[Chem. Pharm. Bull. 18(10)1967—1973(1970)]

UDC 547.94.07 : 547.473.2.07

The Preparation of Fused Ring α,β-Unsaturated Lactones using Lithium Ethoxyacetylide. Syntheses of Dihydroactinidiolide and Actinidiolide, and Partial Synthesis of Dihydrosecurinine

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(Received February 27, 1970)

The syntheses of (±)-dihydroactinidiolide and (±)-actinidiolide, and partial synthesis of dihydrosecurinine were described. Lithium ethoxyacetylide procedure was shown to be a useful method for the preparation of fused ring α,β-unsaturated lactones.

The α,β-unsaturated γ-lactones fused with the homocyclic ring system occur widely in plants, but few synthetic pathways for those α,β-butenolide have been reported while a large number of procedures have been developed for those of non-fused ring system.[2] In connection with the synthetic work of Securinega alkaloids, a group of lactonic alkaloids, there has been developed a new method for the preparation of fused ring α,β-unsaturated γ-lactones which involves an addition of lithium ethoxyacetylide to α-ketol (I) and subsequent lactonization of the resulting β-ethoxyethynylcarbinol (II).[3] The present paper describes the syntheses of some fused ring butenolides of natural source using this procedure.

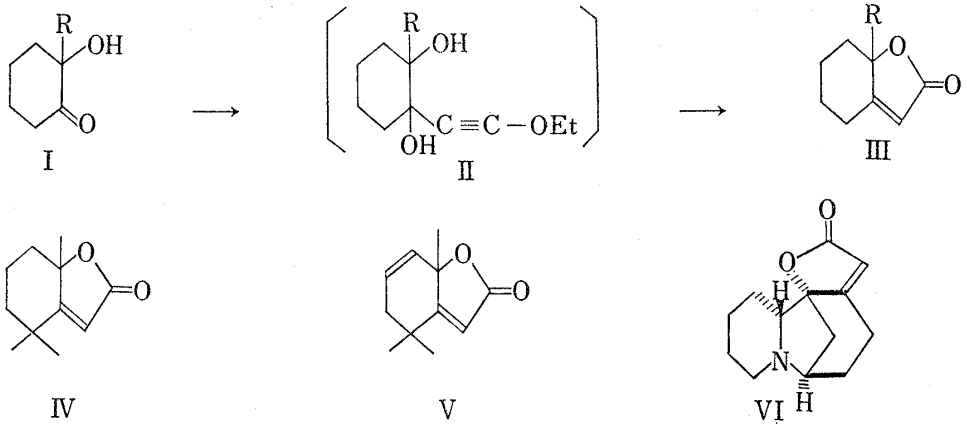


Chart 1

It was found that lithium ethoxyacetylide condensed readily with α-ketol (I) in anhydrous ether at −30°, and treatment of the resulting ethynylcarbinol (II) with dilute sulfuric acid

1) Location: *Toneyama 6-5, Toyonaka, Osaka.*
2) Y.S. Rao, *Chem. Rev.*, **64**, 353 (1964); A relatively useful method has been reported by Epstein, which involves the Reformatsky reaction of α-chlorocyclohexanone followed by pyrolytic cyclization [W.W. Epstein and A.C. Sonntag, *Tetrahedron Letters*, **1966**, 791].
3) It is well known that the condensation of ketone with lithium ethoxyacetylide and subsequent treatment with acid affords the α,β-unsaturated ester as the main product. For a review of this method, see J.F. Arens, "Advances in Organic Chemistry:Methods and Results," Vol. II, Interscience, New York, 1960, p. 203. A transformation of α-acetoxyketone into α,β-butenolide of non-fused system using lithium ethoxyacetylide method has been reported by Deghenghi [R. Deghenghi, A. Philipp, and R. Gaudry, *Tetrahedron Letters*, **1963**, 2045].

in tetrahydrofuran gave the butenolide (III) in a fair yield.[4] The syntheses of securinine[5] and racemic loliolide[6] were achieved by using this useful method. By application of a similar cyclization procedure have been synthesized three additional α,β-butenolides, *i.e.* (±)-dihydroactinidiolide (IV), (±)-actinidiolide (V) and dihydrosecurinine (VI), as described below.

