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(*R*)- and (*S*)-α-Methoxy-(1-naphthyl) acetic acids: resolution by fractional crystallization and use for the NMR stereochemical analysis of alkylsulfoxides

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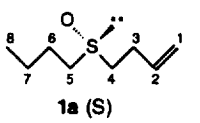
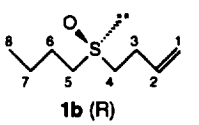
Abstract

Both enantiomers of α-methoxy-(1-naphthyl) acetic acid (1-NMA) were conveniently obtained via fractional crystallization using the enantiomers of 1-(1-naphthyl) ethylamine. 1-NMA was shown to be very powerful for differentiating the enantiomeric signals of quasi-symmetrical aliphatic sulfoxides.

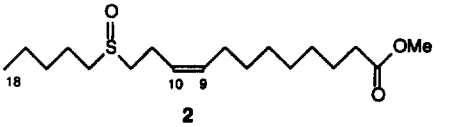
We have recently demonstrated the versatility of (*S*)-α-methoxy-(2-naphthyl) acetic acid for the enantiomeric excess determination of some chiral alkylsulfoxides by NMR.[1] This reagent as well as some other α-methoxyaryl acetic acids has been successfully used to elucidate the absolute configurations of long chain aliphatic secondary alcohols[2] and sulfoxides.[3] The large range of chiral NMR shift reagents reported for the convenient stereochemical analysis of sulfoxides[4] has been essentially applied to the methylaryl- or methylalkyl- sulfoxides. More recently, we have reported[5] that the common anti-inflammatory drugs (*S*)-naproxen and (*S*)-ibuprofen are valuable NMR shift reagents for the configurational analysis of dialkylsulfoxides with complex spin systems such as our chiral sulfoxide models **1a** and **1b**.



1a (S)



1b (R)



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Buist et al.[6] reported the use of (*S*)-α-methoxyphenylacetic acid ((*S*)-MPA) as a universal chiral NMR shift reagent for cyclic and acyclic sulfoxides. The likely complexation of the sulfoxide group with the carboxylic acid function of the (*S*)-MPA, designed as the postulated two point Pirkle-type complexation model[7] should cooperate with the wider-range anisotropic effect of the naphthyl group to discriminate

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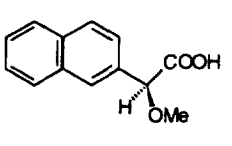
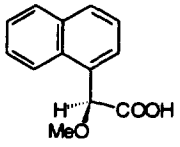
the two diastereotopic hydrogens adjacent to the sulfinyl function. However, no complete stereochemical analysis of the biooxidized thiaoleic acid **2**[8] could be achieved with either (*S*)-MPA or the powerful (*S*)-2-NMA. In order to determine the enantiomeric excess of **2**, we have explored and report here the usefulness of another Trost-like compound,[9] the (*R*)-α-methoxy-(1-naphthyl) acetic acid ((*R*)-1-NMA).



(S)-2-NMA



(S)-1-NMA

First, the racemic form of 1-NMA was synthesized from commercial 1-naphthaldehyde through the trimethylsilylcyanohydrin method,[10] followed by drastic acid hydrolysis (6 N HCl:dioxane=1:3, 4 h, 110°C) to afford the α-hydroxy-(1-naphthyl) acetic acid. The racemic α-methoxy-(1-naphthyl) acetic acid was obtained by treatment of the methyl α-hydroxy-(1-naphthyl) acetate with methyl iodide in the presence of silver oxide, followed by basic hydrolysis (overall yield: 47%). Both pure enantiomers had been previously isolated[2b] from the racemic mixture by chiral HPLC. We first attempted to separate the diastereoisomeric (−)-menthyl esters of 1-NMA by preparative chromatography but the subsequent hydrolysis failed in affording both isomers of the corresponding acids. However, we successfully achieved the resolution of 1-NMA via fractional crystallization of their (*R*)-1-(1-naphthyl) ethylamine salts. To the best of our knowledge, the resolution of aryl substituted carboxylic acids by this classical method has been poorly explored in the past. However, some interesting results such as the enantiomeric resolution of 2-fluorocyclopropanecarboxylic acid with the (*S*)-1-(1-naphthyl) ethylamine has been previously patented.[11] Both enantiomeric forms of 1-(1-naphthyl) ethylamine have been used in order to obtain optically active forms of a hemiphthalic ester, the intermediate in a natural pheromone synthesis.[12]

