ORGANIC LETTERS

2010
Vol. 12, No. 8
1768−1771

Long-Range Shielding Effects in the ^{1}H NMR Spectra of Mosher-like Ester Derivatives

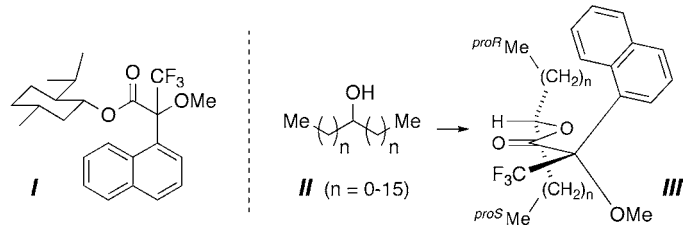
Thomas R. Hoye,* Sara E. Erickson, Sherrie L. Erickson-Birkedahl, Christopher R. H. Hale, Enver Cagri Izgu, Michael J. Mayer, Patrick K. Notz, and Matthew K. Renner

Department of Chemistry, 207 Pleasant Street, SE, University of Minnesota, Minneapolis, Minnesota 55455

hoye@umn.edu

Received February 14, 2010

ABSTRACT



The relative magnitudes of the chemical shift differences ($\Delta\delta$s) in the two diastereomers of menthyl esters of known chiral derivatizing agents (CDAs) were compared to those of the α-methoxy-α-trifluoromethyl-1-naphthylacetyl (MTN$_{(1)}$A) analogues I. Discrimination of the terminal diastereotopic methyl resonances in esters of the homologous, symmetrical carbinols II was evaluated. Remarkably, the methyls differed in the MTN$_{(1)}$A esters III even when $n = 15$; an unexpected crossover in the sign of the $\Delta\delta$ values was also observed.

Mosher ester/amide anaylsis for deducing the absolute configuration of stereogenic carbinol/amino centers of organic compounds, when properly applied, is a very powerful and widely used method.[1] The Mosher method is the prototype of a larger set of analogous ^{1}H NMR-based methods that use chiral auxiliaries that are structurally related to the α-methoxy-α-trifluoromethylphenylacetyl (MTPA) moiety.[2] All of these related methods[3] rely on installation of a chiral derivatizing agent (CDA) into the analyte of interest; the newly installed chiral entity introduces local magnetic anisotropy that differentially influences diastereotopic proton resonances in the derivative. Most typically, one makes a complementary pair of diastereomeric derivatives of the analyte of interest using enantiomerically enriched samples of each antipode of the CDA. Comparison of the sets of differential chemical shifts ($\Delta\delta$s) for analogous proton resonances in the spectrum of each diastereomer allows one to deduce the configuration of the parent alcohol/amine. These empirical methods rely on an understanding, or at least a validated mnemonic construct, of the dominant conformation adopted by the ester/amide derivative.

A related interesting issue is the distance over which the anisotropic differential shielding effects exert themselves. The inherent nature of both the analyte and the derivatizing agent play a role. The studies we report here shed light on some of these issues. In particular, they provide insight about the relative ability of various CDAs (from among **1**−**11**, Figure 1) to discriminate proton resonances distal to the point of attachment. Greater anisotropic reach presumably correlates with an inherently more useful CDA.[4]

Perspective on the choice of CDA (more specifically, on its ability to discriminate analogous protons in a pair of

(1) (a) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519. (b) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

(2) Thomas, J. Wenzel, *Discrimination of Chiral Compounds Using NMR Spectroscopy*; J. Wiley & Sons, Inc.: Hoboken, NJ, 2007.

(3) Seco, M. J.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.

