Synthesis of Optically Active Nicotinoids

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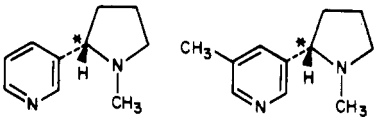
A novel approach to the synthesis of optically active nicotinoids has been developed by utilizing commercial L-proline or L-prolinol as the chiral source. The key steps involve condensation of the anion of (*S*)-(−)-1-methyl-2-(cyanomethyl)pyrrolidine with the appropriately substituted 3-ethoxyacrolein, followed by cyclization of the 1,2-adduct to the 2-bromonicotinoid. In this fashion, the first optically active synthesis of (*S*)-(−)-nicotine was achieved. As a demonstration of the scope of this procedure, (*S*)-(−)-5-methylnicotine was also prepared. The process provides nicotinoids of 56% ee. The site of partial racemization has been investigated and is discussed.

For many years, there has been significant interest in the pharmacological mode of action of nicotine.[1a,b] The classical approach toward this goal relies on the preparation of a variety of nicotine analogues for pharmacological study.[1c,d] Recent efforts have also centered around the definition and characterization of nicotine peripheral and central nervous system receptors by utilizing (−)-nicotine and (+)-nicotine, e.g., to determine binding stereospecificity.[1e-g] As a consequence, we have been particularly interested in the preparation of optically active nicotine analogues.

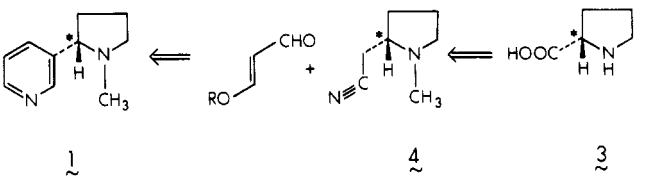
Although a number of methods are available for the preparation of nicotine,[2] its metabolites,[3] and several of its analogues,[1d,4] there exist few approaches to optically active nicotinoids. In particular, no formal asymmetric synthesis has been disclosed. We now report an initial solution to this problem, namely, the syntheses of (*S*)-(−)-nicotine (**1**) and (*S*)-(−)-5-methylnicotine (**2**).



1 **2**

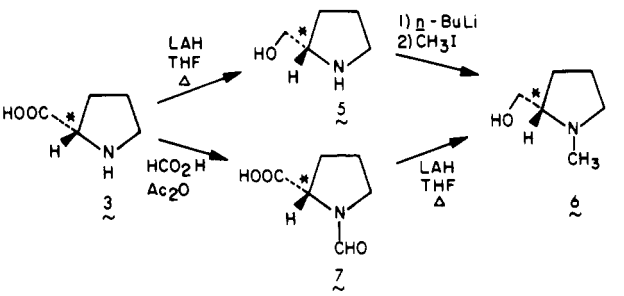
Previous preparations of optically active nicotine analogues have utilized (−)-nicotine as the original starting material. Haglid[4a] developed a low-yield preparation of a structurally isomeric mixture of optically active nicotinoids by the reaction of (−)-nicotine with excess methyllithium. Leete[4d] also utilized this procedure to obtain (−)-4-methylnicotine. Sanders[4b] prepared optically active, pyrrolidine-functionalized derivatives from (−)-cotinine. In all of these methods, the flexibility of pyridine substitution is limited and one is restricted to the preparation of (*S*)-nicotinoids, since (+)-nicotine is not readily available. All other literature syntheses of analogues have been racemic, involving construction of the pyrrolidine ring, following the preparation of the appropriate pyridine ring. None of these methods allows for extension to optically active nicotinoids via asymmetric synthesis.

Scheme I



1 **4** **3**

Scheme II



3 **5** **7** **6**

Our methodology relies on the use of an optically active starting material as the pyrrolidine source onto which is constructed the pyridine ring. The readily available amino acid L-proline (**3**)[5] was chosen as the chiral source. As shown in Scheme I, we envisioned side-chain manipulation of the carboxyl functionality of L-proline (**3**) to the requisite carbon skeleton for further transformation to (−)-nicotine (**1**). Pyridine-substituted nicotine analogues could also be prepared by this process.

The preparation of target intermediate **4** (Scheme I) was undertaken in the following fashion. Reduction of L-proline (**3**) with $LiAlH_4$ provided L-prolinol (**5**)[6] (Scheme II). Formation of the dianion of L-prolinol (**5**) with 2 equiv of *n*-butyllithium followed by treatment with 1 equiv of methyl iodide afforded (−)-1-methyl-2-(hydroxymethyl)-pyrrolidine [**6**; $[\alpha]^{20}_D$ −51° (methanol)][7,8] in 52% yield. An alternate procedure providing **6** was also developed. (−)-1-Formylproline (**7**) was prepared from L-proline, formic acid, and acetic anhydride[9] and then reduced with $LiAlH_4$ to give **6** in 57% overall yield from L-proline.[8]

(1) (a) Barlow, R. B. "Introduction to Chemical Pharmacology", 2nd ed.; Methuen & Co., Ltd.: London, 1964. (b) Ryall, R. W. In "Neuropoisons, Their Pathological Actions"; Simpson, L. L., Curtis, D. R., Eds.; Plenum Press: New York, 1974; Vol. II. (c) Barlow, R. B.; Hamilton, J. T. *Br. J. Pharmacol.* **1962**, *18*, 510. (d) Secor, H. V.; Edwards, W. B., III *J. Org. Chem.* **1979**, *44*, 3136. (e) Aceto, M. C.; et al. *J. Med. Chem.* **1979**, *22*, 174. (f) Abood, L. G.; Reynolds, D. T.; Bidlack, J. M. *Life Sci.* **1980**, *27*, 1307. (g) Romano, C.; Goldstein, A. *Science* **1980**, *210*, 647.

