J|A|C|S COMMUNICATIONS

Published on Web 03/26/2009

A "Shortcut" Mosher Ester Method To Assign Configurations of Stereocenters in Nearly Symmetric Environments. Fluorous Mixture Synthesis and Structure Assignment of Petrocortyne A

Dennis P. Curran* and Bin Sui

Department of Chemistry, University of Pittsburgh, Pittsburgh Pennsylvania 15260

Received February 3, 2009; E-mail: curran@pitt.edu

The configurations of stereocenters of chiral alcohols are commonly assigned by making a pair of diastereomeric Mosher esters and analyzing their ^{1}H NMR spectra by the subtraction protocol of the "advanced Mosher method".[1] In contrast, making Mosher esters of achiral alcohols is pointless. Or is it?

Consider the pairs of methylene protons on either side of the carbinol carbon in the three classes of secondary alcohols **1a**−**3a** shown in Figure 1. Chiral alcohol **1a** bearing different substituents on either side of the carbinol is the usual candidate for the advanced Mosher rule. The (*R*)- and (*S*)-Mosher esters **1e** are made, and the resonances in their ^{1}H NMR spectra are assigned. Subtraction of the corresponding chemical shifts according to the rule provides the configuration. Achiral alcohol **2a** having the same substituents on either side of the carbinol has no stereocenter, and its methylene resonances are equivalent by symmetry.[2] The equivalence is broken in the Mosher ester **2e**, and the resonances can now be assigned by a "backwards" application of the Mosher rule.[3] The second Mosher ester derivative of **2a** is the enantiomer of **2e**, so it provides no new information (its methylene resonances simply exchange places).

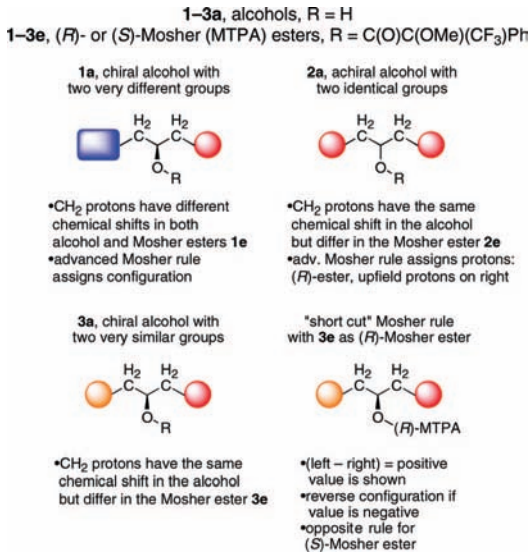


Figure 1. Uses of the Mosher rule for three classes of alcohols.

There is no pressing need to assign proton resonances of Mosher ester derivatives of *achiral* compounds. But the analysis applies directly to *chiral* compounds that have elements of near-symmetry. Consider alcohol **3a**, bearing different but very similar substituents on either side of the carbinol. Because the compound almost has a plane of symmetry, the pairs of methylene protons will be (accidentally) chemical shift equivalent in the alcohol **3a** but different in the Mosher ester **3e**. Now, in a "shortcut" of the usual advanced Mosher rule, subtraction of the pair of resonances *from each other* (rather than from the corresponding resonances in the diastereomeric Mosher ester) provides the absolute configuration of the alcohol. The diastereomeric Mosher ester can be made and the advanced Mosher rule can be applied as usual, but like the enantiomer of **2e**, the diastereomer of **3e** will provide no new information.

We selected the natural product petrocortyne A **4** as a suitable test of the "shortcut" Mosher method (Figure 2). This is a typical representative of a group of related natural products whose members exhibit diverse biological activities.[4] In particular, the dialkynyl carbinol stereocenter at C14 of petrocortyne A has a near-plane of symmetry that extends for seven carbon atoms on either side before being broken. As a consequence of this local symmetry, the formally different protons H11 and H17 are accidentally equivalent, but this equivalence should be broken by making a Mosher ester.

