15 days. Purification by chromatography (CH_2Cl_2-MeOH, 10:1) yielded 110 mg (84%) of the major isomer as a colorless oil.

Major. R_f = 0.35. Anal. Calcd for $C_{14}H_{26}NO_2P$: C, 61.97; H, 9.66; N, 5.16. Found: C, 61.51; H, 9.56; N, 4.85. MS: *m/e* (rel intensity) 271 (M^+, 4), 184 (20), 140 (100), 124 (12), 96 (25), 57 (80). IR (CCl_4): 3080 (w), 2973 (vs), 1626 (w), 1462 (vs), 1164 (s) cm^{-1}. ^{31}P NMR: δ 47.24. ^1H NMR: δ 6.47-6.15 (m, 3 H), 4.37 (ddd, J = 10.8, 6.3, 4.9 Hz, 1 H), 3.88 (m, 1 H), 2.75-2.58 (m, 1 H), 2.46-2.30 (m, 1 H), 2.22-2.06 (m, 1 H), 1.74-1.42 (m, 4 H), 1.28 (s, 3 H), 1.18 (d, J = 15.9 Hz, 9 H), 1.03 (s, 3 H). ^{13}C NMR: δ 137.39 (t), 124.42 (d, J_{PC} = 82.3 Hz) (d), 71.44 (d, J_{PC} = 80.7 Hz) (d), 69.59 (s), 63.46 (d, J_{PC} = 6.3 Hz) (d), 39.30 (t), 36.64 (t), 31.89 (d, J_{PC} = 67.8 Hz) (s), 31.14 (t), 26.78 (q), 23.56 (q).

Minor. ^{31}P NMR: δ 44.90.

Cycloaddition of DMPO to *tert*-Butyldivinylphosphine Sulfide (12). A solution of 26 mg (0.15 mmol) of sulfide **12** and 25 mg (0.22 mmol) of DMPO in 1 mL of $CHCl_3$ was left at 25 °C for 15 days. Purification by chromatography (ethyl acetate-hexane, 1:1, R_f = 0.32) yielded 35 mg (80%) of the major isomer as white crystals.

Major. Mp: 85 °C. Anal. Calcd for $C_{14}H_{26}NOPS$: C, 58.51; H, 9.12; N, 4.87. Found: C, 58.44; H, 9.28; N, 4.82. IR ($CDCl_3$): 2970 (s), 2871 (m), 1460 (s), 1381 (s), 1365 (s), 1157 (m), 1112 (m) cm^{-1}. ^{31}P NMR: δ 62.03. ^1H NMR: δ 6.82-6.26 (m, 3 H), 4.49 (dt, J = 9.5, 6.8 Hz, 1 H), 3.87-3.74 (m, 1 H), 2.66-2.34 (m, 2 H), 2.22-2.01 (m, 1 H), 1.78-1.42 (m, 3 H), 1.28 (d, J = 2.2 Hz, 9 H), 1.20 (s, 3 H), 1.01 (s, 3 H). ^{13}C NMR: δ 138.80 (t), 129.94 (d, J_{PC} = 64.2 Hz) (d), 75.66 (d, J_{PC} = 62.4 Hz) (d), 69.80 (s), 63.65 (d, J_{PC} = 6.3 Hz) (d), 40.82 (t), 36.72 (t), 34.19 (d, J_{PC} = 49.9 Hz) (s), 31.44 (t), 27.02 (q), 25.82 (q), 24.45 (q).

Minor. ^{31}P NMR: δ 61.58.

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Syntheses of 6-Oxodecahydroisoquinoline-3-carboxylates. Useful Intermediates for the Preparation of Conformationally Defined Excitatory Amino Acid Antagonists

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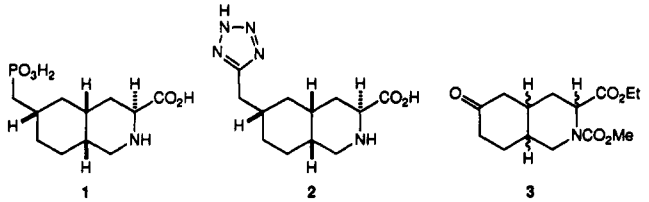
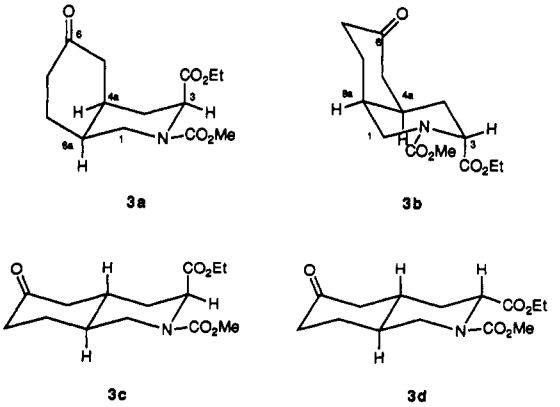
We have prepared three of the four possible diastereomers of ethyl 6-oxo-2-(methoxycarbonyl)decahydroisoquinoline-3-carboxylic acid (two cis- ring and one trans ring juncture ketones, **3a-c**) by a convergent route from (±)-*m*-tyrosine. These ketones are useful intermediates for the preparation of conformationally constrained acidic amino acids as *N*-methyl-D-aspartic acid (NMDA) receptor antagonists, e.g., LY274614 and LY233536 (**1** and **2**, respectively). The cis ring juncture ketones were prepared selectively by hydrogenation of a key tetrahydroisoquinoline intermediate **7**, while the corresponding trans ring juncture ketone was prepared selectively by consecutive dissolving metal reductions of the tetrahydroisoquinoline **8**. One of the ketones, **3b**, that possesses the optimal stereochemical array for NMDA antagonist activity, was resolved via the α-methylbenzylamine salts of the corresponding acid to allow for determination of the active optical isomer of these amino acids. The synthesis and resolution of the keto esters can easily be performed on a multigram scale.

