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CONVERSION OF DIHYDROALANTOLACTONE TO TETRAHYDROLIGULARENOLIDE
A BIOGENETIC-TYPE TRANSFORMATION OF EUDESMANOLIDE TO EREMOPHILANOLIDE

Isao Kitagawa, Hirotaka Shibuya, Yasushi Yamazoe,
Hidekazu Takeno, and Itiro Yosioka

Faculty of Pharmaceutical Sciences, Osaka University
Toyonaka, Osaka, Japan

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In a previous paper[1], we reported a conversion of dihydroalantolactone(1) to the eremophilane-type derivatives(3, 4) via a 5α,6α-epoxide(2), which was the first example of direct transformation from the eudesmanolide to the eremophilanolide. The structure assignment of 3 and 4 has been based mainly on the physicochemical properties and the mechanistic consideration. In this communication, we wish to present a chemical evidence supporting the eremophilane skeleton of 3 and 4, in which a chemical derivation leading to tetrahydroligularenolide(14)[2] has been accomplished.

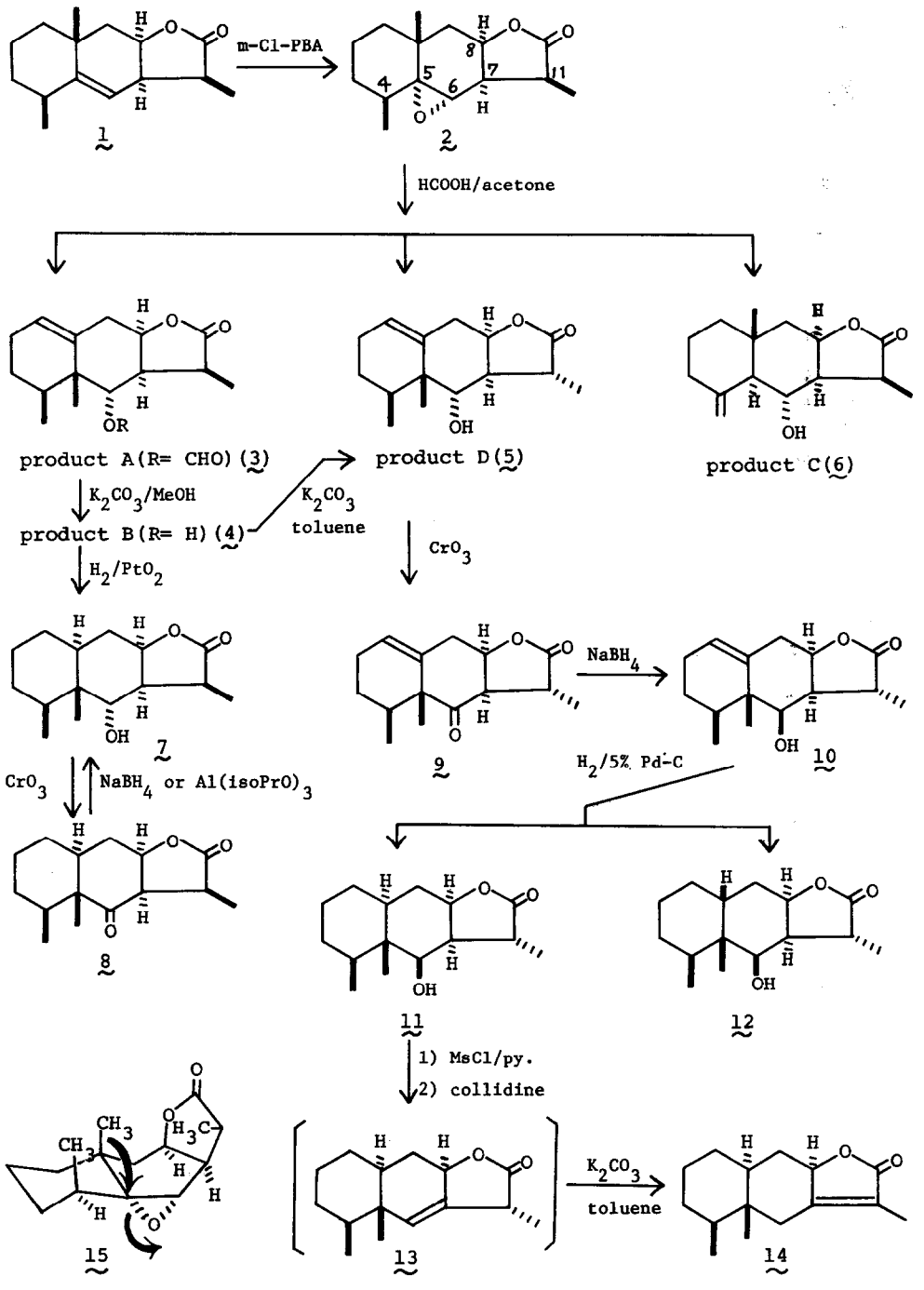
During the continuative study on the reaction products of 2 obtained by HCOOH-acetone treatment at reflux[1], we have isolated three new minor products D(5, 2.0%), E(0.5%), and F(3.4 %) in addition to the previously reported products A(3, 10%), B(4, 34%), and C(6, 2.2%).

