SYNTHESIS OF CINCHONA ALKALOID ANALOGUES AS MECHANISTIC PROBES OF THE OSMIUM–CATALYZED ASYMMETRIC DIHYDROXYLATION OF OLEFINS

by

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ABSTRACT

Synthesis of Cinchona Alkaloid Analogues as Mechanistic Probes of the Osmium–Catalyzed Asymmetric Dihydroxylation of Olefins

by John W. Young, Jr.

Submitted to the Department of Chemistry on August 23, 1991 in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy.

Several features of the osmium-catalyzed asymmetric dihydroxylation of olefins have undergone significant refinement recently. For instance, the development of new oxidants for the Os(VI) to Os(VIII) conversion necessary for the catalytic cycle have improved the reaction dramatically. Additionally, extensive ligand modifications on the parent cinchona alkaloid structures have provided a steady increase in enantioselectivities, and other aspects of ligand-osmium interactions are being studied to help identify the essential structural characteristics of effective ligands.

The synthesis of a series of cinchona alkaloid analogues differentially substituted at C-9 in place of the quinoline moiety is described utilizing two distinct synthetic routes. In the first case, 2-cyanoquinuclidine was used as a common intermediate, and its improved synthesis is detailed. Amino alcohols were produced by reaction of the nitrile with organometallic reagents, followed by stereoselective reduction of the intermediate ketones. Secondly, the one-pot alkylation/in situ reduction of quinuclidine-*N*-oxide is described for the synthesis of similar amino alcohols. Additionally, the syntheses of several related compounds from other intermediates and by degradation of parent alkaloids are discussed. The failure of a kinetic resolution strategy for the resolution of the aforementioned synthetic analogues was a surprising disappointment; however, classical resolution of one analogue followed by suitable derivatization provided material for use in asymmetric dihydroxylations.

Binding studies of racemic alkaloid analogue derivatives using solvent and temperature conditions most relevant to the current catalytic system employing $K_3[Fe(CN)_6]$ were performed by titration with osmium tetroxide in *tert*-butanol at 25°C monitoring by UV. The binding studies indicate that, of the synthetic derivatives prepared, those analogues with structures most similar to those of the parent alkalcids are the best ligands for osmium tetroxide.

Molecular mechanics calculations were performed on several of the synthetic amino alcohol *p*-chlorobenzoate derivatives. Although any relationship between differences in conformational energies and binding constants was not addressed, the failure of some of the alkaloid analogues to interact significantly with osmium tetroxide can be rationalized based on the results of these calculations in light of known cinchona alkaloid derivative conformational dynamics.

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INTRODUCTION

The widespread use of cinchona alkaloid-based ligands and reagents in asymmetric synthesis,[1] and the pharmacologic activity of the alkaloids, particularly quinine and quinidine, make structural analogues attractive synthetic candidates for structure-activity relationship studies. Stereocontrol in a variety of asymmetric transformations, including the formation of cyanohydrins with trimethylsilyl cyanide,[2] heterogeneous hydrogenations,[3] and dihydroxylations with osmium tetroxide[4] is mediated by the readily-available cinchona alkaloids or their simple derivatives. More radical structural variations are likely to prove interesting mechanistically and synthetically.

The osmium-catalyzed dihydroxylation of olefins has proven to be of considerable utility to organic chemists for many years due to its remarkable efficiency, selectivity, and mild reaction conditions. Asymmetric variants, both catalytic[4a,b] and stoichiometric[5] have appeared recently, all of which utilize chiral amine ligands. The significance of an asymmetric dihydroxylation strategy is the same as that already recognized for the Sharpless asymmetric epoxidation of allylic alcohols[6] or the homogeneous asymmetric hydrogenation of acetamido

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[1]For a review, see Wynberg, H. *Top. Stereochem.* **1986**, *16*, 87.

[2]Kobayashi, S.; Tsuchiya, Y.; Mukaiyama, T. *Chem. Lett.* **1991**, 541.

[3]Garland, M.; Blaser, H.-U. *J. Am. Chem. Soc.* **1990**, *112*, 7048.

[4]a) Kwong, H.-L.; Sorato, C.; Ogino, Y.; Chen, H.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, 2999. b) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. c) Hentges, S. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.

[5]a) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. b) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834. c) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1987**, *109*, 6213. d) Yamada, T.; Narasaka, K. *Chem Lett.* **1986**, 131. e) Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, 3951.

[6]a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Do, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. b) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

acrylic acids,[7] namely, the potential for the establishment of two contiguous stereogenic centers in one synthetic operation. One of the most attractive features of osmium-catalyzed asymmetric dihydroxylation is substrate generality. While the substrate pools of various other asymmetric reactions are often rather limited, for instance the restriction of titanium-catalyzed asymmetric epoxidation to allylic alcohols, catalytic asymmetric dihydroxylation (ADH) is compatible with many olefin substitution patterns and varied substituents.

Many features of the catalytic ADH have undergone optimization, including the choice of stoichiometric oxidant,[4a] modes of olefin addition,[8] additives helpful to glycolate hydrolysis,[8,9] and alkaloid derivatization.[10] Currently, the most convenient and effective catalytic conditions use $K_3[Fe(CN)_6]$ as the stoichiometric oxidant in 1:1 *tert*-BuOH:H_2O in the presence of K_2CO_3 at 25°C.[4a] Despite the success in the understanding of the optimization of catalytic cycles, little is understood about the mechanism of asymmetric induction during the ADH using cinchona alkaloid derivatives. While it is unlikely that a readily-available, reasonably-priced, totally-synthetic ligand class will ever emerge to replace the cinchona alkaloids as useful chiral ligands, no studies of synthetic analogues for the purpose of learning what characteristics are necessary for an effective ligand have been undertaken until now.

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[7]a) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746. b) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1980**, 344

[8]Wai, J. S. M.; Marko, I.; Svendsen, J. S.; Finn, M. F.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.

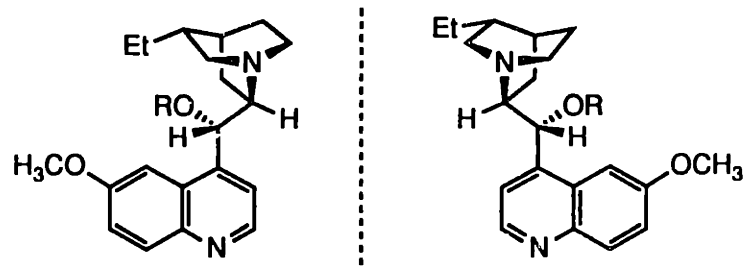
[9]a) Akashi, K.; Palermo, R. E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2063. b) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1976.

[10]a) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lubben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585. b) Shibata, T.; Gilheany, D. G.; Blackburn, B. K.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, 3817.

Numerous amine ligands, both chiral and achiral, are known to modify the reactivity of osmium tetroxide towards olefins in several ways. First, chiral ligands bind to OsO_4 creating a chiral oxidant capable of asymmetry transfer during dihydroxylation. Several notable examples of chiral ligands used for asymmetric dihydroxylation are shown in Figure 1.

Figure 1

Monodentate C_1 ligands

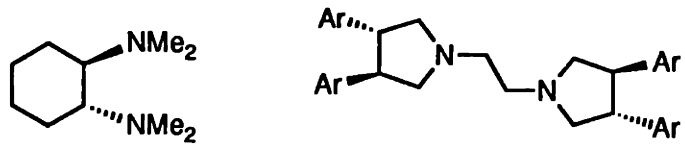


1 dihydroquinidine derivatives

2 dihydroquinine derivatives

R = aromatic acyl, aryl,or heteroaryl

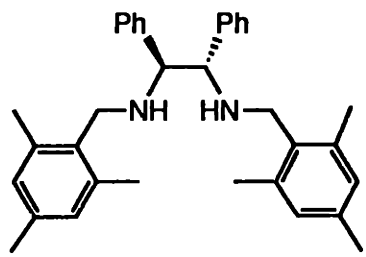
Bidentate C_2 ligands



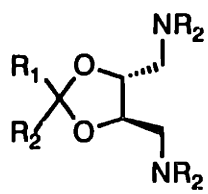
3

4a R = Ph
4b R = mesityl

5 R = neohexyl



6

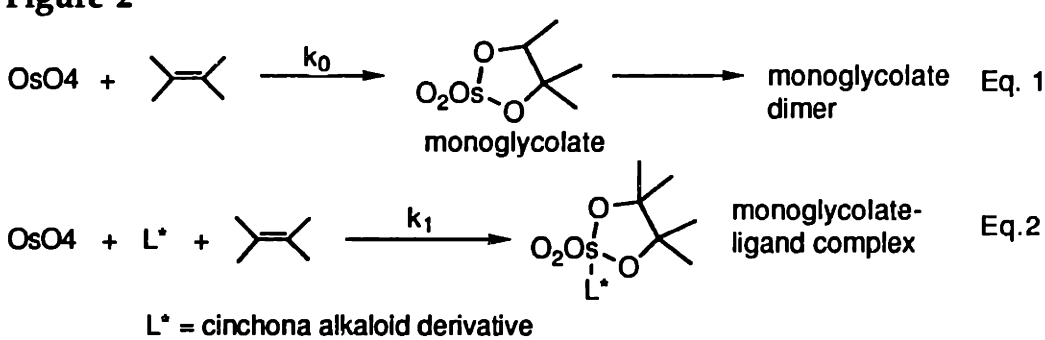


7

Second, amine-osmium complexes are known to increase the rate of formation of osmium(VI) glycolates, the isolable intermediates in stoichiometric and

catalytic dihydroxylations.[11] Since 1988, Sharpless has taken advantage of this ligand acceleration by pairing various known, catalytic dihydroxylation systems with cinchona alkaloid derivatives to produce chiral diols utilizing miniscule amounts of osmium and chiral ligands. High enantioselectivities are observed when the difference in energies of the diastereomeric transition states for the addition step (Figure 2, Eq. 2) is large *and* when the rate of osmylation by the osmium-ligand complex is much faster than the rate of osmylation by osmium tetroxide alone ($k_1 >> k_0$). This second condition is an example of ligand accelerated catalysis.

Figure 2



While the majority of ligands in Figure 1 are bidentate, the monodentate cinchona alkaloid derivatives are the only chiral ligands able to participate in the catalytic processes currently available. It appears that hydrolysis/reoxidation of Os(VI) to Os(VIII) is inhibited by bidentate ligands; hence, they are useful only for stoichiometric osmylations. Additionally, the reactions utilizing bidentate ligands tend to require very low temperatures for complex stability and optimal selectivity. In contrast, catalytic ADH reactions are frequently performed at 0°C or at room temperature. Clearly, the use of cinchona alkaloid derivatives offers two distinct advantages: the use of substoichiometric amounts of reagents which are toxic and/or expensive, and the ability to operate at convenient temperatures.

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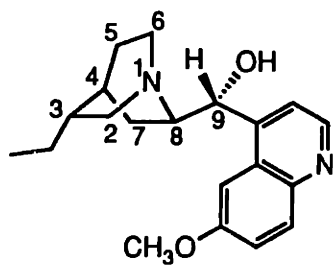
[11]For seminal studies of osmate ester chemistry, see: Criegee, R. *Justus. Liebigs Ann. Chem.*. **1936**, *522*, 75 and Criegee, R.; Marchand, B.; Wannowius, H. *Justus. Liebigs Ann. Chem.* **1942**, *550*, 99.

Dihydroquinidine (**1**, R = H) and dihydroquinine (**2**, R = H), while formally possessing a diastereomeric relationship, have been designated "pseudoenantiomeric" because of their near-mirror-image relationship, which is pictured in Figure 1 and accentuated by the dashed vertical line. All of the stereogenic centers in **1** and **2** possess a mirror-image relationship except C-3, which carries the vinyl substituent (or ethyl for the dihydro derivatives). Indeed, derivatives of **1** and **2** behave as enantiomers in the ADH, with the dihydroquinine derivatives showing slightly lower enantioselectivities than the dihydroquinidine derivatives in ADH reactions. Ligand refinements leading to the use of aryl ether derivatives have decreased the difference in selectivity of **1** and **2** such that it is now negligible.

With the aim of ligand refinement, the cinchona alkaloids, particularly quinidine, have been derivatized extensively at the C-9 hydroxyl group, manipulated at the vinyl group, and to some extent modified on the quinoline moiety. The numbering scheme for the bicyclic portion of quinine is shown in Figure 3 and remains consistent for all analogues and degradation intermediates.

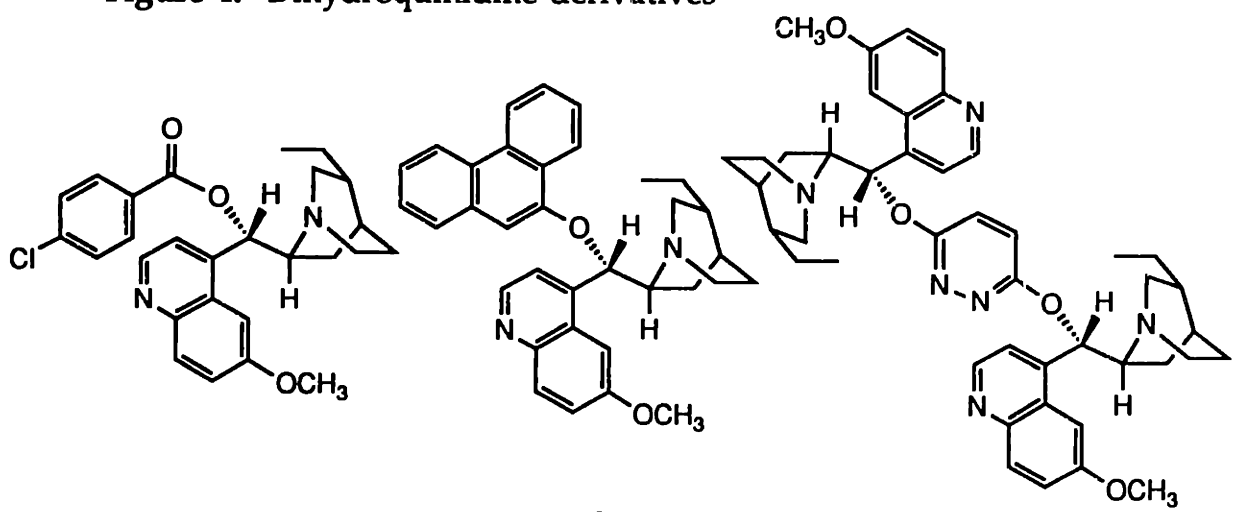
Figure 3. Dihydroquinine



Since the initial reports using dihydroquinidine acetate in dihydroxylations, the improvements in ligand effectiveness for asymmetry transfer during dihydroxylations of a wider variety of olefin classes have been quite dramatic. First, aryl esters[4b] (Figure 4a) proved to be superior to acetate and simple alkyl esters for trans-disubstituted aryl olefins; later, aryl and heteroaryl ethers[10] (Figure 4b) , but not alkyl or silyl ethers, were recognized as exemplary ligands for

both aliphatic and aromatic disubstituted olefins, and for terminal olefins to a somewhat lesser extent. Most recently, bis-cinchona phthalazine derivatives[12] (Figure 4c) have emerged as extraordinarily promising ligands for monosubstituted and 1,1-disubstituted olefins, as well as for all of the previously mentioned olefin classes.

Figure 4. Dihydroquinidine derivatives



a **b** **c**

The requirement of an sp^2-hybridized carbon attached to the C-9 oxygen seems to be a general rule for the success of a ligand, as seen for aryl esters, aryl ethers, and heteroaryl ethers. Currently, the development of equally efficacious ligands for the ADH of cis olefins remains elusive; however, a recently-described catalytic asymmetric epoxidation system[13] handles cis olefins with remarkable selectivity, while acting the complement by performing poorly with typical olefin classes which are amenable to the ADH.

Changes made to the vinyl group of quinine and quinidine are apparently fairly innocuous. For instance, ADH reactions using quinidine, its own vinyl group dihydroxylated during the reaction, still provide high

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[12]Hartung, J.; Sharpless, K. B., unpublished results.

[13]Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.

enantioselectivities.[14] Additionally, elaboration of the vinyl group into a flexible, unsaturated tether, followed by cross-linking with acrylonitrile produces polymeric cinchona derivatives which exhibit only minimally diminished effectiveness.[15]

Some limited studies were undertaken previously to modify the quinoline moiety of quinidine derivatives. The methoxy group, which is oriented, surprisingly, towards osmium in dihydroquinidine derivative–osmium tetroxide crystal structures, and the absence of which causes a modest decrease in enantioselectivities (10-15%) when utilizing cinchonine or cinchonidine derivatives, was cleaved to the phenol and esterified or silylated.[16] Again, enantioselectivities decreased approximately 10-20%. Two experiments were designed to rule out the competitive binding of the quinoline nitrogen to osmium tetroxide (2-substituted pyridines are known, independently, to bind poorly) and to probe the contribution of any electronic effects of the quinoline moiety to enantioselectivity. The quinoline nitrogen was selectively quaternized with alkylating agents in one set of experiments, and the nitrogen was transformed to the *N*-oxide in another set.[16] In both cases, little or no effect was observed in the enantioselectivities of ADH reactions utilizing these ligands.

Two other cinchona alkaloid modifications provide critical information. First, the deoxy-alkaloids (at C-9) give very poor enantioselectivities. Second, the epi-alkaloids (epimeric at C-9, having the threo relative stereochemistry) do not bind to osmium tetroxide, and, as expected, induce no enantioselectivity.

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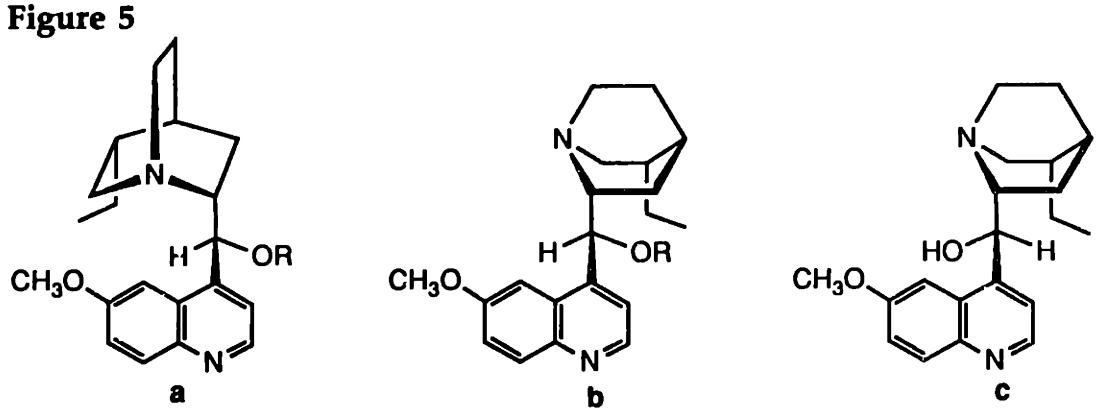
[14]Wai, J. S. M.; Sharpless, K. B., unpublished results.

[15]Kim, B. M.; Sharpless, K. B. *Tetrahedron Lett.* **1990**, 3003.

[16]Zhao, S.; Sharpless, K. B., unpublished results.

Aside from empirical results alone, some insight into cinchona alkaloid derivatives has been gained from molecular mechanics studies in conjunction with NMR techniques.[17] Dihydroquinidine *p*-chlorobenzoate exists primarily in a "closed" conformation (Figure 5a) in solution as determined by inter-ring NOE interactions. Closed conformations are characterized by the lone pair on the quinuclidine nitrogen pointing directly over the quinoline ring. A slightly higher energy "open" conformation (Figure 5b) is possible, however, and this conformation must be accessible in order to allow binding of osmium tetroxide.

Figure 5



R = *p*-C_6H_4CO

It follows that any new, potential ligands must have a corresponding open conformation available to receive the osmium. Identical studies on epi-dihydroquinidine indicate that it exists in a similar open conformation (Figure 5c). However, if this conformation is retained by the corresponding *p*-chlorobenzoate, an explanation for the lack of binding of epi-cinchona alkaloid derivatives to osmium tetroxide is obvious--the *p*-chlorobenzoate moiety is directly in the way. Rotation of the *p*-chlorobenzoyl group away from the binding site would require the quinoline ring to interact severely with the quinuclidine ring system.

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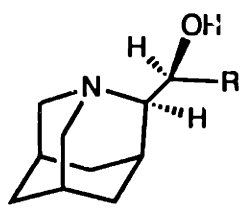
[17]Dijkstra, G. D. H.; Kellogg, R. M.; Wynberg, H.; Svendsen, J. S.; Marko, I.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 8069.

Besides the observation of open and closed conformations, additional X-ray studies,[18] analysis of NMR coupling constants,[17] and molecular mechanics calculations[19] all indicate that the quinuclidine ring system is twisted (20-25° for dihydroquinidine *p*-chlorobenzoate) away from the eclipsed conformation. This twist may be significant to the transfer of asymmetry from cinchona alkaloid-osmium tetroxide complexes. It is unlikely that the C-3 ethyl substituent contributes very much to the twist in the quinuclidine core, since the large substituent at C-8 certainly skews the structure significantly. Hence, a ring system incapable of adopting a twisted geometry is necessary to test the significance of twisting to enantioselectivity, and these results can be compared directly with enantioselectivities observed with an alkaloid analogue lacking the C-3 substituent. Current work is underway by coworkers on the synthesis of substituted azaadamantanes (Figure 6) for this purpose.

Figure 6



There has been considerable debate concerning the mechanism of the addition of olefins to osmium tetroxide centering around whether a four-center, [2+2] cycloaddition or a six-electron, [3+2] cycloaddition occurs. Sharpless proposed a [2+2] cycloaddition mechanism,[20] invoking an oxametallacyclobutane intermediate analogous to the one invoked to explain chromyl chloride reactivity with olefins. A facile insertion of one of the remaining oxo ligands

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[18]Svendsen, J. S.; Marko, I.; Jacobsen, E. N.; Rao, C. P.; Bott, S.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 2263.

[19]Soler, M.; Gutierrez, A.; Sharpless, K. B., unpublished results.