(2) Nakane, M.; Hutchinson, C. R. *J. Org. Chem.* **1978**, *43*, 3922 and references therein.

(3) (a) Bowman, E. R.; McKennis, H., Jr. *Biochem. Prep.* **1963**, *10*, 36. (b) Nguyen, T.-L. Ph.D. Dissertation, Dept. of Pharmaceutical Chemistry, University of California, San Francisco, 1977. (c) Maeda, S.; Matsushita, H.; Mikami, Y.; Kisaki, T. *Agric. Biol. Chem.* **1978**, *42*, 2177. (d) Tsujino, Y.; Matsushita, H.; Saito, A.; Kato, K.; Kisaki, T.; Naguchi, M. *Ibid.* **1979**, *43*, 871.

(4) (a) Haglid, F. *Acta. Chem. Scand.* **1967**, *21*, 329. (b) Sanders, E. B.; DeBardeleben, J. F.; Osdene, T. S. *J. Org. Chem.* **1975**, *40*, 2848. (c) Sanders, E. B.; Secor, H. V.; Seeman, J. I. *Ibid.* **1978**, *43*, 324. (d) Leete, E.; Leete, S. A. S. *Ibid.* **1978**, *43*, 2122. (e) Catka, T. E.; Leete, E. *Ibid* **1978**, *43*, 2125. (f) Secor, H. V.; Chavdarian, C. G.; Seeman, J. I. *Tetrahedron Lett.* **1981**, 3151.

(5) Available from the Aldrich Chemical Co.

(6) Kostyanovsky, R. G.; Gella, I. M.; Markov, V. I.; Samojlova, Z. E. *Tetrahedron* **1974**, *30*, 39. L-Prolinol is also available commercially,[5] and the commercially available material can be used as the starting point for the synthesis.

(7) For a preparation of the racemic compound, see: Blicke, F. F.; Lu, C.-J. *J. Am. Chem. Soc.* **1955**, *77*, 29.

(8) For a detailed report on these approaches, see: Chavdarian, C. G.; Sanders, E. B. *Org. Prep. Proced. Int.* **1981**, *13*, 389.

(9) Sheehan, J. C.; Yang, D.-D. *J. Am. Chem. Soc.* **1958**, *80*, 1154.

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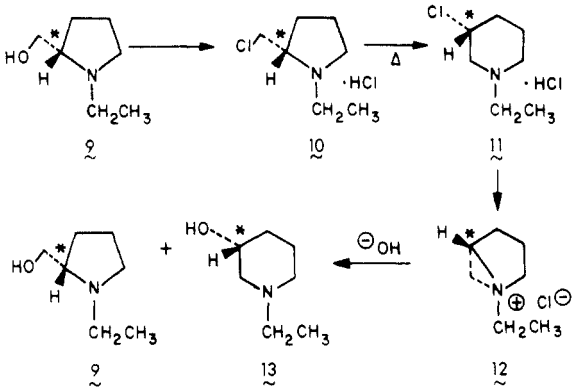
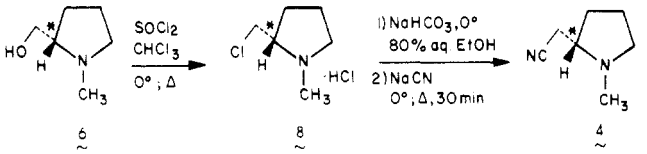
Scheme III



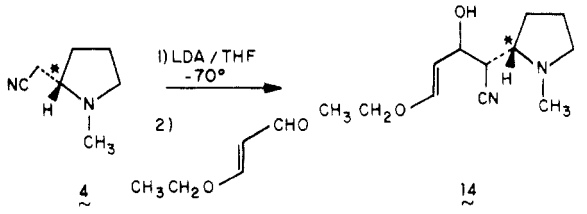
Treatment of **6** with thionyl chloride in chloroform afforded an 88% yield of (−)-1-methyl-2-(chloromethyl)-pyrrolidine hydrochloride [**8**; $[\alpha]^{20}_D$ −6° (methanol)].[10,11]



Neutralization of **8** with aqueous sodium bicarbonate followed by displacement of the chlorine with sodium cyanide in aqueous ethanol resulted in a 51% yield of the target compound, (−)-1-methyl-2-(cyanomethyl)pyrrolidine [**4**; $[\alpha]^{20}_D$ −32.5° (methanol)].[10]