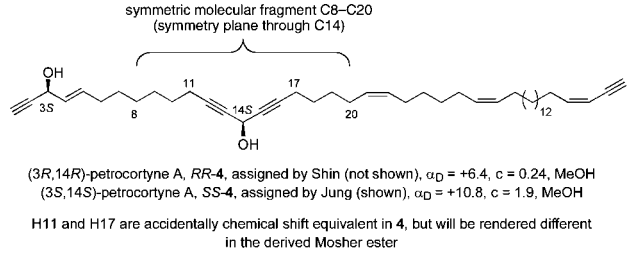


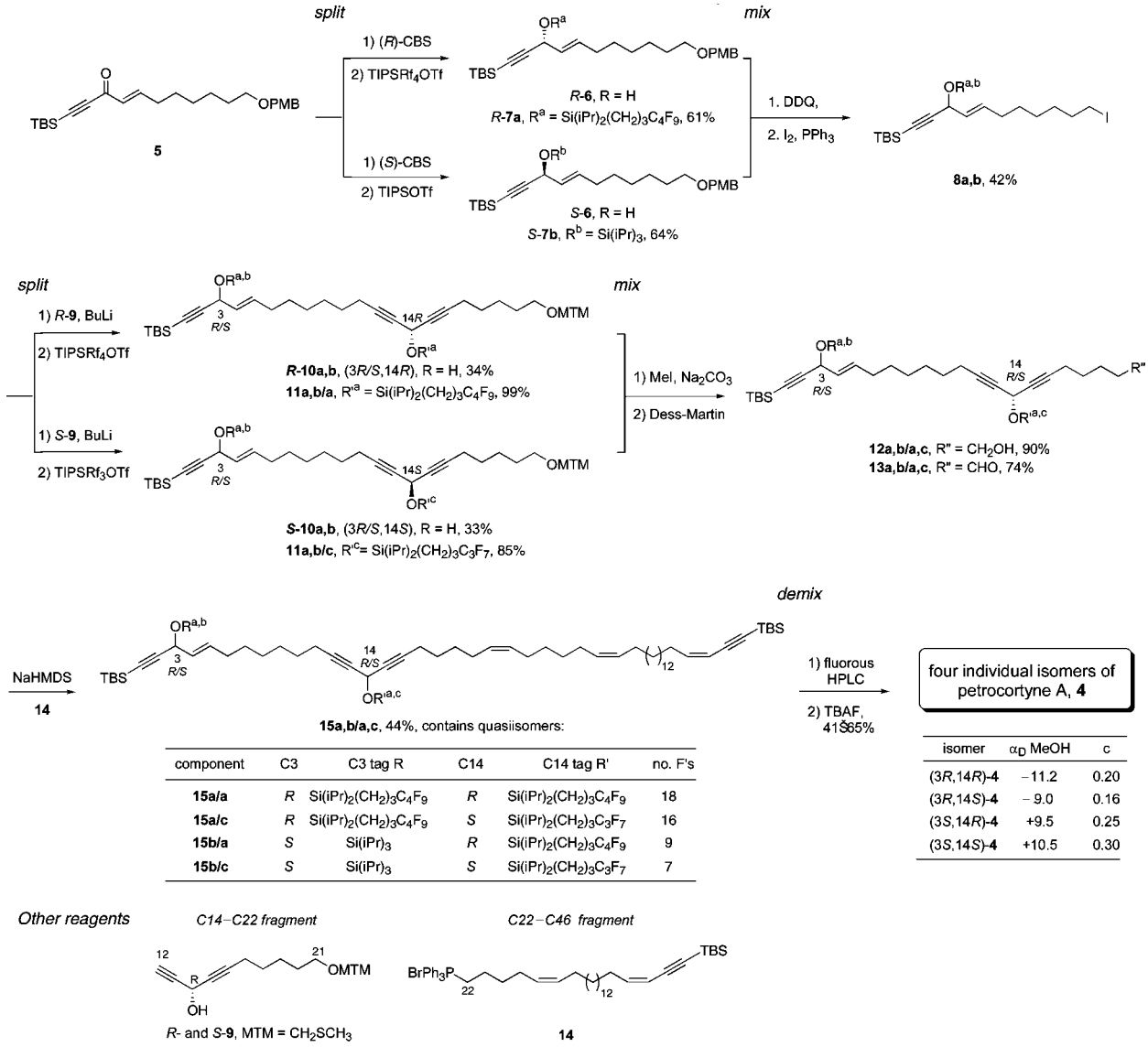
Figure 2. Proposed structures for petrocortyne A.

