JOC Article

Synthesis of Chiral Pilocarpine Analogues via a C-8 Ketone Intermediate

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The synthesis of a chiral pilocarpine analogue **3** in which the lactone ring is replaced by an oxazolidinone and the bridging methylene group is in the ketone oxidation state has been accomplished. The utility of this compound as a key intermediate for the preparation of more complex structures was demonstrated by its reduction to two alcohol epimers and its reaction with a methylene ylide.

Pilocarpine (**1a**, Figure 1), an alkaloid first isolated over 100 years ago, is currently used for the treatment of glaucoma and xerostomia (salivary gland dysfunction). Recently there has been renewed interest in the therapeutic utility of this type of muscarinic agonist, particularly those active in the central nervous system.[1] For example, because of its potential for the treatment of Alzheimer's disease, pilocarpine thiolactone (**1b**) was developed as a clinical candidate.[2] A cyclic carbamate analogue (**2**) of pilocarpine has been prepared using histidine as the chiral educt.[3] Biological evaluation of **2** showed it to be equivalent with pilocarpine using a standard in vitro assay.[3a] However, **2** is expected to have a longer duration of biological action, because two sites for inactivation of pilocarpine (epimerization and lactone hydrolysis) have been eliminated. In addition to its equivalent biological potency, carbamate analogues are more easily synthesized since, in addition to having greater stability, one of the two stereogenic centers has been eliminated. On the basis of these advantages, we sought to prepare a chiral intermediate that could be utilized for the preparation of additional pilocarpine analogues, particularly those with constrained conformations. For this purpose, ketone **3** was selected as a desirable target that might be derived from D-serine (**4a**) and 1-methylimidazole (**6**) as shown in Scheme 1.

The initial approach (Scheme 2) began with the esterification of D-serine (**4a**) to give the benzyl ester as its tosylate salt **4b**,[4] which after conversion to the hydrochloride **4c**, was *N*-alkylated to give **4d** using acetaldehyde and sodium borohydride as described for the correponding L-methyl ester.[5] Initial studies on the formation of oxazolidinone **5a** using the literature procedure (carbonyldiimidazole, CDI)[5] were complicated by partial epimerization.[6] However, substituting 1,1′-carbonylbis(3-methylimidazolium)triflate (CBMIT)[7] for CDI resulted in oxazolidinone formation without significant epimerization. Thus, acid **5b** was obtained by hydrogenolysis with an er > 98/2.

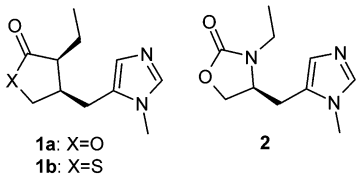
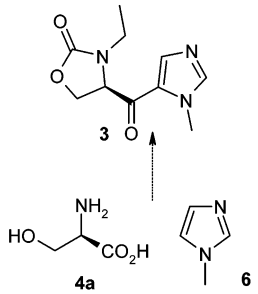


FIGURE 1.

SCHEME 1



The regioselective functionalization of 1-methylimidazole was achieved using a route outlined by El Borai et al.,[8] which was presented without experimental details (Scheme 3). Iodination of the dilithium salt of 1-meth-

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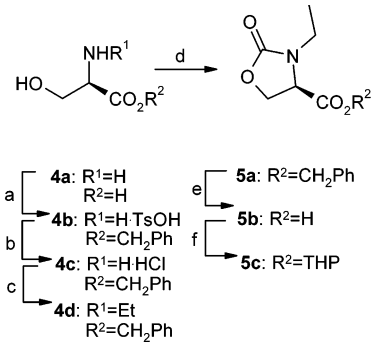
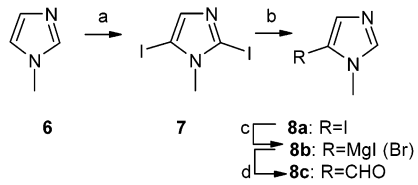
SCHEME 2[a]



[a] (a) $PhCH_2OH$, *p*-TSA, CCl_4, Δ, 9 h, 95%; (b) $NaHCO_3$, then HCl gas, 0 °C, 88%; (c) MeOH, Et_3N, MeCHO, 0 °C, then $NaBH_4$, 58%; (d) CBMIT, 0 °C, 92%; (e) Pd/C, H_2, EtOAc, quantitative; (f) DHP, 10-fold excess, CH_3SO_3H, 0 °C, 88%.

SCHEME 3[a]



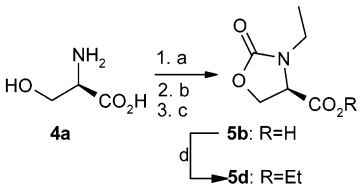
[a] (a) *n*-BuLi, 2.4 equiv, TMEDA, hexanes −20 °C to 22 °C, then I_2, 2.45 equiv in THF, −65°, 89%; (b) *n*-BuLi, THF, 0°, 71%; (c) DCM, EtMgBr in Et_2O; (d) DMF, 0 °C.

ylimidazole (**6)** gave the 2,5-diiodo derivative **7**, which could be selectively deiodinated to the desired 5-iodo-1-methylimidazole (**8a**). After some development, it was possible to carry out the conversion of **6** to **8a** (65%) in a one-flask reaction. Treatment of **8a** with EtMgBr gave the intermediate heterocyclic Grignard reagent **8b**, which produced the known 1-methylimidazole-5-caboxaldehyde (**8c**)[9] on reaction with DMF, thus confirming the regioselectivity of this reaction sequence.

To produce target ketone **3**, acid **5b** was first converted to its THP ester **5c**[10] (Scheme 2), followed by treatment of this material (generated in situ) with Grignard reagent **8b**, produced from **8a**. The product of this reaction, **3**, isolated by chromatography as a crystalline solid in variable yield (54% maximum) depending on reaction conditions, was determined to have an enantiomeric purity of 93−96% using chiral HPLC.