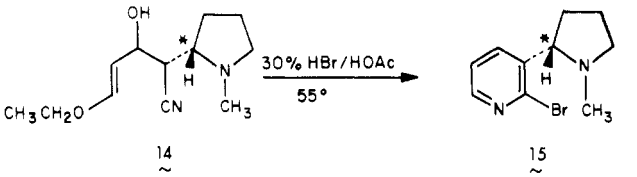
That **4** is formed from **8** with retention is supported by the work of Hammer,[11] who observed that heating (*S*)-1-ethyl-2-(chloromethyl)pyrrolidine hydrochloride (**10**), prepared from (*S*)-1-ethyl-2-(hydroxymethyl)pyrrolidine (**9**), resulted in double internal displacement (with inversion) to yield (*R*)-1-ethyl-3-chloropiperidine hydrochloride (**11**, Scheme III). Neutralization of the acid salt and treatment with hydroxide resulted in displacement of the intermediate, configurationally inverted aziridinium ion **12** to provide a mixture of **9** with 98.5% optical purity and (*R*)-1-ethyl-3-hydroxypiperidine (**13**).

The cyanomethyl moiety of pyrrolidine **4** provides the necessary "handle" for construction of the pyridine ring. For the synthesis of (−)-nicotine, 3-ethoxyacrolein[12] was utilized to complete the carbon skeleton of the pyridine ring. Treatment of **4** with lithium diisopropylamide in THF at −70 °C, followed by the addition of freshly prepared 3-ethoxyacrolein to the resultant anion, afforded hydroxy compound **14** in nearly 40% yield (as a mixture

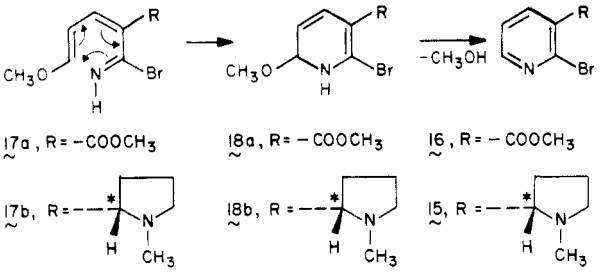


of several stereoisomers). (The stereoselectivity of this condensation and the formation of two additional chiral centers is not pertinent to this work; as demonstrated in the following step, these two chiral centers are eliminated.)

Reaction of **14** with 30–32% hydrobromic acid/acetic acid at 55 °C for 1 h effected ring closure to (−)-2-bromonicotine [**15**; $[\alpha]^{20}_D$ −47° (methylene chloride)] in 46% crude yield.

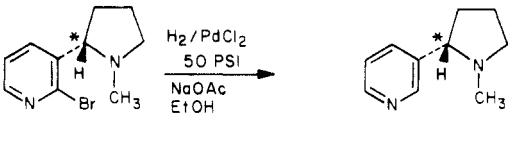


Bryson[13] had cyclized methyl 2-cyano-5-methoxy-2,5-pentadienoate under the same conditions to afford methyl 2-bromonicotinate (**16**). On the basis of this result, Bryson postulated that the ester moiety in the pentadienoate was apparently necessary to promote cyclization. The HBr would initially add to the nitrile functionality to afford the intermediate imino bromide **17a**. The imino bromide could then undergo an intramolecular Michael-like (1,6-addition) reaction followed by loss of methanol to yield methyl 2-bromonicotinate (**16**). As demonstrated, however, our results (**14** → **15**) clearly speak against the necessity of an ester functionality as postulated by Bryson. An alternate mechanism for the Bryson cyclization might simply be an electrocyclic process from imino bromide **17a** to **18a** which



can then lose methanol to afford **16**. This mechanism may also operate in our case. Loss of water from the imino bromide of **14** would yield triene **17b** which could then undergo cyclization to **18b** followed by loss of methanol to yield **15**.

With (−)-2-bromonicotine (**15**) in hand, removal of the halogen would complete the synthesis. Crude **15** was catalytically dehalogenated (H_2, $PdCl_2$, NaOAc, ethanol, at 50 psi) to afford (*S*)-(−)-nicotine [**1**; $[\alpha]^{20}_D$ −41° (methylene chloride)] in a yield of 55%. Based on the specific



rotation, the optical purity of (*S*)-(−)-nicotine obtained by this route is 24% (the $[\alpha]^{20}_D$ of the pure enantiomer is −170° in methylene chloride).

Although this procedure results in optically impure **1**, it nonetheless constitutes the first optically active synthesis of (*S*)-(−)-nicotine. In order to demonstrate the consistency and scope of this approach and its utility in preparing analogues, an analogous preparation of (*S*)-(−)-5-methylnicotine (**2**) was also undertaken.

Generation of the anion of **4**, as before, followed by the addition of 2-methyl-3-ethoxyacrolein afforded condensed product **19** (Scheme IV) in 56% yield. (Of further interest

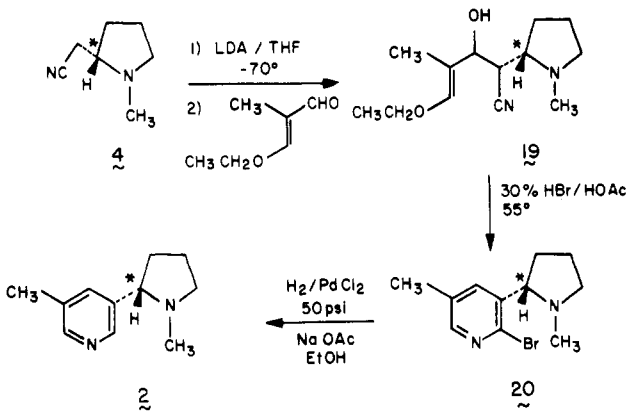
(10) For a preparation of the racemic compound, see: Brain, E. G.; Doyle, F. P.; Mehta, M. D. *J. Chem. Soc.* **1961**, 633.

