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A simple ^{13}C NMR method for determination of the relative stereochemistry of 2,3-dialkylpentenoic acids and related compounds

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Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

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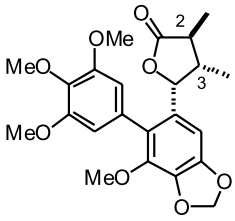
Abstract—The relative stereochemistry of 2,3-dialkylpentenoic acids and derivatives thereof can be easily determined by comparison of ^{13}C NMR spectra of the *syn* and *anti* isomers. The chemical shifts of several of the resonances of the *anti* isomer lie downfield relative to the *syn* isomer.

1. Introduction

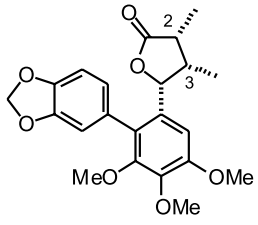
The Ireland Claisen rearrangement is a powerful tool to introduce vicinal stereocenters with high stereoselectivity.[1] In preliminary studies directed toward the total synthesis of members of the eupomatilone family of lignans, we have begun to examine the Ireland Claisen rearrangement as a means of establishing the vicinal stereocenters at C_2 and C_3 of eupomatilone-3 (**1**) and -6 (**2**) (Scheme 1).[2] Since the Ireland Claisen rearrangement can be directed to yield either *syn* or *anti* C_2/C_3 relative stereochemistry by control of the enolate geometry,[1] we anticipated that both targets could be accessed via a common precursor.

A suitably substituted crotyl propionate could be used as the ester precursor of an Ireland Claisen rearrangement. For example, treatment of bis-allylic ester **3** with potassium hexamethyldisilylamide (KHMDS) and triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) afforded a ca. 10:1 mixture of *anti*- and *syn*-dimethylpentenoic acids **5** (Scheme 2) (*anti* and *syn* refer to the relative stereochemistry of the C_2 and C_3 substituents of the pentenoic acid in the extended conformation).[3] Based on our earlier work, we anticipated that the *E*-silylketene acetal would be formed selectively, which would give rise preferentially to acid *anti*-**5**.[3] In order to confirm the predicted relative stereochemistry, acid *anti*-**5** was converted to bromolactone **6**.[4] The structure of bromolactone **6** was determined unambiguously by X-ray crystallographic analysis, verifying that the *anti* isomer was indeed the major product.

The Claisen rearrangement of crotyl propionates and related compounds has often been used to prepare 2,3-dimethylpentenoic acids and their derivatives.[5–11] Although the relative stereochemistry of the products may in some cases be predicted based on the presumed chair-like transition state of the Claisen rearrangement,[1] the problem of unambiguously assigning the relative stereochemistry



Eupomatilone-3 (**1**)



Eupomatilone-6 (**2**)

Scheme 1.

Keywords: NMR; stereochemistry; configuration; conformation.

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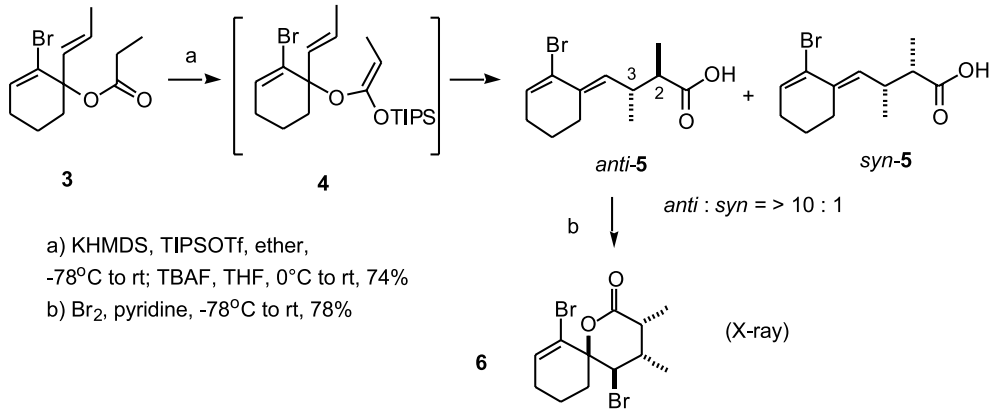


