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The Biogenetic-Type Cyclization of the Unsaturated Monocyclic Alcohol with Formic Acid; Facile Synthesis of the Tricarbocyclic Alcohol, (+)-2-Epi-allo-cedrol

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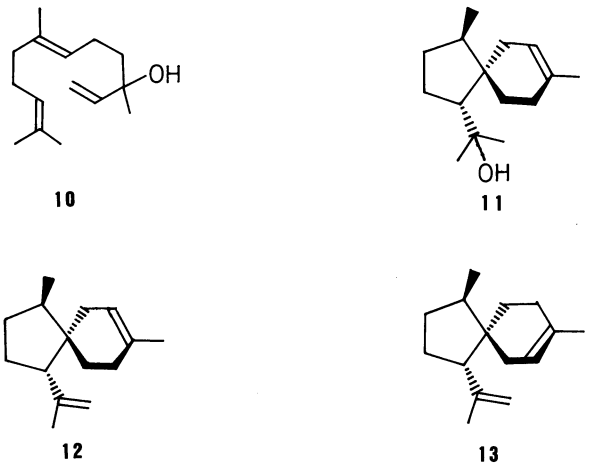
The biogenetic-type cyclization of (+)-(3*S*)-2-(3-hydroxy-3-methyl-4-pentenyl)-1-methyl-3-(1-methylethenyl)-cyclopentene, prepared from *d*-limonene, with formic acid gave stereo and regiospecifically the formates of the tricyclic compounds of the allo-cedrol skeleton, hydrolysis of which gave the unsaturated alcohols, (+)-(1S,5*R*,7*R*,8*S*)-2,6,6,7-tetramethyltricyclo[5.2.2.0^{1,5}]undec-2-en-8-ol (**27**) and (+)-(1*S*,5*R*,7*R*,8*R*)-2,6,6,7-tetramethyltricyclo[5.2.2.0^{1,5}]undec-2-en-8-ol. Hydrogenation of **27** gave (+)-(1*R*,2*S*,5*R*,7*R*,8*S*)-2,6,6,7-tetramethyltricyclo-[5.2.2.0^{1,5}]undecan-8-ol, (+)-2-epi-allo-cedrol.

The carbon skeletons of virtually all the sesquiterpenes can be derived by a cyclization of either *cis*- or *trans*-farnesyl pyrophosphate. The monocarbocyclic sesquiterpen, γ-bisabolene (**2**) can be formed from **1** which is arised from *cis*-farnesyl pyrophosphate and the carbocations **4** and **5** can be biogenetically formed from **2** via **3**.[1]

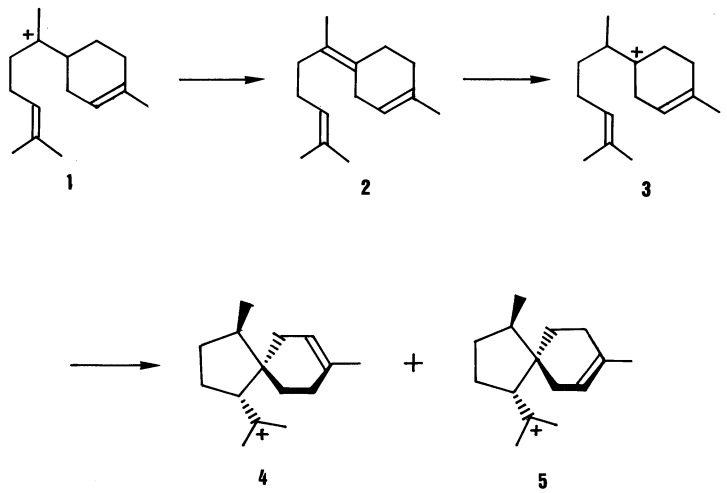
The carbocations **4** and **5** have been also suggested as the precursor of the tricarbocyclic sesquiterpenes, cedrene (**7**) and allo-cedrol (**9**), respectively. It was proposed that **7** is biogenetically derived from **6** which is formed by the consecutive cyclization of **4**.[1,2] Anderson and Syrdal[2] have demonstrated that treatment of nerolidol (**10**) with formic acid gave **2** which was further cyclized to give **7** via **4** and **6**. Tomita and Hirose[3] have reported that both of acorenol (**11**) and **12** were transformed into **7** via **4** by acid treatment. Tomita and Hirose have also proposed the probable biogenetic pathway from **13** to allo-cedrol (**9**) which involves the stereoselective cyclization of **5** leading to **8**,[4] and found the formate of **9** in a mixture of several products which was formed by treatment of **13** with formic acid.

