Received: 26 June 2017 | Revised: 5 September 2017 | Accepted: 8 September 2017

DOI: 10.1002/chir.22775

SPECIAL ISSUE ARTICLE

WILEY

Di(1-naphthyl) methanol ester of carboxylic acids for absolute stereochemical determination

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Funding information
National Science Foundation; Division of Chemistry, Grant/Award Number: CHE-1213759

Abstract

The absolute stereochemistry of chiral carboxylic acids is determined as a di(1-naphthyl)methanol ester derivative. Computational scoring of conformations favoring either *P* or *M* helicity of the naphthyl groups, capable of exciton-coupled circular dichroic coupling, leads to a predicted stereochemistry for the derivatized carboxylic acids.

KEYWORDS

absolute stereochemistry, carboxylic acids, chiral sensing, chirality, computational analysis, ECCD

1 | INTRODUCTION

Over the past 4 decades, chiroptical spectroscopy, and in particular circular dichroism (CD), has played a pivotal role in the absolute stereochemical determination of organic molecules.[1-11] Numerous strategies have been devised to address this important issue; nonetheless, it is clear that a unified solution to the problem is not forthcoming. The best solution for a particular functional group, or a subfamily of molecules, is not necessarily the best choice for another, and thus, the continual optimization of old methods and new creative approaches are needed. Amongst the many different chiroptical techniques, exciton-coupled circular dichroism (ECCD), a method based on the through space electronic coupling between two or more nonconjugated chromophores,[12-14] has enjoyed great success as a result of its ability to directly correlate the sign of the ECCD signal to the helicity of the coupling chromophores.[15-26] Nuclear magnetic resonance (NMR) methods are also widely used in stereochemical determinations, although chemical derivatizations are necessary to convert enantiomers to diastereomers. The Mosher ester analysis is an example of the latter, although they are not without their own limitations.[27,28] The derivatizing agent must be a chiral agent; the reactions are often not microscale and thus require substantial amounts of analyte. The NMR readouts that lead to absolute stereochemical assignments require assumptions regarding the highest populating conformation of a complex system that can have a number of conformers with small energetic differences.[29] Recently, we disclosed the marriage of the latter two approaches, combining the stability in structure of the derivatized sample, with the routine determination of helicity via the ECCD method in determining the absolute stereochemistry of asymmetric amines.[30] Herein, we apply this approach to the absolute stereochemical determination of chiral carboxylic acids.

In our recent report, we demonstrate that 1,1′-(bromomethylene)dinaphthalene (**BDN**) bearing 2 naphthalene groups can easily alkylate an asymmetric amine (Figure 1A). The naphthyl rings of the derivatized molecule adopt a preponderance of either the *P* or *M* helicity as a consequence of intramolecular interactions, yielding either a positive or negative ECCD signal. Low-cost computational analysis provides a theoretical population distribution of conformers. Statistical analysis

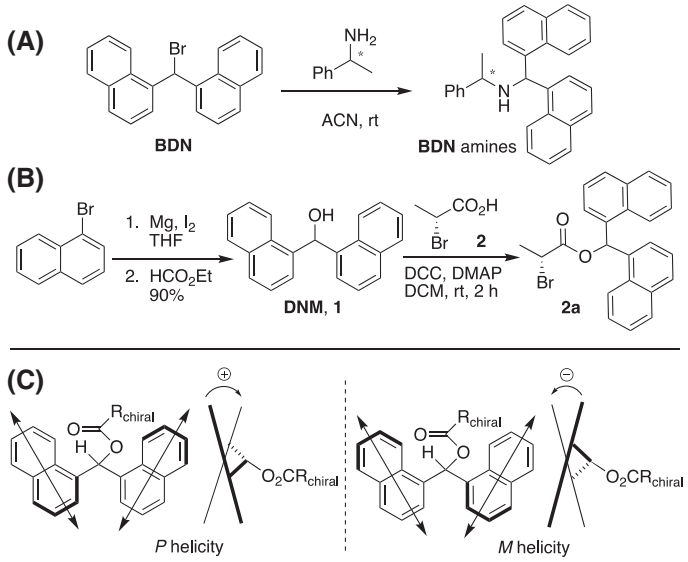


FIGURE 1 A, Chiral amines derivatized with **BDN**; B, Synthesis of **DNM 1** and chiral **DNM** esters; C, *P* and *M* helical conformations of chiral **DNM** esters

