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FORMATION OF STEROIDAL SKELETON FROM RESIN ACID[1]

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Dehydroabietic acid (1) was converted into 14 and 20 having the steroidal skeleton, by the use of its isopropyl group for the formation of the steroidal D-ring.

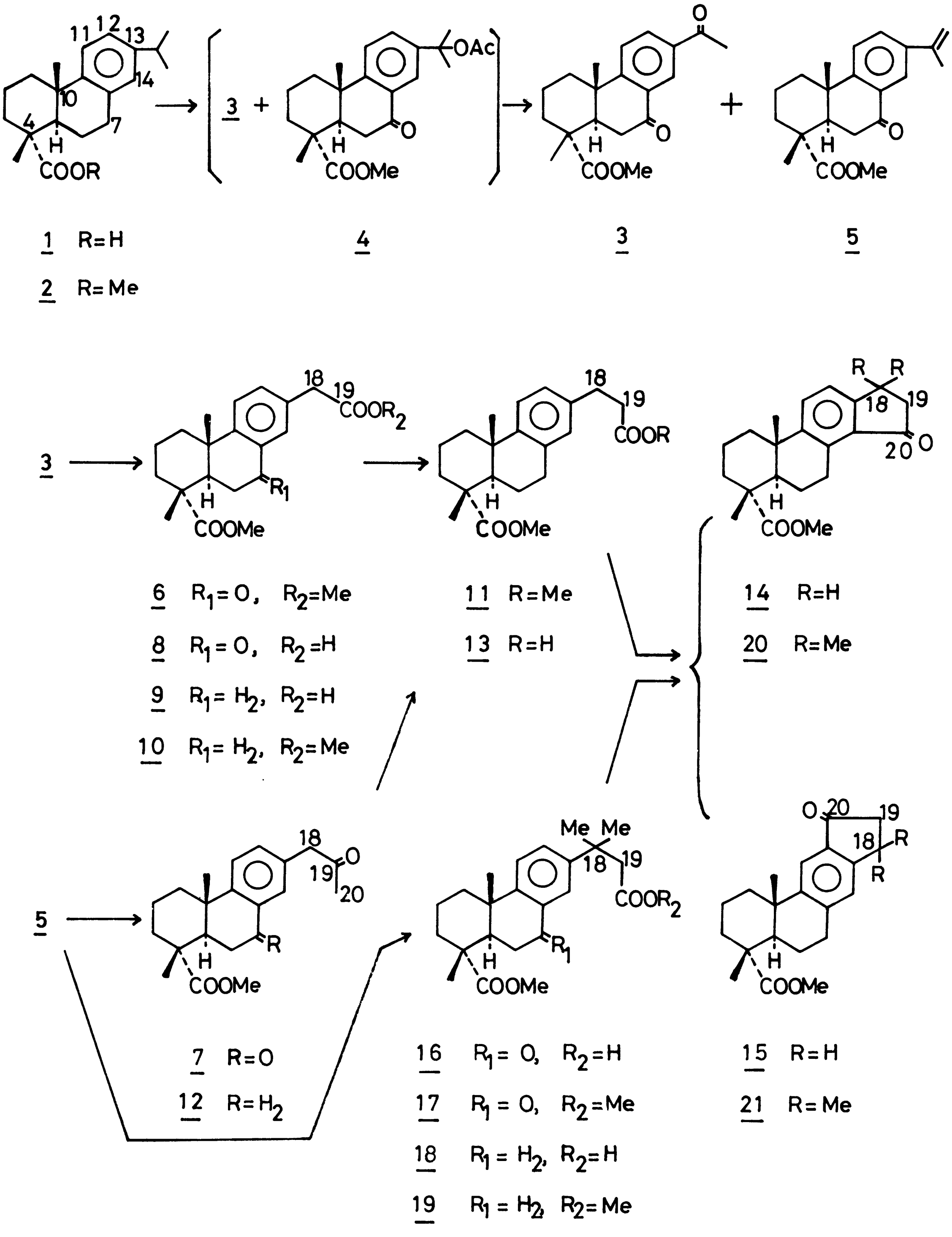
It is attractive to synthesize the steroidal skeleton from diterpene, e.g. dehydroabietic acid (1). Our synthesis reported herein has been achieved by the use of a part or whole of the isopropyl group of 1 to furnish the carbon of the D-ring of the steroidal skeleton.[3]

