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Conversion of Dehydroabietic Acid into a Steroid Skeleton: Formation of the A-ring. III.[1]

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Transformation of dehydroabietic acid (**1**) to a key intermediate for the synthesis of steroids is examined. 13-Isopropyl-15,16-bisnor-5β-podocarpa-8,11,13-trien-3-one (**5**) is synthesized from **1** *via* the ketone (**6**).

Attempts to convert *l*-abietic acid into intermediates suitable for the synthesis of steroids have been carried out in our laboratories. In an earlier paper[3] we reported the conversion of dehydroabietic acid (**1**) derived from *l*-abietic acid into 13β-isopropyl- (**2**) and 13β-acetoxy-9β-methyl-15,16,17-trinor-5β,8α,10α-podocarpa-4-one (**3**) which were expected as key intermediates for the synthesis of antipodal steroids by accompanying with the known procedure.[4] In this synthesis the A, B, and C rings in **1** correspond to the C, B, and A rings in steroids. With the view of utilizing the A, B, and C rings in **1** as the A, B, and C rings in steroids, further, we reported the synthesis of 13-isopropyl-15,16-bisnor-5β-podocarpa-8,11,13-trien-3-one (**5**) from **1** *via* the the keto ester (**4**) which was prepared by several methods.[5] In this connection we now report synthesis of **5** by another procedure starting from the ketone (**6**) which is derived from **1** by oxidative decarboxylation with lead tetraacetate followed by further oxidation of the resulting alkene mixture.[6]

The synthesis of 13-isopropyl-15,16-bisnorpodocarpa-4,8,11,13-tetraen-3-one (**9**) from **6** by the procedure for moving a ring carbonyl group to an adjacent carbon was reported.[7] Since, after carefully repeated examinations of this procedure, it was found that while **6** readily gave the benzylidene ketone (**7**), **7** was fairly unstable and did not afford the Δ^4-benzylidene compound (**8**), we examined anotherpathway from **6**. The ketone (**6**) gave the enone (**13**) in a good yield *via* four steps successively consisted of the Wolff-Kishner reduction (**6**→**10**), oxidation with chromium trioxide (**10**→**11**), bromination (**11**→**12**), and elimination of hydrobromic acid (**12**→**13**).[1]

Dehydrogenation of **13** with chloranil afforded the dienone (**14**) which was characterized by the nuclear magnetic resonance (NMR) spectrum showing signals for three olefinic protons (δ 6.43—6.00), two allylic protons (δ 2.43), and two ring methylene protons (δ 1.80). On epoxidation with *m*-chloroperbenzoic acid (*m*-CPBA), **14** gave the epoxide (**15**) whose NMR spectrum displayed signal for one olefinic proton (δ 6.53). This supports that epoxidation

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[1] This paper constitutes Part XXXIX of Diterpenoids by A. Tahara and co-workers. Part XXXVIII: A. Tahara (the late), M. Shimagaki, M. Itoh, Y. Harigaya, and M. Onda, *Chem. Pharm. Bull.* (Tokyo), 23, 3189 (1975).

