103. The Synthesis and Characterization of New Optically Active 'Dimeric' 'Pineno'-[4,5]-Fused 2,2′-Bipyridines Linked without Spacer or by Small Spacer Groups

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Linked chiral bipyridines **2**–**4** are prepared by combining two optically active 'pineno'-[4,5]-fused 2,2′-bipyridines in a stereoselective reaction (*Scheme 1*). These potential ligands are new members of the 'chiragen' family, and are characterized by NMR spectroscopy and, in the case of **2** and **3** by single-crystal X-ray analysis. A new synthesis of 'dipineno'-[4,5;4′,5′]-fused 2,2′-bipyridine **8** is described, which, when coupled, gives additional four chiral centres to the analogous 'chiragen' series (→ **9**). Analysis of the CD spectra allowed conformational information about the solution species to be determined.

Introduction. – In the last few years, many new and interesting metal complexes of helicating and caging ligands have been described [1]. Many of these ligands lead to chiral complexes or host-guest structures. However, due to the lack of stereoselectivity of the ligands, a racemic mixture of the forms is usually produced. As such systems grow in size, the number of possible diastereoisomers and enantiomeric pairs increases exponentially [2], and consequently it is necessary to develop new systems where the chirality is predetermined prior to complexation so that the exact structure can be predicted in the supramolecular assemblies.

The so-called 'chiragen' ligands have been designed to overcome these problems; these ligands contain a rigid chirality in their bipyridine moieties, introduced by the use of a readily available natural product in their synthesis [3]. Additionally, we have developed a synthetic pathway that allows a wide variety of different linking groups between the bipyridine moieties to be incluced. 'Pineno'-[4,5]-fused 2,2′-bipyridines[1]) linked by alkanediyl groups were initially reported, which were able to control the helical chirality in octahedral metal complexes depending upon the absolute configuration of the starting pinene enantiomer [4]. Subsequently, by replacing the flexible aliphatic groups by more rigid xylenediyl groups, better coordination properties were achieved [5] (*Fig. 1*).

In reducing the size of the spacer unit, it was hoped that the potential linked ligand would have greater intramolecular steric interactions, where the relative orientation of the two bipyridine moieties would influence the average configuration. Secondly, the

[1]) The locants [4,5], [4′,5′], [5,6], and [5′,6′] refer to the numbering of the 2,2′-bipyridine moiety and indicate the fusion sides with the 'pinene' moiety; for systematic names, see *Exper. Part.*

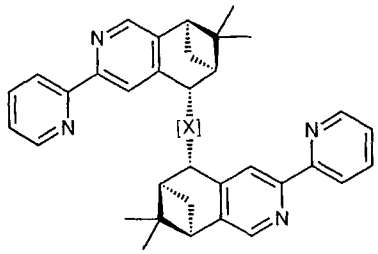

Fig. 1. *The 'chiragen' ligand system.* All molecules have C_2 symmetry and contain six stereogenic C-atoms.

inclusion of additional chiral centres could further direct the configuration. To this end, a new synthesis of 'dipineno'-[4,5;4′,5′]-fused 2,2′-bipyridine[1]) **8** was developed, which led to a new class of bipyridines, linked by a chiral moiety, the 'super chiragens'.

Results and Discussion. – *Synthesis.* The 'pineno'-[4,5]-fused 2,2′-bipyridine[1]) **1** can be obtained using a *Kröhnke*-type synthesis [3]. Linking **1** to a second 'pineno'-[4,5]-fused 2,2′-bipyridine moiety is readily achieved *via* a stereoselective lithiation reaction at position 5[2]) using a sterically-hindered base such as lithium diisopropylamide (LDA). Upon reaction with this lithium salt and a suitable dibromide, linking groups can be inserted in between the two chiral bipyridine moieties. It was observed, however, that if a mild oxidizing agent was present, *e.g.* O_2, a significant quantity of a by-product could be obtained. By adding I_2 to the lithium salt of **1**, it was possible to obtain this by-product in high yield. Characterization indicated it to be 'chiragen[0]' (**2**; *Scheme 1*), which is surprising by virtue of the close proximity of the two large pineno moieties. The preparation of analogous compounds with C_1- and C_2-spacer groups between the two pineno moieties was then attempted. Unfortunately, using reagents such as dibromomethane, diiodomethane, dibromoethane, and ethyl acetate, the desired target molecules were not obtained. The reaction is prevented by the large steric interactions encountered in the second approach of the lithiated species. However, successful reactions were achieved using ethyl formate and dichlorodimethylsilane which yielded the ligands **3** and **4**, respectively, containing a small spacer (*Scheme 1*).

To increase the number of chiral centres in this class of optically active bipyridines, the 'dipineno'-[4,5;4′,5′]-fused 2,2′-bipyridine **8** was synthesized. While **8** was initially prepared in eight steps from (−)-myrtenal according to an analogous reaction sequence recently elaborated by us for the synthesis of the isomeric 'dipineno'-[5,6;5′,6′]-fused 2,2′-bipyridine from (−)-pinocarvone [6], a new synthetic route was developed, taking only three steps. Again the key step of the sequence was a *Kröhnke*-type cyclization of the pyridine ring using the (cyanomethyl)pyridinium salt **5** and (−)-myrtenal to give amine **6** [7]. This amine was then converted to the bromo derivative **7** [8] which was coupled on nickel(II) to produce the desired 'dipineno'-fused bipyridine **8** [9] (*Scheme 2*). The time required and the simplicity of this reaction sequence is greatly improved as compared to the previously used method [6].

