Applications of MTPA (Mosher) Amides of Secondary Amines: Assignment of Absolute Configuration in Chiral Cyclic Amines

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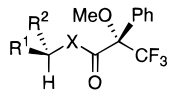
Mosher's MTPA (methoxy(trifluoromethyl)phenylacetyl) technology is applied to the assignment of absolute configuration of several synthetic and natural chiral amines. The substrates are cyclic, secondary amines. The resulting amides usually contain significant populations of two rotamers, readily distinguished by ^{1}H NMR spectroscopy. Thus, two complementary sets of $\Delta\delta$ values are obtained from a single analysis, thereby enhancing the power of the method. A strategy for the MTPA derivatization of (the *N*-methyl tertiary amine in) the tropane alkaloid, cocaine, is also described. The exceptionally large $\Delta\delta$ values observed for these MTPA amides make this a valuable and reliable method for assignment of amine configuration (even in some cases where only one diastereomeric MTPA amide is readily available).

Introduction

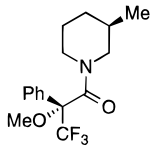
MTPA esters of chiral alcohols and amides of chiral primary amines are well-known.[1] Several other chiral derivatizing agents have been used to determine the absolute configuration of *secondary alcohols* and *primary amines*.[2] We recently described the general principles that permit the use of Mosher's MTPA (methoxy(trifluoromethyl)phenylacetyl) technology for the determination of absolute configuration (as well as the enantiomeric excess) of cyclic *secondary amines*.[3] That work built upon a valuable conformational study of several MTPA amides by Rauk and Tavares[4] and a recent study by Braekman and Daloze, who deduced the absolute configuration of a series of 2,6-dialkylpiperidines using MTPA amide technology.[5] We now present the specific application of these principles to a series of chiral secondary amines that are typical of those encountered in synthetic and natural product studies.

It is generally accepted that the most stable conformation for both MTPA esters and amides of α-branched primary amines is that for which the methine proton, the carbonyl oxygen, and the trifluoromethyl groups are all syn and coplanar.[6] It follows that in conformation **1** protons in R^1 are more highly shielded by the phenyl ring than those in R^2 for both ester and amide derivatives containing an (*S*)-configured MTPA moiety.

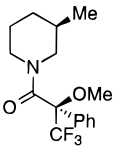
A similar conformation is observed in MTPA amides of secondary amines; that is, the amide carbonyl is syn-periplanar to the trifluoromethyl group. A significant factor is that slow rotation (NMR time scale) about the tertiary amide bond leads to a pair of usually nearly equienergetic rotamers, each observable in the NMR spectrum (see, e.g., **2a** and **2b**). These two diastereomeric conformations (in one the C(3)-methyl substituent is syn to the MTPA α-carbon and in the other anti) provide complementary information. Two distinct ^{1}H NMR spectra are observed at ambient temperature, and deconvolution is usually straightforward because the diastereomers are not equally populated.[3,4]



1 X=O, NH



2a



2b

MTPA amides of cyclic amines generally exhibit much larger differential shielding (or $\Delta\delta$ values) than MTPA esters of secondary alcohols or amides of primary amines. In nearly every example we have studied, there has been at least one (and frequently more) $\Delta\delta$ value greater than 0.9 ppm. These exceptionally large $\Delta\delta$ values make the determination of absolute configuration of cyclic amines via MTPA technology a straightforward and highly reliable technique.

Our previous report dealt with a series of known, simple piperidine and pyrrolidine derivatives.[3] To demonstrate the broader scope of this methodology, we now describe the analysis of amines **1**−**7** containing greater structural complexity (Scheme 1). Most of these compounds were obtained from other research groups and were of known absolute configuration and high enantiomeric purity (>95% ee).[7] (−)-Solenopsin (**5**) was among the piperidine substrates analyzed by Braekman and Daloze.[5] Norcocaine (**7**) was prepared by demethylation of cocaine, a tertiary amine.

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1996.

(1) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Sullivan, G. R.; Dale, J. A.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 2143. (d) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. (e) Kusumi, T.; Fukushima, T.; Ohtani, I.; Kakisawa, H. *Tetrahedron Lett.* **1991**, *32*, 2939.

(2) (a) Trost, B. M.; Bunt, R. C.; Pulley, S. R. *J. Org. Chem.* **1994**, *59*, 4202. (b) Latypov, S. K.; Seco, J. M.; Quiñoá, E.; Riguera, R. *J. Org. Chem* **1995**, *60*, 1538.

(3) Hoye, T. R.; Renner, M. K. *J. Org. Chem.* **1996**, *61*, 2056.

(4) (a) Khan, M. A.; Tavares, D. F.; Rauk, A. *Can. J. Chem.* **1982**, *60*, 2451. (b) Rauk, A.; Tavares, D. F.; Khan, M. A.; Borkent, A. J.; Olson, J. F. *Can. J. Chem.* **1983**, *61*, 2572. (c) These two papers describe the only MTPA amides of secondary amines identified by a Chemical Abstracts Service substructure search [C_2-N−C(=O)−C−C−F].

(5) Leclercq, S.; Thirionet, I.; Broeders, F.; Daloze, D.; Vander Meer, R.; Braekman, J. C. *Tetrahedron* **1994**, *50*, 8465. We regret having overlooked this reference at the time of our initial publication.[3,4c]

(6) For example, see: Fukushi, Y.; Yajima, C.; Mizutani, J. *Tetrahedron Lett.* **1994**, *35*, 9417.

