Friedländer Synthesis of Chiral Alkyl-Substituted 1,10-Phenanthrolines

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The synthetic scope of the Friedländer condensation in the preparation of chiral alkyl-substituted 1,10-phenanthrolines has been investigated. A range of chiral [*x*,*y*-*b*]-cycloalkeno-condensed phenanthrolines has been prepared in one step from steroidal or other cyclic ketones from the chiral pool and 8-amino-7-quinolinecarbaldehyde (**1**) via base-catalyzed condensation. Phenanthroline derivatives are formed in good yields with unhindered ketones, but the reaction proceeds even with sterically congested substrates such as camphor, albeit in low yield. The utility of the Friedländer condensation has been extended to the synthesis of chiral 3-alkyl-substituted phenanthrolines from monoalkyl-substituted acetaldehydes.

Introduction

Transition metal complexes involving 1,10-phenanthroline (phen) or its derivatives are useful catalysts in a wide variety of metal-mediated reactions.[1] Chiral alkyl-substituted phens have been successfully employed as asymmetric auxiliaries in several enantioselective metal-catalyzed processes which include the asymmetric transfer-hydrogenation[2] and hydrosilylation[3] of acetophenone with Rh(I)-catalysts, the allylic alkylation of 1,3-diphenylpropenyl acetate[4] and the alternating CO−styrene copolymerization[5] with Pd-catalysts, and the asymmetric cyclopropanation of styrene with Cu(I) catalysts.[6] The enantioselectivities (ee's) recorded in these reactions range from 63% (H-transfer) to 76% (hydrosilylation) in the Rh-catalyzed reactions, from less than 5% (copolymerization) to more 90% (alkylation) in the Pd-catalyzed reactions, while up to 70% ee's have been obtained in the cyclopropanation with Cu catalysts.

Nevertheless, in comparison with other chiral ligands with a nitrogen donor, the use of phen derivatives as chiral auxiliaries in asymmetric catalysis is less extensive than one might expect. There has been considerable work involving the incorporation of a chiral auxiliary onto the 2,2′-bipyridine (bpy) framework. The resulting chiral bpy ligands embody both C_2 and C_1 symmetry.[7] Particularly elegant is the work of von Zelewsky and co-workers who have fused a pinenyl moiety at the 3,4-position of bpy.[8] They have used this species not only as a simple chelator but also linked two such units to afford a bridging species for dinuclear coordination.[9] By comparison, the use of phen derivatives as chiral auxiliaries in asymmetric catalysis is far less extensive than one might expect.

This shortcoming is due largely to difficulties in synthesizing the prerequisite chiral phens. A notable advance was recently reported by O'Neill and Helquist, who have shown that the samarium diiodide-promoted coupling of phen with chiral ketones affords a moderate yield of the corresponding chiral 2-(1′-hydroxyalkyl)-phen derivative. Depending on the structure of the starting ketone, further elaboration of these compounds may provide access to chiral 2-alkyl and 2,9-dialkyl phens.[10] A significant merit of this new method is that it allows the introduction of a chiral substituent onto the phen

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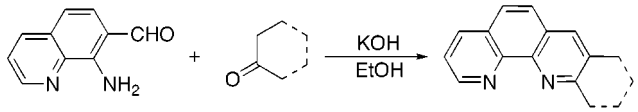
framework in a single step with complete positional selectivity.

However, the presence of 2-substitution is not always well suited for catalysis. In the Rh-catalyzed H-transfer reduction of acetophenone, for instance, the presence of a substituent in close proximity to the nitrogen leads to a less-efficient catalyst, probably because the 2-substituent hampers chelate binding of the phen[11] or bpy[12] ligand to the metal. For catalytic reactions promoted by Pd-phen complexes, the situation is less straightforward. The allylic alkylation of 1,3-diphenylpropenyl acetate is favorably affected by the presence of substituents of increasing stiffness and steric demand in the 2-position.[4] On the contrary, 3-alkyl substituted phens provide a higher activity catalyst in CO−olefin copolymerization.[13]

These considerations prompted us to investigate an expedient synthetic route to chiral 3-monoalkyl- and 2,3-dialkyl-substituted phen derivatives which are not accessible by direct coupling of phen with alkylmetal reagents. It was our aim to provide a simple entry to members of this family with a predetermined substitution pattern of alkyl groups having tunable steric demands.

Scheme 1



1

It has been demonstrated that 8-amino-7-quinolinecarbaldehyde (**1**) is an excellent synthon for the one-step preparation of phen derivatives by way of the Friedländer condensation (Scheme 1).[14] This base-promoted condensation with an enolizable ketone directly affords the desired phen derivative through a double dehydration. This approach has been applied to both enantiomers of nopinone[15] to afford the corresponding enantiomerically pure (2,3-*b*)-pineno-fused phen derivatives which in turn lead to diastereoselective formation of the chiral Cu(I) complex.

This study will investigate the scope and limitation of Friedländer methodology applied to the synthesis of chiral (2,3-*b*)-cycloalkeno-fused phens using ketones from the chiral pool. This approach has also been extended to the synthesis of 3-monoalkyl substituted phens from chiral aldehydes.

Results and Discussion

Both 5α- and 5*β*-cholestan-3-ones (**2** and **5**), which differ only in the geometry of their A−B ring fusion, possess a relatively unhindered carbonyl group which offers two possible regiochemistries for the Friedländer condensation. Since enamine formation at the 4-methylene position is hindered by the adjacent bridgehead, preferential reaction is expected at the more available 2-position.

