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Syntheses of optically Active (+)-Fragrolide and (+)-Bemadienolide from Dehydroabietic Acid[1)]

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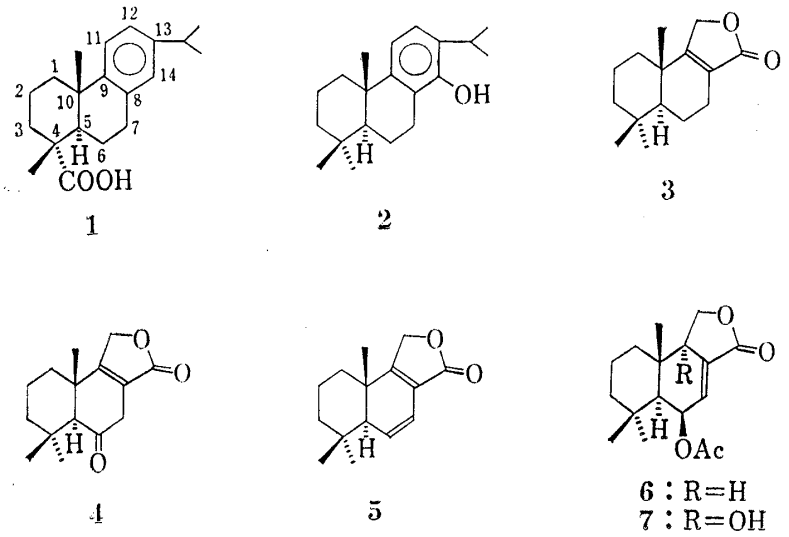
14-Hydroxydehydroabietane derivatives (**8** and **9**), having an oxygen functional group at the 6-position, were obtained from 14-hydroxy-7-oxodehydroabietane (**10**) by transformation of the 7-oxo group into a 6-acetoxyl (or hydroxyl) group. Ozonolysis of the above phenols (**8** and **9**) and subsequent reduction gave the 6-oxygenated confertifolin derivatives **17** and **19**, respectively. Oxidation of 6-hydroxyconfertifolin (**19**) afforded the optically active (+)-fragrolide (**4**). On the other hand, **19** was also converted into (+)-bemadienolide (**5**) by oxidation of the important intermediate, 6β-phenylselenoconfertifolin (**25**).

Keywords——aromatic ring cleavage; drimanic sesquiterpenes; phenolic diterpenes; ozonolysis; transfer of ketone

In the previous paper,[2)] we reported that 14-hydroxy-dehydroabietane (**2**) derived from dehydroabietic acid (**1**) underwent ozonolysis to give confertifolin (**3**), a typical drimanic sesquiterpene. Many other natural products belonging to this class have been isolated. Among them, the structures of (+)-fragrolide (**4**),[3)] (+)-bemadienolide (**5**),[3)] (+)-bemarivolide (**6**),[3)] and (+)-cinnamosmolide (**7**)[4)] are similar to that of **3**, and (±)-**6**[5)] and (±)-**7**[6)] have been synthesized so far. The present paper deals with the syntheses of **4** and **5** by applying the previously reported technique[1,2,7)] of cleaving the aromatic ring selectively to afford the butenolide moiety of these sesquiterpenes.



1 2 3 4 5

6 : R=H
7 : R=OH

Chart 1

The synthesis of the key intermediates (**8** and/or **9**) was achieved as follows. 14-Methoxy-7-oxodehydroabietane (**10**),[2)] having the oxo group on the 7-position, was converted into the 6α-acetoxy compound (**8**) by applying Cambie's method[8)] used in an analogous system. The methoxy ketone (**10**) was treated with isopropenyl acetate in the presence of a catalytic amount

of TsOH to afford the enol acetate (**11**) in 93% yield, and this was oxidized with *m*-chloroperbenzoic acid to give the 6α-acetoxy compound (**12**) in 72% yield and the 6α-hydroxy compound (**13**) in 16% yield. The 6α-acetoxy compound (**12**) was also obtained by acetylation of **13**. The former (**12**) was treated with $AlCl_3$ in benzene to afford the demethylated compound (**14**) in 81% yield in addition to the deisopropyl-demethylated product (**15**) in 4% yield. When the above series of reactions was carried out successively without isolation of the intermediates, **14** was obtained in 89% overall yield from **11**. $NaBH_4$ reduction of **14** in MeOH gave the 7,14-dihydroxy compound (**16**), which was hydrogenated (2.8—2.9 kg/cm²) with 10% Pd–C in the presence of a trace amount of conc. H_2SO_4 to give the desired 6α-acetoxy-14-hydroxy compound (**8**) and the 6α,14-dihydroxy compound (**9**) in yields of 64% and 14%, respectively.[9]

