to room temperature and was stirred overnight. The solution was concentrated, and the crude acetal **17** was taken up in 6 N HCl (100 mL) and heated to reflux for 6.5 h. The solution was concentrated (50 °C) to afford the crude keto phosphinic acid **18** as an orange oil.

The crude ketone was dissolved in aqueous methanol (50%, 200 mL), and ammonium carbonate (28.9 g, 0.3 mol) and potassium cyanide (4.29 g, 66 mmol) were added. The solution was heated at 55 °C for 18 h and at 100 °C for an additional 1.5 h. Half of the crude reaction solution was concentrated and acidified with 2 N HCl. The aqueous solution was saturated with NaCl and extracted with 2-butanol. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated to afford a tan foam (5.40 g, 73%). Formation of the sodium salt or the cyclohexylamine salt of the phosphinic acid did not give analytically pure material. A portion of the cyclohexylamine salt (1.98 g, 5.74 mmol) in ethanol was passed through Dowex 50×8-100 ion-exchange resin. The ethanol solution was concentrated, taken up in water, and lyophilized to a fluffy white solid (0.85 g, 60%) of the hydantoin phosphinic acid: mp 255–259 °C dec; ^{1}H NMR (Me_2SO-d_6, 400 MHz) δ 1.24 (d, 3, J = 12.9 Hz), 1.12–1.32 (m, 2), 1.43–1.98 (series of m, 7), 4.72 (br s, 1), 8.47 (br s, 1), 10.67 (br s, 1); ^{13}C NMR (Me_2SO-d_6, 100.6 MHz, coupled) δ 12.8 (dq, $^1J_{CP}$ = 90.4 Hz), 20.7 (dt, $^3J_{CP}$ = 14.4 Hz), 23.9 (dt, $^2J_{CP}$ = 3.2 Hz), 32.7 (t), 32.9 (t), 33.6 (dd, $^1J_{CP}$ = 97.2 Hz), 62.2 (d, $^3J_{CP}$ = 13.6 Hz), 156.6 (t, J_{CH} = 7.0 Hz, $W_{1/2}$ = 14.0 Hz); ^{31}P NMR (Me_2SO-d_6, 40.3 MHz) δ 49.7 (92%), 50.8 (8%); high-resolution FAB MS (glycerol matrix) calcd for $C_9H_{16}N_2O_4P$ (MH^+) 247.0848, found 247.0896.

1-Amino-3-(hydroxymethylphosphinyl)cyclohexanecarboxylic Acid, Monosodium Salt (20). The remaining half of the crude reaction solution containing **19** was concentrated and dissolved in water (250 mL), barium hydroxide (octahydrate, 37.9 g, 0.12 mol) was added, and the suspension was heated to reflux for 56 h. Ammonium carbonate (16.35 g, 0.17 mol) was added, and reflux was continued for 2 h. The hot suspension was filtered, concentrated, and desalted on Dowex 50×8-100 ion-exchange resin (150 g) eluting with 3 N NH_4OH. The aqueous solution was concentrated to afford the ammonium salt of the phosphinic acid as a light yellow solid (5.50 g, 77% overall, mp 225–230 °C dec). The ammonium salt (1.92 g, 8.1 mmol) was dissolved in methanol (25 mL), and 2.5 N NaOH (3.2 mL, 8.0 mmol) was added. The sodium salt was precipitated by slow addition of acetone. The salt was filtered, dried under high vacuum, taken up in water, concentrated, and dried again to afford 1.53 g (78%) of a white solid: mp 322–324 °C dec; ^{1}H NMR (D_2O, 60 MHz) δ 1.17 (d, 3, J = 14 Hz), 1.10–3.20 (m, 9); ^{13}C NMR (D_2O, 90.5 MHz) δ 13.4 (d, $^1J_{CP}$ = 91.0 Hz), 20.8 (d, $^3J_{CP}$ = 13.8 Hz), 25.0, 32.5 (d, $^3J_{CP}$ = 24.1 Hz), 34.6 (d, $^1J_{CP}$ = 94.6 Hz), 61.1 (d, $^3J_{CP}$ = 12.2 Hz), 179.8; ^{31}P NMR (D_2O, 40.3 MHz) δ 44.5 (96%), 45.1 (4%).

Anal. Calcd for $C_8H_{15}NaNO_4P \cdot 1.5H_2O$: C, 35.56; H, 6.72; N, 5.18. Found: C, 35.65; H, 6.44; N, 5.13.

***trans*-3-(Methoxymethylphosphinyl)-1-[[(*p*-bromophenyl)carbonyl]amino]cyclohexanecarboxylic Acid, Methyl Ester (21).** To a solution of the ammonium salt of **20** (1.00 g, 4.20 mmol) in methanol (30 mL) was added an ethereal solution of diazomethane generated from *N*-nitroso-*N*-methylurea (5.07 g, 49 mmol). The yellow solution was stirred for 5 min, quenched with acetic acid, and concentrated. The crude product was purified on a 4-mm chromatotron plate (10% MeOH (1.5 M NH_3)/$CHCl_3$) to afford a light yellow oil (0.42 g, 40%): ^{1}H NMR ($CDCl_3$, 60 MHz) δ 1.39 (d, 3, J = 13.4 Hz), 1.15–2.80 (m, 11), 3.31 (d, 3, J = 11.0 Hz), 3.67 (s, 3); ^{31}P NMR ($CDCl_3$, 40.3 MHz) δ 58.5 (48%), 58.8 (52%).

The amine (0.42 g, 1.69 mmol) in dry CH_2Cl_2 (15 mL) was treated with *p*-bromobenzoyl chloride (0.41 g, 1.86 mmol), pyridine (0.15 mL, 1.85 mmol), and (dimethylamino)pyridine (20 mg). The reaction mixture was stirred overnight, diluted with CH_2Cl_2, washed with 2 N HCl and saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated to a white solid (0.70 g). The product was purified on a 4-mm chromatotron plate (5% MeOH/$CHCl_3$) to afford the amide as a white solid (0.58 g, 79%): mp 191–195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (d, 1.5, J = 13.2 Hz), 1.42 (d, 1.5, J = 13.2 Hz), 1.50–1.60 (m, 1), 1.77–2.10 (m, 5), 2.23–2.35 (m, 1), 2.62–2.79 (m, 1), 3.63 (d, 1.5, J = 10.8 Hz), 3.70 (d, 1.5, J = 11.0 Hz), 3.74 (s, 1), 6.42 (br s, 1), 7.57–7.69 (m, 4); ^{31}P NMR ($CDCl_3$, 40.3 MHz) δ 59.7, 59.8; CI MS (MH^+) 432, 434.

***trans*-3-(Hydroxymethylphosphinyl)-1-[[(*p*-bromophenyl)carbonyl]amino]cyclohexanecarboxylic Acid, Methyl Ester (22).** A solution of the phosphinate ester **21** (0.31 g, 0.72 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was treated with bromotrimethylsilane (0.19 mL, 1.44 mmol) and was allowed to warm to room temperature overnight. The reaction mixture was concentrated, taken up in CH_2Cl_2, washed with H_2O, dried ($MgSO_4$), and concentrated to afford a white solid (0.26 g, 86%): mp 126–138 °C; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.30 (m, 1, H4a), 1.35 (d, 3, J = 13.8 Hz), 1.54 (m, 1, H5a), 1.77 (m, 3, H2a, H5e, H6a), 11.94 (br d, 1, H4e, J = 12.1 Hz), 2.06 (m, 1, H3a), 2.29 (br d, 1, H6e, J = 12.4 Hz), 2.57 (br d, 1, H2e, J = 13.0 Hz), 3.68 (s, 3), 6.18 (br s, 1), 6.84 (s, 1, NH), 7.59 (d, 2, J = 2.7 Hz), 7.69 (d, 2, J = 2.7 Hz); ^{13}C NMR (CD_3OD, 100.6 MHz) δ 12.5 (d, $^1J_{CP}$ = 92.2 Hz), 22.1 (d, $^3J_{CP}$ = 15.1 Hz), 25.3 (d, $^2J_{CP}$ = 3.4 Hz), 31.2, 33.0, 35.2 (d, $^1J_{CP}$ = 97.5 Hz), 53.1, 60.5 (d, $^3J_{CP}$ = 14.4 Hz), 127.3, 130.6 (2 C), 132.7 (2 C), 134.7, 169.8, 176.1; high-resolution FAB MS (glycerol matrix) calcd for $C_{16}H_{22}NO_5PBr$ (MH^+) 418.0419, found 418.0409.

Acknowledgment. We thank Professor Joseph J. Villafranca (Pennsylvania State University) for many helpful discussions and for a generous gift of *E. coli* glutamine synthetase.

Supplementary Material Available: Synthesis procedures for the acyclic phosphinothricin analogues, a discussion of quantitative 2D NMR routines used in structure elucidation of compound **22**, and glutamine synthetase assay methods (9 pages). Ordering information is given on any current masthead page.