Scheme 2.

invariably arises. Chemical derivatization is frequently used for the determination of the relative stereochemistry.[5–11] Typically the assignments are made by halolactonization coupled with NOE analysis,[5a,9] correlation to known succinic acid derivatives via oxidative cleavage of the alkene,[10,11a–e,m] conversion to known pentenoic acid derivatives,[5c,6a,7,11g,n] or independent chemical synthesis of authentic samples.[5b,8,11i–l] We sought a more direct method which would not require additional chemical operations.

Some limited ^{1}H NMR correlations to the relative stereochemistry of 2,3-dimethylpentenoic acids have previously been noted by other groups, but they are unfortunately too narrow in scope to be generally useful.[11a,j] Analysis of the ^{1}H NMR spectra of several 2,3-dimethylpentenoic acids that we prepared revealed no clear correlation between ^{1}H NMR shifts and *syn* or *anti* stereochemistry. In several cases potentially diagnostic resonances were obscured by overlap with other signals, making determination of any correlations problematic. Bartlett had noted that the ^{13}C NMR chemical shifts of the alkene carbons could be correlated to relative stereochemistry in a limited series of 2-amino-3-methylpentenoic acids.[12] In order to ascertain whether ^{13}C NMR could be used to assign the relative stereochemistry for 2,3-dimethylpentenoic acids, we tabulated the ^{13}C NMR shifts for carbons C_1–C_5 and the C_2 and C_3 methyl groups (i.e. $C_{2'}$ and $C_{3'}$) for all 2,3-dimethylpentenoic acid derivatives for which ^{13}C NMR data were reported (Table 1).[5–11]

2. Results and discussion

2.1. 2,3-Dimethylpentenoic acid derivatives

We felt that it would be useful to assign the C_2 and C_3 methyl resonances for each pair of isomers. Although we found that it is not necessary to make the assignments in order to determine the identity of the *syn* and *anti* isomers, we reasoned that knowing the absolute shifts of the methyl groups of the two isomers might yield additional diagnostic information (*vide infra*). Since those assignments were not made by the authors of the respective papers (with the exception of the dithioesters, entry 5), we assigned the resonances based on calculated ^{13}C NMR shifts using the ChemDraw Ultra™ ^{13}C NMR calculation tool.[13–15] In most cases the C_3 methyl resonances were found to lie downfield of the C_2 methyl resonances.[16,17]

Comparison of the chemical shift differences of all of the ^{13}C resonances yields the following generalizations. With the exception of the C_4 alkene carbon, the *anti* isomer resonances usually lie downfield of the *syn*. The shift differences are in some cases negligible for C_1 and C_2. The C_3 resonances, however, exhibit uniformly positive $\Delta\delta$ values ranging from 0.6 to 2.1 ppm. While the C_4 resonances of the *anti* isomer frequently lie upfield of the *syn*, in two cases either the opposite was true (entry 5) or there was no difference (entry 9). In several cases the C_4 resonances could not be unambiguously assigned on the basis of the chemical shift. The diagnostic signals for this series of compounds are the C_3, the C_2 and C_3 methyls (i.e. $C_{2'}$ and $C_{3'}$) and the C_5 alkene resonances.

