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A Novel Method for Attacking Non-activated C-H Bond and Its Application to the Synthesis of Gibberellin-A_{15} from Enmein

In this comumnication, we wish to report the chemical interconversion between gibberellin-A_{15} and enmein, and also a novel method for attacking non-activated C–H bond.

20-Hydroxykaur-6-en 15α-pyranylether (II) was prepared from enmein (I) as mentioned earlier.[1] Oxidation of II with chromiun trioxide–pyridine gave the aldehyde (III), mp 99—101°; IR ν_{max}^{KBr} cm^{-1}: 2710, 1705. NMR ($CDCl_3$) τ: 0.02 (1H, s, CHO), which was converted with hydroxylamine to the oxime (IV), mp 182—183°. IR ν_{max}^{KBr}: 3340 cm^{-1}. NMR ($CDCl_3$): 2.52 (1H, s, HC=N), 4.25 (2H, s, HC=CH), 6.6 (1H, d, J=4 cps, HC_{15}–OH).

Today, we have many methods for attacking non-activated C–H bond. In order to introduce some functional groups into C_{19}-methyl by these methods, we tried the photolysis of C_{20}-acylazide (V), derived from II. Although V was easily photo decomposed under various conditions to afford two main products, a six-membered lactam and a five-membered lactam, in 13—17% and 5—10% yield, respectively, they were not the products formed by attack on the C_{19}-methyl. Neither the Barton reaction nor lead tetraacetate oxidation of C_{20}-carbinol or C_6-axial hydroxyl gave any desired product. Finally the aromatic amine oxide rearrangements[2] stimulate us to imagine that C_{19}-methyl should be attacked by the photolysis of some nitrone.

From these points of view, IV was converted by the addition of BrN_3[3] into the nitrone (VI), $C_{20}H_{30}O_2NBr$, mp 159—160°. IR ν_{max}^{KBr} cm^{-1}: 3300, 1565 (C=N), 1230 (N–O). NMR ($CDCl_3$) τ: 3.40 (1H, s, HC=N), 5.5 and 6.0 (each 1H, d, J=5 cps, C_6 and C_7H), 6.55 (1H, br., s, C_{15}H), 9.03 (6H, s, C_{18} and C_{19} methyl). UV λ_{EtOH}^{max} mμ (ε): 255 (595.0). Irradiation of the nitrone (VI) with 10W low-pressure mercury lamp (Osawa Shigaisen K.K.) led to the desired product (VII), $C_{20}H_{29}O_2N$, mp 215—218° (from acetone). IR ν_{max}^{KBr}: 3360 cm^{-1}. NMR ($CDCl_3$) τ: 5.55 (1H, s, C_{20}–H), 5.80 and 6,12 (each 1H, d, J=5 cps, C_6 and C_7–H), 6.73 (1H, br., s, C_{15}–H), 8.97 (3H, s, C_{18}–CH_3). This NMR spectrum showed no C_{19}-methyl signal, and AB quartet signals of the methylene adjacent to the nitrogen newly appeared at 7.22 and 7.50 τ with coupling constant of 13 cps. The compound VII was oxidized to the corresponding ketone (VIII), $C_{20}H_{27}O_2N$, mp 202—204°, which showed no N–H or O–H absorption band in its IR spectrum. Therefore, one tertiary nitrogen and one ethereal oxygen are considered as functional groups.

Treatment of VII with mesyl chloride and subsequent demesylation under refluxing in pyridine, gave the N-mesyl-15-dehydroxy product (IX), $C_{21}H_{31}O_4NS$, IR ν_{max}^{KBr} cm^{-1}: 3480, 1330, 1160. NMR ($CDCl_3$) τ: 4.52 (2H, s, C_{15} and C_{20}–H), 5.70 (1H, q, J=2.5 and 8 cps, C_6–H), 6.05 (1H, d, J=2.5 cps, C_7–H), 6.78 (2H, s, C_{19}–H), 7.05 (3H, s, CH_3SO_2), 8.32 (3H, s, =C–CH_3), 8.90 (3H, s, C_{18}-t-CH_3).