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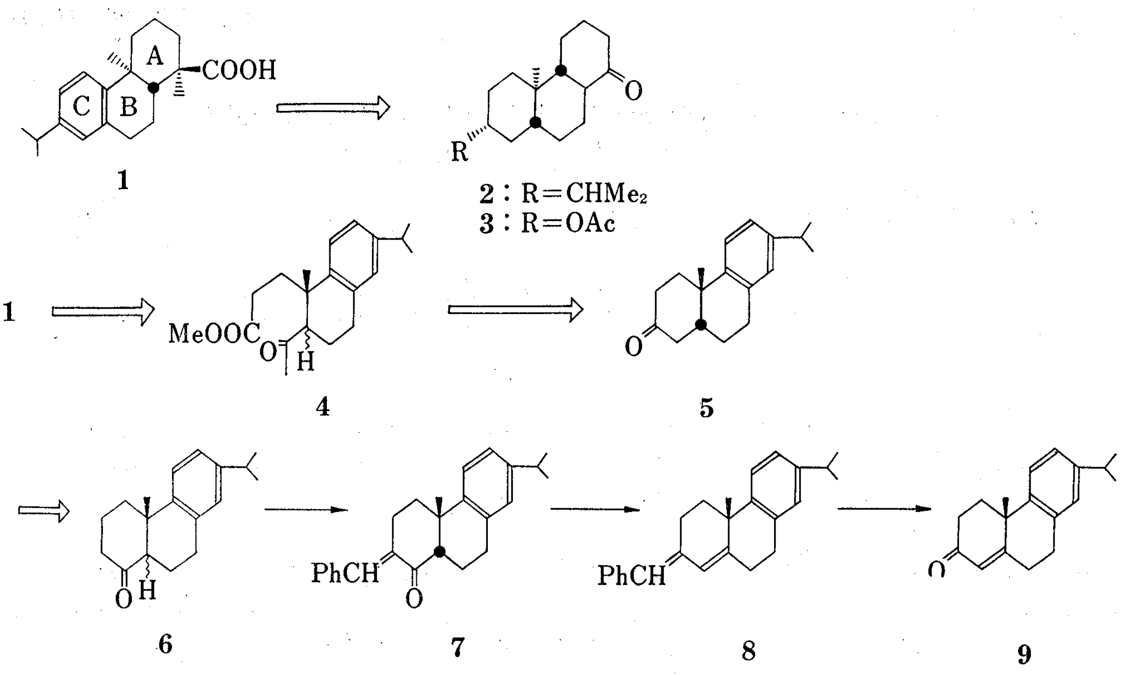
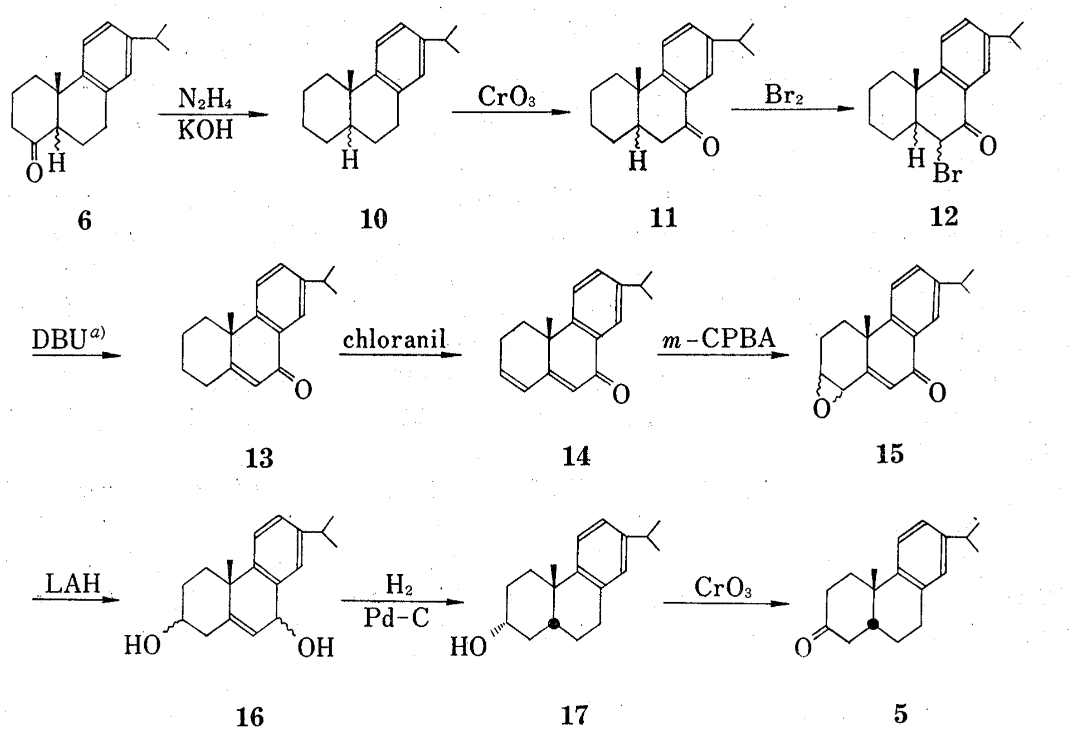


Ph=phenyl

Chart 1



a) 1,5-diazabicyclo[5•4•0]undecene-5

Chart 2

occurred at the 3- and 4-positions in **14**. Since gas chromatography (GLC) of **15** revealed two peaks in an approximate ratio of 2.2: 1, **15** is considered to be a mixture of two isomers.[8] Reduction of **15** with lithium aluminum hydride (LAH) afforded the diol (**16**) which gave

