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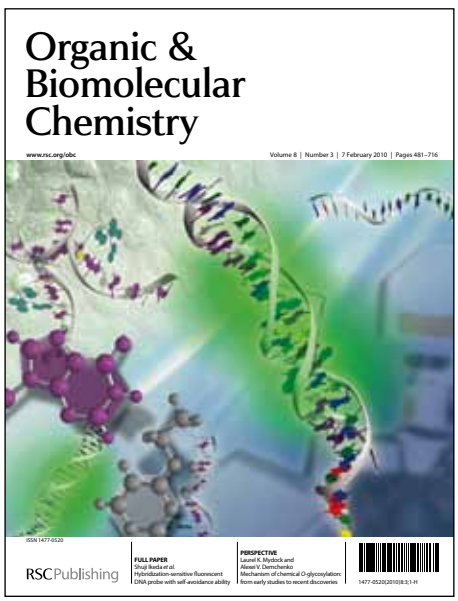

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ARTICLE TYPE

Aminoindanol-based chiral derivatizing agents for the determination of the absolute configuration of carboxylic acids

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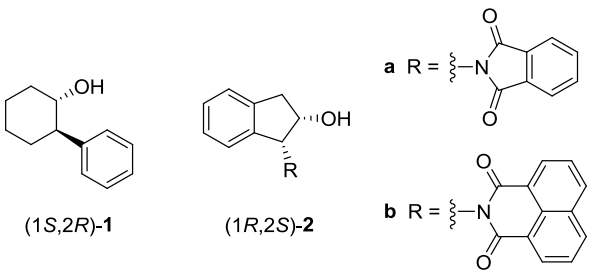
New chiral derivatizing agents have been prepared through a simple, short-step synthesis. The absolute configuration of α-chiral carboxylic acids can be assigned on the basis of the NMR chemical shift difference between diastereomeric esters. Because of the modular structure of the agents, the anisotropic effect could be easily manipulated to afford large chemical shift differences even in polar solvents.

Introduction

With the progress of asymmetric synthesis and natural product chemistry, considerable efforts have been devoted to the development of simple and efficient methods for the absolute configuration assignment of chiral compounds. One of the traditional approaches especially useful for non-crystalline compounds is the NMR anisotropy method[1] in which the chiral compound is derivatized with two enantiomers of a chiral derivatizing agent (CDA) and the NMR spectra are compared to obtain the chemical shift difference (Δδ) between the two resulting diastereomers. Proper analysis of the Δδ values based on the diastereomer conformations and the anisotropic shielding effect produced by the CDA can lead to the absolute configuration assignment of the chiral compound. To reduce possible errors in this analysis, there have been continuous efforts[2] to develop new CDAs with strong anisotropic effects and rigid structures producing large Δδ values.

It is a simple and well accepted concept that the anisotropic effect of a CDA can be improved by increasing the size of the CDA's anisotropic group (an aromatic ring in most cases). In reality, however, the manipulation of the anisotropic effect is not straightforward because most of the CDAs currently used have its anisotropic group directly attached to their chiral centers. With this traditional design, two enantiomers of a new CDA should be prepared by asymmetric synthesis or chiral resolution, and then the absolute configuration of each enantiomer should be assigned without ambiguity.

Exploring alternative approach to develop new CDAs with relatively small amount of time and cost, we have used a modular chiral pool method in which the chiral center and the anisotropic group of a CDA are derived from two separate chiral and achiral starting materials.[3] Because the chiral center is derived directly from chiral pool, a new CDA with improved anisotropic effect



(1*S*,2*R*)-**1** (1*R*,2*S*)-**2**

Fig. 1 Structures of CDAs for the absolute configuration assignment of α-chiral carboxylic acids.

can be prepared simply starting from an achiral material with a strong anisotropic group. Using this approach, we have recently developed tartaric acid-based CDAs for primary amines[3a] and serine-based CDAs for secondary alcohols.[3b] Herein, we would like to report aminoindanol-based CDAs for α-chiral carboxylic acids.

Results and discussion

Among the relatively small number of CDAs developed for the determination of the absolute configuration of carboxylic acids,[4] 2-phenyl-1-cyclohexanol (**1**, Fig. 1) is one of the most widely used and commercially available agents.[4a] We envisioned that aminoindanol derivative **2** could serve as a CDA for carboxylic acids because of its structural similarities with **1**: both are rigid, cyclic secondary alcohols and, once carboxylic acids are connected to the hydroxyl group through an ester bond, the agent's aromatic ring is expected to be positioned close to the attached acid. Unlike compound **1** in which the aromatic group is directly attached to a chiral center, compound **2** has an aromatic group linked through a cyclic imide group to *cis*-1-amino-2-indanol, which is readily available from the chiral pool. Therefore, we expected that the aromatic group of compound **2** could be varied in a simple and straightforward manner.

