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Diastereomeric Reissert Compounds of Isoquinoline and 6,7-Dimethoxy-3,4-dihydroisoquinoline in Stereoselective Synthesis[||]

Harry W. Gibson,* Michael A. G. Berg, Jennifer Clifton Dickson,[†] Pierre R. Lecavalier,[‡] Hong Wang,[§] and Joseph S. Merola

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

hwgibson@vt.edu

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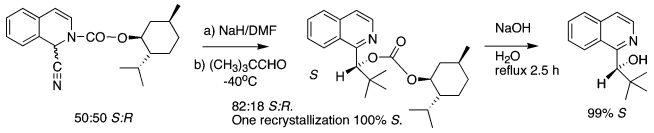
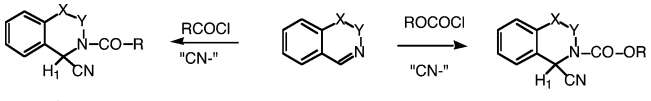


Chiral acid chlorides were reacted with isoquinoline and 6,7-dimethoxy-3,4-dihydroisoquinoline to form diastereomeric Reissert compounds **8**−**11** and **18**−**21**, respectively. The best diastereoselectivity (80:20) was achieved in formation of the 9-phenylmenthyl derivative **20**. The diastereomers of 2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitriles (*S*)-**8**/(*R*)-**8**), formed in equal amounts, were inseparable. However, the individual diastereomers of 2-cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitriles ((*R*)-**11** and (*S*)-**11**) and the 2-*l*-menthoxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinaldonitriles ((*S*)-**19**/(*R*)-**19**)) were each readily purified. (*S*)-**8**/(*R*)-**8** (1:1) via the corresponding anions (NaH, −40 °C, DMF) with pivaldehyde yielded in 82:18 predominance the *S*-diastereomer of 1-isoquinolyl *tert*-butyl carbinyl *l*-menthyl carbonate ((*S*)-**12**), which was obtained in pure form by a single recrystallization; hydrolysis produced 99% pure *S*-(−)-1-isoquinolyl *tert*-butyl carbinol [(*S*)-**16**]. Reactions of the anions of diastereomeric Reissert compounds, either as mixtures or pure single species, with aromatic aldehydes and alkyl halides proceeded with at best modest selectivity (diastereomeric ratios up to 66:34 and 72:28, respectively). Therefore, it is concluded that the Reissert anions are either planar or rapidly inverting tetrahedral structures.

Introduction

Reissert compounds are α-(acylamino)nitriles formed by the formal addition of acyl nitriles to imine bonds.[1] Isoquinoline Reissert compounds, 2-acyl-1-cyano-1,2-dihydroisoquinolines of general structure **1a** (Scheme 1), for example, are prepared by reaction of isoquinoline and acid chlorides in the presence of a cyanide ion source.[2−4] 3,4-Dihydroisoquinolines are converted to analogous compounds **1b**.[5] Aromatic and aliphatic acid chlorides and a variety of heterocycles may be employed to make Reissert compounds.[1,6] Chloroformates produce the corresponding urethane Reissert compounds, for example, **2a** and **2b** (Scheme 1).[1]

SCHEME 1. Syntheses of "Normal" Isoquinoline Reissert Compounds 1 and Urethane Isoquinoline Reissert Compounds 2 from Isoquinoline (a) and 3,4-Dihydroisoquinoline (b)



[||] This article is dedicated to the memory of the late Prof. Frank D. Popp.

[†] Current address: Wikoff Color Corp., 803 Phillips Street, Shelby, NC 28150

[‡] Current address: Defence R&D Canada Suffield, Medicine Hat, AB, Canada T1A 8K6

[§] Current address: Alkermes, Inc., Cambridge, MA 02139

(1) (a) Popp, F. D. In *Quinolines*; Jones, G., Ed.; Wiley and Sons: New York, 1982; pp 353−375. (b) Popp, F. D. *Adv. Heterocycl. Chem.* **1968**, *9*, 1−25. Popp, F. D. *Adv. Heterocycl. Chem.* **1979**, *24*, 187−214. (c) McEwen, W. E.; Cobb, R. L. *Chem. Rev.* **1955**, *55*, 511−549. (d) Cooney, J. V. *Heterocycl. Chem.* **1983**, *20*, 823−837.

(2) Reissert, A. *Chem. Ber.* **1905**, *38*, 1603.

(3) (a) Popp, F. D.; Blount, W. *Chem. Ind.* **1961**, 550. (b) Popp, F. D.; Blount, W.; Melvin, P. *J. Org. Chem.* **1961**, *26*, 4930−4932. (c) Popp, F. D.; Blount, W. *J. Org. Chem.* **1962**, *27*, 297−298. (d) Popp, F. D.; Soto, A. *J. Chem. Soc.* **1963**, 1760−1763.

(4) (a) Ruchirawat, S.; Phadungkul, N.; Chuankamnerdkarn, M.; Thebtaranonth, C. *Heterocycles* **1977**, *6*, 43−46. (b) Bhattacharjee, D.; Popp, F. D. *J. Heterocycl. Chem.* **1980**, *17*, 1211−1212.

(5) (a) Elliot, I. W.; Leflore, J. O. *J. Org. Chem.* **1963**, *28*, 3181−3184. (b) Gibson, H. W.; Popp, F. D. *J. Chem. Soc. C* **1966**, 1860−1864. (c) Shamma, M.; Jones, C. D. *J. Org. Chem.* **1970**, *35*, 3119−3121. (d) Rozwadowska, M. D.; Brózda, D. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1978**, *26*, 33−38. (e) Jackson, Y. A.; Stephenson, E. K.; Cava, M. P. *Heterocycles* **1993**, *36*, 1047−1050.

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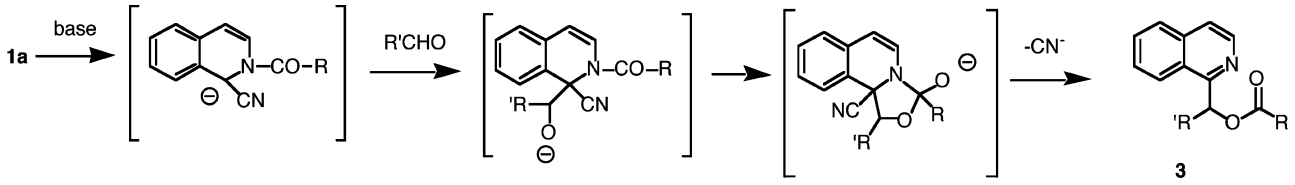
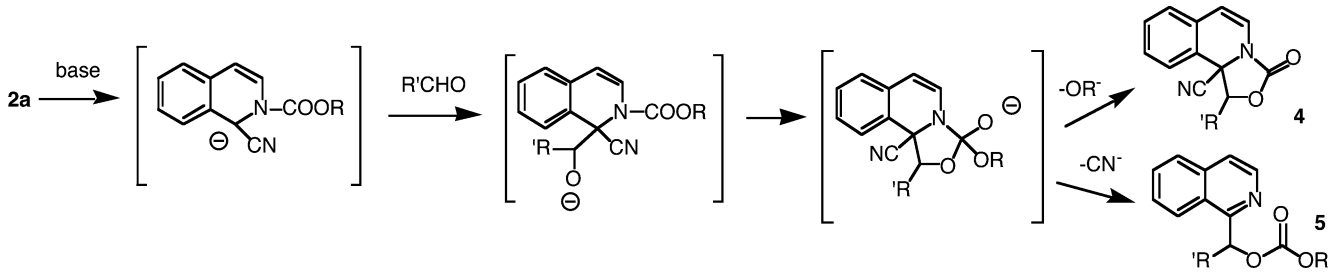
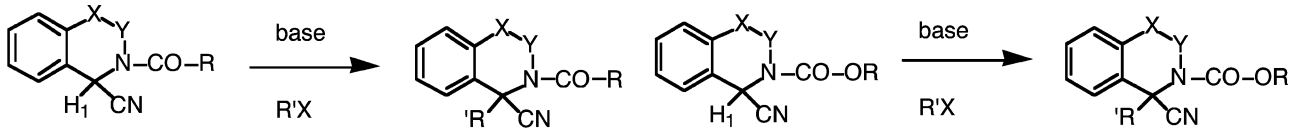
SCHEME 2. Condensation of Isoquinoline Reissert Compound 1a with Aldehydes To Form 1-Isoquinoloyl Carbinyl Esters



SCHEME 3. Condensation of Isoquinoline Urethane Reissert Compounds with Aldehydes To Form Cyclic Urethanes or 1-Isoquinoloyl Carbinyl Carbonates



SCHEME 4 Reactions of Isoquinoline Reissert Compounds 1 and 2 with Primary and Secondary Alkyl Halides, Leading to Derivatives 6 and 7



1a **1b** **a:** X-Y = CH=CH **b.** X-Y = CH_2CH_2 **6a** **6b** **2a** **2b** **a:** X-Y = CH=CH **b.** X-Y = CH_2CH_2 **7a** **7b**

The proton α to the cyano group of Reissert compounds, for example, H_1 of **1** or **2** is acidic and may be abstracted by a variety of bases, and the resultant anions are excellent nucleophiles that undergo a number of reactions with proven utility in elaboration of nitrogen heterocycles.[1] When an isoquinoline Reissert anion from **1a** is treated with an aldehyde, the ester **3** of a 1-(α-hydroxyalkyl)isoquinoline forms via the intermediates shown in Scheme 2. "Dihydro-Reissert compounds" **1b** do not undergo this reaction because of the lack of rearomatization as a driving force.

When urethane Reissert compounds **2a** are treated similarly, an alternate pathway is available, namely, elimination of alkoxide from the cyclic intermediate, resulting in formation of the cyclic urethane **4** (Scheme 3). This process can be circumvented by carrying out the reaction at low-temperature (<0 °C); under these conditions the carbonate **5** is essentially the only product.[7] Note that in **3**, **4**, and **5** a new stereocenter is produced. Again, dihydro-Reissert compounds **2b** do not undergo these processes.

Reissert compound anions also react with alkyl halides as shown in Scheme 4.

In spite of the proven utility of Reissert compounds in syntheses of racemic isoquinoline alkaloids,[8,9] there had been no reports of their utilization in stereoselective synthesis in the late 1980s. The formation of Reissert compounds proceeds through an *N*-acylium intermediate, which undergoes nucleophilic addition of the cyanide ion. Thus, Reissert compounds could conceivably be prepared diastereoselectively if a chiral acyl portion properly influenced the addition of cyanide ion; indeed, preliminary molecular mechanics calculations indicated that this would be the case for some auxiliaries. Also it was our hope that the resulting chiral Reissert compounds could be alkylated with high stereoselectivity, providing a convenient stereoselective route to a number of isoquinoline alkaloids, an ongoing challenge.[10] Preliminary molecular mechanics calculations indicated that this was a real possibility. Therefore, at that time we investigated the use of chiral auxiliaries in the form of the *N*-acyl moiety of isoquinoline Reissert compounds to provide diastereoselective reactions of the corresponding anions.[11]

Recently, the stereoselective synthesis of Reissert compounds using chiral catalysts has been reported and applied.[12] Prompted by this and other recent reports of use of Reissert compounds in stereoselective synthesis,[13,14] here we report our early work on the preparation and use of chiral Reissert compounds derived

(6) (a) Jois, Y. H. R.; Gibson, H. W. *J. Org. Chem.* **1991**, *56*, 865−867. (b) Jois, Y. H. R.; Berg, M. A. G.; Merola, J. S.; Gibson, H. W. *Tetrahedron Lett.* **1991**, *32*, 2997−3000. (c) Pandya, A.; Gibson, H. W. *J. Org. Chem.* **1993**, *58*, 2851−2855. (d) Jois, Y.; Gibson, H. W. *Macromolecules* **1994**, *27*, 2912−2916.

(7) (a) Roswadowska, M. D. *Can. J. Chem.* **1977**, *55*, 164−170. Rozwadowska, M. D.; Brózda, D. *Tetrahedron Lett.* **1978**, 589−592. (b) Rozwadowska, M. D.; Brózda, D. *Can. J. Chem.* **1980**, *58*, 1239−1242.

(8) Popp, F. D. *Heterocycles* **1973**, *1*, 165−180. Popp, F. D. *Heterocycles* **1980**, *14*, 1033−1043.

(9) Blasko, G.; Kerkes, P.; Makleit, S. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 21, pp 1−28.