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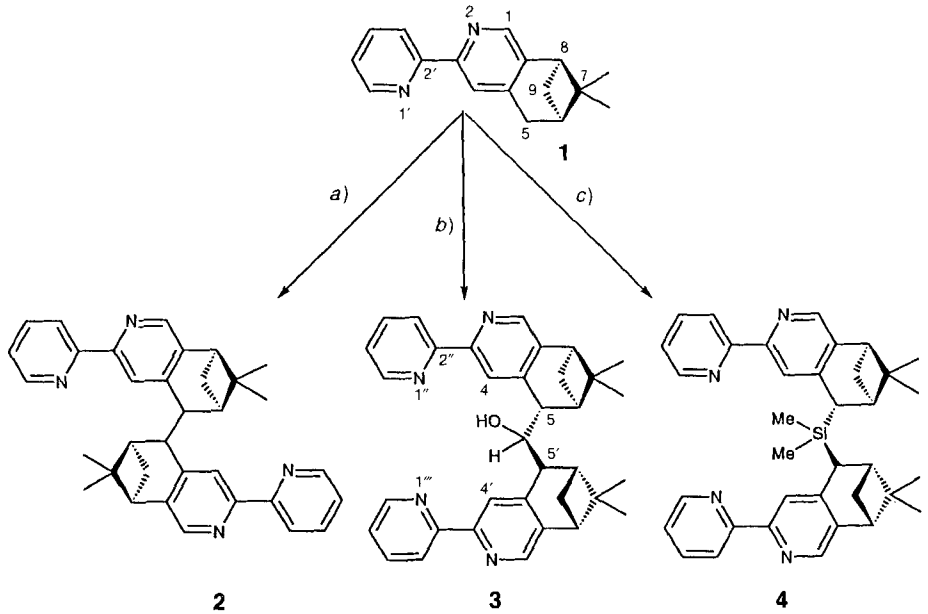
[2]) Systematic numbering as shown for **1** in *Scheme 1* (see also *Exper. Part*).

Scheme 1. *Preparation of the New Small 'Chiragen' Molecules*



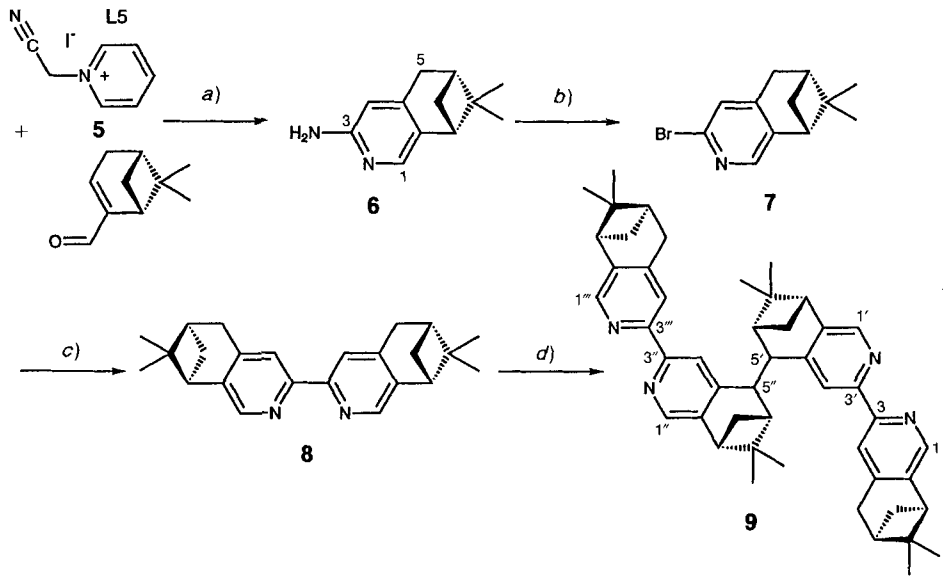
a) 1. LDA, THF, $< -40.°$; 2. I_2, THF. *b*) 1. LDA, THF $< -40°$; 2. HCOOEt. *c*) 1. LDA, THF $< -40°$; 2. $SiMe_2Cl_2$, THF.

The 'dipineno'-[4,5;4′,5′]-fused 2,2′-bipyridine **8** was coupled in an analogous reaction to that of the 'pineno'-[4,5]-fused 2,2′-bipyridine **1** by using 1 equiv. of LDA and then oxidizing the product with I_2. Again, a good yield was achieved, giving the product **9** with ten chiral centres.

NMR Spectroscopy. All the compounds prepared were fully characterized by both ^{13}C- and ^1H-NMR spectroscopy. While the characteristics of the starting bipyridine molecules are evident in all new 'chiragen' compounds, there were several noticeable features. While the silylene-bridged compound **4** had a spectrum very similar to that of the starting bipyridine **1**, **2**, and **9** showed a much greater downfield shift (*ca.* 1 ppm) of the proton at the linking position C(5), along with a noticeable change in peak position of the aromatic protons at C(1) and C(4)[2]). However, there is no loss in C_2 symmetry, despite the great steric hindrance in solution on an NMR time scale. However, the hydroxymethylene link in **3** renders the two bipyridine halves inequivalent. The introduction of the alcohol group removes the C_2 symmetry, which is easily seen in both the ^1H- and ^{13}C-NMR spectra of **3**. Full assignment was carried out using a combination of COSY and HETCOR techniques. It is apparent from the observed shifts that the OH group lies much closer to one of the bipyridine moieties, with protons at C(5) and C(4) being shifted much further downfield when compared to those at C(5′) and C(4′)[2]). The proton of the link, C*H*OH, is in a strongly deshielded position, with a shift of 4.71 ppm.

Structure Determinations. With the exception of **4**, the bipyridine compounds could be recrystallized from EtOH. Ligands **2** and **3** both formed crystals suitable for X-ray structure determination (see *Figs. 2* and *3*).

Scheme 2. *Preparation of the New 'Super Chiragen' Molecules*



a) EtOH/AcOH NH_4OAc. *b*) 1. $NaNO_2$, HBr, 0°; 2. CuBr, HBr, 70°. *c*) Zn/[$Ni(PPh_3)_4Cl_2$], DMF. *d*) 1. LDA, THF < −40°; 2. I_2, THF.

