The Preparation of Fukinane, A New Skeletal Sesquiterpenic Hydrocarbon[1]

Keizo NAYA and Masakazu KOBAYASHI

Department of Chemistry, Faculty of Science, Kwansei Gakuin University, Uegahara, Nishinomiya, Hyogo

(Received August 12, 1970)

A novel skeletal sesquiterpenic hydrocarbon, fukinane (I), has been prepared by conversion from an eremophilane type, fukinone (VIII), *via* fukinan-8-ol (IX). A rearrangement of the fukinane skeleton into an eremophilane type through fukinan-8-ol tosylate (X) has been studied.

We have previously reported the isolation and stereochemistry of several new sesquiterpenoids with a fukinane (I) skeleton (fukinanolide (II),[2] fukinolide (III),[2] *S*-fukinolide (IV),[2] homofukinolide (V),[3] and dihydrofukinolide (VI))[3] from *Petasites japonicus* Maxim. The absolute configurations of these compounds were established by correlation with fukinone (VIII) through fukinan-8-ol (IX).[4] The absolute configuration of fukinone (VIII) had already been settled.[5]

Now we have an interest in preparing a new type of sesquiterpene hydrocarbon, fukinane (I); the present paper will report the results of the following three routes for synthesizing fukinane (I) from fukinan-8-ol (IX).

For the purpose of removing the oxygen function at C-8, we attempted the following three routes: (i) the reduction of fukinan-8-ol tosylate (X) with lithium aluminum hydride, (ii) the Wolff-Kishner reduction of fukinan-8-al semicarbazone (XVI), and (iii) the reduction of fukinan-8-al ethylene thioacetal (XVIII) with Raney nickel.

From Tosylate (X). Fukinan-8-ol (IX),[4] $C_{15}H_{28}O$, mp 38—39°C, was treated with three equivalents of tosyl chloride to give the tosylate (X) quantitatively. An attempt at the further purification of the tosylate (X) by chromatography on silica gel involved a Wagner-Meerwein-type rearrangement[6] to produce a mixture of hydrocarbons XI, XII and XIII. The glc pattern is illustrated in Fig. 2, while the relative ratio of the yield is shown in Table 1. The mixture reacted positively to a tetranitromethane-test and was exclusively converted to eremophilane (XIV) by hydrogenation with Adams' catalyst in acetic acid. Those facts suggest that the rearrangement proceeded stereoselectively, involving the migration of the C-9 methylene to the

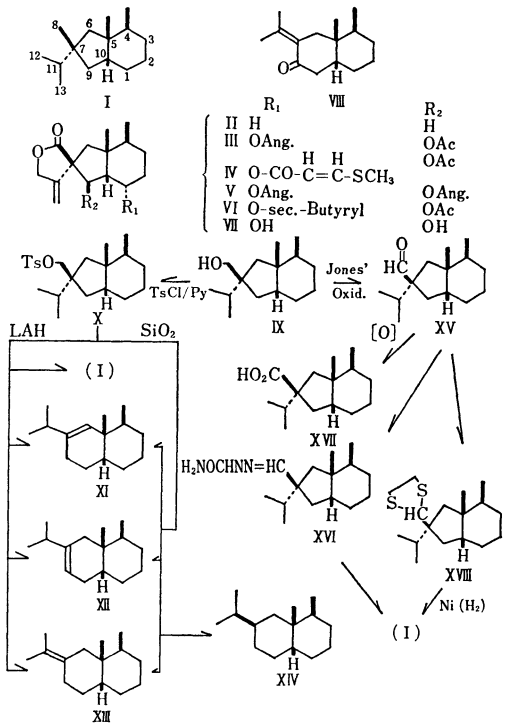


Fig. 1.