Asymmetric Induction in Nitrone Cycloadditions: A Total Synthesis of Acivicin by Double Asymmetric Induction

Shadreck Mzengeza and Ralph Allen Whitney*

Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6

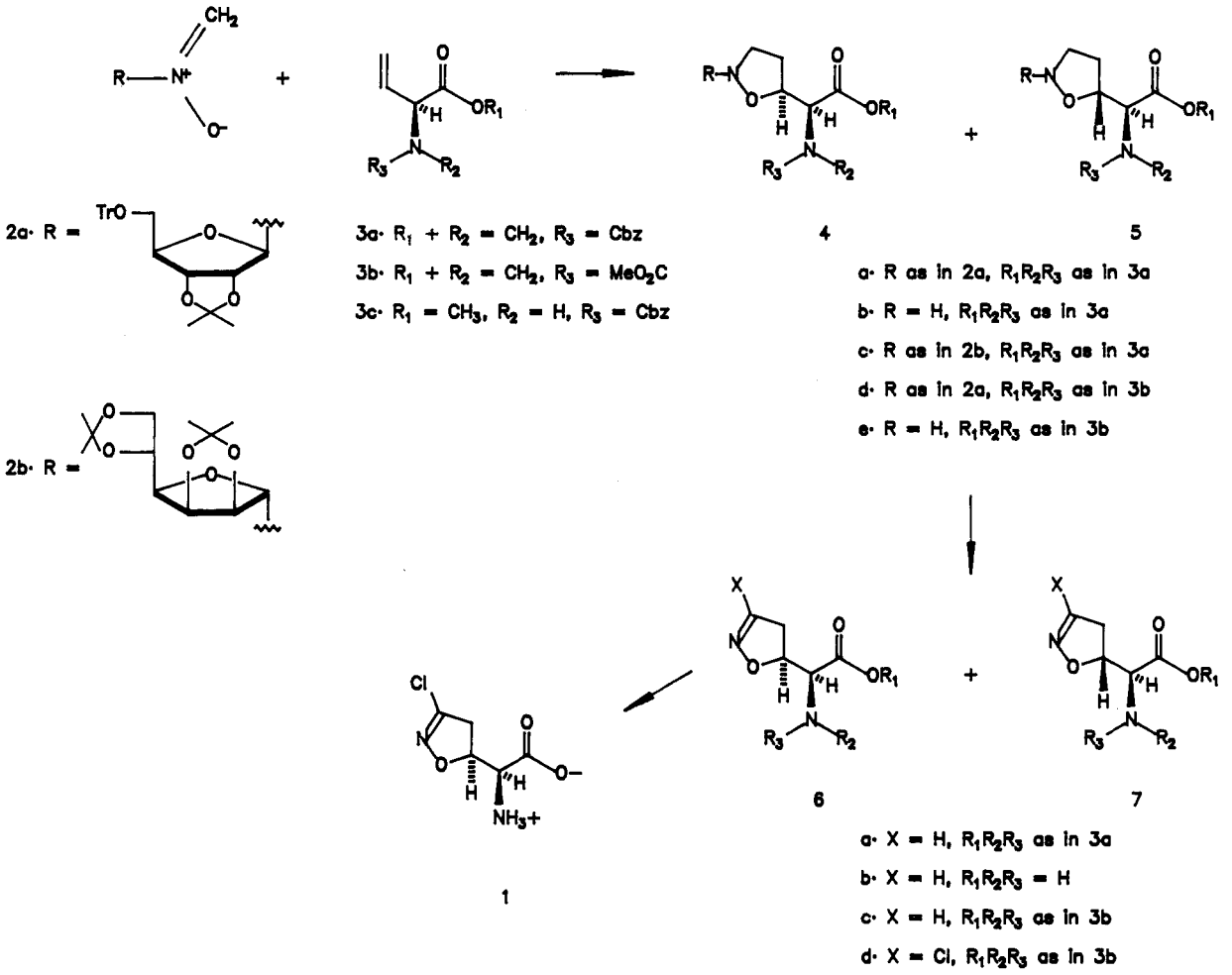
Received December 30, 1987

A total synthesis of acivicin, (αS,5*S*)-α-amino-3-chloro-4,5-dihydroisoxazole-5-acetic acid, has been achieved in 39% overall yield from a derivative of (2*S*)-vinylglycine. The required diastereomer was obtained in an extremely efficient manner (≥19:1) through double asymmetric induction in the reaction of a (2*S*)-vinylglycine derivative with a chiral, nonracemic *N*-glycosylnitrone derived from D-ribose. The origin of the asymmetric induction with respect to the nitrone has been investigated by using semiempirical (MOPAC) computational methods.

Acivicin (AT-125) is an antitumor antibiotic that was isolated in 1973 at the UpJohn Company[1] from fermentation broths of the soil bacterium *Streptomyces sviceus*. The subsequent determination of structure and absolute

0022-3263/88/1953-4074$01.50/0

Scheme I



configuration by Martin et al.[2] showed acivicin to be (αS,5S)-α-amino-3-chloro-4,5-dihydroisoxazole-5-acetic acid (1). Since its isolation and preliminary biological evaluation, acivicin has undergone extensive biochemical and pharmacological evaluation as an antitumor agent.[3] It has been shown to be an inhibitor of several L-glutamine amidotransferases involved in the de novo biosynthesis of purine and pyrimidine nucleotides; antitumor activity is believed to be a consequence of this inhibition. At present, acivicin is undergoing phase II clinical evaluation for the treatment of a number of cancers. Initial results indicate that it may have a role in the treatment of non-small cell lung cancer and that it may be active against colon cancer. The full scope of the drug will emerge as further clinical trials on other tumors are reported.[3]

Although acivicin is available through fermentation, large-scale production has been hampered to some extent by the occurrence of contaminants from which it is not easily separable.[4] This has served to add a further element to the interest in the total synthesis of acivicin. Five total syntheses have been adumbrated[5-9] to date with results ranging from stereorandom to stereoselective formation of the requisite αS,5S stereochemistry. Two general strategies have been explored in these total syntheses. The first has employed tricholomic acid ((αS,5S)-α-amino-3-oxoisoxazolidine-5-acetic acid) derivatives as intermediates and was used successfully by Kelly,[5] Silverman,[6] and Baldwin.[7] The second and potentially most expeditious approach has employed halonitrile N-oxide cycloaddition to vinylglycine derivatives. Initially examined by Baldwin and by Hagedorn,[10] this route has subsequently been the basis of successful total syntheses by Wade[8] and by Vyas.[9] The major limitation of this route, however, has been the poor selectivity for the requisite 5S stereochemistry in the cycloaddition.

Herein we report, as shown in Scheme I, a total synthesis of acivicin that is highly diastereoselective and that is based upon double asymmetric induction[11] in the cycloaddition of a chiral, nonracemic N-glycosylnitrone with a (2S)-vinylglycine derivative. A preliminary account of this work has been reported.[12] In addition, semiempirical

(1) Hanka, L. J.; Dietz, A. *Antimicrob. Agents Chemother.* **1973**, *3*, 425–431.
(2) Martin, D. G.; Duchamp, D. J.; Chidester, C. G. *Tetrahedron Lett.* **1973**, 2549–2552.
(3) Earhart, R. E.; Neil, G. L. *Adv. Enzyme Regul.* **1986**, *24*, 179–205.
(4) Martin, D. G.; Biles, C.; Mizsak, S. A. *J. Antibiot.* **1981**, *34*, 459–461.
(5) Kelly, R. C.; Schletter, I.; Stein, S. J.; Wierenga, W. *J. Am. Chem. Soc.* **1979**, *101*, 1054–1056.
(6) Silverman, R. B.; Holladay, M. W. *J. Am. Chem. Soc.* **1981**, *103*, 757–759.
(7) Baldwin, J. E.; Cha, J. K.; Kruse, L. I. *Tetrahedron* **1985**, *41*, 5241–5260.
(8) Wade, P. A.; Pillay, M. K.; Singh, S. M. *Tetrahedron Lett.* **1982**, *23*, 4563–4567.
(9) Vyas, D. M.; Chang, Y.; Doyle, T. W. *Tetrahedron Lett.* **1984**, *25*, 487–491.
(10) Baldwin, J. E.; Hoskins, C.; Kruse, L. I. *J. Chem. Soc., Chem. Commun.* **1976**, 795–796. Hagedorn, A. A., III; Miller, B. J.; Nagy, J. O. *Tetrahedron Lett.* **1980**, *21*, 229–230.
(11) Masamune, S.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30.
(12) Mzengeza, S.; Yang, C. M.; Whitney, R. A. *J. Am. Chem. Soc.* **1987**, *109*, 276–277.

molecular orbital studies on the conformational preferences of *N*-glycosylnitrones are reported and their relevance to the observed asymmetric induction is discussed.

Results and Discussion

Nitrones bearing a chiral, nonracemic substituent either at carbon[13] or at nitrogen[14] have been shown to undergo cycloaddition to achiral alkenes with moderate to good levels of asymmetric induction. For our purposes we required a chiral auxiliary at nitrogen that was both easily attached prior to cycloaddition and then readily removed after cycloaddition to give an *N*-unsubstituted isoxazolidine. Consequently the *N*-glycosylnitrones studied by Vasella[15] appeared suited to our needs, particularly since the D-ribosyl-derived nitrone **2a** and the D-mannosyl-derived nitrone **2b** were shown to have complementary facial selectivity. In reactions with several achiral alkenes, Vasella obtained isoxazolidines with diastereoselectivity ratios of 2:1–5:1 with nitrone **2a**; the absolute chirality of the cycloadducts was unambiguously determined for methyl acrylate and methyl methacrylate but not for other alkenes. Conversely nitrone **2b** gave the opposite facial selectivity with methyl methacrylate in a 7–9:1 ratio.

(2*S*)-Vinylglycine and certain of its derivatives have recently been prepared by two routes of note; the procedure of Rapoport[16] involves reduced pressure pyrolysis of (2*S*)-methionine sulfoxide derivatives while that of Hanessian[17] involves Kochi oxidative decarboxylation of (2*S*)-glutamic acid derivatives. We have prepared the (2*S*)-vinylglycine derivatives **3** by modification of the former procedure in that the pyrolyses were carried out in refluxing xylenes containing triethyl phosphite. The crude products obtained by this procedure appeared to contain a small amount (<10% by proton NMR) of the alkene isomerization product, a crotonate, which was removed by careful chromatographic purification. In our experience the xylenes pyrolysis procedure works better than the reduced pressure pyrolysis procedure on a moderate scale (10–20 g); the latter procedure appears to give decreased yields with increased scale.

