Special Issue Article

Monomeric and Dimeric 9-*O* Anthraquinone and Phenanthryl Derivatives of Cinchona Alkaloids as Chiral Solvating Agents for the NMR Enantiodiscrimination of Chiral Hemiesters†

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ABSTRACT Mono- and bis-alkaloid chiral auxiliaries with anthraquinone or phenanthryl cores were probed as chiral solvating agents (CSAs) for the enantiodiscrimination of chiral cyclic hemiesters. The dimeric anthraquinone derivative and the monomeric phenanthryl one showed remarkable efficiency in the nuclear magnetic resonance (NMR) differentiation of enantiomeric mixtures of hemiesters. An anthraquinone analogous with a single alkaloid unit was remarkably less effective. The conformational prevalence of the chiral auxiliaries were ascertained by NMR. *Chirality 27:693–699, 2015.*

KEY WORDS: NMR spectroscopy; cinchona alkaloids; hemiesters; enantiodiscrimination phenomena; chiral solvating agents

Applications of cinchona alkaloids as chiral auxiliaries in organic chemistry date back to late 1853,[1] with their use as resolving agents. Since then a great number of applications could be found spanning from asymmetric synthesis and catalysis,[2–7] to chromatographic[7–9] and spectroscopic enantioseparations.[10,11] Cinchona alkaloids enantiodifferentiating ability may be ascribed to their highly preorganized structure, which makes several interaction sites available for the stabilization of supramolecular aggregates with different classes of enantiomeric substrates. In the field of chiral auxiliaries for the analytical enantiodiscrimination by nuclear magnetic resonance (NMR) spectroscopy, both quinine or quinidine and their derivatives at the C-9 hydroxyl site, carbon–carbon double bond, or quinuclidine nitrogen have been extensively exploited as chiral solvating agents (CSAs).[10,11] Often, stimulating hints in this respect have been obtained from the related field of cinchona alkaloid-based selectors for chiral chromatography applications,[7–9] as well as from the growing applications of alkaloid derivatives for asymmetric catalysis. The latter is indeed the case of mono- and bis-quinidine derivatives examined in the present contribution. In the course of a spectroscopic investigation on the mechanism of the asymmetric methanolysis of achiral meso-anydrides,[12] the possibility was suggested of exploiting the chiral discrimination ability of the organocatalytic systems for the in situ NMR determination of enantiomeric purities of reaction products. Therefore, we were encouraged to go deeper in their potentialities as CSAs for the differentiation of NMR signals of chiral hemiesters, focusing in particular on the commercial derivatives $(DHQD)_2AQN$ (**1**) and DHQNPHEN (**2**), as well as DHQDAQN (**3**) as an on-purpose synthesized monomeric analog of **1** (Scheme 1). NMR enantiodiscrimination experiments were performed with different hemiesters **4–8** (Scheme 2), some of which have fluorinated or deuterated probes that lead to remarkable spectral simplification and, hence, better analytical conditions. In an attempt to rationalize the enantiodiscrimination processes, the stereochemical preferences of CSAs were compared by NMR and some relevant complexation parameters were evaluated.

MATERIALS AND METHODS

All the reactions involving sensitive compounds were carried out under dry nitrogen, in flame-dried glassware. Before use, THF, MeOH, and benzyl alcohol were freshly distilled under dry nitrogen from the proper drying agent. The other compounds were commercially available and used as received.

High-performance liquid chromatography (HPLC) analyses were carried out on a Jasco (Tokyo, Japan) PU-1580 chromatograph, equipped with an UV-1575 detector. Optical rotations were measured as solutions in 1 dm cells at the sodium D line, using a Jasco DIP360 polarimeter. For the intermediates in the synthesis of **3**, ^{1}H and ^{13}C NMR spectra were recorded using a Varian (Palo Alto, CA) XL-300 spectrometer operating at 300 MHz and 75 MHz for ^{1}H and ^{13}C, respectively. NMR measurements were performed on a Varian Inova 600 spectrometer operating at 600 MHz, 92 MHz, 150 MHz, and 564 MHz for ^{1}H, ^{2}H, ^{13}C, and ^{19}F, respectively. The temperature was controlled to ±0.1°C. The 2D NMR spectra were obtained using standard sequences with the minimum spectral width required. Proton 2D gradient correlated spectroscopy (gCOSY) spectra were recorded with 256 increments of four scans and 2K data points. The relaxation delay was 2 s. 2D TOCSY spectra were recorded by employing a mixing time of 80 ms. The pulse delay was maintained at 1 s; 256 increments of four scans and 2K data points each were

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†Dedicated to Prof. Francesco Gasparrini, Rome, on the occasion of his 70th birthday.