Although this synthetic route provided **3** in milligram amounts, improvements were needed to produce gram quantities required for analogue synthesis. In particular, the rather lengthy route to **5b**, which presented ester interchange and epimerization problems, suggested that a more direct route via the free acid might have advantages. Also, the preparation of **8a** required 300 mol % of *n*-BuLi and failed to give an acceptable yield on attempted scale-up. The route devised for the preparation of **5b** (Scheme 4) was carried out entirely in aqueous solution. Thus, a solution of molar equivalents of D-serine and acetaldehyde in water was first treated with solid sodium borohydride to give *N*-ethyl-D-serine as the major

SCHEME 4[a]



[a] (a) H_2O, MeCHO then $NaBH_4$, <15 °C; (b) *i*-BuOCOCl, NaOH; (c) Na_2CO_3, Δ; (d) $MeSO_3H$, EtOH, Δ.

product. Only small amounts of starting material and the corresponding *N*,*N*-diethyl derivative were present. This result suggests that the five-membered *N*,*O*-acetal is the dominant species present during the reduction[11]. Acylation with isobutyl chloroformate gave the carbamate, which could be isolated as a glass following extraction with ethyl acetate (73%). However, it was found preferable to cyclize this intermediate directly by heating in the presence of sodium carbonate to give **5b** (60% from D-serine) as a crystalline solid, identical with that produced by the previous route (Scheme 2). Although this method for preparing **5b** is clearly superior, there are two negative factors that must be taken into account: (1) complete hydrolysis back to *N*-ethyl-D-serine is a competing reaction and (2) the high water solubility of **5b** makes extraction (EtOAc/*tert*.-BuOH, 2/1) difficult even after NaCl saturation of the aqueous.

Activation of **5b** as its THP ester **5c** proved problematic because the ester was unstable at room temperature, could not be readily assayed due to decomposition on silica, and often failed to form because of precipitation of the starting material. This problem was circumvented by the use of ethyl ester **5d**, which was stable and could be formed under standard Fischer conditions.

Regioselective activation of the imidazole fragment was achived by direct bromination of 1-methylimidazole with NBS.[8] Although the yield was relatively low, the desired 5-bromo-1-methylimidazole (**9**) could be easily separated from the other major product, 4,5-dibromo-1-methylimidazole, by simple distillation. In addition, the intermediate Grignard product **10** was completely soluble, while that from the iodide formed a suspension and eventually a gum if stirring was interrupted. The solubility of **10** proved to be a considerable advantage, since the reaction sequence required transfer of this material by syringe.

Using these modifications, as shown in Scheme 5, ketone **3** could be prepared in gram quantities. In addition, the product was obtained in high enantiomeric purity (>99/1 as determined by chiral HPLC). Even so, the yield of **3** was modest (49% after chromatography) and could not be significantly improved by using a variety of reaction conditions or substituting a more hindered Girgnard reagent (isopropylmagnesium chloride). In addition to **3**, a small amount (7%) of a more polar product was formed. On the basis of analogy with the stereochemical outcome of hydride reductions of **3** (see below), this product is assigned structure and stereochemistry **11**.

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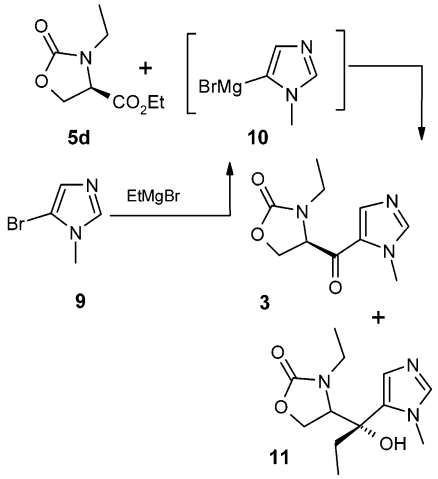
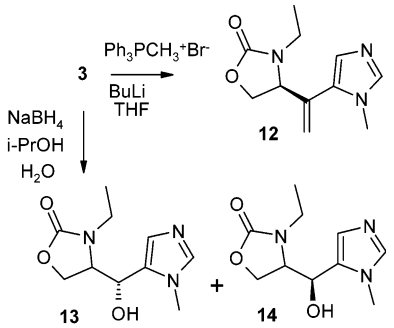
SCHEME 5



SCHEME 6



As shown in Scheme 6, Wittig reaction of **3** gave the expected methylene analogue **12** along with a more polar compound, which appeared to contain elements of the intermediate ylide. When the reaction was conducted in DMSO, the latter was the major product. Low-temperature reduction of **3** with L-Selectride gave predominantly (30/1) alcohol **13** assigned the syn (α) configuration. This is the expected product resulting from approach of a bulky hydride reagent from the less hindered β face of the molecule (away from the *N*-ethyl group). This assignment is also consistent with its ^{1}H NMR vicinal coupling constant (J_{4-8} = 8.2 Hz) compared to the anti (β) epimer **14** with a value of 2.5 Hz, both of which are in agreement with those predicted from molecular modeling. For preparative purposes, it was found that reduction with sodium borohydride was superior even though both epimers were produced (α/β, 1/1.2), since they were easily separated by fractional crystallization and thus readily available for biological evaluation.

It will be of interest to determine the relative muscarinic potency of these pilocarpine analogues and also to investigate the possibility that structures **3**, **13**, and **14** may represent metabolites of **2**. The availability of relatively large amounts of ketone **3** by the synthetic route described makes the synthesis of additional analogues a reasonable goal. This is particularly important because, although well-known and medically useful, pilocarpine has received relatively little attention in terms of structure−activity relationships.