Product D(5), amorphous, Mass: m/e 250(M^+, 3%), 41(base peak); IR($CHCl_3$, cm^{-1}): 3560(hydroxyl), 1768(γ-lactone), 1665(double bond); PMR($CDCl_3$, 90 MHz, δ): 0.95(3H, d, J= 7 Hz, $C_{(4)}$-$C\underline{H}_3$), 1.02(3H, s, $C_{(5)}$-$C\underline{H}_3$), 1.32(3H, d, J= 7, $C_{(11)}$-$C\underline{H}_3$), 1.81(1H, br.s, $W\frac{h}{2}$= 6, O$\underline{H}$), 2.56(1H, m, $C_{(7)}\underline{H}$), 2.84(1H, m, on irradiation at δ1.32 → d, J= 12, $C_{(11)}\underline{H}$), 3.90(1H, d, J= 4, $C_{(6)}\underline{H}$), 4.67(1H, d.t, J= 7 & 10, $C_{(8)}\underline{H}$), 5.70(1H, m, $C_{(1)}\underline{H}$), possesses the similar physicochemical properties to those of product B(4), PMR($CDCl_3$, 90 MHz, δ): 1.01(3H, s, $C_{(5)}$-$C\underline{H}_3$), 1.05(3H, d, J= 5.5, $C_{(4)}$-$C\underline{H}_3$), 1.37(3H, d, J= 7, $C_{(11)}$-$C\underline{H}_3$), 2.91(1H, d, J= 9, $C_{(11)}\underline{H}$, observed on irradiation at δ1.37), 3.88(1H, d.d, J= 9 & 6, on D_2O addition → d, J= 9, $C_{(6)}\underline{H}$), 4.51(1H, q, J= 7, $C_{(8)}\underline{H}$),

5.48(1H, t-like, $W\frac{h}{2}$ = 8, $C_{(1)}\underline{H}$), except $J_{6,7}$ and $J_{7,11}$(9 and 9 Hz in 4, 4 and 12 Hz in 5). Based on the decoupling experiment supporting the eremophilane skeleton of 5, product D has been assumed to be an 11-epimer of 4 and the assumption has been verified by a quantitative isomerization of 4 to 5 by K_2CO_3-toluene treatment at reflux. The structures of product E, $C_{16}H_{24}O_5$, mp. 197° and product F, $C_{15}H_{22}O_3$, mp. 114-115° will be reported in a future paper.

In order to prove chemically the eremophilane skeleton of products A(3), B(4), and D(5), several attempts including the conversion of these to the known eremophilane-type derivatives have been made. For example, a conversion of the major product 4 to tetrahydroligulareno-lide(14) has been tried. Since an elimination reaction of 6α-hydroxyl function of 7(prepared from 4 via catalytic hydrogenation over PtO_2) through mesylation followed by base treatment afforded a rearranged product(unidentified yet), a preparation of 6-epimer of 7 expecting ready trans-elimination of 6β-hydroxyl and 7αH has been attempted. However, reduction of a ketone(8, prepared by CrO_3 oxidation of 7) with either $NaBH_4$ or $Al(isoPrO)_3$ resulted only in the formation of 7 and desired 6-epimer was not obtained. According to the Dreiding model examination keeping in mind the $J_{6,7}$, $J_{7,11}$, and B-ring conformation of 4, 5, 7, and 8, 11β-methyl function has appeared responsible for the orientation of the reduction of 8. Therefore, product D(5) has been then subjected to the conversion.