In this paper we wish to report the facile synthesis of the optically active tricarbocyclic compound with the



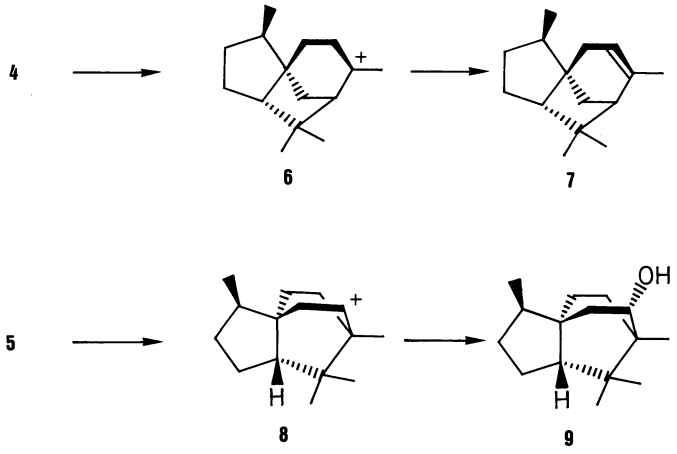
10 11 12 13

Chart 1.

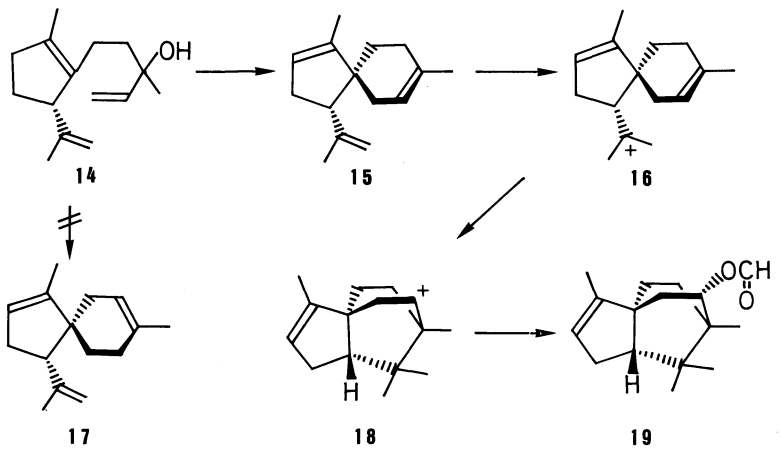


1 2 3 4 5

Scheme 1.



Scheme 2.

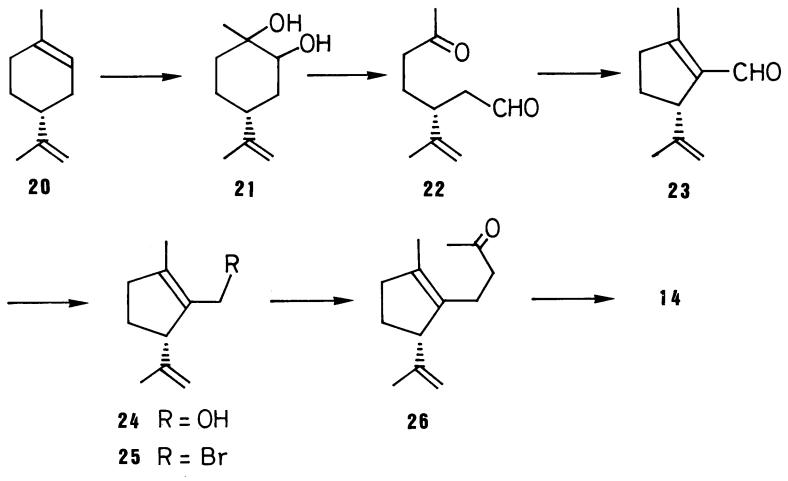


Scheme 3.

allo-cedrol type skeleton by a biogenetic-type cyclization of **14** with formic acid. It would be expected that the initial step of the cyclization of **14** yields stereospecifically the bicarbocyclic triene **15**, the analog of **13**. The alternative cyclization of **14** leading to **17** is unfavorable, since the isopropenyl group prevents attack of C-1 on the *re-si* face of the double bond of the cyclopentene moiety. In analogy with the proposed biosynthesis of **9** from **13**, the consecutive cyclization of **16** derived from **15** by protonation would give regiospecifically **18**, from which the formate **19** and/or its C-8 epimer **28** might be derived.

As the starting material for preparation of the trienol **14**, we chose *d*-limonene (**20**) which has the *R* configuration required to prepare natural allo-cedrol (**9**). Epoxidation of **20** with perbenzoic acid followed by cleavage of the epoxy ring with diluted sulfuric acid gave the diol **21** in 64% yield for two steps, which was treated with sodium periodate to give the keto aldehyde **22**[6] in 71% yield. Cyclization of **22** with piperidinum acetate gave **23**,[7] $LiAlH_4$ reduction of which gave the alcohol **24** in 53% yield for two steps. Bromination of **24** with phosphorus tribromide gave the bromide **25**, treatment of which with ethyl acetoacetate followed by decarboxylation provided the ketone **26** in 58% yield for three steps. The ketone **26** was reacted with vinylmagnesium bromide to give the trienol **14** in 82% yield but as a mixture of epimers at the carbon atom bearing the hydroxyl group. It was permitted to utilize the mixture of epimers in the subsequent cyclization step in our synthetic strategy.