Synthesis of (±)-Dihydroactinidiolide

Dihydroactinidiolide and actinidiolide were isolated from *Actinidia polygama* and their structure were assigned as IV and V, respectively.[7] They have been found to be effective for Felidae animals in a small amount. Recently, much attention has been given to dihydroactinidiolide, one of the principles of tea aroma,[8a-c] because of its isolation[8] from several species of plants. The synthesis of dihydroactinidiolide has already been reported by Sakan, *et al.*,[7,9] Mousseron-Canet, *et al.*,[10] Demole, *et al.*,[11] and Bailey, *et al.*,[8e] and actinidiolide by Sakan, *et al.*,[9a] and Demole, *et al.*[11]

2-Hydroxy-2,6,6-trimethylcyclohexanone (VII)[12] was treated with lithium ethoxyacetylide in anhydrous ether at −30°. Refluxing of the resulting ethynylcarbinol with 15% sulfuric acid in tetrahydrofuran afforded (±)-dihydroactinidiolide (IV) in 47% yield. The synthetic racemic dihydroactinidiolide was shown to be identical with natural dihydroactinidiolide on comparison of the infrared (IR) spectrum and of retention time in gas liquid chromatography (GLC).

Synthesis of (±)-Actinidiolide

Epoxidation of 2,6,6-trimethyl-2-cyclohexenone (VIII)[6,13] with 30% hydrogen peroxide gave the α,β-epoxyketone (IX) in 90% yield. Hydrolysis of the epoxide (IX) with aqueous methanol containing conc. sulfuric acid yielded a dihydroxyketone (X) and a hydroxymethoxyketone (XI) in 42% and 40% yields, respectively. The dihydroxyketone (X) was condensed with lithium ethoxyacetylide and the resulting ethynylcarbinol was treated with dilute sulfuric acid in tetrahydrofuran afforded the butenolide (XII), mp 94—95°, in 50% yield. The α,β-epoxyketone (IX) was also condensed with the ethoxyacetylide according to the procedure described for XII to give the butenolide (XII), in 50% yield, together with an unsaturated ester (XIII). Oxidation of XII with Jones reagent gave the ketobutenolide (XIV), in 60% yield, bromination of which in chloroform containing hydrobromic acid furnished a bromoketone (XV) in 66% yield. On sodium borohydride reduction, XV gave a bromohydrin (XVI), which was treated with mesyl chloride in pyridine to yield the mesylate (XVII). Reduction of XVII with zinc dust in acetic acid afforded (±)-actinidiolide (V), mp 38—39°, in 90% yield. The product showed absorptions at 1750 and 1626 cm^{-1} in the IR spectrum

4) Z. Horii, M. Hanaoka, Y. Tamura, S. Saito, and N. Sugimoto, *Chem. Ind.* (London), **1964**, 664.
5) Z. Horii, M. Hanaoka, Y. Yamawaki, Y. Tamura, S. Saito, N. Shigematsu, K. Kotera, H. Yoshikawa, Y. Sato, H. Nakai, and N. Sugimoto, *Tetrahedron*, **23**, 1165 (1967).
6) Z. Horii, T. Yagami, and M. Hanaoka, *Chem. Commun.*, **1966**, 634; Z. Horii, T. Yagami, M. Ito, and M. Hanaoka, *Chem. Pharm. Bull.* (Tokyo), **16**, 848 (1968).
7) T. Sakan, S. Isoe, and S.B. Hyeon, *Tetrahedron Letters*, **1967**, 1623.
8) *a*) J. Bricout, R. Viani, R. Müggler-Chavan, J.P. Marion, D. Raymond, and R.H. Egli, *Helv. Chim. Acta*, **50**, 1517 (1967); *b*) K. Ina, Y. Sakato, and H. Fukami, *Tetrahedron Letters*, **1968**, 2777; *c*) S. Fukushima, Y. Akahori, and T. Tsuneya, *Yakugaku Zasshi*, **88**, 646 (1968); *d*) H. Kaneko and K. Ijichi, *Agr. Biol. Chem.*, **32**, 1337 (1968); *e*) W.C. Bailey, Jr., A.K. Bose, R.M. Ikeda, R.H. Newman, N.V. Secor, and C. Varsel, *J. Org. Chem.*, **33**, 2819 (1968); *f*) E. Demole, P. Enggist, and M. Stoll, *Helv. Chim. Acta*, **52**, 24 (1969); *g*) R. Viani, J. Bricout, J.P. Marion, F. Müggler-Chavan, D. Reymond, and R.H. Egli, *ibid.* **52**, 887 (1969).
9) *a*) S. Isoe, S.B. Hyeon, H. Ichikawa, S. Katsumura, and T. Sakan, *Tetrahedron Letters*, **1968**, 5561; *b*) S. Isoe, S.B. Hyeon, and T. Sakan, *ibid.*, **1969**, 279.
10) M. Mousseron-Canet, J.C. Mani, and J.P. Dalle, *Bull. Soc. Chim. France*, **1967**, 608.
11) E. Demole and P. Enggist, *Helv. Chim. Acta*, **51**, 481 (1968).
12) C.L. Stevens and A.J. Weinheimer, *J. Am. Chem. Soc.*, **80**, 4072 (1958).
13) J. Meinwald and C.C. Cornwall, *J. Am. Chem. Soc.*, **77**, 5991 (1955).