10.1021/ol1003862
Published on Web 03/25/2010

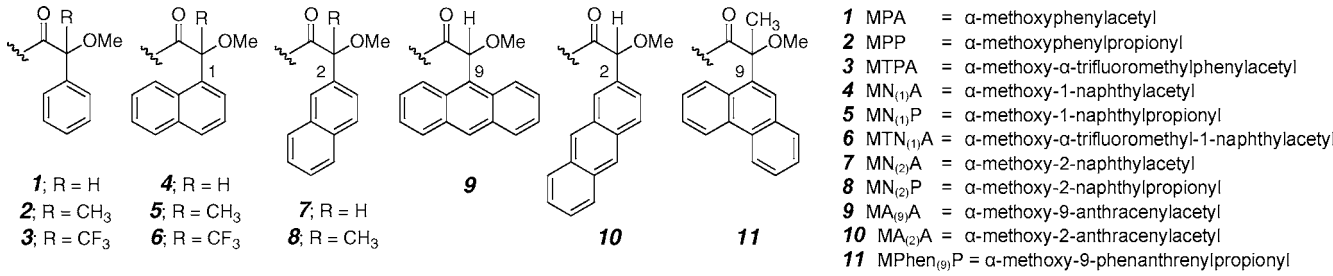
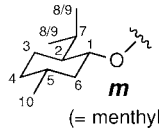


Figure 1. Known Mosher-like chiral derivatizing agents (CDAs).

Table 1. Individual and Mean $\Delta\delta$ Values of Menthyl Esters **1-m**−**11-m** Derived from CDAs **1**−**11**

 *m* (= menthyl)	MPA[5]	MPP[6]	MTPA[5,7]	$MN_{(1)}A$[8]	$MN_{(1)}P$[5,6]	$MTN_{(1)}A$	$MN_{(2)}A$[5]	$MN_{(2)}P$[6]	$MA_{(9)}A$[8,9]	$MA_{(2)}A$[9]	$MPhen_{(9)}P$[6,10]
	1-m	***2-m***	***3-m***	***4-m***	***5-m***	***6-m***	***7-m***	***8-m***	***9-m***	***10-m***	***11-m***
proton #	$\Delta\delta^{SR}$ (= $\delta_S - \delta_R$)										
1	+0.09	+0.05	+0.02	+0.15	+0.16	-0.19	+0.16	+0.06	+0.21	+0.08	+0.14
2	+0.11	+0.06	-0.03	–	+0.26	-0.30	+0.14	+0.06	+0.42	+0.14	+0.28
3eq	+0.07	+0.01	-0.02	–	+0.14	-0.20	+0.10	+0.01	+0.23/+0.26	+0.10/+0.13	+0.16
3ax	+0.07	+0.02	-0.02	–	+0.12	-0.14	+0.10	+0.02	+0.23/+0.26	+0.10/+0.13	+0.13
4eq	0.00	-0.01	0.00	–	-0.01	+0.02	0.00/-0.01	0.00	0.00/-0.10	0.00/-0.02	0.00
4ax	+0.01	+0.03	+0.01	–	-0.03	0.00	0.00/-0.01	-0.01	0.00/-0.10	0.00/-0.02	-0.03
5	-0.04	-0.01	+0.02	–	-0.03	+0.03	-0.03	0.00	-0.04	-0.05	-0.04
6eq	-0.22	+0.01	+0.05	–	-0.28	+0.28	-0.15/-0.23	+0.02	-0.50/-0.51	-0.18/-0.23	-0.30
6ax	-0.14	+0.05	+0.14	–	-0.31	+0.34	-0.15/-023	-0.04	-0.50/-0.51	-0.18/-0.23	-0.37
7	+0.56	+0.07	-0.32	+0.93	+1.21	-1.48	+0.64	+0.09	+1.8	+0.58	+1.20
8/9	+0.26	+0.02	-0.10	+0.51	+0.55	-0.50	+0.35	+0.04	+0.79	+0.36	+0.52
9/8	+0.22	-0.02	-0.13	+0.46	+0.46	-0.67	+0.36	+0.05	+0.85	+0.35	+0.57
10	-0.06	-0.01	+0.03	-0.06	-0.10	+0.18	-0.08	0.00	-0.19	-0.10	-0.12
mean $\lvert\Delta\delta\rvert$	**0.14**	**0.03**	**0.07**	**0.42**	**0.28**	**0.33**	**0.16**	**0.03**	**0.39**	**0.16**	**0.30**

