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THE CONSTITUTION AND STEREOCHEMISTRY OF ENMEIN

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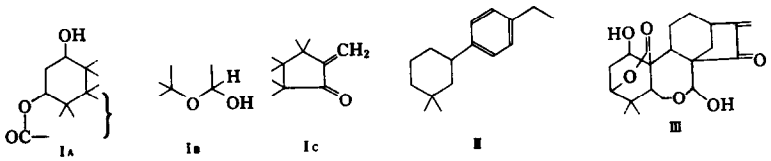
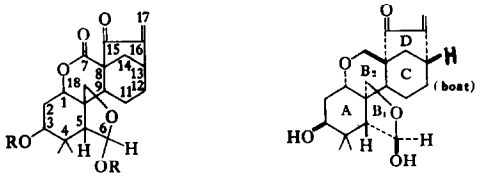
IT has already been reported that, of the six oxygen atoms in enmein[1,2] (=isodonin),[3] $C_{20}H_{26}O_6$,[3] the bitter principle of Isodon trichocarpus KUDO (Japanese name 'Enmeiso'), two form a δ-lactone, one is in the cyclohexanol system (IA),[5] two are in the hemi-acetal ring (IB),[5] and one is in α,β-unsaturated five-membered ketone system (IC).[4] Kanatomo[6] obtained 1-ethyl-4-(3,3-dimethylcyclohexyl)benzene (II), though in a poor yield, by the baryta distillation of enmein, and retene by selenium dehydrogenation of the lithium aluminium hydride reduction product of α-dihydroenmein. Based on these experimental results, Kubota and his collaborators[5] proposed the structural formula (III) for enmein in 1961.



IA Ib Ic II III

Later, however, result of chemical reactions suggested that the planar structural formula of enmein should be I with five-membered acetal ring and that its steric structure should be represented as IJ or IL. These structures conform well with the result of X-ray analysis by Iitaka and Natsume,[16] and reference to this result indicates that the steric structure of enmein should be IL.



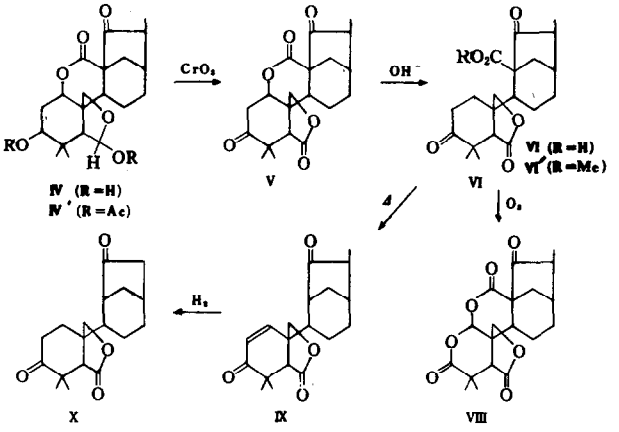
I (R=H)
I' (R=Ac)

IL

1) Nature of Ring A

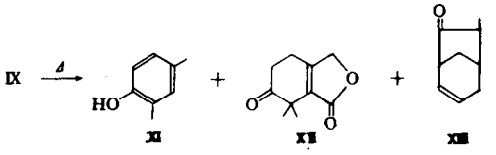
Oxidation of α-dihydroenmein (IV)[1,2,3] with chromium trioxide gives bisdehydro-α-dihydroenmein (V).[3] In contrast to the failure of IV to form a semicarbazone, V forms a monosemicarbazone. Hydrolysis of V with N/60 alkali results in the formation of an isomeric acid (VI) with consumption of 1 mole of alkali. Ultraviolet spectra of VI (λ_{max} 226 mμ) and its semicarbazone (λ_{max} 278 mμ) show the presence of -CO-CH=CH- group in VI. Hydrogenation of VI gives a dihydro compound (VII) and ozonolysis gives a nor compound (VIII), $C_{19}H_{22}O_7$, which consumes 2 moles of alkali, is positive to aldehyde color reaction, and does not show absorption of an enone group in its ultraviolet spectrum. Pyrolysis of VI results in decarboxylation to a compound (IX) of $C_{19}H_{24}O_4$ (λ_{max} 225 mμ), whose catalytic reduction

gives a dihydro compound (X). These experimental results can be explained well by assuming that enmein has a 1,3-dihydroxycyclohexane ring (A ring) and that one of its hydroxyl groups takes part in the formation of a lactone.[5]