The condensation of quinoline aminoaldehyde **1** with cholestanone **2** at 80 °C over 15 h provides a 95% yield of an 87:13 mixture of **3** and **4** (Scheme 2). The major isomer **3** was purified by crystallization and showed the expected six-proton ^{1}H NMR pattern for the 2,3-fused phen ring. The regiochemistry was established from the NMR signal for the C4 methylene protons which showed two distinct doublets of doublets at 3.41 and 3.00 ppm, having a large geminal coupling of 18.9 Hz and smaller vicinal couplings with H5 of 5.4 and 13.2 Hz. The H1 methylene appeared as two geminally coupled (J = 16.1 Hz) doublets at 3.03 and 2.68 ppm. The minor product could not be obtained pure but was tentatively identified in the mixture as regioisomer **4**.

When the same condensation is carried out with 5*β*-cholestan-3-one (**5**), two regioisomers are formed which can be separated by a combination of chromatography and crystallization (Scheme 3). The 3,2-fused isomer **6** is again identified by the multiplicities and chemical shifts of the Cl and C4 methylene groups. The 3,4-fused isomer **7** shows a 2-proton multiplet at 3.35 ppm for the C2 methylene group and a 1-proton singlet at 2.87 ppm for the C5 methine proton. It is noteworthy that the phenanthroline H4 singlet in **6** and **7** is sensitive to its environment and hence diagnostic of regiochemistry. For the more linear isomer **6** this singlet appears at 7.84 ppm; the corresponding 5α-isomer **3** shows a singlet at 7.89 ppm. For the angular isomer **7**, the phen H4 singlet appears at 8.16 ppm. This result is in keeping with the fact that in 5*β*-steroids the 3-ketone enolizes preferentially toward C4.[17]

The steroidal ketone, 5α-androst-2-en-17-one (**8**), has a carbonyl group which is more congested, being adjacent to a quaternary center, but potentially more reactive, being in a five-membered ring. The condensation of **1** with **8** can occur only toward the C16 methylene group and results in a 66% yield of **9** as the sole product (Scheme 4). The phen H4 singlet of **9** appears at 7.98 ppm, being shifted about 0.11−0.14 ppm downfield from what has been observed for other linear steroidal phens. This shift is due to the difference between five- and six-membered ring fusion to phen. The bridgehead carbons on the smaller ring use orbitals with higher s-character to bond to C4 of the phen causing slightly increased acidity of H4 and hence a downfield shift.[16]

It appears that the Friedländer condensation takes place readily even with fairly hindered steroidal ketones and provides a useful method for the incorporation of phen onto a steroid framework.

A second type of ketone which may undergo Friedländer condensation includes a series of chiral cyclohexanone derivatives, **10**, **13**, and **16**, which exhibit increasing steric encumbrance at the carbonyl carbon. Condensation of aminoaldehyde **1** with (+)-*R*-3-methylcyclohexanone (**10a**) affords two possible regiochemistries depending upon whether enamine formation is preferred at the C2 or C6 methylene (Scheme 5). Analysis of the crude reaction mixture indicated complete consumption of **1** resulting in a 3:1 ratio of **11**/**12a** from which a 56%

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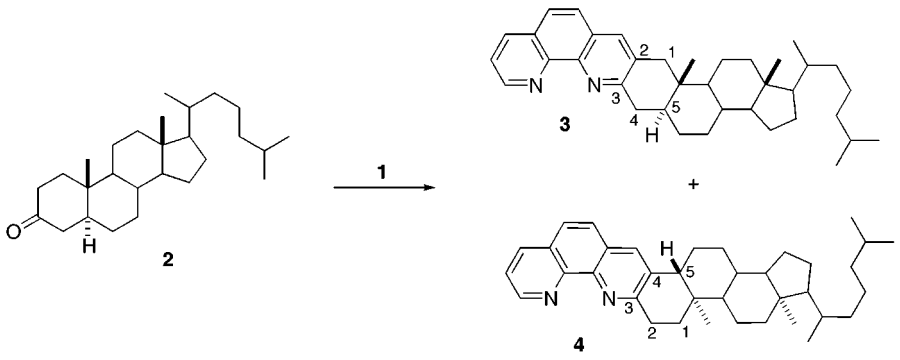
Scheme 2