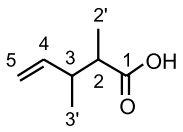
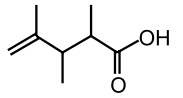
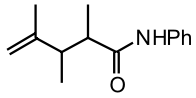
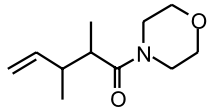
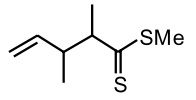
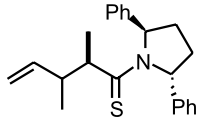
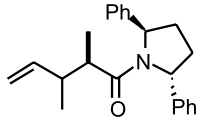
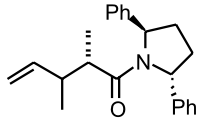
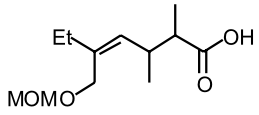
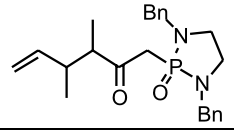
2.2. 2,3-Dialkylpentenoic acid derivatives

In order to further explore the generality of the observed trends, the ^{13}C NMR data for homologous *syn*- and *anti*-pentenoic acid derivatives were also compiled (Table 2). As with the dimethyl series, the $C_{2'}$, $C_{3'}$ and C_5 resonances exhibit significant chemical shift differences between the *anti* and *syn* isomers. The shift differences for the C_5 alkene carbons are on average smaller than for the dimethyl series. The $\Delta\delta$ values for the C_3 carbon are no longer of uniform sign or magnitude. In addition, 2-methyl-3-propylpentenoic acid (entry 14) exhibits an anomalously small and negative $\Delta\delta$ for the C_2 methyl carbon. Nevertheless, the downfield shifts of the $C_{3'}$ and C_5 carbons for the *anti* isomers allow for the stereochemical assignment of the two isomers, although additional examples would be useful in confirming the generality of the trend.

2.3. ^{13}C NMR chemical shift trends

The 2,3-dialkylpentenoic acid derivatives in Tables 1 and 2 all give uniformly positive $\Delta\delta$ (*anti*−*syn*) values for the $C_{2'}$, $C_{3'}$ and C_5 carbons with a single exception ($C_{2'}$, entry 14, Table 2). The generality of the observed trend in ^{13}C chemical shifts is remarkable considering the structural variety of

Table 1. ^{13}C NMR shifts of representative 2,3-dimethylpentenoic acids and derivatives

			C_1	C_2	C_3	C_4	C_5	$C_{2'}$	$C_{3'}$
1[5a]		*anti*	182.6	44.9	40.8	140.5	115.3	14.3	18.3
		syn	182.1	44.5	40.1	141.2	114.6	13.1	16.0
		$\Delta\delta$	0.5	0.4	**0.7**	−0.7	**0.7**	**1.2**	**2.3**
2[5a]		*anti*	183.2	44.6	43.5	146.5	112.4	16.1	18.1
		syn	182.6	43.0	42.9	147.7	111.0	13.0	15.2
		$\Delta\delta$	0.6	1.6	**0.6**	−1.2	**1.4**	**3.1**	**2.9**
3[5b]		*anti*	174.2	46.4	45.1	147.0	112.4	16.8	17.9
		syn	174.1	46.2	43.8	148.5	111.1	14.6	16.3
		$\Delta\delta$	0.1	0.2	**1.3**	−1.5	**1.3**	**2.2**	**1.6**
4[6]		*anti*	174.9	–[a]	–[a]	141.6	115.4	19.3	19.3
		syn	174.7	–[a]	–[a]	142.3	114.3	14.8	16.3
		$\Delta\delta$	0.2	–[a]	–[a]	−0.7	**1.1**	**4.5**	**3.0**
5[7,14]		*anti*	245.0	60.4	45.2	141.8	115.1	21.5	18.8
		syn	246.0	60.2	44.3	141.7	114.1	19.6	17.0
		$\Delta\delta$	−1.0	0.2	**0.9**	0.1	**1.0**	**1.9**	**1.8**
6[8,15]		*anti*	209.8	50.4	46.2	–[a]	114.8	19.7[b]	19.5[b]
		syn	209.5	50.8	44.1	–[a]	114.4	18.4	16.2
		$\Delta\delta$	0.3	−0.4	**2.1**	–[a]	**0.4**	**1.3**	**3.3**
7[8]		*anti*	175.7	43.5	42.3	–[a]	114.6	15.0	18.6
		syn	175.5	43.4	40.8	–[a]	114.2	13.4	15.8
		$\Delta\delta$	0.2	0.1	**1.5**	–[a]	**0.4**	**1.6**	**2.8**
8[8]		*anti*	175.4	43.3	40.5	–[a]	114.4	17.1	19.4
		syn	175.3	43.2	39.4	–[a]	113.6	15.5	16.3
		$\Delta\delta$	0.1	0.1	**1.1**	–[a]	**0.8**	**1.6**	**3.1**
9[9]		*anti*	182.1	45.8	35.2	131.3	138.8	15.1	19.7
		syn	181.3	45.2	34.5	131.3	137.8	13.3	17.6
		$\Delta\delta$	0.8	0.6	**0.7**	0.0	**1.0**	**1.8**	**2.1**
10[10]		*anti*	207.6	52.3	39.9	140.4	115.1	13.3	18.2
		syn	207.4	51.9	39.2	141.5	114.3	12.1	15.5
		$\Delta\delta$	0.2	0.4	**0.7**	−1.1	**0.8**	**1.2**	**2.7**

