CHEMISTRY LETTERS, pp. 1495-1498, 1979.

SYNTHESES OF 24,25-DIDEOXY-FASCICULOL-A AND FASCICULOL-A, CONSTITUENT OF NAEMATOLOMA FASCICULARE (FR.) KARST, A POISONOUS BITTER MUSHROOM

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24,25-Dideoxy-fasciculol-A, fasciculol-A and its C-24 epimer were synthesized from lanosterol and the absolute stereo-structure of fasciculol-A was confirmed.

Three triterpene alcohols, fasciculol-A (1), -B (2) and -C (3) were isolated from the methanol extracts of the fruit bodies of Naematoloma fasciculare (Fr.) KARST (Japanese name : Nigakuri-take) and their structures were elucidated by Ikeda et al.[1] and by us.[2]

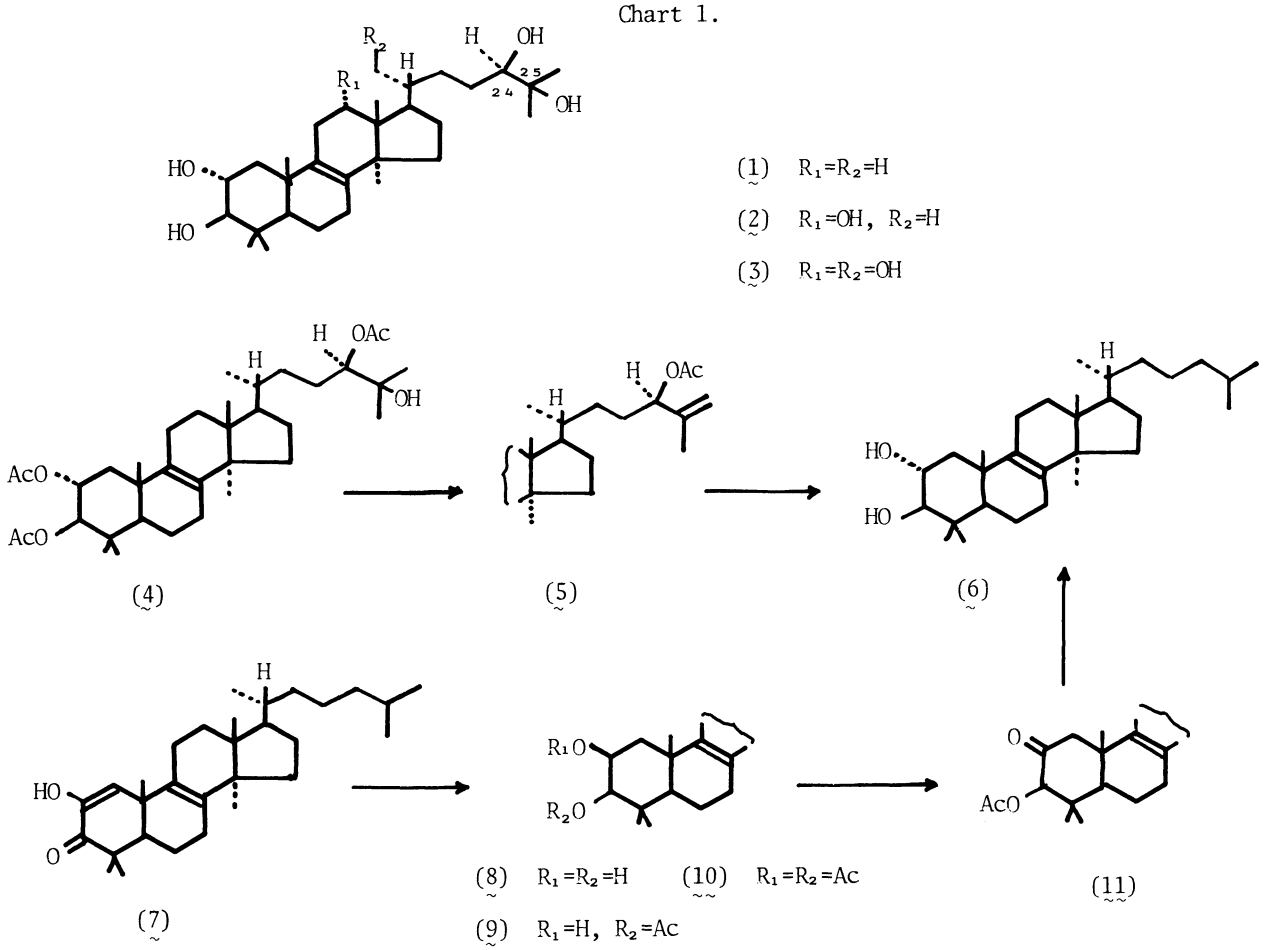
In the course of our structural study,[2] fasciculol-A triacetate (4) was dehydrated with $SOCl_2$ in pyridine to give 5, $C_{36}H_{56}O_6$, mp 179-182°, which on hydrogenation over Pd-C in the presence of HCl, followed by alkaline hydrolysis, afforded 24,25-dideoxy-fasciculol-A (6), $C_{30}H_{52}O_2$, mp 203-206°, $[\alpha]_D^{30}$ +39° (c=0.44, $CHCl_3$), as shown in Chart 1. Here we wish to report the synthesis of the above compound 6 and also of fasciculol-A (1) and its C-24 epimer.