(11) Hammer, C. F.; Heller, S. R.; Craig, J. H. *Tetrahedron* **1972**, *28*, 239.

(12) (a) Kalina, N. N.; Klimko, V. T.; Protopopova, T.-V.; Skoldinor, A. P. *Zh. Obshch. Khim.* **1962**, *32*, 2146. (b) Klimko, V. T.; Protopopova, T.-V.; Smirnova, N. V.; Skoldinov, A. P. *Ibid.* **1962**, *32*, 2961.

(13) Bryson, T. A.; Wisowaty, J. C.; Dunlap, R. B.; Fisher, R. R.; Ellis, P. D. *J. Org. Chem.* **1974**, *39*, 3436.

Scheme IV



is the fact that the presence of a methyl group at the 2-position of the acrolein resulted in a dramatic increase in stereoselectivity[14] and provided **19** greater than 90% isomerically pure based on ^{1}H NMR; however, as stated previously, a stereoselective condensation is not of importance to this synthesis.) Ring closure with 30–32% hydrobromic acid/acetic acid led to a 64% crude yield of (−)-5-methyl-2-bromonicotine [**20**; $[\alpha]^{20}_D$ −22° (methylene chloride)]. Crude **20** was catalytically dehalogenated (H_2, $PdCl_2$, NaOAc, EtOH, at 50 psi) to afford (*S*)-(−)-5-methylnicotine (**2**) in 52% yield [$[\alpha]^{20}_D$ −41 °C (methylene chloride)].

Contrary to (*S*)-(−)-nicotine (**1**), the specific rotation of optically pure (*S*)-(−)-5-methylnicotine (**2**) is unknown. We found that the use of ^{1}H NMR and a chiral lanthanide shift reagent resulted in the successful resolution of a racemic mixture of 5-methylnicotine.[15] When tris[3-(trifluoroacetyl)-*d*-camphorato]europium[16] (Eu(tfac)$_3$) was utilized with synthetic **2**, the enantiomeric *l*/*d* ratio was found to be 62:38 (24% ee), identical with the value for synthetic **1**. Rather fortuitously, the resonances of the pyridine proton at C-6 and the protons of both methyl groups of 5-methylnicotine underwent resolution to the individual enantiomers, greatly simplifying the determination of optical purity.[17] With this question answered, we turned to the determination of the site of partial racemization in the synthetic sequence.

(−)-1-Methyl-2-(hydroxymethyl)pyrrolidine (**6**) should be optically pure due to the fact that two different synthetic routes provide **6** with the same specific rotation. Further proof of optical purity was obtained by subjecting **6** and its racemic counterpart, (*R*,*S*)-1-methyl-2-(hydroxymethyl)pyrrolidine (prepared by the same route by starting with DL-proline[5]), to ^{1}H NMR chiral lanthanide shift analysis. The use of Eu(tfac)$_3$ afforded no resolution of even the racemic material. However, utilization of tris[3-(heptafluorobutyryl)-*d*-camphorato]europium[16] (Eu(hfbc)$_3$) proved successful; the *N*-methyl resonance of the racemic mixture resolved into two singlets. Optically active **6** underwent no such resolution. (*S*)-(−)-1-Methyl-2-(cyanomethyl)pyrrolidine (**4**) and (*R*,*S*)-1-methyl-2-(cyanomethyl)pyrrolidine were also analyzed by chiral lanthanide shift analysis. The use of Eu(tfac)$_3$ resulted in excessive peak broadening and provided no resolution. Utilization of Eu(hfbc)$_3$ proved somewhat successful. The racemic mixture underwent resolution at the *N*-methyl resonance whereas optically active **4** did not. However, due to peak broadening it was difficult to determine whether optically active **4** was indeed optically pure or whether a minor enantiomer was present but obscured by the broadness of the resonance.

At the completion of this work, we noted a report by Shioiri and co-workers[18] concerning a one-pot conversion of primary alcohols to nitriles. One of the examples involved the conversion of (*S*)-(−)-1-methyl-2-(hydroxymethyl)pyrrolidine (**6**) to (*S*)-(−)-1-methyl-2-(cyanomethyl)pyrroldine (**4**) by the use of a multicomponent reaction system consisting of (*n*-Bu)$_3$P, CCl_4, KCN, 18-crown-6, and acetonitrile. Shioiri reported a yield of 81% and an $[\alpha]^{20}_D$ −70.7° (*c* 1.0, methanol). The specific rotation of **4** is substantially greater than that obtained by our process: $[\alpha]^{20}_D$ −32.5° (*c* 2.57, methanol). Shioiri has stated that the preparation of **4** "proceeds without loss of optical activity". We have repeated and confirmed Shioiri's synthesis of **4**. Compound **4** was obtained in a yield of 62% with $[\alpha]^{20}_D$ −73.8° (*c* 0.347, methanol). The slightly greater specific rotation that we observed (compared to −70.7°) may be due to the fact that we utilized a highly pure sample obtained by gas chromatographic trapping.

