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C11 versus C9 carbamoylation of quinine: a new class of versatile polyfunctional chiral solvating agents

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Abstract—Carbamoyl derivatives of quinine obtained by derivatization of its double bond have been prepared and used as chiral solvating agents for NMR spectroscopy: their efficiency reproduces very well that of quinine and its C9 carbamates in enantiodiscriminating underivatized and derivatized chiral substrates, respectively. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

The strong impact of chirality on several fields of chemical research has led to remarkable improvements in the development of stereocontrolled processes and, concomitantly, of analytical methods for the rapid, reliable and accurate determination of the stereoisomeric purities. Of these, NMR methods based on the use of chiral solvating agents (CSAs)[1] have attracted great interest, thanks to the intrinsically simple experimental procedures required in their applications: the preparation, directly in the NMR tube, of the mixture of the CSA and the chiral substrate dissolved in the deuterated solvent and the acquisition of their routine NMR spectrum. When the solvation effects of the CSA generate a differentiated diastereoisomeric environment in the enantiomeric mixture, then their separate resonances can be detected in the spectrum, the integration of which gives the enantiomeric composition of the chiral substrate under analysis. The widespread use of NMR spectrometers, nowadays routine analytical tools in most research laboratories and accessible also to non-specialized users, has made this kind of chiral analysis very popular. Since Pirkle's first work on this topic in 1966,[2] which was a milestone in this field, the literature regarding chiral solvating agents for NMR spectroscopy has flourished.[1] Several types of chiral solvating agents have been proposed, ranging from very simple chiral organic molecules to supramolecular or multiselector systems. Chiral natural products have also gained great popularity, mainly thanks to their availability and cost. Of these cinchona alkaloids, quinine in particular, a very cheap natural material, well known for its therapeutical applications and also used in many research areas concerned with stereocontrolled processes, have been proposed as CSAs.[3] This chiral auxiliary is endowed with several functionalities, which can act independently or behave as a cooperating pool to fit the stereoelectronic features of several kinds of substrates, which account for its versatility in NMR enantiodiscrimination. The multifunctional nature of cinchona alkaloids also allows us to modulate their versatility and efficiency by the selective modification of its functionalities. Among those proposed considerable attention has been dedicated to carbamoylated derivatives, successfully employed also in chiral chromatography.[4] Recently the potential of C9 carbamoyl derivatives of quinine as CSAs for NMR spectroscopy have been suggested.[5] In particular 9-*O*-[(*S*)-1-(1-naphthyl)ethylcarbamate]-10,11-dihydroquinine **1** (Fig. 1), showed superior performances with respect to the underivatized system, in the NMR enantiodiscrimination of simple derivatives of alcohols, amines, acids and aminoacids, bearing a π-acidic moiety.[5a] The versatility and the efficiency of the corresponding diastereoisomeric derivative, bearing the same carbamate residue, but with opposite absolute configuration, was significantly inferior.[5a]

Our aim is to exploit the advantages arising from the introduction of the carbamoyl function, without affecting the nature of the original polar functional groups of quinine, above all the C9 hydroxyl function, the role of which has been widely shown to be fundamental in the

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majority of chiral processes investigated.[3c,6] We therefore propose now the two diastereoisomeric derivatives, 11-*O*-[(*S*)-1-(1-naphthyl)ethylcarbamoyloxy]-10,11-dihydro-11-hydroxyquinine **2** and 11-*O*-[(*R*)-1-(1-naphthyl)ethylcarbamoyloxy]-10,11-dihydro-11-hydroxyquinine **3** (Fig. 1), analogous to **1**, where the carbamate function has been introduced by modification of the double bond of quinine on the C11 carbon atom connected to the quinuclidine ring.

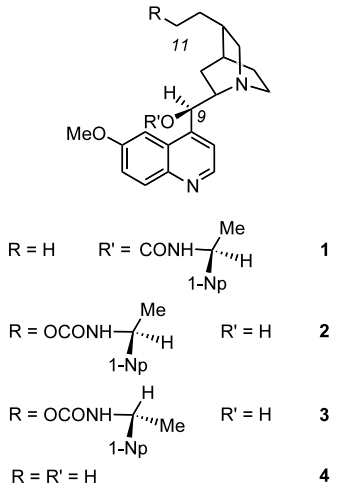


Figure 1. CSAs structures.

The efficiency and versatility of these two carbamate derivatives as chiral solvating agents for the NMR enantiodiscrimination of several classes of chiral organic compounds and their derivatives (Fig. 2) has been probed and compared to that of the underivatized system **4** and of **1** (Fig. 1), the most efficient C9 carbamate derivative previously[5a] considered.