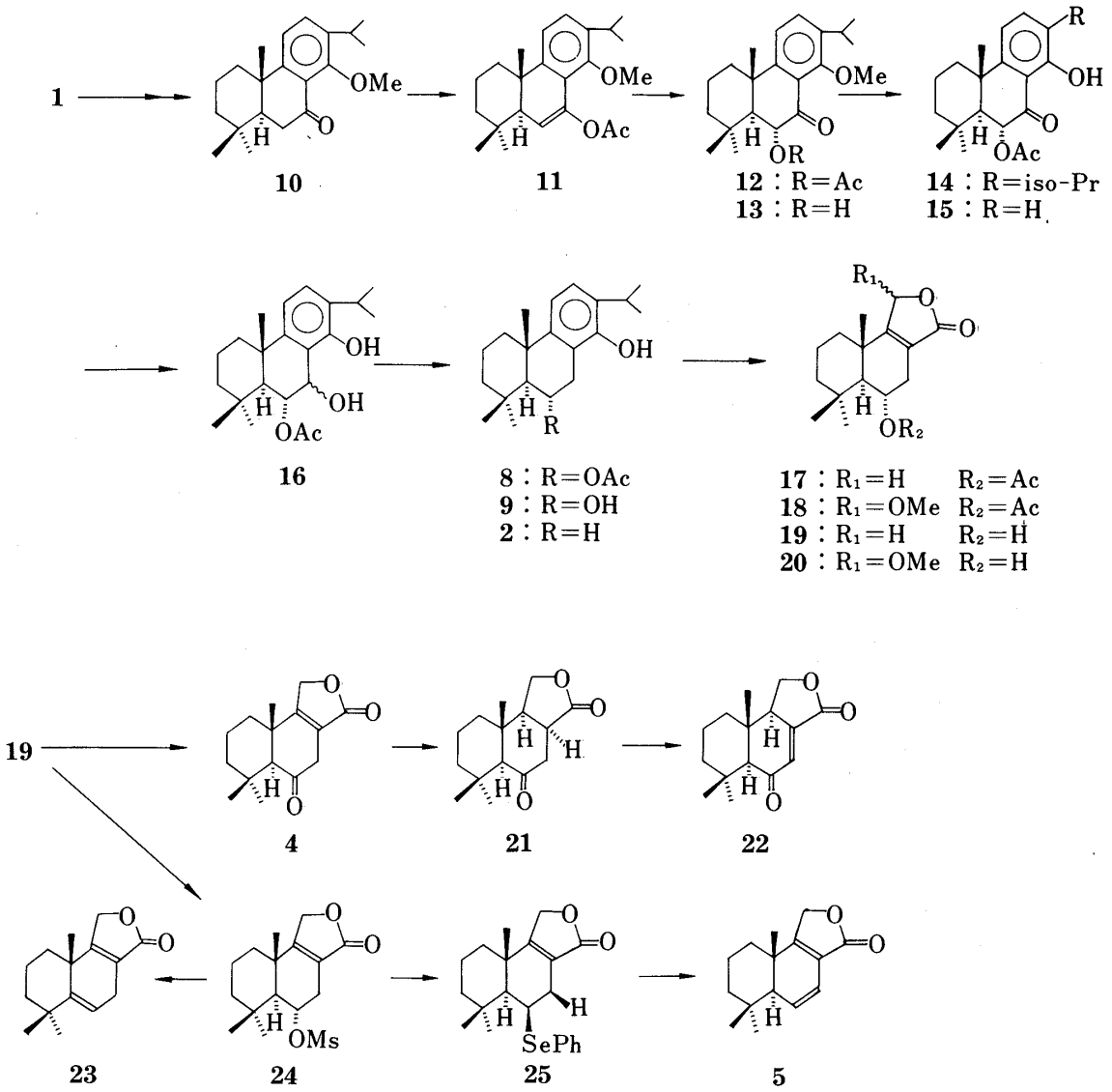


Chart 2

Ozonolysis of **8** in MeOH–CH_2Cl_2 under dry ice–acetone cooling and subsequent $NaBH_4$ reduction gave 6α-acetoxyconfertifolin (**17**; 54% yield) together with a small amount of 6α-acetoxy-11-methoxyconfertifolin (**18**; 11% yield). On the other hand, ozonolysis of **9** afforded only 6α-hydroxyconfertifolin (**19**; 48% yield). The methoxy derivative (**20**) corresponding to **18** could not be isolated. Hydrolysis (1% K_2CO_3–H_2O–MeOH) of 6α-acetoxyconfertifolin