Molecule **2** possesses crystallographic C_2 symmetry (*Fig. 2*); **3**, however, shows strong deviation from C_2 symmetry (*Fig. 3*), demonstrated by the different torsion angles C(4)–C(7)–C(14)–O(15) and C(4a)–C(7a)–C(14)–O(15), being −1.5(9) and 65.7(8)°, respectively[3]). In the solid state, the structures of both compounds **2** and **3** adopt a *trans* position of the two pyridine halves of the bipyridine unit, as is expected, with a torsion angle N(1)–C(2)–C(2′)–N(1′) of 172.5(4)° in **2** and −174.5(7)° in **3** and with N(1a)–C(2a)–C(2a′)–N(1a′) of −176.7(7)° in **3**. Both structures indicate that the alkylation at C(7)[3]) occurred from the sterically less-hindered side of the 'pineno' moiety, thus establishing the stereoselectivity of the reaction, as has been observed previously with this type of reaction [4] [5]. Additionally, it was observed that the two bipyridine units are close enough to affect each other, with the distance between C(7) and C(7a) being 1.55 and 2.59 Å in **2** and **3**, respectively. Additionally, a torsion angle C(4)–C(7)–C(7a)–C(4a) of −159.0(4)° in **2** orientates the two bipyridine moieties to superimpose one another, giving rise to possible stabilizing π–π stacking interactions. In **3**, the two bipyridine moieties adopt a more splayed conformation, with a pseudo torsion angle C(4a)–C(7a)–C(7)–C(4) of 99.8°. The solid-state structure of this compound illustrates that there is a one-dimensional linear arrangement of the molecules held together by intermolecular H-bonds between OH and N(1′) of an adjacent symmetry-related molecule. Surprisingly, the conformation adopted places the two 'pineno' units and the O-atom in an alternate configuration, placing the bulky Me groups in the same plane.

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[3]) Arbitrary numbering as shown in *Figs. 2* and *3*.

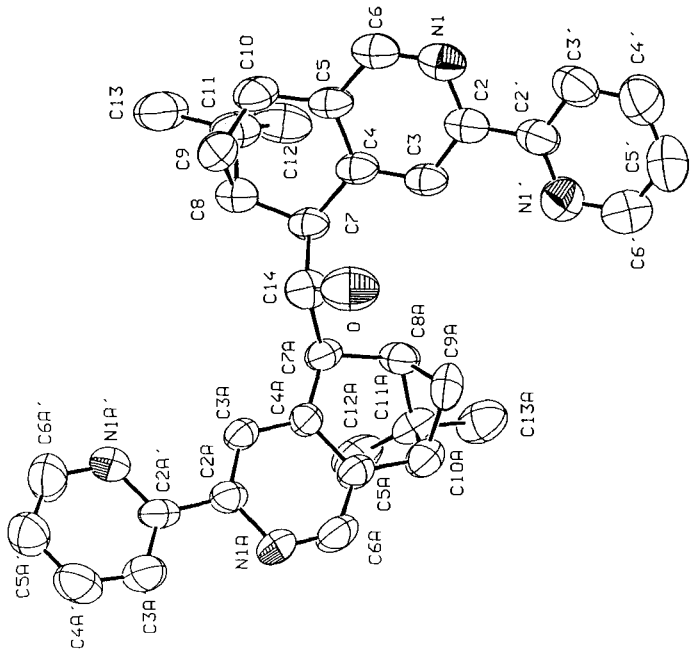

Fig. 3. *Thermal motion ellipsoid plot of* **3**, *with ellipsoids drawn at 50% probability level.* Arbitrary numbering.

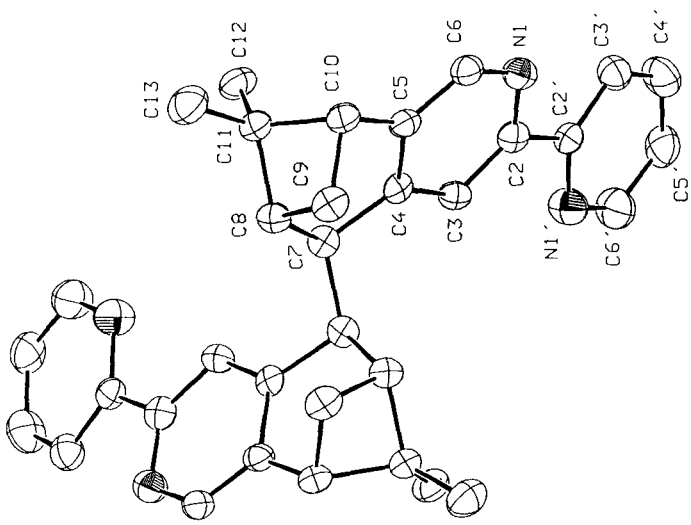

Fig. 2. *Thermal motion ellipsoid plot of* **2**, *with ellipsoids drawn at 50% probability level.* Arbitrary numbering.

Table 1. *UV/VIS Absorption Data for Ligands* **1**–**4**, **8**, *and* **9**[a])

	λ/nm	ε/M^{-1} cm^{-1}	λ/nm	ε/M^{-1} cm^{-1}
1	–	–	291	15900
2	257	12600	291	30500
3	269	11100	304	29500
4	–	–	291	34500
8	262	9900	296	19300
9	264	18600	297	33500

[a]) All spectra were recorded in $CHCl_3$ at a concentration of $2 \cdot 10^{-5}$ M.

Electronic Spectra. All bipyridine-containing ligands were investigated by UV spectroscopy (*Table 1* and *Fig. 4, a*), with the strong π–π^* transitions being evident in each case at 291 nm, except for **3** where it is red-shifted to 304 nm due to the electronegativity of the adjacent OH group. Additionally, there are strong side bands which in several cases resolved into individual peaks.

In the circular dichroism (CD) spectra of both starting bypridines **1** and **8**, very little of the chirality derived from the 'pineno' moiety is observed in the π–π^* transitions (*Fig. 4, b*). However, weak but significant CD spectra are observed for all other ligands (*Fig. 4, b*), due to the orientation of the two adjacent bipyridine groups, while the larger 'chiragens' reported previously demonstrated no effective CD activity [4–6]. It should be stated, however, that these compounds show only small $\Delta\varepsilon$'s, indicating that they adopt different conformations in solution which partially cancel each other in the CD spectrum.