As a part of a program aimed at the synthesis of novel 6-substituted decahydroisoquinoline-3-carboxylic acids, e.g., **1** and **2** (LY274614 and LY233536, respectively),[1] we required large quantities of the four possible diastereomers of 6-keto-3-carboxyisoquinoline **3**. We believed that these



1 **2** **3**

hitherto unknown ketones could be readily elaborated to a variety of substituted amino acids that could serve as novel *N*-methyl-D-aspartic acid (NMDA) receptor antagonists.[2,3] Because of the rigid nature of these bicyclic ketones, the amino acids thus derived would be of limited conformational mobility and therefore provide some useful insight into structural requirements for activity at NMDA receptors. We report here the convergent synthesis of multigram quantities of three of the four possible diastereomers of the title compound **3** and the subsequent resolution of the ketone **3b**.



3a **3b** **3c** **3d**

We envisioned that the cis or trans ring juncture in **3** could be introduced selectively by the appropriate choice of reduction conditions for a suitably protected tetrahydroisoquinoline intermediate such as **4**, which can be obtained from the readily available (±)-*m*-tyrosine. The cis isomers should be available by hydrogenation of **4**,[4] and

(1) Ornstein, P. L.; Schoepp, D. D.; Leander, J. D.; Lodge, D. In *Excitatory Amino Acids 1990* Meldrum, B., Moroni, F., Simon, R., Woods, J., Eds.; Fidia Research Foundation Symposium Series Raven Press: New York, 1991; in press.
(2) Ornstein, P. L.; Schoepp, D. D. *Curr. CNS Patents* **1990**, *1*, 413.
(3) Collingridge, G. L.; Lester, R. A. J. *Pharmacol. Rev.* **1989**, *40*, 143.
(4) Rapala, R. T.; Lavagnino, E. R.; Shepard, E. R.; Farkas, E. *J. Am. Chem. Soc.* **1957**, *79*, 3770.

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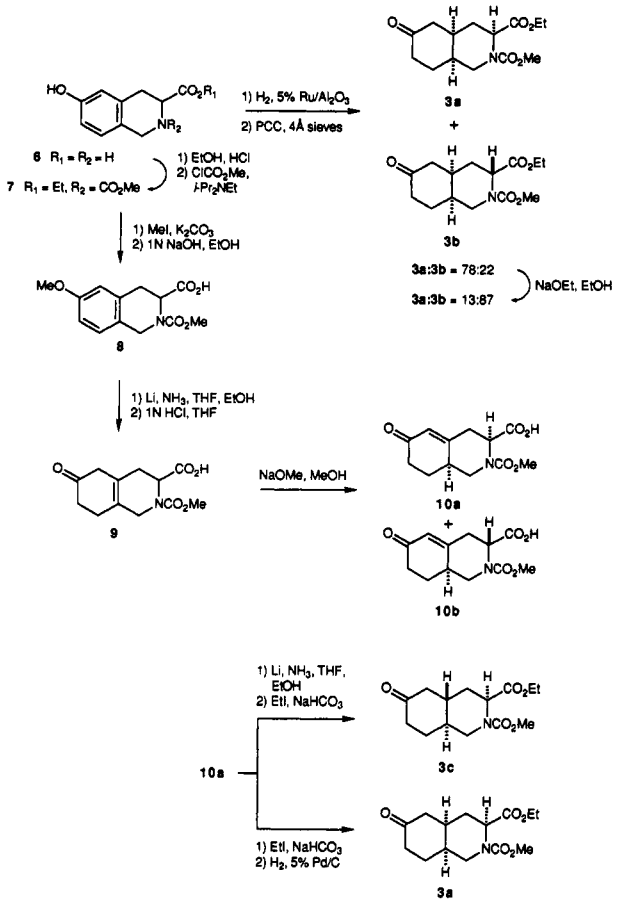
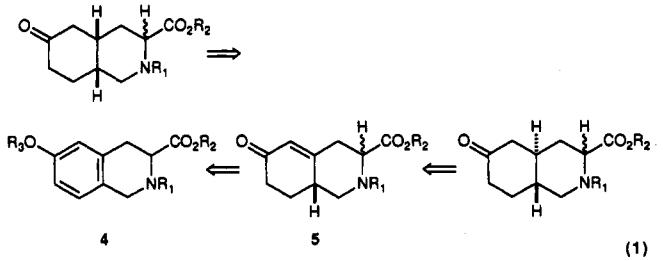
Scheme I



the trans isomers should be available by sequential dissolving metal reductions of **4** via an intermediate enone such as **5**[5] (eq 1).