of the helicity of the computed structures that predict an excess population of either *P* or *M* helicity leads to the prediction of an ECCD signal for the chirality of the computed derivatized compound. Comparison with experimental ECCD data leads to the absolute stereochemical determination of the derivatized amine. In a similar fashion, this methodology is ported for use with chiral carboxylic acids. Instead of **BDN**, di(1-naphthyl) methanol **1** (**DNM**, Figure 1B) is used, enabling complete derivatization of carboxylic acids within 2 hours at room temperature. As described with **BDN** for amines, the induced helical twist of the bisnaphthyl groups in the carboxylic acid derivatized **DNM** complex leads to a distinct ECCD spectrum that is the direct result of the neighboring chiral center. Conformer distribution analysis (MMFF molecular force field) yields prediction for populations that lead to either positive or negative helicity of the bisnaphthyl core. Comparison with the experimentally obtained ECCD signals enables the absolute stereochemical determination of the derivatized carboxylic acid.

2 | MATERIALS AND METHODS

2.1 | Materials

Anhydrous spectral grade solvents used for CD measurements were purchased from Sigma-Aldrich. Acetonitrile was dried over molecule sieves, and THF was dried over sodium. Column chromatography was performed using SiliCycle silica gel. Chiral carboxylic acids not synthesized here were purchased from commercial sources and were used without further purification.

2.2 | Instrument

^{1}H-NMR and ^{13}C-NMR spectra were obtained on Varian 500 MHz and are reported in parts per million (ppm) relative to the solvent resonances (δ), with coupling constants (*J*) in Hertz (Hz). The CD spectra were recorded on a JASCO J-810 spectropolarimeter, equipped with a temperature controller (Neslab 111) and are reported as λ [nm] ($\Delta\varepsilon_{max}$ [mol^{-1} cm^{-1}]). High Resolution Mass Spectrometry (HRMS) analysis was performed on a Q-TOF Ultima system using electrospray ionization in negative mode.

2.3 | CD measurement

Chiral carboxylic acids derivatized with **DNM 1** were dissolved in acetonitrile to make a 0.01 M stock solution. From the stock solution, 1 μL was dissolved in acetonitrile (1 mL), yielding a 10 μM final solution ready for CD measurement. Background spectrum of acetonitrile was recorded from 350 to 200 nm with a scan rate of 100 nm/min at room temperature. The CD spectra of ester samples measured with 10 accumulations were subtracted from the background spectra and normalized based on the concentration to obtain molecular CD (Mol CD).

3 | RESULTS AND DISCUSSION

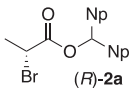
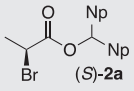
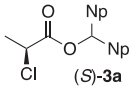
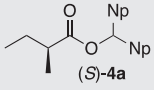
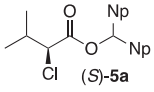
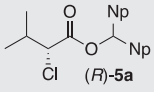
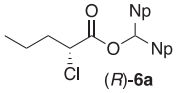
The ECCD signals require coupling of the electric transition dipole moments of 2 or more independently conjugated chromophores. The structure of **DNM 1**, with its 2 naphthyl rings, has the prerequisites for generating an ECCD signal, given that the 2 aryl groups adopt a nonracemic helical population. The methine group that

separates the two rings not only provides a handle for derivatization[31-34] but also aids in reducing the rotational barrier for the two aryl groups, thus enabling them to adopt a preferred conformation as dictated by the chirality of the derivatized carboxylic acid. At the onset, we predict that upon esterification of **DNM 1** with a chiral carboxylic acid, either the *P* or *M* helicity of the bisnaphthyl group would be favored (Figure 1C), resulting in an ECCD signal that can be directly correlated to the chirality of the carboxylic acid.

Although **DNM 1** is commercially available, it can be easily synthesized and purified by recrystallization in gram scale from the Grignard reaction of 1-bromonaphthalene with ethyl formate in 90% overall yield (Figure 1B). The DCC mediated derivatization of **DNM 1** with chiral carboxylic acids requires less than two hours for completion. A short silica plug purification is all that is needed for preparation of the sample for CD analysis.

