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STEREOSELECTIVE ISOPROPYL-METHYL MIGRATION IN l-ABIETIC ACID DERIVATIVE: SYNTHESIS OF l-HIBAENE[1)]

Masayuki Shimagaki and the late Akira Tahara
Rikagaku Kenkyusho (The Institute of Physical and Chemical Research)
Wako-shi, Saitama-ken, Japan

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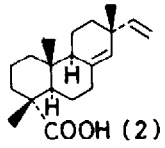
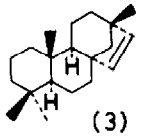
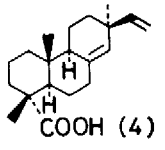
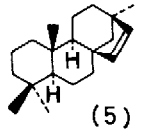
In continuous studies[2a-c)] on the versatile utility of the isopropyl group of l-abietic acid (1), a major component of pine rosin, the isopropyl-methyl migration attracted our attention.

If this objective could be performed and the 13-methyl group possessed a β-configuration, it might be potential intermediate(s) for 18-methyl group, C-16 and C-17 of steroidal skeleton(s), sandaracopimaric acid (2) and d-isohibaene (3), and the 13-methyl group possessed an α-configuration, it might be that (those) for pimaric acid (4) and l-hibaene (5). Moreover, it is of interest that the synthesis of (2) or (4) from (1) is that of a retrograde biogenetic pathway.[3)]





