

113. Analogs of *Cinchona* Alkaloids Incorporating a 9,9'-Spirobifluorene Moiety

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Dedicated to Professor *Vladimir Prelog* on the occasion of his 90th birthday

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The *Cinchona* alkaloid analogs (+)- and (–)-**5** with a quinuclidine-2-methanol residue attached to C(2) of a 9,9'-spirobifluorene moiety were prepared as a racemic mixture by reacting lithiated 2-bromo-9,9'-spirobifluorene **7** with (2-ethoxycarbonyl)quinuclidine (±)-**6** to give ketone (±)-**8**, followed by diastereoselective reduction with diisobutylaluminum hydride (DIBAL-H). The absolute configuration at C(9) and C(8), *i.e.*, at the methanol bridge and the adjacent quinuclidine C-atom, in the two enantiomers of **5** is identical to the configuration at the corresponding centers in (–)-quinine (**1**) and (+)-quinidine (**2**), respectively. For the optical resolution of (±)-**5**, a chiral stationary phase for HPLC was prepared by covalently bonding quinine *via* a thiol spacer to a silica-gel surface. The enantiomer separation was accomplished at an α value of 1.61 with (±)-**5** being eluted last, in agreement with ¹H-NMR studies in CDCl₃ which showed that (+)-**5** underwent a more stable host-guest association with quinine than (–)-**5**. ¹H{¹H} Nuclear Overhauser effect (NOE) difference spectroscopical analysis of the host-guest associations with quinine in CDCl₃, combined with computer-model examinations, allowed the assignment of the absolute configurations as (+)-(8*R*,9*S*)-**5** and (–)-(8*S*,9*R*)-**5**. A detailed conformational analysis displayed excellent agreement between the results of computational methods (Monte Carlo multiple minimum simulations, analyses of the total energy as a function of the flexible dihedral angles in the molecule) and ¹H{¹H}-NOE difference spectroscopical data. It was found that (–)-**5** and (+)-**5** differ significantly in their conformational preference from their natural counterparts quinine (**1**) and quinidine (**2**). Whereas the natural alkaloids prefer the 'open' conformation, with the quinuclidine N-atom pointing away from the quinoline ring, analog (±)-**5** adopts preferentially (by *ca.* 4 kcal mol^{–1}) a 'closed' conformation, in which the quinuclidine N-atom points into the cleft of the 9,9'-spirobifluorene moiety. Since the basic quinuclidine N-atom in the 'closed' conformation is sterically shielded from forming strong H-bonds, the new *Cinchona* alkaloid analogs form less stable host-guest associations *via* H-bonding than quinine or quinidine.

1. Introduction. – *Cinchona* alkaloids [**1**] such as quinine (**1**) and quinidine (**2**) represent some of the most widely used molecular shapes in enantiomer separations [2–7] and asymmetric catalysis [8–17]. Their absolute configurations were determined in the 1940s by *Prelog et al.* [18], and *Wynberg, Kellogg*, and coworkers undertook a detailed conformational analysis in the late 1980s [19], which showed that these alkaloids prefer an 'open' conformation in solution, in which the quinuclidine N-atom is oriented away from the quinoline moiety, over a 'closed' conformation, in which this N-atom points into the aromatic ring (*Fig. 1*). In our chiral recognition studies [20] [21] with H-bonding receptors [22], we previously explored the molecular recognition properties of quinine and quinidine, and observed enantioselective complexation of 1,1'-binaphthyls bearing OH

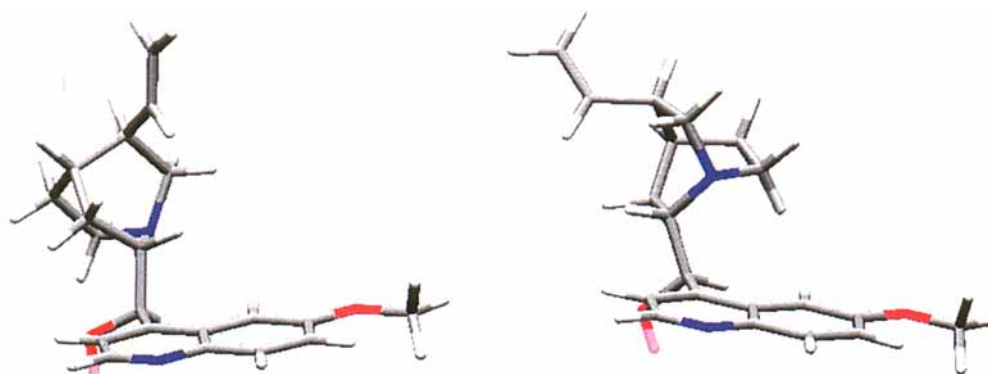
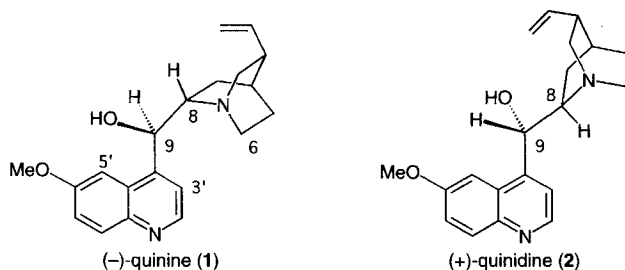
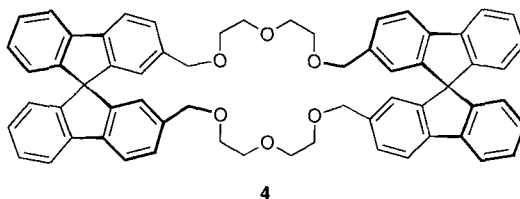
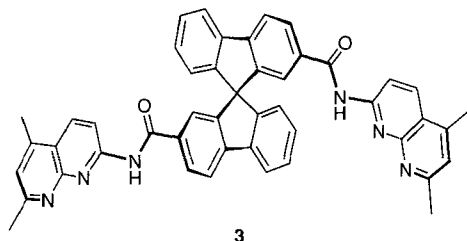


Fig. 1. The natural *Cinchona* alkaloids quinine (1) and quinidine (2) prefer the 'open' conformation (left, shown for quinine) with the quinuclidine *N*-atom pointing away from the quinoline ring over the 'closed' conformation (right) with this *N*-atom pointing towards the aromatic ring ([19])

groups at the 2,2'- (at the minor groove of the 1,1'-binaphthyl cleft) or the 7,7'-positions (at the major groove) [3]. These complexes were stabilized by H-bonds under participation of both the OH group (as a donor) and the quinuclidine *N*-atom (as an acceptor) of the alkaloids as well as by aromatic-aromatic interactions involving their quinoline ring.

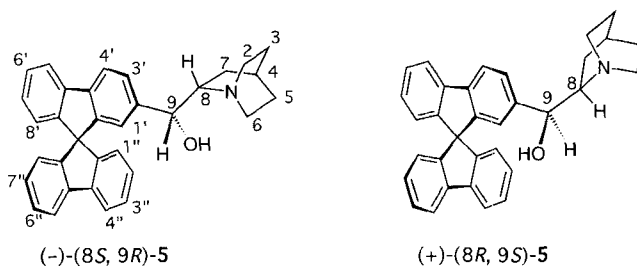
As part of this program, we also prepared chiral H-bonding molecular clefts such as **3**, incorporating 9,9'-spirobifluorene derivatives as rigid molecular spacers [21], and observed high binding strength and significant enantioselection in the complexation of pyranosides and derivatives of excitatory amino acids [21d]. Substituted 9,9'-spirobifluorenes were first introduced into synthetic receptors by *Prelog* and coworkers, who prepared optically active crown ethers such as **4**, incorporating these rigid chiral spacers, and demonstrated their ability to complex amino-acid esters with high enantioselection [23].

In view of the strong performance of both *Cinchona* alkaloids and 9,9'-spirobifluorene derivatives as molecular recognition shapes, we decided to combine both classes of compounds and prepare new analogs of the *Cinchona* alkaloids in which a 9,9'-spirobifluorene moiety replaces the natural quinoline unit. We expected not only enhanced and different receptor properties from such compounds but also felt encouraged in our endeavors by the eminently successful modifications of *Cinchona* alkaloids by *Sharpless* and coworkers for use as ligands in the catalytic asymmetric osmylation reaction [17].



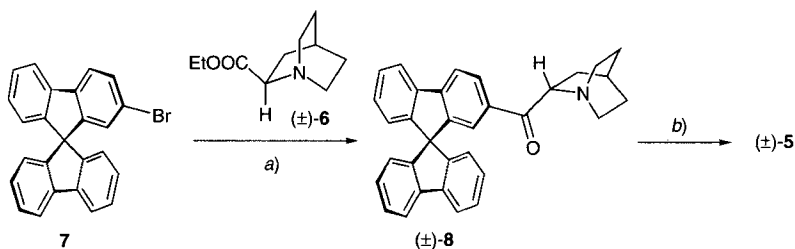
Here, we report the synthesis of the pair of enantiomers $(-)-(8S,9R)$ -**5** and $(+)-(8R,9S)$ -**5** with the same configuration at C(9) and C(8), *i.e.*, at the methanol bridge and the adjacent quinuclidine C-atom, as in $(-)$ -quinine (**1**) and $(+)$ -quinidine (**2**), respectively. We describe the separation of the two enantiomers of **5** on a chiral stationary phase consisting of silica-gel-bound quinine [7], the determination of their absolute configuration based on differential molecular association with quinine in CHCl_3 , a detailed conformational analysis, and an evaluation of their receptor properties.