diastereomeric derivatives of an analyte) is gained from consideration of the $\Delta\delta$ data for the (−)-menthol derivatives (**#-m**) summarized in Table 1. First, the magnitude of the $\Delta\delta$s is enhanced by the replacement of the phenyl with a naphthyl or anthracenyl moeity in the CDA. This is easily seen, for example, in the relative magnitude of the "mean$|\Delta\delta|$" values in the bottom line of Table 1. Within each of the sets MPA vs either $MN_{(1)}A$ or $MA_{(9)}A$, MPP vs $MN_{(1)}P$, and MTPA vs $MTN_{(1)}A$ the discriminating power of naphthyl- or anthracenyl-based CDA is greater [by factors of approximately 3 (cf. **1-m** vs either **4-m** or **9-m**), 10 (cf. **2-m** vs **5-m**), and 5 (cf. **3-m** vs **6-m**), respectively]. Second, whereas MPA shows greater discrimination than MTPA across the mean $|\Delta\delta|$ values for the same set of menthyl protons (cf. **1-m** vs **3-m**), the opposite is true for the $MN_{(1)}A$ vs $MTN_{(1)}A$ pairs (cf. **4-m** vs **6-m**). Third, the difference in the position of substitution on the CDA aromatic moiety (i.e., C1 vs C2 positions for naphthyl and C9 vs C2 positions for anthracenyl groups) also affects the discriminating power of $MN_{(1)}A/MN_{(2)}A$, $MN_{(1)}P/MN_{(2)}P$, and $MA_{(9)}A/MA_{(2)}A$. Specifically, mean $|\Delta\delta|$ values are lower for the "C2"-substituted positional isomers [by factors of approximately 3 (cf. **4-m** vs **7-m**), 10 (cf. **5-m** vs **8-m**), and 2 (cf. **9-m** vs **10-m**), respectively].

Having previously noticed some surprising long-range effects in several Mosher ester derivatives, we decided to investigate the ability of three CDAs [the commonly used

(4) Seco, J. M.; Latypov, Sh.; Quiñoá, E.; Riguera, R. *Tetrahedron Lett.* **1994**, *35*, 2921–2924.
(5) Harada, N; Watanabe, M.; Kuwahara, S.; Kasai, Y.; Ichikawa, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1249–1253.
(6) Kasai, Y.; Sugio, A.; Kuwahara, S.; Matsumoto, T.; Watanabe, M.; Ichikawa, A.; Harada, N. *Eur. J. Org. Chem.* **2007**, *11*, 1811–1826.
(7) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451–2458.
(8) Latypov, Sh.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem.* **1995**, *60*, 504–515.
(9) Kouda, K.; Kusumi, T; Ping, X.; Kan, Y; Hashimoto, T.; Asakawa, Y. *Tetrahedron Lett.* **1996**, *37*, 4541–4544.
(10) Ichikawa, A.; Ono, H.; Harada, N. *Tetrahedron: Asymmetry* **2003**, *14*, 1593–1597.

MPA (**1**) and MTPA (**3**), as well as $MTN_{(1)}A$ (**6**)] to differentially shield distant protons. Specifically, we have examined the resonances of the terminal methyl groups in the ^1H NMR spectra of the series of homologous derivatives **13**, derived from the symmetrical secondary carbinol precursors **12** (Figure 2). These methyls, which are enantiotopic (*pro-R* and *pro-S*) in **12**, become diastereotopic in **13**. Notice that for this study, it makes no difference whether or not the CDAs used were racemic.[11]

