Chiral Recognition of Cinchona Alkaloids at the Minor and Major Grooves of 1,1'-Binaphthyl Receptors†

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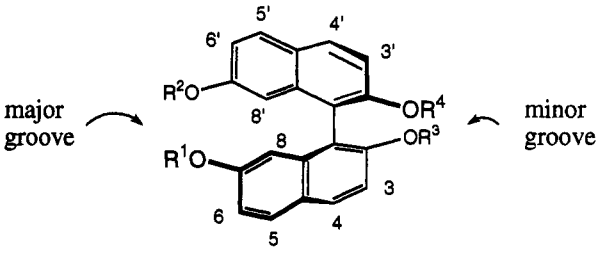
A variety of chiral 1,1'-binaphthyl derivatives with one or two hydroxyl groups at either the 2,2'-(minor groove) or the 7,7'-positions (major groove) were prepared for enantioselective recognition of the cinchona alkaloids quinine and quinidine. The study was initiated when it was found that (±)-7,7'-bis(benzyloxy)-2,2'-dihydroxy-1,1'-binaphthyl ((±)-**1a**) was readily resolved through simple clathrate formation with quinine and quinidine. Optical resolution of (±)-**1a** was also achieved by fractional crystallization of its cyclic phosphate ester with quinidine. The absolute configuration of the optically pure binaphthyl derivatives was established by transformation of (−)-**1a** into a binaphthyl derivative of known absolute configuration (*R*) through reactions of defined stereochemistry. The X-ray crystal structure analysis of the (*S*)-(+)-**1a**·quinidine complex showed that ion pairing is the major interaction between the two components. Complexation of quinine and quinidine at both major and minor grooves of the 1,1'-binaphthyl derivatives occurred in $CDCl_3$ with a significant degree of chiral recognition, and differences in stability between diastereomeric complexes were as large as $\Delta(\Delta G^\circ) \approx 1$ kcal mol^{-1} (293 K). Quinine is consistently better bound by the (*R*)-receptors whereas quinidine always prefers the (*S*)-enantiomers. The structures of the complexes, which are stabilized by hydrogen-bonding and aromatic–aromatic interactions, were analyzed on the basis of the complexation-induced changes in ^{1}H NMR chemical shifts of the binding partners at saturation binding $\Delta\delta_{sat.}$, ^{1}H{^{1}H} nuclear Overhauser effects (NOEs), and molecular modeling.

Introduction

Cinchona alkaloids[1-4] and 1,1'-binaphthyl derivatives[5-7] are among the most versatile and most highly used chiral molecular shapes in asymmetric synthesis and enantiomeric separations. Considerable research has been devoted toward understanding the role of the two cinchona alkaloids quinine and quinidine in these applications.[8-10] In addition, 1,1'-binaphthyl derivatives have been successfully incorporated into optically active crown ethers

Chart 1



1	R^1	R^2	R^3	R^4
a	$PhCH_2$	$PhCH_2$	H	H
b	$PhCH_2$	$PhCH_2$	CH_3	CH_3
c	$PhCH_2$	$PhCH_2$	CH_3	H
d	H	H	CH_3	CH_3
e	H	H	$(CH_2)_{11}CH_3$	$(CH_2)_{11}CH_3$
f	$PhCH_2$	H	CH_3	CH_3
g	$PhCH_2$	H	$(CH_2)_{11}CH_3$	$(CH_2)_{11}CH_3$

† In memory of Jon Reeder.

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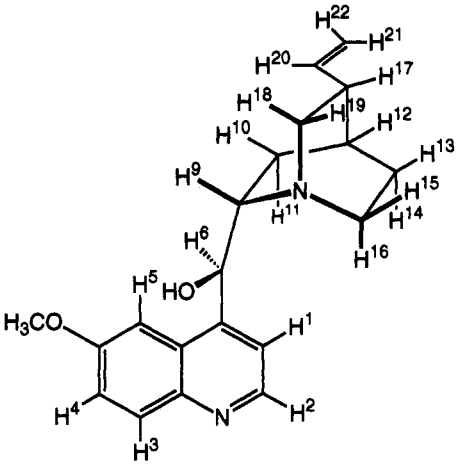
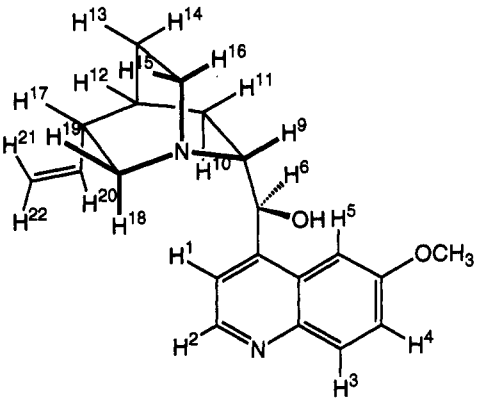
Chart 2



2, quinine



3, quinidine

(arbitrary numbering)[8]

for the enantioselective complexation of amino acid esters and chiral primary ammonium ions.[11]

When we started a research program on chiral recognition of naproxen derivatives with optically active cyclophanes incorporating 2,2′,7,7′-tetrahydroxy-1,1′-binaphthyls as chiral spacers,[12] fractional crystallization of the cinchonine or cinchonidine salts of cyclic phosphate esters[13] was the best method for resolving 2,2′-dihydroxy-1,1′-binaphthyls.[14,15] We became interested in exploring alternate, more facile ways for optical resolution when *Rosini* et al. described the use of quinine as a chiral solvating agent for the determination of the enantiomeric composition of 1,1′-binaphthyl derivatives by ^{1}H NMR spectroscopy.[16] We found that quinine and quinidine effectively resolved binaphthol (±)-**1a** through simple clathrate formation. These findings, in return, led to comprehensive studies of the molecular recognition between 1,1′-binaphthyls and the alkaloids in $CDCl_3$.[17] Here, we describe in detail the optical resolution of (±)-**1a**, the synthesis of the binaphthyl derivatives **1a–g** (Chart 1) in enantiomerically pure form, the X-ray crystal structure of the (*S*)-(+)-**1a**·quinidine complex, and the enantioselective complexation of these cleft-type receptors with quinine (**2**) and quinidine (**3**) in $CDCl_3$ (Chart 2).[18–21]

Results and Discussion

Synthesis and Assignment of the Absolute Configuration of the 1,1′-Binaphthyl Derivatives (*R*)- and (*S*)-1a–g. The synthesis of the various cleft-type receptors started from 7,7′-bis(benzyloxy)-2,2′-dihydroxy-1,1′-binaphthyl (**1a**) which was obtained in 85% yield by coupling 2-(benzyloxy)-7-hydroxynaphthalene (**4**)[12b] with $CuCl_2$/*t*-$BuNH_2$ in CH_3OH (Scheme 1).[22] This method is far superior to the previously described couplings with Mn(acac)$_3$ in CH_3CN (35–40% yield)[12b,23a] or with $FeCl_3$ (≈30% yield) in solution or in the solid state.[23b] Optical resolution of (±)-**1a** was accomplished using the route described for (±)-2,2′-dihydroxy-1,1′-binaphthyl *via* for-

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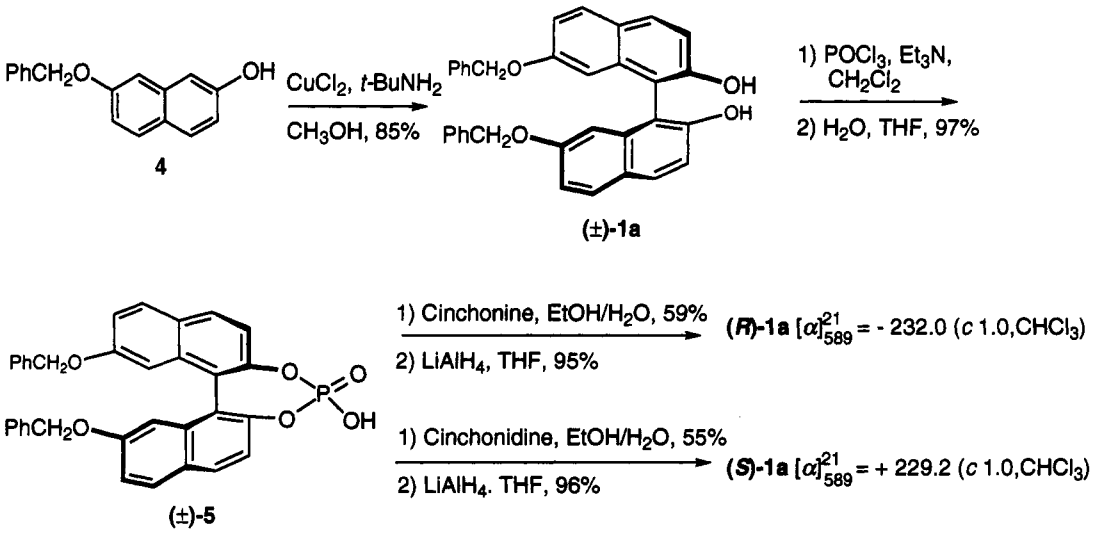
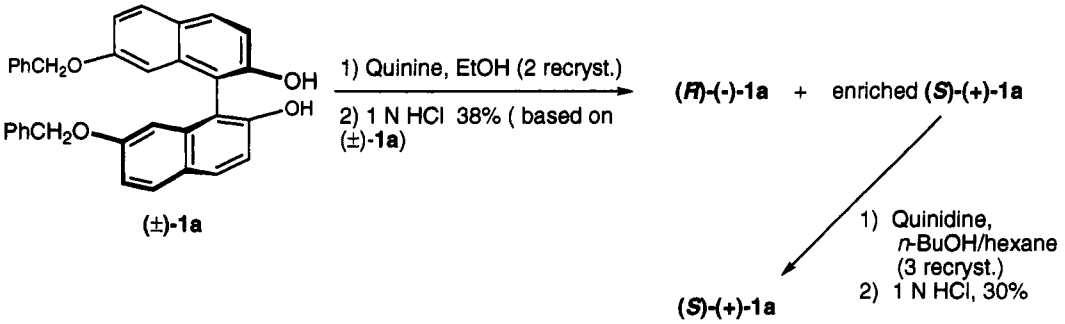
Scheme 1: Synthesis of Optically Pure (*R*)- and (*S*)-1a via the Phosphate Route