(**17**) gave 6α-hydroxyconfertifolin (**19**), which was oxidized with Jones reagent to give the optically active fragrolide (**4**) in quantitative yield. However, the physical data of our synthetic product (**4**) are slightly different from the reported values of the natural product.[3] Therefore, several derivatives of **4** were prepared. Hydrogenation of the synthetic fragrolide (**4**) gave the dihydrofragrolide (**21**),[3] which was dehydrogenated with SeO_2 in AcOH to afford the 6-oxo-$\Delta^{7,8}$ compound (**22**). The spectral data (infrared (IR) and nuclear magnetic resonance (NMR)) of the enone (**22**) thus obtained were identical with those of the authentic racemate (**22**) synthesized by another route by Professor Isoe's group.[10] Therefore, we assigned our synthetic compound (**4**) as (+)-fragrolide.

Next, the conversion of 6α-hydroxyconfertifolin (**19**) into the optically active bemadienolide (**5**) was undertaken. Attempted dehydration of **19** with $SOCl_2$ in pyridine gave an inseparable mixture of double bond isomers (**5** and **23**). Next, **19** was treated with OMsl in pyridine to give 6α-mesylconfertifolin (**24**) in 72% yield; this product was heated in collidine to give the undesired (**23**) in 60% yield, the result being not unexpected. Then, S_N 2 type substitution of the α-OMs group of **24** with the selenophenolate anion liberated by the reduction of ϕ_2Se_2 with $NaBH_4$ was carried out, and although the yield was rather poor, the expected 6β-phenylselenoconfertifolin (**25**) was obtained in 16% yield. In this case, again a mixture of double bond isomers (**5** and **23**) was the main product (63% yield).[11] Oxidation of **25** with 30% H_2O_2 in the presence of a trace amount of AcOH in tetrahydrofuran (THF) afforded the optically active bemadienolide (**5**) in 75% yield. The selective elimination of the 7β-hydrogen located *cis* to the intermediary β-selenoxide must be involved in this transformation.[12] The physical data (mp, $[\alpha]_D$, IR, ultraviolet (UV), and NMR) of the synthetic bemadienolide (**5**) were found to be identical with those of the natural bemadienolide reported by Canonica and his co-workers.[3]

Experimental

Melting points were measured with a Kofler micro melting point apparatus and are uncorrected. IR spectra (CCl_4) were measured on a JASCO A-3 spectrophotometer. NMR spectra were measured either on a Varian HA-100 spectrometer or a JEOL MH-60 instrument. Spectra were taken as 5—10% w/v solutions in $CDCl_3$ with Me_4Si as an internal reference. Gas chromatography–mass spectroscopy (GC–MS) spectra were measured on a Hitachi RMU-6M mass spectrometer and high-resolution mass spectra were taken with a JMS-01SG spectrometer. Gas–liquid chromatography (GLC) was carried out on a column (2 m×4 mm) of 1.5% OV-17 on Shimalite W (80—100 mesh). $[\alpha]_D$ was measured on a Perkin-Elmer model 241 MC polarimeter. UV spectra were measured on a Shimadzu model UV-200 spectrometer.

Enol Acetylation of 14-Methoxy-7-oxoabieta-8,11,13-triene (10)——14-Methoxy-7-oxoabieta-8,11,13-triene (**10**) (3.411 g) was refluxed with isopropenyl acetate (30 ml) and toluene–*p*-sulfonic acid (300 mg) for 48 hr. The cooled mixture was concentrated under reduced pressure and H_2O was added. The resulting solution was extracted with ether. The extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave an oily product (4.727 g), which was chromatographed on silica gel (90 g) to afford 7-acetoxy-14-methoxy abieta-6,8,11,13-tetraene (**11**) as a homogeneous oil (3.590 g, 93% yield) from the petr. ether–ether (19: 1) eluate. *Anal.* high-resolution mass spectrum (MS). Calcd for $C_{23}H_{32}O_3$ (M^+, *m/e*): 356.2351. Found: 356.2346. IR ν_{max} cm^{-1}: 1760, 1655. NMR δ: 0.94, 1.03 (each 3H, s, 4-*gem* Me), 1.15, 1.20 (each 3H, d, J=7.2 Hz, isopropyl Me), 1.18 (3H, s, 10-Me), 2.22 (3H, s, 7-OAc), 3.31 (1H, d, J=3.6 Hz, 5-H), 3.65 (3H, s, 14-OMe), 5.63 (1H, d, J=3.6 Hz, 6-H), 6.93, 7.17 (each 1H, d, J=8.4 Hz, 11-, 12-H).