[20]Sharpless, K. B.; Teranishi, A. Y.; Backvall, J.-E. *J. Am. Chem. Soc.* **1977**, *99*, 3120.

into the osmium-carbon bond completes formation of the glycolate, which yields diol upon hydrolysis. The observation that electron-rich olefins react faster than electron-deficient olefins with osmium tetroxide supports the notion of the olefin acting as a nucleophile, interacting preferentially with the metal center rather than directly and exclusively with the electronegative oxo ligands as required in a [3+2] mechanistic scheme. The [2+2] mechanism is also reasonable considering the well-established chemistry of many high-valent, third-row transition metal species, which act as olefin metathesis catalysts by addition of olefins to metal carbenes in a [2+2] sense to produce metallacyclobutane intermediates, examples of which have been isolated and characterized.[21] To date, no oxametallacyclobutane intermediates[22] in the reaction of olefins with osmium tetroxide have been isolated or observed directly,[23] although some indirect evidence exists. For instance, the presence of intermediate metal-carbon bonds has been inferred from the observation of the ring-opening metathesis polymerization of norbornene by OsO_4.[24] Increasing numbers of oxametallacyclobutanes have been synthesized by alternate routes,[25] and at least

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[21]a) Bazan, G. C.; Khosravi, E.; Schrock, R. R.; Feast, W. J.; Gibson, V. C.; O'Reagan, M. B.; Thomas, J. K.; Davis, W. M. *J. Am. Chem. Soc.* **1990**, *112*, 8378. b) Feldman, J.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2266. c) Feldman, J.; Murdzek, J. S.; Davis, W. M.; Schrock, R. R. *Organometallics* **1989**, *8*, 2260.

[22]For a discussion of metallaoxetanes as possible oxygen atom-transfer intermediates, see Jorgensen, K. A.; Schiott, B. *Chem. Rev.* **1990**, *90*, 1483.

[23]A reported observation of an oxametallacyclobutane intermediate in the ^{1}H-NMR was shown to be incorrect. See Schroder M.; Constable, E. *J. Chem. Soc., Chem. Commun.* **1982**, 734 for the reported observation, and Casey, C. P. *J. Chem. Soc., Chem. Commun.* **1983**, 126 for the alternative explanation.

[24]Hamilton, J. G.; Mackey, O. N. D.; Rooney, J. J.; Gilheany, D. G. *J. Chem. Soc., Chem. Commun.* **1990**, 1600.

[25]a) Bazan, G. C.; Schrock. R. R.; O'Regan, M. B. *Organometallics* **1991**, *10*, 1062. b) Hartwig, J. F.; Bergman, R. G.; Andersen, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3234. c) Day, V. W.; Klemperer, W. G.; Lockledge, S. P.; Main, D. J. *J. Am. Chem. Soc.* **1990**, *112*, 2031. d) Klein, D. P.; Hayes, J. C.; Bergman, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 3704. e) Ho, S. C.; Hentges, S.; Grubbs, R. H. *Organometallics* **1988**, *7*, 780. f)Buchwald, S. L; Grubbs, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 5490.

one has been shown to undergo reversion to olefin and metal oxo by the microscopic reverse of the [2+2] addition.[26]

Proponents of the [3+2] mechanism point to frontier molecular orbital calculations by Jorgensen and Hoffmann[27] which indicate that the [3+2] mechanism is favorable electronically relative to the [2+2] mechanism for the addition of olefins to OsO_4 in the presence of amines, which lower the LUMO engery for the OsO_4–ligand complex, making it more reactive and accounting for the observed rate accelerations. In contrast, most of the indirect mechanistic interpretations present in the literature depend exclusively on the participation of chiral ligands. Tomioka examined Os(VI) glycolate complexes with chiral diamines **4a**[28] and **4b**[29] in light of possible [2+2] and [3+2] cycloaddition transition structures and concluded that the observed enantioselectivities are more consistent with a [2+2] mechanism in which rapid, reversible formation of the oxametallacyclobutane is followed by irreversible oxo insertion induced by the second amine (Figure 7).

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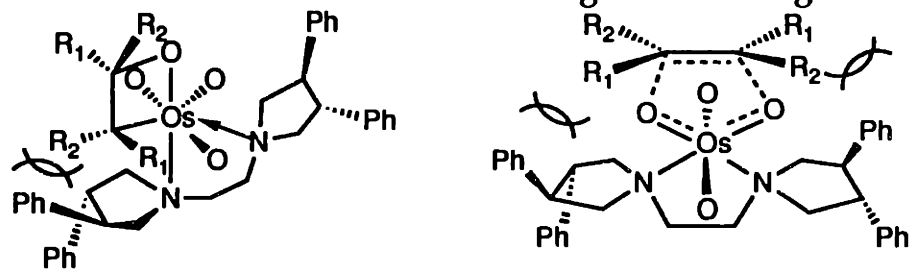
[26]Whinnery, L. L.; Bercaw, J. E. Presented at the Fall 1988 ACS National Meeting. Los Angeles, CA, September 1988; Abstract 160.

[27]Jorgensen, K. A.; Hoffmann, R. *J. Am. Chem. Soc.* **1986**, *108*, 1867.

[28]Tomioka, K.; Nakajima, M.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 573.

[29]Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 1741.

Figure 7. Possible transition structures using Tomioka's ligand **4a**.



[2+2] transition structure [3+2] transition structure

a) R_1 = Ph; R_2 = H
b) R_1 = H; R_2 = Ph

Tomioka's observation that the bis pyridine adduct of racemic hydrobenzoin Os(VI) monoglycolate forms nearly equal amounts of the two possible diastereomers upon addition of **4a** indicates that the enantioselective dihydroxylation must be under kinetic control. While either the [2+2] or the [3+2] mechanisms can account for the observed rate acceleration in the presence of amine ligand, only the [2+2] transition structure predicts the observed selectivity (R_1 = Ph, R_2 = H for stilbene dihydroxylation). In contrast, a [3+2] mechanism has a very late transition structure (product-like), but the most reasonable transition structure based on steric grounds predicts the wrong glycolate stereochemistry (R_1 = H, R_2 = Ph) when using **4a**. Corey, on the other hand, modelled chiral 2° diamine (**5**)–osmium tetroxide–olefin interactions similarly and stated that a [3+2] mechanism must be operative.[30] The conceptual development of a stereochemical model for osmylations involving cinchona alkaloid-based ligands is much less straightforward due to a lack of symmetry in the ligands and the remote location of stereogenic centers. In an effort to explain the stereoselectivity of osmylations involving quinidine and quinine-based ligands in terms of a [3+2] mechanism, Corey proposed additionally the catalytic activity of cinchona alkaloid–osmium(VIII) oxo-bridged dimers (Figure 8);

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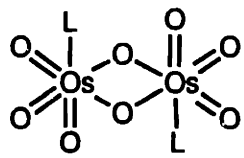
[30]Corey, E. J.; Lotto, G. *Tetrahedron Lett.* **1990**, *31*, 2665.

however, this possibility is inconsistent with published kinetic data[31] which shows clearly first-order dependence of the rate on osmium concentration.

Figure 8



L = dihydrocinchona alkaloid derivative

Certainly, the mechanistic issues surrounding the osmylation reaction are far from resolved, and until the mechanistic puzzle is solved, a stereochemical model allowing full predictability is unlikely to be developed. In the meantime, empirically-derived models based on ligand structure-activity relationships will continue to be refined and applied cautiously to explain selectivity.

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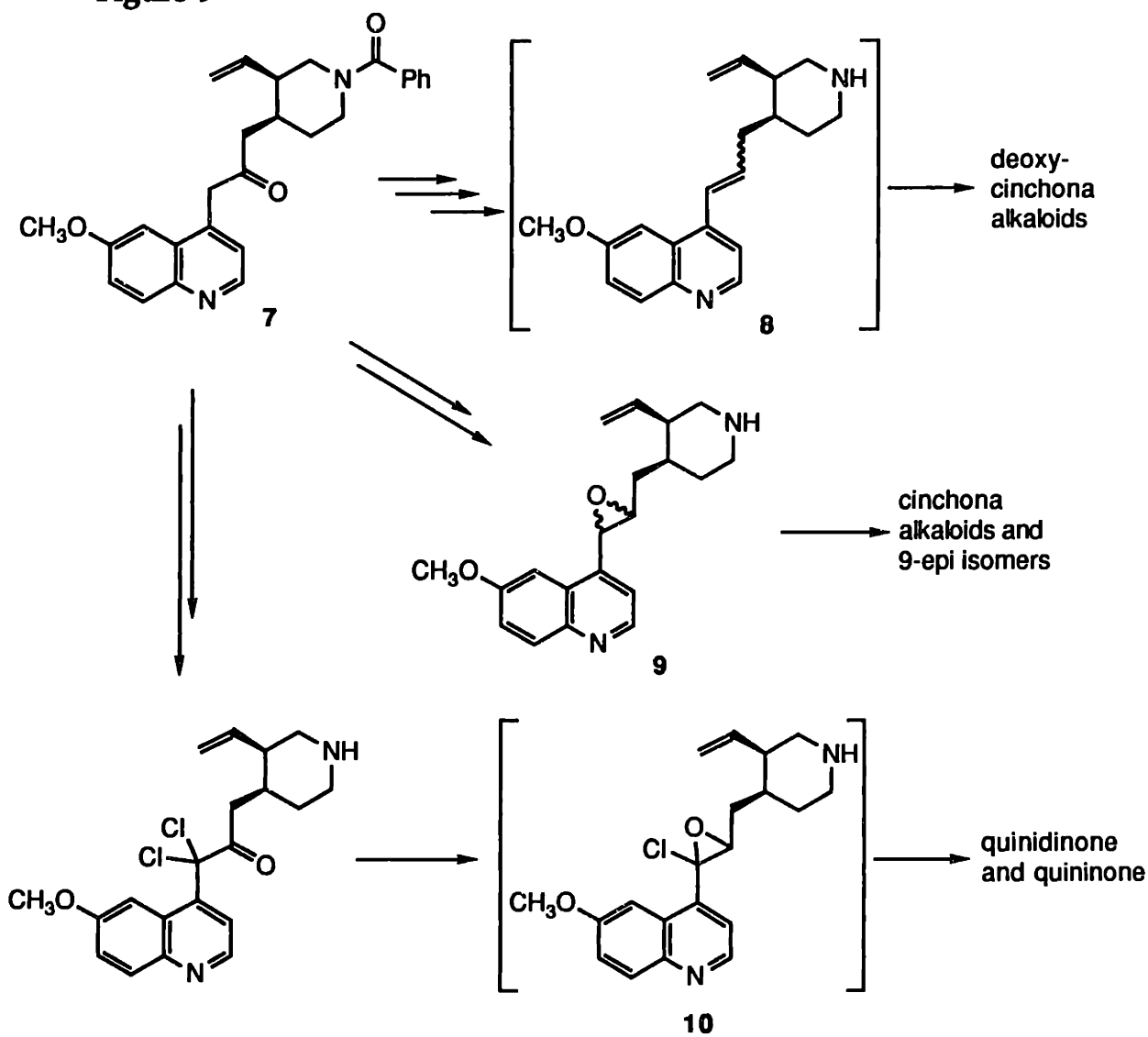
[31]Jacobsen, E. N.; Marko, I.; France, M. B.; Svendsen, J. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 737.

RESULTS AND DISCUSSION

Synthetic Background

The reported total syntheses of cinchona alkaloids have utilized primarily one of two general strategies. The most common approach hinges on the

Figure 9

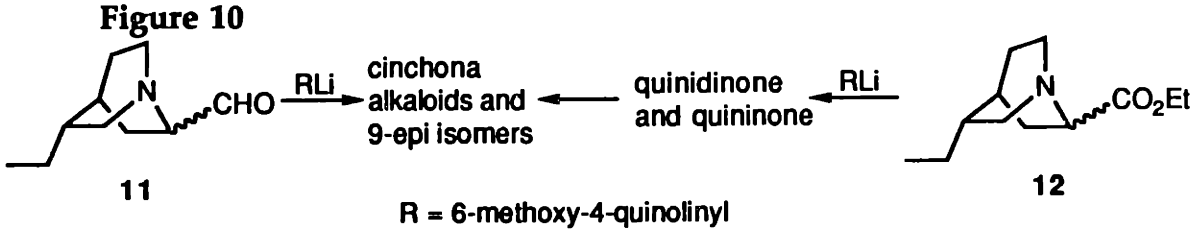


stereoselective formation and subsequent manipulation of a substituted piperidine 7 which can lead to cyclized cinchona derivatives by several pathways (Figure 9).

These cyclization strategies were pioneered by Uskokovic,[32] but several other groups[33] have devised methods for the synthesis of the various intermediates in Figure 9. Each of the cyclization methods have distinct disadvantages, however. Cyclization of olefin **8** is efficient, but reversible, resulting in mixtures of deoxyquinine and deoxyquinidine, which must be separated and then oxidized at C-9 with singlet oxygen. The formation of epoxide **9** is not stereoselective, so complex mixtures of the cinchona alkaloids and their C-9 epimers result upon cyclization. The marginally longer route to quininone and quinidinone via chloroepoxide **10** proceeds in modest yield; however, and stereoselective reduction with DIBAL produces quinine and quinidine.

The second, more convergent general strategy for dihydro cinchona alkaloid synthesis relies on the formation of quinuclidine intermediates[34] which can react with organometallic reagents to form the appropriately functionalized dihydro alkaloids or their 9-keto forms (Figure 10).

Figure 10



11 **12**

R = 6-methoxy-4-quinolinyl

The major drawback of the route outlined above from either the aldehyde or the ester is the very low yield (≈30%) in the condensation step. Additionally, the alkylation of 6-methoxy-4-quinolinyllithium by aldehyde **11** is not

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[32]Gutzwiller, J.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 576.

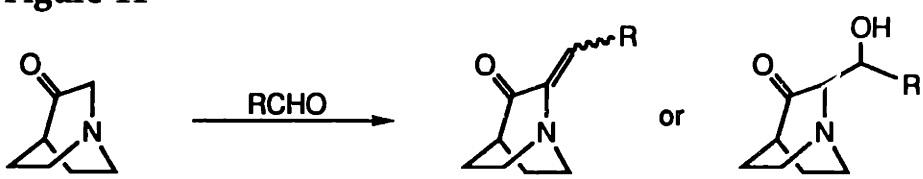
[33]a) Ihara, M.; Taniguchi, N.; Noguchi, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1986**, 573. b) Taylor, E. C.; Martin, S. F. *J. Am. Chem. Soc.* **1974**, *96*, 8095. c) Taylor, E. C.; Martin, S. F. *J. Am. Chem. Soc.* **1972**, *94*, 6218. d) Gates, M.; Sugavanam, B.; Schreiber, W. L. *J. Am. Chem. Soc.* **1970**, *92*, 205.

[34]a) Grethe, G.,; Lee, H. L.; Mitt, T.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 589. b) Grethe, G.; Lee, H. L.; Mitt, T.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 581.

stereoselective, resulting again in a mixture of the dihydro cinchona alkaloids and their 9-epi isomers. To solve the stereoselectivity problem, reaction of the 6-methoxy-4-quinolinyllithium with ester **12** produces dihydroquininone and dihydroquinidinone, which can be reduced stereoselectively with DIBAL[35] to dihydroquinine and dihydroquinidine, respectively.

Various other strategies for the synthesis of functionalized quinuclidines have appeared recently. Several of these strategies involve elaboration of commercially-available 3-quinuclidinone by Wittig[36] or by Aldol[37] methodologies (Figure 11). The removal of the ketone, however, is frequently not trivial.

Figure 11



Although less versatile, 3-quinuclidinol provides a handle for functionalization as well. One of the most elegant approaches to the stereocontrolled synthesis of chiral quinuclidines has been developed by Fleet and coworkers,[38] who utilize carbohydrate precursors to produce quinuclidines enantiospecifically. An example of this approach is depicted retrosynthetically in Figure 12.

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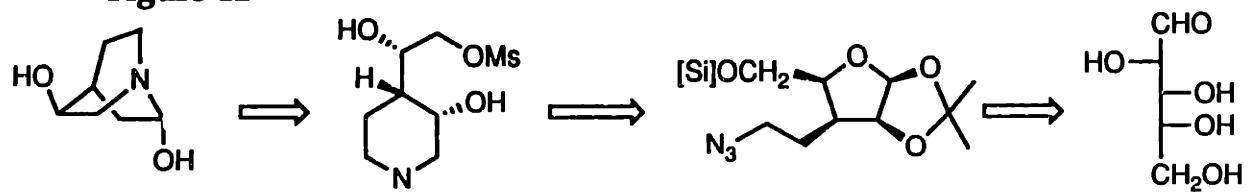
[35]Gutzwiller, J.; Uskokovic, M. R. *Helv. Chim. Acta* **1973**, *56*, 1494.

[36]a) Stotter, P. L.; Friedman, M. D.; Dorsey, G. O.; Shiely, R. W.; Willimans, R. F.; Minter, D. E. *Heterocycles*, **1987**, *25*, 251. b) Stotter, P. L.; Hill, K. A.; Friedman, M. D. *Heterocycles* **1987**, *25*, 259. c) Ricciardi, F. J.; Doukas, P. H. *Heterocycles* **1986**, *24*, 971.

[37]a) Stotter, P. L.; Friedman, M. D. *J. Org. Chem.* **1985**, *50*, 29. b) Bender, D. R.; Coffen D. L. *J. Org. Chem.* **1968**, 33, 2504.

[38]a) Fleet, G. W.; Mathews, C. J.; Seijas, J. A.; Tato, M. P. V.; Brown D. J. *J. Chem. Soc., Perkin Trans. I* **1989**, 1065. b) Fleet, G. W.; Mathews, C. J.; Seijas, J. A.; Tato, M. P. V.; Brown D. J. *J. Chem. Soc., Perkin Trans. I* **1989**, 1067.

Figure 12



(3*S*, 5*S*)-quinuclidine-3,5-diol

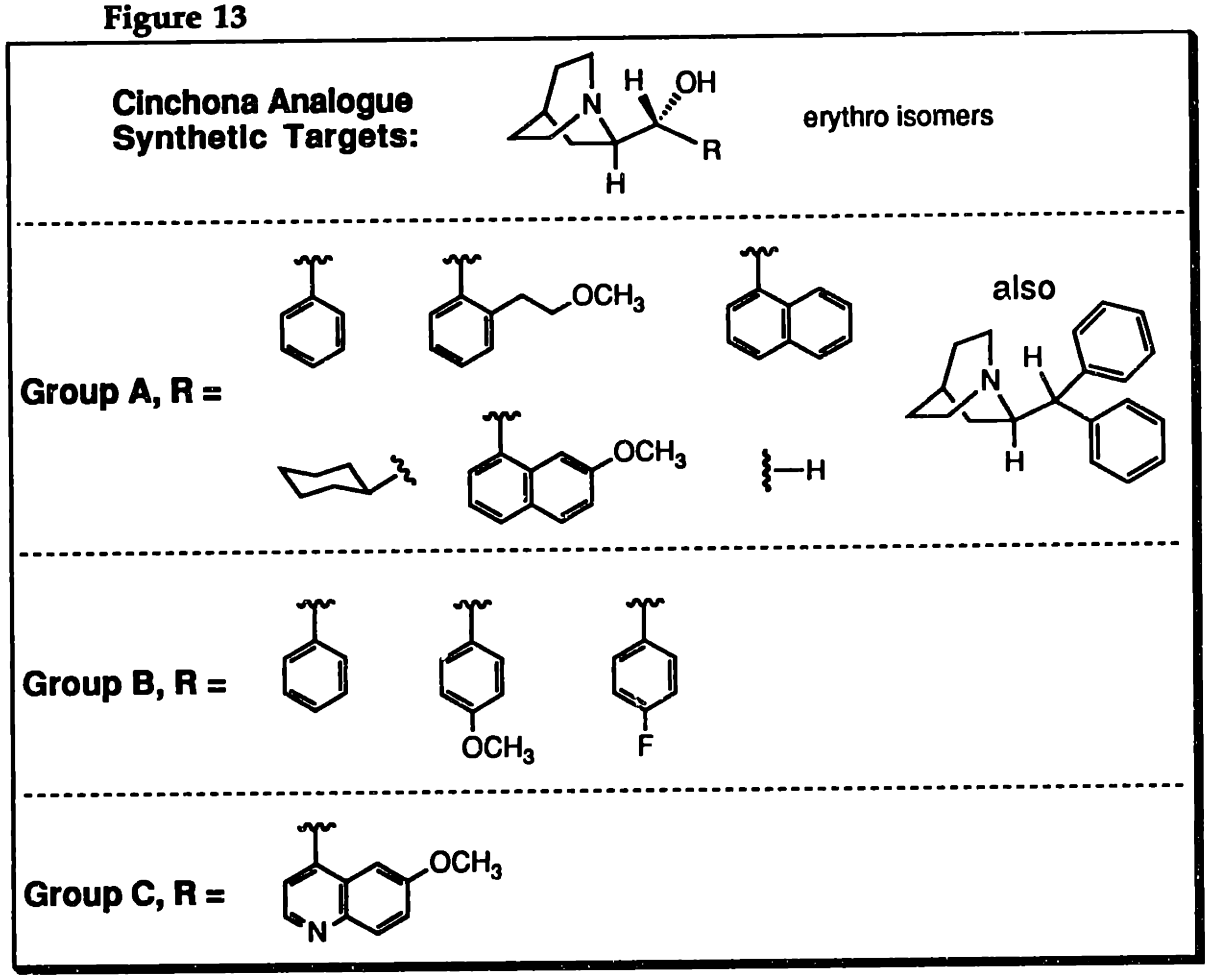
D-arabinose

Two other quinuclidine functionalization tactics were utilized for the synthesis of cinchona analogues and are discussed below.

Synthetic Results

The syntheses of the target molecules in Figure 13 were approached in three different manners. Group A targets were prepared from 2-substituted quinuclidines and appropriate organometallic reagents, with the exception of R=H, which was obtained by direct reduction of quinuclidine-2-carboxylic acid hydrochloride. Group B targets were made by condensation of 2-lithiated quinuclidine-*N*-oxide with aldehydes, followed by reduction to the amino alcohols. The single compound of Group C was envisioned to derive from degradation of quinine in order to take advantage of and to preserve the absolute stereochemistry of the natural alkaloid.