As expected, **DNM 1** is CD silent in acetonitrile. On the other hand, derivatization of carboxylic acid **2** with **DNM 1** yields ester (*R*)-**2a** that generates a positive ECCD spectrum. As expected, its enantiomer (*S*)-**2a** exhibits the opposite ECCD signal (see Figure S1). The observed spectrum is the result of induced helicity of the coupling

TABLE 1 Exciton-coupled circular dichroism data for chiral alkyl **DNM** esters

Entry	Chiral Derivative[a]	Predicted ECCD (*P*:*M*)[b]	λ(nm), Δε[c]	A[d]
1	 (*R*)-**2a**	Pos (54.7/38.8)	226, +14	+18
2	 (*S*)-**2a**	Neg (38.8/54.7)	226, −19	−24
3	 (*S*)-**3a**	Neg (36.5/56.3)	227, −11	−16
4	 (*S*)-**4a**	Neg (44.1/46.4)	226, −10	−16
5	 (*S*)-**5a**	Neg (40.7/49.8)	227, −8	−13
6	 (*R*)-**5a**	Pos (49.8/40.7)	227, +5	+6
7	 (*R*)-**6a**	Pos (51.1/39.3)	226, +8	+10

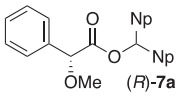
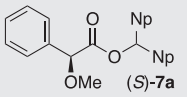
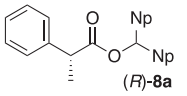
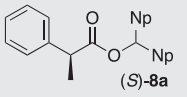
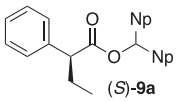
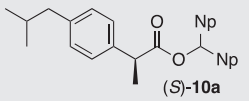
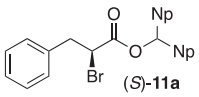
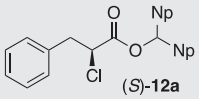
[a]All CD measurements were recorded with 10 μM ester derivative in acetonitrile at rt.

[b]Calculated populations of *P* and *M* helical conformers were obtained via tabulating the population of conformations that yield positive and negative helicity (for computational details, see the text and the Supporting Information).

[c]The reported Δε is from the long wavelength portion of the couplet.

[d]A refers to the amplitude of the ECCD couplet.

TABLE 2 Exciton-coupled circular dichroism data for chiral aryl **DNM** esters

Entry	Chiral Derivative[a]	Predicted ECCD (*P*:*M*)[b]	λ(nm), Δε[c]	A[d]
1	 (*R*)-**7a**	Neg (8.1/83.1)	226, −52	−63
2	 (*S*)-**7a**	Pos (83.1/8.1)	227, +48	+58
3	 (*R*)-**8a**	Neg (32.8/57.5)	227, −30	−48
4	 (*S*)-**8a**	Pos (57.5/32.8)	227, +31	+43
5	 (*S*)-**9a**	Pos (56.9/33.8)	225, +31	+42
6	 (*S*)-**10a**	Pos (51.9/38.3)	227, +70	+92
7	 (*S*)-**11a**	Pos (49.6/43.1)	228, +11	+25
8	 (*S*)-**12a**	Pos (48.1/41.1)	228, +8	+15

[a]All CD measurement were recorded with 10 μM ester derivative in acetonitrile at rt.

[b]Calculated populations of *P* and *M* helical conformers were obtained via tabulating the population of conformations that yield positive and negative helicity (for computational details, see the text and the Supporting Information).

[c]The reported Δε is from the long wavelength portion of the couplet.

[d]A refers to the amplitude of the ECCD couplet.

naphthyl groups, adopting specific conformations as a result of their interaction with the nearby groups attached to the asymmetric center. The asymmetry observed in the ECCD spectra resulting from the coupling of naphthyl groups has been observed before.[35] The asymmetrical shape of the couplet is closely related to the relevant electric transition moment, one of the factors responsible for the Cotton effects.[12] Namely, the transition fall-offs from the vibrational bands reflect the flatness of the shorter wavelength. The shape also seems to be deformed by the strong absorption of solvents and/or minute impurities close to 200 nm, which diminishes the signal because of reduce signal/noise ratio. The spectra remained virtually identical as the temperature was reduced to 0°C. It should be noted that although naphthyl groups have two main transitions (^1L_a ~270 nm and ^1B_b ~220 nm), we observe the coupling from the more intense ^1B_b band (long axis transition) and see no evidence of the short axis ^1L_a transition in the ECCD spectra.