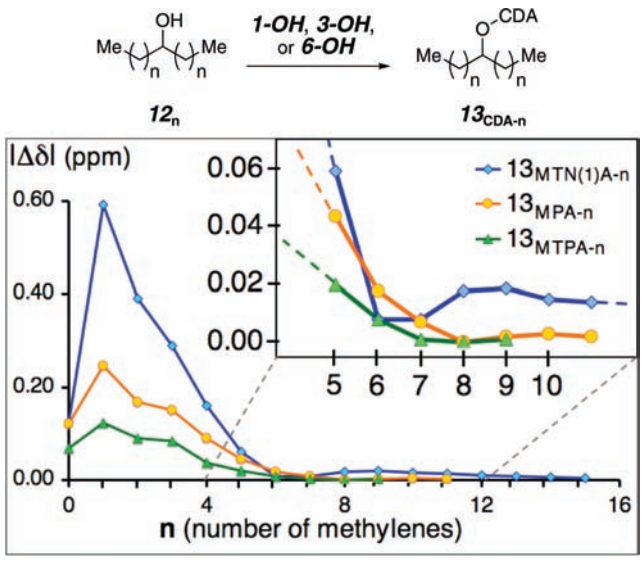


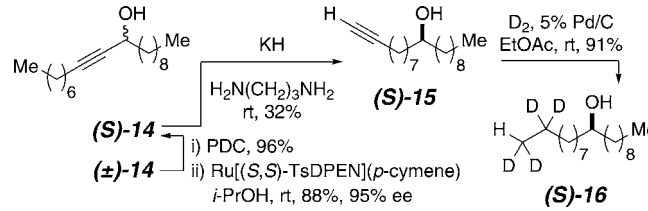
Figure 2. Trends in $\Delta\delta$ values of the terminal methyl groups of the CDA esters **13** derived from symmetric carbinols **12**.

There are a number of noteworthy features seen in the data for these series of compounds. The magnitude of the $\Delta\delta$ values is greatest for $MTN_{(1)}A$ and least for MTPA. For each CDA series, the maximum $\Delta\delta$ value is observed when $n = 1$ (i.e., $\mathbf{13_{CDA\text{-}1}}$ or the 3-pentanol derivative). There is evidence of an "even−odd" effect[12] in the step function (or sawtooth) nature within each of the three series. At values of $n = 6-8$ (i.e., chain lengths of 15−19), the absolute value of $\Delta\delta$ reaches a minimum but, surprisingly, reemerges; that is, the curves show a double maximium. We cannot help but be reminded of the similar, textbook trends for rates of cyclization vs ring size for α,ω-difunctional substrates,[13] wherein transannular effects, maximal at medium ring sizes, mitigate against the reactant residing in the reactive conformation (i.e., with its termini in close proximity). This situation is mitigated as the chain length is further increased.

An additional feature of the data intrigued us. At first glance there is no obvious reason for the crossing of the blue (for $\mathbf{13_{MTN(1)A\text{-}\mathit{n}}}$) with the orange and green curves (for $\mathbf{13_{MPA\text{-}\mathit{n}}}$ and $\mathbf{13_{MTPA\text{-}\mathit{n}}}$, respectively) (see Figure 2 inset). A different way to state this is that there is a discontinuity in the smoothness of the curves, most strongly evident in the $\mathbf{13_{MTN(1)A\text{-}\mathit{n}}}$ data set (blue). However, recall that the data are plotted as the absolute value of $\Delta\delta$. This consideration led us to hypothesize that the relative deshielding effect of the *pro-R* vs *pro-S* methyl groups reverses for each of the series (a *crossover*), causing the sign of $\Delta\delta$ to change for each series. This was testable, assuming we could access (i) nonracemic $MTN_{(1)}A$-OH (**6-OH**, Figure 1) and (ii) an enantiomerically enriched and strategically deuterated analogue of one of the larger ($n \geq 7$) carbinol precursors $\mathbf{12}_n$.

We elected to prepare a nonracemic sample of partially deuterated 10-nonadecanol **16** (the precursor to $\mathbf{13_{MTN(1)A\text{-}8}}$) via the route summarized in Scheme 1. Racemic alcohol (±)-**14** was resolved via PDC oxidation and asymmetric Noyori reduction[14] to give back **(*S*)-14** having 95% ee. Alkyne isomerization to the terminal alkyne **15** was followed by deuteration to provide the alcohol-d_4 **16**.

