CHEMISTRY LETTERS, pp. 1031-1034, 1977. Published by the Chemical Society of Japan

REVISION OF STRUCTURE OF PETASITOLIDES BY THE SYNTHESIS OF 3β-AND 3α-HYDROXY- AND 2β-SENECIOYLOXYEREMOPHILENOLIDES[1]

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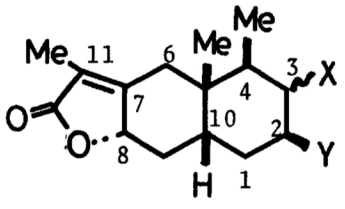
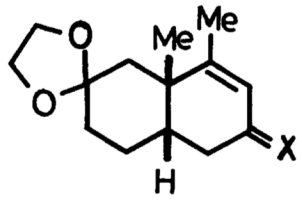
3-Hydroxy-(I, X = β- and α-OH; Y = H) and 2β-senecioyloxy-(I, X = H; Y = $OCOCH{=}CMe_2$) eremophilenolides were synthesized stereoselectively starting from ethylenedioxy octalone derivative (II, X = H_2). The present synthetic study demonstrates unequivocally that the positions of ester groups of petasitolides should be located at C_2- rather than C_3-position.

Due to the marked structural features of eremophilane type sesquiterpenoids, much attention has been focused on the stereoselective synthesis of these synthetically intriguing natural products. Eremophilanes are characterized by the presence of adjacently located cis dimethyl groups on the cis decalin skeleton which is mobile between steroidal and nonsteroidal conformers. After completion of our synthetic studies of two naturally occurring eremophilanes, i.e., eremophilenolide (I, X = Y = H) and furanoeremophilane[2], our first attention was directed toward the synthesis of two epimers of 3-hydroxyeremophilenolide (I, X = OH; Y = H) since a tiglate of one of the epimers had been proposed for the structure of petasitolide-A, isolated from the rhizome of Petasites officinalis Moench[3]. Here we wish to provide synthetic evidence which reveals that the position of the ester groups of petasitolides should be located at C_2- rather than C_3-position.

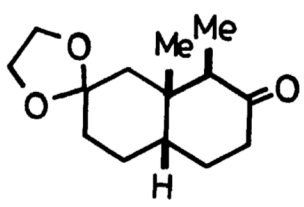
Since stereochemistry at C_3-position of natural petasitolides remained unsolved, we were compelled to synthesize both epimers (I, X = β- and α-OH; Y = H) starting



(I)



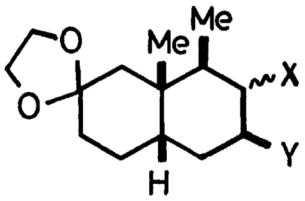
(II)



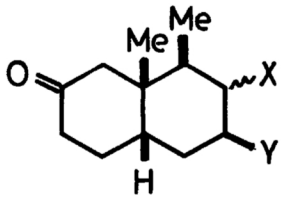
(III)

from our synthetic intermediate (III) derived from ethylenedioxy octalone derivative (II)[4]. By the aid of conformational analysis of III with Dreiding model, the stereoselective reduction conditions were searched and it was found after several trials that both epimers (IV, a and b) were obtainable from III with high stereoselectivity.

When III was reduced with $NaBH_4$ at -4°C in MeOH, a 94:6 mixture of IVa and IVb was obtained[5], from which IVa was isolated in 91% yield by recrystallization. IVa: mp, 95-96°C; PMR ($CDCl_3$), 0.97 (d, 7 Hz, C_4-Me) and 1.12 ppm (C_5-Me)[6]. Deketalization with methanolic HCl afforded a keto alcohol (Va) in 84% yield. Va: mp, 64-65°C; PMR ($CDCl_3$), 0.96 (d, 7 Hz, C_4-Me) and 0.98 ppm (d, 1 Hz, C_5-Me). Esterification with refluxing Ac_2O or PhCOCl in pyridine yielded the corresponding acetate (VIa), oil, and benzoate (VIIa), mp, 111-112°C, respectively. On the meanwhile, reduction of III with Na in refluxing EtOH[7] afforded a 6:94 mixture[8] of IVa and IVb[9], from which the crystalline benzoate (VIIb), mp, 94-95°C, was gained in 42% overall yield by successive treatments with methanolic HCl to an oily isomeric keto alcohol (Vb), followed by esterification with PhCOCl in pyridine. The oily acetate (VIb) was prepared by conventional method. Stereochemistry of C_3-hydroxyl group was deduced on the basis of coupling patterns of C_3-proton in the PMR spectra of VIa and VIb[11]. PMR ($CDCl_3$) of C_3-H: VIa; 5.05 ppm (ddd, 5.5, 5.5, and 11.0 Hz), VIb; 4.76 ppm (ddd, 5.5, 11.0, and 11.0 Hz)



