μL) was injected through a rubber septum into the reaction solution. The subsequent reactions with sulfur and Li_2S were performed exactly as described above for method A. Addition of the latter caused the appearance of a dark green suspension. Workup and DEAE-Sephadex A-25 chromtography was also carried out as above. Thymidine 5′-*O*-(1,1-dithiotriphosphate) eluted between 0.61 and 0.65 M buffer. Yield 125 A_{267} units (13%). This material was identical in all respects with that synthesized by method A.

Guanosine 5′-*O*-(1,1-Dithiotriphosphate). 2′,3′-*O*-Diacetylguanosine (100 μmol, 36.7 mg) was dissolved in pyridine (200 μL) and DMF (800 μL), and the solution was evaporated on a dry evaporator. The residue was dried over P_2O_5 for 1 h, dissolved in a mixture of pyridine (200 μL) and DMF (800 μL), and reacted with salicylphosphochloridite, pyrophosphate, sulfur, and Li_2S as described for compound **15** in method B. Purification on DEAE-Sephadex yielded 290 A_{254}-units (22%) of guanosine 5′-*O*-(1,1-dithiotriphosphate). Its ^{31}P NMR spectrum is virtually identical with that of thymidine 5′-*O*-(1,1-dithiotriphosphate). HPLC retention time, 7.53 min. For comparison that of R_p guanosine 5′-*O*-(1-thiotriphosphate) is 7.22 min.

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Enantioselective Synthesis of Both Enantiomers of Phosphinothricin via Asymmetric Hydrogenation of α-Acylamido Acrylates

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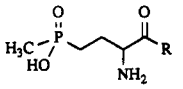
Both enantiomers of phosphinothricin (**1**), a naturally occuring amino acid that contains the unique methylphosphinate moiety, were prepared by asymmetric hydrogenation of α-acylamido acrylate precursors **7**. L-**1** and peptides containing L-**1** are inhibitors of the enzyme glutamine synthetase (GS). Inhibition of GS is responsible for the antibiotical and herbicidal properties of these compounds. Synthesis of substrates **7** and parameters influencing the enantioselectivity are discussed. Substrate concentration and solvent polarity appear to have the most marked effects on enantiomeric excesses for a given catalyst system. Enantiomeric excesses reach 91% for hydrogenations with (*R*,*R*)-NORPHOS- and (*S*,*S*)-CHIRAPHOS-derived catalysts.

Introduction

L-Phosphinothricin (L-**1**), which constitutes the N-terminal amino acid of the antibiotic tripeptides **2**[1] and **3**[2] produced by several streptomycete and actinomycete strains, exhibits strong herbicidal activity.[3]

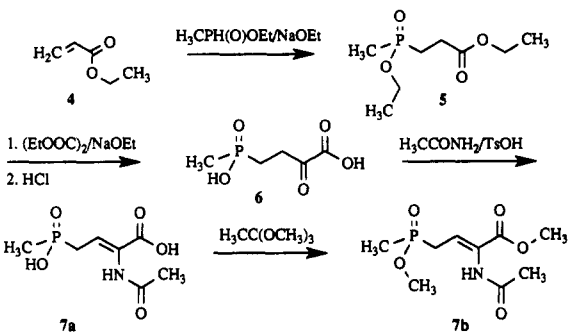


1 R = OH
2 R = Ala-Ala-OH
3 R = Ala-Leu-OH

The biological activity of these compounds is based on the inhibition of glutamine synthetase (EC 6.3.1.2), an enzyme that plays a pivotal role in the ammonia metabolism of plants[4] and bacteria.[5]

Several syntheses of racemic **1** have been reported[6] however L-**1**[7] is claimed to possess twice the biological activity of D,L-**1**.[6b,8]

Scheme I



L-**1** has been obtained with an enantiomeric excess (ee) of 79–94% by enantioselective alkylation of chiral glycine synthons[9] or by enzymatic resolution of racemic precursors.[10]

(1) (a) Bayer, E.; Gugel, K. H.; Haegele, K.; Hagenmeier, H.; Jessipow, S.; Koenig, W. A.; Zaehner, H. *Helv. Chim. Acta* **1972**, *55*, 224. (b) Kondo, Y.; Shomura, T.; Ogawa, Y.; Tsuruoka, T.; Watanabe, H.; Totsukawa, K.; Suzuki, T.; Moriyama, C.; Yoshida, J.; Inouye, S.; Niida, T. *Sci. Rep. Meiji Seika Kaisha* **1973**, *13*, 34.