The products (3) and (5) oxidized on the isopropyl group of methyl dehydroabietate (2) derived from 1 were used as initial materials for our purpose. In order to improve yield and separation of the products, a mixture (3 + 4) obtained from 1 with Sanderson's method,[4] was pyrolyzed (205-210°) without purification to give 3 (28% yield) and 5 (24% yield) by chromatography.[5]

The side chains at C-13 of the both compounds, (3) and (5), were conveniently converted for the formation of the steroidal D-ring. The side chains of 3 (MeOH, 70% $HClO_4$) and 5 (MeOH) were oxidized with thallium trinitrate[6] to give oxo diester (6), bp 151° (bath)/0.0033 mmHg, ν_{max} 1730, 1690; δ (100 MHz, CCl_4) 3.54 (s, $W_{1/2}$=2 Hz; 18-H_2), 3.64 (4, 18-COOMe), 7.25 (d, J=8 Hz; 11-H), 7.40 (d, d, J=2, 8 Hz; 12-H), 7.77 (d, J=2 Hz; 14-H) and dioxo ester (7), mp 131-132°, ν_{max} 1730, 1690; δ (100 MHz, CCl_4) 2.10 (18-COMe), 3.16 (s, $W_{1/2}$=2 Hz; 18-H_2), 5.65 (4-COOMe), 7.28 (s, $W_{1/2}$=3 Hz; 11, 12-H), 7.72 (s, $W_{1/2}$=3 Hz; 14-H) in good yield, respectively.

7-Oxo diester (6) was partially hydrolyzed (KOH, MeOH-H_2O), and successively hydrogenolyzed (H_2, Pd-C, AcOH) to give a half ester (9) [purified as the corresponding diester (10), bp 140-145° (bath)/0.01 mmHg, ν_{max} ($CHCl_3$) 1720; δ (100 MHz, CCl_4) 3.39 (s, $W_{1/2}$=2 Hz; 18-H_2), 3.61 (4, 18-COOMe), 6.84-7.12 (m; 11, 12, 14-H)] *via* oxo half ester (8). The side chain of 9 was converted by Arndt-Eistert reaction (Ag_2O, MeOH) to homo ester (11), ν_{max} ($CHCl_3$) 1725; δ 3.67 (4, 19-COOMe), 6.89-7.14 (m; 11, 12, 14-H).

The resulting diester (11) was also synthesized from dioxo ester (7). The monooxo compound (12), ν_{max} 1730, 1720, derived from 7 (H_2, Pd-C, AcOH) was successively subjected to Willgerodt reaction ($(NH_4)_2S_x$, 170°), hydrolysis (NaOH aq.)


11
12
13
14
10
4
7
H
COOR
1 R=H
2 R=Me
3 +
OAc
O
H
COOMe
4
3
5
+
18
19
COOR2
R1
6 R1=O, R2=Me
8 R1=O, R2=H
9 R1=H2, R2=H
10 R1=H2, R2=Me
COOR
11 R=Me
13 R=H
R R
20
14 R=H
20 R=Me
7 R=O
12 R=H2
Me Me
16 R1=O, R2=H
17 R1=O, R2=Me
18 R1=H2, R2=H
19 R1=H2, R2=Me
15 R=H
21 R=Me

and methylation (CH_2N_2) to give 11.