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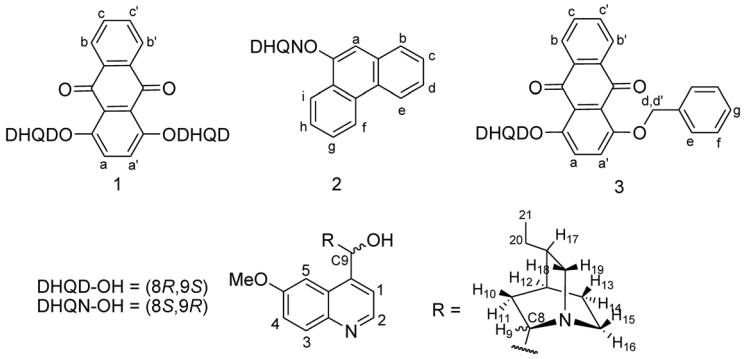
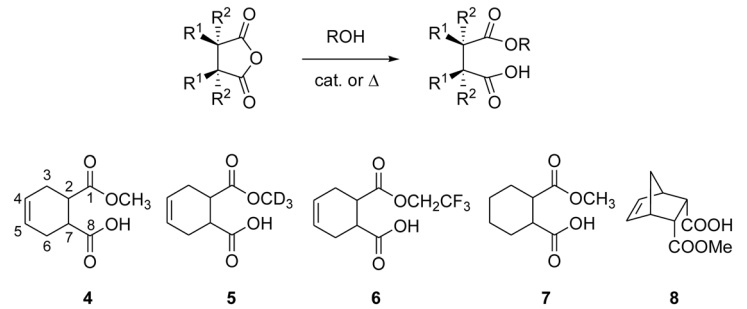


Scheme 1. CSAs **1–3** with numbering scheme for NMR analysis.



Scheme 2. Synthesis of hemiesters **4–8** with numbering scheme for NMR analysis.

collected. The 2D ROESY experiments were performed in the phase-sensitive mode, by employing a mixing time of 0.6/0.3 s. The pulse delay was maintained at 1 s; 256 increments of 16 scans and 2K data points each were collected. Proton 1D TOCSY spectra were recorded using selective pulses generated by means of the Varian Pandora software. The selective 1D TOCSY spectra were acquired with 256 scans in 32K data points with a 1-s relaxation delay and a mixing time of 80 ms. The ^{1}H-^{13}C gradient heteronuclear single quantum correlation (gHSQC) and gradient heteronuclear multiple bond correlation (gHMBC) spectra were recorded with 256 or 128 time increments of 24 scans. The gHMBC experiments were optimized for a long-range ^{1}H-^{13}C coupling constant of 8 Hz and a delay period of 3.5 ms for suppression of one-bond correlation signals. No decoupling was used during the acquisition. The stoichiometry of (1*S*,2*R*)-**4**/**1**, (1*R*,2*S*)-**4**/**1**, (1*S*,2*R*)-**4**/**2,** and (1*R*,2*S*)-**4**/**2** complexes was determined by employing Job's method,[13] by maintaining the total concentration constant (5 mM), and by varying the molar fraction of **4** from 0 to 1. Racemic **4–8** and enantiomerically enriched (1*R*,2*S*)-**4** and (1*S*,2*R*)-**4** were obtained by alcoholysis of the corresponding anhydride, according to published methods.[12,14] The enantiomeric purity of the latter was checked by chiral HPLC (Chiralcel OJ, 1 mL min^{-1} *n*-hexane : 2-propanol : trifluoroacetic acid = 95:5:0.1, 210 nm: $t_{1R,2S\text{-}\mathbf{4}}$ = 11.5 min, $t_{1S,2R\text{-}\mathbf{4}}$ = 14.5 min).[12,14]

Synthesis of 1-benzyloxy-4-fluoroanthraquinone. A 100-mL two-necked flask was charged under nitrogen with 210 μL (2.0 mmol) of benzyl alcohol, 5 mL of THF, and 0.115 g (2.8 mmol) of NaH 60% in oil. The reaction mixture was heated to 60°C and kept under stirring for 30 min. Then 0.491 g (2.0 mmol) of 1,4-difluoroanthraquinone were added and the resulting solution was heated to 75°C overnight. Since the starting anthraquinone was still present (TLC, SiO_2, CH_2Cl_2), a second portion of 0.050 mL (0.5 mmol) of benzyl alcohol and 0.0261 g (0.6 mmol) of NaH (60% in oil) were added and the solution was kept at 75°C overnight. The mixture was quenched by addition of 5 mL of water, and the aqueous layers were extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with water (10 mL), dried (Na_2SO_4), and concentrated with a rotary evaporator. The crude product was purified by flash chromatography (SiO_2/CH_2Cl_2 - n-hexane 2:1) to give 1-benzyloxy-4-fluoroanthraquinone as an orange powder (0.164 g, 25%). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.20-8.13 (m, 2H), 7.75-7.67 (m, 2H), 7.56 (d, J = 8.4 Hz, 2H), 7.44-7.36 (m, 5H), 5.25 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 181.9, 173.6, 172.9, 157.6, 155.6, 154.1, 136.1, 134.3, 134.1, 133.6, 133.2, 128.8, 128.4, 127.0, 126.6, 124.2, 123.8, 122.6, 122.4, 122.3, 122.2, 107.9, 71.8. MS (ESI, *m/z*): = $[M+H]^+$ 333, $[M+MeCN+H]^+$ 374.

