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Determination of the Enantiomeric Excesses of Chiral Acids by ^{19}F NMR Studies of their Esters deriving from (R)-(+)-2-(Trifluoromethyl)benzhydrol

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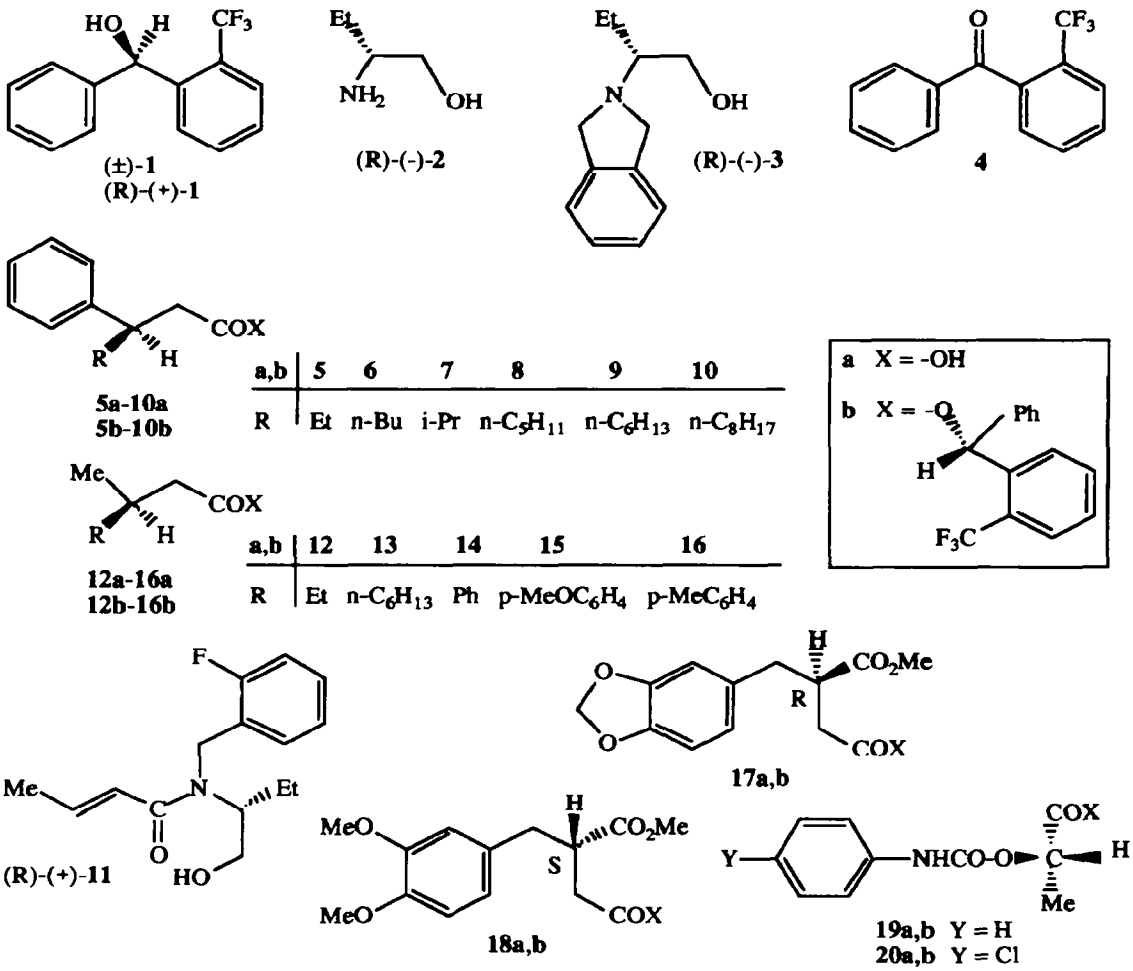
Abstract : 15 Chiral acids were esterified with optically pure (R)-(+)-2-(trifluoromethyl)benzhydrol (R)-(+)-**1**, a readily available reagent. With respect to the carboxy group, the stereogenic centre is in the β position in the case of the acids **5a-10a** and **12a-16a**, and in the α position in the case of the acids **17a-20a**. The diastereomeric excesses of the corresponding esters **5b-10b** and **12b-20b**, respectively, were easily determined by means of ^{19}F NMR. These d.e. values were in very good agreement with the e.e. values of the corresponding acids when the latter were known compounds.

