ORGANIC LETTERS

2005
Vol. 7, No. 24
5485−5487

Structurally Simple, Modular Amino Alcohols for the Recognition of Carboxylic Acids. Application to the Development of a New Chiral Solvating Agent

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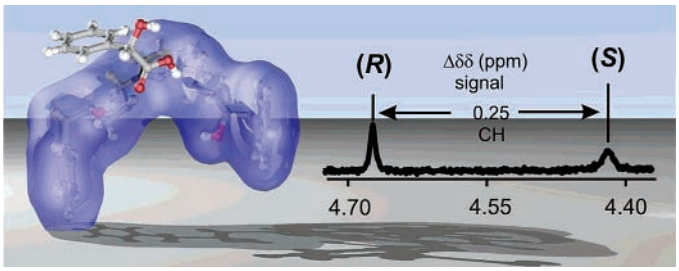
Received October 14, 2005

ABSTRACT



Two flexible receptors for carboxylic acids, based on 1-amino-3-fluoro-2-alcohol functional arrays and built on aminomethylpyridine platforms, are described. The C_2-symmetric one [from 2,6-bis(aminomethyl)pyridine] has been shown to be an efficient CSA due to its ability to form geometrically different diastereomeric complexes enabling the discrimination between the enantiomers of a series of carboxylic acid in the ^{1}H NMR spectra.

While rigid structures with either built-in cages[1] or with strong conformational bias[2] are highly employed tools in the molecular recognition kit, much more simple structures with enough structural flexibility could well show equal or even higher affinity through a wrap-around action mode.[3] Moreover, if these flexible selectors were modular in nature, a structural fine-tuning could allow optimization of the receptor characteristics toward specific substrates.[4]

Nucleophilic ring-opening of enantiopure epoxides provides an easy access to conformationally flexible and spaced functional arrays, and in fact, we have used this principle for the development and optimization of highly efficient ligands for asymmetric catalysis.[5] We wish to report now how fluoroepoxide **1**, readily available in enantiomerically

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(1) (a) Yoshizawa, M.; Kusukawa, T.; Kawano, M.; Ohhara, T.; Tanaka, I.; Kurihara, K.; Niimura, N.; Fujita, M. *J. Am. Chem. Soc.* **2005**, *127*, 2798−2799. (b) Brotin, T.; Lesage, A.; Emsley, L.; Collet, A. *J. Am. Chem. Soc.* **2000**, *122*, 1171−1174. (c) Helgeson, R. C.; Paek, K.; Knobler, C. B.; Maverick, E. F.; Cram, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5590−5604. (d) Kerckhoffs, J.; van Leeuwen, F. W. R.; Spek, A. L.; Kooijman, H.; Crego-Calama, M.; Reinhoudt, D. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5717−5722.

(2) (a) Atwood, J. L.; Szumna, A. *J. Am. Chem. Soc.* **2002**, *124*, 10646−10647. (b) Rudkevich, D. M.; Hilmersson, G.; Rebek, J. *J. Am. Chem. Soc.* **1998**, *120*, 12216−12225.

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(4) Berger, M.; Schmidtchen, F. P. *J. Am. Chem. Soc.* **1996**, *118*, 8947−8948.

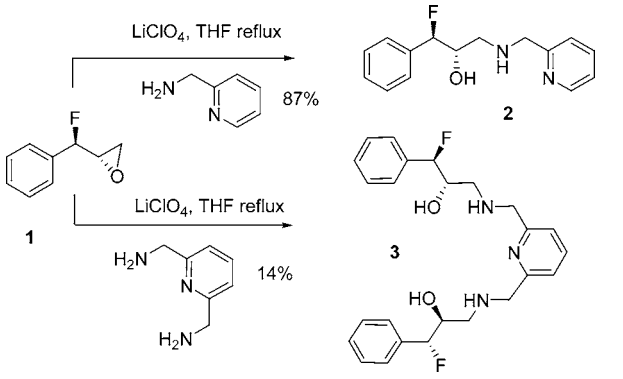
(5) See for instance: Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532−2543 and references therein

