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Revisit to the Samek Rule. A Comparative Study on Lactone Configurations by Synthesis, NMR, and MM2

Motoo TORI, Shin YOSHIMURA,+ Chiaki KURODA,++ and Yoshinori ASAKAWA*

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770
+Department of Chemistry, College of Arts and Science, The University of Tokyo, Komaba, Meguro-ku, Tokyo 153
++Department of Chemistry, St. Paul's (Rikkyo) University, Nishi-Ikebukuro, Toshima-ku, Tokyo 171

Steric energy and the conformation of nepalensolide A and frullanolide, having the *cis* lactones, and four types of possible model lactones as well as some synthetic compounds are calculated by MM2 and the allylic coupling constant of the exomethylenes are estimated to discuss the Samek rule.

The *cis/trans* lactone rule for α-methylene-γ-lactones, reported by Z. Samek in 1970, is now known as "Samek rule", which is used frequently and guides a stereochemistry of fused lactones.[1] The stereochemistry can be assigned by measuring the value of the coupling constant between the exomethylene protons and the allylic proton. It was originally reported as follows:[1] /4J/(*trans*-lactone) $\geqq$ 3 Hz $\geqq$ /4J/(*cis*-lactone) However, exceptions to the above rule have been found since it was reported, especially in the case of pseudoguaianolides.

As we have discovered a new lactone, nepalensolide A (1), and found that this compound is not in accordance with this rule.[2] The most stable conformation of 1 as well as some synthetic lactones were estimated by MM2. We now report the results of the comparative study on lactone configurations.

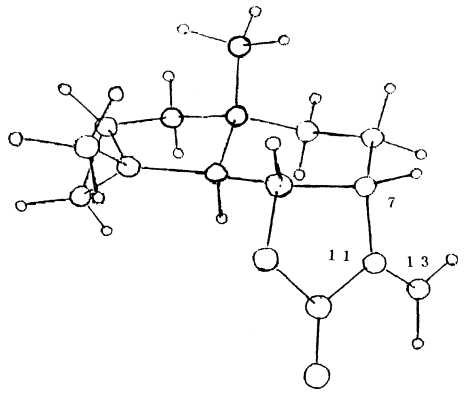
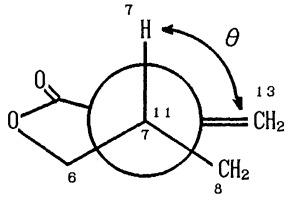


Fig.1. Calculated conformation of nepalensolide A (1). The enantiomer is shown tentatively.

We have isolated and established the structure of nepalensolide A (1) without any doubt, which did not follow the Samek rule.[2] This example was the first one, as the 6/6 membered α-methylene-γ-lactone (eudesmanolide), not to follow the rule. We calculated the steric energy of 1 and found that this molecule adopts a conformation to keep the dihedral angle (H_7-C_7-C_{11}-C_{13}) 91.2° as shown in the Fig.1.[3] The allylic coupling constant is generally between 1.3 and 3.1 Hz at $60° \leqq \theta \leqq 110°$ and is reported to depend upon the dihedral angle between the exomethylene protons and the allylic proton as shown in the Fig.2.[4] This is why the cis-lactone 1 exhibits relatively large coupling constants. Although the conformation to adopt the



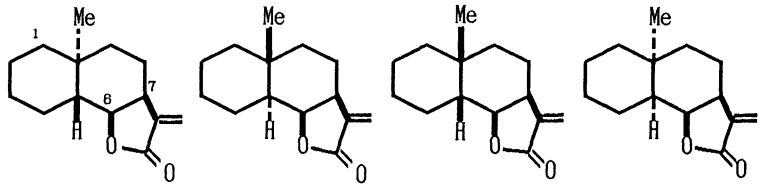
$J=1.3-3.9\sin^2\theta$ ($0 \leqq \theta \leqq 90°$) and $-2.6\sin^2\theta$ ($90° \leqq \theta \leqq 180°$)