Figure 13

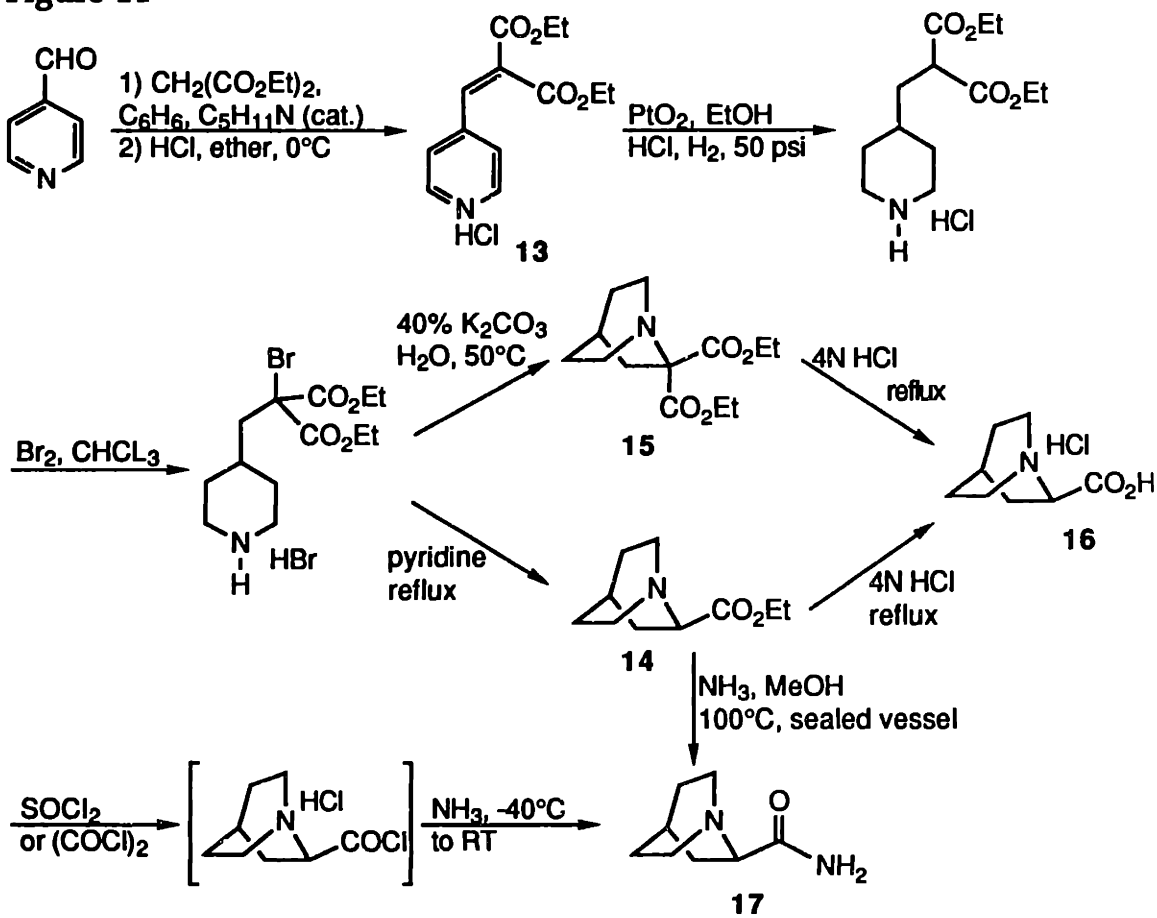


Noticeably absent from the series of ligands in Figure 13 is the structure having a simple 4-pyridyl group attached to C-9. The synthesis of this compound, although straighforward by the quinuclidine-*N*-oxide alkylation strategy, was not pursued because of the likelihood of binding of the pyridyl nitrogen to osmium tetroxide.

Figure 14 shows the synthetic sequence used for the production of the various intermediates relevant to Group A targets. The route to compound **16** is based on the method of Bulacinski[39] with slight modifications, and yields were generally comparable to those published.

[39]Bulacinski, A. B. *Polish J. Chem.* **1978**, *52*, 2181.

Figure 14

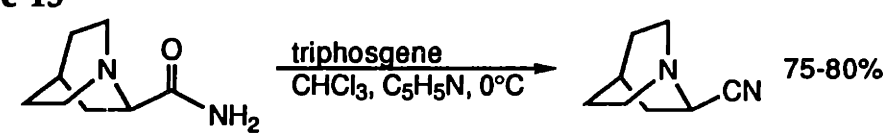


The hydrogenation of **13** was found to proceed in higher yield and catalyst separation was found to be facilitated when a trace of additional concentrated HCl was added prior to hydrogenation. The most significant modification was the use of 4N HCl rather than 12N HCl (concentrated, 36%) for the hydrolysis of monoester **14** or diester **15** to quinuclidine-2-carboxylic acid hydrochloride (**16**). Both Bulacinski[39] and Langström[40] reported the use of concentrated HCl for these hydrolyses; however, after refluxing the diester for 6 hours under these conditions, an ester could still be observed in the ^{1}H-NMR. The use of more dilute HCl always resulted in complete hydrolysis in excellent yield.

[40]Langstrom, B. *Chemica Scripta* **1974**, *5*, 170.

The conversion of acid **16** to the primary amide **17** was reported by Braschler, et al.[41] and by Pluim[42] by the methods indicated in Figure 14; however, for large scale applications, the pathway via the acyl chloride was more convenient. It was found that on a small scale, oxalyl chloride worked well for the acid to acyl chloride transformation under more attractive conditions than those encountered with thionyl chloride. The phosphorous pentoxide method that Braschler, et al. used for the dehydration of quinuclidine-2-carboxamide **17** was found to be completely unsatisfactory in our hands due to an extremely inconvenient workup and low isolated yields (28%). Some other methods tried for the dehydration included trifluoroacetic anhydride in pyridine[43] and thionyl chloride in DMF, pyridine, chloroform/triethylamine, benzene/triethylamine, or chloroform/pyridine. While thionyl chloride in chloroform/pyridine did yield 2-cyanoquinuclidine **18** in modest yield, a much more convenient and efficient set of conditions were developed. The reagent triphosgene, which has been used for a number of types of dehydrations, was found to perform extremely well in chloroform/pyridine at 0°C, affording **18** in 75-80% yield on a multi-gram scale after distillation (Figure 15)

Figure 15



17 **18**

In attempts to expedite the sythesis of 2-cyanoquinuclidine **18**, two alternate routes were devised, each of which derived from analogous, precedented systems. First, the Knoevenagel condensation in Figure 14 with

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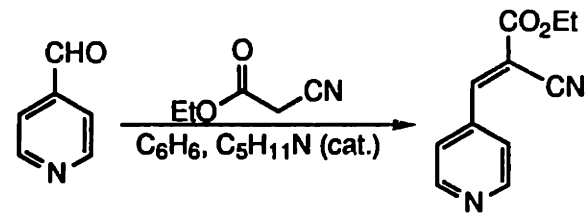
[41]Braschler, V.; Grob, C. A.; Kaiser, A. *Helv. Chim. Acta* **1963**, *46*, 2647.

[42]Pluim, H. Ph.D. Thesis, Rijksuniversiteit te Groningen, December 1982.

[43]Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 1813.

pyridine-4-carboxaldehyde was performed with ethyl cyanoacetate instead of diethyl malonate to yield a solid product in good yield (Figure 16).

Figure 16

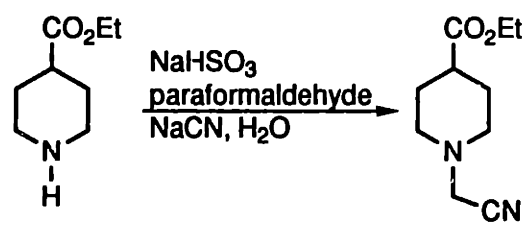


19

The olefin geometry was not determined. It was hoped that a hydrogenation, bromination, cyclization sequence applied to **19** would produce the nitrile **18** directly, thus avoiding several steps in the existing synthesis. Hydrogenation of **19** under the acidic conditions used for **13**, however, resulted in reduction of the nitrile. Considering the ease with which the nitrile was hydrogenated, no exhaustive examination of conditions was undertaken to find appropriate conditions for selective ring reduction.

Second, cyanomethylation of commercially-available ethyl isonipecotate by treament of the formaldehyde bisulfite-addition compound with sodium cyanide in water gave **20** (Figure 17). The analogous diester was prepared previously by Braschler, et al.[41] and cyclized to the β-keto ester, which could be elaborated to monoester **14** in several steps.

Figure 17

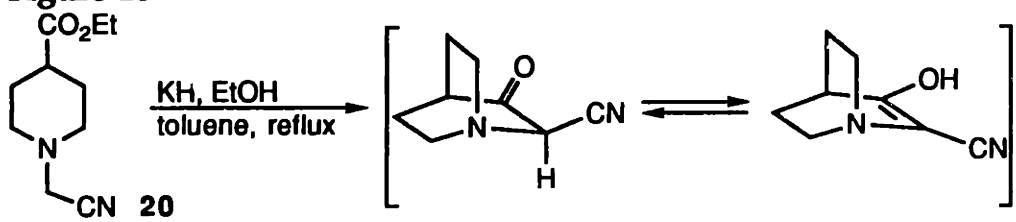


20

Despite the similarities, *N*-cyanomethyl-4-carboethoxypiperidine **20** was reluctant to undergo intramolecular condensation unless treated with 2 equivalents of KH and ethanol in refluxing toluene for prolonged periods. The product, however, could not be fully characterized because it was intractable and resinous. The IR

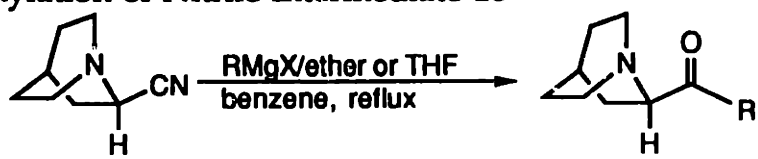
spectrum of the product showed a strong nitrile absorption, no carbonyl absorption, and other strong absorptions in the region of C-O single bond stretches. Additionally, a weak O-H absorption was present. Due primarily to the enhanced nitrile absorption and lack of carbonyl stretch in the IR, an enolized structure is indicated (Figure 18).

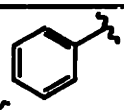
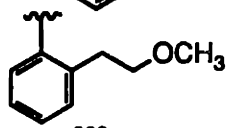
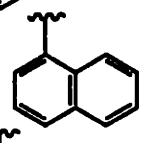
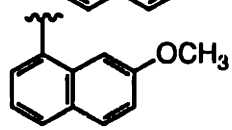
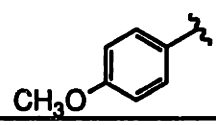
Figure 18



The reaction of quinuclidine-2-carboxamide **17** with phenylmagnesium bromide and with 1-naphthyl magnesium bromide in DME was described by Pluim;[42] however, the conditions reported were tried and the results were not successfully reproduced with phenyl magnesium bromide. A significant drawback of the conditions described by Pluim is the necessity for a large excess of Grignard reagent (typically an 8-fold excess), which would prove to be wasteful with less readily-accessible Grignard reagents. The addition of Grignard reagents to 2-cyanoquinuclidine; however, proceeded beautifully in most cases to yield ketones in good yields, as precendented by Braschler, et al.[41] for entry 1 in Table I.

Table I. Alkylation of Nitrile Intermediate **18**



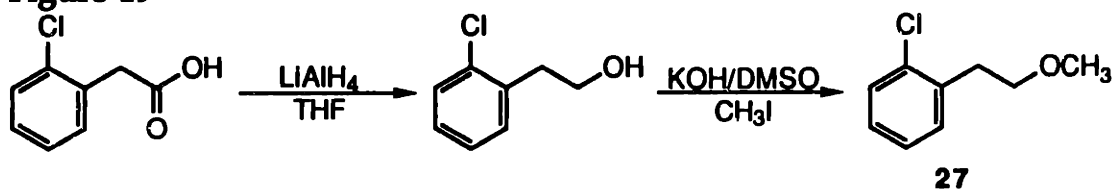
entry	R	yield (%) ketone	compound #
1		89	**21**
2		78	**22**
3		83	**23**
4		95	**24**
5		87	**25**
6		≈80[a]	**26**

[a]decomposed during purification.

Grignard reagents were purchased or were prepared from the appropriate commercially -available halide for entries 1, 3, 5, and 6. For entry 2, α-chlorophenyl acetic acid was reduced with $LiAlH_4$ in THF to give the primary alcohol,[44] which was then alkylated with KOH/DMSO/CH_3I to give the methyl ether **27** in 87% yield after distillation (Figure 19). The reduction of α-bromophenyl acetic acid with $LiAlH_4$, however, resulted in significant debromination.

[44]Glennon, R. A.; Salley, J. J.; Steinsland, O. S.; Nelson, S. *J. Med. Chem.* **1981**, *24*, 678.

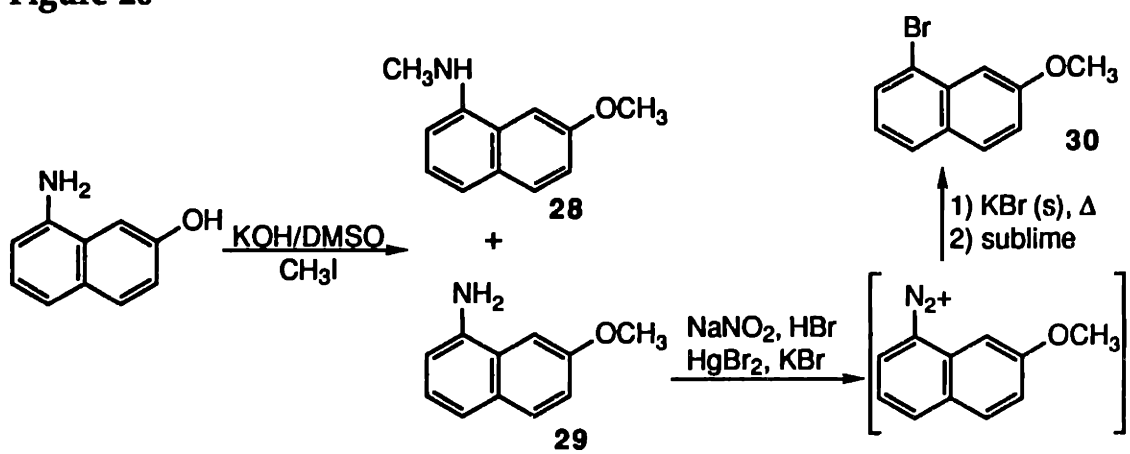
Figure 19



27

The synthesis of the bromide **30** used in entry 5 of Table I was more involved and was precendeted;[45] however, some straighforward modifications were necessary which simplified the synthesis depicted in Figure 20.

Figure 20



Commercially available 8-amino-2-naphthol was available only in 85-90% purity, and the purification was arduous due to the limited solubility of the crude mixture. Chromatography (25% ethyl acetate:hexane) yielded a very small amount of pure starting material, which was methylated as described by Glennon, et al.[46] to yield a mixture of **28** and **29**, chromatographic separation of which was facile. Fortunately, crude 8-amino-2-naphthol subjected to the same methylation conditions gave identical results, presumably because most of the impurities in the starting material were insoluble in methanol and could be separated easily. LaBudde and Heidelberger[44] reported that the usual Sandmeyer

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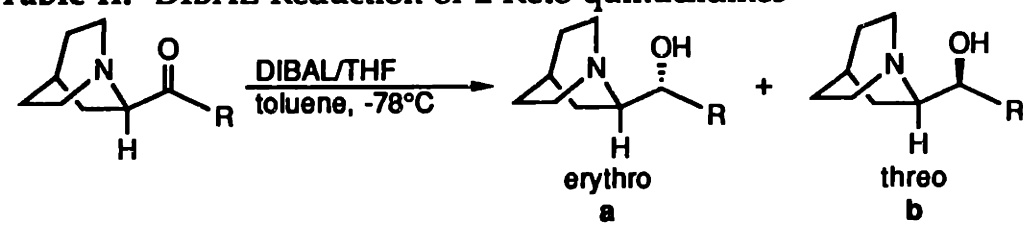
[45]LaBudde, J. A.; Heidelberger, C. *J. Am. Chem. Soc.* **1958**, *80*, 1225.

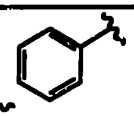
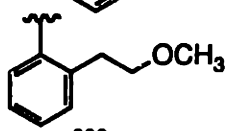
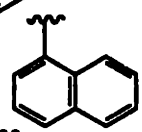
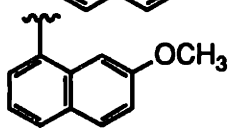
[46]Glennon, R. A.; Naiman, N. A.; Peirson, M. E.; Smith, J. D.; Ismaiel, A. M.; Titeler, M.; Lyon, R. A. *J. Med. Chem.* **1989**, *32*, 1921.

procedure for conversion of **29** to the bromide **30** gave a poor yield of bromide and instead used the Schwechten procedure via the double salt with mercuric bromide. Slight alterations of the literature method by starting with the free amine instead of the hydrochloride and by using 48% HBr instead of using 2N sulfuric acid for the diazotization resulted in a 23% yield of 1-bromo-7-methoxynaphthalene (**30**) after recrystallization from petroleum ether.

Uskokovic's early studies on the stereoselective reduction of quinidinone to quinidine by diisobutyl aluminum hydride[32] (DIBAL) led Pluim to apply these conditions to the reduction of the phenyl ketone **21** with modest selectivity. The selectivity increased dramatically, however, by lowering the reaction temperature to -78°C and by using a toluene/THF solvent mixture, which probably resulted in a less reactive reagent. Indeed, reaction times increased over four-fold. Table II tabulates the results of DIBAL reductions under the modified conditions.

Table II. DIBAL Reduction of 2-Keto-quinuclidines



entry	R	yield (%) alcohols	erythro:threo	compound #
1		93	30:1	**31a, 31b**
2		91	18:1	**32a,32b**
3		96	3:1	**33a,33b**
4		87	1.3:1	**34a,34b**
5		94	8:1[a]	**35a,35b**

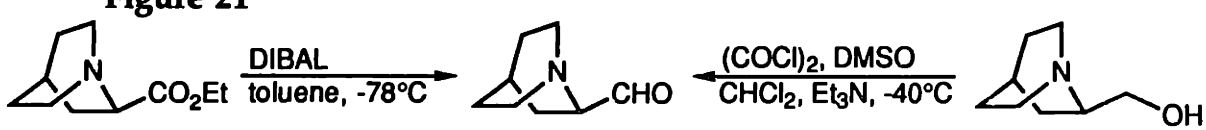
[a]actual relative stereochemistries unconfirmed.

Despite the results reported for quinidinone reduction, it is surprising that the 1-naphthyl and 7-methoxy-1-naphthyl moieties (entries 3 and 4, respectively) seem to decrease the selectivity relative to the smaller phenyl and cyclohexyl groups. The distinct isomeric alcohols could be identified, and the erythro:threo ratios could be determined easily by ^{1}H-NMR for entries 1-4 (R=aryl). The C-9 methine proton of the erythro isomers was consistently shifted downfield relative to that of the threo isomers, and the $^3J_{H(C\text{-}8),H(C\text{-}9)}$ coupling constants were uniformally smaller for the erythro isomers than for the threo isomers. The assignment of relative stereochemistry was ambiguous for entry 5 (R=cyclohexyl), however, since the observed coupling constants for the two isomers were of similar magnitude. Also, considering the increased steric bulk of the cyclohexyl group relative to the planar aryl groups of the other entries in Table II, the

conformational dynamics are likely to be considerably different; hence, the observed trend that the C-9 hydrogen of erythro isomers appear at higher frequency than of the same hydrogen of threo isomers in the ^{1}H-NMR was not applied blindly to the R=cyclohexyl case, and later investigations included derivatives of both isomers.

To avoid the ketone reduction step altogether, quinuclidine-2-carboxaldehyde **36** was considered as another intermediate for producing Group A ligands by reaction with Grignard reagents. In his studies on the total synthesis of quinidine and quinine, Uskokovic[34] used this strategy with an ethyl-substituted quinuclidine-2-carboxaldehyde, **11**, to produce racemic derivatives. However, this method was plagued by poor yields for the addition due to the acidity of the hydrogen at C-2 and by the instability of the aldehyde. Indeed, the reported reduction of 2-carboethoxyquinuclidine **14** by DIBAL proceeded poorly in the hands of several coworkers, as did the attempted Swern oxidation of 2-hydroxymethyl quinuclidine **37** (Figure 21) obtained by $LiAlH_4$ reduction of acid **16**.

Figure 21

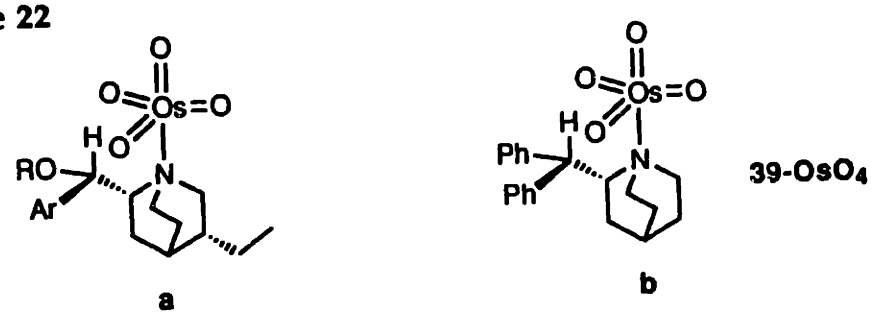


14 **36** **37**

The synthesis of 2-diphenylmethyl quinuclidine **39** was undertaken for two reasons. First, the replacement of the C-9 hydroxyl of cinchona derivatives by a phenyl group would probe the effect of crowding closer to the binding site. Second, a consistent feature of relevant X-ray crystal structures[18] is the orientation of the C-9 hydrogen parallel to the nitrogen lone pair of the quinuclidine bound to osmium such that the hydrogen is situated nearly between two oxo ligands (Figure 22a). This hydrogen may act as a

conformational lock by impeding rotation about the osmium-nitrogen bond. It was hoped that **39** would be able to adopt a similar geometry on binding to osmium tetroxide (Figure 22b), thus allowing discrimination of the oxo ligands by an approaching olefin.