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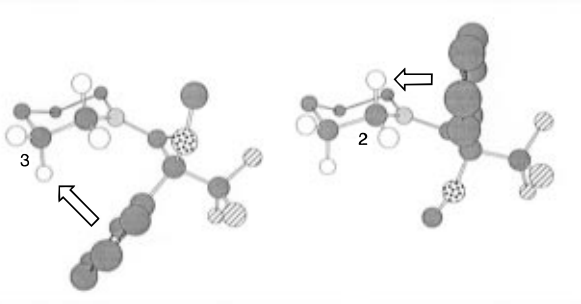
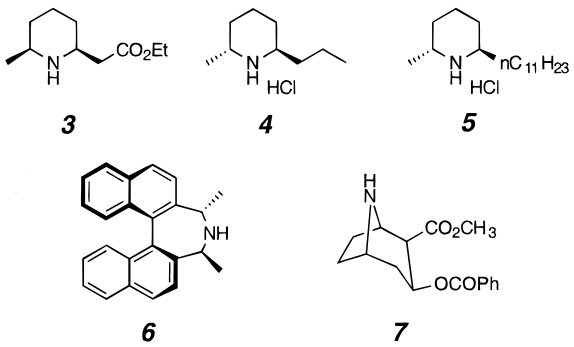


Figure 1. Amide rotamers for a generic piperidine MTPA amide.[10]

Scheme 1



3 **4** **5** **6** **7**

Discussion

In MTPA ester analysis, it is common to consider the molecule roughly as two "halves" divided by the MTPA plane. The substituents on the alcohol carbon occupy opposite halves (i.e., in **1**, R^1 constitutes one half and R^2 the other). Typically, most, if not all, of the protons in R^1 will have $\Delta\delta$ values of the same sign (i.e., positive or negative). Likewise, most, if not all, of the protons in R^2 will have $\Delta\delta$ values of the opposite sign. This is generally not the case with MTPA amides of cyclic amines. Rather, specific spatial relationships must be taken into consideration. Chem3D renderings of the amides (shown in Figures 1−5 throughout) have proven to be very useful. These geometries were identified as minimum energy conformers via Monte Carlo multiconformation searching with the Amber force field in MacroModel.[8]

Our previous work with MTPA amides of piperidines revealed trends for the orientation of the phenyl group in various rotamers. For any given piperidine MTPA amide, the greatest shielding will be experienced at the axial proton of C(3) [or C(5)] for one rotamer and at an axial substituent at C(2) [or C(6)] in the other rotamer.[9] This can be seen in Figure 1, which shows the minimum geometries of the two amide rotamers for the MTPA amide of a generic piperidine. The arrows represent the regions of greatest shielding by the phenyl ring.

Amides **8** and **9** were prepared from (2*S*,6*S*)-2-(carbethoxymethyl)-6-methylpiperidine (**3**)[7a] using a straightforward procedure. The amine was independently treated with (*S*)- and (*R*)-MTPA-Cl in the presence of Hünig's base to afford amides **8** and **9**, respectively, in moderate yields. *It is imperative to not overlook the fact that the absolute configuration of any one enantiomer of Mosher acid chloride (MTPA-Cl) is opposite to that of its precursor acid or the derived ester or amide since the presence of the chlorine atom in MTPA-Cl alters the relative Cahn−Ingold−Prelog priorities.* The ^{1}H NMR data for **8** and **9** are shown in Table 1.

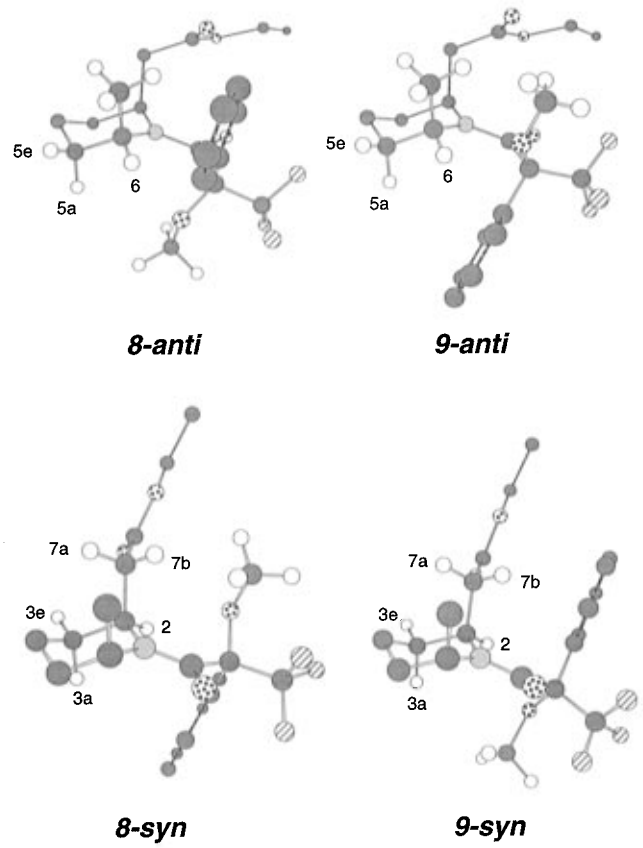


Figure 2. Chem3D Representation of the diastereomers of the anti- and syn-amide rotamers of the (*R*)- and (*S*)-MTPA amides of (2*S*,6*S*)-2-(Carbethoxymethyl)-6-methylpiperidine (**8-anti**, **9-anti**, **8-syn**, and **9-syn**, respectively).

