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Diterpenoids. XLIV. A-Ring Bromination of Abietane Skeleton and the Synthesis of Teideadiol[1]

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Direct introduction of bromine into the A-ring of the phenacylidene derivatives of *l*-abietic acid (**1**) was developed and it was applied to the conversion of **1** into teideadiol (**2**), a naturally occurring diterpene with a hydroxy group on the A-ring of its abietane skeleton.

In the study of the conversion of *l*-abietic acid (**1**) into other naturally occurring diterpenes including Aconitum alkaloids, gibberellins, cytotoxic quinones and kaurenoids, and furthermore into steroids, various types of reactions were employed to introduce an appropriate function into a certain carbon of B-, or C-ring, of C_4-, or C_{10}-angular methyl, or of side chain at C_{13}.[3]

However the problem of the functionalization of the A-ring has long remained untouched, and only the feasible way to realize it seemed to utilize the hydrogen abstraction reaction by securing a foothold on the B-, or C-ring, or on the carboxyl group at C_4.

On the other hand, the study of the reactivity of the phenacylidene derivatives of *l*-abietic acid led to a development of a direct bromination reaction of the A-ring in a unique manner (Chart 1), and it opened a way to synthesize diterpenes with a functionality in the A-ring starting from *l*-abietic acid.[1]

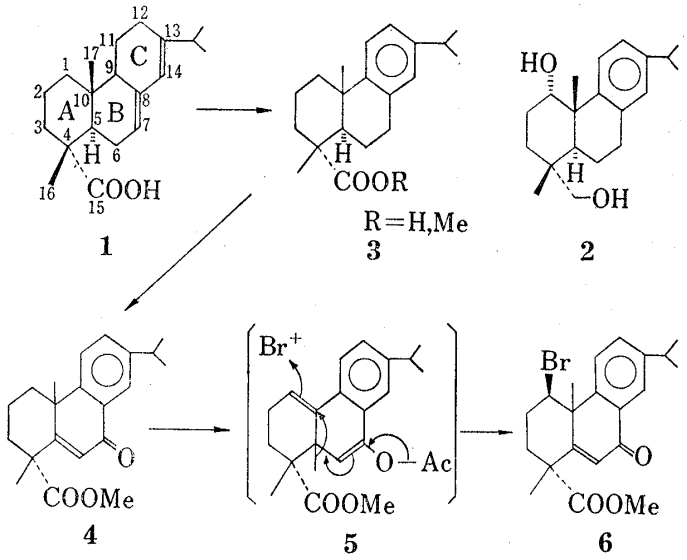

Chart 1

The present paper will deal with, in detail, the synthesis of teideadiol (**2**), a naturally occurring diterpene with a hydroxy group on the A-ring of its abietane skeleton as is illustrated in Chart 2, as one of the applications of the above bromination reaction to syntheses of natural products from *l*-abietic acid.

Teideadiol[4] (**2**) was isolated from a native plant of Canary islands, Nepeta teidea W.B., by Breton in 1970 and it is structurally related to dehydroabietic acid, **3** (R=H). As the

1) Previous communication: A. Tahara and H. Mizuno, *Tetrahedron Letters*, **1974**, 523; Part XLIII: A. Tahara (the late), Y. Harigaya and M. Onda, *Chem. Pharm. Bull.* (Tokyo), **24**, 1497 (1976).

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3) A. Tahara, The proceeding of the 92 nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka (1972) I-p 120, and the references cited in it.

4) J.L. Breton, A.G. Gonzalez, and G. de Leon, *Anales de la Real Sociedad Espanola de Fisica y Quimica, Series B-Quimica*, **66**, 293 (1970) [*Chem. Abstr.*, **73**, 88048 (1970)].

latter is easily derived from **1** and also commercially available as the major component of the disproportionated rosin, **3** (R=H) can be a good starting material for the synthesis of **2**, with some methods of the introduction of the 1α-hydroxy group. Here, new bromination reaction mentioned above should be a pertinent key to solve this problem.