and at 210.5 mμ in the ultraviolet (UV) spectrum, and was shown to be identical with natural actinidiolide in the IR and nuclear magnetic resonance (NMR) spectra. Attempts to obtain (±)-actinidiolide by elimination of 3-hydroxyl or its equivalent in XII were unsuccessful. Although the hydroxymethoxyketone (XI) was assumed not to be the tertiary methoxide from the reaction mechanism, further confirmation of the structure (XI) was given by transformation of the hydroxymethoxyketone (XI) into the methoxybutenolide (XVIII) according to the ethoxyacetylide procedure described above.

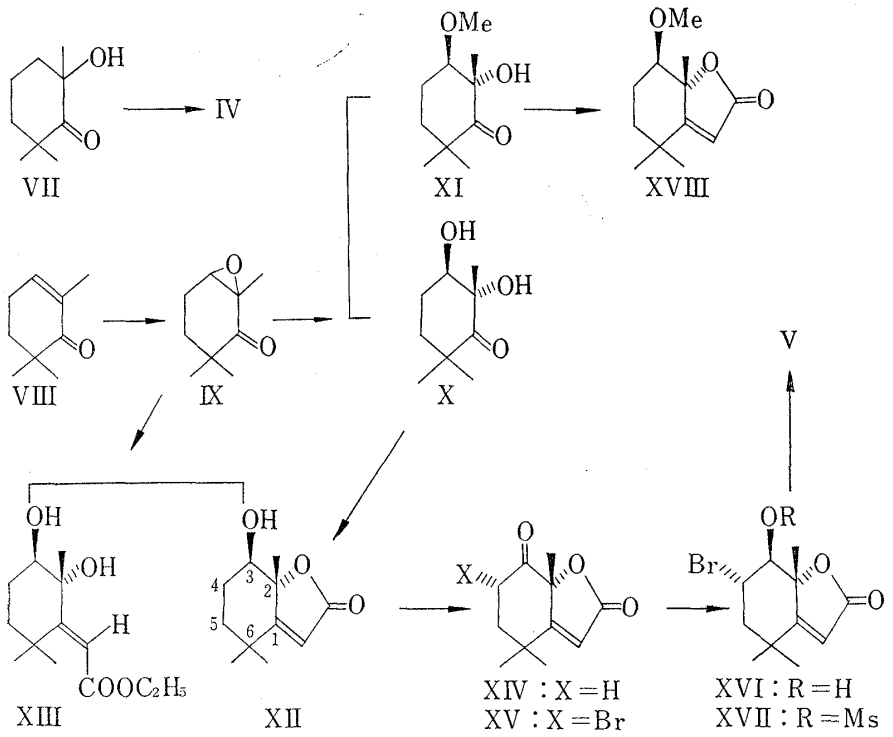


Chart 2

The conformations of the compounds (X, XI, XII, XIII, XVI, XVIII) were assigned from their NMR spectra. From coupling constants determination as shown in Table I, protons at C_3 in X, XI, XII, XIII, XVI, and XVIII are axially oriented.