2. Results and Discussion. – 2.1. *Synthesis of Cinchona Alkaloid Analogs with 9,9'-Spirobifluorene Moieties.* Following the first preparations of *Cinchona* alkaloids by *Rabe* and coworkers between 1910 and 1930 [24], and the first total synthesis of quinine by *Woodward* and *Doering* in 1944 [25], a variety of syntheses for this pharmacologically interesting [1] class of natural products had been developed [26–29]. Among the various protocols, a route developed by *Uskokovic* and coworkers [29d] showed the most promise for the preparation of target compound $(\pm)$ -**5**. Following this procedure, we intended to react quinuclidine ester $(\pm)$ -**6** with lithiated 2-bromo-9,9'-spirobifluorene **7** to yield the



The arbitrary numbering corresponds to that in use for the natural *Cinchona* alkaloids quinine and quinidine (see Fig. 1).

corresponding ketone ($\pm$)-**8** (Scheme 1). Reduction of ($\pm$)-**8** with diisobutylaluminum hydride (DIBAL-H) was expected to yield exclusively the *erythro*-pair of enantiomers ($\pm$)-**5** in analogy to the diastereoselective reduction of quinone and quinidine to give quinine and quinidine, respectively [27b]. In this reaction, the Lewis-acidic Al-atom would coordinate to the quinuclidine N-atom, and hydride transfer from the *Si*-face of the C=O group in (*S*)-**8** would yield the (8*S*,9*R*)-isomer, whereas transfer from the *Re*-face in (*R*)-**8** would afford the (8*R*,9*S*)-enantiomer.

Scheme 1. Synthesis of ($\pm$)-**5**

a) *t*-BuLi, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), THF, -78° , 4 h, 35%. *b*) DIBAL-H, toluene, room temperature, 2 h, 83%.

On the way to ($\pm$)-**5**, 2-bromo-9,9'-spirobifluorene (**7**) was obtained in 78% yield by reacting 2-bromofluoren-9-one [30] with the *Grignard* reagent prepared from 2-iodo-1,1'-biphenyl [31]. Quinuclidine ester ($\pm$)-**6** was prepared in a seven-step synthesis starting from pyridine-4-carbaldehyde according to procedures by *Langström* [32] and *Bulacinski* [33]. Compound ($\pm$)-**6** was obtained, as described, as a colorless liquid, but after storage for two years at room temperature, some large and very pretty crystals of dimensions up to $5 \times 4 \times 1$ mm had formed. The X-ray structural analysis rapidly demonstrated that these crystals consisted of monohydrated quinuclidine-2-carboxylic acid ($\pm$)-**9** which presumably had formed by partial hydrolysis of ester ($\pm$)-**6**. Apparently, ($\pm$)-**6** is hygroscopic and attracts moisture from the atmosphere. The molecular structure showed that proton transfer had occurred, and that ($\pm$)-**9** was present in its zwitterionic form (Fig. 2, *a*). The space group *C2/c* indicated that the crystal is a racemate. Identical enantiomers of **9** form dimers (Fig. 2, *b*) which are stabilized by two ionic $\text{CO}^{-} \cdots \text{H}-\text{N}^{+}$ H-bonds ($\text{O} \cdots \text{N}$ distance 2.71 Å) orienting into the direction of the *anti* lone pairs of the carboxylate O-atoms. Dimers formed by identical enantiomers are linked together in a *zig-zag* fashion through H-bonding to the H_2O molecules in the crystal. The two nearly linear $\text{CO}^{-} \cdots \text{H}-\text{O}$ H-bonds ($\text{O} \cdots \text{O}$ distance 2.85 Å) between two dimers and one H_2O molecule are oriented into the direction of the *syn* lone pairs of the two carboxyl O-atoms that participate in the H-bonding array of the dimers (Fig. 2, *c*). The crystal packing shows infinite parallel chains of H_2O -bridged dimers. Each chain is composed of identical enantiomers, and the chirality of the zwitterionic molecules alternates in a regular fashion from chain to chain.

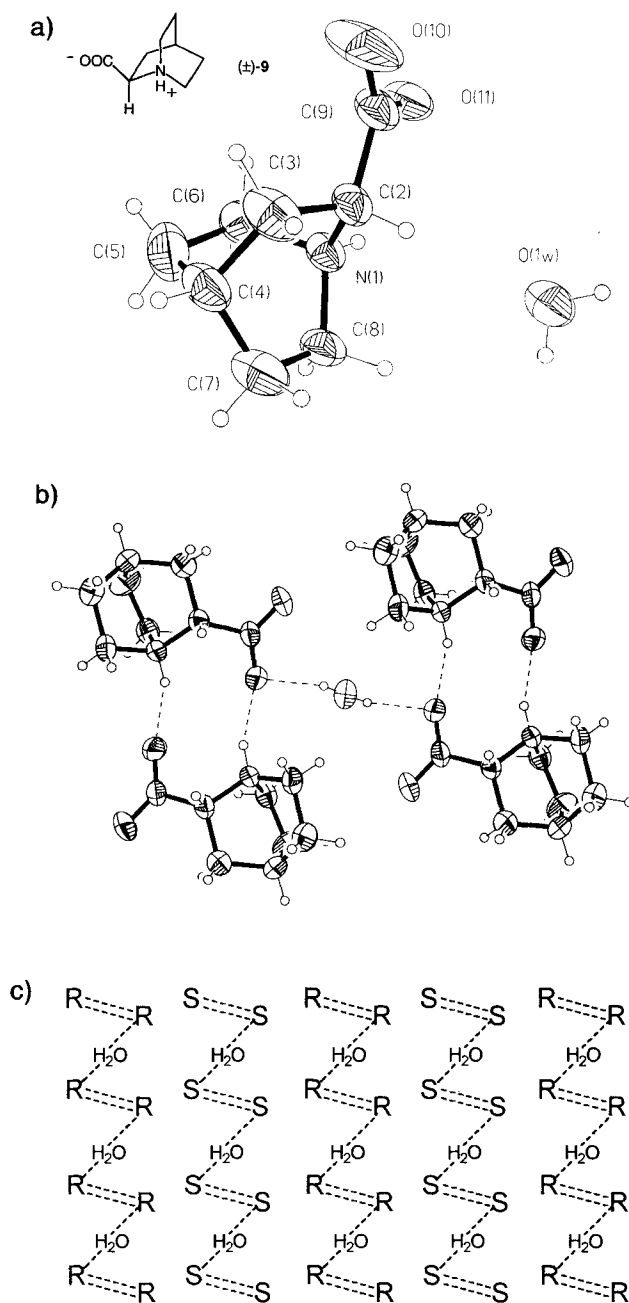
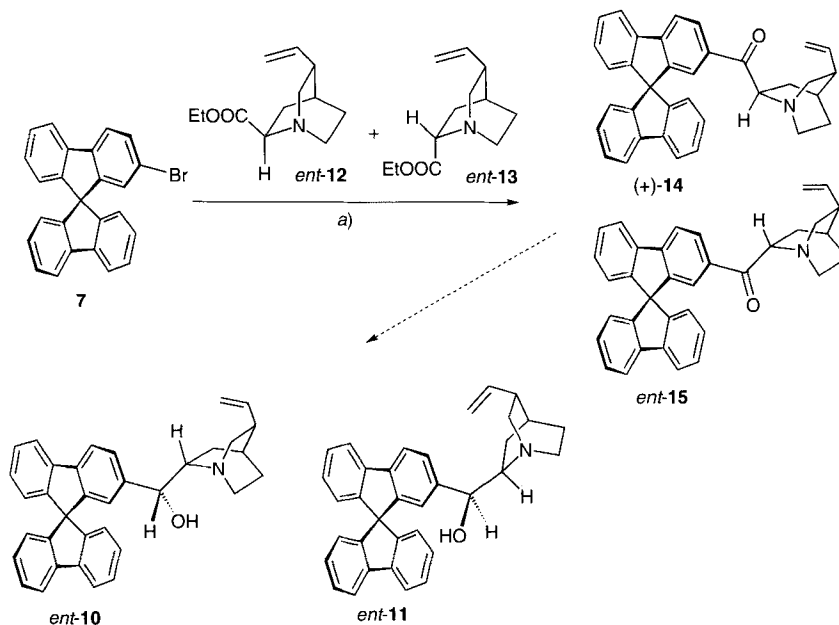


Fig. 2. a) Molecular structure of monohydrated ($\pm$)-9. Arbitrary numbering. b) View of the crystal structure showing the H_2O molecule which bridges two dimers formed by identical enantiomers. c) Schematic depiction of the infinite chains formed by H_2O -bridged dimers in the crystal. Each chain is formed by one enantiomer, and the chirality of the quinuclidine-carboxylic acid alternates between parallel chains.

Lithiated **7** was reacted with ester ($\pm$)-**6** to give ketone ($\pm$)-**8** in 35% yield. Reduction of ($\pm$)-**8** with DIBAL-H in toluene at room temperature proceeded with complete diastereoselection ($^1\text{H-NMR}$) and provided in 83% yield the *erythro*-pair of enantiomers (8*S*,9*R*)-**5** and (8*R*,9*S*)-**5**.