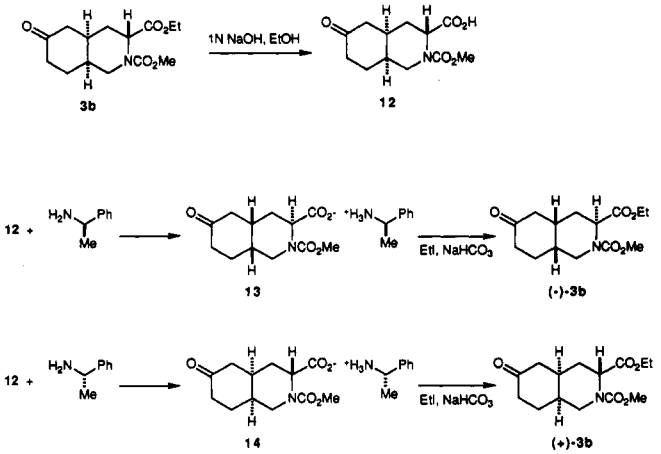


(1)

Condensation of (±)-*m*-tyrosine (Scheme I) using standard Pictet–Spengler reaction conditions[6] (5% HCl, 37% formaldehyde, 90 °C bath, 45 min) was capricious, and although the desired product **6** was obtained, it was always contaminated with byproducts that were difficult to remove after subsequent transformations. However, when the reaction was performed under weakly acidic conditions (0.05 N HCl, 37% formaldehyde, 90 °C bath, 45 min), the amino acid **6** could be directly isolated (as the inner salt) from the reaction mixture by filtration. The only significant byproduct was the 8-hydroxy isomer, and this could be removed by washing the solid with water to afford a 70% yield of the desired amino acid **6**.[6] This compound was esterified and then N-protected to afford a 69% yield of tetrahydroisoquinoline **7**. High-pressure hydrogenation of **7** with 5% ruthenium on alumina[7] cleanly afforded the desired decahydroisoquinoline as a mixture of alcohol epimers. The mixture of diastereomers was oxidized without purification to afford a 78:22 (by GC[8]) mixture of ketones **3a** and **3b**. None of the trans-ring juncture ketones were observed. Ketone (±)-**3a** could be obtained in >99% diastereomeric purity[8] by recrystallization from this mixture with ether and was shown to possess the stereochemistry as shown previously by ^{1}H NMR analysis.[9] The mixture of ketones could be equilibrated to a 13:87 (by GC[8]) mixture of **3a:3b** by treatment with sodium ethoxide in ethanol at reflux, and ketone (±)-**3b** could be crystallized from this mixture with ether in >99% diastereomeric purity.[8] The structure of this ketone (as shown previously) was also confirmed by ^{1}H NMR analysis.[9] The use of the methyl carbamate as a nitrogen protecting group was essential, as the equilibrated ratio of the two cis ring juncture ketones was diminished to 40:60 with the *tert*-butoxycarbonyl group.

The trans ring juncture ketone **3** (Scheme I) was obtained by conversion of **7** to the methyl ether and subse-

Scheme II[a]



[a] The absolute stereochemistry of (−)- and (+)-**3b** is unknown. One enantiomer was arbitrarily chosen for clarity.

(5) Smith, H. A.; Huff, B. J. L.; Powers, W. J., III; Caine, D. *J. Org. Chem.* **1967**, *32*, 2851.

(6) (a) Kato, H.; Koshinaka, E.; Nishikawa, T.; Arata, Y. *J. Pharm. Soc. Jpn.* **1974**, *94*, 934. (b) Saxena, A. K.; Jain, P. D.; Anand, N. *Ind. J. Chem.* **1975**, *13*, 230.

(7) Hydrogenations of tetrahydroisoquinolines with 5% rhodium on alumina are reported to give exclusively the cis decahydroisoquinoline (see ref 4). While we have used this catalyst, we found that more consistent results were obtained with 5% ruthenium on alumina. The products obtained from both hydrogenations were identical.

(8) Gas chromatographic analyses were performed on an HP5890 Series II capillary GC with an Ultra 1 cross-linked methyl silicone column, 25 m × 0.32 mm × 0.52 μM. For ketones **3a** and **3b**, the column was held at 210 °C. The retention times for **3a** and **3b** were 7.12 and 6.53 min, respectively. For the amides formed from **13** and **14**, a temperature program of 180 °C for 1 min, increased by 10 °C/min to 260 °C, then held at 260 °C for 5 min was employed. The retention times were 14.47 min for **13**-amide and 15.34 min for **14**-amide.