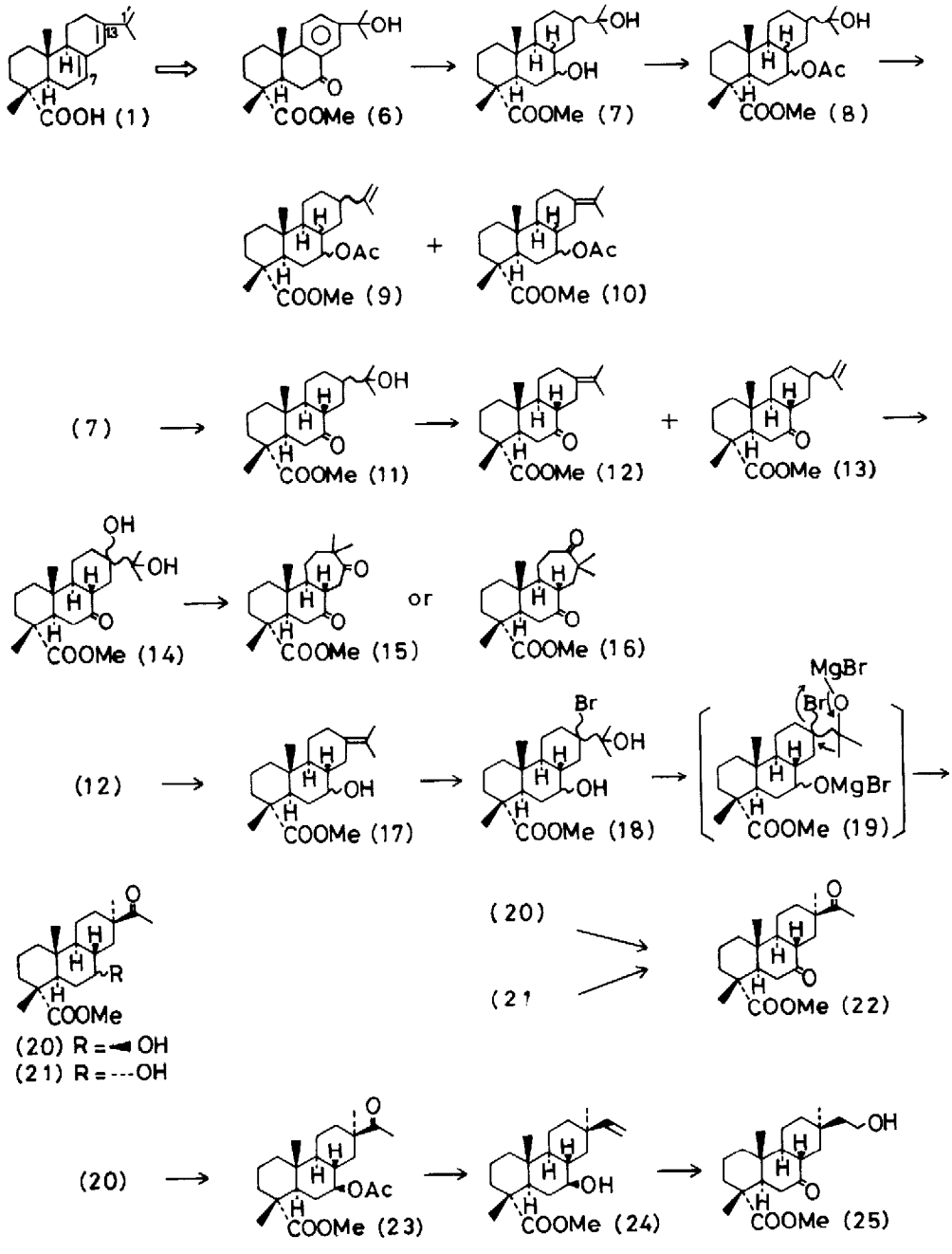




The pinacol rearrangement casts a light to the methyl migration, but there is a tendency that a more substituted group is easier to migrate than a less substituted one.[4)] It might be anticipated that the desired product was difficult to be obtained in this method. Moreover, from a consideration of the mechanism of the Wagner-Meerwein rearrangement, the isopropyl-methyl migration is one of a method in which less stable compound is introduced from more stable one.

We succeeded in a stereoselective isopropyl-methyl migration to a 13α-position by using (19), derived from (1), to give (20) and (21). The former (20) was interrelated to l-hibaene (5), via (25).

In order to prepare a compound having an oxygen function at the 7- and 1'-positions (benzylic positions of the C-ring of (6)), an oxo oxy ester (6), derived


COOH (1)
COOMe (6)
COOMe (7)
COOMe (8)
COOMe (9)
COOMe (10)
(7)
COOMe (11)
COOMe (12)
COOMe (13)
COOMe (14)
COOMe (15)
or
COOMe (16)
(12)
COOMe (17)
COOMe (18)
COOMe (19)
(20) R = OH
(21) R = OH
(20)
(21)
COOMe (22)
(20)
COOMe (23)
COOMe (24)
COOMe (25)

from (1) was catalytically hydrogenated over ruthenium oxide[2c] to give a dioxy ester (7) (δ: 1.08, 1.16 (each s, 4,10-Me), 1.19 (s, 1'-Me), 3.66 (s, COOMe), 3.82 (centered at, b.s, 7-H); ν_{max}: 3630, 1725). The dioxy ester (7) was converted with Ac_2O-pyridine to a mono acetate (8), and successively with $POCl_3$-pyridine to give two kinds of product whose NMR spectrum showed 1.2 vinyl protons (δ: 4.6-5.2), which indicated that a major product was an isopropenyl acetate (9), but not an isopropylidene acetate (10). Then (7) was oxidized with CrO_3·pyridine complex in CH_2Cl_2[2a,c,5] and chromatographed on Florisil eluting with ether to give a B,C-trans oxo oxy ester (11) (mp 123-125.5°; δ: 1.06, 1.22 (each s, 4,10-Me), 1.26 (s, 1'-Me), 3.70 (s, COOMe); $\nu_{max}^{CHCl_3}$: 3625, 1715, 1700 (shoulder); ORD (dioxane); $[\alpha]_{318}$: trough, $[\alpha]_{290}$: last reading)), having an 8β-H, which was a more thermodynamically stable product. The configuration of the 8-position was supported by its ORD curve which indicated a weak negative Cotton effect.[2c,6] Treatment of (11) with $POCl_3$-pyridine gave two kinds of product (GC-MS M^+; m/e: 332 (both)), whose NMR showed 0.3-0.4 vinyl proton (δ: 4.7-5.2) which indicated that the proportion of an isopropyridene oxo ester (12) (mp 124-126.5°; δ(100 MHz): 1.05, 1.23 (each s, 4,10-Me), 1.61, 1.68 (each s, 1'-Me), 3.66 (s, COOMe); ν_{max}: 1725, 1705) and an isopropenyl oxo ester (13) was 4.0-5.6:1. This value was nearly as same as that integrated by GLC. Although the mixture of (12) and (13) could be separated by fractional recrystallizations, preparative sequences were performed without separation of them because of their instability (it might be caused by the double bond isomerization(s)), and the structures in chart were indicated which were obtained from the major product (12).