Synthesis of 1-benzyloxy-4-[9-O-(10,11-dihydroquinidinyl)]anthraquinone (3). A 50-mL two-necked flask was charged under nitrogen with dihydroquinidine (0.147 g, 0.45 mmol), NaH 60% in oil (0.027 g, 0.67 mmol), and 3 mL of DMF. The reaction mixture was heated to 60°C for 30 min, then 1-benzyloxy-4-fluoroanthraquinone (0.149 g, 0.45 mmol) was added. The resulting solution was kept at 60°C overnight, monitoring the reaction course by TLC (SiO_2, AcOEt:MeOH = 7:1). The mixture was quenched by adding 5 mL of water and 10 mL of HCl (10%) and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with water (3 × 10 mL), dried (Na_2SO_4), and concentrated with a rotary evaporator. The crude product (0.245 g) was purified by flash chromatography (SiO_2/AcOEt - CH_2Cl_2 7:1) to give **4** as an orange powder (0.171 g, 59%). ^{1}H NMR (600 MHz, $CDCl_3$, δ): 8.65 (d, $J_{2\text{-}1}$ = 4.6 Hz, 1H, H2), 8.23 (m, 1H, Hb'), 8.20 (m, 1H, Hb), 8.05 (d, $J_{3\text{-}4}$ = 9.2 Hz, 1H, H3), 7.77 (m, 1H, Hc'), 7.76 (m, 1H, Hc), 7.61 (d, $J_{1\text{-}2}$ = 4.6 Hz, 1H, H1), 7.61 (br s,1H, H5) 7.50 (d, $J_{e\text{-}f}$ = 7.5 Hz, 2H, He), 7.42 (dd, $J_{4\text{-}3}$ = 9.2 Hz, $J_{4\text{-}5}$ = 2.3 Hz, 1H, H4), 7.36 (t, $J_{f\text{-}g}$ = $J_{f\text{-}e}$ = 7.5 Hz, 2H, Hf), 7.28 (d, $J_{g\text{-}f}$ = 7.5 Hz, 1H, Hg), 7.07 (br s, 2H, Ha/Ha'), 6.75 (br s, 1H, H8), 5.14 (m, 2H, Hd/Hd'), 4.06 (s, 3H, OMe), 3.36 (m, 1H, H9), 3.25 (m, 1H, H19), 3.13 (m, 1H, H16), 3.06 (m, 1H, H18), 2.91 (m, 1H, H15), 2.85 (m, 1H, H10), 1.95 (m, 1H, H12), 1.76 (m, 1H, H20), 1.66 (m, 2H, H13/H14), 1.60 (m, 1H, H17), 1.46 (m, 1H, H11), 0.92 (t, $J_{21\text{-}20}$ = 7.2 Hz, 3H, H21). ^{13}C NMR (150 MHz, $CDCl_3$, δ): 177.9, 177.2, 142.1, 139.1, 130.8, 128.8, 128.7, 127.9, 127.7, 126.6, 123.1, 122.4, 121.4, 121.2, 120.9, 120.5, 118.3, 118.0, 117.1, 115.4, 113.7, 95.0, 71.8, 66.3, 54.7, 45.2, 44.4, 20.9, 18.6. MS (ESI, *m/z*): = $[M+H]^+$ 639. $[\alpha]_D^{25}$ = -310 deg cm^3 g^{-1} dm^{-1} (*c* = 0.5 and gcm^{-3} in dichloromethane).

RESULTS AND DISCUSSION

Synthesis of Chiral Auxiliaries and Substrates

CSAs **1** and **2** are commercially available, whereas for the preparation of the monomeric compound **3** a synthetic route analogous to that of Zhang and colleagues was followed.[15] Accordingly, the sodium salt of benzyl alcohol was reacted in THF with 1,4-difluoroanthraquinone. After work-up, the monosubstituted product was separated from the disubstituted one and from unreacted substrate by flash chromatography. A second nucleophilic substitution with the sodium salt of 10,11-dihydroquinidine in DMF afforded **3** in 59% yield after chromatographic purification.

Racemic hemiesters **4–8** (Scheme 2) were obtained by alcoholysis of the corresponding anhydride with an excess of MeOH, CD_3OD, or CF_3CH_2OH; in the case of **5** and **6**, quinuclidine (5 mol%) was added as an achiral catalyst. Enantiomerically enriched (1*R*,2*S*)-**4** (95% *ee*) and (1*S*,2*R*)-**4** (91% *ee*) were obtained by asymmetric methanolysis of *cis*-1,2,3,6-tetrahydrophthalic anhydride in Et_2O, in the presence of **1** (10 mol%) and **2** (20 mol%), respectively.[12,14]

Conformational Analysis of Chiral Auxiliaries

Following the well-known Burgi's protocol,[16] stereochemical preference of cinchona alkaloids is commonly described by means of mostly populated conformers identified as Closed (1), Closed(2), Open(3), and Open(4) (Fig. 1). Closed conformations have almost anti H8-C9 and C8-H9 bonds, leading quinuclidine nitrogen in proximity of the quinoline ring. On the contrary, the same bonds are cisoid (dihedral angle H8-C9-C8-H9 about of 78°) in Open-like conformations, making the basic quinuclidine nitrogen better predisposed for the interaction with suitable hydrogen bond donor groups. Inside each family of conformations (Closed or Open), rotation about the C9-C16 bond is possible, leading the C9-H8 bond bent at the H1 quinoline proton in Closed(1) or Open(4) or at its H5 proton Closed(2) or Open(3). The values of the vicinal coupling constant $^3J_{H8\text{-}H9}$ and through space dipolar interactions allow the definition of the conformational preference, which is strongly affected by the nature of any derivatizing group at the hydroxyl function or quinuclidine nitrogen and is often remarkably dependent on the solvent.