(9) Structural assignments for **3a** and **3b** were made from analysis of coupling constants in the ^{1}H NMR. Because of doubling due to amide rotamers, these NMR experiments were performed in DMSO-d_6 at 90 °C. In this solvent and at this temperature, the doubled signals all coalesced to one set of peaks. For **3a**, we observed couplings between H_3 and axial (ax)-H_4 and equatorial (eq)-H_4 of 6.07 Hz each, indicative of equatorial orientation for the proton at C_3, thereby requiring the axial ester. Coupling constants between H_{4a} and ax-H_4 and eq-H_4 of 4.95 and 5.77 Hz indicate an equatorial orientation for H_{4a}, and coupling constants of 11.5 Hz for H_{8a} and ax-H_1 and 5.22 Hz for H_{8a} and eq-H_1 indicate that H_{8a} is axial. Assuming a chairlike conformation for the piperidine ring, the stereochemistry for **3a** would be as shown in the text. For **3b**, we observed couplings between H_3 and ax-H_4 and eq-H_4 of 6.05 and 0.0 Hz, indicative of equatorial orientation for the proton at C_3, again requiring the axial ester. A coupling constant between H_{4a} and ax-H_4 of 13.75 Hz indicates an axial orientation for H_{4a}, and coupling constants of 3.30 and 0.0 Hz for H_{8a} and ax-H_1 and eq-H_1 indicate that H_{8a} is equatorial. Assuming a chairlike conformation for the piperidine ring, the stereochemistry for **3b** would be as shown in the text. For both **3a** and **3b**, we believe that $A_{1,3}$ strain between the ester and carbamoyl group forces the ester into an axial orientation.

quent hydrolysis of the ester to the acid 8 (83%). Dissolving metal reduction of 8 (Li, NH_3, THF, ethanol) afforded an air-sensitive enol ether that was hydrolyzed directly to the unconjugated enone 9. The double bond was brought into conjugation to give the diastereomeric enones 10a (59%) and 10b (12%), which were separable by flash chromatography. The enone 10a was reduced again with lithium in ammonia as in the previous text (91%) and the acid esterified to afford 72% of the desired trans ketone 3c. If 10a was first esterified and then reduced by catalytic hydrogenation (5% Pd/C, ethyl acetate, rt, 60 psi), we obtained the cis ketone 3a, thereby establishing the stereochemistry at C_3 as shown for 10a. Reduction of the enone 10b under the same dissolving metal reduction conditions as for 10a gave an 80:20 mixture (by GC[10]) of the cis ketone 3b and what we presumed was the other trans ketone diastereomer 3d. This mixture was inseparable by chromatography,[10] so that the pure trans ketone diastereomer 3d remains elusive at this point.

We found that amino acids derived from ketone 3b possess the optimal stereochemical arrangement for NMDA antagonist activity and felt that it was important to resolve this compound in order to determine which optical isomer of both LY274614 and LY233536 was most active.[1] Ketone 3b could be easily resolved by conversion (Scheme II) to the corresponding acid 12 and then formation of the diastereomeric salts 13 and 14 with either (*R*)- or (*S*)-α-methylbenzylamine, respectively, in ethyl acetate. One recrystallization from tetrahydrofuran provided material that was ≥98% one diastereomer (vide infra). The salts 13 and 14 were converted to the esters (−)- and (+)-3b, respectively, by treatment with iodoethane in DMF. Thus, resolution with (*R*)-α-methylbenzylamine gave (−)-3b and (*S*)-α-methylbenzylamine gave (+)-3b. We found it convenient to assess the optical purity of the derived ketones through conversion of the salts 13 and 14 to the corresponding amides by treatment with isobutyl chloroformate and *N*-methylmorpholine in dichloromethane. GC analysis of the crude amides showed them to be ≥98% of one diastereomer.[8] We also knew that no epimerization at C_3 had occurred during the hydrolysis, resolution, or esterification, as this would have afforded the ketone 3a, easily detected but not observed by GC.[8]

The synthesis described herein allows for the easy preparation of large quantities of three of the four possible diastereomers of 3, starting from (±)-*m*-tyrosine. The formation of the cis or trans ring juncture is readily controlled by the choice of reduction conditions. These ketones should prove to be useful conjunctive reagents for the preparation of a variety of conformationally restricted amino acids with well-defined stereochemistry. The further elaboration of these compounds to various acidic amino acids, including LY274614 and LY233536, will be described in subsequent publications.

Experimental Section

General Procedures. All experiments were run under a positive pressure of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium prior to use. All other solvents and reagents were used as obtained. ^1H and ^{13}C NMR spectra were obtained at 300.15 and 75.48 MHz, respectively, with TMS as an internal standard. Where necessary, a small amount of 40% potassium deuteroxide in D_2O was added to NMR samples to aid in solution.

6-Hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (6). A suspension of 123 g (0.68 mol) of (±)-*m*-tyrosine and 96 mL of 37% formaldehyde in 1010 mL of 0.05 N HCl was heated to 90 °C (external bath temperature) for 45 min then cooled to rt. The solid was filtered and washed twice with 400 mL each of water and twice with 400 mL each of acetone, then dried in vacuo to afford 91.4 g (70%) of 6. ^1H NMR (D_2O/KOD): δ 6.75 (d, J = 8.2 Hz, 1 H), 6.35 (d, J = 8.2 Hz, 1 H), 6.30 (s, 1 H), 3.77 (d, J = 15.3 Hz, 1 H), 3.69 (d, J = 15.3 Hz, 1 H), 3.26 (dd, J = 10.9, 4.4 Hz, 1 H), 2.79 (dd, J = 16.4, 4.4 Hz, 1 H), 2.60 (dd, J = 16.4, 10.9 Hz, 1 H). Anal. Calcd for $C_{10}H_{11}NO_3 \cdot 0.85H_2O$: C, 57.60; H, 6.13; N, 6.71. Found: C, 57.70; H, 6.43; N, 6.69.