Experimental Section

General. TLC analyses were performed on silica gel plates, and the products were visualized with UV light followed by iodine staining. Column chromatography was carried out on silica gel (28−200 or 70−230 mesh) or alumina. ^{1}H and ^{13}C NMR spectra are reported in ppm (δ) downfield from tetramethylsilane. Melting points were determined on an open capillary apparatus and are uncorrected. Elemental analyses were conducted by the Analytical Laboratory at the University of California at Berkeley.

D-Serine Benzyl Ester, *p*-Toluenesulfonic Acid Salt (4b). A mixture of D-serine (21 g, 0.2 mol), *p*-TsOH (41.8 g, 0.22 mol), and benzyl alcohol (100 mL) in carbon tetrachloride (100 mL) was heated at reflux until the formation of water ceased (9 h). The mixture was concentrated in vacuo, and the residue was treated with diethyl ether (300 mL). After being seeded with a small sample of **4b**, the mixture was placed in the refrigerator for 1−2 days. Additional diethyl ether (900 mL) was added, and the mixture was stirred at 0 °C for 30 min, filtered, and washed with diethyl ether to give 70.0 g (95%) of **4b** as a white solid: mp 80 °C (lit. 94−95°);[4] it has been reported that the reaction product is frequently difficult to crystallize due to byproducts resulting from self-esterification and O-benzylation); $[\alpha]^{20}_D$ +2.3° (*c* 4.55, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 2.29 (s, 3H), 3.78−3.91 (m, 2H), 4.23 (s, 1H). 5.24 (ABq, J = 12.55 Hz, 2H), 7.12, 7.49 (AA′BB′, J = 7.77 Hz, 4H), 7.31−7.41 (m, 5H), 8.40 (s, 2H).

D-Serine Benzyl Ester, Hydrochloride Salt (4c). D-Serine benzyl ester *p*-toluenesulfonic acid salt (**4b**, 70 g, 0.19 mol) was carefully dissolved in 5% sodium bicarbonate solution (350 mL) at 0 °C. The resulting solution was extracted with $CHCl_3$/*i*-PrOH (4:1, 3 × 300 mL), dried over sodium sulfate, and evaporated to a residue. The residue was dissolved in dichloromethane (500 mL), and HCl gas was bubbled into the solution at 0 °C for 10−15 min followed by stirring for 1 h. The solid formed was filtered, washed with dichloromethane and diethyl ether, and dried to yield 38.68 g (87.6%) of **4c** as a white solid. A sample of this material was further purified by recrystallization from *i*-PrOH/MeOH (13:1) in 78% yield, mp 172−174 °C; $[\alpha]^{20}_D$ + 4.03° (*c* 4.63, MeOH); ^{1}H NMR (400 MHz, DMSO) δ 3.80−3.90 (m, 2H), 4.19 (brs, 1H), 5.24 (ABq, J = 12.67 Hz, 2H), 5.69 (brs, 1H), 7.30−7.50 (m, 5H); ^{13}C NMR (100 MHz, DMSO) δ 54.9, 60.0, 67.3, 128.4, 128.9, 135.8, 168.4.

D-*N*-Ethylserine Benzyl Ester (4d). D-Serine benzyl ester hydrochloride salt (**4c**, 78.8 g, 0.34 mol) was treated with dry methanol (300 mL) followed by dry triethylamine (47.5 mL, 0.34 mol). The reaction was carried out under nitrogen at 0 °C with stirring. Cold acetaldehyde (20 mL, 0.36 mol) was added via syringe and stirring at 0 °C was continued for 2 h. Sodium borohydride (25.8 g, 0.68 mol) was then slowly added over 3 h, keeping the internal temperature at −7 to −13 °C. After being stirred for an additional 20 min, the reaction mixture was slowly added to a stirred solution of 3 M HCl (340 mL) at 0 °C; $CHCl_3$/*i*-PrOH (3:1, 800 mL) was then added followed by 5 M NaOH to pH 10.5. After saturation with solid NaCl, the organic phase was separated, and the aqueous was extracted with $CHCl_3$/*i*-PrOH (3:1, 2 × 600 mL) while maintaining the pH of the aqueous at 10.5. The combined organic phases were dried over sodium sulfate and evaporated below 35 °C until precipitation occurred. Filtration gave 44.3 g (58.2%) of **4d** as a white solid. Evaporation of the mother liquor, followed by crystallization from dichloromethane, gave an additional 3.8 g (5.0%) of **4d**, mp 100−101 °C; $[\alpha]^{20}_D$ +17.7° (*c* 1.17, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (t, J = 7.13 Hz, 3H), 1.64 (brs, 1H), 2.57 (dq, J = 11.21, 7.18 Hz, 1H), 2.74 (dq, J = 11.21, 7.06 Hz, 1H), 3.43 (dd, J = 6.60, 4.57 Hz, 1H), 3.59 (dd, J = 10.60, 6.63 Hz, 1H), 3.79 (dd, J = 10.60, 4.52 Hz, 1H), 5.19 (s, 2H), 7.33−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 42.6, 62.6, 66.9, 128.2, 128.7, 135.7, 173.6. Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.65; H, 7.80; N, 6.27.