The compound IX was further oxidized to the six-membered lactone (X), $C_{21}H_{29}O_4NS$, mp 235—236°. IR ν_{max}^{KBr} cm^{-1}: 1740, 1325, 1160. NMR ($CDCl_3$) τ: 4.45 (1H, s, C=CH), 6.80 and 7.00 (2H, AB, q, J=10 cps, CH_2–N), 7.05 (3H, s, CH_3SO_2), 8.30 (3H, d, J=1 cps C=C–CH_3), 8.90 (3H, s, C_{18}–CH_3). This indicates the ethereal oxygen is linked to the position C_{20} and C_7. From these facts, the structure of VII is proved unequivocally.

We propose the photolysis of a nitrone as a new method for attacking a nonactivated C–H bond. Generalization of the reaction is now in progress.

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2) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Company, Amsterdam, 1967.
3) A. Hassner and F. Boerwinkle, *J. Am. Chem. Soc.*, **90**, 218 (1968).

Table I. Photolysis of Nitrone

No.	Nitrone (mg)	Solvent (ml)	Gas	Reaction time (hr)	Yield of VII (mg)	(%)
1	55	abs. THF, 41	Ar	3	1.5	3.4
2	56	99% EtOH, 40	Ar	3	8.5	19.2
3	250	99% EtOH, 87	N_2	3	44.0	22.2
4	1003	J. P. EtOH, 75	Ar	28	216.0	27.3
5	282	J. P. EtOH, 40	N_2	28	85.0	38.1
6	900	J. P. EtOH, 70 and H_2O, 14	N_2	25	351.0	46.6
7	592	J. P. EtOH, 25 and H_2O, 25	N_2	25	112.0	23.6

10 W low-pressure lamp; in an ice bath

Yield of VII under various conditions is summarized in Table I.

The reaction is explained by the two possible mechanisms; (a) nitrene formation, insertion into C_{19}-methyl and dehydrobromination *via* α-amino alcohol, and (b) homolytic oxazilizine N–O bond fission, abstraction of C_{19}–H, and recombination, which do not conflict with the observed solvent effect (Chart 1).