Ethyl 6-Hydroxy-2-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7). HCl gas was bubbled through a suspension of 177.9 g (0.92 mol) of 6 in 2000 mL of ethanol for 20 min, and then the solution was heated to reflux overnight. The resultant mixture was concentrated in vacuo, and then CH_2Cl_2 was added and the mixture again concentrated in vacuo. This procedure was repeated three times (removes the last traces of HCl) to afford 237.3 g of a solid. ^1H NMR (D_2O/DCl): δ 6.73 (d, J = 8.4 Hz, 1 H), 6.41 (d, J = 8.4 Hz, 1 H), 6.34 (s, 1 H), 3.96 (m, 5 H), 2.96 (dd, J = 17.4, 5.4 Hz, 1 H), 2.81 (dd, J = 17.4, 10.8 Hz, 1 H), 0.92 (t, J = 7.1 Hz, 3 H). To this solid in 1200 mL of CH_2Cl_2 and 422 mL (313 g, 2.42 mol) of *i*-Pr_2NEt at 0 °C was added dropwise 71 mL (87 g, 0.92 mol) of methyl chloroformate in 30 mL of CH_2Cl_2. After the mixture was stirred for 20 min more at 0 °C, TLC (silica gel, 5% EtOH/EtOAc) showed a complete reaction. The mixture was diluted with 500 mL of ether and washed once with 1500 mL of 10% aqueous $NaHSO_4$ and once with 500 mL of 10% aqueous $NaHSO_4$. The combined aqueous washes were extracted 3× with 500 mL each of ether, and then the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting solid was triturated with ether and filtered to afford 176.4 g (69%) of 7, mp 123–125 °C. ^1H NMR ($CDCl_3$): δ (doubling due to amide rotamers) 6.95 (m, 1 H), 6.67 (d, J = 8.3 Hz, 1 H), 6.61 (s, 1 H), 5.76 (s, 1 H), 5.06 and 4.85 (m, 1 H), 4.65 (dd, J = 15.7, 6.8 Hz, 1 H), 4.48 (d, J = 15.7 Hz, 1 H), 4.05 (m, 2 H), 3.78 and 3.73 (s, 3 H), 3.11 (m, 2 H), 1.11 (t, J = 7.3 Hz, 3 H). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02. Found: C, 60.49; H, 6.24; N, 4.98.

Ethyl (3*SR*,4a*RS*,8a*SR*)-6-Oxo-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (3b). A 158.9-g (0.57-mol) portion of 7 in 1760 mL of absolute ethanol was hydrogenated with 80 g of 5% Ru/Al_2O_3 at 180 °C and 2000 psi for 16 h. The mixture was cooled, filtered through Celite, and concentrated in vacuo. The resultant oil was redissolved in EtOAc, filtered through Celite, and concentrated in vacuo to afford 156.7 g (97%) of an oil. This material was dissolved in 300 mL of CH_2Cl_2 and added dropwise to a suspension of 260.5 g (1.21 mol) of PCC and 260.5 g of powdered 4-Å molecular sieves in 1400 mL of CH_2Cl_2 (which were stirred 1 h prior to addition of the previous alcohol). After the reaction was judged complete by TLC (50% EtOAc/hexane), it was diluted with ether and filtered through a layer each of Celite and silica gel in a sintered glass funnel, the solids washed well with ether, and the filtrate concentrated in vacuo. The resultant oil was dissolved in ether, filtered again through Celite and silica gel, and the filtrate concentrated in vacuo to afford 128.8 g (83%) of a mixture of 3b and the epimeric 3*RS*,4a*RS*,8a*SR* ketone 3a (3b:3a = 22:78, by GC[8]). This mixture was dissolved in 1000 mL of ethanol and treated with 1.82 g (45.5 mmol) of NaH in 100 mL of ethanol and the mixture heated to reflux for 1.5 h, at which time GC shows an 87:13 mixture of 3b:3a. The mixture was cooled, concentrated in vacuo, dissolved in 800 mL of 1:1 CH_2Cl_2/ether and washed with 600 mL of 10% aqueous $NaHSO_4$. The aqueous wash was extracted 3× with 250 mL each of ether, and then the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. PREP 500 HPLC (gradient elution with hexane to 25% ethyl acetate/hexane) afforded 106.9 (66%) of the mixture of 3b and 3a (3b:3a = 87:13, by GC[8]). Recrystallization from ether gave 67.0 g (41% overall) of 3b, >99% one isomer by GC[8] (mp 78–79 °C). ^1H NMR (DMSO,

(10) GC analysis of the crude reaction mixture from the dissolving metal reduction of 10a (as for 10b) followed by esterification (EtI, $NaHCO_3$, DMF, 60 °C) showed two peaks (same GC conditions[8] as for 3a and 3b) at t_R = 6.29 and 6.53 min in a 20:80 ratio, respectively. The peak at 6.29 min was unique, based on coinjection with 3a–c, and the peak at 6.53 was identical with 3b; the ^1H NMR was also supports the assignment of 3b as the major product from this reduction. On the basis of this evidence, the tentative assignment of 3d as the minor product was made, although we do lack confirmatory ^1H NMR evidence. Thin-layer chromatography with a variety of different ethyl acetate/hexane mixtures showed no separation of these two compounds.