As a consequence of the above, it is clear that the chlorination–cyanation sequence (thionyl chloride–sodium cyanide) proceeds with only partial retention of configuration, in contrast to the chlorination–hydroxylation procedure of Hammer[11] cited earlier.

In order to demonstrate that nicotinoids of higher optical purity could be prepared, we undertook the synthesis of **2** from Shioiri's **4** and obtained **2** with $[\alpha]^{20}_D$ −90° (*c* 0.508, methylene chloride); chiral lanthanide shift analysis of **2** with Eu(tfac)$_3$ revealed an enantiomeric ratio of 78:22, i.e., 56% ee.

As we have shown, the optical yield of the nicotinoid can be significantly improved by the use of Shioiri's compound **4**. However, partial racemization within the synthetic route is still prevalent.

We also addressed the possibility of partial racemization during the condensation step, e.g., **4** to **19**. It is conceivable that the anion of **4** could potentially induce ring opening through β elimination of the amino moiety to afford an open-chain ϵ-amino-α,β-unsaturated nitrile. This intermediate could in turn undergo an intramolecular Michael reaction back to racemized **4**. To test this possibility, we treated optically active **4** with lithium diisopropylamide in THF at −70 °C. After the reaction mixture was warmed to 0 °C and quenched with water, **4** was recovered in good yield without the loss of any optical activity. Therefore, the condensation step does not appear to lead to any racemization.

On the basis of the preceding information, partial racemization appears to occur during the cyclization process. The cyclization of **14** to **15** and **19** to **20** are effected in a strong acidic medium. The intermediate triene could undergo double bond isomerization toward the chiral

(14) This observation should be of interest in light of recent studies in the area of stereoselective aldol condensations; see (a) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. (b) Buse, C. T.; Heathcock, C. H. *Ibid.* **1977**, *99*, 8109. (c) Evans, D. A.; Vogel, E.; Nelson, J. V. *Ibid.* **1979**, *101*, 6120. (d) Heathcock, C. H.; Pirrung, M. C.; Buse, C. T.; Hagen, J. P.; Young, S. D.; Sohn, J. E. *Ibid.* **1979**, *101*, 7077.

(15) For the preparation of racemic 5-methylnicotine, see: Seeman, J. I.; Secor, H. V.; Chavdarian, C. G.; Sanders, E. B.; Bassfield, R. L.; Whidby, J. F. *J. Org. Chem.* **1981**, *46*, 3040.

(16) Available from the Norell Chemical Co., Inc.; all ^{1}H NMR analyses were performed in $CDCl_3$ with a Bruker WP-80.

(17) As a check on the NMR method of resolution, the synthetic (*S*)-(−)-nicotine (**1**) was also treated with Eu(tfac)$_3$. Resolution was successful, and a value of 24% ee. was obtained. This is identical with the value obtained from the specific rotation of synthetic **1** and the known specific rotation of optically pure **1**.

(18) Mizuno, A.; Hamada, Y.; Shioiri, T. *Synthesis* **1980**, 1007.

center of the pyrrolidine ring, resulting in racemization. When the conversion of **19** to **20** was carried out at room temperature (in contrast to 50–60 °C), a slightly lower yield resulted (58%) but without a change in the degree of racemization (catalytic dehalogenation of this product afforded **2** with the same specific rotation). It is apparent that rather substantially different conditions may need to be developed in order to achieve cyclization without concurrent partial racemization.

In conclusion, we have developed a general route to functionalized nicotinoids which provides a distinct alternative to literature approaches. The synthesis is brief and is the first formal optically active synthesis of (*S*)-(−)-nicotine. Although the optical purity of synthetic (*S*)-(−)-nicotine and (*S*)-(−)-5-methylnicotine is not high, some optical retention is maintained. Nicotinoids approaching 56% ee are attainable by this process.

Experimental Section

Melting points and boiling points are uncorrected. The ^{1}H NMR spectra were determined on a Bruker WP-80 or a Varian XL-100 spectrometer. IR spectra were determined on a Perkin-Elmer 735B infrared spectrophotometer. Low-resolution mass spectra were obtained on a Finnigan 3300 mass spectrometer. Microanalyses were performed by Galbraith Laboratories, Inc.

(*S*)-(−)-1-Methyl-2-(hydroxymethyl)pyrrolidine (6). This compound was prepared by either of two methods reported elsewhere.[8] L-Proline and L-prolinol were obtained from Aldrich.

(*S*)-(−)-1-Methyl-2-(chloromethyl)pyrrolidine Hydrochloride (8). To a solution of 12.0 g (0.1043 mol) of **6** in 60 mL of ethanol-free chloroform under nitrogen at 0 °C was added a solution of 9.53 mL (0.1304 mol) of thionyl chloride in 30 mL of ethanol-free chloroform over 10 min. The resultant clear, brown solution was stirred at room temperature for 30 min and refluxed for 30 min. After cooling, the dark solution was evaporated to provide a tan, solid residue. The residue was dissolved in absolute ethanol, and excess ether was added, resulting in the crystallization of a white solid. The solid was suction filtered under nitrogen and dried in vacuo to afford 14.30 g (88%) of **8**: mp 154–156 °C (racemic **8**: lit.[7] mp 151–153 °C); $[\alpha]^{20}_D$ −6° (*c* 2.35, methanol); ^{1}H NMR δ (D_2O) 3.5–4.15 (m, 4), 3.08–3.48 (m, 1), 3.0 (s, 3), 1.75–2.58 (m, 4).