As reported in the preceding papers,[5] the phenacylidene derivative of *l*-abietic acid, **4**, gave 1β-acetyl derivative with acid in acetic anhydride. It suggested the possibility of the introduction of other functional groups to C_1 position of **4** with other electrophilic reagents. Then N-bromosuccinimide was chosen as Br^+ source and **4** was treated with it in acetic anhydride containing sulfuric acid at room temperature for 6 hr to give **6** as an oil in 85% yield as is illustrated in Chart 1;[6] $C_{21}H_{25}O_3Br$; IR cm^{-1}; 1725, 1655; NMR δ: 3.74 (s, COOMe), 4.84 (m, $\Delta W_{1/2}$= 12 Hz, 1-H), 6.15 (s, 6-H), 7.41 (q, J=2 and 8 Hz, 12-H), 7.85 (d, J=2 Hz, 14-H), 8.08 (d, J=8 Hz, 11-H). The structure **6** was determined by analogy to the 1β-acetyl phenacylidene, considering the mechanistic point of view. Furthermore, the retention of the original skeleton was confirmed by the formation of methyl dehydroabietate by the hydrogenolysis as will be mentioned later. The position, C_1, and the configuration, β, of the bromine was also supported by the observation of the nuclear Overhauser effect (NOE) between C_1–H and C_{11}–H; 9.9% increase of C_1–H signal by the irradiation of C_{11}–H, and 17.1% increase of C_{11}–H signal by the irradiation of C_1–H. Moreover, very large chemical shift, 0.66 ppm, between the signals of C_{11}–H in **6** (δ 8.08) and that in **7** (δ 7.42), C_1 isomer of **6** mentioned in the following section, can be reasonably explained by the above assignment. In **6**, C_{11}–H is located very close to 1β-bromine atom, suffering from paramagnetic effect, but in **7**, this situation does not exist and C_{11}–H appears in the normal field. Comparison of the half-height band width ($\Delta W_{1/2}$) of C_1–H in **6** with that of C_1–H in **7** also supports the assignment. That is, the former is 12 Hz, corresponding to an axial proton and the latter is 6 Hz, corresponding to an equatorial proton. Conclusively, **6** has 1β-Br and **7** has 1α-Br, based on a chair conformation of A-ring with large COOMe group at C_4 in equatorial.

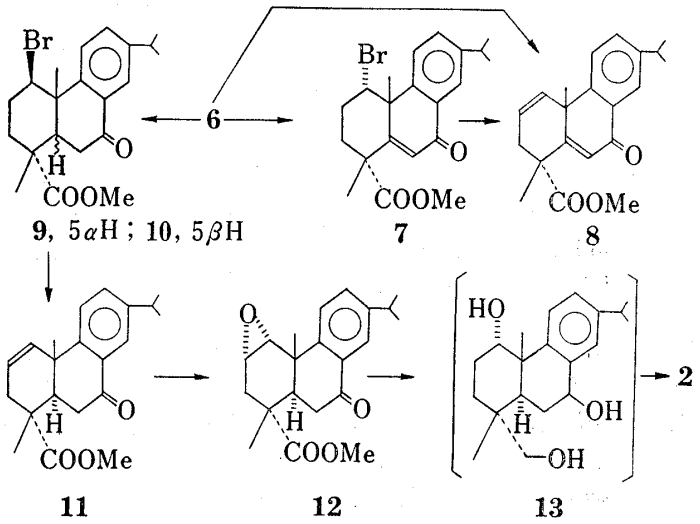

Chart 2

In order to clarify the reactivity of the bromine atom against dehydrobromination reaction, **6** was refluxed in pyridine or heated at 120° in collidine for 4 hr, giving crystals of **7**, mp 124—125°, $C_{21}H_{25}O_3Br$, in 67 and 69%, respectively. Heated at 150° in collidine for 2 hr, **6** was transformed to a mixture of **7** in 23% and the olefin **8**, mp 84—86°, NMR δ: 5.89 and 6.33 (C_2– and C_1–H, respectively) in 38%. Far better yield of the olefin, 88%, was obtained by treating **6** in diazabicyclo[5,4,0]-undecene (DBU) at 100° for 2 hr. Not only **6**, but also **7** were dehydrobrominated to **8** with DBU, supporting that these two bromides are stereoisomers at C_1-position.