(2) Omura, S.; Hinotozawa, K.; Imamura, N.; Murata, M. *J. Antibiot.* **1984**, *37*, 939.

(3) Weissermel, K.; Kleiner, H. J.; Finke, M.; Felcht, U. H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 223.

(4) Koecher, H. *BCPC Monogr.* **1989**, *42*, 63.

(5) Colanduoni, J. A.; Villafranca, J. J. *Bioorg. Chem.* **1986**, *14*, 163.

(6) (a) Suzuki, A.; Tsuruoka, T.; Mizutami, K.; Inouye, S. *Sci. Rep. Meiji Seika Kaisha* **1981**, *20*, 33. (b) Maier, L.; Lea, P. J. *Phosphorus Sulfur* **1983**, *17*, 1. (c) Minowa, N.; Fukatsu, S.; Niida, T.; Takada, M.; Sato, K. *Tetrahedron Lett.* **1983**, *24*, 2391. (d) Logusch, E. W. *Tetrahedron Lett.* **1986**, *27*, 5935.

(7) It has been shown by X-ray analysis that at least in the crystalline state L-**1** has two centers of chirality. While the α-carbon atom is *S* configurated, the phosphorus atom has *R* configuration: Paulus, E. F.; Grabley, S. *Z. Kristallogr.* **1982**, *160*, 63.

(8) Takematsu, T.; Konnai, M.; Tachibana, K.; Tsuruoka, T.; Inouye, S.; Watanabe, T. U.S. Patent 4265654, 1981; *Chem. Abstr.* **1979**, *91*, 103741a.

(9) (a) Minowa, N.; Hirayama, M.; Fukatsu, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1761. (b) Zeiss, H. J. *Tetrahedron Lett.* **1987**, *28*, 1255.

(10) (a) Grabley, S.; Sauber, K. U.S. Patent 4389488, 1983; *Chem. Abstr.* **1982**, *97*, 125725z. (b) Natchev, I. A. *J. Chem. Soc., Perkin Trans. I* **1989**, 125.

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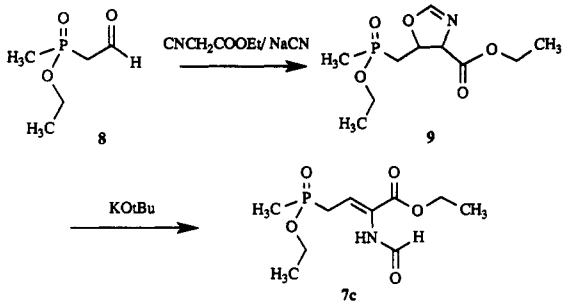
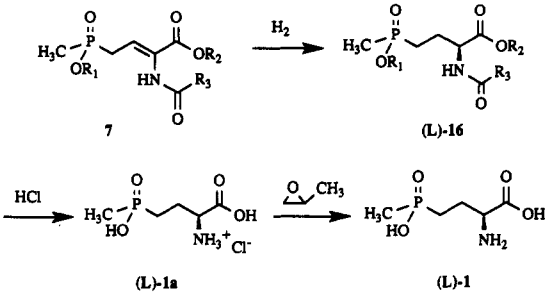
Scheme II



Scheme III



We wish to report here a catalytic enantioselective synthesis of L-1 and its enantiomer D-1 via asymmetric hydrogenation of α-acylamido acrylate precursors that avoids the use of stoichiometric amounts of a chiral auxiliary as well as the sometimes difficult manipulation of enzyme preparations.