In order to perform a pinacol rearrangement, (12) was converted to a dioxy ester (14) (δ: 1.07, 1.12 (each s, 4,10-Me), 1.24 (s, 1'-Me), 3.67 (s, COOMe); $\nu_{max}^{CHCl_3}$: 3650-3200, 1720-1700) with OsO_4, followed by $NaHSO_3$-treatment. The dioxy ester (14) was treated with H_2SO_4 to give a methylene-migration product, (15) or (16), (mp 129.5-132°; δ(100 MHz): 1.02, 1.06, 1.10, 1.21 (each s, Me), 3.67 (s, COOMe); ν_{max}: 1725, 1710) and not to give a methyl-migration product. Then the isopropylidene oxo ester (12) was reduced with $NaBH_4$ to an isopropylidene oxy ester (17) (7α-OH:7β-OH=1:3) and treated successively with NBS (N-bromosuccinimide) in dioxane-H_2O to give a bromohydrin (18)[7] (δ: 0.97, 1.20 (each s, 4,10-Me), 1.40 (s, 1'-Me), 3.67 (s, COOMe); $\nu_{max}^{CHCl_3}$: 3560-3200, 1710; Beilstein test: positive). The bromohydrin (18) was treated with excess isopropyl magnesium bromide (ca. 3 eq. mole) in ether at 25-30° for 20 hr to give, via a magnesium salt (19), two kinds of an isopropyl-methyl migration product, (20) (δ(100 MHz): 0.80, 1.07, 1.17 (each s, 4,10,13-Me), 2.13 (s, $COCH_3$), 2.67 (d.d.d, J=3, 3 and 13 Hz, 14-H_{eq}), 3.21 (m, W/2=12 Hz, 7-H_{ax}), 3.64 (s, COOMe); ν_{max}: 3670, 1725, 1705) and (21) (mp 148-148.5°; δ(100 MHz): 0.77, 1.07, 1.16 (each s, 4,10,13-Me), 2.10 (s, $COCH_3$), 3.65 (s, COOMe), 3.79 (b.s, W/2=7 Hz, 7-H_{eq}); ν_{max}: 3670, 1725, 1705) in 18.0% and 6.8% yields, respectively, from (17) (the reac-

tion in refluxing benzene[7] decreased the yield of the product). Respective oxidation of (20) and (21) with the CrO_3·pyridine complex[2a,c,5] gave a same dioxo ester (22) (bp 135° (bath, 0.04 mmHg); δ: 0.99, 1.10, 1.20 (each s, 4,10,13-Me), 2.08 (s, $COCH_3$), 3.64 (s, COOMe); ν_{max}^{film}: 1725, 1705), which indicated that (20) and (21) possessed the same configuration at the 13-position and the opposite configuration at the 7-position.

The confirmation of the configuration at the 13-position was performed as follows. The 7β-acetoxy acetyl ester (23) (bp 145° (bath, 0.03 mmHg); δ(100 MHz): (0.81, 1.14, 1.15 (each s, 4,10,13-Me), 2.05 (s, $OCOCH_3$), 2.10 (s, $COCH_3$), 3.65 (s, COOMe), 4.50 (m, W/2=13 Hz, 7-H_{ax}); ν_{max}: 1740 (shoulder), 1735, 1710), prepared from (20) by Ac_2O-pyridine treatment was treated successively with $NaBH_4$-EtOH, MsCl-pyridine, KOH-MeOH-H_2O and γ-collidine, to give 7β-oxy vinyl ester (24) (δ: 0.86, 0.97, 1.19 (each s, Me), 3.2 (centered at, m, 7-H), 3.66 (s, COOMe), 4.76-5.92 (m, 3H, vinyl-H); ν_{max}: 3650, 3450 (b), 1730, 1640 (w)). Hydroboration of (24), followed by NBA (N-bromoacetamide, 1.1 eq. mole)-t-BuOH-H_2O-treatment, gave a known oxy oxo ester (25)[6] (δ: 0.94, 1.11, 1.22 (each s, Me), 3.66 (t, J=7.5 Hz, CH_2OH), 3.66 (s, COOMe); ν_{max}: 3675, 3450 (b), 1730, 1710; 2,4-DNP: mp 135-137°, mixed mp 134-137°). The acetyl 7α-oxy ester (21) may be converted to (25) by the same procedures. Since an interrelation from (25) to (5) had been published,[6] a synthesis of l-hibaene (5), by using three carbon units of the isopropyl group of l-abietic acid (1), via the isopropyl-methyl migration, has been accomplished.

The acetyl oxy esters, (20) and (21), are also a hopeful intermediate to synthesize pimaric acid (4) or its derivative(s).

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References and Footnote

1) New compounds indicated by mp or bp gave satisfactory analytical values. NMR (δ) and IR (ν_{max}) spectra, when not mentioned, were measured at 60 MHz in $CDCl_3$ vs. Me_4Si as internal reference and in CCl_4, respectively.
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