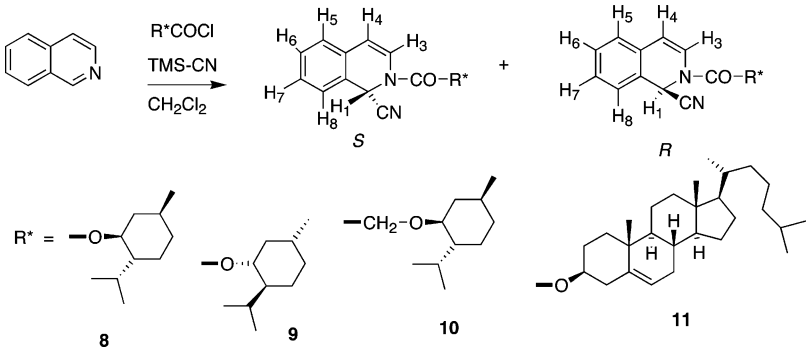
(10) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341−3370.

(11) (a) Clifton, J. Studies in Stereoselective Synthesis via Reissert Compound Chemistry. M.S. Thesis, Virginia Polytechnic Institute and State University, 1991. (b) Berg, M. A. G. Studies in Stereoselective Synthesis of 1,2,3,4-Tetrahydroisoquinolines. Ph.D. Dissertation, Virginia Polytechnic Institute and State University, 1992.

(12) (a) Takamura, M.; Funabashi, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6327−6328. (b) Funabashi, K.; Ratni, H.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 10784−10785.

(13) Sieck, O.; Schaller, S.; Grimme, S.; Liebscher, J. *Synlett* **2003**, *3*, 337−340.

SCHEME 5. Synthesis of Chiral Isoquinoline Reissert Compounds



from commercially available, cheap, chiral auxiliaries, and the condensation reactions of Schemes 2, 3, and 4.

Results and Discussion

A. Synthesis of Diastereomeric Reissert Compounds from Isoquinoline. With chiral acid chlorides and chloroformates, either commercially available or easily derived from commercial materials, and isoquinoline (Scheme 5) we prepared the Reissert compounds summarized in Table 1.

1. 2-(Menthoxycarbonyl)-1-,2-dihydroisoquinaldonitriles (8). It was originally believed that the *l*-menthyl chloroformate Reissert compound was a single diastereomer because both the melting point (96−97 °C) and the optical rotation ($[\alpha]_D^{25} = -63.4$, CH_2Cl_2) were constant upon repeated recrystallization, and high performance liquid chromatography (HPLC) on Pirkle covalent phenylglycine and Chiralcel OD columns afforded only one peak. The $[\alpha]_D^{25}$ value is very close to that recently reported (−59.6°) for what is claimed to be **8** of >95% diastereomeric purity.[13]

However, examination of the ambient-temperature 270 (or 400) MHz ^{1}H NMR spectrum in $CDCl_3$ (Figure 1a,b) indicated that signals for H_3 were comprised of two broad peaks at 6.87 and 7.01 in a ratio of 39:61, respectively. H_4 appeared as a multiplet at 6.0 ppm and H_1 was represented by three distinct signals at 6.18, 6.22, and 6.38 ppm in a ratio of 62:19:19, respectively, clearly indicative of a mixture of both diastereomers and urethane isomers (rotamers about the N−CO bond with its partial double bond character). For comparison, in the analogous urethane Reissert compound **2a**, R = C_2H_5,[15] H_1, H_3, and H_4 were observed as simple signals at 6.43 (d, $J \sim 1$ Hz), 7.03 (dd, $J \sim 1,8$ Hz), and 6.07 (d, $J \sim 8$ Hz) ppm at ambient temperature, respectively. The four possible isomers of chiral Reissert compounds **8**−**11** are shown in Scheme 6; here *E* and *Z* refer to the relative positions of the carbonyl oxygen atom and the cyano group.

Low-temperature (253 K) proton NMR spectroscopy in $CDCl_3$ demonstrated that both diastereomers of **8** and in each case both urethane isomers were present. In Figure 1c there are three signals for H_1 at 6.43 (a larger peak, presumably two superimposed signals), 6.25, and 6.20 ppm. The assignment of the H_1 signals was verified by deuteration (see Supporting Information, Figure S14). H_3 appears as a nearly equal pair of doublets at 6.90 ppm and another nearly equal pair of doublets at 7.05 ppm ($J_{1,3} = 1$, $J_{3,4} = 8$ Hz). The signal for H_4 consists of seven peaks at 6.05−6.10 ppm ($J_{3,4} = 8$ Hz); two peaks are

TABLE 1. Synthesis of Diastereomeric Reissert Compounds

Reissert compd	yield (%)	diastereomeri ratio
8	96	50:50[a]
9	98	50:50[a]
10	67	47:53[b]
11	91	41:59[c]
(*S*)-**11**[d]	37	100:0
(*R*)-**11**[d]	54	100:0

[a] Determined by integrations of H_1, H_3, and H_4 signals in the ^{1}H proton NMR spectra as discussed in the text. [b] Determined by integration of C(=O)CH_2O signals in the ^{1}H proton NMR spectrum; in one diastereomer the signal is an AB quartet and in the other it is a singlet. The identities of the diastereomers are not known. [c] Determined by HPLC with a Pirkle phenylglycine column (99:1 hexane/isopropanol, 1 mL/min); listed in order of elution (see Supporting Information, Figure S2). [d] The diastereomers of **11** were easily separated morphologically; the identity of the minor *S*-isomer was established by X-ray crystallography (see Supporting Information, Figure S3).

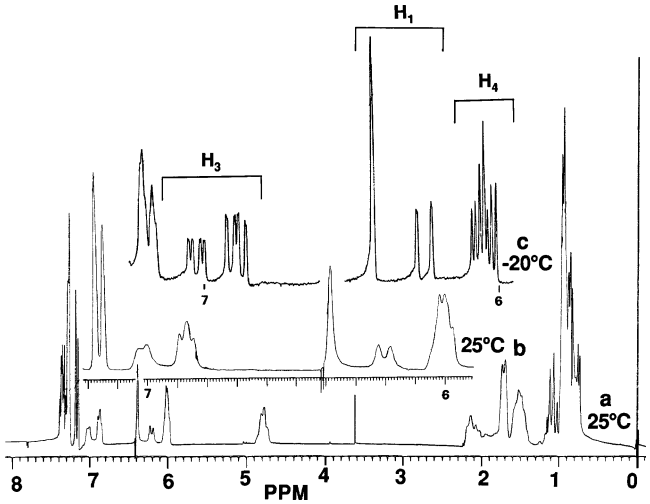
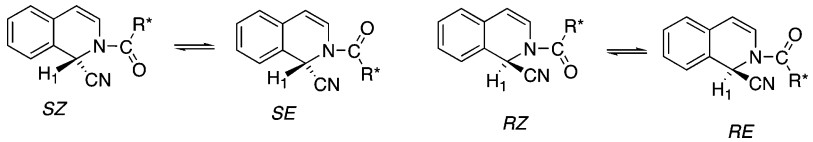


FIGURE 1. 270 MHz ^{1}H NMR spectra of 2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile [1:1 (*S*)-**8**/(*R*)-**8**] in $CDCl_3$: (a) bottom, at 25 °C; (b) middle, expanded region 5.9−7.2 ppm at 25 °C; (c) top, expanded region from 6.0 to 7.2 at −20 °C. The peak at ca. 7.27 ppm in (a) is due to $CHCl_3$.

(14) (a) Reimann, E.; Erdle, W.; Weigl, C.; Polborn, K. *Monatsh. Chem.* **1999**, *130*, 313−326. (b) Reimann, E.; Grasberger, F.; Polborn, K. *Monatsh. Chem.* **2000**, *131*, 73−84. (c) Reimann, E.; Grasberger, F.; Polborn, K. *Monatsh. Chem.* **2000**, *134*, 991−1014. (d) Evain, M.; Pauvert, M.; Collet, S.; Guingant, A. *Acta Crystallogr., Sect. E* **2002**, *E58*, o1121−o1122. (e) Pauvert, M.; Collet, S. C.; Bertrand, M.-J.; Guingant, A. Y.; Evain, M. *Tetrahedron Lett.* **2005**, *46*, 2983−2987. (f) Brózda, D.; Hoffman, K.; Rozwadowska, M. D. *Heterocycles* **2006**, *67*, 119−122. (g) Kanemitsu, T.; Yamashita, Y.; Nagata, K.; Itoh, T. *Synlett* **2006**, 1595−1597. (h) Reimann, E.; Renz, M. *Monatsh. Chem.* **2007**, *138*, 211−218.

(15) Popp, F. D.; Katz, L. E.; Klinowski, C. W.; Wefer, J. M. *J. Org. Chem.* **1968**, *33*, 4447−50.

SCHEME 6. Four Stereoisomers of Chiral Reissert Compounds 8−11



apparently overlapping. The integrations of the H_3 signals (corroborated by the H_1 signals) indicate that the four isomers have relative populations of 20, 20, 30, and 30%. Changes in temperature from −45 to +25 °C did not reveal significant changes in these proportions.

NMR analyses were recently conducted in toluene-d_8 in order to observe aromatic solvent induced shifts to confirm these assignments. Protons *cis* to the carbonyl moieties of the urethane linkage are expected to undergo small downfield or perhaps upfield shifts upon switching from $CDCl_3$ to toluene-d_8, whereas protons *trans* to the carbonyl oxygen are expected to undergo large upfield shifts.[16] At −20 °C in toluene-d_8 the minor pair (37%) of doublets for H_3 shifts upfield 0.47 ppm (with respect to its position in $CDCl_3$ at −20 °C), while the major pair (63%) of H_3 doublets moves upfield by 0.27 ppm (Figure 2), indicating that the former correspond to the (*E*)-urethanes and the latter to the (*Z*)-urethanes (consistent with our deduction based on chemical shift patterns of other Reissert compounds). H_1 appears as three distinct peaks at 6.09, 6.03, and 5.77 ppm in a ratio of 30:33:37; due to preferential solvation of the partially positive nitrogen atom (a consequence of the resonance contribution of the $=N^+=C(O^-)-$ structure) by the toluene,[16] now the (*Z*)-urethane isomers (63%) are resolved as the downfield pair of H_1 peaks with upfield shifts of only 0.35 and 0.41 ppm, respectively, while the H_1 signals for both (*E*)-urethanes are now merged into the peak at 5.77 ppm (37%), representing shifts of 0.52 and 0.46 ppm. Thus, the large H_1 signal at 6.43 ppm at −20 °C in $CDCl_3$ (Figure 1c) includes the (*Z*)-urethane isomers of both diastereomers, *RE* and *RZ*. These NMR results also demonstrated that even after 17 years no epimerization occurred.

Therefore, we conclude that in the original sample of **8** the ratio of *R/S* diastereomers was 1:1 and the ratio of (*E*)- to (*Z*)-urethane isomers was 4:6 for both diastereomers. The OCH methine signal of the menthyl group at 4.8 ppm also separated into four separate multiplets at −20 °C (Figure 2), supporting the existence of the four stereoisomers in these ratios. Although chromatography did not result in complete separation of the diastereomers of **8**, changes were observed in the optical rotations. By careful use of flash chromatography, the NMR spectra (see Supporting Information, Figure S1) exhibited changes consistent with these conclusions.

From *d*-menthyl chloroformate and isoquinoline in the presence of trimethylsilyl cyanide (TMSCN) was produced 2-*d*-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (**9**). The diastereomeric mixture of Reissert compounds **9** had an NMR spectrum identical to that of **8** and an optical rotation equal and opposite in sign to that of 1:1 (*S*)-**8**/(*R*)-**8**. Therefore, (*R*)-**9**/(*S*)-**9** is also of 1:1 composition.

2. Model Study: 2-Methoxyacetyl-1,2-dihydroisoquinaldonitrile. As a model for use of chiral alkoxyacetyl Reissert compounds, we prepared 2-methoxyacetyl-1,2-dihydroisoquinaldonitrile (**1a**, R = CH_2OCH_3), whose proton NMR spectrum revealed H_1 as a broad singlet at 6.65 ppm, H_3 as a broadened doublet at 6.90 ppm ($J_{3,4}$ = 8 Hz, $J_{1-3} \sim$ 1 Hz), and H_4 as a doublet at 6.15 ppm ($J_{3,4}$ = 8 Hz); the amide isomers were not detected at 25 °C. The diastereotopic $C(=O)CH_2O$ protons of the methoxyacetyl moiety produced an AB quartet.