As DBU was proved effective for the dehydrobromination, saturation of the 5,6-double bond of **6** was next examined. In the presence of sulfuric acid, 10% palladium charcoal in

5) A. Tahara, H. Mizuno and T. Ohsawa, *Chemistry Letters*, **1972**, 1163; T. Ohsawa, H. Mizuno, T. Takizawa, M. Itoh, S. Saito, and A. Tahara (the late), *Chem. Pharm. Bull.* (Tokyo), **24**, 705 (1976).

6) The detail concerning this type reaction will be reported in the following paper.

ethanol reduced **6** into methyl dehydroabietate, **3** (R=Me), in 36% yield in hydrogen atmosphere at 1 atm at room temperature for 2.5 hr, proving abietane skeleton of **6**. Without acid, a dihydro compound, IR cm^{-1}: 1736, 1690, mp 105—106°, was obtained in 87% yield by hydrogenation with 10% palladium charcoal in methanol at 1 atm of hydrogen at room temperature for 12 hr. Nevertheless, the examination of its nuclear magnetic resonance (NMR) spectrum revealed that this dihydro compound has undesirable *cis* A/B ring juncture. That is, the signal of the methyl of the methoxy carbonyl group appeared at δ 2.96, suffering from the diamagnetic anisotropic effect of the aromatic C-ring and C_7-carbonyl group, and the structure is given as **10**. On the other hand, with platinum oxide in methanol containing acetic acid, hydrogenation of **6** at 1 atm at room temperature for 2 hr gave another dihydro compound, mp 139—140°, IR cm^{-1}: 1736, 1690, in 53% and **10** in 26%. The NMR spectrum of the former shows a methyl signal of the methoxy carbonyl at ordinary position, δ 3.64, indicating the desirable A/B *trans* ring juncture, therefore, structure **9**. Higher yield, 77%, of the trans isomer, **9**, was obtained at 5 atm with platinum oxide in methanol containing acetic acid for 5 min.

Successively, dehydrobromination of **9** was done by heating at 100° in DBU for 3 hr to give the olefin **11**, mp 84—85°, in 87% yield, NMR δ: 5.73 and 6.30 (C_2-, and C_1–H, respectively).

Then **11** was treated with peracetic acid in acetic acid at room temperature for 34 hr to yield 1α,2α-epoxide **12**, mp 154—156°, in 81% yield, by the attack of the reagent from the less hindered side.

The epoxide **12** was reduced with lithium aluminum hydride in tetrahydrofuran for 16 hr into the triol **13**, which was submitted, without purification, to hydrogenolysis with 10% palladium charcoal at 1 atm at room temperature for 20 hr. After work-up in the usual manner, the reaction product was chromatographed on silica gel column to give colorless needles, mp 127—128°, in 79% yield. The melting point of this crystal is the same as that of the reported teideadiol, 128°, and this specimen was sent to Prof. Breton and identified with the authentic teideadiol.

Above conversion of *l*-abietic acid, **1**, to teideadiol completed, at the same time, the total synthesis of the latter in formal sense as the total synthesis of the former was already done.[7]

Experimental[8]

Bromination of Phenacylidene Compound (4); Methyl 1β-Bromo-13-isopropyl-7-oxo-10β-podocarp-5,8,11,13-tetraen-15-oate (6)——To a solution of phenacylidene compound (**4**) (10.0 g) in Ac_2O (700 ml), N-bromosuccinimide (8.9 g) and 5% H_2SO_4–Ac_2O (200 ml) were added, and the mixture was left at room temperature for 6 hr. Then it was poured on ice flakes containing a little $NaHCO_3$, followed by extraction with ether. The ethereal extract was washed successively with H_2O, 10% Na_2CO_3 aq. and satd. NaCl aq. Work-up gave 13.6 g of an oil, which was chromatographed on a silica gel column (500 g) to give **6** as an oil in 85% yield in the *n*-hexane–ether (10: 1) eluate. IR cm^{-1}: 1725, 1655. NMR δ: 3.74 (s, COOMe), 4.84 (m, $\Delta W_{1/2}$=12 Hz, 1-H), 6.15 (s, 6-H), 7.41 (q, J=2 and 8 Hz, 12-H), 7.85 (d, J=2 Hz, 14-H), 8.08 (d, J=8 Hz, 11-H).