(*R*)-3-Ethyl-2-oxo-4-oxazolidinecarboxylic Acid Benzyl Ester (5a). D-*N*-Ethylserine benzyl ester (**4d**, 45 g, 0.2 mol) was suspended in dry nitromethane[12] (262 mL), cooled to 0 °C, and treated with 1-methylimidazole (2.1 mL, 0.026 mol). To the stirred suspension at 0 °C was added a CBMIT solution [prepared by adding methyl triflate[13] (86 g, 0.52 mol) to a suspension of CDI (42.5 g, 0.26 mol) in nitromethane (205 mL) at 0 °C and stirring for 30 min] over 2−3 h. The reaction mixture was concentrated in vacuo, diluted with chloroform (3 L), washed with 1 M HCl, water, 5% $NaHCO_3$, water, and brine in succession, dried over sodium sulfate, and evaporated to a residue. Chromatography (EtOAc/hexane, 1:1) gave 46.11 g (92%) of **5a**: $[\alpha]^{20}_D$ +40.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (t, J = 7.28 Hz, 3H), 3.19 (dq, J = 14.20, 7.12 Hz, 1H), 3.61 (dq, J = 14.27, 7.30 Hz, 1H), 4.31 (dd, J = 8.02, 4.11 Hz, 1H), 4.37−4.47 (m, 2H), 5.23 (ABq, J = 12.04, Hz, 2H), 7.34−7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 38.3, 56.6, 64.2, 67.8, 128.5, 128.8, 128.9, 134.6, 157.4, 169.6. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.63; H, 6.07; N, 5.62. Found: C, 62.81; H, 6.21; N, 5.79.

(*R*)-3-Ethyl-2-oxo-4-oxazolidinecarboxylic Acid (5b). Benzyl ester **5a** (23.1 g, 93 mmol) in EtOAc (125 mL) was hydrogenated in the presence of 5% Pd/C (3.5 g) at 60 psi and room temperature. Hydrogen was consumed rapidly, but the reaction was allowed to continue for 1.5 h. Filtration through Celite followed by evaporation of the solvent gave 14.4 g (quantitative) of **5b** as a white solid: mp 103−109 °C (crude), 110−111.5 °C after recrystallization (EtOAc/diethyl ether); $[\alpha]^{21}_D$ +47.8° (*c* 1.025, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.31 Hz, 3H), 3.27 (dd, J = 14.22, 7.14 Hz, 1H), 3.65 (dd, J = 14.28, 7.37 Hz, 1H), 4.41−4.45 (m, 2H), 4.54 (like t, J = 10.02 Hz, 1H), 8.94 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 38.3, 56.3, 64.9, 158.5, 172.6.

Determination of Enatiomeric Purity of 5b. Carboxylic acid **5b** (1 mmol) was dissolved in dry THF (12 mL), cooled to −20 °C, and treated with isobutylchloroformate (1.2 mmol) with stirring, under a nitrogen atmosphere for 40−60 min. To the reaction mixture was added (*R*)-(+)-α-methylbenzylamine (1.1 mmol), and the reaction was then allowed to warm to room temperature. The solvent was removed in vacuo, and the residue was dissolved in EtOAc, washed successively with 1 M HCl, water, 5% $NaHCO_3$, water and brine, dried over sodium sulfate, and evaporated. The crude amide residue was evaluated for enatiomeric purity using HPLC (Microsorb Si, mobile phase EtOAc/*n*-hexane, 3:1); the er was found be be approximately 98/2. When CDI was used in place of CBMIT for formation of the oxazolidinone, the enantiomeric purity was determined to be in the range of 80−88% and could not be substantially improved by recrystallization.

(*R*)-3-Ethyl-2-oxo-4-oxazolidinecarboxylic Acid, Tetrahydropyranyl Ester (5c). To a stirred solution of **5b** (159 mg, 1.0 mmol) in dichloromethane (5 mL) at 0 °C were added dihydropyran (0.91 mL, 10 mmol) and methanesulfonic acid (0.65 μL, 0.01 mmol). After being stirred for 1 h at 0 °C, the reaction was quenched by addition of 1,2-ethylenediamine (2.67 μL, 0.04 mmol) followed by chilled $NaHCO_3$ solution (H_2O/brine/sat. $NaHCO_3$, 1:1:1, 0.5 mL). After dilution with dichloromethane (30 mL), the organic phase was washed with $NaHCO_3$ and brine and dried over Na_2SO_4/Na_2CO_3. Evaporation of the solvent gave 215 mg (88%) of **5c** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20, 1.21 (two t, J = 7.2 Hz, 3H, diastereomeric mixture), 1.61−1.88 (m, 6H), 3.24 (approximately sextet, 1H), 3.62−3.87 (m, 3H), 4.35−4.40 (m, 2H), 4.41−4.51 (m, 1H), 6.11, 6.12 (two s, 1H, diastereomeric mixture).

2,5-Diiodo-1-methylimidazole (7). 1-Methylimidazole (4.45 mL, 52.8 mmol) was added over 20 min to a well-stirred solution of TMEDA (20.0 mL, 135 mmol, 240 mol %) and *n*-BuLi (52 mL, 2.54 M in hexanes, 132 mmol, 237 mol %) in pentane (55 mL) under nitrogen at −20 °C. The stirred, cloudy, yellow, heterogeneous mixture was warmed to 22 °C for 1 h and then diluted with anhydrous THF (50 mL) and cooled to −65 °C. A solution of iodine (34.7 g, 137 mmol, 245 mol %) in anhydrous THF (180 mL) was added over 90 min. During the addition, the internal temperature of the thick, light-brown reaction mixture rose to −39 °C. The stirred reaction mixture was allowed to warm to 22 °C over 9 h. During this process, the reaction mixture suddenly became a dark, homogeneous solution at −19 °C. The reaction was quenched by the addition of ethyl acetate (10 mL) followed by water (10 mL), dichloromethane (250 mL), and saturated Na_2SO_3 solution (125 mL). The organic layer was separated, washed with saturated Na_2SO_3 (3 × 50 mL) and brine (3 × 25 mL), dried over $MgSO_4$, filtered, and evaporated to yield **7** (16.7 g, 89%) as a golden-brown solid which could be recrystallized from chloroform: mp 150−152 °C (lit. 154 °C):[8] R_f 0.62 (CH_2Cl_2/MeOH/NH_4OH, 88:10:2); ^{1}H NMR ($CDCl_3$) δ 7.21 (s, 1H, CH, C-4), 3.65 (s, 3H, CH_3).

