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An NMR method for determination of configuration of β-substituted carboxylic acids

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Abstract

The absolute configuration of the stereogenic center at the β-position of a carboxylic acid can be determined via derivatization with chiral benzylic amines [PhCH(Me)NH_2 or 1-NpCH(Me)NH_2]. Acids of known configuration and with a variety of β-substituents were subjected to derivatization. Analysis of the signs of the chemical shift differences of substituent protons permits determination of the absolute configuration. © 2000 Elsevier Science Ltd. All rights reserved.

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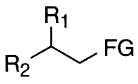
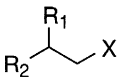
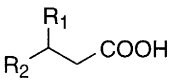
NMR-based methods for determination of the absolute configuration of stereogenic centers are popular in modern organic chemistry.[1] Their main advantages are availability of instrumentation, low cost, and easy derivatization techniques. Typically, the derivatization is necessary to convert a compound with an isolated stereogenic center into a pair of diastereomers, which possess different NMR properties. Several methods for assignment of absolute configuration of the stereogenic center in a position beta to the site of functionalization (**1**) have been developed. These include the Mosher MTPA/Eu(fod)$_3$[2a] or the anthryl-methoxyacetate (AMA)[2b] analyses of primary alcohols (**2a**), the Pirkle isocyanate method for amines (**2b**),[3] and the ephedrine-derived oxazolidinone method for aldehydes (**2c**).[4] We have recently reported the use of amides derived from 1-phenylethylamine or 1-(1-naphthyl)ethylamine for determination of absolute configuration of β-methyl-substituted carboxylic acids (**3**, R_1=Me, $R_2 \neq$Me).[5]







1 ***2a*** X = OH, ***2b*** X = NHR, ***2c*** X = CHO ***3***

Carboxylic acids **3** with substituents other than a methyl group at C(3) were of interest to us since they are abundantly present in natural compounds.[6] We decided to investigate the extension of our method

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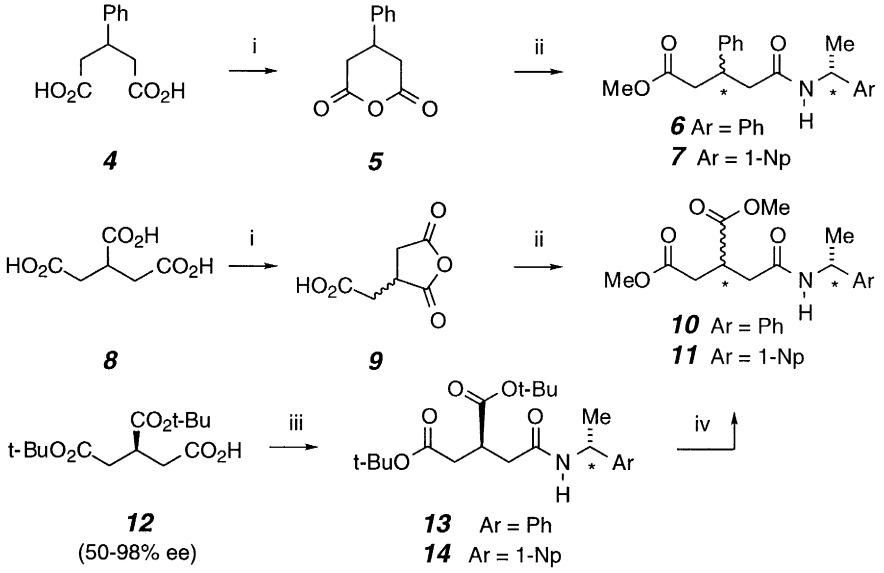
to include this broader spectrum of acid substrates. Chemical shift trends in the diastereomeric pairs of 1-phenylethylamides and 1-(1-naphthyl)ethylamides derived from several such β-substituted carboxylic acids have now been studied and we present the results here.

The synthesis of the diastereomeric amides is shown in Scheme 1. 3-Phenylglutaric acid (**4**) was converted into 3-phenylglutaric anhydride (**5**) and then ring-opened with *R*-1-phenylethylamine or *R*-1-(1-naphthyl)ethylamine to give diastereomeric mono-amide mono-acids (~2:1 ratio of diastereomers in each case). The acids were esterified with DMF·dimethyl acetal. Diastereomers of each phenyl- (**6**) and naphthyl-containing (**7**) amide were separated by MPLC on silica gel. The relative configuration for the two diastereomers of **6** and of **7** is assigned by analogy with the sense of ring opening of 3-methylglutaric anhydride (to provide **15** and **16**) as we previously reported.[5] A similar strategy was employed starting with tricarballylic acid (**8**) to give (after opening of anhydride **9**[7] and esterification) diastereomeric mixtures of amides **10** and **11**.