(*S*)-(−)-1-Methyl-2-(cyanomethyl)pyrrolidine (4). To a solution of 7.0 g (0.045 mol) of *S* in 35 mL of 80% aqueous ethanol at 0 °C, was added, in portions, a solution of 3.81 g (0.045 mol) of sodium bicarbonate in 50 mL of water. The mixture was stirred at 0 °C for 15 min, followed by the addition of a solution of 2.52 g (0.052 mol) of sodium cyanide in 65 mL of 80% aqueous ethanol. This mixture was refluxed for 30 min. The resultant solution was cooled, evaorated to a small volume, and extracted with ether (2 × 25 mL). The combined ethereal layer was dried with magnesium sulfate and evaporated to a clear, brown oil. Bulb-to-bulb distillation [oven temperature 40–55 °C (0.25 torr)] yielded 2.62 g (51%) of **4**, a clear, colorless, mobile oil: $[\alpha]^{20}_D$ −32.5° (*c* 2.57, methanol); picrate, mp 175–178 °C; ^{1}H NMR ($CDCl_3$) δ 2.93–3.25 (m, 1), 2.48 (s (br with fine coupling), 2), 2.38 (s, 3), 1.5–2.33 (m, 6); IR (film) 2225 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}N_5O_7$ (picrate): C, 44.19; H, 4.28; N, 19.83. Found: C, 44.00; H, 4.31; N, 19.61.

Compound **4** was also prepared directly from **6** by the method of Shioiri.[18] Optical rotation of **4**: $[\alpha]^{20}_D$ −73.8° (*c* 0.347, methanol).

5-Ethoxy-3-hydroxy-2-(1-methyl-2-pyrrolidinyl)-4-pentenenitrile (14). To a solution of 2.43 mL (1.76 g, 0.0174 mol) of diisopropylamine, in 50 mL of dry tetrahyrofuran under nitrogen at −20 °C was added 7.0 mL (0.016 mmol) of 2.3 M *n*-butyllithium in hexane such that the temperature did not rise above −10 °C. After being stirred below −20 °C for 15 min, the solution was cooled to −70 °C. To the solution of lithium diisopropylamide was added a solution of 1.723 g (0.0139 mol) of **4** in 10 mL of dry tetrahydrofuran over 10 min. The residue was washed in with an additional 1 mL of tetrahydrofuran, and the resultant cloudy mixture was stirred for 30 min at −70 °C. To this mixture was added a solution of 1.391 g (0.0139 mol) of 3-ethoxyacrolein[12] in 10 mL of dry tetrahydrofuran over 10 min. The residue was washed in with an additional 1 mL of tetrahydrofuran. The resultant clear solution was stirred at −70 °C for 5 min, 0 °C for 30 min, and room temperature for 2 h. The yellow solution was quenched with 50 mL of water and extracted with ether (3 × 50 mL). The ethereal layers were combined, dried with magnesium sulfate, and evaporated to a red, viscous oil. Bulb-to-bulb distillation [oven temperature 115–135 °C (0.15 torr)] afforded 1.212 g (39%) of **14**, a viscous, yellow oil: ^{1}H NMR revealed a mixture of several stereoisomers ($CDCl_3$) δ 1.3 and 1.34 (2 t, J = 7 Hz, 3), 1.5–2.2 (m, 5), 2.26, 2.38, 2.43, 2.48, 2.54 (5 s, 3), 2.5–3.3 (m, 3), 3.8 and 3.95 (2 q, J = 7 Hz, 2), 4.25–4.58 (m, 1, α to OH), 4.73–5.13 (m, 1, vinyl), 4.88 (br, OH, variable, 1), 6.5–7.0 (m, 1, vinyl).

(*S*)-(−)-2-Bromonicotine (15). To a solution of 1.0 g (4.46 mmol) of **14** in 12 mL of glacial acetic acid under nitrogen at 40 °C was added, dropwise, 24 mL of 30–32% hydrobromic acid/acetic acid while the temperature was maintained at 40–45 °C. The red-brown solution was then heated at 55–60 °C for 1 h. After being allowed to cool, the solution was poured into 100 mL of ice-cold water and carefully basified with excess sodium carbonate. The aqueous mixture was extracted with methylene chloride (3 × 100 mL). The methylene chloride solution was dried with magnesium sulfate and evaporated to 0.493 g (46%) of crude **22**, a viscous, dark-red oil: $[\alpha]^{20}_D$ −47° (*c* 0.559, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 8.26 (dd, 1, J = 4.7, 2 Hz), 7.94 (dd, 1 J = 8, 2 Hz), 7.30 (dd, 1 J = 8, 4.7 Hz), 3.55 (t, 1, J = 8 Hz), 3.26 (m, 1), 1.25–2.73 (m, 5), 2.25 (s, 3). The crude material was utilized directly in the next step.