Upon the formation of the D-ring, the half ester (13) obtained from 11 (KOH, MeOH-H_2O) was cyclized (AcCl, $AlCl_3$, CS_2) to give two kinds of product (14) (48% yield), bp 185-190° (bath)/0.013 mmHg, ν_{max} ($CHCl_3$) 1720, 1695; δ 1.20, 1.26 (4, 10-Me), 3.62 (4-COOMe), 7.24 (d, J=8.5 Hz; 12-H), 7.49 (d, J=8.5 Hz; 11-H), and (15) (16% yield), bp 180-185° (bath)/0.012 mmHg, ν_{max} 1730, 1715; δ 1.19, 1.27 (4, 10-Me), 3.63 (4-COOMe), 7.13 (s; 14-H), 7.68 (s; 11-H). The structures of 14 and 15 were determined by analyses of their nmr spectra due to aromatic protons.

On the other hand, addition (8% BF_3-Et_2O/H_2SO_4)$^{7)}$ of 1,1-dichloroethylene to double bond of 5 gave a product (16) (77% yield) [purified as the corresponding diester (17), bp 170° (bath)/0.0029 mmHg, ν_{max} 1735, 1730, 1685; δ (CCl_4) 1.26, 1.32 (4, 10-Me), 1.45 (s; 18-Me_2), 3.53 (19-COOMe), 3.64 (4-COOMe), 7.20 (d, J=8 Hz; 11-H), 7.46 (d,d, J=2, 8 Hz; 12-H), 7.88 (d, J=2 Hz; 14-H)], which is also suitable for our purpose. Deoxo compound (18) [purified as the corresponding diester (19), mp 74.5-76.5°, ν_{max} 1730] obtained by hydrogenolysis (H_2, Pd-C, AcOH) of 16 was treated under the same condition as that of 13 to give two cyclized compounds (20) (51% yield), mp 125-126°, ν_{max} 1724, 1710; δ 1.21, 1.26 (4, 10-Me), 1.34, 1.37 (each s; 18-Me_2), 2.50 (s; 19-H_2), 3.63 (4-COOMe), 7.26 (d, J=8.5 Hz; 12-H), 7.55 (d, J=8.5 Hz; 11-H) and (21)$^{8)}$ (15% yield), mp 106-108° (recrystallized from MeOH-H_2O), ν_{max} ($CHCl_3$) 1725, 1705; δ 1.17, 1.25 (4, 10-Me), 1.36 (s; 18-Me_2), 2.51 (19-H_2), 3.64 (4-COOMe), 7.12 (s; 14-H), 7.60 (s; 11-H). The cyclization reaction mentioned above is similar to that of 13. In conclusion, it is noticeable that the cyclization to 14-position in 13 and 18 is always predominant over that to 12-position. The main products, (14) and (20), have a steroidal skeleton and can be considered to be hopeful intermediates for the chemical conversion of diterpene to steroid.

References and Footnotes

1) The physical constants of new compounds (elemental or mass-spectroscopic analysis) gave satisfactory analytical values for their molecular weight. Nmr (δ) and ir (ν_{max}) spectra not stated in it, were measured at 60 MHz in $CDCl_3$ and in CCl_4, respectively. Nomenclature of the steroid in this report, was used according to that of diterpenoid.

2) To whom inquiries regarding this communication should be addressed.

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4) T. F. Sanderson, U. S. Pat. 2750368 (1956) [Chem. Abst., 51, 1278 (1957)]. Oxidation condition was slightly improved in our laboratory.

5) P. F. Ritchie, T. F. Sanderson and L. F. McBurney, J. Am. Chem. Soc., 76, 723 (1954).

6) A. McKillop, B. P. Swann and E. C. Taylor, J. Am. Chem. Soc., 93, 4919 (1971); A. McKillop, J. D. Hunt, E. C. Taylor and F. Kienzle, Tetrahedron Letters, 1970, 5275.

7) K. Bott and H. Hellmann, Angew. Chem. (Internat. Edit.), 5, 870 (1966).

8) Physical constants of 21 were identical with those of the compound, mp 125-127° and 136-137° (recrystallized from $CHCl_3$-MeOH), ν_{max} 1725, 1705; δ 1.19, 1.28, 1.38, 2.52, 3.64, 7.12, 7.61, described in Cambie's report except melting point. The difference can be considered to result from polymorphism or crystal solvent.

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