Oxidation of 7-Acetoxy-14-methoxy Abieta-6,8,11,13-tetraene (11) with *m*-Chloroperbenzoic Acid——The enol acetate (**11**) (1.302 g) in CH_2Cl_2 (10 ml) was treated with *m*-chloroperbenzoic acid (0.789 g), and the mixture was allowed to stand at 0° for 24 hr. The reaction mixture was extracted with ether after H_2O had been added. The extract was washed with sat. $NaHCO_3$ aq. and sat. NaCl aq., then dried over Na_2SO_4. Removal of the solvent gave an oily product (1.438 g), which was chromatographed on silica gel (50 g) to provide two fractions from the petr. ether–ether (9: 1) eluate.

The first fraction (**13**) (188 mg, 16% yield) was recrystallized from petr. ether to give 6α-hydroxy-14-methoxy-7-oxoabieta-8,11,13-triene (**13**) as colorless prisms, mp 139—146°. *Anal.* Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.39; H, 9.11. IR ν_{max} cm^{-1}: 3450, 1680. NMR δ: 1.20 (6H, d, J=7.2 Hz, isopropyl Me), 1.22 (6H, s, 4-*gem* Me), 1.36 (3H, s, 10-Me), 1.79 (1H, d, J=13.2 Hz, 5-H), 3.82 (3H, s, 14-OMe), 3.99 (1H, d, J=3 Hz, 6α-OH), 4.60 (1H, dd, J=3, 13.2 Hz, 6β-H), 7.15, 7.47 (each 1H, d, J=8.4 Hz, 11-, 12-H).

The second fraction (**12**) (978 mg, 72% yield) was recrystallized from petr. ether to afford 6α-acetoxy-14-methoxy-7-oxoabieta-8,11,13-triene (**12**) as colorless prisms, mp 107—108.5°. *Anal.* Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.88; H, 8.78. IR ν_{max} cm^{-1}: 1750, 1695, 1223. NMR δ: 1.01, 1.11 (each 3H, s, 4-*gem* Me), 1.17, 1.20 (each 3H, d, J=7.2 Hz, isopropyl Me), 1.29 (3H, s, 10-Me), 2.07 (1H, d, J=12 Hz, 5-H), 2.14 (3H, s, 6α-OAc), 3.39 (1H, m, isopropyl methine), 3.76 (3H, s, 14-OMe), 5.66 (1H, d, J=12 Hz, 6β-H), 7.10, 7.44 (each 1H, d, J=8.4 Hz, 11-, 12-H).

Acetylation of 6α-Hydroxy-14-methoxy-7-oxoabieta-8,11,13-triene (13)——A mixture of **13** (679 mg), pyridine (5 ml) in acetic anhydride (5 ml) was allowed to stand for 24 hr at 0°. The reaction mixture was concentrated under reduced pressure after H_2O had been added and the residue was extracted with ether. The extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave an oily product (790 mg), which was chromatographed on silica gel (30 g) to afford a homogeneous oil (**12**) (761 mg, quantitative yield) from the petr. ether–ether (4: 1) eluate. A part of the above oil was crystallized from petr. ether to give colorless prisms (**12**), whose physical data (IR, NMR, and GLC) were identical with those of the previously obtained sample (**12**).

Treatment of 6α-Acetoxy-14-methoxy-7-oxoabieta-8,11,13-triene (12) with Aluminum Chloride——A mixture of **12** (3.05 g) and aluminum chloride (3 g) in anhydrous benzene (100 ml) was stirred for 3.5 hr at room temperature. The reaction mixture was extracted with ether after H_2O had been added. The extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave an oily product (2.998 g), which was chromatographed on silica gel (80 g) to provide two fractions from the petr. ether–ether (19: 1) eluate. The first fraction (**14**) (2.381 g, 81% yield) was recrystallized from petr. ether to give 6α-acetoxy-14-hydroxy-7-oxoabieta-8,11,13-triene (**14**) as pale yellow prisms, mp 108—111°. *Anal.* Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.77; H, 8.42. IR ν_{max} cm^{-1}: 1755, 1645, 1230. NMR δ: 1.07 (6H, s, 4-*gem* Me), 1.20 (6H, d, J=7.2 Hz, isopropyl Me), 1.34 (3H, s, 10-Me), 2.17 (1H, d, J=13.2 Hz, 5-H), 2.24 (3H, s, 6α-OAc), 3.32 (1H, m, isopropyl methine), 5.95 (1H, d, J=13.2 Hz, 6β-H), 6.79, 7.39 (each 1H, d, J=8.4 Hz, 11-, 12-H). From the second fraction, 6α-acetoxy-14-hydroxy-13-deisopropyl-7-oxoabieta-8,11,13-triene (**15**) (110 mg, 4% yield) was obtained as an oily product. *Anal.* high-resolution MS. Calcd for $C_{19}H_{24}O_4$ (M^+, *m/e*): 316.1674. Found: 316.1678. IR ν_{max} cm^{-1}: 1752, 1645, 1230. NMR δ: 1.08 (6H, s, 4-*gem* Me), 1.35 (3H, s, 10-Me), 2.19 (1H, d, J=13.2 Hz, 5-H), 2.24 (3H, s, 6α-OAc), 5.95 (1H, d, J=13.2 Hz, 6β-H), 6.62—7.50 (3H, m, 11-, 12-, 13-H).

