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BROMINATION OF A-RING IN DEHYDROABIETIC ACID DERIVATIVES. TOTAL SYNTHESIS OF TEIDEADIOL[*1]

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Substitution of the A-ring in dehydroabietic acid is regarded as one of attractive problems, but no report has been found till quite recently. In our previous work,[1] an interesting methyl migration of benzonilidene compound[2] (**2**) derived from methyl dehydroabietate (**1**) was found ($\mathbf{2} \rightleftarrows \mathbf{3}$) and an acetyl cation could be attacked successfully to C_1-position ($\mathbf{2} \longrightarrow \mathbf{4}$) by the application of this migration. The acetyl group in **4** is less reactive, so that **4** is not expected as a relay compound for the syntheses of various derivatives having substituents in the A-ring. Thus, an introduction of other electrophilic reagents, e.g., bromine cation, into the A-ring was examined in **2**.

The benzonilidene ester[2] (**2**) was readily brominated (N-bromosuccinimide, Ac_2O-H_2SO_4, room temp., 6 hr) to yield β-bromide (**5**)(85% yield), ir: 1725, 1655; nmr: 1.65, 1.80 (s, 3H each; C_4- and C_{10}-Me), 4.84 (m, 1H, $W^h/_2$=12 Hz; C_1-H), 6.15 (s, 1H; C_6-H), 7.41 (q, 1H, _J_=2, 8 Hz; C_{12}-H), 7.85 (d, 1H, _J_=2 Hz; C_{14}-H), 8.08 (d, 1H, _J_=8 Hz; C_{11}-H). For an elimination of hydrobromide from **5**, the bromide (**5**) was treated with a base [collidine (120°) or pyridine (reflux), 4 hr], but it did not give the desired unsaturated compound and gave an unexpected isomeric α-bromide (**6**)(67-69% yield), mp 124-125°, ir: 1736, 1665; nmr: 1.66, 1.68 (s, 3H each; C_4- and C_{10}-Me), 5.01 (m, 1H, $W^h/_2$=6 Hz; C_1-H), 6.10 (s, 1H; C_6-H),

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[*1] New compounds gave satisfactory analytical values. Nmr (δ, 60 MHz) and ir (cm^{-1}) spectra were measured in CCl_4.

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7.42 (br.s, 2H; C_{11}- and C_{12}-H), 7.92 (br.s, 1H; C_{14}-H).

Configuration at C_1-position of both isomers (5; β C_1-Br and 6; α C_1-Br) was assumed by comparison of the width of half-height ($W^h/_2$)(5, 12 Hz; axial C_1-H, and 6, 6 Hz; equatorial C_1-H) of nmr peak due to C_1-H. This assumption was evidently supported by the nuclear Overhauser effect (NOE) between C_1-H and C_{11}-H. Any changes of integration value were not detected in 5, but distinct increases of the integration value (9.9% increase in C_1-H and 17.1% increase in C_{11}-H by irradiation at C_{11}-H and C_1-H, respectively) were observed in 6.[*3]

Retention of the original skeleton in the bromides (5 and 6) was confirmed by the following reaction. Dehydrobromination of the bromides (5 and 6) was carried out with 1,5-diazabicyclo[5.4.0]undecene-5 (DBU)(100°, 2 hr) and easily gave the same product (7)(88-92% yield), mp 84-86°, nmr: 5.89 (octet, 1H, *J*=4, 5, 10 Hz; C_2-H), 6.33 (d, 1H, *J*=10 Hz; C_1-H), 6.11 (s, 1H; C_6-H), 7.46 (br.s, 2H; C_{11}- and C_{12}-H), 7.90 (br.s, 1H; C_{14}-H), and then 7 could be reverted to the starting methyl dehydroabietate (1) by catalytic hydrogenation (Pd-C, MeOH, H_2).

The benzonilidene system of β-bromide (5) is so reactive that it should be removed firstly for the synthesis of diterpenoids having a substituted A-ring from 5. The system was eliminated under the optimum condition (Pt, AcOH-MeOH, 5 atm. pressure of H_2) and gave a bromide (8) having *trans*-A/B ring fusion, mp 139-140° (67% yield), nmr: 3.64 (s, 3H; COOMe), 4.59 (q, 1H, *J*=8, 9 Hz; C_1-H), 7.32 (q, 1H, *J*=2, 8 Hz; C_{12}-H), 7.69 (d, 1H, *J*=2 Hz; C_{14}-H), 8.10 (d, 1H, *J*=8 Hz; C_{11}-H). In the hydrogenation, *cis*-isomer (9), mp 105-106° (10% yield), nmr: 2.96 (s, 3H; COOMe), 5.35 (m, 1H, $W^h/_2$=7 Hz; C_1-H), 7.14 (d, 1H, *J*=8 Hz; C_{11}-H), 7.35 (q, 1H, *J*=8, 2 Hz; C_{12}-H), 7.79 (d, 1H, *J*=2 Hz; C_{14}-H) was also produced in