Table 1 illustrates a set of diverse chiral alkyl carboxylic acids derivatized with DMN **1** (**2a**-**6a**) that produce ECCD active species. Notably, the system is sensitive to the discrimination of substituents with similar size such as a methyl vs ethyl group (Table 1, entry 4). Our approach to the prediction of ECCD relies on evaluating conformational distribution of populations that adopt either the *P* (leading to positive ECCD) or the *M* (leading to negative ECCD) helicity. The estimate for the percentage of *P* and *M* populations for conformers with over 90% abundance (spanning 2.3 Kcal/mol from the most stable conformer) was calculated by routine and expeditious conformational modeling (MMFF94S force field). For example, molecular modeling of ester (*R*)-**2a** (Table 1, entry 1) leads to a set of conformers, of which 93.5% reside within 1.12 Kcal/mol. Conformational analysis of this group of molecules shows a *P*:*M* calculated ratio of 54.7:38.8. The dominance of the *P* helical population would predict a positive ECCD spectrum, which in fact is in agreement with the experimentally observed data (A = +18). The same analysis for molecules listed in Table 1 yields predictions that are in line with the ECCDs obtained for each molecule.

Table 2 summarizes the extension of the same principles and analysis to chiral carboxylic systems that are aryl substituted. As expected, enantiomeric esters (*R*)-**7a** and (*S*)-**7a** show opposite ECCD signals (Figure 2A). Interestingly, the aryl substituted esters yield the opposite ECCD sign in comparison to their alkyl carboxylic acid derivatives. For example, ester (*S*)-**5a**, with its medium sized chloride and large sized isopropyl substituent, yields a negative ECCD signal. Ester (*S*)-**8a**, having the same disposition of substituents based on size as determined by A-value steric parameters (medium sized methyl group and large sized aryl group), produces a positive ECCD. Importantly, the conformational analysis for both leads to the correct prediction, thus providing an operationally expedient system that considers all mechanical interactions that lead to a preferred helicity. In general, the derivatized aryl substituted carboxylic acids (Table 2) exhibits a stronger ECCD signal as compared to the aliphatic substituted carboxylic acid derivatives listed in Table 1. This is presumably the result of stronger interactions of the bisnaphthyl group with the aryl substituents. Similar to that discussed with aliphatic substrates, computational studies also predict the correct *P*:*M* ratio, matching the observed ECCD signals. Of note, the benzyl substituted derivatives (*S*)-**11a** and (*S*)-**12a** (Table 2, entries 7 and 8) do lead to observable ECCD spectra, albeit weaker in strength as compared to other aryl-substituted examples. This is presumably the result of having the phenyl group further away from the dinaphthyl moiety, thus lessening its influence on dictating the *P*:*M* population difference. A greater difference in helical population should translate to the higher ECCD amplitudes. As depicted in Figure 2B, a trend was observed between the *P* and *M* populations for esters **2a**-**12a** (alkyl and aryl systems), plotted as a function of the observed amplitude.

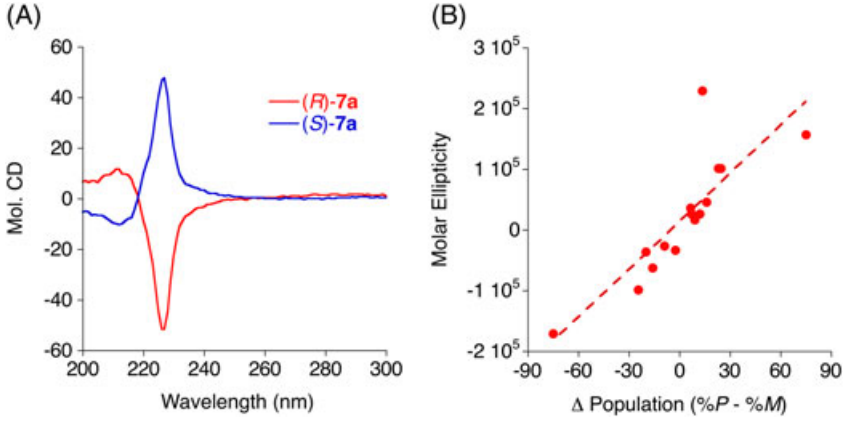


FIGURE 2 A, Circular dichroism spectra of chiral **DNM** esters (*R*)-**2a** and (*S*)-**2a** show the opposite exciton-coupled circular dichroism (ECCD) signals. B, A correlation is observed for the strength of the ECCD spectra (Δε of the high wavelength cotton effect) and the population difference calculated for *P* and *M* helicities