The trienol **14** was treated with 98% formic acid at room temperature and the reaction was monitored by GLC which revealed that the reaction was complete in less than 2 h and elongation of the reaction period changed scarcely the ratio of the products. The GC mass spectrum of the products showed a major peak together with three minor peaks. A molecular ion peak of the major component appeared at m/z 248 ($C_{16}H_{24}O_2$) and all minor components showed their molecular ion peaks at m/z 202 ($C_{15}H_{22}$). The major product could be



Scheme 4.

separated from the minor components in 55% isolated yield by chromatography on silica gel. The observation of strong absorption bands at 1720 and 1180 cm^{-1} in its IR spectrum showed that the major product was the formate.

Hydrolysis of the major product with KOH in methanol gave an easily separable mixture of two alcohols, silica-gel chromatography of which gave the unsaturated alcohols **27**, mp 119—121 °C; $[\alpha]_D$ +127° (18% overall yield based on **14**) and **29**, mp 71 °C; $[\alpha]_D$ +63.0° (30% overall yield). ^1H NMR spectrum of **27** showed three singlet signals (δ=0.76, 0.88, and 0.96) and one doublet signal (δ=1.52, J=2.0 Hz) due to the four methyl groups, an octet signal at δ=4.05 due to the proton on the carbon atom bearing the hydroxyl group, and a double doublet signal at δ=5.30 due to the olefinic proton. The spectrum of **29** exhibited three singlet signals (δ=0.92, 0.93, and 1.15) and one doublet signal (δ=1.50) due to the four methyl groups and double doublet signals at δ=3.75 and 5.30 due to the protons at C-8 and at C-3, respectively. On the basis of these ^1H NMR spectra together with IR spectra and elementary analyses, the structures **27** and **29** were assigned to the hydrolysis products and the structure **33** with the cedran type skeleton was excluded. The structures assigned to **27** and **29** were well supported on the basis of spectral data of the hydrogenated products **30** and **32**, respectively.

The alcohol **27** was hydrogenated with hydrogen over 10% Pd on carbon in ethanol and with sodium, hexamethylphosphoric triamide in *t*-butyl alcohol. In both cases, the saturated alcohol **30**, mp 89—90 °C; $[\alpha]_D$ +112° was isolated as a sole product, whose structure was unambiguously confirmed on the basis of its ^1H NMR and ^{13}C NMR spectra. The ^{13}C NMR spectrum showed well-resolved resonances for all 15 carbons (see Table 1) and the ^1H NMR spectral data are also summarized in Table 1. The long-range coupling between the C-9 β-methylene proton (δ=1.67) and the C-10 α-methylene proton through four bonds planar "W" pathway was observed, but the "W" long-range coupling was not observed in the signal (δ=1.38) due to the C-9 α-methylene proton. These spectral data were thoroughly consistent with the structure assigned to **30** and excluded its isomer **34**, since it is presumed that the "W" long-range coupling is observed in both signals due to the protons of the C-9 methylene group in ^1H NMR spectrum of **34**.

Table 1. ^1H and ^{13}C Resonances for the Alcohol **30**

Position	^{13}C	^1H
1	42.94 (s)	No
2	42.44 (d)	1.45 (tq, J=9.4, 6.4)
3	31.82 (t)	H —[a]
		H 1.79 (tdd, J=9.4, 5.9, 13.0)
4	22.63 (t)	H 1.52 (ddd, J=5.9, 9.2, 14.4)
		H —[a]
5	54.07 (d)	1.34 (ddd, J=1.6, 9.2, 10.8)
6	34.84 (s)	No
7	39.66 (s)	No
8	71.06 (d)	3.92 (ddd, J=2.3, 5.5, 9.6)
		-OH 1.40 (s)
9	44.44 (t)	H 1.38 (dd, J=5.5, 13.1)
		H 1.67 (ddd, J=2.5, 9.6, 12.6)
10	20.14 (t)	—[b]
11	23.23 (t)	—[c]
12	16.27 (q)	0.78 (d, J=6.9)
13	26.51 (q)	0.88 (s)
14	21.50 (q)	0.87 (s)
15	14.34 (q)	0.76 (s)

a) Overlapping resonances at δ=1.49—1.61. b) Overlapping resonances at δ=1.23—1.30. c) Overlapping resonances at δ=1.15—1.24.

Assignment of the *S* configuration to the stereocenter C-2 of **30** was established by relating this unknown stereocenter to the *R* configuration at C-5 which was assigned on the basis of the stereochemistry of *d*-limonene (**20**). The C-5 angular methine proton showed NOE correlation (see Fig. 1) with the β-proton of the C-3 methylene group, but not with the α-proton. The

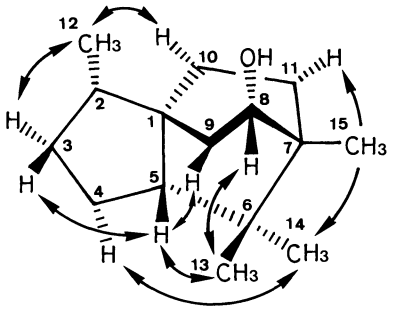


Fig. 1. Summary of observed ^1H–^1H NOE enhancements in **30**.

protons of the C-12 methyl group showed NOE correlation with the C-3 α-methylene proton and with the C-10 α-methylene proton, but not with the both protons of the C-9 methylene group. The stereochemical assignment of C-8 was based on the appearance of a signal due to the C-8 methine proton as an octet (δ=3.92), which suggested the existence of the "W" long-range coupling (J=2.3 Hz) between this proton and the C-11 α-methylene proton. Additional supportive evidence came from the fact that NOE correlation was observed between the C-8 methine proton and the protons of the C-13 methyl group. These spectral data permitted us to assign the 1*R*,2*S*,5*R*,7*R*,8*S* configuration to **30**, which is the C-2 epimer of natural allo-cedrol (**9**) (Lit,[5] mp 81.5 °C; $[\alpha]_D$ +68°).