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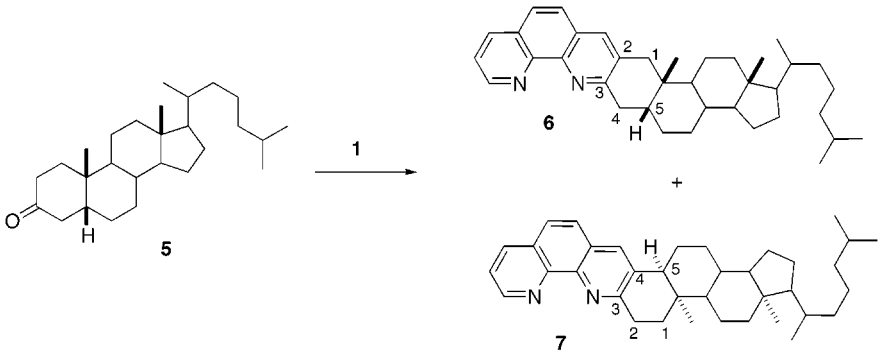
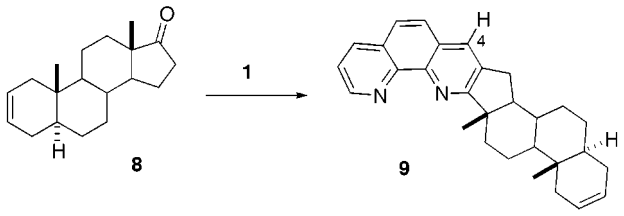
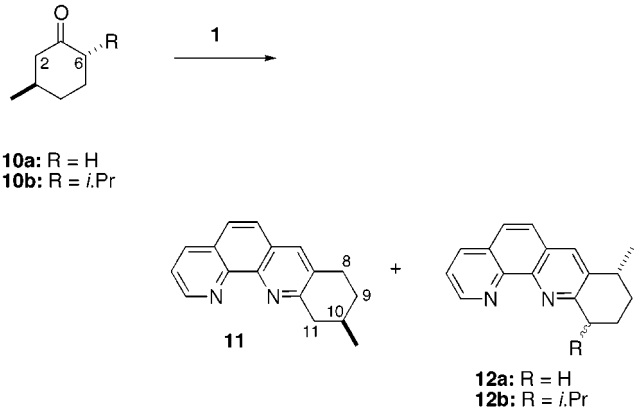


Scheme 4



Scheme 5



10a: R = H
10b: R = *i*.Pr

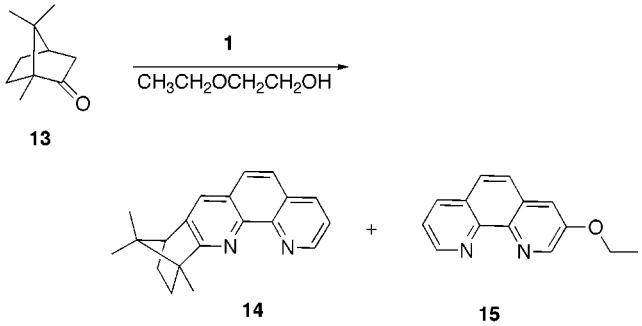
12a: R = H
12b: R = *i*.Pr

yield of **11** could be isolated. The identity of **11** was ascertained from its ^{1}H NMR which revealed four benzylic methylene protons. The C11 methylene appears as two 1-proton signals at 3.56 and 2.92 ppm with a geminal coupling of 17.4 Hz and vicinal couplings of 4.8 and 10.2 Hz to the C10 methine proton. The C8 methylene is an unresolved 2-proton multiplet at 3.08 ppm.

The condensation of **1** with cyclohexanone derivatives is quite sensitive to the steric congestion at the carbonyl group. In the case of a 2-alkyl-substituted cyclohexanone such as (2*R*,5*S*)-menthone (**10b**), a reaction time of 90 h was required to obtain a reasonable consumption of the substrate. The expected phen **12b**, obtained in only 15% yield and as a 3:1 mixture of epimers at C11, could not be purified or adequately characterized.

When the cyclohexanone is incorporated into a rigid bicyclic framework as in (+)(1*R*,4*R*)-camphor (**13**), only the C3 α-methylene site is available for condensation and hence a single Friedländer product is expected. As the attack of the aminoaldehyde at the C2 carbonyl of **13** is hindered by the adjacent quaternary C1 center, higher temperatures are required for the reaction to proceed. Six hours reflux in 2-ethoxyethanol (135 °C) indicated two phen products in a 22:78 ratio (Scheme 6). Chromatography on alumina provided the camphenyl-fused phen **14**[18] as the minor product in an overall 5% yield. The major product was identified as 3-ethoxyphen (**15**), apparently produced by the condensation of **1** with ethoxyacetaldehyde that is formed by oxidation of the solvent. The isolation of this byproduct gave us a clue into the use of aldehydes as Friedländer partners, a reaction which will be discussed in more detail below.

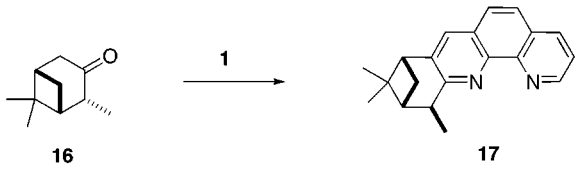
Scheme 6



(18) This compound has been recently obtained in higher yield through a related synthetic route. Chelucci, G.; Thummel, R. P. *Synthetic Commun.* **1999**, *29*, 1665.

A closely related isomer of **13** is the pinanone **16** which possesses three chiral centers one of which may epimerize through enolization. Indeed epimerization does occur during the course of condensation with **1**. The condensation proceeds at 80 °C, but higher yields are obtained when the reaction is run at 135 °C for a shorter time. The only possible regioisomer **17**, isolated in 16% yield, consisted of a single stereoisomer, possessing an equatorial methyl group, arising from complete epimerization at C2 (Scheme 7).