90 °C): δ 4.76 (d, J = 6.0 Hz, 1 H), 4.14 (q, J = 7.2 Hz, 2 H), 3.80 (d, J = 13.5 Hz, 1 H), 3.61 (s, 3 H), 3.21 (b d, J = 13.5 Hz, 1 H), 2.65 (dd, J = 14.3, 6.0 Hz, 1 H), 2.43 (dt, J = 14.0, 7.2 Hz, 1 H), 2.19 (m, 1 H), 2.14 (m, 2 H), 1.98 (ddd, J = 14.3, 5.0, 2.5 Hz, 1 H), 1.88 (m, 1 H), 1.85 (m, 1 H), 1.75 (m, 1 H), 1.65 (dt, J = 6.0, 13.5 Hz, 1 H), 1.20 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$) (doubling due to amide rotamers): δ 210.2 and 210.0, 170.8, 157.1 and 156.6, 61.3, 54.1 and 53.9, 52.9, 46.2, 45.5 and 45.3, 40.1, 33.5, 33.3, 26.8 and 26.7, 24.6, 14.1 Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.62; H, 7.61; N, 4.97.

Ethyl (3*RS*,4a*RS*,8a*SR*)-6-Oxo-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (3a). A 3.35-g portion of the crude ketone (prior to equilibration) from the previous preparation was recrystallized from ether to afford 2.0 g of **3a**, one isomer by GC.[8] The mother liquors afforded a second crop of 0.33 g, one isomer by GC.[8] The total recovery of **3a** was 2.33 g (70%), mp 79–81.5 °C. ^1H NMR (DMSO, 90 °C): δ 4.45 (t, J = 6.1 Hz, 1 H), 4.13 (m, 2 H), 3.78 (dd, J = 13.5, 5.2 Hz, 1 H), 3.62 (s, 3 H), 3.26 (dd, J = 13.5, 11.5 Hz, 1 H), 2.30 (m, 1 H), 2.24 (m, 1 H), 2.19 (m, 1 H), 2.12 (m, 1 H), 2.10 (m, 1 H), 2.01 (m, 1 H), 1.99 (m, 1 H), 1.88 (m, 1 H), 1.81 (m, 1 H), 1.77 (m, 1 H), 1.20 (t, J = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$) (doubling due to amide rotamers): δ 210.4, 172.4, 156.9 and 156.6, 61.4, 52.9, 51.6, 41.8, 40.6 and 40.3, 37.0, 34.1, 32.6, 30.6, 27.9, 14.1. Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.56; H, 7.62; N, 4.91.

6-Methoxy-2-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (8). A solution of 12.8 g (45.9 mmol) of **7**, 15 mL (34.2 g, 240.9 mmol) of methyl iodide, and 6.4 g (45.9 mmol) of K_2CO_3 in 120 mL of acetone was heated to reflux for 6 h, at which time 12 mL more of methyl iodide was added and reflux was continued overnight. The mixture was cooled and filtered through Celite, and EtOAc was added, the mixture filtered again through Celite, and then concentrated in vacuo. The residue was taken up in EtOAc and filtered through Celite and the filtrate concentrated in vacuo to afford 13.5 g (100%) of ethyl 6-methoxy-1-(methoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate. This ester was treated with 46 mL of 1 N NaOH in 120 mL of ethanol overnight at rt. The mixture was concentrated in vacuo then partitioned between EtOAc and 10% aqueous $NaHSO_4$. The aqueous layer was extracted twice more with EtOAc, and then dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was triturated with ether to afford 10.1 g (83%) of **8**, mp 141–142 °C. ^1H NMR ($CDCl_3$) (doubling due to amide rotamers): δ 7.60 (b s, 1 H), 7.03 and 6.98 (d, J = 8.5 Hz, 1 H), 6.75 (d, J = 8.5 Hz, 1 H), 6.65 (s, 1 H), 5.09 and 4.91 (m, 1 H), 4.65 (dd, J = 15.8, 10.4 Hz, 1 H), 4.46 (d, J = 15.8 Hz, 1 H), 3.76 and 3.71 (s, 3 H), 3.76 (s, 3 H), 3.14 (m, 2 H). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.77; H, 5.65; N, 5.21.