Parallel to the synthesis of ($\pm$)-**5**, we also pursued the preparation of diastereoisomers *ent*-**10** and *ent*-**11** (Scheme 2) which more closely resemble quinine (**1**) and quinidine (**2**) by bearing an additional vinyl group at the quinuclidine moiety. The diastereoisomeric quinuclidine-ester precursors *ent*-**12** and *ent*-**13** were obtained by degradation of quinone following a procedure described by Woodward *et al.* [26a] and Evstigneeva *et al.* [34]. This multi-step transformation, which included oxidation of quinine to quinone, conversion of quinone into the corresponding *trans*-oxime, Beckmann rearrangement to the quinuclidine-carboxamide, amide hydrolysis, and esterification yielded *ent*-**12** together with *ent*-**13** (ca. 1:1 mixture) in 12% yield, a value close to the 14% reported in the literature [34] (Scheme 2). Although not entirely pure, *ent*-**12** and *ent*-**13** together were reacted on a small scale with lithiated **7** to afford a product mixture from which a single fraction could be isolated by chromatography as an oil in low yield (ca. 5%). Upon addition of hexane, the oil solidified overnight, affording, besides a powdery fraction, a few larger, regular crystals which were analyzed by X-ray crystallography. The crystals possess the non-centrosymmetrical space group $P2_12_12_1$, and, therefore, are chiral. They only contain one diastereoisomer (+)-**14** with the (*R*)-configuration at C(8) (Fig. 3, a). The dihedral angle C(1')–C(2')–C(9)–O is 178.2° , indicating near-coplanarity and full conjugation between

Scheme 2. Synthesis of (+)-**14**



a) *t*-BuLi, TMEDA, THF, -78° , 4 h, ca. 5%.

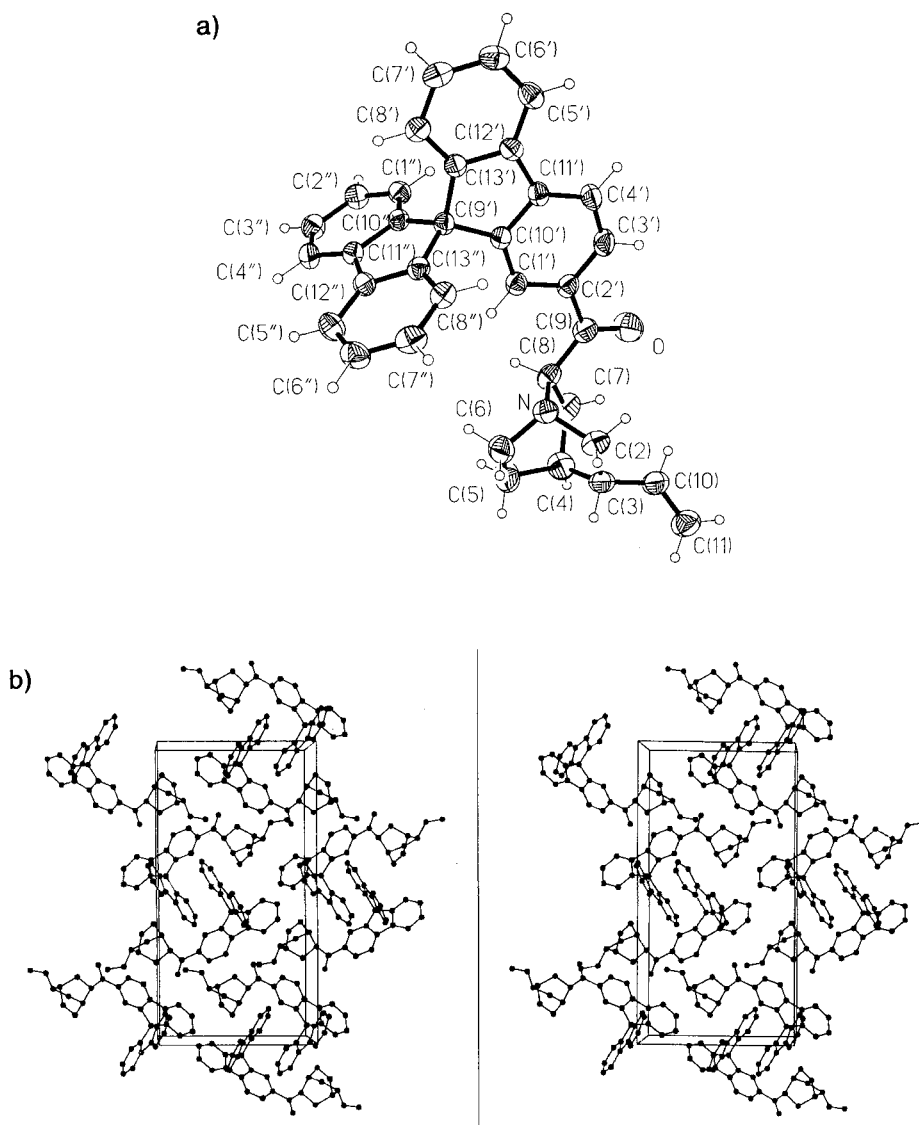


Fig. 3. a) Molecular structure of (+)-**14**. The numbering in use for *Cinchona* alkaloids is shown. b) Stereoview of the crystal packing of (+)-**14** showing the exclusive edge-to-face aromatic interactions between fluorene rings of neighboring molecules.

the C=O group and the adjacent fluorene ring. Molecules of (+)-**14** interact in the crystal exclusively *via* edge-to-face aromatic interactions involving both substituted and unsubstituted fluorene rings (Fig. 3, b).

Whereas the ^1H -NMR spectrum obtained by dissolution of the crystals was in agreement with the presence of pure diastereoisomer (+)-**14**, the number and complexity of the

resonances in the spectrum of the isolated powdery product fraction suggested that both diastereoisomers (+)-**14** and *ent*-**15** had formed and precipitated out. This was also indicated by measurements of the optical rotation: whereas pure crystals of (+)-**14** gave a specific rotation of $[\alpha]_D^{25} = +34.1$ ($c = 0.1$, $\text{CHCl}_3/\text{EtOH}$ 99:1), a different value of $[\alpha]_D^{25} = +51.2$ ($c = 0.25$, $\text{CHCl}_3/\text{EtOH}$ 99:1) was measured for the powder. In view of low yields in various steps, the synthesis of *ent*-**10** and *ent*-**11** was discontinued.

2.2. *Optical Resolution of ($\pm$)-5*. Enantiomer separation of ($\pm$)-**5** proved to be extremely difficult. Conventional methods such as diastereoisomeric-salt formation with chiral acids or covalent derivatization to diastereoisomeric esters or carbamates were unsuccessful [35]. Similarly, HPLC on a variety of commercial chiral stationary phases (CSPs) failed [36–38]¹⁾. Attempted TLC separations on reversed-phase silica gel with $\text{H}_2\text{O}/\text{MeCN}$ mixtures as eluent containing poly(hydroxypropyl)- β -cyclodextrin as chiral receptor [39] did not give positive results. Crystallization from optically active solvents was equally unsuccessful [40].

A preliminary molecular recognition study in solution by ^1H -NMR spectroscopy [3] ultimately showed the way towards a successful optical resolution of ($\pm$)-**5**. When quinine was added to a solution of ($\pm$)-**5** in CDCl_3 , differential interactions between the natural alkaloid and the two unnatural enantiomeric analogs became visible in the ^1H -NMR spectrum. Selected resonances of ($\pm$)-**5**, in particular the *doublet* of $\text{H}-\text{C}(9)$, appeared twice in the spectrum, which indicated formation of two diastereoisomeric associations, (+)-**5**·quinine and (–)-**5**·quinine. The difference in chemical shift between the two *doublets* for $\text{H}-\text{C}(9)$ was strongly dependent on the concentration of quinine. In a 0.2M solution of pure ($\pm$)-**5**, the *doublet* of $\text{H}-\text{C}(9)$ was measured at 4.615 ppm. Upon addition of 0.1M quinine, this resonance split into two *doublets* at 4.603 and 4.730 ppm. The two *doublets* appeared at 4.597 and 4.758 ppm in the presence of 0.2M quinine and at 4.593 and 4.803 ppm in the presence of excess quinine (1.0M). Clearly, only one *doublet* significantly shifted, whereas the second one was nearly unaffected by the presence of the chiral solvating agent. These differential changes in chemical shift suggested that diastereoisomeric associations of differential stabilities had formed [3]. Only one of the two complexes has significant stability, and the signal of $\text{H}-\text{C}(9)$ of the enantiomer of **5** in this complex is shifted downfield. The absence of any significant change in chemical shift of the second *doublet* suggests that the second complex is much less stable in the chosen concentration range. The second enantiomer of **5** is mainly present in unbound form, and its resonance for $\text{H}-\text{C}(9)$ remains essentially in the position seen for pure ($\pm$)-**5** (near 4.60 ppm).