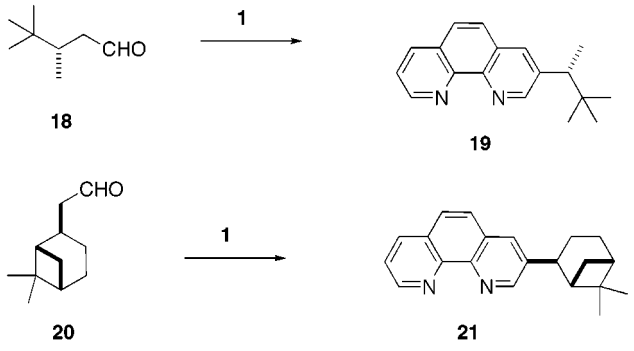
Scheme 7



16 **17**

The few chiral 3-alkyl phenanthrolines thus far reported have been prepared from chiral carbonyl compounds through multistep synthetic routes.[2,11] The one-step condensation of aminoquinoline carbaldehyde **1** with a monoalkyl-substituted acetaldeyde, if feasible, would provide a more efficient alternative. Unfortunately, aldehydes have not been widely considered as suitable substrates for the Friedländer condensation because under basic conditions they often undergo self-condensation leading to impractical product mixtures. Such unwanted side reactions were observed upon initial attempts with the chiral aldehydes **18** and **20**, which gave disappointingly low yields of phen derivatives under typical reaction conditions. Better results were obtained when it was realized that the extent of self-condensation could be limited by running the reaction at more moderate temperature (30−35 °C) and fairly low concentration of aldehyde. Portionwise addition of the substrate and long reaction times (120 h) led to improved yields of phen derivatives.

Scheme 8



18 **19**

20 **21**

In this manner (+)-(*S*)-3,4,4-trimethylpentanal (**18**) and the pinenyl carbaldehyde **20** give the corresponding phens **19** and **21** in 52% and 77% yields, respectively (Scheme 8). Thus the overall yield in an aldehyde Friedländer condensation was improved 4−5-fold over previous results.[2,11] The epimeric composition of the phen **21** (9:1) closely corresponds to the isomeric purity of the starting aldehyde **20**, as obtained from the hydroformylation of 2*R*,5*S*-*β*-pinene.[19]

This study has shown that the Friedländer condensation is a valuable and versatile synthetic protocol for the preparation of chiral (2,3-*b*)-cycloalkeno-fused phens using ketones from the chiral pool. It should be stressed that these phen derivatives are mostly inaccessible by any other known route.

The rate of the reaction is heavily dependent upon steric hindrance near the carbonyl group. Nevertheless, even congested ketones such as camphor can be converted, albeit in low yield, into the desired phen at more elevated temperatures.

When two positional isomers are possible, the regioselectivity of the condensation is dictated by the direction of the enamine formation. Consequently, for those ketones where enamine formation is subject to kinetic and thermodynamic control, the ratio of isomeric phens can be regulated, to a large extent, by choosing the appropriate reaction temperature. A study on the regiochemistry of the Friedländer reaction is in progress.

Under well-controlled conditions, the Friedländer condensation is well suited to the production of 3-alkyl phens from chiral monoalkyl-substituted acetaldeydes. This finding expands the synthetic scope of this reaction and makes readily accessible a class of previously rare chiral ligands.

The utility of the chiral phens prepared in this study as auxiliaries in transition metal-catalyzed reactions is under current investigation. From results obtained in a preliminary screening, allylic alkylation with Pd seems to promise high enantioselectivity,[20] whereas the prospects seem less encouraging for transfer hydrogenation (Rh) and cyclopropanation (Cu).

Experimental Section

General. Nuclear magnetic resonance spectra were obtained on a Varian VXR-300 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts are reported in ppm downfield from internal Me_4Si in $CDCl_3$. Gas chromatographic analysis were performed using a Hewlett-Packard 5890/A gas chromatograph equipped with a HP 3396 integrator. Optical rotations were measured on a Perkin-Elmer Model 241 polarimeter. Melting points were obtained with a Leitz Laborlux S melting point apparatus and are not corrected. Elemental analyses were performed with a Perkin-Elmer Analyzer 240B by Mr. A. Canu (Dipartimento di Chimica, Università di Sassari). MS Spectra were recorded with a HP 5988A spectrometer. The 8-amino-7-quinolinecarbaldehyde was prepared as reported.[14a]

(+)-5′α-Cholesteno-[3′,2′-*b*]-1,10-phenanthroline (3) and 5′α-Cholesteno-[3′,*4*′-*b*]-1,10-phenanthroline (4). Into a 100 mL round-bottom flask, equipped with a condenser, a magnetic stirrer, and a serum cap, under an atmosphere of nitrogen was introduced a mixture of 8-amino-7-quinolinecarbaldehyde (0.43 g, 2.50 mmol), 5α-cholestan-3-one (0.97 g, 2.50 mmol), and saturated ethanolic KOH (0.24 mL) in absolute EtOH (37 mL), and the solution was refluxed for 15 h. The course of the reaction was followed by TLC on neutral alumina eluting with EtOAc (R_f(phen) = 0.70, R_f(ketone) = 0.97, R_f(aminoaldehyde) = 0.89). After cooling, the mixture was concentrated and diluted with water to produce a white precipitate which was extracted with CH_2Cl_2. The combined organic phase was washed with water and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. An ^{1}H NMR of the crude material indicated an 87:13 mixture of two products. Crystallization from CH_2Cl_2/Et_2O provided the major product **3** (0.47 g, 36%): mp 235−237 °C; $[\alpha]^{20}_D$ +65.2° (*c* 1, $CHCl_3$); ^{1}H NMR *δ* 9.17 (dd, 1H, *J* 4.5 Hz, 1.8 Hz), 8.20 (dd, 1H, *J* 8.1 Hz, 1.8 Hz), 7.89 (s, 1H), 7.68 (ab, 2H, *J* 9.0 Hz), 7.57 (dd, 1H, *J* 8.1