Corresponding 2,4-dinitrophenylhydrazone of **6** was synthesized by the usual method as yellow needles, mp 95.5—97.5° from MeOH aq. *Anal.* Calcd. for $C_{27}H_{29}O_6N_4Br$: C, 55.39; H, 4.99; N, 9.57; Br, 13.65. Found: C, 55.48; H, 5.02; N, 9.83; Br, 12.54.

Base Treatment of Methyl 1β-Bromo-13-isopropyl-7-oxo-10β-podocarp-5,8,11,13-tetraen-15-oate (6)——i) With Pyridine: A solution of **6** (180 mg) in anhydrous pyridine (24 ml) was refluxed for 4 hr. After the removal of the solvent by distillation under reduced pressure, the product was extracted with ether, and the ethereal extract was washed successively with 10% HCl aq., satd. $NaHCO_3$ aq. and satd. NaCl aq. The resulting oil (160 mg) was chromatographed on a silica gel column (8 g) to give 120 mg of crystals of **7** in 67% yield in the *n*-hexane–ether (10: 1) eluate. Recrystallization from MeOH aq. gave colorless needles, mp

7) E. Wenkert, A. Afonso, J.B. Brendenberg, C. Kaneko, and A. Tahara, *J. Am. Chem. Soc.*, **86**, 2038 (1964).

8) All melting points were measured on a Kofler block and not corrected. NMR spectra were measured at 60 MHz in CCl_4 *vs.* Me_4Si, unless stated otherwise, and singlet, broad singlet, doublet, double doublet, triplet, quartet and multiplet were abbreviated as "s", "br s", "d", "d.d", "t", "q", and "m", respectively. Infrared (IR) spectra were measured usually in CCl_4.

124—125°. *Anal.* Calcd. for $C_{21}H_{25}O_3Br$: C, 62.66; H, 6.22; Br, 19.71. Found: C, 62.49; H, 6.21; Br, 19.73. IR cm^{-1}: 1736, 1655. NMR δ: 3.77 (s, COOMe), 5.01 (m, $\Delta W_{1/2}$=6 Hz, 1-H), 6.10 (s, 6-H), 7.42 (br s, 11-, and 12-H), 7.92 (br s, 14-H).

ii) With γ-Collidine: A solution of **6** (160 mg) in anhydrous γ-collidine (4 ml) was heated at 120° for 4 hr. Work-up in the same manner as in i) gave 155 mg of an oil, which was chromatographed on a silica gel column (8 g) to give 110 mg of crystals of **7** in 69% yield in the *n*·hexane–ether (10: 1) eluate. Recrystallization from MeOH aq. gave colorless needles, mp 124—125°, which were identified with **7** obtained in i) by mixed melting point, IR and NMR spectra.

iii) With γ-Collidine: A solution of **6** (200 mg) in γ-collidine (6 ml) was heated at 150° for 2 hr. Work-up in the same manner as above gave 160 mg of an oil, which was chromatographed on a silica gel column (8 g) to give 45 mg of crystals in 23% yield in the *n*·hexane–ether (10: 1) eluate. Recrystallization from MeOH aq. gave colorless needles, mp 124—125°, identical with **7**. Further elution with the same solvent gave 60 mg of crystals of **8** in 38% yield. Recrystallization from MeOH aq. gave colorless needles, mp 84—86°. *Anal.* Calcd. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.76; H, 7.35. IR cm^{-1}: 1740, 1665. NMR δ: 3.64 (s, COOMe), 5.89 (q, J=4 and 10 Hz, 2-H), 6.11 (s, 6-H), 6.33 (d, J=10 Hz, 1-H), 7.46 (br s, 11-, and 12-H), 7.90 (br s, 14-H).

