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^{1}H NMR evaluation of the enantiomeric purity of a series of heterocyclic β-dimethylamino esters and amides by using (*S*)-mandelic acid derivatives as chiral solvating agents

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Abstract

(*S*)-OR-Mandelic acid derivatives have been used as chiral solvating agents to induce significant non-equivalences in the ^{1}H NMR spectra of several heterocyclic structures bearing a β-dimethylamino ester or amide pattern.

Recently, we described the asymmetric synthesis (100% ee) of the (*R,R*)-5,6-dihydro-*4H*-1,3-thiazine **1** via a diastereoselective Lewis acid mediated hetero Diels–Alder reaction.[1] Cleavage of the external N–CO bond in the oxazolidinone precursor **2** (100% de) constituted the ultimate step of our synthesis. In order to ensure that the chiral auxiliary recovery was effected without erosion of the chirality at C-5, recourse to NMR techniques appeared highly desirable as compound **1** is prone to a facile β-elimination process with loss of dimethylamine. Use of chiral lanthanide shift reagents (CLSR) proved ineffective in the case at hand as broadening of all signals resulted after addition of very small amounts of these reagents in various solvents ($CDCl_3$, CD_3CN, CD_3COCD_3). Consequently, we turned our attention to an alternative strategy involving the use of chiral solvating agents (CSAs) and after screening of a series of chiral acids we finally discovered that the enantiomeric purity of dihydrothiazine **1** could be satisfactorily evaluated in $CDCl_3$ by using an excess (two to three equivalents) of (*S*)-mandelic acid (Scheme 1).[2,3]

Encouraged by this result and due to the current interest of our laboratory in methods for constructing chiral heterocyclic structures of synthetic importance, we have now examined a series of racemic heterocycles[4] (5,6-dihydro-*4H*-1,3-thiazines **4** and **5**; 5,6-dihydro-*4H*-1,3-selenazine **6**; 3,4-dihydro-*2H*-thiopyrans **7**–**10**, Scheme 2), all having in common a β-dimethylamino ester or amide pattern as shown by the general formula **3** in Scheme 1. The purpose of our study was to determine the generality of the 'mandelic acid effect' on heterostructures related to **1** and to delineate the main structural factors

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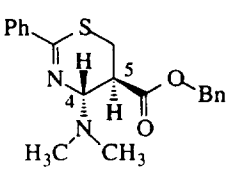

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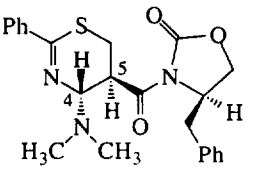

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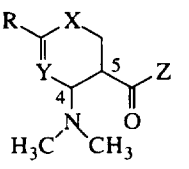

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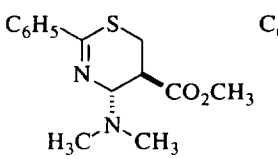
X = S, Se Y = N, CH, C-CO_2CH_3
R = Ph, CO_2CH_3
Z= OCH_3, N (oxazolidinone residue)

Scheme 1.

involved in such an effect. Herein, we disclose our results showing, *inter alia*, that (*S*)-O-methyl and (*S*)-O-acetyl mandelic acids act, as a general rule, as superior CSAs[5] for enantiomeric purity evaluation of the compounds outlined in Scheme 2.



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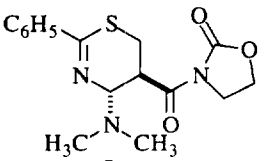

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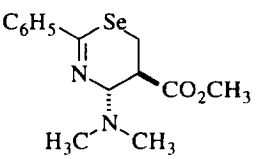

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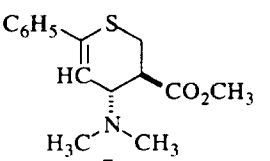

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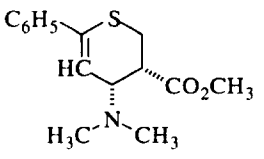

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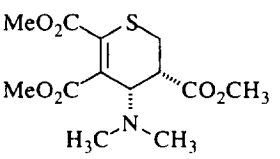

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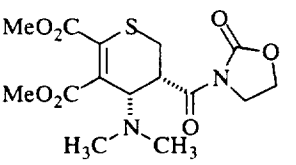

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Scheme 2.