The same catalytic hydrogenation of **29** gave the saturated alcohol **32**, mp 30—31 °C; $[\alpha]_D$ +60.9°. ^1H NMR spectrum of **32** showed a doublet signal (J=6.9 Hz) at δ=0.76 and three singlet signals at δ=0.82, 0.89, and 1.11 due to the methyl protons and a double doublet signal at δ=3.62 due to the C-8 methine proton. The spectral data revealed that **32** was the C-8 epimer of **30**, and this stereochemical relationship was unambiguously confirmed by the chemical conversions as follows.

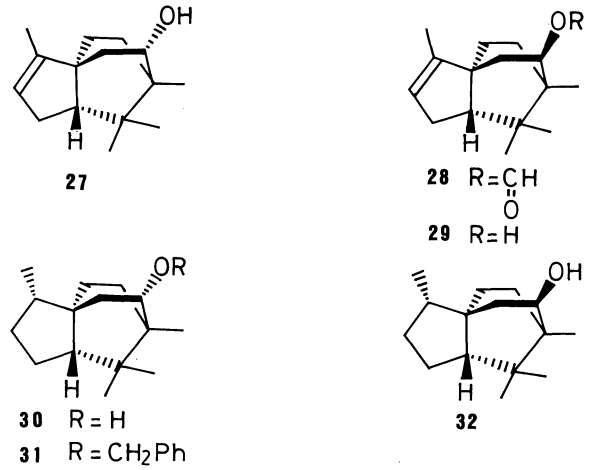


Chart 2.

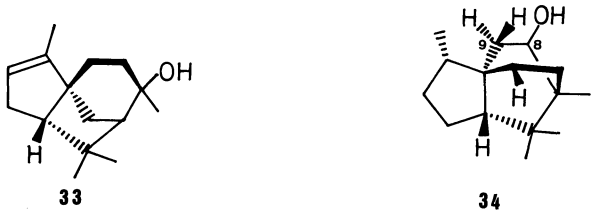


Chart 3.

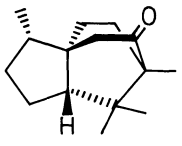
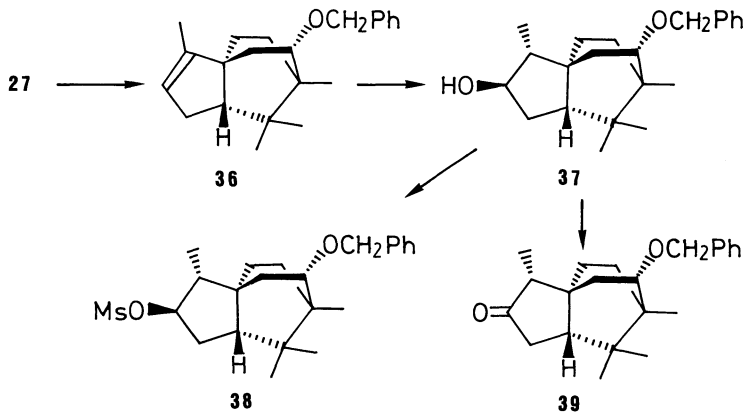


Chart 4.

Oxidation of **32** with Jones reagent afforded the ketone **35**, reduction of which with sodium and ethanol[9] gave the 3:2 mixture of **30** and **32**.



Scheme 5.

Next our attention was preparation of natural allo-cedrol (**9**) with the 2*R* configuration from **27**. After **27** was converted into the benzyl ether **36**, hydroboration of **36** with diborane followed by hydrogen peroxide oxidation in aqueous NaOH solution gave a single product **37** in 54% yield for three steps. The methane sulfonate **38** was treated with $LiAlH_4$ to yield **30** and the benzyl ether **31**. Hydrogenolysis of **31** with hydrogen over 10% Pd on carbon gave **30**.

Next, we attempted to isomerize **39** to its C-2 epimer. The ketone **35** was treated with NaOMe in methanol and with $KOBu^t$ in *t*-butyl alcohol. In both cases, no evidence of the formation of the desired C-2 epimer of **39** was observed and only the starting material **39** was recovered. The Huang-Minlon modification of the Wolff-Kishner reduction of **39** yielded a single product **31** in 66% yield.

In summary, compared with the analogous cyclization of **10**, the acyclic analog of **14**, leading to cedrene (**7**) and its C-7 epimer, the formic acid mediated cyclization of the monocyclic trienol **14**, which was readily prepared from *d*-limonene (**20**), gave stereo and regiospecifically the products with the allo-cedrol type skeleton in moderate yield.