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Hz, 4.5 Hz), 3.41 (dd, 1H, *J* 18.9 Hz, 5.4 Hz), 3.03 (d, 1H, *J* 16.1 Hz), 3.00 (dd, 1H, *J* 18.9 Hz, 13.2 Hz), 2.68 (d, 1H, *J* 16.1 Hz), 2.07 (dt, 1H, *J* 13.2 Hz), 1.64−1.84 (overlapping m), 1.02−1.57 (overlapping m), 0.94 (d, 3H, *J* 6.6 Hz), 0.87 (d, 6H, *J* 6.6 Hz), 0.82 (s, 3H), 0.71 (s, 3H); ^{13}C NMR δ 155.7, 147.0, 143.0, 141.1, 133.0, 132.7, 129.1, 125.2, 124.1, 123.1, 122.1, 119.3, 53.3, 53.2, 50.5, 40.5, 39.4, 39.1, 36.9, 36.4, 34.6, 33.1, 32.7, 32.5, 32.0, 28.5, 25.7, 25.1, 24.9, 21.1, 20.7, 19.7, 19.5, 18.3, 15.6, 8.9, 8.6; MS: *m*/*e* 522 (100, M^+), 507 (43), 245 (43). Anal. Calcd for $C_{37}H_{50}N_2 \cdot H_2O$: C, 82.17; H, 9.69; N, 5.18. Found: C, 82.65; H, 9.18; N, 5.36.

The mother liquor from the crystallization was chromatographed on neutral alumina eluting with EtOAc to provide a mixture of the two regiosiomers **3** and **4** (0.77 g, 59%) for an overall yield of 95%.

(+)-5′*β*-Cholesteno-[3′,2′-*b*]-1,10-phenanthroline (6) and (−)-5′*β*-Cholesteno-[3′,4′-*b*]-1,10-phenanthroline (7). In the manner described above for **3** and **4**, a mixture of 8-amino-7-quinolinecarbaldehyde (0.10 g, 0.58 mmol), 5*β*-cholestan-3-one (0.27 g, 0.70 mmol), and saturated ethanolic KOH (0.30 mL) in absolute EtOH (9 mL) was stirred at 25 °C for 48 h. The course of the reaction was followed by TLC on neutral alumina eluting with EtOAc/petroleum ether (1:2) (R_f(phen) = 0.46, R_f(ketone) = 0.79, R_f(aminoaldehyde) = 0.65). After cooling, the precipitate was collected and purified by chromatography on neutral alumina eluting with EtOAc/petroleum ether (1:2). Crystallization from CH_2Cl_2/EtOH afforded **7** (0.12 g; 40%): mp 283−285 °C; $[\alpha]^{25}_D$−62.3 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 9.18 (dd, 1H, *J* 4.5 Hz, 1.8 Hz), 8.21 (dd, 1H, *J* 8.1 Hz, 1.8 Hz), 8.16 (s, 1H), 7.71 (ab, 2H, *J* 8.7 Hz), 7.58 (dd, 1H, *J* 8.1 Hz, 4.5 Hz), 3.35 (d, 1H, *J* 4.8 Hz), 3.32 (d, 1H, *J* 5.4 Hz), 2.87 (s, 1H), 1.21−2.41 (overlapping m), 1.19 (s, 3H), 0.86 (d, 3H, *J* 6.6 Hz), 0.83 (d, 6H, *J* 6.6 Hz), 0.67 (s, 3H); ^{13}C NMR δ 156.9, 147.0, 142.8, 140.3, 132.8, 131.9, 130.7, 125.3, 124.3, 123.5, 112.0, 119.3, 53.1, 52.8, 42.5, 39.5, 38.9, 36.8, 36.3, 32.9, 32.7, 32.5, 31.3, 26.8, 26.6, 25.1, 24.8, 23.4, 21.0, 20.8, 20.1, 19.7, 19.4, 18.3, 15.4, 8.9; MS: *m*/*e* 522 (100, M^+), 507 (48), 245 (68). HRMS calcd for $C_{37}H_{50}N_2$ 522.397400, found 522.397084.

When the reaction was performed at 135 °C in ethoxyethanol, workup as described above afforded **6** as the major product. Crystallization from CH_2Cl_2/EtOH gave **6** (0.10 g; 24%): mp 224−226 °C; $[\alpha]^{25}_D$ = +124.0° (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 9.18 (dd, 1H, *J* 4.5 Hz, 1.8 Hz), 8.21 (dd, 1H, *J* 8.1 Hz, 1.8 Hz), 7.84 (s, 1H), 7.70 (ab, 2H, *J* 9.0 Hz), 7.58 (dd, 1H, *J* 8.1 Hz, 4.5 Hz), 3.53 (dd, 1H, *J* 19.5 Hz, 10.5 Hz), 3.40 (dd, 1H, *J* 19.8 Hz, 8.1 Hz), 3.02 (d, 1H, *J* 16.2 Hz), 2.69 (d, 1H, *J* 15.6 Hz), 1.22−2.17 (overlapping m), 0.87−1.19 (overlapping m), 0.82 (d, 6H, *J* = 6.6 Hz), 0.79 (d, 3H, *J* = 6.9 Hz), 0.64 (s, 3H); ^{13}C NMR δ 157.0, 147.0, 142.9, 141.3, 132.8, 131.5, 128.5, 125.2, 124.1, 123.2, 122.0, 119.2, 53.0, 53.0, 39.5, 38.8, 38.1, 37.1, 36.7, 36.3, 32.9, 32.6, 32.1, 31.6, 25.1, 24.8, 22.8, 22.4, 21.0, 20.7, 19.7, 19.4, 19.4, 18.0, 15.4, 8.9, MS: *m*/*e* 522 (100, M^+), 507 (48), 245 (68). HRMS calcd for $C_{37}H_{50}N_2$ 522.397400, found 522.397121.