2. Results and discussion

The (*S*)- or (*R*)-1-(1-naphthyl)ethylcarbamoyl moiety was introduced at the C11 position of quinine by modifying the vinyl group in four steps to synthesize the quinine derivatives **2** and **3** (Scheme 1). Quinine was protected at the C9 position as *tert*-butyldimethylsilyl (TBDMS) ether and subsequently converted into the

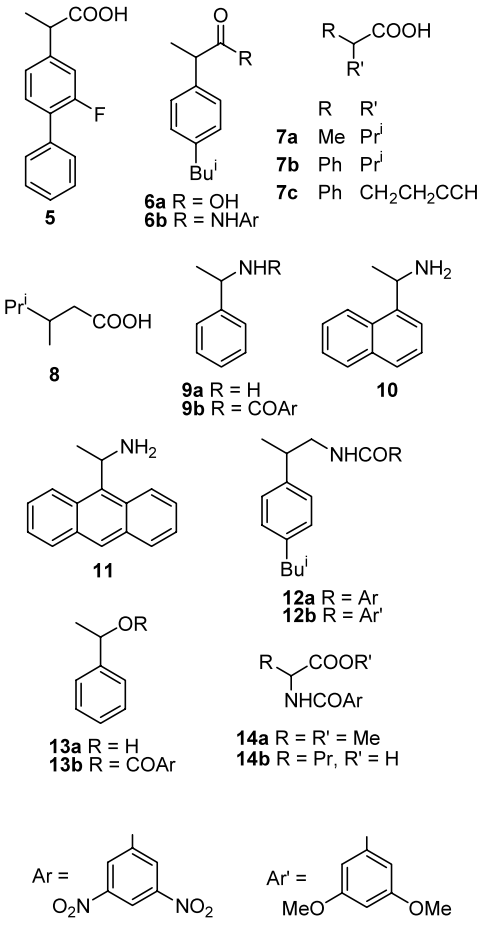
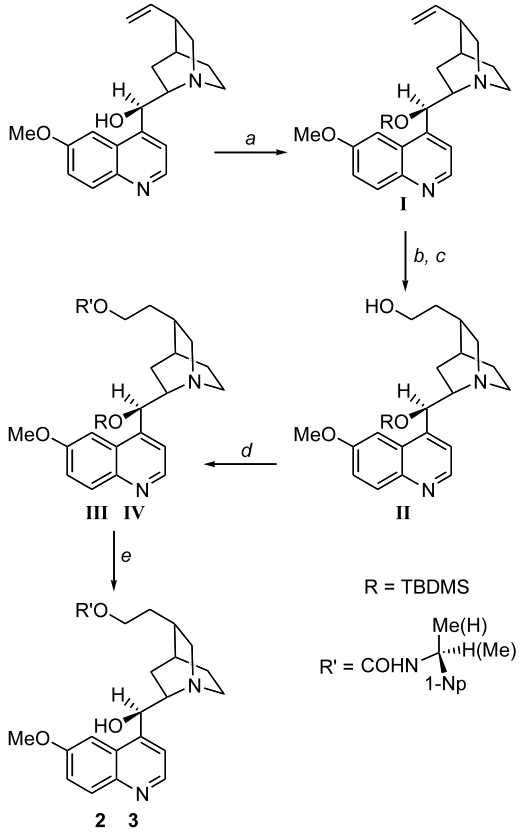


Figure 2. Chiral substrates.



Scheme 1. Synthesis of CSAs **2** and **3**. *Reagents and conditions*: (a) TBDMSCl, DMAP, Et_3N, DMF; (b) BH_3THF, diglyme; (c) Et_3NO, 100°C; (d) (*S*)- or (*R*)-1-NpCHMeNCO, toluene; (e) TBAF, THF.

Table 1. Unequivalence ($\Delta\delta$[a] 300 MHz, $CDCl_3$, 25°C) data measured for the chiral underivatized substrates (120 mM) in equimolar mixtures with the CSAs **1**–**4**.

	Proton	**1**		**2**		**3**		**4**	
5	Me	0.9		8.2		7.0		9.6	
	CH	–		7.2		–		4.2	
6a	CH	1.4		6.6		2.9		3.2	
	CH_2	6.8		9.7		9.8		13.1	
7a	Me	2.8		7.2		7.2		7.2	
	CH	1.8		3.7		2.9		1.2	
	Me (^{i}Pr)	–	1.5	3.3	–	2.6	–	4.3	–
7b	Me	4.2	1.7	–	–	3.3	3.6	1.8	2.4
	CH	–		4.2		11.1		15.9	
7c	CH	3.0		9.0		5.5		5.4	
8	C*H*H	5.7		9.0		8.6		9.0	
9a	CH	–		0.9		2.0		2.1	
10	Me	–		0.4		0.7		0.7	
	CH	–		2.8		3.5		3.6	
11	CH	–		1.8		2.2		2.0	
13a	Me	1.4		1.1		0.9		2.0	
	CH	4.1		0.9		1.8		2.1	