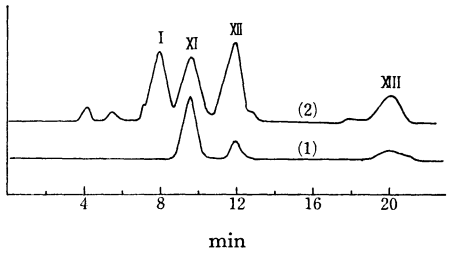


Fig. 2. Glc of hydrocarbons I, XI, XII, and XIII.
(1) Rearrangement of the tosylate (X) through SiO_2
(2) $LiAlH_6$ reduction of the tosylate (X)
(PEG 6000, 2.6 m. 170°C, H_2: 54.5 ml/min)

TABLE 1. RELATIVE RATIO OF HYDROCARBONS I, XI, XII, AND XIII

Run	Product			
	I	XI	XII	XIII
1	—	5	1.4	1
2	1.9	1.9	2.4	1

Run 1) Rearrangement of the tosylate (X) through SiO_2
Run 2) $LiAlH_4$ reduction of the tosylate (X)

1) This report is dedicated to Professor Munio Kotake for his 75th birthday, "Kiju".

2) K. Naya, I. Takagi, M. Hayashi, S. Nakamura, and M. Kobayashi, 11th Symposium on the Chemistry of Natural products, Symposium Papers (1967), p. 88; N. Abe, R. Onoda, K. Shirahara, T. Kato, M. C. Woods, and Y. Kitahara, *ibid.*, p. 96; N. Abe, R. Onoda, K. Shirahara, T. Kato, M. C. Woods, and Y. Kitahara, 11th Symposium on the Chemistry of Terpenes, Essential Oils and Aromatics, Symposium Papers (1967), p. 147; K. Naya, I. Takagi, M. Hayashi, S. Nakamura, M. Kobayashi, and S. Katsumura, *Chem. Ind.* (London), **1968**, 318.

3) M. Hayashi, S. Katsumura, I. Takagi, and K. Naya, 18th Annual Meeting of Chemical Society of Japan (1968), Collective Papers, Vol. 3, p. 2152.

4) K. Naya and M. Kobayashi, *ibid.*, p. 1836.

5) K. Naya, I. Takagi, Y. Kawaguchi, Y. Asada, N. Shinoda, and Y. Hirose, *Tetrahedron*, **24**, 5871 (1968).

6) W. G. Dauben and J. B. Rogan, *J. Amer. Chem. Soc.*, **79**, 5002 (1957).

electron-deficient C-8, but not to the C-6. Each hydrocarbon was isolated by preparative glc. The structures of the hydrocarbons XI, XII, and XIII, were determined as will be described below.

The NMR spectrum[7] of the compound XI shows a singlet at 5.03, suggesting a C=CH–C– grouping. The structure was settled as in formula XI from the MS fragmentation shown in Fig. 3.

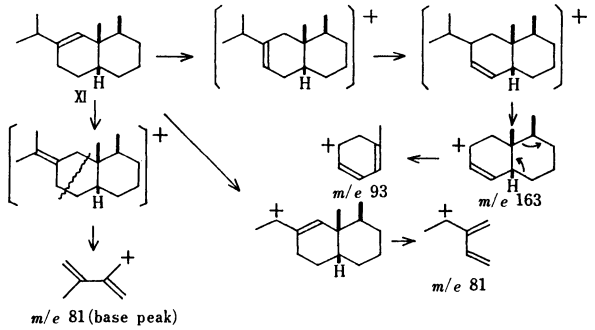


Fig. 3. Mass fragmentation of hydrocarbon XI.

The NMR spectrum of the compound XII shows a multiplet signal centered at 5.24 which was presumed to be the result of the long-range coupling between the vinyl proton at C-8 and the protons at C-6 and C-11. In the MS spectrum, the base peak at *m/e* 110 was derived from a retro-Diels-Alder rupture of the molecular ion. The structure was, then, represented by the stereoformula XII, based on the MS fragmentation, shown in Fig. 4.[8]

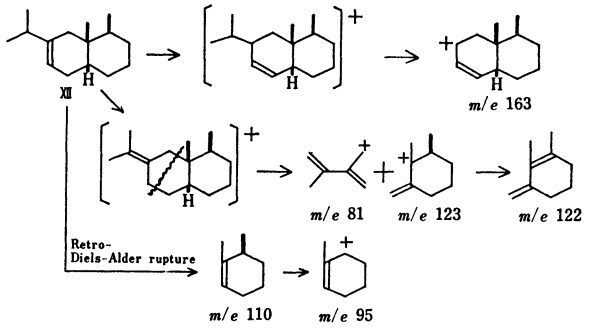


Fig. 4. Mass fragmentation of hydrocarbon XII.