Direct comparison of the ^1H NMR spectra recorded at 400 MHz in deuterated chloroform solution[6] reveals that (*S*)-OMe and (*S*)-OAc mandelic acids induce a significant resolution of the absorptions due to the H-4, $N(CH_3)_2$ and CO_2CH_3 protons. Since the $N(CH_3)_2$ and CO_2CH_3 signals, as opposed to the H-4 signal, are sharp singlets appearing in almost free spectral regions, they represent the ideal probes for the measurements and particular attention was devoted towards conditions that allow optimum signal separations ($\Delta\delta$). The data summarised in Table 1 deserve the following comments: (1) In all heterocyclic structures considered, it was possible to find conditions that permit clear baseline separation of the CO_2CH_3 and (or) $N(CH_3)_2$ protons, thus allowing for accurate quantifiable measurements. As a general rule, the CO_2CH_3 signals are best separated although, in some examples (particularly in cases where the CO_2CH_3 grouping is replaced by an oxazolidinone residue), the NMe_2 signal separation is large enough for measurements. As an illustration of the efficacy of the method, Fig. 1 displays the CO_2CH_3 and $N(CH_3)_2$ signal discriminations for compound **8** in the presence of two equivalents of (*S*)-OMe mandelic acid ($\Delta\delta$=0.057 ppm and 0.016, respectively). (2) Addition of two or three CSA equivalents increases, in some cases, the enantiomer signal separation. At an equal number of CSA equivalents added, the signal separation is always superior with the (*S*)-OMe and (*S*)-OAc mandelic acids than with mandelic acid itself. On one occasion (entry 6), use of (*S*)-OBn mandelic acid gave results comparable to those displayed by the (*S*)-OMe analogue. (3) CO_2CH_3 chemical shift differences recorded for compound cis-**8** (axial NMe_2) are significantly greater than those exhibited by its stereoisomer trans-**7** (equatorial $N(CH_3)_2$). (4) The presence of both the carboxylic acid functionality and the phenyl substituent in (*S*)-

Table 1
Shift non-equivalences ($\Delta\delta$) induced in the $N(CH_3)_2$ and CO_2CH_3 (if present) protons (400 MHz, 0.05 M solution in $CDCl_3$, 20°C) of racemic heterocyclic structures **1**, **4–10** in the presence of (*S*)-mandelic acid (MAc) and its (*S*)-OMe and (*S*)-OAc derivatives

Entries	Heterocycles	CSAs (equiv.)	$\Delta\delta$ (NMe_2)	$\Delta\delta$ (CO_2Me)
1	**1**	MAc (2)	0.010	
2	-	OMe-MAc (3)	0.020	
3	**4**	MAc (1)	0.008	0.004
4	-	OMe-MAc (1)	0.012	0.033
5	-	OAc-MAc (1)	0.005	0.016
6	-	OBn-MAc (2)	0.010	0.030
7	**5**	OMe-MAc (1)	0.016	
8	-	OMe-MAc (2)	0.028	
9	-	OMe-MAc (3)	0.036	
10	-	OAc-MAc (1)	0.026	
11	**6**	OMe-MAc (1)	0.007	0.023
12	-	OAc-MAc (2)	0.010	0.007
13	**7**	OMe-MAc (2)	0.010	0.012
14	-	OAc-MAc (1)	0.004	0.013
15	**8**	MAc (3)	0	0.033
16	-	OMe-MAc (1)	0	0.018
17	-	OMe-MAc (2)	0.016	0.057
18	-	OAc-MAc (1)	0	0.039
19	-	OAc-MAc (3)	0.014	0.06
20	**9**	OMe-MAc (3)	0.007	0.013
21	-	OAc-MAc (3)	0.009	0.020
22	**10**	OMe-MAc (3)	0.032	

mandelic acid and its (*S*)-OR-derivatives are key elements for the effect to be observed. Indeed, use of (*S*)-lactic acid or (*S*)-mandelic acid methyl ester resulted in no significant chemical shift non-equivalences for all of the compounds considered. The position of the phenyl substituent relative to the carboxylic acid moiety is also of great importance as shown by the very small $\Delta\delta$ displayed by (*S*)-phenyl lactic acid (not shown in Table 1). (5) In addition to chemical shift non-equivalences it was noted that addition of CSAs induced pronounced chemical shift variations in the NMR spectra of substances **4–10** and that the H-4 proton and the β-dimethylamino ester moiety were principally affected by the chiral additives. Thus, large chemical shift variations were noted (2 equivalents of OR-MAc) for H-4 (0.4 to 0.8 ppm, downfield), $N(CH_3)_2$ (0.2 to 0.3 ppm, downfield) and CO_2CH_3 (0.1 to 0.2 ppm, upfield) whereas the other protons were less or not affected. One notable exception is the downfield shift displacement experienced by the H-5 proton in dihydropyrans **7** and **8** (0.3 to 0.4 ppm). Also noteworthy is the rather similar effect displayed by the H-4 proton in trans-**7** (0.6 to 0.7 ppm) and cis-**8** (0.5 to 0.6 ppm).