Methyl 13-Isopropyl-7-oxo-10β-podocarp-1,5,8,11,13-pentaen-15-oate (8)——A solution of **6** (100 mg) in 1,5-diazabicyclo[5,4,0]undecene-5 (DBU) (2 ml) was heated at 100° for 2 hr. After dilution with H_2O, the reaction mixture was extracted with ether. The ethereal extract was washed successively with 10% HCl aq., satd. $NaHCO_3$ aq. and satd. NaCl aq. Work-up in the usual manner gave 85 mg of crystals, which was recrystallized from MeOH aq. to give 70 mg of **8** in 88% yield. Further recrystallization yielded colorless needles, mp 86—87°. IR and NMR spectra, and mixed melting point showed the identity of the above crystals with **8** obtained by dehydrobromination of **6** with γ-collidine.

Dehydrobromination of Methyl 1α-Bromo-13-isopropyl-10β-podocarp-5,8,11,13-tetraen-15-oate (7)——A solution of **7** (100 mg) in DBU (2 ml) was heated at 100° for 2 hr. Work-up in the same manner as the dehydrobromination of 1β-isomer gave 85 mg of crystals, which were recrystallized from MeOH aq. to give 70 mg of colorless needles in 88% yield. Further recrystallization gave a melting point of 84—86°. The identification of these crystalls with **7** was done by IR and NMR spectra, and mixed melting point.

Catalytic Reduction of 6——i) H_2, 1 atm/Pd-C/H_2SO_4–EtOH: Compound **6** (200 mg) was reduced at 1 atm with 10% Pd-C (1.0 g) in EtOH (30 ml) containing H_2SO_4 (0.4 ml) at room temperature for 2.5 hr. Work-up in the usual manner gave 120 mg of an oil, which was chromatographed on a silica gel column (6 g) to give crystals in 36% yield in the *n*·hexane–ether (20: 1) eluate. Recrystallization from MeOH aq. gave colorless needles, mp 57—59°. These were identified with the authentic **3** (R=Me) by IR and NMR spectra, and mixed melting point.

ii) H_2, 1 atm/Pd-C/MeOH: Compound **6** (200 mg) was reduced at 1 atm with 10% Pd-C (200 mg) in MeOH (10 ml) at room temperature for 12 hr. After the filtration of the catalyst and removal of the solvent, the residue was crystallized from *n*·hexane to give 210 mg of crystals, which were recrystallized from the same solvent to give 175 mg of **10** in 87% yield. Upon further recrystallization gave a melting point of 105—106°. *Anal.* Calcd. for $C_{21}H_{27}O_3Br$: C, 61.90; H, 6.68; Br, 19.62. Found: C, 62.10; H, 6.68; Br, 19.42. IR cm^{-1}: 1736, 1690. NMR δ: 2.96 (s, COOMe), 5.35 (m, $\Delta W_{1/2}$=7 Hz, 1-H), 7.14 (d, J=8 Hz, 11-H), 7.35 (q, J=2 and 8 Hz, 12-H), 7.79 (d, J=2 Hz, 14-H).

iii) H_2, 1 atm/PtO_2/MeOH+AcOH: Compound **6** (200 mg) was reduced at 1 atm with PtO_2 (40 mg) in MeOH (15 ml) containing AcOH (0.1 ml) at room temperature for 2 hr. The residue (200 mg) from the work-up in the usual manner was crystallized from *n*·hexane to give 105 mg of crystals of **9** in 53% yield. A melting point of 139—140° was obtained upon further recrystallization. *Anal.* Calcd. for $C_{21}H_{27}O_3Br$: C, 61.90; H, 6.68; Br, 19.62. Found: C, 62.16; H, 6.47; Br, 19.84. IR cm^{-1}: 1736, 1690. NMR δ: 3.64 (s, COOMe), 4.59 (q, J=8 and 9 Hz, 1-H), 7.32 (q, J=2 and 8 Hz, 12-H), 7.69 (d, J=2 Hz, 14-H), 8.10 (d, J=8 Hz, 11-H).