Experimental

All melting and boiling points are uncorrected. Infrared spectral data were taken on a Hitachi 260-10 spectrophotometer, and ^1H NMR and ^{13}C NMR spectra were obtained from a JNM-MH-100 and JNM-GX-500. Chemical shifts are reported in parts per million (δ) down field from tetramethylsilane. Optical rotations were measured with a JASCO DIP-140 automatic polarimeter. Mass spectra were taken with a JEOL-DX-303 HF spectrometer. Elemental analyses were determined on a Yanagimoto CHN-Corder, Type II.

(*S*)-5-Isopropenyl-2-methyl-1-cyclopentene-1-carbaldehyde (23). A mixture of the aldehyde[6] **22** (47.4 g, 0.282 mol), piperidine (3.1 ml), acetic acid (2.7 ml), and benzene (720 ml) was refluxed for 80 min. During this period, water generated was removed from the reaction mixture as the azeotrope with benzene. After cooling to room temperature, the reaction mixture was washed with 5% sulfuric acid, 5% aqueous solution of sodium hydrogencarbonate, and water. The solvent was removed and the residue was distilled to yield **23** (27.2 g, 58% yield), bp 52—53.5 °C (0.3 mmHg (1 mmHg=133.322 Pa)) (Lit,[7] bp 56—58 °C (0.5 mmHg)); $[\alpha]_D^{25}$ +45.9° (*c* 1.16 $CHCl_3$); IR (neat film) 1665, 1630, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.05—2.75 (4H, m), 1.68 (3H, s), 2.18 (3H, s), 3.60 (1H, m), 4.63 (2H, s), 9.52 (1H, s).

Found: C, 79.73; H, 9.30%. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39%.

(*S*)-5-Isopropenyl-2-methyl-1-cyclopentene-1-methanol (24). A solution of **23** (39.7 g, 0.264 mol) in dry ether (450 ml) was added dropwise to a suspension of lithium aluminum hydride (7.00 g, 0.184 mol) in dry ether (300 ml), and the mixture was refluxed for 14 h. The reaction mixture was cooled with ice, and saturated aqueous solution of ammonium chloride was added carefully to the chilled reaction mixture. The precipitated inorganic solid was filtered off, and the filtrate was dried ($MgSO_4$). After removal of the solvent, the residue was distilled to yield **24** (37.0 g, 92% yield), bp 56—58 °C (0.3 mm Hg); $[\alpha]_D^{28}$ +167° (*c* 1.14, $CHCl_3$); IR (neat film) 3320, 1640, 990, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.15—2.55 (5H, m), 1.62 (3H, s), 1.73 (3H, s), 3.46 (1H, m), 4.10 (2H, s), 4.72 (2H, s).

Found: C, 78.61; H, 10.54%. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59%.

(*S*)-2-Bromomethyl-1-methyl-3-isopropenyl-1-cyclopentene (25). Phosphorus tribromide (12.0 g, 44.3 mol) was added to a mixture of **24** (15.0 g, 98.5 mol), pyridine (2.3 ml), and petroleum ether (bp 40—60 °C) (200 ml) with stirring at 0—5 °C, and the mixture was stirred for 7 h at the same temperature. After the reaction mixture was carefully poured into 5% aqueous solution of sodium hydrogencarbonate with ice cooling, the organic layer was separated and the aqueous phase was extracted with ether. The combined organic solutions were washed with saturated aqueous solution of sodium hydrogencarbonate and water, and dried ($MgSO_4$). The solvent was removed in vacuo to yield **25** (19.2 g, 91% yield) as an oil, which was used for the next reaction without further purification.

(*S*)-4-(5-Isopropenyl-2-methyl-1-cyclopenten-1-yl)-2-butanone (26). To a solution of sodium ethoxide in ethanol, prepared from sodium (3.00 g, 0.125 mol) and abs. ethanol (90 ml), was added ethyl acetoacetate (17.0 g, 0.131 mol), and then the mixture was stirred for 1 h at room temperature. The mixture was cooled with ice and **25** (19.2 g) was added to the chilled mixture. After the resulting mixture was stirred for 5 h at room temperature and then for an additional 1 h under reflux, the white precipitate was filtered off. To the filtrate was added ethanol (250 ml) and 4% aqueous solution of sodium hydroxide (135 ml), and then the resulting mixture was refluxed for 48 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to yield **26** (12.1 g, 64% yield), bp 65—67 °C (0.3 mmHg); $[\alpha]_D^{25}$ +120° (*c* 0.952, EtOH); IR (neat film) 1720, 1640, 1160, 885 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.20—2.65 (8H, m), 1.55 (3H, s), 1.66 (3H, s), 2.10 (3H, s), 3.27 (1H, m), 4.67 (2H, s).

Found: C, 80.98; H, 10.39%. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48%.