Scheme 2: Optical Resolution of (±)-1a via Clathrate Formation with Quinine and Quinidine, Respectively



mation of the cyclic phosphate (±)-**5**, fractional crystallization of the diastereomeric salts formed with cinchonine and cinchonidine, and dephosphorylation with lithium aluminum hydride.[13] The optical purity of (−)-**1a** prepared this way was determined as ≥99% ee from the 500-MHz ^{1}H NMR spectra of the diastereomeric Mosher esters formed with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) in the presence of dicyclohexylcarbodiimide (DCC) and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2.[24,25]

An easier way to demonstrate that the optical purity of (*R*)- and (*S*)-**1a** was ee ≥ 99% involved the formation of diastereomeric complexes with quinine in $CDCl_3$.[16,17] The ^{1}H NMR spectra of the two complexes showed large differential complexation-induced shifts (see Table 2 below), which is indicative of different complex geometries. This observation led us to consider, whether the complexes would also exhibit significantly different stabilities, and this reasoning initiated the molecular recognition studies described below. In addition, the initial finding of the chiral solvating power of the alkaloid led to a much faster route to the optical resolution of (±)-**1a** through clathrate formation with quinine (**2**) and quinidine (**3**) (Scheme 2). When (±)-**1a** together with 1 equiv of quinine was recrystallized twice from ethanol, one crystalline diastereomeric complex was obtained in pure form. Subsequent acidic workup to remove the alkaloid yielded enantiomerically pure (−)-**1a**, $[\alpha]^{21}_{589}$ = −232.0° (*c* 1.0, $CHCl_3$) in 38% yield (based on (±)-**1a**).

The assignment of the absolute configuration of this enantiomer as (*R*)-(−)-**1a** was based on its conversion in stereochemically known steps *via* (−)-**5** and (−)-**6** into (*R*)-(−)-**7** (Scheme 3). The absolute configuration of (−)-**7** had previously been assigned by Pirkle and Schreiner based on the elution sequence of a series of 1,1′-binaphthyl derivatives on the chiral stationary phase CSP 2.[26a] HPLC analysis on a Pirkle CSP prepared from D-phenylglycine with 2-propanol/hexane (1:9) as the eluent showed that the optical purity of (*R*)-(−)-**1a** (retention time *t* = 37.5 min; (*S*)-enantiomer: *t* = 30.4 min) was ee ≥ 99.9%.

The mother liquors enriched in (*S*)-(+)-**1a** were evaporated to dryness, and this enantiomer ($[\alpha]^{21}_{589}$ (*c* 1.0, $CHCl_3$) = +229.2°) was obtained in low yield by multiple recrystallizations (5×) of the quinine clathrate from C_2H_5OH/H_2O (4:1). A better method was the formation of the quinidine clathrate. After quinine was removed by acidic extraction from the mother liquors enriched in (*S*)-(+)-**1a**, quinidine was added and three crystallizations of the formed clathrate from *n*-BuOH/hexane yielded the (*S*)-enantiomer in 30% yield (based on (±)-**1a**) with >99% ee.

Starting from (*R*)- and (*S*)-**1a**, the other binaphthyl clefts (*R*)- and (*S*)-**1b–g** were readily obtained in optically pure form following the short conversions shown in Scheme 4. The derivatives **1e** and **1g** with long alkyl chains were

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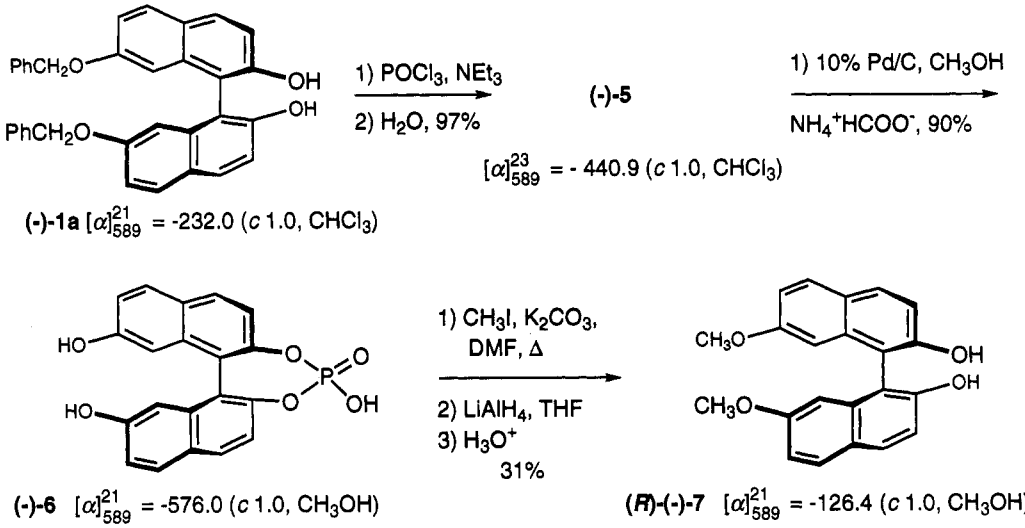
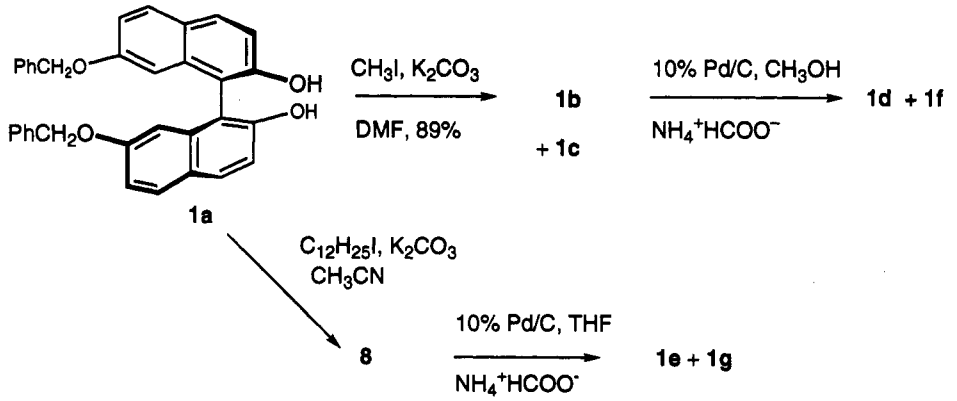
Scheme 3: Assignment of Absolute Configuration of (−)-1a as *R* by Chemical Correlation to (*R*)-(−)-7



Scheme 4: Synthesis of 1,1′-Binaphthyl Cleft Receptors



prepared for future exploration of chiral recognition processes in monolayers at air–water interfaces;[6a] also, the alkyl chains provided enhanced solubility properties which was beneficial in the ^{1}H NMR studies of the alkaloid complexes.

X-ray Crystal Structure of the Complex of Cyclic Phosphate (*S*)-5 with Quinidine. In addition to the optical resolution of (±)-5 with cinchonine and cinchonidine, the (*S*)-enantiomer of the phosphate was readily obtained in highest purity (35% yield based on (±)-5) as an ethanol solvate by three crystallizations with quinidine from a minimum amount of 95% C_2H_5OH. The X-ray crystal structure of the ethanol solvate of the (*S*)-5-quinidine complex (Figure 1) demonstrated the correctness of the configurational assignment shown in Scheme 3.[26b] The alkaloid adopts the "open conformation 3" according to the definitions introduced by Dijkstra et al.[8] The dihedral angle C(13)–C(14)–C(33)–C(32) about the chirality axis in the binaphthyl component is remarkably small and amounts to only 57(2)°. The greatest deviation of a naphthyl C-atom from a least-squares plane through the 10 naphthalene C-atoms is 0.10(2) Å. The two components interact in a typical acid–base relationship with the closest intermolecular contact being observed between one phosphate O-atom and the quinuclidine N-atom (N(55)···O(3) 2.64(2) Å).[27] Ethanol is hydrogen bonded to another phosphate O-atom (O(3E)···O(2) 2.65(2) Å, H(3E)···O(2) 2.0(2) Å, O(3E)–H(3E)···O(2) 117(13)°.