While the asymmetric hydrogenation of α-acylamido cinnamic acid derivatives, which leads to the formation of phenylalanines, has been extensively investigated,[11] only a few reports have appeared on the synthesis of aliphatic amino acids that bear a polar group in their side chain.[12]

A reason for this lack of effort may be due to the inaccessibility of the respective α-acylamido acrylic acid derivatives that are needed as substrates for the asymmetric hydrogenation reaction.

Results and Discussion

Base-catalyzed addition[13] of ethyl methylphosphinate to ethyl acrylate (4) afforded **5**[14] in 81% yield (Scheme I). Reaction of **5** with diethyl oxalate followed by saponification and decarboxylation furnished the α-keto acid **6**,[15] which upon acid-catalyzed condensation with acetamide provided the N-acylated dehydroamino acid **7a** as a single stereoisomer.[16,17] Simultaneous esterification of both acid functionalities to yield **7b**[17] quantitatively was accomplished by refluxing **7a** with an excess of 1,1,1-trimethoxyethane.

A second approach to dehydroamino acid derivatives is outlined in Scheme II. Cyanide-mediated reaction of aldehyde **8**[18] with ethyl isocyanoacetate furnished **9**, which was converted into **7c** in 66% yield by treatment[19] with equimolar amounts of potassium *tert*-butoxide.

Table I. Asymmetric Hydrogenation of Dehydrophosphinothricin Derivatives 7 with Chiral Rhodium–Phosphine Catalysts[a]

entry	substr	phosphine	solvent[b]	ee, %[c]	confign
1[d,e]	7c	10	MeOH	39.0	*S*
2[f,g]	7a	10	MeOH	60.0	*S*
3[f]	7a	10	MeOH	69.5	*S*
4	7a	10	MeOH/H_2O	71.4	*S*
5[f,h]	7a	10	MeOH	71.6	*S*
6	7a	11	MeOH	81.8	*S*
7[i]	7a	11	MeOH	81.4	*S*
8[i]	7a	11	MeOH/H_2O	83.2	*S*
9[f,h,i]	7a	11	MeOH	83.2	*S*
10[h,i]	7a	11	THF/MeOH	67.2[j]	*S*
11[k]	7a	11	MeOH	82.4	*S*
12[l]	7a	11	MeOH	no reaction	
13[f,i]	7b	11	MeOH	80.4	*S*
14	7a	12	MeOH	87.2	*S*
15	7a	12	MeOH/H_2O	87.2	*S*
16[k]	7a	12	MeOH/H_2O	88.2	*S*
17[e,m]	7a	12	MeOH/H_2O	90.8	*S*
18	7b	12	MeOH	84.4	*S*
19	7a	13	MeOH	91.0	*R*

[a] For reaction conditions, see Experimental Section. [b] MeOH/H_2O 9:1; THF/MeOH 2:1. [c] Enantiomeric excess of the crude hydrochlorides **1a**, which were >98% pure by ^{31}P NMR. The deviation of ee values for two consecutive hydrogenations with the same substrate/catalyst combination under identical experimental conditions was found to be 0.4%. The accuracy of the HPLC determination[28] was checked to be ±0.4% ee with a racemic mixture of D-**1a** and L-**1a**. [d] Reaction time 45 h. [e] Substrate/catalyst ratio 150:1. [f] Substrate/catalyst ratio 250:1. [g] Crude **7a** was used as substrate. [h] Reaction at 50 °C. [i] Crystalline catalyst **15** was used. [j] Turnover after 22 h: 88%. [k] 1 equiv of Et_3N added. [l] 2 equiv of Et_3N added. [m] Substrate solution 0.0125 M.