5-Iodo-1-methyimidazole (8a). To a stirred solution of **7** (2.80 g, 8.39 mmol) in anhydrous THF (90 mL) at −78 °C under nitrogen was slowly added *n*-BuLi (3.45 mL, 2.55 M in hexanes, 105 mol %) during 18 min. After being stirred for an additional 40 min, the reaction was quenched by the addition of methanol (3 mL) and diluted with dichloromethane (150 mL). The organic layer was washed with brine (2 × 20 mL), dried ($MgS0_4$), filtered, and evaporated to give a yellow-brown solid (1.92 g, >100%), which was recrystallized from chloroform to yield **8a** (1.23 g, 71%): mp 104−105 °C (lit. 107 °C):[8] R_f 0.4 (EtOAc/MeOH/NH_4OH, 88:10:2); ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H), 7.08 (s, 1H), 3.61 (s, 3H, CH_3).

5-Iodo-1-methylimidazole (8a), Directly from 1-Methylimidazole. To a stirred solution of TMEDA (32.3 mL, 214 mmol, 237 mol %) in dry pentane (75 mL) under nitrogen at −20 °C was added *n*-BuLi (94.4 mL, 2.3 M in hexanes, 217 mmol, 240 mol %). 1-Methylimidazole (7.21 mL, 90.4 mmol, 100 mol %) was added dropwise over 25 min, and the cooling bath (−25 °C) was removed approximately halfway through the addition. The stirred cloudy, yellow mixture was warmed to 22 °C for 1 h, whereupon a yellow/white precipitate formed. The suspension was cooled to −65 °C and anhydrous THF (220 mL) was added at such a rate that the internal temperature remained below −20 °C. A solution of iodine (33.3 g, 131 mmol, 145 mol %) in anhydrous THF (140 mL) was added to the vigorously stirred suspension at such a rate that the internal temperature (initially at −65 °C) did not rise above −20 °C. Stirring was continued as the reaction was gradually warmed to 0 °C over 2 h while the solids dissolved. TLC indicated virtually no diiodoimidazole remaining. After 0.5 h at 0 °C, the reaction mixture was quenched by adding methanol (15 mL) followed by brine (70 mL). After addition of dichloromethane (350 mL), the organic phase was separated, washed with saturated Na_2SO_3 (2 × 50 mL) and brine (3 × 25 mL), dried (Na_2SO_4), filtered, and evaporated to yield **8a** (12.3 g, 65%) as a yellow-brown solid (mp 104 °C), which was recrystallized from chloroform to give 7.93 g: mp 104−5 °C, identical with the product derived from **7**.

1-Methylimidazole-5-carboxaldehyde (8c). To a stirred solution of **8a** (104 mg, 0.50 mmol, 100 mol %) in dichloromethane (2.2 mL) at 20 °C under nitrogen was added ethylmagnesium bromide (203 μL, 2.7 M in ether, 110 mol %) over 2 min. After stirring for 1 h, the heterogeneous reaction mixture was cooled to 0 °C, and dimethylformamide (77 μL, 1.0 mmol, 200 mol %) was added. After being warmed to 22

(12) Dry nitromethane was prepared by treating with $CaCl_2$ or $CaSO_4$ for one day followed by molecular sieves (3 Å, freshly activated at 400° C) twice for two days and stored in the dark. It has been reported that nitromethane may explode when heated with basic impurities.

(13) This was prepared according to the following procedure: trifluoromethanesulfonic acid (1 mol) was added via a dropping funnel into stirred dimethyl sulfate (1.2 mol, previously distilled from P_2O_5). The reaction mixture was then distilled to give colorless methyl triflate (bp 92-100° C/760 mm Hg). Methyl triflate is a powerful methylating agent and is thus a suspected carcinogen that should be handled with appropriate care.

°C and stirring for 2 h, the reaction was quenched with saturated Na_2HPO_4 (4 mL) and extracted with dichlormethane/2-propanol (DCM/IPA, 3:1,1 × 35 mL, then 4 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to give **8c** (55 mg, ∼100%, containing a small amount of DMF): ^{1}H NMR (400 MHz, CD_3OD) δ 9.07 (d, 1H, CHO), 7.72 (s, 1H), 7.58 (s, 1H), 3.88 (s, 1H, CH_3). This material was identical to an authentic sample of 1-methylimidazole-5-carboxaldehyde previously prepared by an unambiguous route[14].