Although diastereoisomeric complexes of differential stability apparently formed in solution, attempted enantiomer separations by chiral enclathration [3] [41] remained unsuccessful. Fractional crystallizations of mixtures of quinine and ($\pm$)-**5** from various solvents did not lead to enrichment of one of the two diastereoisomeric complexes. Therefore, we followed a protocol developed by *Salvadori* and coworkers [7] and prepared a chiral stationary phase consisting of silica-gel-bound quinine with the objective to resolve ($\pm$)-**5** by HPLC on this phase. First, (3-mercaptopropyl)trimethoxysilane was

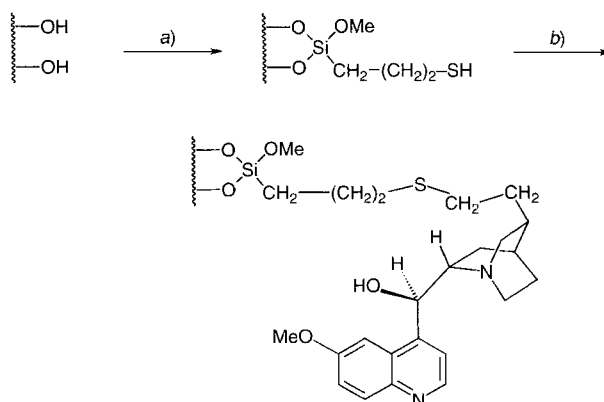
¹⁾ The following commercial CSPs were tried: *Chiracel OD-R* (cellulose carbamate reversed phase) and *Chiralcel OD* (cellulose carbamate) from *Daicel Chemical Industries Ltd.* (*J. T. Baker*); *Pirkle Covalent (S,S)-Whelk-O1* (spherical silica gel) from *Regis*; *Cyclobond I2000-SN* (spherical β -cyclodextrin) from *Alltech Associates, Inc.*

attached as a spacer to the surface of silica gel (*LiChrosorb Si60*, particle size 5 μm , *E. Merck*) (Scheme 3), then in a second step, quinine was bound to this spacer by radical chain addition of the thiol residue to the vinyl group of the alkaloid. A test of the performance of the new phase with $(\pm)$ -1-(9-anthryl)-2,2,2-trifluoroethanol gave a separation factor of $\alpha = 1.08$, compared to $\alpha = 1.11$ for the similar phase prepared by *Salvadori* and coworkers [7e]. The characterization of the modified silica gel according to *Berendsen* and *de Galan* [42] afforded for the degree of surface functionalization by spacer molecules a value of 1.36 mmol/g silica gel and for the amount of covalently bound quinine a value of 0.61 mmol/g or 1.22 $\mu\text{mol}/\text{m}^2$. Separations on an analytical column (25 cm $\times$ 7 mm internal diameter (ID)) (Fig. 4) demonstrated that the optical resolution of $(\pm)$ -5 was successful on the new phase: with hexane/ CH_2Cl_2 /EtOH 65:33:2 as eluent, a near-baseline separation with an α value of 1.61 was achieved. This α value is much larger than the best one ($\alpha = 1.16$) obtained in the separations on the quinine-derived CSP described in the literature [7].

In runs on a preparative HPLC column (25 cm $\times$ 2 cm ID), 12–15-mg quantities of the racemate could be separated affording 80–90% of each enantiomer with an ee value of $\sim 100\%$. Measurement of the optical rotation showed that $(-)$ -5 ($[\alpha]_{\text{D}}^{25} = -57.7^\circ$ ($c = 1.05$, $\text{CHCl}_3/\text{EtOH}$ 99:1)) was eluted first and thus interacted less efficiently with the silica-gel-bound quinine than $(+)$ -5 ($[\alpha]_{\text{D}}^{25} = +57.3^\circ$ ($c = 1.01$, $\text{CHCl}_3/\text{EtOH}$ 99:1)). A similar differential interaction can be assumed for the liquid phase, and we, therefore, assign the ^1H -NMR resonances of $(\pm)$ -5, that shift significantly in the presence of quinine (see above), to those in the diastereoisomeric complex $(+)$ -5·quinine. This assignment was confirmed by the ^1H -NMR spectra recorded from solutions containing only either pure $(+)$ - or $(-)$ -5 besides quinine.

2.3. *Conformational Analysis of 5*. As mentioned in the *Introduction*, the natural *Cinchona* alkaloids prefer in solution an ‘open’ conformation, with the quinuclidine N-atom turned away from the quinoline ring, over a ‘closed’ conformation, in which this N-atom points towards the aromatic surface. In the case of quinine (1), the ‘open’

Scheme 3. Chiral Stationary Phase Mode from Silica-Gel-Bound Quinine



a) 3-(Mercaptopropyl)trimethoxysilane, pyridine, toluene, 90°, 24 h. b) Quinine (1), α, α' -azobis[isobutyronitrile] (AIBN), CHCl_3 , 80°, 30 h.

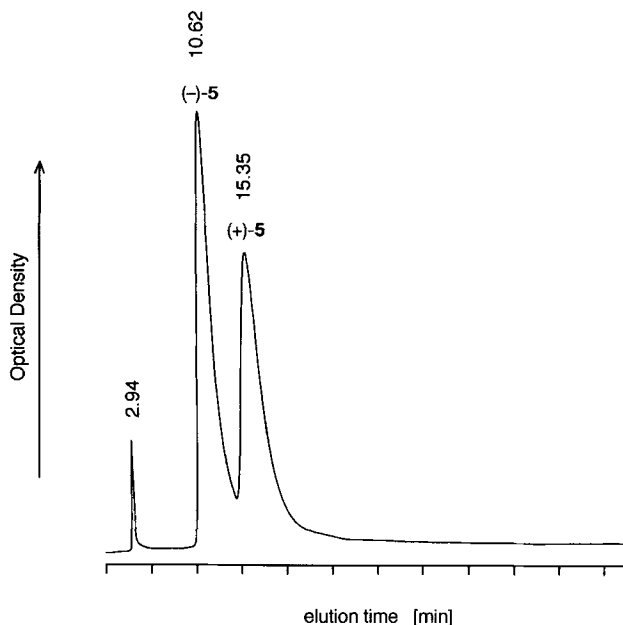


Fig. 4. Chromatographic optical resolution of $(\pm)$ -5 on an analytical column (25 cm $\times$ 7 mm ID) packed with a CSP made from silica-gel-bound quinine. Eluent: hexane/ CH_2Cl_2 /EtOH 95:33:2; flow rate: 1 ml min^{-1} , UV detection at 260 nm.

conformation is preferred by *ca.* 2 kcal mol^{-1} . The preference for the 'open' conformation is crucial for the performance of *Cinchona* alkaloids in molecular recognition or as ligands to metal ions, since this geometry allows the quinuclidine N-atom to undergo H-bonding or ligation in a sterically non-encumbered way. It was, therefore, of great interest to explore the conformational preference of the new unnatural analog $(\pm)$ -5.

2.3.1. Computational Studies. Computer simulations were performed on $(8S,9R)$ -5 with the AMBER* force field [43] in the program package MacroModel/BatchMin V. 4.0 [44] and with AMBER [45] in Insight II V. 2.3.5 [46]. Monte Carlo (MC) multiple minimum simulations (1000 steps) were executed in CHCl_3 using the column-based continuum model (GB/SA) for the solvent as implemented in MacroModel/BatchMin [47]. Changes in the total energy of $(8S,9R)$ -5 as a function of the molecular geometry were analyzed in gas-phase simulations within the Insight II program.

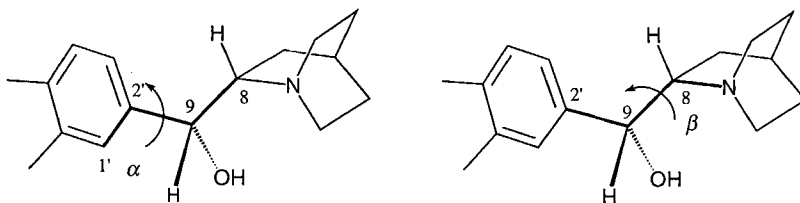


Fig. 5. Definition of the torsional angles α and β in $(8S,9R)$ -5

In (8*S*,9*R*)-**5**, bond rotation is only possible around the two bonds C(2')–C(9) and C(9)–C(8) connecting the two rigid quinuclidine and 9,9'-spirobifluorene moieties as well as around the C(9)–O bond. Only the rotation around the two C,C bonds was investigated in detail, and the relevant torsional angles C(1')–C(2')–C(9)–C(8) and C(2')–C(9)–C(8)–N were defined as α and β , respectively (Fig. 5).

The MC search identified for (8*S*,9*R*)-**5** a total of 25 conformers within 1.1 kcal mol⁻¹ of the global minimum which is shown in Fig. 6. The relevant torsional angles in the lowest-energy conformer ($E_{\text{total}} = 35.24$ kcal mol⁻¹) are -116.6° (α) and $+54.0^\circ$ (β). In a control run, the MC search afforded very similar values for the other enantiomer (8*R*,9*S*)-**5** ($E_{\text{total}} = 35.44$ kcal mol⁻¹, $\alpha = +117.9^\circ$ and $\beta = -54.2^\circ$).

The analysis of the 25 lowest-energy conformers of (8*S*,9*R*)-**5** (Fig. 7) revealed that the torsional angle β varied only within 10° (between 49.8° and 59.5°), whereas angle α displayed a greater variation with a preference for values either between -110° and -140° or between $+50^\circ$ and $+70^\circ$. Fig. 7 visualizes that the small changes in β together with the preference of α for two angle ranges translates into two distinct, preferred orientations of the quinuclidine-methanol moiety with respect to the 9,9'-spirobifluorene unit. Due to the small variation in β , the overall orientation of the quinuclidine moiety with respect to the aromatic unit is very similar in all conformers. As a result of the preference of α for two angle ranges, the OH group and the quinuclidine N-atom adopt two preferred orientations with respect to the aromatic cleft. These two functional groups are located above the unsubstituted fluorene ring and on opposite sides, respectively, of the second substituted fluorene ring. The quinuclidine moiety avoids a location within the plane of the adjacent fluorene ring, since this would lead to significant steric interactions with the aromatic protons H–C(1') and H–C(3').

