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1-Arylethylamino-substituted *s*-triazine derivatives as chiral solvating agents for the determination of the enantiomeric composition of chiral compounds

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Abstract

The development of 2-[(*R*)-1-(9-anthryl)ethylamino]-4-chloro-6-methoxy-1,3,5-triazine, 2-[(*R*)-1-(9-anthryl)ethylamino]-4-chloro-6-[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine and 2-[(*R*)-1-(9-anthryl)ethylamino]-4,6-bis-[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine as chiral solvating agents (CSAs) for the determination of the enantiomeric composition of derivatized and underivatized chiral compounds is presented. The comparison between the efficiency of these chiral auxiliaries with the corresponding 1-(1-naphthyl)-ethylamino substituted *s*-triazine derivatives is also discussed. © 2000 Published by Elsevier Science Ltd.

1. Introduction

The growing use of enantiomerically pure materials as chiral auxiliaries in asymmetric synthesis[1] has given rise for about 15 years to the need for the development of fast and accurate methodologies for the determination of the enantiomeric composition of chiral compounds.[2] A satisfactory answer to this demand is afforded by the use of chiral solvating agents (CSAs) for NMR spectroscopy,[3] which represents, together with the chromatographic methods,[4] one of the most employed techniques for the rapid assessment of the enantiomeric excesses.

Although a great number of CSAs are reported in the literature,[3] systems showing applicability towards a wide range of substrates are still a challenge. In searching for enantiomerically pure compounds having these properties[5] we have recently dealt with a new class of CSAs, obtained by linking to the *s*-triazine nucleus enantiomerically pure 1-(1-naphthyl)ethylamine.[6] The mono-, di- and tri-1-(1-naphthyl)ethylamino-substituted *s*-triazine derivatives **1**, **2** and **3** (Fig. 1) have proven to be promising CSAs, inducing appreciable non-equivalences on the enantiotopic protons of

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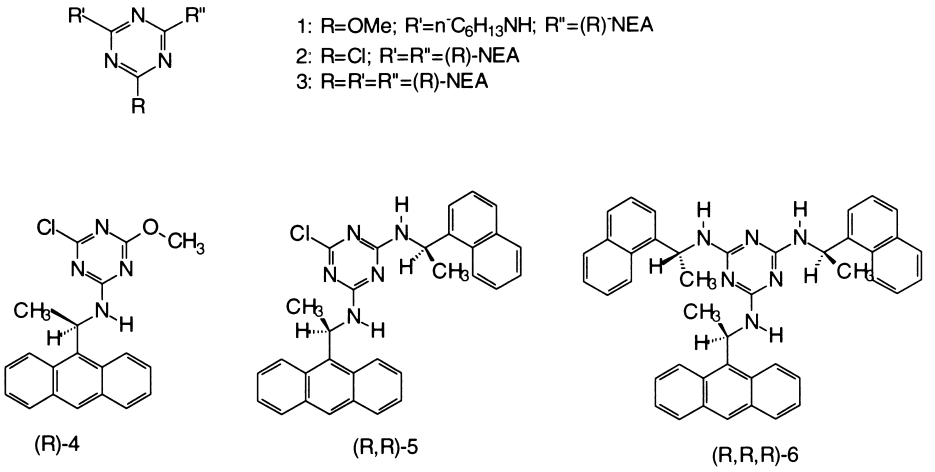


Figure 1.

3,5-dinitrophenyl derivatives of various racemic compounds, and, in the case of the trisubstituted one, being able to enantiodiscriminate some underivatized compounds.[6] The effectiveness of these kinds of CSAs is attributable to their high degree of conformational homogeneity[7] and to the presence of π-basic aromatic rings able to establish π–π interaction with π-acidic substrates.

The encouraging results obtained with the above CSAs have prompted us to synthesize mono-, di- and tri-1-(9-anthryl)ethylamino-substituted *s*-triazine derivatives in order to introduce into the molecule a higher degree of conformational homogeneity and a more polarizable moiety, which could afford a new class of *s*-triazine-based CSAs having an improved efficiency with respect to the 1-(1-naphthyl)ethylamino-substituted *s*-triazine derivatives.