In general cycloadditions of the nitrones **2** with the vinylglycine derivatives **3** were carried out by the procedure of Vasella.[15] Assessment of the cycloaddition diastereoselectivity was difficult on both the *N*-glycosyl and *N*-unsubstituted isoxazolidines **4** and **5** due to complexities in the ^{1}H NMR spectra of these compounds. This was in part due to dynamic properties associated with amide rotation (in the carbamate) and nitrogen inversion (in the isoxazolidine) that were slow on the NMR time scale. Since the cycloadducts could be converted by hydrolysis (formic acid) and oxidation (*N*-chlorosuccinimide in CH_2Cl_2) to isoxazolines **6** and **7** in high yield (70–80% for the three steps), this proved to be a convenient point at which to assess diastereoselectivity. The H–C_3 signal in the ^{1}H NMR spectra of the isoxazolines showed moderate line-broadening at 25 °C; however, at a probe temperature of 50 °C the resonances were considerably sharpened and had baseline separation which allowed quantification of the diastereomers. Additionally the *N*-unsubstituted isoxazolidines were susceptible to slow air oxidation (discoloration) while the isoxazolines proved to be much more stable.

Reaction of the nitrone **2a**, generated in situ by the procedure of Vasella[15] from 5-*O*-trityl-2,3-*O*-isopropylidene-D-ribose oxime and paraformaldehyde, with vinylglycine derivative **3a** in chloroform at reflux for 1.5 days gave a single cycloadduct (**4a**) in 93% yield. Hydrolysis of the chiral auxiliary in 98% formic acid gave the isoxazolidine **4b** (84% yield), which was oxidized with *N*-chlorosuccinimide[15] in CH_2Cl_2 (94% yield) to the dihydroisoxazole **6a**. The extent of the double asymmetric induction was such that only one diastereomer was detectable by 400-MHz proton NMR; conservatively the diastereoselectivity was ≥19:1. The stereochemistry of this diastereomer was initially inferred on the basis of the H_5–H_α coupling constant (J = 3.8 Hz) for the free amino acid **6b** (obtained by deprotection with boron tris(trifluoroacetate) in CF_3CO_2H, 89% yield); the H_5–H_α coupling for acivicin is 3.0 Hz while the epimer has a coupling constant of 8.0 Hz.[7] This assignment was subsequently confirmed upon the total synthesis of acivicin.

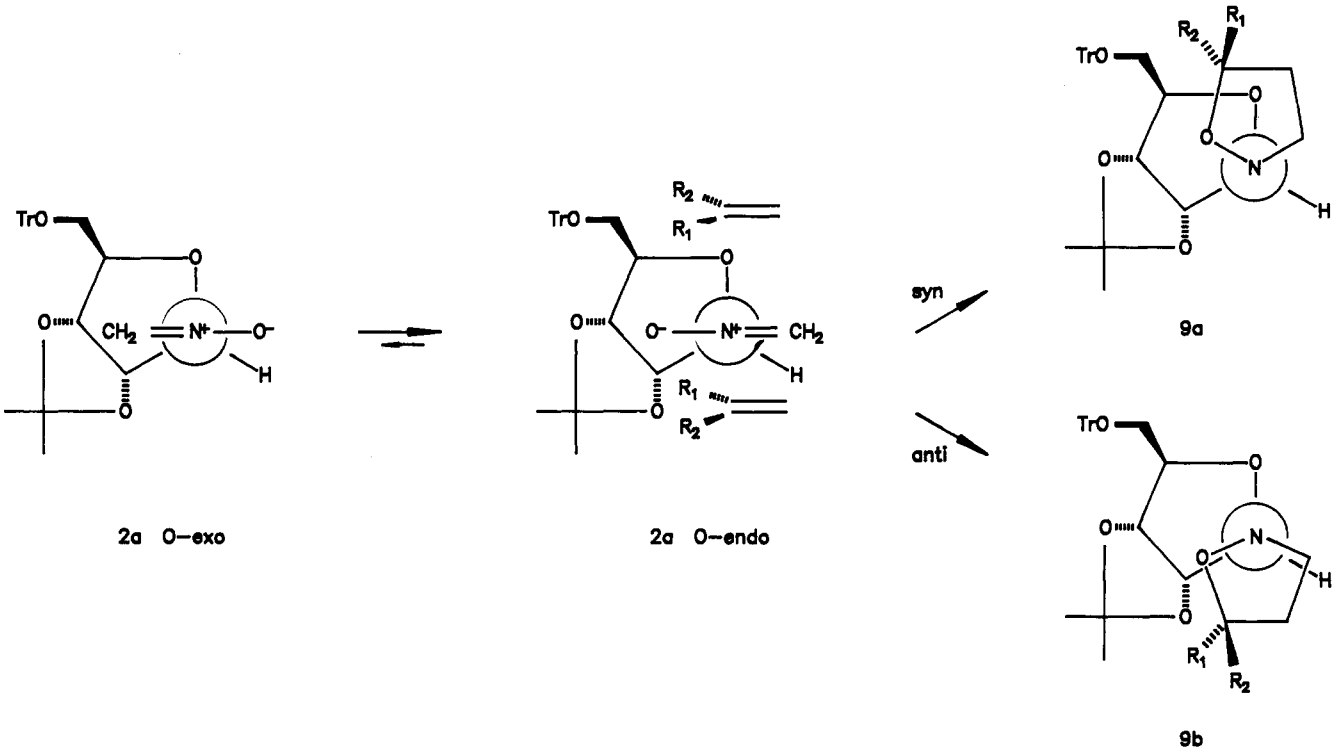
Conversely reaction of nitrone **2b**, also generated in situ by the procedure of Vasella,[15] with vinylglycine derivative **3a** followed by hydrolysis and oxidation as before gave only a 3:1 mixture of diastereomers **6a** and **7a**, presumably as a consequence of their mismatched chirality. The H_3 resonances for **6a** and **7a** occurred at δ 7.15 and 7.09, respectively. The deprotected amino acids **6b** and **7b** had H_5–H_α coupling constants of 3.5 and 6.0 Hz, respectively, consistent with the presumed stereochemistry.

In general nitrone cycloadditions are thermally reversible so that kinetic or thermodynamic product control may be observed. While we have not examined in detail this aspect of nitrone cycloaddition, we have observed that prolonged reaction times (2.5 days instead of 1.5 days) for the cycloaddition of nitrone **2a** with vinylglycine derivative **3a** led to a decrease in diastereoselectivity from ≥19:1 to 6:1 in favor of the 5*S* isomer. This indicates that the optimum stereoselectivity is likely kinetically controlled and that variations in reaction conditions may alter this selectivity.

With the (5*S*,α*S*)-4,5-dihydroisoxazole **6** efficiently in hand our attention was turned to the chlorination of the 3-position of the isoxazoline. Since it is known[18] that aldoximes can be chlorinated under strongly acidic conditions, we initially examined the chlorination of the free amino acid **6b** under acidic conditions but without reproducible success. Consequently other derivatives of the amino acid **6** were examined, particularly those with protecting groups that were likely to be more stable under chlorination conditions than the carbobenzyloxy derivative **6a**. The carbomethoxy derivative **6c** was ultimately found to be the optimum compound. This was prepared from nitrone **2a** and (2*S*)-vinylglycine methylidene ester **3b** in 82% overall yield for the three steps described previously (cycloaddition, hydrolysis, and oxidation). Again only a single diastereomer was obtained in the cycloaddition as evidenced by proton NMR. Deprotection of **6c** with BBr_3 in CH_2Cl_2 gave, as evidenced by proton NMR, the same amino acid **6b** as obtained previously. Chlorination of **6c** was examined under a wide variety of conditions; ultimately Cl_2 in dry *t*-BuOH at room temperature gave the acivicin derivative **6d** (79% yield) in a reproducible manner and an acceptable yield. Our previous stereochemical

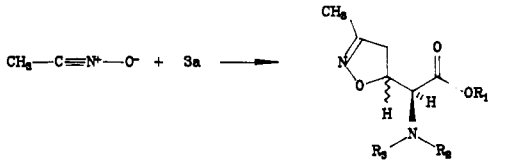
(13) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598–5602, and references therein.
(14) Wovkulich, P. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956–3958. Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134–1145. Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5048–5050. Kametani, T.; Nagahara, T.; Honda, T. *J. Org. Chem.* **1985**, *50*, 2327–2331. Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am. Chem. Soc.* **1986**, *108*, 4647–4648.
(15) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273–1295.
(16) Afzali-Ardakami, A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4817–4820.
(17) Hanessian, S.; Sahoo, S. P. *Tetrahedron Lett.* **1984**, *25*, 1425–1428.
(18) Ulrich, H. *The Chemistry of Imidoyl Halides*; Plenum Press: New York, 1968; pp 158–159.

Scheme II



assignments were confirmed when **6d** was deprotected with BCl_3 in CH_2Cl_2 to give acivicin, identical with an authentic sample. Thus acivicin was obtained in 39% overall yield starting from the (2*S*)-vinylglycine derivative **3b**.

Previous work has shown that acyclic ester **3c** and related (2*S*)-vinylglycine derivatives give moderate diastereoselectivity in dipolar cycloadditions with achiral dipoles for 4,5-dihydroisoxazoles with 5*R* stereochemistry,[8,9,19] the wrong stereochemistry for acivicin. Consequently, the diastereofacial selectivity of the cyclic methylidene ester **3b** was investigated; reaction with acetonitrile *N*-oxide gave a 3:1 ratio of diastereomers **8a**. The stereochemistry of



8a $R_1R_2R_3$ as in **3a**
8b $R_1R_2R_3$ = H

the major isomer was again assigned as 5*S* on the basis of the H_5–H_α coupling constant in the free amino acid **8b** obtained by deprotection with BBr_3 in CH_2Cl_2; the major isomer had a coupling constant of 3.5 Hz, while the minor isomer had a coupling constant of 8.0 Hz. Apparently the facial selectivity of (2*S*)-vinylglycine in dipolar cycloadditions is readily influenced by the type of protecting groups used.