Conversion of 7-Acetoxy-14-methoxy Abieta-6,8,11,13-tetraene (11) to 6α-Acetoxy-14-methoxy-7-oxoabieta-8,11,13-triene (14)——Oxidation of **11** (3.106 g) in CH_2Cl_2 (40 ml) with *m*-chloroperbenzoic acid (1.882 g) gave a mixture of **12** and **13**, which was acetylated with acetic anhydride in pyridine to afford a single product (**12**) by the same treatment as in the case of the conversion of **11** to **12**. The treatment of **12** in anhydrous benzene with aluminum chloride gave an oily product (3.442 g) on treatment as in the case of the conversion of **12** into **14**. The oily product was subjected to chromatography on silica gel (80 g) to give the demethylated compound (**14**) (2.783 g, 89% yield from **11**) from the petr. ether–ether (19: 1) eluate.

Reduction of 6α-Acetoxy-14-hydroxy-7-oxoabieta-8,11,13-triene (14)——i) 6α-Acetoxy-14-hydroxy-7-oxoabieta-8,11,13-triene (**14**) (14.4 g) in MeOH (20 ml) was treated with $NaBH_4$ (2 g) and the solution was stirred at room temperature for 3.5 hr. The solution was diluted with H_2O, and extracted with $CHCl_3$ after acidification with 10% HCl aq. The extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave 6α-acetoxy-7ξ,14-dihydroxyabieta-8,11,13-triene (**16**) as an oily product (14.383 g), which was used for the next reaction without further purification.

ii) A part of the above oily product (**16**) (*ca.* 3 g) was catalytically hydrogenolyzed in EtOH (30 ml)–conc. H_2SO_4 (4 drops) in the presence of 10% Pd–C (3 g) under a hydrogen atmosphere (2.8—2.9 kg/cm^2) with shaking for 4 hr. The filtrate was diluted with H_2O, and the whole was extracted with ether. The extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave an oily product. The experiment was repeated on a five times larger scale. Finally, a crude reduction product (**16**) (14.492 g) was obtained from **14** (14.383 g), and subjected to chromatography on silica gel (200 g) to provide three fractions. The first fraction was eluted with petr. ether–ether (19: 1) and gave 14-hydroxyabieta-8,11,13-triene (**2**) as a homogeneous oil (1.023 g, 9% yield from **14**). The physical data (IR, NMR, and GLC) were identical with those of an authentic sample (**2**).[2] The second fraction was eluted with petr. ether–ether (4: 1) and afforded a homogeneous oil (**8**) (8.815 g, 64% yield from **14**), which was crystallized from petr. ether–ether to give 6α-acetoxy-14-hydroxyabieta-8,11,13-triene (**8**) as colorless prisms, mp 143.5—144.5°. *Anal.* Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.76; H, 9.31. IR ν_{max} cm^{-1}: 3610, 1735, 1240. NMR δ: 0.98, 1.05 (each 3H, s, 4-*gem* Me), 1.18 (3H, s, 10-Me), 1.24 (6H, d, J=7.2 Hz, isopropyl Me), 1.61 (1H, d, J=9.6 Hz, 5-H), 2.05 (3H, s, 6α-OAc), 5.78—5.30 (1H, m, 6β-H), 5.37 (1H, br s, 14-OH), 6.83, 7.09 (each 1H, d, J=8.4 Hz, 11-, 12-H). The third fraction (**9**) (1.673 g, 14% yield from **14**) was obtained from the ether eluate. It was recrystallized from *n*-hexane–ether to give 6α,14-dihydroxyabieta-8,11,13-triene (**9**) as colorless needles (905 mg), mp 126.5—129°. *Anal.* Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.41; H, 10.02. IR ν_{max} cm^{-1}: 3625. NMR δ: 1.14 (9H, s, 4-*gem* Me, 10-Me), 1.19, 1.21 (each 3H, d, J=7.2 Hz, isopropyl Me), 4.16—4.58 (1H, m, $W_{h/2}$=15.6 Hz, 6β-H), 5.38 (1H, s, 6α-OH), 6.91, 7.06 (each 1H, d, J=8.4 Hz, 11-, 12-H).