Such an analysis has been described in the case of derivative **1**.[12] In toluene-d_8, the solvent employed in meso-anhydride desymmetrizzation experiments, the Open(3) conformation of each alkaloid unit prevails. In spite of the molecular C_2 symmetry, which leads to complete isochronism of alkaloids units, an anti-disposal of the two DHQD moieties could be nonetheless ascertained thanks to reciprocal ROEs between anthraquinone Ha/H8 protons and Hb/methyl group of the ethyl groups.

With the plan of carrying out chiral discrimination measurements also in a solvent less expensive than toluene-d_8 (vide infra), at the outset of the present study the conformational characterization of **1** was repeated in $CDCl_3$. Even though extensive signal superimposition was found under these conditions, a selective H1–H10 dipolar interaction could be detected, which is diagnostic for the Open(3) conformation.

Regarding the monomeric derivatives, a strong preference for the Open(3) conformation was ascertained also in the case of **2** on the basis of the analysis of ROEs. In particular, some dipolar interactions which support the Open(3) conformer were detected (Fig. 2a–c), like the ROE between H11 quinuclidine proton and H1 quinoline moiety (Fig. 2a). The orientation of the phenantryl moiety with respect to the alkaloid fragments was defined on the basis of inter-ROEs Ha-H8 (Fig. 2b) and Hi-H11,H14 (Fig. 2e), which suggest that the former lays almost perpendicular to the quinoline ring with its Ha proton bent at H8 nucleus and its Hi proton in proximity of the quinuclidine moiety.

A similar conformational analysis could not be performed for the anthraquinone monomeric derivative **3**, due to the extensive line-broadening and signals superimposition that made impossible the univocal interpretation of ROEs interactions.

Enantiodiscrimination Experiments

NMR spectra of pure hemiesters **4–8** and their mixtures with the chiral auxiliaries **1–3** were compared in enantiodiscrimination experiments. The efficiency of each chiral auxiliary was evaluated in terms of the chemical shift nonequivalence ($\Delta\delta$), i.e., the magnitude of the separation of corresponding signals of the two enantiomeric substrates in their mixtures with the CSA. In this regard it is noteworthy that within each chiral substrate a suitable probe nucleus was present, which originates very simple NMR signals: the methoxy singlet for **4**, **7,** and **8** or the deuterium or fluorine nucleus in **5** and **6**, respectively.

Preliminary optimization of the analytical conditions was performed for racemic hemiester **4**, starting with solvent selection. Comparison of the results in toluene-d_8 with those in $CDCl_3$ revealed significant advantages in the use of the latter. In the equimolar mixture containing the racemic substrate **4** and the dimeric anthraquinone auxiliary **1** at 10 mM concentration, a relevant differentiation of 0.055 ppm of methoxy resonances of rac-**4** was observed in toluene-d_8, which nearly doubled when the spectrum was recorded in

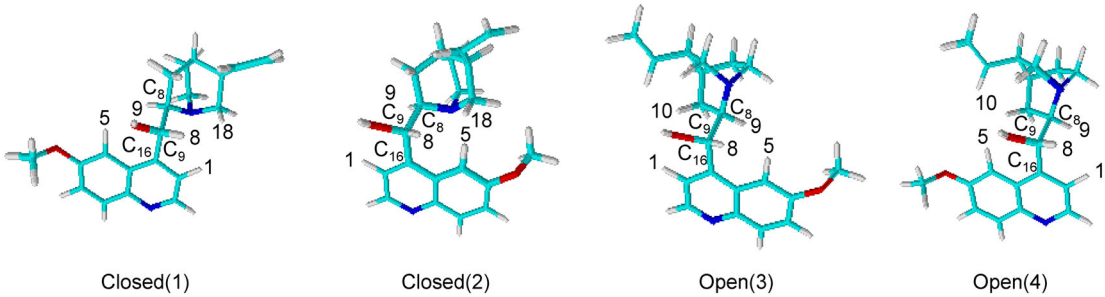


Fig. 1. Limit conformers according to Burgi's protocol for quinidine.