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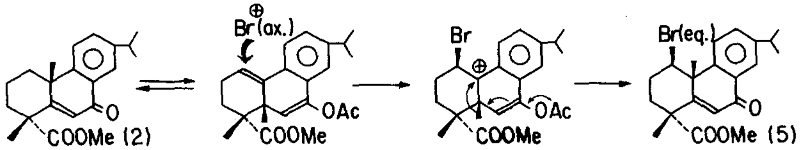
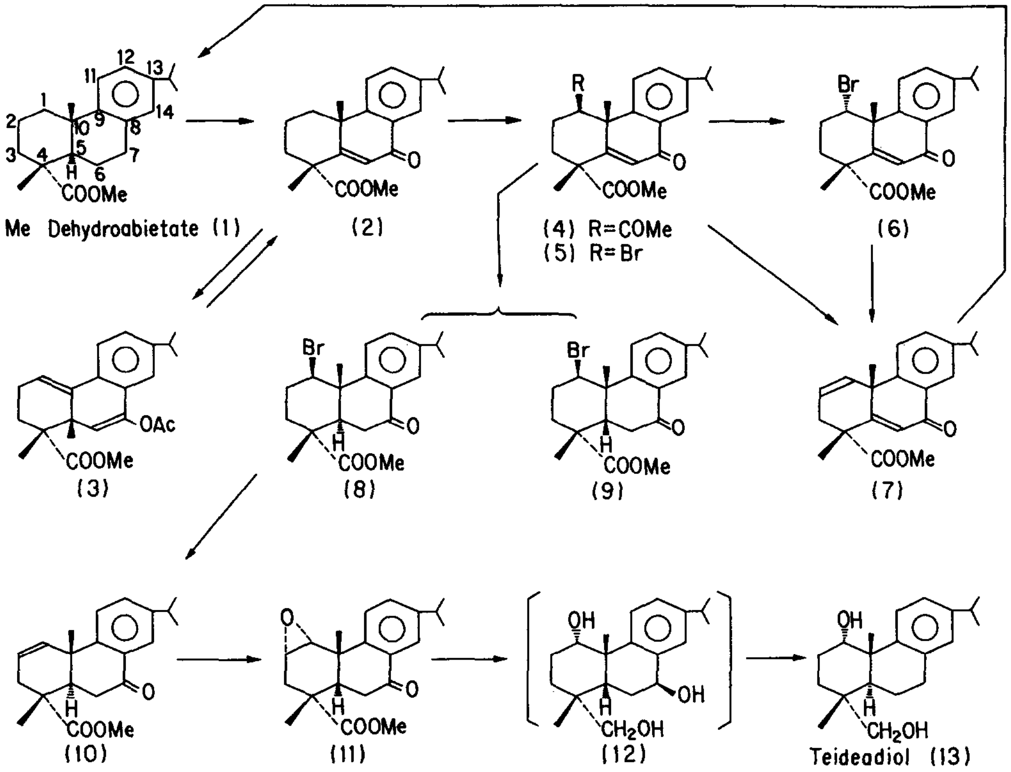
[*3] For explanation of β configuration of C_1-bromine atom in 5, a following mechanism can be considered at present.





company with the major product (8).

Stereostructure of the A/B ring juncture of both isomers (8 and 9) was determined by comparison of their nmr spectra. The lower chemical shift due to methoxycarbonyl group in 9 (cis) than that of 8 (trans) shows that the group in 9 is located on the benzene ring in its nonsteroidal conformation and is affected by the diamagnetism.

The bromide (8) can be considered as an important intermediate for our purpose. As a simple example for its utilization, synthesis of teideadiol,[3] isolated from Nepeta teydea W. B. (an endemic plant of Canary Islands), was accomplished from 8. Dehydrobromination of 8 by DBU as in 6 gave an unsaturated ester (10)(87% yield), mp 84-85°, nmr: 3.64 (s, 3H; COOMe), 5.73 (octet, 1H, *J*=2, 5, 11 Hz; C_2-H), 6.30 (q, 1H, *J*=2, 11 Hz; C_1-H), 7.26 (br.s, 2H; C_{11}- and C_{12}-H), 7.75 (br.s, 1H; C_{14}-H), and **10** was oxidized ($MeCO_3H$, AcOH, 34 hr, room temp.) to give an epoxide (**11**)(81% yield), mp 154-156°, nmr: 3.2-3.8 (m, 2H; C_1- and C_2-H), 3.67 (s, 3H; COOMe), 7.40 (br.s, 2H; C_{11}- and C_{12}-H), 7.75 (br.s, 1H; C_{14}-H). The oxide ring of **11** was cleaved by $LiAlH_4$ and the resulting triol (**12**) was hydrogenated (Pd-C, AcOH, H_2) to give an alcohol (**13**)(79% yield from **11**), mp 127-128°, nmr: 2.87, 3.27 (d, 1H each, *J*=9 Hz; CH_2OH), 4.11 (m, 1H, $W^h/_2$=7 Hz; C_1-H), 6.78-7.10 (m, 3H; C_{11}-, C_{12}- and C_{14}-H). The product (**13**) was completely identical with natural teideadiol.[3]

Study on the interesting reactivity at C_1-position of benzonilidene system (e.g., **2**) and its application are in progress.

References

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