Complexation of Quinine and Quinidine at the 1,1′-Binaphthyl Minor Groove. All complexation studies with the two cinchona alkaloids and the 1,1′-binaphthyl derivatives (*R*)- and (*S*)-1a–g involved 500-MHz ^{1}H NMR titrations in dry $CDCl_3$ (293 K) at constant binaphthyl concentration, which were evaluated by a nonlinear least-squares curve fitting procedure.[28] The alkaloid concentration ranges were chosen to provide approximately 10–90% complexation of the binaphthyl derivative. All binaphthyl protons that could be monitored during the entire titration and showed complexation-induced shifts at saturation binding larger than $\Delta\delta_{sat.}$ = 0.1 ppm were evaluated, and the binding data shown below in Tables 1 and 2 are averaged data. We consistently find that evaluation of smaller complexation-induced shifts ($\Delta\delta_{sat.}$ < 0.1 ppm) leads to large uncertainties in the thermodynamic data. In the minor groove complexes, most binaphthyl protons showed sufficiently large $\Delta\delta_{sat.}$ values (≫0.1 ppm) to be evaluated with confidence, whereas $\Delta\delta_{sat.}$ values of this magnitude were generally only observed for one or two binaphthyl protons in the major groove complexes. Therefore, the uncertainties of the $-\Delta G^\circ$ values for major groove complexes are larger (±0.20 kcal mol^{-1}) than for minor groove complexes (±0.10 kcal mol^{-1}). The stoichiometry of the complexes was shown to be 1:1 by Job plot analysis. We believe that the uncertainties in

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(28) Associate V.1.4.1, Blake Peterson, ETH Zürich.

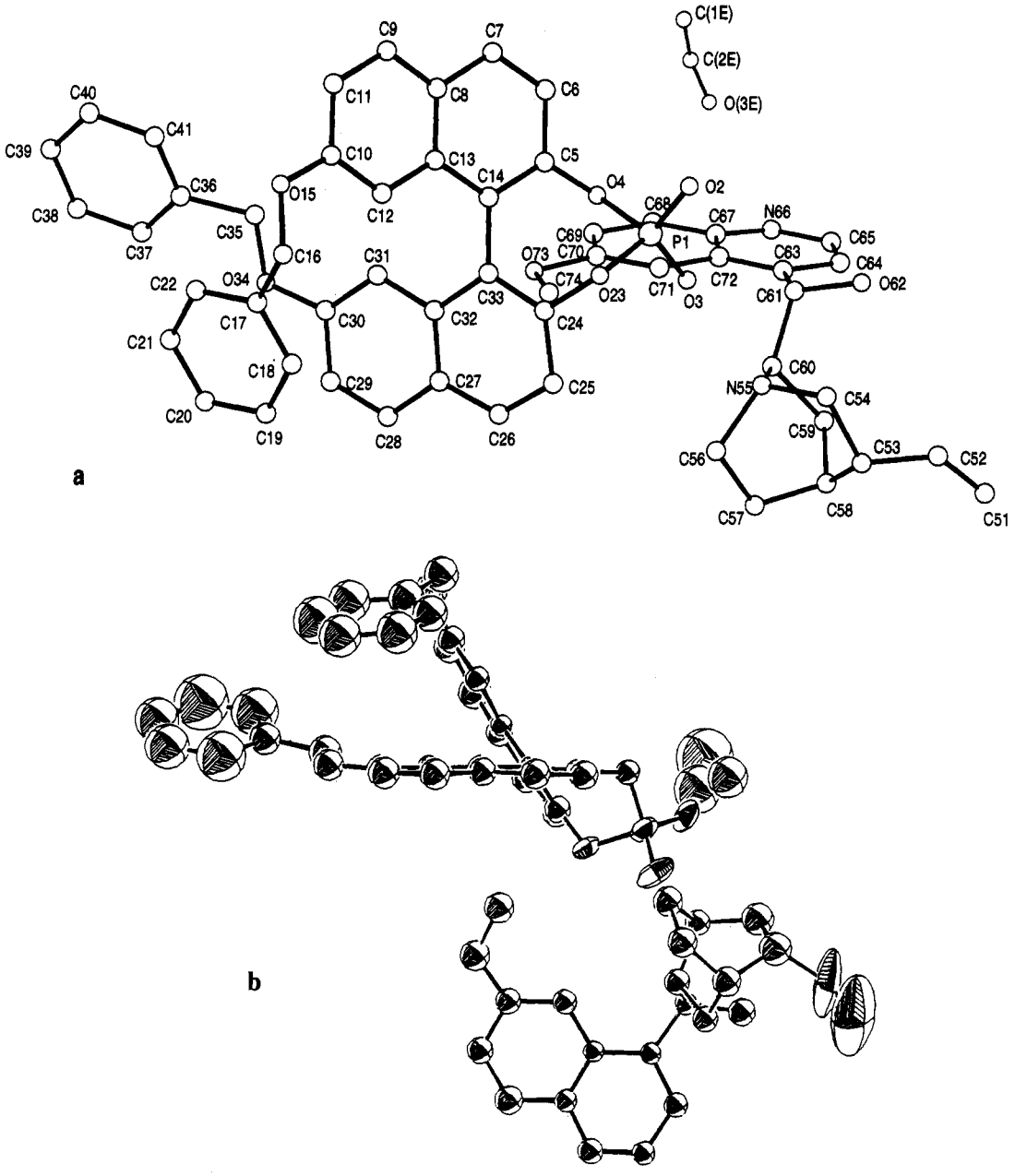


Figure 1. X-ray crystal structure of the complex between (*S*)-**5** and quinidine (a) in a view perpendicular to the binaphthyl chirality axis and (b) along the binaphthyl chirality axis.

Table 1. Association Constants, K_a, and Free Energies of Formation, $-\Delta G°$, of the Diastereomeric Complexes between (*R*)- and (*S*)-1a–c and Cinchona Alkaloids in $CDCl_3$, T = 293 K.[a] The Calculated Differences in Stability between Diastereomeric Complexes, $\Delta(\Delta G°)$, are Given

alkaloid	K_a (L mol^{-1})	$-\Delta G°$ (kcal mol^{-1})	K_a (L mol^{-1})	$-\Delta G°$ (kcal mol^{-1})	$\Delta(\Delta G°)$ (kcal mol^{-1})
	(*R*)-**1a**[b]		(*S*)-**1a**		
quinine	86	2.59	46	2.23	0.36
quinidine	25	1.89	71	2.48	0.59
	(*R*)-**1b**		(*S*)-**1b**		
	no measurable complexation				
	(*R*)-**1c**		(*S*)-**1c**		
quinine	33	2.04	13	1.49	0.55
quinidine	13	1.49	25	1.89	0.40

[a] Errors in $\Delta G°$: ± 0.10 kcal mol^{-1}. [b] Minor deviations of the binding data for (*R*)- and (*S*)-**1a** from those reported in the preliminary communication (ref 17) are due to sampling and averaging of thermodynamic data over additional binding titrations.

the evaluation of very small changes in chemical shift ($\Delta\delta_{sat.}$ < 0.1 ppm) are not due to instrumental errors but to competing self-association equilibria of the binding partners[29] as well as to higher complex stoichiometries, which start becoming relevant at the higher concentration ranges of the titrations. All binding data were confirmed in duplicate or triplicate runs.

Table 1 shows the association constants, K_a, and free energies of formation, $-\Delta G°$, of the complexes formed by (*R*)- and (*S*)-**1a–c** with the two cinchona alkaloids as well as the differences in stability between diastereomeric complexes, $\Delta(\Delta G°)$. Table 2 and Figure 2 show the complexation-induced changes in ^{1}H-NMR chemical shift, $\Delta\delta_{sat.}$, of the binding partners at saturation binding. The following conclusions can be drawn from these data:

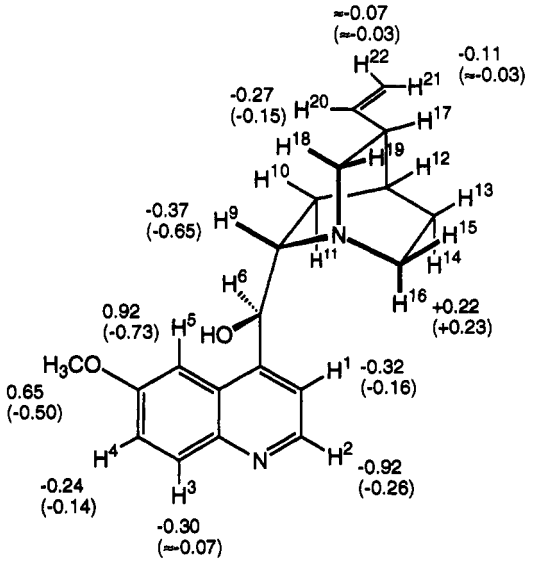
(1) The binaphthyl clefts (*R*)- and (*S*)-**1a/c** form complexes of moderate association strength with both

(29) At [alkaloid] = 1 mM, autoaggregation in $CDCl_3$ is negligible; it becomes, however, significant in concentration ranges above 5 mM. Uccello-Barretta, G.; Di Bari, L.; Salvadori, P. *Magn. Reson. Chem.* **1992**, *30*, 1054–1063.