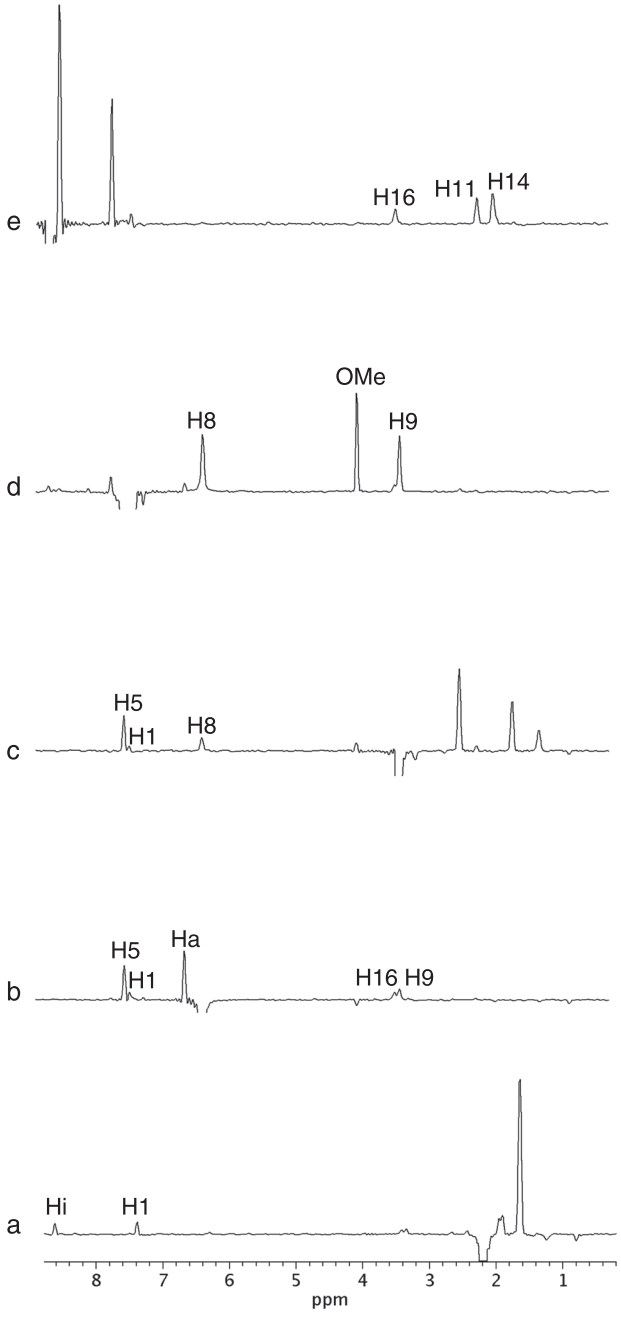


Fig. 2. 2D ROESY traces (600 MHz, $CDCl_3$, 25°C) of selected protons of **2** (5 mM): (**a**) H11, (**b**) H8, (**c**) H9, (**d**) H5, and (**e**) Hi.

$CDCl_3$ (0.100 ppm, Table 1, entries 1 and 2). An analogous solvent effect was found for the chiral auxiliary **2**, with an increase from 0.029 ppm in toluene-d_8 to 0.076 ppm in $CDCl_3$ (Table 1, entries 7 and 8).

The effect of total concentration was negligible in the 10-0.7 mM range for **1** and 10-5 mM range for **2** (Table 1, entries 2–4 and 8–9, respectively). In the case of the latter, the nonequivalence in $CDCl_3$ was still remarkable at the 0.7 mM concentration (0.043 ppm, Table 1, entry 10). For practical reasons, however, most of the subsequent enantiodiscrimination experiments were performed at a 5 mM concentration.

Concerning the influence of the analyte/CSA ratio, it is noteworthy that accurate enantiomeric purity determinations could be performed also in experimental conditions that are

TABLE 1. Nonequivalences ($\Delta\delta = |\delta_{ent\text{-}1} - \delta_{ent\text{-}2}|$, ppm) measured for the OMe group of rac-4 in rac-4/CSAs mixtures

Entry	CSA	Solvent	rac-**4**/CSA	[rac-**4**] (mM)	Δδ (ppm)
1	**1**	Toluene-d_8	1:1	10	0.055
2	**1**	$CDCl_3$	1:1	10	0.100
3	**1**	$CDCl_3$	1:1	5	0.101
4	**1**	$CDCl_3$	1:1	0.7	0.092
5	**1**	$CDCl_3$	5:1	10	0.035
6	**1**	$CDCl_3$	10:1	10	0.013
7	**2**	Toluene-d_8	1:1	10	0.029
8	**2**	$CDCl_3$	1:1	10	0.076
9	**2**	$CDCl_3$	1:1	5	0.077
10	**2**	$CDCl_3$	1:1	0.7	0.043
11	**2**	$CDCl_3$	5:1	10	0.020
12	**2**	$CDCl_3$	10:1	10	0.070
13	**3**	$CDCl_3$	1:1	5	0.020

closer to catalysis experiments, since methoxy signals of **4** were clearly differentiated even with a sub-stoichiometric amount (0.1–0.2 equivalents) of the chiral auxiliary **1** or **2** (Table 1, entries 5, 6 and 11, 12, respectively).

The change from the dimeric structure of **1** to its monomeric counterpart **3** caused a 5-fold decrease of nonequivalence of the methoxy protons of the enantiomers of **4** (0.020 ppm in the presence of **3** to be compared to 0.100 ppm in the presence of **1**, Table 1, entries 13 and 3); nonetheless, the splitting magnitude was still high and suitable for the accurate determination of enantiomeric purity of the chiral analyte.

Further enantiodiscrimination experiments in $CDCl_3$ with substrates **5–8** (Supporting Table S1) demonstrated the generality of the approach and confirmed the superior performance of chiral auxiliaries **1** and **2** with respect to **3**. In detail, the presence of the double bond in the chiral substrates did not turn out to be mandatory for enantiomer differentiation, since substrate **7**, analogous of **4**, but with a saturated cyclic moiety, underwent remarkably large doubling of the methoxy resonance both in the presence of **1** (0.092 ppm) and **2** (0.106 ppm). The anthraquinone monomer **3** (0.019 ppm) was confirmed less effective in comparison to **1** and **2**.