To investigate the utility of compound **2** as a new CDA, we prepared the corresponding esters of α-chiral carboxylic acids of known absolute configuration. First, both enantiomers of compound **2** were synthesized in high yields by reacting corresponding enantiomers of *cis*-1-amino-2-indanol with phthalic or 1,8-naphthalic anhydride. These indanol derivatives were then coupled with chiral carboxylic acids using conventional carboxylic-acid activating reagents.[5] The ^{1}H NMR

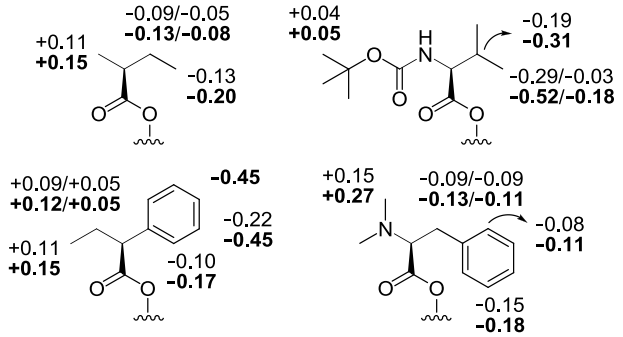


Fig. 2 Δδ values of **2a** (in lightface) and **2b** (in boldface) esters of chiral carboxylic acids. The ^{1}H NMR spectra were recorded in $CDCl_3$.

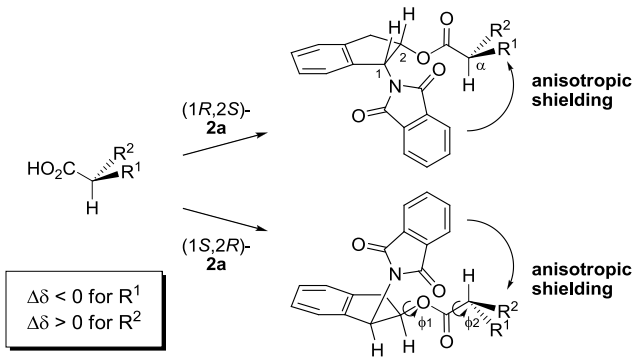


Fig. 3 Conformational analysis of (*1R,2S*)- and (*1S,2R*)-**2a** esters and the expected shielding effect on the carboxylic acid substituents.

signals of the prepared esters were assigned using COSY and NOESY NMR spectroscopic methods and the chemical shifts were compared between the two diastereomeric esters to calculate chemical shift differences (Δδ = δ(1*R*,2*S*) - δ(1*S*,2*R*)).

As summarized in Fig. 2, all the tested compounds showed the same trend in their Δδ values: if the general structure of carboxylic acids is represented as in Fig. 3, the chemical shift difference between the diastereomeric esters are always negative for the R^1 substituent and positive for the R^2 substituent. This consistent and uniform distribution of the Δδ values could be explained on the basis of conformer search calculations.[6] In the lowest energy conformation of the **2a** ester of isobutyric acid[7] (**sp1** in Fig. 4), the (C2—O)—(C—Cα) ester bond adopts an *anti* planar conformation, and the (H—C2)—(O—C) and (O—C)—(Cα—H) bonds (with dihedral angles ϕ1 and ϕ2, respectively) adopt *syn* periplanar conformations. This overall arrangement around the ester bond is consistent well with the general conformational preference of carboxylic esters.[1a,4a] The aromatic ring of the phthalimide group faces toward the ester group and this orientation is preferred to minimize the steric interaction between the cyclic imide and indanol ring structures. In this representative conformation, the phthalimide group is positioned more closely to the methyl group corresponding to the R^1 substituent than to the other methyl group corresponding to the R^2 substituent. Therefore, it is expected that the Δδ value should be positive for the R^1 substituent and negative for the R^2 substituent, and this is in good agreement with the experimental results (Fig. 2).