Table 2. Complexation-Induced Changes in ^{1}H NMR Chemical Shift at Saturation Binding, $\Delta\delta_{sat.}$ [ppm], of Binaphthyl Protons in Minor and Major Groove Complexes[a]

binaphthyl	alkaloid	H-C(3)	H-C(4)	H-C(5)	H-C(6)	H-C(8)	H-C(3′)	H-C(4′)	H-C(5′)	H-C(6′)	H-C(8′)
					Minor Groove Complexes						
(*R*)-**1a**	quinine	−0.15	−0.28	−0.39	−0.39	+0.11					
(S)-**1a**	quinidine	−0.12	−0.27	−0.35	−0.42	+0.11					
(*R*)-**1c**[c]	quinine	−0.17	−0.27	−0.37	−0.40	≈+0.09	≈−0.07	≈−0.07	≈−0.04	≈−0.07	≈+0.04
(*S*)-**1c**[d]	quinidine	−0.16	−0.29	−0.41	−0.45	≈+0.09	≈−0.07	*b*	–	–	–
(*S*)-**1a**	quinine	−0.24	−0.32	−0.18	−0.18	≈+0.02					
(*R*)-**1a**	quinidine	−0.26	−0.31	−0.16	−0.14	≈+0.04					
(*S*)-**1c**[e]	quinine	−0.37	−0.30	−0.11	−0.12	≈+0.06	–	–	–	–	–
(*R*)-**1c**[f]	quinidine	−0.36	−0.27	−0.13	−0.10	≈+0.06	–	–	–	–	–
					Major Groove Complexes						
(*R*)-**1d**	quinine	−0.19	≈−0.19	≈−0.06	≈−0.07	≈+0.07					
(*S*)-**1d**	quinine	≈−0.09	≈−0.07	−0.11	−0.14	≈+0.04					
(*R*)-**1d**	quinidine	−0.10	≈−0.09	−0.11	–	≈+0.02					
(*S*)-**1d**	quinidine	−0.17	≈−0.09	≈−0.07	–	≈+0.05					

[a] For the proton labeling, see formula drawings **1a–g**; – = upfield shift. [b] Not determined since $\Delta\delta_{sat.}$ very small (≤0.1 ppm) or too much signal overlap during the titration. [c] OCH_3: $\Delta\delta_{sat.}$ = ≈−0.08. [d] OCH_3: $\Delta\delta_{sat.}$ = −0.10. [e] OCH_3: $\Delta\delta_{sat.}$ = −0.35. [f] OCH_3: $\Delta\delta_{sat.}$ = −0.34.

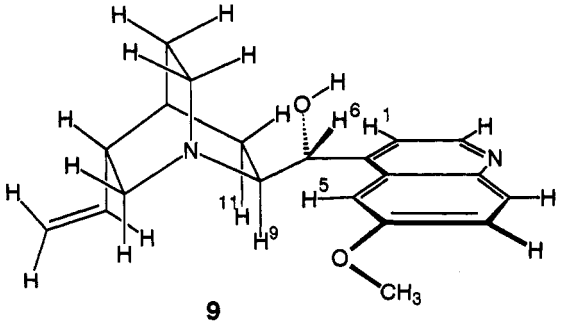


free quinine [ppm]

H^1	7.54	H^{13}	1.67
H^2	8.78	H^{14}	1.56
H^3	8.04	H^{15}	2.69
H^4	7.39	H^{16}	3.38
H^5	7.29	H^{17}	2.29
CH_3O	3.95	H^{18}	2.71
H^6	5.55	H^{19}	3.13
H^9	3.22	H^{20}	5.80
H^{10}	1.55	H^{21}	4.96
H^{11}	1.70	H^{22}	5.01
H^{12}	1.84		

Figure 2. Changes in ^{1}H NMR chemical shift at saturation binding, $\Delta\delta_{sat.}$, in the quinine complexes of (*R*)-**1a** (first numbers) and (*R*)-**1c** (second numbers, in parentheses). As a reference, the spectrum of 0.001 M quinine in $CDCl_3$ (293 K) is shown.

Scheme 5: Open Conformation Preferred by Quinine in the Uncomplexed and Complexed State[8]



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quinine and quinidine, and significant differential stabilities of the diastereomeric complexes are observed. Generally, the (*R*)-clefts prefer binding to quinine, and the (*S*)-clefts prefer quinidine. Thus, the (*R*)-**1a**-quinine complex, which showed the higher tendency to form an insoluble clathrate in the optical resolution process (Scheme 2), is also the more stable of the two diastereomeric complexes formed by (*R*)- and (*S*)-**1a**.

(2) The H-bond donor center at the minor groove is essential for complexation. Alkylation of all four binaphthyl hydroxy groups in **1b** leads to the complete disappearance of any measurable binding interactions. Although the complexes became less stable upon reduction of the H-bond donor centers from two (in (*R*)- and (*S*)-**1a**) to one (in (*R*)- and (*S*)- **1c**), the degree of chiral recognition as measured by $\Delta(\Delta G^o)$ remains approximately the same.

(3) Similar to the free alkaloids, complexed quinine and quinidine greatly prefer the "open" conformation **9** (Scheme 5). The preference of cinchona alkaloids for this conformation in solution had previously been elegantly demonstrated by Dijkstra et al. using 1D and 2D NMR techniques as well as AM1 computations.[8] Conclusive evidence for the preference for the "open" conformation **9** in the binaphthyl complexes of quinine and quinidine was obtained by NMR techniques[30] including $^1H\{^1H\}$ NOE difference spectroscopy[31] and ROESY[32] experiments. In the spectra of quinine, characteristic NOEs were observed between H(1) and H(11), H(5) and H(6), H(5) and H(9), and H(6) and H(9).[8]

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(31) (a) Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 5627–5628. (b) Williamson, M. P.; Williams, D. H. *J. Chem. Soc. Chem. Commun.* **1981**, 165–166.

(32) Pochapsky, T. C.; Stone, P. M.; Pochapsky, S. S. *J. Am. Chem. Soc.* **1991**, *113*, 1460–1462.

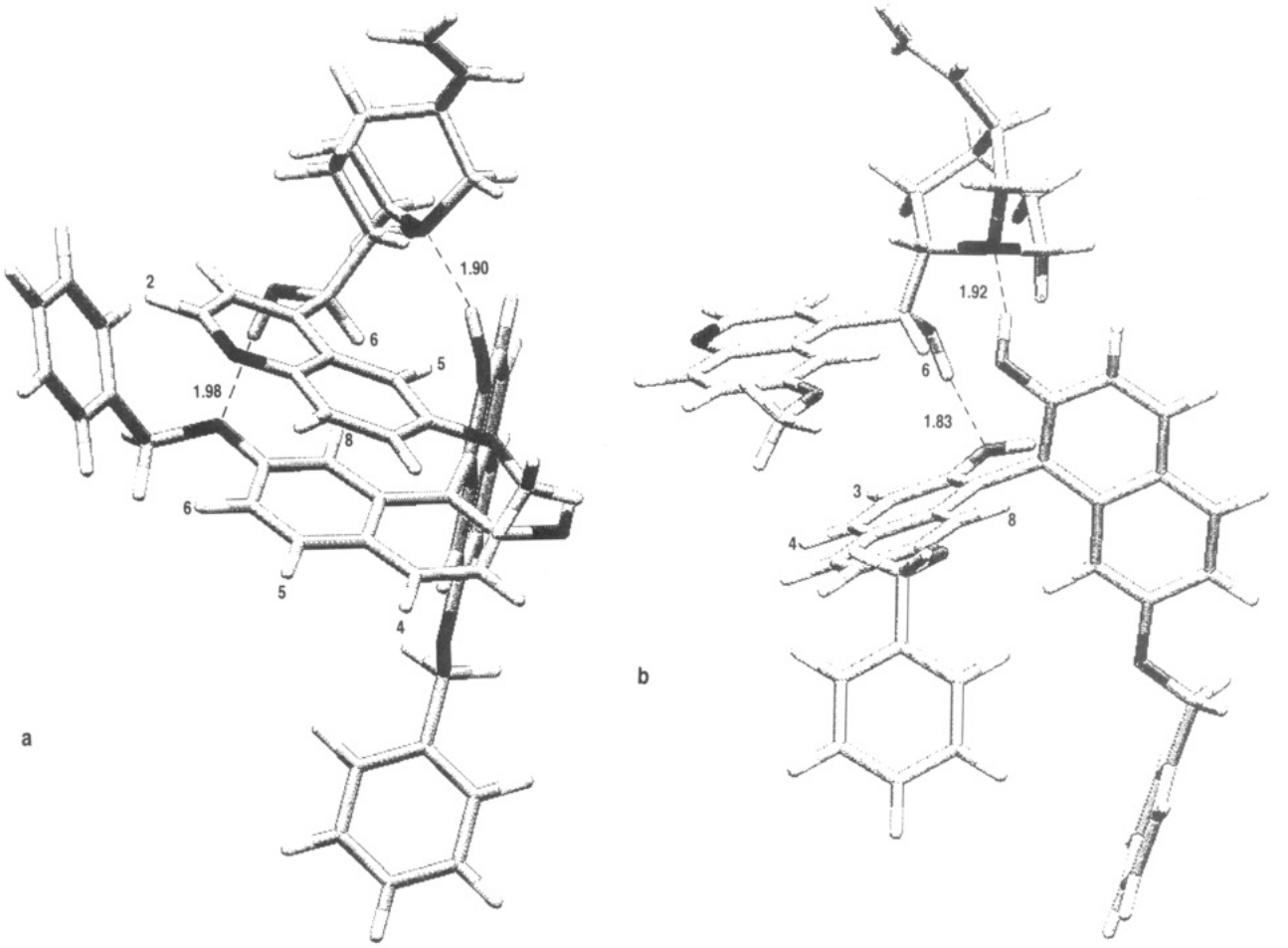

Figure 3. MacroModel geometries (OPLS* force field) of the two diastereomeric complexes (*R*)-**1a**-quinine (a) and (*S*)-**1a**·quinine (b), supported by experimental NOE and $\Delta\delta_{sat.}$ data.

