ORGANIC LETTERS

2010
Vol. 12, No. 4
880−882

Cyclic Ketals of Tartaric Acid: Simple and Tunable Reagents for the Determination of the Absolute Configuration of Primary Amines

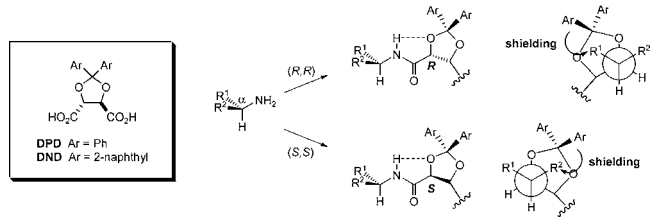
You-Jin Shim and Kihang Choi*

Department of Chemistry, Korea University, Seoul 136-701, Republic of Korea

kchoi@korea.ac.kr

Received December 23, 2009

ABSTRACT



2,2-Diphenyl-[1,3]dioxolane-4,5-dicarboxylic acid (DPD) and 2,2-dinaphthalen-2-yl-[1,3]dioxolane-4,5-dicarboxylic acid (DND) have been synthesized starting from dimethyl tartrate. DPD and DND amides of α-chiral primary amines showed significantly different ^{1}H chemical shift values depending on the stereochemistry of the derivatizing agent. On the basis of this chemical shift difference, the absolute configuration of amine substrates could be assigned. DND amides showed significantly larger chemical shift differences than the corresponding DPD amides allowing for a more error-free assignment.

In the advent of asymmetric synthesis and natural product chemistry, there is a growing demand for simple and efficient methods to determine absolute configurations of chiral molecules. One of the traditional approaches for absolute configuration assignment is to use NMR spectroscopy:[1] a chiral compound is derivatized with two enantiomers of a chiral derivatizing agent (CDA), and the chemical shift difference ($\Delta\delta$) between the two resulting diastereomers is obtained by comparing the NMR spectra. Proper analysis of the $\Delta\delta$ values based on the diastereomer conformations and the anisotropic effect produced by the CDA can lead to the absolute configuration assignment of the chiral compound.

Various CDAs have been developed for several classes of chiral compounds, and for the case of primary amines, Mosher's α-methoxytrifluoromethylphenylacetic acid (MTPA, **1**) and Trost's α-methoxyphenylacetic acid (MPA, **2**) are the two most widely used reagents.[2] Because of the conformational flexibility, however, the diastereomeric amides derived from these reagents usually show small $\Delta\delta$ values, and the development of more efficient reagents producing large $\Delta\delta$ values is still an active area of research.[3]

In a continuing effort to develop efficient CDAs,[4] we report here that 2,2-diaryl-[1,3]dioxolane-4,5-dicarboxylic acid **3** can be used as a simple and reliable reagent for the

(1) (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17. (b) Wenzel, T. J. *Discrimination of Chiral Compounds Using NMR Spectroscopy*; Wiley-Interscience: Hoboken, 2007.

(2) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (c) Trost, B. M.; Belletire, J. L.; Godleski, S.; Mcdougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 2370.

(3) (a) Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1999**, *64*, 4669. (b) Porto, S.; Duran, J.; Seco, J. M.; Quiñoá, E.; Riguera, R. *Org. Lett.* **2003**, *5*, 2979. (c) García, R.; Seco, J. M.; Vázquez, S. A.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **2006**, *71*, 1119. (d) Takeuchi, Y.; Segawa, M.; Fujisawa, H.; Omata, K.; Lodwig, S. N.; Unkefer, C. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4617. (e) Thillaye du Boullay, O.; Alba, A.; Oukhatar, F.; Martin-Vaca, B.; Bourissou, D. *Org. Lett.* **2008**, *10*, 4669.

(4) Ahn, H. C.; Choi, K. *Org. Lett.* **2007**, *9*, 3853.