(+)-5′α-2′-Androstadieno-[17′,16′-*b*]-1,10-phenanthroline (9). In the manner described above for **3** and **4** a mixture of 8-amino-7-quinolinecarbaldehyde (0.33 g, 1.92 mmol), 5α-androst-2-en-17-one (0.52 g, 1.92 mmol), and saturated ethanolic KOH (1.06 mL) in absolute EtOH (29 mL) was stirred at reflux for 22 h. The course of the reaction was followed by TLC on neutral alumina eluting with Et_2O (R_f(phen) = 0.37, R_f(ketone) = 0.80, R_f(aminoaldehyde) = 0.71). After cooling, the mixture was concentrated and diluted with water. The resulting white solid was extracted with CH_2Cl_2. The combined organic phase was filtered through Celite, washed with water, and dried (Na_2SO_4). The solvent was evaporated, and the reddish-brown crude product was flash chromatographed on neutral alumina eluting with CH_2Cl_2. The product was finally purified by recrystallization from Et_2O to afford **9** (0.51 g, 66%): mp 255−57 °C; $[\alpha]^{25}_D$ +152.6° (*c* 1.2, $CHCl_3$); ^{1}H NMR δ 9.23 (dd, 1H, *J* 4.2 Hz, 1.5 Hz), 8.22 (dd, 1H, *J* 8.1 Hz, 1.5 Hz), 7.98 (s, 1H), 7.72 (AB quartet, 2H, *J* 9.0 Hz), 7.56 (dd, 1H, *J* 8.1 Hz, 4.2 Hz), 5.62 (s, 2H), 2.96 (dd, 1H, *J* 15.3 Hz, 6.3 Hz), 2.72 (m, 2H), 0.89−2.17 (overlapping m), 1.16 (s, 3H), 0.87 (s, 3H); ^{13}C NMR δ 171.8, 147.0, 143.2, 141.6, 134.1, 132.9, 128.4, 125.3, 124.7, 123.8, 122.8, 122.6, 122.1, 119.0, 52.7, 51.4, 43.3, 38.5, 36.5, 31.8, 31.7, 30.6, 28.4, 27.3, 27.2, 25.5, 17.5, 14.5, 8.6; MS: *m*/*e* 408 (M^+, 58), 393 (100), 231 (33). Anal. Calcd for $C_{29}H_{32}N_2$: C, 85.25; H, 7.78; N, 6.86. Found: C, 85.56; H, 8.01; N, 6.62.

(+)-(*R*)-10′-Methyl-8′,9′,10′,11′-tetrahydrobenzo[*b*]-1,10-phenanthroline (11) and (*R*)-8′-Methyl-8′,9′,10′,11′-tetrahydrobenzo[*b*]-1,10-phenanthroline (12). In the manner described above for **3** and **4**, a mixture of 8-amino-7-quinolinecarbaldehyde (0.58 g, 3.37 mmol), (+)-*R*-3-methylcyclohexanone (0.38 g, 3.37 mmol), and saturated ethanolic KOH (1.70 mL) in absolute EtOH (51 mL) was stirred at reflux for 15 h. The course of the reaction was followed by TLC on neutral alumina eluting with Et_2O (R_f(phenanthrolines) = 0.54, 0.60, R_f(ketone) = 0.88, R_f(aminoaldehyde) = 0.86). After cooling, the mixture was concentrated and diluted with water. The resulting white solid was extracted with CH_2Cl_2. The combined organic phases were washed with water and dried (Na_2SO_4). The crude reaction product consisted of a mixture of regioisomers which was purified by chromatography on neutral alumina, eluting with EtOAc to afford **11** (0.47 g, 56%) and a mixture of **11** and **12** (0.35 g) for an overall yield of 97%. **11**: mp 128−30 °C; $[\alpha]^{25}_D$ +85.4° (*c* 1, $CHCl_3$); ^{1}H NMR δ 9.17 (dd, 1H, *J* 4.5 Hz, 1.8 Hz), 8.20 (dd, 1H, *J* 8.1 Hz, 1.8 Hz), 7.91 (s, 1H), 7.69 (ab, 2H, *J* 9.0 Hz), 7.58 (dd, 1H, *J* 8.1 Hz, 4.5 Hz), 3.56 (ddd, 1H, *J* 17.4 Hz, 4.8 Hz, 1.8 Hz), 3.08 (m, 2H), 2.92 (dd, 1H, *J* 17.4 Hz, 10.2 Hz), 2.17−2.00 (overlapping m, 2H), 1.56 (m, 1H), 1.17 (d, 3H, *J* 6.6 Hz); ^{13}C NMR δ 156.2, 147.0, 143.0, 141.0, 132.8, 132.1, 129.1, 125.1, 124.1, 123.1 122.2, 119.3, 39.2, 27.7, 26.3, 25.4, 18.7; MS: *m*/*e* 248 (M^+, 100), 233 (92), 206 (78). Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.22; H, 6.49; N, 11.28. Found: C, 82.32; H, 6.59; N, 11.31.