Figure 22



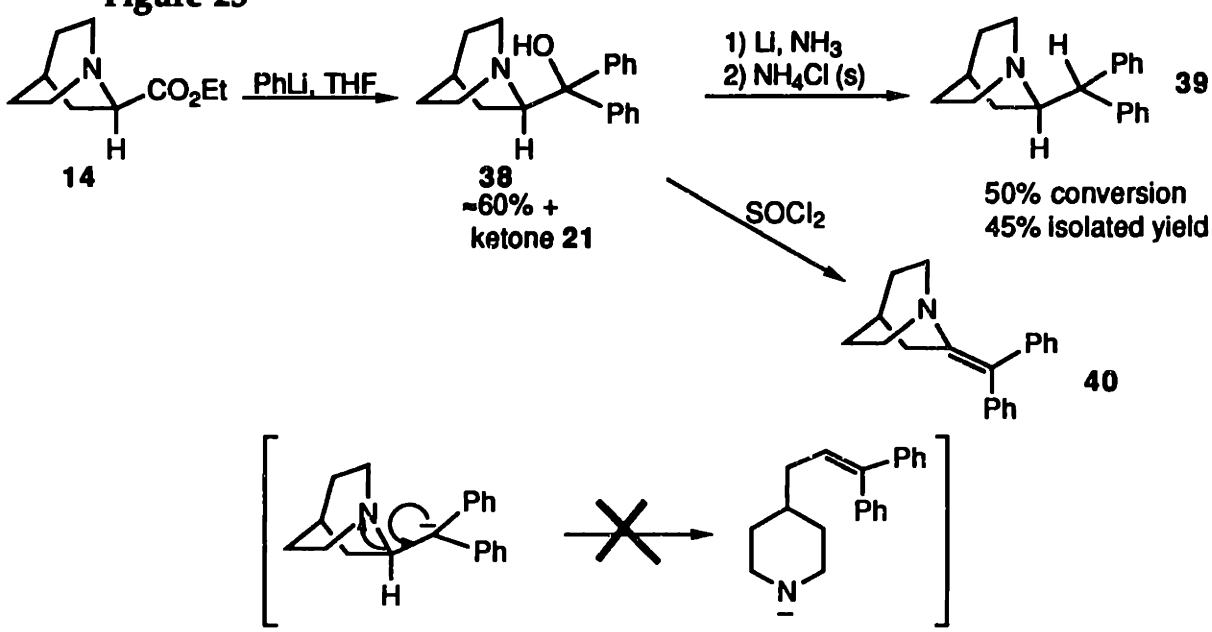
a **b**

Preparation of the 3° alcohol **38** (Figure 23) from the monoester **14** and phenyl lithium was accompanied by significant formation of phenyl ketone **21**, which could be recycled. No conditions were found which allowed complete reaction indicating that a portion of the ketone must exist as the enolate under the basic reaction conditions, thus arresting further addition of PhLi. The 3° benzylic alcohol was very resistant to hydrogenolysis over palladium, even in the presence of trifluoroacetic anhydride. Additionally, mixed aluminum chloride-aluminum hydride reagents[47] were ineffective for the hydrogenolysis. Hoping that the 3° benzylic chloride would undergo hydrogenolysis more readily, attempts to form the chloride from the alcohol using thionyl chloride, for instance, resulted only in dehydration (or perhaps dehydrohalogenation) to the alkene **40**, which was impervious to all hydrogenation conditions applied. Finally, hydrogenolysis was achieved by dissolving metal reduction with lithium/ammonia.[48] The alcohol was converted cleanly to **39** despite concerns about elimination of the putative intermediate anion (Figure 23).

[47a] Brewster, J. H.; Bayer, H. O.; Osman, S. F. *J. Org. Chem.* **1964**, *29*, 110. b) Nystrom, R. F.; Berger, C. R. A *J. Am. Chem. Soc.* **1958**, *80*, 2896.

[48]Small, G. H.; Minnella, A. E.; Hall, S. S. *J. Org. Chem.* **1975**, *40*, 3151.

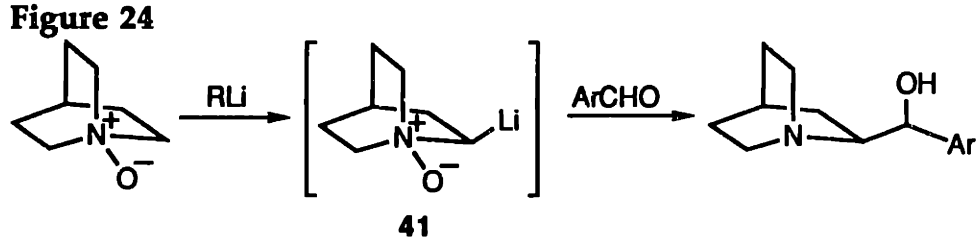
Figure 23



Unfortunately, the hydrogenolysis would not proceed beyond 50% conversion at -78°C, and raising the temperature to -42°C resulted simply in overreduction. The starting alcohol and the product could be separated easily by silica gel chromatography, however, and **38** was recycled in this manner.

The second tactic used for the synthesis of cinchona analogues pertained to the Group B members and was based on the preliminary work of Beugelmans[49] on the alkylation of lithiated quinuclidine-*N*-oxide (**41**) by aldehydes (Figure 24).

Figure 24



41

Beugelmans reported that the condensation products between lithiated quinuclidine-*N*-oxide and benzaldehyde were isolated in 50% yield as a 1:1 mixture of erythro and threo isomers. Subsequently, the amino alcohols were

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[49]Barton, D. H. R.; Beugelmans, R.; Young, R. N. *Nouveau J. Chim.* **1978** 2, 363.

produced by reduction of the N-oxides with hexachlorodisilane in unreported yield. Initial attempts to reproduce the same reaction were unsuccessful using the scant information available in the literature reference; however, the problem at the outset was probably that the N-oxide was not completely anhydrous. Quinuclidine-*N*-oxide is made by hydrogen peroxide oxidation in methanol, followed by destruction of the excess peroxide with platinum black, removal of water and methanol, and drying with gentle heating under high vacuum.[50] While studying the reduction of N-oxides by hexachlorodisilane, Mislow reported that quinuclidine-*N*-oxide (QNO) decomposed at temperatures above 50°C; hence, it was important to monitor the temperature diligently during the dehydration. Recrystallization of the wet QNO from acetone/hexane, followed by several days of heating at 40-45°C in a round-bottomed flask under vacuum was sufficient to dehydrate the material, which was stored at room temperature under a nitrogen atmosphere in a drybox.

The report of an anhydrous preparation of 3° amine N-oxides[51] seemed attractive since the dehydration of QNO was so long and difficult. The oxidation of quinuclidine by TBHP catalyzed by $VO(acac)_2$ in acetone proceeded smoothly; however, ^{1}H-NMR analysis of the product showed a strong singlet that was likely due to a *tert*-butanol adduct. The product could not be recrystallized, and even after a week of heating at 45°C under vacuum, the ^{1}H-NMR showed little change.

Once anhydrous material was in hand, the condensation proceeded in moderate yield, but isolation of the N-oxides was inconvenient. It was clear that the utility of an N-oxide alkylation strategy could be vastly improved by

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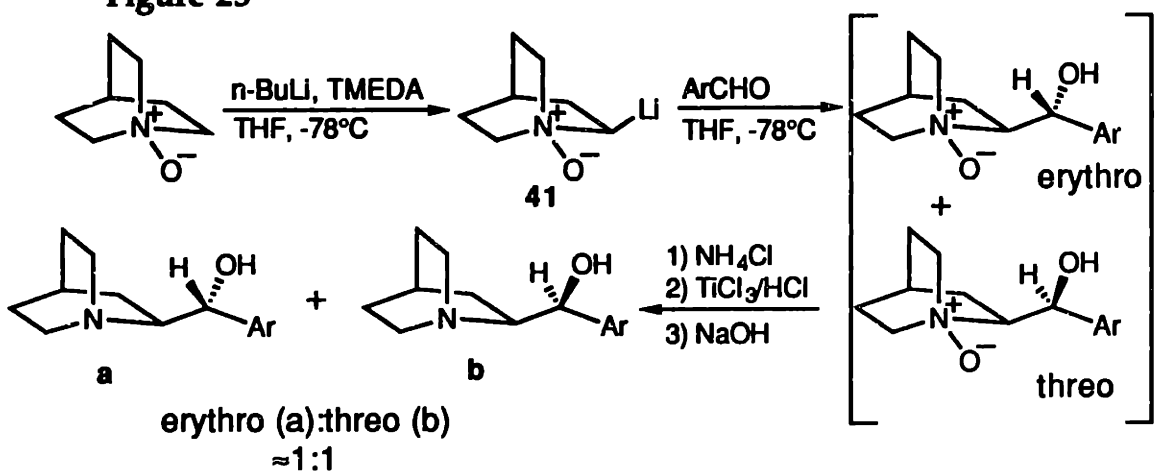
[50]Naumann, K.; Zon, G. Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7012.

[51]Sheng, M. N.; Zajacek, J. G. *J. Org. Chem.* **1968**, *33*, 588.

incorporating an in situ reduction so that the N-oxide condensation products would not need to be handled. Titanium trichloride was chosen as the reducing agent since it is known to react quickly with N-oxides[52] and is stable to the acidic conditions used to quench the alkylation. Figure 25 outlines the approach developed for the one-pot alkylation/in situ reduction.

Figure 25



Upon quenching the reaction at 0°C with aqueous NH_4Cl, an aqueous solution of $TiCl_3$ in HCl was added dropwise until the purple color of the reagent persisted. After vigorous stirring for approximately one hour, excess NaOH was added to neutralize the acid and to convert any titanium species to TiO_2, which could be separated by filtration. Because the condensation yields were somewhat low, we thought that an additive to stabilize the lithiated QNO might be beneficial. Indeed, the addition of TMEDA to the reaction mixture improved yields and facilitated product isolation. The effects of each of the above modifications are tabulated in Table III.

[52]Seaton, Q. F.; Lawley, C. W.; Akers, H. A. *Anal. Biochem.* **1984**, *138*, 238.

Table III. Alkylation of Quinuclidine-*N*-Oxide with Aldehydes.

entry	Aldehyde	Constraints	Yield (%) amino alcohols	compound #
1	Ar = Ph	--	77	**31a,31b**
2		2 steps	63	
3		no TMEDA	51	
4		no TMEDA, 2 steps	42	
5		1.5 g scale	71	
6	Ar = *p*-MeO-C_6H_4	2.0 g scale	68	**42a,42b**
7	Ar = *p*-F-C_6H_4	2.0 g scale	63	**43a,43b**

Entry 1 is the newly-developed, one-pot alkylation/in situ reduction using TMEDA as an additive. The yields are obviously improved, although there is still essentially no stereoselectivity. Entry 3 indicates that without TMEDA, the yield of the one-pot procedure drops dramatically. Entries 2 and 4 (with TMEDA and without, respectively) show how the yields are affected by isolating the N-oxides, then reducing them with $TiCl_3$ in a separate step. Perhaps most important from a synthetic perspective, entry 5 indicates that the yields are not affected dramatically by increasing the reaction scale.

The lack of stereoselectivity observed for the QNO alkylations presented a considerable drawback since only the erythro isomers were desired for studies with osmium tetroxide. Two experiments were designed to determine whether the unwanted threo isomers could be manipulated to yield erythro compounds. First, a Swern oxidation[53] of **31a** was attempted in the hope of obtaining ketone **21**, which could be stereoselectively reduced as mentioned above. Analysis of the crude product indicated that starting material and an unidentified olefinic product, which decomposed during chromatography, were present; however, no

[53]Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

evidence of **21** was observed by TLC or by ^{1}H-NMR. While no precedent for the Swern oxidation of cinchona alkaloids was found, it is known that oxidation of the C-9 hydroxyl of cinchona alkaloids is notoriously difficult, and only a modified Oppenauer oxidation method seems to give reasonable yields.[54] Second, a Mitsunobu reaction[55] using *p*-chlorobenzoic acid as the acidic component was attempted on the threo alcohol **32b**. A mixture of erythro and threo *p*-chlorobenzoate esters identified in the ^{1}H-NMR of the crude product quickly dismissed hopes of utilizing such a simple alcohol inversion method, however.

Preparative scale alkylations were performed with *p*-anisaldehyde (entry 6) and *p*-fluorobenzaldehyde (entry 7) to give **42** and **43** in good yields considering the expedient construction of the carbon skeleton. Unfortunately, it was not possible to separate the erythro (**42a**) and threo (**42b**) isomers of **42** by recrystallization or by chromatography, but the *p*-fluorophenyl products could be separated easily by fractional crystallization. Although nitro groups are known to be reduced by $TiCl_3$, attempts to run just the condensation step with *p*-nitrobenzaldehyde resulted in numerous products, which may arise from lithiation of the electron-deficient aldehyde by *n*-butyl lithium under the reaction conditions. In addition, attempts to apply the strategy to methyl benzoate gave a very poor yield (<10%) of the ketone **21**.

Since the mirror-image relationship of quinine and quinidine is disrupted only by the vinyl substituent at C-3, attempts to remove the vinyl group to produce **44** (Figure 26) by degradation were undertaken.

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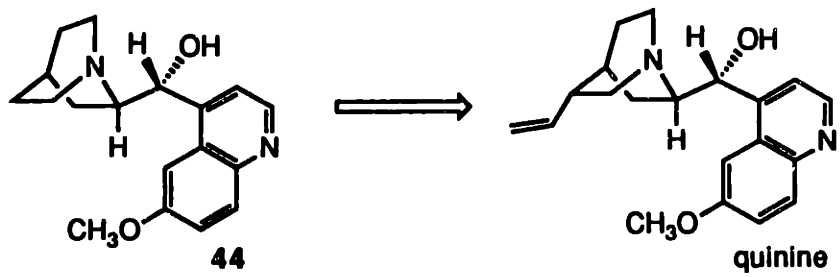
[54]Woodward, R. B.; Wendler, N. L.; Brutschy, F. J. *J. Am. Chem. Soc.* **1945**, *67*, 1425.

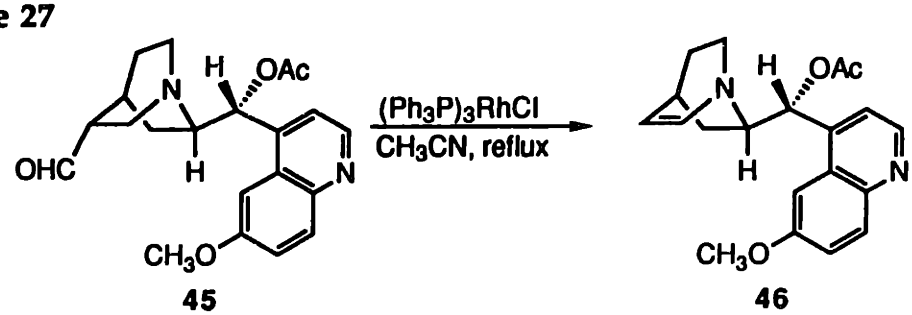
[55]Mitsunobu, O. *Synthesis* **1981**, 1.

Figure 26



Quinine was chosen for these degradation studies because its vinyl group is more accessible than that of quinidine, as can be seen by comparing the structures of the dihydro forms **1** and **2** in Figure 1. The first method involved oxidative cleavage of *O*-acetyl quinine to the 3-formyl derivative **45** using $OsO_4/NaIO_4$ in THF. Formyl derivatives such as **45** that have been elaborated to contain an unsaturated tether have been copolymerized with acrylonitrile to produce solid-phase chiral supports for OsO_4. Stoichiometric decarbonylations with Wilkinson's catalyst, $(Ph_3P)_3RhCl$,[56] were found to proceed only in refluxing acetonitrile after trying many solvents, although conversion remained very low. In fact, the typical canary-yellow color of insoluble $(Ph_3P)_2Rh(CO)Cl$, which typically idicates the end-point of the reaction, was observed only to a small extent. After chromatography to remove Rh-containing materials, a product was isolated which had spectral characterstics consistent with the β-hydride elimination product **46** (Figure 27).

Figure 27

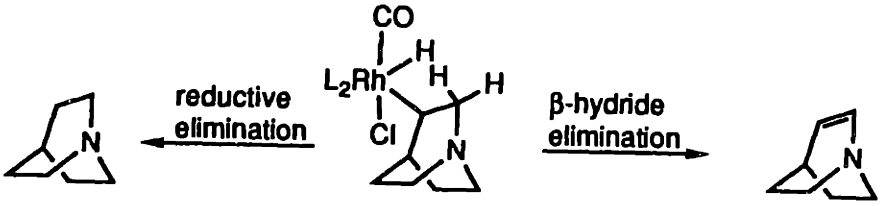


The isolation of such competitive elimination products during decarbonylations

[56]Baird, M. C.; Nyman, C. J.; Wilkinson, G. *J. Chem. Soc. (A)* **1968**, 348.

with Wilkinson's catalyst is not uncommon for substrates that have accessible β-hydrogens. In these cases, β-hydride elimination is faster than reductive elimination from the intermediate formed after oxidative addition of the formyl–H bond and migration of the alkyl fragment from CO to metal (Figure 28).

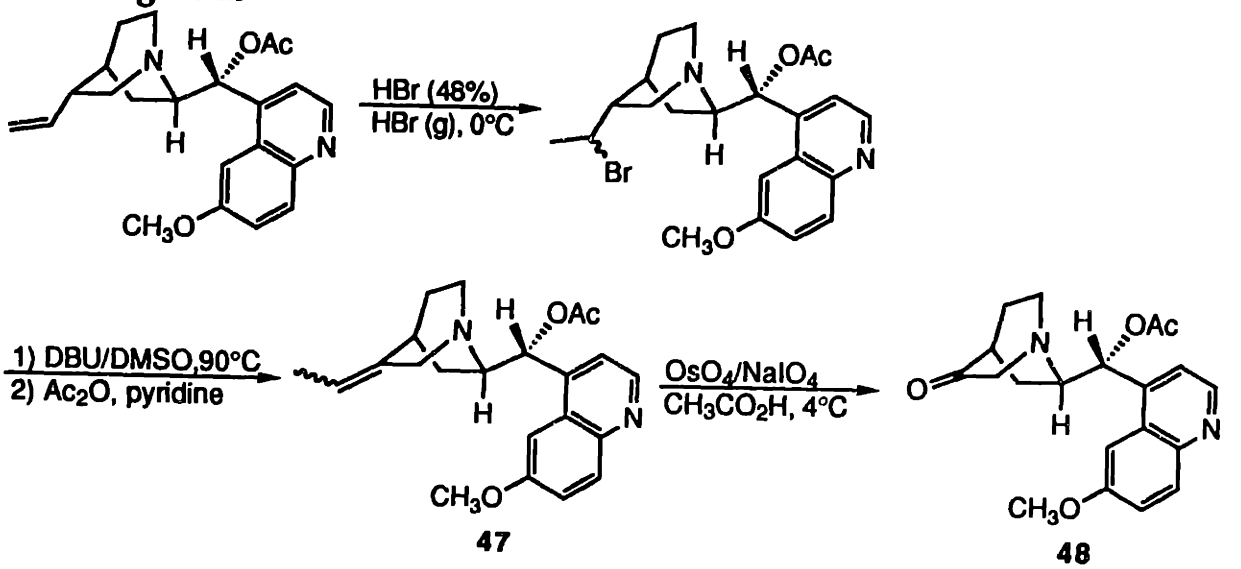
Figure 28



Disappointingly, hydrogenation of **46** under acidic conditions led to decomposition. Considering the expense of the stoichiometric rhodium complex required and the low yield of **46** (≈15%) this method was abandoned.

The second quinine degradation attempt started with quinine acetate once again. The known conversion of quinine acetate to apoquinine acetate **47**, followed by oxidative cleavage of the isomerized olefin to give the ketone **48** is depicted in Figure 29.

Figure 29

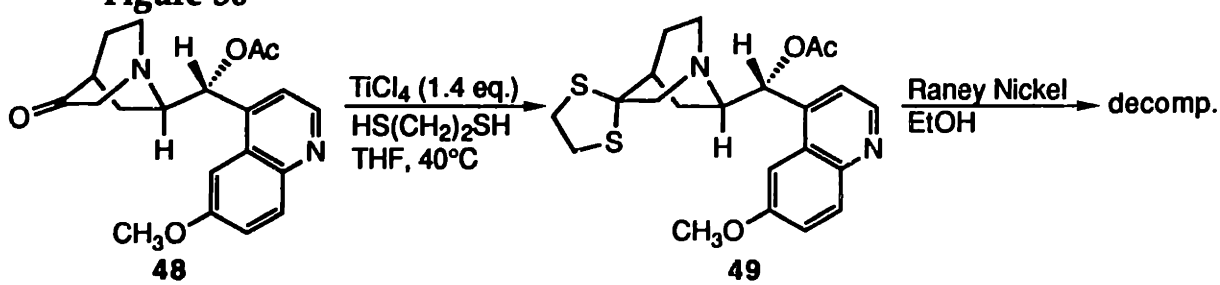


47 **48**

Ketone **48** prepared by this method has been used to synthesize quinine

metabolites[57] by addition of vinyl lithium to produce the 3° allylic alcohol. Reduction of the ketone to a methylene group was necessay to reach the target compound **44**, however. Wolff-Kishner conditions were inappropriate for this transformation, since the α-amino-ketones would be expected to undergo cleavage under the reaction conditions. Reduction of the tosylhydrazone with $NaBH_3CN$[58] resulted in a plethora of products, presumably due to cleavages as well. Despite a report that dithioketal formation on another 3-keto quinuclidine proceeded abnormally,[37b] dithioketalization did occur on **48** to produce **49** (Figure 30); however, because of coordination of the quinuclidine nitrogen, an *excess* of $TiCl_4$[59] was required for the transformation, which is usually catalytic in Lewis Acid.

Figure 30



48 **49**

Neither BF_3 nor anhydrous $FeCl_3/SiO_2$[60] were effective for this dithioketalization. Raney Nickel desulfurization of **49** again resulted in numerous products; however, it was apparent by ^{1}H-NMR that the acetate group was missing, probably due to hydrogenolysis at the benzylic position.

One final attempt to reduce the carbonyl group of **48** was initiated. Hoping to perform a radical deoxygenation of a suitable derivative of a 2° alcohol, the

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[57]a) Diaz-Arauzo, H.; Cook, J. M. *J. Natural Prod.* **1990**, *53*, 112. b) Guengerich, F. P.; Müller-Enoch, D.; Blair, I. A. *Mol. Pharmacol.* **1986**, *30*, 287. c) Carroll, F. I.; Philip, A.; Coleman, M. C. *Tetrahedron Lett.* **1976**, 1757.

[58]Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662.

[59]Kumar, V.; Dev, S. *Tetrahedron Lett.* **1983**, 1289.