(IV)
a: X = β-OH, Y = H
b: X = α-OH, Y = H
c: X = H, Y = OH

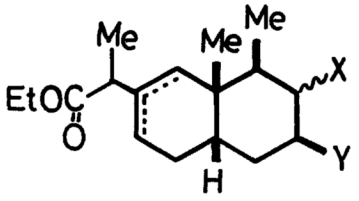


(V) a: X = β-OH, b: X = α-OH, c: Y = H
(VI) a: X = β-OAc, b: X = α-OAc
(VII) a: X = β-OCOPh, b: X = α-OCOPh, c: Y = β-OCOPh
a and b, Y = H; c, X = H

Both epimers of 3-hydroxyeremophilenolide (I, X = β- and α-OH; Y = H) were easily derived from each of the benzoate [VIIa (b)] by the similar procedure as described previously.

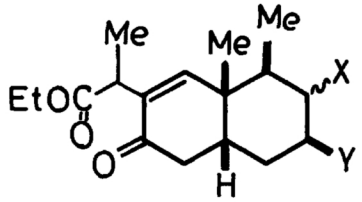
VIIa (b)[12] was submitted to the Reformatsky reaction with ethyl α-bromopropionate in refluxing mixture of toluene-benzene (1:1) in the presence of $HgCl_2$ followed by dehydration with $SOCl_2$ in pyridine at ambient temperature to give an unsaturated ester, VIIIa (b), in 80 (85)% overall yield. Allylic oxidation of VIIIa (b) with t-butyl chromate in refluxing CCl_4 containing AcOH-Ac_2O (10:1)[13] produced an oily conjugated ketone, IXa (b), in 42 (46)% yield. The position of the double bond in IX was supported by the observation of a singlet at 6.5 ppm in the PMR spectra of both compounds. Hydrolysis with 2N KOH in MeOH at room temperature overnight and subsequent esterification with CH_2N_2 gave a hydroxy ester, Xa (b), in 73 (66)% yield. Xa (b) was allowed to react with $NaBH_4$ in MeOH at room temperature to yield dl-3β (α)-hydroxyeremophilenolide (Ia, X = β-OH; Y = H. Ib, X = α-OH; Y = H) in 50 (70)% yield. Ia: mp, 171-

172°C; IR ($CHCl_3$), 3600, 1747, 1690, and 1032 cm^{-1}; PMR ($CDCl_3$), 1.01 (d, 7 Hz, C_4-Me), 1.29 (s, C_5-Me), 1.80 (t, 1.5 Hz, C_{11}-Me), 3.80 (1H, ddd, each 3 Hz, C_3-H), and 4.65 ppm (1H, m, C_8-H). Ib: mp, 147°C; IR ($CHCl_3$), 3620, 3480, 1742, 1690, and 1039 cm^{-1}; PMR ($CDCl_3$), 0.99 (d, 6.5 Hz, C_4-Me), 1.05 (s, C_5-Me), 1.79 (t, 1.0 Hz, C_{11}-Me), 3.45 (1H, ddd, 5.0, 10.0, and 10.0 Hz, C_3-H), and 4.65 ppm (1H, m, C_8-H).

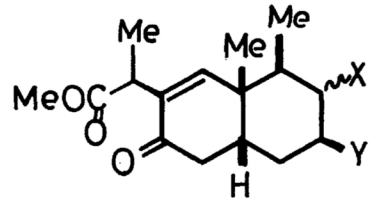


(VIII)

a: X = β-OCOPh, b: X = α-OCOPh, c: Y = β-OCOPh
a and b, Y = H; c, X = H



(IX)



(X)

a: X = β-OH, b: X = α-OH,
c: Y = β-OH
a and b, Y = H; c, X = H

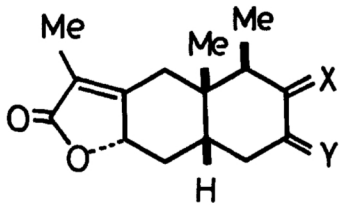
Oxidation of each epimer of I (X = OH; Y = H) with Jones reagent gave the same 3-oxoeremophilenolide, XI (X = O; Y = H_2): IR ($CHCl_3$), 1750, 1707, 1691, and 1033 cm^{-1}; PMR ($CDCl_3$), 0.96 (d, 7 Hz, C_4-Me), 1.00 (s, C_5-Me), 1.84 (t, 1 Hz, C_{11}-Me), 2.85 (d, 15 Hz, $C_{6\alpha}$-H), and 4.77 ppm (bt, C_8-H). Chemical shifts in the PMR spectrum of dl-3-oxoeremophilenolide was not completely identical with that of the oxoeremophilenolide derived from natural petasitolides. In particular, chemical shift of C_5-Me is diagnostic. The ketone derived from the natural compound was 1.29 ppm. Detailed inspection of PMR spectrum of the natural compound suggested that the ester group might be located at C_2- instead of C_3-position. This deduction was proved unequivocally by the synthesis of 2-hydroxyeremophilenolide and its derivatives as follows.