(4) The binaphthyl protons in the four more-stable diastereomeric complexes (*R*)-**1a**·quinine, (*R*)-**1c**·quinine, (*S*)-**1a**·quinidine, and (*S*)-**1c**-quinidine show similar $\Delta\delta_{sat.}$ values (Table 2, Figure 2) which indicates high structural similarity. The same observation also holds for the four weaker complexes. NOE difference spectroscopy and ROESY experiments, together with the analysis of the $\Delta\delta_{sat.}$ values, provide a clear picture of the bonding situation in the two types of complexes (Figure 3). In the four more-stable complexes, a strong intermolecular NOE indicates a close proximity between H(6) of the alkaloid and H(8) of the binaphthyl. This NOE is not observed in the four weaker diastereomeric complexes. Molecular modeling (CPK models, MacroModel)[33] shows that this proximity occurs when one binaphthyl OH-group forms an H-bond to the quinuclidine N-atom (Figure 3a). To establish this essential binding interaction, the quinoline ring and the naphthalene ring bearing the second OH-group (in **1a**) or the CH_3O-group (in **1c**) adopt a π-stacking arrangement. This, in return, orients the OH-group of the alkaloid toward the benzylic O-atom of the π-stacking naphthalene ring, leading to a second, weaker H-bond. In this complex geometry, protons H(4,5,6) of the π-stacking naphthalene ring shift upfield by ≈0.27–0.45 ppm (Table 2). In contrast, the chemical shift of protons H(4′,5′,6′) of the naphthalene moiety in **1c**, which is not π-stacking and forms with its OH-group the H-bond to the quinuclidine, are almost unaffected by complexation (Table 2). Correspondingly, the protons of the π-stacking quinoline moiety of the alkaloid move upfield with H(2), H(5), and the CH_3O-protons showing the largest shifts (Figure 2). The significant upfield shift (–0.92 ppm) of H(2) in the (*R*)-**1a**-quinine complex could be explained by additional shielding from the benzyl ring attached to the stacking naphthalene moiety (Figure 3a). As an additional characteristic feature in the (*R*)-**1a**-quinine and (*R*)-**1c**-quinine complexes, proton H(16) of the quinuclidine moiety shifts downfield presumably due to deshielding effects of the binaphthyl cleft.

No intermolecular NOE was observed between H(6) of the alkaloid and H(8) of the binaphthyl in the four less-stable diastereomeric complexes formed by (*R*)-**1a**/**c** with quinidine and by (*S*)-**1a**/**c** with quinine. Again, modeling, combined with the analysis of the $\Delta\delta_{sat.}$ values (Table 2), suggests that the major binding modes in these complexes are (a) a N···HO hydrogen bond between the quinuclidine N-atom and the OH-group at one naphthalene, (b) π–π-stacking between the quinoline ring and the second naphthalene, and (c) a second H-bond between the OH-group of the alkaloid and the OH (OCH_3) O-atom of the π-stacking naphthalene of **1a** (**1c**) (Figure 3b). Such geometry orients the protons H(6) of the alkaloid and H(8) of the binaphthyl far away from each other, and a NOE is not observed. Chiral recognition presumably occurs

(33) MacroModel V. 4.0, Still, W. C., Columbia University, New York. Input structures were generated based on experimental NOE and chemical shift data. The OPLS* force field was used for energy minimizations, and conformational space was sampled using Monte-Carlo searches in BatchMin. For details, see ref 19c.

Table 3. Association Constants, K_a, and Free Energies of Formation, $-\Delta G^0$, of the Diastereomeric Complexes between (*R*)- and (*S*)-1d–g and Cinchona Alkaloids in $CDCl_3$, $T = 293$ K.[a] The Calculated Differences in Stability between Diastereomeric Complexes, $\Delta(\Delta G^0)$, are Given

alkaloid	K_a (L mol^{-1})	$-\Delta G^0$ (kcal mol^{-1})	K_a (L mol^{-1})	$-\Delta G^0$ (kcal mol^{-1})	$\Delta(\Delta G°)$ (kcal mol^{-1})
	(*R*)-**1d**		(*S*)-**1d**		
quinine	1270	4.16	650	3.77	0.39
quinidine	625	3.75	850	3.93	0.18
	(*R*)-**1e**		(*S*)-**1e**		
quinine	793	3.89	436	3.54	0.35
quinidine	348	3.41	507	3.63	0.18
	(*R*)-**1f**		(*S*)-**1f**		
quinine	775	3.87	140	2.88	0.99
quinidine	105	2.72	550	3.67	0.95
	(*R*)-**1g**		(*S*)-**1g**		
quinine	1174	4.11	$\ll$500[b]	$\ll$3.61	$\gg$0.50
quinidine	$\ll$500[b]	$\ll$3.61	1050	4.05	$\gg$0.44

[a] Errors in ΔG^0: ±0.20 kcal mol^{-1} except for the weaker complexes formed by (*R*)- and (*S*)-**1g**. [b] Estimated values since all protons of the binaphthyl derivative, held at constant concentration, show $\Delta\delta_{sat.}$ $\ll$0.1 ppm.

since π–π-stacking is less effective in the less-stable than in the more-stable diastereomeric complexes. The $\Delta\delta_{sat.}$ values (Table 2) show that the quinoline ring undergoes π-stacking with only a reduced area of a naphthalene ring: only H(3) and H(4) (besides the CH_3O protons in **1c**) show larger upfield shifts with $\Delta\delta$ values between 0.24 and 0.37 ppm. The modeling clearly shows that no pair of protons of the two binding partners in the proposed bonding geometry is sufficiently close to produce a significant NOE.

4. Complexation of Quinine and Quinidine at the 1,1′-Binaphthyl Major Groove. Complexes of quinine and quinidine at the major groove of the 1,1′-binaphthyl clefts are generally more stable than those formed at the minor groove (Table 3). Interestingly, the binaphthyls **1f**/**g** with one H-bond donor site show a higher degree of chiral recognition than the derivatives **1d**/**e** with two OH-groups. Similar to the bonding at the minor groove, quinine prefers to bind to the *R*-binaphthyls, and quinidine to the *S*-binaphthyls. However, the geometries of the major groove complexes are less defined than those formed at the minor groove, and the origin of chiral recognition in the liquid phase remains unclear. The $\Delta\delta_{sat.}$ values measured for the binaphthyl protons in all complexes (Table 2) are rather similar and much smaller than those measured for the corresponding protons in the minor groove complexes. This either means that the quinoline moiety of the alkaloids does not interact closely with the binaphthyl clefts or that a population of several favorable binding conformations leads to small, averaged-out $\Delta\delta_{sat.}$ values.

NOE data from both ROESY experiments and NOE difference spectroscopy indeed indicate that several low-energy binding geometries are populated in the major groove complexes. In the (*R*)-**1g**·quinine and (*S*)-**1g**·quinidine complexes, intermolecular NOEs are observed between H(8′) of the binaphthyl unit and the alkaloid protons H(6), H(15), H(19), and H(16) (quinine) or H(18) (quinidine). These NOEs suggest that the quinuclidine N-atom forms a H-bond to the OH-group of (*R*)-**1g** but that no additional stabilizing aromatic–aromatic contacts are involved. In addition, in both complexes, a strong intermolecular NOE is also visible between the binaphthyl proton H(8′) and the quinoline proton H(2) of the alkaloid. Figure 4 shows a low-energy conformation for the (*R*)-**1f**·quinine complex which was generated with the OPLS* force field in MacroModel and which would explain the observed NOE. This conformation is stabilized by two H-bonds, one between the naphthalene OH-group and the quinoline N-atom and a second between the alkaloid OH-group and the O-atom of the (benzyloxy)naphthalene. In this geometry, as in any of the geometries where the quinuclidine N-atom is H-bonded, aromatic interactions are weak which would explain the small $\Delta\delta_{sat.}$ values of the binaphthyl protons.

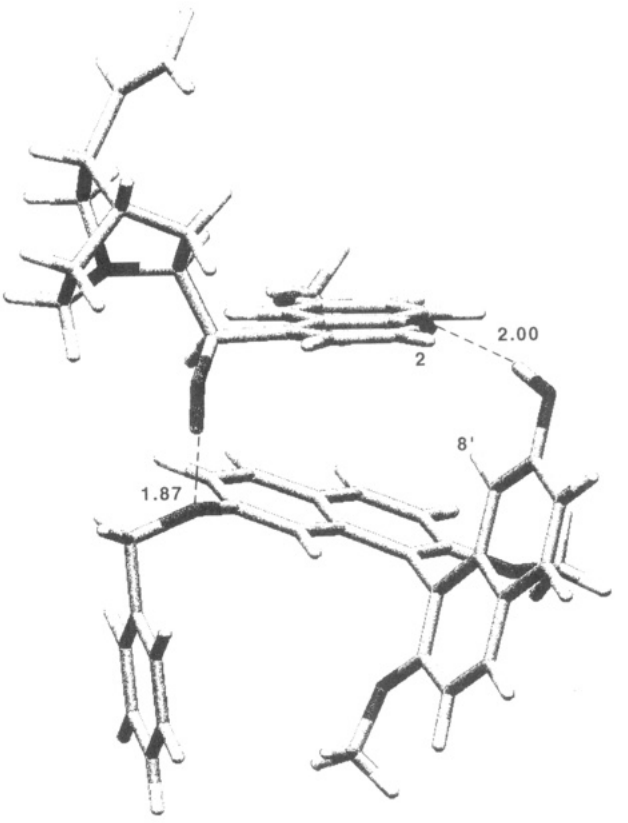

Figure 4. Favorable MacroModel (OPLS* force field) geometry of the (*R*)-**1f**-quinine complex which explains the observed NOE between H(8′) of the binaphthyl and H(2) of the alkaloid.

