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Application of deuterated THENA for assigning the absolute configuration of chiral secondary alcohols

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ABSTRACT

The structure of a constrained bicyclic chiral derivatizing agent (CDA), 1,2,3,4-tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid, THENA **1**, was modified by replacing both *exo*-methylene protons with deuterium atoms. The modified CDA, THENA-*d*₂ **2**, could be used to assign the absolute configuration of chiral secondary alcohols with good reliability. Compared with THENA, the multiplicity of the methylene proton signals in the ¹H NMR spectra of THENA-*d*₂ derivatives is less complicated and the new CDA thus offers simpler NMR spectra for data interpretation.

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Introduction

The determination of the absolute configuration of chiral compounds is a challenging question for chemists. With the development of high field NMR, derivatization of chiral secondary alcohols with both enantiomers of chiral derivatizing agents (CDAs) [1], such as Mosher's acid (MTPA) [2], has widely been used as a method to identify the absolute configuration of the alcohol of interest. However, in response to the particular limitations of each CDA, a variety of CDAs have continuously been developed [3].

In principle, the differentiation of ¹H NMR signals in both diastereomeric MTPA esters results from the anisotropic effect of an aromatic group and the chemical shift difference values ($\Delta\delta$) can be used for assigning the absolute configuration. However, due to the rotation of an anisotropic group in certain CDA designs [4], each conformer can contribute to the anisotropic influence on the proton of interest and therefore cause small $\Delta\delta$. 1,2,3,4-Tetrahydro-1,4-epoxynaphthalene-1-carboxylic acid, THENA **1**, (Fig. 1) was recently introduced as a CDA with restricted rotation of the anisotropic group caused by the bicyclic core structure [5].

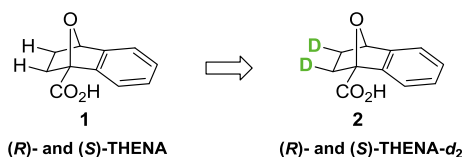
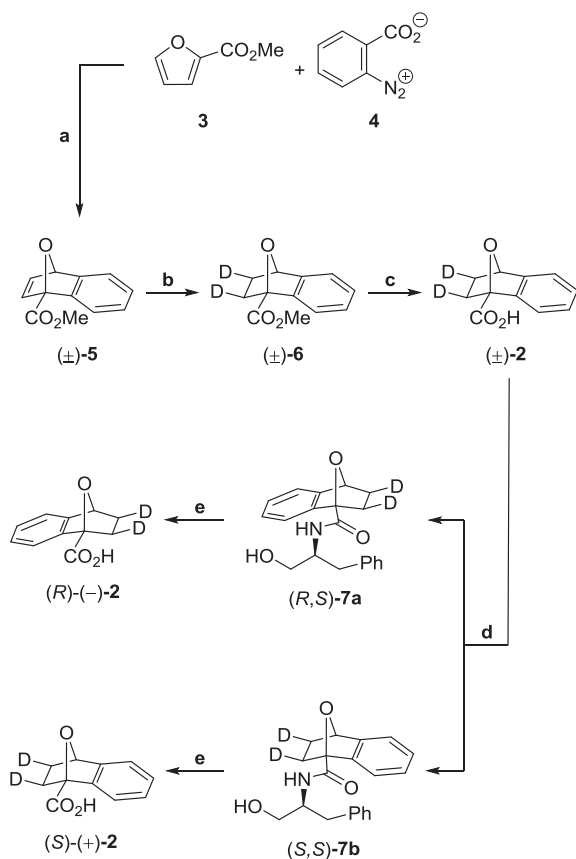
Although THENA has been used successfully as a CDA, its four methylene protons may pose difficulty in interpreting the ¹H NMR spectrum of the THENA ester, especially in the high field region. Herein, we report a means of reducing the complexity of the ¹H NMR spectrum of THENA itself without sacrificing the simplicity and efficiency of its synthetic utility. THENA-*d*₂ **2**, in which the *exo* protons on the methylene carbon atoms have been replaced by deuterons, is proposed and tested with natural chiral secondary alcohols to prove its efficiency as a CDA.