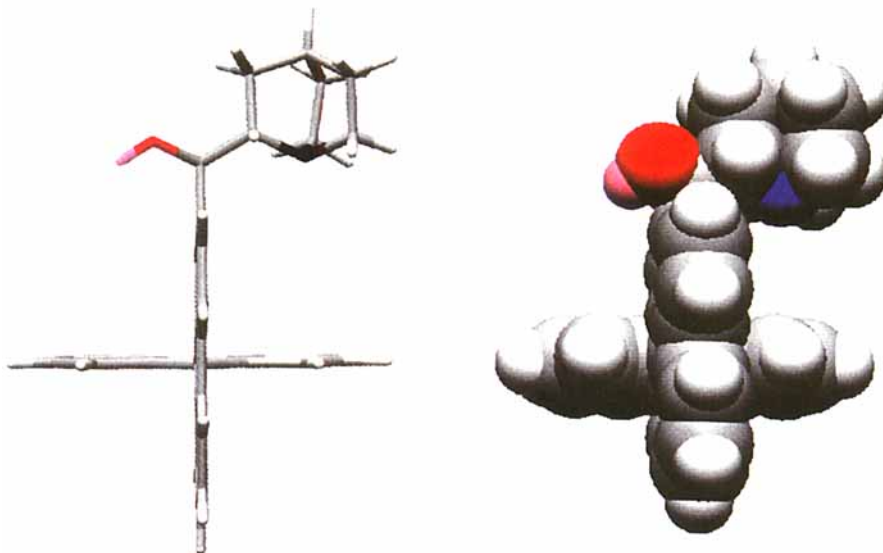


Fig. 6. 'Polytube' (left) and space-filling (right) models of the lowest-energy conformer of (8*S*,9*R*)-**5** in CHCl_3 as revealed in a MC search within MacroModel V. 4.0

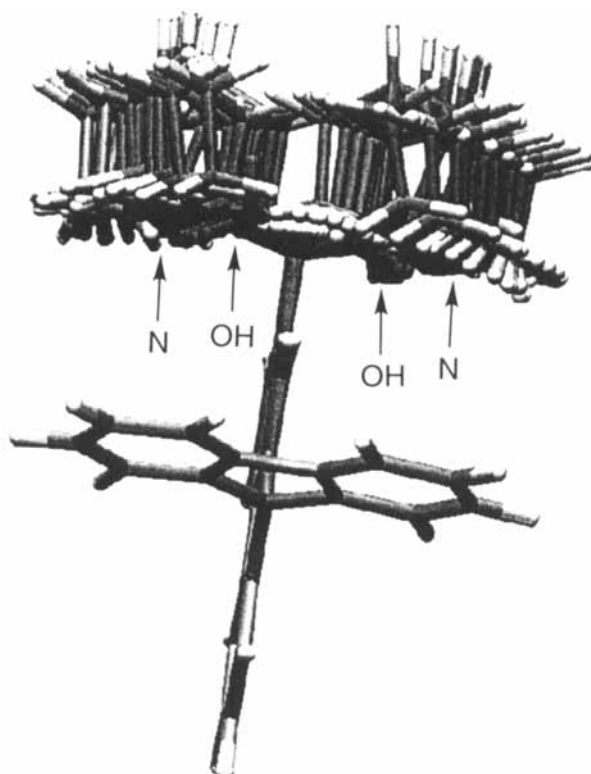


Fig. 7. Superimposition of the 25 lowest-energy conformers of (8S,9R)-5 found in a MC search in CHCl_3 within MacroModel V. 4.0

For a further validation of these results, we conducted a complete gas-phase investigation within Insight II of the dependency of the total energy on the two torsional angles α and β . When the lowest-energy conformation from the MacroModel MC search in CHCl_3 with the AMBER* force was minimized in Insight II with the AMBER force field, torsional angles of -110.2° (α) and $+53.2^\circ$ (β) were obtained. They compare well with gas-phase values calculated with AMBER* within MacroModel ($\alpha = 115.1^\circ$ and $\beta = +52.7^\circ$), which shows good correspondence between the results obtained with the two force fields.

In a first step, the torsional angle β , which was found in the MC search to undergo only small variations, was held constant at $+53.2^\circ$. The angle α was subsequently rotated in 1° steps, and the new geometry was energy-minimized (100 iterations). Alternatively, α was rotated by 1° steps and only the energy of the new conformation calculated. Since the rotation around all other bonds, except the C–O(H) bond, is frozen, both procedures led to identical two-dimensional energy schemes.

The analysis of the total energy as a function of α ($\beta = \text{constant}$) yielded minima for values of -110° ($E_{\text{total}} = 101.0 \text{ kcal mol}^{-1}$) and $+66^\circ$ ($E_{\text{total}} = 101.6 \text{ kcal mol}^{-1}$) of this

torsional angle. These values are close to the one found for the lowest-energy conformer in the MC search ($\alpha = -116.6^\circ$). In further confirmation of the previous results, the quinuclidine ring clearly prefers a location outside the plane of the adjacent (substituted) fluorene moiety. The energy maxima are found at $\alpha = +26^\circ$ ($E_{\text{total}} = 138.0 \text{ kcal mol}^{-1}$) and $+155^\circ$ ($E_{\text{total}} = 142.9 \text{ kcal mol}^{-1}$), at which the quinuclidine is positioned in the fluorene plane. The very high barriers of *ca.* 40 kcal mol^{-1} indicate that the molecule does not change its conformation from one minimum to the other by changes of the dihedral angle α only.

A more accurate and complete description of the total energy of (8*S*,9*R*)-**5** was obtained, when rotations around both torsional angles were permitted. In this simulation, each angle was changed in 5° steps and the energy of the new conformation calculated. Specifically, angle α was rotated, and, subsequently, β was rotated in 72 steps by 360° , then α was changed again followed by a stepwise 360° rotation of β , *etc.* This way, over five thousand data points were obtained, which are represented in the energy diagram in Fig. 8. Four energy minima are clearly visible (Table 1).

Table 1. The Four Energy Minima of (8*S*,9*R*)-**5** Obtained by Systematic Variation of Both Torsional Angles α and β

Minimum	α [$^\circ$]	β [$^\circ$]	E_{total} [kcal mol $^{-1}$]
1	-110	+55	101.0
2	+65	+55	101.6
3	+75	+155	105.0
4	-100	+155	105.1

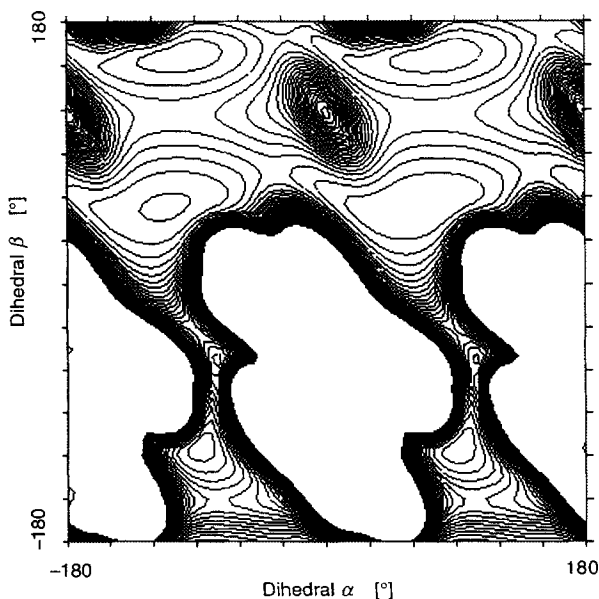


Fig. 8. Calculation of the total energy of (8*S*,9*R*)-**5** as a function of torsional angles α and β . The separation between potential lines is $2.5 \text{ kcal mol}^{-1}$.

The two lowest-energy minima in *Fig. 8* correspond to those seen in the two-dimensional graph calculated at constant β . At a β value close to 60° , the substituents at the C(8)–C(9) bond adopt a synclinal (*gauche*) orientation. At the two higher-energy minima, β adopts a value of 155° , which corresponds to an orientation of these substituents in between anticlinal and antiperiplanar. The second torsional angle α is of nearly identical magnitude in all four conformers.

The energetic minima observed in *Fig. 8* are not narrow but rather correspond to elongated valleys. Changes in the torsional angle α by as much of 50° (energy minimum $\pm 25^\circ$) change the total energy only within 1 kcal mol $^{-1}$. Changes in β have a more profound effect on the total energy with a variation by 1 kcal mol $^{-1}$ already being observed at an angle change of $\pm 15^\circ$. This confirms the findings of the MC simulations.

The structures corresponding to the four energy minima are shown in *Fig. 9*. Conformers 1 and 2 differ from 3 and 4 by the value of β , whereas differences between conformers 1 and 2 or between 3 and 4 result from differences in α . The geometries of conformers 1 and 2 resemble each other closely, whereas the geometries of conformers 3 and 4 differ by the orientation of the quinuclidine N-atom with respect to the 9,9'-spiro-bifluorene cleft. In analogy to the conformational description proposed for the natural *Cinchona* alkaloids (*Fig. 1*) [19], we name the two lowest-energy conformers 1 and 2 as 'closed', since the quinuclidine N-atom points into the cleft towards both fluorene moieties. Similarly, the two higher-energy conformers 3 and 4 are called 'open', since the N-atom points away from the aromatic spacer. Thus, the preferred geometrical preference of the new *Cinchona* alkaloid analogs is opposite to that of the natural systems. Quinine and quinidine prefer the 'open' (*Fig. 1*) over the 'closed' conformation by *ca.* 2 kcal mol $^{-1}$, whereas (8*S*,9*R*)-**5** prefers the 'closed' over the 'open' conformation by *ca.* 4 kcal mol $^{-1}$. The interconversion between the two 'closed' conformers of (8*S*,9*R*)-**5** is facilitated by a rotation of both torsional angles α and β ; an increase of the latter angle from 55° to 75° generates an interconversion pathway with an activation barrier of *ca.* 8 kcal mol $^{-1}$. Thus, the two lowest-energy conformers are in a rapid equilibrium at room temperature.