3. 2-*l*-Menthoxyacetyl-1,2-dihydroisoquinaldonitrile (10). *l*-(−)-Menthoxyacetyl chloride[17] yielded Reissert compounds (*R*)-**10**/(*S*)-**10** (Scheme 5), whose proton NMR spectrum (Figure 3b) contained two peaks for H_1 at 6.58 and 6.63 ppm of nearly equal (47:53) proportion. For H_4, doublets ($J_{3,4}$ = 8 Hz) were observed at 6.08 and 6.11 ppm. H_3 appeared as two doublets at 6.95 and 6.98 ppm ($J_{3,4}$ = 8 Hz) broadened by coupling ($J_{1,3} \sim$ 1 Hz) to H_1. The diastereotopic $C(=O)O-CH_2$ protons of the menthoxyacetyl moiety of one of the isomers appeared as an AB quartet centered at 4.31 ppm; the other $C(=O)OCH_2$ signal of the menthoxyacetyl moiety was a singlet at 4.34 ppm (Figure 3c). At −20 °C this region became more complex, presumably

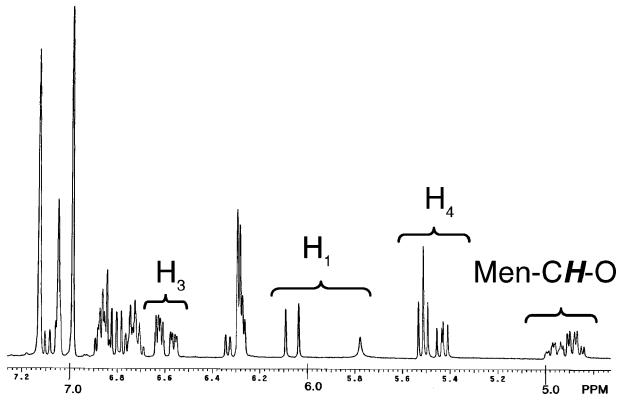


FIGURE 2. Partial 400 MHz ^1H NMR spectrum of 2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile [1:1 (*R*)-**8**/(*S*)-**8**] in toluene-d_8 at −20 °C.

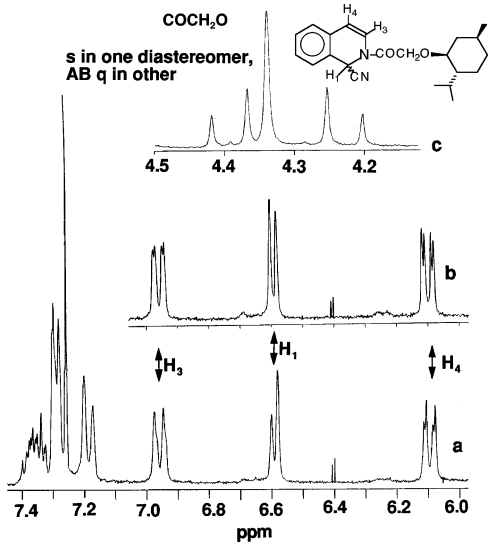
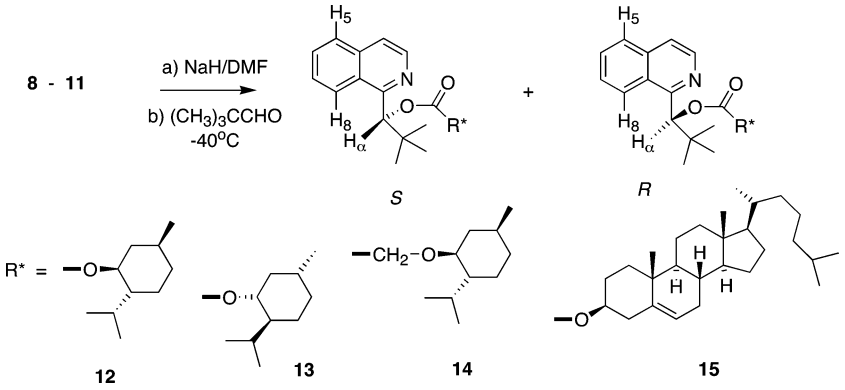


FIGURE 3. Partial 270 MHz ^1H NMR spectra of 2-*l*-menthoxyacetyl-1,2-dihydroisoquinaldonitrile [(*R*)-**10**/(*S*)-**10**] at 25 °C in $CDCl_3$: (a) bottom, region from 6.0 to 7.4 ppm after chromatography; (b) middle, region from 6.0 to 7.0 ppm, as synthesized; (c) top, region from 4.1 to 4.5 ppm as synthesized. The peak at ca. 7.27 ppm in (a) is due to $CHCl_3$.

SCHEME 7. Reactions of Chiral Reissert Compounds 8−11 with Pivaldehyde via the Corresponding Anions



in part due to the resolution of amide isomers, and revealed the former C(═O)OCH$_2$ singlet as a closely spaced (0.01 ppm) equal pair of singlets; corresponding minor (10%) signals also appeared for H$_1$, H$_3$, and H$_4$. Aromatic solvent induced shift (ASIS) studies[16] in deuterated toluene showed that the two H$_1$ signals at ambient temperature were not from different amide isomers; from the shifts (0.25 upfield for H$_1$, nearly zero for H$_3$) it was concluded that the (*E*)-amide form predominates in both time averaged diastereomers, even at −20 °C. The diastereomers (*R*)-**10** and (*S*)-**10** were both formed predominantly in the (*E*)-amide configuration. It appears from modeling that this unusual preference for the *E*-isomer may arise, in part, from hydrogen bonding between H$_1$ and the menthoxy oxygen atom, forming a six-membered ring (see Supporting Information, Figure S31).

The mixture of (*R*)-**10** and (*S*)-**10** was chromatographed on silica gel. The ratio of the two NMR peaks for H$_1$ at 6.58 and 6.63 δ changed from 47:53 (Figure 3b) to 65:35 (Figure 3a) in the first fraction, respectively. This was accompanied by similar changes in the ratio of doublets for protons H$_3$ and H$_4$ and the AB patterns of the C(═O)O−CH$_2$ protons. These results confirmed that the two diastereomers were responsible for signal doubling. These changes are attributed to separation of the diastereomers and not to epimerization.

4. 2-Cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitriles (11). ^{1}H NMR and HPLC analyses demonstrated that the chemically pure cholesteryl chloroformate-based isoquinoline Reissert compounds **11** were a 57:43 mixture of diastereomers, basically unchanged from the crude product. Recrystallization from ethyl acetate followed by separation of the diastereomers with the help of forceps and a lens (à la Pasteur) and further recrystallizations afforded both diastereomers in their pure forms, as confirmed by HPLC (see Supporting Information, Figure S2). X-ray structural analysis (see Supporting Information, Figure S3) showed that the minor diastereomer was (*S*)-**11** and, by inference, the predominant diastereomer was (*R*)-**11**.

B. Synthesis of Diastereomeric Esters and Carbonates by Condensation of Reissert Compounds with Aldehydes. These reactions were initially carried out with pivaldehyde using NaH as the base at −40 °C (to avoid formation of cyclic urethanes and to produce the carbonates in the cases of **8**, **9**, and **11**) in DMF as indicated in Scheme 7 and summarized in Table 2.

1. Reaction of 2-*l*-Menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (8) with Pivaldehyde. The crude product carbonates (*R*)-**12**/(*S*)-**12** from the 1:1 mixture of (*S*)-**8** and (*R*)-**8** were examined using HPLC on a Pirkle phenylglycine column, which revealed two peaks with retention times of 371 (82%) and 414 s (18%) (see Supporting Information, Figure S4). The proton NMR spectrum (Figure 4a) of the crude product **12** contained two peaks at 6.18 and 6.24 ppm for the methine proton (H$_\alpha$) at the newly formed carbinyl center in a ratio of 77:23. After a single recrystallization from hexanes, the proton NMR spectrum (Figure 4b) of the compound exhibited only one peak for the methine proton (H$_\alpha$) at 6.18 ppm; the HPLC trace exhibited only the peak at 371 s (see Supporting Information, Figure S4). The X-ray structure of this pure major diastereomer (see Supporting Information, Figure S5) established the *S*-configuration of the newly formed stereocenter by reference to the known configurations of the *l*-menthyl stereocenters.

Reactions of **8** with aromatic aldehydes under similar conditions afforded carbonates and esters with up to 66:34 diastereoselectivity (see Supporting Information, Table S1, Figures S6 and S7); the resultant compounds were found to epimerize quite rapidly (hours−days) even in the solid state (presumably via S$_N$1 processes since these esters are doubly benzylic).

2. Reaction of 2-*d*-Menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (9) with Pivaldehyde. The 1:1 *R*/*S* mixture of the *d*-menthyl Reissert compound **9** led to a 77:23 (by ^{1}H NMR) mixture of (*R*)-**13**/(*S*)-**13**. A single recrystallization produced

TABLE 2. Reactions of Diastereomeric Reissert Compounds with Pivaldehyde

Reissert compd	product	yield (%)	diastereomeric ratio
1:1 (*R*)-**8**/(*S*)-**8**	**12**	100	77:23 *S*/*R*,[a] 82:18 *S*/*R*[b]
1:1 (*R*)-**9**/(*S*)-**9**	**13**	100	77:23 *R*/*S*[a]
47:53 (*R*)-**10**/(*S*)-**10**	**14**	97	50:50[c,d]
(*S*)-**11**	**15**	100	52:48[c,e]

[a] Determined by integration of the H$_\alpha$ signals in the ^{1}H proton NMR spectrum (Figure 4a). [b] Determined by HPLC with a Pirkle phenylglycine column (99:1 hexane/isopropanol, 1 mL/min); listed in order of elution (see Supporting Information, Figure S4). The identity of the major *S*-isomer was established by X-ray crystallography (see Supporting Information, Figure S5). [c] Determined by integration of the H$_\alpha$ signals in the ^{1}H proton NMR spectrum. [d] Confirmed by HPLC with a Pirkle phenylglycine column (99:1 hexane/isopropanol, 1 mL/min); listed in order of elution. [e] Confirmed by HPLC with a Pirkle phenylglycine column (99:1 hexane/isopropanol, 1 mL/min); listed in order of elution (see Supporting Information, Figure S8).

(16) (a) Hatton, J. V.; Edwards, R. E. *Mol. Phys.* **1962**, *5*, 139−152. (b) Shvo, Y.; Taylor, E. C.; Mislow, K.; Raban, M. *J. Am. Chem. Soc.* **1967**, *89*, 4910−4917. (c) Monro, A. M.; Sewell, M. J. *Tetrahedron Lett.* **1969**, 595−598. (d) Stewart, W. E.; Siddall, T. H., III. *Chem. Rev.* **1970**, *70*, 517−551.

(17) Leffler, M. T.; Calkins, A. E. *Organic Synthesis;* Wiley: New York, 1955; *Coll. Vol. 3*; (a) p 544, (b) p 547.

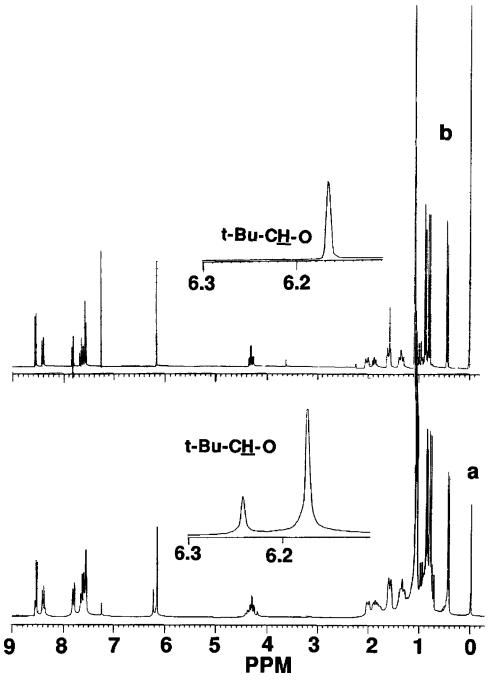
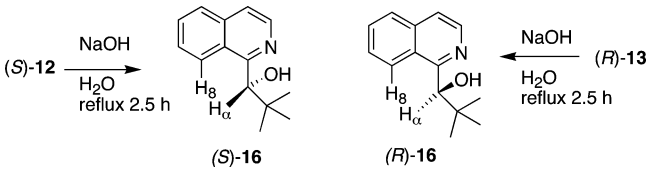


FIGURE 4. 270 MHz ^{1}H NMR spectra of 1-isoquinolyl *tert*-butyl carbinyl *l*-menthyl carbonate (**12**) in $CDCl_3$ at 25 °C: (a) bottom, as synthesized mixture of (*S*)-**12** and (*R*)-**12**; (b) top, pure (*S*)-**12** obtained after one recrystallization.