[a] $\Delta\delta = |\delta_S - \delta_R|$, difference between the chemical shifts (Hz) of corresponding nuclei of the two enantiomers of the chiral substrate in the presence of the CSA.

corresponding C11 alcohol by hydroboration followed by oxidation, as reported by Rowan and Sanders.[7] Carbamoylation of this primary hydroxyl group by reacting it with (*S*)- or (*R*)-1-(1-naphthyl)ethyl isocyanate in toluene gave the diastereoisomeric carbamate derivatives, which were deprotected using TBAF/THF, yielding the C11 carbamoylated quinines **2** and **3** (Scheme 1).

The enantiodiscrimination experiments have been carried out comparing the ^{1}H NMR spectra (300 MHz, $CDCl_3$, 25°C, 120 mM) of the pure racemic substrates shown in Fig. 2 and those of their equimolar mixtures with the chiral auxiliaries **1**–**4**, at the same concentration and temperature. The magnitudes of the splittings (unequivalence, $\Delta\delta$, Hz) of corresponding signals of the two enantiomers of **5**–**14**, due to the presence of the chiral auxiliaries **1**–**4**, have been measured and are shown in Tables 1 and 2.

To begin with the underivatized racemic substrates, the enantiodiscriminating abilities of the two diastereoisomeric quinines **2** and **3** carbamoylated at the C11 carbon atom resemble that of underivatized quinine more closely than the C9 carbamate does. In fact the methyl resonance of flurbiprofen **5** undergoes splittings of 7–10 Hz in the presence of **2**, **3** or **4**, whereas **1** produces a very small doubling of 0.9 Hz (Fig. 3, Table 1). In the mixtures containing the analogous anti-inflammatory drug ibuprofen **6a** the unequivalences produced by **2**–**4** are significant for all the alkyl protons and superior to those due to the chiral auxiliary **1**. The same trend occurs in the cases of the acids **7b** and **7c**, having bulkier alkyl groups bound to the stereogenic centre, or for **7a** and **8**, both devoid of aromatic substituents and with the carboxyl function respectively in α- and β-positions with respect to the stereogenic centre (Table 1, Fig. 3).

In any case, no relevant differences were found in the enantiodiscriminating efficiency of the two diastereoisomers **2** and **3**.

The carbamates at C11 duplicate the resonances of all the three chiral amines **9a**, **10** and **11**. The extent of the splittings are comparable to those obtained in the presence of dihydroquinine (Table 1).

Very low unequivalences are produced in the enantiomers of the aromatic alcohol **13a** in the presence of dihydroquinine and the three carbamates.

The unequivalences induced in the enantiomeric mixtures of derivatized chiral substrates by the two diastereoisomeric C11 carbamates are very similar to those obtained by using the C9 derivative as CSA and remarkably superior to the splittings produced by **4**. In

Table 2. Unequivalence ($\Delta\delta$[a] 300 MHz, $CDCl_3$, 25°C) data measured for the chiral derivatized substrates (120 mM) in equimolar mixtures with the CSAs **1**–**4**

	Proton	**1**	**2**	**3**	**4**
6b	H_{para}	40.4	42.9	30.9	0.8
	H_{ortho}	86.2	86.5	75.3	0.6
9b	H_{para}	34.5	26.8	22.6	–
	H_{ortho}	35.6	29.5	26.1	–
12a	H_{para}	12.3	4.0	3.0	0.8
	H_{ortho}	5.0	2.1	1.7	0.9
13b	H_{para}	–	1.2	1.2	–
	H_{ortho}	–	1.3	1.1	–
14a	H_{para}	33.0	23.7	29.9	–
	H_{ortho}	23.2	19.8	26.8	–
14b	H_{para}	98.6	28.1	18.6	2.4
	H_{ortho}	30.6	28.1	14.8	–

[a] $\Delta\delta = |\delta_S - \delta_R|$, difference between the chemical shifts (Hz) of corresponding nuclei of the two enantiomers of the chiral substrate in the presence of the CSA.