Allylic oxidation of II (X = H_2) with $CrO_3 \cdot 2Py$ in CH_2Cl_2 (room temperature, overnight) gave an oily conjugated ketone (II, X = O): IR (neat), 1660 and 1620 cm^{-1}; PMR ($CDCl_3$), 5.70 (s, C_3-H). The Birch reduction (Li/NH_3/t-BuOH) afforded a hydroxy ketal (IVc) as a stereoisomeric mixture concerning C_2- and C_4-positions, which was converted to the known ketone (Vc) by successive treatments with CrO_3-2Py in CH_2Cl_2 followed by the Wolff-Kishner reduction and subsequent deketalization with HCl in MeOH. The vapor phase chromatography of the resultant ketone showed that it was a 3:1 mixture of Vc and its C_4-epimer. From the mixture of hydroxy ketal (IVc, epimeric mixture at C_2- and C_4-positions) was isolated a crystalline benzoate (VIIc) by successive treatments with HCl in MeOH and then PhCOCl in pyridine in 34% overall yield from II (X = O). VIIc: mp, 143-144°C. The 2β-equatorial configuration of the benzoate group of VIIc was reasonable expected by assuming that the reduction of II (X = O) might proceed through the more stable steroidal conformation.

The γ-lactone moiety of the eremophilenolide skeleton was constructed by the similar procedure as described precedingly. Hydroxy ester (Xc):oil; PMR ($CDCl_3$), 0.97 (d, 7 Hz, C_4-Me), 1.15 (s, C_5-Me), 1.27 (d, 8 Hz, C_{11}-Me), ca 3.9 (m, C_2-H), and 6.64 ppm (s, C_6-H). dl-2β-Hydroxyeremophilenolide (I, X = H; Y = OH): mp, 146-148°C; IR ($CHCl_3$), 3430, 1720, and 1680 cm^{-1}; PMR ($CDCl_3$), 0.84 (d, 6 Hz, C_4-Me), 1.10 (s, C_5-Me), 1.79 (t, 1.5 Hz, C_{11}-Me), 2.90 (d, 15 Hz, $C_{6\alpha}$-H), 3.78 (1H, dddd, 5.5, 5.5, 11.0, and 11.0 Hz, C_2-H), and 4.60 ppm (dd, 7 and 9 Hz, C_8-H).

Esterification of I (X = H; Y = OH) with senecioyl chloride in pyridine gave the corresponding 2β-senecioyloxyeremophilenolide (I, X = H; Y = $OCOCH=CMe_2$). PMR and IR ($CHCl_3$) spectra of the synthetic ester are completely superimposable with those of natural senecioyloxyeremophilenolide. Furthermore, dl-2-oxoeremophilenolide (XI, X = H_2; Y = O), derived easily from dl-I (X = H; Y = OH) was identical with that obtained from natural petasitolides in their PMR and IR ($CHCl_3$) spectra.

All the evidence presented so far leads to the conclusion that senecioyloxy and other ester groups of petasitolides should be located at C_2 position of eremophilenolide skeleton. Inspection of the possible conformers of 2β-senecioyloxyeremophilenolide with Dreiding model suggests that the steroidal conformation is sterically more favorable than the corresponding nonsteroidal conformer. This suggestion is partly supported by the coupling pattern of $C_{2\alpha}$-H (dddd, 11.0, 11.0, 5.5, and 5.5 Hz) although exact conformation could be determined only after measurement of PMR spectra under variable temperature[14].



(XI)

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#1. Present address, Bioscience Lab., Central Research Labs., Mitsubishi Chem. Ind. Ltd., Kamoshidacho, Yokohama.
#2. Faculty of Art and Science, Yamagata University, Yamagata.
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4. On the synthesis of II and III, see ref. 2.
5. When reduced with $NaBH_4$ in refluxing EtOH, the ratio of IVa and IVb was 3:2.
6. Numbering of the synthetic intermediates were conventionally based on that of eremophilenolide.
7. D. N. Kirk and A. Mudd, J. Chem. Soc. C, 1969, 968.
8. The formation ratio was estimated by gas liquid chromatography.
9. Possibility of the epimerization at C_4-position of III under the reduction conditions is ruled out by the evidence described in ref 2 and also by the comparison of Va and Vb with 3β-hydroxy-4α, 5β-dimethyl derivative[10].
10. Ph. D. Thesis of Dr. I. Nagakura, Tohoku University (1970).
11. Master Thesis of S. Maeda, Tohoku University (1972).
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13. K. Heusler and A. Wettstein, Helv. Chem. Acta, 35, 284 (1952).
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(Received June 3, 1977)