Table I

	X	XI	XII	XIII	XVI	XVIII
C_3-H (τ)	6.31q J=5.8, 9.6	6.83q J=6.3, 10.2	6.42q J=4.9, 10.2	6.2—6.5m $W_{1/2}$=16	6.47q J=3.5, 10.9	6.93q J=4.3, 10.3

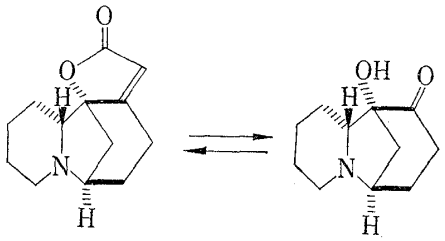
q: quartet m: multiplet J, $W1/2$: in cps

Partial Synthesis of Dihydrosecurinine

In order to verify the applicability of the present method to an aminoketol, the partial synthesis of dihydrosecurinine (VI) was undertaken. The α-ketol (XIX)[14] derived from dihydrosecurinine (VI) was condensed with lithium ethoxyacetylide in anhydrous ether at −30°. The resulting product was refluxed with 15% sulfuric acid in tetrahydrofuran for

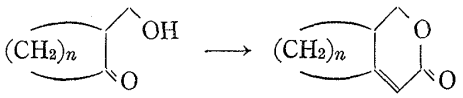
14) I. Satoda, M. Murayama, T. Tsuji, and E. Yoshii, *Tetrahedron Letters*, **1962**, 1199; Z. Horii, M. Ikeda, Y. Yamawaki, Y. Tamura, S. Saito, and K. Kotera, *Tetrahedron*, **19**, 2101 (1963).

30 min. Distillation of the crude product gave the aminobutenolide (VI) in 25% yield. The butenolide was identical with natural dihydrosecurinine in the IR spectrum and in retention time in GLC.



VI XIX

Chart 3



XX: $n=3$ XXII: $n=3$
XXI: $n=4$ XXIII: $n=4$

Chart 4

It may be concluded from the results obtained that the present method is a useful one for the preparation of a fused-ring α,β-unsaturated γ-lactone because of its fair yield or its simple procedure. Furthermore, the applicability of the ethoxyacetylide procedure to the synthesis of fused-ring α,β-unsaturated δ-lactones was established by transformations of the 2-hydroxymethylcyclopentanone (XX)[15] and the 2-hydroxymethylcyclohexanone (XXI)[15] into the unsaturated δ-lactones, (XXII) and (XXIII),[16] respectively.

Further investigation to clarify the reaction mechanism of this butenolide synthesis is now in progress.

Experimental[17]

(±)-Dihydroactinidiolide (IV)——A solution of ethoxyacetylene (2.8 g) in dry ether (8 ml) was added to a stirred solution of MeLi (prepared from Li (0.56 g) and MeI (5.6 g)) in dry ether (20 ml) under N_2 at −10——15° over a period of 10 min. The mixture was stirred for an additional 15 min, and to this was added a solution of 2-hydroxy-2,6,6-trimethylcyclohexanone (VII)[12] (1.4 g) in dry ether (10 ml) at −25——30° with stirring over a period of 30 min. After the addition was complete, stirring was continued for 2 hr at −30° and then 2 hr at room temperature. The resulting complex in the reaction mixture was decomposed with saturated aqueous NH_4Cl solution. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layer was dried and evaporated to give a yellow oil (1.8 g), which was refluxed with 15% H_2SO_4 (4.5 ml) in tetrahydrofuran (19 ml) for 15 min. The mixture was neutralized with $NaHCO_3$, evaporated, and extracted with $CHCl_3$. Evaporation of the dried extract and chromatography of the residue (2.2 g) on silica gel (22 g) in $CHCl_3$ gave two fractions. The first fraction gave crystals, which were recrystallized from petr. ether (bp 30—50°) to give (±)-dihydroactinidiolide (IV, 750 mg, 47%) as colorless plates, mp 41—42°. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1752 (conjugated γ-lactone), 1627, 862 (C=C). *Anal.* Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.80; H, 9.13. This product was identical with natural dihydroactinidiolide in IR (CCl_4) and in retention time in GLC.

The second fraction gave crystals, which were recrystallized from *n*-hexane–benzene to give a β-hydroxy-γ-lactone (60 mg, 3.4%) as colorless needles, mp 112—113°. IR ν_{max}^{KBr} cm^{-1}: 3453 (OH), 1748 (γ-lactone). NMR ($CDCl_3$) τ: 9.01 (3H, singlet, C–Me), 8.96 (3H, singlet, C–Me), 8.51 (3H, singlet, C–Me), 7.88 (1H, singlet, OH), 7.34 (2H, AB quartet, $J=17.1$ cps, $-CH_2CO-$). *Anal.* Calcd. for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 67.11; H, 9.06. This compound was dehydrated with $SOCl_2$ in pyridine to give the butenolide (IV) in 60% yield.