Conclusions

1,1′-Binaphthyl clefts with one or two OH-groups at the major or minor groove recognize enantioselectively the cinchona alkaloids quinine and quinidine in $CDCl_3$, and the degree of chiral recognition varies between $\Delta(\Delta G^o) \approx$ 0.2 and 1.0 kcal mol^{-1}. The analysis of $\Delta\delta_{sat.}$ and NOE data provided a clear picture of the geometries of the complexes formed at the narrow minor groove. Two H-bonds, one between the quinuclidine N-atom and the OH-group of one naphthalene and a second between the OH-group of the alkaloid and an O-atom of the second naphthalene stabilize these complexes in addition to π–π-stacking interactions between the quinoline and a naphthalene ring. Chiral recognition presumably originates from differences in π–π-stacking interactions in the diastereomeric complexes. The geometries of the major groove complexes are less defined, and NOE data suggest that more than one favorable conformation is populated, in which H-bonding of the binaphthyl OH-groups occurs to either quinuclidine or quinoline N-atoms. π–π-Stacking interactions are less effective in the major groove than in the minor groove complexes. This study was initiated by the finding that one of the clefts, (±)-**1a**, was easily resolved

through clathrate formation with quinine and quinidine. It was subsequently determined that the preferentially formed diastereomeric clathrate also corresponds to the more stable complex in $CDCl_3$. Although the solvents employed in the optical resolution via enclathration (EtOH, BuOH) and the liquid phase complexation studies ($CDCl_3$) were very different, this investigation suggests that solid state complex formation is preceded by specific recognition in solution and that it may be worthwhile to investigate chiral recognition in solution in cases where facile enantioselective clathrate formation is observed. For most successful chiral enclathrations, liquid phase recognition studies have not been reported.

Experimental Section

General. ^1H NMR spectra (δ[ppm], J[Hz]) were measured at 293 K in $CDCl_3$ is not stated otherwise. Assignments of proton resonances were supported by ^1H–^{13}C-HETCOR spectra[34] and intramolecular NOEs seen in NOE difference spectra and ROESY experiments. Electron impact mass spectra (EI-MS) were obtained at 20 eV. The m/z values listed below are followed by relative intensities given in parentheses. IR spectra were recorded for all compounds but are not reported. Melting points are uncorrected. Elemental analyses were carried out by Spang Microanalytical Laboratory. Eagle Harbor, MI, Desert Analytics, Tucson, AZ, and the Mikrolabor in the Laboratorium für Organische Chemie at ETHZ. Column chromatography was performed on silica gel 70–230 mesh from E. Merck. Reagents and solvents used were reagent-grade. The Pirkle CSP 2 was purchased from Alltech Associates. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) and acetonitrile (CH_3CN) were distilled from calcium hydride prior to use. Dimethylformamide (DMF) was dried by storage over basic alumina (Merck, act. I). Reactions were performed under argon unless otherwise noted. The general reaction workup included separation of the product-containing organic phase from aqueous layers, drying with $MgSO_4$, and evaporation of the solvent *in vacuo* (at water aspirator pressure). All ^1H NMR titration data was obtained at 500 MHz at 293.0 K following previously reported procedures.[35]

(±)-7,7′-Bis(benzyloxy)-2,2′-dihydroxy-1,1′-binaphthyl ((±)-1a). A solution of 4 (23.6 g, 0.094 mol) and $CuCl_2$ (25.6 g, 0.19 mol) in degassed CH_3OH (600 mL) was stirred while Ar was bubbled through for 10 min. *t*-Butylamine (0.77 mol, 250 mL of a 3.08 M freshly prepared solution in CH_3OH) was added over a period of 1.5 h, and the reaction was stirred for 20 h. After cooling in an ice-bath, 6 N HCl (200 mL) was slowly added and CH_3OH removed *in vacuo*. The residue was taken up in $CH_3COOC_2H_5$ and washed with saturated aqueous NaCl solution (2×). Workup followed by recrystallization from toluene/cyclohexane (5:95) afforded (±)-**1a** (20 g, 85%) as a yellow solid with spectral and physical properties identical to those of the material previously reported:[12b] ^1H NMR (200 MHz, $CDCl_3$) δ 4.69 and 4.83 (AB, J = 11.8, 4 H), 4.99 (s, 2 H), 6.48 (d, J = 2.4, 2 H), 7.10 (dd, J = 9.0 and 2.4, 2 H), 7.15–7.25 (m, 12 H), 7.80 (d, J = 9.0, 2 H), 7.89 (d, J = 9.0, 2 H).

Optical Resolution of (±)-1a via the Phosphate Esters (*R*)- and (*S*)-5. To a stirred solution of (±)-**1a** (33.7 g, 67.7 mmol) in CH_2Cl_2 (100 mL) was added dropwise $POCl_3$ (16 mL, 171.7 mmol) followed by NEt_3 (25 mL, 179.2 mmol). The solution began to reflux gently and stirring was continued at 20 °C for 1 h, after which the reaction mixture was poured into ice–water (200 mL). After phase separation, the organic solution was washed with H_2O (2 × 100 mL) and the solvent removed *in vacuo*. The residue was refluxed for 2 h in THF/H_2O (300 mL) and the resulting solution extracted with $CH_3COOC_2H_5$ (3 × 100 mL). The combined organic phases were combined and washed with H_2O (100 mL) and saturated aqueous NaCl solution (100 mL). Workup yielded (±)-**5** (36.7 g, 97%) of sufficient purity for optical resolution: ^1H NMR (200 MHz, $CDCl_3$) δ 4.58 (s, 4 H), 6.73 (d, J = 2.4, 2 H), 7.03 (m, 4 H), 7.18 (m, 8 H), 7.35 (d, J = 8.7, 2 H), 7.78 (d, J = 8.7, 2 H), 7.71 (d, J = 8.7, 2 H); FAB-MS (*m*-nitrobenzyl alcohol) 561 ([M^+ + H]; $C_{34}H_{26}PO_6$).

A solution of (±)-**5** (27.1 g, 48.4 mmol) and cinchonine (14.3 g, 48.6 mmol) in boiling C_2H_5OH (300 mL) was prepared and subsequently cooled down slowly, which led to the precipitation of the (−)-**5**-cinchonine salt (16.5 g) as a beige solid. The mother liquor was reduced in volume to yield an additional 3.7 g of the salt. The solids were combined and recrystallized from C_2H_5OH/H_2O (4:1) to yield the pure (−)-**5**·cinchonine salt (12.1 g, 59%), $[\alpha]^{21}_{589}$ = −279.5° (*c* 1.0, $CHCl_3$). A similar resolution with cinchonidine yielded the (+)-**5**·cinchonidine salt, $[\alpha]^{21}_{589}$ = +274.9° (*c* 1.0, $CHCl_3$).

The (−)-**5**·cinchonine salt (12 g, 14 mmol) was dissolved in $CHCl_3$ (200 mL) and extracted with 6 N HCl (3 × 75 mL). The organic phase was washed with water (100 mL) and workup yielded (−)-**5** (7.9 g, 100%, $[\alpha]^{23}_{589}$ = −440.9° (*c* 1.0, $CHCl_3$) which was dissolved in THF (150 mL). To the cooled solution (0 °C) of (−)-**5** (6.0 g, 10.7 mmol) in THF (150 mmol) was added $LiAlH_4$ (2 g, 50 mmol) in small portions. After refluxing for 2 h, the mixture was cooled to 0 °C and water was carefully added. Following exhaustive extraction of the formed slurry with $CH_3COOC_2H_5$, the combined organic phases were washed with saturated aqueous NaCl solution (100 mL) and worked up: 5.05 g (95%) of (−)-**1a**, $[\alpha]^{21}_{589}$ = −232.0° (*c* 1.0, $CHCl_3$). A similar procedure starting from the (+)-**5**·cinchonidine salt gave (+)-**5** (55%) ($[\alpha]^{21}_{589}$ = +438.6° (*c* 1.0, $CHCl_3$)) and then (+)-**1a** (96%) ($[\alpha]^{21}_{589}$ = +229.2° (*c* 1.0, $CHCl_3$).