There are relatively few methods for the NMR determination of enantiomeric excess (e.e., %) of chiral carboxylic acids.[1] The e.e. of such acids can be determined by ^1H NMR studies of the corresponding diastereomeric amides[1-3] or esters.[1] There are reports of the use of amines,[1] such as (1R, 2R)-1,2-diamino-1,2-diphenylethane[4,5] as chiral solvating agents for the analysis of carboxylic acids. Chiral carboxylates can be analyzed by ^1H NMR examination of their adducts formed with an achiral praseodymium complex.[6] It must be emphasized that in most cases, the stereogenic centre of the carboxylic acid is in the α position with respect to the carboxy group. The e.e. of such acids can be also determined by examination of the ^1H NMR spectra of their methyl esters run in the presence of the chiral shift reagent Eu(hfc)3. In our hands, this method failed in the case of β-substituted alkanoic acids, presumably because the β−stereogenic centre is too far from the carboxy group. However, we eventually found that the e.e.'s of these acids could be determined with a fair accuracy from the ^{19}F NMR spectra of their esters deriving from (R)-(+)-2-(trifluoromethyl)benzhydrol (R)-(+)-**1**. We describe here the results we have obtained.

Preparation of (R)-(+)-2-(trifluoromethyl)benzhydrol (R)-(+)-1

Equimolecular amounts of (R)-(-)-2-aminobutan-1-ol (R)-(-)-**2**[7] and α,α'-dichloro-ortho-xylene in toluene were refluxed for 3h, followed by the addition of a twofold molar amount of Na_2CO_3. After refluxing for a further 15 h, the tertiary base (R)-(-)-**3**[7] was isolated and purified by sublimation. In the next step, 2-(trifluoromethyl)phenylmagnesium bromide was prepared from commercial 1-bromo-2-trifluoromethyl benzene in refluxing ether and reacted with benzaldehyde, thus leading to the benzhydrol (±)-**1**[7] in high yields. Oxidation of the latter with Jones' reagent at 0°C readily afforded the crystalline benzophenone **4**.[7] The asymmetric reduction of the ketone **4** was next carried out as follows. To a molar, ethereal solution of $LiAlH_4$ (6.0 mmol),[8] a solution of the alcohol (R)-(-)-**3** (15 mmol) in dry ether (40 mL) was added with stirring under argon for 1 h at room temperature. After stirring for a further 30 min, the mixture was cooled to -15°C and a solution of the benzophenone **4** (5.0 mmol) in dry ether (6 mL) was added dropwise in 1 h 15 min. After stirring for a another 30 min, the mixture was hydrolyzed with aqueous 1N NaOH (5 mL). The resulting

benzhydrol (+)-1[7] was isolated and purified by molecular distillation (see Scheme). The ^1H NMR spectrum of (+)-1 run in the presence of Eu(hfc)3 (0.5 molar equ.) revealed that (+)-1 was enantiomerically pure. The absolute configuration of (+)-1 was determined using Horeau's method.[9] Thus, a sample of (+)-1 was totally esterified using a twofold molar amount of racemic 2-phenylbutyric anhydride in dry pyridine. (S)-(+)-2-Phenylbutyric acid, $[\alpha]_D$ +5.7 (c 2, PhMe), e.e. = 6%, was isolated from the aqueous phase after hydrolytic work-up. Therefore the alcohol (+)-1 has the (R) configuration.



Scheme

Synthesis and ^{19}F NMR studies of esters deriving from (R)-(+)-1 and various chiral acids

The optically active acids **5a-10a** were obtained by asymmetric synthesis as described earlier.[10] The optically active acids **12a-16a** were similarly obtained by Michael addition of the Grignard reagent RMgX to the chiral crotonamide (R)-(+)-**11**, followed by acidic hydrolysis.[11] The half-esters (R)-(+)-**17a** and

(S)-(-)-**18a** were obtained by resolution of their racemates.[12] The acids (S)-(-)-**19a**[13] and (S)-(-)-**20a**[14] were obtained by reaction of the corresponding arylisocyanate with ethyl (S)-(-)-lactate, followed by alkaline hydrolysis at -10°C. The afore-mentioned acids **5a-10a** and **12a-20a** were each esterified with equimolecular quantities of the alcohol (R)-(+)-**1** by means of dicyclohexyl carbodiimide in the presence of catalytic amounts of p-(dimethylamino) pyridine in methylene chloride for 24 h at room temperature. The resulting oily esters **5b-10b** and **12b-20b**, respectively, were purified by column chromatography over silica gel using cyclohexane/ether (ca. 9:1) for the elution.