Reduction of 2-hydroxy-lanosta-1,8-dien-3-one (7)[3] with $NaBH_4$ gave solely lanost-8-ene-2β,3β-diol (8), $C_{30}H_{52}O_2$, mp 182-186°, which was treated with acetic anhydride in pyridine to give a monoacetate 9 (34% yield), $C_{32}H_{54}O_3$, mp 185-189°, $[\alpha]_D^{28}$ +77.9° (c=1.02, $CHCl_3$), NMR ($CDCl_3$): δ 4.55 (1H, d, J=4 Hz, C<u>H</u>-OAc), 4.10 (1H, q, J=4 Hz, C<u>H</u>-OH), 2.10 (3H, s, Ac) and a diacetate 10 (28% yield), $C_{34}H_{56}O_4$, mp 165-167°, $[\alpha]_D^{20}$ +83° (c=1, $CHCl_3$).

Collins oxidation of the monoacetate 9 afforded a ketone 11, $C_{32}H_{52}O_3$, mp 152-153°, which was then reduced with metallic sodium[4] in refluxing n-AmOH to yield the desired compound 6, $C_{30}H_{52}O_2$, mp 203-205°, $[\alpha]_D^{25}$ +36° (c=0.75, $CHCl_3$), NMR ($CDCl_3$): δ 3.75 (1H, dt, J=5, 11, 11 Hz, C<u>H</u>-OH), 3.05 (1H, d, J=11 Hz, C<u>H</u>-OH), 1.05-0.70 (CH_3 x 8). This compound was identified with 24,25-dideoxy-fasciculol-A (6) in all respects.

Turning to the synthesis of fasciculol-A (1), 2-hydroxy-lanosta-1,8,24-trien-3-one (12)[3] was used as the starting material. $NaBH_4$ reduction of 12 gave a 2β,3β-diol (13), $C_{30}H_{50}O_2$, mp 165-166°, $[\alpha]_D^{25}$ +78.8° (c=1.6, $CHCl_3$), which was acetylated in mild condition to give mainly a monoacetate 14

Chart 1.