With a knowledge of the respective diastereoselectivities (D.S.) of each of the chiral reactants **2a** and **3b** with an achiral reagent, a qualitative assessment[11] of nitrone **2a** (D.S. = 2:1–5:1) and (2*S*)-vinylglycine derivative **3b** (D.S. = 3:1) as a matched pair of chiral reactants suggests that reaction of **2a** and **3b** would give a selectivity for the desired 5*S* isomer **4d** of 6:1–15:1. Indeed the experimental reality proved to be immensely gratifying in that the observed selectivity was ≥19:1.

In view of the fact that the *N*-glycosylnitrones **2a** and **2b** readily give access to isoxazolidines and, through oxidation, isoxazolines[20] that are enantiomerically enriched, the nature of the asymmetric induction associated with these nitrones is of some interest. Previously Vasella[15,21] has suggested that a product-like transition state may be important in these cycloadditions in the following manner (Scheme II): if conformations in which the C_1–O bond of the furanosyl ring is perpendicular to the plane of the nitrone are considered, and if it is assumed that the "O-endo" conformation is sterically preferred over the "O-exo" conformation, then the dipolarophile may add either syn or anti to the C_1–O bond to give an anomerically stabilized product **9a** or **9b** (note that **9a** and **9b** can be interconverted through nitrogen inversion). Initially it was suggested that this "kinetic anomeric effect" would favor the syn transition state leading to **9a** on stereoelectronic grounds due to an antiperiplanar arrangement of the nitrogen lone pair and C_1–O σ^*-orbital in **9a**. Subsequent experimental work[22] on a more conformationally rigid spironitrone indicated, however, that anti addition was likely the preferred mode.

Since nitrone cycloadditions are considered[23] to have an early or reactant-like transition state, we have chosen to examine the conformational properties of *N*-glycosylnitrones and related model compounds by using the MNDO semiempirical molecular orbital method.[24]

(19) Wade, P. M.; Singh, S. M.; Pillay, M. K. *Tetrahedron* **1984**, *40*, 601–611.

(20) For leading references on the use of isoxazolines in organic synthesis, see: Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410–416. Jager, V.; Schohe, R. *Tetrahedron* **1984**, *40*, 2199–2210. Curran, D.; Scanga, S. A.f; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474–3478.

(21) Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730–1747.

(22) Bernet, B.; Krawczyk, E.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 2299–2311.

(23) Leroy, G.; Nguyen, M. T.; Sana, M. *Tetrahedron* **1978**, *34*, 2459–2468.

Table I. MNDO Heats of Formation for *N*-Glycosylnitrones

nitrone	ΔH_f and $\Delta\Delta H_f$ (kcal mol^{-1})	$\vartheta_{C\text{-}N\text{-}C\text{-}O}$
10a	−93.90	−107.4
	−3.32	
10b	−90.58	44.5
11a	−18.93	−102.2
	−1.67	
11b	−17.26	39.8
12a	−11.28	−131.0
	1.61	
12b	−12.89	54.2

Starting geometries for these calculations were generated with the MMPMI molecular mechanics program;[25] energy-minimized structures were obtained with the MOPAC program[26] (MNDO version 2.0) running on an IBM 3081 computer. Energy-minimized geometries were found by minimizing all parameters and were characterized by calculating force constants. Model nitrones **10–12** were examined and the results are listed in Table I.

Two features are readily seen from these results. First, the conformational preference of the cyclic *N*-(alkoxyalkyl)nitrones **10** and **11** is opposite to that of the acyclic nitrone **12**, with the former preferring an "O-endo" nitrone (**10a** and **11a**) by 1.6 to 3.3 kcal mol^{-1}. Second, the preferred conformations of the cyclic nitrones **10a** and **11a** do indeed have an orientation of the C_1–O bond that is nearly perpendicular to the plane of the nitrone, while the acyclic nitrone **12b** shows a much larger deviation from orthogonality (Scheme III). The large difference in conformational preference between cyclic and acyclic *N*-(alkoxyalkyl)nitrones suggests that steric factors are largely responsible for the conformations of these cyclic nitrones.

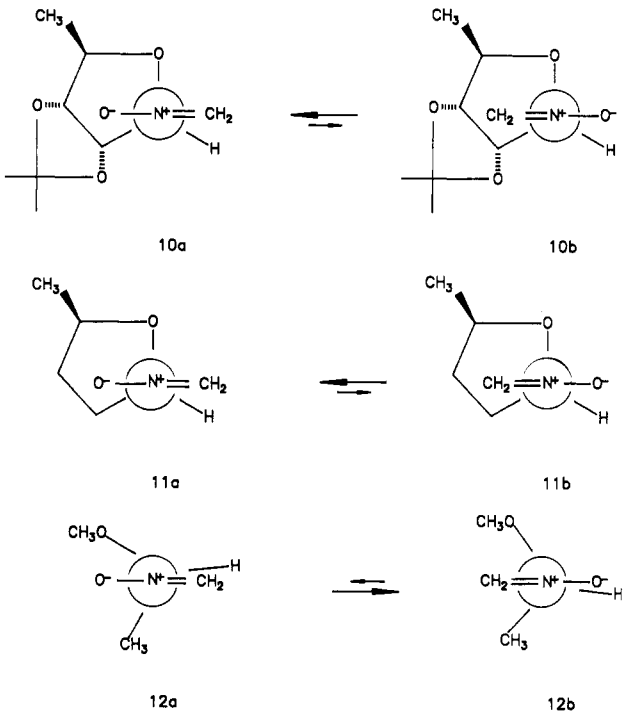
In light of these results, it is entirely reasonable to assume a reactivity model in which cycloaddition to *N*-glycosylnitrones occurs via a preferred "O-endo" conformation with the dipolarophile adding anti to the C_1–O bond, as shown in Scheme II. Presumably, in a reactant-like transition state, anti addition is preferred over syn addition on steric grounds. It follows that the cycloaddition of (2*S*)-vinylglycine methylidene esters **3a/b** to nitrone **2a** occurs via an anti transition state in which the sterically demanding substituent on the dipolarophile (R_1 = H, R_2 = α-amino residue, Scheme II) is remote from the furanosyl ring; this is consistent with normal steric effects in nitrone cycloadditions.

In summary, *N*-glycosyl residues constitute a useful class of chiral auxiliaries for nitrone cycloadditions applied to organic syntheses. We are currently examining further the synthetic potential of chiral, nonracemic *N*-glycosylnitrones.

Experimental Section

General. Melting points are uncorrected. Proton and carbon-13 NMR spectra were obtained at 400 and 100.6 MHz respectively. Unless otherwise stated NMR spectra were run in $CDCl_3$ with TMS as internal standard. When deuterium oxide was used as solvent, the DOH peak was used as the reference and was set at δ 4.70. Column chromatography was performed with Merck Kieselgel 60, 70–230-mesh silica gel, while high performance liquid chromatography was performed on Merck prepacked Lobar columns. Ion exchange column chromatography was performed with Dowex 50X8-400 cationic exchange resin of mesh size 200–400. The resin was packed in a column and regenerated with

Scheme III



2 N NaOH, H_2O, 2 N HCl, and H_2O. Thin layer chromatography was performed on Merck 60F-254 (0.25 mm) silica gel plates. The spots on the TLC were observed under short wave ultraviolet light or were visualized with iodine vapor or by heating the TLC plates to about 150 °C after they had been sprayed with either ninhydrin (for the free amino acids) or with a solution of 10% aqueous sulfuric acid containing 1% cerium sulfate and 1.5% molybdic acid. Unless otherwise stated organic solutions were dried over Na_2SO_4 and were evaporated under reduced pressure at water bath temperatures of <40 °C.

An authentic sample of acivicin (mp 182–191 °C [lit.[7] 188–96 °C]; ^{1}H NMR (D_2O) 5.36 (ddd, J = 11, 8, 3 Hz, 1 H, H_5), 4.12 (d, J = 3 Hz, 1 H, H_α), 3.60 (dd, J = 18, 11 Hz, 1 H, H_4), 3.52 (dd, J = 18, 8 Hz, 1 H, H_4) was kindly provided by Dr. D. G. Martin of the Upjohn Company, Kalamazoo, MI. *N*-Chlorosuccinimide was recrystallized from water before use. Solvents were distilled before use and were dried, as necessary, by literature procedures. All reaction products given structure numbers were homogeneous according to TLC analyses and the purity was estimated to be ≥95% from their ^{1}H NMR spectra.

(2*S*)-*N*-(Alkoxycarbonyl)methionine Methylidene Esters. These were prepared by using the modified Schotten–Baumann procedure[27] to give the (2*S*)-*N*-(alkoxycarbonyl)methionine; the method of Ben-Ishai[28] was used to prepare the methylidene esters.

(2*S*)-*N*-(Benzyloxycarbonyl)methionine methylidene ester was obtained as an oil (27.83 g, 91%): $[\alpha]_D$ +133° (*c* 0.98, $CHCl_3$); IR (neat) 1780 (C=O, methylidene ester), 1700 (C=O, carbamate) cm^{-1}; ^{1}H NMR δ 7.38 (s, 5 H, Ar H), 5.52 (br, 1 H, methylidene CH), 5.25 (br d, J = 4 Hz, 1 H, methylidene CH), 5.14 (AB q, J = 12 Hz, 2 H, benzyl CH_2), 4.38 (t, J = 6 Hz, 1 H, H_α), 2.52 (br m, 2 H, SCH_3), 2.35–2.14 (br m, 2 H, H_β), 1.99 (br s, 3 H, CH_3).