SCHEME 8. Hydrolysis of 1-Isoquinolyl *tert*-Butyl Carbinyl Menthyl Carbonates to 1-Isoquinolyl *tert*-Butyl Carbinols



99% diastereomerically pure *R*-(+)-1-isoquinolyl *tert*-butyl carbinyl menthyl carbonate [(*R*)-**13**].

3. Reaction of Methoxyacetyl-1,2-dihydroisoquinaldonitrile (1a, R = CH_2OCH_3) with Pivaldehyde. In a model reaction of **1a** (R = CH_2OCH_3) with pivaldehyde, product **3** (R = CH_2OCH_3, R′ = *t*-Bu) was obtained in quantitative yield. In the NMR spectrum the methine proton (H_α) singlet appeared at 6.5 ppm. In the aromatic region one doublet each [8.6 ppm (J = 6 Hz), 8.4 ppm (J = 7 Hz)] was found for the aromatic protons H_5 and H_8. The diastereotopic C(=O)OCH_2 protons of the methoxyacetyl group were observed as an AB quartet centered at 4.2 ppm.

4. Reaction of 2-*l*-Menthoxyacetyl-1,2-dihydroisoquinaldonitrile (10) with Pivaldehyde. The diastereomeric esters (*R*)-**14**/(*S*)-**14** from 1:1 (*R*)-**10**/(*S*)-**10** and pivaldehyde were formed with no diastereoselectivity as determined by the NMR analysis of the methine proton (H_α) singlets (6.48 and 6.53 ppm) and the four sets of doublets of equal intensity observed for H_5 and H_8 in the range 8.3−8.7 ppm. HPLC analysis confirmed this composition. The product was passed through a silica gel column, and the ratio of diastereomers changed to 70:30. In the proton NMR spectrum the downfield H_α signal (6.53 ppm) predominated; likewise the downfield signals for H_5 and H_8 were enhanced. A second sample purified by simply washing the crude material with hexanes was found to be a 90:10 mixture of diastereomers by HPLC. These changes in diastereomeric ratio are again attributed to selective separation of the diastereomers and not to epimerization, since there was no evidence for epimerization over time.

5. Reaction of 2-Cholesteryloxycarbonyl-1-,2-dihydroisoquinaldonitrile [(*S*)-11] with Pivaldehyde. From diastereomerically pure (*S*)-**11** and pivaldehyde, carbonate **15** was isolated in quantitative yield. Both ^{1}H NMR and HPLC (see Supporting Information, Figure S8) demonstrated that there was no stereoselectivity in this reaction.

D. Synthesis of Optically Pure 1-isoquinolyl *tert*-Butyl Carbinols [(*R*)-16, (S)-16]. A 10-fold excess of base and a 2.5 h reaction period allowed hydrolysis of the pure diastereomeric carbonate (*S*)-**12** to produce 99% optically pure *S*-(−)-1-isoquinolyl *tert*-butyl carbinol [(*S*)-**16**] (Scheme 8). The optical purity was determined using quinine as a chiral solvating agent (CSA)[18] (see Supporting Information, Figures S9 and S10). A sample of 99% diastereomerically pure carbonate (*R*)-**13** was hydrolyzed to form *R*-(+)-1-isoquinolyl *tert*-butyl carbinol [(*R*)-**16**] with 98% optical purity as determined by use of quinine as a CSA.

E. Synthesis of Diastereomeric Reissert Compounds from 6,7-Dimethoxy-3,4-dihydroisoquinoline. Using standard conditions, we prepared the dihydro-Reissert compounds **18**−**21** from 6,7-dimethoxy-3,4-dihydroisoquinoline and chiral acid chlorides (Scheme 9), and the results are summarized in Table 3.

F. Alkylation of Diastereomeric Reissert Compounds. Alkylation reactions of diastereomeric Reissert compounds **8** and **11** (Scheme 10) are summarized in Table 4. Benzylation of **8** proceeded with modest diastereoselectivity to produce **22c**. However, with methyl iodide neither **8** nor pure (*S*)-**11** afforded any selectivity. This finding for **22a** from **8** contradicts the recent claim of "excellent yield and stereoselectivity" for this particular alkylation reaction using LDA as the base.[13]

SCHEME 9. Synthesis of Dihydro-Reissert Compounds 18−21 from 6,7-Dimethoxy-3,4-Dihydroisoquinoline (17)

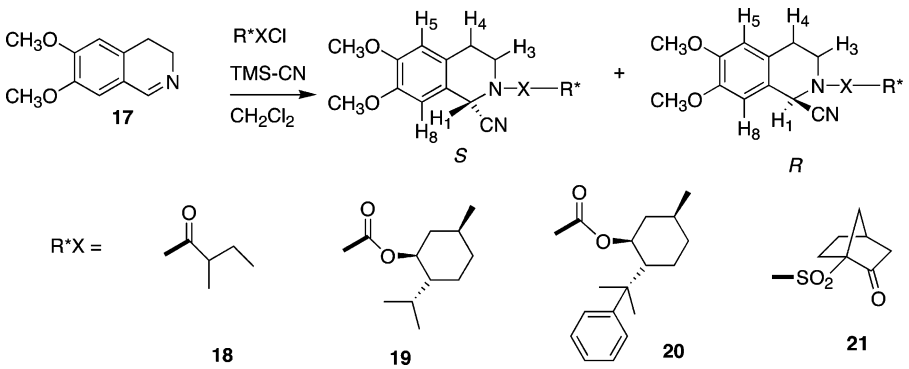


TABLE 3. Synthesis of Diastereomeric Dihydro-Reissert Compounds

Reissert compd	yield (%)	diastereomeric ratio
18	37	50:50[a]
19	77	65:35[b]
(*S*)-**19**[c]	51	100
(*R*)-**19**[c]	26	100
20	80	20:80[d]
21	66	?

[a] Determined by integrations of methyl triplets at 0.85 and 0.95 ppm and methyl doublets at 1.13 and 1.18 ppm in the ^{1}H proton NMR spectra in $CDCl_3$ (see Supporting Information, Figure S15) and toluene-d_8 (see Supporting Information, Figure S16), and confirmed by X-ray crystallography (see Supporting Information, Figure S17). [b] Mixture confirmed qualitatively by HPLC with a Pirkle phenylglycine column (99:1 hexane/isopropanol, 1 mL/min); listed in order of elution (see Supporting Information, Figure S18). [c] The diastereomers of **19** were easily separated by recrystallization; the identity of the major isomer was established by X-ray crystallography (see Supporting Information, Figure S21). [d] Determined by HPLC with a normal phase silica column (85:15 hexane/ethyl acetate, 1 mL/min); listed in order of elution (see Supporting Information, Figure S22).

TABLE 4. Alkylation of Diastereomeric Isoquinoline Reissert Compounds[a]

Reissert compd	alkyl halide	product	yield (%)	diastereomericratio
1:1(*S*)-**8**/(*R*)-**8**	CH_3I	**22a**	92	50:50[b,c]
1:1(*S*)-**8**/(*R*)-**8**	*n*-BuCl	**22b**	10	36:64[b]
1:1(*S*)-**8**/(*R*)-**8**	*n*-BuBr	**22b**	90	36:64[b,d]
1:1(*S*)-**8**/(*R*)-**8**	$C_6H_5CH_2I$	**22c**	72	72:28[e]
(*S*)-**11**	CH_3I	**23a**	100	55:45[b,f]

[a] In DMF at −40 °C using NaH as the base. [b] By HPLC with a Pirkle phenylglycine column (99:1 hexane/isopropanol, 1 mL/min); listed in order of elution. [c] See Supporting Information, Figure S11. [d] See Supporting Information, Figure S12. [e] By integration of ^{1}H NMR spectrum; arbitrary designations. [f] See Supporting Information, Figure S13.

Alkylation reactions of the dihydro-Reissert compounds **18**−**21** were also examined (Scheme 11). The results (Table 5) reveal modest diastereoselectivty in the case of 9-phenylmenthyl product **26a**. Pure diastereomer (*S*)-**19** was methylated with some selectivity in formation of **25a**. With isopropyl iodide **25b** was formed nondiastereoselectively. Alkylation of (*S*)-**19** with benzyl iodide proceeded in high yield, but the diastereomeric ratio of **25c** could not be determined.

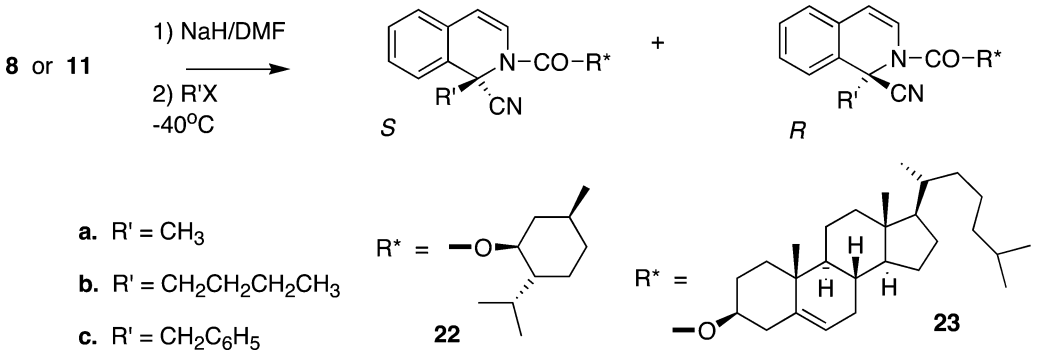
As with other *N*-sulfonyl Reissert compounds[19] attempted methylation of **21** led to elimination of the sulfinate moiety from the Reissert anion and formation of the 1-cyano-3,4-dihydroisoquinoline **27** (Scheme 12). Upon treatment with NaH in DMF, the fully aromatized 6,7-dimethoxyisoquinoline (**28**) was isolated, apparently a result of removal of HCN from **27** (Scheme 12), perhaps by elimination of HCN from the 4-anion of the 1,4-dihydro-isomer of **27**; there is some precedent for such processes in dihydroisoquinolines.[20]

Compounds **25a**, **25c,** and **26a** were prepared by cyanoacylation[21] of the corresponding 1-alkyl-6,7-dimethoxy-3,4-dihydroisoquinolines (Scheme 13) in hopes that greater selectivity could be achieved; however, this proved not to be the case (see Supporting Information).

G. Nature of the Reissert Anions. There are three possible geometries for the anions of isoquinoline Reissert compounds: (1) planar sp^2 carbon at C_1 (i. e., through ArC(N)═C═N$^-$) as is common for benzylic[22] and other[23] carbanions, (2) tetrahedral/pyramidal C_1 but equilibrating,[24] and 3) tetrahedral/pyramidal C_1 but not equilibrating.