2,3-Epoxy-2,6,6-trimethylcyclohexanone (IX)——To a stirred mixture of 2,6,6-trimethyl-2-cyclohexenone (VIII)[6,13] (10 g), 30% H_2O_2 (20.8 ml), and MeOH (72 ml) was added 6N NaOH (6 ml) dropwise at 15°, and the mixture was stirred at 20—25° for 3 hr, poured into 90 ml of H_2O and extracted with ether. The ether

15) F.H. Case, *J. Org. Chem.*, **21**, 1069 (1956).
16) B. Belleau, *Can. J. Chem.*, **35**, 673 (1957).
17) Melting points and boiling points are uncorrected. The extracts were dried over Na_2SO_4 unless otherwise specified. NMR spectra were taken on Hitachi H-6013 spectrometer with Me_4Si as the internal standard. GLC was carried on Perkin-Elmer gas chromatograph model 800, employing SE-30 column.

layer was washed with satd. NaCl, dried, evaporated, and fractionated to give IX (10 g, 90%) as a colorless oil, bp 95—97° (22 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1701 (C=O), 898. *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.84; H, 9.17.

2,3-Dihydroxy-2,6,6-trimethylcyclohexanone (X) and 2-Hydroxy-3-methoxy-2,6,6-trimethylcyclohexanone (XI)——A solution of IX (3.7 g) in 65% MeOH (20 ml) containing 20 drops of sulfuric acid was refluxed for 5 hr and then was diluted with H_2O (20 ml). The solution was made slightly alkaline with anhyd. K_2CO_3 and extracted with $CHCl_3$. Evaporation of the dried extract gave a yellow oil, which was chromatographed on silica gel in $CHCl_3$. The first fraction gave a yellow oil of XI (1.8 g, 40%), bp 120—123° (bath temp., 18 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1695 (C=O). NMR ($CDCl_3$) τ: 8.88 (3H, singlet, C–Me), 8.80 (3H, singlet, C–Me), 8.66 (3H, singlet, C–Me), 6.83 (1H, quartet, J=6.3, 10.2 cps, C<u>H</u>OMe), 6.51 (3H, singlet, O–Me), 5.94 (1H, singlet, OH). The 2,4-dinitrophenylhydrazone: yellow crystals (from EtOH), mp 189—190°. *Anal.* Calcd. for $C_{16}H_{22}O_6N_4$: C, 52.45; H, 6.05; N, 15.29. Found: C, 52.73; H, 5.73; N, 15.63.

The second fraction gave crystals, which were recrystallized from *n*-hexane to yield X (1.7 g, 42%) as colorless plates, mp 58—59°. IR ν_{max}^{KBr} cm^{-1}: 3353 (OH), 1702 (C=O). NMR ($CDCl_3$) τ: 8.89 (3H, singlet, C–Me), 8.79 (3H, singlet, C–Me), 8.64 (3H, singlet, C–Me), 6.31 (1H, quartet, J=5.8, 9.6 cps, C<u>H</u>OH). *Anal.* Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.84; H, 9.19.

2,3-Dihydroxy-2,6,6-trimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid γ-Lactone (XII)——a) From X: A solution of ethoxyacetylene (1.8 g) in dry ether (8 ml) was added to a stirred solution of MeLi (prepared from Li (0.36 g) and MeI (3.6 g)) in dry ether (15 ml) under N_2 at −15° over a period of 10 min. The reaction mixture was stirred for an additional 15 min, followed by addition of a solution of X (0.9 g) in dry ether (10 ml) at −25——30° with stirring over a period of 30 min. After the addition was complete, stirring was continued for 2 hr at −30° and 3 hr at room temperature. The resulting complex in the mixture was decomposed with satd. NH_4Cl. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether layer was dried and evaporated to give a reddish brown oil (1.0 g), a solution of which in tetrahydrofuran (17.5 ml) was refluxed with 15% H_2SO_4 (2.5 ml) for 15 min. The solution was neutralized with $NaHCO_3$, evaporated and extracted with $CHCl_3$. Evaporation of the dried extract and chromatography of the residue (1.0 g) on silica gel (10 g) in $CHCl_3$ gave the first crop of crystals, which were recrystallized from petr. benzene–benzene to yield XII (520 mg, 50%) as colorless plates, mp 94—95°. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1745 (unsatd. γ-lactone), 1621, 857 (C=C). NMR ($CDCl_3$) τ: 8.77 (3H, singlet, C–Me), 8.72 (3H, singlet, C–Me), 8.48 (3H, singlet, C–Me), 6.94 (1H, singlet, OH), 6.42 (1H, quartet, J=4.9, 10.2 cps, C<u>H</u>OH), 4.33 (1H, singlet, =CH). *Anal.* Calcd. for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.42; H, 8.12.