10.1021/ol052490b CCC: $30.25
Published on Web 11/01/2005

pure form,[6] can be converted in a single step into flexible structures involving one or more stereodefined 1-amino-3-fluoro-2-alcohol moieties and how the resulting products show outstanding features in the complexation of carboxylic acids.[7] As an application of this behavior, we have developed a new chiral solvating agent (CSA)[8] for the fast evaluation of enantiomeric composition of carboxylic acids.[9]

Ring-opening of **1** with 2-aminomethylpyridine leads to the extremely simple receptor **2** (Scheme 1). According to

Scheme 1. Synthesis of Receptors **2** and **3**



our design, binding to the carboxy group would take place through the 2-aminomethylpyridine unit by a combination of acid−base and hydrogen-bonding interactions. In addition, it was expected that the polar substituents at the stereogenic centers near the binding unit could modulate the enantioselectivity and the binding affinity to structurally different carboxylic acids. The binding affinity (molecular recognition) of receptor **2** for a series of enantiomerically pure (*R*)-α-substituted chiral carboxylic acids, phenylacetic acid, and phenylglyoxylic acid (Figure 1) in $CDCl_3$ was next studied by ^{1}H NMR titration methods. In all cases, the titration data obtained for the methine proton α to the hydroxyl in **2** could be fitted to a 1:1 binding model.[10]

The calculated association constants and complexation-induced shift (CIS) are summarized in Table 1. Very gratifyingly, the data in Table 1 indicate that receptor **2** is selective in the molecular recognition of carboxylic acids with different α substituents. For example, while receptor **2** binds phenylacetic acid (**7**) with a K_a of 163 M^{-1} (ΔG =

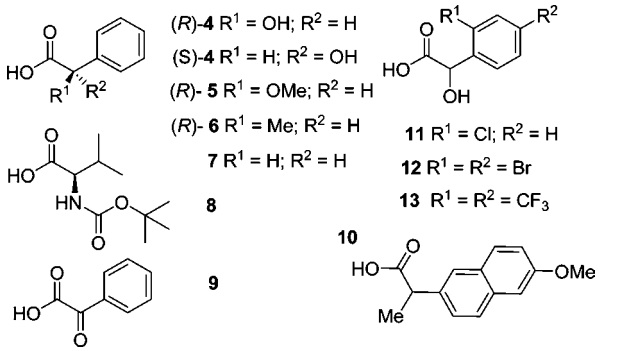


Figure 1. Molecular structures of the carboxylic acids used in the titrations.

−3.0 kcal/mol), its binding affinity toward α-hydroxyphenylacetic acid (*R*)-**4** and α-ketophenylacetic (**9**) increases to −5.5 and −6.5 kcal/mol, respectively. These results demonstrate that the affinity is modulated by the hydrogen bonding capabilities of the α-susbtituent of the carboxylic acid and also suggest the implication of the hydroxyl group of **2** in the stabilization of some complexes. We believe that the selectivity and high affinity observed for such a structurally simple receptor like **2** is truly remarkable.

Next, we investigated the enantioselectivity of receptor **2** toward the two enantiomers of mandelic acid (**4**). Using ^{1}H NMR titrations, we calculated the association constant values of 7100 M^{-1} for the *S* enantiomer and 12700 M^{-1} for the *R* enantiomer ($\Delta\Delta G^o$ = 0.4 kcal/mol). Although receptor **2** shows low enantioselectivity toward the mandelic acid enantiomers, the addition of 1 equiv of the receptor to a racemic mixture of **2** in $CDCl_3$ produces a chemical shift difference of 0.013 ppm for the methine proton assigned to each enantiomer, clearly indicating a conformational adaptability in the receptor. The crystal structure of the diastereomeric complex **2**·(*S*)-**4** sheds some light on the factors governing this behavior (see the Supporting Information).