As anticipated, the anisotropic effect of CDA **2** could be manipulated effectively by installing different anisotropic groups

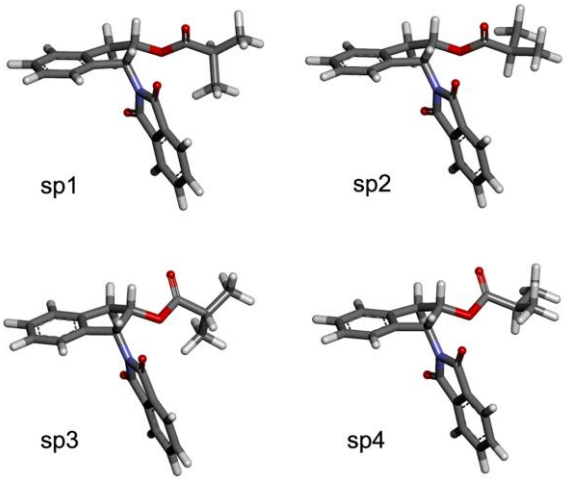


Fig. 4 Stable conformers of (1*R*,2*S*)-**2a** ester of isobutyric acid (R^1 = R^2 = Me). The energy differences between the most stable conformer **sp1** and the next three stable conformers **sp2**-**4** are less than 5 kJ/mol.

Table 1 Δδ values of **2a** and **2b** esters of (*S*)-2-methylbutyric acid obtained in various NMR Solvents

Solvent	ε[a]	**2a**		**2b**	
		CH_3CH-	CH_3CH_2-	CH_3CH-	CH_3CH_2-
$CDCl_3$	4.8	+0.11	–0.13	+0.15	–0.20
[D_8]toluene	2.4	+0.08	–0.10	+0.13	–0.18
[D_6]acetone	20.7	+0.13	–0.14	+0.16	–0.21
[D_4]methanol	32.7	+0.13	–0.14	+0.18	–0.23
[D_3]acetonitrile	37.5	+0.14	–0.16	+0.20	–0.26
[D_6]DMSO	46.7	+0.16	–0.18	+0.20	–0.27

[a] Solvent dielectric constant from ref.[9]

through simple and straightforward synthesis. The Δδ values obtained with compound **2a** in $CDCl_3$ are similar or slightly greater in magnitude than the corresponding values reported with compound **1**.[4a] A second version compound **2b** with a lager anisotropic group afforded significantly enhanced Δδ values.[8] These values have same signs as those of corresponding **2a** esters suggesting that the anisotropic group change has little effect on the overall conformational preference and, therefore, the structure analysis shown in Fig. 3 is also applicable to **2b** esters.

Next, we tested the solvent dependence of the Δδ value to find out whether the agents could be used as effective CDAs in various solvents. The Δδ values of **2a** and **2b** esters of (*S*)-2-methylbutyric acid (R^1 = Et, R^2 = Me) were measured in commonly used NMR solvents (Table 1). All these values have same signs as those obtained in $CDCl_3$ indicating that the esters retain the same conformational preference in the tested solvents. Interestingly, the Δδ values of this simple carboxylic acid get increased with the solvent polarity suggesting that compound **2** could be used as a reliable CDA even in polar solvents.

To further understand the solvent effect on the Δδ values, we examined solvation energies of the stable conformations **sp1**-**4** of the isobutyric acid **2a** ester (Fig. 4). According to Table 2 comparing the energies of solvation in $CHCl_3$ and in DMSO, conformers **sp1** and **sp2** show relatively large changes in solvation energy (ΔE_{sol}). This is presumably because these conformers with positive dihedral angle ϕ1 have larger solvent-accessible polar surface areas, especially around the indanol

Table 2 Solvation energy (E_{sol}) of the **2a** ester of isobutyric acid[a]

Conformer	ϕ1/ϕ2 (degree)	E_{sol} (kJ/mol) $CHCl_3$	E_{sol} (kJ/mol) DMSO	ΔE_{sol}[b] (kJ/mol)
sp1	+39.6/+53.8	–67.85	–68.55	–0.70
sp2	+37.7/–36.1	–69.47	–70.45	–0.98
sp3	–45.2/–44.3	–68.05	–68.04	+0.01
sp4	–38.9/+39.3	–68.70	–69.13	–0.43

[a] Calculated using an empirical solvation model, SM8, parameterized for the 6-31G* basis set.[10] [b] $\Delta E_{sol} = E_{sol}(DMSO) - E_{sol}(CHCl_3)$.

