Cytidin-3′-yl Uridin-5′-yl Phosphorothioate (R_p Isomer) [8b(R_p), Cp(S)U(R_p)] [from 6b(S_p)]. Yield: 26 mg (88%). ^{31}P NMR data, see Table I. ^{1}H NMR (D_2O; ∂ in ppm): 8.04 (d, ^3J = 8.2 Hz, 1 H, 6-H_U), 7.91 (d, ^3J = 7.5 Hz, 1 H, 6-H_C), 5.92 (d, ^3J = 7.5 Hz, 1 H, 5-H_C), 5.86 (d, ^3J = 2.7 Hz, 1 H, 1′-H_C), 5.82 (d, ^3J = 8.1 Hz, 1 H, 5-H_U), 5.75 (d, ^3J = 2.4 Hz, 1 H, 1′-H_U), 4.61 (ddd, $^3J_{PH}$ = 12.6 Hz, ^3J = 4.9 and 7.7 Hz, 1 H, 3′-H_C), 4.47 (dd, ^3J = 2.5 and 4.7 Hz, 1 H, 2′-H_C), 4.3–4.1 (m, 6 H, 2′-H_U, 3′-H_U, 4′-H_U, 5′-H_U, 4′-H_C), 4.03 (dd, ^2J = 13.2 Hz, ^3J = 2.5 Hz, 1 H, 5′-H_C), 3.90 (dd, ^2J = 13.2 Hz, ^3J = 3.8 Hz, 1 H, 5′-H_C). FAB-mass (negative) 564.1 (M – Na).

Cytidin-3′-yl Uridin-5′-yl Phosphorothioate (S_p Isomer) [8b(S_p), Cp(S)U(S_p)] [from 6b(R_p)]. Yield: 27 mg (92%). ^{31}P NMR data, see Table I. ^{1}H NMR (D_2O; ∂ in ppm): 8.00 (d, ^3J = 8.1 Hz, 1 H, 6-H_C), 7.94 (d, ^3J = 8.0 Hz, 1 H, 6-H_U), 6.12 (d, ^3J = 7.8 Hz, 1 H, 5-H_C), 5.93 (d, ^3J = 3.3 Hz, 1 H, 1′-H_U), 5.89 (d, ^3J = 8.0 Hz, 1 H, 5-H_U), 5.88 (d, ^3J = 3.8 Hz, 1 H, 1′-H_C), 4.71 (dt, $^3J_{PH}$ = 11.0 Hz, ^3J = 5.5 Hz, 1 H, 3′-H_C), 4.47 (t, ^3J = 4.0 Hz, 1 H, 2′-H_C), 4.3–4.1 (m, 6 H, 2′-H_U, 3′-H_U, 4′-H_U, 5′-H_U, 4′-H_C), 3.96 (dd, ^2J = 12.8 Hz, ^3J = 2.6 Hz, 1 H, 5′-H_C), 3.85 (dd, ^2J = 12.8 Hz, ^3J = 4.0 Hz, 1 H, 5′-H_C). FAB-mass (negative) 564.1 (M – Na).

Guanosin-3′-yl Uridin-5′-yl Phosphorothioate (R_p Isomer) [8c(R_p), Gp(S)U(R_p)] [from 6c(S_p)]. Yield: 25 mg (81%). ^{31}P NMR data, see Table I. ^{1}H NMR (D_2O; ∂ in ppm): 8.0 (s, 1 H, 8-H_G), 7.9 (d, ^3J = 8.2 Hz, 1 H, 6-H_U), 5.91 (d, ^3J = 4.7 Hz, 1 H, 1′-H_G), 5.90 (d, ^3J = 2.6 Hz, 1 H, 1′-H_U), 5.80 (d, ^3J = 8.1 Hz, 1 H, 5-H_U), 4.46 (m, 1 H, 3′-H_G), 4.8 (t, ^3J = 4.8, 1 H, 2′-H_G), 4.46 (t, ^3J = 3.3, 1 H, 2′-H_U), 4.2–4.1 (m, 5 H, 3′-H_U, 4′-H_U, 5′-H_U, 4′-H_G), 3.98 (dd, ^2J = 12.8 Hz, ^3J = 2.9 Hz, 1 H, 5′-H_G), 3.89 (dd, ^2J = 12.8 Hz, ^3J = 4.0 Hz, 1 H, 5′-H_G). FAB-mass (negative) 604.2 (M – Na).

Guanosin-3′-yl Uridin-5′-yl Phosphorothioate (S_p Isomer) [8c(S_p), Gp(S)U(S_p)] [from 6c(R_p)]. Yield: 28 mg (89%). ^{31}P NMR data, see Table I. ^{1}H NMR (D_2O; ∂ in ppm): 8.0 (s, 1 H, 8-H_G), 7.9 (d, ^3J = 8.1 Hz, 1 H, 6-H_U), 5.93 (d, ^3J = 4.0 Hz, 1 H, 1′-H_U), 5.91 (d, ^3J = 5.5 Hz, 1 H, 1′-H_G), 5.85 (d, ^3J = 8.1 Hz, 1 H, 5-H_U), 5.0 (m, 1 H, 3′-H_G), 4.90 (t, ^3J = 5.5 Hz, 1 H, 2′-H_G), 4.4–4.1 (m, 6 H, 2′-H_U, 3′-H_U, 4′-H_U, 5′-H_U, 4′-H_G), 3.95 (dd, ^2J = 12.8 Hz, ^3J = 2.9 Hz, 1 H, 5′-H_G), 3.85 (dd, ^2J = 12.8 Hz, ^3J = 4.0 Hz, 1 H, 5′-H_G). FAB-mass (negative), 604.2 (M – Na).