(*R*)-3-Ethyl-4-(1′-methyl-5′-imidazoyl)-2-oxazolidinone (3). To a stirred solution of **5b** (139 mg, 1.0 mmol) in dichlomethane (8 mL) at −20 °C under nitrogen were added dropwise dihydropyran (0.11 mL, 1.2 mmol) and methanesulfonic acid (0.65 μL, 0.01 mmol). The reaction was allowed to warm to 0 °C during 1.5 h and stirred for 2 h. Separately, a Grignard reagent was prepared by adding ethylmagnesium bromide solution (2.0 mL, 2.3 mmol) to a stirred solution of **8a** (437 mg, 2.1 mmol) in dichloromethane (9 mL) at 20 °C under nitrogen over 1 h. After stirring for an additional 20 min, the resulting suspension was transferred via cannula to the previously prepared solution of **5c**. The addition was carried out at −20 °C over 10−15 min, and the reaction was allowed to warm to 0 °C over 1−1.5 h. After stirring over.night at 4 °C (cold room), the reaction was stirred at room temperature for 1 h and then poured into a stirred mixture of 1 M KH_2PO_4/dichoromethane (1:1, 30 mL) at 5 °C. The pH was adjusted to 5.5, the organic phase was separated, and the aqueous phase was extracted with dichloromethane (3 × 30 mL). The combined organic phases were washed with saturated $NaHCO_3$/water (1:1, 10 mL), dried over sodium sulfate, and evaporated to give **3** (216 mg, 97%). The crude product was purified by column chromatography (chloroform/methanol, 15:1) to afford **3** (120 mg, 54%) as a white solid: mp 93−98 °C (before recrystallization), mp 102.5−103 °C (after recrystalliztion from EtOAc/hexane); $[\alpha]^{20}_D$ +82.0° (*c* 1.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, J = 7.3 Hz, 3H), 3.12-(approximately sextet, 1H), 3.63 (approximately sextet, 1H). 3.98 (s, 3H), 4.22 (dd, J = 8.8, 5.5 Hz, 1H), 4.57 (approximately t, J = 8.90 Hz, 1H), 4.99 (dd, J = 9.8, 5.4 Hz, 1H), 7.70 (s, 1H), 7.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 35.0, 38.2, 59.4, 64.9, 128.5, 139.2, 145.1, 157.8, 185.8. Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.72; H, 5.91; N, 18.78.

Determination of Stability and Enantiomeric Purity of 3. The purity of **3** was evaluated using a CHIRACEL OD-R reverse phase chiral column, 250 × 4.6 mm. The HPLC conditions were as follows: flow rate, 0.5 mL/min; mobile phase, CH_3CN/H_2O (1:9); injection volume, 20 μL; detector, 260 nm; retention time, 28 min for minor and 32 min for major enantiomer. The sample of ketone **3** used in this analysis was found to have an enantiomeric ratio of 96:4.

Three samples of **3** were treated under various conditions to investigate the conformational stability of the ketone. The first sample was kept neat at 50 °C for 2 h, the second sample was subjected to column chromatography using $CHCl_3$/*i*-PrOH (7:1) as eluant (column residence time 2 h), and the third sample was treated with diisopropylethylamine (100 mol %) in THF at room temperature for 3 h. As shown by chiral HPLC, all samples were stable under the described conditions.

(*R,S*)-1-(3-Ethyl-2-oxo-4-oxazlidinyl-1-(1′-methyl-5′-imidazolyl)methanol (13) by Reduction of 3 with L-Selectride. To a stirred solution of **3** (30 mg, 0.13 mmol) in THF (5 mL) under nitrogen at −78 °C was slowly added a solution of L-Selectride (0.72 mL, 1.0 M, 0.72 mmol). After 2 h at −78 °C, the reaction was quenched by the addition of phosphate buffer (pH 6.0, 2 mL) and extracted with $CHCl_3$/*i*-PrOH (3:1, 3 × 20 mL). The combined organic phases were dried over sodium sulfate and evaporated to yield a crude product, which was purified by column chromatography ($CHCl_3$/methanolic NH_3, 14:1) to give **13** (30 mg, ∼quantitative). This material appeared to be a diastereomeric mixture by NMR (**13**/**14**, 30/1). The oily product crystallized on standing, and on trituration with diethyl ether produced pure **13** as a white solid: mp 128−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J = 7.1 Hz, 3H), 3.54−3.65 (m, 2H), 3.74 (s, 1H), 3.78−3.80 (m, 1H), 4.20−4.80 (m, 2H), 4.70 (d, J = 8.2 Hz, 1H), 6.81 (s, 1H), 7.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 32.3, 39.3, 57.5, 64.8, 68.5, 126.6, 130.7, 139.2, 158.4.

(*R,R*)-1-(3-Ethyl-2-oxo-4-oxazolidinyl)-1-(1′-methyl-5′-imidazolyl)methanol (14), by Reduction of 3 with Lithium Borohydride. A 2.0 M solution of $LiBH_4$ (135 μL, 0.27 mmol) was added dropwise to a stirred solution of **3** (40 mg, 0.18 mmol) in THF (7 mL) at −78 °C. After being stirred at −78 °C for 2 h, the reaction mixture was warmed to −10 °C and quenched with phosphate buffer (pH 6, 2 mL). Extraction with $CHCl_3$/*i*-PrOH (3:1, 3 × 20 mL) followed by washing of the combined organic phase with phosphate buffer (pH 6.0, 10 mL), drying (Na_2SO_4), and evaporation gave the crude product, which was purified by column chromatography ($CHCl_3$/methanolic NH_3, 13:1). ^{1}NMR analysis of the separated components indicated a mixture of **13** and **14** (21 mg, 51%, **13**/**14**, 1/1.3) and a borane complex (14 mg, **13**/**14**, 1/1.7). The borane complex was dissolved in $CHCl_3$/*i*-PrOH (3:1, 15 mL) and stirred with 1 M phosphoric acid. The pH was adjusted to 6.0 with $NaHCO_3$ and the aqueous phase was extracted with $CHCl_3$/*i*-PrOH (3:1, 2 × 10 mL). The combined organic extracts were dried over sodium sulfate and evaporated to give additional **13** and **14** (6 mg, 15%, **13**/**14**, 1/1.3): total yield 66%. A 12 mg sample of the mixture was recrystallized from EtOAc/MeOH to give 5 mg of **14** as a white solid: mp 203−204 °C, ^{1}H NMR (400 MHz, CD_3OD) δ 1.18 (t, J = 7.2 Hz, 3H), 3.16 (approximately sextet, 1H), 3.55 (approximately sextet, 1H), 3.75 (s, 3H), 4.33−4.35 (m, 1H), 4.45 (approximately d, J = 7.1 Hz, 2H), 5.01 (like d, 1H), 6.18 (s, 1H), 7.63 (s, 1H).