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[8] This result is contrary to that 13-isopropyl-15-norpodocarpa-3,5,8,11,13-pentaen-7-one gave 3α,4α-epoxy-13-isopropyl-15-norpodocarpa-5,8,11,13-tetraen-7-one.[5]

the carbinol (**17**) on hydrogenation over 10% palladium-carbon. The A/B *cis* configuration with the axial 10β-methyl group to the B ring and the 3-position of the hydroxy group in **17** are confirmed on the basis of the structure of the ketone (**5**) derived from **17** (*vide infra*). Configuration of the 3-hydroxy group in **17** is determined to be α (equatorial) by the half-height width (32 Hz) of the 3-hydrogen in the NMR spectrum of **17**. The carbinol (**17**) was oxidized with the Jones reagent to give the ketone (**5**), the structure of which was established as 13-isopropyl-15,16-bisnor-5β-podocarpa-8,11,13-trien-3-one by comparisons of the infrared (IR) and NMR spectra and the circular dichroism (CD) curve of an authentic sample.$^{5)}$

Experimental

IR spectra were taken on a JASCO IR-G. NMR spectra were measured with a Varian T-60 (60 MHz) and a JEOL JNM PS-100 (100 MHz) in a carbon tetrachloride solution. Mass spectra were recorded on a JEOL TMS-OlS. GLC was carried out with a Shimadzu GC-3AF. A glass column of 2 m × 4 mm was packed with 1.5% OV-17 on Shimalite W (80—100 meshes). Operating temperature was 230°. CD curves were taken on a JASCO J-20.

13-Isopropyl-15,16-bisnorpodocarpa-5,8,11,13-tetraen-7-one (13)——The enone (**13**) was prepared by the procedure described in lit. 1. **6→10**: A mixture of **6**$^{6)}$ (2.0 g), hydrazine hydrate (5.0 ml), and KOH (7.5 g) in diethylene glycol (100 ml) was treated. After alumina-chromatography, **10** (1.6 g, 88%) was obtained. **10→11**: To a solution of **10** (1.6 g) in acetic acid (50 ml) was added a solution of CrO_3 (2.2 g) in H_2O–acetic acid (1: 2, v/v) (30 ml). After work-up, **11** (1.5 g, 88%) was obtained. **11→12→13**: To a solution of **11** (2.0 g) in carbon tetrachloride (50 ml) was added a solution of Br_2 in carbon tetrachloride (100 mg/ml) (15 ml) with cooling. After stirring for 30 min and then removal of solvent, the resulting residue was dissolved in benzene (50 ml). To this solution was added DBU (5 ml) and the reaction mixture was refluxed for 1.5 hr. After work-up, **13** (1.13 g, 56%) was obtained as colorless oil. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1}: 1660, 1625 (enone system). Mass Spectrum: M^+, *m/e* 254.168. Calcd. for $C_{18}H_{22}O$: M, 254.167.

13-Isopropyl-15,16-bisnorpodocarpa-3,5,8,11,13-pentaen-7-one (14)——A mixture of **13** (1.4 g), chloranil (1.7 g), and *p*-toluene sulfonic acid (0.37 g) in acetic acid (30 ml) was refluxed for 3 hr. After removal of solvent, the resulting residue was treated with ether. The ethereal solution was worked up to give an oil (720 mg) whose chromatography on neutral alumina (grade III, 30 g) gave **14** (350 mg) as light yellow oil from benzene–*n*–hexane (1: 5—2: 5, v/v) eluate. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1}: 1645, 1625 (dienone system). NMR (60 MHz): δ 7.95 (bs, W_H 4 Hz, 14-H), 7.42 (d, *J* 7 Hz) and 7.32 (d, *J* 7 Hz) (11- and 12-H), 6.43—6.21 (m, 3- and 4-H), 6.12 (s, 6-H), 2.97 (septet, *J* 8 Hz, $C\underline{H}Me_2$), 2.43 (m, 2-H_2), 1.80 (m, 1-H_2), 1.39 (s, 10β-Me), 1.32 (d, *J* 8 Hz, $CH\underline{Me}_2$). Mass Spectrum: M^+, *m/e* 252.150. Calcd. for $C_{18}H_{20}O$: M, 252.151.