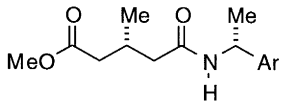
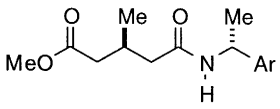
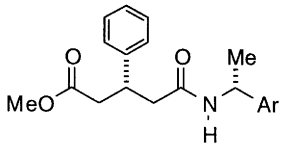
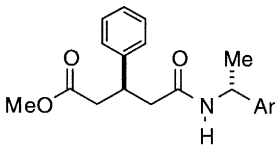
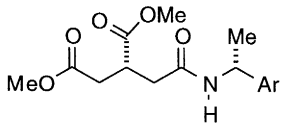
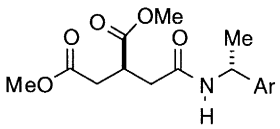
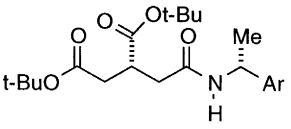
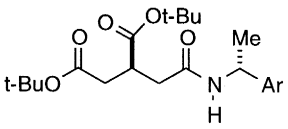


Scheme 1. Reagents and conditions: (i) Ac_2O solvent, rt, 24 h; (ii) (1) *R*-1-phenylethylamine or *R*-1-(1-naphthyl)ethylamine, 2 equiv., 24 h, CH_2Cl_2;[8] (2) dimethylformamide dimethyl acetal, CH_2Cl_2, 24 h, 45–55% for two steps; (iii) *R*-1-phenylethylamine or *R*-1-(1-naphthyl)ethylamine, DCC, DMAP cat., CH_2Cl_2, 24 h, 60–65%; (iv) MeCOCl/MeOH, 1 h, rt, 52–95%

To unambiguously prove the relative configuration of the *syn*- and *anti*-diastereomers of **10** and of **11**, *S*-tricarballylic acid bis-*t*-butyl ester (**12**) was synthesized in an enantiomerically enriched form according to the literature procedure.[9] DCC-mediated coupling under standard conditions led to the formation of amides **13** and **14**. Each of these amides was treated with HCl in methanol to form their corresponding diastereomeric esters **10** and **11**, thereby permitting unambiguous assignment of the relative configuration of each.

As expected, meaningful differences were observed in chemical shifts of various protons associated with the R^1 and R^2 substituents at C(3) in each pair of diastereomeric amides. These results are presented in Table 1,[10] along with those of the 3-methyl glutaramide derivatives **15** and **16** we reported earlier.[5] The difference [expressed in $\Delta\delta$ units, where $\Delta\delta=\delta$ (*syn*)$-\delta$ (*anti*)] is always positive for the R^1 substituent and negative for the R^2 substituent (cf. Fig. 1). Observed magnitudes of chemical shift differences are consistent with our earlier observation that the 1-naphthyl group usually provides a larger anisotropic shielding effect than the phenyl group.[5]

Table 1
^{1}H NMR $\Delta\delta$ values for amides derived from β-chiral acids with known relative configurations

***syn*-Amides**	***anti*-Amides**		$\Delta\delta$ = δ (***syn***) - δ (***anti***)	
			$\Delta\delta$(Me)	$\Delta\delta$(CO_2Me)
		15 Ar = Ph[a]	+ 0.013	-0.015
		16 Ar = 1-Np[a]	+ 0.019	-0.032
			$\Delta\delta$(Ph)	$\Delta\delta$(CO_2Me)
		6 Ar = Ph	not	-0.019
		7 Ar = 1-Np	resolved	-0.070
			$\Delta\delta$($CHCO_2$Me)	$\Delta\delta$(CH_2CO_2Me)
		10 Ar = Ph	+0.034	-0.016
		11 Ar = 1-Np	+0.062	-0.037
			$\Delta\delta$($CHCO_2$*t*-Bu)	$\Delta\delta$(CH_2CO_2*t*-Bu)
		13 Ar = Ph	+0.019	-0.013
		14 Ar = 1-Np	+0.025	-0.037

A useful conformational model that accounts for the observed signs of the chemical shift differences between the *syn* and *anti* diastereomers is shown in Fig. 1. It is based on two assumptions: (i) the predominant rotamer around the benzylic carbon to nitrogen bond is that having the benzylic proton eclipsed with the carbonyl group; (ii) one of the two non-hydrogen substituents at C(3) essentially always occupies the *anti* position relative to the carbonyl group, forcing the other non-hydrogen substituent *gauche* to the carbonyl. In the case of the *anti*-diastereomer, this results in preferential anisotropic shielding of the R^1 substituent by the aromatic phenyl or 1-naphthyl group. In the case of the *syn*-