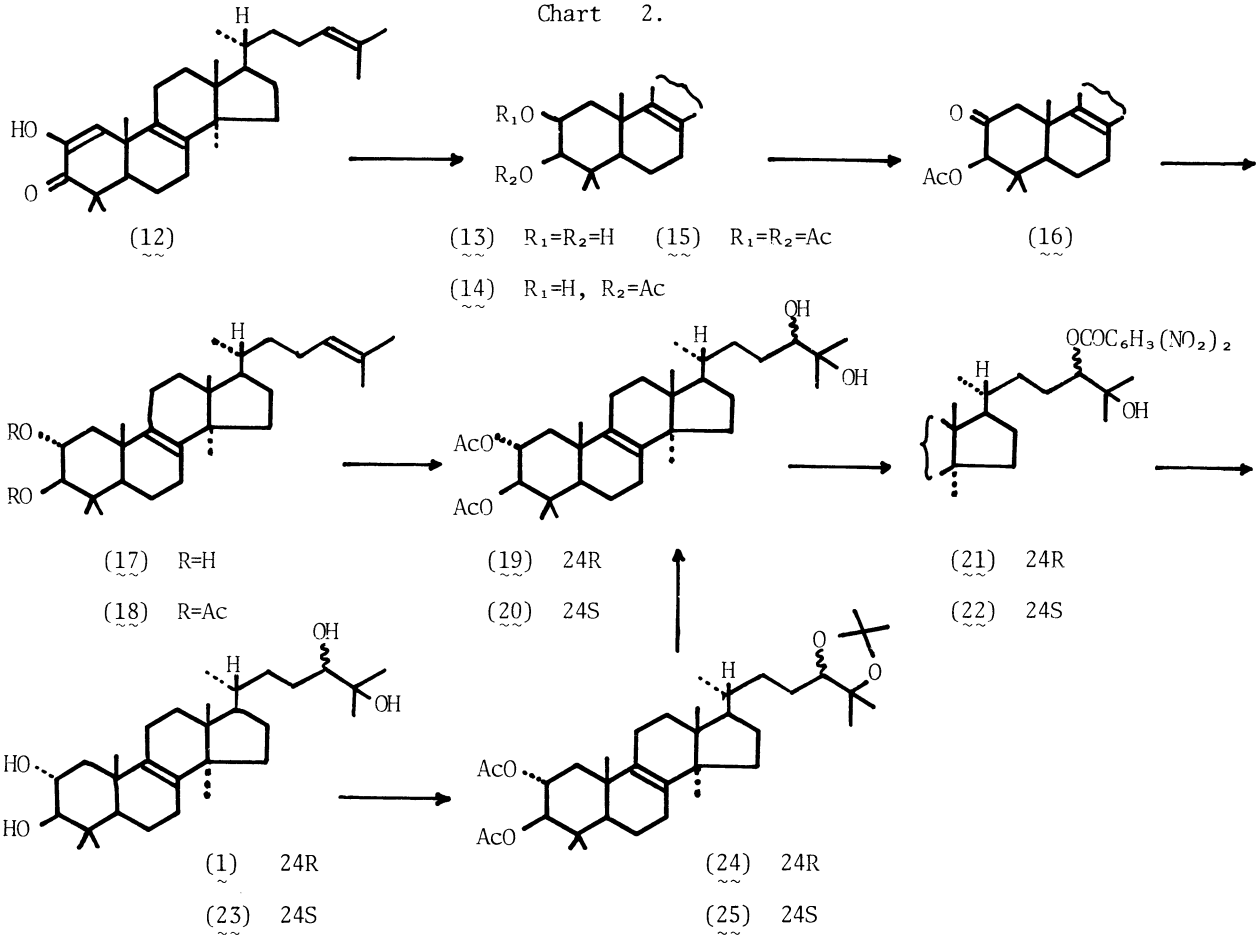


(80% yield), $C_{32}H_{52}O_3$, mp 166-168°, $[\alpha]_D^{26}$ +69.8° (c=0.9, $CHCl_3$), NMR ($CDCl_3$): δ 4.65 (1H, d, J=4 Hz, C<u>H</u>-OAc), 4.15 (1H, q, J=4 Hz, C<u>H</u>-OH), 2.18 (3H, s, Ac) accompanied with a small amount of diacetate 15, $C_{34}H_{54}O_4$, mp 146-149°, $[\alpha]_D^{26}$ +78.8° (c=1.2, $CHCl_3$). Oxidation of the monoacetate 14 by Collins procedure afforded a ketone 16, $C_{32}H_{50}O_3$, mp 154-156°, $[\alpha]_D^{25}$ +105.4° (c=1, $CHCl_3$).

Reduction of 16 with metallic sodium[4] in refluxing n-AmOH gave a 2α,3β-diol 17 (55% yield), $C_{30}H_{50}O_2$, mp 183-185°, $[\alpha]_D^{14}$ +53.7° (c=1, 10% MeOH-$CHCl_3$), which was then acetylated in the usual manner to afford a diacetate 18, $C_{34}H_{54}O_4$, mp 98-101°, $[\alpha]_D^{20}$ +12° (c=1, $CHCl_3$), NMR ($CDCl_3$): δ 5.15 (1H, dt, J=5, 11, 11 Hz, C<u>H</u>-OAc), 4.83 (1H, J=11 Hz, C<u>H</u>-OAc), 2.00 and 2.10 (each 3H, s. Ac x 2).