Optical Resolution of (±)-1a through Clathrate Formation with Quinine and Quinidine. Quinine (18.1 g, 0.057 mol) and (±)-**1a** (24.6 g, 0.049 mol) were dissolved in boiling C_2H_5OH (600 mL). On cooling, the (−)-**1a**·quinine complex (14.5 g) precipitated out and was collected and dried at 0.5 Torr. Recrystallization from C_2H_5OH (500 mL) yielded the pure complex (^1H NMR, 14.3 g) which was dissolved in $CHCl_3$ (300 mL). Quinine was removed by extraction with 2 N HCl (3 × 250 mL). The aqueous layers were combined and extracted with $CHCl_3$; the combined organic layers washed with H_2O (300 mL) and worked up: (−)-**1a** (9.3 g, 38% based on (±)-**1a**, >99% ee). The mother liquor of the initial recrystallization, which was enriched in (+)-**1a**, was evaporated, the residue taken up in $CHCl_3$, and the remaining quinine removed by extraction with 2 N HCl. The aqueous layers were combined and extracted with $CHCl_3$, and the combined organic layers were washed with H_2O and worked up to yield enriched (+)-**1a** (10.7 g, 0.021 mol). This material together with quinidine (6.56 g, 0.021 mol) was suspended in hexane (200 mL) and the solution brought to reflux. *n*-Butanol was added dropwise until complete dissolution (≈60 mL), slow cooling, and subsequent standing in the freezer at −30 °C afforded the (+)-**1a**·quinidine complex. Two recrystallizations of the clathrate from the same solvent yielded the pure diastereomeric complex from which the alkaloid was freed as described above for quinine. Workup yielded (+)-**1a** (7.38 g, 30% based on (±)-**1a**, 99% ee).

Preparation of the Mosher's Ester of (−)-1a.[25] To a stirred solution of (−)-**1a** (10 mg, 0.020 mmol) and MTPA (22 mg, 0.095 mmol) in dry CH_2Cl_2 (3 mL) were added DMAP (10 mg, 0.082 mmol) and DCC (40 mg, 0.20 mmol). After refluxing for 2 h, the mixture was cooled and the formed dicyclohexylurea was removed by filtration. The solution was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (2 × 10 mL), 5% CH_3COOH (2 × 10 mL), and H_2O (2 × 10 mL). Workup yielded the Mosher's ester as colorless crystals: ^1H NMR (500 MHz, $CDCl_3$) δ 2.97 (s, 6 H, α-OCH_3), 4.64 and 4.79 (AB, J = 11.5, 4 H), 6.55 (d, J = 2.4, 2 H, H(8)), 7.10 (dd, J = 9.0 and 2.4, 2 H), 7.15–7.25 (m, 22 H), 7.81 (d, J = 9.0, 2 H), 7.87 (d, J = 9.0 Hz, 2 H). When the Mosher's ester of (±)-**1a** was prepared, two sets of signals for the protons α-OCH_3 (2.79 and 2.97 ppm) and H(8) (6.55 and 6.60 ppm), respectively, were visible in the ^1H NMR spectrum.

(−)-7,7′-Dihydroxy-1,1′-binaphthyl-2,2′-diyl Hydrogen Phosphate ((−)-6). To a stirred suspension of (−)-**5** (0.50 g, 0.89 mmol) in dry CH_3OH (7 mL) was added 5% Pd/C (0.21 g, 0.10 mmol) followed by $NH_4^+HCOO^-$ (0.98 g, 15.5 mmol), and the

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(35) Tam-Chang, S.-W.; Jimenez, L.; Diederich, F. *Helv. Chim. Acta* **1993**, *76*, 2616–2639.

mixture was refluxed for 1 h. Filtration through Celite with CH_3OH and solvent evaporation yielded (−)-**6** (0.30 g, 90%) as a colorless foam: $[\alpha]^{21}_{589}$ = −576.0° (*c* 1.0, CH_3OH); ^1H NMR (360 MHz, $(CD_3)_2SO$) δ 3.15 (s, 3 H), 6.56 (d, *J* = 2.1, 2 H), 6.95 (dd, *J* = 9.0 and 2.1, 2 H), 7.10 (d, *J* = 9.0, 2 H); 7.80 (d, *J* = 9.0, 2 H), 7.83 (d, *J* = 9.0, 2 H); MS 380 (100, M^+); HRMS (M^+, $C_{20}H_{13}PO_6$) calcd 380.0450, obsd 380.0457.

(−)-7,7′-Dimethoxy-2,2′-dihydroxy-1,1′-binaphthyl ((−)-7). Methyl iodide (5 mL, 80.1 mmol) was added to a stirred solution of (−)-**6** (0.30 g, 0.79 mmol) and K_2CO_3 (1.1 g, 7.97 mmol) in DMF (5 mL), and the mixture was stirred at 50 °C for 4 d. Filtration through a pad of Celite, washing the pad with CH_3OH (2 × 25 mL) and removal of the solvents *in vacuo* yielded (−)-7,7′-dimethoxy-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate (0.32 g, 100%) as a brownish foam which was used in the next step without further purification: ^1H NMR (200 MHz, $CDCl_3$) δ 3.39 (s, 6 H), 6.65 (d, *J* = 2.1, 2 H), 7.06 (dd, *J* = 9.0 and 2.1, 2 H), 7.57 (d, *J* = 9.0, 2 H), 7.72 (d, *J* = 9.0, 2 H), 7.79 (d, *J* = 9.0, 2 H). The crude phosphate (0.38 g, 0.93 mmol) was dissolved in dry THF and $LiAlH_4$ (1.0 g, 26.0 mmol) was added in small portions. After refluxing for 2 h, the mixture was cooled to 0 °C and 2 N HCl was carefully added. Extraction with Et_2O (2 × 50 mL) and workup followed by flash chromatography (SiO_2, CH_2Cl_2) gave (−)-7 (100 mg, 31%) as a white solid: mp 149–151 °C (lit.[26] mp 151–152 °C); $[\alpha]^{21}_{589}$ = −126.4° (*c*, 1.0, CH_3OH); ^1H NMR (200 MHz, CD_3COCD_3) δ 2.81 (br s, 2 H), 3.49 (s, 6 H), 6.49 (d, *J* = 2.1, 2 H), 6.95 (dd, *J* = 9.0 and 2.1, 2 H), 7.16 (d, *J* = 9.0, 2 H), 7.78 (d, *J* = 9.0, 2 H), 7.81 (d, *J* = 9.0, 2 H); HRMS (*M*$^+$, $C_{22}H_{18}O_4$) calcd 346.1205, obsd 346.1205. Anal. Calcd for $C_{22}H_{18}O_4$ (346.3): C, 76.29; H, 5.24. Found: C, 76.37; H, 5.21.

(*R*)-(−)-7,7′-Bis(benzyloxy)-2,2′-dimethoxy-1,1′-binaphthyl ((*R*)-(−)-1b). A solution of (−)-**1a** (0.99 g, 1.98 mmol), K_2CO_3 (0.80 g, 5.8 mmol), and CH_3I (2.5 mL, 40.0 mmol) in DMF (50 mL) was stirred at 50 °C for 24 h. Filtration through a pad of Celite, washing the pad with $CH_3COOC_2H_5$ (2 × 25 mL), and evaporation of the solvent gave a solid which was redissolved in $CH_3COOC_2H_5$ (25 mL) and washed with 2 N HCl (2 × 25 mL). The aqueous phase was extracted with $CH_3COOC_2H_5$ (2 × 25 mL) and the combined organic layers were worked up to yield, after recrystallization from CH_3OH, (−)-**1b** (0.92 g, 88%) as a white solid: mp 119–121 °C; $[\alpha]^{21}_{589}$ = −129.7° (*c*, 1.0, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 3.66 (s, 6 H), 4.69 (s, 4 H), 6.43 (d, *J* = 2.1, 2 H), 7.06 (dd, *J* = 9.0 and 2.1, 2 H), 7.10–7.15 (m, 4 H), 7.15–7.20 (m, 6 H), 7.26 (d, *J* = 9.0, 2 H), 7.77 (d, *J* = 9.0, 2 H), 7.88 (d, *J* = 9.0, 2 H); MS 526 (100, M^+); HRMS (M^+, $C_{36}H_{30}O_4$) calcd 526.2144, obsd 526.2130. Anal. Calcd for $C_{36}H_{30}O_4$ (526.2); C, 82.11; H, 5.74. Found: C, 81.80; H, 5.46. (*S*)-(+)-**1b** $[\alpha]^{21}_{589}$ = +125.6° (*c* 1.0, $CHCl_3$) was prepared in the same way starting from (+)-**1a**.

(*R*)-(−)-7,7′-Bis(benzyloxy)-2-hydroxy-2′-methoxy-1,1′-binaphthyl ((*R*)-(−)-1c. To a mixture of (−)-**1a** (0.075 g, 0.14 mmol) and K_2CO_3 (0.041 g, 0.30 mmol) in CH_3CN (8 mL) at 45 °C was added a solution of CH_3I (0.028 mL, 0.45 mmol) in CH_3CN (2 mL) over a 10-h period via syringe pump. After refluxing for 6 h, the mixture was filtered through a pad of Celite, the Celite was washed with boiling $CH_3COOC_2H_5$ (2 × 15 mL), and the solvents were evaporated. The residue, consisting of a mixture of (−)-**1b** and (−)-**1c**, was chromatographed (SiO_2, $CH_3COOC_2H_5$/hexane (15:85) to yield (−)-**1c** as a light yellow oil (48 mg, 63%): $[\alpha]^{21}_{589}$ = −196.4° (*c*, 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.72 (s, 3 H), 4.73 (AB, *J* = 12.0, 4 H), 4.85 (s, 1 H), 6.41 (d, *J* = 2.5, 1 H), 6.52 (d, *J* = 2.5, 1 H), 7.0–7.3 (m, 14 H), 7.7-8.0 (m, 4 H); HRMS (M^+, $C_{35}H_{28}O_4$) calcd 512.1988, obsd 512.1989. (*S*)-(+)-**1c**, $[\alpha]^{21}_{589}$ = +190.5° (*c* 1.0, $CHCl_3$), was prepared in the same way from (+)-**1a**.