Ozonolysis of 6α-Acetoxy-14-hydroxy Abieta-8,11,13-triene (8)——A solution of **8** (2.063 g) in 40 ml of

1: 1 MeOH–CH_2Cl_2 was subjected to ozonolysis under dry ice–acetone cooling for 1 hr. A solution of $NaBH_4$ (1.5 g) in 50% (v/v) EtOH–H_2O (30 ml) was added to the above ozonolyzed product and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was extracted with $CHCl_3$ after acidification with 10% HCl aq. and the extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave an oily product (2.207 g), which was chromatographed on silica gel (90 g) to provide two fractions from the petr. ether–ether (1: 1) eluate. The first fraction (**18**) (217 mg, 11% yield) provided 6α-acetoxy-11ξ-methoxyconfertifolin as an oily product. *Anal.* high-resolution MS. Calcd for $C_{18}H_{26}O_5$ (M^+, *m/e*): 322.178. Found: 322.176. IR ν_{max} cm^{-1}: 1766, 1740, 1235. NMR δ: 1.00, 1.10 (each 3H, s, 4-*gem* Me), 1.30 (3H, s, 10-Me), 1.57 (1H, d, $J=12$ Hz, 5-H), 2.09 (3H, s, 6α-OAc), 3.59 (3H, s, 11ξ-OMe), 5.19—5.58 (1H, m, 6β-H), 5.66 (1H, br s, $W_{h/2}=4.8$ Hz, 11ξ-H). The second fraction (**17**) (941 mg, 54% yield) was also an oily product, 6α-acetoxyconfertifolin. *Anal.* high-resolution MS. Calcd for $C_{17}H_{24}O_4$ (M^+, *m/e*): 292.167. Found: 292.167. IR ν_{max} cm^{-1}: 1765, 1685, 1740, 1235. NMR (100 MHz) δ: 0.96, 1.11 (each 3H, s, 4-*gem* Me), 1.26 (3H, s, 10-Me), 1.70 (1H, d, $J=12$ Hz, 5-H), 2.06 (3H, s, 6α-OAc), 1.94—2.32, 2.70—3.03 (each 1H, m, 7-H_2), 4.63—4.72 (4.67) (2H, m, 11-H_2), 5.23—5.51 (1H, octet, 6β-H).

Ozonolysis of 6α,14-Dihydroxy Abieta-8,11,13-triene (9)——A solution of **9** (2.278 g) in 44 ml of 1: 1 MeOH–CH_2Cl_2 was subjected to ozonolysis under dry ice–acetone cooling for 1.5 hr. A solution of $NaBH_4$ (1.7 g) in 50% (v/v) EtOH–H_2O (33 ml) was added to the above ozonolyzed product and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was treated as in the case of the ozonolysis of **8** to give an oily product, which was chromatographed on silica gel (30 g) to afford colorless crystals (**19**) (897 mg, 48% yield) from the ether–*n*-hexane (2: 1) eluate. This product was recrystallized from ether–*n*-hexane to give 6α-hydroxyconfertifolin (**19**) as colorless plates, mp 190.5—191.5°. *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.03; H, 8.87. $[\alpha]_D$ +79° ($CHCl_3$, $c=1.00$). IR ν_{max}^{KBr} cm^{-1}: 3440, 1736, 1677. NMR (100 MHz) δ: 1.13 (3H, s, 4β-Me), 1.22 (3H, s, 4α-Me, 10-Me), 1.44 (1H, d, $J=10$ Hz, 5-H), 1.97—2.36, 2.66—2.98 (each 1H, m, 7-H_2), 4.65—4.74 (4.68) (2H, m, 11-H_2), 4.30 (1H, br s, $W_{h/2}=20$ Hz, 6β-H).

Hydrolysis of 6α-Acetoxyconfertifolin (17)——6α-Acetoxyconfertifolin (**17**) (1.210 g) was hydrolyzed with a solution of 24 ml of 1% K_2CO_3–H_2O–MeOH [K_2CO_3 (1 g), H_2O (9 ml), MeOH (90 ml)] for 24 hr at room temperature. The reaction mixture was extracted with ether after dilution with H_2O and the extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave crystals (900 mg), which were recrystallized from ether to afford 6α-hydroxyconfertifolin (**19**) as colorless plates (831 mg, 80% yield). The physical data (NMR and TLC) were identical with those of the previous authentic sample (**19**).