(*R*)-3-Ethyl-2-oxo-4-oxazolidinecarboxylic Acid (5b), Directly from D-Serine. A solution of D-serine (52.5 g, 0.50 mol) and acetaldehyde (24.2 g, 0.55 mol) in water (500 mL) was stirred at 0 °C while solid sodium borohydride (19.0 g, 0.50 mol) was added at such a rate that the internal temperature did not rise above 15 °C. After 2 h, stirring was stopped, and the reaction mixture (heavy white precipitate) was allowed to stand overnight at room temperature. To destroy excess borohydride, the cooled reaction mixture was carefully treated with 20% HCl until strongly acidic (pH 1−2). Following adjustment of the pH to 6.5 with 50% NaOH and then to 8.5 with 4 M NaOH, the stirred reaction mixture was treated alternately with isobutyl chloroformate and 4 M NaOH, keeping the pH between 7.5 and 9.0 (about 7 h). After standing overnight, the reaction mixture was filtered, and the filtrate was treated with saturated sodium carbonate solution (450 mL) and distilled during 2 h to give approximately 500 mL of a mixture of isobutanol and water. The cooled pot residue was acidified to pH 1−2, treated with sodium chloride (250 g), and extracted with ethyl acetate (9 × 100 mL). Evaporation of the combined and dried (sodium sulfate) organic phases gave 39.51 g of crude product. Re-extraction of the aqueous with ethyl acetate/*tert*-butyl alcohol (2:1, 6 × 100 mL) gave, after drying and evaporation, an additional 8.48 g for a total of 47.99 g (0.302 mol, 60%). The crude product could be recrystallized from ethyl acetate/cyclohexane or methylene chloride (chilled in freezer at − 20 °C) to give **5b** identical with that prepared by the benzyl ester route.

(*R*)-3-Ethyl-2-oxo-4-oxazolidinecarboxylic Acid Ethyl Ester (5d). A solution of acid **5b** (15.90 g, 0.10 mol) in 99.5% ethanol (100 mL) containing methanesulfonic acid (0.48 g, 0.05 mol) was slowly distilled over 2 h, collecting 45 mL of distillate. More 99.5% ethanol (50 mL) was added to the pot residue, and distillation was continued for another 2 h. The cooled reaction mixture was treated with sodium bicarbonate and evaporated to near dryness. The residue was taken up in

(14) Dener, J. M.; Zang, L. -H.; Rapoport, H. *J. Org Chem*., **1993**, *58*, 1159.

ethyl acetate (30 mL) and water (15 mL). After the organic phase was separated, the aqueous was extracted with ethyl acetate (2 × 20 mL), and the combined organic phases were dried (sodium sulfate) and evaporated to give 17.83 g of **5d** (0.0956 mol, 95%). A sample of this material was distilled (bp 125−129°, 2 mm) to give a clear oil: R_f = 0.74 (methylene chloride/ethyl acetate, 7:3). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.3; H, 7.0; N, 7.5. Found: C, 51.22; H, 6.99; N, 7.50.

5-Bromo-1-methylimidazole (9). This was prepared essentially as described in the reference[8] except that purification did not involve chromatography, and the yield of product was consistently lower than reported. To a stirred solution of 1-methylimidazole (76.8 g, 0.80 mol) in chloroform (500 mL) was added *N*-bromosuccinimide (171 g, 0.96 mol) in portions such that the reaction temperature remained just below reflux. The reaction mixture was then heated at reflux for 2 h. The cooled reaction mixture was stirred with saturated sodium carbonate (200 mL) and filtered. The organic phase was separated and washed with 0.25 M trisodium phosphate (2 × 175 mL), and the aqueous phases were extracted, with methylene chloride (2 × 50 mL). The combined organic phases were dried (sodium sulfate) and evaporated to give 80.66 g of crude **9**. Distillation (89−121 °C at 2.5 mm) gave material (48.71 g, 0.30 mol, 38%) that was predominantly **9** (R_f = 0.31, methylene chloride/ethyl acetate, 7:3) but was contaminated with some starting material; the pot residue was mainly 4,5-dibromo-1-methylimidazole (R_f = 0.61). Attempted removal of 1-methylimidazole by extraction with aqueous base was only partially successful; however, redistillation at 68−71 °C/ 2 mm gave a low melting solid. Crystals from this source were washed with cold 1,1,1-trichloroethane and distilled via a short-path apparatus to give an analytical sample, mp 47−49 °C (reported[8] as an oil). Anal. Calcd for $C_4H_5N_2Br$: C, 29.84; H, 3.13; N, 17.40. Found: C, 29.82; H, 3.08; N, 17.36.