Uridin-3′-yl Uridin-5′-yl Phosphorothioate (R_p Isomer) [8d(R_p), Up(S)U(R_p)] [from 6d(S_p)]. Yield: 25 mg (85%). ^{31}P NMR data, see Table I. ^{1}H NMR (D_2O; ∂ in ppm, symbol * indicates protons in the uridin-5′-yl unit of the dimer): 7.97 (d, ^3J = 8.1 Hz, 1 H, 6-H_{U*}), 7.86 (d, ^3J = 8.2 Hz, 1 H, 6-H_U), 5.91 (d, ^3J = 3.7 Hz, 1 H, 1′-H_{U*}), 5.88 (d, ^3J = 8.2 Hz, 1 H, 5-H_U), 5.85 (d, ^3J = 4.3 Hz, 1 H, 1′-H_U), 5.84 (d, ^3J = 8.2 Hz, 1 H, 5-H_{U*}), 4.72 (dt, $^3J_{PH}$ = 11.4 Hz, ^3J = 5.5 Hz, 1 H, 3′-H_U), 4.44 (t, ^3J = 4.8 Hz, 1 H, 2′-H_U), 4.3–4.2 (m, 6 H, 2′-H_{U*}, 3′-H_{U*}, 4′-H_{U*}, 5′-H_{U*}, 4′-H_U), 3.94 (dd, ^2J = 13.0 Hz, ^3J = 2.7 Hz, 1 H, 5′-H_U), 3.84 (dd, ^2J = 13.0 Hz, ^3J = 4.2 Hz, 1 H, 5′-H_U). FAB-mass (negative), 565.0 (M – Na).

Uridin-3′-yl Uridin-5′-yl Phosphorothioate (S_p Isomer) [8d(S_p), Up(S)U(S_p)] [from 6d(R_p)]. Yield: 27 mg (92%). ^{31}P NMR data, see Table I. ^{1}H NMR (D_2O; ∂ in ppm, symbol * indicates protons in the uridin-5′-yl unit of the dimer): 7.93 (d, ^3J = 8.2 Hz, 1 H, 6-H_{U*}), 7.84 (d, ^3J = 8.2 Hz, 1 H, 6-H_U), 5.92 (d, ^3J = 3.8 Hz, 1 H, 1′-H_{U*}), 5.89 (d, ^3J = 8.5 Hz, 1 H, 5-H_{U*}), 5.87 (d, ^3J = 4.7 Hz, 1 H, 1′-H_U), 5.86 (d, ^3J = 8.4 Hz, 1 H, 5-H_U), 4.74 (dt, $^3J_{PH}$ = 10.6 Hz, ^3J = 5.1 Hz, 1 H, 3′-H_U), 4.45 (t, ^3J = 5.1 Hz, 1 H, 2′-H_U), 4.3–4.2 (m, 6 H, 2′-H_{U*}, 3′-H_{U*}, 4′-H_{U*}, 5′-H_{U*}, 4′-H_U), 3.91 (dd, ^2J = 12.8 Hz, ^3J = 2.7 Hz, 1 H, 5′-H_U), 3.81 (dd, ^2J = 12.8 Hz, ^3J = 4.0 Hz, 1 H, 5′-H_U). FAB-mass (negative), 565.0 (M – Na).

Enzymatic Hydrolysis of 8a–d Using Snake Venom Phosphodiesterase (SVPD). One milligram of each diastereomer of the phosphorothioate 8 was dissolved in a buffer solution (100 μL; 2 mM $MgCl_2$ and 50 mM Tris-HCl, pH = 8.9) and snake venom phosphodiesterase (SVPD) from *C. atrox* (1 mg of the enzyme dissolved in the same buffer; 100 μL) was added. The samples were kept on a water bath at 37 °C overnight. TLC analysis (2-propanol–ammonia–water, 7:1:2, v/v/v) revealed that all samples of **8a–d** obtained from the diastereomers of **6** that had more downfield ^{31}P NMR signals were cleaved to a substantial degree (hence, identified as the R_p isomers of 8), whereas the phosphorothioates **8a–d** deriving from the diastereomers of H-phosphonates **6a–d** with more upfield ^{31}P NMR shifts were completely resistant toward enzymatic hydrolysis (the S_p diastereomers of 8).

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Registry No. **1a**, 58-61-7; **1b**, 65-46-3; **1c**, 118-00-3; **1d**, 58-96-8; **3**, 143294-18-2; **4a**, 143294-14-8; **4b**, 143294-15-9; **4c**, 143294-16-0; **5a**, 143294-19-3; **5b**, 143294-20-6; **5c**, 143294-21-7; (R_p)-**6a**, 143294-22-8; (S_p)-**6a**, 143344-21-2; (R_p)-**6b**, 143294-23-9; (S_p)-**6b**, 143344-22-3; (R_p)-**6c**, 143294-24-0; (S_p)-**6c**, 143344-23-4; (R_p)-**6d**, 143294-25-1; (S_p)-**6d**, 143344-24-5; (R_p)-**7a**, 143294-26-2; (S_p)-**7a**, 143344-25-6; (R_p)-**7b**, 143294-27-3; (S_p)-**7b**, 143344-26-7; (R_p)-**7c**, 143294-28-4; (S_p)-**7c**, 143344-27-8; (R_p)-**7d**, 143294-29-5; (S_p)-**7d**, 143344-28-9; (R_p)-**8a**, 143344-29-0; (S_p)-**8a**, 143344-30-3; (R_p)-**8b**, 143059-90-9; (S_p)-**8b**, 143059-89-6; (R_p)-**8c**, 143294-30-8; (S_p)-**8c**, 143344-31-4; (R_p)-**8d**, 143344-32-5; (S_p)-**8d**, 143344-33-6; SiOMb-Cl, 129452-86-4; phosphodiesterase, 9025-82-5.

Asymmetric Synthesis of (*S*)-4-Aminohex-5-enoic Acid: A Potent Inhibitor of 4-Aminobutyrate-2-oxoglutarate Aminotransferase[1a]

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The potent inhibitor of 4-aminobutyrate-2-oxoglutarate aminotransferase (GABA-T), 4-aminohex-5-enoic acid (vinyl GABA), has been synthesized with excellent enantioselectivity in six steps from L-glutamic acid in an overall yield of 33%. This is the most efficient synthesis of this important compound and illustrates the use of a novel alkenyl protecting group for pyroglutamate. This allowed the preparation and manipulation of the key (*S*)-2-oxopyrrolidine-5-carboxaldehyde intermediate.