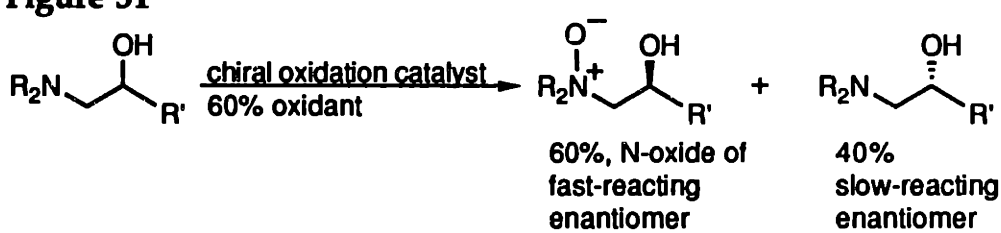
[60]Patney, H. *Tetrahedron Lett.* **1991**, 2259.

ketone **48** was reduced with $NaBH_4$ in ethanol at room temperature to give a marginally soluble product that was missing the acetate functionality once again. Although these initial degradation trials were disappointing, it is likely that mild conditions can be found for the reduction of a derivative of **48** other than acetate.

Ligand Resolution, Derivatization, and Reactivity.

In 1983, Miyano, et al.[61] reported an efficient kinetic resolution of racemic β-hydroxy amines by enantioselective N-oxide formation. This system utilized a titanium–tartrate catalyst similar to the one used for the asymmetric epoxidation of allylic alcohols, except that the optimal titanium:tartrate ratio was found to be close the 2:1 for the kinetic resolution rather than the 2:2 ratio for epoxidation. Later, other reports of the β-hydroxy amine kinetic resolution[62,63] included more refined studies of the titanium:tartrate ratio and found that, for the substrates studied, a ratio of about 2:1.4 was best. Figure 31 shows the general scheme for the kinetic resolution of β-hydroxy amines. The use of a chiral oxidation catalyst and only 0.6 eq. of oxidant makes possible the isolation of an unreacted portion of the starting material which is optically enriched. The highest enantioselectivities result when the rate of oxidation of the fast-reacting enantiomer is much greater than that of the other enantiomer.

Figure 31



The cinchona alkaloid analogues prepared as reported above possessed the necessary structural characteristics to be ideal candidates for kinetic resolution. A study of the kinetic resolution of **31a** revealed that the kinetic resolution efficiency was poor for this substrate (Table IV, entry 5), as evidenced by only moderate enantioselectivity (73%) at 58% conversion.

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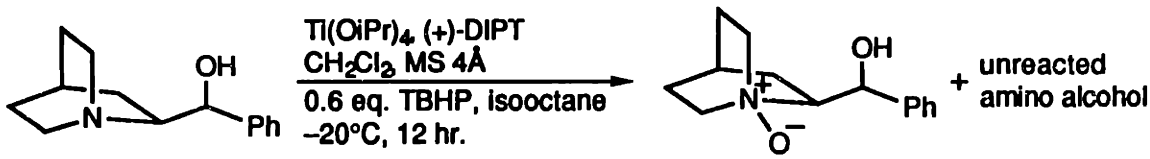
[61]Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1983**, *48*, 3608.
[62]Miyano, S.; Lu, L. D.-L.; Viti, S. M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 4350.
[63]Hayashi, M.; Okamura, F.; Toba, T.; Oguni, N.; Sharpless, K. B. *Chem. Lett.* **1990**, 547.

Table IV. Variation of Ti:DIPT Ratios for Kinetic Resolution of **31a**



entry	Ti:DIPT	conversion crude (%)[a]	yield[b] amine (%)	amine ee (%)
1	2:1.1	43.0	48	–
2	2:1.2	46.5	48	–
3	2:1.3	47.4	43	34
4	2:1.4	55.4	36	64
5	2:1.4	57.8	35	73
6	2:1.4	39.6	41	50
7	2:1.4	51.0	35	56
8	2:1.5	37.5	59	–

[a]by ^{1}H-NMR integration. [b] isolated yield.

Examination of the data in Table IV suggests, however, that there may have been inherent problems with the substrate. Varying the titanium:tartrate ratio did not lead to any improvements in enantioselectivity. The addition of powdered molecular sieves to the reaction mixture showed no deleterious effects and was simply precautionary since the catalyst was likely to be very susceptible to hydrolysis by adventitious water as observed for the asymmetric epoxidation of allylic alcohols, in which molecular sieves were found to be quite essential.[64] Most revealing, however, was the observation that the conversion to product rarely proceeded to the theoretical 60% even after 12 hours. Generally, kinetic resolutions such as these are complete in a matter of a couple of hours. Additionally, side-by-side kinetic resolutions of **31a** and *d,l-N*-methyl ephedrine resulted in spurious results for the substituted quinuclidine (entries 4-7) but consistently good results (complete conversions, and enantioselectivities >95%)

[64]Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

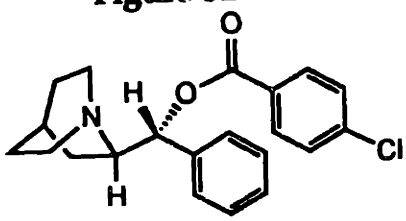
for *N*-methyl ephedrine. Hence, it is likely that some feature of the substrate inhibited catalyst turnover, or perhaps induced a completely different coordination environment about titanium. No examples of the kinetic resolution of substituted quinuclidines were reported previously, so it may be that this class of amino alcohols is inappropriate for the kinetic resolution.

The failure of the kinetic resolution of **31a** to provide useful enantioselectivities left classical resolution techniques as the next most viable alternative for producing optically pure material. The resolution of **31a**[42] was accomplished by repetitive fractional crystallization of the 1:1 D-(+)-tartaric acid:**31a** salt from 95% ethanol. The optical purity was checked by converting the resolved alcohol to its Mosher's ester and examining the ^{1}H-NMR for traces of the other diastereomer. After four crystallizations, a sharp-melting salt was obtained (further recrystallizations did not raise the melting point) which showed only one diastereomer in the ^{1}H-NMR. Other attempted resolutions (of **33a** and **35a**) were unsuccessful after trying to isolate crystalline derivatives of numerous chiral acids from a variety of solvents.

Among the choices for derivatization of the synthetic cinchona analogues, the most attractive was conversion to the *p*-chlorobenzoate ester, since a large amount of data for comparison was available on the reactivity of the *p*-chlorobenzoates of dihydroquinidine and dihydroquinine. The aryl ethers, while very effective derivatives, can be prepared in only moderate yield (70-75%), which is an unattractive feature for the derivatization of a small amount of precious, resolved ligand. Hence, resolved **31a** was esterified with *p*-chlorobenzoyl chloride to give **50**. The catalytic asymmetric dihydroxylations of *trans*-stilbene and of *trans*-5-decene were performed with resolved **50** using the potassium ferricyanide oxidant system in 1:1 *tert*-butanol:water.[4a] Figure 32

shows the results of the dihydroxylations along with the enantioselectivities using dihydroquinidine *p*-chlorobenzoate.

Figure 32



50

[from (+)-tartaric acid resolution]

Catalytic ADH using $K_3Fe(CN)_6$ in t-BuOH/H2O:

substrate	ee (config.)	using dihydroquinidine *p*-chlorobenzoate:
trans-stilbene	78% (*S,S*)	99% (*R,R*)
trans-5-decene	59% (*S,S*)	79% (*R,R*)

Although the absolute configuration of resolved **50** was not determined, its sense of enantioselection in the ADH parallels that of dihydroquinine derivatives, hence it is likely that they share the same absolute stereochemistry at C-8 and C-9. Clearly, the size of the aromatic moiety at C-8 of the ligand has a large effect on enantioselectivity, assuming that the effect of the ethyl group at C-3 of dihydroquinidine derivatives is small. Considering that simply the absence of the methoxy group on the quinoline moiety of dihydrocinchonine esters results in a decrease in enantioselectivity of 10-15% relative to the selectivities observed for dihydroquinidine esters, the decrease in selectivity is perhaps less than might have been expected.

Binding and Conformational Studies.

The nature of the interaction between amine ligands and osmium tetroxide is of extraordinary importance to catalytic asymmetric dihydroxylation. The rate acceleration observed for the addition of olefins to osmium tetroxide in the presence of amine ligands is well-documented; however, some amines will inhibit catalysis by preventing hydrolysis of the Os(VI) glycolate. For instance, Tomioka's bidentate ligand **4a** enhances the rate of stoichiometric osmylation, but it is not able to participate in the catalytic version,[31] presumably because the Os(VI) glycolate–diamine complex is so stable. One commonly used ligand relevant to cinchona alkaloid derivatives is quinuclidine. Both DABCO and quinuclidine possess bicyclic bridgehead amine structures that keep the nitrogen lone pair unobstructed for interaction with metal centers, resulting in strong binding. In fact, quinuclidine shows the requisite rate enhancement for osmylation but binds so strongly that it inhibits catalysis.[64]

The measurement of the strength of the interaction between osmium and amine gives valuable information about the likelihood of the ligand permitting catalysis. Despite the presence of a quinuclidine bicyclic core in cinchona alkaloid derivatives, catalysis is not inhibited, thus leading to the qualitative conclusion that the cinchona derivatives do not bind as strongly to osmium as quinuclidine does. Jacobsen's measurement of equilibrium binding constants[65] for OsO_4 and simple 3° amines in toluene at 25°C (Table V) supports this assertion.

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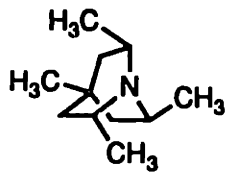
[64]Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 766.
[65]Jacobsen, E. N.; Sharpless, K. B., unpublished results.

Table V. Binding Constants for Ligands with OsO_4 at 25°C in *tert*-Butanol.

Entry	Amine Ligand	$K_{eq}(M^{-1})$
1	pyridine	69
2	quinuclidine	≈80,000
3	*O*-acetyl dihydro-quinidine	50
4	*O*-acetyl epidihydro-quinidine	≈0
5		≈0

Clearly, the binding affinity of cinchona derivatives for OsO_4 is precariously balanced between being strong enough to assert a stereochemical influence and being weak enough to permit hydrolysis and catalytic turnover. Quinuclidine's own binding affinity can be masked altogether by appropriate substitution. Although epiquinidine derivatives have the same atomic constitution and connectivity as quinidine derivatives, the epi isomers show no evidence of binding to OsO_4 due to their inability to adopt low-energy conformations which can accomodate close approach of osmium.[17] As an indication of the steric sensitivity of binding at the quinuclidine nitrogen, even the presence of three small methyl groups on the C_3-symmetric quinuclidine shown in entry 5 prohibits interaction of the nitrogen with OsO_4.[66]

For new ligands, it is obviously desirable to retain the charactersitics that make cinchona derivatives useful, namely, the stereochemical information necessary for asymmetric induction and the moderate binding affinity which

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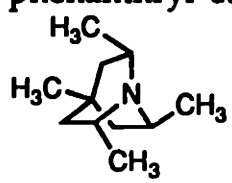
[66]The synthesis of this C_3-symmetric quinuclidine was described by Burns, C. J. Ph.D. Thesis, Massachusetts Institute of Technology, June, 1989.

makes both asymmetric induction and catalysis possible. Binding constant data provided by Kwong[67] for the most commonly used ligands in the ADH is given in Table VI.

Table VI. Binding Constants for Cinchona Alkaloid Derivatives with OsO_4 at 25°C in *tert*-Butanol.

Entry	Ligand	$K_{eq}(M^{-1})$
1	dihydroquinidine *p*-chlorobenzoate	38.1
2	dihydroquinine *p*-chlorobenzoate	22.1
3	dihydroquinidine *O*-9-phenanthryl ether	18.6
4	dihydroquinine *O*-9-phenanthryl ether	15.5
5		≈0

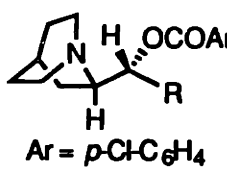
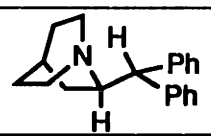
Entries 1 and 2 (as well as entries 3 and 4) reveal the slight decrease in binding affinity of dihydroquinine derivatives relative to the corresponding dihydroquinidine derivatives. These differences exemplify the fact that ligand binding to OsO_4 is exquisitely sensitive to subtle structural features.

Table VII discloses the results of binding studies of the newly prepared cinchona analogues, all of which were *p*-chlorobenzoate derivatives except for 2-diphenylmethyl quinuclidine **39**. The binding constant measurements were performed in a thermostated UV cuvette at 25°C by titration of a known amount of racemic ligand in *tert*-butanol by aliquots of OsO_4 solution in *tert*-butanol. Addition of excess OsO_4 and observation of the absorbance at 480 nm until

[67]Kwong, H. L.; Sharpless, K. B., unpublished results.

saturation was reached provided a data set which was put into a computer program (designed on the principles that Drago[68] reported) for the estimation and correction for the absorbance of the osmium-ligand adduct. The resulting information produced a new set of absorbance data. The calculated absorbance points, along with the experimental data and an initial estimate of the binding constant were used in an iterative, non-linear least-squares method to obtain a value for the equilibrium binding constant (K_{eq}). Minimization of the χ^2 statistical factor by refining the estimated K_{eq} value gave the values in Table VII.

Table VII. Binding Constants for Cinchona Analogue Derivatives with OsO_4 at 25°C in *tert*-Butanol.

Ligand		Entry	Compound #	K_{eq} (M^{-1})
 Ar = *p*-Cl-C_6H_4	R = phenyl	1	**50**	16.4
	R = phenyl (threo isomer)	2	**51**	3
	R = *p*-fluorophenyl	3	**52**	12.5
	R = 2-(2-methoxyethyl) phenyl	4	**53**	16.3
	R = 1-naphthyl	5	**54**	(22.5)[a]
	R = 6-methoxy-1-naphthyl	6	**55**	26.7
	R = H	7	**56**	24.4
	R = cyclohexyl (from **35a**)	8	**57**	1.7
	R = cyclohexyl (from **35b**)	9	**58**	0
	2-diphenylmethyl quinuclidine	10	**39**	0

[a]precipitate formed prior to reaching saturation

The comparison of entries 1 and 2 for the two phenyl-substituted stereoisomers shows once again that the threo stereochemistry (entry 2) is detrimental to ligand binding to osmium tetroxide. Whereas the epicinchona derivatives (i.e threo relationship at C-8/C-9) show no evidence of binding to osmium tetroxide, a small but measureable interaction is apparent for the threo

[68]Long, J. R.; Drago, R. S. *J. Chem. Educ.* **1982**, *59*, 1037.

isomer in this case, probably because the phenyl group is less sterically demanding than the methoxyquinoline substituent of the epicinchona derivatives, thus permitting slighly more conformational freedom. It is quite clear, however, that the larger aromatic substituents present on erythro isomers provide a stabilizing interaction (entries 5 and 6). The data for **54** in entry 5 was taken only from initial absorbance measurements before saturation was reached, however, because a precipitate formed during the titration, even when the experiment was repeated with repurified **54**. Hence, there may be considerable error in that particular measurement.

Despite the ambiguity in assigning the relative stereochemistries of the cyclohexyl-substituted analogues **35a** and **35b**, the binding constant data indicates that the *p*-chlorobenzoate derivatives of neither stereoisomer can bind efficiently to osmium tetroxide. Thus, moving an sp^3 center closer to the binding site is extremely disadvantageous.

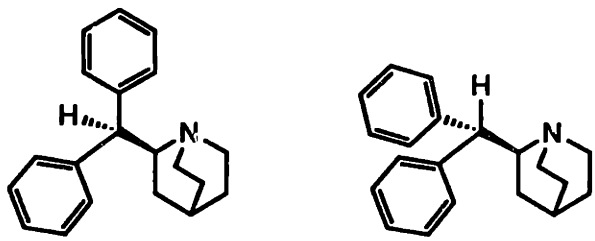
A small electronic effect on binding to osmium tetroxide may be indicated by the results of entry 3, since there is a noticeable drop in K_{eq} compared to the phenyl-substituted derivative (entry 1). The lack of data for the *p*-methoxyphenyl analogue is unfortunate; however, the erythro and threo isomers could not be separated for that case.

Removal of the stereogenic center at C-9 (entry 9) had an interesting effect on the binding constant. As stated above, the larger 7-methoxy-1-naphthyl group has a stabilizing influence on binding relative to the smaller phenyl group. The even smaller hydrogen atom permitted more efficient binding than did phenyl.

After considerable investment in the synthesis of 2-diphenylmethyl quinuclidine, its absolute lack of interaction with osmium tetroxide was extremely disconcerting. A closer look at the conformational properties of **39**

indicated an explanation, however. MM2 force field calculations[69] on **39** revealed that the lowest energy conformation resembled one of the closed conformations of cinchona alkaloids, whereas a conformation which would allow OsO_4 access to the lone pair on nitrogen is over 6 kcal/mol higher in energy (Figure 33).

Figure 33



"closed" 9.50 kcal/mol

"open" 15.56 kcal/mol

To probe the conformational similarities of the cinchona analogues to the natural alkaloids quickly, MM2 calculations on the amino alcohols *erythro*-**31a** and *threo*-**31b** were performed. The lowest energy conformer for the erythro isomer was closed (12.3 kcal/mol), while the threo isomer possessed an open conformation (15.2 kcal/mol) analogous to that of epidihydroquinidine (Figure 5c).

Similar calculations on the erythro *p*-chlorobenzoate derivative **50** (R = Ph) affirmed that the lowest energy conformer (9.7 kcal/mol) was closed, as expected; however, an open conformation was only 1.1 kcal/mol higher in energy. Thus OsO_4 can bind readily to this ligand.

A molecular mechanics study of the erythro cyclohexyl-substituted *p*-chlorobenzoate structure (assumed to be **57** since it was the only isomer that showed any interaction with osmium tetroxide) revealed three interesting conformations depicted in Figure 34.

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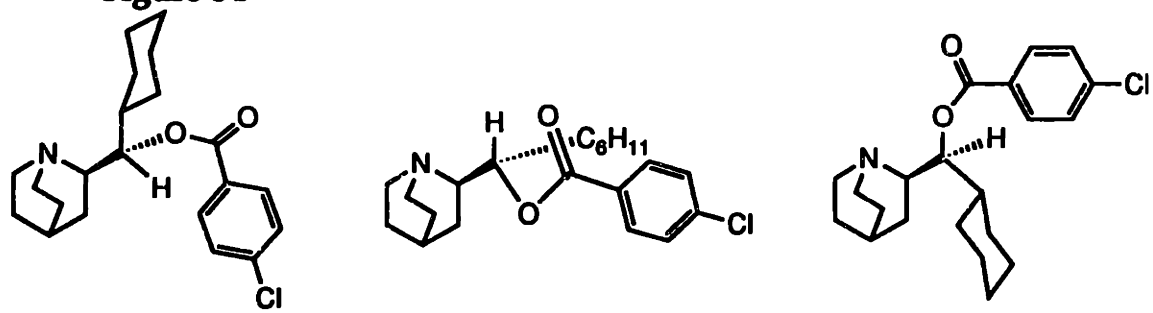
[69]Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

Figure 34



a 28.2 kcal/mol

b 28.4 kcal/mol

c 33.0 kcal.mol

Typically, the lowest energy conformer (Figure 34a) possessed a closed structure. Two semi-open conformers were interesting, however. In each case, the bulky cyclohexyl group caused deviations from the expected structures. The first open conformer was nearly isoenergetic (Figure 34b) with the closed conformer. The *p*-chlorobenzoyl moiety was in an unusual orientation in this case, however, such that it could interfere with binding. The second open conformer (Figure 34c), unlike the open conformers of quinidine derivatives, resembled the open epidihydroquinidine conformer (Figure 5c) more closely. Thus, the derivatized C-9 oxygen protruded into the space that bound osmium tetroxide would occupy. Hence, the inaccessibility of suitable conformations for binding to osmium tetroxide for either the erythro or threo cyclohexyl-substituted *p*-chlorobenzoate structures neatly explains the results for entries 8 and 9 in Table VII.

EXPERIMENTAL

General.

All moisture- or oxygen-sensitive reactions were carried out under argon in glassware flame-dried under vacuum or oven-dried at 130°C. All reactions were stirred magnetically unless otherwise noted. Hydrochloride salts of amines were prepared by treating a solution of the amine in ether or ether/toluene at 0°C with anhydrous HCl in ether (1.0 M, Aldrich Chemical). Mosher's esters[70] were prepared from group stock of *S*-Mosher's chloride (prepared from *R*-Mosher's acid, Aldrich Chemical or Fluka Chemical).

Reagents from commerical sources were used without further purification unless otherwise noted. Dry solvents were obtained as follows: benzene, toluene, and THF were distilled under argon from sodium-benzophenone ketyl; dichloromethane, ether, TMEDA, and triethylamine were distilled under argon from calcium hydride; pyridine was distilled under argon from barium oxide and stored over activated 3A molecular sieves, acetonitrile was distilled under argon from CaH_2, and dimethyl sulfoxide was used from an anhydrous Sure/Seal™ reagent bottle (Aldrich Chemical). Molecular sieves were activated by heating at 150°C in a vacuum oven for at least 12 hours. Dehydrated quinuclidine-N-oxide was stored under nitrogen in a Vacuum Atmospheres drybox.

NMR spectra were recorded on Bruker WM-250, AC-250, and Varian XL-300, Gemini-300, and Unity-300 spectrometers. Deuterochloroform for NMR sample preparation was passed through a plug of basic alumina immediately prior to use to remove acidic impurities. Other deuterated solvents were used directly from freshly cracked ampoules. NMR spectra were referenced to TMS using $CDCl_3$ or benzene-d_6 as solvents, to 3-(trimethylsilyl)propionic-2,2,3,3-d_4

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[70]Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

acid, sodium salt using D_2O as solvent, and to residual proton signals using other solvents. Melting points were determined either in open glass capillaries using a Thomas-Hoover melting point apparatus, or between thin glass slides using a Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were performed by Roberston Laboratories, Inc., Madison, N.J. Analytical TLC was performed using glass plates coated with Merck silica gel 60-F254. Tertiary amines were visualized by dipping developed TLC plates into Dragendorff's Reagent. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh) as described by Still.[71] Infrared spectra were recorded on a Perkin-Elmer 1600 series FT-IR with internal referencing. Capillary gas chromatography was performed using 28-30 meter fused silica capillary columns with DB-5 (5% cross-linked methyl silicone) stationary phase.