Petrocortyne A **4** has been isolated by two different groups from similar sponges collected in similar locations.[5] The optical rotations of both samples had the same sign though different magnitudes. And both groups applied the advanced Mosher method to assign configurations to their samples. The Shin group[5a] assigned the 3*R*,14*R* configuration to petrocortyne A **4**, while the Jung group[5b] deduced the enantiomer 3*S*,14*S*. It seems likely that one of these assignments is incorrect. And because of the difficulty of assigning the C14 stereocenter, we also considered the possibility that both were incorrect.

To rigorously assign the configuration of petrocortyne A, we decided to make all four possible stereoisomers of **4** in individual, pure form by fluorous mixture synthesis[6] and then to convert these isomers to Mosher esters for comparison with each other and with the data for the natural samples. The preparation of the starting quasiracemate[7] **7a**,**b** and the mixture and postmixture phases of the synthesis are summarized in Scheme 1.

Straightforward preparations of the fragments (**5**, **9**, and **14**) are briefly summarized in the Supporting Information. Ketone **5** (C1−C11) was divided in half and reduced with the (*R*)- and (*S*)-CBS reagents.[8] The resulting alcohols **6** were directly tagged with a fluorous diisopropylsilyl triflate[9,10] bearing the C_4F_9 group

Scheme 1. Fluorous Mixture and Postmixture Stages of the Synthesis of Four Isomers of Petrocortyne A



component	C3	C3 tag R	C14	C14 tag R'	no. F's
15a/a	*R*	$Si(iPr)_2(CH_2)_3C_4F_9$	*R*	$Si(iPr)_2(CH_2)_3C_4F_9$	18
15a/c	*R*	$Si(iPr)_2(CH_2)_3C_4F_9$	*S*	$Si(iPr)_2(CH_2)_3C_3F_7$	16
15b/a	*S*	$Si(iPr)_3$	*R*	$Si(iPr)_2(CH_2)_3C_4F_9$	9
15b/c	*S*	$Si(iPr)_3$	*S*	$Si(iPr)_2(CH_2)_3C_3F_7$	7

isomer	α_D MeOH	c
(3*R*,14*R*)-**4**	−11.2	0.20
(3*R*,14*S*)-**4**	−9.0	0.16
(3*S*,14*R*)-**4**	+9.5	0.25
(3*S*,14*S*)-**4**	+10.5	0.30

($TIPSRf_4OTf = Si(iPr)_2(CH_2)_3C_4F_9$) or the standard triisopropylsilyl triflate (TIPSOTf) to give quasienantiomers *R*-**7a** and *S*-**7b** in 61 and 64% overall yield, respectively, for the two steps. The quasienantiomers were mixed, and the resulting quasiracemate was deprotected with DDQ to provide an alcohol, which was immediately converted to the iodide **8a,b** (42% overall yield).

Quasiracemate **8a**,**b** was divided in half and used to alkylate the propargyl anions derived from *R*-**9** and *S*-**9** (C12−C21) to give *R*-**10a**,**b** (14*R* mixture) and *S*-**10a**,**b** (14*S* mixture) in 34 and 33% yields, respectively, after careful purification. Fluorous tagging of these products with silyl triflates bearing C_4F_9 and C_3F_7 groups encoded the configurations at C14 in products **11a,b/a** (99%) and **11a,b/c** (85%). These two-compound mixtures were in turn mixed and the resulting four-compound mixture **11a,b/a,c** was treated with MeI to remove the MTM group, giving an alcohol **12a,b/a,c** (90%). Subsequent Dess−Martin oxidation provided an aldehyde **13a,b/a,c** (74%), which was coupled with the ylide derived from phosphonium salt **14** (C22−C46) to provide *Z*-alkene **15a,b/a,c** in 44% yield.

This final mixture was demixed by fluorous HPLC,[10] and the four individual quasiisomers (**15a/a**, **15a/c**, **15b/a**, **15b/c**) were detagged and purified by flash chromatography to give the four petrocortyne A stereoisomers **4**. These four samples exhibited substantially identical ^1H (600 MHz) and ^{13}C (125 MHz) spectra. All four spectra in turn matched the spectra reported for both natural samples of petrocortyne A,[5] thereby confirming the two-dimensional structure of **4**. Like the spectra, the optical rotations (Scheme 1) did not differentiate the two possible diastereomers of petrocortyne A. But they did of course differentiate the enantiomers. The (3*S*) pair of petrocortyne diastereomers is dextrorotatory, supporting the assignment of Jung[5b] rather than Shin.[5a]

Next, we converted the pair of diastereomers with the (3*S*) configuration to both the *bis*-(*R*)- and *bis*-(*S*)-Mosher esters, and recorded a set of 1D and 2D ^1H NMR spectra for assignment and analysis. The structures of the Mosher esters and their spectra are shown in the Supporting Information. Our expectation that all the 1D spectra might be substantially identical in the region of the C14 stereocenter proved to be wrong; there were small yet clear differences. Thanks to these differences, we could clearly show that both natural samples have the *syn* relative configuration between C3 and C14 by comparing Mosher spectra from natural and synthetic samples.