The hydrocarbon XIII shows a singlet at 1.62 (6H) due to an isopropylidene group in its NMR spectrum. The structure XIII was established with the aid of the MS fragmentation shown in Fig. 5.[8]

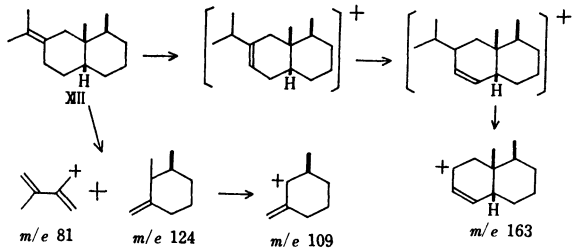
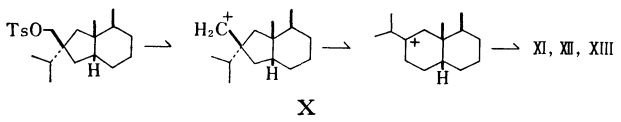


Fig. 5. Mass fragmentation of hydrocarbon XIII.

7) All NMR spectra were taken in CCl_4 on a JEOL C-60 spectrometer, otherwise mentioned, with TMS as an internal reference. The values are reported in ppm.

8) H. Budzikiewics, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day Inc., San Francisco (1967), p. 71.



X

Fig. 6. The scheme of rearrangement of the tosylate (X).

The rearrangement should occur by means of the scheme shown in Fig. 6.

Because the tosylate (X) yielded predominantly migration products with an eremophilane sekeleton when submitted to chromatography over silica gel, the tosylate (X) was submitted to lithium aluminum hydride reduction without further purification. The glc pattern of the hydrocarbons obtained by the reduction is shown in Fig. 2. The products proved to include mainly the migration hydrocarbons, plus a small amount of fukinane (I).

From Fukinan-8-al Semicarbazone (XVI). Fukinan-8-al (XV) was obtained in a comparatively good yield by Jones' oxidation[9] under controlled conditions. The product XV was appreciably air-oxidized to the carboxylic acid (XVII), mp 125.5—126.0°C, by leaving it overnight in the air at room temperature, or by preparative tlc. The crude aldehyde (XV) was, therefore, quickly transformed to the semicarbazone (XVI). The product XVI was submitted to Wolff-Kishner reduction to afford fukinane (I) (10% yield; 3.7% overall yield from fukinan-8-ol). We turned to an alternate approach to produce fukinane (I) in a good yield.

From Fukinan-8-al Ethylene Thioacetal (XVIII). The third route involved the reduction of the ethylene thioacetal of fukinan-8-al (XVIII). The condensation of fukinan-8-al (XV) with ethanedithiol afforded the ethylene thioacetal (XVIII) in a 70.2% yield. Its reduction with Raney nickel proceeded readily to give fukinane (I) (yield, 79%), which was identical with the sample prepared by the other routes described

Table 2. Physical properties of fukinane (I)

n_D^{17}	n_D^{20}	$n_D^{24.5}$	d_4^{20}	$[\alpha]_D^{23a)}$
1.4761	1.4750	1.4734	0.89077	+41.8°

a) (*c*, 1.42, CCl_4)

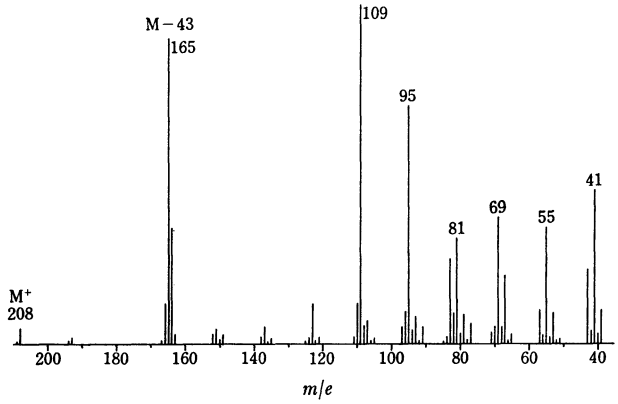


Fig. 7. Mass spectrum of fukinane (I).

9) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **1946**, 39.

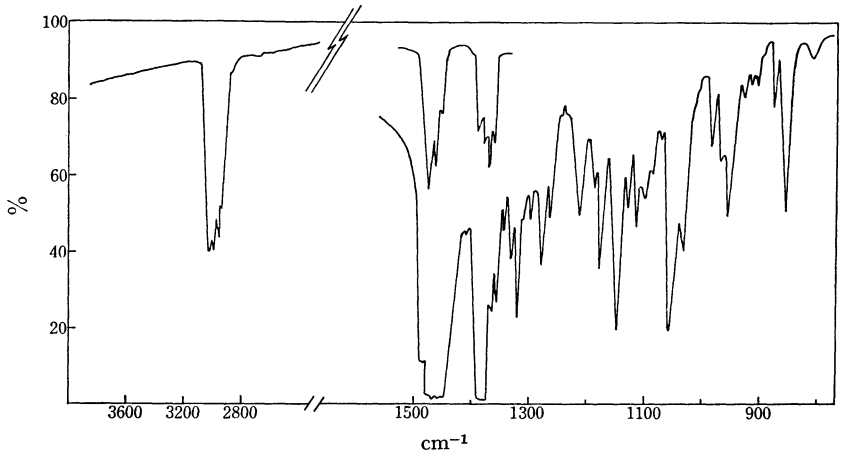


Fig. 8. IR spectrum of fukinane (I).

above. The physical properties of fukinane (I) are listed in Table 2. The MS spectrum is shown in Fig. 7, and the IR spectrum, in Fig. 8.

Experimental

All the melting points are uncorrected. The MS spectra were measured with a Hitachi RMU-6 MS spectrometer: ion-source temperature 250°C; evaporation temperature, 150°C. The IR spectra were recorded with a JASCO DS-402G spectrophotometer, and the optical rotations were measured with a Hitachi EPU-2A spectrophotometer. Glc was carried out using a Shimadzu GC-1C apparatus on a stainless steel column (ϕ=3 mm).

Fukinan-8-ol (IX)[4] was prepared from fukinolidol (VII),[2] which had been derived by alkaline hydrolysis from fukinolide (III),[2] *S*-fukinolide (IV),[2] homofukinolide (V),[3] and dihydrofukinolide (VI),[3] and also from fukinanolide (II)[2] and fukinone (VIII).[5]

Tosylate of Fukinan-8-ol (IX). To a solution of fukinan-8-ol (IX) (346 mg, 1.54 mmol) in dry pyridine (6.8 m*l*), was added tosyl chloride (909 mg, 4.8 mmol); the reaction mixture was then left at room temperature for 19 hr. Subsequent working up in the usual manner yielded the tosylate (X) (560 mg, yield 95.2%); almost one spot by tlc analysis with R_f=0.35 (light petroleum: benzene=3 : 1). IR (film): 1600, 1379, 1190, 1100, 960, 845, 820 cm^{-1} (characteristic of a tosylate).

Rearrangement of Tosylate (X) by Silica Gel. Fukinan-8-ol tosylate (X) (1.21 g, 3.45 mmol) was chromatographed on silica gel (30 g). The light petroleum-benzene (5 : 1) eluates were combined to give a mixture of the hydrocarbons XI, XII, and XIII (457 mg, 70%). Their pure specimens were furnished by preparative glc (PEG-20M on Celite 545; 2.6 m; H_2 37 m*l*/min; column temperature, 160°C).

Compound XI, $[\alpha]_D^{23}$ +23.1° (*c*, 0.91, CCl_4); n_D^{15} 1.4901; NMR: 0.78 (d, 3H, *J*=6 Hz), 0.86 (s, 3H), 1.02 ppm (d, 6H, *J*=6.6 Hz); MS: M$^+$ *m/e* 206, base peak *m/e* 81.

Found: C, 87.41; H, 12.54%. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70%.

Compound XII, $[\alpha]_D^{23}$ −16.4° (*c*, 1.70, CCl_4); $n_D^{15.5}$ 1.4919; NMR: 0.85 (s, 3H), 0.89 (d, 3H, *J*=4.5 Hz), 0.98 (d, 6H, *J*=6.6 Hz), 5.24 ppm (br. s, 1H); MS: M$^+$ *m/e* 206, base peak *m/e* 110.