The results described above and formation of mixed diastereomeric products from quenching diastereomerically pure

SCHEME 10. Alkylation of Chiral Reissert Compounds 8 and 11



SCHEME 11. Alkylation of Chiral Dihydro-Reissert Compounds 18−20

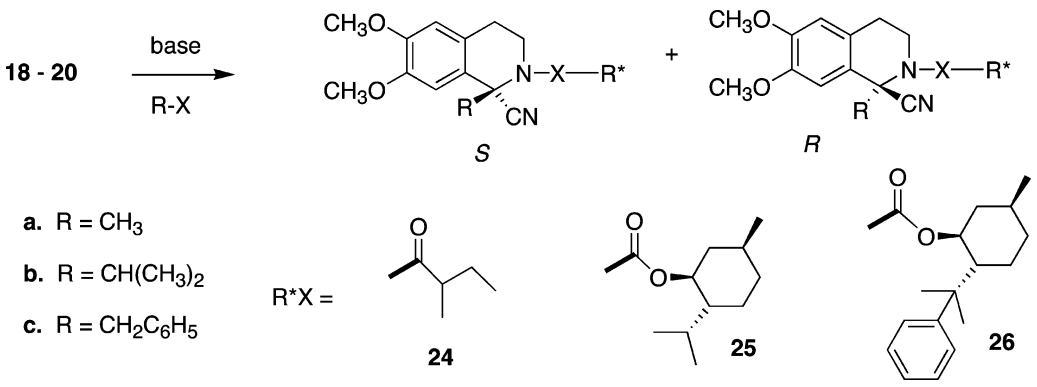
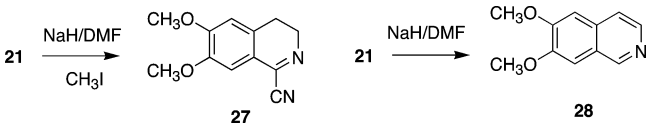


TABLE 5. Alkylation of Diastereomeric Dihydro-Reissert Compounds

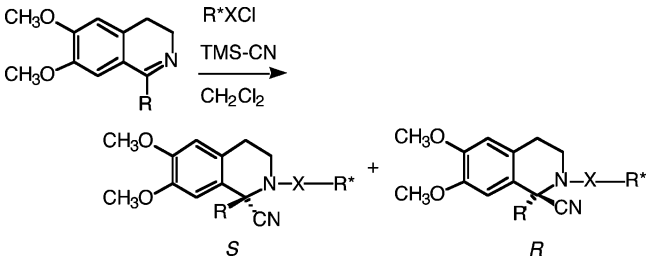
Reissert compd	RX	conditions	product	yield (%)	diasteromeric ratio
1:1 (*R*)-**18**/(*S*)-**18**	CH_3I	*n*-BuLi/THF, −100 °C	**24a**	90	50:50[a,b]
(*S*)-**19**	CH_3I	NaH/DMF, 0 °C	**25a**	83	36:64[c]
(*S*)-**19**	CH_3I	*n*-BuLi/THF, −100 °C[d]	**25a**	100	54:46[c]
(*S*)-**19**	$(CH_3)_2CHI$	NaH/DMF, 0 °C	**25b**	100	50:50[e]
(*S*)-**19**	$(CH_3)_2CHI$	LDA/THF, −78 °C	**25b**	98	∼50:50[f]
(*S*)-**19**	$C_6H_5CH_2I$	NaH/DMF, 25 °C	**25c**	89	??
4:1 (*R*)-**20**/(*S*)-**20**[g]	CH_3I	NaH/DMF, 25 °C	**26a**	100	67:33[c]
21	CH_3I	NaH/DMF, −40, 25 °C	*h*		

[a] Determined by integration of the pair of 1-methyl singlets at ∼1.9 ppm in the ^{1}H NMR spectrum of the product in $CDCl_3$ (see Supporting Information, Figures S24 and S25). [b] Confirmed by integration of the pair of α-methyl doublets at 1.17 and 1.20 ppm in the ^{1}H NMR spectrum of the product in $CDCl_3$ (see Supporting Information, Figure S25) and the X-ray crystal structure (see Supporting Information, Figure S26). [c] Determined by integration of the pair of 1-methyl singlets at ∼1.9 ppm in the ^{1}H NMR spectrum of the product in toluene-d_8 (see Supporting Information, Figures S27 and S29); configuration of major diastereomer unknown. [d] See Supporting Information for procedure. [e] Established by X-ray crystallography (see Supporting Information, Figure S28). $[\alpha]_D^{25} = -46.2$ ($c = 15.6$, CH_2Cl_2). [f] See Supporting Information. $[\alpha]_D^{25} = -53.1$ ($c = 0.700$, $CHCl_3$). [g] Arbitrary designation; configuration of major diastereomer unknown. [h] No alkylation occurred; see text and Supporting Information.

SCHEME 12. Transformations of Camphorsulfonyl Dihydro-Reissert Compound 21



SCHEME 13. Cyanoacylation of 1-Alkyl-6,7-Dimethoxy-3,4-Dihydroisoquinolines as a Route to 24−26



Reissert anions with D_2O or H_2O (see Supporting Information) clearly demonstrate that nonequilibrating anions can be ruled out. The modest stereoselectivity observed in some cases can be attributed to the effects of the chiral auxiliary in terms of selective blocking of one face of the carbanion (see Supporting Information, Figure S32).

Conclusions

Reissert compounds bearing chiral substituents were prepared from isoquinoline (**8**−**11**) and 6,7-dimethoxy-3,4-dihydroisoquinoline (**18**−**21**) (Tables 1 and 3). Low-temperature proton NMR was used to determine the ratio of diastereomers (1:1 *R*/*S*) and also the ratio of (*E*)- to (*Z*)-urethane rotational isomers (4:6) of 2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (**8**). Thus, contrary to a recent report,[13] this reaction is not >95% diastereoselective. Notably, 2-cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitriles (**11**) were similarly produced as a mixture of diastereomers, 41% *S* and 59% *R*, which could be morphologically separated quite easily. Similarly, the diastereomers of 2-*l*-menthoxycarbonyl-1,2,3,4-tetrahydroisoquinaldonitrile (**19**) were readily separated and purified.

The reaction of 1:1 (*S*)-**8**/(*R*)-**8** with pivaldehyde gave the carbonate **12**, whose major (82%) diastereomer (*S*)-**12** was easily separated from the minor diastereomer (*R*)-**12** (18%) by a single recrystallization from hexanes. Diastereomerically pure (*S*)-**12** was hydrolyzed to the 99% enantiomerically pure 1-isoquinolyl *tert*-butyl carbinol [(*S*)-**16**]. Starting from the *d*-menthyl Reissert compounds (*R*)-**9** and (*S*)-**9**, we synthesized (*R*)-1-isoquinolyl *tert*-butyl carbinol [(*R*)-**16**] with 98% optical purity in an analogous fashion. Aromatic aldehydes react with similar stereoselectivities, but the products epimerize rather rapidly. 2-Cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitrile [(*S*)-**11**], as the pure diastereomer, in condensation with pivaldehyde was totally nonselective, yielding equal amounts of the two diastereomers.

The mixture (1:1) of diastereomers of 2-*l*-menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (**8**) was alkylated with butyl and benzyl halides with modest diastereoselectivities (Table 4). With methyl iodide no selectivity was observed, contrary to a recent claim.[13] However, methylation of dihydro-Reissert compounds **18**−**20** proceeded with modest selectivities, up to 2:1 (Table 5).

The lack of highly selective reactions of these Reissert anions is explained by the fact that they are not static tetrahedral species but are rather either planar or equilibrating tetrahedral species.

Experimental Section

Caution: *Trimethylsilyl cyanide (TMSCN) is toxic and should be used in an efficient fume hood.*

2-*l*-Menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (8). General Method for Reissert Compound Synthesis. To a stirred solution (0 °C, N_2) of isoquinoline (9.68 g, 75.0 mmol) in methylene chloride (150 mL), was added *l*-menthyl chloroformate (18.04 g, 82.5 mmol) followed after 15 min by TMSCN (7.81 g, 76.0 mmol). The reaction was monitored by TLC (silica gel, EtOAc/hexanes, 2:8). Stirring was continued for 48 h at rt, and the reaction was terminated by the addition of water (150 mL) and stirring overnight. The organic layer was separated and washed with water (2 × 30 mL), 10% HCl (2 × 20 mL), saturated $NaHCO_3$ (2 × 30 mL), and

(18) Rosini, C.; Uccello-Barretta, G.; Pini, D.; Abete, C.; Salvadori, P. *J. Org. Chem.* **1988**, *53*, 4579−4581.
(19) Wefer, J. M.; Catala, A.; Popp, F. D. *J. Org. Chem.* **1965**, *30*, 3075−7.
(20) Li, W.-D. Z.; Yang, H. *Tetrahedron* **2005**, *61*, 5037−5042.
(21) Berg, M. A. G.; Gibson, H. W. *J. Org. Chem.* **1992**, *57*, 748−750.
(22) (a) Brooks, J. J.; Stucky, G. D. *J. Am. Chem. Soc.* **1972**, *94*, 7333−7338. (b) Peoples, P. R.; Grutzner, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 4709−4715. (c) Jernigan, M. T.; Eliel, E. L. *J. Am. Chem. Soc.* **1995**, *117*, 9638−9644. (d) Enders, D.; Kirchoff, J.; Gerdes, P.; Mannes, D.; Raabe, G.; Runsink, J.; Boche, G.; Marsch, M.; Ahlbrecht, H.; Sommer, H. *Eur. J. Org. Chem.* **1998**, 63−72. (e) Binev, Y. I.; Petrova, R. R.; Tsenov, J. A.; Binev, I. G. *J. Mol. Struct.* **2000**, *516*, 23−29.
(23) (a) Zimmerman, H. E.; Ignatchenko, A. *J. Org. Chem.* **1999**, *64*, 6635−6645. (b) Karazi, Y.; Vertgoten, G.; Supateanu, *J. Mol. Structure* **1999**, *476*, 121−131.
(24) Carlier, P. *Chirality* **2003**, *15*, 340−347.

water (2 × 30 mL). It was dried over Na_2SO_4 and concentrated by rotary evaporation to give the crude product (27.17 g, 96%). Analytically pure product, mp 96−97 °C, $[\alpha]_D^{25} = -63.5$ (c = 1.53, CH_2Cl_2), was obtained by three recrystallizations from hexanes. HPLC on a Pirkle phenylglycine column gave one signal at 10.6 min (99:1 hexanes/isopropanol, flow rate 1 mL/min). HPLC on a Chiralcel OD column produced one signal at 22 min (95:5 hexanes/isopropanol, flow rate 0.25 mL/min). FTIR: ν 2950 (C−H), 1713 (C═O), and 1150 (C−O) cm^{-1}. ^1H NMR ($CDCl_3$, −20 °C, see Figure 1c): δ 0.5−2.2 (m, 18H), 4.60−4.90 (m, 1H, OCH), 6.03 (d, J = 8 Hz, 0.2H, H_4), 6.04 (d, J = 8 Hz, 0.2H, H_4), 6.07 (d, J = 8 Hz, 0.3H, H_4), 6.08 (d, J = 8 Hz, 0.3H, H_4), 6.23 (s, 0.2H, H_1), 6.28 (s, 0.2H, H_1), 6.43 (s, 0.6H, H_1), 6.87 (d, J = 8 Hz, 0.3H, H_3), 6.92 (d, J = 8 Hz, 0.3H, H_3), 7.03 (d, J = 8 Hz, 0.2H, H_3), 7.04 (d, J = 8 Hz, 0.2H, H_3), 7.15 (d, J = 8 Hz, 1H), 7.20−7.38 (m, 3 H). ^{13}C NMR ($CDCl_3$): δ 16.4, 16.6, 20.7, 21.8, 23.7, 23.9, 26.4, 26.8, 31.5, 34.2, 41.0, 41.3, 46.3, 47.4, 78.5, 108.6, 116.5, 124.1, 124.4, 125.7, 126.5, 126.8, 128.0, 130.0, 130.5, 151.9. LR EIMS *m/z*: 338 (M^+, 7%), 183 ($M^+ - C_{10}H_7N_2$, 12%) 156 ($M^+ - C_{11}H_{18}O_2$, 100%). HRMS−FAB (NBA-PEG) *m/z*: 338.1983 (calcd For M^+ 338.1994). Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.51; H, 7.74; N, 8.30. Careful column chromatography of 1.0 g of this mixture on 100 g of silica gel by elution with 5% ethyl acetate in hexanes afforded 22 fractions with $[\alpha]_D^{25}$ ranging from −58.7 to −22.5 (c = 1.1−1.5, CH_2Cl_2). Automated flash chromatography yielded fractions with quantitatively different NMR spectra (see Supporting Information, Figure S1), but neither pure diastereomer was isolated.

2-*d*-Menthoxycarbonyl-1,2-dihydroisoquinaldonitrile (9). The above method with isoquinoline and *d*-(+)-menthyl chloroformate gave a 98% yield of crude product. Pure product, mp 96−97 °C, $[\alpha]_D^{25} = +63.4$ (c = 2.00, CH_2Cl_2), was obtained by three recrystallizations from hexanes. Spectral data of **9** were identical to those of **8**.

2-Methoxyacetyl-1,2-dihydroisoquinaldonitrile (1, R = CH_2OCH_3). The method above using isoquinoline and methoxyacetyl chloride afforded a quantitative yield. The product was purified by column chromatography on silica gel (5:95 EtOAc/hexanes) followed by three recrystallizations from EtOAc/hexanes. mp 103−104 °C. FTIR (KBr): ν 2957 (C−H), 1680 (C═O), 1630 (Ar C−H), 1344, and 1130 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.5 (s, 3H), 4.23 and 4.41 (1H each, d, J = 14 Hz), 6.10 (d, J = 8 Hz, 1H), 6.65 (s, 1H), 6.90 (d, J = 8 Hz, 1H), 7.2−7.5 (m, 4H). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.30; N, 12.28. Found: C, 68.48; H, 5.32; N, 12.30.