However, the poor solubility of the di-1-(9-anthryl)ethylamino-substituted *s*-triazine derivative in the most commonly employed solvents for NMR analysis, such as $CDCl_3$, which strongly limits its use, and the difficulty in obtaining the trisubstituted derivative, discouraged us from preparing homo-substituted *s*-triazine derivatives. Nevertheless, the above-mentioned characteristics of the 1-(9-anthryl)ethylamino moiety make interesting even the use of mixed *s*-triazine derivatives containing both 1-(1-naphthyl)ethylamino and 1-(9-anthryl)ethylamino groups, which are synthetically accessible and readily soluble in the most common organic solvents.[8,9] Therefore, the aim of this work is the development as CSAs of the *s*-triazine derivatives **4**, **5** and **6** (Fig. 1) containing only one 1-(9-anthryl)ethylamino moiety, in order to check if this structural characteristic could afford new 1-arylethylamino-substituted *s*-triazine derivatives to be used as more convenient CSAs than the 1-(1-naphthyl)ethylamino-substituted *s*-triazine derivatives.

2. Results and discussion

The *s*-triazine derivatives **4**, **5** and **6** were prepared by regioselective nucleophilic displacement of the chlorine atoms of *s*-trichlorotriazine by means of enantiomerically pure (*R*)-1-(1-naphthyl)-ethylamine and (*R*)-1-(9-anthryl)ethylamine as reported previously.[8,9]

Racemic 3,5-dinitrobenzoyl alanine methyl ester **7a** has been chosen as a probe for comparing the efficiency of **4**, **5** and **6** with respect to the corresponding mono-, di- and tri-1-(1-naphthyl)-ethylamino-substituted *s*-triazine derivatives **1**, **2** and **3**.

Splitting of the resonances of most of the protons of **7a** is observed in the presence of an equimolar amount of **4** (Fig. 2 and Table 1). The non-equivalences produced on the aromatic protons are, respectively, 15 Hz for Ha and 11.2 Hz for Hb, the doubling of the signal of the proton on the stereogenic centre affords two partially superimposed multiplets ($\Delta\Delta\delta$ 5.8 Hz) and two well separated singlets are observed for the methoxy protons ($\Delta\Delta\delta$ 3.4 Hz). By comparing these non-equivalences with those measured for the same protons, in the presence of an equimolar amount of the mono-1-(1-naphthyl)ethylamino-substituted *s*-triazine derivative **1** (Fig. 2 and Table 1), it is clear that **4** is more efficient than **1**, and, due to the baseline separation of the 3,5-dinitrophenyl signals, an accurate determination of the enantiomeric composition of **7a** can be carried out, whereas this was difficult with the mono-1-(1-naphthyl)ethylamino derivative.

The non-equivalences produced by **5** are greater than those measured for **4**, but no significant differences are observed in comparison to **2** (Fig. 2 and Table 1); however, it is noteworthy that the proton on the stereogenic centre gives rise, in this case (mixtures **7a** and **5**), to two partially superimposed multiplets ($\Delta\Delta\delta$ 4.4 Hz), whereas in the presence of the 1-(1-naphthyl)ethylamino derivative **2** no splitting of this signal is observed. As far as the trisubstituted derivative is concerned, only the non-equivalences induced on the methoxy protons are significantly higher than those measured with **4** and **5** (Fig. 2). The signals of the other protons, in particular the aromatic ones, are less split: this fact makes the use of **6** as CSA for **7a** less attractive than the use of **4** and **5**. However, also in this case, at least as far as Ha and methoxy protons are concerned, compound **6** results in being more efficient than the tri-1-(1-naphthyl)ethylamino analogue **3**, so confirming the trend of **4** and **5**. The comparison between the two classes of *s*-triazine derivatives can be made, taking into consideration the shift of the proton signals of **7a** in the presence of the two kinds of compounds. All the signals undergo an upfield shift in the presence of both classes of CSAs, which is found to be more marked when the CSAs contain the 1-(9-anthryl)ethylamino moiety: this probably happens because of the stronger diamagnetic anisotropy exerted by the anthracene moiety on the protons of the substrate, which produces larger upfield shifts with respect to those observed in the presence of the 1-(1-naphthyl)ethylamino-substituted *s*-triazine derivatives.