(−)-1′,1′,7′-Trimethyl[2.2.1]bicycloheptano[2′,3′-*b*]-1,10-phenanthroline (14). In the manner described above for **3** and **4**, a mixture of 8-amino-7-quinolinecarbaldehyde (0.40 g, 2.32 mmol) and (+)-(1*R*,4*R*)-camphor (0.35 g, 2.32 mmol) in 2-ethoxyethanol (35 mL) was combined with a solution of saturated KOH in 2-ethoxyethanol (1.03 mL), and the mixture was refluxed for 6 h. The course of the reaction was followed by TLC on neutral alumina eluting with EtOAc (R_f(phenanthroline) = 0.61, R_f(ketone) = 0.78, R_f(aminoaldehyde) = 0.86). After cooling, the mixture was concentrated, diluted with water, and extracted with Et_2O. The combined organic phases were filtered through Celite, washed with water, and dried (Na_2SO_4). After evaporation of the solvent, an ^{1}H NMR of the crude reaction mixture revealed the presence of two products (22:78). Chromatography on neutral alumina provided the minor product **14** (0.03 g, 5%): mp 169−170 °C; $[\alpha]^{25}_D$ −30.2 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 9.20 (dd, 1H, *J* 4.5 Hz, 2.1 Hz), 8.23 (dd, 1H, *J* 8.1 Hz, 1.8 Hz), 7.85 (s, 1H), 7.75 (ab, *J* 8.7 Hz), 7.56 (dd, 1H, *J* 7.8 Hz, 4.2 Hz), 3.06 (d, 1H, *J* 4.2 Hz), 1.64 (s, 3H), 1.10 (s, 3H), 0.60 (s, 3H); ^{13}C NMR δ 169.0, 147.2, 143.2, 140.9, 138.9, 132.8, 124.9, 124.8, 123.9, 123.7, 121.7, 118.7, 53.2, 51.8, 48.3, 28.6, 23.1, 17.2, 16.0, 7.7. MS: *m*/*e* 288 (50, M^+), 273 (43), 245 (100). Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.14. Found: C, 83.56; H, 7.61; N, 9.16. A second fraction contained 0.11 g of 3-ethoxy-1,10-phenanthroline: ^{1}H NMR δ 9.16 (dd, 1H, *J* = 4.5 Hz, 1.8 Hz), 8.93 (d, 1H, *J* = 6.9 Hz), 8.21 (dd, 1H, *J* = 8.1 Hz, 1.8 Hz), 7.73 (ab, 2H, *J* = 8.14 Hz), 7.51 (d, 1H, *J* = 6.9 Hz), 7.36 (dd, 2H, *J* = 8.1 Hz, 4.5 Hz), 3.48 (q, 2H, *J* = 7.3 Hz), 1.51 (t, 3H, *J* = 7.3 Hz).

(+)-(1*S*,2*R*,5*S*)-(3′,4′-*b*)-2′,7′,7′-Trimethyl[2.1.1]bicyclohepteno-1,10-phenanthroline (17). In the manner described above for **3** and **4**, a mixture of 8-amino-7-quinolinecarbaldehyde (0.11 g, 0.64 mmol), (−)-(1*S*,2*S*,5*R*)-3-pinanone (0.10 g, 0.64 mmol), and potassium *tert*-butoxide (0.50 g, 4.46 mmol) in 2-ethoxyethanol (29 mL) was heated at reflux for 15 h. The course of the reaction was followed by TLC on neutral alumina, eluting with EtOAc/petroleum ether (4:1, R_f(phen) = 0.58, R_f(ketone) = 0.88, R_f(aminoaldehyde) = 0.76). The reaction mixture was cooled, diluted with water (100 mL), and extracted with Et_2O:CH_2Cl_2 (3:1). The combined organic phase was filtered through Celite, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave a crude product which showed a mixture of phens by NMR. An acid−base extraction was

followed by chromatography on neutral alumina, eluting with EtOAc/petroleum ether (4:1) to provide unreacted aminoaldehyde in the early fractions followed by **17** (0.03 g, 16%) as a single stereoisomer: mp 77−78 °C; $[\alpha]^{25}_D$ +2.3 (*c* 0.7, $CHCl_3$); ^{1}H NMR δ 9.17 (dd, 1H, *J* 4.5 Hz, 2.1 Hz), 8.19 (dd, 1H, *J* 8.1 Hz, 1.8 Hz), 7.70 (s, 1H), 7.68 (d, 2H, *J* 7.5 Hz), 7.55 (dd, 1H, *J* 8.1 Hz, 4.5 Hz), 3.64 (qd, 1H, *J* 6.9 Hz, 2.4 Hz), 3.00 (t, 1H, *J* 6.0 Hz), 2.66 (dt, 7.55 (dt, 1H, *J* 10.5 Hz, 6.0 Hz), 2.25 (td, 1H, *J* 6.0 Hz, 2.4 Hz), 1.62 (d, 3H, *J* 6.9 Hz), 1.46 (s, 3H), 1.43 (d, 1H, *J* 10.0 Hz), 0.67 (s, 1H);); ^{13}C NMR δ 163.1, 150.1, 146.0, 144.3, 142.1, 136.1, 131.1, 128.2, 127.1, 126.5, 125.5, 122.1, 47.7, 46.8, 41.4, 39.6, 28.8, 26.3, 21.1, 19.2; MS: *m*/*e* 288 (54, M^+), 273 (62), 245 (100).

