.12 (d, 3, J=6.5 Hz, CH_3), 1.10—1.67 (m, 3, CH_2, CH), 1.79 (s, 1, OH), 1.87 (s, 3, C=CCH_3), 2.03—2.50 (m, 3, CH_2), 2.11 (s, 3, C=CCH_3), 2.93 (d, 1, J=14 Hz, C=CCH), 3.60 (d, d, d, 1, J=10, 5, 5 Hz, CH-O), 5.82 (br s, 1, HC=C); ^{13}C NMR δ 10.8 (q, C-9), 17.3 (q, C-10), 22.1 (q, C-13), 22.6 (q, C-12), 30.5 (t, C-8), 35.3 (t, C-7), 41.2 (t, C-4), 42.0 (s, C-4a), 49.1 (d, C-5), 71.3 (d, C-6), 126.5 (d, C-1), 127.2 (s, C-3), 143.2 (s, C-11), 166.1 (s, C-8a), 191.7 (s, C-2).

Similarly, *dl*-isopetasol (**1a**) was obtained in 71% yield by hydrolysis of **1c** at room temperature for 2 h with KOH in aqueous MeOH. IR and ^1H NMR spectra data were identical with those of an authentic sample.[16]

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16) We are gratefull to Professor K. Naya, Kwansei Gakuin University, for providing ^{1}H NMR and IR spectra of natural isopetasol (**1a**).

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