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Tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid: a chiral derivatizing agent for the determination of the absolute configuration of secondary alcohols

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ABSTRACT

A new chiral derivatizing agent, tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid (THENA), with a represented *syn*-periplanar disposition of O–C_α–C=O as a part of the bicyclic system to lock the aromatic residue conformation and the availability of an internal reference proton for ^{1}H NMR spectral alignment, is introduced. In the determination of the absolute configuration of chiral secondary alcohols, THENA offered good uniformity of $\Delta\delta$ with high reliability, resulting in unambiguous assignment of the absolute configuration.

The introduction of chiral derivatizing agents (CDAs),[1] such as Mosher's acid **1**,[2] MPA **2**,[3] MαNP **3**,[4] 2-NMA **4**,[5] 2-ATMA **5**[6] and 9-ATMA **6**,[7] has provided chemists with a set of tools for the determination of absolute configuration by analysis of diastereotopic NMR shifts ($\Delta\delta$). In general, these CDAs apply the favored conformational equilibrium of the *syn*-periplanar array of L_k–C_α–C=O,[1a] for example, L_k = OMe in **2**–**6** (known as MPA array) (Fig. 1), and the aromatic anisotropic effect from the Ar group to differentiate the substitution patterns of the chiral substrate. Rotation around the C_α–Ar bond, however, may generate additional conformational options[8] and, in some cases, result in ambiguous absolute stereochemistry assignment.[9] Here we report the design and synthesis of tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid (THENA) **7** as a new CDA for the determination of the absolute configuration of chiral secondary alcohols. The key features of THENA include (i) the analogous MPA array as a part of the bicyclic system, to limit the rotational degree of freedom of the aromatic moiety, (ii) the observed anisotropic deshielding effect on the substituents, due to the bicyclic tether, (iii) the presence of an internal reference proton (H_{ref}) to facilitate spectral alignment, and (iv) the low cost straightforward synthesis.

The optically active acid **7** was prepared from commercially available and low cost starting materials. As summarized in Scheme 1, methyl furan-2-carboxylate (**8**) was reacted with benzenediazonium-2-carboxylate (**9**), generated from the reaction between anthranilic acid and *iso*-pentyl nitrite, in boiling 1,2-dichloroethane to yield the racemic bicyclic ester **10** in 87% yield.[10] The ester was then subjected to catalytic hydrogenation with H_2 over Pd-C (97% yield) followed by ester hydrolysis with KOH in MeOH/1,4-dioxane

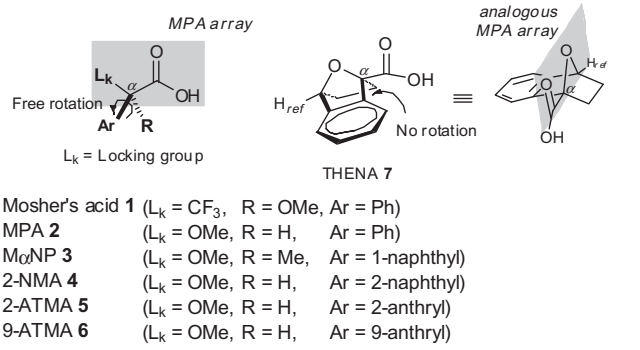

Figure 1. Common chiral derivatizing agents (CDAs) **1**–**6** and tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid (THENA) (**7**). The MPA and the analogous MPA arrays are highlighted in shade.

to give the acid **7** in 95% yield. The resulting acid was then resolved by formation of an ester with (+)-(*S*)-menthol to yield a pair of diastereomers (*S*,*S*)-**12** (47%) and (*R*,*S*)-**12** (46%). Finally, hydrolysis of each diastereomer furnished the desired (*S*)- and (*R*)-THENA **7** in 95% and 97% yields, respectively.

X-ray analysis[11] of the THENA ester (*R*,*S*)-**12** (Fig. 2) established the absolute configuration of the THENA acid. In addition, the X-ray structure confirmed the conservation of the analogous MPA plane (the *syn*-periplanar disposition of the O–C_α–CO–O–C^*–H) in the THENA ester derivative.