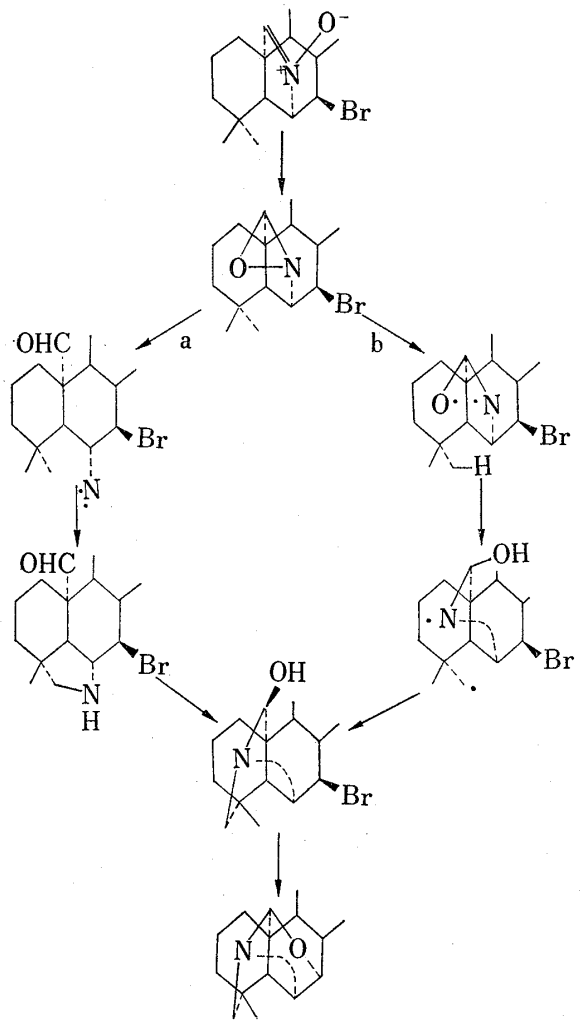

Chart 1

The compound (VII) was isomerized on heating at slightly higher temperature than its melting point to the imine (XI), mp 254—255°. IR ν_{max}^{KBr}: 1630 cm^{-1}. NMR ($CDCl_3$): 2.55 (1H, br, s, HC=N), 6.60 (2H, s, CH_2–O). 5,55 (1H, q, C_6–H) 5.95 (1H, d, J=3.5 cps C_7–H). The ring system of the imine (XI) was contracted to the gibbane skeleton by its treatment with sodium nitrite. Immediate oxidation of the products mixture with the Jones' reagent afforded XII, $C_{20}H_{26}O_4$, mp 265—268°. IR ν_{max}^{KBr}: 1735 cm^{-1}. NMR ($CDCl_3$) τ: 4.65 (1H, q, J=2 and 5 cps O–CH–O) 6.20 and 6.50 (2H, AB, q, J=14 cps, CH_2–O), and XIII, $C_{20}H_{26}O_4$, mp 205—207°. IR ν_{max}^{KBr}: 1732 cm^{-1}. NMR ($CDCl_3$) τ: 4.78 (1H, d, J=2 cps O–CH–O), 6.40 (2H, s, CH_2–O), 6.72 (1H, d, J=7.5 cps, C_{10}–H). The compounds XII and XIII were led to the corresponding 9-hydroxyl compounds (XIV and XV) by reduction with $NaBH_4$, XIV: $C_{20}H_{28}O_4$, mp 270—272°. IR ν_{max}^{KBr} cm^{-1}: 3560, 1720. NMR (d_5-py) τ: 4.35 (1H, q, J=2 and 4 cps O–CH–O), 5.75 (1H, d, J=10 cps C_9–H), 5.98 and 6.35 (2H, AB q, J=12.5 cps, CH_2–O) XV: $C_{20}H_{28}O_4$, mp 204—206°. IR ν_{max}^{KBr} cm^{-1}: 3480, 1715. NMR (d_5-py) τ: 4.6 (1H, d, J=2.5 cps), 5.64 (1H, d, J=10 cps, C_9–H), 6.15 and 6.33 (2H, AB, q, J=12.5 cps), 6.62 (1H, d, J=7.5 cps, C_{10}–H). The compound XIV was led to its mesylate (XVI), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740, 1360, 1175. NMR (d_5-py) τ: 4.47 (1H, br, s, O–CH–O), 4.97 (1H, d, J=10