Given the good results obtained in the enantiodiscrimination of **7a** when **4** and **5** are used as CSAs, we were interested in checking the applicability of these compounds towards various 3,5-dinitrobenzoyl amino acid alkyl esters and, for this reason, the ^{1}H NMR spectra of the amino acid derivatives **7b–g** in the presence of equimolar amounts of **4** and **5** were analysed (Table 2).

The data listed in Table 2 show that both **4** and **5** are able to induce such non-equivalences on the enantiotopic protons of the substrates **7b–g** that an easy determination of the enantiomeric composition of enriched samples can be performed. The non-equivalences induced on the enantiotopic protons are higher in the presence of **5** and depend on the nature of the amino acid. The best results are obtained in both cases with the derivative **7g**, where the phenyl group is present on the stereogenic centre of the amino acid, whereas the branching of the alkyl group of the amino acid moiety is detrimental for the enantiodiscrimination, as clearly deducible by comparing the non-equivalences measured for **7a** and **7f**. On the contrary, the nature of the ester group has little influence on the enantiodiscrimination process, as similar non-equivalences are measured for **7b**, **7c** and **7d**. As far as the effect of the molar ratio CSA/substrate is concerned, it is noteworthy that **4** and **5** also work when this ratio is lowered. In fact, appreciable non-equivalences are still induced by **4** on the protons of **7a** (Table 1) also when the molar ratio CSA/substrate is lowered from 1:1 to 1:2, although the values are smaller than those obtained in the case of the 1:1 mixture; much more interesting results are obtained with **5**, which is able to produce separation of the

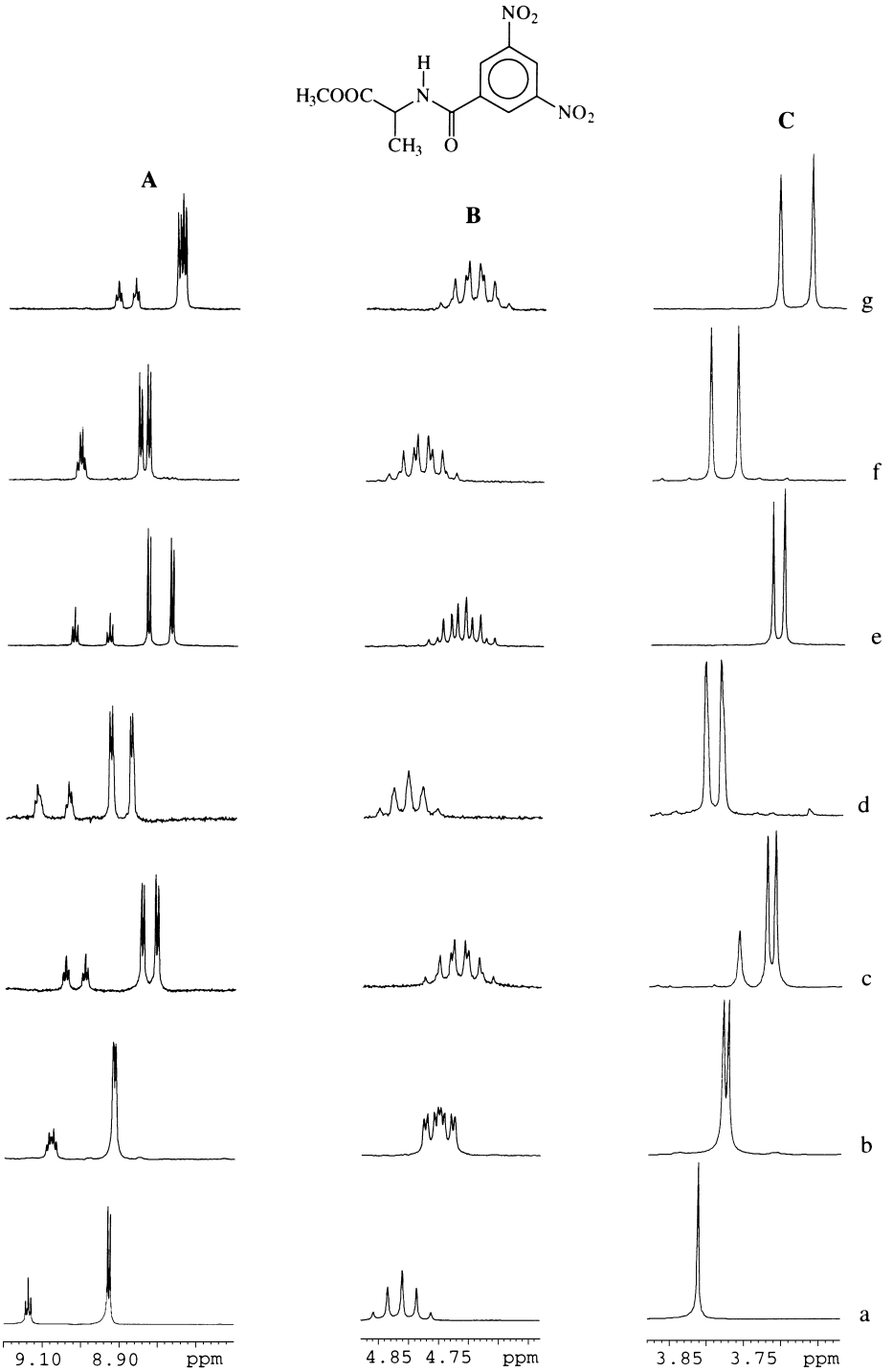
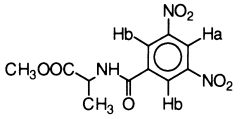