Chem3D renderings for the anti rotamers[11] **8-anti** and **9-anti** are shown in Figure 2. In these conformations, both the methyl and carbethoxymethyl substituents are in the axial position to minimize $A^{1,3}$ strain with the amide substituents.[12] Using these models, the $\Delta\delta$ ($\Delta\delta = \delta_S - \delta_R$) values observed for the anti rotamers are conveniently rationalized. In rotamer **8-anti**, the phenyl group is aimed directly at the axial methyl group, resulting in a large $\Delta\delta$ value of +0.99 ppm. Rotamer **9-anti**, on the other hand, has the phenyl group oriented toward the axial proton at C(5) [H(5a)], which is shielded upfield to 0.55 ppm. H(5a) could not be assigned with confidence in rotamer **8-anti**; thus the exact $\Delta\delta$ value is not available, but it must be between +0.9 and +1.3 ppm. The $\Delta\delta$ value of −0.39 ppm for H(6) is also consistent with these models. For the syn-amide rotamers **8-syn**

(7) (a) Munchhof, M. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1995**, *117*, 5399. (b) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (c) Comins, D. L.; Benjelloun, N. R. *Tetrahedron Lett.* **1994**, *35*, 829. (d) Meyers, A. I.; Nguyen, T. H. *Tetrahedron Lett.* **1995**, *36*, 5873. (e) Rychnovsky, S. D.; McLernon, T. L.; Rajanpakse, H. *J. Org. Chem.* **1996**, *61*, 1194.

(8) While useful, the modeling techniques described here are nonessential for successful determination of absolute configuration of most chiral secondary amines.

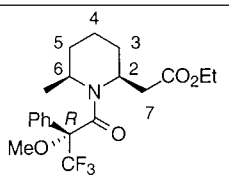
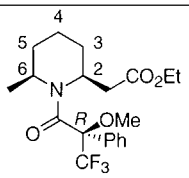
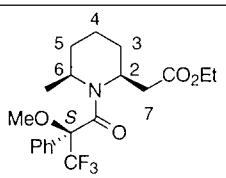
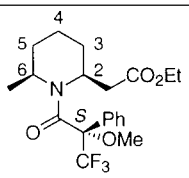
(9) Shielding is greater for protons on an axial substituent at C(2) than that for axial protons at C(2).

(10) Some protons have been removed for clarity in each of the figures.

(11) We refer to individual rotamers as syn or anti on the basis of the relationship of the MTPA α-carbon and the largest ring substituent (e.g., the carbethoxymethyl group in **8** or **9**).

(12) (a) Lunazzi, L.; Macciantelli, D.; Tassi, D.; Dondoni, A. *J. Chem. Soc., Perkin Trans. 2* **1980**, 717. (b) Chow, Y. L.; Colon, C. J.; Tam, J. N. S. *Can. J. Chem.* **1968**, *46*, 2821.

Table 1. Chemical Shifts (in ppm) and Δδ Values (in ppm) for the Individual Rotamers of the (*R*)- and (*S*)-MTPA Amides of (2*S*,6*S*)-2-(Carbethoxymethyl)-6-methylpiperidine (8 and 9)

H	 **8-anti**	 **8-syn**	 **9-anti**	 **9-syn**	Δδ = $\delta_S - \delta_R$ (*anti*)	Δδ = $\delta_S - \delta_R$ (*syn*)
2	5.10	4.34	5.34	4.84	+0.24	+0.50
3a		0.52		1.4-1.7[a]		+0.9 to +1.3[a]
3e		1.05				
5a	1.4-1.7[a]		0.55		-0.8 to -1.2[a]	
5e			0.88			
6	4.47	5.05	4.08	4.87	-0.39	-0.18
7a	2.59	2.83	2.68	2.38	+0.09	-0.45
7b	2.54	2.43	2.64	1.14	+0.10	**-1.29**
$C\underline{H}_2CH_3$	4.19, 4.15	4.14, 4.10	4.16, 4.12	3.85, 3.85		
$CH_2C\underline{H}_3$	1.29	1.26	1.28	1.14	-0.01	-0.12
Me	0.26	1.24	1.25	1.17	**+0.99**	-0.07

[a] This chemical shift and, therefore, the Δδ value fall within the indicated range.

and **9-syn** (Figure 2), the largest Δδ values are those for the protons at C(7), alpha to the ester carbonyl. Protons in the ethoxy group are also relatively shielded in **9-syn**. In rotamer **9-syn** the phenyl group is directed toward H(7b), resulting in a large Δδ of −1.29 ppm. H(7a) and H(2) also have large Δδ values. In **8-syn** the phenyl group is oriented toward H(3a). Once again, H(3a) could not be assigned with confidence in **9-syn**, but the Δδ value must be between −0.8 and −1.2 ppm.

It is worth reinforcing the fact that the magnitudes of the Δδ values exhibited by these MTPA amides are huge. In Mosher esters, for example, Δδ's greater than 0.3 ppm are rare and values even as small as 0.01−0.03 ppm can be used with confidence in making configurational assignments.

One limitation of this technique is that steric bulk around nitrogen can make the derivatization troublesome.[13] *trans*-2,6-Disubstituted piperidines have proven more difficult to derivatize than *cis*-2,6-disubstituted piperidines. For example, (2*R*,6*R*)-6-methyl-2-propylpiperidine (*epi*-dihydropinidine, **4**)[7b] and the analogous (2*R*,6*R*)-6-methyl-2-undecylpiperidine [(−)-solenopsin A, **5**][7b,c] were successfully derivatized with the *R* enantiomer of MTPA-Cl. However, amide formation using the (*S*)-acid chloride was quite slow, and competing side reactions that consumed the MTPA-Cl predominated. Despite this drawback, the anisotropic shieldings are so large within the single diastereomeric amides **10** and **11** that the absolute configuration of these molecules can still be confirmed/assigned with confidence even when only one amide is available. An analysis follows.