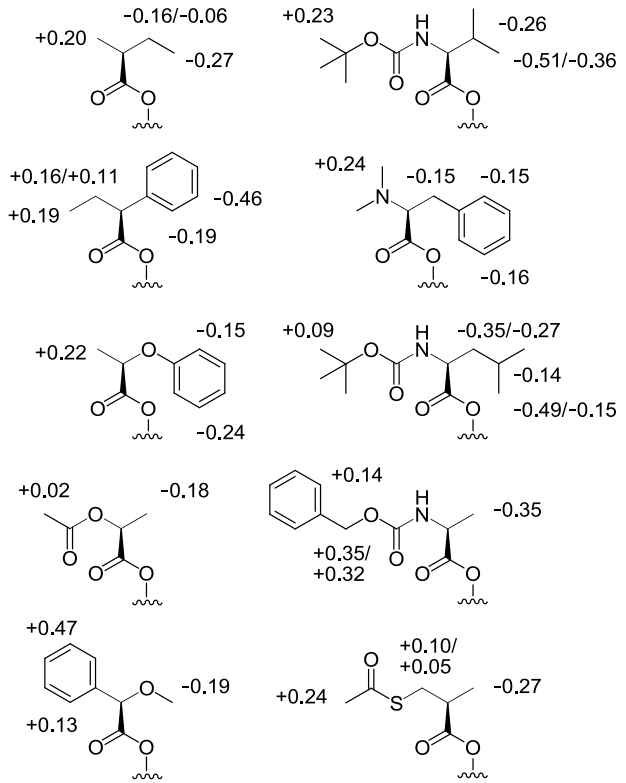


Fig. 5 Δδ values of **2b** esters of chiral carboxylic acids. ^{1}H NMR spectra were recorded in [D_6]DMSO.

oxygen atom. As a result, conformers **sp1** and **sp2** are expected to be populated more in DMSO than in $CHCl_3$. The phthalic group and the attached acid get slightly closer in conformers **sp1** and **sp2** than in **sp3** and **sp4** so that the Δδ values are expected to be increased in DMSO.

The results obtained in [D_6]DMSO with diverse carboxylic acids (Fig. 5) clearly show that compound **2b** could be used as a reliable CDA in this polar NMR solvent also. Although the solvent effect strongly depends on the acid structure (Fig. 2 vs. Fig. 5) presumably because of the variation in conformational flexibility and intramolecular interaction, large Δδ values with consistent signs are observed not only for the protons close to the chiral center but also for the protons six or seven bonds away.

Conclusions

In summary, we have presented aminoindanol-based CDAs for the determination of the absolute configuration of α-chiral carboxylic acids. The agents were prepared through efficient one-step reaction between an achiral cyclic anhydride and readily available *cis*-aminoindanol, and the anisotropic effect of the agent could be changed easily by employing different cyclic anhydrides in the synthesis. The diastereomeric esters of compound **2** showed significantly large chemical shift differences in various NMR solvents suggesting that this CDA could be used as a reliable and versatile reagent for the absolute configuration assignment of α-chiral carboxylic acids.

Experimental

2-((1*R*,2*S*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)isoindoline-1,3-dione ((1*R*,2*S*)-**2a**): (1*R*,2*S*)-1-Amino-2-indanol (0.50 g, 3.3 mmol) and phthalic anhydride (0.51 g, 1.0 equiv.) were suspended in toluene (30 mL), and *N*,*N*-diisopropylethylamine (DIEA, 0.59 mL, 1.0 equiv.) was added. The mixture was refluxed overnight while the water formed was removed using a Dean-Stark apparatus. After cooling down to room temperature, the resulting mixture was washed with aqueous HCl (1 N), saturated $NaHCO_3$ solutions and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by SiO_2 chromatography to give the title compound as a yellowish-white solid (0.81 g, 87 %). m.p. 138–141℃. $[\alpha]_D^{22}$ = –52 (*c* = 0.5 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.88 (m, 2 H), 7.72–7.77 (m, 2 H), 7.28–7.35 (m, 2 H), 7.10–7.23 (m, 2 H), 5.82 (d, ^3J = 6.3 Hz, 1 H, C1H), 4.75–4.81 (m, 1 H, C2H), 3.36 (dd, ^2J = 16.6 Hz, ^3J = 6.2 Hz, 1 H, C3H), 3.26 (dd, ^2J = 16.6 Hz, ^3J = 3.3 Hz, 1 H, C3H'), 2.70 (d, ^3J = 10.8 Hz, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 140.2, 137.2, 134.4, 132.0, 128.7, 127.2, 125.7, 124.3, 123.6, 74.4, 57.9, 41.4. HRMS (FAB) calcd. for $[M+H]^+$ $C_{17}H_{14}NO_3$: 280.0974, found: 280.0969.