Scheme 1. Synthesis of (*S*)-10-Nonadecanol-*1,1,2,2-d*$_4$ [(*S*)-**16**]



Acids **(*R*)-6-OH** and **(*S*)-6-OH** (Scheme 2) are the nonracemic versions of $MTN_{(1)}A$ acid. These were prepared from alkenol **(±)-17**, which was *O*-methylated and oxidatively cleaved to give the primary alcohol **(±)-19**. Partial kinetic resolution was achieved with a lipase-induced acetylation. Although the levels of enantiopurity of the derived samples of **(*R*)-19** [via acetate **(*R*)-20**] and **(*S*)-19** were marginal [86% ee and 28% ee, respectively (from MTPA analysis)], they were sufficiently high to serve our purposes. Oxidation of each gave the carboxylic acids **(*R*)-6-OH** and **(*S*)-6-OH**. Alternatively, we prepared racemic acid **6-OH** (by the method of Bourissou:[15] 1-NphthMgBr + CF_3COCO_2Et; K_2CO_3, MeI; KOH, EtOH), derivatized it as the diasteromeric menthyl esters **6-m**, and separated these by MPLC (silica gel) to provide **(*R*)-6-m** (>99.8% de) and **(*S*)-6-m** (94% de), which were used to collect the data summarized in Table 1.

The preparation of the diastereomeric $MTN_{(1)}A$ esters **(*S,R*)-** and **(*S,S*)-21**, each derived from nonracemic acid chlorides prepared in situ and derived from nonracemic samples of acids **(*R*)-6-OH** or **(*S*)-6-OH**, is outlined in

(11) For development of another unorthodox ("shortcut") Mosher ester analysis that was used on "nearly symmetrical" carbinols, see: Curran, D. P.; Sui, B. *J. Am. Chem. Soc.* **2009**, *131*, 5411–5413.

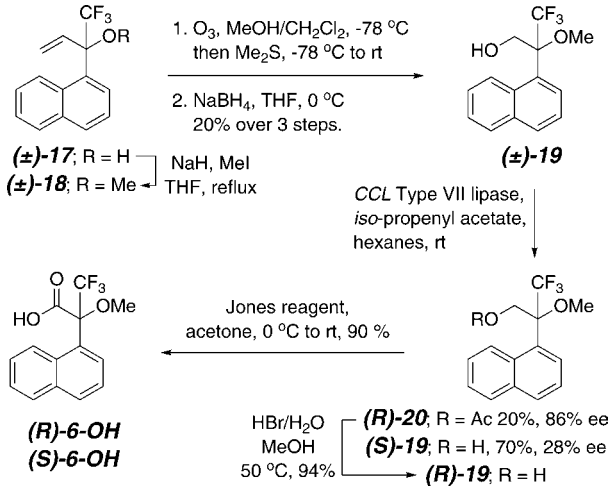
(12) (a) Baeyer, A. *Ber. Chem. Ges.* **1877**, *10*, 1286–1288. (b) von Sydow, E. *Ark. Kemi* **1955**, *9*, 231–254. (c) Breusch, F. L. *Fortschr. Chem. Forsch.* **1969**, *12*, 119–184.

(13) E.g.: Smith, M. B., March, J. *March's Advanced Organic Chemistry*, 5th Ed.; J. Wiley & Sons, Inc.: New York, 2001; pp 281−284.

(14) Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285–288.

(15) du Boullay, O. T.; Alba, A.; Oukhatar, F.; Martin-Vaca, B.; Bourissou, D. *Org. Lett.* **2008**, *10*, 4669–4672.

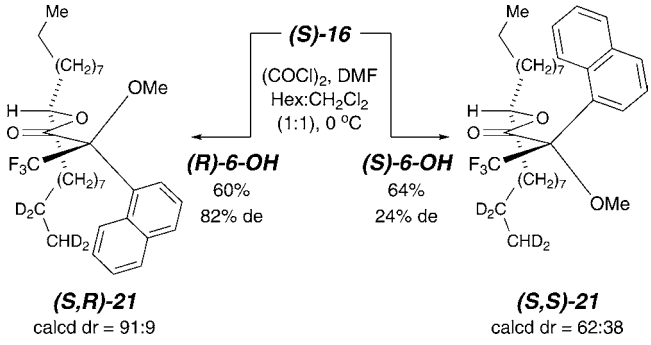
Scheme 2. Enantioselective Synthesis of $MTN_{(1)}A$ Acid



Scheme 3. With these two esters in hand, we were in a position to evaluate the hypothesis laid out above.

