New Monoterpene Lactones of the Iridane Type from *Actinidia polygama* Miq.

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(Received May 29, 1980)

Fourteen iridoid monoterpene lactones including eight new compounds were isolated from the volatile oil of fresh fruits of the cat- and lacewing-attracting plant *Actinidia polygama* Miq., and their structures were established on the basis of spectral evidence and chemical transformation.

In continuous investigation of the constituents of the cat- and lacewing-attracting plant *Actinidia polygama* Miq.,[1,2] we isolated from the volatile oil of its fresh fruits eight new iridoid monoterpene lactones, which we named dihydroepinepetalactone (**1a**), isodihydroepinepetalactone (**1b**), isoepiiridomyrmecin (**2b**), isoneonepetalactone (**3b**), dehydroiridomyrmecin (**4a**), isodehydroiridomyrmecin (**4b**), actinidialactone (**5a**), and isoactinidialactone (**5b**), together with five previously isolated lactones.[3] The known compounds were identified as neonepetalactone (**3a**),[2] dihydronepetalactone (**6a**), isodihydronepetalactone (**6b**), iridomyrmecin (**7a**), and isoiridomyrmecin (**7b**). In addition, nepetalactone (**8**)[4] was also isolated from this oil.

The present paper deals with the structural elucidation of these new compounds.

*Structures of Three New Saturated Lactones **1a**, **1b**, and **2b**.* These new saturated lactones **1a**, **1b**, and **2b** were isolated by repeated preparative gas chromatography. They have the molecular formula $C_{10}H_{16}O_2$ according to high resolution mass spectra, and a characteristic IR band at 1740—1735 cm^{-1} indicated the presence of a saturated δ-lactone group. The mass spectra of **1a**, **1b**, and **2b** were almost identical to those of **6a**, **6b**, and **7b**, respectively. In their NMR spectra, the C-1 methyl protons signals were observed at δ 1.01, 1.01, and 0.83, while the analogous protons of natural **6a**, **6b**, and **7b** had signals at δ 1.19, 1.19, and 1.05. By comparison of the chemical shifts of the new lactones with those of lactones **6a**, **6b**, and **7b**, we deduced that they were the C-2 epimers of **6a**, **6b**, and **7b**.

The structures and stereochemistry of these new saturated lactones were confirmed by the following chemical evidence. When the lactones **1a** and **1b** were refluxed with sodium methoxide in methanol or potassium carbonate in xylene and followed by acidification with dil HCl, they were converted into **6a** and **6b**. As these conversions were analogous to that of epinepetalactone (**9**) into nepetalactone (**8**),[5] the lactones **1a** and **1b** were assigned as the dihydro derivatives of epinepetalactone, for which we proposed the names dihydroepinepetalactone (**1a**) and isodihydroepinepetalactone (**1b**). LAH reduction of **1a** and **1b** gave the corresponding saturated diols **10a** and **10b**. Their optical rotation data were in accord with those of β-iridodiol (**10a**) and γ-iridodiol (**10b**).[6] The lactone **2b** was also reduced with LAH to give γ-iridodiol (**10b**). From the above spectral and chemical evidence, **2b** was confirmed as the C-2 epimer of isoiridomyrmecin (**7b**) and named isoepiiridomyrmecin.

No epiiridomyrmecin (**2a**) was detected by GC-MS analysis of the oil.

*Structures of Five New Unsaturated Lactones **3b**, **4a**, **4b**, **5a**, and **5b**.* These new unsaturated lactones were also isolated by preparative gas chromatography. They were an α-unsaturated δ-lactone **3b** (MS: M^+ 166, $C_{10}H_{14}O_2$; IR: 1710, 1638 cm^{-1}), a pair of diastereomers of the unsaturated δ-lactones **4a** and **4b** (MS: M^+ 166; IR: 1730 cm^{-1}), and a pair of diastereomers of the unsaturated γ-lactones **5a** and **5b** (MS: M^+ 166; IR: 1770—1760 cm^{-1}). The mass spectrum of **3b** agreed with that of **3a**. The mass spectra of **4a** and **4b** and of **5a** and **5b** were almost identical to each other.