(*R*)-(−)-7,7′-Dihydroxy-2,2′-dimethoxy-1,1′-binaphthyl ((*R*)-(−)-1d). A mixture of (*R*)-(−)-**1b** (0.30 g, 0.57 mmol), 5% Pd/C (0.17 g, 0.08 mmol), and $NH_4^+HCOO^-$ (0.85 g, 13.49 mmol) in dry CH_3OH (10 mL) was refluxed for 1 h. Filtration through a pad of Celite, washing the Celite with CH_3OH (2 × 25 mL), and removal of the solvent yielded (*R*)-(−)-**1d** as a white solid which was recrystallized from CH_3OH: 0.122 g (62%), mp 210–212 °C, dec; $[\alpha]^{21}_{589}$ = −46.6° (*c* 1.0, DMF); ^1H NMR (360 MHz, $CDCl_3$) δ 3.75 (s, 6 H), 4.83 (s, 2 H), 6.35 (d, *J* = 2.1, 2 H), 6.92 (dd, *J* = 9.0 and 2.1, 2 H), 7.27 (d, *J* = 9.0, 2 H), 7.75 (d, *J* = 9.0, 2 H), 7.87 (d, *J* = 9.0, 2 H); HRMS (M^+, $C_{22}H_{18}O_4$) calcd 346.1205, obsd 346.1217. Anal. Calcd for $C_{22}H_{18}O_4$ (346.4): C, 76.29; H, 5.24. Found: C. 76.37; H, 5.21. (*S*)-(+)-**1d**, $[\alpha]^{21}_{589}$ = +45.9° (*c*, 1.0, DMF), was prepared in the same way from (+)-**1b**.

(*R*)-(−)-7′-Mono(benzyloxy)-7′-monohydroxy-2,2′-dimethoxy-1,1′-binaphthyl ((*R*)-(−)-1f). A mixture of (*R*)-(−)-**1b** (0.22 g, 0.42 mmol), 5% Pd/C (0.030 g, 0.014 mmol), and $NH_4^+HCOO^-$ (0.50 g, 7.9 mmol) in dry CH_3OH (10 mL) was refluxed for 5 min. Filtration of the hot solution through a pad of Celite, washing the Celite with $CHCl_3$ (4 × 25 mL), and removal of the solvent yielded a mixture of starting material, (*R*)-(−)-**1d**, and (*R*)-(−)-**1f**, which was chromatographed (SiO_2, $CHCl_3$ then $CHCl_3/CH_3OH$, 8:1) to yield (*R*)-(−)-**1f** (55 mg, 31%): mp 168–170 °C (CH_3OH); $[\alpha]^{21}_{589}$ = −112.5° (*c* 1.0, $CHCl_3$); ^1H NMR (360 MHz, $CDCl_3$) δ 3.68 (s, 3 H), 3.75 (s, 3 H), 4.65 (s, 2 H), 6.43 (d, *J* = 2.1, 1 H), 6.45 (d, *J* = 2.1, 1 H), 6.95 (dd, *J* = 9.0 and 2.1, 1 H), 7.05 (dd, *J* = 9.0 and 2.1, 1 H), 7.10–7.15 (m, 2 H), 7.19–7.21 (m, 3 H), 7.27 (d, *J* = 9.0, 1 H), 7.28 (d, *J* = 9.0, 1 H), 7.76 (d, *J* = 9.0, 1 H), 7.78 (d, *J* = 9.0, 1 H), 7.87 (d, *J* = 9.0, 1 H), 7.89 (d, *J* = 9.0, 1 H); MS 436 (100, M^+); HRMS (M^+, $C_{29}H_{24}O_4$) calcd 436.1675, obsd 436.1671. (*S*)-(+)-**1f**, $[\alpha]^{21}_{589}$ = +113.3° (*c* 1.0, $CHCl_3$), was prepared in the same way from (+)-**1b**.

(*R*)-(−)-7,7′-Bis(benzyloxy)-2,2′-bis(dodecyloxy)-1,1′-binaphthyl ((*R*)-(−)-8). A solution of (−)-**1a** (0.074 g, 0.15 mmol), K_2CO_3 (0.18 g, 1.30 mmol), and 1-iodododecane (0.255 mL, 1.03 mmol) was refluxed in dry CH_3CN (5.7 mL) for 16 h. Filtration through a pad of Celite, washing the Celite with boiling $CH_3COOC_2H_5$ (2 × 15 mL), and removal of the solvents yielded (−)-**8**, which was chromatographed (SiO_2, hexane then $CH_3COOC_2H_5$/hexane, 2:8) to afford a light yellow oil (80 mg, 65%): $[\alpha]^{21}_{589}$ = −47.0° (*c* 1.1, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.7–1.6 (m, 46 H), 3.6–4.0 (m, 4 H), 4.70 (s, 4 H), 6.49 (d, *J* = 2.1, 2 H), 7.04 (dd, *J* = 9.0 and 2.1, 2 H), 7.1–7.3 (m, 12 H), 7.74 (d, *J* = 9.0, 2 H), 7.82 (d, *J* = 9.0, 2 H); HRMS (M^+, $C_{58}H_{74}O_4$) calcd 834.5587, obsd 834.5615. Anal. Calcd for $C_{58}H_{74}O_4$ (835.2): C, 83.41; H, 8.93. Found: C, 82.63; H, 9.17. (*S*)-(+)-**8**, $[\alpha]^{21}_{589}$ = +46.0° (*c* 1.0, $CHCl_3$), was prepared in the same way from (+)-**1a**.

(*R*)-(−)-2,2′-Bis(dodecyloxy)-7,7′-dihydroxy-1,1′-binaphthyl ((*R*)-(−)-1e). A mixture of (−)-**8** (0.074 g, 0.089 mmol), 5% Pd/C (0.035 g, 0.016 mmol), and $NH_4^+HCOO^-$ (0.205 g, 3.25 mmol) in dry THF (4.5 mL) was refluxed for 30 min. Filtration through a pad of Celite, washing the Celite with boiling $CH_3COOC_2H_5$ (2 × 15 mL), and removal of the solvent yielded (−)-**1e** as a light pink oil (50 mg, 86%): $[\alpha]^{21}_{589}$ = −28.2° (*c* 1.6, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) 0.80–1.60 (m, 46 H), 3.8–4.0 (m, 4 H), 4.61 (s, 2 H), 6.41 (d, *J* = 2.5, 2 H), 6.92 (dd, *J* = 8.8 and 2.5, 2 H), 7.22 (d, *J* = 8.8, 2 H) 7.74 (d, *J* = 8.8, 2 H) 7.83 (d, *J* = 8.8, 2 H); HRMS (M^+, $C_{44}H_{62}O_4$) calcd 654.4648, obsd 654.4640. Anal. Calcd for $C_{44}H_{62}O_4$ (655.0): C, 80.69; H, 9.59. Found: C, 80.87; H, 9.69. (*S*)-(+)-**1e**, $[\alpha]^{21}_{589}$ = +27.1° (*c* 1.6, $CHCl_3$), was prepared in the same way from (+)-**8**.

(*R*)-(−)-7,7′-(Benzyloxy)-2,2′-bis(dodecyloxy)-7′-hydroxy-1,1′-binaphthyl ((*R*)-(−)-1g). To a mixture of (−)-**1e** (0.032 g, 0.049 mmol) and K_2CO_3 (0.014 g, 0.098 mmol) in CH_3CN (2.6 mL) at reflux was added a solution of benzyl chloride (0.004 mL, 0.034 mmol) in CH_3CN (0.650 mL) over a 5-h period via syringe pump. The reaction mixture was then refluxed for 3 h. Filtration through a pad of Celite, washing the Celite with boiling $CH_3COOC_2H_5$ (2 × 15 mL), and removal of the solvent yielded a mixture of (−)-**1g** and (−)-**8** which was chromatographed (SiO_2, $CH_3COOC_2H_5$/hexane, 15:85) to yield (−)-**1g** as a yellow oil (18 mg, 50%): $[\alpha]^{21}_{589}$ = −32.0° (*c*, 0.126, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 0.8–1.6 (m, 46 H), 3.7–4.0 (m, 4 H), 4.6 (br s, 1 H), 4.74 (s, 2 H), 6.38 (d, *J* = 2.5, 1 H), 6.51 (d, 2.5, 1 H), 6.93 (dd, *J* = 9.0 and 2.5, 1 H), 7.03 (dd, *J* = 9.0 and 2.5, 1 H), 7.1–7.3 (m, 7 H), 7.7–7.9 (m, 4 H); HRMS (M^+, $C_{51}H_{68}O_4$) calcd 744.5118, obsd 744.5136. Anal. Calcd for $C_{51}H_{68}O_4$ (745.1): C, 82.21; H, 9.20. Found: C, 81.99; H, 9.20. (*S*)-(+)-**1g**, $[\alpha]^{21}_{589}$ = +30.8° (*c* 0.126, $CHCl_3$), was prepared in the same way from (+)-**1e**.

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