Fig.2. The dihedral angle θ.

dihedral angle *ca.*30° is possible (expected value 0.3 Hz), the steric energy is much higher than the most stable one from MM2 calculation. We then calculated the steric energy of the four types of *cis* model lactones depicted in the Fig. 3 and estimated the conformation of the lactone rings. The figures show the dihedral angles between the exomethylene and the proton at the 7 position, which correspond to allylic coupling constants (in the parentheses). In the case of 6B, the coupling constant is inferred to be small, as shown by the rule. However, the other cases show relatively large coupling constants as *cis* fused lactones, although they are still smaller than 3 Hz. The synthetic compound 7 (type 6B)[5] shows small coupling constants (1.5 and 1.0 Hz) as predicted by the rule. However, compound 6 (type 6A)[5] has large coupling constants (2.9 Hz) as suggested by the calculation. Brothenolide (2), isolated from the liverwort *Frullania brotherii*, shows $J_{7,13}=0.6$ Hz, suggesting the *cis* fused ring due to the rule.[6] This was unambiguously confirmed by chemical degradations and partial synthesis.[6] The structure of frullanolide (3),[7] isolated from the liverwort *Frullania dilatata*, was established as depicted in the Fig. 4 and the coupling constant, $J_{7,13}=2$ Hz, was observed, relatively large but still following the rule. The conformation of frullanolide (3) was then calculated and the value of allylic coupling constant was estimated to be 0.9 Hz (49.2°). Since (+)-β-frullanolide (5)[7] belongs to type 6B, the coupling constants were also small following the Samek rule. These results show that calculations can predict the most stable conformation and receive validity, although these results only show an ideal model. In the actual cases, there

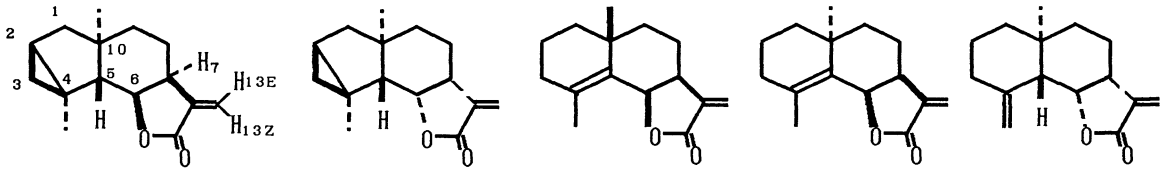
are a lot of factors, such as other functional groups, hydrogen bonds etc.[3]

We then synthesized the isomer of frullanolide, 4, having the opposite configuration (but still *cis*-lactone) of the lactone ring.[8] The coupling constant between H-7 and H-13 were 2.6 and 2.3 Hz, showing relatively large values. The MM2 calculation shows that the dihedral angle of this compound is 82.3° (2.5 Hz). This case again shows relatively large values.



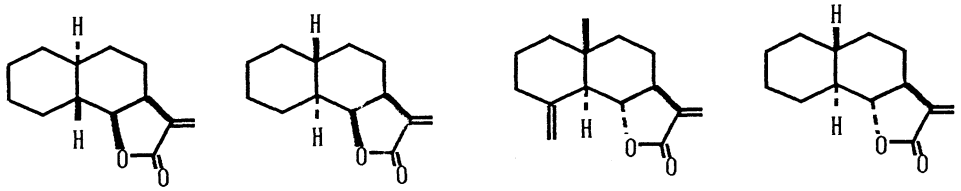
type	6A	6B	6C	6D
Samek rule	J<3	J<3	J<3	J<3
Dihedral angle calcd by MMP2 (coupling const.)	83.7° (2.5 Hz)	48.0° (0.85 Hz)	84.0° (2.6 Hz)	83.9° (2.6 Hz)

Fig.3. Calculated data for 6A-6D.