(3*SR*,8a*SR*)-6-Oxo-2-(methoxycarbonyl)-1,2,3,4,6,7,8,8a-octahydroisoquinoline-3-carboxylic Acid (10a) and (3*SR*,8a*RS*)-6-Oxo-2-(methoxycarbonyl)-1,2,3,4,6,7,8,8a-octahydroisoquinoline-3-carboxylic Acid (10b). To a solution of 2.0 g (7.5 mmol) of **8** and 0.88 mL (15.1 mmol) of anhydrous ethanol in 25 mL of anhydrous ammonia was added 0.194 g (27.9 mmol) of lithium wire in small (ca. 20-mg) pieces over 25 min. The mixture was stirred for an additional 45 min following addition then quenched with water to discharge the blue color. The solution was concentrated under a stream of dry nitrogen at rt. To the residue was added 15 mL of THF and 30 mL of 1 N HCl, and the mixture was stirred for 45 min and then extracted 3× with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 1.9 g (98%) of **9** as a very air-sensitive oil, used without purification. The unconjugated enone **9** was dissolved in 30 mL of degassed methanol and treated with a solution of 0.33 g (8.1 mmol) of sodium hydride in 10 mL of degassed methanol. After 3.5 h at rt, 20 mL of EtOAc and 20 mL of 10% aqueous $NaHSO_4$ were added, the organic layer was separated and the aqueous layer was extracted 3× more with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on 130 g of silica gel, eluting with 4% HOAc/Et_2O to afford 1.1 g (59%) of **10a** (mp 146–147 °C, ether) and 0.23 g (12%) of **10b**. ^1H NMR **10a** ($CDCl_3$) (doubling due to amide rotamers): δ 8.06 (b s, 1 H), 5.96 (s, 1 H), 5.19 and 5.03 (d, J = 6.9 Hz, 1 H), 4.33 and 4.18 (dd, J = 13.1, 6.0 Hz, 1 H), 3.75 and 3.73 (s, 3 H), 2.2–3.1 (m, 6 H), 2.08 (m, 1 H), 1.60 (m, 1 H). ^1H NMR **10b** ($CDCl_3$): δ 7.39 (b s, 1 H), 5.95 (s, 1 H), 4.61 (m, 1 H), 3.87 (m, 1 H), 3.71 (s, 3 H), 3.19 (m, 1 H), 2.95 (m, 2 H), 2.85 (m, 1 H), 2.43 (m, 2 H), 2.03 (m, 1 H), 1.70 (m, 1 H).

Ethyl (3*SR*,4a*RS*,8a*SR*)-6-Oxo-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (3c). To a −78 °C solution of 0.35 g (50.3 mmol) of lithium wire in 140 mL of anhydrous ammonia was added a solution of 2.6 g (10.2 mmol) of **10b** and 0.60 mL (10.2 mmol) of ethanol in 30 mL of THF. After 15 min at −78 °C, the reaction turned from dark blue to yellow. After being stirred 1 h, the reaction was quenched with 3.3 g (61.2 mmol) of NH_4Cl, and the ammonia was evaporated under a stream of nitrogen. The residue was partitioned between EtOAc and 10% aqueous $NaHSO_4$, the organic layer separated, and the aqueous layer extracted 3× with EtOAc. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 2.4 g (91%) of the desired keto acid. This compound was heated for 2 days at 45 °C with 4.6 g (55.2 mmol) of $NaHCO_3$ and 50 mL of iodoethane in 20 mL of DMF then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 and water, the organic layer separated, and the aqueous layer extracted 3× with CH_2Cl_2. The combined organics were dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was chromatographed on 100 g of silica gel, eluting with 45% EtOAc/hexane to afford 1.9 g (72%) of **3c**. ^1H NMR ($CDCl_3$, doubling due to amide rotamers): δ 5.00 and 4.83 (d, J = 6.5 Hz, 1 H), 4.18 (m, 2 H), 4.04 (m, 1 H), 3.73 and 3.69 (s, 3 H), 2.71 (m, 1 H), 1.90–2.50 (m, 6 H), 1.30–1.65 (m, 4 H), 1.24 (t, J = 7.1 Hz, 3 H). ^{13}C NMR ($CDCl_3$) (doubling due to amide rotamers): δ 209.3, 171.0, 156.7 and 156.3, 61.4, 54.0 and 53.7, 53.0, 47.1, 46.3, 40.7, 39.2, 37.9, 33.9 and 33.7, 29.5, 14.2. Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.29; H, 7.23; N, 4.89.

(−)- and (+)-6-Oxo-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic Acid α-Methylbenzylamine Salts (13, from (*R*)-α-Methylbenzylamine, and 14, from (*S*)-α-Methylbenzylamine). A solution of 20.0 g (70.6 mmol) of **3b** and 77.7 mL of 1 N NaOH in 185 mL of absolute ethanol was stirred overnight at rt then concentrated in vacuo. The residue was partitioned between 200 mL each of EtOAc and 10% aqueous $NaHSO_4$ and the aqueous layer separated and extracted twice with 100 mL each of EtOAc and once with 100 mL of CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 13.6 g (100%) of the acid **12**, used without purification. To this acid **12** in 550 mL of EtOAc was added 9.11 mL (8.56 g, 70.6 mmol) of (*S*)-α-methylbenzylamine and the mixture allowed to stand at rt overnight. The resultant solid was filtered and rinsed with EtOAc to afford 10.8 g of crude **14** (96:4 ratio of diastereomers, as determined by conversion to the amide and GC analysis. See the following procedure.) Recrystallization from THF gave 3.45 g (13%) of **14** (>99% one diastereomer, as determined by conversion to the amide and GC analysis. See the following procedure.) $[\alpha]_D$ = +55.0 (c = 1, H_2O). Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.57; H, 7.42; N, 7.55. The mother liquors from the original crystallization and subsequent recrystallization were combined, concentrated in vacuo, then partitioned between 300 mL of CH_2Cl_2 and 300 mL of 1 N HCl. After being stirred for 0.5 h at rt, the organic layer was separated and the aqueous layer extracted 3× with 50 mL each of CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 7.2 g (28.3 mmol, 40%) of the acid **12**. This acid was dissolved in 280 mL of EtOAc and treated with 3.65 mL (3.49 g, 28.3 mmol) of (*R*)-α-methylbenzylamine. Treatment as for **14** gave 7.71 g (29%) of **13** (99% one diastereomer, as determined by conversion to the amide and GC analysis. See the following procedure.) $[\alpha]_D$ = −57.0 (c = 1, H_2O). Anal. Calcd for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50; N, 7.44. Found: C, 63.87; H, 7.33; N, 7.33.