	Acids (a)					Esters (b)			
R		Abs. conf.	$[\alpha]_D$ obs. a)	Lit. $[\alpha]_D$ a)	e.e. (%) b)		Yield (%) c)	$[\alpha]_D$ obs. d)	d.e. (%) e)
Et	**5a**	(R)	-45	-49.96[16]	90	**5b**	60	+9.5	87.5
n-Bu	**6a**	(R)	-38	+37.05[16]	100	**6b**	65	+12.2	89.6
i-Pr	**7a**	(R)	-34.4	-40.5[17]	85 (77)[f]	**7b**	78	+6.4	72.5
n-C_5H_{11}	**8a**	(R)?	-30.52			**8b**	42	+12	88
n-C_6H_{13}	**9a**	(R)?	-26.45			**9b**	50	+15.7	89
n-C_8H_{17}	**10a**	(R)?	-21.5			**10b**	79.4	+10.7	88.4
Et	**12a**	(R)	-7.83	-8.15 (neat)[16]		**12b**	78	+16.3	87.8
n-C_6H_{13}	**13a**	(R)	+7.57	+5.10 (neat)[16]		**13b**	63	+18.47	91.8
Ph	**14a**	(S)	+51	+57.23[16]	89.1	**14b**	76	+34.12	90.8
p-$MeOC_6H_4$	**15a**	(S)	+31.5 (MeOH)	+36.5 (MeOH)[18]	86.3	**15b**	75	+33.32	91.2
p-MeC_6H_4	**16a**	(S)	+57.69	+65 (PhH)[19]	88.75	**16b**	72	+35.37	93.5
	17a	(R)	+29.2 (MeOH)	+30.4 (MeOH)[12]	96	**17b**	67.5	+9.4	>98[14]
	18a	(S)	-26.9 (MeOH)	-27.6 (EtOH)[12]	93	**18b**	62	-14.1	90.2
	19a	(S)	-12 (EtOH)	-13±1 (EtOH)[13]	100	**19b**	66	-13.1	>98
	20a	(S)	-20 (MeOH)	-21.5 (MeOH)[14]	93	**20b**	74.5	-32.3	91.6

a) Taken in PhH as a solvent unless otherwise stated. b) Determined as the ratio of the observed $[\alpha]_D$ to that reported for the optically pure compound. c) Yield after chromatography. d) Taken in EtOH as a solvent. e) Determined from the integration of the ^{19}F NMR signals of both diastereomeric esters.[15] f) The value in brackets corresponds to the d.e. of an amide precursor of **7a**.[11]

Table. Diastereomeric excesses of esters of (R)-(+)-2-(trifluoromethyl) benzhydrol (R)-(+)-**1** deriving from various chiral acids.

The proton decoupled ^{19}F NMR spectra (376.5 MHz) of these 15 esters were next run in $CDCl_3$ using $CFCl_3$ as a standard. In most cases, the ^{19}F NMR spectra of these esters revealed the presence of two signals of unequal areas corresponding to each enantiomer of the acyl moiety.[15] The diastereomeric excesses (d.e., %) of the esters were determined from the integration of the ^{19}F NMR signals (see Table).

Conclusion

Assuming that both enantiomers, coexisting in a given chiral acid, can be esterified with an optically pure alcohol at the same rate or in the same yield, then the d.e. of the corresponding ester should be equal to the e.e. of the starting acid. It can be seen from the Table that the e.e. of each known acid **5a** and **15a-20a** was in very good agreement (within 3%) with the d.e. value of the corresponding esters **5b** and **14b-20b** deriving from (R)-(+)-2-(trifluoromethyl)benzhydrol (R)-(+)-**1**. Since the latter can be readily synthesized in optically pure form and on a multi-gram scale, we believe that it should arouse interest as a tool for the determination of the e.e.'s of chiral acids by means of ^{19}F NMR spectrometry.

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