In order to get more information concerning the mode of interaction arising between the two partners we undertook an IR study and first considered, as a simplified model, a 1/1 mixture of triethylamine and (*S*)-OMe mandelic acid. The IR spectrum, taken in chloroform solution at a concentration similar to that used in NMR experiments, clearly shows the disappearance of the hydroxyl and carbonyl bands[7]

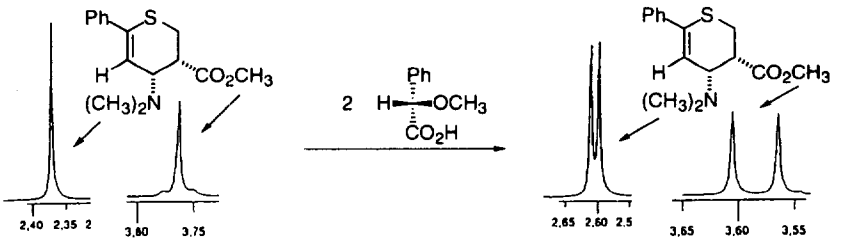

Fig. 1. ^{1}H NMR resonances of the CO_2CH_3 and $N(CH_3)_2$ protons in free *rac*-**8** and the 1/2 mixture of *rac*-**8**/(*S*)-OMe mandelic acid, (400 MHz, 0.05 M solution in $CDCl_3$, 20°C)

and the concomitant appearance of bands corresponding to the formation of an ammonium salt (ν NH^+: 2475 cm^{-1}; ν_{as} CO_2^-: 1622 cm^{-1} and ν_s CO_2^-: 1398 cm^{-1}). By comparison the IR spectrum of the 1/1 dihydrothiazine **3**/OMe–MAc mixture could be interpreted the same way. In particular, carboxylate bands were detected at 1625 and 1400 cm^{-1}, respectively. In this example, we also made the interesting observation that the disappearance of the hydroxyl and carbonyl bands, although quite significant, were not complete in contrast to what we had previously observed for the NEt_3/OMe–MAc mixture. Given the NMR observation that addition of one CSA equivalent resulted in complete transformation of compound **3**, a reasonable interpretation is that two species principally coexist in chloroform solution, i.e., the ammonium salt $[R(CH_3)_2NH^+ \cdot {}^-O_2CR'^*]$ in equilibrium with the hydrogen bonded complex $[R(CH_3)_2N \cdots HO_2CR'^*]$, the role of the extra CSA equivalents being to displace this equilibrium toward the ammonium salt species.

To sum up, the addition of (*S*)-mandelic acid and (*S*)-OR-derivatives to the compounds outlined in Scheme 2 results in the formation of ammonium salts in which both the chemical shift non-equivalences and the chemical shift variations observed by ^{1}H NMR analysis are primarily due to anisotropic effects exerted by the CSA groupings (principally the phenyl one) on the β-dimethylamino ester or amide moieties. However, despite the amount of data accumulated in this study, it is still difficult to propose a simple and coherent model for the ammonium salt structure that takes into account all of the spectroscopic observations and we prefer not to speculate on this point. Nevertheless, the present method offers a useful solution to the difficult problem of enantiomeric excess determination for a class of heterocyclic β-dimethylamino esters and amides where the use of CLSR agents cannot be envisaged.

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References

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2. Previous examples of the use of carboxylic acids as chiral solvating agents for amines and amino alcohols can be found in the following review: Parker, D. *Chem. Rev.* **1991**, *91*, 1441–1457.
3. Previous use of carboxylic acids as CSAs for the determination of enantiomeric excess of chiral α-amino esters (three examples) and γ-amino ester (one example) by NMR spectroscopy, see: Benson, S. C.; Cai, P.; Colon, M.; Haiza, M. A.; Tokles, M.; Snyder, J. K. *J. Org. Chem.* **1988**, *53*, 5335–5341. Shapiro, M. J.; Archinal, A. E.; Jarema, M. A. *J. Org. Chem.* **1989**, *54*, 5826–5828.
4. All of these heterocycles were obtained following a hetero Diels–Alder protocol. Details of their preparation will be reported in a forthcoming full paper.

5. The superiority of OAc mandelic acid compared to mandelic acid or MTPA as a CSA was first pointed out by Parker et al. for a series of β-amino alcohols: Parker, D.; Taylor, R. J. *Tetrahedron*, **1987**, *43*, 5451–5456.
6. The $\Delta\delta$ values are smaller in deuterated benzene solution.
7. (*S*)-OMe Mandelic acid displays three distinct hydroxyl bands (ν OH). A broad one centered around 3000 cm^{-1} corresponding to its dimer and two sharper ones located at 3503 and 3402 cm^{-1} corresponding to the free acid and its internal hydrogen bonded analogue, respectively. Two carbonyl bands (ν CO) are present at 1774 cm^{-1} (free and internal hydrogen bonded analogue) and 1726 cm^{-1} (dimer).