(*S*)-5-(5-Isopropenyl-2-methyl-1-cyclopentenyl)-3-methylpent-1-en-3-ol (14). A solution of vinyl bromide (17.5 g, 0.161 mol) in dry tetrahydrofuran (THF) (40 ml) was added to a mixture of magnesium (3.40 g, 0.140 mol) and dry THF (25 ml) and the mixture was refluxed for 30 min. To the solution of vinylmagnesium bromide in THF was added a solution of **26** (17.6 g, 91.5 mmol) in dry THF (100 ml) at room temperature and the resulting mixture was heated for 5 h under reflux. The reaction mixture was cooled with ice and saturated aqueous solution of ammonium chloride was added to the chilled reaction mixture. After the precipitated inorganic solid was removed by filtration, the filtrate was concentrated in vacuo and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was distilled to yield **14** as a mixture of epimers (16.6 g, 82% yield), bp 78—81 °C (0.2 mmHg); $[\alpha]_D^{22}$ +126° (*c* 1.07, $CHCl_3$); IR (neat film) 3390, 1640, 1105, 885 cm^{-1}.

Found: C, 81.06; H, 10.87%. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98%.

The mixture of epimers was used for the next reaction without further separation.

Treatment of 14 with Formic Acid. A mixture of **14** (2.21 g, 10.0 mmol) and 98% formic acid (220 ml) was stirred for 4 h at room temperature (25 °C) and then 60% aqueous solution of potassium hydroxide (300 ml) was slowly added to the reaction mixture at 0—5 °C. The mixture was extracted with ether and the extract was washed with saturated aqueous solution of sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated in vacuo to give an oil, which was chromatographed on silica gel. The fractions eluted with hexane–benzene (1/1 v/v) gave a mixture of **19** and **28** as a pale yellow oil 1.36 g (55% yield), IR (neat film) 1725, 1640, 1180, 800 cm^{-1}; MS m/z 248 (M^+). The mixture was used for the next reaction without further purification.

Hydrolysis of the Mixture of Formates 19 and 28. A mixture of **19** and **28** (980 mg, 3.95 mmol) and 5% methanolic solution of potassium hydroxide (15 ml) was stirred for 12 h at room temperature. The mixture was neutralized with hydrochloric acid, concentrated in vacuo, and extracted with ether. The extract was washed with saturated aqueous solution of sodium hydrogencarbonate and water, and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was chromatographed on silica gel. The fractions eluted with hexane–benzene (1/2 v/v) gave a solid, which was recrystallized from hexane to yield **27** (284 mg), and the subsequent fractions eluted with benzene–ether (3/1 v/v) gave a solid, which was recrystallized from hexane to give **29** (474 mg).

27: Mp 119—121 °C; $[\alpha]_D^{26}$ +127° (c 0.553, $CHCl_3$); IR (KBr) 3350, 1640, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.76 (3H, s), 0.88 (3H, s), 0.96 (3H, s), 1.52 (3H, d, J=2.0 Hz), 1.2—2.2 (10H, m), 4.05 (1H, octet, J=2.2, 5.5, 9.6 Hz), 5.30 (1H, dd, J=2.2, 4.2 Hz).

Found: C, 81.93; H, 11.01%. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98%.

29: Mp 71 °C; $[\alpha]_D^{25}$ +63.0° (c 0.338, $CHCl_3$); IR (KBr) 3600, 3410, 1640, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.92 (3H, s), 0.93 (3H, s), 1.15 (3H, s), 1.50 (3H, d, J=2.0 Hz), 0.9—2.2 (10H, m), 3.75 (1H, dd, J=10.2, 2.2 Hz), 5.30 (1H, dd, J=2.2, 4.1 Hz).

Found: C, 81.87; H, 10.99%. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98%.

(1*R*,2*S*,5*R*,7*R*,8*S*)-2,6,6,7-Tetramethyltricyclo[5.2.2.0^{1,5}]-undecan-8-ol (30). A solution of **27** (100 mg, 0.454 mmol) in 99% ethanol (30 ml) was shaken at room temperature with 10% Pd on carbon (48 mg) at 1 atm of hydrogen. After hydrogen uptake had ceased, the catalyst was removed by filtration. The solvent was evaporated in vacuo to give a solid, which was chromatographed on alumina (dichloromethane eluent) to yield a white solid **30** (96 mg, 95% yield), mp 89—90 °C (recrystallized from hexane); $[\alpha]_D^{23}$ +112° (c 0.306, $CHCl_3$); IR (KBr) 3330 cm^{-1}.

Found: C, 80.80; H, 11.73%. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79%.

(1*R*,2*S*,5*R*,7*R*,8*S*)-2,6,6,7-Tetramethyltricyclo[5.2.2.0^{1,5}]-undecan-8-ol (32). By using the same procedure described for the preparation of **30**, **29** (100 mg, 0.454 mmol) was hydrogenated with 1 atm of hydrogen over 10% Pd on carbon to give **32** (96 mg, 95% yield), mp 30—31 °C (recrystallized from hexane in a refrigerator); $[\alpha]_D^{22}$ +60.9° (c 1.06, $CHCl_3$); IR (KBr) 3040 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.83—1.80 (11H, m), 0.76 (3H, d, J=6.9 Hz), 0.82 (3H, s), 0.89 (3H, s), 1.11 (3H, s), 1.68 (1H, s), 2.14 (1H, dd, J=13.1, 9.7 Hz), 3.62 (1H, dd, J=9.7, 3.0 Hz).