4-Aminobutanoic acid (γ-aminobutyric acid, GABA, 1) is an important neurotransmitter in mammalian systems.[2] GABA deficiency has been associated with a variety of neurological disorders including Parkinson's disease,[3] ep-

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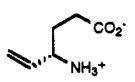
ilepsy,[2] and Huntington's chorea.[4] GABA is metabolized by 4-aminobutyrate-2-oxoglutarate aminotransferase (GABA aminotransferase, GABA-T), a mitochondrial enzyme found in synaptic neurons, to succinic semialdehyde. This is further metabolized to succinimide and γ-hydroxybutyrate.[5] Inhibitors of GABA-T are of interest as anticonvulsant agents.[6] Treatment of neurological disorders with GABA is severely limited due to the inability of GABA to efficiently cross the blood–brain barrier (BBB) and the poor synaptic uptake of synthetic GABA.[7] Attempts to circumvent this problem have focused on development of GABA mimics such as baclofen[8] and muscimol,[8c,9] which have had some success. A highly attractive alternative focuses on irreversible inactivation of the enzyme GABA-T, a pyridoxal phosphate-dependent enzyme which operates via tautomerism of the Schiff base formed between GABA and pyridoxal phosphate.[5] It has been shown that (*S*)-4-aminohex-5-enoic acid (vinyl GABA, **2**) inactivates GABA-T by selective reaction with the pyridoxal aldehyde moiety.[10] The net result of GABA-T inhibition by **2** (or by other related inhibitors) is an increase in the levels of GABA in the central nervous system (CNS) and the brain. (*S*)-4-Aminohex-5-enoic acid (**2**) therefore functions as a selective catalytic inhibitor of GABA-T.[10]

1

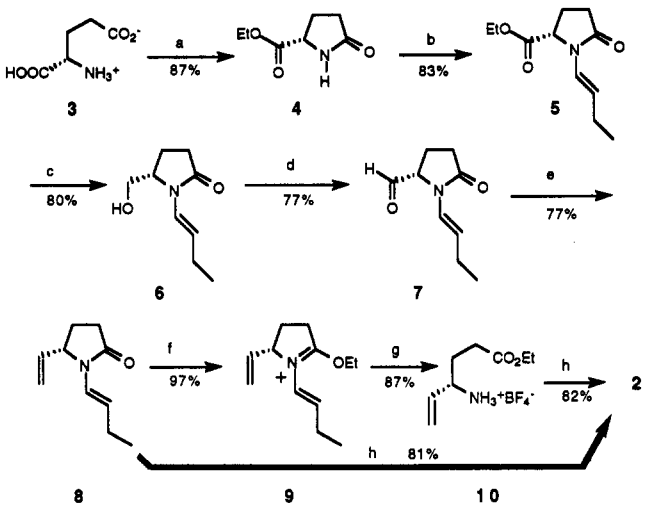


2

Our work with asymmetric Diels–Alder reactions and radical cyclizations used functionalized alkenyl lactams, and this suggested an efficient and enantioselective synthesis of vinyl GABA, **2**. The chiral precursor used for this synthesis is L-glutamic acid (**3**), and the key feature of the synthesis is the use of an *N*-alkenyl moiety to both protect the lactam nitrogen and function as a trigger for facile conversion of the protected lactam to the required GABA derivative. This alkenyl protecting group allowed the formation of a (*S*)-2-oxopyrrolidine-5-carboxaldehyde moiety (**7**) which allowed a Wittig reaction to proceed with great facility, incorporating the requisite ethenyl group.

Metcalf synthesized racemic **2** by converting propargyl amine to a triply protected alkynyl derivative of 4-amino-5-hexynoic acid in six steps.[10,11] Deprotection of an intermediate silylalkyne was followed by reduction of the triple bond (Li/NH_3) to produce racemic **2**. An asymmetric synthesis has also been reported in the patent literature. In Frieben and Fritz's synthesis,[12] glutamic acid (**3**) was converted to (*S*)-ethyl pyroglutamate (**4**) with thionyl chloride and ethanol.[13] Reduction of the ester with lithium borohydride produced 5-(hydroxymethyl)-2-pyrrolidinone. Mesylation and reaction with cyanide gave the cyanomethyl derivative, which was converted to the (dimethylamino)methyl derivative. Oxidation to the *N*-oxide was followed by a Cope elimination to produce 5-vinyl-2-pyrrolidinone. Acid hydrolysis gave **2** in a total of nine steps.[12] This is a very reasonable synthesis, but our work with pyroglutamate suggested a similar but more efficient route.

Scheme I[a]



[a] (a) $SOCl_2$, EtOH; (b) butanal, P_2O_5, PhMe, reflux; (c) $NaBH_4$, EtOH, 0 °C → rt, 18 h; (d) DMSO/DCC, py, cat. TFA; (e) $Ph_3P^+–CH_3Br^-$, t-BuOK, THF; (f) $Et_3O^+BF_4^-$, ether; (g) H_2O, 25 °C; (h) 5% aqueous HCl.

Our synthesis also began with (*S*)-ethyl pyroglutamate ((*S*)-5-carbethoxy-2-pyrrolidinone, **4**) and is outlined in Scheme I. In our first attempt at this synthesis, **4** was reacted with butanal (toluene, catalytic amount of *p*-TsOH, 5 h, Dean–Stark head)[14] to generate the *N*-butenyl derivative, **5**. The butenyl group is a very effective protecting group for lactams of this type. Subsequent reduction with borohydride gave **6**. An analysis of the MPTA (Mosher's) ester[15] of this alcohol as well as an analysis of the ester derived from menthoxyacetyl chloride indicated a 70:30 *S*:*R* mixture of **6**. The tosic acid catalyst required for the alkenylation reaction had caused partial racemization of the ester moiety. Subsequent steps (vide infra) did not lead to racemization. Racemization in this early step was easily corrected by changing the catalyst from tosic acid to phosphorus pentoxide. Identical treatment of **4** with butanal in the presence of P_2O_5 gave **5** in 83% yield. Reduction with sodium borohydride then

(1) (a) Presented, in part, at the 195th National Meeting of the American Chemical Society, ORGN 273, June 8, 1988, Toronto, Canada. (b) Taken, in part, from the Ph.D. Thesis of T.W.K., current address: Department of Chemistry, Kyung Sung University, Pusan, Korea.

(2) (a) Krogsgaard-Larsen, P.; Scheel-Kruger, J.; Kofid, H. *GABA-Neurotransmitters*; Munksgaard: Copenhagen, 1979. (b) Enna, S. J., Ed. *The GABA Receptors*; The Humana Press: Clifton, NJ, 1983.

(3) Lloyd, K. G.; Sheman, L.; Hornykiewicz, O. *Brain Res.* **1977**, *127*, 269–278.

(4) (a) Perry, T. L.; Hansen, S.; Kloster, M. N. *N. Engl. J. Med.* **1973**, *288*, 337–342. (b) Perry, T. L.; Hansen, S.; Urquhart, N. *Lancet* **1974**, *7*, 995–996.