10.1021/ol902942k
Published on Web 01/22/2010

determination of the absolute configuration of chiral amines. Unlike MTPA and MPA, compound **3** has C_2 symmetry, and the carboxylic acid and aromatic groups are constrained through a [1,3]dioxolane ring (Figure 1). Once the dicarboxylic acid is linked to 2 equiv of a primary amine substrate through amide bonds, the dioxolane oxygen and amide hydrogen atoms will be located in close proximity, and intramolecular hydrogen bonds are expected to be formed between these atoms.[5,6] Both the cyclic structure and the intramolecular interaction might help to reduce the conformational flexibility of the amide molecule and, as a result, to induce large $\Delta\delta$ values.

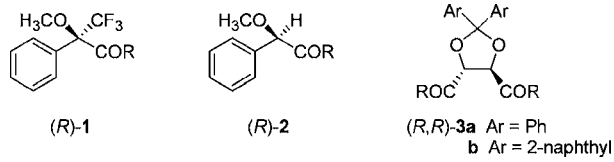


Figure 1. Structures of MTPA, MPA, DPD, and DND reagents (R = OH).

To test the utility of compound **3** as a CDA, we first synthesized (*R,R*)- and (*S,S*)-2,2-diphenyl-[1,3]dioxolane-4,5-dicarboxylic acid (DPD, **3a**) starting from dimethyl L- and D-tartrate, respectively; the dioxolane ring was constructed through an acid-catalyzed condensation reaction with benzophenone dimethylketal, and the resulting dimethyl ester was hydrolyzed under basic conditions.[7] The dicarboxylic acid **3a** was then coupled with 2 equiv of α-chiral primary amines of known absolute configuration. The ^{1}H NMR signals were assigned by using COSY and NOESY spectroscopy, and the chemical shift values were compared between the diastereomeric amides to obtain $\Delta\delta^{RS}$ values (Figure 2). Because of molecular symmetry, only one set of NMR signals were observed from the amine substrate.

All the tested compounds showed the same trend in their $\Delta\delta^{RS}$ values. If the structure of amine substrates is represented as in Figure 3a, the $\Delta\delta^{RS}$ values of DPD amides are always negative for the R^1 substituent and always positive for the R^2 substituent. These consistent $\Delta\delta^{RS}$ values could be explained on the basis of the conformational analysis summarized in Figure 3. In the representative conformation of DPD amides, the C═O bond and the ajacent C−O bond are depicted in an *anti* conformation because this arrangement could be stabilized by the intramolecular interaction between the amide hydrogen and dioxolane oxygen atoms. In (*R,R*)-DPD amides, the aryl group of the CDA and the R^1 substituent of the amine substrate are located on the same

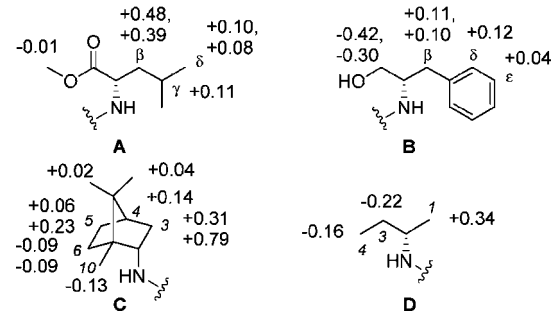


Figure 2. $\Delta\delta^{RS}$ values ($\delta(R,R) - \delta(S,S)$) of DPD amides (**3a**, R = **A**−**D**) of chiral amines.

side of the amide plane, and the anisotropic shielding is expected for the R^1 substituent. In (*S,S*)-DPD amides, on the other hand, it is the R^2 substituent that is on the same side with the aryl group, and therefore the R^2 substituent is under the shielding effect. As a result, the $\Delta\delta^{RS}$ value should be negative for the R^1 substituent and positive for the R^2 substituent. This analysis is in good agreement with the experimental data shown in Figure 2.