Elution with AcOEt gave the second crop of crystals, which were recrystallized from AcOEt to yield a dihydroxy-γ-lactone (135 mg, 12%) as colorless crystals, mp 220°. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1754 (γ-lactone). NMR (D_5-pyridine) τ: 8.90 (3H, singlet, C–Me), 8.78 (3H, singlet, C–Me), 8.09 (3H, singlet, C–Me), 7.00 (2H, AB quartet, J=17.0 cps, –C<u>H</u>$_2$CO–), 3.18 (1H, singlet, OH). *Anal.* Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 62.13; H, 8.33.

b) From IX: The epoxy-ketone (IX, 0.9 g) was condensed with lithium ethoxyacetylide in the same manner as described in a). Crude oil obtained was chromatographed on silica gel in $CHCl_3$. The first fraction gave XII (510 mg, 50%). The second fraction, a yellow oil, was further chromatographed on silica gel. Elution with $CHCl_3$ afforded crystals, which were recrystallized from petr. ether to yield XIII (290 mg, 21%) as colorless crystals, mp 56—56.5°. IR ν_{max}^{KBr} cm^{-1}: 3411 (OH), 1716 (unsatd. ester), 1630 (C=C). NMR ($CDCl_3$) τ: 8.74 (6H, singlet, C–Me), 8.63 (3H, singlet, C–Me), 8.71 (3H, triplet, J=7.2 cps, $CH_2C\underline{H}_3$), 5.80 (2H, quartet, J=7.2 cps, $C\underline{H}_2CH_3$), about 7.78 (2H, multiplet, OH), 6.2—6.5 (1H, multiplet, $W_{1/2}$=16 cps, C<u>H</u>OH), 3.61 (1H, singlet, =CH). *Anal.* Calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.48; H, 9.17.

2-Hydroxy-3-oxo-2,6,6-trimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid γ-Lactone (XIV)——To a stirred solution of XII (1.0 g) in acetone (20 ml) was added an excess of Jones reagent at room temperature. After 5 hr, the excess of the reagent was decomposed with MeOH and the solution was diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried, and evaporated to give a yellow oil, which was chromatographed on silica gel in CH_2Cl_2. The first fraction gave crystals, which were recrystallized from *n*-hexane–benzene to yield XIV (610 mg, 61%) as colorless needles, mp 99.0—99.5°. IR ν_{max}^{KBr} cm^{-1}: 1746 (unsatd. γ-lactone), 1728 (C=O), 1624, 856 (C=C). *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.94; H, 7.00.

The second eluted component (210 mg, 21%) was identical with the starting material (XII).

4-Bromo-2-hydroxy-3-oxo-2,6,6-trimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid γ-Lactone (XV)——To a stirred solution of XIV (800 mg) in $CHCl_3$ (50 ml) containing one drop of 25% HBr was added dropwise a solution of Br_2 (650 mg) in $CHCl_3$ (5 ml) at 40°. After the color of Br_2 disappeared, the mixture was diluted with $CHCl_3$ (40 ml), washed with H_2O, and dried. Evaporation of the dried extract and chromatography of the residue on silica gel in CH_2Cl_2 gave crystals, which were recrystallized from *n*-hexane–benzene to yield XV (700 mg, 66%) as colorless needles, mp 161—163°. IR ν_{max}^{KBr} cm^{-1}: 1742 (unsatd. γ-lactone), 1624, 869 (C=C). NMR ($CDCl_3$) τ: 4.97 (1H, quartet, J=5.7, 12.5 cps, C<u>H</u>Br), 4.23 (1H, singlet, =CH). *Anal.* Calcd. for $C_{11}H_{13}O_3Br$: C, 48.37; H, 4.80. Found: C, 48.73; H, 4.73.