The *trans* geometry of the substituents at the C(2) and C(6) positions dictates two possibilities for the rotamers of the MTPA amides of these compounds. If the amine is of the (2*S*,6*S*) geometry, then the phenyl of the (*S*)-MTPA amide will be oriented toward H(2) and H(6) in the two rotamers. Alternatively, (2*R*,6*R*) geometry will lead to two rotamers for which the phenyl is oriented toward the alkyl substituents rather than the ring protons. The ^{1}H NMR chemical shifts for the (*S*)-MTPA amide of *epi*-dihydropinidine **10** (Table 2) show that the protons in the substituents rather than the ring protons are being shielded. The C(6) methyl group, for example, resonates at 1.43 ppm in the syn rotamer but greatly upfield at 0.20 ppm in the anti rotamer. Likewise, the methyl triplet for the syn rotamer is shielded to 0.39 ppm while the triplet for the anti rotamer is at 0.96 ppm. Thus, the ^{1}H NMR data are consistent with the structures in Figure 3, and therefore with the reported (2*R*,6*R*) configuration.[7b]

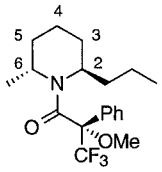
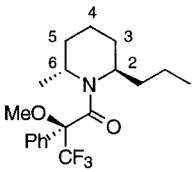
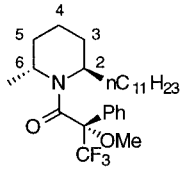
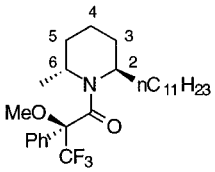
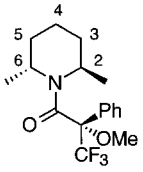
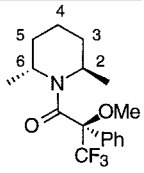
The ^{1}H NMR spectrum for the (*S*)-amide of (−)-solenopsin A (**11**)[5] is quite similar to that of **10**. The highly shielded methyl group in the minor rotamer **11-anti** is again indicative of the (2*R*,6*R*) configuration of the piperidine ring. Several proton resonances appear upfield of 1.0 ppm in the major rotamer **11-syn**, consistent with shielding of the C_{11} alkyl chain, but these resonances could not be assigned with certainty.

The ^{1}H NMR data for each of **10** and **11** are comparable with the data for the (*R*)-MTPA amide of (2*R*,6*R*)-dimethylpiperidine (**12**), which has been previously described.[3,14] For example, in the anti rotamers **10-anti** and **11-anti** (methyl groups syn to the MTPA α-carbons), the chemical shifts of the methyl groups are 0.20 and 0.19 ppm, respectively. The appropriate comparison is to that of the C(2) methyl group in **12** (methyl group syn to the

(13) 2,2,6,6-Tetramethylpiperidine, for example, could not be derivatized. So far we have been unsuccessful in derivatizing a mixture of *cis*- and *trans*-2,6-bis(carbomethoxymethyl)piperidine.

(14) The two amide rotamers for compound **13** (and **12**) can interconvert by chair−chair ring flip, thus, only one set of resonances is observed in the ambient temperature ^{1}H NMR spectrum.

Table 2. Partial Listing of Chemical Shifts (in ppm) for the Individual Rotamers of *epi*-Dihydropinidine (*S*)-MTPA Amide (10-syn and 10-anti), Solenopsin A (*S*)-MTPA Amide (11-syn and 11-anti), and the (*S*)- and (*R*)-MTPA Derivatives of (2*R*,6*R*)-Dimethylpiperidine 12 and 13

H	 **10-syn**	 **10-anti**	 **11-syn**	 **11-anti**	 **12**[a]	 **13**
2	4.0	3.90	4.05	3.88		
6	4.0	4.37	4.03	4.37		
Me(6)	1.43	0.20	1.43	0.19	1.40	1.54
$CH_2C\underline{H}_3$	0.39	0.96	0.892	0.885		
Me(2)					0.21	1.20

[a] The chemical shift data are actually those of the enantiomer of **12**.[3]

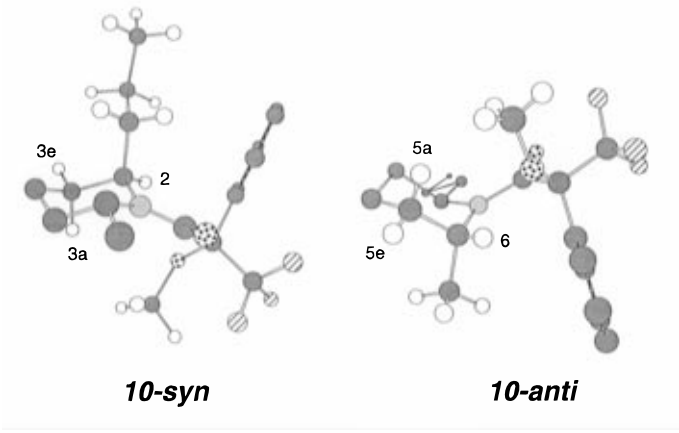


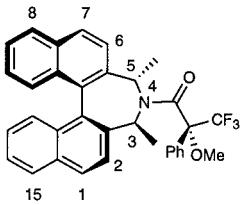
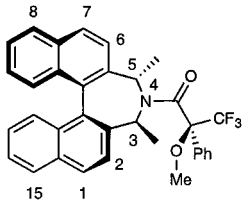
Figure 3. Chem3D representation of the syn- and anti-amide rotamers of the (*S*)-MTPA amide of (2*R*,6*R*)-6-methyl-2-propylpiperidine (**10-syn** and **10-anti**, respectively).

MTPA α-carbon), which resonates at 0.20 ppm. Similarly, the methyl groups in the syn rotamers **10-syn** and **11-syn** can be compared to the C(6) methyl group in **12** (methyl groups are anti to the MTPA α-carbon for all). The chemical shifts for these methyl groups are 1.43, 1.43, and 1.40 ppm, respectively. Thus, the configuration of the precursor amines is unambiguously confirmed, even though only one derivatized amide was available.