3,4-Epoxy-13-isopropyl-15,16-bisnorpodocarpa-5,8,11,13-tetraen-7-one (15)——To a solution of **14** (230 mg) in chloroform–ether (1: 1, v/v) (10 ml) added *m*-CPBA (200 mg) and the resulting solution was allowed to stand for 10 days at room temperature. *m*-CPBA (100 mg) was added after every 3 days in this duration. The reaction mixture was diluted with ether and washed successively with 5% aq. KOH, saturated aq. NaCl, and H_2O. The residue (242 mg) obtained from the ethereal solution purified by chromatography on neutral alumina (grade III, 20 g). The benzene–*n*–hexane (4: 1, v/v) eluate gave **15** (105 mg) as colorless oil, whose GLC showed 2 peaks in an approximate ratio of 2.2: 1 at t_R 9.6 and 6.5 min. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1}: 1658, 1630 (enone system). NMR (60 MHz): δ 7.91 (bs, W_H 3 Hz, 14-H), 7.37 (d, *J* 8 Hz) and 7.27 (d, *J* 8 Hz) (11- and 12-H), 6.53 (s, 6-H), 3.50 (m, 3- and 4-H), 2.97 (septet, *J* 8 Hz, $C\underline{H}Me_2$), 2.23 (m, 2-H_2), 1.90 (m, 1-H_2), 1.38 (s, 10β-Me), 1.31 (d, *J* 8 Hz, $CH\underline{Me}_2$). Mass Spectrum: M^+, *m/e* 268.144. Calcd. for $C_{18}H_{20}O_2$: M, 268.146.

13-Isopropyl-15,16-bisnorpodocarpa-5,8,11,13-tetraen-3,7-diol (16)——To a solution of **15** (150 mg) in dry tetrahydrofuran (15 ml) was added LAH (90 mg) and the reaction mixture was stirred for 1 hr at room temperature. After work-up, **16** (166 mg) was obtained as colorless oil. Mass Spectrum: M^+, *m/e* 272.179. Calcd. for $C_{18}H_{24}O_2$: M, 272.178.

13-Isopropyl-15,16-bisnor-5β-podocarpa-8,11,13-trien-3α-ol (17)——A solution of **16** (45 mg) in ethanol (3.5 ml) was hydrogenated over 10% Pd-C (20 mg) for 1.5 hr at room temperature. After work-up, the remaining residue (38 mg) was purified by preparative thin–layer chromatography (silica gel plates, 0.4 mm; benzene–ethyl acetate = 3: 1, v/v). The zone with *Rf* 0.68 gave **17** (14 mg) as colorless oil. IR $\nu_{\text{max}}^{\text{film}}$ cm^{-1}: 3325 (OH). NMR (100 MHz): δ 7.13 (d, *J* 8 Hz) and 6.93 (d, *J* 8 Hz) (11- and 12-H), 6.84 (bs, W_H 3 Hz, 14-H), 3.52 (m, W_H 32 Hz, 3β-H), 2.80 (m, 7-H_2 and $C\underline{H}Me_2$), 2.48—1.48 (9 × H), 1.22 (d, *J* 8 Hz, $CH\underline{Me}_2$), 1.13 (s, 10β-Me), 1.10 (OH).$^{9)}$ Mass Spectrum: M^+, *m/e* 258.198. Calcd. for $C_{18}H_{26}O$: M, 258.198.

13-Isopropyl-15,16-bisnor-5β-podocarpa-8,11,13-trien-3-one (5)——To a solution of **17** (12 mg) in acetone (0.5 ml) was added the Jones reagent (2 drops) with cooling and the reaction mixture was stirred for 15 min at room temperature. After work-up, there was obtained an oil (11 mg) which was purified by preparative

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9) This signal disappeared on addition of deuterium oxide.

thin-layer chromatography (silica gel plates, 0.3 mm; benzene–ethyl acetate=100: 1, v/v). The zone with *Rf* 0.42 gave **5** (9 mg) as colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1720 (C=O). NMR (100 MHz): δ 7.25 (d, *J* 8 Hz) and 7.03 (d, *J* 8 Hz) (11- and 12-H), 6.89 (bs, W_H 4 Hz, 14-H), 2.90 (m, 7-H_2 and C$\underline{H}$Me$_2$), 2.68—1.60 (9×H), 1.36 (s, 10β-Me), 1.24 (d, *J* 8 Hz, CH$\underline{Me}_2$). CD (c=0.06, MeOH [θ] (mμ): −660 (293) (negative maximum), −1536 (265) (negative maximum). These spectra were superimposed on those of an authentic sample.[5] Mass Spectrum: M$^+$, *m/e* 256.179. Calcd. for $C_{18}H_{24}O$: M, 256.183.