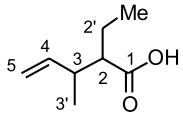
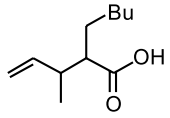
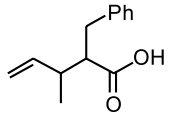
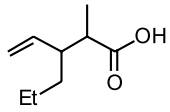
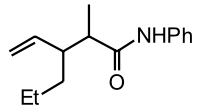
[a] The resonances could not be unambiguously assigned.
[b] The assignments for $C_{2'}$ and $C_{3'}$ may be reversed.

the pentenoic acid derivatives. These structures include pentenoic acids and derivatives containing terminal, 1,1-di-, 1,2-di- and trisubstituted alkenes. Likewise, carboxylic acids, secondary and tertiary amides, a thioamide, a dithioester and a ketone follow the same trend. Cyclic and acyclic amides, alkyl and phenyl amides, and chiral and achiral amides also follow the same trend. Also noteworthy are the pairs of amides in entries 7 and 8 (Table 1) which exhibit the chemical shift trend irrespective of the relative stereochemistry between the chiral auxiliary and the pentenoyl side chain. Finally, pentenoic acids bearing methyl, ethyl, propyl, pentyl and benzyl substituents at C_2 and C_3 follow the chemical shift trend with the one exception of the $C_{2'}$ carbon of 2-methyl-3-propylpentenoic acid (entry 14, Table 2). In compounds of this type it may be necessary to rely upon the $C_{3'}$ and C_5 carbons to make the stereochemical assignment.

For all of the examples, the $\Delta\delta$ values for the $C_{2'}$ and $C_{3'}$ carbons are large enough so that both isomers can be easily distinguished by ^{13}C NMR. The values range from 1.2 to 4.5 ppm for the C_2 methyl resonances and 1.6–3.3 ppm for the C_3 methyl resonances in the dimethyl series. For the higher homologs, the $C_{2'}$ resonances range from 0.8 to 1.4 ppm and the $C_{3'}$ resonances from −0.1 to 1.5 ppm. The C_5 alkene carbon exhibits a $\Delta\delta$ range from 0.3 to 1.2 ppm.