[71]Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Synthesis.

Preparation of quinuclidine-2-carboxylic acid hydrochloride (16).[38]

Starting from either 2-carboethoxy quinuclidine (**15**) or 2,2-dicarboethoxy quinuclidine (**16**), for each gram of starting ester, 10 mL of 4N HCl was placed in a round-bottomed flask with a magnetic stir bar and a reflux condenser leading to a KOH trap. The mixture was refluxed gently for 6 hr., after which the HCl was removed by rotary evaporation. Drying under high vacuum yielded 95-98% of a chunky, white solid, mp 294-296°C (lit.[38] 292-295°C).

Preparation of 2-cyanoquinuclidine (18).[41]

An ice-cooled, 300-mL round-bottomed flask equipped with a magnetic stir bar, an addition funnel, and an argon inlet was charged with 5.25 g (34.0 mmol) quinuclidine-2-carboxamide (**17**) and 5.50 mL dry pyridine (68.1 mmol; 2 eq.) in 160 mL $CHCl_3$. Triphosgene (4.39 g; 14.8 mmol; 0.44 eq.) in 20 mL $CHCl_3$ was added dropwise over 10 min. After stirring for 10 additional min., water (100 mL) was added and the biphasic mixture was stirred vigorously for 10 min. to destroy any unreacted phosgene. Washing with brine (100 mL) and removal of the solvent in vacuo gave a slightly yellow oil. Kugelrohr distillation (85°C oven temperature, 1 mm Hg; lit.[41] 105-121°C/13 mm Hg) yielded 3.62 g (78%) **18** as a clear, colorless oil which solidified on cooling in storage.

^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	3.85 (dd, J=10.5 Hz,5.9 Hz, 1H), 3.17-3.32 (m,1H), 2.8-2.95(m,3H), 1.73-2.05 (m,3H), 1.43-1.71 (m,4H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	120.6, 47.6, 47.3, 43.6, 30.9, 25.3, 24.5, 20.0

Preparation of 4-(2-carboethoxy-2-cyano)vinylpyridine (19).

In a one liter flask equipped with a magnetic stir bar, a Dean-Stark apparatus, and a reflux condenser, 44.27 g pyridine-4-carboxaldehyde (0.413 mol; Aldrich), 46.72 g ethyl cyanoacetate (0.413 mol, 1.0 eq.; Aldrich), and 2 mL piperidine were combined with 500 mL benzene. The mixture was refluxed for 18 hr. while collecting water. The yellow reaction mixture was washed with water (300 mL) and brine (300 mL) and dried over Na_2SO_4. Removal of the solvent gave a yellow solid which was recrystallized from 200 mL 95% EtOH to give fine, slightly yellow needles (72.8 g, 87%).

melting point	98-99.5°C
^{1}H-NMR ($CDCl_3$, 300 MHz)	8.83 (d, J=6.2 Hz, 2H), 8.22 (s, 1H), 7.78 (d, J=6.2 Hz, 2H), 4.42 (q, J=6 Hz, 2H), 1.42 (t, J=6 Hz, 3H)
^{13}C-NMR ($CDCl_3$, 75.5 MHz)	161.4, 152.2, 151.2, 138.1, 123.3, 114.2, 108.3, 63.1, 13.7
Anal.	Calc'd for $C_{11}H_{10}N_2O_2$: C 65.34, H 4.98, N 13.85 Found: C 65.26, H 4.93, N 13.84

Preparation of *N*-cyanomethyl-4-carboethoxy piperidine (20).

A 3-necked, 100 mL round-bottomed flask equipped with a reflux condenser, an addition funnel, and a magnetic stir bar was charged with 3.31 g $NaHSO_3$ (31.8 mmol) and 50 mL water. Paraformaldehyde (2.39 mL, 0.995 g, 31.8 mmol, 1.0 eq., 37% aqueous, Aldrich) was added dropwise, and the mixture was heated at 40°C for 15 min. Neat ethyl isonipecotate (4.90 mL, 31.8 mmol, 1.0 eq., Aldrich) was added dropwise. The reaction mixture was stirred vigorously for 2 hr. at 40°c. Sodium cyanide (1.56 g, 31.8 mmol, 1.0 eq.) in 10 mL water was added dropwise. Heating was suspended and, the reaction mixture became cloudy while stirring. After 15 min., 30 mL diethyl ether was added and the layers separated. The aqueous phase was extrated twice with ether (25 mL). The

combined ether layers were washed with brine and dried over Na_2SO_4. Removal of the solvent in vacuo gave a slightly yellow oil. Kugelrohr distillation (110°C oven temperature, 1 mm Hg) yielded 5.37 g (86%) of a white solid.

melting point	39.5-41°C
^{1}H-NMR ($CDCl_3$, 300 MHz)	δ 4.14 (q, J=10.4 Hz, 2H), 3.54 (s, 2H), 2.78-2.85 (m, 2H), 2.25-2.41 (m, 3H), 1.91-2.02 (m, 2H), 1.60-1.85 (m, 2H), 1.25 (t, J=10.4 Hz, 3H)
^{13}C-NMR ($CDCl_3$, 75.5 MHz)	δ 174.5, 114.5, 60.0, 51.1, 45.8, 39.5, 27.4, 13.6
IR (cm^{-1})	2900, 2228 , 1718, 1210
Anal.	Calc'd for $C_{10}H_{16}N_2O_2$: C 61.20, H 8.22, N 14.27 Found: C 61.41, H 8.10, N 14.32

Preparation of 2-benzoyl quinuclidine (21).

The procedure of Braschler, et al.[41] was followed with slight modifications. A flame-dried, 100-mL, 3-necked round-bottomed flask equipped with a magnetic stir bar, a reflux condenser, an addition funnel, and an argon inlet was charged with 9.80 mL phenyl magnesium bromide (29.4 mmol, 3.0M in ether, Aldrich) and 20 mL dry benzene. 2-cyanoquinuclidine (2.0 g., 14.7 mmol, 0.5 eq.) in 25 mL benzene was added dropwise, and the reaction mixture was refluxed under argon for 3 hr. With ice cooling, the reaction was quenched by first adding 10 mL saturated NH_4Cl dropwise and then pouring the crude mixture into 30 mL saturated NH_4Cl. The flask was rinsed with water and benzene, and the mixture was acidified with 10 mL concentrated HCl and 10 mL water. The layers were separated, and the organic phase was extracted twice with 25 mL portions of 2N HCl. The combined aqueous extracts were warmed gently on a stirring hot plate for 2 hr., after which the water was removed in vacuo. The residue was placed in 30 mL water, made alkaline with saturated K_2CO_3 solution, and extracted four

times with 50 mL ether. The ether solution was dried over solid K_2CO_3, and the solvent was removed. The residue crystallized on cooling to yield, after recrystallization from ether, 2.81 g (89%) 2-benzoyl quinuclidine.

melting point	88-90°C (lit.[41] 88-89.5°C)
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	8.0-8.08 (m, 2H), 7.39-8.57 (m,3H), 4.30 (dd, J=, 1H), 3.12-3.23 (m, 1H), 9.94-3.05 (m, 1H), 2.62-2.83 (m, 2H), 2.19-2.28 (m, 1H), 1.91 (m, 1H), 1.38-1.67 (m, 5H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	199.5, 136.6, 133.0, 129.1, 128.6, 60.4, 49.3, 43.3, 26.6, 26.0, 25.9, 21.2
IR (cm^{-1})	1675 (C=O)

Preparation of 2-quinuclidinyl (2'-(2"-methoxyethyl)phenyl) ketone (22).

A flame-dried, 50-mL, 2-necked round-bottomed flask equipped with a magnetic stir bar, a reflux condenser with an argon inlet, and an addition funnel was charged with 0.800 g magnesium turnings (32.9 mmol, 1.5 eq., Aldrich) and stirred vigorously under vacuum overnight. A crystal of iodine was added. 2-(2-methoxyethyl)chlorobenzene **27** (4.88 g, 28.6 mmol, 1.3 eq.) in 5 mL dry ether was added dropwise, and the funnel was rinsed with 3 mL ether. After refluxing 1 hr., GC analysis of a quenched aliquot showed minimal conversion. The reaction mixture began to look cloudy and discolored after 4 hr., at which time GC analysis indicated ≈40% conversion to the Grignard. After refluxing for 6 additional hours, the same conversion was observed, and 15 mL dry benzene was added. After refluxing the very discolored reaction mixture for a total of 20 hours, GC analysis showed 92% conversion, and the Grignard solution was used at that stage. The Grignard was transferred via cannula into a 300-mL 3-necked round-bottomed flask, and 60 mL benzene was added that had been used to rinse the Grignard flask. The mixture was heated to reflux, and 2-cyanoquinuclidine

(3.00 g, 22.0 mmol, 1.0 eq.) was added in 10 mL benzene. After refluxing for 5 hr., the reaction was quenched, with ice cooling, by first adding 10 mL saturated NH_4Cl dropwise and then pouring the crude mixture into 40 mL saturated NH_4Cl. The flask was rinsed with water and benzene, and the mixture was acidified with 10 mL concentrated HCl and 10 mL water. The layers were separated, and the organic phase was extracted twice with 40 mL portions of 2N HCl. The combined aqueous extracts were warmed gently on a stirring hot plate for 2 hr., after which the water was removed by rotary evaporation. The residue was placed in 30 mL water, made alkaline with saturated K_2CO_3 solution, and extracted four times with 50 mL ether. The ether solution was dried over solid K_2CO_3, and the solvent was removed to yield a yellow oil (4.69 g, 78%). An impurity was evident by ^{1}H-NMR, indicated by a complex multiplet at 3.8-3.9 ppm. Chromatography on silica gel (EtOAc, 5% Et_3N) did not provide adequate separation from the impurity. The hydrochloride salt was prepared in ether and was recrystallized from absolute ethanol, then the free base was recovered by treating an aqueous solution of the hydrochloride with 40% K_2CO_3, extracting into ether, drying over K_2CO_3, and removing the ether by rotary evaporation.

melting point (HCl salt)	194-195.5°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.64-7.70 (d, 2H), 7.20-7.39 (m, 3H), 4.20 (dd, J=9.5Hz, 14.2Hz, 1H), 3.60-3.68 (m, 2H), 3.35 (s 3H), 2.62-3.15 (m, 6H) 2.0-2.12 (m, 1H), 1.85-1.92 (m, 1H), 1.38-1.68 (m, 5H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	203.2, 138.7, 137.9, 131.4, 130.6, 128.4, 125.8, 73.4, 62.1, 58.3, 49.3, 43.3, 33.9, 27.3, 26.1, 25.7, 21.4
IR (cm^{-1})	1675 (C=O)
Anal. (HCl salt)	Calc'd for $C_{17}H_{24}ClNO_2$: C 65.90, H 7.81, N 4.49, Cl 11.44 Found: C 65.76, H 7.74, N 4.45, Cl 11.24

Preparation of 2-quinuclidinyl (1'-naphthyl) ketone (23).

A flame-dried, 50-mL, 3-necked round-bottomed flask equipped with a magnetic stir bar, a reflux condenser with an argon inlet, and an addition funnel was charged with 0.750 g magnesium turnings (30.9 mmol, 2.1 eq., Aldrich) and stirred vigorously under vacuum overnight. 1-Bromonaphthalene (4.09 mL, 29.4 mmol, 2.0 eq.) in 5 mL dry THF was added dropwise, and the funnel was rinsed with 3 mL THF. After refluxing 3 hr., 7 mL dry THF was added. to the dark reaction mixture. 2-cyanoquinuclidine (2.00 g, 14.7 mmol, 1.0 eq.) was added in 10 mL benzene. After refluxing for 3 hr., the reaction was quenched, with ice cooling, by first adding 10 mL saturated NH_4Cl dropwise and then pouring the crude mixture into 30 mL saturated NH_4Cl. The flask was rinsed with water and benzene, and the mixture was acidified with 10 mL concentrated HCl and 10 mL water. The layers were separated, and the organic phase was extracted twice with 25 mL portions of 2N HCl. The combined aqueous extracts were warmed gently on a stirring hot plate for 2 hr., after which the water was removed by rotary evaporation. The residue was placed in 30 mL water, made alkaline with saturated K_2CO_3 solution, and extracted four times with 50 mL ether. The ether solution was dried over solid K_2CO_3, and the solvent was removed to yield a slightly yellow solid 3.24 g, 83%). Recrystallization from ether:petroleum ether (1:1) gave white crystals.

melting point	126-127.5°C (lit.[72] 125-127°C)

[72]This ketone was prepared previously by Pluim (ref. 42) by reaction of 1-naphthyl magnesium bromide with the primary amide 17.

^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	8.43 (d, J=8.5 Hz, 1H), 7.82-7.96 (m, 3H), 7.45-7.60 (m, 3H), 3.33 (dd, J=10.8 Hz, 12 Hz, 1H), 2.90-3.18 (m, 3H), 2.64-2.78 (m, 1H), 2.10-2.20 (m, 1H), 1.9 (m, 1H), 1.40-1.72 (m, 5H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	204.0, 136.0, 134.2, 132.2, 130.9, 128.6, 127.7, 126.3, 125.6, 124.6, 62.6, 49.4, 43.5, 27.4, 26.0, 25.7, 21.4
IR (cm^{-1})	1670 (C=O)

Preparation of 2-quinuclidinyl (7'-methoxy-1'-naphthyl) ketone (24).

A flame-dried, 50-mL, 3-necked round-bottomed flask equipped with a magnetic stir bar, a reflux condenser with an argon inlet, and an addition funnel was charged with 0.246 g magnesium turnings (10.1 mmol, 1.2 eq., Aldrich) and stirred vigorously under vacuum overnight. A crystal of iodine was added to the flask along with 9 mL dry THF. 7-methoxy-1-bromonaphthalene (2.00g., 8.44 mmol, 1.0 eq.) in THF (3 mL) was added dropwise. The reaction initiated rapidly, and was complete within 30 min., at which time 36 mL benzene was added. A THF solution of 2-cyanoquinuclidine (4 mL) was added dropwise, and the reaction mixture was refluxed for 30 min. during which time the mixture turned deep purple. The dark purple color dissipated rapidly as the reaction was quenched by first adding 10 mL saturated NH_4Cl dropwise and then pouring the crude mixture into 30 mL saturated NH_4Cl. The flask was rinsed with water and benzene, and the mixture was acidified with 10 mL concentrated HCl and 10 mL water. The layers were separated, and the organic phase was extracted twice with 25 mL portions of 2N HCl. The combined aqueous extracts were warmed gently on a stirring hot plate for 2 hr., then allowed to cool to room temperature before being made alkaline with saturated K_2CO_3 solution and extracted four times with 50 mL portions of ether. The combined ether extracts were dried over solid K_2CO_3, and the solvent was removed to yield 2.01 g (95%) of the ketone. The

hydrochloride salt was prepared in ether and was recrystallized from absolute ethanol, then the free base was recovered by treating an aqueous solution of the hydrochloride with 40% K_2CO_3, extracting into ether, drying over K_2CO_3, and removing the ether by rotary evaporation.

melting point (HCl salt)	261°C (decomp.)
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.72-8.06 (m, 4H), 7.14-7.35 (m, 2H), 4.36 (dd, J=8.6 Hz) 3.93 (s, 3H), 3.04-3.18 (m, 1H), 2.88-3.0 (m, 2H), 2.65-2.78 (m, 1H), 2.15-2.25 (m, 1H), 1.90 (m, 1H), 1.40-1.70 (m, 5H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	203.2, 159.3, 133.4, 129.8, 129.6, 128.8, 122.0, 118.8, 104.0, 62.3, 55.2, 49.5, 43.6, 27.4, 26.2, 25.9, 21.6
IR (cm^{-1})	1672 (C=O)
Anal. (HCl salt)	Calc'd for $C_{19}H_{22}ClNO_2$: C 68.77, H 6.68, N 4.22 Found: C 68.49, H 6.70, N 4.02

Preparation of 2-quinuclidinyl cyclohexyl ketone (25).

A flame-dried, 100-mL, 3-necked round-bottomed flask equipped with a magnetic stir bar, a reflux condenser with an argon inlet, and an addition funnel was charged with 14.7 mL cyclohexyl magnesium chloride (29.4 mmol, 2.0M in ether, Aldrich) and 20 mL dry benzene. 2-cyanoquinuclidine (2.0 g., 14.7 mmol, 0.5 eq.) in 20 mL benzene was added dropwise, and the reaction mixture was refluxed under argon for 3 hr. With ice cooling, the reaction was quenched by first adding 10 mL saturated NH_4Cl dropwise and then pouring the crude mixture into 30 mL saturated NH_4Cl. The flask was rinsed with water and benzene, and the mixture was acidified with 10 mL concentrated HCl and 10 mL water. The layers were separated, and the organic phase was extracted twice with 25 mL portions of 2N HCl. The combined acidic extracts were warmed gently on a stirring hot plate for 2 hr., then allowed to cool to room temperature before

being made alkaline with saturated K_2CO_3 solution and extracted four times with 50 mL portions of ether. The combined ether extracts were dried over solid K_2CO_3, and the solvent was removed to yield a yellow oil. Kugelrohr distillation (140°C oven temperature, 0.5 mm Hg) gave 2.83 g (87%) of the ketone as a clear, colorless oil. The HCl salt was prepared as described in the general experimental section, and was recrystallized from absolute EtOH before analyses.

melting point (HCl salt)	196-199.5°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	3.50 (dd, J=8.1, 8.1 Hz, 1 H), 2.50-3.10 (m, 5H), 1.12-2.10 (m, 17 H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	214.1, 62.6, 49.4, 46.9, 44.2, 29.7, 27.8, 26.2, 26.1, 25.9, 25.84, 25.77, 25.2, 21.3
IR (cm^{-1})	1693 (C=O)
Anal.(HCl salt)	Calc'd for $C_{14}H_{24}ClNO$: C 65.23, H 9.38, N 5.43 Found: C 65.17, H 9.22, N 5.39

Preparation of 2-(2'-methoxyethyl) chlorobenzene (27).

Reduction of α-chlorophenyl acetic acid by $LiAlH_4$ according to literature procedures gave 2-(2'-hydroxyethyl) chlorobenzene, which was methylated to give **27**. A 3-necked, 300-mL round-bottomed flask with a magnetic stir bar, an argon inlet, and an addition funnel was charged with 6.00 g (38.3 mmol) 2-(2'-hydroxyethyl) chlorobenzene and 100 mL anhydrous DMSO (Aldrich). Powdered KOH (3.00 g, 53.5 mmol, 1.4 eq.) was added, and the suspension was stirred vigorously while adding methyl iodide (3.10 mL, 49.8 mmol, 1.3 eq.) in 5 mL DMSO dropwise. The reaction mixture was stirred under argon for 5 hr., then it was quenched by the addition of 200 mL of ice water. Extraction with two 100 mL portions of ether, drying of the combined ether extracts over K_2CO_3, and removal

of the solvent by rotary evaporation gave crude **27** (5.93 g, 91%). Distillation at 85°C/1.5 mm Hg yielded 5.22 g **27** (80%) as a clear, colorless liquid.

^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.08-7.35 (m, 4 H), 3.60 (t, J=6.9 Hz, 2H), 3.34 (s, 3H), 3.01 (t, J=6,9 Hz, 2H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	136.3, 133.9, 130.8, 129.2, 127.5, 126.5, 71.4, 58.3, 33.6
IR, cm^{-1} ($CHCl_3$)	3029, 2941, 2820, 1603, 1508, 1142
Anal.	Calc'd for $C_9H_{11}ClO$: C 63.35, H 6.50, Cl 20.78 Found: C 63.09, H 6.50, Cl 20.49

Preparation of 7-methoxy-1-naphthylamine (29).

The method of Glennon[46] was used with slight modifications to the stoichiometry and starting with 87% 8-amino-2-naphthol (Aldrich) rather than purified material. In a flame-dried, 3-necked, 500-mL round-bottomed flask with a magnetic stir bar, an argon inlet, and an addition funnel, 21.0 g 8-amino-2-naphthol (0.132 mol) and 50 mL dry MeOH were treated with 1.1 eq. NaOMe in 50 mL MeOH (from 3.33 g Na, 0.145 mol). The mixture was stirred for 10 min., then filtered to remove insoluble starting material impurities. The solvent was removed to yield the sodium salt as a light brown residue. Dimethyl sulfate (11.25 mL, 0.119 mol, 0.9 eq.) was added dropwise to an acetone solution of the sodium salt, and the mixture was stirred for 3 hr. The solvent was removed by rotary evaporation to yield an oil. The crude product was dissolved in methylene chloride and washed with 10% NaOH to remove any unreacted starting material. Chromatography on silica gel (20% EtOAc:hexane) to remove dimethylated side-product gave 11.73 g (51%) of **29**.

melting point	73.5-75.5°C (lit.[45] 75-77°C)

^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.63 (d, J=11.6 Hz, 1H), 6.95-7.25 (m, 4H), 6.67 (d, J=9.2 Hz, 1H), 3.90 (br, 2H), 3.80 (s, 3H),
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	157.1, 141.0, 130.0, 129.8, 124.7, 123.8, 118.9, 118.0, 110.5, 100.1, 55.2

Preparation of 1-bromo-7-methoxynaphthalene (30).

The procedure of LaBudde[45] was used with slight modifications. In a 1 L round-bottomed flask, a suspension of 9.70 g **29** (56.0 mmol) in 95 mL water and 95 mL 48% HBr was cooled to 0°C and diazotized by slowly adding $NaNO_2$ (4.25 g, 61.6 mmol, 1.1 eq.) in 20 mL water. The clear, bright yellow solution was diluted with 120 mL ice-water and a solution of mercuric bromide (60.55 g, 168 mmol, 3.0 eq.) and potassium bromide (60.0 g, 504 mmol, 9.0 eq.) in 240 mL water was added. A forest green precipitate formed immediately. After standing one hour at 0°C, the double salt was filtered and dried under high vacuum at room temperature for 3 days. It was then mixed with with an equivalent weight of potassium bromide (31 g) and heated gradually to 150°C at 1 mm Hg in a large sublimation apparatus, whereupon rapid decomposition of the salt occured. The entire mixture was sublimed at 165°C to give a white solid (5.58 g, 42%) which was recrystallized from 35 mL petroleum ether to give 4.38 g (33%) **30** as white crystals.

melting point	67-68.5°C (lit.[45] 68-69°C)
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.65-7.75 (m, 3H), 7.46 (br, 1H), 7.10-7.18 (m, 2H), 3.93 (s, 3H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	158.8, 133.1, 130.2, 129.94, 129.86, 127.5, 123.7, 121.4, 119.5, 105.2, 55.3

The general procedure for the DIBAL reduction of 2-ketoquinuclidines is based on the method of Pluim[42] for the reduction of 2-benzoyl quinuclidine

(21) to 2-hydroxybenzyl quinuclidines 30a and 30b with minor modifications. The details below typify the procedure.

