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# ASSIGNMENT OF ABSOLUTE CONFIGURATION OF 2-SUBSTITUTED-1-PROPANOLS BY $^1$H NMR SPECTROSCOPY

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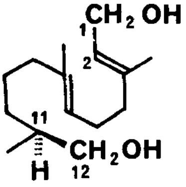
Summary: $^1$H NMR coupling pattern of α-methylene group in the MTPA esters of the title compounds has been successfully correlated to the absolute configuration of the original alcohols.

In the course of continuing studies of sesquiterpene oligosaccharides, Mukuroziosides, we have found that $^1$H NMR signal of $C_{12}$-methylene proton for the diastereomeric pairs of (R)- and (S)-MTPA[α-methoxy- α-trifluoromethylphenyl acetic acid]$^{1)}$ esters of Mukurozidiol(1) appears as distinctly different coupling pattern('doublet' vs. 'multiplet').



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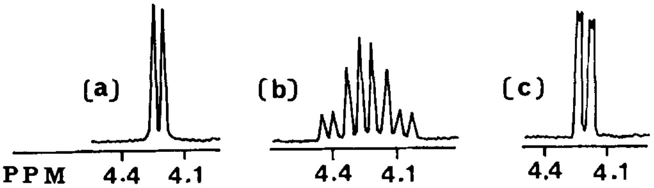
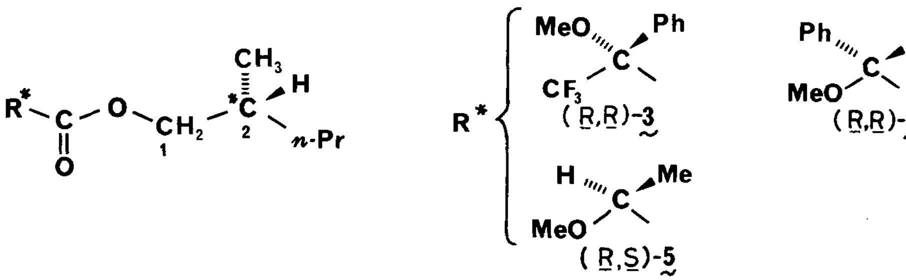


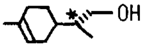
Fig. 1 Coupling pattern difference of $C_9$-methylene signals of diastereomeric (R)- and (S)-MTPA esters of 14. (90 MHz).

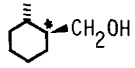
In order to examine a usefulness and a limitation of this coupling pattern difference for determining absolute stereochemistry of primary alcohols with chiral center at the $C_2$-position, we have carried out extensive investigation for various types of substrates. As shown in Fig. 1[(a),(b)], $C_9$-methylene signals for diastereomeric (R)- and (S)-MTPA esters of p-1-menthen-9-ols(14) appear as 'doublet'[(R,8S) pair, AA' part of AA'X pattern, $\delta_A \fallingdotseq \delta_{A'}$, $\delta_A$= 4.24 ppm] and 'multiplet'[(S,8S) pair, AB part of ABX pattern, $\delta_A$=4.36, $\delta_B$=4.14 ppm], respectively. The presence of additional chiral center(S) in $R_1$, $R_2$ does not interfere with the application of this method(13~17, 19~21). The method is accessible for the compounds carrying cycloalkyl ring(e.g. 13, 14, 16, 17) for which MTPA/LSR method$^{2)}$ gave an ambiguous result because of small lanthanide induced shift difference($\Delta \mathrm{LIS}_{\mathrm{OMe}} \leqq 0\sim0.2$).$^{3)}$ The presence of Ph group in the chiral auxiliary(R*CO group) plays an important role for the observed coupling



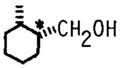
pattern difference, since (i) a reversal of the correlation scheme [(R,R):'d', (R,S):'m'] is observed for OMe-mandelate(4) in which the phenyl group is $\alpha$-oriented in its preferred conformation,[1)] and (ii) the coupling pattern difference disappears when $R^*CO$ group is replaced by OMe lactic acid moiety(5)[(R,R):'m', (R,S):'m'].

Table 1. $^1H$ NMR Coupling Pattern[a] of $\alpha$-Methylene Proton for (R)-,(S)-MTPA-$OCH_2CH\langle^{R_1}_{R_2}$ , 4 and 5.

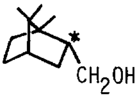
| Compound | $R_1$ | $R_2$ | (R,R) pair | (R,S) pair |
|---|---|---|---|---|
| 1 | Mukurozidiol | | 'm' | 'd',(S)-(-)[MeOH][f,g] |
| 2 | Me | Et | 'm' | 'd' |
| 3 | Me | n-Pr | 'm' | 'd' |
| 4 | Me | n-Pr[b] | 'd' | 'm' |
| 5 | Me | n-Pr[c] | 'm' | 'm' |
| 6 | Me | n-Bu | 'm' | 'd' |
| 7 | Me | t-Bu | 'm' | 'm' |
| 8 | Me | Ph | 'm' | 'm' |
| 9 | Me | COOMe[d] | 'dd'[e] | 'm' |
| 10 | Me | n-$C_8H_{17}$ | 'm' | 'd' |
| 11 | Me | n-$C_{12}H_{25}$ | 'm' | 'd',(R)-(+)[MeOH][f] |
| 12 | Et | n-Bu | 'd' | 'd' |
| 13 |  | | 'm' | 'd' |
| 14 |  | | 'm' | 'd' |
| 15 |  | | 'm' | 'dd'[e],(S)-(+)[MeOH][f] |



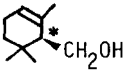
(R,S):'d',(S,S):'m'
(S)-(+) [MeOH][f]
16



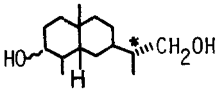
(R,R):'m',(S,R):'d'
(R)-(+) [MeOH][f]
17



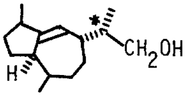
(R,R):'d',(S,R):'d'
18



(R,S):'m',(S,S):'d'[d]
19



$(OH)_{ax}$: (R,R):'m',(S,R):'dd'[e]
$(OH)_{eq}$: (R,R):'m',(S,R):'dd'[e]
20



(R,S):'d',(S,S):'m'
(S)-(+) [MeOH][f]
21[h]

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[a] Spectra were measured on Hitachi R-90H(90M Hz) in $CDCl_3$(35°C). [b] OMe mandelate. [c] OMe lactate. [d] (R,R) pair is configurationally related to the other (R,S) one. [e] A doublet accompanied by small split[Fig.1(C)]. [f] These configurations were assigned based on the present method. [g] O. Tanaka et al., Phytochemistry, 25, 871(1986). [h] Derived from (+)-$\gamma$-Gurjunene via hydroboration.

Although there are several cases which do not follow this correlation scheme(7, 8, 12, and 18) and a role of the phenyl group in the $R^*CO$ moiety remains to be clarified, the present method will offer a simple and a convenient procedure for determining absolute configuration of 2-substituted-1-propanols and their related compounds, so far as the $\alpha$-methylene signal appears as a distinctly different coupling pattern.

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