(+)-nepalensolide A (1) (+)-brothenolide(2) (-)-frullanolide(3) 4 (+)-β-frullanolide (5)

type	6A	6B	-	-	6B
Samek rule	J<3	J<3	J<3	J<3	J<3
Observed δ (J)	5.47(d,3.3)	5.52(d,0.6)	5.60(d,2)	5.33(d,2.3)	5.52(d,0.6)
	6.26(d,3.3)	6.09(d,0.6)	6.18(d,2)	6.19(d,2.6)	6.07(d,0.6)
Calculated	91.2° (2.6 Hz)	-	49.2° (0.9 Hz)	82.3° (2.5 Hz)	-



	6	7	8	9
type	6A	6B	-	-
Samek rule	J<3	J<3	J>3	J>3
Observed δ (J)	5.47(d,2.9)	5.50(d,1.0)	5.38(d,3)	5.37(d,3.4)
	6.27(d,2.9)	6.06(d,1.5)	6.00(d,3)	6.06(d,2.9)

Fig.4. Data for natural and synthetic lactones.

The natural compound 8[9] as well as the synthetic compound 9[5] having the *trans* lactone clearly show the larger coupling constants (3 Hz for 8 and 3.4 and 2.9 Hz for 9, respectively), although we have not studied *trans* lactones in detail yet.

This study clearly shows that when we use the Samek rule, a great care should be given, especially when we isolate a compound having the types 6A, 6C, and 6D. We have to think about the molecular conformation and predict the coupling constants. When two conformations are possible, we have to use another method to determine the structure, for instance NOE, as demonstrated in the previous paper.[2]

References

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2)Refer to the previous paper.

3)MM2 calculations were carried out in the University of Tokyo and some parameters were substituted by similar functional groups.

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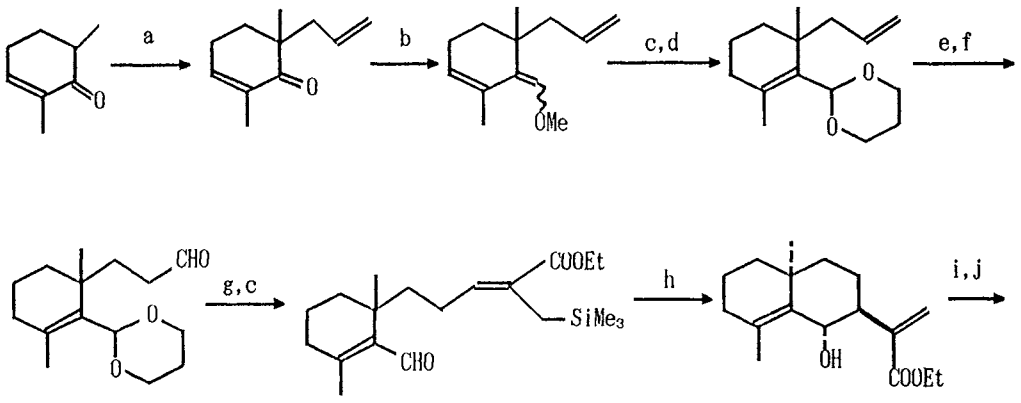
8)This compound was synthesized as follows[5] and the configuration was confirmed by NOE experiments.[5]



a)LDA/$BrCH_2CH{=}CH_2$; b)$Ph_2(O)CH_2OCH_3$/LDA; c)H^+; d)$HOCH_2CH_2CH_2OH$/PPTS; e)Sia_2BH, H_2O_2/NaOH; f)PDC; g)$(EtO)_2P(O)CH(COOEt)CH_2SiMe_3$/NaH; h)$^nBu_4NF$; i)$HO^-$; j)$[Me_2NClNMe_2]^+Cl^-$

9)G. W. Perold, J. -C. Müller, and G. Ourisson, *Tetrahedron*, **28**, 5797 (1972).

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