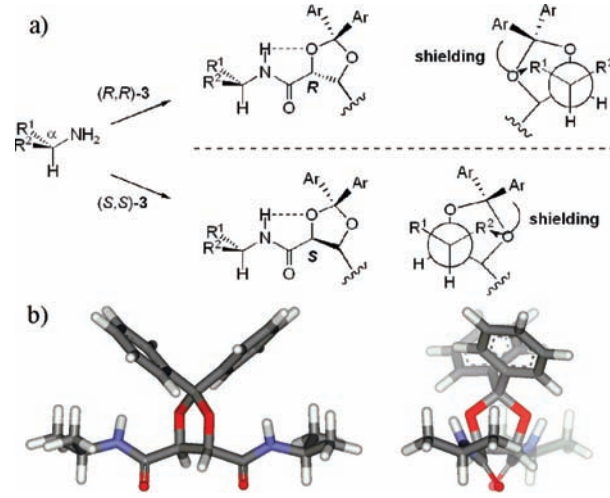


Figure 3. (a) Representative conformations of (*R,R*)- and (*S,S*)-**3** amides. In the Newman projection, the amide bond is omitted for clarity. (b) The calculated structure of the (*S,S*)-DPD amide of isopropylamine: a side view (left) and a front view (right with depth cues) onto the [1,3]dioxolane ring. Atoms are colored following the CPK color code (C, gray; H, white; O, red; N, blue).

The conformation preference of DPD amides was investigated further by computational modeling studies.[8] In the lowest-energy structure of the (*S,S*)-DPD amide of isopropylamine (Figure 3b), the (H−Cα)−(N−H) and (O═C)−(C−O)

(5) For an example of a CDA using the intramolecular hydrogen bond included in a five-membered quasi-ring, see ref 3e.

(6) (a) The role of an intramolecular hydrogen bond in determination of molecular conformation has been well considered.[6b] (b) *The Hydrogen Bond*; Schuster, P., Zundel, G., Sandorfy, C., Eds.; North-Holand: Amsterdam, 1976.

(7) The detailed synthesis and chracterization are described in the Supporting Information.

(8) Spartan'06 (Wavefunction, Inc.) was used for the calculation. A Monte Carlo conformation search was performed by using the MMFF force field to find the lowest-energy conformation, which was then used as an initial structure for the ab initio geometry optimization (RHF/6-31G**). No symmetry contraints were used in the calculations.

bonds are in *anti* arrangements. The calculated distance between the NH hydrogen atom and the proximal oxygen atom of the dioxolane ring is 2.3 Å. Two diastereotopic methyl groups of each isopropylamine substrate are located on the opposite sides of the amide plane, and the benzene ring faces toward the methyl group corresponding to the R^2 substituent. In this lowest-energy structure, little, if any, difference was observed between the local conformations of the two isopropylamide groups.

The $\Delta\delta^{RS}$ values are considerably larger for the DPD amides than for the corresponding MTPA and MPA amides (Table 1), with a few exceptions especially of the values for

Table 1. Selected $\Delta\delta^{RS}$ Values of Chiral Amines **A**−**D** Obtained with Different CDAs[a]

	amine	MTPA (**1**)[b]	MPA (**2**)[c]	DPD (**3a**)	DND (**3b**)
A	OCH_3	−0.02	−0.06	−0.01	−0.16
	β-CH_2	0.15/0.03	0.07/0.07	0.48/0.39	0.72
	γ-CH	0.23	[d]	0.11	0.31
	δ-CH_3	0.10/0.08	0.13/0.08	0.10/0.08	0.42/0.35
B	OCH_2	−0.06/−0.05	[d]	−0.42/−0.30	−0.60/−0.49
	β-CH_2	0.03	[d]	0.11/0.10	0.24/0.13
	δ-CH	0.13	[d]	0.12	0.22
C	3-CH_{endo}	0.07	0.11	0.79	1.22
	CH_{exo}	0.07	0.08	0.31	0.61
	6-CH_{endo}	[d]	−0.06	−0.09	−0.23
	CH_{exo}	[d]	−0.07	−0.09	−0.29
	10-CH_3	−0.08	−0.19	−0.13	−0.30
D	4-CH_3	[d]	−0.09	−0.16	−0.34
	3-CH_2	[d]	−0.05	−0.22	−0.41/−0.31
	1-CH_3	[d]	0.06	0.34	0.57

[a] $\delta(R) - \delta(S)$ for MTPA and MPA amides; $\delta(R,R) - \delta(S,S)$ for DPD and DND amides. [b] From ref 10. The values originally reported in ref 10a are $\Delta\delta^{SR}$ rather than $\Delta\delta^{RS}$ values. [c] From ref 9b and ref 3c. [d] Not available.