Treatment of 18 with one equivalent of OsO_4 in ether-pyridine afforded an epimeric mixture of 24,25-diol (19 and 20) in 57% yield. Separation of this C-24 epimers was unsuccessful at this stage, but it could be achieved effectively with the corresponding 3,5-dinitrobenzoate mixture (21 and 22), which was prepared as usual (92% yield) and showed two peaks in approximate intensity ratio 55 : 45 (in the order of increasing polarity) in HPLC.[5] Thus, the 3,5-dinitrobenzoate mixture (21 and 22) was subjected to preparative HPLC[6] and fractions were recrystallized from ether to afford the less polar epimer 21, $C_{41}H_{58}N_2O_{11}$, mp 219-221°, $[\alpha]_D^{30}$ +10.2° (c=1, $CHCl_3$) and the more polar one 22

Chart 2.



$C_{41}H_{58}N_2O_{11}$, mp 226°, $[\alpha]_D^{28}$ +1.2° (c=1, $CHCl_3$), in about 20-25% yield, respectively. It should be noted here that the NMR spectra of the above epimers (21 and 22) are almost superimposable with each other, but the 18-methyl signal[7] of 21 appears at slightly lower field (δ 0.70) than that of 22 (δ 0.65).

Alkaline hydrolysis of these isomers (21 and 22) afforded the corresponding tetrols: 1, $C_{30}H_{52}O_4$, mp 209°, $[\alpha]_D^{23}$ +50.4° (c=1, MeOH) and 23, $C_{30}H_{52}O_4$, mp 236-238°, $[\alpha]_D^{26}$ +22.3° (c=1, MeOH), respectively. Of these, 1 was shown to be identical with natural fasciculol-A (1) by mixed fusion and IR (KBr) and MS comparisons.

Absolute configuration of the C-24 position of fasciculol-A was suggested to be "R" by Ikeda et al.[1] based on the lanthanide-induced Cotton effect of fasciculol-A 2,3-diacetate according to the modified Nakanishi's method.[8] However, a possibility that the 2,3-diacetoxyl moiety in the latter compound may have influence to some extent on the induced Cotton effect due to 24,25-glycol grouping could not be excluded. Therefore, we converted the tetrols (1 and 23) to the corresponding 2,3-diacetates (19 and 20) in order to compare their CD spectra.

Treatment of 1 and 23 with anhydrous acetone and p-toluenesulfonic acid, followed by acetylation

in the usual manner, afforded the corresponding monoacetonide-2,3-diacetate (24, $C_{37}H_{60}O_6$, mp 167-171° and 25, $C_{37}H_{60}O_6$, mp 190-192°), which on hydrolysis with methanolic HCl gave the 2,3-diacetate 19, $C_{34}H_{56}O_6$, mp 153-154°, $[\alpha]_D^{21}$ +12.9° (c=1, MeOH) and 20, $C_{34}H_{56}O_6$, mp 159-160°, $[\alpha]_D^{28}$ -9.2° (c=1, MeOH), respectively.

The CD spectra of 19 and 20 in CCl_4 in the presence of Eu(fod)$_3$ showed a negative Cotton effect at 305 nm ($\Delta\varepsilon$ -10.4) and a positive one at 306 nm ($\Delta\varepsilon$ +11.3), respectively. These observations led to the conclusion that the compound 19 has the 24R absolute configuration and 20 the 24S configuration. In addition, this assignment is supported by the above mentioned NMR behavior of 18-methyl group in 21 and 22.[9]

Thus the structure of fasciculol-A was unambiguously assigned to the formula 1.

Acknowledgment The authors are indebted to Dr. Kaoru Kuriyama and Mr. Tatsuo Iwata, Shionogi Research Laboratory, Shionogi Co., Ltd., for CD measurements, Mr. Hiroyuki Matsunaga, Nihon Waters Ltd., for carrying out preparative HPLC, and Mr. Masahiro Morikoshi, this University, for NMR spectra measurements.

References and Notes

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5) HPLC (High Performance Liquid Chromatography) was done on a Shimadzu LC-1 equipped with a UV detector (240 nm) and a Zorbax SIL column (25cm x 2.1mmφ), using hexane/CH_2Cl_2 (2/8) - i-PrOH (99.55 : 0.45) at 100kg/cm^2.

6) Preparative HPLC was performed on a Waters System 500 with a prep PAK-500 SILICA column, using hexane/CH_2Cl_2(2/8) - i-PrOH (99.5 : 0.5) at 5kg/cm^2.

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(Received October 18, 1979)