The precursor to the diastereomeric amides **14** and **15** is the C_2-symmetric amine **6**.[7d,e] As a result of this symmetry, both amide rotamers for each diastereomer are identical so only one set of resonances is observed in the ^{1}H NMR spectrum of each amide. The models shown in Figure 4 clearly indicate that the phenyl group is directed at the C(3) methyl in the (*R*)-amide **14** but not in the (*S*)-amide **15**. Indeed, the Δδ value for the C(3) methyl group is +1.05 ppm, confirming the proposed absolute configuration (Table 3).[7d,e]

In the (*S*)-amide, however, the phenyl group is aimed directly at the naphthyl proton at C(2), shielding it to 5.23 ppm. This results in a Δδ of −2.44 ppm, the largest differential shielding effect we know of for any Mosher derivative. The average C(2) proton−phenyl carbon distance in the model for **15** is 2.97 Å. This dramatic shielding effect is easily seen from the minimized structures shown in Figure 4, reinforcing their utility.

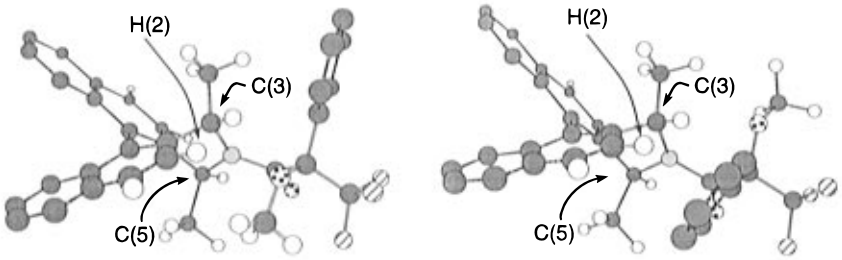
Table 3. Chemical Shifts (in ppm) and Δδ Values (in ppm) for the (*R*)- and (*S*)-MTPA Amides of (3*S*,5*S*)-3,5-Dihydro-3,5-dimethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine (14 and 15, Respectively)

H	 **14**	 **15**	Δδ = **S** - δ**R**
1	7.93	7.46	-0.47
2	7.67	5.23	**-2.44**
3	5.52	5.05	-0.47
5	5.90	5.74	-0.16
6	7.67	7.58	-0.09
7	7.95	7.96	0.01
8	7.93	7.92	-0.01
15	7.87	7.80	-0.07
Me(3)	-0.34	0.71	**1.05**
Me(5)	0.91	0.84	-0.07

All of the amides described thus far are derivatives of secondary amines. Many *N*-methyl tertiary amines can be conveniently demethylated using chloroformates. For example, cocaine was demethylated using trichloroethyl chloroformate, followed by zinc reduction to give the secondary amine, norcocaine (**7**).[15] The amine was then derivatized with MTPA-Cl to form amides **16** and **17**.

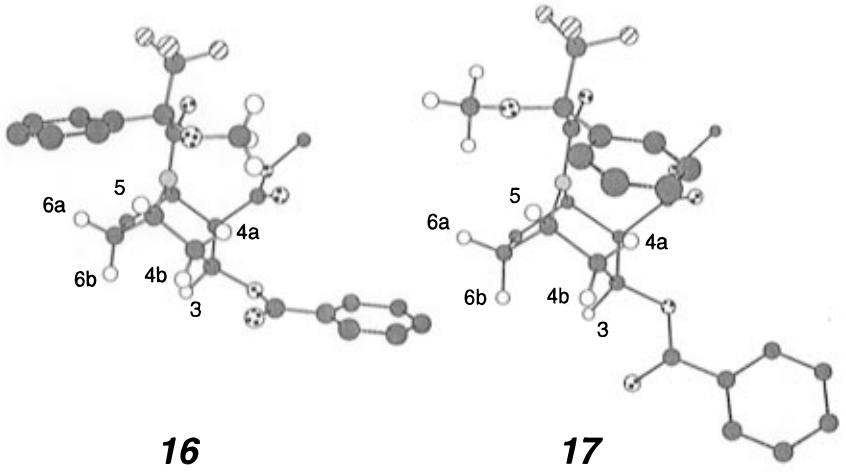
Each MTPA amide of norcocaine (**16** or **17**) shows only one rotamer in its ^{1}H NMR spectrum.[16] The NMR data for each amide are consistent with a rotamer in which the amide carbonyl is syn to the carbomethoxy group at

(15) Baldwin, S. W.; Jeffs, P. W.; Natarajan, S. *Synth. Commun.* **1977**, *7*, 79.



14 **15**

Figure 4. Chem3D representation of the diastereomers of the (*R*)- and (*S*)-MTPA amides of (3*S*,5*S*)-3,5-dihydro-3,5-dimethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine (**14** and **15**, respectively).



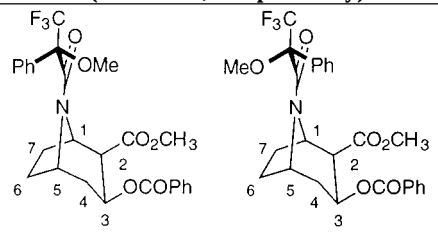
16 **17**

Figure 5. Chem3D representation of the diastereomers of the (*R*)- and (*S*)-MTPA amides of norcocaine (**16** and **17**, respectively).

C(2). We assume that this conformation is adopted to minimize steric interactions between the bulky MTPA α-carbon substituents and the carbomethoxy group (Figure 5). In the (*R*)-MTPA amide of norcocaine (**16**), the phenyl group is oriented toward C(6) [$\Delta\delta$ values of +1.17 and +0.44 ppm for H(6a) and H(6b), respectively (Table 4)]. Conversely, the phenyl group is oriented toward C(4) in the (*S*)-MTPA amide (**17**) ($\Delta\delta$ values of −1.05 and −0.57 ppm for H(4a) and H(4b), respectively). Thus, the data are entirely consistent with the known absolute configuration of cocaine.