Figure 2. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, ppm referred to TMS as external standard) spectral regions corresponding to the 3,5-dinitrobenzoyl (A), CH (B) and COOMe (C) proton absorptions of racemic **7a** (20 mM): (a) free compound; (b) equimolar mixture **1**/(*RS*)-**7a**; (c) equimolar mixture **4**/(*RS*)-**7a**; (d) equimolar mixture **2**/(*RS*)-**7a**; (e) equimolar mixture **5**/(*RS*)-**7a**; (f) equimolar mixture **3**/(*RS*)-**7a**; (g) equimolar mixture **6**/(*RS*)-**7a**

Table 1
^{1}H NMR (300 MHz, $CDCl_3$, 25°C) non-equivalences ($\Delta\Delta\delta$, hertz, difference between the chemical shifts of corresponding protons of the two enantiomers) for protons of **7a** in the presence of CSAs **1**–**6** (molar ratio 1:1; 20 mM)

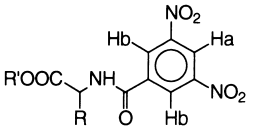


7a

	ΔΔδ								
	4	**1**	**5**	**2**	**6**	**3**	**4**[(a)]	**5**[(a)]	**5**[(b)]
Ha	15	3.5	27.2	24.3	13.5	2.1	5.9	29.8	27.4
Hb	11.2	-	18.0	15.8	4.0	6.5	3.8	19.6	18.0
CH[(c)]	5.8	1.9	4.4	-	5.3	5.3	2.0	4.1	3.6
OCH_3	3.4	2.0	4.7	6.5	13.1	11	1.2	4.8	4.1

a) molar ratio CSA/substrate 1:2. b) molar ratio CSA/substrate 1:3. c) proton on the stereogenic centre.

Table 2
^{1}H NMR (300 MHz, $CDCl_3$, 25°C) non-equivalences ($\Delta\Delta\delta$, hertz, difference between the chemical shifts of corresponding protons of the two enantiomers) for some protons of the amino acid derivatives **7b**–**g** in the presence of CSAs **4** and **5** (molar ratio 1:1; 20 mM)