Oxidation of 6α-Hydroxyconfertifolin (19)——A solution of **19** (425 mg) in acetone (10 ml) was oxidized with Jones reagent (1 ml) under stirring for 30 min at room temperature. After addition of both MeOH (10 ml) and H_2O, the reaction mixture was evaporated to dryness and the residue was extracted with ether. The extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave crystals (420 mg, quantitative yield), which were recrystallized from isopropylether to afford fragrolide (**4**) as colorless plates, mp 163—164°. *Anal.* Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.50; H, 8.15. $[\alpha]_D$ +145.1° ($CHCl_3$, $c=1.00$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1755, 1720, 1675. NMR (100 MHz) δ: 1.04 (3H, s, 4α-Me), 1.18 (3H, s, 10-Me), 1.30 (3H, s, 4β-Me), 2.44 (1H, s, 5-H), 3.00—3.14 (2H, m, 7-H_2), 4.80—4.88 (2H, m, 11-H_2).

Conversion of (+)-Fragrolide (4) into (+)-6-Oxocinnamolide (22)——i) A mixture of **4** (42 mg), PtO_2 (40 mg) in AcOH (5 ml) was stirred under a hydrogen atmosphere at room temperature. The filtrate was evaporated to dryness, and the residue was extracted with ether. The extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave crystals, which were recrystallized from isopropylether to give dihydrofragrolide (**21**) as colorless needles, mp 156—157°. *Anal.* high-resolution MS. Calcd for $C_{15}H_{22}O_3$ (M^+, *m/e*): 250.157. Found: 250.158. $[\alpha]_D$ +56.4° ($CHCl_3$, $c=1.00$), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1778, 1712. NMR δ: 0.83, 1.02 (each 3H, s, 4α-Me, 10-Me), 1.21 (3H, s, 4β-Me), 2.01 (1H, s, 5-H), 4.28 (2H, d, $J=3.6$ Hz, 11-H_2).

ii) A solution of **21** (100 mg) and SeO_2 (400 mg) in AcOH (10 ml) was refluxed for 1 hr with stirring. The filtrate was evaporated to dryness, and the residue was extracted with ether. The extract was washed with sat. NaCl aq. then dried over Na_2SO_4. Removal of the solvent gave crystals, which were chromatographed on silica gel (25 g) to give crystals (**22**) (58 mg) from the petr. ether–ether (4: 1) eluate. The product was recrystallized from *n*-hexane–ether to afford 6-oxofragrolide (**22**) as colorless prisms, mp 120—123.5°. The physical data (IR and NMR) were identical with those of authentic racemate (**22**) prepared by Isoe's group.[10] *Anal.* high-resolution MS. Calcd for $C_{15}H_{20}O_3$ (M^+, *m/e*): 248.141. Found: 248.143. $[\alpha]_D$ +63.6° ($CHCl_3$, $c=1.00$). IR ν_{max} cm^{-1}: 1785, 1690. NMR δ: 0.97, 1.19 (each 3H, each 6H, s, 10-Me, 4-*gem* Me), 2.19 (1H, s, 5-H), 3.30 (1H, sextet, $J=3.6$, 8.4 Hz, 9-H), 4.16, 4.57 (each 1H, t, $J=8.4$ Hz, 11-H_2), 6.54 (1H, d, $J=3.6$ Hz, 7-H).

Preparation of 6α-Mesylconfertifolin (24)——A mixture of 6α-hydroxyconfertifolin (**19**) (547 mg) and mesyl chloride (2 ml) in pyridine (3 ml) was allowed to stand for 20 hr at room temperature. The reaction mixture was extracted with ether after H_2O had been added and the extract was washed with 10% HCl aq., sat. $NaHCO_3$ aq., and sat. NaCl aq., then dried over Na_2SO_4. Removal of the solvent gave an oily product (779 mg), which was chromatographed on silica gel (40 g) to give 6α-mesylconfertifolin (**24**) as a homogeneous oil (518 mg, 72% yield) from the *n*-hexane–ether (2: 1) eluate. *Anal.* GC–MS Calcd for $C_{16}H_{24}O_5S$ (M^+, *m/e*): 328. Found: 232 (M^+ − MsOH). IR ν_{max} cm^{-1}: 1771, 1690, 1382, 1180. NMR δ: 1.16, 1.29 (each 6H,

each 3H, s, 4-*gem* Me, 10-Me), 3.10 (3H, s, $-OSO_2Me$), 4.71 (2H, t(d,d), $J=3$ Hz, 11-H_2), 5.02—5.48 (1H, m, 6β-H).