(5) Roberts, E. *Biochem. Pharmacol.* **1974**, *23*, 2637–2649.

(6) Hammond, E. J.; Wilder, B. J. *Gen. Pharmacol.* **1985**, *16*, 441–447.

(7) (a) Bodor, N.; Brewster, M. E. *Pharm. Ther.* **1983**, *19*, 337–386. (b) Pardridge, W. M. *Annu. Rep. Med. Chem.* **1985**, *20*, 305–313. (c) Pardridge, W. M. *J. Cereb. Blood Flow Metab.* **1983**, *3*, 400–401. (d) Pardridge, W. M. *Directed Drug Delivery* **1985**, 83–96. (e) Oldendorf, W. H. *Res. Methods Neurochem.* **1981**, *5*, 91–112. (f) Bodor, N. In *Optimization of Drug Delivery*; Bundgaard, H., Hanser, A. B., Kofod, H., Eds.; Munksgaard: Copenhagen, 1982; p 156. (g) Oldendorf, W. H. *Adv. Physiol. Sci. Proc. Int. Congr., 28th* **1980**, *7*, 349–353.

(8) (a) Curtis, D. R.; Duggan, A. W.; Felix, D.; Johnston, G. A. R. *Brain Res.* **1971**, *32*, 69–96. (b) Davies, J.; Watkins, J. C. *Ibid.* **1974**, *70*, 501–505. (c) Curtis, D. R.; Lodge, D.; Bornstein, J. C.; Peet, M. J. *Exp. Brain Res.* **1981**, *42*, 158–170. (d) Bernard, P. S.; Sobiski, R. E.; Dawson, K. M. *Brain Res. Bull.* **1980**, *5* (Suppl 2), 519–523.

(9) (a) Krogsgaard-Larsen, P.; Johnston, G. A. R. *J. Neurochem.* **1978**, *30*, 1377–1382. (b) Johnston, G. A. R.; Curtis, D. R.; DeGroat, W. C.; Duggan, A. W. *Biochem. Pharmacol.* **1968**, *17*, 2488–2489.

(10) Lippert, B.; Metcalf, B. W.; Jung, M. J.; Casara, P. *Eur. J. Biochem.* **1977**, *74*, 441–445.

(11) (a) Metcalf, B. W.; Casara, P. *Tetrahedron Lett.* **1975**, 3337–3340. (b) Metcalf, B. W. *Biochem. Pharmacol.* **1979**, *28*, 1705–1712. (c) Metcalf, B. W.; Jung, M. U.S. Patent 3 960 927; *Chem. Abstr.* **1976**, *85*, 143512j. (d) U.S. Patent 4 041 041; *Chem. Abstr.* **1977**, *87*, 200807b. (e) U.S. Patent 4 039 549; *Chem. Abstr.* **1977**, *87*, 184965u.

(12) Frieben, W.; Fritz, G. Brit. UK Patent Appl. GB 2 133 002; *Chem. Abstr.* **1984**, *101*, 231027j.

(13) (a) Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815–818. (b) Adkins, H.; Billica, H. R. *J. Am. Chem. Soc.* **1948**, *70*, 3121–3125.

(14) Zezza, C. A.; Smith, M. B. *Synth. Commun.* **1987**, *17*, 729–740.

(15) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–2549.

produced 6 in 80% yield. Analysis of the Mosher's ester of this alcohol showed greater than 99% retention of configuration at C_5.

The importance of the butenyl group in the synthesis is apparent in the next step, which involved oxidation of the hydroxymethyl moiety of 6 to the 5-carboxaldehyde derivative, 7. If the nitrogen of 5-carbethoxy-2-pyrrolidinone is unprotected, it is subject to facile racemization under very mild conditions. The *N*-alkenyl aldehyde 7, however, is remarkably stable to neutral and basic conditions. Presumably, the linear nature of the alkenyl lactam moiety and the orthogonal nitrogen lone electron pair diminishes the acidity of the C_5 hydrogen. In addition, there is no special stability of the enolate that would result from removal of that hydrogen, due to electron repulsion of the adjacent filled orbitals on nitrogen. A variety of oxidation methods were used to convert 6 to 7, but only Moffatt oxidation provided reasonable yields. Oxidation of 6 with PCC or PDC gave only 15% and 10%, respectively, of 7. Collin's oxidation led to 40% of 7. Moffatt oxidation (DMSO, DCC)[16] gave 85% of the desired aldehyde, but surprisingly, Swern oxidation (oxalyl chloride, DMSO, −60 °C) gave only 21% of 7. The C_5-hydroxymethyl group in 6 is rather hindered, accounting for the low yields with the chromium-based oxidants. Swern oxidation[17] is supposedly the reaction of choice for hindered alcohols,[17] but it gave poorer yields than Moffatt oxidation in this case. We do not, at this time, have a reasonable explanation for this observation. Our results stand in sharp contrast to the oxidation of prolinol derivatives, which gave good yields of the aldehyde with a variety of oxidation agents.[18]

No racemization of the C_5 center in 7 was observed with any of our oxidation procedures. Isolation of the pure aldehyde required several passes through a silica gel column due to the presence of DMSO and dicyclohexylurea. Although effective for purification, this repeated chromatography led to diminished yields of 7. Aldehyde 7 could be stored, under desiccation, in the refrigerator for several weeks without a problem. At room temperature and exposed to the air, however, it showed signs of racemization in 1–2 days. An expedient that improved the overall yield of 2 was to remove the dicyclohexylurea by filtration and immediately subject the aldehyde to Wittig conditions. Reaction of 7 with methyltriphenylphosphonium bromide (THF, potassium *tert*-butoxide, 10 h, ambient temperatures) provided a 77% yield of the requisite (*S*)-5-ethenyl-1-(1-butenyl)-2-pyrrolidinone, 8. This proved to be the best method for generating the ylid.[19] The use of *n*-butyllithium in THF, for example, gave only 43% of 8, and NaH in DMSO at 80 °C gave 15% of 8.