***(R)*-3-Ethyl-4-(1′-methyl-5′-imidazoyl)-2-oxazolidinone (3) and (*R,S*)-1-(3-Ethyl-2-oxo-4-oxazolidinyl)-1-(1′-methyl-5′-imidazolyl)propanol (11).** A stirred solution of 5-bromo-1-methylimidazole (**9**, 1.93 g, 12 mmol) in anhydrous methylene chloride (10 mL), under an argon atmosphere, was treated with a 3 M solution of ethylmagnesium bromide (4.0 mL, 12 mmol) at such a rate that the reaction mixture was kept just below reflux. A precipitate began to form during the addition but redissolves at completion to give a clear golden solution. After an additional 15 min, the solution of **10** was added in portions, via syringe, to a stirred solution of oxazoldinone ester **5d** (1.87 g, 10 mmol) in methylene chloride (10 mL), which was maintained under an argon atmosphere at 0 °C. The addition took place over 1 h, during which time a dense precipitate formed and eventually turned into sticky clumps that inhibited stirring. After stirring for an additional 1 h at 0 °C, the reaction was quenched by the addition of 1 M hydrochloric acid (15 mL) to give an aqueous solution with a pH of 6.0−6.5. The organic phase was separated, dried (sodium sulfate), and evaporated to give 2.11 g. Extraction of the aqueous with ethyl acetate/*tert*-butyl alcohol (2 × 20 mL) gave 0.52 g. The aqueous was treated with 3.0 g of ammonium chloride, adjusted to pH 8.0−8.5, and extracted with ethyl acetate/*tert*-butyl alcohol (3 × 20 mL) to give an additional 0.19 g. Since all three factions contained **3** (R_f = 0.50, methylene chloride/ethyl acetate/ethanol, 5:3:2, strong UV), they were combined and chromatographed on neutral, activity III alumina (50 g). Early fractions eluted with hexanes/methylene chloride 1:1 and methylene chloride contained mostly starting materials (**9** and **5d** along with 1-methylimidazole and products resulting from the addition of 1 or 2 mol of ethylmagneium bromide to ester **5d**) totaling 1.52 g. Fractions eluting later, with methylene chloride and 2% ethanol in methylene chloride, contained mostly **3** (1.10 g, 4.93 mmol, 49%). Recrystallization from ethyl acetate/cyclohexane gave pure **3**, mp 117−119 °C, which, except for its higher melting point, appeared identical with **3** prepared via the THP ester route. Further elution of the column with 5% ethanol in methylene chloride gave **11** (0.22 g, 0.87 mmol, 7%), which was purified by recrystallization from ethyl acetate/ether, mp 161−162 °C, (R_f = 0.28, methylene chloride/ethyl acetate/ethanol, 5:3:2). Anal. Calcd for $C_{12}H_{19}N_3O_3$: C, 56.9; H, 7.56; N, 16.59. Found: C, 56.87; H, 7.65; N, 16.45.

***(R)*-1-(Ethyl-2-oxo-4-oxazolidinyl)-1-(1′-methyl-5′-imidazolyl)ethene (12).** To a stirred suspension of methyltriphenylphosphonium bromide (0.90 g, 2.4 mmol) in anhydrous THF (5 mL) under an argon atmosphere at 0 °C was added 2 M *n*-butyllithium in cyclohexane (1.15 mL, 2.3 mmol). After stirring for 30 min, a solution of **3** in THF (3 mL) was added gradually over a few minutes. The reaction mixture was allowed to stir for 1 h while it warmed to room temperature. After being stirred at reflux for 3 h, the cooled reaction mixture was stirred with 1 mL of 50% sodium hydroxide for 15 min and then neutralized with 20% hydrochloric acid. Evaporation of most of the solvent gave a residue, which was distributed between water (10 mL) and methylene chloride (10 mL). Additional acid was added to bring the aqueous pH to 1−2. This was extracted with methylene chloride (2 × 10 mL) to remove neutrals (triphenylphosphine and triphenylphosphine oxide). The aqueous was made basic (pH 9) with 4 M sodium hydroxide and extracted with methylene chloride/2-propanol, 3:1 (4 × 10 mL), dried (sodium sulfate), and evaporated to give 0.44 g of crude product which contained **12** (R_f = 0.53, methylene chloride/ethyl acetate/ethanol, 5:3:2) and an unidentified product (R_f = 0.46). Despite their similar R_fs on silica, these materials were easily separated by chromatography on activity III, neutral alumina (20 g). Elution with methylene chloride and 1% ethanol in methylene chloride gave **12** (0.27 g, 61%), which was purified by recrystallization from ethyl acetate/hexanes, mp 98−98 °C. Anal. Calcd for $C_{11}H_{15}O_2N_3$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.68; H, 7.05; N, 19.00.

***(R,S)*-1-(3-Ethyl-2-oxo-4-oxazolidinyl)-1-(1′-methyl-5′-imidazolyl)methanol (13) and (*R,R*)-1-(3-Ethyl-2-oxo-4-oxazoldinyl)-1-(1′-methyl-5′-imidazolyl)methanol (14) by Reduction of 3 with Sodium Borohydride.** To a stirred solution of sodium borohydride (0.084 g, 2.2 mmol) in water (3 mL) at 0 °C was added a solution of **3** (0.45 g, 2.0 mmol) in 2-propanol (2 mL) during 3 min. After being stirred for 1 h while the reaction mixture warmed to room temperature, it was treated dropwise with 20% hydrochloric acid until the pH reached 1−2. After 10 min, the pH was adjusted to 8−9 with 4 M NaOH and extracted with methylene chloride (6 mL) followed by methylene chloride/2-propanol (3:1, 2 × 6 mL). The combined organic phases were dried (sodium sulfate) and evaporated (0.48 g, >100%). Chromatography on 30 g of neutral, activity III alumina gave only partial separation of the epimeric alcohols, both eluting with methylene chloride containing increasing amounts of ethanol (1.5−15%). However, recrystallization from ethanol/ethyl acetate gave pure **13** (R_f = 0.25, methylene chloride/ethyl acetate/ethanol, 5:3:2), mp 135−136 °C. Anal. Calcd for $C_{10}H_{15}O_3N_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.26; H, 6.74; N, 18.61. Pure **14** could be obtained by recrystallization of the mother liquor residue from ethanol/ethyl acetate (R_f = 0.18), mp 207−208 °C. Anal. Calcd for $C_{10}H_{15}O_3N_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.06; H, 6.92; N, 18.31. Except for small differences in melting points, these samples of **13** and **14** were identical with those produced with other reducing agents.

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Supporting Information Available: Chiral HPLC data on samples of ketone **3** prepared under different reaction conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

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