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STRUCTURE OF KADSURIC ACID. A NEW SECO-TRITERPENOID FROM KADSURA JAPONICA DUNAL

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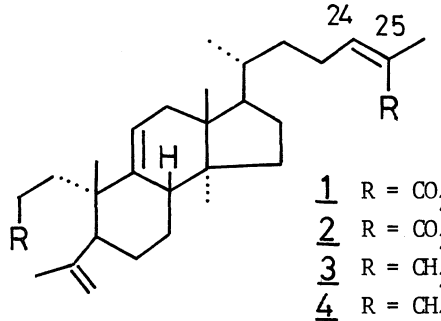
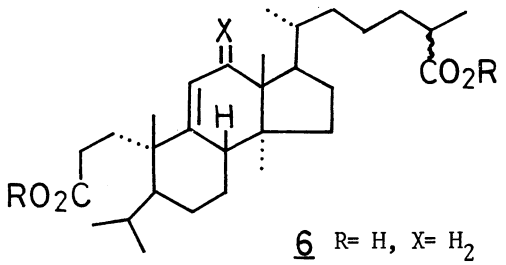
A new A-seco-lanostane type triterpenoid, kadsuric acid, was isolated from Kadsura japonica Dunal and its structure was elucidated as 1 on the basis of the spectroscopic data and the chemical transformations.

The dry stems of Kadsura japonica Dunal (Magnoliaceae) is widely used as a herb in Taiwan[1]. From this plant Yamamura et al. reported the isolation of lignanes, kadsurin and kadsurarin[2]. In the course of our investigation of the herb, a new seco-triterpenoid, which we name kadsuric acid, has been isolated from the $CHCl_3$ extract. Now we report the structure of kadsuric acid.

Kadsuric acid 1, $C_{30}H_{46}O_4$ (M^+ m/e 470.339, calcd. 470.340), m.p. 185°, $[\alpha]_D^{20}$ +77.3°(c 1.1, MeOH), IR(KBr) 3400-2600, 1700, 1640 and 895 cm^{-1}, UV(EtOH) 222 nm (sh), ^{1}H-NMR(DMSO-d_6) δ 0.65, 0.76, 1.00(each 3H,s,tertiary CH_3), 0.91(3H,d,secondary CH_3), 1.72, 1.80(each 3H,br.s,olefinic CH_3), 4.71, 4.86(each 1H,br.m,$\succ C=CH_2$), 5.30, 5.89(each 1H,m,$\succ C=CH-$), and 12.2(2H,br,$-CO_2H$) ppm, was treated with CH_2N_2 to give dimethyl kadsurate 2[3], IR(KBr) 1710 cm^{-1}, UV(EtOH) 220 nm(sh), ^{1}H-NMR($CDCl_3$) δ 3.67 and 3.73(each 3H,s,OCH_3) ppm. Reduction of 2 with $LiAlH_4$ afforded kadsuradiol 3, IR($CHCl_3$) 3600 cm^{-1}, which upon acetylation yielded the diacetate 4, IR ($CHCl_3$) 1720 cm^{-1}, ^{1}H-NMR($CDCl_3$) 2.05 and 2.08(each 3H,s) ppm. The UV absorption at 220-222 nm observed in 1 and 2 was disappeared in the reduction products 3 and 4. Hydrogenation of 1 over Pd-C afforded dihydro derivative 5, which was further hydrogenated over Pt to yield tetrahydro derivative 6. Chromic acid oxidation of the dimethyl ester 7, obtained from 6, afforded the conjugated enone 8, M^+ m/e 516.384(calcd. 516.381), UV(MeOH) 244 nm, ^{1}H-NMR($CDCl_3$) δ 3.68(6H,s) and 5.65(1H,



1 R = CO_2H
2 R = CO_2Me
3 R = CH_2OH
4 R = CH_2OAc
5 R = CO_2H
24,25-dihydro



6 R= H, X= H_2
7 R= Me, X= H_2
8 R= Me, X= O

d,J=2.0 Hz) ppm. From these chemical transformations and spectroscopic data of these compounds, kadsuric acid 1 can be regarded as a seco-triterpenoid having two carboxyl groups,one of which is conjugated with a C-C double bond.