We resolved the racemic 1-NMA with (*R*)-1-(1-naphthyl) ethylamine to give a crystalline salt m.p. 208–210°C, $[\alpha]_D^{20}$ −80.36 (MeOH, c 0.494) after three repeated recrystallizations from MeOH. Acidification of the salt with 0.5 N HCl:ethyl ether (2:1, v/v) afforded the resolved (*R*)-1-NMA with 31% yield, m.p. 115°C, $[\alpha]_D^{20}$ −176.8 (EtOH, c 0.328),[13] lit.[2b] −130.66 (EtOH, c 0.30).

Similarly, resolution with (*S*)-1-(1-naphthyl) ethylamine gave another crystalline salt m.p. 178–180°C, $[\alpha]_D^{20}$ +80.8 (MeOH, c 0.50), which yielded (*S*)-1-NMA with 34% yield, m.p. 115°C, $[\alpha]_D^{20}$ +177.4 (EtOH, c 0.303), lit.[2b] +134.55 (EtOH, c 0.4). Enantiomeric purities of both enantiomers were determined by the use of the bonded chiral stationary phase Whelk-0 1.[14]

In order to measure an enantiomeric excess of those alkylsulfoxides, we were first concerned with the splitting effect of the terminal methyl signals in ^{1}H-NMR spectra. Figure 1 illustrates the very wide anisotropic effect on these protons of the racemic butylbutene sulfoxide **1** in C_6D_6 using (*R*)-1-NMA, compared to the (*R*)-2-NMA and to the common MPA reagent. Consequently, we observe the effect of these shift reagents on the difference of carbon chemical shifts between enantiomers **1a** and **1b** in the ^{13}C-NMR spectrum (Table 1). (*R*)-1-NMA was shown to be much more efficient than MPA and 2-NMA on the whole of the carbon signal splittings.

Similarly, (*R*)-1-NMA appeared to be extremely efficient in the enantiomer differentiation of most of the carbon signals of methyl (*S*)-oxide-13-thiaoleate **2** (Table 2). The splitting of the CH_3 (C_{18}) signal (Fig. 2) should be sufficient to measure the ee of an optically active sample from our biocatalysis experiments.[8]

In conclusion, (*R*)-1-NMA appears to be a powerful shift reagent in the discrimination of the enantiomeric signals of quasi-symmetrical aliphatic sulfoxides. Moreover, the results presented here suggest a very important influence of the aryl substitution (1-NMA or 2-NMA) on the building of the

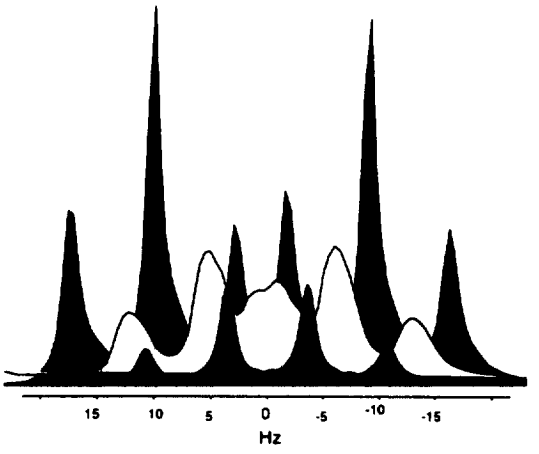


Fig. 1. Splitting of the ^{1}H-NMR CH_3 signal of **1** with added shift reagent (grey: MPA; white: 2-NMA; black: 1-NMA)[15]

Table 1
Effect of the shift reagent on the magnitude of the non-equivalence in the ^{13}C-NMR spectra of **1a** and **1b**

	| δ(1a) - δ(1b) | (ppm)							
^{13}C Position	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
MPA	0.015	0.023	0.034	0.027	0.027	0.015	0.023	0.008
2-NMA	0.027	0.030	0.030	0.023	0.023	0.011	0.019	0.023
1-NMA	0.046	0.049	0.072	0.068	0.064	0.038	0.053	0.038