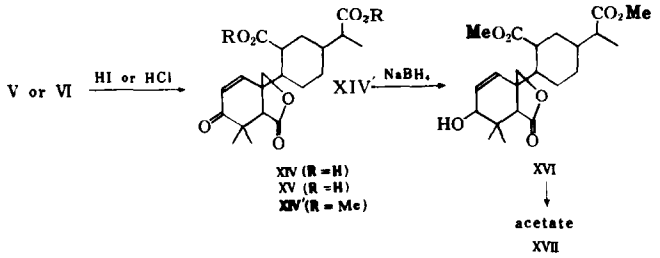


2) Nature of Rings C and D

Presence of an α,β-unsaturated ($=CH_2$) five-membered ketone ring is assumed for enmein,[1,2,3,4] and the C and D rings in enmein is thought to be a phyllocladen type from the result of the aforementioned selenium dehydrogenation and baryta decomposition. These assumptions were confirmed by the following experiments.[b] Pyrolysis of the decarboxylated compound (IX) in a sealed tube at 350-360° results in isolation of 2,4-dimethylphenol (XI) (3,5-dinitrobenzoate, m.p. 153-156°), keto-lactone (XII), m.p. 95-98°, $C_{10}H_{12}O_3$, an unsaturated ketone (XIII) (2,4-dinitrophenylhydrazone, $C_{15}H_{16}O_4N_4$, m.p. 136-140°), and the dihydro compound (semicarbazone, $C_{10}H_{17}N_3O$, m.p. 180-186°) of XIII from the reaction products. XIII was confirmed by the synthesis of its dihydro compound.

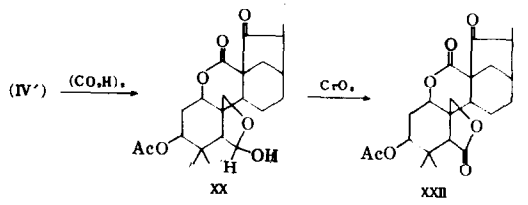


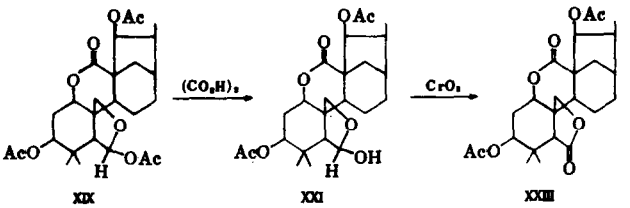
Treatment of V or VI with hydriodic or hydrochloric acid in acetic acid gives two kinds of isomeric dicarboxylic acid, $C_{20}H_{26}O_7$ (λ_{max} 228 mμ in both), one (XIV) of m.p. 302-303° (pKa_1' 6.22, pKa_2' 7.82) and the other (XV) of m.p. 268° (pKa_1' 6.20, pKa_2' 7.85). This reaction may be explained as the cleavage of the D ring by acid decomposition of β-ketocarboxylic acid.[a)]



3) Nature of the Hemiacetal Ring (Ring B_1)

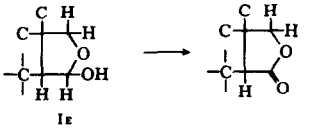
Kubota and other[(5)] assumed that this hemiacetal ring is seven-membered (III) but this did not satisfy the infrared absorption data of various derivatives of enmein. For example, hydrolysis of dihydroenmein diacetate (IV') or tetrahydroenmein triacetate (XIX) with oxalic acid results in the hydrolysis of the acetyl group in hemiacetal alone, and the lactones (XXII and XXIII), obtained by oxidation of XX and XXI, exhibit absorption at 1780 cm^{-1} region in their infrared spectra, indicating the formation of a five-membered lactone ring.[a)]





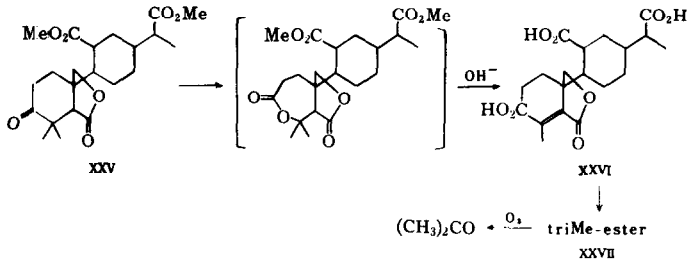
Infrared spectra of all the derivatives in which this kind of a five-membered lactone ring is considered to be still present show absorption at 1780 cm^{-1} region so that the hemiacetal ring (ring B_1) must be five-membered.[a,b,c]