The presence of the partial structures I – III (Fig.1) in kadsuric acid was strongly supported by the decoupling experiment of the ^{1}H-NMR spectrum of 1 and by the analysis of the ^{13}C-NMR spectrum of 2. Irradiation at 5.89 ppm (partial structure I) converted the broad singlet at 1.80 ppm to a sharp singlet, and irradiation at 1.80 ppm converted the olefinic proton signal at 5.89 ppm to a sharp signal. Similar change was observed on the terminal methylene protons at 4.71 and 4.86 ppm (partial structure II) on irradiation at 1.72 ppm. Six olefinic carbon signals were observed in the ^{13}C-NMR spectrum (15.1 MHz, $CDCl_3$) of 2 , indicating the presence of three carbon-carbon double bonds, and these signals were unequivocally assignable to each carbon atom in the partial structures I – III by off-resonance measurements and single-frequency measurements together with the consideration of the chemical shifts. The geometry of the double bond in I was elucidated by

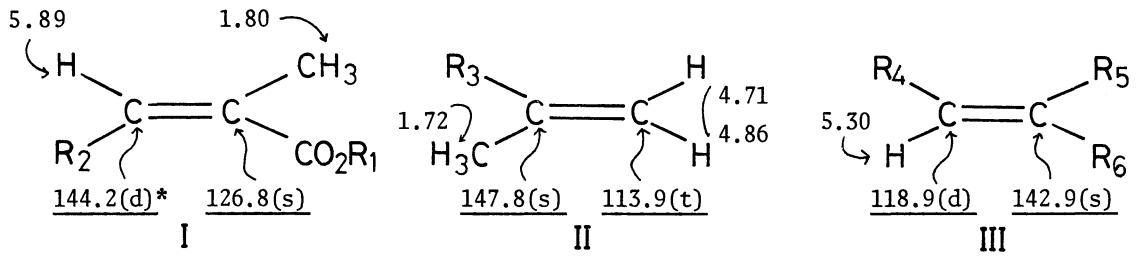


Fig.1. ^{1}H-NMR Chemical shifts of kadsuric acid 1(R_1=H) and ^{13}C-NMR chemical shifts (underlined values) of the olefinic carbons of dimethyl kadsurate 2(R_1=CH_3).
* Splitting patterns observed by the off-resonance measurements were indicated in parentheses.

comparison of ^{1}H-NMR chemical shift of the olefinic proton (5.89 ppm) with those of the corresponding protons of methyl angelate(5.97 ppm) and methyl tiglate(6.72 ppm)[4].

These results, coupled with the detailed analyses of the mass spectra of the compounds 1 – 8, led to the conclusion that kadsuric acid was expressed by the A-seco-triterpenoid structure 1. The fragmentation patterns of kadsuric acid 1, dimethyl kadsurate 2 and the conjugated enone 8 are depicted in Fig. 2 and 3, respectively. The elemental compositions of the main fragment ions were confirmed by high resolution measurements, and these fragmentation patterns are fully self-explanatory.

Stereochemistry was deduced from the spectroscopic data and the biogenetic consideration. The lanostane-type stereochemistry of the C/D ring juncture was