Compound XIII, $n_D^{16.5}$ 1.5060; NMR: 0.78 (d, 3H, *J*=6 Hz), 0.85 (s, 3H), 1.62 ppm (s, 6H); MS: M$^+$ *m/e* 206, base peak *m/e* 81.

Catalytic Reduction of the Hydrocarbons XI, XII, and XIII. A mixture of the hydrocarbons XI, XII, and XIII (99.4 mg) was hydrogenated in glacial acetic acid (3 m*l*) with Adams' catalyst (22 mg) at room temperature and at atmospheric pressure. After the hydrogen uptake had ceased, the catalyst was filtered. The filtrate was diluted with aqueous sodium hydrogen carbonate, and the product was extracted with benzene. The evaporation of the solvent *in vacuo* then gave a hydrocarbon (88 mg) which was found to be identical with eremophilane (XIV) in glc analysis; retention time, 6.1 min; PEG-6000 on Celite 545 (2.5 m, 60—80 mesh); carrier gas, H_2, flow rate, 120 m*l*/min; column temperature, 160°C.

Lithium Aluminum Hydride Reduction of Tosylate (X). To a stirred and refluxed mixture of lithium aluminum hydride (147 mg, 3.87 mmol) in absolute ether (10 m*l*), a solution of the tosylate (X) (289 mg, 0.76 mmol) in absolute ether (7 m*l*) was added, drop by drop over a 45 min period. The mixture was then maintained at that temperature for an additional 7 hr. After being cooled to room temperature, the reaction mixture was treated with moist ether and aqueous 10% hydrochloric acid, and then washed thoroughly with water. The ethereal extract was dried over anhydrous sodium sulfate. The evaporation of the solvent gave an oily residue (163 mg), which was then chromatographed over silica gel (7 g). Elution with light petroleum afforded a mixture of hydrocarbons (30 mg, 19%), which was proved by glc analysis to be a mixture of fukinane I, XI, XII, and XIII. Further elution with benzene-ethyl acetate (40 : 1) afforded fukinan-8-ol (IX) (104 mg; yield, 60%).

Semicarbazone of Fukinan-8-al (XV). Into a solution of fukinan-8-ol (IX) (334 mg, 1.5 mmol) in acetone (7.6 m*l*), 0.57 m*l* of Jones' reagent (containing 157 mg of chromium trioxide) was stirred in a single portion at −16°C. The mixture was kept for 30 min, methanol (4 m*l*) was added, and the solvent was removed under reduced pressure. The residue was then extracted with ether, and the ethereal extract was washed with aqueous sodium hydrogen carbonate and then with water. The ethereal solution was dried over anhydrous sodium sulfate, after which the solvent was evaporated to give a crude aldehyde, fukinan-8-al (XV); positive to tetrazolium test; IR (film): 1720 cm^{-1}. The residual oil was treated in ethanol (2 m*l*) with semicarbazide hydrochloride (400 mg) and freshly-fused sodium acetate (60 mg) as soon as possible. The reaction mixture was then left at room temperature for 16 hr to afford crystalline semicarbazone

(XVI) (208 mg, 49%); mp 189—190°C (decomp.). Recrystallization from aqueous methanol gave a pure semicarbazone; mp 206.0—206.5°C (decomp.); $[\alpha]_D^{23}$ +19.1° (*c*, 1.1, $CHCl_3$); IR (KBr disk): 3500, 3300 (sh), 3240, 3180, 1695, 1625 (sh), 1580, 1565 (sh), 1143, 1045, 1008, 948, 772 cm^{-1}; NMR:[10] 0.79 (d, 3H, J=6.1 Hz), 0.89 (d, 6H, J=6.0 Hz), 0.89 (s, 3H), 5.53 (br. s, 2H, $-CO-NH_2$), 7.01 (s, 1H, $-CO-NH-N=$), 8.96 ppm (s, 1H, $-N=CH$).

Found: C, 68.92; H, 10.42; N, 15.39%. Calcd for $C_{16}H_{29}N_3O$: C, 68.77; H, 10.46; N, 15.04%.