It is well known that 2-pyrrolidinone reacts with 6 N HCl to give GABA, and it was also known that 5-ethenyl-2-pyrrolidinone reacted with 5% HCl to give vinyl GABA in the synthesis of Frieben and Fritz.[12] This suggested direct treatment of 8 with 5% HCl, and this procedure produced an 81% yield of 2. The spectral data were completely consistent with the structure of 2 and the specific rotation ($[\alpha]^{25}_D = +12.5°$, $c = 0.095$ g/mL, H_2O at pH 6.6) was identical to that reported by Merrel Dow ($[\alpha]^{23}_D = +12.3 \pm 0.3°$, $c = 0.200$ g/mL, H_2O at pH 6.6).[20]

We initially believed that a mild hydrolysis was required for the conversion of 8 to 2. In previous work we discovered that *N*-alkenyl-2-pyrrolidinone derivatives could be converted to a pyrrolidiniminium salt upon treatment with triethyloxonium tetrafluoroborate.[21] Subsequent dissolution in neutral water generated the ethyl ester of GABA (ethyl 4-aminobutanoate, 1) with a half-life of 8 min.[21] Prior to the more convenient conversion of 8 to 2, we believed this "milder" procedure would be the best method. Reaction of 8 with triethyloxonium tetrafluoroborate generated 9 in 97% yield. Subsequent dissolution of 9 in water provided the ethyl ester of vinyl GABA as the ammonium tetrafluoroborate (10) in 87% yield. Although the saponification of 10 to 2 was successful (82%), the free amino acid was difficult to separate in pure form from the tetrafluoroborate salts and tetrafluoroboric acid. Passage through Dowex 200 provided some purification but also gave 5-vinyl-2-pyrrolidinone as a significant byproduct. The severe problems with isolation and the propensity for cyclization of the interemediate product clearly indicated that the iminium salt hydrolysis procedure was inferior to the direct hydrolysis of 8. We were concerned about the integrity of the chiral center after the oxidation and Wittig olefination sequence. We therefore treated a sample of 10 (derived from 8) with methoxyacetyl chloride and showed, by GC/MS and HPLC analysis, that the resulting amide existed as a single diastereomer, confirming that no racemization had occurred during the oxidation or Wittig steps.

This straightforward synthetic route supplies (*S*)-4-amino-5-hexanoic acid (2) in 33% overall yield from 3 in six synthetic steps, and the last three can be performed without isolation of the intermediate products. The synthesis provides enantiomerically pure 2 in an highly efficient manner. A salient feature of this synthesis is the use of the butenyl protecting group, which allows manipulation of the 5-carboxaldehyde (7) and also unmasking vinyl GABA from 8 with aqueous acid. In addition, this is the most efficient route to this important CNS agent yet reported and provides a route to both 7 and 8, which can be used as intermediates for the asymmetric synthesis of other biologically important 2-pyrrolidinone derivatives.

Experimental Procedures

Melting points were taken on a Thomas-Hoover capillary melting point apparatus. All melting and boiling points are uncorrected. Infrared spectra were recorded with a Perkin-Elmer infrared spectrophotometer Model 283 and recorded in reciprocal centimeters. ^{1}H NMR spectra were determined in chloroform-*d* solution on a IBM 270-MHz spectrometer and determined in ppm using tetramethylsilane as an internal standard. High-resolution mass spectra were measured on an AEI MS-902 mass spectrometer and are accurate to 5 mmu. The specific rotations were obtained on an O.C. Rudolph polarimeter using the sodium D line. All specific rotation concentrations are reported in grams per milliliter. The apparatus for experiments requiring anhydrous conditions was flame-dried, allowed to cool in a desiccator over calcium chloride, and flushed with argon prior to use. L-Glutamic acid, L-menthoxyacetic acid, thionyl chloride, *n*-butyllithium, potassium *tert*-butoxide, (methyl)triphenylphosphonium bromide, sodium borohydride, and lithium bromide were purchased from Aldrich. Absolute ethanol was obtained from USI Chemicals Co. Absolute ether and THF were distilled from sodium/benzophenone. Methylene chloride was distilled from calcium hydride. During workup of the reactions, general drying of the solvent was per-

(16) (a) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5661–5670. (b) *Ibid.* **1965**, *87*, 5670–5678.

(17) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

(18) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654–655.

(19) Other C_5-alkenyl derivatives can be prepared via this procedure. One additional example is the reaction of 7 with benzyltriphenylphosphonium bromide and *t*-BuOK, in THF, giving a 65% yield of 5-(phenylethenyl)-*N*-(1-butenyl)-2-pyrrolidinone.

(20) $[\alpha]^{23}_D = +12.3°$, $c = 0.200$ g/mL, H_2O at pH 6.6. We thank Dr. N. Seiler and Merrel-Dow (Strasbourg, France) for kindly providing specific rotation data for both (*S*)- and (*R*)-vinyl GABA (2).

(21) (a) Smith, M. B.; Shroff, H. N. *J. Org. Chem.* **1984**, *49*, 2900–2906. (b) *Tetrahedron Lett.* **1983**, *24*, 2091–2094.

formed over anhydrous magnesium sulfate or anhydrous sodium sulfate as indicated. Thin-layer plates were made of E. Merck AG Darmstadt silica gel pf-254. In all cases, the products were purified by column chromatography to a single spot on TLC. Column chromatography was performed with silica gel 60 (70–230 mesh) from E. Merck.

(*S*)-(+)-5-Carbethoxy-2-pyrrolidinone (4). The procedure of Adkins and Billica[13] was modified as follows. Sixty milliliters (0.8 mol) of freshly distilled thionyl chloride was added to a suspension of L-glutamic acid (**3**, 51.2 g, 0.4 mol) in 500 mL of commercial absolute ethanol cooled in an ice bath. The solution was stirred at room temperature for 1 h. The pale yellow solution was neutralized by potassium hydroxide in ethanol, the potassium chloride was filtered, and the ethanol was distilled off under reduced pressure. The crude product was heated to 140–150 °C under reduced pressure for 3 h or until frothing and bubbling ceased. The ester was first distilled through a Vigreux column 6–8 cm in length at 155–156 °C (3 mmHg), and subsequent crystallization from ethanol gave **4** as colorless needles, mp 50–51 °C (lit. mp 51–52 °C,[13b] 48–50 °C[13a]) (47.8 g, 0.3 mol, 87%): ^{1}H NMR ($CDCl_3$) δ 1.3 (3 H, t), 2.3 (4 H, m), 4.1 (3 H, m), 7.2 (1 H, br); ^{13}C NMR ($CDCl_3$) δ 14.4 (q), 22 (t), 29.5 (t), 56 (d), 61.6 (t), 152 (2), and 180 (s) ppm; IR (neat, KBr) 3230 (br), 1740 (s), 1700 (s), 1200 (s), 1100 (m), 1040 (m), and 740 (br) cm^{-1}; mass spectrum (m/z, relative intensity) P^+ 157 (14), 135 (8), 129 (80), 127 (6), 99 (8), 95 (8), 84 (10), 83 (100), 73 (8), 56 (44), and 55 (6); $[\alpha]^{25}_D$ = +2.4° (c = 10, EtOH).