Found: C, 79.88; H, 11.79%. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79%.

Reduction of 27 with Sodium, Hexamethylphosphoric Triamide and *t*-Butyl Alcohol. A mixture of sodium (75 mg, 3.3 mmol), hexamethylphosphoric triamide (9 ml), and **27** (100 mg, 0.454 ml) was stirred at room temperature until a blue color appeared. To the blue reaction mixture was added a 0.15 ml portion of dry *t*-butyl alcohol (0.45 ml) every 1.5 h under a nitrogen atomsphere. After the reaction mixture was stirred for an additional 20 h at room temperature, it was carefully poured into water (50 ml) and extracted with hexane. The extract was washed with water, dried ($MgSO_4$), and concentrated to give a solid, which was chromatographed on silica gel (hexane–ethyl acetae 95/5 v/v eluent) to give **30** (78 mg, 77% yield).

(1*R*,2*S*,5*R*,7*R*)-2,6,6,7-Tetramethyltricyclo[5.2.2.0^{1,5}]-undecan-8-one (35). To a solution of **32** (1.02 g, 4.65 mmol) in acetone (40 ml) was added slowly excess of Jones reagent[10] with ice cooling and then the mixture was stirred for 3 h. After a small amount of isopropyl alcohol was added to the reaction mixture, the reaction mixture was extracted with ether and the extract was washed with aqueous sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel (benzene eluent) to give **35** (860 mg, 61% yield); mp 101—103 °C; $[\alpha]_D^{20}$ +53.9° (c 0.577, $CHCl_3$); IR (KBr) 1710, 1640 cm^{-1}.

Found: C, 82.35; H, 10.14%. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16%.

Reduction of 35 with Sodium and Ethanol. To a solution of **35** (49 mg, 0.23 mmol) in ethanol (3 ml) was slowly added sodium (32 mg, 1.4 mmol) in a small portion. After the mixture was refluxed for 24 h, it was acidified with hydrochloric acid and concentrated in vacuo. The residue was extracted with chloroform and the extract was washed with water and dried ($MgSO_4$). Removal of the solvent gave a solid, which was chromatographed on silica gel to yield the ketone **35** (19 mg) and a 3:2 mixture of alcohols **30** and **32** (27 mg 55% yield).

(1*S*,5*R*,7*R*,8*S*)-8-Benzyloxy-2,6,6,7-tetramethyltricyclo-[5.2.2.0^{1,5}]undec-2-ene (36). To a suspension of sodium hydride (125 mg, 5.21 mmol) in dry THF (10 ml) was added **27** (570 mg, 2.59 mmol), and the mixture was refluxed for 2 h. After the mixture was cooled to room temperature, a solution of benzyl bromide (1.10 mg, 6.43 mmol) in dry THF (2 ml) was added to the mixture and the resulting mixture was refluxed for 15 h. The reaction mixture was cooled with ice and a small amount of water was added to the chilled reaction mixture. The mixture was extracted with chloroform, and the extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel and the fractions eluted with benzene gave **36** (696 mg, 88% yield) as a colorless oil, $[\alpha]_D^{21}$ +123° (c 1.49, $CHCl_3$); IR (neat film) 3090, 3070, 3030, 1640, 1600, 1500, 1070, 800, 735, 695 cm^{-1}.

Found: C, 84.58; H, 9.72%. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74%.

(1*S*,2*R*,3*R*,5*R*,7*R*,8*S*)-8-Benzyloxy-2,6,6,7-tetramethyltricyclo[5.2.2.0^{1,5}]undecan-3-ol (37). A freshly prepared solution of diborane in dry THF (9.0 ml, 0.424 mol dm^{-3})[11] was added to a solution of **36** (1.35 g, 4.35 mmol) in dry THF (40 ml) and then the mixture was stirred for 4 h at room temperature. After a small amount of water was carefully added to the reaction mixture, the mixture was concentrated in vacuo. The

residue was extracted with ether, and the extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was dissolved in THF (35 ml) and to the solution was added 3M aqueous solution of sodium hydroxide (9.8 ml) and 30% aqueous solution of hydrogen peroxide (2.2 ml). The mixture was heated for 3 h at 40—45 °C. After water (7 ml) and ether (140 ml) was added to the reaction mixture, the organic layer was separated and the aqueous solution was extracted with ether. The combined ethereal solutions were washed with water, dried ($MgSO_4$), and concentrated in vacuo to yield an oily product, which was chromatographed on silical gel. The fractions eluted with benzene–ether (95/5 v/v) gave a solid, which was recrystallized from hexane to yield **37** (870 mg, 61% yield), mp 98—99 °C; $[\alpha]_D^{23}$ +121° (*c* 1.14, $CHCl_3$); IR (KBr) 3340, 1600, 1070, 735, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.83 (3H, s), 0.84 (3H, s), 0.85 (3H, s), 0.89 (3H, d, *J*=6.8 Hz), 1.0—2.2 (11H, m), 3.5—3.7 (1H, m), 4.0—4.3 (1H, m), 4.36 (1H, d, *J*=12.0 Hz), 4.58 (1H, d, *J*=12.0 Hz), 7.29 (5H, s).