Table 2
Effect of the shift reagent on the magnitude of the non-equivalence in the ^{13}C-NMR spectra of **2**

	| Δδ | (ppm)											
^{13}C Position	**6**[a)]	**7**[a)]	**8**	**9**	**10**	**11**	**12**	**14**	**15**	**16**	**17**	**18**
MPA	0.000	0.000	0.019	0.023	0.011	0.046	0.019	0.034	0.015	0.027	0.000	0.000
2-NMA	0.019	0.019	0.034	0.038	0.030	0.049	0.027	0.049	0.038	0.034	0.019	0.030
1-NMA	0.023	0.023	0.046	0.053	n.m.	0.083	0.049	0.084	0.046	0.065	0.042	0.030

a) not attributed ; b)not measured .

interaction with our sulfoxides, and consequently on the anisotropic effect exerted by the naphthyl group on the different NMR signals.

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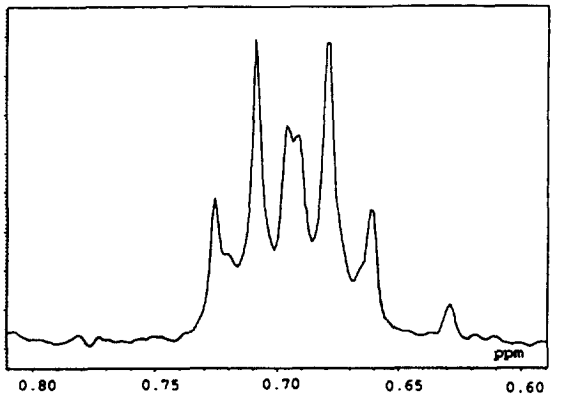

Fig. 2. Splitting of the ^{1}H-NMR CH_3 (C_{18}) signal of **2** with added (*R*)-1-NMA

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13. (*R*)-1-(1-Naphthyl) ethylamine (1 g) was added to a stirred solution of racemic 1-NMA (1.4 g) in ethyl ether. The obtained crystals were collected by filtration and dried at r.t. The resulting filtrate was recovered and submitted to another crystallization. The operation was repeated until the specific rotation of the salt turned positive. The collected (*R*)-1-NMA-(*R*)-amine salt fractions were recrystallized several times from MeOH until the specific rotation became constant. This salt (260 mg) was added to a stirred and ice-cooled mixture of diethyl ether (10 mL) and 0.5 N HCl aq. (20 mL). The mixture was stirred for 3 h under ice-cooling and extracted with ethyl ether. After drying ($MgSO_4$) and evaporation of the solvent under vacuum, the (*R*)-1-NMA (137 mg) was obtained. HRMS calcd for $C_{13}H_{12}O_3$: 216.0786, obsd: 216.0793.
14. The Whelk-0 1 CSP, Pirkle-type chiral stationary phase HPLC was used to separate both enantiomeric forms of 1-NMA. UV detection was accomplished at 254 nm. An isocratic mobile phase (hexane:isopropanol=98:2) was used with a flow rate of 1 mL/min. Enantiomers were separated by approximately 5.5 min. This Pirkle concept enantiomeric resolution has been developed specifically for the separation of 2-arylpropionic acid, including non-steroidal anti-inflammatory drugs such as naproxen and ibuprofen. See for examples: Blum, A. M.; Lynam, K. G.; Nicolas, E. C. *Chirality* **1994**, *6*, 302–313. Nicoll-Griffith, D.; Scartozzi, M.; Chiem, N. *J. Chromatogr.* **1993**, *653*, 253–259.
15. NMR spectra were recorded with an ARX-400 Bruker Spectrometer. The correct assigments were established using routine COSY and HMQC experiments. All the samples were prepared as follows: to 1 mg of the sulfoxide in 0.5 mL of solvent, was added 3 equiv. of the desired NMR shift reagent. All the spectra were recorded at 298 K, after thermal stabilization of the samples. The same splitting effects were observed in the ^{1}H- and ^{13}C-NMR spectra with both enantiomers of the tested shift reagents (1-NMA or 2-NMA).