Accordingly, a pair of diastereomers derived from both enantiomers of THENA **7** with an optically active secondary alcohol should provide distinctive NMR characteristics. The presence of H_{ref} which is not influenced by the diastereotopic environment can serve as an internal reference for spectral alignment and thus

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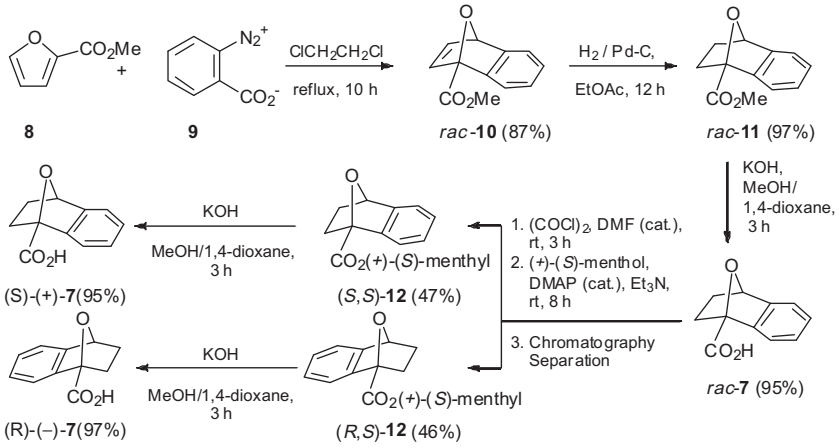

Scheme 1. Synthesis and resolution of optically active THENA 7.

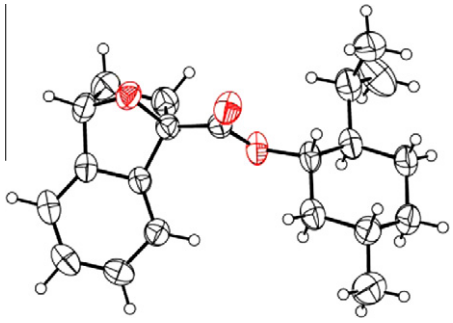

Figure 2. ORTEP diagram of the X-ray crystal structure of (*R*,*S*)-**12**, indicating the *R* configuration of the THENA moiety and the analogous MPA plane.

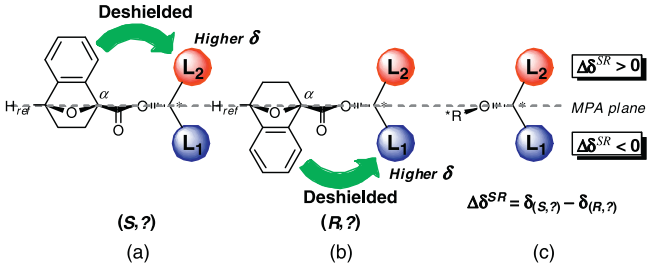

Figure 3. Influence of the anisotropic deshielding effect on subsituents L_1 and L_2 in a pair of diastereomeric esters derived from (a) (*S*)-THENA and (b) (*R*)-THENA. (c) The proposed model to correlate between the $\Delta\delta^{SR}$ value ($\Delta\delta^{SR} = \delta_{(S,?)} - \delta_{(R,?)}$ where *?* denotes an unknown absolute configuration of the chiral alcohol) and the absolute configuration. Dashed line represents the plane.

the chemical shift difference ($\Delta\delta$) can then be calculated explicitly. A model to correlate $\Delta\delta$ with the absolute configuration assignment is proposed as follows (Fig. 3). Related to MPA and its analogs, the THENA ester should adopt a *syn*-periplanar arrangement of the O–C_α–CO–O–C^*–H (dashed line)[12] and therefore position the substituents L_1 and L_2 on either the left or the right side of the plane. It should be emphasized that, since the aromatic moiety of the bicyclic ester is conformationally locked, a deshielding anisotropic effect, as opposed to a shielding effect from the phenyl ring of the MPA, is observed exclusively. Moreover, the structural rigidity in the bicyclic system eliminates the conformational equilibrium around the C_α–Ar bond, leading to an unambiguous calculation of the $\Delta\delta$ values.

