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Graphical Abstract

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Determination of the relative configuration of *vic*-amino alcohols

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The relative configuration of *vic*-amino alcohols can easily be determined by ¹H NMR. Derivatization or shift reagents are not needed.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100

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Determination of the relative configuration of *vic*-amino alcohols

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Abstract— A large set of *syn*- and *anti*-1,2-amino alcohols has been synthesized. Upon comparison of the CHO and CHN ^1H NMR shifts a general trend has been observed, making it possible to determine the relative configuration of 1,2-amino alcohols without derivatization or shift reagents. © 2002 Elsevier Science. All rights reserved

The β -amino alcohol moiety is found in a wide variety of biologically active alkaloids and peptides,¹ it is consequently a common building block in the synthesis of natural products.² The importance of vicinal amino alcohols is also well recognized in asymmetric synthesis, as many chiral auxiliaries and ligands contain this substructure.³

Development of methods for configurational assignment of 1,2-amino alcohols has remained an interesting task. Shapiro recently reported an NMR method of determining enantiomeric purity and relative configuration by (R)-(+)-*t*-butylphenylphosphinothioic acid complexation.⁴ Absolute configuration can be determined by circular dichroism measurements of dirhodium tetraacetate complexes.⁵ Several methods to determine relative configuration of β -amino alcohols require derivatization prior to NMR or CD analysis.^{6,7} In the most common of these procedures, the amino alcohol is converted to the corresponding oxazolidinone (Scheme 1).^{8,9} The ring protons (H_4, H_5) of these compounds have coupling constants that are larger for *cis*- than *trans*-configuration. The configuration can also be confirmed by NOE experiments.⁸ As the differences in coupling constants and NOE values between *cis*- and *trans*-oxazolidinones can be rather small, both isomers of the amino alcohol are often needed, especially if it contains a vinyl substituent.^{10,11}

Scheme 1: Transformation of an *anti*-amino alcohol into a *cis*-oxazolidinone.

In our work with a regio- and stereodivergent synthesis of *vic*-amino alcohols, we have transformed all amino alcohols to the corresponding oxazolidinones for determination of relative configuration (Scheme 2).^{12,13} As this was a rather tedious operation, we sought a simplified method of configuration assignment without need for derivatization.

Scheme 2: Divergent synthesis of *vic*-amino alcohols.

Seven substrates (**a-g**), each with four amino alcohols isomers (**2**, **3**, **5**, **6**), were used in the study (Figure 1, Table 1). NMR spectroscopy data of the amino alcohols was examined in order to find general trends that could be used to distinguish *syn*- and *anti*-amino alcohols. To our

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Table 1: ^1H NMR shift (ppm) of CH-O / CH-N protons in vinylic *vic*-amino alcohols.

Amino alcohol ^a	Shift (ppm) of CH-O / CH-N protons						
	a	b	c	d	e	f	g
2 	3.61	3.78	3.77	3.73	3.83	3.74	3.53
	3.36	3.50	3.51	3.29	3.63	3.42	3.40
3 	3.32	3.50	3.58	3.45	3.70	3.53	3.29
	3.14	3.40	3.43	3.06	3.40	3.34	3.14
5 	4.07	4.11	4.15	4.00	4.10	4.04	4.24
	2.94	3.06	3.06	3.00	3.12	3.03	2.85
6 	3.85	4.08	4.08	3.73	3.92	3.96	3.91
	2.67	2.97	2.94	2.81	3.04	2.88	2.72

^a **a:** $\text{R}^1=\text{PhCH}_2$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{H}$; **b:** $\text{R}^1=\text{BnO}$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{H}$; **c:** $\text{R}^1=\text{BnO}$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{CH}_2\text{OPMB}$; **d:** $\text{R}^1=\text{H}$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{CH}_2\text{OBn}$; **e:** $\text{R}^1=\text{PMBO}$, $\text{R}^2=\text{CH}_2\text{OBn}$, $\text{R}^3=\text{H}$; **f:** $\text{R}^1=\text{BnO}$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{C}_{13}\text{H}_{27}$; **g:** $\text{R}^1=\text{C}_{13}\text{H}_{27}$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{BnO}$.

disappointment, no such tendency was found in coupling constants between methine protons H_3 and H_4 or ^{13}C NMR shifts of C_3 and C_4 .

Figure 1: *Anti*-amino alcohols **2a–g**.

Surprisingly, there was instead a trend in the ^1H NMR shifts, where H_3 and H_4 shifted more downfield in *anti*-amino alcohols **2** and **5** than in the corresponding *syn*-amino alcohols **3** and **6**. For example, the shift of CH-O in **2a** and **3a** is 3.61 and 3.32 ppm, respectively. For the same compounds, the shift of CH-N is 3.36 and 3.14 ppm, respectively (Table 1).

To broaden the scope of this observation, the amino alcohols of substrates **a**, **b**, **d**, **f** and **g** were reduced to the corresponding saturated compounds (Scheme 3).¹⁴

Scheme 3: Reduction of the vinyl group.

To our satisfaction, saturated amino alcohols **2'**, **3'**, **5'**, **6'** showed the same trend in ^1H NMR shifts (Table 2).

Table 2: ^1H NMR shift (ppm) of CH-O / CH-N protons in saturated *vic*-amino alcohols.

Amino alcohol ^a	Shift (ppm) of CH-O / CH-N protons				
	a	b	d	f	g
2' 	3.50	3.67	3.72	3.65	3.46
	2.64	2.79	2.78	2.87	2.77
3' 	3.31	3.53	3.41	3.51	3.25
	2.52	2.73	2.44	2.80	2.55
5' 	3.39	3.47	3.43	3.55	3.47
	2.81	3.02	2.96	3.00	2.76
6' 	3.24	3.42	3.19	3.48	3.26
	2.60	2.91	2.73	2.86	2.53

^a **a:** $\text{R}^1=\text{PhCH}_2$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{H}$; **b:** $\text{R}^1=\text{BnO}$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{H}$; **d:** $\text{R}^1=\text{H}$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{CH}_2\text{OBn}$; **f:** $\text{R}^1=\text{BnO}$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{C}_{13}\text{H}_{27}$; **g:** $\text{R}^1=\text{C}_{13}\text{H}_{27}$, $\text{R}^2=\text{H}$, $\text{R}^3=\text{BnO}$.

To summarize, we have presented a rapid way of determining relative configuration of *vic*-amino alcohols when both the *syn*- and *anti*-isomer of a given amino alcohol is present. The ^1H NMR shifts of CH-O and CH-N protons are more downfield in the *anti*-amino alcohol than in the corresponding *syn*-isomer. This method of configurational assignment should be of substantial use

when amino alcohols are formed by diastereoselective reactions.

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