Results and discussion

The preparation of enantiopure THENA-*d*₂ **2** followed the synthesis of THENA **1** [5a], as shown in Scheme 1. A Diels-Alder reaction between methyl furan-2-carboxylate **3** and benzyne, produced by the decomposition of diazonium salt **4** at high temperature, in 1,2-dichloroethane at reflux, formed the racemic mixture of bicyclic compound (\pm)-**5** in 88% yield. Subsequent, deuteration of compound (\pm)-**5** was affected using a H-Cube[®] continuous-flow hydrogenation reactor [6], with Pd/C catalyst and 99% D₂O as the deuterium source to afford compound (\pm)-**6** in 99% yield (99% atom D [7]) [8]. The hydrolysis of ester (\pm)-**6** gave acid (\pm)-**2** (80% yield), which was transformed into the corresponding acid chloride with oxalyl chloride and then reacted with L-Phenylalaninol to form an amide [9]. The separation of amide diastereomers was achieved

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Fig. 1. Structures of THENA and THENA-*d*₂.

Scheme 1. Preparation of optically active THENA-*d*₂ (*R*)-(-)-**2** and (*S*)-(+)-**2**. Reagents and conditions: (a) 1,2-dichloroethane, reflux, overnight, 88%; (b) D₂, Pd/C, CH₂Cl₂, 30 °C, 99%; (c) KOH (5 eq), MeOH:1,4-dioxane (1:1), rt, overnight, 80%; (d) (i) (COCl)₂, DMF (cat.), CH₂Cl₂, 0 °C to rt, 3 h; (ii) L-phenylalaninol, NEt₃, DMAP (cat.), CH₂Cl₂, rt, overnight, (*R,S*)-**7a** (31%) and (*S,S*)-**7b** (30%); (e) KOH (30 eq), MeOH:1,4-dioxane (1:1), reflux, overnight, 90% and 98% for (*R*)-(-)-**2** and (*S*)-(+)-**2**, respectively.

by column chromatography to provide pure diastereomeric compounds (*R,S*)-**7a** [10] and (*S,S*)-**7b** [11] in 31% and 30% yield, respectively. Each diastereomer was then hydrolyzed to finally obtain optically active THENA-*d*₂ (*R*)-(-)-**2** (90%) and (*S*)-(+)-**2** (98%).

Compound (*S,S*)-**7b** provided a good single crystal suitable for X-ray diffraction analysis [12]. The asymmetric unit contains two molecules of the same enantiomer with very similar conformations and slight disorder of the benzyl entity. As shown in Fig. 2, the alignment of the amide C=O and the C^α-O is anti-periplanar [13]. Although the absolute configuration of the molecule could not be confirmed independently by the diffraction experiment, the known configuration of the L-(*S*)-phenylalaninol used as a resolving agent could be applied in constructing the model for the crystal structure refinement, from which it was possible to confirm the absolute configuration of THENA-*d*₂ as the (*S*)-isomer. It should be noted that the position of deuterium cannot be confirmed by X-ray crystallography. However, the *syn* hydrogenation at the *exo*-position of the bridge of the [2.2.1] alkene was prece-

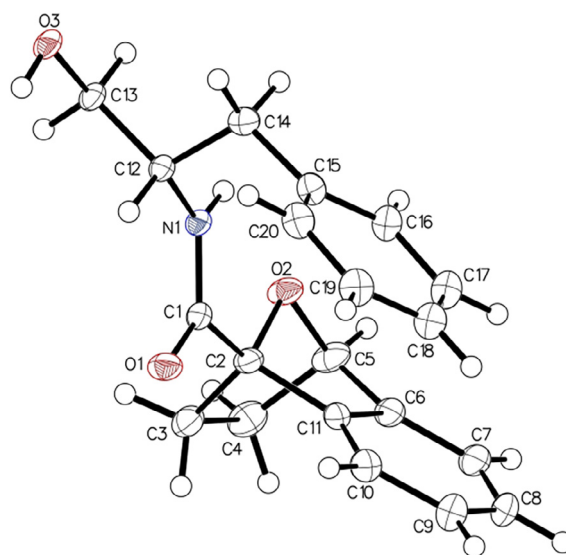


Fig. 2. ORTEP diagram of the major disorder conformation of one of the two symmetry-independent molecules in the crystal structure of (*S,S*)-**7b** (drawn with 30% probability displacement ellipsoids).

ented [14] and *exo*-deuteration could be confirmed, based on the disappearance of the *J*-coupling between the *exo*-proton H-3 and the bridgehead proton H-4 [15].