Found: C, 80.23; H, 9.73%. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82%.

(1*S*,2*R*,3*R*,5*R*,7*R*,8*S*)-8-Benzyloxy-2,6,6,7-tetramethyltricyclo[5.2.2.0^{1,5}]undec-3-yl Methanesulfonate (38). To a chilled mixture of **37** (135 mg, 0.411 mmol), triethylamine (150 mg, 1.48 mmol), and dichloromethane (10 ml) was added methanesulfonyl chloride (140 mg, 1.22 mmol), and the mixture was stirred overnight at room temperature. The reaction mixture was poured into ice-water, acidified with hydrochloric, acid, and extracted with dichloromethane. The extract was washed with aqueous solution of sodium hydrogencarbonate and water, dried ($MgSO_4$), and concentrated in vacuo to give **38** (158 mg, 95% yield) as an oil, which was used for the next reaction without further purification.

Reaction of 38 with Lithium Aluminum Hydride. A soluion of **38** (156 mg, 0.384 mmol) in dry ether (30 ml) was carefully added to a suspension of lithium aluminum hydride (80 mg, 2.1 mmol) in dry ether (10 ml) and the mixture was heated under reflux for 24 h. After saturated aqueous solution of ammonium chloride (0.5 ml) was added to the reaction mixture with ice cooling, the precipitated inorganic solid was removed by filtration. The filtrate was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by a preparative TLC (silica gel) to give **31** (90 mg, 75% yield) as an oil and **35** (10 mg, 12% yield) as a white solid.

31: $[\alpha]_D^{24}$ +182° (*c* 0.177, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.80 (3H, d, *J*=6.8 Hz), 0.82 (6H, s), 0.88 (3H, s), 1.0—1.9 (12H, m), 3.5—3.7 (1H, m), 4.12 (1H, d, *J*=12.0 Hz), 4.58 (1H, d, *J*=12.0 Hz), 7.24 (5H, s).

Found: C, 84.35; H, 10.22%. Calcd for $C_{22}H_{32}O$: C, 84.56; H, 10.32%.

Hydrogenolysis of 31. A mixture of **31** (39 mg, 0.13 mmol), *p*-toluenesulfonic acid (1 mg), 10% Pd on carbon (10 mg), and 1,4-dioxane (6 ml) was shaken under 1 atm of hydrogen at room temperature. After hydrogen uptake had ceased, the catalyst was removed by filtration. To the filtrate was added sodium carbonate (10 mg), and the resulting mixture was stirred for 1 h. The solid was removed by filtration and the filtrate was concentrated in vacuo. The product was purified by a preparative TLC (silica gel) to give **30** (19 mg, 83% yield).

(1*S*,2*R*,5*R*,7*R*,8*S*)-8-Benzyloxy-2,6,6,7-tetramethyltricyclo[5.2.2.0^{1,5}]undecan-3-one (39). By the similar procedure described for the preparation of **35**, **37** (625 mg, 1.90 mmol) was oxidized with excess of Jones reagent. The product was chromatographed on silical gel (hexane–ethyl acetate 95/5 v/v eluent) to give an oily product, which was crystallized from hexane (at −15 °C) to give **39** (500 mg, 81% yield), mp 38—39 °C; $[\alpha]_D^{24}$ +37.0° (*c* 1.16, $CHCl_3$); IR (neat film) 1735, 1070, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.88 (3H, d, *J*=3.4 Hz), 0.89 (6H, s), 0.93 (3H, s), 1.0—2.3 (6H, m), 3.6—3.9 (1H, m), 4.42 (1H, d, *J*=12.0 Hz), 4.62 (1H, d, *J*=12.0 Hz), 7.30 (5H, s).

Found: C, 79.75; H, 9.21%. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26.

Treatment of 39 with Sodium Methylate. A solution of sodium methylate, prepared from sodium (3.3 mg, 0.14 mmol) and abs. methanol (1.5 ml), was added to **39** (50 mg, 0.15 mmol) under a nitrogen atmosphere and the mixture was stirred for 1 h at room temperature. A small amount of diluted hydrochloric acid was added to the mixture and the methanol was removed in vacuo. The residue was extracted with chloroform. After a usual work up, removal of the solvent gave the starting material **39** (46 mg) as a sole product.

The Wolff-Kishner Reduction of 39. A mixture of **39** (200 mg, 0.613 mmol), potassium hydroxide (150 mg, 2.67 mmol), and triethylene glycol (4 ml) was heated for 1 h at 70—80 °C. After the reaction mixture was cooled to room temperature, 80% hydrazine hydrate (176 mg, 3.52 mmol) was added to the mixture and the resulting mixture was heated in an oil bath. During 1 h, the bath temperature was gradually raised to 200 °C and this temperature was kept for an additional 1 h. After the mixture was cooled to room temperature, the inner wall of the condenser was rinsed with chloroform and the reaction mixture was extracted with chloroform. The combined chloroform solutions were washed with water, dried ($MgSO_4$), and concentrated to give an oily product. The product was purified by a preparative TLC (silica gel) to provide **31** (126 mg, 66% yield) as a colorless oil.

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