These results stimulated us to prepare (see Scheme 1) and study the behavior of **3**, the C_2-symmetric version of receptor

Table 1. Calculated Association Constants and Complexation Induced Shift (CIS) for the Binding of Receptors **2** and **3** with a Series of Carboxylic Acids

carboxylic acid	receptor	K_a[a] (M^{-1})	CIS[b]	$\Delta G°$ (kcal mol^{-1})
(*R*)-**4**	**2**	12700	4.54	−5.5
(*S*)-**4**	**2**	7100	4.54	−5.1
5	**2**	1000	4.53	−4.0
6	**2**	570	4.19	−3.7
7	**2**	163	4.28	−3.0
8	**2**	850	4.45	−3.9
9	**2**	74000	4.63	−6.5
(*R*)-**4**	**3**	26000	4.51	−5.9
(*S*)-**4**	**3**	25000	4.39	−5.9

[a] All association constants were determined in $CDCl_3$ solution by ^{1}H NMR titrations. Estimated errors are ±10%. [b] Complexation-induced shift for the methine proton of the receptor in ppm.

(6) Rodriguez-Escrich, S.; Popa, D.; Jimeno, C.; Vidal-Ferran, A.; Pericàs, M. A. *Org. Lett.* **2005**, *7*, 3829−3832.

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(8) (a) Parker, D. *Chem. Rev.* **1991**, *91*, 1441−1457. (b) Wenzel, T. J.; Wilcox, J. D. *Chirality* **2003**, *15*, 256−70.

(9) For recent examples of CSA for carboxylic acids, see: (a) Yang, D.; Li, X.; Fan, Y.-F.; Zhang, D.-W. *J. Am. Chem. Soc.* **2005**, *127*, 7996−7997. (b) Zheng, Y. S.; Zhang, C. *Org. Lett.* **2004**, *6*, 1189−1192. (c) Port, A.; Virgili, A.; Alvarez-Larena, A.; Piniella, J. F. *Tetrahedron: Asymmetry* **2000**, *11*, 3747−3757.

(10) Titration data were analyzed by fitting to a simple 1:1 binding isotherm using the software SPECFIT 3.0: (a) Gampp, H.; Maeder, M.; Meyer, C. J.; Zuberbühler, A. D. *Talanta* **1985**, *32*, 95−101. (b) Gampp, H.; Maeder, M.; Meyer, C. J.; Zuberbühler, A. D. *Talanta* **1986**, *33*, 943−951. Job plots are also in agreement with the exclusive formation of 1:1 stoichiometry complexes.