(2*S*)-*N*-(Methoxycarbonyl)methionine methylidene ester was obtained as an oil (34.0 g, 98%): $[\alpha]_D$ +162° (*c* 12.5, $CHCl_3$); IR (neat) 1790 (C=O, methylidene ester), 1710 (C=O, carbamate) cm^{-1}; ^{1}H NMR δ 5.53 (br, 1 H, methylidene CH), 5.27 (d, J = 4 Hz, 1 H, methylidene CH), 4.39 (t, J = 6 Hz, 1 H, H_α), 3.81 (s, 3 H, OCH_3), 2.59 (m, 2 H, SCH_2), 2.28 (m, 2 H, H_β), 2.08 (s, 3 H, SCH_3).

General Procedure for the Preparation of Sulfoxides of (2*S*)-*N*-(Alkoxycarbonyl)vinylglycine Methylidene Esters.

(24) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907.
(25) Serena Software, P. O. Box 3076, Bloomington, IN 47402-3076.
(26) Stewart, J. J. P. *QCPE Bull.* **1985**, *5*, 133; QCPE Program 455.
(27) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; John Wiley and Sons: New York, 1961; Vol. 2, pp 887–895.
(28) Ben-Ishai, D. *J. Am. Chem. Soc.* **1957**, *79*, 5736–5738.

To a mechanically stirred ice-cold solution of the (2*S*)-*N*-(alkoxycarbonyl)methionine methylidene ester (0.10 mol) in methanol (600 mL) was added dropwise a solution of sodium metaperiodate (0.12 mol) in water (400 mL). The mixture was stirred with cooling for 5 h, after which time the mixture was filtered and the filtrate was concentrated to about 400 mL, then extracted with dichloromethane (5 × 200 mL), dried, and evaporated under reduced pressure to give the sulfoxide. After drying under high vacuum a viscous oil was obtained.

Sulfoxide of (2*S*)-*N*-(benzyloxycarbonyl)methionine methylidene ester was obtained as an oil (28.03 g, 96%): IR (neat) 1780 (C=O, methylidene ester), 1690 (C=O, carbamate) cm^{-1}; ^1H NMR δ 7.39 (s, 5 H, Ar H), 5.56 (br, 1 H, methylidene CH), 5.29–5.11 (m, 3 H, methylidene CH and benzyl CH_2), 4.45 (t, 1 H, H_α), 2.79 (br m, 2 H, SCH_2), 2.57 and 2.55 (br s, 3 H, $S(O)CH_3$), 2.40 (br, 2 H, H_β).

Sulfoxide of (2*S*)-*N*-(methoxycarbonyl)methionine methylidene ester was obtained as an oil (29.54 g, 86%): IR (neat) 1790 (C=O, methylidene ester), 1710 (C=O, caramate) cm^{-1}; ^1H NMR δ 5.53 (br s, 1 H, methylidene CH), 5.28 (br s, 1 H, methylidene CH), 4.44 (br s, 1 H, H_α), 3.80 (s, 3 H, OCH_3), 2.85 (br m, 2 H, SCH_2), 2.62 (s, 3 H, $S(O)CH_3$), 2.40 (br m, 2 H, H_β).

General Procedure for the Pyrolysis of (2*S*)-*N*-(Alkoxycarbonyl)methionine Sulfoxide Methylidene Esters. A solution of the sulfoxide (0.05 mol) and triethyl phosphite (0.10 mol) in dry xylenes (300 mL) was heated at reflux under a nitrogen atmosphere. Refluxing was continued until all the sulfoxide had been pyrolyzed as observed by TLC, usually after 2 days. The mixture was then washed with water (5 × 150 mL), dried, and evaporated under reduced pressure to give the crude product containing triethyl phosphite. Drying under high vacuum removed most of the triethyl phosphite. Purification by chromatography (hexanes–ethyl acetate, 9:1) gave the (2*S*)-*N*-(alkoxycarbonyl)-vinylglycine methylene ester derivatives as a clear oil homogeneous by TLC.

(2*S*)-*N*-(Benzyloxycarbonyl)vinylglycine methylidene ester (3a) was obtained as an oil (6.71 g from 13.08 g of sulfoxide, 65%); $[\alpha]_D$ +78° (*c* 0.93, $CHCl_3$); IR (neat) 1790 (C=O, methylidene ester), 1700 (C=O, carbamate) cm^{-1}; ^1H NMR δ 7.36 (s, 5 H, Ar H), 5.88 (ddd, *J* = 17, 10, 5 Hz, 1 H, H_β), 5.61 (br s, 1 H, methylidene CH), 5.44–5.41 (m, 2 H, H_γ), 5.27 (d, *J* = 4 Hz, 1 H, methylidene CH), 5.20 (AB q, *J* = 12 Hz, 2 H, benzyl CH_2), 4.83 (br d, *J* = 5 Hz, 1 H, H_α).

(2*S*)-*N*-(Methoxycarbonyl)vinylglycine methylidene ester (3b) was obtained as an oil (11.12 g from 24.7 g of sulfoxide, 62%); $[\alpha]_D$ +94° (*c* 1.0, $CHCl_3$); IR (neat) 1800 (C=O, methylidene ester), 1710 (C=O, carbamate) cm^{-1}; ^1H NMR 5.89 (ddd, *J* = 17, 10.5, 5 Hz, 1 H, H_β), 5.61 (br s, 1 H, methylidene CH), 5.46–5.41 (m, 2 H, H_γ), 5.27 (d, *J* = 4.5 Hz, 1 H, methylidene CH), 4.82 (br s, 1 H, H_α), 3.81 (s, 3 H, OCH_3); ^{13}C NMR 169.9, 153.4, 129.4, 118.9, 77.8, 57.0, 53.3.

General Procedure for 1,3-Dipolar Cycloaddition Reactions of *N*-(5-*O*-Trityl-2,3-*O*-isopropylidene-β-D-ribofuranosyl)nitrone (2a) and *N*-(2,3;5,6-Di-*O*-isopropylidene-α-D-mannofuranosyl)nitrone (2b). A mixture of 5-*O*-trityl-2,3-*O*-isopropylidene-D-ribose oxime[15] (5.5 mmol) *or* 2,3;5,6-di-*O*-isopropylidene-D-mannose oxime[15] (5.5 mmol), paraformaldehyde (7.5 mmol), and the (2*S*)-vinylglycine derivative (5.0 mmol) in chloroform (30 mL) was heated at reflux under a nitrogen atmosphere. The refluxing was continued until all the alkene had been consumed as observed by TLC, usually after ca. 1.5 days. The reaction mixture was filtered and then evaporated under reduced pressure to give the cycloadduct.

(αS,5S)-2-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-α-D-ribofuranosyl)-α-[(benzyloxycarbonyl)amino]-5-isoxazolidineacetic Acid Methylidene Ester (4a). The cycloaddition of **2a** to (2*S*)-*N*-(benzyloxycarbonyl)vinylglycine methylidene ester (**3a**) in chloroform gave the cycloadduct **4a**, which was purified by chromatography (hexanes–ethyl acetate, 7:3) to give a white solid (6.86 g, 93%): R_f 0.22 (hexanes–ethyl acetate, 7:3); mp 75–78 °C; $[\alpha]_D$ +57.1° (*c* 0.98, $CHCl_3$); IR (KBr) 1790 (C=O, methylidene ester), 1705 (C=O, carbamate) cm^{-1}; ^1H NMR 7.50–7.20 (m, 20 H, Ar H), 5.48 (d, *J* = 4 Hz, 1 H, methylidene CH), 5.22–5.12 (m, 3 H, methylidene CH and benzyl CH_2), 4.63 (br m, 1 H, H_5), 4.58 (dd, *J* = 6, 2 Hz, 1 H, $H_{2'}$), 4.52 (dd, *J* = 6, 2.5 Hz, 1 H, $H_{3'}$), 4.47 (d, *J* = 2 Hz, 1 H, $H_{1'}$), 4.25 (br s, 1 H, H_α), 4.19 (ddd, *J* = 6, 6, 2.5 Hz, 1 H, $H_{4'}$), 3.22 (m, 2 H, $H_{5'}$), 3.05 (m, 1 H, H_3), 2.95 (m, 1 H, H_3), 2.50 (m, 1 H, H_4), 2.30 (m, 1 H, H_4), 1.47 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3); ^{13}C NMR 169.3, 152.2, 143.7, 135.2, 128.6, 128.5, 127.9, 127.7, 127.0, 112.9, 98.3, 86.7, 85.5, 83.5, 81.7, 77.9, 68.0, 64.3, 57.1, 48.5, 29.1, 26.8, 25.3.

(αS,5S)-2-(2′,3′-*O*-Isopropylidene-5′-*O*-trityl-α-D-ribofuranosyl)-α-[(methoxycarbonyl)amino]-5-isoxazolidineacetic Acid Methylidene Ester (4d). The cycloaddition of **2a** to (2*S*)-*N*-(methoxycarbonyl)vinylglycine methylidene ester (**3b**) in chloroform gave the cycloadduct **4d**, which was purified by chromatography (hexanes–ethyl acetate, 7:3) to give a white solid (5.97 g, 97%); R_f 0.42 (hexanes–ethyl acetate, 1:1); mp 72–76 °C; $[\alpha]_D$ +68° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 1790 (C=O, methylidene ester), 1700 (C=O, carbamate) cm^{-1}; ^1H NMR 7.47–7.21 (m, 15 H, trityl), 5.49 (br s, 1 H, methylidene CH), 5.20 (d, *J* = 4 Hz, 1 H, methylidene CH), 4.65 (br m, 1 H, H_5), 4.63 (dd, *J* = 6.5, 1.5 Hz, 1 H, $H_{2'}$), 4.54 (dd, *J* = 6.5, 1.5 Hz, 1 H, $H_{3'}$), 4.48 (d, *J* = 1.5 Hz, 1 H, $H_{1'}$), 4.29 (br s, 1 H, H_α), 4.24 (m, 1 H, $H_{4'}$), 3.78 (s, 3 H, OCH_3), 3.28–3.10 (m, 3 H, $H_{5'}$ and H_3), 2.91 (m, 1 H, H_3), 2.51 (m, 1 H, H_4), 2.35 (m, 1 H, H_4), 1.50 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3); ^{13}C NMR 169.3, 152.8, 143.7, 128.6, 127.7, 127.0, 112.8, 98.4, 86.7, 85.5, 83.5, 81.8, 77.9, 64.3, 60.2, 57.1, 53.0, 48.5, 29.1, 26.9, 25.3, 20.9, 14.1. Anal. Calcd. for $C_{35}H_{38}N_2O_9$: C, 66.65; H, 6.07; N, 4.44. Found: C, 66.58; H, 6.27; N, 4.33.