The α-unsaturated δ-lactone **3b** was reduced with LAH to give the corresponding unsaturated diol **11b**, which was identified as isodehydroiridodiol of known absolute configuration.[2] Catalytic hydrogenation of **3b** with Adams catalyst or Raney nickel catalyst gave a mixture of 1-epi-isodihydronepetalactone (**12b**) and the double bond migrated product **13b**, which were characterized on the basis of spectral data. The IR spectrum of **12b** was similar to that of **6b** and the NMR spectrum of **12b** closely resembled that of **6b**, except for the signals of the C-1 methyl protons: the (1*R*)-methyl signals of **12b** appeared at about 0.20 ppm higher field than the (1*S*)-methyl signals of **6b**. The IR, NMR, and mass spectra of **13b** closely resembled those of the lactone **13a** obtained from **3a**.[2] Spectral and chemical evidence showed that the lactone **3b** was the C-8 epimer of neonepetalactone (**3a**) and it was named isoneonepetalactone.

The unsaturated δ-lactones **4a** and **4b** were reduced with LAH to give dehydroiridodiol (**11a**) and isodehydroiridodiol (**11b**), respectively. Catalytic hydrogenation of **4b** gave an unsaturated carboxylic acid.[7] Lactonization of this acid with *p*-toluenesulfonic acid in benzene afforded a mixture of two new saturated γ-lactones **14b** and **15b** in a ratio of 3 : 4, which were determined by spectral analysis. Thus, the lactones **4a** and **4b** were assigned as the $\Delta^{1,2}$-dehydro derivatives of **7a** and **7b**, and designated as dehydroiridomyrmecin (**4a**) and isodehydroiridomyrmecin (**4b**).

The NMR spectra of the new unsaturated γ-lactones **5a** and **5b** showed the presence of a secondary methyl group, a methyl group on a tertiary carbon-bearing oxygen, and a trisubstituted olefinic proton. Spectral characteristics and biogenetic consideration show these compounds to be a pair of diastereomers having an

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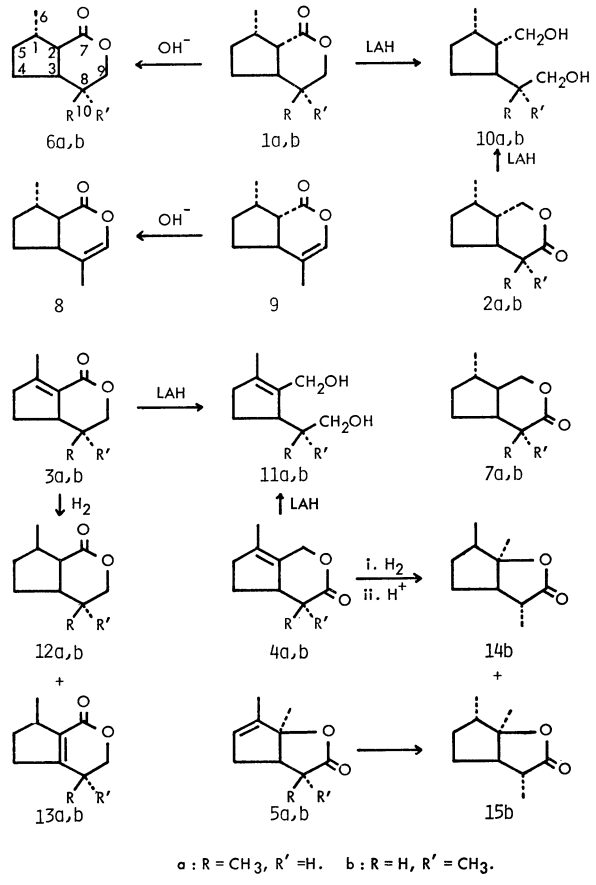

iridane skeleton with a γ-lactone group and a double bond, *i.e.*, structures **5a** and **5b**, for which we propose the names actinidialactone (**5a**) and isoactinidialactone (**5b**). The stereochemistry of **5a** and **5b** was established by the following evidence. (a) Reduction of **5b** with Adams catalyst in ether yielded a mixture of two saturated γ-lactones in a ratio of 12 : 1, which were identical in all respects (IR, NMR, MS, and CD) to the lactones **14b** and **15b** derived from **4b** with the (3*R*,8*R*)-configuration. (b) The CD spectrum of the new lactone **5a** exhibited a positive Cotton curve while **5b** showed a negative one. According to Snatzke's rule,[8] the molecules corresponding to **5a** and **5b** are supposed to show positive and negative Cotton effects, respectively. (c) Close correspondence of the ^{1}H- and ^{13}C-NMR spectra of **5a** and β-episantonin derivatives and of **5b** and α-episantonin derivatives[9,10] definitely confirmed the stereochemistry of the α-methyl-γ-lactone moiety in **5a** and **5b**.[11]

These newly isolated lactones have not yet evaluated for their bioactive effects against Felidae animals.