(+)-(*R*)-3-(1′,2′,2′-Trimethylpropyl)-1,10-phenanthroline (19). In the manner described above for **3** and **4**, a mixture of 8-amino-7-quinolinecarbaldehyde (0.20 g, 1.16 mmol) and saturated ethanolic KOH (1.0 mL) in absolute EtOH (17.5 mL) was warmed to 35 °C and (+)-(*S*)-3,4,4-trimethylpentanal (0.52 g, 4.06 mmol, ee 67%)[2] was slowly added in decreasing portions at 10 h intervals during the course of the reaction. The reaction was followed by TLC on neutral alumina eluting with EtOAc (R_f(phen) = 0.36, R_f(aminoaldehyde) = 0.89). After 120 h, the mixture was concentrated, diluted with water, and extracted with CH_2Cl_2. The combined organic phase was filtered through Celite, washed with water, and dried (Na_2SO_4). After the solution was concentrated, the crude residue was extracted with 25% HCl, and the acid extracts were neutralized with 25% NaOH to provide a precipitate which was extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), the solvent was evaporated, and the final product was purified by filtration through neutral alumina using EtOAc to afford **19** (0.17 g, 55%) which was recrystallized from CH_2Cl_2: mp 138−140 °C (lit.[2] mp 138−140 °C), $[\alpha]^{25}_D$ = +6.5° (*c* 1.03, 95% EtOH) corresponds to an optical purity of 88%:[2] ^{1}H NMR δ 9.17 (dd, 1H, *J* 4.5 Hz, 1.8 Hz), 9.02 (d, 1H, *J* 2.4 Hz), 8.23 (dd, 1H, *J* 8.1 mHz, 1.8 Hz), 8.00 (d, 1H, 2.4 Hz), 7.77 (ab, 2H, *J* 8.4 Hz), 7.61 (dd, 1H, *J* 8.1 Hz, 4.5 Hz), 2.89 (q, 1H, *J* 7.2 Hz), 1.43 (d, 3H, *J* 7.2 Hz), 0.95 (s, 9H); ^{13}C NMR δ 149.0, 147.0, 143.1, 141.4, 137.0, 132.7, 131.6, 125.0, 124.9, 123.5, 123.1, 119.5, 44.4, 30.9, 24.5, 12.5.

(+)-3-[(1*S*,2*R*,5*S*)-Pinenyl]-1,10-phenanthroline (21). In the manner described above for **3** and **4**, a mixture of 8-amino-7-quinolinecarbaldehyde (0.20 g, 1.16 mmol) and saturated ethanolic KOH (1.0 mL) in absolute EtOH (17.5 mL) was treated slowly with (−)-(1*S*,2*R*,5*S*)-pinenylcarbaldehyde (0.37 g, 2.22 mmol)[17] at 25−30 °C added in decreasing portions, at 10 h intervals, during the course of the reaction. The reaction was followed by TLC on neutral alumina eluting with EtOAc (R_f(phen) = 0.42, R_f(aminoaldehyde) = 0.89). After 120 h, the mixture was concentrated, diluted with water, and extracted with CH_2Cl_2. The combined organic phase was filtered through Celite, washed with water, and dried (Na_2SO_4). After the solution was concentrated, the crude residue was extracted with 25% HCl, and the acid extracts were neutralized with 25% NaOH to provide a precipitate which was extracted with CH_2Cl_2. The combined organic phase was dried (Na_2SO_4), and the solvent was evaporated to provide a material (0.27 g, 77%) which NMR indicated to be a 9:1 mixture of epimeric phens. This crude product was dissolved in benzene/*n*-hexane (1:1), and the brown solid which formed was filtered. The mother liquor was concentrated, and the major product **21** was purified by recrystallization from CH_2Cl_2/*n*-hexane. Some drops of benzene were added to dissolve a yellow oil which formed with the crystals; **21**: mp 170 °C (lit.[11] mp 173 °C); $[\alpha]^{25}_D$ +28.4 (*c* 2.0, EtOH) (lit.[11] $[\alpha]^{25}_D$ +28.1 (*c* 2, EtOH)); ^{1}H NMR δ 9.09 (dd, 1H, *J* 4.5 Hz, 1.8 Hz), 9.02 (d, 1H, *J* 2.1 Hz), 8.21 (dd, 1H, *J* 8.1 Hz, 1.8 Hz), 8.00 (d, 1H, *J* 2.1 Hz), 7.74 (s, 2H), 7.58 (dd, 1H, *J* 8.1 Hz, 4.5 Hz), 3.51 (t, 1H, *J* 8.1 Hz), 1.77−2.37 (overlapping m, 8H), 1.31 (s, 3H), 1.03 (s, 3H); ^{13}C NMR δ 147.9, 147.0, 143.2, 141.3, 139.7, 132.7, 129.1, 125.5, 125.0, 123.5, 123.1, 119.4, 42.7, 36.8, 36.5, 35.1, 23.7, 21.6, 20.9, 20.6, 17.1. Anal. Calcd for $C_{21}H_{22}N_2$: C, 81.37; H, 6.81; N, 11.82. Found: C, 81.54; H, 6.55; N, 11.61.

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Supporting Information Available: NMR spectra of compounds **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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