(*S*)-(−)-Nicotine (1). A mixture of 0.451 g (1.87 mmol) of crude **15**, 0.133 g (0.4 equiv, 0.75 mmol) of palladium chloride, 0.615 g (4 equiv, 7.5 mmol) of sodium acetate, and 10 mL of absolute ethanol was shaken under hydrogen at 50 psi for 10.5 h. The mixture was filtered through Celite and evaporated to a small volume which was basified and extracted with methylene chloride. The methylene chloride solution was dried with magnesium sulfate and evaporated to a mobile, red-brown oil. Bulb-to-bulb distillation [oven temperature 55–65 °C (0.15 torr)] afforded 0.234 g (55%) of **1**, a clear, colorless oil: $[\alpha]^{20}_D$ −41° (*c* 0.561, methylene chloride); identical by ^{1}H NMR, GC, and TLC to natural (*S*)-(−)-nicotine.

5-Ethoxy-3-hydroxy-4-methyl-2-(1-methyl-2-pyrrolidinyl)-4-pentenenitrile (19). To a solution of 2.54 mL (1.83 g, 0.0181 mol) of diisopropylamine in 50 mL of dry tetrahydrofuran under nitrogen at −20 °C was added 7.26 mL (0.0167 mol) of 2.3 M *n*-butyllithium in hexane such that the temperature did not rise above −10 °C. After stirring below −20 °C for 15 min, the solution was cooled to −70 °C. To the solution of lithium diisopropylamide was added a solution of 1.8 g 0.0145 mol) of **4** in 10 mL of dry tetrahydrofuran over 10 min. The residue was washed in with an additional 1 mL of tetrahydrofuran, and the resultant white, cloudy mixture was stirred for 20 min at −70 °C. To this mixture was added a solution of 1.655 g (0.0145 mol) of freshly distilled 3-ethoxy-2-methylacrolein in 10 mL of dry tetrahydrofuran over 10 min. The residue was washed in with an additional 1 mL of tetrahydrofuran. The resultant clear, nearly colorless solution was stirred at −70 °C for 5 min, 0 °C for 30 min, and room temperature for 2 h. The yellow solution was quenched with 30 mL of water and extracted with 50 mL of ether and methylene chloride (2 × 50 mL). The organic layers were combined, dried with magnesium sulfate, and evaporated to a dark yellow, viscous oil. Two bulb-to-bulb distillations [oven temperature 115–130 °C (0.05 torr)] removed the forerun of 3-ethoxy-2-methylacrolein and provided 1.94 g (56%) of **19**, a viscous, yellow oil; $[\alpha]^{20}_D$ −7° (*c* 0.56, methylene chloride); ^{1}H NMR ($CDCl_3$) δ 6.31 (m, 1, J = 1 Hz), 4.25 (br d, 1, J = 4 Hz), 3.85 (q, 2, J = 7 Hz), 3.13 (m, 1), 2.63–2.90 (m, 2, includes variable OH), 2.53 (s, 3), 1.63–2.5 (m, 5), 1.6 (d, 3, J = 1 Hz), 1.27 (t, 3, J = 7 Hz); EI mass spectrum, m/e 238 (M^+), 220 ($M^+ - H_2O$), 209 ($M^+ - CH_2CH_3$), 84 (1-methylpyrrolidinyl).

(*S*)-(−)-1-Methyl-2-(cyanomethyl)pyrrolidine (**4**) of high optical activity, prepared by the method of Shioiri,[18] was also utilized as above to provide **19**: $[\alpha]^{20}_D$ −20° (1.171, methylene chloride).

(*S*)-(−)-5-Methyl-2-bromonicotine (20). To a solution of 1.78 g (7.5 mmol) of **19** in 20 mL of glacial acetic acid under nitrogen at 40 °C was added, dropwise, 40 mL of 30–32% hydrobromic acid/acetic acid while the temperature was maintained at 40–45

°C. The red-brown solution was then heated at 55 °C for 1 h. After being cooled, the solution was poured into 150 mL of ice-cold water and carefully basified with excess sodium carbonate. The aqueous mixture was extracted with methylene chloride (3 × 100 mL). The methylene chloride solution was dried with magnesium sulfate and evaporated to give 1.215 g (64%) of crude **20**, a viscous, red-brown oil: $[\alpha]^{20}_D$ (*c* 0.413, methylene chloride); picrate, mp 187–192 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, 1, *J* = 3 Hz), 7.71 (d, 1, *J* = 3 Hz), 3.51 (t, 1, *J* = 8 Hz), 3.20 (m, 1), 1.25–2.63 (m, 5), 2.31 (s, 3), 2.24 (s, 3); EI mass spectrum, *m/e* 256, 254 (M^+), 84 (1-methylpyrrolidinyl). The crude material was utilized directly in the next step.

Anal. Calcd. for $C_{17}H_{18}BrN_5O_7$ (picrate): C, 42.16, H, 3.72; N, 14.47. Found: C, 42.64; H, 3.87; N, 14.66.

Compound **19**, prepared from Shioiri's compound **4**,[18] was also converted as above to **20**; $[\alpha]^{20}_D$ −66° (*c* 0.435, methylene chloride).