2-*l*-Menthoxyacetyl-1,2-dihydroisoquinaldonitrile [(*R*)-10/(*S*)-10]. Application of the above procedure to isoquinoline and *l*-(−)-menthoxyacetyl chloride (see Supporting Information) produced a 67% yield of an oily product. The ratio of the diastereomers in the crude compound was 1:1 (by NMR). The product was dissolved in EtOAc, and the solution treated twice with activated charcoal and filtered through Celite. The compound was then subjected to silica gel column chromatography, eluting consecutively with hexanes, hexanes/EtOAc (99.75:0.25), and hexanes/EtOAc (99.50:0.50). This resulted in partial separation of the diastereomers. The first fraction (mp 79−81 °C) was a 65:35 mixture of diastereomers as deduced from the NMR spectrum (Figure 3a). The ratio then went to 48:52 within a few fractions with mp 79−81 °C and $[\alpha]_D^{25} = -51.4$ (c = 2.0, CH_2Cl_2). FTIR: ν 2960−2860 (C−H), 1738 (C═O), 1630 (Ar C−H), 1450, 1221, and 1124 (C−O) cm^{-1}. ^1H NMR (~50:50 sample, $CDCl_3$, −20 °C, Figure 3b): δ 0.60−2.4 (m, 17H), 3.22 (q, J = 12 Hz, 0.5H, OCH), 3.26 (q, J = 12 Hz, 0.5H, OCH), 4.27 and 4.42 (0.5H each, J = 14 Hz, $COCH_2$), 4.37 (s, 0.5H, $COCH_2$), 4.38 (s, 0.5H, $COCH_2$), 6.13 (d, J = 8 Hz, 0.5H, H_4), 6.14 (d, J = 8 Hz, 0.5H, H_4), 6.61 (br s, 0.5 H, H_1), 6.64 (br s, 0.5H, H_1), 6.90 (dd, J = 1 Hz, 8; 0.5H, H_3), 6.91 (dd, J = 1 Hz, 8; 0.5H, H_3), 7.15−7.5 (m, 3H). Anal. Calcd for $C_{22}H_{28}N_2O_2 \cdot 0.25CH_3COOCH_2CH_3$: C, 73.76; H, 8.08; N, 7.48. Found: C, 73.35; H, 7.74; N, 7.56.

2-Cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitrile (11). Isoquinoline and cholesteryl chloroformate gave the crude product (91%) as a cream colored solid, mp 167−173 °C, $[\alpha]_D^{25} = -2.32$ (c = 2.76, CH_2Cl_2). HPLC on a Pirkle column (99:1 hexanes/isopropanol, flow rate 1.0 mL/min) gave signals at 12.6 and 13.5 min with nearly baseline separation in a ratio of 41:59, respectively (see Supporting Information, Figure S2). Two recrystallizations from ethyl acetate produced a sample with two types of crystals; these were separated by means of a magnifiying glass and forceps and recrystallized individually to diastereomeric purity (see Supporting Information, Figure S2). The sample with the lower retention time on HPLC had mp 184−186 °C and $[\alpha]_D^{25} = -95.5$ (c = 2.41, CH_2Cl_2); X-ray crystallography (see Supporting Information, Figure S3) demonstrated that this was the *S*-diastereomer. The *R*-diastereomer had mp 200−201 °C and $[\alpha]_D^{25} = +80.9$ (c = 2.75, CH_2Cl_2). FTIR (KBr): ν 2950 (C−H), 1715 (C═O), and 1150 (C−O) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.6−2.1 (m, 43H), 4.70 (m, 1H, OCH), 5.44 (br s, 1H, ═CH−), 6.00 (overlapping d, J = 7.4 Hz, 1H, H_4), 6.22 (br s, 0.45H, H_1), 6.37 (br s, 0.55H, H_1), 6.87 (d, J = 7.4 Hz, 0.55H, H_3), 6.99 (d, J = 7.4 Hz, 0.45H, H_3), 7.16 (d, J = 7.3 Hz, 1H, H_5), 7.20−7.38 (m, 3H). Anal. Calcd for $C_{38}H_{52}N_2O_2$: C, 80.23; H, 9.22; N, 4.92. Found: C, 80.12; H, 9.38; N 4.81.

***S*-(−)-1-Isoquinolyl *tert*-Butyl Carbinyl *l*-Menthyl Carbonate [(*S*)-12]. General Method for Reactions of Reissert Compounds with Pivaldehyde and Alkyl Halides.** A well stirred solution of 1:1 mixture of diastereomers of the Reissert compound **8** (500 mg, 1.3 mmol) and pivaldehyde (0.17 mL, 1.6 mmol) in DMF (15 mL) was cooled to −40 °C under nitrogen. After addition of 80% NaH (80 mg, 2.7 mmol), the mixture was allowed to stir for 5 h and quenched into water (100 mL). The ether extract (3 × 20 mL) was washed with water (4 × 20 mL) and evaporated to yield the crude product: 516 mg (100%), mp 90−100 °C, and $[\alpha]_D^{25} = -42.5$ (c = 2.00, CH_2Cl_2). HPLC was performed on a Pirkle covalent phenylglycine column (99:1 hexanes/isopropanol, flow rate 1 mL/min): two peaks, one at 371 s and another at 414 s (ratio 82:18, see Supporting Information, Figure S4). Upon recrystallization from hexanes once, the *S*-enantiomer was isolated with mp 122−123 °C and $[\alpha]_D^{25} = -35.5$ (c = 1.78, CH_2Cl_2). HPLC for the pure compound showed only the peak at 371 s (see Supporting Information, Figure S4). X-ray crystallography (see Supporting Information, Figure S5) showed the configuration at C_1 to be *S*. FTIR (KBr): ν 2887−2964 (C−H), 1779 (C═O), 1170 (C−O), 1166, and 1128 cm^{-1}. ^1H NMR ($CDCl_3$, Figure 4b, pure diastereomer): δ 0.44 (d, J = 7 Hz, 3 H, CH_3), 0.80 (d, J = 7 Hz, 3H, CH_3), 0.88 (d, J = 7 Hz, 3H, CH_3), 1.09 [s, 9 H, $C(CH_3)_3$], 0.70−2.1 (underlying m, 9 H), 4.32 (m, 1H, ring OCH), 6.18 (s, 1H, IQ-CHO) [in the mixture of diastereomers: 6.18 (s, 0.70 H, IQ-CHO), 6.24 (s, 0.30 H, IQ-CHO)], 7.58 (d, J = 8 Hz, 1H), 7.60−7.70 (m, 2H), 7.83 (d, J = 8 Hz, 1H), 8.40 (d, J = 8 Hz, 1H), 8.55 (d, J = 8 Hz, 1H). Anal. Calcd for $C_{25}H_{35}NO_3$: C, 75.46; H, 8.87; N, 3.52. Found: C, 75.44; H, 8.90; N, 3.51.

***R*-(+)-1-Isoquinolyl *tert*-Butyl Carbinyl *d*-Menthyl Carbonate [(*R*)-13].** From the 50:50 mixture of *R*/*S* diastereomers of Reissert compound **9** and pivaldehyde (*R*)-**13** was isolated (70%) and purified analogously, with mp 122−123 °C and $[\alpha]_D^{25} = +35.5$ (c = 1.50, CH_2Cl_2). Spectral data were identical to those of (*S*)-**12**.

1-Isoquinolyl *tert*-Butyl Carbinyl Methoxyacetate (3, R = CH_2OCH_3, R′ = tert-Bu). Reissert compound **1**, R = CH_2OCH_3, and pivaldehyde produced (98%) the ester, which was purified by silica gel chromatography (90:10 hexanes/EtOAc). mp 116−117 °C. FTIR (neat): ν 2960, 2932, 1750, 1627, 1382, 1273, and 1128 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.10 (s, 9H), 3.40 (s, 3H), 4.20 (s, 2H), 6.55 (s, 1H), 7.6−8.05 (m, 4H), 8.40 (d, J = 8 Hz, 1H), 8.60 (d, J = 8 Hz, 1H). Because of its instability, we were unable to obtain a satisfactory elemental analysis.

1-Isoquinolyl *tert*-Butyl Carbinyl 1-Menthoxyacetate (14). A 1:1 diastereomeric mixture of Reissert compounds (*R*)-**10** and (*S*)-

10 and pivaldehyde produced a 97% yield of an oil (1:1 *S/R* by ^{1}H NMR). Column chromatography on silica gel (9:1 hexanes/EtOAc) afforded chemically pure product as a clear oil that crystallized slowly; mp 65−75 °C, $[\alpha]_D^{25} = -49.0$ ($c = 3.3$, CH_2Cl_2), and 70:30 dr by NMR. HPLC on a Pirkle phenylglycine column (99:1 hexanes/isopropanol, 1 mL/min) gave the major peak at 533 s (71%) and the minor peak at 550 s (29%). FTIR (neat): ν 2955, 2924, 1756, 1126 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.60−2.30 (m, 27H), 3.20 (m, 1H), 4.24 and 4.38 (0.15H each, d, $J = 14$ Hz), 4.34 (s, 0.7H), 6.43 (s, 0.3H), 6.53 (s, 0.7H), 7.65−7.90 (m, 4H), 8.15 (d, $J = 8$ Hz, 0.3H), 8.39 (d, $J = 8$ Hz, 0.7H), 8.49 (d, $J = 8$ Hz, 0.3H), 8.55 (d, $J = 8$ Hz, 0.7H). Anal. Calcd for $C_{25}H_{37}NO_3$: C, 75.15; H, 9.33; N, 3.51. Found: C, 75.17; H, 9.03; N, 3.66.

1-Isoquinolyl *tert*-Butyl Carbinyl Cholesteryl Carbonate (15). Conversion of (*S*)-**11** and pivaldehyde to **15** was quantitative. Both NMR and HPLC analyses (Pirkle phenylglycine column, 99:1 hexanes/isopropanol, 1 mL/min) indicated the two diastereomers were formed in 52:48 ratio (see Supporting Information, Figure S8). ^{1}H NMR ($CDCl_3$): δ 0.60−2.5 (m, 52H), 4.30 (m, 1H), 5.27 (d, $J = 7$ Hz, 0.5H), 5.29 (d, $J = 7$ Hz, 0.5H), 6.20 (s, 1H), 7.5−7.7 (m, 2H), 7.82 (d, $J = 8$ Hz, 1H), 8.35 (d, $J = 8$ Hz, 1H), 8.56 (d, $J = 8$ Hz, 1H). Recrystallized from acetone, mp 123−124 °C. Anal. Calcd for $C_{42}H_{61}NO_3 \cdot {}^1/_3H_2O$: C, 79.57; H, 9.80; N, 2.21. Found: C, 79.66; H, 9.71; N, 2.18. HRMS−FAB (NBA-PEG) *m/z:* 628.4742 [calcd for $(M + H)^+$ 628.4730].

***S*-(−)-1-Isoquinolyl *tert*-Butyl Carbinol [(*S*)-16].** A stirred solution of 318 mg (0.80 mmol) of *S*-(−)-isoquinolyl *tert*-butyl *l*-menthyl carbonate [(*S*)-**12**] and 324 mg (8.0 mmol) of NaOH in 25 mL each of water, THF, and ethanol was heated at reflux for 2.5 h (monitored by TLC, 1:1 ethyl acetate/hexanes), cooled, and extracted with ether. The ether extract was in turn extracted with 10% HCl, and the aqueous solution was made basic (pH 10) by addition of NaOH and extracted with ether. The ethereal extract was washed with water and brine and dried over sodium sulfate. Removal of the ether under vacuum yielded 90 mg (80%) of the alcohol, mp 100−101 °C, $[\alpha]_D^{25} = -70.6$ ($c = 1.17$, CH_2Cl_2), after two recrystallizations from EtOAc/hexanes. Optical purity was established by utilization of quinine as a chiral solvating agent[18] in ^{1}H NMR as described in the Supporting Information (Figures S9 and S10). FTIR (KBr): ν 3300−3500 (O−H), 2810−2600 (C−H) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.98 (s, 9H), 4.57 (d, $J = 7$ Hz, 1H), 5.3 (d, $J = 7$ Hz, 1H), 7.50−7.70 (m, 3H), 7.83 (d, $J = 8$ Hz, 1H), 8.15 (d, $J = 8$ Hz, 1H), 8.50 (d, $J = 8$ Hz, 1H). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.98; N, 6.51. Found: C, 77.97; H, 7.98; N, 6.34.

***R*-(+)-1-Isoquinolyl *tert*-Butyl Carbinol [(*R*)-16].** Hydrolysis of *R*-(+)-1-isoquinolyl *tert*-butyl *d*-menthyl carbonate ((*R*)-**13**) similarly produced (70%) (*R*)-**16**, with mp 100−101 °C and $[\alpha]_D^{25} = +68.9$ ($c = 1.00$, CH_2Cl_2). The optical purity as measured by the use of quinine as outlined above was 98%. Spectral data of the pure (+)-enantiomer were identical to those of the racemate and the (−)-enantiomer (*S*)-**16**.