The more rigid bicyclic hemiester **8** showed the highest nonequivalences among the substrates examined in this study. As already found for **7**, in this case the optimal CSA was found to be the phenanthryl ether **2**, which caused a chemical shift nonequivalence of the methoxy groups of **8** (0.155 ppm) remarkably larger than observed in the presence of the anthraquinone dimer **1** (0.104 ppm). As before, the anthraquinone monomer **3** proved to be the least effective CSA in the series (0.014 ppm), in accordance with the general trend noted above.

The anthraquinone moiety in the dimer structure of **1** and phenanthryl moiety in the monomer alkaloid **2** caused analogous enantiomer differentiation, but diverse complexation shifts (Table 2). As a matter of fact, both chiral auxiliaries strongly shielded the methoxy nuclei of both enantiomers of **4**, but the low-frequency shifts were remarkably higher in the presence of **1** than in the presence of **2**. By contrast, **3,** the monomeric analog of **1,** not only caused lower differentiation of the enantiomers of **4**, but also lower complexation

TABLE 2. Complexation shifts of enantiomers (ent-1 and ent-2) of hemiesters 4, 7 and 8 ($\Delta\delta = \delta_{mix} - \delta_f$, ppm) in the presence of equimolar amount of CSAs 1-3 (5 mM, $CDCl_3$)

		Substrate/**1**		Substrate/**2**		Substrate/**3**	
Entry	Substrate	$\Delta\delta_{ent-1}$	$\Delta\delta_{ent-2}$	$\Delta\delta_{ent-1}$	$\Delta\delta_{ent-2}$	$\Delta\delta_{ent-1}$	$\Delta\delta_{ent-2}$
1	**4** (OMe)	–0.45	–0.55	–0.22	–0.29	–0.13	–0.15
2	**7** (OMe)	–0.45	–0.54	–0.16	–0.27	–0.14	–0.16
3	**8** (OMe)	–0.44	–0.54	–0.14	–0.29	–0.13	–0.14

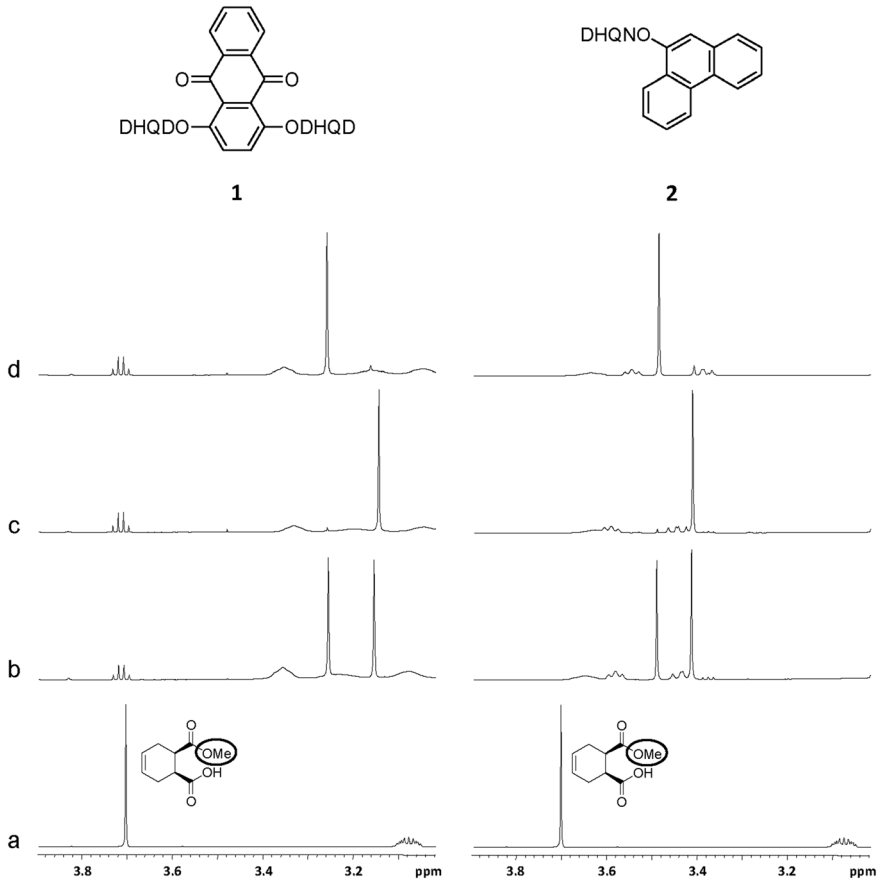


Fig. 3. ^{1}H NMR (600 MHz, $CDCl_3$, 25°C) of OMe resonance of **4** (5 mM) in (**a**) pure rac-**4**, (**b**) rac-**4**/CSA 1:1, (**c**) (1*R*,2*S*)-**4**/CSA 1:1, and (**d**) (1*S*,2*R*)-**4**/CSA 1:1.

shifts (Table 2, entry 1). The same general trend was observed in the analysis of the hemiesters **7** and **8** (Table 2, entries 2 and 3).