NMR spectra[a,b,c] (cf. Table 1) of enmein diacetate (I') (τ 3.85) and dihydroenmein diacetate (IV') (τ 3.84) show sharp singlet of hydrogen in $-CH\langle^{O-}_{O-}$, while those of dihydroenmein monoacetate (XX) and O-methyldehydrodihydroenmein (XXIV)[5] show weakly split (J=2 c.p.s.) absorption at τ 5.28. These facts indicate the presence of one hydrogen atom (dihedral angle of two hydrogen atoms is close to 90°) whose steric configuration does not allow its coupling with the adjacent proton $-CH\langle^{O-}_{O-}$. This fact is also understood from the presence of a singlet of one proton at τ value (6.80-7.53) corresponding to -CH-CO-O- in the compounds (VI', XIV', XVII, XXII, XXV) formed by oxidation of the hemiacetal. Naturally, absorption corresponding to $-CH\langle^{O-}_{O-}$ has disappeared in these compounds. On the other hand, C_{18}-H_2 (τ around 5.8) is a typical AB type, as seen in XXIV, XXV, XXVII, XIV' and XVII, forming two pairs of doublet ($J\approx10$ c.p.s.). Appearance as a singlet in I', IV', VI' and XXI is probably the result of chemical shift of two protons becoming equal by chance.[7] Considering these facts, the structure of B_1 ring can be extended to IE.



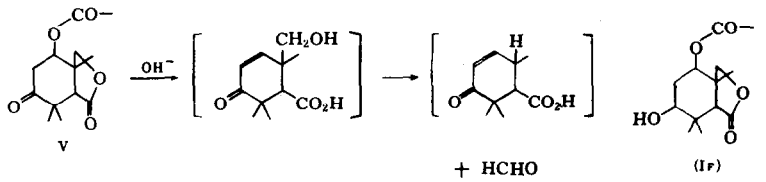
4) Presence of gem-Dimethyl and the Relation of Ring A to Ring B

The dimethyl ester (XXV) of the dihydro compound, obtained by catalytic reduction of XIV, when oxidized with perbenzoic acid in the presence of a minute amount of p-toluenesulfonic acid and subsequent treatment with dilute alkali, produces a crystalline acid (XXVI), $C_{20}H_{28}O_8$.[a] The ultraviolet (λ_{max} 236 mμ) and infrared spectra of the trimethyl ester (XXVII) of XXVI suggest that tetrasubstituted double bond is conjugated with the carbonyl of a γ-lactone.[8] Chemical shift of the methyl proton in the NMR spectra of XXV ⟶ XXVII indicates that the gem-dimethyl in XXV has changed to isopropylidene in XXVII, which is conjugated with lactone carbonyl in s-cis form. The presence of isopropylidene group was confirmed by the formation of acetone



by ozonolysis of XXVII.[a] The existence of gem-dimethyl is also shown by the fact that dimethyl malonic acid is obtained from the permanganate oxidation products of IX.[b] The presence of gem-dimethyl group in enmein itself can be assumed from its infrared absorptions[9] (1370 and 1392 cm^{-1} in KBr).

Treatment of V with 1N alkali results in the formation of formaldehyde.[c] The same treatment of VI and IX gives formaldehyde[a] but it is not formed by treatment of α-dihydroenmein (IV) and the saturated compound (X) of IX.[c] This reaction may be considered as elimination of primary alcohol at C-18 by retro-aldol reaction, as shown below.



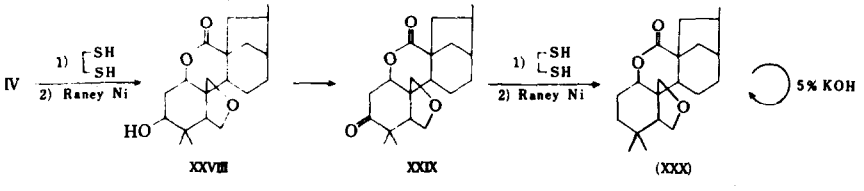
V (IF)

These experimental results show that the rings A and B_1 would be in relative positions shown by the formula IF.