1-Methyl-2-(*l*-menthoxycarbonyl)-1,2-dihydroisoquinaldonitrile (22a). A glassy material that would not crystallize was obtained in 92% yield. By both ^{1}H NMR spectroscopy and HPLC (99:1 hexanes/isopropanol, flow rate 1 mL/min, see Supporting Information, Figure S11) the product was shown to be comprised of equal amounts of the two possible diastereomers. ^{1}H NMR ($CDCl_3$) δ 0.70−2.2 (m, 21 H, including a sharp singlet @ 1.91 ppm), 4.88 (m, 1H), 5.69 (d, $J = 8$ Hz, 0.5H), 5.71 (d, $J = 8$ Hz, 0.5H), 6.89 (d, $J = 8$ Hz, 1H), 7.00 (m, 1H), 7.26 (m, 2H), 7.59 (m, 1H). FAB MS (NBA-PEG) *m/z:* 352 (M^+, 32%), 327 [$(M + H - CN)^+$, 100%]. HRMS−FAB (NBA-PEG) *m/z:* 352.2145 (calcd for M^+ 352.2152).

1-Methyl-2-cholesteryloxycarbonyl-1,2-dihydroisoquinaldonitrile (23a). Starting from pure diastereomer (*S*)-**11** only ~15% conversion was obtained after 5 h at −40 °C. By both ^{1}H NMR spectroscopy and HPLC (Pirkle phenylglycine column, 99:1 hexanes/isopropanol, flow rate 1 mL/min, see Supporting Information, Figure S13) the product was comprised of a 55:45 mixture of the two diastereomers. A reaction at rt for 20 h led to complete conversion with formation of the two diastereomeric products in a 55:45 ratio. ^{1}H NMR ($CDCl_3$): δ 0.60−2.2 (m, 41H, including a sharp singlet at 1.91 ppm), 2.50 (m, 2H), 3.64 (m, 2H), 4.76 (m, 1H), 5.44 (br s, 1H), 5.68 (d, $J = 7$ Hz, 1H), 6.87 (d, $J = 8$ Hz, 1H), 7.01 (m, 1H), 7.23 (m, 3H), 7.59 (m, 1H). Recrystallized from acetone, mp 178−180 °C. Anal. Calcd for $C_{39}H_{54}N_2O_2$: C, 80.37; H, 9.34; N, 4.81. Found: C, 80.02; H, 9.22; N, 4.79. HRMS−FAB (NBA-PEG) *m/z:* 583.4225 [calcd for $[M + H]^+$ 583.4264].

2-[(*S*)-α-Methylbutyryl]-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (18). General Procedure for Preparation of Dihydro-Reissert Compounds. To a stirred solution of 6,7-dimethoxy-3,4-dihydroisoquinoline (**17**)[25] (1.08 g, 5.65 mmol), TMSCN (0.62 g, 6.2 mmol), and anhyd $AlCl_3$ (0.08 g, 0.6 mmol) in CH_2Cl_2 (30 mL) was added (*S*)-α-methylbutyryl chloride (0.75 g, 6.2 mmol, see Supporting Information). The mixture was stirred for 5 days. Water (1 mL) was added to the mixture and stirring continued for 1 day. The organic phase was washed three times each with H_2O, 10% aq HCl, H_2O, 10% aq NaOH, H_2O, and once with brine. The CH_2Cl_2 was removed in vacuo to give 0.64 g (37% yield) of a yellow solid, which was recrystallized twice from ethanol and once from ethyl acetate to afford colorless crystals. mp 140−141 °C. $[\alpha]_D^{25} = +16.7$ ($c = 0.773$, $CHCl_3$). IR (KBr): ν 2236, 1684 cm^{-1}. ^{1}H NMR: δ 0.85 (t, $J = 7$ Hz, 1.5H), 0.95 (t, $J = 7$ Hz, 1.5H), 1.13 (d, $J = 7$ Hz, 1.5H), 1.18 (d, $J = 7$ Hz, 1.5H), 1.47 (m, 1H), 1.73 (m, 1H), 2.70 (m, 1H), 2.89 (m, 2H), 3.62 (m, 1H), 3.86 (s, 3H), 3.88 (s, 3H), 4.09 (m, 1H), 6.40 (br s, 0.5H), 6.43 (br s, 0.5H), 6.63 (s, 1H), 6.77 (s, 1H). ^{13}C NMR: δ 11.58, 11.74, 16.94, 26.81, 27.12, 28.47, 37.28, 37.65, 41.28, 43.64, 56.06, 56.18, 109.91, 111.73, 118.08, 120.53, 126.03, 148.82, 149.71, 175.71. Anal. Calcd for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33. Found: C, 67.43; H, 7.28. X-ray crystallography (see Supporting Information, Figure S17) demonstrated that this was a 1:1 mixture of diastereomers.

(1*S*)-2-(*l*-Menthoxycarbonyl)-l-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*S*)-19]. From 6,7-dimethoxy-3,4-dihydroisoquinoline (**17**)[25] and *l*-menthyl chloroformate, the crude solid was treated with hexanes and ethanol until it dissolved. White crystals formed immediately. The suspension was filtered to afford a yellowish-white solid (51% yield), which was recrystallized twice from ethanol to give colorless crystals of (*S*)-**19**. mp 185−187 °C. $[\alpha]_D^{25} = -152.3$ ($c = 1.79$, $CHCl_3$). IR (KBr): ν 2232, 1721 cm^{-1}. ^{1}H NMR: δ 0.90 (br m, 10H), 1.11 (m, 2H), 1.48 (br m, 2H), 1.69 (br d, $J = 11$ Hz, 2H), 2.04 (br m, 2H), 2.73 (d, $J = 16$ Hz, 1H), 2.89 (br m, 1H), 3.33 (br m, 1H), 3.87 (s, 3H), 3.88 (s, 3H), 4.21 (m, 1H), 4.68 (m, 1H), 5.81 (br s, 0.5H), 6.04 (br s, 0.5H), 6.64 (s, 1H), 6.75 (s, 1H). ^{13}C NMR: δ 16.6, 20.8, 22.0, 23.7, 26.6, 27.7, 31.4, 34.3, 39.6, 41.4, 46.1, 47.5, 56.1, 56.2, 109.6, 111.9, 118.2, 126.8, 148.6, 149.7 (20 peaks; theory, 22). Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05. Found: C, 68.73; H, 8.06. The structure was established by X-ray crystallography (see Supporting Information, Figure S21) and diastereomeric purity was confirmed by HPLC (see Supporting Information, Figure S18).

(1*R*)-2-(*l*-Menthoxycarbonyl)-l-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*R*)-19]. The mother liquor from the recrystallizations above yielded crystals (26%), which from ethanol produced fine needle shaped crystals of (*R*)-**19**. mp 140−142 °C. $[\alpha]_D$ +49.9° ($c = 0.680$, $CHCl_3$). IR (KBr): ν 2235, 1693 cm^{-1}. ^{1}H NMR: δ 0.89 (br m, 12H), 1.45 (br m, 2H), 1.66 (br d, $J = 11$ Hz, 2H), 2.08 (br m, 2H), 2.71 (m, 1H), 2.84 (br m, 1H), 3.31 (br m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.21 (m, 1H), 4.64 (m, 1H),

(25) (a) Haworth, R. D. *J. Chem. Soc.* **1927**, 2281−2284. (b) Whaley, W. M.; Meadow, M. *J. Chem. Soc.* **1953**, 1067−1070. (c) Popp, F. D.; McEwen, W. E. *J. Am. Chem. Soc.* **1957**, *79*, 3773−3777. (d) Openshaw, H. T.; Whittaker, N. *J. Chem. Soc.* **1963**, 1461−1471. (e) Whaley, W. M.; Govindachari, T. R. *Org. React.* **1969**, *6*, 74−150. (f) Warrener, R. N.; Liu, L.; Russell, R. A. *Tetrahedron* **1998**, *54*, 7485−74960.

5.86 (br s, 0.5H), 6.03 (br s, 0.5H), 6.62 (s, 1H), 6.74 (s, 1H). ^{13}C NMR: δ 16.5, 20.7, 21.9, 23.6, 26.5, 27.7, 31.4, 34.2, 39.5, 41.4, 45.9, 46.0, 47.4, 56.0, 56.1, 109.6, 111.8, 118.1, 126.7, 148.5, 149.6 (21 peaks; theory, 22). Anal. Calcd for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; Found: C, 68.78; H, 8.13. Diastereomeric purity was established by HPLC (see Supporting Information, Figure S18).

2-(8′-Phenyl-*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (20). The crude light yellow wax (80%) from 6,7-dimethoxy-3,4-dihydroisoquinoline (**17**)[25] and 8-phenyl-*l*-menthyl chloroformate (see Supporting Information) was examined by normal phase HPLC using a mixed solvent system of 10% ethyl acetate in hexanes, affording baseline separation of two peaks at retention times of 11.7 and 12.5 min with relative peak areas 20:80, respectively (see Supporting Information, Figure S22). Attempts to recrystallize the solid failed. The material was purified by flash column chromatography using 40% ethyl acetate in hexanes to give a colorless amorphous solid that exhibited a phase-transition at 70 °C. $[\alpha]_D^{25} = -70.5$ ($c = 0.440$, $CHCl_3$). IR (KBr): ν 2234, 2254, 1698 cm^{-1}. ^{1}H NMR: δ 0.85 (m, 6H), 1.20 (m, 6H), 1.49 (m, 1H), 1.72 (m, 1H), 2.00 (m, 2H), 2.59 (m, 2H), 3.00 (m, 0.5H), 3.28 (m, 0.5H), 3.85 (m, 7H), 4.18 (m, 0.5H), 4.87 (m, 1H), 5.91 (m, 0.5H), 6.42 (m, 1H), 6.59, (m, 1H), 6.92 (t, $J = 8$ Hz, 1H), 7.14 (m, 1H), 7.28 (m, 4H). The ^{1}H NMR spectrum revealed the presence of ethyl acetate. ^{13}C NMR: δ 13.9, 20.9, 21.6, 22.5, 26.2, 26.8, 27.4, 27.9, 28.9, 29.9, 30.8, 31.3, 31.4, 34.5, 38.9, 39.1, 39.2, 41.9, 42.3, 44.8, 45.5, 45.8, 50.5, 50.9, 55.9, 56.0, 109.6, 110.1, 111.4, 118.1, 119.4, 120.2, 124.8, 125.2, 126.6, 127.3, 127.8, 128.1, 148.4, 149.2, 149.6, 152.6, 153.3. LR EIMS *m/z:* 476 (M^+), 450 $(M - CN)^+$, 380 $(M - C_7H_{12})^+$, 357 $[M - C_6H_5C(CH_3)_2]^+$, 262 {100%, $[M - C_6H_5C(CH_3)_2 - C_7H_8]^+$}, 245, 237, 217, 190, 176, 149, 119 {100%, $[(C_6H_5C(CH_3)_2]^+$}, 105 [100%, $(C_8H_9)^+$], 91 (100%), 85, 79, 71, 65, 55. Anal. Calcd for $C_{29}H_{36}N_2O_4 \cdot 0.50(CH_3COOC_2H_5)$: C, 71.50; H, 7.74; N, 5.38; Found: C, 71.06; H, 7.55; N, 5.54.

2-[(+)-10-Camphorsulfonyl]-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (21). 6,7-Dimethoxy-3,4-dihydroisoquinoline (**17**)[25] and (+)-10-camphorsulfonyl chloride produced a peach colored solid (66%), which was recrystallized from ethanol three times to afford colorless, needle shaped crystals. mp 193−194 °C. $[\alpha]_D^{25} = +24.9$ ($c = 0.447$, $CHCl_3$). IR (KBr): ν 2233, 1748, 1149 cm^{-1}. ^{1}H NMR: δ 0.91 (d, $J = 7$ Hz, 3H), 1.14 (d, $J = 7$ Hz, 3H), 1.46 (m, 1H), 1.78 (m, 1H), 2.00 (d, 1H), 2.09 (m, 2H), 2.45 (m, 2H), 2.79 (m, 1H), 3.01 (m, 2H), 3.45 (m, 1H), 3.59 (m, 1H), 3.87 (s, 6H), 4.12 (m, 1H), 5.80 (d, $J = 7$ Hz, 1H), 6.64 (d, $J = 8$ Hz, 1H), 6.70 (d, $J = 8$ Hz, 1H). ^{13}C NMR: δ 19.9, 20.0, 25.3, 25.4, 27.0, 27.2, 28.0, 28.2, 41.2, 42.8, 43.3, 46.9, 47.8, 48.1, 48.3, 49.2, 56.2, 56.3, 58.4, 58.6, 109.4, 112.1, 117.5, 117.7, 119.3, 119.7, 125.8, 148.8, 150.0, 214.1. Anal. Calcd for $C_{22}H_{28}N_2O_5S$: C, 61.09; H, 6.52; N, 6.48; S, 7.42. Found: C, 61.16; H, 6.50; N, 6.54; S, 7.49.