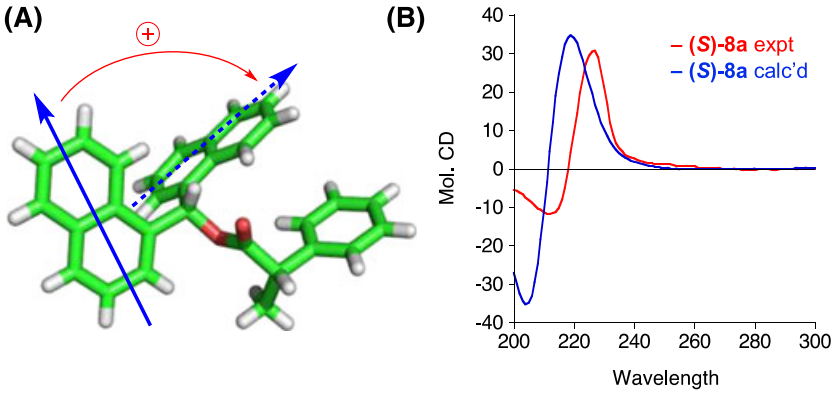


FIGURE 3 A, Crystal structure of (*S*)-**8a** (CCDC deposition number: 1441836) exhibits the *P* helicity that would yield a positive exciton-coupled circular dichroism (ECCD) signal. B, Theoretical calculation of ECCD for (*S*)-**8a**, overlapped with the experimentally observed spectrum

Although we find that a simple conformational analysis, requiring less than a few hours per substrate, is sufficient to yield predictable populations for absolute stereochemical determinations, a higher-level calculation was also performed for substrate (*S*)-**8a**. For this purpose, all conformers above 1% population, obtained from MMFF minimization, were further optimized by DFT calculation (hybrid functional B3LYP, double-zeta basis set 6-31G(d) in gas phase). The energetically most stable conformers accounting for 91.0% of the population (4 conformers) were then subject to TDDFT calculation with a hybrid functional B3LYP and a double-zeta basis set cc-pVDZ. The calculated ECCD spectra were integrated by considering their population, resulting a theoretical ECCD spectrum for substrate (*S*)-**8a** as shown in Figure 3B. As anticipated, the calculated ECCD matches the Cotton effects observed experimentally for (*S*)-**8a**, thus confirming that the calculated *P*:*M* ratios results in the observed sign for the ECCD spectra. Fortuitously, ester (*S*)-**8a** succumbed to crystallization, exhibiting the *P* helical conformation, matching the predicted dominant population by modeling (66.8% *P* helicity, Figure 3A and Supporting Information).

4 | CONCLUSION

A simple and microscale derivatization of chiral carboxylic acids with **DNM 1** yields ECCD active species. The observed signal is the result of interactions that lead to a specific orientation of the naphthyl groups, adopting either *P* or *M* helicity. Low-cost conformational modeling of the derivatized carboxylic acid yields energetically preferred populations; a weighted average of conformers that lead to *P* and *M* helicity yields a prediction for the absolute stereochemistry of the parent carboxylic acid. In all cases, computational modeling for alkyl and aryl carboxylic acids yields predictions that are in agreement with the observed ECCD spectra. Ongoing studies with other functional groups are underway, along with alterations to the chromophore to redshift absorption.

ACKNOWLEDGMENTS

We are grateful to the NSF (CHE-1213759) for funding. We also thank Dr Richard Staples (MSU) for the X-Ray crystallography.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Zhang J, Sheng W, Gholami H, Nehira T, Borhan B. Di(1-naphthyl) methanol ester of carboxylic acids for absolute stereochemical determination. *Chirality*. 2017;1–6. https://doi.org/10.1002/chir.22775