(*S*)-(+)-5-Carbethoxy-*N*-(1-butenyl)-2-pyrrolidinone (5). A solution of 170 mL of dry toluene (distilled from sodium), 22.6 g (144.5 mmol) of (*S*)-(+)-5-carbethoxy-2-pyrrolidinone (**4**), and 10.4 g (19 mL, 144.5 mmol) of butanal (distilled from calcium chloride) was stirred at ambient temperature and then treated with 21.29 g of P_2O_5 (150 mmol). A Dean–Stark trap was added to remove water, and the solution was refluxed for 12 h. The solution was cooled to room temperature, the toluene was decanted, and the product was washed with 2 × 100 mL of saturated sodium bicarbonate solution. The remaining semisolid was dissolved in water, neutralized with sodium bicarbonate, and extracted with 3 × 100 mL of ether. The organic phases were combined and dried with magnesium sulfate. The solution was filtered and concentrated under vacuum. The mixture was distilled (Kugelrohr, oven temperature 155–160 °C, 3 mmHg; chromatography: SiO_2/ether) to give 25.1 g (118.5 mmol, 82%) of (*S*)-(+)-5-carbethoxy-*N*-(1-butenyl)-2-pyrrolidinone (**5**) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 0.99 (3 H, t, J = 7.4 Hz), 1.29 (3 H, t, J = 7.15 Hz), 2.09–2.20 (2 H, m), 2.30–2.47 (2 H, m), 2.60 (2 H, m), 4.21 (2 H, q, J = 7.15 Hz), 4.36 (1 H, dd, J = 2.0, 9.1 Hz), 4.91 (1 H, dt, J = 6.7, 14.7 Hz), and 6.82 ppm (1 H, d, J = 14.7 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2 (q), 14.3 (q), 22.9 (t), 23.3 (t), 29.8 (t), 58.7 (t), 61.6 (d), 114.4 (d), 122.2 (d), 171.6 (s), and 172.9 ppm (s); IR (neat, KBr) 3230 (br), 1740 (s), 1700 (s), 1200 (s), 1100 (m), 1040 (m), and 740 (br) cm^{-1}; mass spectrum (m/z, relative intensity) P^+ 211 (3), 196 (3), 183 (1), 168 (2), 139 (9), 138 (100), 122 (1), 110 (8), 95 (3), 94 (4), 84 (6), 80 (3), 70 (4), 68 (5), 67 (4), 55 (9), 54 (5), and 51 (1); HRMS calcd for $C_{11}H_{17}NO_3$ 211.1218, found 211.1209 (±0.9 mmu); $[\alpha]^{25}_D$ = −16.4° (c = 0.052, CH_2Cl_2).

(*S*)-(+)-5-(Hydroxymethyl)-*N*-(1-butenyl)-2-pyrrolidinone (6). A mixture of 0.09 g (2.38 mmol) of $NaBH_4$ in 5 mL of anhydrous ethanol was stirred under argon for 20 min at room temperature and treated with a solution of 0.43 g (2.2 mol) of (*S*)-(+)-5-carbethoxy-*N*-(1-butenyl)-2-pyrrolidinone (**5**) in 5 mL of ethanol at 0 °C. The solution was stirred 18 h at room temperature, cooled in an ice bath, and quenched by the slow addition of 50 mL of acetone. The reaction mixture was filtered, the solvents were evaporated under reduced pressure, and the remaining oil was purified by silica gel chromatography (5% methanol + 95% CH_2Cl_2, R_f = 0.2) to give 0.27 g (1.76 mmol, 80%) of (*S*)-5-(hydroxymethyl)-*N*-(1-butenyl)-2-pyrrolidinone (**6**): ^{1}H NMR ($CDCl_3$) δ 0.99 (3 H, t, J = 7.4 Hz), 2.21 (2 H, m), 2.34 (2 H, m), 2.60 (2 H, m), 3.6–3.9 (3 H, m), 4.41 (1 H, dd, J = 1.1, 9.3 Hz), 4.94 (1 H, dt, J = 6.2, 14.7 Hz), and 6.70 ppm (1 H, dd, J = 1.1, 14.8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4 (q), 21.7 (t), 23.6 (t), 30.8 (t), 58.4 (t), 61.2 (d), 115.1 (d), 121.8 (d), and 174.0 ppm (s); IR (neat) 3400 (br), 1680 (s), 1410 (m), 1280 (m), and 1110 (m) cm^{-1}; mass spectrum (m/z, relative intensity) P^+ (22), 138 (100), 110 (8), 126 (5), 96 (12), 84 (15), 70 (18), and 55 (25); HRMS calcd for $C_9H_{15}NO_2$ 169.1104, found 169.1095 (±0.9 mmu); $[\alpha]^{25}_D$ = −2.0° (c = 0.056, CH_2Cl_2).