Table 2. $^1\text{H-NMR}$ Chemical Shifts of ($\pm$)-**5** in CDCl_3 , 298 K, 500 MHz. The arbitrary numbering corresponds to that in use for the natural *Cinchona* alkaloids.

	H-Atom	δ	H-Atom	δ
(8<i>S</i>,9<i>R</i>)-5	H–C(1')	6.73	H $_{\alpha}$ –C(2)	2.50–2.40
	H–C(3')	7.17	H $_{\beta}$ –C(2)	2.60–2.55
	H–C(4')	7.73	H $_{\alpha}$ –C(3)	1.30–1.20
	H–C(5')	7.85–7.80	H $_{\beta}$ –C(3)	1.30–1.20
	H–C(6')	7.31	H–C(4)	1.30–1.20
	H–C(7')	7.10–7.05	H $_{\alpha}$ –C(5)	1.30–1.20
	H–C(8')	6.70–6.65	H $_{\beta}$ –C(5)	1.30–1.20
	H–C(1'')	6.70–6.65	H $_{\alpha}$ –C(6)	3.00–2.95
	H–C(2'')	7.10–7.05	H $_{\beta}$ –C(6)	2.25–2.20
	H–C(3'')	7.34	H $_{\alpha}$ –C(7)	1.30–1.20
	H–C(4'')	7.85–7.80	H $_{\beta}$ –C(7)	1.45–1.40
	H–C(5'')	7.85–7.80	H–C(8)	2.75–2.70
	H–C(6'')	7.34	H–C(9)	4.62
	H–C(7'')	7.10–7.05	OH	1.67
	H–C(8'')	6.70–6.65		

Table 3. Signal Enhancements Observed in the $^1\text{H}\{^1\text{H}\}$ -NOE Difference Spectra of $(\pm)$ -**5**^{a)}

Proton irradiated	Proton resonances showing signal enhancement
H–C(1')	H–C(8) and H–C(9); weak: H _a –C(7) and H _b –C(7)
H–C(3')	H–C(8), H–C(9), H–C(4')
H–C(4')	H–C(3')
H _a –C(2)	H _b –C(2), H–C(3)
H _b –C(2)	H _a –C(2), H–C(3), H–C(8)
H _a –C(6)	H _a –C(5), H _b –C(6), H–C(9)
H _b –C(6)	H _a –C(5), H _a –C(6)
H–C(8)	H–C(1'), H–C(3'), H _b –C(2), H _b –C(7), H–C(9)
H–C(9)	H–C(1'), H–C(3'), H _a –C(6), H–C(8); weak: H _a –C(7)

^{a)} For numbering, see Table 2.

2.3.2. *¹H-NMR Conformational Studies.* A complete assignment of the ¹H-NMR resonances of $(\pm)$ -**5** was obtained with the help of both $\{^1\text{H}, ^1\text{H}\}$ -COSY and $^1\text{H}\{^1\text{H}\}$ -NOE (nuclear Overhauser effect) difference spectra at 500 MHz (Table 2). The observed intramolecular NOEs are shown in Table 3; they provide strong and independent experimental evidence for the preference of the molecule to adopt the rapidly equilibrating 'closed' conformations 1 and 2 shown in Fig. 9.

The protons H–C(8) and H–C(9) both displayed strong NOEs of equal intensity, when the aromatic protons H–C(1') and H–C(3') were irradiated. We take this as strong experimental evidence for the presence of rapidly equilibrating, approximately equimolar quantities of conformers 1 and 2 (Fig. 9). In one conformer, H–C(9) is in close contact with H–C(1'), whereas, at the same time, H–C(8) is close to H–C(3'). In the other conformer, H–C(9) is close to H–C(3'), whereas H–C(8) now approaches H–C(1'). The simultaneous appearance of these NOEs also provides strong support for the *gauche* alignment of the substituents at the C(8)–C(9) bond, which is characteristic for the two 'closed' conformers 1 and 2 (see Sect. 2.3.1). The strong NOE observed between H–C(9) and H_a–C(6) is additional evidence for this *gauche* alignment. Thus, the experimental and computational conformational analyses both agree that $(\pm)$ -**5** prefers adopting the two 'closed' conformations (conformers 1 and 2 in Fig. 9) which rapidly equilibrate and are nearly equally populated.

2.4. *Assignment of the Absolute Configurations of (+)-5 and (–)-5 from Host-Guest Association Studies with Quinine in CDCl₃.* A convenient way to determine the absolute configuration of a new optically active base is the X-ray crystallographic analysis of crystals formed by co-crystallization with optically active acids [35], receptors [3] [4], or clathrate-forming agents [41]. Since all co-crystallization attempts with (+)-**5** or (–)-**5** were unsuccessful, we turned to host-guest experiments in solution to obtain this essential stereochemical information. In the chromatographic optical resolution on the CSP consisting of silica-gel-bound quinine (Sect. 2.2), (–)-**5** eluted much faster ($\alpha = 1.61$) than (+)-**5**, which suggested that the host-guest interaction between (+)-**5** and quinine was stronger than the interactions between (–)-**5** and the natural alkaloid. The same conclusion had been drawn from ¹H-NMR complexation studies, which showed much larger complexation-induced changes in chemical shift for solutions containing (+)-**5** than for solutions of (–)-**5** (Sect. 2.2). We, therefore, hoped that structural information from

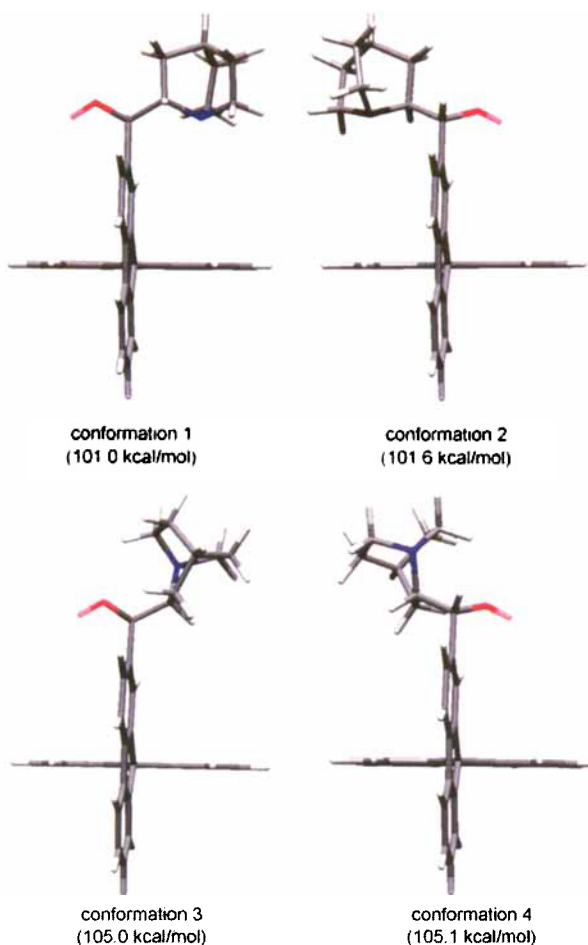


Fig. 9. The four minimum-energy conformations of (8S,9R)-5

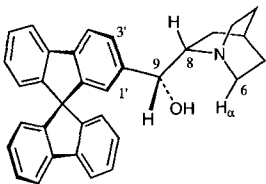
NOE experiments, combined with modeling, would enable us to identify the absolute configuration of the enantiomers of **5** present in the two diastereoisomeric associations.

NOE Difference spectra of 0.2M solutions of (+)-**5** or (–)-**5** with quinine were recorded in CDCl₃ at 300 MHz (Table 4). An analysis of the intramolecular NOEs demonstrated that the interacting binding partners preferred the same conformation as in the pure state. Intramolecular NOEs for (+)-**5** and (–)-**5** were identical to those measured for pure (±)-**5** (Table 3); hence the ‘closed’ conformation was maintained. Strong intramolecular NOEs between H–C(9) and H–C(8), H–C(5'), H_a–C(6) provided evidence for the preferred ‘open’ conformation of quinine in both solutions [3] [19].

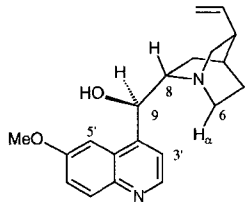
The observed intermolecular NOEs, three for the more stable association of (+)-**5** and only one for the less stable one of (–)-**5**, are shown in Table 4. The complete absence

Table 4. Observed Intermolecular NOEs in Solutions of (–)-**5** or (+)-**5** with Quinine (**1**) in CDCl₃

(–)- 5	Quinine (1)	(+)- 5	Quinine (1)
H–C(9)	H–C(9)	H–C(9)	H–C(9)
		H _a –C(6)	H–C(9)
		H–C(9)	H _a –C(6)



(+)-**5**/(-)-**5**



1

of intermolecular NOEs involving aromatic protons suggests that aromatic interactions between fluorene and quinoline rings do not provide a significant contribution to the stability of the associations found in solution. Rather, the observed NOEs are best explained by the proximity of specific protons as a result of host-guest H-bonding interactions. Examinations of *Corey-Pauling-Koltun* (CPK) and computer models (MacroModel) indicate that two N⋯HO host-guest H-bonds can form in the quinine complex of (8*R*,9*S*)-**5** (Fig. 10). As a result of these H-bonds, both quinine protons H–C(9) and H_a–C(6) come close to proton H–C(9) of (8*R*,9*S*)-**5** and H–C(9) of