2-(2′,3′;5′,6-Di-*O*-isopropylidene-α-D-mannofuranosyl)-α-[(benzyloxycarbonyl)amino]-5-isoxazolidineacetic Acid Methylidene Ester (4c and 5c). The cycloaddition of **2b** to (2*S*)-*N*-(benzyloxycarbonyl)vinylglycine methylidene ester (**3a**) in chloroform gave the cycloadducts **4c** and **5c** ($R_1 + R_2 = CH_2$, R_3 = Cbz), which were purified by chromatography (hexanes–ethyl acetate, 7:3) to give a viscous oil (1.50 g, 71%); IR (KBr) 1800 (C=O, methylidene ester), 1720 (C=O, carbamate) cm^{-1}; ^1H NMR 7.36 (s, 5 H, Ar H), 5.68 and 5.55 (br, 1 H, methylidene CH), 5.28–5.13 (m, 3 H, methylidene CH and $PhCH_2$), 4.87–4.65 (m, 3 H), 4.54 and 4.47 (s, 1 H, H_α), 4.38–4.23 (m, 2 H), 4.05 (m, 2 H), 3.15 (m, 1 H, H_3), 3.00 (m, 1 H, H_3), 2.70 and 2.40 (m, 2 H, H_4), 1.47, 1.45, 1.38 and 1.33 (s, 12 H); ^{13}C NMR 170.0, 169.4, 152.1, 135.2, 134.9, 128.5, 128.4, 128.1, 128.0, 112.5, 112.3, 108.9, 98.8, 96.5, 83.7, 83.6, 82.6, 82.5, 80.1, 80.0, 79.0, 78.1, 77.7, 73.3, 73.1, 68.3, 67.8, 66.4, 66.3, 58.1, 57.0, 49.4, 49.3, 29.3, 29.2, 26.7, 25.9, 25.8, 25.1, 24.5, 24.4.

General Procedures for the Hydrolysis of Cycloadducts Using 98% Formic Acid. The cycloadduct (5 mmol) was dissolved in 98% formic acid (20 mL), stirred at room temperature for 10–16 h, and then filtered to remove trityl alcohol if necessary. The reaction mixture was then concentrated, dissolved in ice-cold 2 N hydrochloric acid (20 mL), washed with cold ether (3 × 20 mL), neutralized with sodium bicarbonate, saturated with sodium chloride, and extracted with dichloromethane (5 × 20 mL). The organic phase was dried and evaporated under reduced pressure to give the *N*-unsubstituted isoxazolidine.

(αS,5S)-α-[(Benzyloxycarbonyl)amino]-5-isoxazolidineacetic Acid Methylidene Ester (4b). Hydrolysis of cycloadduct **4a** gave the *N*-unsubstituted isoxazolidine **4b** as an oil (1.71 g, 84%). A sample was purified by chromatography (hexanes–ethyl acetate, 1:1): R_f 0.19 (hexanes–ethyl acetate, 1:1); $[\alpha]_D$ +176° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3400 (NH), 1790 (C=O, methylidene ester), 1705 (C=O, carbamate) cm^{-1}; ^1H NMR 7.37 (m, 5 H, Ar H), 5.48 (br s, 1 H, methylidene CH), 5.32 (d, *J* = 4 Hz, 1 H, methylidene CH), 5.19 (AB q, *J* = 12 Hz, 2 H, benzyl CH_2), 4.54 (br m, 1 H, H_5), 4.47 (s, 1 H, H_α), 4.20 (br, 1 H, NH), 3.26 (m, 1 H, H_3), 3.12 (m, 1 H, H_3), 2.61 (m, 1 H, H_4), 2.40 (m, 1 H, H_4); ^{13}C NMR 169.8, 152.2, 135.2, 128.6, 128.5, 128.2, 79.6, 78.0, 67.9, 57.2, 49.2, 32.1; MS, *m/e* (relative intensity) 292 (20, M^+), 221 (18), 92 (37), 91 (100), 86 (16), 72 (37), 65 (21).

(αS,5S)-α-[(Methoxycarbonyl)amino]-5-isoxazolidineacetic Acid Methylidene Ester (4e). Hydrolysis of cycloadduct **4d** gave the *N*-unsubstituted isoxazolidine **4e** as an oil (1.78 g, 92%). A sample was purified by chromatography (ethyl acetate): R_f 0.08 (hexanes–ethyl acetate, 1:1); $[\alpha]_D$ +226° (*c* 0.805, $CHCl_3$); IR ($CHCl_3$) 3380 (NH), 1780 (C=O, methylidene ester), 1690 (C=O, carbamate) cm^{-1}; ^1H NMR 5.54 (br s, 1 H, methylidene CH), 5.32 (br s, 1 H, methylidene CH), 5.02 (br, 1 H, NH), 4.51 (br m, 1 H, H_5), 4.47 (s, 1 H, H_α), 3.80 (s, 3 H, OCH_3), 3.26 (br m, 1 H, H_3), 3.16 (br m, 1 H, H_3), 2.62 (m, 1 H, H_4), 2.43 (br m, 1 H, H_4); ^1H NMR (at 50 °C) 5.52 (d, *J* = 4.5 Hz, 1 H, methylidene

CH), 5.29 (d, J = 4.5 Hz, 1 H, methylidene CH), 4.92 (br, 1 H, NH), 4.51 (br t, J = 8.5 Hz, 1 H, H_5), 4.43 (s, 1 H, H_α), 3.79 (s, 3 H, OCH_3), 3.25 (m, 1 H, H_3), 3.13 (m, 1 H, H_3), 2.61 (m, 1 H, H_4), 2.41 (m, 1 H, H_4); ^{13}C NMR 170.0, 153.0, 79.9, 78.3, 57.5, 53.2, 49.3, 32.3.

(αS,5S)- and (αS,5R)-α-[(Benzyloxycarbonyl)amino]-5-isoxazolidineacetic Acid Methylidene Esters (4b and 5b). The hydrolysis of a mixture of **4c** and **5c** gave the N-unsubstituted isoxazolidine as a mixture of the 5S and 5R diastereomers **4b** and **5b** as an oil (1.29 g, 90%). A sample was purified by chromatography (hexanes–ethyl acetate, 1:1): IR ($CHCl_3$) 3400 (NH), 1790 (C=O, methylidene ester), 1710 (C=O, carbamate) cm^{-1}; ^1H NMR 7.36 (m, 5 H, Ar H), 5.68 and 5.52 (br, 1 H, methylidene CH), 5.32–5.14 (m, 3 H, $PhCH_2$ and methylidene CH), 4.81 (br, 1 H, H_5), 4.51 and 4.47 (br s, 1 H, H_α), 3.24 and 3.12 (m, 2 H, H_3), 2.61 and 2.35 (m, 2 H, H_4).

General Procedure for the Oxidation of N-Unsubstituted Isoxazolidines to 4,5-Dihydroisoxazoles. A solution of the isoxazolidine (1 mmol) and N-chlorosuccinimide (1.2 mmol) in CH_2Cl_2 was stirred at room temperature for about 1 h. The reaction mixture was then concentrated and treated with carbon tetrachloride (20 mL). The precipitated succinimide was removed by filtration and the solution was evaporated under reduced pressure to give the 4,5-dihydroisoxazole.

(αS,5S)-α-[(Benzyloxycarbonyl)amino]-4,5-dihydro-5-isoxazoleacetic Acid Methylidene Ester (6a). The crude product was purified by chromatography (hexanes–ethyl acetate, 6:4) to give an oil (800 mg,94%): R_f 0.46 (hexanes–ethyl acetate, 1:1); $[\alpha]_D$ +251.5° (c 0.994, $CHCl_3$); IR ($CHCl_3$) 1790 (C=O, methylidene ester), 1710 (C=O, carbamate) cm^{-1}; ^1H NMR (at ambient temperature) 7.38 (m, 5 H, Ar H), 7.15 (s, 1 H, H_3), 5.52 (br, 1 H, methylidene CH), 5.38 (d, J = 4 Hz, 1 H, methylidene CH), 5.20 (AB q, J = 12 Hz, 2 H, benzyl CH_2), 5.08 (br m, 1 H, H_5), 4.32 (br s, 1 H, H_α), 3.49 (dd, J = 18, 7.5 Hz, 1 H, H_4), 3.19 (br m, 1 H, H_4); ^1H NMR (at 50 °C) 7.35 (m, 5 H, Ar H), 7.12 (s, 1 H, H_3), 5.54 (d, J = 4 Hz, 1 H, methylidene CH), 5.37 (d, J = 4 Hz, 1 H, methylidene CH), 5.21 (AB q, J = 12 Hz, 2 H, benzyl CH_2), 5.03 (m, 1 H, H_5), 4.30 (s, 1 H, H_α), 3.48 (ddd, J = 18, 7.5, 2 Hz, 1 H, H_4), 3.15 (ddd, J = 18, 11.5, 1.5 Hz, 1 H, H_4); ^{13}C NMR 168.7, 152.1, 146.7, 135.1, 128.6, 128.3, 78.3, 77.5, 68.1, 57.4, 37.4; MS, m/e (relative intensity) no M^+, 221 (80), 107 (30), 92 (90), 91 (100), 86 (84), 83 (90), 70 (51), 65 (79).

