DETERMINATION OF THE STEREOSTRUCTURE OF THE δ-LACTONES OF 5,7-DIHYDROXY-2,3-UNSATURATED ACIDS BY $^1$H NMR SPECTROSCOPY

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The stereostructures of the syn- and anti-δ-lactones of 5,7-dihydroxy-2,3-unsaturated acids were assigned by a structure-specific $^1$H NMR splitting pattern of the C-4 protons of the corresponding acetate.

KEYWORDS — stereostructure determination; δ-lactone of 5,7-dihydroxy 2,3-unsaturated acid; syn-, anti-isomer; $^1$H NMR; structure-specific splitting pattern

Recently, the optically active δ-lactones, 5,7-syn-1 and 5,7-anti-isomer 2, were synthesized by a strategy for 1,3-polyol synthesis.1) The $^1$H NMR spectrum of the former proved to be identical with that of (-)-tarchonanthuslactone. Thus, the relative and absolute configurations of the natural lactone were established as shown in structure 1. During the comparison studies using the $^1$H NMR (400 MHz) technique, we found that the splitting pattern of the C-4 and C-6 protons of 5,7-syn-1 was clearly different from that of 5,7-anti-2 (Fig. 1).

To examine whether a similar spectral pattern difference is observed in other isomer pairs of this type, we synthesized several stereochemically well-defined C-7 mono- and C-7,9 diacetates (3 ~ 10) by an authenticated method.2,3) On comparison of their $^1$H NMR spectra, all of the 5,7-syn- and anti-isomers examined proved to have characteristic splitting patterns similar to 1 and 2, respectively.4)
The $^1$H NMR spectra (400 MHz) of the C-4 protons of the synthetic 6-lactones are shown in Fig 2. Two protons at C-4 in the 5,7-syn-lactones appeared separately at $\delta$ 2.29~2.33 and 2.45~2.53 with each dddd splitting pattern, while the protons of 5,7-anti-lactones appeared overlapped at ca. $\delta$ 2.35. These results show that the pattern strongly depends on the relative configuration at C-5 and C-7 but is not affected by the configuration at the other positions. As for the C-6 protons, the spectral characteristic of $\underline{3}$ and $\underline{4}$ holds well for 3, 4 and for 5, 6, respectively. However, the signals of these protons in the diacetoxy lactones (7~10) overlapped those of other protons (acetyl and/or methylene protons). So the use of the spectral pattern of C-6 protons for structural study is rather limited.

The chemical shifts of the acetyl groups of the above stereoisomers are shown in Table I. It is noteworthy that signals of the acetyl groups of 5,7-syn-isomers 3, 4 appeared at a slightly lower field than those of anti-isomers 5, 6, respectively. The same trend appeared in the chemical shifts of 7,9-syn- and anti-isomer pairs (7/8 and 9/10).

Clearly the present findings serve as a very simple and reliable method for determining the relative configuration at C-5 and C-7 of the naturally occurring $\alpha,\beta$-unsaturated 6-lactones having a functionalized side chain of unknown configuration. The method's applicability was confirmed in the following cases. The absolute stereostructures of (+)-cryptocaryalactone and ACRL Toxin I was
recently determined to be 5,7-anti-11 and 10,12-syn-12, respectively, by physicochemical methods. The reported NMR data of the C-4 protons of anti-acetate 16b,8) and the C-13 protons of syn-acetate 17b) show the characteristic patterns for 5,7-anti- and 10,12-syn-compounds, respectively. Thus, the above spectral trends for determining the relative configurations were found to hold well even for compounds having double bonds on the side chain and/or a methoxy group on the lactone ring.

The spectral pattern and the chemical shift of the C-4 protons of 14 having no oxygen function at the C-7 position are similar to those of 5,7-anti-isomers (5, 6, 9, and 10). This shows that the acyloxy group at the C-7 position in these isomers should be located far from the C-4 protons in the preferred conformation, while in the 5,7-syn-isomers (3, 4, 7, and 8), 4a(equatorial)-H is apparently shifted to a lower field influenced by the near-by acyloxy group at the C-7 position. The structure of the preferred conformers should serve to rationalize the observed structure-specific spectral pattern at the C-4 and C-6 protons. Examination of the preferred conformation of these isomers is in progress.

Other special cases where the present findings are effectively used for elucidation of stereostructure of natural lactones will be reported elsewhere. Furthermore, based on the above structure-specific 1H NMR spectra, development of a general method for determination of the stereostructure of the 1,3-polyol system is now being investigated in our laboratory.

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REFERENCES AND NOTES
3) The stereoisomers (3~10) were synthesized based on the synthetic method for
1,3-syn- and anti-polyol as shown below. Alcohols 16 and 18 were prepared from cetyl alcohol. See, reference 1.

\[
\text{3, 4} \quad \text{OH} \quad \text{COOMe} \\
\text{3: } R=\text{Me} \\
\text{4: } R=\text{C}_{15}H_{31}
\]

\[
\text{15: } R=\text{Me} \\
\text{16: } R=\text{C}_{15}H_{31}
\]

\[
\text{19: } R=\text{C}_{15}H_{31}
\]

\[
\text{21: } R^*=\text{PrPh}_{2}Bu \\
\text{22: } \text{COOSiBu}_{2} \\
\text{23: } R^*=\text{PrPh}_{2}Bu \\
\text{24: } \text{COOSiBu}
\]

\[
\text{7, 9} \\
\text{8} \\
\text{10}
\]

a) 1N HCl/THF; NaBH4/MeOH/THF; CSA/PhH; Ac2O/DMAP/Py/CH2Cl2; DBU/PhH, b) HS(CH2)3SH/ BF3Et2O/CH2Cl2; c) t-BuPh2SiCl/imidazole/DMF; LDA/MeCOO-t-Bu/THF; CH(OMe)3/CSA/MeOH/CH2Cl2; NBS/AgNO3/Na2CO3/aq MeCN; n-Bu4NBH4/aq THF, d) 1N HCl/THF; NaBH4/MeOH/THF; CSA/PhH; n-Bu4NF/THF; Ac2O/DMAP/Py/CH2Cl2; DBU/PhH.

4) In the corresponding C-7 hydroxy compounds, there was no spectral pattern difference between the syn- and anti-isomers.

5) In the case of 5,7-syn-3, signals centered at δ 2.33 and at δ 2.46 were assigned as C-4 axial and equatorial protons, respectively, since the coupling constant between the C-4 and C-5 protons in the former was found to be 12 Hz and that in the latter, 6 Hz by an extensive decoupling experiment. 5,7-syn-3: δ 2.33 (dddd, J4,4 = 18 Hz, J3,4 = 12 Hz, J2,4 = J4,5 = 2 Hz; 4-H), 2.46 (dddd, J4,4 = 18 Hz, J4,5 = 6 Hz, J2,4 = 4 Hz, J3,4 = 1 Hz; 4a-H).


8) Both anti-acetate 11 and syn-acetate 25 were synthesized for comparison in this laboratory. The \(^1H\) NMR (400 MHz) data of synthetic 11 were identical with those of natural 11. The C-4 protons of syn-25 exhibit a typical splitting pattern for 5,7-syn-compounds.

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