Exciton theory has been used to elucidate the conformations and configurations of molecules in solution and has proved to be useful with a variety of organic compounds [10] and metal complexes [11]. With high-intensity electric dipole moment allowed transitions, exciton CD is supposed to correlate well with absolute configurations [10], as recently demonstrated by *Lightner* and coworkers [12]. An almost identical UV spectrum for the different ligands **1**–**4**, **8**, and **9** (*Fig. 4, a*) shows that the electronic transitions of the molecules containing two bipyridine moieties result from the sum of the transitions in two individual mono-bipyridines, and thus, the exciton model can be applied. ZINDO Calcu-

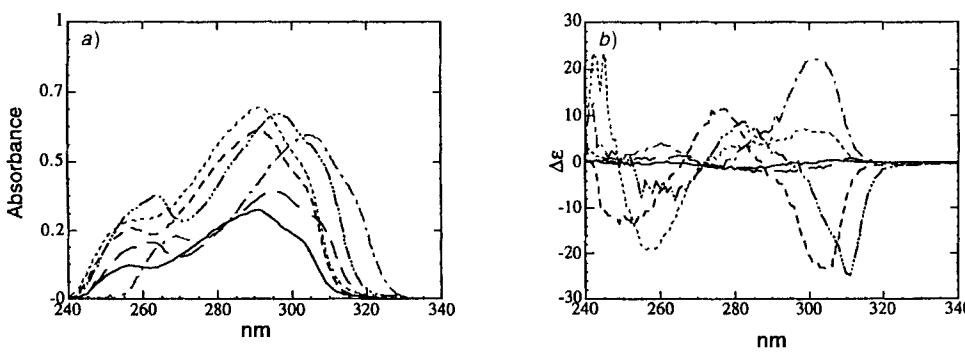

Fig. 4. a) *UV Spectra of ligands* **1**–**4**, **8**, *and* **9** ($c = 2 \cdot 10^{-5}$ M in $CHCl_3$), *and* b) *circular dichroism spectra of* **1**–**4**, **8**, *and* **9** ($c = 1 \cdot 10^{-4}$ M in $CHCl_3$). ——**1**; – – –**2**; –·–·–**3**; ----**4**; – – –**8**; –···–···–**9**.

lations (INDO/1 parametrization [13]) including the orbitals from HOMO−11 to LUMO+11 in the configuration interaction (CI) active space with an INDO/1 geometry-optimized 'pineno'-[4,5]-fused 2,2′-bipyridine show that the UV/VIS bands arise primarily from long-axis polarized π–π^* transitions. The calculated spectra correspond reasonably well with those observed (*Fig. 5*). Therefore, the CD bands observed for the linked molecules arise from intramolecular electrostatic coupling of electric transition dipole moments of the two bipyridine moieties.

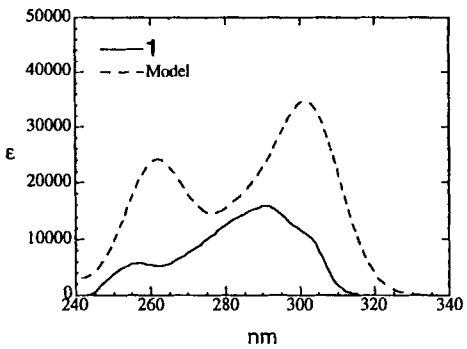

Fig. 5. *Calculated UV spectrum for 'pineno'-[4,5]-fused 2,2′-bipyridine, using geometry-optimized ZINDO(INDO/1) calculations*

The CD spectra of ligands **2** and **9** in solution (*Fig. 4, b*) indicate that the relative arrangement of the two bipyridines in the molecules are very similar. From the application of the exciton theory, the configuration adopted can be assigned as a left-handed helix (see *Fig. 6*), whereas, in the ligands **3** and **4**, a right-handed conformation is preferred. This fact is also observed in the optical rotation of the compounds, where **2** and **9** give a negative value, while **3** and **4** give positive values of $[\alpha]$. This feature is due to the difference in the relative torsion angles along the link between the 'pineno' moieties, and it is apparent that only a small rotation in the angle can turn one helicity into the other thus inverting the CD transition (*Fig. 6*).

The modelled solution conformation of **3** derived from analysis of the CD spectrum agrees with the configuration observed in the X-ray-determined solid-state structure. Surprisingly, this is not the case for **2** having a link without spacer. However, in the solid state, **3** takes up a configuration where the two bipyridine units overlay each other, which would lead to a different CD spectrum as modelled with exciton theory. It can be assumed that upon crystallization, intermolecular H-bonding plays a more important role, leading to the change in average configuration.

Conclusions. – The successful synthesis of 'dipineno'-[4,5;4′,5′]-fused 2,2′-bipyridine **8** allowed us to extend the number of chiral centres appended to a bipyridine group. Using this and the previously reported 'pineno'-[4,5]-fused 2,2′-bipyridine **1**, new configurationally defined potential linked bidentate ligands of the 'chiragen' family containing up to ten chiral centres were prepared and characterized. Due to the shortness of the linking spacers between the two halves of the structure, there is helicity transferred to the relative position of the bipyridine units, since free rotation along the spacers is prevented on steric grounds. This was illustrated by both X-ray structure determinations and by circular

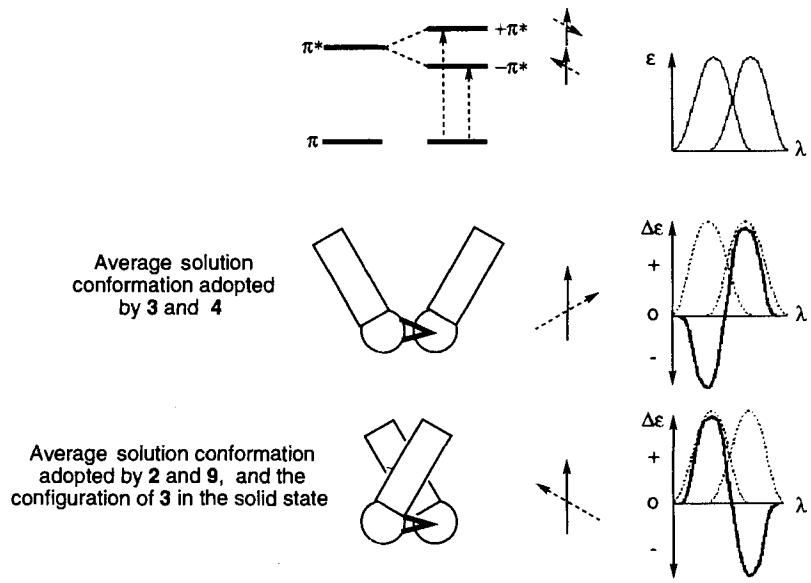

Fig. 6. The relative configurations of the two bipyridine moieties in the linked ligands **2**–**4** *and* **9** *and the expected CD spectra*

dichroism spectroscopy in solution. Additionally, it appears that only a small change in the angle between the two bipyridine moieties is required to invert the helicity of the overall molecule. These new small 'chiragens' and 'super chiragens' are believed to be able to produce chiral coordination compounds, in combination with transition metals, and currently investigations are in progress to demonstrate this.