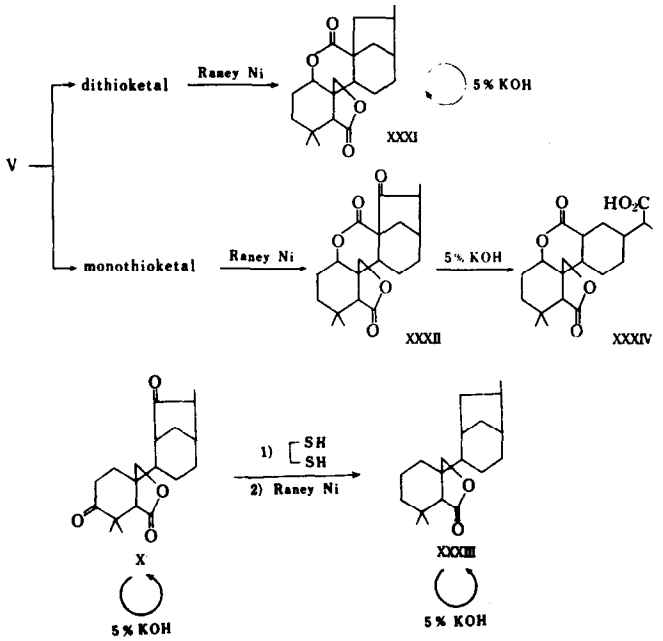
5) Relation of Rings C and D to Ring B_2

It is easy to presume that the carbonyl of δ-lactone in the partial structural formula (IF) is the carbonyl in β-position of the ketone group in ring D (cf. section 2) and this was confirmed by the following experiment.[b] Desulfuration of monothioketal of IV with Raney nickel results in concurrent reduction of the acetal-hydroxyl to form hydroxy-monolactone (XXVIII). Oxidation of XXVIII to XXIX, its derivation to monothioketal again, and its desulfuration gives a monolactone (XXX), $C_{20}H_{30}O_3$.

Dithioketal and monothioketal are obtained from V and desulfuration of these two thioketals respectively gives a dilactone (XXXI), $C_{20}H_{28}O_4$, and monoketodilactone (XXXII), $C_{20}H_{26}O_5$. Similar treatment of X gives a monolactone (XXXIII), $C_{19}H_{30}O_2$. When these compounds are refluxed with 5% potassium hydroxide, XXXII alone undergoes acid hydrolysis and forms XXXIV, while other compounds, XXX, XXXI, X and XXXIII, are all recovered unchanged.



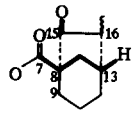
XXVIII XXIX (XXX)



These experimental results indicate that the group adjacent to C and D rings is not the γ-lactone ring but a δ-lactone ring, and it may be concluded that the planar structure of enmein is represented by I.

6) Stereochemistry of Enmein

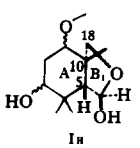
(i) C-D Ring From the structure of C and D rings, the linkage between C_8-C_{15} and C_{13}-C_{16} can take only cis and the diaxial configuration. Takahashi and others[4] reported that the optical rotatory dispersion curve of α-dihydroenmein (IV) shows a negative Cotton effect and, with reference to the report of Kline,[10] C and D rings of IV must be indicated by the absolute configurational formula (IG), same as that of phyllocladen.[11] It follows, therefore that the C_7-C_8 linkage is equatorial to the C ring.



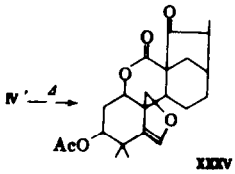
Ig

(ii) A-B Ring It was shown in the foregoing section (3) from consideration of NMR spectra that the small value of the coupling constant of C_6-H and C_5-H (0 or 2 c.p.s.) suggests the dihedral angle of these two hydrogen atoms to be about 90°. For the hydrogen atoms to take this configuration, A-B ring must be in cis bonding, C_{10}-C_{18} bonding must be axial to A ring, and C_5-C_6 must be equatorial.

The foregoing facts are not inconsistent with the relationship between C_6-OH and C_5-H. Pyrolysis of α-dihydroenmein diacetate (IV') results in facile deacetylation and an enol ether (XXXV) is formed.[b] This indicates that C_5-H and C_6-OH are in syn-parallel (cis elimination) and, therefore, A-B ring must be represented as IH or its enantiomer. This in turn would indicate that C_9-C_{10} linkage is equatorial to the A ring and C_5-H would be axial.