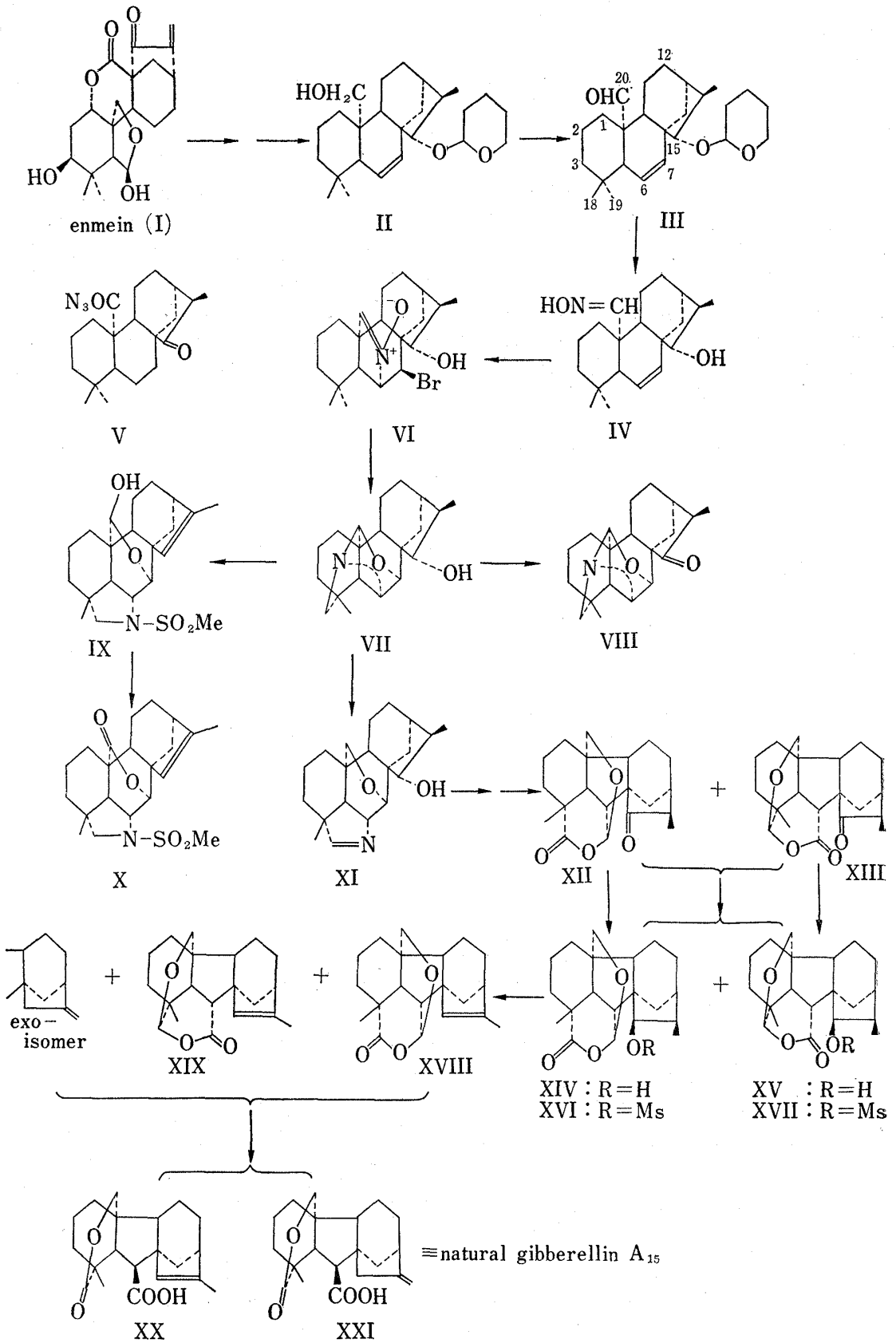

Chart 2

cps CH–OMs), 6.65 (3H, s, CH_3SO_3). XVI was demesylated by refluxing in collidine to XVIII, $C_{20}H_{26}O_3$, mp 201—203°. IR ν_{max}^{KBr}: 1745 cm^{-1}. NMR ($CDCl_3$) τ: 4.42 and 4.55 (each 1H, br., s, C_9–H and O–CH–O), 6.21 and 6.45 (2H, AB, q, J=12.5 cps), 8.30 (3H, d, J=1 cps, C=C–CH_3).

Because of the difficulty and no necessity of separation, further reactions were carried out with the mixture of XII and XIII, which was reduced, mesylated, and demesylated as mentioned above, and its NMR spectrum showed the presence of products consisting of 1:1 mixture of XVIII and XIX, and also a small amount of exo double bond isomers. The mixtire, treated with KOH in abs. diethlene glycol under refluxing, gave a mixture of the acids (XX and XXI). The NMR spectra of the acid mixture and also of its methyl esters showed signals for 2:1 mixture of XX and XXI. Among them the spectrum of XXI was identical with that of natural gibberellin-A_{15}.[4] From the acid mixture, XXI separated out from acetone–hexane as crystals and was recrystallized from acetone to prisms, mp 262—264°.

Characteristic fluorescence, thin-layer chromatogram with 10% $AgNO_3$-silica gel, ORD curve, and IR spectrum of XXI were identical with those of natural gibberellin-A_{15}, and showed no depression of mp on admixture.

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The Reactions of 4-Nitroquinoline 1-Oxide Derivatives with Nucleophiles in the Presence of Potassium Cyanide

During an investigation of reaction of 4-nitroquinoline 1-oxide derivatives,[1] it happened to be found that treatment with some nucleophiles in the presence of potassium cyanide led to formation of 4-substituted quinoline-3-carbonitrile derivatives.

When potassium cyanide (0.7 g, 0.01 mole) was added with stirring to a solution of 4-nitroquinoline 1-oxide (0.95 g, 0.005 mole) and ethyl cyanoacetate (2.2 g, 0.019 mole) in dimethyl sulfoxide (30 ml) and the whole was stirred for 6 hours at room temperature, ethyl α-(3-cyano-4-quinolyl)-cyanoacetate (I) was obtained in 27.3% yield after treatment with ice–water and 10% hydrochloric acid. Recrystallization from methanol–chloroform gave orange-red powder of mp 218° (decomp.), IR ν_{max}^{KBr} cm^{-1}: 2230, 2176 (CN), 1654 (C=O). *Anal.* Calcd. for $C_{15}H_{11}O_2N_3$: C, 67.91; H, 4.18; N, 15.84. Found: C, 67.64; H, 4.13; N, 16.03.

The structure of I was confirmed by direct comparison with an authentic sample prepared from 4-chloroquinoline-3-carbonitrile and ethyl cyanoacetate.

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