Experimental Part

General. Unless otherwise stated, commercial-grade reagents were used without further purification. THF was pre-dried by distillation from Na. (−)-(1*R*)-Myrtenal was obtained from *Fluka* (> 97%, $[\alpha]_D^{20°} = -14.6$). Column chromatography = CC. M.p.: *Büchi-520* melting-point apparatus, uncorrected. Optical rotations: *Perkin-Elmer-MC 241* polarimeter; 10-cm cell; sample concentration *ca.* $1 \cdot 10^{-2}$ M in $CHCl_3$. UV/VIS Spectra: *Perkin-Elmer-Lambda-2* in spectrometer; λ_{max} (ε) in nm. CD Spectra: *Jobin-Yvon* spectrophotometer; λ_{max} ($\Delta\varepsilon$) in nm. NMR Spectra: *Varian-Gemini-300* spectrometer (300 (^{1}H) and 75.46 MHz (^{13}C)); in $CDCl_3$; δ in ppm using the solvent as internal ref. rel. to $SiMe_4$, J in Hz. MS: *VG-Instruments-7070E* mass spectrometer equipped with a FAB inlet system m/z (rel.%). The elemental analyses were performed in the Research Centre, of *Ciba AG*, Marly.

5,6,7,8-Tetrahydro-7,7-dimethyl-3-(pyridin-2-yl)-6,8-methanoisoquinoline (**1**) was prepared according to [3] [4].

5,5′,6,6′,7,7′,8,8′-Octahydro-7,7,7′,7′-tetramethyl-3,3′-di(pyridin-2-yl)-5,5′-bi[6,8-methanoisoquinoline] ('*Chiragen(0)*'; **2**). To a soln. of **1** (504 mg, 2.01 mmol) in dry THF (10 ml) was added at −40° 1.5M lithium diisopropylamide (LDA; 1.5 ml, 2.25 mmol) in dry THF (10 ml) over 30 min. The mixture was kept at −40° for 4 h, then I_2 (254 mg, 1.0 mmol) in dry THF (10 ml) was added. At the end of the addition, the colour changed from blue to red. The mixture was stirred overnight, quenched with H_2O (2 ml), and concentrated *in vacuo*. After addition of sat. aq. $NaHCO_3$ soln. (30 ml), the mixture was extracted with CH_2Cl_2 (3 × 30 ml), the org. phase dried ($MgSO_4$) and evaporated, and the residue purified by CC (silica gel, hexane/Et_2O/Et_3N 14:6:1): 302 mg (60%) of **2**. Recrystallization from MeOH gave colourless crystals. M.p. 290–292° (dec.) $[\alpha]_D^{22°} = -115$. ^{1}H-NMR: 8.65 (*dd*, J = 3.9, 0.9, H–C(6″)); 8.45 (*s*, H–C(1)); 8.36 (*d*, J = 8.0, H–C(3″)); 8.26 (*s*, H–C(4)); 7.79 (*ddd*, J = 8.0, 8.0, 1.7,

H–C(4″)); 7.26 (*m*, H–C(5‴)); 4.03 (*s*, H–C(5)); 2.82 (*dd*, *J* = 5.4, 5.4, H–C(8)); 2.50 (*ddd*, *J* = 9.8, 5.6, 5.6, H_b–C(9)); 2.09 (*dd*, *J* = 5.7, 5.7, H–C(6)); 1.28 (*s*, Me_a–C(7)); 1.24 (*d*, *J* = 9.6, H_a–C(9)); 0.70 (*s*, Me_b–C(7)). ^{13}C-NMR: 156.3, 154.9 (C(3), C(2″)); 149.2 (C(6″)); 147.3 (C(4a)); 145.6 (C(4)); 143.8 (C(8a)); 136.8, 123.4, 120.8, 118.4 (C(4″), C(5″), C(3″), C(1)); 43.8, 43.5, 42.2 (C(8), C(5), C(6)); 41.9 (C(7)); 28.7 (C(9)); 26.0 (*Me*–C(7)); 20.9 (*Me*$_b$–C(7)). FAB-MS: 499 (6, MH^+), 456 (2, $[M - Me_2C]^+$), 249 (75, 0.5 M^+), 207 (100, $[249 - Me_2C]^+$). Anal. calc. for $C_{34}H_{34}N_4$: C 81.9, H 6.8, N 11.2; found: C 81.0, H 6.7, N 11.3.