γ and δ protons. We envisioned that a similar CDA with larger aromatic rings, like naphthalene, might produce stronger anisotropic effect and, as a result, larger $\Delta\delta^{RS}$ values.[9] Preparation of this second version of reagent was simple and straightforward; 2,2-dinaphthalen-2-yl-[1,3]dioxolane-4,5-dicarboxylic acid (DND, **3b**) was synthesized following a similar pathway for **3a** except that 2,2′-dinaphthyl ketone was used instead of benzophenone. The $\Delta\delta^{RS}$ values obtained with a new set of DND amides (Figure 4) have the same signs as those obtained with DPD amides ($\Delta\delta^{RS} < 0$ for R^1, $\Delta\delta^{RS} > 0$ for R^2), indicating that DND amides have similar conformational preference as DPD amides. As expected, $\Delta\delta^{RS}$ values are significantly larger for the DND amides than for the corresponding DPD amides (Table 1).

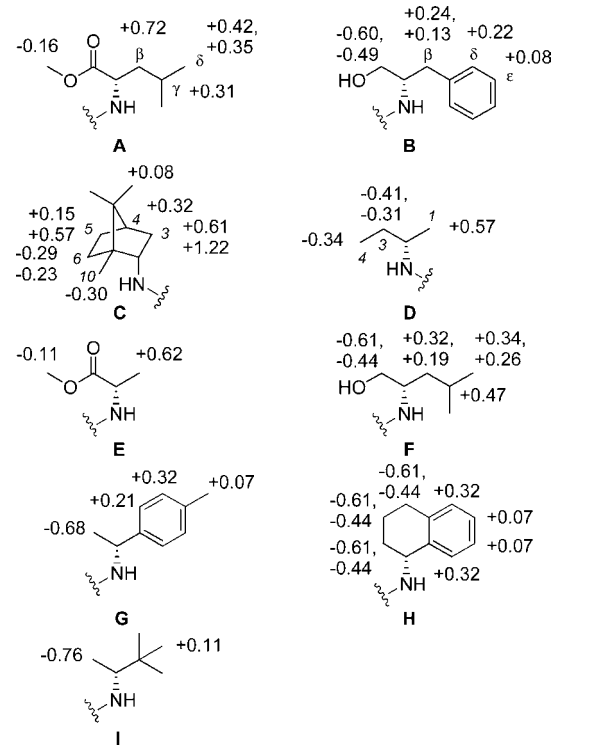


Figure 4. $\Delta\delta^{RS}$ values of DND amides of chiral amines **A**−**I**.

In conclusion, we have presented new CDAs **3** which can be prepared from dimethyl tartrate and diaryl ketones through a simple, two-step synthesis. The reagents were found to produce large $\Delta\delta$ values with a wide range of α-chiral primary amines. Because of the modular structure of **3**, a more efficient reagent with stronger anisotropic effect can be readily prepared by using a dirayl ketone with larger aromatic rings. DND amides showed significantly larger chemical shift differences than the corresponding MTPA, MPA, and DPD amides, providing a more reliable way to determine the absolute configuration of primary amines.

Acknowledgment. This work was supported by a grant (No. 2009-0059321) of MEST/NRF.

Supporting Information Available: Synthetic details and characterization data for compounds **3a** and **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902942K

(9) (a) Similar appoaches using larger aryl groups have been explored to increase the efficiency of MPA.[9b] However, arylmethoxyacetic acids with a naphthalene or anthracene ring produce small $\Delta\delta$ values of amine substrates and have no advantages over MPA or MTPA.[1a] (b) Latypov, Sh. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 1538.

(10) (a) Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2939. (b) Seco, J. M.; Latypov, S. K.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1997**, *62*, 7569.