We next analyzed the Mosher spectra by applying the standard advanced method and the short-cut method. The shortcut method

does not apply to C3 (no local symmetry), but its configuration is correctly assigned by the standard Mosher rule (see Supporting Information). The subtraction data for key protons needed to validate the two methods for assigning C14 are shown in Table 1.[11] In the standard analysis, data from both *bis*-(*R*) and *bis*-(*S*)-Mosher esters are used, and the usual subtraction ($\delta S - \delta R$) validates that the Mosher method does correctly assign the C14 configuration of both diastereomers.

Table 1. Chemical Shifts of H11 and H17 in Mosher Esters and Application of the Advanced ($\delta S-\delta R$) and Shortcut (δH11$-\delta$H17) Mosher Methods

config.	H#	δ *S*-MTPA	δ *R*-MTPA	$\delta S-\delta R$[a]	δH11$-\delta$H17[b]
3*S*,14*R*	11	2.214	2.190	+0.024[c]	−0.043[c]
3*S*,14*R*	17	2.204	2.233	−0.029[c]	
3*S*,14*S*	11	2.185	2.219	−0.034[d]	+0.015[d]
3*S*,14*S*	17	2.220	2.204	+0.026[d]	

[a] The standard advanced Mosher method. [b] The shortcut Mosher method with the *R*-MTPA ester. [c] Indicates 14*R*. [d] Indicates 14*S*.

In the shortcut analysis, data of symmetry-related pairs from a single Mosher ester are subtracted from each other (δH11 $-$ δH17). Accordingly, having two Mosher esters generates two sets of data. If the 1D spectra of the Mosher esters are identical (as in truly symmetric systems), then the subtraction results will give the same magnitude with opposite signs. The Mosher ester spectra of the petrocortyne derivatives are not identical, so the magnitudes of the subtractions are slightly different. But the signs of the subtractions are the opposite, so both analyses correctly indicate the known configurations of the compounds. This validates the applicability of the shortcut Mosher method.

With the optical rotations and Mosher spectra of all isomers of petrocortyne A **4** in hand, we can confirm that the (3*S*,14*S*) configuration assignment of Jung is correct and that the (3*R*,14*R*) assignment of Shin must be reversed;[12] his sample of petrocortyne also must have the (3*S*,14*S*) configuration since his data (optical rotation, Mosher spectra) match ours for that isomer.

This assignment of the (3*S*,14*S*)-configuration to petrocortyne A is rigorous and is based solely on comparison of data derived from natural and synthetic samples and Mosher derivatives; it does not depend on applying Mosher rules. At the same time, we have validated that both the standard and shortcut Mosher methods are applicable to assigning the configuration of the challenging C14 stereocenter in petrocortyne and related molecules. So previous assignments in related compounds can now be confirmed or revised, and future assignments can be made without recourse to a complete stereoisomer library.

The "shortcut" method should be generally applicable to assigning stereocenters in molecules or molecular fragments with local symmetry, and the method should be generalizable beyond Mosher esters to the family of related chiral ∝-trifluoromethyl ∝-aryl esters[1c,d] and beyond. The method conserves precious natural product samples because only one derivative is made. If the pairs(s) of protons that are related by local symmetry can be unambiguously assigned,[13] then a reliable assignment of configuration will follow from the shortcut method.

Acknowledgment. We thank the National Institutes of Health, National Institute of General Medical Sciences, for funding. We thank Dr. J. H. Jung, Pusan National University, for copies of spectra of natural petrocortyne A.

Supporting Information Available: Contains summary schemes for synthesis of fragments **5**, **9**, and **14** and copies of NMR spectra of the petrocortyne isomers and derived Mosher esters. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(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. (c) Seco, J. M.; Quinoa, E.; Riguera, E. *Tetrahedron: Asymmetry* **2000**, *11*, 2781–2791. (d) Kusumi, T.; Ooi, T.; Ohkubo, Y.; Yabuuchi, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 965–980.