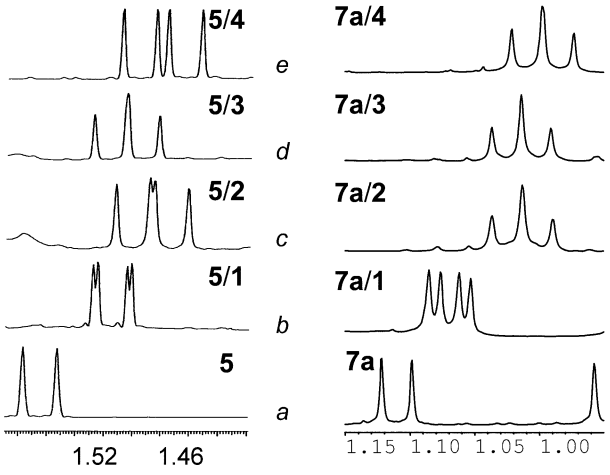


Figure 3. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) spectral regions corresponding to the methyl resonances of **5** and **7a** (120 mM) in the free state (*a*) and in the presence of equimolar amount of **1** (*b*), **2** (*c*), **3** (*d*) and **4** (*e*).

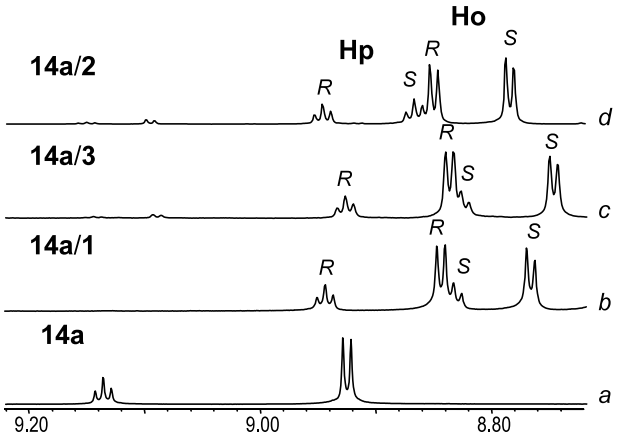


Figure 4. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C) spectral regions corresponding to 3,5-dinitrophenyl resonances of **14a** (120 mM) in the free state (*a*) and in the presence of equimolar amount of **1** (*b*), **3** (*c*) and **2** (*d*)

fact, in the case of the very simple derivative **6b** of the acid **6a**, unequivalences ranging from 30 to 90 Hz are measured for the 3,5-dinitrophenyl protons in the presence of **1-3**, whereas underivatized **4** produces very small unequivalences of about 1 Hz (Table 2).

The derivatives **9b** and **12a** of amines having the stereogenic centre respectively in the α- and β-position relatively to the nitrogen, are satisfactorily enantiodiscriminated by the C9 and C11 carbamates, whereas remarkably smaller splittings are produced by the underivatized dihydroquinine. It is worthy of note, that the presence of a π-acidic aromatic moiety seems to be a prerequisite for the enantiodiscrimination by the derivatized alkaloids, indeed compound **12b** having a π-basic nucleus is not discriminated at all.

It is noteworthy that only the C11 diastereoisomeric derivatives are able to differentiate the enantiomers of the ester derivative **13b**.

No pure aminoacids have been analysed due to their low solubility in $CDCl_3$. Therefore their simple derivatives **14a** and **14b** have been considered, the first having both the amino and carboxyl groups derivatized and the latter having the free carboxyl function. In both cases only the three carbamates of quinine **1**–**3** produced very efficient enantiodiscriminations. Figure 4 shows the enantiodiscrimination experiments referring to derivative **14a**.

3. Conclusion

The functionalization of the double bond of quinine, already exploited[8] in chromatography as an efficient way to bind the alkaloid to silica support without disturbing its original polar functions, is also an efficient means of expanding the potentialities of quinine as a chiral auxiliary in NMR spectroscopy. The simple carbamate derivatives of quinine, obtained on derivatization of the double bond, are chiral solvating agents for NMR spectroscopy able to enantiodiscriminate acids, alcohols, amines and their derivatives as well as very simple derivatives of aminoacids. The efficiency in enantiodiscriminating underivatized chiral substrates reproduces that of underivatized quinine better than previously reported[5a] C9 carbamates do, whereas their ability to induce unequivalences in derivatized substrates closely resembles the behaviour of the corresponding C9 carbamate.

It is noteworthy that the efficiency and versatility of previously reported[5a] diastereoisomeric carbamates obtained by derivatization at the C9 site was strongly dependent on the absolute configuration of the new stereogenic centre. By contrast no significant differences are found in the two diastereoisomeric derivatives at C11, probably due to the greater conformational freedom of their carbamoyl group, which is bound to the quinuclidine moiety by two methylene groups. The superior versatility of the C11 carbamates can be assumed to be due not only to the increase in the sites available for controlling stabilizing and enantiodifferentiating interactions, which probably occur essentially independently, but also to the extent of conformational changes induced in the relative stereochemistry of the functional groups, originating from functionalization in the proximity of the quinuclidine ring in place of that produced by the more common derivatization at the C9 site.