Bis[5,6,7,8-tetrahydro-7,7-dimethyl-3-(pyridin-2-yl)-6,8-methanoisoquinolin-5-yl]methanol (*'Chiragen(OH)'*; **3**). As described for **2**, using **1** (508 mg, 2.03 mmol), 1.5M LDA/THF (1.8 ml, 2.7 mmol), and HCOOEt (75.6 mg, 1.02 mmol) added in three portions over 15 min: 419 mg (78%) of **3**. Recrystallization from MeOH/CH_2Cl_2 gave colourless crystals. M.p. 245–246° $[\alpha]_D^{22°} = +119$. ^{1}H-NMR: 8.78 (*s*, H–C(4)); 8.48 (*d*, *J* = 4.1, H–C(6″)); 8.44 (*d*, *J* = 4.1, H–C(6‴)); 8.34 (*d*, *J* = 8.0, H–C(3″)); 8.21 (*d*, *J* = 8.0, H–C(3‴)); 8.19 (*s*, H–C(1)); 8.17 (*s*, H–C(4′), H–C(1′)); 7.70–7.61 (*m*, H–C(4″), H–C(4‴)); 7.16–7.10 (*m*, H–C(5″), H–C(5‴)); 4.71 (*d*, *J* = 7.8, *CH*OH); 3.21 (*dd*, *J* = 7.8, 8.9, H–C(5)); 3.10 (*s*, H–C(5′)); 3.01 (*d*, *J* = 4.0, OH); 2.89 (*dd*, *J* = 5.2, 5.2, H–C(8′)); 2.84 (*dd*, *J* = 5.2, 5.2, H–C(18)); 2.72–2.59 (*m*, H_b–C(9), H_b–C(9′)); 2.39 (*dd*, *J* = 5.1, 5.1, H–C(6)); 2.17 (*ddd*, *J* = 5.1, 5.1, 1.7, H–C(6′)); 2.03 (*d*, *J* = 9.9, H_a–C(9)); 1.53 (*d*, *J* = 9.7, H_a–C(9′)); 1.46 (*s*, Me_a–C(7)); 1.44 (*s*, Me_a–C(7′)); 0.64 (*s*, Me_b–C(7), Me_b–C(7′)); assigned by COSY. ^{13}C-NMR: 156.7, 154.7, 156.2, 154.5 (C(3), C(3′), C(2″), C(2‴)); 148.9, 148.7 (C(6″), C(6‴)); 147.4, 146.7 (C(4a), C(4′a)); 145.8, 145.4 (C(1), C(1′)); 143.8, 142.2 (C(8a), C(8′a)); 136.7, 136.6, 123.2, 123.0, 122.3, 120.9, 120.8, 118.1 (C(4‴), C(4″), C(5‴), C(5″), C(4), C(3″), C(3‴), C(4′)); 75.9 (CHOH); 45.1, 44.7, 43.8, 42.6, 42.6 (C(8), C(8′), C(5), C(6), C(5′)); 42.2, 41.4 (C(7′), C(7)); 40.1 (C(6′)); 29.1, 28.2 (C(9′), C(9)); 26.7, 26.2 (*Me*$_a$–C(7′), *Me*$_a$–C(7)); 21.0, 20.7 (*Me*$_b$–C(7′), *Me*$_b$–C(7)); assigned by DEPT and HETCOR. FAB-MS: 551 (24, $[M + Na]^+$), 529 (100, MH^+), 279 (72, $[0.5M + CH_2OH]^+$). Anal. calc. for $C_{34}H_{34}N_4 \cdot H_2O$: C 76.9, H 7.0, N 10.2; found: C 77.4, H 7.1, N 10.3.

5,5′-(Dimethylsilylene)bis[5,6,7,8-tetrahydro-7,7-dimethyl-3-(pyridin-2-yl)-6,8-methanoisoquinoline] (*'Chiragen(SiMe$_2$)'*; **4**). As described for **2** using **1** (502 mg, 2.01 mmol), 1.5M LDA/THF (1.5 ml, 3.00 mmol), and dichlorodimethylsilane (128 mg, 0.99 mmol), added over 5 min: 256 mg (46%) of **4** (50% of **1** was recovered from the 1st fraction of CC). M.p. 72–75° (dec.). $[\alpha]_D^{22°} = +146$. ^{1}H-NMR: 8.55 (*dd*, *J* = 4.8, 0.9, H–C(6″)); 8.25 (*d*, *J* = 7.8, H–C(3‴)); 8.19 (*s*, H–C(1)); 8.15 (*s*, H–C(4)); 7.67 (*ddd*, *J* = 8.0, 7.4, 0.9, H–C(4‴)); 7.17 (*dd*, *J* = 4.8, 7.3, H–C(5‴)); 3.07 (*s*, H–C(5)); 2.83 (*dd*, *J* = 5.5, 5.5, H– C(8)); 2.68 (*ddd*, *J* = 9.8, 5.5, 5.5, H_b–C(9)); 2.63 (*dd*, *J* = 5.6, 5.6, H–C(6)); 1.38 (*s*, Me_a–C(7)); 1.29 (*d*, *J* = 9.6, H_a–C(9)); 0.64 (*s*, Me_b–C(7)); 0.12 (*s*, Me_2Si). ^{13}C-NMR: 156.4, 154.2 (C(3), C(2″)); 148.9 (C(6″)); 147.8 (C(4a)); 145.7 (C(4)); 142.3 (C(8a)); 136.5, 123.0, 120.5, 119.7 (C(4″), C(5″), C(3″), C(1)); 44.2, 42.7 (C(8), C(6)); 38.9 (C(7)); 32.9 (C(5)); 29.3 (C(9)); 25.7 (*Me*$_a$–C(7)); 21.0 (*Me*$_b$–C(7)); 0.6 (Me_2Si). FAB-MS: 579 (17, MNA^+), 557 (100, MH^+), 399 (97, $[M - 2Py]^+$). Anal. calc. for $C_{34}H_{34}N_4 \cdot H_2O$: C 75.1, H 7.4, N 9.7; found: C 74.7, H 7.3, N 9.4.

(Cyanomethyl)pyridinium Iodide (**5**). For 4 h, 2-chloroacetonitrile (42.69 g, 565 mmol) and KI (100.00 g, 602 mmol) were refluxed in MeOH (100 ml). The mixture was cooled to r.t. and evaporated. The residual yellow oil was taken up in CH_2Cl_2 (100 ml) and filtered to remove inorg. residues. The filtrate was dried ($MgSO_4$) and filtered, and pyridine was added dropwise (200 ml) over 1 h. The mixture was stirred at r.t. for 16 h. The resulting precipitate was collected by filtration, washed with Et_2O (3 × 50 ml), and dried *in vacuo*: 105.85 g (76%) of **5**. Yellow crystalline solid. M.p. 162–163°. ^{1}H-NMR ((D_6)DMSO): 9.19 (*d*, *J* = 6.5, H–C(2), H–C(6)); 8.75 (*t*, *J* = 7.4, H–C(4)); 8.27 (*dd*, *J* = 6.5, 7.5, H–C(3), H–C(5)); 6.01 (*s*, CH_2). ^{13}C-NMR ((D_6)DMSO): 147.6, 145.4, 128.6 (C(2), C(3), C(4), C(5), C(6)); 114.2 (CN); 47.8 (CH_2). FAB-MS: 365 (100, $[2M + I]^+$).