(*S*)-(−)-5-Methylnicotine (2). A mixture of 1.177 g (4.62 mmol) of crude **20**, 0.327 g (0.4 equiv, 1.85 mmol) of palladium chloride, 1.52 g (4 equiv, 18.5 mmol) of sodium acetate, and 25 mL of absolute ethanol was shaken under hydrogen at 50 psi in a Parr apparatus for 8 h. The mixture was filtered through Celite and evaporated to a small volume which was basified with 15 mL of 10% aqueous sodium hydroxide. The aqueous mixture was extracted with methylene chloride (3 × 25 mL). The combined methylene chloride solution was dried with magnesium sulfate and evaporated to a mobile, red-brown oil. Bulb-to-bulb distillation of the oil [oven temperature 70–90 °C (0.15 torr)] yielded 0.421 g (52%) of **2**, a clear, colorless oil: $[\alpha]^{20}_D$ −41° (*c* 0.504, methylene chloride); dipicrate, mp 202–205 °C; ^{1}H NMR ($CDCl_3$) δ 8.35, (br s, 1), 8.33 (br s, 1), 7.53 (s (v br, approximating a t), 1), 3.13 (m, 1), 3.06 (t, *J* = 6.5 Hz, 1), 2.34 (s, 3), 2.19 (s, 3), 1.5–2.5 (m, 5); EI mass spectrum, *m/e* 176 (M^+), 84 (1-methylpyrrolidinyl).

Nicotinoid **2** was also prepared by the same sequence starting with Shioiri's compound **4**.[18] Optical rotation of **2**: $[\alpha]^{20}_D$ −90° (*c* 0.5075, methylene chloride).

Anal. Calcd for $C_{23}H_{22}N_8O_{14}$ (dipicrate): C, 43.53; H, 3.47; N, 17.67. Found: C, 43.27; H, 3.55, N, 17.38.

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Registry No. 1, 54-11-5; 2, 77629-31-3; 2 dipicrate, 80294-08-2; 4, 67824-39-9; 4 picrate, 80294-09-3; 6, 34381-71-0; 8, 67824-38-8; 14, 80301-18-4; 15, 80294-10-6; 19, 80294-11-7; 20, 80294-12-8; 20 picrate, 80294-13-9; 3-ethoxyacrolein, 19060-08-3; 3-ethoxy-2-methylacrolein, 42588-57-8.

Nitrones. 6.[1] Reactions of Nitrones with Cyclic Phosphonates. Influence of the Phosphonate Ring Size upon the Course of the Reaction[2]

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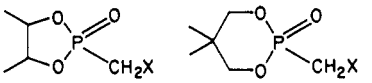
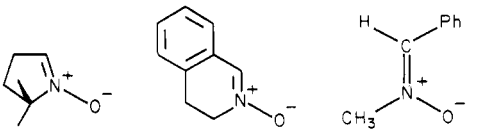
Nitrones, 5,5-dimethyl-Δ^1-pyrroline *N*-oxide (**5**), and 3,4-dihydroisoquinoline *N*-oxide (**6**) were reacted with the five-membered cyclic phosphonates 2-[(ethoxycarbonyl)methyl]-2-oxo-4,5-dimethyl-1,3,2-dioxaphospholane (**1**) and 2-(cyanomethyl)-2-oxo-4,5-dimethyl-1,3,2-dioxaphospholane (**2**) and with the six-membered cyclic phosphonates 2-[(ethoxycarbonyl)methyl]-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (**3**) and 2-(cyanomethyl)-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (**4**). The reactions of the five-membered phosphonates gave aziridines as products, except that of **6** and **2**. The reactions of the six-membered phosphonates gave exclusively or predominantly enamines. The reactions of *C*-phenyl-*N*-methylnitrone (**7**) with **2** gave only *trans*-1-methyl-2-cyano-3-phenylaziridine (**22**). Cyclic phosphates 2-hydroxy-2-oxo-4,5-dimethyl-1,3,2-dioxaphospholane (**20**) and 2-hydroxy-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (**21**) were isolated as byproducts from the reactions of the corresponding phosphonates.

Previously, we reported that the aziridines formed in the reactions of nitrones with phosphonates or phosphine oxides are exclusively of trans stereochemistry.[1-5] This appears to be reminiscent of the phosphonate or phosphine oxide modification of the Wittig reaction,[6] which also leads predominantly to trans products (olefins).[7] Consequently, some time ago we expressed the assumption[5] that, similarly to the olefin synthesis, the stereoselectivity of the aziridine formation is a result of thermodynamic control upon the reversible formation and interconversion of the two possible diastereoisomeric erythro and threo reaction intermediates. Recently we succeeded in changing the steric course of the phosphonate modification of the Wittig reaction by the use of cyclic phosphonates (**1–4**), achieving



1, X = CO_2Et 3, X = CO_2Et
2, X = CN 4, X = CN

in some cases predominant formation of cis olefins.[8] Consequently, it was of interest to examine the reactions of representative nitrones with our cyclic phosphonates. In this paper we describe the results obtained from the reactions of the cyclic phosphonates with the representative nitrones 5,5-dimethyl-Δ^1-pyrroline *N*-oxide (**5**), 3,4-dihydroisoquinoline *N*-oxide (**6**), and *C*-phenyl-*N*-methylnitrone (**7**).



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