(αS,5S)-α-[(Methoxycarbonyl)amino]-4,5-dihydro-5-isoxazoleacetic Acid Methylidene Ester (6c). The crude product was purified by chromatography (hexanes–ethyl acetate 1:1) to give an oil (805 mg, 92%); R_f 0.21 (hexanes–ethyl acetate, 1:1); $[\alpha]_D$ +269° (c 0.49, $CHCl_3$); IR ($CHCl_3$) 1790 (C=O, methylidene ester), 1700 (C=O, carbamate) cm^{-1}; ^1H NMR (ambient temperature) 7.20 (br s, 1 H, H_3), 5.56 (br, 1 H, methylidene CH), 5.39 (d, J = 4 Hz, 1 H, methylidene CH), 5.08 (br m, 1 H, H_5), 4.33 (br s, 1 H, H_α), 3.84 (s, 3 H, OCH_3), 3.54 (ddd, J = 18, 7.5, 2 Hz, 1 H, H_4), 3.22 (ddd, J = 18, 11.5, 2 Hz, 1 H, H_4); ^1H NMR (at 50 °C) 7.15 (s, 1 H, H_3), 5.54 (d, J = 4 Hz, 1 H, methylidene CH), 5.36 (d, J = 4 Hz, 1 H, methylidene CH), 5.05 (m, 1 H, H_5), 4.33 (s, 1 H, H_α), 3.83 (s, 3 H, OCH_3), 3.51 (ddd, J = 18, 7.5, 2 Hz, 1 H, H_4), 3.19 (ddd, J = 18, 11.5, 2 Hz, 1 H, H_4); ^{13}C NMR 168.9, 152.9, 146.7, 78.5, 77.1, 57.3, 53.3, 37.5.

Mixture of (αS,5S)- and (αS,5R)-α-[(Benzyloxycarbonyl)amino]-4,5-dihydro-5-isoxazoleacetic Acid Methylidene Esters (6a and 7a). The oxidation of a mixture of **4b** and **5b** gave a 3:1 mixture of the 5S and 5R isomers **6a** and **7a**, respectively, as an oil (1.03 g, 95%): IR ($CHCl_3$) 1790 (C=O, methylidene ester), 1710 (C=O, carbamate) cm^{-1}; ^1H NMR (at 35 °C) 7.42–7.32 (m, Ar H), 7.17 (br s, H_3, 5S isomer), 7.07 (br s, H_3, 5R isomer), 5.66 (br, methylidene CH, 5R isomer), 5.53 (br, methylidene CH, 5S isomer), 5.38 (d, J = 4 Hz, methylidene CH, 5S isomer), 5.25–5.01 (m, PhCH, methylidene CH and H-5), 4.44 (br s, H_α, 5R isomer), 4.32 (br s, H_α, 5S isomer), 3.55–3.33 (m, H_4), 3.19 (m, H_4); ^1H NMR (at 50 °C) 7.41–7.30 (m, Ar H), 7.17 (s, H_3, 5S isomer), 7.07 (s, H_3, 5R isomer), 5.66 (d, J = 4 Hz, methylidene CH, 5R isomer), 5.54 (d, J = 4 Hz, methylidene CH, 5S isomer), 5.37 (d, J = 4 Hz, methylidene CH, 5S isomer), 5.25–5.13 (m, $PhCH_2$ and methylidene CH), 5.02 (m, H_5), 4.40 (s, H_α, 5R isomer), 4.30 (s, H_α, 5S isomer), 3.48 (ddd, J = 18, 11.5, 1.5 Hz, H_4, 5S isomer), 3.30 (br, H-4, 5R isomer), 3.19–3.07 (m, H-4).

(αS,5R)-α-[(Benzyloxycarbonyl)amino]-4,5-dihydro-5-isoxazoleacetic Acid Methylidene Ester (7a). Separation of the mixture of **6a** and **7a** by column chromatography (hexanes–ethylacetate, 7:3) gave an oil: R_f 0.49 (hexanes–ethyl acetate, 1:1); $[\alpha]_D$ +23.4° (c 1.11, $CHCl_3$); IR ($CHCl_3$) 1790 (C=O, methylidene ester), 1705 (C=O, carbamate) cm^{-1}; ^1H NMR (ambient temperature) 7.37 (m, 5 H, Ar H), 7.09 (s, 1 H, H_3), 5.66 (br, 1 H, methylidene CH), 5.25–5.11 (br m, 3 H, methylidene CH and benzyl CH_2), 5.07 (br m, 1 H, H_5), 4.45 (s, 1 H, H_α), 3.42 (br m, 1 H, H_4), 3.16 (br m, 1 H, H_4); ^1H NMR (at 50 °C) 7.35 (m, 5 H, Ar H), 7.02 (s, 1 H, H_3), 5.66 (d, J = 4 Hz, 1 H, methylidene CH), 5.22 (d, J = 4 Hz, 1 H, methylidene CH), 5.19 (AB q, J = 12 Hz, 2 H, benzyl CH_2), 5.03 (dd, J = 11, 6 Hz, 1 H, H_5), 4.41 (s, 1 H, H_α), 3.32 (br m, 1 H, H_4), 3.15 (ddd, J = 18, 11 Hz, 1 H, H_4); ^{13}C NMR 170.0, 152.2, 146.6, 134.9, 128.7, 128.3, 79.2, 77.6, 68.6, 58.7, 37.7.

(αS,5S)-α-[(Methoxycarbonyl)amino]-3-chloro-4,5-dihydro-5-isoxazoleacetic Acid Methylidene Ester (6d). A solution of (αS,5S)-α-[(methoxycarbonyl)amino]-4,5-dihydro-5-isoxazoleacetic acid methylidene ester (**6c**) (1.38 mmol) in dry *tert*-butyl alcohol (15 mL) was saturated with chlorine gas. The reaction mixture was stirred at room temperature with the progress of the reaction being monitored by TLC. After 3 h and 6 h the reaction mixture was resaturated with chlorine gas. After 8 h the solution was concentrated under reduced pressure and then dissolved in small volume of dichloromethane and purified by chromatography (hexanes–ethyl acetate, 1:1) to give the 3-chloro-4,5-dihydroisoxazole (**6d**) as an oil (271 mg, 1.09 mmol, 79%): R_f 0.34 (hexanes–ethyl acetate, 1:1); $[\alpha]_D$ +227° (c 0.61, $CHCl_3$); IR ($CHCl_3$) 1790 (C=O, methylidene ester), 1700 (C=O, carbamate) cm^{-1}; ^1H NMR (at ambient temperature) 5.54 (br, 1 H, methylidene CH), 5.36 (d, J = 4 Hz, 1 H, methylidene CH), 5.29 (br, 1 H, H_5), 4.35 (br s, 1 H, H_α), 3.82 (s, 3 H, OCH_3), 3.69 (dd, J = 18, 8 Hz, 1 H, H_4), 3.40 (dd, J = 18, 11 Hz, 1 H, H_4); ^1H NMR (at 50 °C) 5.53 (d, J = 4 Hz, 1 H, methylidene CH), 5.33 (d, J = 4 Hz, 1 H, methylidene CH), 5.26 (m, 1 H, H_5), 4.32 (s, 1 H, H_α), 3.81 (s, 3 H, OCH_3), 3.67 (dd, J = 18, 8 Hz, 1 H, H_4), 3.40 (dd, J = 18, 11 Hz, 1 H, H_4); ^{13}C NMR 168.6, 152.8, 150.1, 80.2, 78.5, 57.2, 53.5, 40.0.

General Procedure for the Deprotection of the 4,5-Dihydro-5-isoxazoleacetic Acid Derivatives. Method A: Using Boron Tris(fluoroacetate) in Trifluoroacetic Acid. This was carried out by following the literature procedure.[29] To a stirred ice-cold solution of the protected amino acid (1 mmol) in dry trifluoroacetic acid (10 mL) was added dropwise a solution of boron tris(trifluoroacetate) in trifluoroacetic (6 mL of 0.8 M solution) under a nitrogen atmosphere. The resulting mixture was stirred at 0 °C for 1 h and then evaporated to dryness under reduced pressure. The resulting mixture was treated three times with methanol and evaporated to dryness. The resulting solid was dissolved in 2 N HCl (5 mL), filtered, and then loaded onto an ion-exchange column (5 × 2.5 cm). The column was washed with water (200 mL) and then eluted with 0.5 N NH_4OH. The ninhydrin positive fractions were pooled and then lyophilized to give the free amino acid. Recrystallization from aqueous methanol gave the pure product.

(αS,5S)-α-Amino-4,5-dihydro-5-isoxazoleacetic Acid (6b). The deprotection of (αS,5S)-α-[(benzyloxycarbonyl)amino]-4,5-dihydro-5-isoxazoleacetic acid methylidene ester (**6a**) gave **6b** as a white powder (35 mg, 89%): mp 171–173 °C dec; $[\alpha]_D$ +148° (c 1.0, H_2O); IR (KBr) 3100–2500, 1590, 1400 cm^{-1}; ^1H NMR (D_2O) 7.44 (s, 1 H, H_3), 4.95 (ddd, J = 12, 8, 3.5 Hz, 1 H, H_5), 3.94 (d, J = 3.5 Hz, 1 H, H_α), 3.20 (dd, J = 18, 12 Hz, 1 H, H_4), 3.07 (dd, J = 18, 8 Hz, 1 H, H_4). Anal. Calcd for $C_5H_8N_2O_3$: C, 41.67; H, 5.60; N, 19.44. Found: C, 41.72; H, 5.73; N, 19.42.