The absolute ^{13}C NMR shifts of the methyl groups in the dimethyl series also exhibit some uniformity. With the

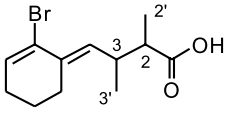
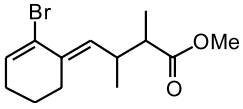
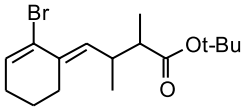
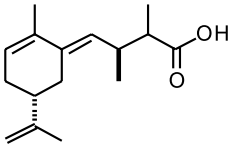
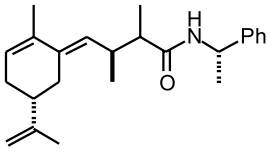
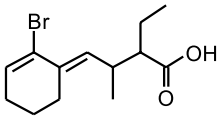
Table 2. ^{13}C NMR shifts of 2,3-dialkylpentenoic acids and derivatives

			C_1	C_2	C_3	C_4	C_5	$C_{2'}$	$C_{3'}$
11[18]		*anti*	181.7	53.1	40.6	141.5	115.3	23.6	18.8
		syn	181.4	53.0	40.1	141.3	114.9	22.4	17.5
		Δδ	0.3	0.1	0.5	0.2	**0.4**	**1.2**	**1.3**
12[18]		*anti*	181.6	51.5	40.9	141.5	115.3	30.4	18.8
		syn	181.3	51.3	40.3	141.3	114.9	29.2	17.5
		Δδ	0.3	0.2	0.6	0.2	**0.4**	**1.2**	**1.3**
13[18]		*anti*	180.4	53.5	40.9	–[a]	115.9	36.4	18.5
		syn	179.8	53.0	40.2	–[a]	115.6	35.2	17.7
		Δδ	0.6	0.5	0.7	–[a]	**0.3**	**1.2**	**0.8**
14[5a]		*anti*	182.9	46.5	43.8	138.8	117.0	13.9	34.7
		syn	182.1	46.7	43.9	139.4	116.4	14.0	33.3
		Δδ	0.8	−0.2	−0.1	−0.6	**0.6**	**−0.1**	**1.4**
15[5b]		*anti*	174.1	47.5[b]	47.1[b]	139.6	117.2	15.8	34.8
		syn	173.5	47.4[b]	47.0[b]	139.6	116.6	15.3	33.6
		Δδ	0.6	0.1	0.1	0.0	**0.6**	**0.5**	**1.2**

[a] The resonances could not be unambiguously assigned.
[b] The assignments for C_2 and C_3 may be reversed.

exception of *syn* dienic amide **9** (Table 3) and one *anti* dienic amide (entry 3, Table 1), the *anti* C_3 methyl resonances appear above 18 ppm and the *syn* C_3 methyl resonances below 18 ppm. The C_2 methyl resonances are more variable and are not sufficiently uniform to be diagnostic.

Table 3. ^{13}C NMR shifts of 2,3-dialkylcyclohexenylidenoic acids and derivatives[3b]

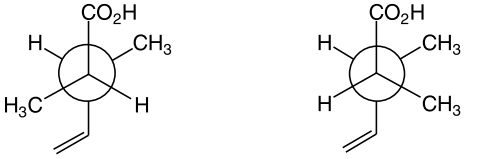
Cmpd			$C_{2'}$	$C_{3'}$
5[19]		*anti*	15.3	19.3
		syn	13.5	17.2
		Δδ	**1.8**	**2.1**
6[20]		*anti*	15.6	19.2
		syn	13.9	17.4
		Δδ	**1.7**	**1.8**
7[20]		*anti*	15.8	18.9
		syn	14.4	17.7
		Δδ	**1.4**	**1.2**
8[21]		*anti*	15.5	19.7
		syn	13.6	17.8
		Δδ	**1.9**	**1.9**
9[22]		*anti*	16.5	19.5
		syn	15.4	18.4
		Δδ	**1.1**	**1.1**
10[23]		*anti*	24.0	19.3
		anti	22.5	18.0
		Δδ	**1.5**	**1.3**

2.4. Model studies

The observed ^{13}C NMR shift trends proved to hold for the series of dienic pentenoic acid derivatives that we prepared in the course of our model studies (Table 3). In these cases only the $C_{2'}$ and $C_{3'}$ resonances were examined, since they were most easily distinguishable and exhibited the greatest chemical shift differences. The ^{13}C NMR shifts of the C_2 and C_3 methyl carbons of dienic acids *anti*-**5** and *anti*-**8** were confirmed by ^{1}H–^{1}H COSY and ^{1}H–^{13}C HETCOR.