To determine the absolute configuration of an enantiopure secondary alcohol of interest, it was first coupled with THENA-*d*₂ to form a pair of diastereomers. As shown in Fig. 3, the array of O-C^α-CO-O-C^β-H bonds of the THENA-*d*₂ ester was assigned to be in a plane, called the THENA plane [5a]. Accordingly, the ¹H NMR chemical shifts of the protons in the alcohol substituent on the same side of this plane as the rigid aromatic group of the THENA-*d*₂ entity will shift to a lower field, because of the deshielding anisotropic effect. In contrast, the protons of the alcohol substituent on the other side of the THENA plane are further away from the aromatic ring, and their chemical shifts will be influenced less. Thus, the protons on substituent L₂ in the (*S*,?) [16] THENA-*d*₂ ester (Fig. 3b) and on L₁ in the (*R*,?) THENA-*d*₂ ester (Fig. 3c) are deshielded to different extents, which results in negative and positive signs for the chemical shift difference values ($\Delta\delta^{SR}$; $\Delta\delta^{SR} = \delta_{(-S,?)}$ - $\delta_{(R,?)}$) for protons on the substituents L₁ and L₂, respectively (Fig. 3d).

In accordance with the above concept, THENA-*d*₂ (*R*)-(-)-**2** and (*S*)-(+)-**2** were activated with oxalyl chloride before treatment with a variety of optically active secondary alcohols to generate a diastereomeric pair of (*R*,?)- and (*S*,?)-THENA-*d*₂ esters **8-27** in moderate yields. The chemical shifts of the protons in the alcohol substituent of each corresponding diastereomer were used to calculate the chemical shift difference values ($\Delta\delta^{SR}$). If the signs of the $\Delta\delta^{SR}$ values for most of the protons on one side of the alcohol substituent (as separated by THENA plane) were negative, this group was assigned as substituent L₁ in the model (Fig. 3d). Conversely, the other side of the alcohol substituent, where the $\Delta\delta^{SR}$ values for most of the protons were positive, was assigned as substituent L₂. Overall, the absolute configurations determined by the THENA-*d*₂ method were found to be identical when compared with the known configurations of the chiral secondary alcohols (**8-27**) used for testing (Fig. 4).

Not only can THENA-*d*₂ be used in the assignment of the absolute configuration of chiral secondary alcohols, the high field region in the ¹H NMR spectra of these compounds is less complicated. For example, comparison of the high field regions in the

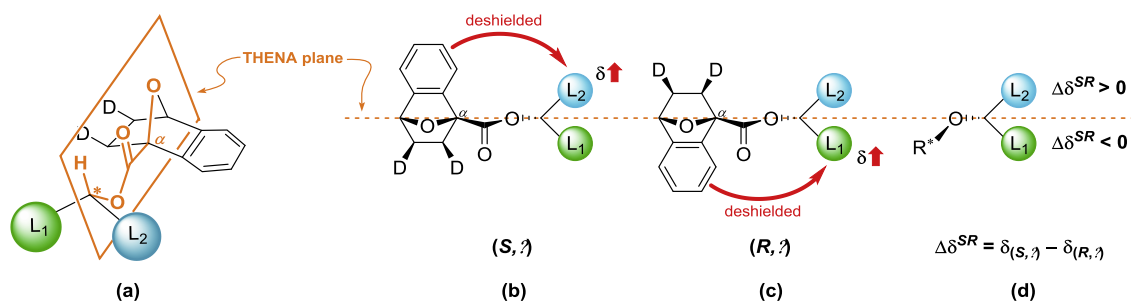


Fig. 3. (a) The THENA plane in the structure of the (*S*,?)-THENA-*d*₂ ester. (b, c) The influence of the anisotropic group on the L₂ and L₁ substituents of (*S*,?)- and (*R*,?)-THENA-*d*₂ esters, respectively. (d) The model for assigning the absolute configuration (?) of an enantiopure secondary alcohol by the sign of the $\Delta\delta^{SR}$ value.