Treatment of 6α-Mesylconfertifolin (24) with γ-Collidine——Crude 6α-mesylconfertifolin (**24**) (66 mg) obtained by the reaction of 6α-hydroxyconfertifolin (**19**) (50 mg) and mesyl chloride (0.2 ml) in pyridine (0.3 ml), was refluxed with γ-collidine (3 ml) for 8 hr under a nitrogen atmosphere. The reaction mixture was extracted with ether and the extract was washed with 10% HCl aq., sat. $NaHCO_3$ aq., and sat. NaCl aq., then dried over Na_2SO_4. Removal of the solvent gave an oily product (43 mg), which was chromatographed on silica gel (6 g) to afford $\Delta^{5,6}$-confertifolin (**23**) as a homogeneous oil (28 mg, 60% yield from **19**) from the *n*-hexane–ether (5: 1) eluate. *Anal.* GC–MS Calcd for $C_{15}H_{20}O_2$ (M^+, *m/e*): 232. Found: 232. IR ν_{max} cm^{-1}: 1770, 1702. NMR δ: 1.17, 1.24, 1.38 (each 3H, s, 4-*gem* Me, 10-Me), 2.77—2.97 (2H, m, 7-H_2), 4.71—4.85 (2H, m, 11-H_2), 5.76 (1H, t, $J=4$, 4 Hz, 6-H).

Preparation of 6β-Phenylselenoconfertifolin (25)——A solution of 6α-mesylconfertifolin (**24**) (48 mg) in absolute EtOH (1 ml) was added to a solution of sodium phenylselenide [prepared from $NaBH_4$ (9 mg) and diphenyldiselenide (35 mg) in absolute EtOH (1 ml)] and the reaction mixture was stirred for 30 min at room temperature then refluxed for 2 hr under a nitrogen atmosphere. The reaction mixture was extracted with ether after acidification with 0.1 N HCl aq. The extract was washed with sat. $NaHCO_3$ aq. and sat. NaCl aq., then dried over Na_2SO_4. Removal of the solvent gave an oily product (56 mg), which was separated by preparative silica gel TLC, using ether–*n*-hexane (1: 1) as the solvent. From the upper band was obtained a mixture (21 mg, 63% yield) of $\Delta^{5,6}$-confertifolin (**23**) and bemadienolide (**5**). From the middle band was obtained the desired 6β-phenylselenoconfertifolin (**25**) (9 mg, 16% yield). *Anal.* GC–MS Calcd for $C_{21}H_{26}O_2Se$ (M^+, *m/e*): 389. Found: 389. IR ν_{max} cm^{-1}: 1770, 1680. NMR δ: 1.11, 1.47, 1.51 (each 3H, s, 4-*gem* Me, 10-Me), 2.63—2.87 (2H, m, 7-H_2), 3.87—4.13 (1H, m, 6α-H), 4.78 (2H, br s, $W_{h/2}=6$ Hz, 11-H_2), 7.13—7.70 (5H, m, aromatic H). The lower band provided unchanged starting material (**24**) (4 mg, 9% recovery).

Preparation of (+)-Bemadienolide (5)——A solution of 6β-phenylselenoconfertifolin (**25**) (73 mg) in 6 ml of dry THF–AcOH [prepared from dry THF (10 ml) and AcOH (2 drops)] was treated with 30% hydrogen peroxide (304 μl) under ice cooling. The reaction mixture was stirred for 30 min under ice cooling, then stirred for 15 min at room temperature. The reaction mixture was extracted with ether and the extract was washed with sat. NaCl aq., then dried over Na_2SO_4. Removal of the solvent gave an oily product (61 mg), which was chromatographed on silica gel (6 g) to give an oil (50 mg) from the *n*-hexane–ether (5: 1) eluate. This was again separated by preparative TLC, using *n*-hexane–ether (1: 1) as the solvent. From the upper band was obtained bemadienolide (**5**) (33 mg, 75% yield), which was crystallized from *n*-hexane–ether as colorless needles, mp 124—124.5°. Its physical data (mp, $[\alpha]_D$, IR, NMR, and UV) were identical with those of natural bemadienolide (**5**).[3] *Anal.* Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.52; H, 8.69. $[\alpha]_D$ +20.4° ($CHCl_3$, $c=1.00$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1755, 1646. UV λ_{max}^{MeOH} nm (log ε): 273 (3.65). NMR (100 MHz) δ: 1.02, 1.05 (each 6H, each 3H, s, 4-*gem* Me, 10-Me), 2.22 (1H, t, $J=2$, 3 Hz, 5-H), 4.78 (2H, br s, $W_{h/2}=4$ Hz, 11-H_2), 6.04 (1H, dd, $J=2$, 10 Hz, 7-H), 6.33 (1H, dd, $J=3$, 10 Hz, 6-H).

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