7

			ΔΔδ							
			4				**5**			
Compound	R	R'	Ha	Hb	CH[(a)]	OR	Ha	Hb	CH[(a)]	OR
7b	^{i}Pr	CH_3	8.7	7.9	-	2.6	12.2	13.0	1.8	2.1
7c	^{i}Pr	^{i}Pr	9.3	7.1	1.8	4.0	11.5	13.0	1.1	-
7d	^{i}Pr	^{n}Bu	8.8	7.5	1.1	-	11.2	11.9	1.4	-
7e	^{s}Bu	CH_3	8.3	7.2	1.0	2.4	12.9	14.1	-	5.6
7f	^{t}Bu	CH_3	3.5	3.6	1.2	-	3.8	9.9	-	n.d.
7g	Ph	CH_3	18.6	58.5	-	21.0	25.1	59.9	-	79.2

a) proton on the stereogenic centre

proton signals of **7a** to the same extent also when the molar ratio CSA/substrate is lowered from 1:1 until 1:3. This behaviour is very different with respect to most common CSAs which require a 1:1 or even higher molar ratio CSA/substrate in order to induce appreciable non-equivalences on the enantiotopic protons of the substrates. This feature makes the CSA **5** very attractive, as a small amount (≅2 mg) is sufficient for carrying out an accurate determination of the ee of a chiral compound.

Considering the effectiveness of **4**, **5** and **6** in enantiodiscriminating the 3,5-dinitrobenzoyl derivatives of amino acid alkyl esters, we addressed our attention towards 3,5-dinitrophenyl derivatives of other compounds (Fig. 3).

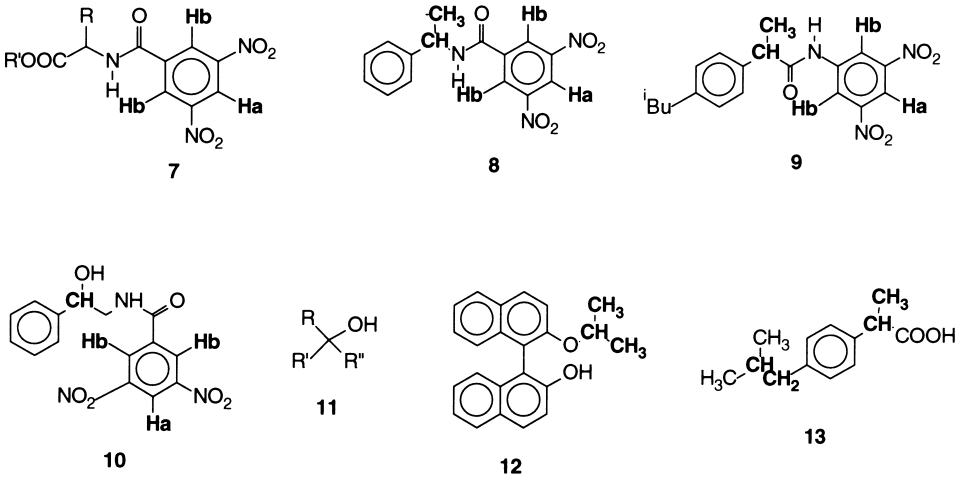


Figure 3.

The data concerning the enantioselectivity exhibited towards 3,5-dinitrophenyl derivatives of an amine, an aminoalcohol and a carboxylic acid are reported in Table 3.

Table 3
^{1}H NMR (300 MHz, $CDCl_3$, 25°C) non-equivalences ($\Delta\Delta\delta$, hertz, difference between the chemical shifts of corresponding protons of the two enantiomers) for the protons marked in Fig. 3 of compounds **8**–**13** in the presence of the CSAs **4**–**6** (molar ratio 1:1; 20 mM)

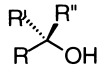
	ΔΔδ			
	Ha	Hb	CH	CH_3
8/4	2.3	2.0	-	-
8/5	-	-	-	-
8/6	1.4	3.6	1.2	7.3
9/4	-	-	2.1	-
9/5	-	-	-	-
9/6	12.4	5.9	7.0	nd
10/4	2.9	2.4	-	-
10/5	4.2	1.9	3.1	
10/6	23.2	-	5.1	
12/6			1.9	1.2
13/6			7.3[a]	9.2
			2.4	3.1[b]

a) proton on the stereogenic centre.
b) protons of the methylene group

The proton signals of these derivatives are well separated in the presence of an equimolar amount of **6**, whereas in the presence of **4** and **5** poor or no non-equivalences are measured for **8** and **9** and only **10** is enantiodiscriminated, although to a lesser extent than in the presence of **6**. On the basis of these results the conclusion which can be drawn is that an additional polar function, such as the OH group of **10** or the ester moiety of **7**, is required in order for enantiodiscrimination to take place in the cases of **4** and **5**. On the contrary, this function is not necessary in the case of **6**, which is able to enantiodiscriminate all three derivatives.