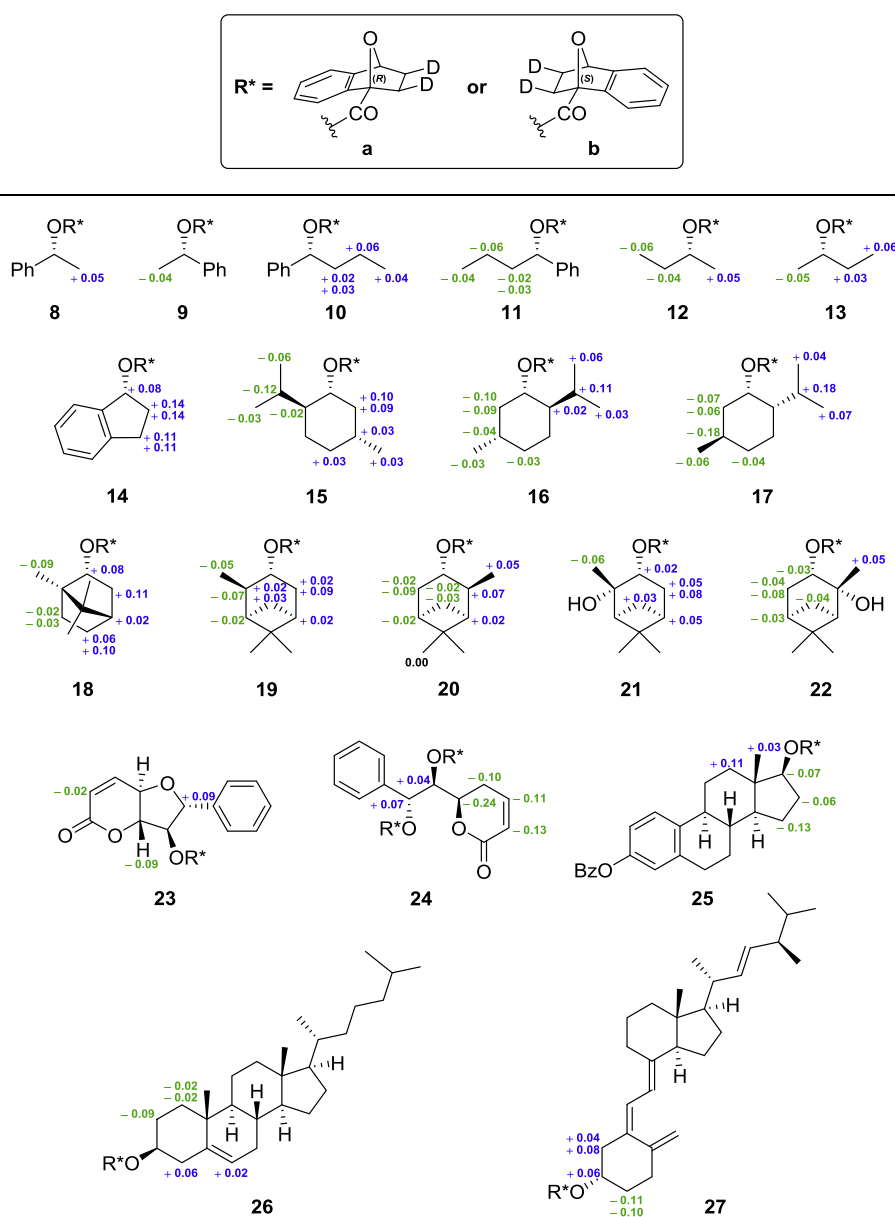


Fig. 4. The $\Delta\delta^{SR}$ values of the THENA-*d*₂ esters of alcohols 8–27. Difference values of less than 0.01 ppm have been omitted as they are considered to be within instrument precision.

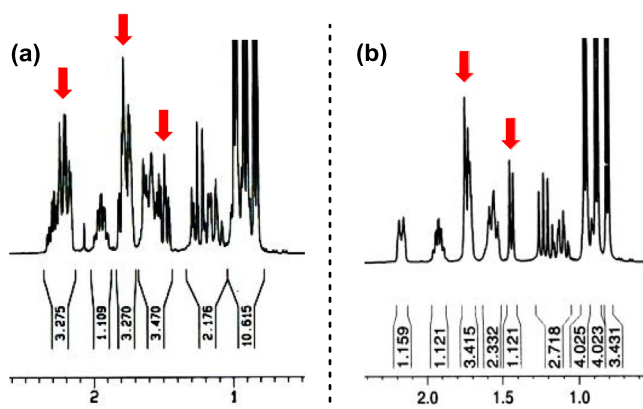


Fig. 5. ^1H NMR spectra in high field region of the (a) (S)-THENA and (b) (S)-THENA- d_2 esters of (1R,2S,5R)-(-)-menthol **15** [17].

^1H NMR spectra of the (1R,2S,5R)-(-)-menthol esters of (S)-THENA [5a] and (S)-THENA- d_2 **15** illustrates clearly the decrease in the multiplicity of the methylene signals from 3 multiplet signals (the arrows in Fig. 5a) to 2 doublet signals (the arrows in Fig. 5b).

Conclusion

Optically active (R)-(-)-THENA- d_2 and (S)-(+)-THENA- d_2 were successfully prepared in high yield. Similar to THENA, THENA- d_2 can be used to determine the absolute configuration of chiral secondary alcohols with good reliability. Incorporation of deuterium in THENA- d_2 decreased the complexity of the ^1H NMR spectra. These results demonstrate the increased utility afforded by constrained bicyclic CDAs when used as a means to establish the absolute configuration of compounds with more complicated structures.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tetlet.2019.01.013>.