Ethyl (−)-6-Oxo-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((−)-3b). A mixture of 5.1 g (13.6 mmol) of **13**, 1.71 g (20.3 mmol) of $NaHCO_3$, and 10.8 mL (21.1 g, 135.5 mmol) of iodoethane in 27 mL of DMF was heated at 60 °C overnight. The mixture was cooled and partitioned between 150 mL of CH_2Cl_2 and 150 mL of 10% aqueous $NaHSO_4$. The aqueous layer was separated and extracted twice

with 100 mL of CH_2Cl_2 and once with 100 mL of ether. The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was chromatographed on 200 g of silica gel, eluting with 50% EtOAc/hexane, to afford 3.36 g (88%) of the desired ketone (-)-**3b**. $[\alpha]_D = -51.3$ ($c = 1$, CH_2Cl_2). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.11; H, 7.20; N, 4.90. ^1H NMR in $CDCl_3$ was identical with racemic **3b**.

Ethyl (+)-6-Oxo-2-(methoxycarbonyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate ((+)-3b). As for (-)-**3b**, 5.9 g (15.7 mmol) of **14**, 1.98 g (23.5 mmol) of $NaHCO_3$, and 12.5 mL (24.4 g, 156.7 mmol) of iodoethane in 31 mL of DMF gave 3.96 g (89%) of (+)-**3b**. $[\alpha]_D = +53.4$ ($c = 1$, CH_2Cl_2). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.50; H, 7.46; N, 4.72. ^1H NMR in $CDCl_3$ was identical with racemic **3b**.

Determination of Optical Purity of 13 and 14. To a suspension of 63 mg (0.17 mmol) of **13** in 1.5 mL of CH_2Cl_2 at 0 °C was added 22 μL (0.17 mmol) of isobutyl chloroformate. After being stirred for 30 min, 37 μL (0.34 mmol) of *N*-methylmorpholine was added and the mixture stirred for another 2 h. Another 11 μL of isobutyl chloroformate was added and the mixture stirred for another 20 min, and then 22 μL of (*R*)-α-methylbenzylamine was added and the mixture stirred overnight while warming to rt. TLC (10% HOAc/EtOAc) showed complete reaction. To the reaction mixture was added 10 mL of CH_2Cl_2 and 10 mL of 10% aqueous $NaHSO_4$, and the aqueous layer was separated and extracted twice with 5 mL each of CH_2Cl_2. The combined organics were dried (Na_2SO_4), filtered, and concentrated in vacuo. GC[8] of the crude material shows a 99:1 ratio of epimers (98% ee). By use of the same experimental conditions, **14** showed a >99:<1 ratio of epimers (by GC,[8] >99% ee).

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Synthesis of 1-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (F-ddC). A Promising Agent for the Treatment of Acquired Immune Deficiency Syndrome

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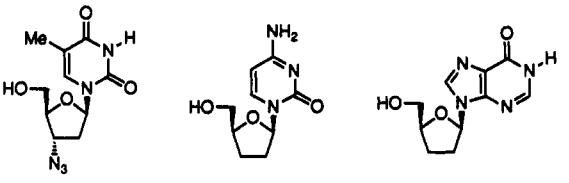
A new and practical synthesis of a fluorinated analogue of 2',3'-dideoxycytidine (ddC), 1-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (F-ddC), is described. The key feature in the synthesis is the use of the selectively protected 2,4,5-trihydroxypentanoic acid derivative **15** as a chiral pool synthon.

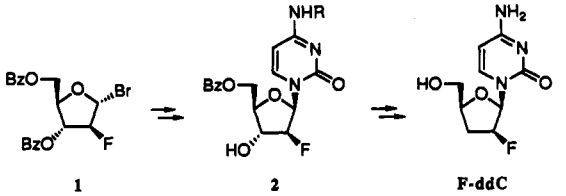
A variety of fluorinated 2',3'-dideoxynucleosides has been prepared by several groups[1] in order to seek out agents that effectively inhibit HIV reverse transcriptase. Other reverse transcriptase inhibitors, such as 3'-deoxy-3'-azidothymidine (AZT),[2] 2',3'-dideoxycytidine (ddC),[3] and 2',3'-dideoxyinosine (ddI)[4] have thus far proven to be the most effective therapeutic agents for the treatment of acquired immune deficiency syndrome (AIDS).[5] As part of our program concerned with finding new ways to prepared dideoxynucleosides with anti-HIV activity,[6] a fluorinated analogue of ddC, 1-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (F-ddC) was prepared. F-ddC has shown significant anti-HIV activity[1b-d] and potentially could show diminished clinical side effects.



AZT ddC ddI

Results and Discussion

In the original preparation of F-ddC,[1a-c] protected 1-(2-deoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine **2** was prepared from 3,5-*O*-dibenzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**1**),[7] and then the 3-hydroxy group was removed by Barton's deoxygenation reaction.



1 2 F-ddC

The requirement for tributyltin hydride in the deoxygenation step is especially vexing as it results in tin contam-

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