Experimental

NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard on a JEOL JNM-FX100 instrument. IR spectra were taken as thin films between NaCl plates on a Hitachi EPI-G2 spectrometer equipped with a beam condenser. Optical rotations were measured in $CHCl_3$ on a Perkin-Elmer Model 141 polarimeter. Mass spectra were obtained on a Hitachi RMU-6 mass spectrometer (for GC-MS) or a JEOL JMS-01SG (for high resolution mass spectra) instrument. Gas liquid chromatography (GLC) was performed on a Hitachi 163 (for analytical work) or a Varian aerograph 920 (for preparative work) instrument, using a 40 m × 0.25 mm glass capillary column coated with Thermon 600T (analytical and GC-MS) or a 3 m × 10 mm aluminum column packed with 5% Thermon 1000 on Chromosorb W (preparative).

Isolation of Lactones. Fresh fruits (5.5 kg, collected in Toyama Pref. in August 1979) were steam distilled to give the volatile oil (4.5 g). Figure 1 shows its gas chromatogram.

Its components were separated by repeated preparative GLC (column temp, 180 °C; injector temp., 220 °C; helium flow rate, 40 ml/min). Eight new oily substances and six known lactones were isolated in their pure states. The known lactones were identified by direct comparison with authentic samples.

*Dihydroepinepetalactone (**1a**).* Content: 0.31%;[12] Relative retention time: 1.49;[13] $[\alpha]_D^{25}$ +31.3° (*c* 0.55); IR: 1740 cm^{-1}; NMR: δ 1.00, 1.03 (each 3H, d, J=7 Hz, C-8 Me and C-1 Me), 4.02, 4.35 (each 1H, AB q of ABX, J_{AX}=3 Hz, J_{BX}=4 Hz, J_{AB}=11 Hz, C-9 H_2); MS: 168 (22%, M$^+$), 153 (41), 139 (7), 126 (31), 113 (70), 95 (45), 81 (100), 67 (60), 55 (22), and 41 (36). [Found, M$^+$ 168.1142. $C_{10}H_{16}O_2$ requires, M$^+$ 168.1148].

*Isodihydroepinepetalactone (**1b**).* Content: 0.30%; RRT: 1.16; $[\alpha]_D^{25}$ +90.3° (*c* 0.74); IR: 1740 cm^{-1}; NMR: δ 1.01 (6H, d, J=7 Hz, C-8 Me and C-1 Me), 3.81, 4.35 (each 1H, AB q of ABX, J_{AX}=9 Hz, J_{BX}=5 Hz, J_{AB}=11 Hz, C-9 H_2); MS: 168 (17%, M$^+$), 153 (53), 139 (5), 126 (18), 123 (15), 113 (100), 109 (25), 95 (56), 81 (81), 69 (30), 67 (54), 55 (20), and 41 (30). [Found, M$^+$ 168.1145].

*Isoepiiridomyrmecin (**2b**).* Content: 0.73%; RRT: 1.47; $[\alpha]_D^{25}$ +6.17° (*c* 0.47); IR: 1730 cm^{-1}; NMR: δ 0.86, 1.31 (each 3H, d, J=7 Hz, C-1 Me and C-8 Me), 4.21, 4.48 (each 1H, AB q of ABX, J_{AX}=8 Hz, J_{BX}=5 Hz, J_{AB}=11 Hz, C-7 H_2); MS: 168 (8%, M$^+$), 109 (33), 95 (48), 81 (100), 68 (55), 67 (64), 55 (19), and 41 (25). [Found, M$^+$ 168.1146].

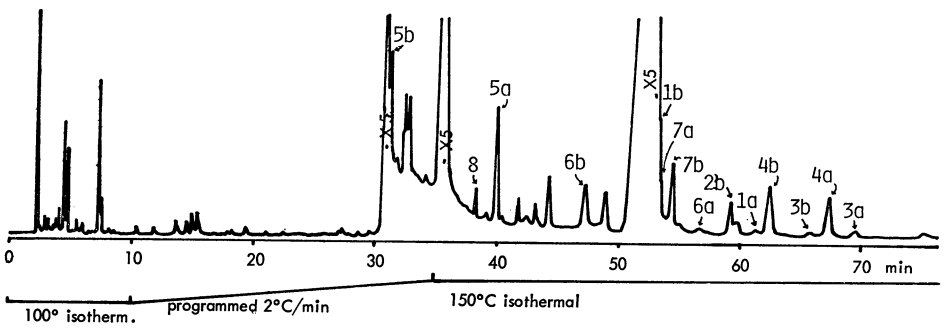

Fig. 1. The gas chromatogram of the volatile oil of fresh fruits.