References

- [1] (a) J.M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* 104 (2004) 17–117; (b) J.M. Seco, E. Quiñoá, R. Riguera, *Tetrahedron: Asymmetry* 12 (2001) 2915–2925.
- [2] J.A. Dale, H.S. Mosher, *J. Am. Chem. Soc.* 95 (1973) 512–519.
- [3] (a) S. Kuwahara, J. Naito, Y. Yamamoto, Y. Kasai, T. Fujita, K. Noro, K. Shimanuki, M. Akagi, M. Watanabe, T. Matsumoto, M. Watanabe, A. Ichikawa, N. Harada, *Eur. J. Org. Chem.* (2007) 1827–1840; (b) Y. Kasai, H. Taji, T. Fujita, Y. Yamamoto, M. Akagi, A. Sugio, S. Kuwahara, M. Watanabe, N. Harada, A. Ichikawa, V. Schurig, *Chirality* 16 (2004) 569–585; (c) J.M. Seco, E. Quiñoá, R. Riguera, *Tetrahedron* 55 (1999) 569–584; (d) Y. Takeuchi, H. Fujisawa, R. Noyori, *Org. Lett.* 6 (2004) 4607–4610; (e) S. Pérez-Estrada, P. Joseph-Nathan, H.A. Jiménez-Vázquez, M.E. Medina-López, F. Ayala-Mata, L.G. Zepeda, *J. Org. Chem.* 77 (2012) 1640–1652.
- [4] S.K. Latypov, J.M. Seco, E. Quiñoá, R. Riguera, *J. Org. Chem.* 61 (1996) 8569–8577.
- [5] (a) S. Sungsuwan, N. Ruangsapichart, S. Prabpai, P. Kongsaree, T. Thongpanchang, *Tetrahedron Lett.* 51 (2010) 4965–4967; (b) J. Kornsakulkarn, K. Dolsophon, N. Boonyuen, T. Boonruangprapa, P. Rachtawee, S. Prabpai, P. Kongsaree, C. Thongpanchang, *Tetrahedron* 67 (2011) 7540–7547; (c) C. Daengrot, V. Rukachaisirikul, C. Tansakul, T. Thongpanchang, S. Phongpaichit, K. Bowornwiriyan, J. Sakayaroj, *J. Nat. Prod.* 78 (2015) 615–622; (d) K. Dolsophon, N. Ruangsapichat, J. Soponpong, S. Sungsuwan, S. Prabpai, P. Kongsaree, T. Thongpanchang, *Tetrahedron: Asymmetry* 27 (2016) 1113–1120.
- [6] Ö. Sándor, H. Chi-Ting, W. Yang-Chang, L. Jih-Heng, C. Fang-Rong, F. Ferenc, *Molecules* 21 (2016) 318.
- [7] The % atom D of compound (\pm)-**6** was calculated from the intensity of its [M+Na⁺] signal and the intensity of the [M+Na⁺] signal of THENA methyl ester in the HRMS spectrum of compound (\pm)-**6**.
- [8] It should be noted that conventional deuteration with D₂ on Pd/C also gave the deuterated product in excellent yield.
- [9] S. Arita, T. Yabuuchi, T. Kusumi, *Chirality* 15 (2003) 609–614.
- [10] Diastereomeric purity of compound (R,S)-**7a** is >99% de, which was calculated from a comparison of the intensity of its signal with that of the other diastereomer in the HPLC trace of compound (R,S)-**7a**.
- [11] Diastereomeric purity of compound (S,S)-**7b** is >99% de, which was calculated from a comparison of the intensity of its signal with that of the other diastereomer in the HPLC trace of compound (S,S)-**7b**.
- [12] CCDC-1841008 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.
- [13] B.M. Trost, R.C. Bunt, S.R. Pulley, *J. Org. Chem.* 59 (1994) 4202–4205.
- [14] (a) J.G. Smith, P.W. Dibble, *J. Org. Chem.* 53 (1988) 1841–1848; (b) J.G. Smith, S.S. Welankiwar, B.S. Shantz, E.H. Lai, N.G. Chu, *J. Org. Chem.* 45 (1980) 1817–1824.
- [15] (a) N.K. Cokol, S. Kaya, M. Balci, *Tetrahedron Lett.* 58 (2017) 2732–2735; (b) C.N. Rowley, T.K. Woo, N.J. Mosey, *J. Chem. Educ.* 86 (2009) 199–201.
- [16] “?” refers to the unknown configuration of an enantiopure secondary alcohol.
- [17] For more examples, see the [Supplementary Material](#) (page 141–149).