In conclusion we have described here a powerful tool for the determination of absolute configuration of chiral cyclic amines. Quite often differential shieldings in the (*R*)- and (*S*)-Mosher amides are enormous. So large, in fact, that it is possible to determine absolute configuration based on derivatization with a single enantiomer of MTPA-Cl. Proper use of molecular modeling provides complementary information useful for understanding the chemical shift trends. Tertiary methyl amines can be demethylated and then subjected to the same analysis. We predict that this technology will become the method of choice for determination of absolute configuration in many amines.

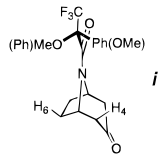
Table 4. Chemical Shifts (in ppm) and $\Delta\delta$ Values (in ppm) for the (*R*)- and (*S*)-MTPA Amides of Norcocaine (16 and 17, Respectively)



$\Delta\delta$ =

H	*16*	*17*	$\delta S - \delta R$
1	5.23	5.15	-0.08
2	3.19	3.16	-0.03
3	5.36	5.30	-0.06
4a	2.52	1.47	**-1.05**
4b	1.87	1.30	-0.57
5	4.33	4.47	+0.14
6a	0.86	2.03	**+1.17**
6b	1.38	1.82	+0.44
7a	1.83	2.03	+0.20
7b	1.73	1.82	+0.09
CO_2Me	3.70	3.79	+0.09

(16) We also prepared the MTPA amide of nortropinone (i). Nortropinone is achiral (*cf. cis*-dimethylpiperidine).[3,4] The ^{1}H NMR spectrum of the resulting amide shows two rotamers, present in a ratio of 2.5:1. In the major rotamer, the phenyl is directed toward the C(4) methylene group, while in the minor rotamer it is oriented principally toward the C(6) methylene group.



i

Experimental Section

In the ^{1}H NMR data (δ values are in ppm) for **8**−**11** resonances associated with the major amide rotamer are indicated with * and those for the minor amide rotamer with **; resonances comprising protons from both rotamers bear no asterisk. Proton assignments were consistent with DQ-COSY experiments for **8**, **9**, **10**, **11**, and **15** and DQ-COSY and NOESY spectra for **16** and **17**.

(2*S*,6*S*)-2-(Carbethoxymethyl)-6-methylpiperidine (*R*)-MTPA Amide (8). (Carbethoxymethyl)methylpiperidine **3** (3.9 mg, 0.021 mmol) and Hünig's base (6.7 mg, 0.052 mmol, 2.5 equiv) were dissolved in deuteriochloroform (200 μL) and stirred slowly in a tapered screw-capped vial under argon. (*S*)-MTPA-Cl (13.5 mg, 0.053 mmol, 2.5 equiv) was added, and the mixture was stirred at ambient temperature for 96 h. The solvent was evaporated, and the resulting residue was taken up in 1 M NH_4Cl and stirred vigorously for 30 min. The mixture was extracted with methylene chloride (4 × 1 mL), dried over $MgSO_4$, and flashed through a short plug of silica. The resulting oil was purified by preparative HPLC (90:10 Hex:EtOAc) to give **8** as a clear oil (5.1 mg, 61%). ^{1}H NMR ($CDCl_3$, 500 MHz, 2.5:1 ratio of rotamers): δ 7.56−7.53 (m, 4H), 7.41−7.37 (m, 6H), 5.10* (m, 1H), 5.05** (m, 1H), 4.47* (m, 1H), 4.34** (m, 1H), 4.19* (dq, 1H, J = 11 and 7 Hz), 4.15* (dq, 1H, J = 11 and 7 Hz), 4.14** (dq, 1H, J = 11 and 7 Hz), 4.10** (dq, 1H, J = 11 and 7 Hz), 3.76* (q, 3H, J = 1.5 Hz), 3.70** (q, 3H, J = 2 Hz), 2.83** (dd, 1H, J = 11 and 16 Hz), 2.59* (dd, 1H, J = 10 and 15 Hz), 2.54* (dd, 1H, J = 4 and 15 Hz), 2.43** (br d, 1H, J = 16 Hz), 1.8−1.4 (m, many H's), 1.29* (t, 3H, J = 7.5 Hz), 1.26** (t, 3H, J = 7.5 Hz), 1.24** (d, 3H, J = 7.5 Hz), 1.05** (br d, 1H, J = 13.5 Hz), 0.52** (m, 1H), and 0.26* (d, 3H, J = 7 Hz). HRMS (FAB): calcd for $C_{20}H_{26}F_3NO_4$ (M + H$^+$) 402.1892, found 402.1884.

(2*S*,6*S*)-2-(Carbethoxymethyl)-6-methylpiperidine (*S*)-MTPA Amide (9). Amide **9** was prepared from amine **3** and (*R*)-MTPA-Cl using a procedure analogous to that used for the preparation of **8** from **3**. ^{1}H NMR ($CDCl_3$, 500 MHz, 2:1 ratio of rotamers): δ 7.56−7.51 (m, 4H), 7.39−7.36 (m, 2H), 7.36−7.33 (m, 4H), 5.34** (m, 1H), 4.87* (m, 1H), 4.84* (m, 1H), 4.16** (dq, 1H, J = 11 and 7.5 Hz), 4.12** (dq, 1H, J = 11 and 7.5 Hz), 4.08** (m, 1H), 3.85* (q, 2H, J = 7.5 Hz), 3.79* (q, 3H, J = 1.5 Hz), 3.74** (q, 3H, J = 2 Hz), 2.68** (dd, 1H, J = 7 and 15 Hz), 2.64** (dd, 1H, J = 8 and 15 Hz), 2.38* (dd, 1H, J = 12 and 17 Hz), 1.7−1.4 (m, many H's), 1.28** (t, 3H, J = 7.5 Hz), 1.25** (d, 3H, J = 7.5 Hz), 1.17* (d, 3H, J = 7 Hz), 1.16* (br d, 1H, J = 17 Hz), 1.14* (t, 3H, J = 7 Hz), 0.88** (br d, 1H, J = 15 Hz), and 0.55** (m, 1H). HRMS (FAB): calcd for $C_{20}H_{26}F_3NO_4$ (M + H$^+$) 402.1892, found 402.1893.