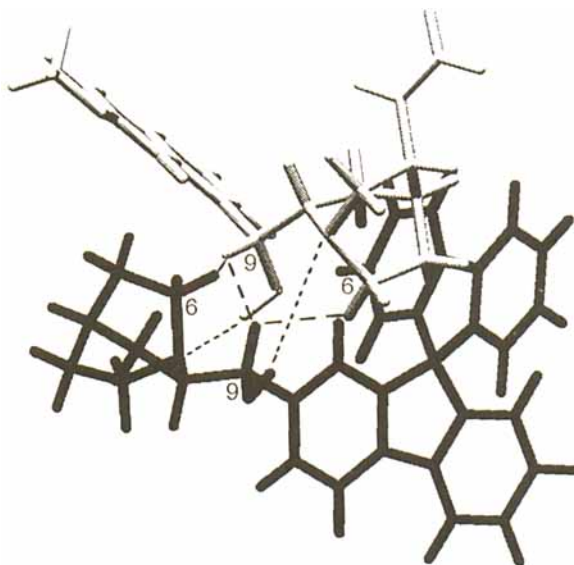


Fig. 10. Computer model of the more stable diastereoisomeric complex formed between (8*R*,9*S*)-**5** and quinine (**1**). Shown are the three observed intermolecular NOEs (----) and the two host-guest H-bonds (.....).

the natural alkaloid approaches $H_a-C(6)$ of the binding partner. These proximities give rise to three strong NOEs such as measured for the more stable diastereoisomeric complex, and, therefore, we assign the (8*R*,9*S*)-configuration to the (+)-**5** enantiomer in this complex. The model examinations also suggest that steric hindrance between quinine and spirobifluorene moieties allows formation of only one stable $N \cdots HO$ H-bond in the association between (–)-quinine (**1**) and (8*S*,9*R*)-**5**. Only one close intermolecular proton proximity is established giving rise to only one NOE, as observed for the weaker diastereoisomeric association. Therefore, we assign the (8*S*,9*R*)-configuration to the (–)-**5** enantiomer in the less stable complex. There exists a correlation between the sign of the specific optical rotation and the absolute configuration in the natural (–)-quinine (**1**) and (+)-quinidine (**2**) [18], and their unnatural counterparts (–)-**5** and (+)-**5**. The absolute configurations at the stereogenic methanol center (*R*) and the adjacent quinuclidine C-atom (*S*) in (–)-quinine (**1**) and (–)-**5** are identical and opposite at those of these centers in (+)-quinidine and (+)-**5**.

Attempts to quantify the strength of the interaction between quinine (**1**) or quinidine (**2**) with (+)-**5** and (–)-**5** in $CHCl_3$ by various binding titration methods (1H -NMR, fluorescence, UV/VIS, microcalorimetry, and CD) showed that the host-guest association, even in the more stable diastereoisomeric complexes, was weak. Mainly due to practical reasons such as solubility or inadequate concentration ranges, accurate association constants could not be determined. We estimate the association constant at 300 K for the more stable complex between (+)-**5** and quinine in $CDCl_3$ as $K_a < 20 \text{ l mol}^{-1}$. In view of the almost complete absence of complexation-induced changes in chemical shift at high concentration ranges (see *Sect. 2.3*), the stability of the diastereoisomeric complex (–)-**5**·quinine should even be much smaller. Self-association between identical enantiomers of **5** was found to be much weaker than between quinine molecules. For quinine, we determined by 1H -NMR dilution studies [48] an equilibrium constant for self-association of $K = 15 \text{ l mol}^{-1}$ (association free energy $\Delta G^\circ = -1.6 \text{ kcal mol}^{-1}$, $T = 300 \text{ K}$), which is in agreement with literature data [49]. In contrast, no self-association of the enantiomers of **5** was observed below $c = 0.1 \text{ M}$.

The binding studies, together with the difficulties encountered in the optical resolution of (±)-**5**, suggest that the new *Cinchona* alkaloid analogs (+)-**5** and (–)-**5** are inferior to the natural counterparts quinine and quinidine [3] in their ability to interact with other molecules *via* H-bonding. This difference can be explained by the different conformational preferences of the two types of molecules. Quinine (**1**) and quinidine (**2**) prefer the 'open' conformation, in which both the OH group and the quinuclidine N-atom are readily accessible for H-bonding. In contrast, (+)-**5** and (–)-**5** greatly prefer adopting the 'closed' conformation, in which the quinuclidine N-atom points into the adjacent 9,9'-spirobifluorene cleft and thus is sterically shielded. As a result, strong H-bonds with the participation of the quinuclidine N-atom as H-bond donor are disfavored.

3. Conclusions. – By attachment of a quinuclidine-2-methanol moiety at C(2) of a 9,9'-spirobifluorene unit, a novel pair of enantiomeric unnatural *Cinchona* alkaloid analogs (±)-**5** with the same configuration at the two stereogenic centers in the methanol bridge and the adjacent quinuclidine C-atom as in quinine (**1**) and quinidine (**2**), respectively, was obtained. Optical resolution of (±)-**5** was accomplished by HPLC on a chiral stationary phase prepared by covalently binding quinine *via* a thiol spacer to a silica-gel

surface. A detailed computational and ^1H -NMR spectroscopic conformational analysis demonstrated that (+)-**5** and (–)-**5** differed greatly in their conformational preference from their natural counterparts **1** and **2**, respectively. Whereas quinine (**1**) and quinidine (**2**) prefer an ‘open’ conformation, with the quinuclidine N-atom pointing away from the quinoline ring, (+)-**5** and (–)-**5** prefer adopting a ‘closed’ conformation in which this N-atom is pointing into the 9,9′-spirobifluorene cleft. A combined experimental ($^1\text{H}\{^1\text{H}\}$ -NOE difference spectroscopy) and computer-modeling analysis of the diastereoisomeric complexes formed by (+)-**5** and (–)-**5** with quinine (**1**) in CDCl_3 revealed that the (+)-enantiomer in the more stable association has the (8*R*,9*S*)-configuration, whereas the (–)-enantiomer in the less stable association is (8*S*,9*R*)-configured. As a result of the large preference (by *ca.* 4 kcal mol $^{-1}$) for the ‘closed’ over the ‘open’ conformation, the quinuclidine N-atom in (+)-**5** and (–)-**5** is sterically not well accessible for H-bonding, which provides these new chiral shapes with inferior molecular recognition properties, as compared to quinine (**1**) or quinidine (**2**). The most useful result of this investigation is the demonstration of the excellent agreement between the computational and experimental conformational analysis of **5**. Therefore, we are now taking advantage of the predictive power of the computing to identify as future synthetic targets unnatural *Cinchona* alkaloid analogs in which the quinoline moiety is replaced by interesting recognition shapes such as 2,2′-binaphthyl units but which demonstrate a clear preference for the desired ‘open’ conformation.

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Experimental Part

General. See [20b] [21d]. CH_2Cl_2 was freshly distilled over CaCl_2 and Et_2O and toluene over NaH prior to use. HPLC on commercial CSPs was performed on a *Perkin-Elmer Series 400 Liquid Chromatograph*, coupled with a *Perkin-Elmer LCI Laboratory Computing Integrator* and a *LC90-UV Spectrophotometric Detector*. HPLC Separations on silica-gel-bound quinine were performed on *Merck-Hitachi* instruments using a *L-6200A* pump and a *L-4250-UV-VIS* detector for anal. runs and a *L-6250* pump and a *L-4000-UV* detector for prep. runs. M.p.: Dr. Tottoli (Büchi 510) apparatus; uncorrected. CD Spectra: *Jasco J-710* spectropolarimeter; $c = 10^{-4}$ M in CHCl_3 , λ_{max} , λ_{min} , and shoulders (sh) in nm ($\Delta\epsilon$). UV/VIS Spectra: *Varian Cary-5* spectrophotometer; λ_{max} in nm (ϵ). ^{13}C -NMR: multiplicity of signals in DEPT-spectra reported as *s* (C), *d* (CH), *t* (CH_2), and *q* (Me). EI-MS (m/z , %): *Hitachi-Perkin-Elmer RMU 6M* instrument, 70 eV. FAB-MS (m/z , %): *VG ZAB2-SEQ* instrument, *m*-nitrobenzyl alcohol as matrix.

X-Ray Crystal Structure of (±)-9**.** X-ray crystal data for $2 (\text{C}_8\text{H}_{13}\text{NO}_2) \cdot \text{H}_2\text{O}$ ($M_r = 328.4$): monoclinic space group $C2/c$ (No. 15), $D_c = 1.331 \text{ g cm}^{-3}$, $Z = 4$, $a = 7.620(9)$, $b = 9.975(7)$, $c = 21.76(4) \text{ Å}$, $\beta = 97.90(12)^\circ$, $V = 1638(4) \text{ Å}^3$, MoK_α radiation, $\lambda = 0.71073 \text{ Å}$, $3 \leq 2\theta \leq 40^\circ$, 759 unique reflections, $T = 293 \text{ K}$. The structure was solved by direct methods (SHELXTL PLUS) and refined by full-matrix least squares analysis using experimental weights (heavy atoms anisotropic, H-atoms fixed, whereby H-positions are based on stereochemical considerations). Final $R(F) = 0.0631$, $wR(F) = 0.0697$ for 105 variables and 656 observed reflections with $F > 4.0\sigma(F)$.

X-Ray Crystal Structure of (+)-14**.** X-ray crystal data for $\text{C}_{35}\text{H}_{29}\text{NO}$ ($M_r = 479.6$): orthorhombic space group $P2_12_12_1$, $D_c = 1.214 \text{ g cm}^{-3}$, $Z = 4$, $a = 9.583(10)$, $b = 11.879(15)$, $c = 23.05(3) \text{ Å}$, $V = 2624(6) \text{ Å}^3$, MoK_α radiation, $\lambda = 0.71073 \text{ Å}$, $3 \le$

of the crystal-structure investigations are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ (UK), on quoting the full journal citation.