4-Bromo-2,3-dihydroxy-2,6,6-trimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid γ-Lactone (XVI)——To a stirred solution of XV (400 mg) in MeOH (30 ml) was added $NaBH_4$ (150 mg) at 0°. The mixture was stirred for 1 hr, diluted with H_2O (30 ml), neutralized with conc. HCl, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and evaporated. Chromatography of the residue on silica gel in CH_2Cl_2 gave crystals, which were recrystallized from *n*-hexane–benzene to yield XVI (200 mg, 50%) as colorless needles, mp 173.5—174.5°. IR ν_{max}^{KBr} cm^{-1}: 3331 (OH), 1737 (unsatd. γ-lactone), 1624, 865 (C=C). NMR ($CDCl_3$) τ: 8.74 (3H, singlet, C–Me), 8.70 (3H, singlet, C–Me), 8.48 (3H, singlet, C–Me), 6.72 (1H, doublet, J=3.5 cps, OH), 6.47 (1H, quartet, J=3.5, 10.9 cps, CHOH), 5.86 (1H, octet, J=5.5, 13.1, 10.9 cps, CHBr), 8.20 (1H, quartet, J=13.1, 13.6 cps, C_5–H_{axial}), 7.73 (1H, quartet, J=5.5, 13.6 cps, C_5–$H_{equatorial}$), 4.29 (1H, singlet, =CH). *Anal.* Calcd. for $C_{11}H_{15}O_3Br$: C, 48.04; H, 5.13; Br, 29.04. Found: C, 47.79; H, 5.35; Br, 29.46.

4-Bromo-2-hydroxy-3-mesyloxy-2,6,6-trimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid γ-Lactone (XVII)——To an ice cooled-solution of XVI (300 mg) in pyridine (10 ml) was added mesyl chloride (770 mg), and the mixture was warmed at 60° for 3 hr, poured into H_2O (20 ml), and extracted with CH_2Cl_2. The extract was washed with 10% HCl, dried, and evaporated. Chromatography of the residue on silica gel in $CHCl_3$ gave two fractions. The first fraction gave crystals, which were recrystallized from acetone–petr. ether to yield XVII (240 mg, 60%) as colorless crystals, mp 254—255°. IR ν_{max}^{KBr} cm^{-1}: 1761 (unsatd. γ-lactone), 1623, 841 (C=C), 1370, 1179 (mesyl). *Anal.* Calcd. for $C_{12}H_{17}O_5SBr$: C, 40.82; H, 4.85. Found: C, 41.14; H, 4.54.

The second fraction gave crystals (50 mg, 17%), which was identical with the starting material (XVI).

(±)-Actinidiolide (V)——A mixture of XVII (180 mg), zinc dust (900 mg) and AcOH (30 ml) was refluxed for 30 min with vigorous stirring. The precipitates were separated and washed with AcOH. The combined AcOH solution was diluted with H_2O (20 ml), neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated. Chromatography of the residue on silica gel in $CHCl_3$ gave (±)-actinidiolide (V, 80 mg, 90%) as a colorless oil, bp 115° (bath temp., 0.002 mmHg), which solidified on standing. mp 38—39° (from petr. ether). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1757 (unsatd. γ-lactone), 1629 (C=C). ν_{max}^{KBr} cm^{-1}: 1748 (unsatd. γ-lactone), 1631 (C=C). UV $\lambda_{max}^{n\text{-hexane}}$ mμ (log ε): 210.5 (4.12). NMR ($CDCl_3$) τ: 8.71 (3H, singlet, C–Me), 8.69 (3H, singlet, C–Me), 8.42 (3H, singlet, C–Me), 7.81 (2H, doublet, J=2 cps, CH_2), 4.36 (1H, singlet, =CH), 4.15—4.33 (2H, multiplet, CH=CH). *Anal.* Calcd. for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.11; H, 7.88.