This consideration prompted us to check the enantiodiscriminating capability of **6**, also towards underivatized compounds, such as alcohols, the free acid ibuprofen **13** and the binaphthol derivative **12** (Fig. 3 and Table 4).

Table 4
^{1}H NMR (300 MHz, $CDCl_3$, 25°C) non-equivalences ($\Delta\Delta\delta$, hertz, difference between the chemical shifts of corresponding protons of the two enantiomers) for some protons of alcohols **11a**–**e** in the presence of **6** (molar ratio 1:1; 20 mM)



11

				ΔΔδ		
Compound	R	R'	R"	R	R'	R"
11a	^{t}Bu	H	C≡CH	1.1	-	3.5
11b	Ph	H	C≡CH		nd	8.1
11c	Ph	CH_3	C≡CH		2.0	7.5
11d	^{t}Bu	CH_3	4-OMePh	0.9	1.4	
11e	^{i}Pr	H	1-naphthyl	3.4 (CH) 2.8 (CH_3)	1.8	

CSAs **4** and **5**, as expected, did not achieve enantiodiscrimination of this kind of racemate, whereas **6** showed both efficiency and versatility. The data reported in Table 4 demonstrate that compound **6** is able to split the signals of some protons of alkylarylcarbinols **11d** and **11e** and propargyl alcohols **11a**–**c**: the values of the non-equivalences, for signals having simple structure or acetylenic protons, are sufficient to allow accurate determination of the enantiomeric composition of these compounds (Fig. 4).

The case of the free acid ibuprofen looks quite interesting: in fact, this compound was enantiodiscriminated by the tri-1-(1-naphthyl)ethylamino-substituted *s*-triazine derivative **3** but, as shown in Fig. 5, this derivative was able to split only the signal of the proton on the stereogenic centre, which produces two partially superimposed quartets.

On the contrary, in the presence of an equimolar amount of **6** the signals of several protons of ibuprofen are split (Fig. 5). Therefore, the replacement of one 1-(1-naphthyl)ethylamino moiety with the 1-(9-anthryl)ethylamino one produces a remarkable improvement of the efficiency of this class of CSAs also with respect to underivatized substrates.

In summary, the *s*-triazine derivatives **4**, **5** and **6** are convenient CSAs for the determination of the enantiomeric purity of 3,5-dinitrobenzoyl derivatives of amino acid alkyl esters; compound **6** is also a suitable CSA for other kinds of 3,5-dinitrophenyl derivatives and for various underivatized compounds. The data reported clearly demonstrate that this class of CSAs shows better efficiency

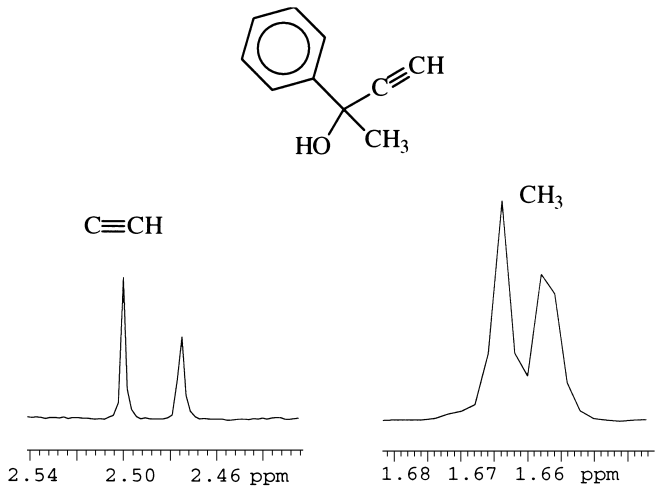


Figure 4. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, ppm referred to TMS as external standard) spectral regions corresponding to the acetylene and methyl proton absorptions of racemic **11c** (20 mM) in the presence of an equimolar amount of **6**