*Isoneonepetalactone (**3b**).* Content: 0.003%; RRT: 1.77; $[\alpha]_D^{23}$ −66.2° (*c* 0.34); IR: 1710, 1638 cm^{-1}; NMR: δ 0.94 (3H, d, J=7 Hz, C-8 Me), 2.20 (3H, t, J=1 Hz, C-1 Me), 3.89, 4.24 (each 1H, AB q of ABX, J_{AX}=11 Hz, J_{BX}=5Hz, J_{AB}=11 Hz, C-9 H_2); MS: 166 (93%, M^+), 151 (21), 136 (8), 124 (90), 121 (30), 107 (24), 105 (13), 93 (60), 91 (26), 87 (42), 79 (100), 77 (30), 67 (15), 65 (10), 55 (12), 53 (14), 41 (30), and 39 (26). [Found, M^+ 166.0995. $C_{10}H_{14}O_2$ requires: M^+ 166.0993].

*Dehydroiridomyrmecin (**4a**).* Content: 0.80%; RRT: 1.79; $[\alpha]_D^{25}$ −105.6° (*c* 0.90); IR: 1730, 1650 cm^{-1}; NMR: δ 1.14 (3H, d, J=7 Hz, C-8 Me), 1.73 (3H, t, J=1 Hz, C-1 Me), 4.91 (2H, br s, C-7 H_2); MS: 166 (20%, M^+), 151 (1), 138 (5), 122 (22), 121 (18), 107 (57), 105 (26), 93 (100), 91 (42), 81 (21), 79 (36), 77 (34), 67 (12), 55 (14), and 41 (30). [Found, M^+ 166.0998].

*Isodehydroiridomyrmecin (**4b**).* Content: 1.40%; RRT: 1.59; $[\alpha]_D^{25}$ −79.2° (*c* 1.06); IR: 1730 cm^{-1}; NMR : δ 1.27 (3H, d, J=7 Hz, C-8 Me), 1.68 (3H, t, J=1 Hz, C-1 Me), 4.96 (2H, br s, C-7 H_2); MS: 166 (32%, M^+), 151 (2), 138 (9), 121 (6), 109 (12), 107 (13), 98 (14), 93 (100), 81 (25), 67 (7), 55 (11), and 41 (6). [Found, M^+ 166.0993].

*Actinidialactone (**5a**).* Content: 1.38%; RRT: 0.70; $[\alpha]_D^{25}$ −18.3° (*c* 1.15); IR: 1760 cm^{-1}; NMR: δ 1.23 (3H, d, J=7 Hz, C-8 Me), 1.47 (3H, s, C-2 Me), 1.75 (3H, t, J=1 Hz, C-1 Me), 5.56 (1H, br s, C-5H); MS: 166 (3%, M^+), 151 (2), 122 (50), 107 (100), 105 (16), 95 (10), 93 (22), 91 (44), 79 (28), 67 (6), 55 (6), and 43 (4). [Found, M^+ 166.0993].

*Isoactinidialactone (**5b**).* Content: 0.51%; RRT: 0.40; $[\alpha]_D^{25}$ −13.9° (*c* 0.94); IR: 1770 cm^{-1}; NMR: δ 1.29 (3H, d, J=7 Hz, C-8 Me), 1.46 (3H, s, C-2 Me), 1.73 (3H, t, J=1 Hz, C-1 Me), 5.41 (1H, br s, C-5 H); MS: 166 (5%, M^+), 151 (4), 122 (51), 107 (100), 95 (16), 93 (11), 91 (30), 79 (20), 67 (8), 55 (7), and 43 (11). [Found, M^+ 166.1009].

*Conversion of Dihydroepinepetalatone (**1a**) into Dihydronepetalactone (**6a**).* A mixture of 8 mg of **1a**, 10 mg of Na_2CO_3, and 0.5 ml of xylene was heated at 230 °C in a sealed tube for 2 h. The mixture was separated by preparative GLC to give an oily substance (6 mg), $[\alpha]_D^{25}$ +40.8° (*c* 0.60); IR: 1725 cm^{-1}; NMR: δ 0.90, 1.19 (each 3H, d, J=7 Hz, C-8 Me and C-1 Me); MS: 168 (17%, M^+), 153 (36), 139 (6), 126 (23), 113 (42), 95 (46), 81 (100), 67 (75), 55 (32), and 41 (68). The spectral data and the retention time in GLC were identical to those of natural lactone **6a**.