In order to correlate the position of the observed resonances with the absolute configuration of the corresponding stereoisomer of the substrate, mixtures of **1** and **2** with enantiomerically enriched (1*R*,2*S*)-**4** or (1*S*,2*R*)-**4** were examined next (Fig. 3).

The two chiral auxiliaries **1** and **2** have opposite absolute configurations at the C8-C9 alkaloid sites and behave as pseudo-enantiomers in catalysis.[12,14] Nonetheless, in the NMR experiments they gave the same sense of nonequivalence, i.e., relative positions of the enantiomeric substrates. In particular, (1*R*,2*S*)-**4** had the more shielded methoxy resonance in the presence of either **1** or **2**. Given the demonstrated uniform conformational preferences of **1** and **2**, this result could be the consequence of the different nature of the high-anisotropy groups bound to 9-*O*.

Substrate **5**, the deuterated analog of **4**, was selected for ^{2}H NMR enantiodiscrimination experiments (Fig. 4). The influence of the structure of the chiral auxiliary on the magnitude of nonequivalence reproduced the trend found in the ^{1}H NMR spectra of **4**. In particular, the effectiveness of the different CSAs in splitting the CD_3 ^{2}H NMR signals of **5** was found to vary in the order: **1** > **2** > **3**, with **1** producing a 5-fold larger nonequivalence (0.103 ppm) than its monomeric counterpart **3** (0.020 ppm) and the phenanthryl ether **2** (0.079 ppm) just between the two anthraquinone derivatives. Moreover, the correlation between the sense of nonequivalence and absolute configuration of each enantiomer of **5** was the same as that found for **4**.

Both **4** and **5** showed analogous nonequivalences of the olefin proton in the presence of each chiral auxiliary (Supporting Table S1) which, however, were less useful for analytical purposes due to their complex spectral patterns and, in some cases, partial superimposition of the resonances.

Fluorinated hemiester **6** gave us the opportunity of detecting enantiodiscrimination phenomena in the ^{19}F spectra. Pure **6** originated a triplet centered at –10.18 ppm due to the trifluoromethyl group. This signal underwent analogous splittings in the presence of **1** and **2** (0.032 ppm in **1**/**6** and 0.026 ppm in **2**/**6**, Fig. 5), with complexation shifts that were remarkably larger in the presence of **1** than in the mixture containing **2**. Once again, the monomeric ether **3** was less effective of the corresponding dimer in differentiating the two enantiomers of the substrate, with a nonequivalence of 0.016 ppm only. In view of the spectral simplification attained in ^{2}H and ^{19}F experiments, application of these results for in situ investigation of catalytic processes may be foreseen.

Finally, the complexation stoichiometry was determined for the monomeric CSA **2** and compared with that of the dimeric CSA **1**. Job's plots (Fig. 6) clearly demonstrated that a 1:1 supramolecular assembling was given by each stereoisomer of the substrate **4** and the monomeric CSA **2**, whereas a 1:2

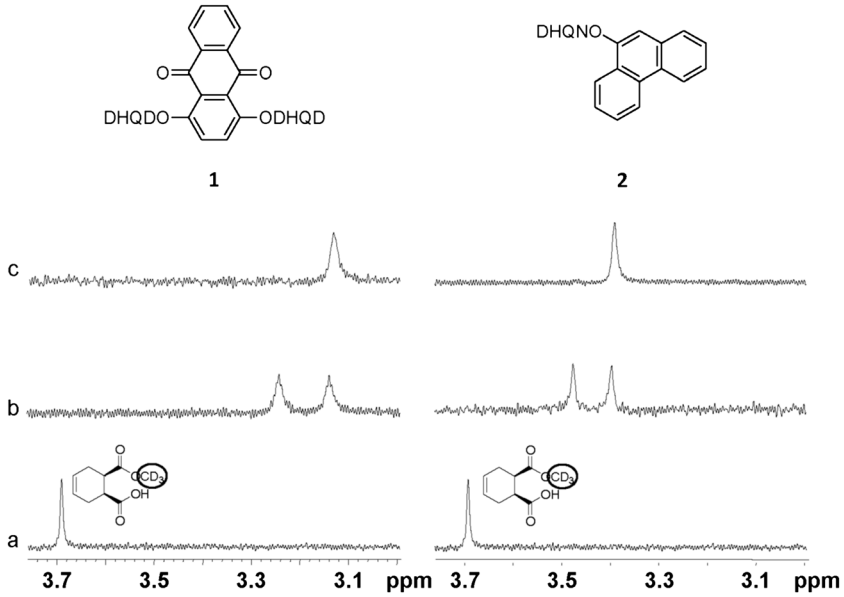


Fig. 4. ^{2}H NMR (92 MHz, $CDCl_3$, 25°C) of OCD_3 resonance of **5** (5 mM) in (**a**) pure rac-**5**, (**b**) rac-**5**/CSA 1:1, and (**c**) (1*R*,2*S*)-**5**/CSA 1:1.