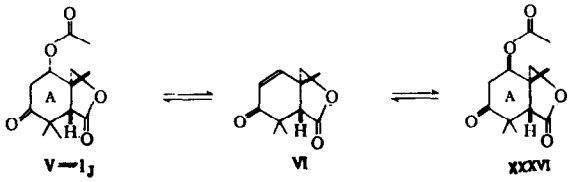
Ih



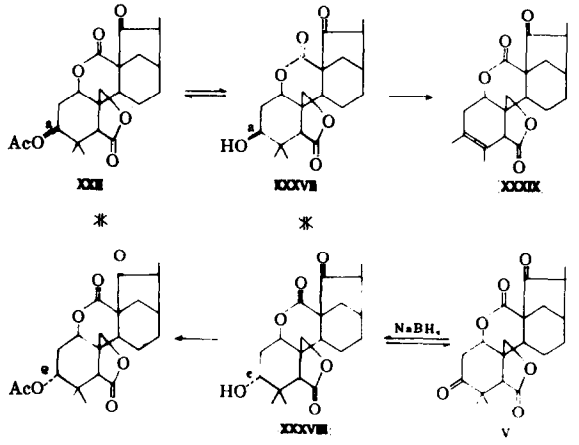
XXXV

(iii) δ-Lactone[a] Application of hydrogen bromide to bisdehydro-α-dihydroenmein (V) in acetic acid gives, besides the acid (VI) and recovered V, a neutral substance (XXXVI), $C_{20}H_{24}O_6$, which produces the same acid (VI) as that formed from V by the action of dilute alkali. This fact shows that V and XXXVI are epimers in relation to C_1 (OH of δ-lactone). That these three substances are in equilibrium is clear from the formation of V, VI and XXXVI in 14:21:30 ratio (total yield, 65%) by the treatment of VI with boron trifluoride. Isomerization of V and XXXVI to VI by the ap-

plication of 0.5 equivalent of alkali and examination of its rate through ultraviolet spectrum shows that the isomerization rate of the XXXVI is about twice that of V. This fact indicates that the alcoholic hydroxyl in C_1 formed from the lactone is equatorial to the A ring in V (IJ or its antipode) and axial in XXXVI. Consequently, hydroxyl group in the δ-lactone of enmein is equatorial to the A ring.



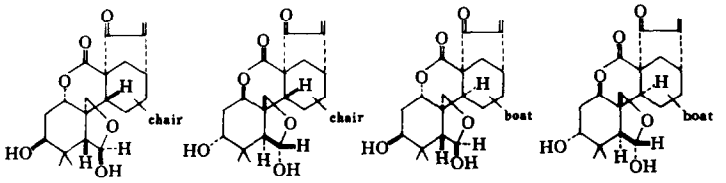
(iv) C_3-Hydroxyl Chromium trioxide oxidation of α-dihydroenmein monoacetate (XX) and hydrolysis of its product, dilactone acetate (XXII), with dilute acid or dilute alkali gives dehydrodihydroenmein (XXXVII), m.p. 272°, $C_{20}H_{26}O_6$, which reverts to XXII on acetylation, showing that the configuration of its C_3 position is the same as that of enmein. On the other hand, reduction of bisdehydro-α-dihydroenmein (V) with sodium borohydride gives only XXXVIII, m.p. 297-300°, $C_{20}H_{26}O_6$, an isomer of XXXVII.



XXXVII and XXXVIII forms V on oxidation with chromium trioxide, showing that they are isomers relative to C_3-OH. The same thing can be seen with dehydrotetrahydro-enmein series. It is known generally that equatorial hydroxyl is formed chiefly by the reduction of unhindered ketone with sodium borohydride,[12] so that the hydroxyl in XXXVIII is equatorial and that in XXXVII is probably axial.[a,b,c]

Solvolysis of the mesylate of XXXVII with acetic acid,sodium acetate under drastic conditions results in the formation of 3,4-dimethyl-$\Delta^{3,4}$ compound (XXXIX) with rearrangement of the methyl group.[c] This fact also suggests axial configuration for the C_3-OH.

(v) C_9-C_{10} Linkage Molecular model of enmein based on foregoing facts shows that both the chair and boat forms are possible for the C ring but a more stable conformation can be obtained when the C ring is in a chair form and C_9-C_{10} linkage is equatorial (IJ or IK), and when the C ring is in a boat form and C_9-C_{10} linkage is equatorial (IL and IM). Consequently, four formulae, IJ to IM, are possible for the steric structure of enmein.