2-Hydroxy-3-methoxy-2,6,6-trimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid γ-Lactone (XVIII)——The methoxyketone (XI, 1.2 g) was condensed with ethoxyacetylene in the same manner as described for XII. Crude product was chromatographed on silica gel. Elution with $CHCl_3$ gave crystals, which were recrystallized from *n*-hexane to yield XVIII (790 mg, 51%) as colorless crystals, mp 74.0—74.5°. IR ν_{max}^{KBr} cm^{-1}: 1749 (unsatd. γ-lactone), 1621, 875 (C=C). NMR ($CDCl_3$) τ: 8.78 (3H, singlet, C–Me), 8.72 (3H, singlet, C–Me), 8.50 (3H, singlet, C–Me), 6.93 (1H, quartet, J=4.3, 10.3 cps, CHOMe), 6.49 (3H, singlet, O–Me), 4.31 (1H, singlet, =CH). *Anal.* Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.69; H, 8.46.

Elution with AcOEt gave crystals, which were recrystallized from *n*-hexane to yield a γ-lactone (300 mg, 22%) as colorless crystals, mp 141—142°. IR ν_{max}^{KBr} cm^{-1}: 3478 (OH), 1755 (γ-lactone). NMR ($CDCl_3$) τ: 9.01 (3H, singlet, C–Me), 8.98 (3H, singlet, C–Me), 8.57 (3H, singlet, C–Me), 7.40 (2H, AB quartet, J=18.0 cps, $-CH_2CO-$), 7.51 (1H, singlet, OH), 6.84 (1H, quartet, J=3.6, 9.1 cps, HCOMe), 6.56 (3H, singlet, O–Me). *Anal.* Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.37; H, 8.72.

Dihydrosecurinine (VI)——A solution of ethoxyacetylene (1.25 g) in dry ether (5 ml) was added to a stirred solution of MeLi (prepared from Li (0.25 g) and MeI (3.0 g)) in dry ether (10 ml) under N_2 at −10° over a period of 10 min. The mixture was stirred for an additional 20 min, followed by addition of a solution of 1,2,3,4,7,8,10,10aβ-octahydro-10-hydroxy-6,10-methanopyrido[1,2-*a*]azepin-9(6*H*)-one[14] (XIX, 0.5 g) in dry ether (10 ml) at −30° with stirring over a period of 30 min. After the addition was complete, stirring was continued for 1 hr at −30° and for 3 hr at room temperature. The resulting complex in the mixture was decomposed with satd. NH_4Cl. The ether layer was separated and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was dried and evaporated to give a reddish brown oil (0.6 g), which was refluxed with 15% H_2SO_4 (2.4 ml) in tetrahydrofuran (14 ml) for 30 min. The solvent was removed *in vacuo* and the residual liquid was made alkaline with K_2CO_3, and extracted with $CHCl_3$. Evaporation of the dried extract and distillation of the residue under reduced pressure gave VI (140 mg, 25%), bp 165—170° (bath temp., 0.4—0.5 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1815, 1770 (unsatd. γ-lactone), 1652 (C=C). This product was identical with the natural dihydrosecurinine in the IR spectrum (CCl_4) and in retention time in GLC. The perchlorate: colorless needles (from EtOH), mp 214—216°. *Anal.* Calcd. for $C_{13}H_{18}O_6NCl$: C, 48.83; H, 5.67; N, 4.38. Found: C, 49.04; H, 5.62; N, 4.22. This salt did not depress the melting point of the perchlorate of natural dihydrosecurinine on admixture and the IR spectra of both specimens were identical in Nujol.

2-Hydroxymethyl-$\Delta^{1,\alpha}$-cyclopentaneacetic Acid δ-Lactone (XXII)——2-Hydroxymethylcyclopentanone[15] (XX, 0.75 g) was condensed with ethoxyacetylene in the same manner as described for XII. Chromatography of the crude product on silica gel in $CHCl_3$ gave XXII (322 mg, 35%) as a colorless oil, bp 145° (bath temp., 2 mmHg). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730 (unsatd. δ-lactone), 1654 (C=C). *Anal.* Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.55; H, 7.20.

2-Hydroxymethyl-$\Delta^{1,\alpha}$-cyclohexaneacetic Acid δ-Lactone (XXIII)——2-Hydroxymethylcyclohexanone[15] (XXI, 0.9 g) was treated according to the method described for XII to give XXIII[16] (368 mg, 34%) as colorless plates, mp 62.0—62.5° (*n*-hexane), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1734 (unsatd., δ-lactone), 1642 (C=C). *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.65: H, 7.72.

Acknowledgement The authers are grateful to Professor T. Sakan for providing the sample of natural dihydroactinidiolide and the IR and NMR spectra of natural actinidiolide.