(*S*)-(+)-*N*-(1-Butenyl)-2-oxopyrrolidine-5-carboxaldehyde (7). Dissolution of 0.5 g (3.0 mmol) of (*S*)-(+)-5-(hydroxymethyl)-*N*-(1-butenyl)-2-pyrrolidinone (**6**) in 10 mL of dry benzene was followed by addition of 10 mL of dry dimethyl sulfoxide. The clear solution was then treated with 0.2 mL (3.0 mmol) of anhydrous pyridine (distilled from calcium hydride), 0.1 mL (1.5 mmol) of distilled trifluoroacetic acid (TFA), and 1.7 g (9.0 mmol) of dicyclohexylcarbodiimide (distilled under reduced pressure, bp 140 °C, 5 mmHg), in that order. The flask was tightly stoppered and left at room temperature for 18 h under an argon atmosphere. Benzene (80 mL) was added, and the crystalline dicyclohexylurea was removed by filtration. The solids were washed with benzene, and the combined filtrates and washings were extracted with water (3 × 50 mL) to remove dimethyl sulfoxide. The organic layer was dried with sodium sulfate and evaporated to dryness under reduced pressure. The crude product was purified by flash chromatography (silica gel, 5% MeOH–95% CH_2Cl_2, R_f = 0.35) and that portion further purified by bulb-to-bulb distillation (oven temperature 145–150 °C, 4–5 mmHg) to give 0.4 g (2.3 mmol, 77%) of (*S*)-(+)-*N*-(1-buenyl)-2-oxopyrrolidine-5-carboxaldehyde (**7**): ^{1}H NMR ($CDCl_3$) δ 0.99 (3 H, t, J = 7.4 Hz), 2.1 (2 H, m), 2.3–2.6 (4 H, m), 4.3 (1 H, dd, J = 2.3, 13.7 Hz), 5.1 (1 H, dt, J = 6.8, 14.8 Hz), 6.9 (1 H, dd, J = 1.1, 14.8 Hz), and 9.60 ppm (1 H, d, J = 1.1 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3 (q), 19.9 (t), 23.4 (t), 29.9 (t), 64.0 (d), 115.3 (d), 122.4 (d), 173.0 (s), and 200.0 ppm (s); IR (neat) 3100–2800 (s), 1730 (s), 1680 (s), 1410 (s), 1070 (w), and 950 cm^{-1}; mass spectrum (m/z, relative intensity) P^+ 167 (16), 138 (100), 124 (2), 110 (7), 95 (6), 84 (8), 68 (12), and 55 (21); HRMS calcd for $C_9H_{13}NO_2$ 167.0947, found 167.0939 (±0.8 mmu).

(*S*)-5-Ethenyl-1-butenyl-2-pyrrolidinone (8). A stirred suspension of 3 equiv of methyltriphenylphosphonium bromide (1.20 g, 3.36 mmol) in 4 mL of THF was treated with 0.4 g (3.4 mmol) of potassium *tert*-butoxide at room temperature. After the mixture was stirred for 10 min, a THF solution of aldehyde **9** (0.2 g, 1.10 mmol, in 5 mL of THF) was injected via syringe at room temperature, and the whole reaction mixture was stirred for 10 h at that same temperature and then quenched with distilled water. The aqueous layer was extracted with ether, washed with brine, dried (magnesium sulfate), filtered, and concentrated. The product was purified by silica gel (CH_2Cl_2, R_f = 0.3) and Kugelrohr distillation (oven temperature = 125–130 °C, 3 mmHg) to give 1.10 g of (*S*)-5-ethenyl-1-(1-butenyl)-2-pyrrolidinone, **8** (0.8 mmol, 77%), as a clear oil: ^{1}H NMR ($CDCl_3$) δ 0.99 (3 H, t, J = 7.4 Hz), 1.8–2.6 (6 H, m), 4.35 (1 H, t, J = 7.4 Hz), 5.1 (1 H, m), 5.19 (1 H, m), 5.70 (2 H, m), and 6.77 ppm (1 H, d, J = 14.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.4 (q), 23.5 (t), 25.8 (t), 29.7 (t), 59.4 (d), 115.7 (t), 116.0 (d), 121.9 (d), 136.7 (d), and 174.0 ppm (s); mass spectrum (m/z, relative intensity) P^+ 165 (32), 151 (6), 150 (52), 138 (12), 137 (55), 136 (73), 122 (17), 110 (29), 108 (22), 97 (10), 95 (18), 84 (16), 82 (35), 68 (36), 67 (65), 56 (25), 55 (33), 54 (39), 53 (23), 48 (3); HRMS calcd for $C_{10}H_{15}NO$ 165.1154, found 165.11632 (±0.7 mmu); $[\alpha]^{25}_D$ = −46.3° (c = 0.032, CH_2Cl_2).

(*S*)-4-Aminohex-5-enoic Acid (2). A solution of 0.38 g (2.08 mmol) of triethyloxonium tetrafluoroborate in 8 mL of methylene chloride was cooled to 0 °C (ice bath) under argon, and a solution of 0.3 g (1.7 mmol) of (*S*)-4-ethenyl-*N*-(1-butenyl)-2-pyrrolidinone (**8**) in 8 mL of dry methylene chloride was added over a period of 3 min. The solution was stored at 0 °C for 17 h. The removal of solvent under reduced pressure (3 mmHg) gave 0.46 g (1.6 mmol, 97%) of crude (*S*)-5-ethenyl-2-ethoxy-1-butenylpyrrolidiminium tetrafluoroborate (**9**) as a viscous oil, which was used for next step without further purification: *crude* (contains ether) ^{1}H NMR ($CDCl_3$) δ 1.0 (3 H, t, J = 7.5 Hz), 1.5 (3 H, t, J = 6.8 Hz), 2.1 (2 H, t), 2.8 (2 H, m), 3.3 (2 H, t), 4.8 (2 H, q, J = 6.8 Hz), 4.9 (1 H, m), 5.2 (3 H, m), 5.9 (2 H, m), and 6.45 (1 H, d) ppm; ^{13}C NMR ($CDCl_3$) δ 12.5 (q), 13.8 (q), 23.0 (t), 24.7 (2 C, t), 66.3 (t), 83.6 (d), 118.9 (t), 119.5 (t), 130.7 (d), 134.1 (d), and 177.5 (s) ppm; IR (neat, KBr) 870 (w), 960 (m), 1090 (m), 1300 (m), 1480 (m), 1650 (s), 3000–2900 (s) cm^{-1}.

The crude hydrolysis product was dissolved in 10 mL (0.5 mol) of water and stirred at 25 °C for 15 h. The mixture was extracted with 2 mL of pentane (2 times). The pentane layer was dicarded, and the water layer was evaporated under vacuum (3 mmHg for

overnight) leaving 0.3 g of a colorless oil. Dissolution in 5% NaOH solution was followed by heating to 65 °C for 3 h. The solution was cooled to 0 °C and neutralized with 5% HCl using a pH meter (pH = 6.6). The water layer was evaporated under pressure (3 mmHg) at ambient temperature, and the resulting yellow powder was recrystallized from ethanol/water to give 0.07 g of (*S*)-4-aminohex-5-enoic acid, **2** (0.75 mmol, 44%): mp 190–205 °C (lit.[12] mp 208 °C); $[\alpha]^{25}_D = -13.5°$ (*c* 0.02 g/mL, H_2O at pH 6.6) [lit.[19] $[\alpha]^{22}_D = +12.3 \pm 0.3$, *c* = 0.200, H_2O at pH 6.6].