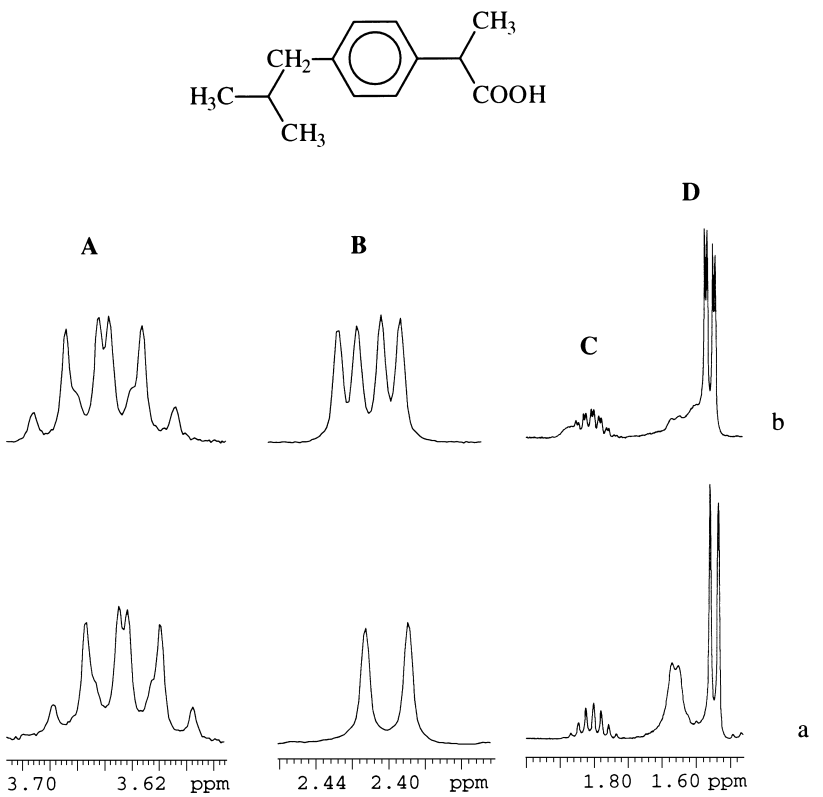


Figure 5. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, ppm referred to TMS as external standard) spectral regions corresponding to the proton on the stereogenic centre (A), CH_2 (B), CH (C) and CH_3 (D) absorptions of racemic **13** (20 mM) in the presence of: (a) an equimolar amount of **3**; and (b) an equimolar amount of **6**

than the 1-(1-naphthyl)ethylamino-substituted *s*-triazine derivatives. In fact, the presence of the 1-(9-anthryl)ethylamino moiety produces two effects: the first one is the greater conformational homogeneity which characterizes these derivatives with respect to the 1-(1-naphthyl)ethylamino-substituted ones, the other is the stronger diamagnetic anisotropy exerted by the anthracene moiety on the protons of the substrates. These synergic effects result in an increase of the non-equivalence values and, hence, in the effectiveness of these CSAs.

3. Experimental

NMR measurements were performed on a Varian VXR-300 spectrometer, operating at 300 MHz, equipped with a temperature control unity (±1°C). Typical sample concentrations were 20 mM.

3.1. Materials

2-[(*R*)-1-(9-anthryl)ethylamino]-4-chloro-6-methoxy-1,3,5-triazine, 2-[(*R*)-1-(9-anthryl)ethylamino]-4-chloro-6-[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine and 2-[(*R*)-1-(9-anthryl)ethylamino]-4,6-bis-[(*R*)-1-(1-naphthyl)ethylamino]-1,3,5-triazine were prepared as described elsewhere and matched the reported characteristics.[8,9] 1,2-Dihydroxyphenylethane was purchased from the Fluka Chemical Co.

Literature methods were used to prepare the 3,5-dinitrobenzoylamides of amino acid alkyl esters[10] **7**, and of the 2-amino-1-hydroxy-1-phenylethane[11] **10**, the alkylarylcarbinols[12] **11d–e**, and the propargyl alcohols[13] **11a–c**. The binaphthyl derivative **12** was prepared according to the procedure of Pirkle.[14] The preparation of 3,5-dinitrophenylanilide of ibuprofen **9** has been described elsewhere.[15]

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