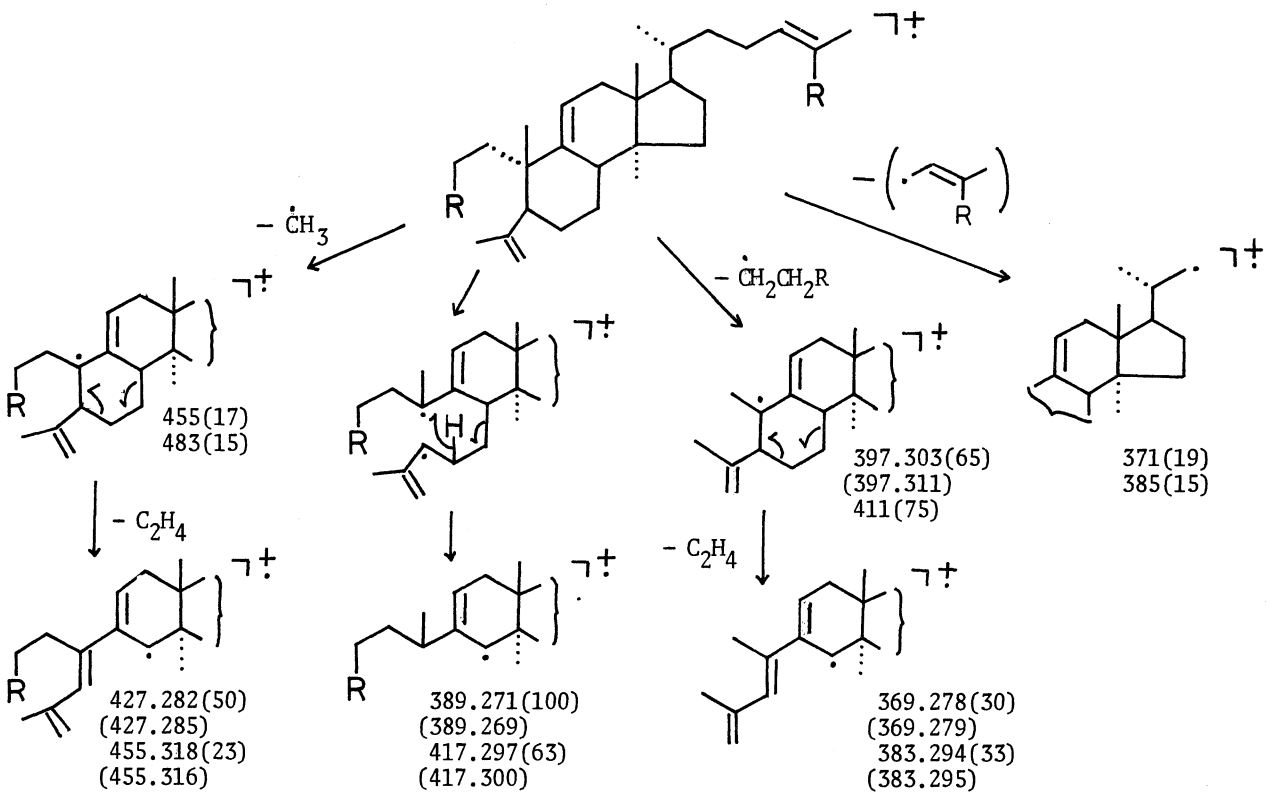


Fig.2. Mass fragmentations of kadsuric acid 1(R=CO_2H) and dimethyl kadsurate 2(R=CO_2Me). The values, indicating the m/e of fragment ions, are given in the order of 1 and 2. The values in parentheses in the same array indicate % intensity relative to base peak. Numerals in parentheses in the next array indicate the value calculated for high resolution measurements.

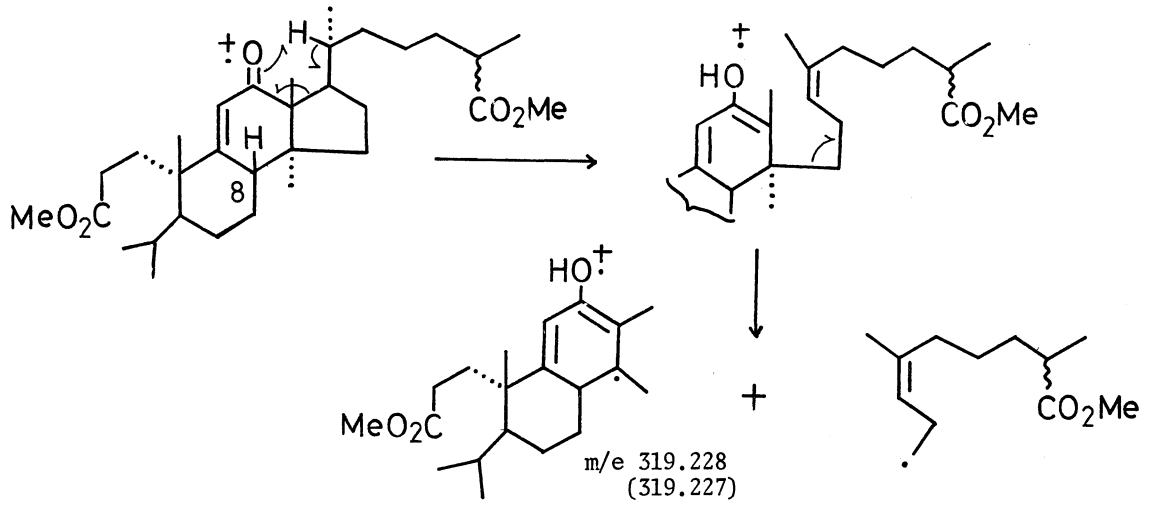


Fig.3. Mass fragmentation of the conjugated enone 8.
The numeral in parenthesis indicate the value calculated for high resolution measurement.

clarified by the CD spectrum of the conjugated enone 8 ; negative Cotton-effect caused by $n\rightarrow\pi^*$ transition at 333 nm ($\Delta\varepsilon$ -3.6) and positive Cotton-effect caused by $\pi\rightarrow\pi^*$ transition at 245 nm ($\Delta\varepsilon$ +11.4). The signs of the Cotton-effects[5] were agreement with those predicted from the structure 1. The β configuration of the C-8 proton was supported by the allylic coupling constant (J=2.0 Hz)[6] between C-8 proton and C-11 olefinic proton in the ^{1}H-NMR spectrum of 8. Stereochemistry at the remaining asymmetric carbon centers in 1 is based on the biogenesis; kadsuric acid is presumably derived from the lanostane-type triterpenoid by the cleavage of the A ring. In order to confirm the full structure involving the absolute configuration of some asymmetric carbon centers, the chemical transformation of lanosterol to kadsuric acid is currently under investigation.

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