Preparation of *erythro*- and *threo*- 2-hydroxybenzyl quinuclidine (30a, 30b).

A flame-dried, 300-mL, 3-necked round-bottomed flask equipped with a magnetic stir bar, an addition funnel, and an argon inlet was charged with 3.30 g **21** (15.3 mmol) and 60 mL dry toluene. The solution was cooled to -78°C with an acetone/CO_2 bath and 20 mL DIBAL (20.0 mmol, 1.3 eq., 1.0M in THF, Aldrich) was added dropwise over 15 min. The reaction mixture was stirred at -78°C for 3 hr., then allowed to warm slowly to room temperature. The reaction was quenched by adding 50 mL methanol, and the solvent was removed by rotary evaporation. The residue was dissolved in 100 mL dichloromethane, washed with 1N NaOH and with brine, and dried over K_2CO_3. The solvent was removed by rotary evaporation to give 3.09 g (93%) of a white solid, which proved to be a mixture of erythro and threo 2-hydroxybenzyl quinuclidines (**30a:30b** ratio 29:1 by ^{1}H-NMR). Recrystallization from acetone (25 mL) gave the pure erythro isomer (2.31 g, 69%). Silica gel chromatography (87.5:10:2.5 $CHCl_3$:Et_3N:MeOH) allowed isolation of the threo isomer (R_f = 0.39; erythro R_f = 0.11).

Spectral data for *erythro*-2-hydroxybenzyl quinuclidine (**30a**):

melting point	142-144°C (lit.[42] 143-144°C)
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.20-7.38 (m, 5H), 4.77 (d, J=6.6 Hz, 1H), 4.05 (br, 1H), 3.18-3.30 (m, 1H), 2.45-3.0 (m, 4H), 1.30-1.85 (m, 7H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	144.5, 127.9, 126.9, 126.1, 75.7, 61.3, 50.2, 43.1, 26.9, 26.3, 25.4, 21.8

Spectral data for *threo*-2-hydroxybenzyl quinuclidine (**30b**):

^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.21-7.43 (m, 5H), 4.37 (d, J=9.9 Hz, 1H), 4.0 (br, 1H), 2.7-3.10 (M, 5H), 1.70-1.80 (m, 1H), 1.05-1.55 (m, 6H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	141.0, 127.8, 127.5, 126.8, 74.2, 62.4, 49.3, 41.1, 29.1, 26.1, 25.2, 21.3
IR (cm^{-1})	3320, 2944, 1612, 1519, 1080

Preparation of *erythro*-2-(2'-(2''-methoxyethyl)phenyl) hydroxymethyl quinuclidine (32a).

By the procedure described for the preparation of **31a**, 1.70 g of **22** (6.22 mmol) was reduced with DIBAL to yield 1.56 g (91%) of a mixture of **32a** and **32b** (ratio 18:1 by ^{1}H-NMR). Silica gel chromatography (87.5:10:2.5 $CHCl_3$:Et_3N:MeOH) gave the pure erythro isomer **32a**. The hydrochloride salt was prepared in ether/toluene and was recrystallized from absolute EtOH for analysis.

melting point (HCl salt)	178-179°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.38-7.45 (m, 1H), 7.10-7.28 (m, 3H), 4.97 (d, J=7.8 Hz, 1H), 3.30-3.7 (m, 3H), 3.28 (s, 3H), 2.55-3.0 (m, 7H), 1.38-1.90 (m, 7H) threo isomer **32b** has a doublet at 4.75, J=10.1 Hz
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	141.9, 136.9, 129.7, 127.4, 126.7, 126.4, 73.8, 71.6, 59.1, 58.8, 50.0, 43.0, 32.5, 29.7, 26.6, 25.7, 21.8
IR (cm^{-1})	
Anal. (HCl salt)	Calc'd for $C_{17}H_{26}ClNO_2$: C 65.48, H 8.40, N 4.49 Found: C 64.71, H 8.50, N 4.51

Preparation of *erythro*-2-(1'-naphthyl) hydroxymethyl quinuclidine (33a).

By the procedure described for the preparation of **31a**, 3.21 g of **23** (12.1 mmol) was reduced with DIBAL to yield 3.10 g (96%) of a mixture of **33a** and **33b** (ratio 2.7:1 by ^{1}H-NMR). Recrystallization from 100 mL toluene gave the pure erythro isomer **33a**.

melting point	198.5-200°C (lit.[42] 199.5-199.9°C)
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.1-8.1 (m, 7H), 5.79 (d, J=3.9 Hz, 1H), 3.8 (br, 1H), 3.47-3.60 (m, 1H), 3.10-3.25 (m, 1H), 2.48-3.0 (m, 3H), 1.75-1.95 (m, 2H), 1.55-1.70 (m, 1H), 1.30-1.50 (m, 4H) threo isomer **33b** has a doublet at 4.95, J=6.1 Hz)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	140.8, 135.4, 131.8, 129.9, 128.7, 127.0, 126.4, 126.3, 124.7, 124.0, 73.0, 61.3, 49.3, 44.8, 27.1, 27.0, 26.4, 23.3

Preparation of *erythro*- 2-(7'-methoxy-1'-naphthyl) hydroxymethyl quinuclidine (34a).

By the procedure described for the preparation of **31a**, 1.25 g of **24** (4.23 mmol) was reduced with DIBAL to yield 1.09 g (87%) of a mixture of **34a** and **34b** (ratio 1.3:1 by ^{1}H-NMR). Recrystallization from 25 mL toluene gave the pure erythro isomer **34a**.

melting point	191.5-193°C
^{1}H-NMR, ppm (CD_2Cl_2, 300 MHz)	7.10-7.80 (m, 6H), 5.57 (d, J=5.2 Hz), 3.90 (s, 3H), 3.80 (br, 1H), 3.30-3.42 (m, 1H), 3.18-3.28 (m, 1H), 2.40-2.88 (m, 3H), 2.0 (br, 1H), 1.75-1.83 (m, 1H), 1.30-1.60 (m, 5H) threo isomer **34b** has a doublet at 5.02, J=9.6 Hz)
^{13}C-NMR, ppm (CD_2Cl_2, 75.5 MHz)	158.0, 139.2, 132.2, 130.5, 129.5, 127.6, 124.7, 123.3, 118.2, 102.6, 73.3, 60.5, 55.7, 50.7, 43.9, 28.1, 27.0, 26.0, 22.6
IR (cm^{-1})	

Anal.	Calc'd for $C_{19}H_{23}NO_2$: C 76.74, H 7.80, N 4.71 Found: C 76.02, H 7.67, N 4.64

Preparation of 2-((cyclohexyl) hydroxymethyl) quinuclidines (35a, 35b--mixture of erythro and threo isomers).

By the procedure described for the preparation of **31a**, 2.58 g **25** (11.6 mmol) was reduced with DIBAL to yield 2.45 g (94%) of a mixture of **35a** and **35b** (ratio 8.2:1 by ^{1}H-NMR). Recrystallization from 25 mL acetone/ether (5:1) gave one pure stereoisomer (**35a**) as fine needles. Silica gel chromatography (87.5:10:2.5 $CHCl_3$:Et_3N:MeOH) allowed isolation of the other stereoisomer, **35b** (R_f = 0.41, R_f = 0.15 for **35a**). The hydrochloride salt of **35b** was prepared in ether and was recrystallized from absolute EtOH for analysis.

Spectral data for **35a**:

melting point	113-114°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	3.52 (dd, J=7.3, 3.5), 2.60-3.20 (m, 5H), 1.40-1.90 (m, 14H), 1.07-1.38 (m, 5H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	78.0, 56.9, 50.2, 43.0, 30.3, 29.7, 26.5, 26.4, 26.0, 25.9, 25.6, 21.6
IR, cm^{-1} ($CHCl_3$)	3300, 2946, 1108, 1085
Anal.	Calc'd for $C_{14}H_{25}NO$: C 75.28, H 11.28, N 6.27 Found: C 75.14, H 11.05, N 6.27

Spectral data for **35b**:

melting point (HCl salt)	251-253°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	3.80 (br, 1H), 3.25 (dd, J=11.9 Hz, 1.9 Hz, 1H), 2.82-3.0 (m, 3H), 2.58-2.74 (m, 2H), 1.0- 1.90 (m, 18H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	75.1, 57.8, 49.5, 41.2, 39.0, 30.9, 30.1, 26.9, 26.7, 26.5, 26.4, 25.9, 25.8, 21.5

IR, cm^{-1} ($CHCl_3$)	3300, 2944, 1105, 1090
Anal.(HCl salt)	Calc'd for $C_{14}H_{26}ClNO$: C 64.72, H 10.09, N 5.39 Found: C 64.68, H 9.93, N 5.36

Preparation of 2-diphenylmethyl quinuclidine (39).

Following the method of Nelson,[73] 2-diphenylhydroxymethyl quinuclidine **38** was prepared in 60% yield. A flame-dried, 25-mL, 2-necked flask equipped with a magnetic stir bar, a dry ice condenser, and an argon inlet was charged with 0.500 g **38** (1.70 mmol), 4 mL THF, and 7 mL NH_3 (distilled from Na) at -78°C. With vigorous stirring, lithium wire (36 mg, 3.19 mmol, 3.05 eq.) was added in small pieces, resulting in a blue color which dissipated slowly with the formation of a suspension over the course of 1 hr. The reaction was quenched with solid NH_4Cl, and the ammonia was allowed to evaporate in the hood. The residue was dissolved in dichloromethane, washed with water and brine, and dried over K_2CO_3. The solvent was removed by rotary evaporation to give an off-white solid. ^{1}H-NMR analysis showed the presence of starting material and a new resonance at 3.94 ppm (benzylic hydrogen) indicating a 47% conversion for the reaction. Silica gel chromatography (87.5:2.5:1.0 $CHCl_3$:MeOH:NH_4OH) allowed isolation of pure **39**.

melting point	108-109°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.05-7.30 (m, 10H), 3.94 (d, J=12.1 Hz, 1H), 3.55-3.67 (m, 1H), 3.0-3.15 (m, 1H), 2.88-2.97 (m, 2H), 2.6-2.7 (m, 1H), 1.7 (br, 1H), 1.35-1.55 (m, 5H), 1.0-1.1 (m, 1H)
^{13}C-NMR, ppm ($CDCl_3$, 62.9 MHz)	143.1, 128.6, 128.4, 127.6, 126.1, 58.4, 56.2, 50.0, 41.2, 33.3, 27.0, 25.7, 22.2

[73]Nelson, P. H.; Stosberg, A. M.; Untch, K. G. *J. Med. Chem.* **1980**, *23*, 180.

IR, cm^{-1} (KBr)	3035, 2938, 1614, 1603, 1505
Anal.	Calc'd for $C_{20}H_{23}N$: C 86.59, H 8.36, N 5.05 Found: C 85.76, H 8.25, N 5.08

The general procedure for the alkylation/in situ reduction of quinuclidine-*N*-oxide is illustrated below by the experimental details for the preparation of 31a.

Preparation of *erythro*-2-hydroxybenzyl quinuclidine (31a) by the alkylation/in situ reduction of quinuclidine-*N*-oxide.

A flame-dried, 300-mL, 3-necked round-bottomed flask equipped with a magnetic stir bar, an addition funnel, and an argon inlet was charged with 1.50 g quinuclidine-*N*-oxide (11.8 mmol), 1.96 mL freshly distilled TMEDA (13.0 mmol, 1.1 eq.), and 80 mL dry THF. The suspension was stirred vigorously under argon for 30 min. at room temperature until all the N-oxide was in solution. The reaction mixture was cooled to -78°C, and *n*-BuLi (7.20 mL, 1.1 eq., 1.80M in hexane, Aldrich) was added dropwise. The reaction mixture turned pale yellow while stirring for 45 min. Freshly distilled benzaldehyde (1.32 mL, 13.0 mmol, 1.1 eq.) in 20 mL THF was added dropwise over 15 min. The bright yellow solution was stirred for 1 hr. at -78°C, then allowed to warm to 0°C over the course of an hour. The reaction was quenched with 20 mL saturated aqueous NH_4Cl and stirred for 5 min. $TiCl_3$ (1.9M in 2.0M HCl, Aldrich) was added dropwise via syringe until the purple color of the reagent persisted. The mixture was allowed to warm to room temperature, and 15% NaOH was added until the pH of the aqueous phase was ≈10. Stirring at room temperature was continued until the solids in the reaction mixture were white. The crude mixture was filtered through Celite, and the filtrate was extracted with 3-75 mL portions of ether. The combined ether extracts were washed with brine and dried over K_2CO_3. Rotary evaporation of the solvent and passage of the crude product through a short silica gel column (4:1 $CHCl_3$:MeOH, 1% NH_4OH) gave a 1:1 mixture of **31a**

(erythro) and **31b** (threo), which could be separated by fractional crystallization from acetone to give the pure erythro isomer, which was identical to material prepared by DIBAL reduction of **21** described above.

Preparation of *erythro*- and *threo*-2-(*p*-methoxyphenyl) hydroxymethyl quinuclidine (42a, 42b).

By the procedure described for the preparation of **31a** by the alkylation/in situ reduction of quinuclidine-*N*-oxide, 2.0 g quinuclidine-*N*-oxide (15.7 mmol) was alkylated with freshly distilled *p*-anisaldehyde (2.11 mL, 17.3 mmol, 1.1 eq.). Isolation of the product after the reduction and work-up gave 2.64 g (68%) of a nearly 1:1 mixture of erythro (**42a**) and threo (**42b**) amino alcohols which could not be separated by chromatography or fractional crystallization.

^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	benzylic proton resonances: erythro isomer 4.65 (d, J=6.7Hz) threo isomer 4.30 (d, J=9.7 Hz)
Anal. (mixture)	Calc'd for $C_{15}H_{21}NO_2$: C 72 84, H 8.56, N 5.66 Found: C 72.56, H 8.68, N 5.75

Preparation of *erythro*-2-(*p*-fluorophenyl) hydroxymethyl quinuclidine (43a).

By the procedure described for the preparation of **31a** by the alkylation/in situ reduction of quinuclidine-*N*-oxide, 2.0 g quinuclidine-*N*-oxide (15.7 mmol) was alkylated with *p*-fluorobenzaldehyde (1.86 mL, 17.3 mmol, 1.1 eq., Aldrich). Isolation of the product after the reduction and work-up gave 2.33 g (63%) of a crude mixture containing erythro and threo isomers along with several side-products which made integration of the benzylic proton resonances in the ^{1}H-NMR difficult. Recrystallization from 15 mL acetone gave the pure erythro isomer (**43a**, 872 mg, 24% from quinuclidine-*N*-oxide).

melting point	139-140°C

^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.22-7.38 (m, 2H), 6.9-7.05 (m, 2H), 4.71 (d, J=7.2 Hz, 1H), 3.50-3.10 (m, 5H), 1.40-1.9 (m, 8H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	162.3 (d, $^1J_{F,C}$=246 Hz), 139.6 (d, $^4J_{F,C}$=2.9 Hz), 128.1 (d, $^3J_{F,C}$=7.8 Hz), 115.1 (d, $^2J_{F,C}$=21 Hz), 76.1, 61.7, 50.7, 43.3, 29.5, 27.0, 25.9, 22.1
IR (cm^{-1})	3310, 3017, 2949, 1612, 1514, 1235
Anal.	Calc'd for $C_{14}H_{18}FNO$: C 71.46, H 7.71, N 5.95, F 8.07 Found: C 71.39, H 7.80, N 5.98, F 8.33

Dithioketalization of 3-oxo-6'-methoxyrubanol acetate (48).

A flame-dried, 15-mL , 2-necked round-bottomed flask equipped with a magnetic stir bar, a rubber septum, and an argon inlet was charged with 0.200 g **48**,[56] 65 μL 1,2-dithioethane (0.775 mmol, 1.3 eq.), and 5 mL $CHCl_3$ that had been passed through basic alumina. The flask was cooled to -15°C using an ethylene glycol/CO_2 bath, and $TiCl_4$ (91 μL, 1.4 eq.) was added slowly. The reaction mixture turned orange immediately. After 10 min. the cooling bath was removed, and the reaction was allowed to warm to room temperature. No evidence of reaction was apparent after 6 hr., so the mixture was heated to 40°C overnight. The reaction was quenched by the addition of 5 mL saturated $NaHCO_3$, followed by extraction with $CHCl_3$ (3 x 5 mL). The combined organic layers were washed with water and brine, then dried over Na_2SO_4. Removal of the solvent by rotary evaporation gave the crude dithioketal, which was purified by flash chromatography on silica gel (EtOAc, 5% Et_3N) to give 0.150 g (59%) of the dithioketal **49**.

melting point	74-75°C

^{1}H-NMR, ppm ($CDCl_3$, 250 MHz)	8.75 (d, J=6.4 Hz, 1H), 8.02 (d, J=11.5 Hz, 1H), 7.40 (m, 3H), 6.45 (d, J=8.3 Hz, 1H), 3.95 (s, 3H), 5.52-3.70 (m, 1H), 3.0-3.4 (m, 7H), 2.7 (m, 1H), 1.93-2.35 (m, 6H), 1.65-1.85 (m, 3H)

Ligand Resolution, Derivatization, and Reactivity.

Kinetic resolution of *erythro*-2-hydroxybenzyl quinuclidine (31a).

A 20-mL Schlenk tube equipped with a magnetic stir bar was flame-dried under vacuum and flushed with argon while cooling. The vessel was charged with 0.030 g **31a** (0.138 mmol), (+)-DIPT (386 μL of a 0.500M solution in CH_2Cl_2, 0.193 mmol, 1.4 eq.), 1.0 mL CH_2Cl_2, and Ti(O*i*-Pr)$_4$ (82 μL, 0.276 mmol, 2.0 eq.). The mixture was stirred at room temperature for 30 min., after which the flask was cooled to -20°C with a cryogenic cooler. TBHP (3.0M in isooctane, 27.6 μL, 0.828 mmol, 0.6 eq.) was added, and the reaction was allowed to stir for 13 hr. The reaction was quenched by the addition of 2 mL ether, 0.25 mL water, and 0.25 mL 40% NaOH. This mixture was stirred vigorously for several hours at room temperature, then filtered through Celite to remove the gelatinous precipitate, which was washed with $CHCl_3$. The combined filtrates were concentrated to leave a white solid which was dried under vacuum. The conversion was determined by ^{1}H-NMR to be 57.8% by integration of the N-oxide resonance at 6.0 ppm relative to the unreacted amino alcohol resonance at 6.03 ppm. The residue was triturated with ether, and the suspension was filtered. The solids were rinsed with ether, and the combined ether extracts were washed with nearly-saturated brine and dried over Na_2SO_4. The solvent was removed by rotary evaporation to leave 0.0106 g (35%) of partially resolved **31a**. Analysis of the (*R*)-Mosher's ester by ^{1}H-NMR revealed a 73% ee (methine doublet at 5.90

ppm in $CHCl_3$ corresponded to the predominant diastereomer; methine doublet at 5.99 ppm related to the minor diastereomer).

Resolution of *erythro*-2-hydroxybenzyl quinuclidine (31a).

Pluim's resolution[42] of **31a** by the following method provided material with different reported physical characteristics. A solution of 2.11 g (9.71 mmol) **31a** in 20 mL absolute EtOH was mixed at room temperature with 1.46 g (9.73 mmol) D-tartaric acid in 25 mL absolute EtOH. The first crystals were collected, and subsequent crystallizations were performed in 95% EtOH. The salt had a constant melting point after 4 crystallizations.

crystallization #	yield (g)	melting point (°C)
1	1.57	188-190
2	1.25	193-194
3	1.03	196-198
4	0.750	199.5-200.5
5	0.643	199-200
mixed (4,5)		199-200

The crystals from the fifth crystallization were dissolved in water, and 15% NaOH was added to pH 10-11. The free base was extracted into ether, washed with brine, and dried over K_2CO_3 to give 0.295 g (14%) of resolved-**31a**. Analysis of the (*R*)-Mosher's ester by ^{1}H-NMR revealed only one diasteromer (methine doublet 5.90 ppm in $CHCl_3$; methine resonances for the (*R*)-MTPA derivative of racemate: doublet 5.99 ppm, doublet 5.90 ppm).

melting point	155-156°C (lit.[42] 145-146°C)
$[\alpha]^{23}_D$	–58.72° (*c* 0.0904, $CHCl_3$)
Anal.	Calc'd for $C_{14}H_{19}NO$: C 77.38, H 8.81, N 6.45 Found: C 77.24, H 8.98, N 6.60

The general procedure for the derivatization of cinchona analogues with *p*-chlorobenzoyl chloride is typified by the experimental details for the esterification of resolved 31a to form resolved *erythro*-2-hydroxybenzyl quinuclidine *p*-chlorobenzoate (res-50).

Preparation of resolved *erythro*-2-hydroxybenzyl quinuclidine *p*-chlorobenzoate(res-50).