4. Experimental

4.1. General methods

NMR measurements were performed on a spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively and the temperature was controlled to ±0.1°C. All ^{1}H and ^{13}C NMR chemical shifts are referenced to TMS as external standard. The 2D NMR spectra were

obtained by using standard sequences. The double-quantum-filtered (DQF) COSY experiments were recorded with the minimum spectral width required; 512 increments of 8 scans and 2K data points were acquired. The relaxation delay was 5 s. The data were zero-filled to 2K×1K and a Gaussian function was applied for processing in both dimensions. The HETCOR spectra were acquired with the minimum spectral width required in F_2 and in F_1 in 2K data points using 64 scans of the 512 increments. The relaxation delay was 1 s. The data were zero-filled to 2K×1K and a Gaussian function was applied for processing in both dimensions. The NOESY (Nuclear Overhauser and Exchange SpectroscopY) spectra were recorded in the phase-sensitive mode, by employing a mixing time of 0.6 s. The spectral width used was the minimum required in both dimensions. The pulse delay was maintained at 8 s; 512 hypercomplex increments of 8 scans and 2K data points each were collected. The data matrix was zero-filled to 2K×1K and a Gaussian function was applied for processing in both dimensions. The $^1H\{^1H\}$-NOE experiments were performed in the difference mode. The decoupler power used was the minimum required to saturate the spin of interest. A waiting time of 5–10 s was used to allow the system to reach the equilibrium. Each NOE experiment was repeated at least four times.

Compounds **I** and **II** (Scheme 1) were prepared as described elsewhere[7] and matched the reported characteristics.

4.2. Synthesis of compounds III–IV

To a solution of **II** (4.0 mmol) in anhydrous toluene (30 mL) was added the (*R*)- or (*S*)-1-(1-naphthyl)ethyl isocyanate (4.8 mmol). The reaction mixture was refluxed for 20 h. The solvent was removed in vacuo and the derivatives **III** and **IV** were obtained in high yields (90%).

4.2.1. 9-*O*-(*tert*-Butyldimethylsilyl)-11-[(*S*)-1-(1-naphthyl)ethylcarbamoyloxy]-10,11-dihydroquinine (III). ^1H NMR (300 MHz, DMSO, 25°C), δ −0.42 (3H, MeSi, s); 0.08 (3H, MeSi, s); 0.80 (9H, Bu^t, s); 1.25–1.70 (3H, H_{11}, H_{12} and H_{17}, m); 1.30 (1H, H_{13}, m); 1.41 (3H, Me, br. s); 1.63 (1H, H_{14}, m); 2.03 (1H, H_{10}, m); 2.19 (1H, H_{18}, m); 2.45 (1H, H_{16}, m); 2.47 (2H, H_{20}–H_{21}, m); 2.75 (1H, H_{19}, m); 3.23 (1H, H_{15}, m); 3.43 (1H, H_9, m); 3.80 (2H, H_{22}–H_{23}, br. s); 3.90 (3H, OMe, s); 4.88 (1H, H_8, d, $J_{8-9}=9.9$ Hz); 5.42 (1H, CH, dq, $J_{CH-Me}=7.5$ Hz, $J_{CH-NH}=7.5$ Hz); 7.31–7.54 (2H, Np, m); 7.34 (1H, H_5, br. s); 7.47 (1H, $H_{2'}$, m); 7.51 (1H, H_1, d, $J_{1-2}=4.7$ Hz); 7.54 (1H, $H_{7'}$, m); 7.75–7.94 (2H, Np, m); 7.82 (1H, NH, br. s); 7.84 (1H, H_4, dd, $J_{4-3}=8.9$ Hz, $J_{4-5}=2.6$ Hz); 7.92 (1H, H_3, d, $J_{3-4}=8.9$ Hz); 8.10 (1H, $H_{8'}$, d, $J_{8'-7'}=5.9$ Hz); 8.69 (1H, H_2, d, $J_{2-1}=4.7$ Hz). Anal. calcd for $C_{39}H_{51}N_3O_4Si$: C, 72.14; H, 7.72; N, 6.31. Found: C, 72.17; H, 7.70; N, 6.27.