(2) Formally, the spin system is ABXA′B′, but here we use A_2XA_2 for illustration. The same analysis holds whether or not the actual spectrum shows an AB or A_2 appearance for the methylene protons.

(3) "Backwards" because the resonances are usually used to make the assignment, but here they are instead being assigned. See: Curran, D. P.; Zhang, Q. S.; Lu, H. J.; Gudipati, V. *J. Am. Chem. Soc.* **2006**, *128*, 9943–9956.

(4) (a) Shin, J.; Seo, Y.; Cho, K. W. *J. Nat. Prod.* **1998**, *61*, 1268–1273. (b) Lim, Y. J.; Kim, J. S.; Im, K. S.; Jung, J. H.; Lee, C.-O.; Hong, J.; Kim, D.-k. *J. Nat. Prod.* **1999**, *62*, 1215–1217. (c) Lim, Y. J.; Lee, C.-O.; Hong, J.; Kim, D.-k.; Im, K. S.; Jung, J. H. *J. Nat. Prod.* **2001**, *64*, 1565–1567. (d) Lim, Y. J.; Park, H. S.; Im, K. S.; Lee, C.-O.; Hong, J.; Lee, M.-Y.; Kim, D.-k.; Jung, J. H. *J. Nat. Prod.* **2001**, *64*, 46–53. (e) Kim, D.-K.; Lee, M.-Y.; Lee, H. S.; Lee, D. S.; Lee, J.-R.; Lee, B.-J.; Jung, J. H. *Cancer Lett.* **2002**, *185*, 95–101. (f) No petrocortynes have been synthesized, but a synthesis of dideoxypetrosynol A has recently been reported. Gung, B. W.; Omollo, A. O. *Eur. J. Org. Chem.* **2008**, *28*, 4790–4795.

(5) (a) Seo, Y.; Cho, K. W.; Rho, J.-R.; Shin, J.; Sim, C. J. *Tetrahedron* **1998**, *54*, 447–462. (b) Kim, J. S.; Lim, Y. J.; Im, K. S.; Jung, J. H.; Shim, C. J.; Lee, C. O.; Hong, J.; Lee, H. *J. Nat. Prod.* **1999**, *62*, 554–559.

(6) (a) Luo, Z. Y.; Zhang, Q. S.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766–1769. (b) Fukui, Y.; Brueckner, A. M.; Shin, Y.; Balachandran, R.; Day, B. W.; Curran, D. P. *Org. Lett.* **2006**, *8*, 301–304. (c) Dandapani, S.; Jeske, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 9447–9462. (d) Curran, D. P.; Zhang, Q. S.; Richard, C.; Lu, H. J.; Gudipati, V.; Wilcox, C. S. *J. Am. Chem. Soc.* **2006**, *128*, 9561–9573. (e) Yang, F.; Newsome, J. J.; Curran, D. P. *J. Am. Chem. Soc.* **2006**, *128*, 14200–14205.

(7) Zhang, Q. S.; Curran, D. P. *Chem.—Eur. J.* **2005**, *11*, 4866–4880.

(8) (a) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org, Chem.* **1988**, *53*, 2861–2863. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

(9) (a) Zhang, Q. S.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774–5781. (b) Zhang, W.; Luo, Z.; Chen, C. H. T.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 10443–10450.

(10) (a) Precursors for the silyl tags and fluorous HPLC columns for the demixing were purchased from Fluorous Technologies, Inc., www.fluorous.com. (b) DPC owns an equity interest in this company.

(11) The proton assignments are crucial because protons come in nearly symmetric pairs, and reversing the assignments reverses the subtraction outcome and hence the assignment. We used TOCSY spectra to unambiguously differentiate pairs of protons on either side of the dialkynyl carbinol (H^{11} and H^{17}).

(12) The incorrect assignment emantes from an error in CIP assignment of the stereocenter of the Mosher esters. We will discuss implications of these data on configurational assignments of other petrocortynes in a forthcoming full paper.

(13) Very long range assignments are possible with modern NMR experiments. For an impressive example, see: Duret, P.; Waechter, A.-I.; Figadère, B.; Hocquemiller, R.; Cavé, A. *J. Org. Chem.* **1998**, *63*, 4717–4720.

JA900849F