2-((1*S*,2*R*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)isoindoline-1,3-dione ((1*S*,2*R*)-**2a**): The procedure described for (1*R*,2*S*)-**2a** was followed except that (1*S*,2*R*)-1-amino-2-indanol was used instead of (1*R*,2*S*)-1-amino-2-indanol. The spectral data were virtually identical to those of (1*R*,2*S*)-**2a** except $[\alpha]_D^{22}$ = +53 (*c* = 0.5 in $CHCl_3$).

2-((1*R*,2*S*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-benzo-[*de*]isoquinoline-1,3(2*H*)-dione ((1*R*,2*S*)-**2b**): The procedure described for (1*R*,2*S*)-**2a** was followed except that 1,8-naphthalic anhydride was used instead of phthalic anhydride. Yield: 88%. m.p. 207–214℃. $[\alpha]_D^{22}$ = –123 (*c* = 0.5 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45–8.74 (m, 2 H), 8.23–8.28 (m, 2 H), 7.71–7.84 (m, 2 H), 7.36 (d, ^3J = 6.4 Hz, 1 H), 7.27 (t, ^3J = 7.4 Hz, 1 H), 7.18 (t, ^3J = 7.4 Hz, 1 H), 7.04 (d, ^3J = 7.4 Hz, 1 H), 6.67 (d, ^3J = 7.1 Hz, 1 H, C1H), 4.90–4.97 (m, 1 H, C2H), 3.49 (dd, ^2J = 16.8 Hz, ^3J = 6.7 Hz, 1 H, C3H), 3.31 (dd, ^2J = 16.8 Hz, ^3J = 2.7 Hz, 1 H, C3H'), 3.18 (d, ^3J = 11.3 Hz, 1 H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 165.3, 139.6, 138.9, 134.4 (2 C), 132.1, 131.8, 131.6, 128.4, 127.8, 127.3, 127.2, 126.8, 125.6, 123.2, 123.0, 122.6, 74.2, 59.8, 42.4. HRMS (FAB) calcd. for $[M+H]^+$ $C_{21}H_{16}NO_3$: 330.1130, found: 330.1126.

2-((1*S*,2*R*)-2-Hydroxy-2,3-dihydro-1*H*-inden-1-yl)-1*H*-benzo-[*de*]iso-quinoline-1,3(2*H*)-dione ((1*S*,2*R*)-**2b**): The procedure

described for (1*R*,2*S*)-**2a** was followed except that (1*S*,2*R*)-1-amino-2-indanol and 1,8-naphthalic anhydride were used instead of (1*R*,2*S*)-1-amino-2-indanol and phthalic anhydride, respectively. The spectral data were virtually identical to those of (1*R*,2*S*)-**2b** except $[\alpha]_D^{22}$ = +121 (*c* = 0.5 in $CHCl_3$).

General Procedure for the Preparation of compound 2 esters: A carboxylic acid, bis(2-oxo-3-oxazolidinyl)-phosphinic chloride (BOP-Cl, 1.5 equiv.), and 4-(dimethylamino)pyridine (0.1 equiv.) were dissolved in DMF. To the solution was added DIEA (2.5 equiv.) followed by compound **2a** or **2b** (1.0 equiv.). After stirring overnight, the mixture was diluted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by SiO_2 chromatography.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Copies of the NMR spectra and characterization data for **2a**, **2b**, and their esters. See DOI: 10.1039/b000000x/

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5 Partial epimerizaton (< 10%) at the chiral center of carboxylic acids was observed during the synthesis of **2a** or **2b** esters of α-aryl carboxylic acids.

6 Spartan'10 (Wavefunction, Inc.) was used for the calculation. A Monte Carlo conformation search was performed by using the MMFF force field to find stable conformations, which were then used as initial structures for the density functional geometry optimization (B3LYP/6-31G*).

7 In the computational studies, isobutyric acid was chosen as the simplest model of α-branched carboxylic acids.

8 For the case of compound **1**, the size of the aromatic group has little effect on the chemical shift difference: replacing the benzene ring with naphthyl or anthryl rings did not produce higher shift.[4a] This was ascribed due to the direction of maximum shielding focused on the immediate neighbour of the chiral center.

9 *NMR Solvent Data Chart*, Cambridge Isotope Laboratories, Inc., Andover, MA.

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