(2*R*,6*R*)-6-Methyl-2-propylpiperidine (*S*)-MTPA Amide (10). *epi*-Dihydropinidine hydrochloride (**4**) (4.2 mg, 0.024 mmol) was suspended in deuteriochloroform (100 μL). Hünig's base (6.7 mg, 0.052 mmol, 2.2 equiv) and (*R*)-MTPA-Cl (8.8 mg, 0.035 mmol, 1.5 equiv) were added, and the mixture was stirred overnight at ambient temperature. The solvent was evaporated, and the residue was taken up in 1 M NH_4Cl. The mixture was extracted with methylene chloride (6 × 2 mL), dried over $MgSO_4$, and concentrated to yield a yellow oil, which was purified by preparative HPLC (96:4 Hex:EtOAc) to give **10** as a clear oil (3.4 mg, 40%). ^{1}H NMR ($CDCl_3$, 500 MHz, 6:5 ratio of rotamers): δ 7.60−7.57 (m, 4H), 7.39−7.35 (m, 6H), 4.37** (m, 1H), 4.07−4.01* (m, 2H), 3.90** (m, 1H), 3.75 (s, 6H), 1.96−1.45 (m, many H's), 1.43* (d, 3H, J = 6.5 Hz), 1.38* (m, 1H), 1.26** (m, 1H), 0.96** (t, 3H, J = 7.5 Hz), 0.79** (m, 1H), 0.39* (t, 3H, J = 7 Hz), 0.20** (d, 3H, J = 6.5 Hz), and 0.17−0.10 (m, 2H). HRMS (FAB): calcd for $C_{19}H_{26}F_3NO_2$ (M + H$^+$) 358.1994, found 358.2006.

(2*R*,6*R*)-6-Methyl-2-undecylpiperidine (*S*)-MTPA Amide (11). Amide **11** was prepared from (−)-solenopsin A hydrochloride (**5**) using a procedure analogous to that used for the preparation of **10** from **4** (7.3 mg, 62%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60−7.57 (m, 4H), 7.38−7.35 (m, 6H), 4.37** (m, 1H), 4.05* (m, 1H), 4.03* (m, 1H), 3.88** (m, 1H), 3.75* (s, 3H), 3.74** (s, 3H), 2.0−1.4 (m, many H's), 1.43* (d, 3H, J = 6.5 Hz), 1.4−1.2 (m, many H's), 1.10 (m, 2H), 0.94 (m, 2H), 0.892* (t, 3H, J = 7.5 Hz), 0.885** (t, 3H, J = 7.5 Hz), 0.8−0.6 (m, 2H), 0.19** (d, 3H, J = 7 Hz), 0.16 (m, 1H), and 0.05 (m, 1H). HRMS (FAB): calcd for $C_{27}H_{42}F_3NO_2$ (M + H$^+$) 470.3246, found 470.3227.

(3*S*,5*S*)-3,5-Dihydro-3,5-dimethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine (*R*)-MTPA Amide (14). Azepine **6** (4.7 mg, 0.15 mmol) and Hünig's base (2 mg, 0.16 mmol, 1.1 equiv) were dissolved in methylene chloride (200 μL) and stirred slowly in a tapered screw-capped vial under argon. (*S*)-MTPA-Cl (5.4 mg, 0.21 mmol, 1.5 equiv) was added, and the reaction mixture was stirred at ambient temperature for 14 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (10:1 Hex:EtOAc) to give a white solid (5.2 mg, 67%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (d, 1H, J = 8.5 Hz), 7.93 (br d, 2H, J = 8.5 Hz), 7.87 (br d, 1H, J = 8.5 Hz), 7.67 (br d, 2H, J = 7.5 Hz), 7.56 (d, 1H, J = 8.5 Hz), 7.52 (d, 1H, J = 8.5 Hz), 7.48 (ddd, 1H, J = 1.5, 7, and 7 Hz), 7.34−7.43 (m, 4H), 7.24−7.30 (m, 2H), 7.15 (br d, 2H, J = 3.5 Hz), 5.90 (q, 1H, J = 6.5 Hz), 5.52 (q, 1H, J = 6.5 Hz), 3.71 (q, 3H, J = 1.5 Hz), 0.91 (d, 3H, J = 7 Hz), and −0.34 (d, 3H, J = 7 Hz). IR (thin film): 1737 (w), 1642 (s), 1254 (m), 1181 (s), and 1163 (s) cm^{-1}. MS (EI): *m*/*z* 539 (21), 525 (5), 524 (20), 350 (30), 307 (42), 291 (20), 280 (57), 265 (41), 189 (75), and 105 (100). HRMS (EI): calcd for $C_{34}H_{28}F_3NO_2$ 539.2072, found 539.2054.