4.2.2. 9-*O*-(*tert*-Butyldimethylsilyl)-11-[(*R*)-1-(1-naphthyl)ethylcarbamoyloxy]-10,11-dihydroquinine (IV). ^1H NMR (300 MHz, DMSO, 25°C), δ −0.43 (3H, MeSi, s); 0.09 (3H, MeSi, s); 0.80 (9H, Bu^t, s); 1.25–1.75 (3H, H_{11}, H_{12} and H_{17}, m); 1.31 (1H, H_{13}, m); 1.42 (3H, Me, d, $J_{Me-CH}=7.2$ Hz); 1.62 (1H, H_{14}, m); 1.96 (1H, H_{10}, m); 2.19 (1H, H_{18}, m); 2.46 (1H, H_{16}, m); 2.49 (2H, H_{20}–H_{21}, m); 2.77 (1H, H_{19}, m); 3.23 (1H, H_{15}, m); 3.42 (1H, H_9, m); 3.83 (2H, H_{22}–H_{23}, br. s); 3.92 (3H, OMe, s); 4.90 (1H, H_8, d, $J_{8-9}=9.1$ Hz); 5.40 (1H, CH, br. s); 7.32–7.56 (2H, Np, m); 7.37 (1H, H_5, br. s); 7.48 (1H, $H_{2'}$, m); 7.49 (1H, H_1, d, $J_{1-2}=4.9$ Hz); 7.51 (1H, $H_{7'}$, m); 7.74–7.96 (2H, Np, m); 7.80 (1H, NH, br. s); 7.86 (1H, H_4, dd, $J_{4-3}=8.9$ Hz, $J_{4-5}=2.5$ Hz); 7.93 (1H, H_3, d, $J_{3-4}=8.9$ Hz); 8.10 (1H, $H_{8'}$, d, $J_{8'-7'}=6.0$ Hz); 8.70 (1H, H_2, d, $J_{2-1}=4.9$ Hz). Anal. calcd for $C_{39}H_{51}N_3O_4Si$: C, 72.14; H, 7.72; N, 6.31. Found: C, 72.12; H, 7.75; N, 6.25.

4.3. Synthesis of quinine derivatives 2–3

To a solution of **III** or **IV** (4 mmol) in THF (50 mL) was added TBAF (1 M in THF, 12 mL). The mixture was allowed to stir at room temperature for 15 h and then ethyl acetate was added. The organic layer was washed with brine (×3) and dried over Na_2SO_4. Once the solvent was removed, **2** and **3** were purified (70% yield) by chromatography (SiO_2; AcOEt/MeOH 9:1).

4.3.1. 11-[(*S*)-1-(1-naphthyl)ethylcarbamoyloxy]-10,11-dihydroquinine 2. $[\alpha]_D$ −73.0 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, DMSO, 25°C), δ 1.30 (1H, H_{13}, m); 1.44 (3H, CH_3, d, $J_{Me-CH}=7.2$ Hz); 1.50 (1H, H_{17}, m); 1.54 (2H, H_{20}–H_{21}, m); 1.61 (1H, H_{12}, m); 1.65 (1H, H_{14}, m); 1.67 (1H, H_{10}, m); 1.71 (1H, H_{11}, m); 2.20 (1H, H_{18}, br. d, $J_{18-19}=13.2$ Hz); 2.38 (1H, H_{16}, m); 2.80 (1H, H_{19}, dd, $J_{19-18}=13.2$ Hz, $J_{19-17}=8.7$ Hz); 3.03 (1H, H_9, m); 3.16 (1H, H_{15}, m); 3.87 (3H, OMe, s); 3.93 (2H, H_{22}–H_{23}, br. s); 5.22 (1H, H_8, d, $J_{8-9}=6.6$ Hz); 5.43 (1H, CH, dq, $J_{CH-NH}=J_{CH-Me}=7.2$ Hz); 5.62 (1H, OH, br. s); 7.38 (1H, H_4, dd, $J_{4-3}=9.2$ Hz, $J_{4-5}=2.6$ Hz); 7.44 (1H, $H_{2'}$, br. dd); 7.47 (1H, $H_{3'}$, br. dd); 7.48 (1H, H_1, d, $J_{1-2}=4.4$ Hz); 7.49 (1H, $H_{6'}$, br. dd); 7.50 (1H, $H_{7'}$, br. dd); 7.51 (1H, H_5, d, $J_{5-4}=2.6$ Hz); 7.79 (1H, $H_{4'}$, d, $J_{4'-3'}=7.8$ Hz); 7.81 (1H, NH, d, $J_{NH-CH}=7.2$ Hz); 7.90 (1H, $H_{5'}$, d); 7.91 (1H, H_3, d, $J_{3-4}=9.2$ Hz); 8.11 (1H, $H_{8'}$, d, $J_{8'-7'}=7.8$ Hz); 8.65 (1H, H_2, d, $J_{2-1}=4.4$ Hz); ^{13}C NMR (75 MHz, DMSO, 25°C), δ CH_3: 55.4, 22.1; CH_2: 62.3, 57.3, 41.7, 33.8, 28.0, 23.7; CH: 70.9, 60.4, 46.1, 31.9, 25.5; aromatic CH: 147.4, 131.1, 128.6, 127.0, 126.0, 125.5, 125.4, 122.9, 122.1, 120.9, 119.1, 102.5; quaternary C: 156.8, 155.5, 149.3, 143.9, 140.8, 133.3, 130.1. ^1H NMR (300 MHz, $CDCl_3$, 25°C), δ 1.34 (1H, H_{10}, m); 1.35 (1H, H_{13}, m); 1.38 (1H, H_{17}, m); 1.46 (2H, H_{20}–H_{21}, m); 1.57 (3H, CH_3, d, $J_{Me-CH}=5.1$ Hz); 1.70 (1H, H_{12}, m); 1.72 (1H, H_{14}, m); 1.76 (1H, H_{11}, m); 2.37 (1H, H_{18}, m); 2.56 (1H, H_{16}, m); 2.98 (1H, H_{19}, m); 3.02 (1H, H_9, m); 3.47 (1H, H_{15}, m); 3.75 (3H, OMe, s); 3.92 (2H, H_{22}-H_{23}, br. s); 4.63 (1H, OH, br. s); 5.11 (1H, NH, d, $J_{NH-CH}=7.7$ Hz); 5.56 (1H, CH, br. s); 5.56 (1H, H_8, br. s); 7.12 (1H, H_5, br. s); 7.21 (1H, H_4, dd, $J_{4-3}=9.3$ Hz; $J_{4-5}=2.5$ Hz); 7.39 (1H, $H_{3'}$, br. dd); 7.42 (1H, $H_{2'}$, br. d); 7.44 (1H, H_1, d, $J_{1-2}=4.5$ Hz); 7.45 (1H, $H_{6'}$, br. dd); 7.46 (1H, $H_{7'}$, br. dd); 7.73 (1H, $H_{4'}$, br. d, $J_{4'-3'}=7.2$ Hz); 7.81 (1H, $H_{5'}$, d, $J_{5'-6'}=7.2$ Hz); 7.90 (1H, H_3, d, $J_{3-4}=9.3$ Hz); 8.05 (1H, $H_{8'}$, br. d,