Preparation of Silica-Gel-Bound Quinine as CSP for Optical Resolutions. [7d]. A suspension of *LiChrosorb Si60* silica gel (4.80 g, *E. Merck*, particle size 5 μm) in a mixture of (3-mercaptopropyl)trimethoxysilane (20 ml), abs. toluene (10 ml), and dry piperidine (10 ml) was stirred mechanically for 24 h at 90°. After cooling, the suspension was centrifuged for 1 h at 5000 rpm. The supernatant soln. was removed *via* pipette, and the modified silica gel was subsequently washed exhaustively on a glass frit with toluene, acetone, Et_2O , and pentane. After drying in high vacuum (10^{-2} Torr), the modified silica gel was suspended in CHCl_3 (25 ml), which had been freshly distilled over P_2O_5 , and quinine (**1**; 3.20 g) together with AIBN (164 mg) were added. The suspension was stirred mechanically under the exclusion of light for 30 h in a 80° warm oil bath. After cooling to r.t., the mixture was centrifuged for 1 h at 5000 rpm. The supernatant was removed *via* pipette, and the modified silica gel was washed exhaustively on a glass frit with MeOH, until the washing liquids no longer showed an UV absorption at 325 nm, characteristic for **1**. After drying at high vacuum (10^{-2} Torr), the derivatized silica gel was packed into HPLC columns with CCl_4 using the slurry method.

2-Bromo-9,9'-spirobifluorene (7). A mixture of Mg (4.24 g, 173.7 mmol) and 2-iodo-1,1'-biphenyl (48.70 g, 173.7 mmol) [31] in abs. Et_2O (80 ml) was heated to reflux for 2.5 h. After addition of Et_2O (100 ml) and filtration, a soln. of 2-bromofluoren-9-one (37.56 g, 145.0 mmol) [30] in abs. toluene (1 l) was added, and the mixture was heated to reflux for 65 h. The cooled (r.t.) soln. was poured onto ice (250 g); conc. aq. HCl soln. (500 ml) and toluene (500 ml) were added, and the mixture was stirred at r.t. for 2 h. Extraction with toluene (300 ml), washing with sat. aq. NaHCO_3 soln. and sat. aq. NaCl soln., drying (MgSO_4), evaporation, and chromatography (SiO_2 ; hexane) yielded colorless **7** (44.89 g, 78%). M.p. 180.5–181°. R_f (SiO_2 , hexane) 0.48. IR (KBr): 3059w, 2360m, 1594w, 1473w, 1445s, 1402m, 1262m, 1155w, 1104w, 1057w, 1028w, 1004w, 955w, 868w, 823m, 773w, 749s, 728s, 667m, 634m, 620w, 574w, 472w, 420m. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.84 (d, $J = 7.5$, 2 H); 7.80 (d, $J = 7.5$, 1 H); 7.69 (d, $J = 8.1$, 1 H); 7.47 (dd, $J = 8.1$, 1.8, 1 H); 7.37 (td, $J = 7.5$, 1.0, 2 H); 7.35 (td, $J = 7.5$, 1.0, 1 H); 7.11 (td, $J = 7.5$, 1.0, 3 H); 6.85 (d, $J = 1.8$, 1 H); 6.72 (d, $J = 7.5$, 2 H); 6.71 (d, $J = 7.5$, 1 H). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3): 150.79, 148.52 (2s); 147.88 (2s); 141.71 (2s); 140.74, 140.62 (2s); 130.87, 128.23 (2d); 127.97 (2d); 127.93 (2d); 127.89, 127.26, 124.08 (3d); 124.03 (2d); 121.39 (s); 121.29 (d); 120.11 (2d); 120.03 (d); 65.77 (s). EI-MS: 396/394 (79/75, M^+ ($^{81}\text{Br}/^{79}\text{Br}$)), 315 (100, $[M - \text{Br}]^+$). Anal. calc. for $\text{C}_{25}\text{H}_{15}\text{Br}$ (395.30): C 75.96, H 3.82, Br 20.21; found: C 75.38, H 4.12, Br 19.96.

($\pm$)-Ethyl Quinuclidine-2-carboxylate (($\pm$)-6). A soln. of diethyl quinuclidine-2,2-dicarboxylate (11.13 g, 43.5 mmol) [33] in conc. aq. HCl soln. (110 ml) was stirred for 22 h at reflux. A cycle of evaporation to dryness, suspension of the residue in EtOH, and re-evaporation was performed three times, after which conc. H_2SO_4 soln. (0.7 ml) was added to the residue suspended in EtOH (225 ml). The mixture was stirred for 15 h at 80°, the solvent was evaporated, and sat. aq. NaHCO_3 soln. was added. Extraction with CH_2Cl_2

25.98 (5r); 21.43 (d). EI-MS: 453 (38, M^+), 82 (100). HR-MS: 453.2073 (M^+ , $C_{33}H_{27}NO^+$; calc. 453.2092). Anal. calc. for $C_{33}H_{27}NO$ (453.58): C 87.38, H 6.00, N 3.09, O 3.53; found: C 86.79, H 6.52, N 3.05, O 3.50.

(+)- and (-)-(1-Azabicyclo[2.2.2]oct-2-yl)(9,9'-spirobifluoren-2-yl)methanol ((+)-5 and (-)-5). To (±)-8 (500 mg, 1.1 mmol) in toluene (10 ml) was slowly added dropwise at r.t. a soln. of 1.5M DIBAL-H in toluene (1.25 ml, 1.8 mmol). After stirring for 3 h, H_2O (10 ml) was added and the mixture was filtered over *Celite*. H_2O was added to the residue obtained by evaporation, and extraction with CH_2Cl_2 , washing with 2N aq. NaOH soln. (3×) and H_2O , drying ($MgSO_4$), followed by chromatography (SiO_2 ; hexane/ CH_2Cl_2 / Et_3N 3:3:1) gave colorless hygroscopic (±)-5 (416 mg, 83%). Optical resolution by HPLC on silica-gel-bound quinine (see Sect. 2.2) afforded pure (+)-5 and (-)-5. M.p. ((±)-5) 169–170°. R_f (SiO_2 ; hexane/ CH_2Cl_2 / Et_3N 3:3:1) 0.22. (+)-5: $[\alpha]_D^{25} = +57.3$ ($c = 1.017$, $CHCl_3$ / $EtOH$ 99:1). (-)-5: $[\alpha]_D^{25} = -57.7$ ($c = 1.052$, $CHCl_3$ / $EtOH$ 99:1). UV ($CHCl_3$): 312 (14000), 300 (10450). CD ($CHCl_3$): (+)-5: 313 (0.127), 306 (0.010), 302 (0.016), 291 (-0.013), 280 (0.033), 268 (0.063), 260 (0.071). (-)-5: 313 (-0.130), 306 (-0.010), 302 (-0.015), 292 (0.012), 280 (-0.036), 269 (-0.058), 260 (-0.068). IR ($CHCl_3$): 3688m, 3602w, 3007m, 2935s, 2864m, 1719m, 1602m, 1448m, 1381w, 1282m, 1138m, 1075m, 1006m, 988m, 909w, 829w, 692w, 660w, 637w, 621w. 1H -NMR (500 MHz, $CDCl_3$): 7.85–7.80 (m, 3 H); 7.73 (d, $J = 7.9$, 1 H); 7.34 (td, $J = 7.5$, 1.0, 2 H); 7.31 (td, $J = 7.5$, 1.0, 1 H); 7.17 (dd, $J = 7.9$, 1.3, 1 H); 7.10–7.05 (m, 3 H); 6.73 (d, $J = 1.3$, 1 H); 6.70–6.65 (m, 3 H); 4.62 (d, $J = 5.4$, 1 H); 3.00–2.95 (m, 1 H); 2.75–2.70 (m, 1 H); 2.60–2.55 (m, 1 H); 2.50–2.40 (m, 1 H); 2.25–2.20 (m, 1 H); 1.67 (br. s, 1 H); 1.45–1.40 (m, 1 H); 1.30–1.20 (m, 6 H). ^{13}C -NMR (100 MHz, $CDCl_3$): 149.02, 148.85, 148.79, 144.13 (4s); 141.79 (2s); 141.65, 140.99 (2s); 127.72 (d); 127.65 (s + d); 127.63 (2d); 126.14, 124.04 (2d); 124.01 (2d); 123.98 (2d); 121.90, 119.98, 119.96, 119.86, 119.69, 75.82 (6d); 65.95 (s); 61.29 (d); 50.14, 43.12, 27.28, 26.35, 25.51 (5t); 21.85 (d). EI-MS: 455 (100, M^+). HR-MS: 455.2217 (M^+ , $C_{33}H_{29}NO^+$; calc. 455.2249). Anal. calc. for $C_{33}H_{29}NO \cdot 3 H_2O$ (509.65): C 77.77, H 6.92, N 2.75; found: C 77.31, H 6.59, N 2.76.

(+)- and (-)-(1-Aza-5-vinylbicyclo[2.2.2]oct-2-yl)(9,9'-spirobifluoren-2-yl)methanone ((+)-14; diastereoisomeric mixture with *ent*-15). To TMEDA (273 mg, 2.3 mmol) in abs. THF (1 ml) was added at -78° a 1.7M soln. of *t*-BuLi in pentane (1.4 ml, 2.4 mmol), then 7 (0.909 g, 2.3 mmol) in abs. THF (5 ml) was added dropwise, leading to a change in color from yellow to orange. The mixture was stirred for 1.5 h at -78° , then a ca

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