(3*S*,5*S*)-3,5-Dihydro-3,5-dimethyl-4*H*-dinaphth[2,1-*c*:1′,2′-*e*]azepine (*S*)-MTPA Amide (15). Compound **15** was prepared from azepine **6** using a procedure analogous to that used for the preparation of **14** from **6** (9.2 mg, 88%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (d, 1H, J = 7 Hz), 7.92 (br d, 1H, J = 7.5 Hz), 7.80 (br d, 1H, J = 8 Hz), 7.61 (tt, 1H, J = 1.5, 1.5, 7.5, and 7.5 Hz), 7.58 (br d, 3H, J = 8 Hz), 7.50 (d, 1H, J = 8 Hz), 7.48 (br d, 2H, J = 8 Hz), 7.44 (ddd, 1H, J = 1, 7, and 7 Hz), 7.43 (ddd,1H, J = 1, 7, and 7 Hz), 7.35 (br d, 1H, J = 8 Hz), 7.25 (br d, 1H, J = 8.5 Hz), 7.22 (ddd, 1H, J = 1.5, 7, and 7 Hz), 7.21 (ddd, 1H, J = 1.5, 7, and 7 Hz), 5.74 (q, 1H, J = 7 Hz), 5.23 (d, 1H, J = 8.5 Hz), 5.05 (q, 1H, J = 7 Hz), 3.70 (q, 3H, J = 1.5 Hz), 0.84 (d, 3H, J = 7 Hz), and 0.71 (d, 3H, J = 7 Hz). IR (thin film): 1737 (w), 1641 (s), 1254 (m), 1181 (s), and 1163 (s) cm^{-1}. MS (EI): *m*/*z* 539 (46), 525 (14), 524 (33), 350 (47), 307 (70), 291 (32), 280 (100), 265 (69), and 189 (52). HRMS (EI): calcd for $C_{34}H_{28}F_3NO_2$ 539.2072, found 539.2077.

Norcocaine *N*-(*R*)-MTPA Amide (16). Cocaine base (500 mg, 1.65 mmol) was dissolved in dry benzene (10 mL) over anhydrous potassium carbonate (50 mg). 2,2,2-Trichloroethyl chloroformate (385 mg, 1.82 mmol) was added to the stirred mixture, and the mixture was heated to reflux for 36 h. The reaction mixture was poured into ice water, the layers were separated, and the aqueous layer was extracted with chloroform (3 × 20 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated to give norcocaine *N*-(trichloroethyl)carbamate as an oil. The carbamate (166 mg, 0.357 mmol) was dissolved in 95% acetic acid (30 mL) and stirred at ambient temperature. Zinc dust (250 mg, 3.82 mmol) was added slowly, and the mixture was stirred for 48 h. The mixture was diluted with water (75 mL), basified with solid sodium carbonate, and extracted with methylene chloride (3 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give norcocaine (**7**) as a clear oil (75 mg, 74%), which slowly decomposed upon standing in air. The oil (18.5 mg, 0.064 mmol) and Hünig's base (18.5 mg, 0.14 mmol, 2.2 equiv) were dissolved in methylene chloride (500 μL) under argon. (*S*)-MTPA-Cl (19 mg, 0.075 mmol, 1.2 equiv) was added slowly to the stirred mixture, and the reaction mixture was stirred overnight. The solvent was evaporated, and the residue was taken up in 1 M NH_4Cl. The mixture was extracted into methylene chloride (3 × 2 mL), dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil (35 mg). The oil was purified by flash chromatography (4:1 Hex:EtOAc) to provide **16** as a clear oil (22.4 mg, 70%), which solidified (mp 149−152 °C) upon standing. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (dd, 2H, J = 1 and 8.5 Hz), 7.56 (tt, 1H, J = 1, 1, 7.5, and 7.5 Hz), 7.53 (m, 2H), 7.42 (dd, 2H, J = 7.5 and 8 Hz), 7.35−7.39 (m, 3H), 5.36 (ddd, 1H, J = 6, 6, and 11.5 Hz), 5.23 (m, 1H, Σ J's = 11 Hz), 4.33 (m, 1H, Σ J's = 12.5 Hz), 3.94 (q, 3H, J = 2 Hz), 3.70 (s, 3H), 3.19 (dd,

1H, J = 2.5 and 6.5 Hz), 2.52 (ddd, 1H, J = 3, 12, and 12 Hz), 1.87 (dddd, 1H, J = 1, 3, 6.5, and 9.5 Hz), 1.83 (ddd, 1H, J = 4, 7.5, and 12.5 Hz), 1.73 (ddd, 1H, J = 5, 9.5, 14 Hz), 1.38 (ddd, 1H, J = 5, 9.5, and 14 Hz), and 0.86 (ddddd, 1H, J = 1, 5, 7, 12.5, and 12.5 Hz). IR (thin film): 2953 (m), 1740 (s), 1718 (s), 1653 (s), 1272 (s), and 1110 (s) cm^{-1}. MS (EI): m/z 474 (1), 352 (2), 316 (20), 194 (23), 189 (10), 126 (17), 105 (100), and 77 (11). HRMS (CI): calcd for $C_{26}H_{26}F_3NO_6$ 505.1712, found 505.1732.

Norcocaine *N*-(*S*)-MTPA Amide (17). Compound **17** (mp 155−157 °C) was prepared from norcocaine (**7**) using a procedure analogous to that used for the preparation of **16** (23 mg, 72%). ^1H NMR ($CDCl_3$, 500 MHz): δ 7.91 (dd, 2H, J = 1 and 8 Hz), 7.71 (bd, 2H, J = 8 Hz), 7.55 (tt, 1H, J = 1, 1, 7.5, and 7.5 Hz), 7.47 (bt, 2H, J = 7 and 7 Hz), 7.39−7.43 (m, 3H), 5.30 (ddd, 1H, J = 6, 6, and 12 Hz), 5.15 (m, 1H, $\sum J$'s = 15 Hz), 4.47 (m, 1H, $\sum J$'s = 16.5 Hz), 3.79 (s, 3H), 3.64 (q, 3H, J = 1.5 Hz), 1.99−2.06 (m, 2H), 1.76−1.89 (m, 2H), 1.47 (ddd, 1H, J = 3, 12, and 12 Hz), and 1.30 (ddd, 1H, J = 3, 6, and 12 Hz). IR (thin film): 2952 (m), 1745 (s), 1718 (s), 1654 (s), 1274 (s), 1179 (s), and 1111 (s) cm^{-1}. MS (EI): m/z 474 (1), 316 (18), 194 (20), 189 (9), 126 (17), 105 (100), and 77 (16). HRMS: calcd for $C_{26}H_{26}F_3NO_6$ 505.1712, found 505.1727.

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