$J_{8'-7'}=6.5$ Hz); 8.54 (1H, H_2, d, $J_{2-1}=4.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C), δ CH_3: 55.6, 21.6; CH_2: 63.1, 57.9, 43.0, 33.9, 27.6, 20.9; CH: 71.1, 59.7, 46.5, 32.1, 25.7; aromatic CH: 147.4, 131.4, 128.8, 128.1, 126.3, 125.7, 125.2, 123.1, 122.1, 121.4, 118.4, 101.2; quaternary C: 157.7, 155.6, 147.4, 144.0, 138.7, 133.9, 130.7, 126.5. Anal. calcd for $C_{33}H_{37}N_3O_4$: C, 73.44; H, 6.91; N, 7.79. Found: C, 73.40; H, 6.86; N, 7.82.

4.3.2. 11-[(*R*)-1-(1-naphthyl)ethylcarbamoyloxy]-10,11-dihydroquinine 3. $[\alpha]_D$ −70.6 (*c* 1, $CHCl_3$). ^1H NMR (300 MHz, DMSO, 25°C), δ 1.29 (1H, H_{13}, m); 1.44 (3H, CH_3, d, $J_{Me-CH}=7.1$ Hz); 1.51 (1H, H_{17}, m); 1.52 (2H, H_{20}–H_{21}, m); 1.61 (1H, H_{12}, m); 1.64 (1H, H_{14}, m); 1.65 (1H, H_{11}, m); 1.69 (1H, H_{10}, m); 2.21 (1H, H_{18}, br. d, $J_{18\text{-}19}=12.6$ Hz), 2.40 (1H, H_{16}, m); 2.82 (1H, H_{19}, br. dd, $J_{19-18}=12.6$ Hz, $J_{19-17}=8.9$ Hz); 3.06 (1H, H_9, m); 3.18 (1H, H_{15}, m); 3.88 (3H, OMe, s); 3.91 (2H, H_{22}–H_{23}, br. s); 5.23 (1H, H_8, br. d, $J_{8-9}=6.7$ Hz); 5.43 (1H, CH, dq, $J_{CH-Me}=J_{CH-NH}=7.1$ Hz); 5.64 (1H, OH, br. s); 7.38 (1H, H_4, dd, $J_{4-3}=9.2$ Hz, $J_{4-5}=2.6$ Hz); 7.44 (1H, $H_{2'}$, br. dd); 7.47 (1H, $H_{3'}$, br. d); 7.49 (1H, H_1, d, $J_{1-2}=4.4$ Hz); 7.50 (1H, H_5, br. s); 7.50 (1H, $H_{6'}$, br. dd); 7.51 (1H, $H_{7'}$, br. dd); 7.78 (1H, $H_{4'}$, br. d, $J_{4'-3'}=8.9$ Hz); 7.82 (1H, NH, d, $J_{NH-CH}=7.1$ Hz); 7.91 (1H, $H_{5'}$, br. d); 7.92 (1H, H_3, d, $J_{3-4}=9.2$ Hz); 8.11 (1H, $H_{8'}$, br. d, $J_{8'-7'}=7.8$ Hz); 8.66 (1H, H_2, d, $J_{2-1}=4.4$ Hz); ^{13}C NMR (75 MHz, DMSO, 25°C), δ CH_3: 22.1, 55.5; CH_2: 62.4, 57.3, 41.8, 34.0, 28.1, 23.6; CH: 70.9, 60.4, 46.2, 32.0, 25.7; aromatic CH: 147.5, 131.2, 128.7, 127.1, 126.1, 125.6, 125.5, 123.0, 122.2, 121.0, 119.1, 102.5; quaternary C: 156.9, 155.6, 149.3, 143.9, 140.9, 133.4, 130.2, 127.1. ^1H NMR (300 MHz, $CDCl_3$, 25°C), δ 1.34 (1H, H_{13}, m); 1.35 (1H, H_{10}, m); 1.51 (2H, H_{20}–H_{21}, m); 1.53 (1H, H_{17}, m); 1.57 (3H, CH_3, d, $J_{Me-CH}=5.9$ Hz); 1.66 (1H, H_{14}, m); 1.71 (1H, H_{11}, m); 1.74 (1H, H_{12}, m); 2.33 (1H, H_{18}, br. d, $J_{18-19}=11.8$ Hz); 2.53 (1H, H_{16}, m); 2.96 (1H, H_{19}, m); 2.99 (1H, H_9, m); 3.44 (1H, H_{15}, m); 3.79 (3H, OMe, s); 3.93 (2H, H_{22}–H_{23}, br. s); 4.62 (1H, OH, br. s); 5.12 (1H, NH, d, $J_{NH\text{-}CH}=7.9$ Hz); 5.50 (1H, H_8, br. s); 5.57 (1H, CH, dq, $J_{CH-Me}=5.9$ Hz, $J_{CH-NH}=7.9$ Hz); 7.15 (1H, H_5, br. s); 7.23 (1H, H_4, dd, $J_{4-3}=9.1$ Hz, $J_{4\text{-}5}=2.6$ Hz); 7.40 (1H, $H_{3'}$, br. dd); 7.43 (1H, $H_{2'}$, br. d); 7.46 (1H, H_1, d, $J_{1\text{-}2}=4.5$ Hz); 7.47 (1H, $H_{6'}$, br. dd); 7.49 (1H, $H_{7'}$, br. dd); 7.73 (1H, $H_{4'}$, d, $J_{4'-3'}=7.6$ Hz); 7.82 (1H, $H_{5'}$, d, $J_{5'-6'}=7.6$ Hz); 7.88 (1H, H_3, d, $J_{3-4}=9.2$ Hz); 8.06 (1H, $H_{8'}$; br. d, $J_{8'-7'}=7.5$ Hz); 8.52 (1H, H_2, d, $J_{2-1}=4.5$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$, 25°C), δ CH_3: 55.7, 21.6; CH_2: 63.2, 58.0, 43.0, 34.0, 27.8, 21.1; CH: 71.4, 59.7, 46.5, 32.2, 25.9; aromatic CH: 147.4, 131.4, 128.8, 128.1, 126.3, 125.7, 125.2, 123.1, 122.1, 121.4, 118.4, 101.3; quaternary C: 157.7, 155.6, 147.6, 144.1, 138.7, 133.9, 130.8, 126.5. Anal. calcd for $C_{33}H_{37}N_3O_4$: C, 73.44; H, 6.91; N, 7.79. Found: C, 73.38; H, 6.85; N, 7.74.

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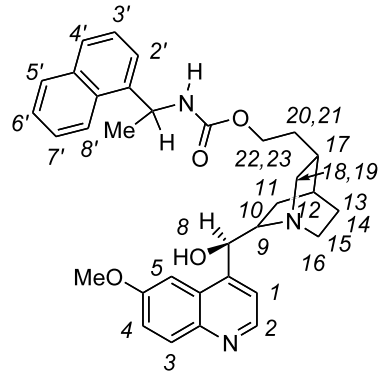

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