Mixture of (αS,5S)- and (αS,5R)-α-Amino-4,5-dihydro-5-isoxazoleacetic Acids (6b and 7b). The deprotection of the mixture of (αS,5S)- and (αS,5R)-α-[(benzyloxycarbonyl)-amino]-4,5-dihydro-5-isoxazoleacetic acid methylidene esters (**6a** and **7a**) gave the trifluoroacetate salt as a 3:1 mixture of the 5S and 5R isomers **6b** and **7b**, respectively, as a white solid (120 mg, 92%): ^1H NMR (D_2O) 7.35 (s, H_3, 5S isomer), 7.30 (s, H_3, 5R isomer), 4.96 (m, H_5, 5S isomer), 4.89 (m, H_5, 5R isomer), 4.18

(29) Pless, J.; Bauer, W. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 147–148.

(d, J = 3.5 Hz, H_α, 5S isomer), 3.99 (d, J = 6 Hz, H_α, 5R isomer), 3.34–3.13 (m, H_4).

Method B: Using Boron Tribromide in Dichloromethane. This was carried out by using the procedure of Felix.[30] To a stirred solution of the protected amino acid (0.5 mmol) in dry CH_2Cl_2 (15 mL) cooled to −10 °C was added dropwise BBr_3–CH_2Cl_2 (3 mL of a 1 M solution). Stirring was continued at −10 °C for 1 h and at room temperature for 2–5 h, after which the reaction mixture was cautiously treated with H_2O (5 mL). The aqueous phase was collected and the organic phase was extracted with H_2O (5 × 5 mL). The combined aqueous extracts were evaporated to dryness under reduced pressure. The resulting solid was dissolved in H_2O (2 mL) and then loaded onto an ion-exchange column that had earlier been equilibrated with 0.4 M pyridine acetate buffer (pH 4). The column was eluted with 0.4 M pyridine acetate buffer (pH 4). The ninhydrin fraction positive fractions were pooled and then lyophilized to give the free amino acid. Recrystallization from aqueous methanol gave the pure product.

(αS,5S)-α-Amino-4,5-dihydro-5-isoxazoleacetic Acid (6b). The deprotection of **6c** gave **6b** (88% yield; mp 171–173 °C dec) identical by ^1H NMR with that obtained previously.

Method C: Using Boron Trichloride in Dichloromethane. (αS,5S)-α-Amino-3-chloro-4,5-dihydro-5-isoxazoleacetic Acid (Acivicin) (1). To s stirred ice-cold solution of the 3-chloro-4,5-dihydroisoxazole (**6d**) (88 mg, 0.35 mmol) in dry CH_2Cl_2 (5 mL) under a nitrogen atmosphere was added dropwise a solution of BCl_3 in CH_2Cl_2 (2 mL of a 1 M solution). The resulting reaction mixture was stirred at room temperature for 20 h and then cautiously treated with water (5 mL). The aqueous layer was separated and then the organic layer was extracted with water (5 × 5 mL). The combined aqueous extracts were evaporated to dryness under reduced pressure and then the resulting solid was dissolved in 2 N HCl (2 mL) and loaded onto an ion-exchange column. The column was eluted with 0.5 N NH_4OH. The ninhydrin positive fractions were pooled and then lyophilized to afford acivicin as a white solid (35 mg, 59.5%). Recrystallization from aqueous methanol gave a white powder: mp 180–192 °C dec; R_f 0.56 (MeOH–H_2O–pyridine, 20:5:1); $[\alpha]^{20}_D$ +139° (c 0.14, H_2O), [lit.[6] $[\alpha]^{20}_D$ +148° (c 0.845, H_2O)]; $[\alpha]^{20}_{578}$ +146° (c 0.14, H_2O), [lit.[7] $[\alpha]^{20}_{578}$ +135° (c 0.159, H_2O)]; IR (KBr) 3500–2500, 1590, 1480, 1390, 1300 cm^{-1}; ^1H NMR (D_2O) 5.36 (ddd, J = 11, 8, 3 Hz, 1 H, H_5), 4.12 (d, J = 3 Hz, 1 H, H_α), 3.60 (dd, J = 18, 11 Hz, 1 H, H_4), 3.52 (dd, J = 18, 8 Hz, 1 H, H_4).

(30) Felix, A. M. *J. Org. Chem.* **1974**, *39*, 1427–1429.

(αS,5S)- and (αR,5R)-α-[(Methoxycarbonyl)amino]-3-methyl-4,5-dihydroisoxazole-5-acetic Acid Methylidene Ester (8a). To a stirred ice-cold solution of (2S)-*N*-(methoxycarbonyl)vinylglycine methylidene ester (**3b**) (1.54 g, 9.0 mmol) and phenyl isocyanate (2.5 mL, 2.737 g, 23 mmol) in dry benzene (20 mL) under nitrogen was added dropwise a solution of dry nitroethane (3 mL, 3.135 g, 42 mmol) and dry triethylamine (0.4 mL, 0.29 g, 2.8 mmol) in dry benzene (10 mL). The resulting mixture was stirred at room temperature overnight. Purification by column chromatography (hexanes–ethyl acetate, 1:1) gave the cycloadduct **8a** (1.51 g, 74%) as a mixture of two isomers: ^1H NMR 5.65 and 5.52 (br, 1 H, methylidene CH), 5.38 and 5.26 (d, J = 4 Hz, 1 H, methylidene CH), 5.10 (m, 1 H, H_5), 4.43 and 4.27 (br s, 1 H, H_α), 3.82 (s, 3 H, OCH_3), 3.42 (dd, J = 18, 6 Hz, 1 H, H_4), 3.16 (dd, J = 18, 11 Hz, 1 H, H_4), 2.01 and 1.99 (s, 3 H, CH_3).

(αS,5S)- and (αS,5R)-α-Amino-3-methyl-4,5-dihydroisoxazole-5-acetic Acid (8b). Deprotection of 4,5-dihydroisoxazole-5-acetic acid methylidene ester (**8a**) (555 mg, 2.4 mmol) by method B (BBr_3/CH_2Cl_2) gave (αS)-α-amino-3-methyl-4,5-dihydroisoxazole-5-acetic acid (**8b**) as a solid (298 mg, 74%): ^1H NMR (D_2O) 4.98 (m, H_5, 5S isomer), 4.80 (m, H_5, 5R isomer), 3.90 (d, J = 3.5 Hz, H_α, 5S isomer), 3.66 (d, J = 8 Hz, H_α, 5R isomer), 3.31–3.01 (m, H_4), 1.92 (s, CH_3, 5R isomer), 1.87 (s, CH_3, 5S isomer). Recrystallization from aqueous methanol gave a white powder consisting largely of the αS,5R diastereomer: ^1H NMR (D_2O) 4.83 (m, 1 H, H_5), 3.69 (d, J = 8 Hz, 1 H, H_α), 3.30 (dd, J = 18, 11 Hz, 1 H, H_4), 3.15 (dd, J = 18, 6 Hz, 1 H, H_4), 1.95 (s, 3 H, CH_3). Anal. Calcd for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.71. Found: C, 45.67; H, 6.29; N, 18.14. The mother liquor was freeze-dried to give a solid consisting largely of the αS,5S diastereomer: ^1H NMR (D_2O) 5.00 (m, 1 H, H_5), 3.93 (d, J = 3.5 Hz, 1 H, H_α), 3.22 (dd, J = 18, 11 Hz, 1 H, H_4), 3.07 (dd, J = 18, 7 Hz, 1 H, H_4), 1.89 (s, 3 H, CH_3).

Acknowledgment. We are grateful to Dr. D. G. Martin of The UpJohn Company, Kalamazoo, MI, for kindly providing an authentic sample of acivicin. Financial support of the Natural Sciences and Engineering Research Council of Canada, the Clare Nelson Bequest, and Mr. and Mrs. J. A. Whitney is gratefully acknowledged. The experimental assistance of Chang-Mo Yang, Pacific Chemical Industrial Co. Ltd., Seoul, Korea, in preliminary aspects of this work is also gratefully acknowledged. Professor Saul Wolfe is sincerely thanked for many fruitful discussions, particularly those concerning computational methods.

Asymmetric Synthesis of Both Enantiomers of Tomoxetine and Fluoxetine. Selective Reduction of 2,3-Epoxycinnamyl Alcohol with Red-Al

Y. Gao and K. B. Sharpless*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Received February 16, 1988

Both enantiomers of tomoxetine **7a,7b** and fluoxetine **8a,8b** (as their hydrochloride salts) have been synthesized from cinnamyl alcohol by asymmetric epoxidation, and their absolute configurations have been established. Optimal conditions for regioselective Red-Al reduction at C-2 of 2,3-epoxycinnamyl alcohol are discussed.

Tomoxetine is the first norepinephrine (NE) reuptake-inhibiting antidepressant without strong affinity for α- or β-adrenergic receptors.[1] Fluoxetine is also a potent antidepressant with potential applications in treatment of other symptoms.[1b,2] The enantiomers of both compounds have been synthesized relying upon resolution of appropriate racemic precursors, and recently (S)-fluoxetine has

(1) (a) *Drugs Future* **1986**, *11*, 134. (b) Ankier, S. I. *Prog. Med. Chem.*, **1986**, *23*, 121.

(2) Robertson, D. W.; Krushinski, J. H.; Fuller, R. W.; Leander, J. D. *J. Med. Chem.*, in press. The authors have developed a method for determination of enantiomeric excess of fluoxetine.

0022-3263/88/1953-4081$01.50/0