A 25-mL, 2-necked round-bottomed flask equipped with a magnetic stir bar, an addition funnel, and an argon inlet was charged with 0.293 g (1.35 mmol) **31a**, 0.300 mL triethylamine (2.15 mmol, 1.6 eq.), a pinch of DMAP, and 8 mL dry CH_2CL_2. With cooling to 0°C using an ice bath, 0.290 mL *p*-chlorobenzoyl chloride (1.50 mmol, 1.1 eq.) in 1 mL CH_2Cl_2 was added dropwise. The ice bath was removed, and the reaction was stirred for 5 hr. The reaction was quenched by the addition of 1 mL 10% HCl and shaking in an addition funnel. The mixture was washed with saturated $NaHCO_3$, water, and brine, then dried over Na_2SO_4. The solvent was removed by rotary evaporation, and the crude product was chromatographed on silica gel (EtOAC, 5% Et_3N). After isolating the product fractions (0.447 g, 93%) and removing the solvent, the hydrochloride salt was prepared by dissolving the ester in ether at 0°C and adding a slight excess of 1.0M HCl in ether (Aldrich) with vigorous stirring. Filtration of the salt and recrystallization from 5 mL absolute EtOH afforded the hydrochloride salt of **res-50**, which was suspended in water, treated with saturated $NaHCO_3$, extracted into ether, and dried over Na_2SO_4. Removal of the ether by rotary evaporation gave pure **res-50** (0.379 g, 79%).

melting point	122-123°C
^{1}H-NMR, ppm ($CDCl_3$, 250 MHz)	8.05 (d, J=12.1 Hz, 2H), 7.20-7.50 (m, 7H), 6.03 (d, J=9.2 Hz, 1H), 3.30-3.40 (m, 1H), 3.0-3.18 (m, 1H), 2.65-2.90 (m, 3H), 1.78-1.9 (m, 2H), 1.40-1.62 (m, 5H)

^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	164.9, 139.6, 139.4, 130.9, 128.8, 128.7, 128.4, 128.1, 127.0, 78.9, 60.0, 50.3, 42.6, 30.6, 26.7, 25.6, 21.6
IR, cm^{-1} ($CHCl_3$)	3019, 2941, 1728, 1595, 1489, 1456, 1400, 1278, 1115
$[\alpha]^{21}_D$	+13.96° (*c* 0.285, $CHCl_3$, 21°C)
Anal.	Calc'd for $C_{21}H_{22}ClNO_2$: C 70.88, H 6.23, N 3.94, Cl 9.96 Found: C 70.58, H 6.22, N 3.93, Cl 10.27

Preparation of racemic *erythro*-2-hydroxybenzyl quinuclidine *p*-chlorobenzoate (50).

According to the above procedure, 0.250 g **31a** (1.15 mmol) was esterified with *p*-chlorobenzoyl chloride to give 0.340 g (83%) **50** after chromatography of the crude ester (EtOAc, 5% Et_3N), recrystallization of the hydrochloride salt, and isolation of the free base.

melting point	130-131°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	8.05 (d, J=12.1 Hz, 2H), 7.20-7.50 (m, 7H), 6.03 (d, J=9.2 Hz, 1H), 3.30-3.40 (m, 1H), 3.0-3.18 (m, 1H), 2.65-2.90 (m, 3H), 1.78-1.9 (m, 2H), 1.40-1.62 (m, 5H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	164.9, 139.6, 139.4, 130.9, 128.8, 128.7, 128.4, 128.1, 127.0, 78.9, 60.0, 50.3, 42.6, 30.6, 26.7, 25.6, 21.6
IR, cm^{-1} ($CHCl_3$)	3016, 2933, 2927, 1730, 1598, 1489, 1270
Anal.	Calc'd for $C_{21}H_{22}ClNO_2$: C 70.88, H 6.23, N 3.94 Found: C 71.05, H 6.11, N 3.87

Preparation of *threo*-2-hydroxybenzyl quinuclidine *p*-chlorobenzoate (51).

According to the above procedure, 0.250 g **31a** (1.15 mmol) was esterified with *p*-chlorobenzoyl chloride to give 0.340 g (83%) **50** after chromatography of the crude ester (EtOAc, 5% Et_3N), recrystallization of the hydrochloride salt, and isolation of the free base.

melting point	117-118°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.95 (d, J=13.1 Hz, 2H), 7.42-7.50 (m, 2H), 7.25-7.40 (m, 5H), 5.98 (d, J=10.1 Hz, 1H), 3.35 (q, J=9.2 Hz, 1H), 3.10-3.25 (m, 1H), 2.87-3.0 (m, 2H), 2.68-2.80 (m, 1H) 1.70 (m, 1H), 1.40-1.55 (m, 4H), 1.08-1.26 (m, 1H), 0.95-1.05 (m, 1H)
IR, cm^{-1} ($CHCl_3$)	3014, 2942, 2932, 1727, 1595, 1468, 1265
Anal.	Calc'd for $C_{21}H_{22}ClNO_2$: C 70.88, H 6.23, N 3.94, Cl 9.96 Found: C 70.60, H 6.10, N 3.94, Cl 9.82

Preparation of *erythro*-2-(*p*-fluorophenyl) hydroxymethyl quinuclidine *p*-chlorobenzoate (52).

According to the above procedure, 0.271 g **31a** (1.14 mmol) was esterified with *p*-chlorobenzoyl chloride to give 0.362 g (85%) **50** after chromatography of the crude ester (EtOAc, 5% Et_3N), recrystallization of the hydrochloride salt, and isolation of the free base.

melting point	127-128°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.96 (d, J=10 Hz, 2H), 7.40 (m, 4H), 7.02 (t, $^3J_{H,F}$=11.5 Hz, 2H), 5.99 (d, J=9.6 Hz, 1H), 3.25-3.38 (m, 1H), 3.0-3.10 (m, 1H), 2.65-2.9 (m, 3H), 1.78-1.95 (m, 2H), 1.40-1.60 (m, 5H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	164.9, 162.4 ($^1J_{C,F}$=246 Hz), 139.55, 135.4 ($^4J_{C,F}$=3.6 Hz), 130.9, 128.8 ($^3J_{C,F}$=10.2 Hz) 128.7, 128.6, 115.4 ($^2J_{C,F}$=21.5 Hz), 78.2, 59.9, 50.3, 42.6, 30.9, 26.7, 25.6, 21.6
IR, cm^{-1} ($CHCl_3$)	3022, 2944, 1730, 1585, 1470, 1263, 1244, 1205
Anal.	Calc'd for $C_{21}H_{21}ClFNO_2$: C 67.47, H 5.66, N 3.75, F 5.08 Found: C 67.20, H 5.73, N 3.57, F 5.20

Preparation of *erythro*-2-(2'-(2''-methoxyethyl)phenyl) hydroxymethyl quinuclidine *p*-chlorobenzoate (53).

According to the above procedure, 0.880 g **31a** (3.20 mmol) was esterified with *p*-chlorobenzoyl chloride to give 1.15 g (87%) **50** after chromatography of the crude ester (EtOAc, 5% Et_3N), recrystallization of the hydrochloride salt, and isolation of the free base.

melting point (HCl salt)	238-240°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	8.0 (d, J=10 Hz, 2H), 7.38-7.45 (m, 2H), 7.2 (m, 2H), 6.3 (d, J=7.8 Hz), 3.58-3.80 (m, 2H), 3.37 (s, 3H), 3.35 (m, 1H), 3.0-3.2 (m, 3H), 2.7-2.85 (m, 3H), 1.75-1.9 (m, 2H), 1,45-1.70 (m, 5H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	164.7, 139.4, 138.3, 136.6, 130.9, 128.8, 128.7, 127.9, 126.6, 126.5, 75.6, 73.0, 60.5, 58.6, 50.4, 43.3, 32.6, 29.5, 26.8, 25.6, 21.8
IR, cm^{-1} ($CHCl_3$)	3028, 2937, 1725, 1589, 1490, 1448, 1272, 1119
Anal. (HCl salt)	Calc'd for $C_{24}H_{29}Cl_2NO_3$: C 64.00, H 6.49, N 3.11, Cl 15.74 Found: C 63.92, H 6.64, N 3.13, Cl 15.52

Preparation of *erythro*-2-(1'-naphthyl) hydroxymethyl quinuclidine *p*-chlorobenzoate (54).

According to the above procedure, 1.33 g **31a** (4.97 mmol) was esterified with *p*-chlorobenzoyl chloride to give 1.76 g (87%) **50** after chromatography of the crude ester (EtOAc, 5% Et_3N).

melting point	161-162.5°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.38-8.38 (m, 11H), 6.86 (d, J=7 Hz, 1H), 3.45-3.62 (m, 1H), 3.15-3.28 (m, 1H), 2.62-2.85 (m, 3H), 1.40-1.95 (m, 8H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	164.8, 139.5, 137.8, 135.6, 133.9, 131.0, 130.8, 129.0, 128.8, 126.3, 125.5, 125.2, 124.3, 123.3, 76.4, 59.7, 50.6, 43.2, 29.2, 25.6, 21.8
IR, cm^{-1} ($CHCl_3$)	3032, 2946, 1728, 1570, 1483, 1448, 1260, 1110

Anal.	Calc'd for $C_{25}H_{24}ClNO_2$: C 73.97, H 5.96, N 3.45 Found: C 72.91, H 5.89, N 3.44

Preparation of *erythro*- 2-(7'-methoxy-1'-naphthyl) hydroxymethyl quinuclidine *p*-chlorobenzoate (55).

According to the above procedure, 0.635 g **31a** (2.14 mmol) was esterified with *p*-chlorobenzoyl chloride to give 0.765 g (82%) **50** after chromatography of the crude ester (EtOAc, 5% Et_3N), recrystallization of the hydrochloride salt, and isolation of the free base.

melting point (HCl salt)	253°C (decomp.)
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.10-8.05 (m, 10H), 6.84 (d, J=6.8 Hz, 1H), 3.95 (s, 3H), 3.50-3.60 (m, 1H), 3.15-3.25 (m, 1H), 2.63-2.90 (m, 3H), 1.38-1.93 (m, 7H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	164.6, 157.7, 139.3, 134.0, 131.8, 130.8, 130.2, 129.2, 128.6, 128.2, 124.5, 122.8, 118.0, 101.9, 76.0, 59.1, 55.2, 50.4, 43.1, 28.9, 26.7, 25.4, 21.7
IR, cm^{-1} ($CHCl_3$)	3030, 2947, 2934, 1731, 1564, 1491, 1253
Anal. (HCl salt)	Calc'd for $C_{26}H_{27}Cl_2NO_3$: C 66.10, H 5.76, N 2.96, Cl 15.01 Found: C 65.87, H 5.83, N 2.80, Cl 14.81

Preparation of 2-hydroxymethyl quinuclidine *p*-chlorobenzoate (56).

The method of Långström was used to prepare 2-hydroxymethyl quinuclidine by $LiAlH_4$ reduction of quinuclidine-2-carboxylic acid (**16**). According to the above esterification procedure, 0.300 g 2-hydroxymethyl quinuclidine (2.12 mmol) was esterified with *p*-chlorobenzoyl chloride to give 0.433 g (73%) **50** after chromatography of the crude ester (EtOAc, 5% Et_3N), recrystallization of the hydrochloride salt, and isolation of the free base.

melting point (HCl salt)	278-280°C

^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.90 (d, J=8.5 Hz, 2H), 7.32 (d, J=8.5 Hz, 2H), 4.30-4.36 (m, 1H), 4.14-4.20 (m, 1H), 3.10-3.22 (m, 1H), 2.82-3.02 (m, 3H), 2.60-2.86 (m, 1H), 1.60-1.80 (m, 2H), 1.38-1.51 (m, 4H), 1.05-1.20 (m, 1H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	165.8, 139.3, 131.1, 129.0, 128.6, 66.6, 54.9, 50.0, 42.2, 30.2, 26.9, 25.9, 21.7
IR, cm^{-1} ($CHCl_3$)	3026, 2943, 2929, 1729, 1566, 1482, 1241
Anal. (HCl salt)	Calc'd for $C_{15}H_{19}Cl_2NO_2$: C 56.97, H 6.06, N 4.43, Cl 22.42 Found: C 56.73, H 5.77, N 4.31

Preparation of 2-((cyclohexyl) hydroxymethyl) quinuclidine *p*-chlorobenzoate from isomer 35a.

According to the above procedure, 0.260 g **31a** (1.16 mmol) was esterified with *p*-chlorobenzoyl chloride to give 0.327 g (78%) **50** after chromatography of the crude ester (EtOAc, 5% Et_3N), recrystallization of the hydrochloride salt, and isolation of the free base.

melting point (HCl salt)	247-248.5°C
^{1}H-NMR, ppm ($CDCl_3$, 250 MHz)	8.0 (d, J=8.3 Hz, 2H), 7.42 (d, J=10 Hz, 2H), 5.24 (dd, J=12 Hz, 2.1 Hz, 1H), 2.65-3.15 (m, 5H), 0.95-2.0 (m, 18H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	165.7, 139.3, 131.0, 128.9, 128.7, 80.4, 55.1, 50.0, 42.5, 39.2, 30.54, 30.48, 26.6, 26.4, 26.3, 26.1, 25.8, 25.7, 21.3
IR, cm^{-1} ($CHCl_3$)	3014, 2948, 2941, 1729, 1256
Anal. (HCl salt)	Calc'd for $C_{21}H_{29}Cl_2NO_2$: C 63.32, H 7.34, N 3.52, Cl 17.80 Found: C 63.15, H 7.21, N 3.31, Cl 17.53

Preparation of 2-((cyclohexyl) hydroxymethyl) quinuclidine *p*-chlorobenzoate from isomer 35b.

According to the above procedure, 0.360 g **31b** (1.61 mmol) was esterified with *p*-chlorobenzoyl chloride to give 0.425 g (73%) **50** after chromatography of the crude ester (EtOAc, 5% Et_3N), recrystallization of the hydrochloride salt, and isolation of the free base.

melting point (HCl salt)	249-250°C
^{1}H-NMR, ppm ($CDCl_3$, 300 MHz)	7.95 (d, J=7.9 Hz), 7.40 (d, J=7.9 Hz), 5.07 (dd, J=12.6 Hz, 3.9 Hz, 1H), 3.10-3.22 (m, 1H), 2.95-3.08 (m, 1H), 2.80 (m, 2H), 2.58-2.70 (m, 1H), 1.0-1.80 (m, 18H)
^{13}C-NMR, ppm ($CDCl_3$, 75.5 MHz)	165.5, 138.9, 131.1, 129.3, 128.5, 78.4, 56.1, 50.1, 42.5, 38.1, 30.5, 29.8, 26.8, 26.77, 26.3, 26.2, 26.1, 25.7, 21.7
IR, cm^{-1} ($CHCl_3$)	3021, 2945, 2932, 1728, 1564, 1491, 1261
Anal. (HCl salt)	Calc'd for $C_{21}H_{29}Cl_2NO_2$: C 63.32, H 7.34, N 3.52, Cl 17.80 Found: C 63.32, H 7.52, N 3.54, Cl 17.61

Asymmetric dihydroxylation of *trans*-stilbene using resolved 50.

In a 5-mL round-bottomed flask, 0.025 g **resolved 50** (0.0703 mmol, 0.5 eq), 3.5 µL of OsO_4 solution (0.500M in toluene, 0.0125 eq), 0.058 g K_2CO_3 (0.423 mmol, 3.0 eq), and 0.140 g $K_3[Fe(CN)_6]$ (0.423 mmol, 3.0 eq.) were stirred vigorously at room temperature in 2 mL 1:1 *tert*-butanol:water. *Trans*-stilbene (0.025 g, 0.141 mmol, 1.0 eq) was added all at once, and the reaction mixture was stirred for 24 hr. at room temperature. Solid Na_2SO_3 (0.150 g) was added, and the mixture was stirred for an additional hour. The reaction mixture was diluted with water (10 mL) and extracted 3 times with 10 mL portions of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated. The crude product was run through a short plug of silica gel (1:1 CH_2Cl_2:ether) to yield 0.028 g (93%) stilbene diol. Analysis of the bis-Mosher's ester derivative by ^{1}H-NMR indicated a product of

78% ee with the selectivity observed for dihydroquinine derivatives [(*S*),(*S*)-hydrobenzoin benzilic proton of bis-(*R*)-MTPA derivative: singlet, 6.32 ppm in $CHCl_3$].

Asymmetric dihydroxylation of *trans*-5-decene using resolved 50.

In a 5-mL round-bottomed flask, 0.025 g **resolved 50** (0.0703 mmol, 0.5 eq), 3.5 μL of OsO_4 solution (0.500M in toluene, 0.0125 eq), 0.058 g K_2CO_3 (0.423 mmol, 3.0 eq), and 0.140 g $K_3[Fe(CN)_6]$ (0.423 mmol, 3.0 eq.) were stirred vigorously at room temperature in 2 mL 1:1 *tert*-butanol:water. *Trans*-5-decene (0.027 mL, 0.020 g, 0.141 mmol, 1.0 eq) was added all at once, and the reaction mixture was stirred for 24 hr. at room temperature. Solid Na_2SO_3 (0.150 g) was added, and the mixture was stirred for an additional hour. The reaction mixture was diluted with water (10 mL) and extracted 3 times with 10 mL portions of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated. The crude product was run through a short plug of silica gel (1:1 CH_2Cl_2:ether) to yield 0.023 g (95%) *trans*-5-decene diol. Analysis of the bis-Mosher's ester derivative by ^{1}H-NMR indicated a product of 59% ee with the selectivity observed for dihydroquinine derivatives [(*S*),(*S*)-hydrobenzoin benzilic proton of bis-(*R*)-MTPA derivative: triplet, 5.23 ppm in $CHCl_3$].

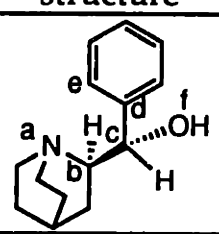
Binding Studies.

Binding constants were measured by taking a known concentration of ligand in *tert*-butanol at 25°C and titrating with 25 μL aliquots of osmium tetroxide solution in *tert*-butanol while monitoring UV absorbance changes at 480 nm. The raw absorbance verses concentration data was put into an iterative program based on the principles set forth by Drago[68] for estimating the equilibrium binding constant.

Molecular Mechanics Calculations.

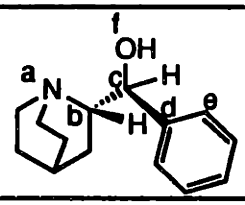
A Tektronix CAChe™ system was used for molecular mechanics calculations using Allinger's standard MM2 force field parameters.[69] All energy minimizations were performed using a conjugate gradient (first derivative) method in an iterative manner until convergence to 0.001 kcal/mol. Conformational energy mapping was performed by the concurrent searching of relevant dihedral angles through a range of values determined by local symmetry. Once a particular conformation of interest was identified from the conformational energy map, the structure of that conformation was reminimized to obtain the reported energy values.

Minimization of *erythro*-2-hydroxybenzyl quinuclidine (31a).

structure	dihedral angle	reminimized dihedral value
	abcf	-170.86°
	bcde	-69.9°

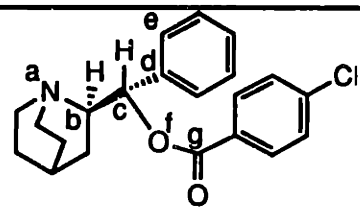
Reminimized energy: 12.3352 kcal/mol.

Minimization of *threo*-2-hydroxybenzyl quinuclidine (31b).

structure	dihedral angle	reminimized dihedral value
	abcf	-51.84°
	bcde	-34.06°

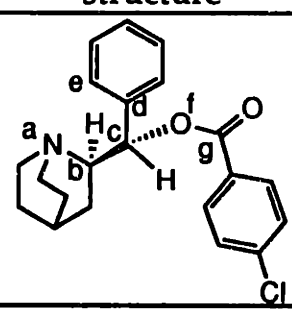
Reminimized energy: 15.1863 kcal/mol.

Minimization of *erythro*-2-hydroxybenzyl quinuclidine *p*-chlorobenzoate (50) OPEN conformer.

structure	dihedral angle	reminimized dihedral value
	abcf	80°
	bcde	89.25°
	bcfg	-157°

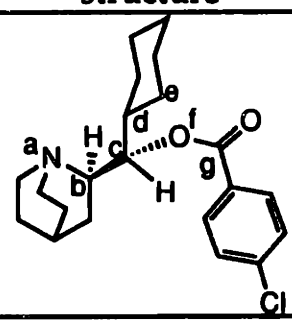
Reminimized energy: 10.7990 kcal/mol.

Minimization of *erythro*-2-hydroxybenzyl quinuclidine *p*-chlorobenzoate (50) CLOSED conformer.

structure	dihedral angle	reminimized dihedral value
	abcf	-173°
	bcde	107.55°
	bcfg	-162°

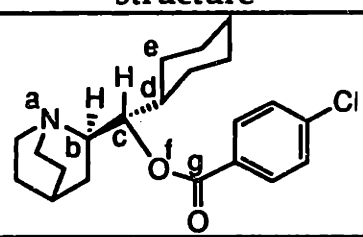
Reminimized energy: 9.6663 kcal/mol.

Minimization of *erythro*-2-((cyclohexyl) hydroxymethyl) quinuclidine *p*-chlorobenzoate (57) CLOSED conformer (from Figure 34a).

structure	dihedral angle	reminimized dihedral value
	abcf	166.33°
	bcde	61.49°
	bcfg	71.72°

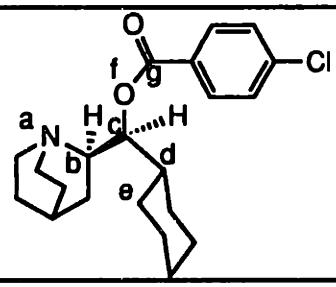
Reminimized energy: 28.2131 kcal/mol.

Minimization of *erythro*-2-((cyclohexyl) hydroxymethyl) quinuclidine *p*-chlorobenzoate (57) OPEN conformer (from Figure 34b).

structure	dihedral angle	reminimized dihedral value
	abcf	70°
	bcde	62°
	bcfg	-129.64°

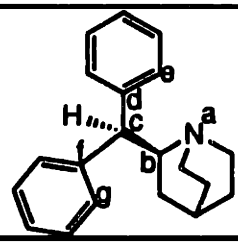
Reminimized energy: 28.3873 kcal/mol.

Minimization of *erythro*-2-((cyclohexyl) hydroxymethyl) quinuclidine *p*-chlorobenzoate (57) OPEN conformer (from Figure 34c).

structure	dihedral angle	reminimized dihedral value
	abcf	-64°
	bcde	63.62°
	bcfg	-83.55°

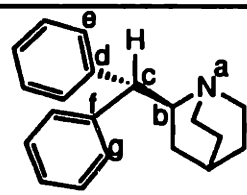
Reminimized energy: 33.0595 kcal/mol.

Minimization of 2-diphenylmethyl quinuclidine (39) CLOSED conformer (from Figure 33).

structure	dihedral angle	reminimized dihedral value
	abcf	-173.9°
	bcde	126.3°
	bcfg	90.6°

Reminimized energy: 9.5017 kcal/mol.

Minimization of 2-diphenylmethyl quinuclidine (39) OPEN conformer (from Figure 33).

structure	dihedral angle	reminimized dihedral value
	abcf	54.5°
	bcde	73.5°
	bcfg	100.2°

Reminimized energy: 15.5641 kcal/mol.