CrO_3 oxidation of 5 gave quantitatively a keto-lactone(9), mp. 85-86°, IR($CHCl_3$, cm^{-1}): 1775(γ-lactone), 1718(ketone), 1676(double bond); PMR($CDCl_3$, 90 MHz, δ): 0.89(3H, d, J= 6.5, $C_{(4)}$-$C\underline{H}_3$), 1.07(3H, s, $C_{(5)}$-$C\underline{H}_3$), 1.30(3H, d, J= 7, $C_{(11)}$-$C\underline{H}_3$), 2.91(1H, d.d, J= 3 & 8, $C_{(7)}\underline{H}$), 3.29(1H, d.q, J= 3 & 7, $C_{(11)}\underline{H}$), 4.83(1H, q-like, J= 8, $C_{(8)}\underline{H}$), 5.72(1H, m, $C_{(1)}\underline{H}$), which, on $NaBH_4$ reduction, was converted in an excellent yield to 6-epimer(10), mp. 155°, IR($CHCl_3$, cm^{-1}): 3650(hydroxyl), 1770(γ-lactone), 1610(double bond); PMR($CDCl_3$, 90 MHz, δ): 0.93(3H, d, J= 6.5, $C_{(4)}$-$C\underline{H}_3$), 0.98(3H, s, $C_{(5)}$-$C\underline{H}_3$), 1.32(3H, d, J= 7, $C_{(11)}$-$C\underline{H}_3$), 3.81(1H, d, J= 3, $C_{(6)}\underline{H}$), 4.81(1H, q-like, J= 7, $C_{(8)}\underline{H}$), 5.40(1H, m, $C_{(1)}\underline{H}$). Catalytic hydrogenation of 10 over 5% Pd-C in EtOH furnished two products: 11(64%), mp. 175-176°, IR($CHCl_3$, cm^{-1}): 3640(hydroxyl), 1768(γ-lactone); PMR($CDCl_3$+ d_6-benzene, 90 MHz, δ): 0.68(3H, s, $C_{(5)}$-$C\underline{H}_3$), 1.13(3H, d, J= 6.5, $C_{(4)}$-$C\underline{H}_3$), 1.31(3H, d, J= 7, $C_{(11)}$-$C\underline{H}_3$), 2.22(1H, d.t, J= 7 & 12, $C_{(7)}\underline{H}$), 2.64(1H, d.q, J= 7 & 12, $C_{(11)}\underline{H}$), 3.38(1H, d, J= 7, $C_{(6)}\underline{H}$), 4.12(1H, d.t, J= 7 & 11, $C_{(8)}\underline{H}$), and its 10-epimer(12, 33%). Mesylation of the major reduction product(11) followed by collidine treatment at reflux furnished a fairly labile product(13) which, without further purification[3], was treated


m-Cl-PBA
HCOOH/acetone
product A(R= CHO) (3)
product D(5)
product C(6)
K_2CO_3/MeOH
product B(R= H) (4)
K_2CO_3 toluene
CrO_3
H_2/PtO_2
$NaBH_4$
H_2/5% Pd-C
CrO_3
$NaBH_4$ or $Al(isoPrO)_3$
1) MsCl/py.
2) collidine
K_2CO_3 toluene

with K_2CO_3-toluene at reflux to yield a product(74% from 11), being identical with tetrahydroligularenolide(14)[2] in all respects(mmp, IR, TLC, GLC, PMR, and $[\alpha]_D$).

Since products A(3) and B(4) are converted to product D(5) quantitatively, it follows that the above mentioned conversion from dihydroalantolactone(1) to tetrahydroligularenolide(14) has been accomplished in 15% overall yield. The total synthesis of (±)-14 has been reported very recently from two groups independently[4]. The present conversion would provide a new synthetic route of eremophilane-type sesquiterpenoid via an eudesmane-type precursor.

As for the reason of successful transformation from 2 to 3, 4, and 5, two factors would be considered: i) the location of epoxide function, since the 4α,5α-epoxide had been shown already not to give the eremophilane-type derivative[5], and ii) the presence of cis-γ-lactone, which would force the B-ring to take a boat-like conformation(15)[6] and to be sterically more congested so that $C_{(10)}$-CH_3 appears to be in the favorable location for 1,2-shift to release the strain(including 1,3-diaxial interaction of $C_{(4)}$-CH_3). To solve these problems, the further investigation is under way.

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