Wolff-Kishner Reduction of Semicarbazone (XVI). The semicarbazone (XVI) (325 mg, 1.17 mmol) and powdered potassium hydroxide (233 mg, 4.2 mmol) were heated under reflux for 9 min to give a brownish-yellow syrup. After being cooled, the reaction mixture was diluted with water and extracted with ether. Then the solvent was removed. The IR spectrum of the residue (219 mg) showed an absorption band at 1640 cm^{-1}, presumably due to the C=N group. The residual oil was heated under reflux again with potassium hydroxide (197 mg, 3.5 mmol). After the evolution of the gas had subsided, the solution was diluted with water and extracted with ether, and the ethereal solution was dried over anhydrous sodium sulfate. The evaporation of the solvent gave a crude oil (188 mg), which was then chromatographed on preparative tlc to give fukinane (I) (24 mg, 10%; total yield from IX, 4.9%).

Ethylene Thioacetal of Fukinan-8-al (XV). Fukinan-8-ol (IX) (574 mg, 2.6 mmol) was treated with 1.3 m*l* of Jones' reagent (containing 364 mg of chromium trioxide) at −13°C for 7 min to give a crude aldehyde (XV). After being dried throughly by azeotropic evaporation with dry benzene, the aldehyde (XV) was dissolved in ethanedithiol (1 m*l*) and to this a catalytic amount of BF_3-etherate was added. The reaction mixture was then left at room temperature for 1.5 hr. Methanol (2 m*l*) was added, and the mixture was diluted with 5% aqueous potassium hydroxide, extracted with ether, washed with water and dried over anhydrous sodium sulfate. The evaporation of the solvent gave an oil (1.24 g), which was chromatographed over silica gel (10 g) and eluted with light petroleum to afford fukinan-8-al ethylene thioacetal (XVIII) (536 mg, yield, 70.2%); $[\alpha]_D^{23}$ +22.5° (*c*, 1.1, CCl_4); $n_D^{18.5}$ 1.5544; IR (film): 1392, 1386, 1376, 1315, 1280, 1185, 1165, 1125, 1107, 1023, 944, 860, 840, 783 cm^{-1}; NMR; 0.78 (d, 3H, J=6 Hz), 0.92 (s, 3H), 0.99 (d, 6H, J=6.9 Hz), 3.11 (fine splitting, s, 4H, $-S-CH_2-CH_2-S-$), 4.81 ppm (s, 1H, $-S-CH-S-$); glc: retention time, 9 min; Thermol-3 (1.1 m) on Shimalite (60—80 mesh); carrier gas, H_2; flow rate, 200 m*l*/min; column temperature, 170°C.

Found: C, 68.72; H, 10.13: S, 21.30%. Calcd for $C_{17}H_{30}S_2$: C, 68.39; H, 10.13; S, 21.48%.

Raney Nickel Reduction of Ethylene Thioacetal (XVIII). A solution of the ethylene thioacetal (XVIII) (534 mg, 1.8 mmol) in ethyl acetate (3 m*l*) was stirred drop by drop into a suspension of Raney nickel (10 g) in ethyl acetate (10 m*l*) over a 12-min period. The reaction mixture was then refluxed for an additional hour, and subsequently filtered. The filtrate was evaporated *in vacuo* to give fukinane (I) (303 mg, 79%); single peak by glc analysis; retention time, 4.1 min; PEG-20M (2.6 m) on Celite 545 (60—80 mesh); carrier gas, H_2; flow rate, 37.3 m*l*/min; column temperature, 168°C. The pure specimen was obtained by preparative glc. MS: M^+ *m/e* 208, base peak *m/e* 109; NMR; 0.70—0.91 (15H, five methyls).

Found: C, 86.90; H, 13.26%. Calcd for $C_{15}H_{28}$: C, 86.46; H, 13.54%. The physical properties are listed in Table 2. The MS spectrum is shown in Fig. 7, and the IR spectrum, in Fig. 8.

The authors wish to thank the Shionogi Research Laboratory, Shionogi & Co., Ltd., for the microanalysis and the Institute of Food Chemistry for the measurements of the MS and NMR spectra.

10) This spectrum was taken in $CDCl_3$ on H-6013 (Hitachi) spectrometer.