*Conversion of Isodihydroepinepetalactone (**1b**) into Isodihydronepetalactone (**6b**).* A solution of 28 mg of **1b** in 4 ml of methanol containing sodium methoxide (240 mg) was refluxed with stirring for 17 h. Next, 2 ml of water was added to the cooled solution, and it was refluxed for another 4 h then acidified with dil HCl. After the usual work-up, the resulting oily material (18 mg) was separated by preparative GLC into two components. The major product (13 mg) showed $[\alpha]_D^{25}$ +1.6° (*c* 0.94); IR: 1725 cm^{-1}; NMR: δ 0.97, 1.18 (each 3H, d, J=7 Hz, C-8 Me and C-1 Me); MS: 168 (17%, M^+), 153 (58), 139 (12), 126 (21), 123 (18), 113 (100), 95 (36), 81 (79), 67 (53), 55 (20), and 41 (37). The spectral data and the GLC retention time were identical to those of natural lactone **6b**.

*LAH Reduction of Dihydroepinepetalactone (**1a**), Isodihydroepinepetalactone (**1b**), and Isoepiiridomyrmecin (**2b**).* Each lactone was refluxed in ether with LAH for 2 h. After the usual work-up, the residual oil was chromatographed over silicic acid. Elution with ether afforded a pure saturated diol. The diol **10a** derived from **1a** showed $[\alpha]_D^{22}$ −49.4° (*c* 0.66); IR: 3320 cm^{-1}; NMR: δ 0.85, 0.95 (each 3H, d, J=7 Hz, C-8 Me and C-1 Me), 3.38, 3.72 (each 1H, AB q of ABX, J_{AX}=5 Hz, J_{BX}=5 Hz, J_{AB}=10 Hz, C-7 H_2), 3.51 (2H, d, J=7 Hz, C-9 H_2), 4.12 (2H, br s, 2×OH); MS: 154 (0.1%, M^+ −18), 123 (38), 109 (10), 95 (60), 81 (100), 67 (45), 55 (77), and 41 (75). This diol had the same $[\alpha]_D$ as authentic β-iridodiol ($[\alpha]_D^{23}$ −62°).[6] The diol **10b** derived from **2b** was identical in all respects to the diol prepared from **1b**. The diol **10b** showed $[\alpha]_D^{24}$ −19.5° (*c* 0.64); IR: 3320 cm^{-1}; NMR: δ 0.91, 0.93 (each 3H, d, J=7 Hz, C-8 Me and C-1 Me), 3.41, 3.70 (each 2H, m, C-7 and C-9 H_2); MS: 154 (0.5%, M^+ −18), 139 (2), 136 (2). 123 (81), 109 (16), 95 (72), 81 (100), 67 (34), 55 (39), and 41 (23). The diol was identical to authentic γ-iridodiol ($[\alpha]_D^{23}$ −19°).[6]

*LAH Reduction of Isoneonepetalactone (**3b**), Dehydroiridomyrmecin (**4a**), and Isodehydroiridomyrmecin (**4b**).* Each lactone was refluxed in ether with LAH for 2 h. The lactone **4a** was reduced with LAH to yield the diol **11a**, $[\alpha]_D^{24}$ −20.7° (*c* 2.28), which was identical in all respects to the authentic sample of dehydroiridodiol.[2] The lactones **3b** and **4b** were reduced with LAH to yield the same diol **11b**, $[\alpha]_D^{24}$ −15.6° (*c* 1.08), which was identical in all respects to the authentic sample of isodehydroiridodiol.[2]