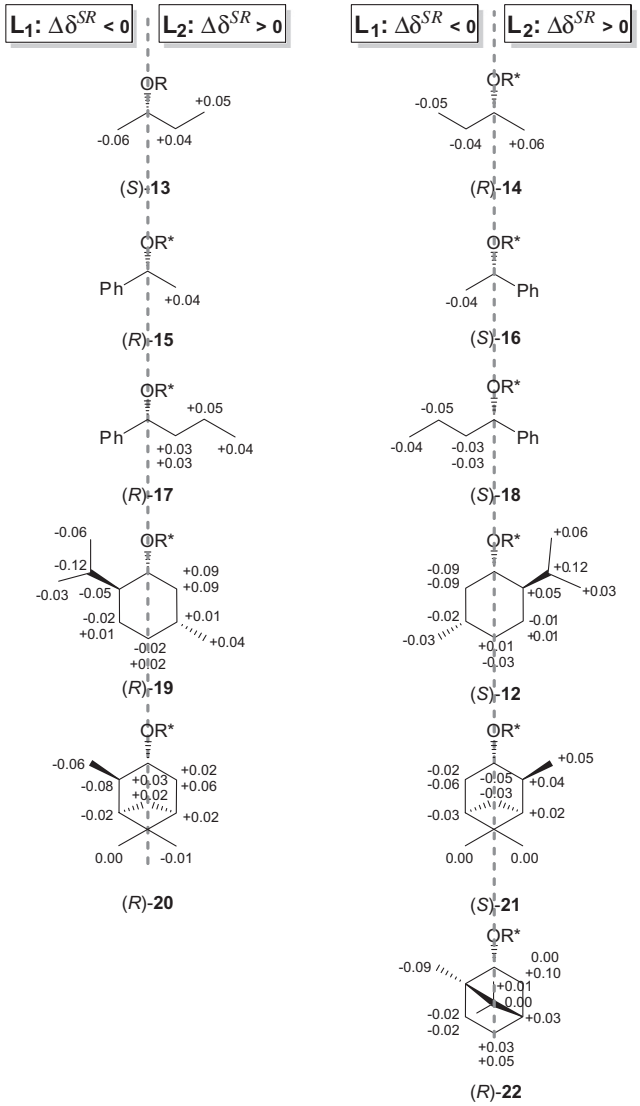

Figure 4. Chemical shift difference values ($\Delta\delta^{SR}$) and the assigned absolute configuration of the tested chiral alcohols. Substituents with positive values are on the right while those with negative values are on the left. Dashed line represents the plane.

Thus substituents L_2 of the diastereomer derived from (*S*)-THENA should be influenced by the anisotropic deshielding effect and their chemical shifts should appear at a lower field (Fig. 3a). In analogy, the chemical shifts of substituents L_1 of the diastereomer derived from (*R*)-THENA should also be shifted to a lower field (Fig. 3b). Consequently, given $\Delta\delta^{SR} = \delta_{(S,?)} - \delta_{(R,?)}$ where *?* represents the unknown configuration of chiral alcohols (Fig. 3c), the protons on L_1 should have negative $\Delta\delta^{SR}$ values ($\Delta\delta^{SR}$ <0) while the protons on L_2 should have positive $\Delta\delta^{SR}$ values ($\Delta\delta^{SR}$ >0) and the absolute configuration can then be deduced.

Application of THENA as a CDA for the determination of the absolute configuration of chiral secondary alcohols was demonstrated. Eleven chiral secondary alcohols with known absolute configuration were esterified with the acid chloride of both (*S*)- and (*R*)-THENA **7**, following a modified Trost method,[3a] to give the corresponding esters in 69–92% yields. The spectra of both diastereomers were aligned with respect to the chemical shift of H_{ref}, and the chemical shift difference ($\Delta\delta^{SR}$) of the corresponding protons in the diastereomeric (*S*)- and (*R*)-esters, respectively, was computed and the values shown in Figure 4. It is worth mentioning that, although the $\Delta\delta^{SR}$ values of the THENA esters were relatively smaller than those of the MPA analogs due to the weaker deshielding effect, the use of H_{ref} as an internal reference facilitated reliable calculation of the $\Delta\delta^{SR}$ value. In addition, the signs of $\Delta\delta^{SR}$ of the protons situated on the same side of the plane were observed with uniformity. Thus, according to the proposed model, substituents with positive $\Delta\delta^{SR}$ values (L_2) were placed on the right side of the plane (dashed line) while substituents with negative $\Delta\delta^{SR}$ values (L_1) were on the left, and the absolute configurations of the chiral alcohols were then assigned. It was found that, in all cases, the absolute configurations derived from the experimental data and the proposed model were all satisfactorily in good agreement with the known configuration.

In conclusion, a new chiral derivatizing agent, THENA (**7**), has been prepared. The application of THENA (**7**) as a CDA in the NMR shift difference method is realized, and its potential as a candidate for single derivative methods[3b,c] to determine the absolute configuration is very promising. Further investigations on the application of THENA **7** in determining the absolute configuration of chiral secondary alcohols and of other systems, as well as its application in natural products chemistry are currently in progress.

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Supplementary data

Supplementary data (detailed experimental procedures and ^1H and ^{13}C NMR spectra of compounds **7**, and **10**–**22**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.062.

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11. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 772662. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.
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