2.5. Conformations of *syn*- and *anti*-2,3-dimethylpentenoic acids

In order to rationalize the observed ^{13}C shift differences between the two isomers, a conformational search of the *anti* and *syn* isomers of 2,3-dimethylpentenoic acid was performed at the MM2 level (Scheme 3).[24] The two lowest energy conformers (E_{rel}=0.0–0.67 kcal/mol) of the *anti* isomer have the C_2 and C_3 methyl groups oriented antiperiplanar to one another.[24b] The C_2 methyl group is oriented *gauche* to the vinyl substituent and the C_3 methyl group



anti ΔE_{rel} = 0.0-0.67 kcal/mol

syn ΔE_{rel} = 0.0-0.41 kcal/mol

Scheme 3.

gauche to the carboxyl substituent. By contrast, the three lowest energy conformers of the *syn* isomer (E_{rel}=0.0–0.41 kcal/mol) have the two methyl groups oriented *gauche* to one another.[24c] In addition, the C_2 methyl group is *gauche* to the vinyl group and the C_3 methyl group is *gauche* to the carboxyl group. These conformations are consistent with the relative ^{13}C shifts of the *anti* and *syn* isomers, since the methyl groups with two *gauche* interactions should lie upfield of those with only one.[25–27] The reason for the downfield shift of the C_5 carbon is less clear.

3. Conclusion

In summary, a simple and general ^{13}C NMR method for determination of the relative stereochemistry of 2,3-dimethylpentenoic acids and derivatives thereof has been demonstrated.[28] The ^{13}C NMR signals of the methyl carbons of *anti* isomers invariably lie downfield relative to those of *syn* isomers. Homologous 2,3-dialkylpentenoic acid derivatives exhibit similar trends, but further study is required to determine the reliability of the method for these cases.

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14. The authors of Ref. 7 assigned the C_2 and C_3 methyl resonances as shown in entry 5, Table 1. No rationale was given for the assignments. The ChemDraw ^{13}C NMR calculation tool yielded the opposite assignment, with the $\Delta\delta$ (*anti*−*syn*)=1.1 ppm. However, since examination of the calculation protocol revealed that it was not explicitly parameterized for the dithioester functional group, the original authors' assignments were retained.
15. Because the shifts of the C_2 and C_3 methyl resonances of the *anti*-thioamide isomers in entry 6, Table 1 are so similar, the assignments and hence the $\Delta\delta$ values could not be firmly established on the basis of the reported data and ^{13}C NMR calculations. Since the shift difference is only 0.2 ppm, however, the $\Delta\delta$ values would be very similar irrespective of the actual assignments. The assignments for the C_2 and C_3 methyl resonances of the *syn*-thioamide isomer were made as shown based on the ChemDraw ^{13}C NMR calculation tool. The calculations are parameterized for the thioamide functional group.
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20. Esters **6** and **7** were prepared by treatment of acid **5** with oxalyl chloride followed by triethylamine and the corresponding alcohol in CH_2Cl_2.
21. Dienic acid **8** was prepared in 72% yield analogously to acid **5**. The ratio of *anti*-**8** to *syn*-**8** was 12:1.
22. Amide **9** was prepared by treatment of acid **8** with triethylamine, DPPA and (*S*)-α-methylbenzylamine in DMF.
23. Dienic acid **10** was prepared in 72% yield analogously to acid **5**. The ratio of *anti*-**10** to *syn*-**10** was >10:1. The assignments of the $C_{2'}$ methylene carbons were made by comparison to the dimethyl acid **5**.
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