An Alternative Preparation of (*S*)-4-Aminohex-5-enoic Acid (2). Ten milliliters of 10% aqueous HCl solution was added to 0.252 g (1.53 mmol) of 5-ethenyl-*N*-(1-butenyl-2-pyrrolidinone (8) and heated to 90 °C in a steam bath for 5 h. The clear solution was cooled to room temperature, and the solvents were evaporated under reduced pressure to give a yellow oil. The oil was dissolved in 50 mL of water, treated with about 5 g of activated charcoal, and filtered. Evaporation of the water under reduced pressure gave 0.160 g (1.24 mmol, 81%) of an oil that gave all spectral characteristics of pure (*S*)-4-aminohex-5-enoic acid, **2**. Recrystallization from aqueous acetone provided 0.124 g (0.96 mmol, 63%) of **2**: mp 207–209 °C (lit.[12] mp 208 °C); ^1H NMR (D_2O) δ 2.03 (2 H, m), 21.6 (2 H, m), 2.57 (2 H, dist t), 4.97 (2 H, bd s), 5.53 (1 H, m), 5.86 (1 H, m), and 9.60 ppm (1 H, bd s); ^{13}C NMR (D_2O) δ 29.7 (t), 32.4 (t), 58.1 (d), 124.5 (t), 134.9 (d), and 179.4 ppm (s); IR (neat, film) 3100–2800 (s), 1730 (s), 1680 (s), 1410 (m), 1070 (m), and 950 cm^{-1} (m); $[\alpha]^{25}_D = +12.2°$, *c* = 0.095, H_2O at pH 6.4–6.8 [lit.[19] $[\alpha]^{23}_D = +12.3 \pm 0.3°$, *c* = 0.200, H_2O at pH 6.6].

Organoboranes for Synthesis. 14. Convenient Procedures for the Direct Oxidation of Organoboranes from Terminal Alkenes to Carboxylic Acids[1]

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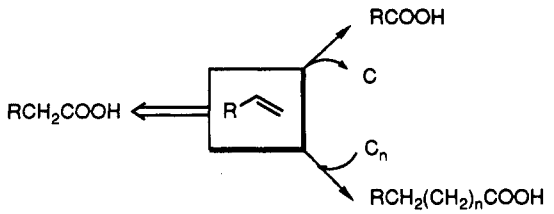
For the first time, a highly efficient and direct oxidation of a variety of organoborane intermediates into carboxylic acids has been demonstrated, without an increase or decrease of carbon atoms. Synthetically useful procedures have been developed for the ready conversion of representative terminal alkenes into carboxylic acids via oxidation of the organoboranes obtained by hydroboration of the terminal alkenes. The oxidation works well with a variety of organoboranes derived from reagents such as dibromoborane–methyl sulfide ($HBBr_2 \cdot SMe_2$), monobromoborane–methyl sulfide ($H_2BBr \cdot SMe_2$), monochloroborane–methyl sulfide ($H_2BCl \cdot SMe_2$), borane–methyl sulfide ($H_3B \cdot SMe_2$), thexylborane (H_2BThx), and dicyclohexylborane ($HBChx_2$). The oxidation is achieved in a convenient manner with pyridinium dichromate (PDC), sodium dichromate in aqueous sulfuric acid ($Na_2Cr_2O_7$–H_2SO_4) and chromium trioxide in 90% aqueous acetic acid (CrO_3–HOAc–H_2O). These oxidations afford carboxylic acids in very good yields with complete retention of the structure of the organic group attached to boron.

Carboxylic acids and their derivatives are valuable for organic synthesis as well as biological studies.[3] Many procedures are available for the synthesis of carboxylic acids from olefinic precursors involving oxidative cleavage of the carbon–carbon double bond and a loss of carbon atoms.[4] Similarly, the preparation of higher homologous carboxylic acids from terminal olefins is also well-known.[5] However, highly efficient and practically useful procedures are not available for the synthesis of carboxylic acids from olefinic precursors without skeletal cleavage or side reactions.[6-8]

Scheme I



The importance of organoboranes as versatile intermediates in organic synthesis is well established.[9] In the past, organoboranes have been shown to undergo oxidation to

(1) For a preliminary account of this work, see: Racherla, U. S.; Khanna, V. V.; Brown, H. C. *Tetrahedron Lett.* **1992**, *33*, 1037. Oxidation of primary alcohols to carboxylic acids without concurrent formation of carboxylic esters with chromium trioxide in 90% aqueous acetic acid was reported earlier. See ref 8a.

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(3) Rieu, J. P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095.

(4) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989; pp 596, 828–829.

(5) (a) Hara, S.; Kishimura, K.; Suzuki, A.; Dhillon, R. S. *J. Org. Chem.* **1990**, *55*, 6356. (b) Brown, H. C.; Imai, T.; Desai, M. C.; Singaram, B. *J. Am. Chem. Soc.* **1985**, *107*, 4980. (c) See also ref 4, pp 849–850.

(6) Wiberg, K. B. *Oxidations in Organic Chemistry*; Academic Press: New York, 1965; Part A, pp 69–184.

(7) (a) Lee, D. G. In *Oxidation*; Augustine, R. L., Ed.; Dekker: New York, 1969; Vol I. (b) Lee, D. G. *The Oxidation of Organic Compounds by Permanganate Ion and Hexavalent Chromium*; Open Court: La Salle, IL, 1980. (c) See: Haines, A. H. *Methods of Oxidation of Organic Compounds*; Academic Press: New York, 1988, pp 148–165 and 391–401. (d) Periasamy, M.; Narayana, C.; Anitha, N. *Ind. J. Chem.* **1986**, *25B*, 844.

(8) A number of excellent methods are available for the synthesis of carboxylic acids from primary alcohols. See: (a) Pattison, F. L. M.; Stothers, J. B.; Woolford, R. G. *J. Am. Chem. Soc.* **1956**, *78*, 2255. (b) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399. (c) Firouzabadi, H.; Tamani, B.; Goudarzian, N.; Lakouraj, M. M. *Synth. Commun.* **1991**, *21*, 2077.

(9) Pelter, A.; Smith, K.; Brown, H. C. *Borane Reagents*; Academic Press: New York, 1988; pp 1–27.

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