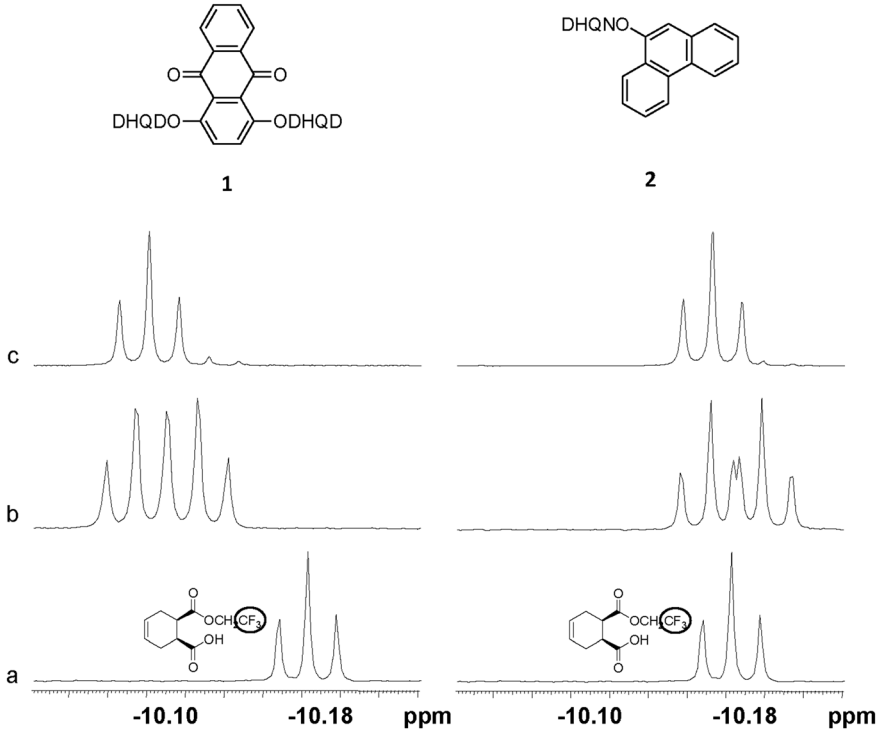


Fig. 5. ^{19}F NMR (564 MHz, $CDCl_3$, 25°C) of CF_3 resonance of **6** (5 mM) in (**a**) pure rac-**6**, (**b**) rac-**6**/CSA 1:1, and (**c**) (1*R*,2*S*)-**6**/CSA 1:1.

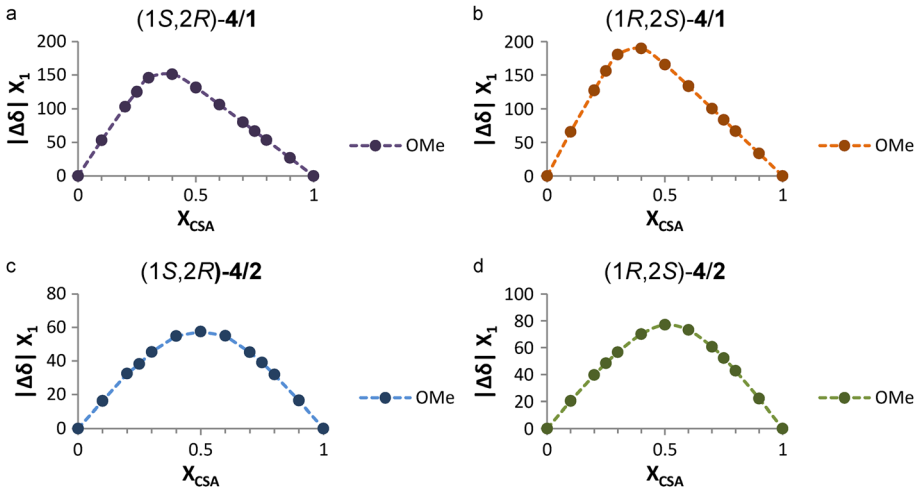


Fig. 6. Determination of stoichiometry for (**a**) (1*S*,2*R*)-**4**/**1**, (**b**) (1*R*,2*S*)-**4**/**1**, (**c**) (1*S*,2*R*)-**4**/**2**, and (**d**) (1*R*,2*S*)-**4**/**2** complexes.

CSA/substrate complexation stoichiometry was involved in the interaction with the dimeric chiral auxiliary **1**.

CONCLUSION

Chiral auxiliaries **1** and **2** are very efficient in the differentiation of corresponding nuclei of enantiomeric hemiesters and, hence, can be reliably employed in the determination of enantiomeric purity for this class of substrates. Very high nonequivalences were obtained, which encourage their use for ex situ and, potentially, in situ chiral analysis of enantiomeric products. Application of the latter idea for monitoring of the course of desymmetrization reactions of prochiral anhydrides is currently under examination.

The dimer vs. monomer arrangement of alkaloids units seem fundamental in the enantiodiscrimination phenomena in the case of **1** vs. **3**, whereas, in selected cases, phenanthryl monomer **2** was even more effective than anthraquinone dimer **1**. It is noteworthy that, at least for CSAs **1** and **2**, the prevalence of open conformations was demonstrated, where the quinuclidine nitrogen is more available for the interaction with hydrogen bond donor groups of the enantiomeric substrates, accounting for the relevant enantiodiscriminating efficiency of both chiral auxiliaries. Noticeably, different complexation shifts produced similar nonequivalence in the mixtures containing **1** and **2**, which once again[11] demonstrated the relevance of stereochemical differentiation rather than thermodynamics differentiation in NMR enantiodiscrimination processes.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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