5,6,7,8-Tetrahydro-7,7-dimethyl-6,8-methanoisoquinolin-3-amine (**6**) [7]. A soln. of **5** (10.03 g, 38.0 mmol), (–)-myrtenal (5.09 g, 33.9 mmol), and NH_4OAc (15.67 g, 203.4 mmol) in 50% EtOH/AcOH (50 ml) was refluxed for 6 h. The resulting black soln. was allowed to stand overnight and then the volume reduced to *ca.* 15 ml. H_2O (50 ml) was added and the soln. taken to pH 14 with sat. NaOH soln. The mixture was extracted with Et_2O (10 × 100 ml) and the org. phase dried ($MgSO_4$) and concentrated to *ca.* 250 ml. This was then extracted with 2M HCl (5 × 100 ml), the aq. phase made basic with sat. NaOH soln., the alkaline soln. extracted with CH_2Cl_2 (5 × 100 ml), and the org. phase dried ($MgSO_4$) and evaporated. The resulting black oil was then further purified by CC (silica gel, gradient CH_2Cl_2/MeOH containing 2% of Et_3N): 2.42 g (38%) of **6**. Yellow oily solid. To avoid decomposition, **6** was stored under N_2 at –30° and used as quickly as possible after preparation. ^{1}H-NMR: 7.42 (*s*, H–C(1)); 6.22 (*s*, H–C(4)); 4.26 (br., NH_2); 2.70 (*d*, *J* = 2.2, H–C(5)); 2.51 (*dd*, *J* = 5.4, 5.4, H–C(8)); 2.47 (*m*, H_b–C(9)); 2.06 (*m*, H–C(6)); 1.21 (*s*, Me_a–C(7)); 1.00 (*d*, *J* = 8.5, H_a–C(9)); 0.47 (*s*, Me_b–C(7)). ^{13}C-NMR: 157.0 (C(3)); 146.5 (C(4a)); 142.9 (C(1)); 132.8 (C(8a)); 108.1 (C(4)); 43.8, 39.7 (C(8), C(6)); 39.6 (C(7)); 32.5, 32.3 (C(5), C(9)); 25.9 (*Me*$_a$–C(7)); 21.3 (*Me*$_b$–C(7)). EI-MS: 188 (15, M^+), 173 (19, $[M - NH_2]^+$), 145 (100, $[M - Me_2C]^+$).

3-Bromo-5,6,7,8-tetrahydro-7,7-dimethyl-6,8-methanoisoquinoline (**7**) [8]. A soln. of **6** (3.44 g, 0.222 mol) in 33% HBr soln. (60 ml) was cooled to below 0°. To this was added dropwise $NaNO_2$ (1.70 g, 0.246 mol) in H_2O

(10 ml) over 15 min, and the mixture was stirred for a further 15 min. CuBr (5.00 g, 0.349 mol) was added over 30 min and the mixture heated at 70° for 3 h. After cooling to r.t., the soln. was taken to pH 14 by the addition of 3M aq. NaOH. The resulting precipitate was extracted with Et_2O (5 × 100 ml), the extract dried ($MgSO_4$) and evaporated, and the resulting brown oil purified by CC (silica gel, hexane containing 5% of Et_3N): 1.27 g (28%) of **7**. Yellow oil. ^{1}H-NMR: 7.82 (*s*, H–C(1)); 7.18 (*s*, H–C(4)); 2.87 (*d*, J = 2.8, H–C(5)); 2.72 (*dd*, J = 5.5, 5.5, H–C(8)); 2.61 (*m*, H_b–C(9)); 2.22 (*m*, H–C(6)); 1.32 (*s*, Me_a–C(7)); 1.09 (*d*, J = 9.8, H_a–C(9)); 0.54 (*s*, Me_b–C(7)). ^{13}C-NMR; 147.8 (C(4a)); 145.8 (C(1)); 141.8 (C(3)); 139.1 (C(8a)); 127.0 (C(4)); 43.9, 39.5 (C(8), C(6)); 38.7 (C(7)); 32.4, 31.4 (C(5), C(9)); 25.9 (Me_a–C(7)); 21.3 (Me_b–C(7)). EI-MS: 251/253 (10/9, M^+), 236/238 (5/4, $[M - Me]^+$), 208/210 (100/96, $[M - Me_2C]^+$).

5,5′,6,6′,7,7′,8,8′-Octahydro-7,7,7′,7′-tetramethylbi[6,8-methanoisoquinoline] (*'Super Chiragen(0)'*; **8**) [9]. To a soln. of $NiCl_2 \cdot 6H_2O$ (0.372 g, 1.56 mmol) and PPh_3 (1.640 g, 6.25 mmol) in degassed DMF (8 ml) was added Zn powder (0.130 g, 1.99 mmol). The mixture was heated at 60° for 2 h, during which time the colour changed from blue to red. Then **7** (0.393 g, 1.57 mmol) in DMF 810 ml) was added. The mixture was heated for a further 18 h and then poured into 10% NH_3/H_2O (50 ml). The resulting precipitate was extracted with CH_2Cl_2 (6 × 50 ml), dried ($MgSO_4$), and evaporated . The resulting orange oil was purified by CC (silica gel, CH_2Cl_2 containing 1% of MeOH): PPh_3, then crude product containing a significant amount of PPh_3. The latter mixture was taken up in