*Catalytic Hydrogenation of Isoneonepetalactone (**3b**).* A mixture of 100 mg of **3b** in 3 ml of ether and 25 mg of PtO_2 catalyst was stirred under a hydrogen pressure of 1 atm at room temp for 5 min. Filtration of the catalyst and evaporation of the solvent afforded a mixture of the reduction products. GLC indicated the presence of 84% of **12b** and 16% of **13b**. A pure sample of **12b** showed $[\alpha]_D^{28}$ −66.1° (*c* 0.46); IR: 1725 cm^{-1}; NMR: δ 0.98 (6H, d, J=7 Hz, C-8 Me and C-1 Me), 3.85, 4.19 (each 1H, AB q of ABX, J_{AX}=10 Hz, J_{BX}=4 Hz, J_{AB}=11 Hz, C-9 H_2); MS: 168 (6%, M^+), 153 (5), 126 (7), 123 (7), 113 (100), 95 (27), 81 (35), 67 (35), 55 (20), and 41 (34). A pure sample of **13b** showed $[\alpha]_D^{24}$ −89.1° (*c* 1.94); IR: 1720, 1640 cm^{-1}; UV: λ_{max}^{EtOH} 235 nm (log ε 4.10); NMR: δ 1.14 (3H, d, J=7 Hz, C-8 Me), 1.18 (3H, d, J=7 Hz, C-1 Me), 4.06, 4.37 (each 1H, AB q of ABX, J_{AX}=6 Hz, J_{BX}=5 Hz, J_{AB}=11 Hz, C-9 H_2); MS: 166 (100%, M^+), 151 (50), 136 (49), 123 (25), 121 (61), 107 (58), 95 (36), 93 (40), 91 (38), 81 (18), 79 (40), 77 (30), 67 (18), 65 (13), 53 (13), 41 (25), and 39 (26).

*Transformation of Isodehydroiridomyrmecin (**4b**) into the New Saturated γ-Lactones **14b** and **15b**.* The lactone **4b** (40 mg) was hydrogenated in ether over PtO_2 catalyst for 40 min. After the usual work-up, the residue was purified by preparative GLC to give a single product. It showed the following spectral data; IR: 3500—2500, 1700 cm^{-1} (COOH); NMR: δ 0.95 (3H, d, J=7 Hz, C-8 Me), 1.61, 1.64 (each 3H, s, C-1 Me and C-2 Me); MS: 168 (10%, M^+), 113 (13), 95 (100), 81 (10), 67 (17), 55 (13), and 41 (9). A solution of 38 mg of the acid in 4 ml of benzene containing 30 mg of *p*-toluenesulfonic acid was refluxed with stirring for 40 min. The solution was washed with 10% $NaHCO_3$ aq and water, then dried over Na_2SO_4. After the solvent was removed, the mixture was separated by preparative GLC into two saturated γ-lactones **14b** and **15b** in a ratio of 3 : 4. A pure sample of **14b** showed $[\alpha]_D^{19}$ +43.3° (*c* 0.09); IR: 1760 cm^{-1}; NMR: δ 1.05 (3H, d, J=6 Hz, C-1 Me), 1.37 (3H, d, J=7 Hz, C-8 Me), 1.48 (3H, s, C-2 Me); MS: 168 (23%, M^+), 153 (1), 140 (6), 125 (100), 109 (22), 95 (23), 81 (6), 72 (23), 69 (15), 55 (31), and 43 (22). A pure sample of **15b** showed $[\alpha]_D^{19}$ +13.8° (*c* 0.08); IR: 1760 cm^{-1}; NMR: δ 0.99 (3H, d, J=6 Hz, C-1 Me), 1.34 (3H, d, J=7 Hz, C-8 Me), 1.35 (3H, s, C-2 Me); MS: 168 (21%, M^+), 153 (1), 140 (5), 125 (100), 109 (22), 95 (28), 81 (7), 72 (32), 69 (18), 55 (45), and 43 (30).

*Catalytic Hydrogenation of Isoactinidialactone (**5b**).* The lactone **5b** (20 mg) was hydrogenated in ether over PtO_2 catalyst for 1.5 h. The reaction mixture was worked up in the usual manner to give a mixture of the lactones **14b** and **15b**

in a ration of 12 : 1. These lactones were identical in all respects to the lactones prepared from **4b** as described above.

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7) Spectral data confirmed that this acid was (1*R*, α*R*)-2,3,α-trimethyl-2-cyclopenteneacetic acid.

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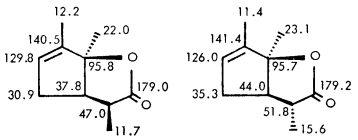
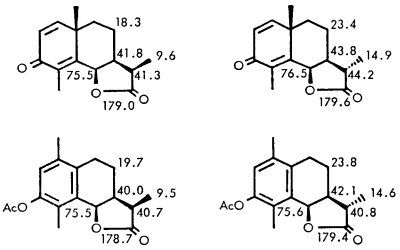
11) ^{13}C-NMR data of **5a** and **5b**.



5a 5b

Cf. ^{13}C chemical shifts of the α- and β-episantonin derivatives.[9,10]



12) The content of lactone was calculated using a GC/computer system from the peak area of GLC.

13) Relative retention time was evaluated with isodihydronepetalactone (**6b**) as the standard substance.