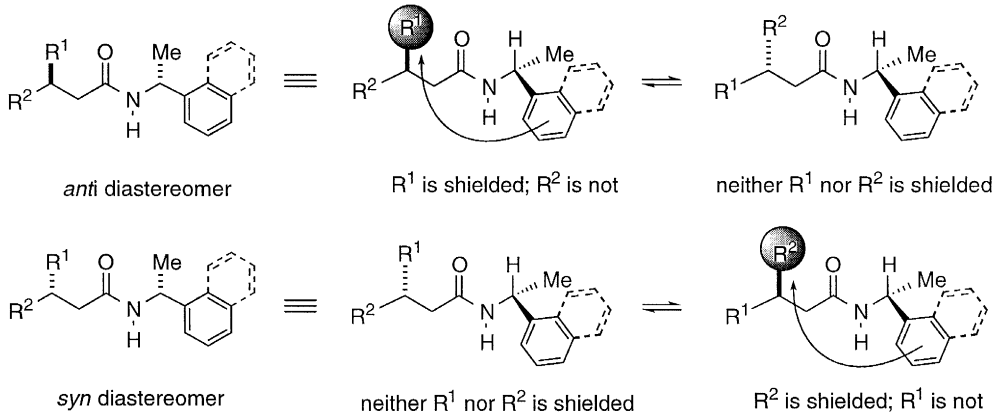


Fig. 1. Conformational model for determination of the sign of $\Delta\delta$=δ (*syn*)–δ (*anti*) or protons in R^1 and R^2

diastereomer, preferential shielding of the R^2 substituent is observed. It follows that the $\Delta\delta$ [=δ (*syn*)–δ (*anti*)] values of protons in R^1 are positive and those in R^2 are negative (cf. Table 1).

In conclusion, the NMR strategy for determination of the absolute configuration of a stereogenic center in the β-position of a carboxylic acid has been extended to include a variety of (non-methyl) β-substituents. The strategy involves derivatization of the acid with each enantiomer of 1-phenylethylamine or 1-(1-naphthyl)ethylamine and measurement of the chemical shifts of groups attached to C(3).

Acknowledgements

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6. A search of the Beilstein database indicates that there are over 350 known natural products that contain the substructure shown in **3** in which R^1 and R^2 are both carbon substituents. A nearly equal number are known in which one of the two is a hetereoatom substituent.
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8. In the case of tricarballylic acid anhydride, products arising from α- and β-openings were separated using MPLC.
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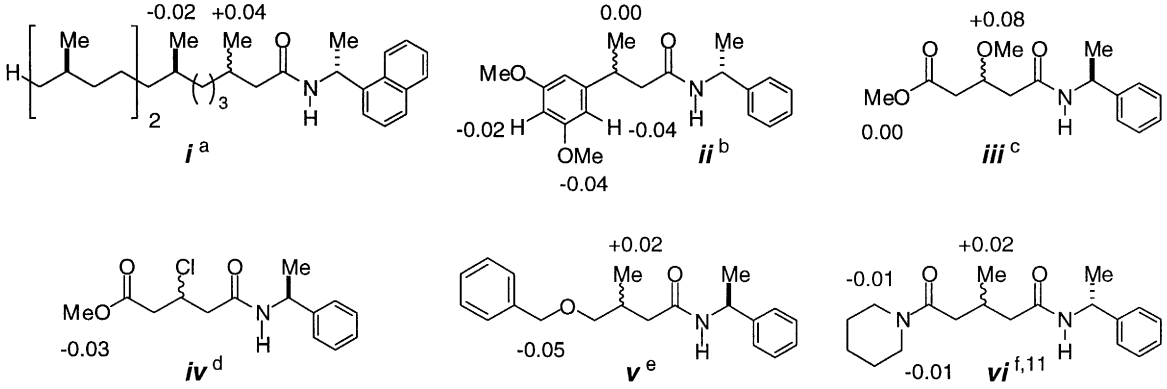
10. We have found additional examples of analogous amide derivatives of 3-substituted carboxylic acids (**i**–**vi**) that complement the NMR data reported in Table 1. The $\Delta\delta$ [=δ (*syn*)–δ (*anti*)] value for the relevant protons of the two diastereomers is indicated (with sign) directly beside the relevant proton.



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11. The signs of the $\Delta\delta$ values for diastereomers **vi** deduced from Ref. 10f are opposite to those that our method predicts. Concerned that this represents an exception to our method, we independently synthesized each of *syn*-**vi** and *anti*-**vi** and unambiguously determined the relative configuration of *syn*-**vi** by single crystal X-ray analysis. It is now clear that the ^{1}H NMR data in Ref. 10f are reversed for *syn*-**vi** and *anti*-**vi** (although the mp and specific rotation values as reported are associated with the correct diastereomeric structures). The signs and magnitudes of the $\Delta\delta$ values shown in structure **vi** above are from our NMR data and are unambiguously consistent with the method.