1-Methyl-2-[(*S*)-α-methylbutyryl]-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (24a). To a stirred solution of **18** (0.20 g, 0.66 mmol) in 10 mL of dry THF under argon at −78 °C was added *n*-butyllithium (0.66 mmol). The light yellow mixture was stirred at −78 °C for 15 min. Iodomethane (0.14 g, 1.0 mmol) was added via syringe. The mixture was stirred at −78 °C for 3 h, during which time the color slowly faded. The mixture was allowed to warm to rt. CH_2Cl_2 (50 mL) was added to the mixture, and the solution was washed with brine (five times) and dried over anhyd Na_2SO_4. The solvent was removed in vacuo to give 0.19 g (90%) of a glassy solid, which was recrystallized from ethanol to afford large chunky crystals. mp 139−142 °C. $[\alpha]_D^{25} = +34.1$ ($c = 0.507$, $CHCl_3$). IR (KBr): ν 2237, 1661 cm^{-1}. ^{1}H NMR: δ 0.92 (m, 3H), 1.17 (m, 3H), 1.48 (m, 1H), 1.79 (m, 1H), 1.92 (s, 1.5H), 1.93 (s, 1.5H), 2.71 (m, 1H), 2.83 (m, 2H), 3.68 (m, 2H), 3.87 (s, 3H), 3.91 (s, 3H), 6.61 (s, 1H), 7.05 (s, 1H). ^{13}C NMR: δ 11.7, 16.8, 26.8, 27.1, 28.1, 28.5, 29.4, 38.7, 42.2, 56.1, 56.2, 110.1, 110.9, 126.0, 148.8, 149.1, 176.2. Anal. Calcd for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65. Found: C, 68.38; H, 7.69. X-ray crystallography (see Supporting Information, Figure S26) demonstrated that this was a 1:1 mixture of the two diastereomers.

1-Methyl-2-(*l*-menthoxycarbonyl)-l-cyano-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (25a). General Alkylation Procedure with NaH/DMF. To a stirred solution of (*S*)-**19** (0.50 g, 1.3 mmol) in DMF (40 mL) at 0 °C was added 60% NaH (0.050 g, 1.3 mmol). The solution was stirred for 5 min. Iodomethane (0.19 g, 1.3 mmol) was added via syringe and stirring continued at rt for 14 h. The reaction mixture was poured into ice H_2O (400 mL) and filtered to give 0.43 g (83% yield) of white solid, which was recrystallized from hexanes to afford a colorless powder. mp 110−114 °C. $[\alpha]_D^{25} = -52.3$ ($c = 12.7$, $CHCl_3$). IR (KBr): ν 2234, 1705 cm^{-1}. ^{1}H NMR (toluene-d_8): δ 0.81 (d, $J = 6$ Hz, 1.92H), 0.82 (d, $J = 6$ Hz, 1.08H), 0.93 (d, $J = 7$ Hz, 1.08H), 0.95 (d, $J = 7$ Hz, 1.92H), 0.96 (d, $J = 7$ Hz, 1.08H), 1.00 (d, $J = 7$ Hz, 1.92H), 1.24 (m, 3H), 1.53 (m, 3H), 1.87 (s, 1.92H), 1.90 (s, 1.08H), 2.11 (m, 2H), 2.31 (m, 3H), 3.36 (s, 3H), 3.40 (s, 3H), 3.85 (t, $J = 6$ Hz, 2H), 5.02 (m, 1H), 6.15 (s, 1H), 7.01 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 16.3, 20.8, 21.9, 23.5, 26.3, 26.5, 28.9, 29.3, 29.7, 31.4, 34.2, 40.8, 41.0, 41.1, 41.4, 47.2, 54.6, 56.0, 56.2, 110.1, 111.0, 121.1, 126.4, 127.1, 148.5, 149.0, 154.8 (27 peaks; theory, 24 for each diastereomer). Anal. Calcd for $C_{24}H_{34}N_2O_4$: C, 69.54; H, 8.27. Found: C, 69.60; H, 8.31. The integration ratio of the two 1-methyl signals at 1.90 and 1.87 ppm in the NMR spectrum of the crude product in toluene-d_8 was 36:64 (see Supporting Information, Figure S27).

1-Isopropyl-2-(*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroiso-quinoline (25b). (*S*)-**19** with 2-iodopropane (NaH, DMF, 0 °C) gave a quantitative yield of a colorless solid, which was recrystallized twice from ethanol. mp 132−134 °C. $[\alpha]_D^{25} = -46.2°$ ($c = 15.6$, CH_2Cl_2). IR (KBr): ν 2242, 1700 cm^{-1}; ^{1}H NMR: δ 0.63 (dd, $J = 3.3$, 6.8 Hz, 3H), 0.81 (dd, $J = 0.9$, 6.9 Hz, 3H), 0.91 (m, 6H), 1.08 (dd, $J = 2.9$, 6.9 Hz, 6H), 1.47 (m, 2H), 1.69 (d, $J = 11.5$ Hz, 2H), 1.90 (m, 1H), 2.13 (m, 1H), 2.64 (d, $J = 15.7$ Hz, 1H), 2.88 (m, 1H), 3.20 (m, 2H), 3.89 (s, 6H), 4.25 (m, 1H), 4.75 (m, 1H), 6.63 (s 1H), 7.05 (d, $J = 2.4$ Hz, 1H), ^{13}C NMR: δ 16.1, 16.5, 18.9, 20.7, 22.0, 23.6, 26.6, 29.1, 31.5, 34.3, 36.7, 41.3, 41.9, 47.5, 55.9, 56.2, 63.2, 63.4, 111.0, 112.3, 119.8, 122.0, 128.4, 147.2, 149.0, 155.0. Anal. Calcd for $C_{26}H_{30}N_2O_4$: C, 70.56; H, 8.65. Found: C, 70.62; H, 8.70. The X-ray structure (see Supporting Information, Figure S28) revealed this to be a 1:1 mixture of the two diastereomers.

l-Benzyl-2-(*l*-menthoxycarbonyl)-l-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (25c). (*S*)-**19** and benzyl iodide (NaH, DMF, rt) yielded (89%) a white powder, which was recrystallized twice from hexanes as colorless needles. mp 109−111 °C. $[\alpha]_D^{25} = -41.7$ ($c = 7.60$, $CHCl_3$). IR (KBr): ν 2231, 1696 cm^{-1}. ^{1}H NMR: δ 0.97 (m, 12H), 1.13 (m, 1H), 1.54 (m, 2H), 1.72 (d, $J = 11$ Hz, 2H), 2.03 (br s, 1H), 2.22 (q, $J = 13$ Hz, 2H), 3.15 (t, $J = 11$ Hz, 1H), 3.31 (dd, $J = 13$, 19 Hz, 1H), 3.70 (m, 1H), 3.86 (m, 6H), 4.10 (br, 1H), 4.83 (br, 1H), 6.42 (d, $J = 4$ Hz, 1H), 6.59 (dd, $J = 7$, 4 Hz, 2H), 6.94 (br s, 1H), 7.07 (dd, $J = 8$, 14 Hz, 2H), 7.18 (m, 1H). ^{13}C NMR: δ 16.4, 20.8, 22.0, 23.5, 23.6, 26.4, 26.7, 28.0, 31.6, 34.4, 41.4, 41.5, 41.6, 46.8, 47.3, 47.4, 56.0, 56.2, 58.8, 59.1, 110.5, 110.6, 110.8, 120.1, 120.4, 124.2, 127.4, 127.7, 127.8, 128.5, 128.7, 130.9, 133.8, 148.1, 148.2, 149.1, 154.8. Anal. Calcd for $C_{30}H_{38}N_2O_4$: C, 73.44; H, 7.81. Found: C, 73.45; H, 7.85.

1-Methyl-2-(8′-phenyl-*l*-menthoxycarbonyl)-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (26a). 20 and iodomethane (NaH, DMF, rt) afforded a quantitative yield of a yellow oil; flash chromatography using 30% ethyl acetate in hexanes as the eluent yielded a colorless oil. IR (neat): ν 2235, 2254, 1698, 1693 cm^{-1}. ^{1}H NMR: δ 0.85 (d, $J = 7$, 3H), 1.05 (m, 2H), 1.19 (m, 4H), 1.36 (d, $J = 7$ Hz, 3H), 1.48 (m, 1H), 1.70 (m, 2H), 1.87 (d, $J = 7$ Hz, 3H), 1.95 (m, 1H), 2.10 (m, 1H), 2.47 (m, 2.5H), 2.50 (m, 0.5H), 2.88 (m, 0.5H), 3.08 (m, 0.5H), 3.87 (m, 6H), 4.92 (m, 1H), 6.53 (d, $J = 8$ Hz, 1H), 6.98 (d, $J = 8$ Hz, 1H), 7.08 (m, 1H), 7.31 (m, 4H). ^{13}C NMR: δ 21.7, 23.2, 24.5, 26.5, 28.5, 28.7, 29.2, 29.5, 31.3, 34.6, 39.4, 39.6, 39.9, 40.1, 42.3, 50.5, 50.7, 54.5, 55.9, 56.2, 109.9, 110.9, 120.9, 124.8, 125.2, 125.3, 126.33, 126.9,

127.1, 127.8, 127.9, 128.0, 148.4, 149.0, 152.6, 153.7, 153.9. LR EIMS *m/z:* 490.2 (M^+), 475.2 ($M - CH_3)^+$, 464.3 ($M - CN)^+$, 394.2 ($M - C_7H_{12})^+$, 371.2 [$M - C_6H_5C(CH_3)_2]^+$, 276.1 [$M - C_6H_5C(CH_3)_2 - C_7H_8$]$^+$, 261.2 [$M - C_6H_5C(CH_3)_2 - C_7H_9 - CH_3]^+$, 248.1, 217.1, 119.1 {100%, [$(C_6H_5C(CH_3)_2]^+$}, 105.1 $(C_8H_9)^+$, 91.0 $(C_7H_7)^+$. HR EIMS *m/z*: calcd for $C_{30}H_{38}N_2O_4$ (M^+), 490.2832; found, 490.2825 (see Supporting Information, Figure S30). The integration of the two 1-methyl signals at 1.90 and 1.87 ppm in toluene-d_8 was 67:33, respectively (see Supporting Information, Figure S29).

Attempted Alkylation of 2-[(+)-10-Camphorsulfonyl]-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (21). 21 and iodomethane (NaH, DMF, −40 °C for anion formation and rt for alkylation) gave (40%) fine white needles of **27**. mp 148−149 °C. IR (KBr): ν 1609, 1286 cm^{-1}. ^{1}H NMR: δ 2.73 (t, J = 7 Hz, 2H), 3.93 (m, 8H), 6.68 (s, 1H), 7.12 (s, 1H). ^{13}C NMR: δ 24.2, 48.7, 56.2, 56.3, 109.4, 110.6, 114.6, 119.1, 130.0, 145.9, 148.5, 153.1. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 66.64; H, 5.61; N, 12.98.

Alternatively, treatment of **21** alone with NaH/DMF at rt yielded a yellow oil (60%), which was purified by flash chromatography using ethyl acetate and then by recrystallization from ethyl acetate/hexanes, affording colorless crystals of **28**. mp 85−90 °C (lit.[26a] mp 89−91 °C, 90−91 °C[26b]). IR (KBr): ν 1507, 1254 cm^{-1}. ^{1}H NMR: δ 4.02 (s, 6H), 7.05 (s, 1H), 7.18 (s, 1H), 7.49 (d, J = 8 Hz, 1H), 8.37 (d, J = 8 Hz, 1H), 9.03 (s, 1H). ^{13}C NMR: δ 55.5, 55.8, 104.1, 104.9, 118.8, 124.4, 132.1, 144.4, 149.4, 149.9, 152.7.

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Supporting Information Available: General experimental and synthetic procedures (including known starting materials); pertinent ^{1}H NMR spectra, HPLC traces, and X-ray structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) (a) Spath, E.; Polgar, N. *Monatsh. Chem.* **1929**, *51*, 190−204. (b) Birch, A. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, *19*, 2185−2190.