Table 2. *Experimental Crystallographic Data for Compounds* **2** *and* **3**

	2	**3**
Molecular formula	$C_{34}H_{34}N_4$	$C_{35}H_{36}N_4O$
Molecular weight	498.65	528.68
Crystal system	Monoclinic	Orthorhombic
Space group	*I*2	$P2_12_12_1$
Cell parameters *a* [Å]	11.880(5)	11.307(4)
b [Å]	6.360(2)	14.594(7)
c [Å]	17.828(10)	17.762(14)
α	90°	90°
β	93.43(3)°	90°
γ	90°	90°
Volume [Å^3]	1344.6(10)	2931.0(28)
Z	2	4
Calculated density [gcm^{-3}]	1.232	1.198
Diffractometer used	*Stoe AED* 4-circle	*Syntex P2$_1$* [14]
Radiation and wavelength [Å]	MoK_α 0.71073	MoK_α 0.71073
Temp. [°C]	193(2)	293(2)
Linear absorption coefficient	0.073	0.073
Scan mode	$\omega/2\theta$	$\omega/2\theta$
Max./Min. value of θ	$2.01 < \theta < 24.99$	$2.28 < \theta < 22.57$
Method used to solve / refine structure	direct methods using SHELXS-86 / SHELXL-93 with calculated H-positions using a 'riding model' for H [15] removed 'for H'	
No. of reflections measured	2599	2946
No. of independent reflections	2362	2676
No. of unique reflections	1334	1717
Criterion for classification of observed reflections	$> 2\sigma(I)$	$> 2\sigma(I)$
No. of parameters refined	175	368
Final refinement on F^2:		
Final *R*	0.0733	0.0700
Final *wR*	0.1599	0.1523
Goodness of fit	1.097	1.231
Max.+/-electron density in *Fourier* synthesis [eÅ^{-3}]	0.176/−0.158	0.509/−0.203
Plotting software used	PLUTON and PLATON [16]	

25% CH_2Cl_2/Et_2O (50 ml) and extracted with 2M HCl (4 × 50 ml). The acidic soln. was taken to pH 13 with sat. aq. NaOH soln., the resulting basic soln. extracted with CH_2Cl_2 (4 × 200 ml), and the organic soln. dried ($MgSO_4$) and evaporated. The final acid/base extraction was repeated to remove traces of P-containing impurities: 0.204 g (76%) of **8**. Further purification can be achieved by CC (silica gel, hexane containing 5% of Et_3N). M.p. 179–180°. $[\alpha]_D^{22} = -104$. ^{1}H-NMR: 8.17 (*s*, H–C(1)); 8.14 (*s*, H–C(4)); 3.03 (*d*, *J* = 2.7, H–C(5)); 2.84 (*dd*, *J* = 5.5, 5.5, H–C(8)); 2.67 (*m*, H_b–C(9)); 2.29 (*m*, H–C(6)); 1.39 (*s*, Me_a–C(7)); 1.23 (*d*, *J* = 9.8, H_a–C(9)); 0.62 (*s*, Me_b–C(7)). ^{13}C-NMR: 154.8 (C(4a)); 145.5 (C(3)); 145.2 (C(1)); 142.6 (C(8a)); 120.3 (C(4)); 44.5, 40.1 (C(8), C(6)); 39.3 (C(7)); 3.29, 31.8 (C(5), C(9)); 26.0 (*Me*$_a$–C(7)); 21.3 (*Me*$_b$–C(7)). EI-MS: 344 (11, M^+), 301 (86, $[M - Me_2C]^+$). Anal. calc. for $C_{24}H_{28}N_2 \cdot 1/2\,H_2O$: C 81.5, H 8.3, N 7.9; found: C 81.9, H 8.5, N 7.5.

4,4′,4″,4‴,5,5′,5″,5‴,6,6′,6″,6‴,7,7′,7″,7‴-Hexadecahydro-7,7,7′,7′,7″,7″,7‴,7‴-octamethyl-3,3′:5′,5″:3″,3‴-quater[6,8-methanoisoquinoline] (**9**). As described for **2**, using **8** (602 mg, 1.742 mmol) in dry THF (20 ml), 1.5M LDA/THF (1.2 ml, 1.8 mmol), and I_2 (227 mg, 0.89 mmol) in dry THF (15 ml). The crude product was purified by CC (silica gel, hexane/Et_3N 20:1): 400 mg (67%) of **9** and 192 mg (32%) of recovered **8**. **9**: $[\alpha]_D^{22} = -138$. M.p. 200–204°. ^{1}H-NMR: 8.41 (*s*, H–C(1′)); 8.19 (*s*, H–C(1)); 8.22 (*s*, H–C(4′)); 8.14 (*s*, H–C(4)); 4.03 (*s*, H–C(5)); 3.04 (*d*, *J* = 1.0, H–C(5′)); 2.86 (*t*, *J* = 5.7, H–C(8′)); 2.78 (*t*, *J* = 5.5, H–C(8)); 2.76 (*m*, H_b–C(9)); 2.48 (*m*, H_b–C(9′)); 2.31 (*t*, *J* = 5.6, H–C(6)); 2.07 (*t*, *J* = 5.6, H–C(6′)); 1.41, 1.28 (*s*, Me_a–C(7), Me_a–C(7′)); 1.24 (*m*, H_a–C(9)); 1.22 (*m*, H_a–C(9′)); 0.68, 0.66 (*s*, Me_b–C(7), Me_b–C(7′)). ^{13}C-NMR: 155.6, 154.9 (C(3), C(3′)); 147.1 (C(4′a)); 145.5, 145.4 (CH(1), CH(1′)); 145.3 (C(4a)); 143.2, 142.5 (C(8a), C(8′a)); 120.1, 118.1 (CH(4), CH(4′)); 44.5, 43.7, 43.4, 42.2 (CH(8), CH(8′), CH(5′), CH(6′)); 41.8 (C(7′)); 40.1 (CH(6)); 39.3 (C(7)); 32.9, 31.9, 28.8 (CH_2(9), CH_2(9′), CH_2(5)); 26.0 (*Me*$_a$–C(7), *Me*$_a$–C(7′)); 21.3, 20.9 (*Me*$_b$–C(7), *Me*$_b$–C(7′)). FAB-MS (NBA): 688 (100, MH^+). Anal. calc. for $C_{48}H_{54}N_4 \cdot 1\,H_2O$: C 81.8, H 8.0, N 7.9; found: C 81.9, H 8.7, N 7.9.

Single Crystal Structure Determinations see *Table 2*.

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