I_J I_K I_L I_M

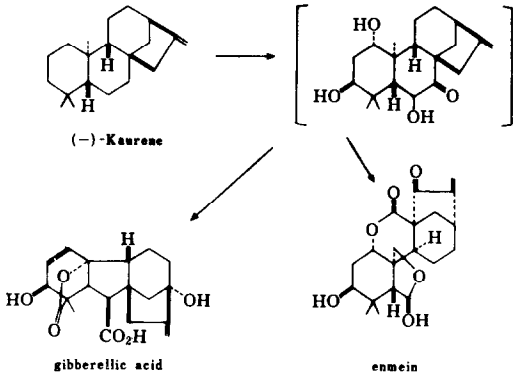
(vi) Absolute Configuration In order to determine whether the structure of enmein should be IJ or IL, or IK or IM amount the four possible formulae, the atrolactic acid method of Prelog[13] was applied to dehydro-a-dihydroenmein (XXXVII).[a] Formation of dextrorotatory atrolactic acid, $[\alpha]_D$ +9.2° (24% excess), showed that the structure of enmein should be IJ or IL.

Iitaka and Natsume[16] had concluded from the X-ray analysis of the

monobromoacetate of α-dihydroenmein monoacetate (XX) that the structure of enmein should be II. or its antipode so that the absolute configuration of enmein should be represented by II.

7) Biogenesis

Enmain, from its structure, may be considered as a diterpene of (-)-kaurene homolog[14] and it is the first example of naturally occurring diterpenes formed by the cleavage of carbon linkage in the B ring. Birch and others[15] assumed that the B ring of gibberellic acid was formed by the Favorskii rearrange of its precursor α-hydroxy-ketone or the benzilic acid rearrangement of α-diketone, and it may also be assumed in the case of enmein that it was formed by the oxidative cleavage of the B ring in its precursor, 6-hydroxy-7-ketone.



								the others
(I')	8.94(s)	8.80 (sholder)	5.93(s)	5.10(t?) 5.40(m)	3.85(s)	---	---	3.92(s) 4.47(s)
(IV')	8.94(s)	8.86(d) (J=9)	5.94(s)	5.11(t?) 5.34(q?)	3.84(s)	---	---	-OAc 7.89(s) 7.98(s)
(XX)	9.00(s)	8.88(d) (J=6.5)	6.02(s)	5.15(m) 5.40(m)	4.62(d) (J=2.0)	---	---	-OAc 7.90(s) -OH 7.10(s)
(XXII)	8.83, 8.87, 8.80		5.72 two pair(d)	4.93(t?) 5.31(q?)	---	7.50(s)	---	-OAc 7.85(s)
(XXIV)	8.83(s)	8.77(d) (J=8)	5.94(d) 6.10(d)	4.93(m)	5.28(d) (J=2)	---	---	-OMe 6.68(s)
(VI')	8.60(s) 8.71(s)	8.87(d) (J=7)	5.80(s)	---	---	6.80(s)	3.24(d) 3.92(d) (J=11.4)	-COOMe 6.22(s)
(XIV')	8.57(s) 8.83(s)	8.90(d) (J=8)	5.62(d) 5.87(d) (J=11.4)	---	---	7.22(s)	3.63(d) 4.08(d) (J=11.4)	-COOMe 6.32(s) 6.47(s)
(XVII)	8.71(s) 9.03(s)	8.91(d) (J=7)	5.79(d) 6.05(d) (J=10)	4.76(q) (Jα=2.5) (Jβ=1.5)	---	7.53(s)	4.55(t)	-COOMe 6.32(s) 6.37(s) -OAc 7.87(s)
(XXV)	8.67(s) 8.71(s)	8.89(d) (J=7)	5.75(d) 6.08(d) (J=10)	---	---	7.44(s)	---	-COOMe 6.32(s)
(XXVII)	7.73(s) 8.05(s)	8.70(d) (J=7)	5.67(d) 6.28(d) (J=12)	---	---	---	---	-COOMe 6.35(s) (6H) 6.46(s) (3H)

Table 1. NMR Spectra (τ value, p.p.m.)

Solvent : $CDCl_3$ Internal standard : TMS J=(c.p.s.)

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