The proton NMR data for the terminal methyl regions of **(*S*,*R*)-21** and **(*S*,*S*)-21**, each having a diastereomeric purity reflective of the level of enantiopurity of its precursors, are

Scheme 3. Synthesis of Diastereomeric C-19 Carbinyl $MTN_{(1)}A$ Esters **(*S*,*R*)-21** and **(*S*,*S*)-21**



shown in Figure 3. For comparison, the same spectral region of the nondeuterated analogue of **21** (i.e., $\mathbf{13}_{MTN(1)A\text{-}8}$, blue data point, $n = 8$, Figure 2) is also shown. From the method of synthesis we know that the chain with the deuterated terminus occupies the *pro-S* position in the structures in Scheme 3. From the spectral data in Figure 3, we learn that the nondepleted methyl resonance in the *unlike* diasteromer [**(*S*,*R*)-21**] is further upfield and that in the *like* diastereomer [**(*S*,*S*)-21**] further downfield. This confirms that indeed there is a crossover-a change in the sign of $\Delta\delta$ for $\mathbf{13}_{MTN(1)A\text{-}8}$.

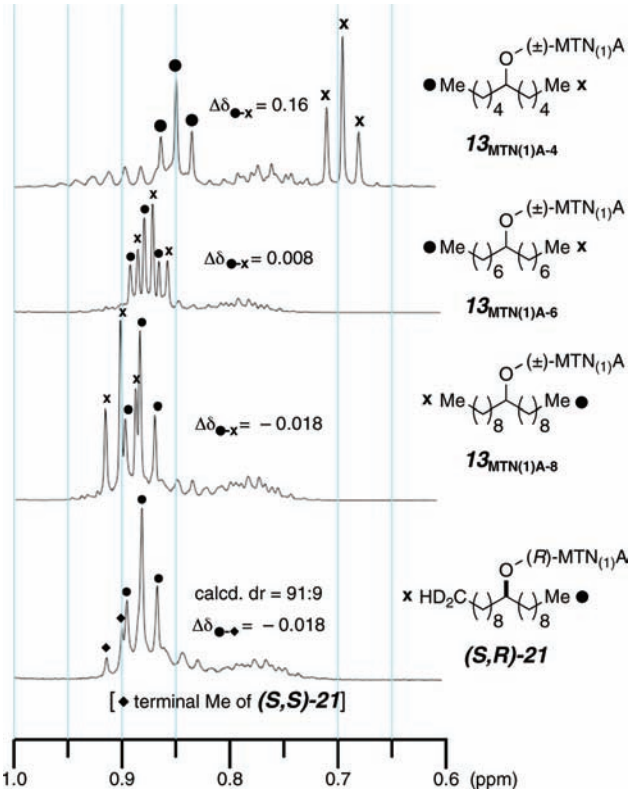


Figure 3. Methyl resonances in the ^1H NMR spectra ($CDCl_3$, 500 MHz) for selected members of the $MTN_{(1)}A$ ester series.

In conclusion, trends in the relative discriminating power of a wide variety of Mosher-like esters were identified by analysis of the data in Table 1. Three homologous series of esters $\mathbf{13}_{CDA\text{-}n}$ (derived from the symmetrical carbinols $\mathbf{12}_n$) were used to establish that the anistropic effects extend over remarkably long molecular distances. An interesting crossover effect was uncovered.

Acknowledgment. These studies were supported by the National Institute of General Medical Sciences (GM-65597) and the National Cancer Institute (CA-76497) of the National Institutes of Health.

Supporting Information Available: Detailed experimental procedures and spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1003862