From the mother liquid of the first crystallization, 50 mg of crystals were obtained as the second crop in 26% yield. These crystals were further recrystallized to colorless needles, mp 105—106°, and identified as **10**.

iv) H_2, 5 atm/PtO_2/MeOH+AcOH: Compound **6** (2 g) was reduced at 5 atm with PtO_2 (400 mg) in MeOH (80 ml) containing AcOH (0.6 ml) at room temperature for 5 min. The resulting oil (1.9 g) from the work-up in the usual manner was crystallized from *n*·hexane to give 1.36 g of crystals of **9** in 67% yield, which were recrystallized from the same solvent to colorless needles, mp 139—140°.

From the mother liquid of the first crystallization, 200 mg of crystals were obtained as the second crop in 10% yield. These crystals were further recrystallized to colorless needles, mp 105—106°, and identified as **10**.

Methyl 13-Isopropyl-7-oxo-5α,10β-podocarp-1,8,11,13-tetraen-15-oate (11)——A solution of **9** (1.26 g) in DBU (10 ml) was heated at 100° for 3 hr. Then 10% HCl aq. was added and the separated oily product was extracted with ether. Work-up of the ethereal extract yielded 960 mg of an oil, which was chromatographed on neutral alumina (50 g) to give 880 mg of crystals of **11** in 87% yield in the *n*·hexane–ether (20: 1) eluate. Recrystallization from MeOH aq. gave colorless needles, mp 84—85°. *Anal.* Calcd. for $C_{21}H_{26}O_3$:

C, 77.27; H, 8.03. Found: C, 76.94; H, 7.97. IR cm^{-1}: 1735, 1690. NMR δ: 3.64 (s, COOMe), 5.73 (m, $J=2$, 5, and 11 Hz, 2-H) 6.30 (q, $J=2$ and 11 Hz, 1-H), 7.26 (br s, 11-, and 12-H), 7.75 (br s, 14-H).

Methyl 1α,2α-Epoxy-13-isopropyl-7-oxo-5α,10β-podocarp-8,11,13-trien-15-oate (12)——A solution of **11** (250 mg) in 10% AcO_3H in AcOH (32 ml) was left at room temperature for 34 hr. An oil precipitated by the addition of H_2O was extracted with ether. Work-up of the ethereal extract yielded 168 mg of crystals of **12** in 81% yield. Recrystallization from a mixture of ether and *n*-hexane gave colorless needles, mp 154—156°. *Anal.* Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.24; H, 7.41. IR cm^{-1}: 1730, 1685. NMR δ: 3.2—3.8 (m, 1-, and 2-H), 3.67 (s, COOMe), 7.40 (br s, 11-, and 12-H), 7.75 (br s, 14-H).

Teideadiol (2)——To a solution of $LiAlH_4$ (180 mg) in anhydrous tetrahydrofuran (5 ml), a solution of **12** (180 mg) in the same solvent (10 ml) was added dropwise under stirring, and the stirring was continued at room temperature for 16 hr. The excess reagent was decomposed by the careful addition of H_2O and the resulting precipitate was removed. After the solvent was evaporated, the residue was extracted with ether. The product from the work-up of the ethereal extract was dissolved in AcOH (15 ml) and reduced with 10% Pd-C (170 mg) in an atmosphere of H_2 under 1 atm at room temperature for 20 hr. After the catalyst was filtered off, the reaction mixture was diluted with H_2O to precipitate an oil, which was extracted with ether. The product from the work-up was chromatographed on a silica gel column (10 g) to give 125 mg of crystals in 79% yield in the *n*-hexane–ether (2: 1) eluate. Recrystallization from *n*-hexane gave colorless needles, mp 127—128°. These crystals were identified by Dr. Breton with the authentic sample of teideadiol by IR and NMR spectra, and mixed melting point. *Anal.* Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.01; H, 10.08. IR cm^{-1}: 3630, 3580, 3450. NMR δ: 0.72 (s, 4-Me), 1.11 (s, 10-Me), 2.87 and 3.27 (AB q. $J=9$ Hz, 4-CH_2O-), 4.11 (m, $\Delta W_{1/2}=7$ Hz, 1-H), 6.78—7.10 (m, 11-, 12-, and 14-H).

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