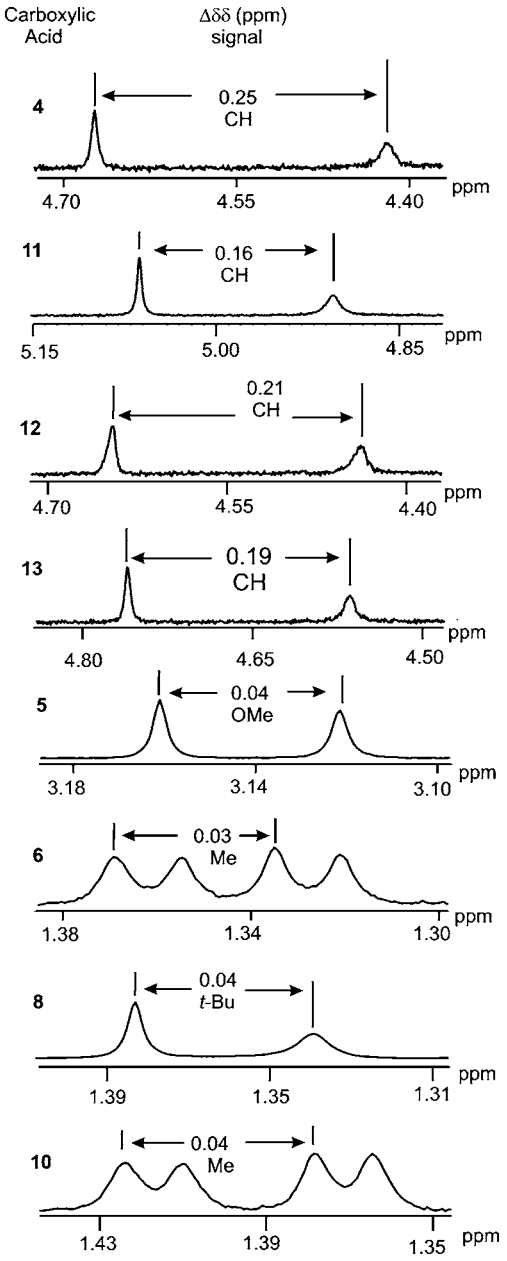

Figure 2. Selected regions of the ^{1}H NMR spectra and measurement of the ^{1}H chemical shift nonequivalences ($\Delta\Delta\delta$) for a series of racemic carboxylic acids in the presence of 1 equiv of **3** at 25 °C using a 500 MHz instrument.

2 with the expectation of facilitating a multitopic interaction with the carboxylic acid. This, in turn, could produce a higher binding affinity, greater geometrical differentiation between diastereomeric complexes and, hence, a larger signal separation in the NMR spectra. Compared to **2**, the binding affinity of **3** for mandelic acid enantiomers, (*R*)-**4** and (*S*)-**4**, increased 2-fold and 3-fold, respectively. The crystal structure of the diastereomeric complex formed between **3** and (*S*)-**4** shows the establishment of a ditopic interaction between the amino and hydroxyl groups of **3** and the carboxy function of (*S*)-**4** and,as in the case of **2**, the conformational adaptability of the receptor (see the Supporting Information). On the other hand, while the enantioselectivity toward the two enantiomers of mandelic acid (Table 1 last two entries) was reduced, *the difference in the chemical shift of the methine protons on the two enantiomers of mandelic acid in the presence of one equivalent of **3** increased to 0.25 ppm* (Figure 2), a value 19 times greater that the observed shift with receptor ***2***.

In view of this observation, we decided to investigate the properties of **3** as CSA in the determination of the optical purity of other chiral carboxylic acids using ^{1}H NMR spectroscopy. To this end, we selected a variety of racemates of α-substituted carboxylic acids, including the pharmacologically relevant naproxen (**10**).

Figure 2 summarizes the obtained results in deuterated chloroform in the presence of 1 equivalent of **3** with respect to the racemate at 2 mM concentration. In all cases the separation of a proton signal for both enantiomers is large enough to have baseline resolution in the spectra measured on a 500 MHz NMR instrument at room temperature. The discrimination of signals for each enantiomer of the carboxylic acid can also be achieved with **3** even when the substituent in the α position is not a hydroxyl group. Altogether, these results indicate that **3** is capable of forming diasteromeric complexes with intrinsically different geometries. This in turn yields a good separation of proton signals for each enantiomer, thus making **3** a most efficient CSA for chiral carboxylic acids.

In summary, we have reported the straightforward preparation of enantiomerically pure (1*R*,2*S*)-1-fluoro-1-phenyl-3-(pyridin-2-ylmethylamino)propan-2-ol **2** and its C_2-symmetric version **3**, two flexible receptors based on 1-amino-3-fluoro-2-alcohol functional arrays. These compounds, which are structurally very simple, represent the first examples of receptors for carboxylic acids assembled through the regioselective ring-opening of enantiomerically pure epoxides. Despite its structural simplicity, both bind carboxylic acids in deuterated chloroform with high affinity and remarkable selectivity. Furthermore, receptor **3** has been shown to be an efficient CSA due to its ability to form geometrically different diastereomeric complexes enabling the discrimination between the enantiomers of a series of carboxylic acid in the ^{1}H NMR spectra.

Acknowledgment. We thank Dirección General de Investigación, Ministerio de Ciencia y Tecnología (Grant Nos. BQU2002-02459 and BQU2002-04651), DURSI (Grant No. 2001SGR50), Fundación Ramon Areces and ICIQ Foundation for financial support. We also thank the Torres-Quevedo program for a contract to F.C.

Supporting Information Available: Experimental procedures and characterization data for receptors **2** and **3**. Curve fittings of the ^{1}H NMR titration data and Job plots. Figures of the X-ray structures for the complexes **2**·(*S*)-**4** and **3**·(*S*)-**4**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052490B