The assignment of *Z* stereochemistry to **7a**, **7b**, and **7c** is based on the comparison of their olefinic proton NMR chemical shift values with dehydroamino acid derivatives whose structures have been confirmed by X-ray analysis.[12b,20]

Enantioselective hydrogenation of the substrates **7** was performed with rhodium(I) complexes derived from the chiral bis(phosphines) (*S*,*S*)-DIOP (**10**),[21] (*R*)-PROPHOS (**11**),[22] (*R*,*R*)-NORPHOS (**12**),[23] and (*S*,*S*)-CHIRAPHOS (**13**).[24]

Catalysts were usually prepared in situ by mixing equimolar amounts of chloro–norbornadiene–rhodium

(11) (a) Brunner, H. *Synthesis* **1988**, 645. For recent reviews, see: (b) Williams, R. M. *Synthesis of optically active α-amino acids*; Pergamon: Oxford, 1989; p 239. (c) Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* **1989**, *45*, 6901.

(12) (a) Achiwa, K. *Tetrahedron Lett.* **1978**, 2583. (b) Scott, J. W.; Keith, D. D.; Nix, D.; Parish, D. R.; Remington, S.; Roth, G. P.; Townsend, J. M.; Valentine, D.; Yang, R. *J. Org. Chem.* **1981**, *46*, 5086. (c) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J. *J. Mol. Catal.* **1983**, *19*, 159.

(13) Gehrmann, K.; Ohorodnik, A.; Rosenthal, J. U.S. Patent 4560518, 1985; *Chem. Abstr.* **1984**, *101*, 192199v.

(14) Khairullin, V. K.; Sobchuk, T. I.; Pudovik, A. N. *Zh. Obshch. Khim.* **1967**, *37*, 710, Engl. 666.

(15) Baillie, A. C.; Wright, B. J.; Wright, K.; Earnshaw, C. G. U.S. Patent 4399287, 1983; *Chem. Abstr.* **1981**, *95*, 214152x.

(16) The uncatalyzed condensation of **6** with acetamide is claimed to yield **7a** in ref 15, but data confirming either the purity or the structure of the product are not given there.

(17) The mother liquors of the crystallization of (*Z*)-**7a** contained varying amounts (5–10%) of (*E*)-**7a**. A mixture of (*Z*)-**7b** and (*E*)-**7b** can be obtained by prolonged heating of (*Z*)-**7b** to 100 °C. The proton NMR spectra of these mixtures served as basis for the assignment of the stereochemistry, cf. ref 12b.

(18) Razumov, A. I.; Liorber, B. G.; Pavlov, V. A.; Sokolov, M. P.; Zykova, T. V.; Salakhutdinov, R. A. *Zh. Obshch. Khim.* **1977**, *46*, 243, Engl. 224.

(19) (a) Schoellkopf, U.; Gerhart, F.; Schroeder, R.; Hoppe, D. *Liebigs Ann. Chem.* **1972**, *766*, 116. (b) Hoppe, I.; Schoellkopf, U. *Synthesis* **1982**, 129.

(20) The stereochemical assignments for α-formamidoacrylic acid derivatives given in ref 19 are inconsistent with those established in ref 12b for α-acetamidoacrylic acid compounds. The stereochemical conclusions in ref 19 are drawn only on the basis of proton NMR data, while those in ref 12b are based on X-ray analysis. Since we observed a very strong solvent dependence of the proton NMR signals, which led to an inversion of the olefinic proton NMR shift values for (*E*)-**7b** and (*Z*)-**7b** when changing the solvent from $CDCl_3$ to DMSO-d_6, we believe this to be a possible explanation for the contradictory assignments in ref 19.

(21) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.

(22) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.

(23) Brunner, H.; Pieronczyk, W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 620.

(24) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262.

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dimer (14) and the respective bis(phosphine).[12b] In the case of (*R*)-PROPHOS (11) also the crystalline rhodium(I) tetrafluoroborate complex 15[25] was employed for the purpose of comparison.

Since the N-acylated derivatives 16[26] of both L-1 and D-1 proved to be hygroscopic oils that were difficult to manipulate,[27] the crude hydrogenation products were converted into hydrochlorides 1a (Scheme III).

The yields of the primary hydrogenation products 16 were quantitative, except in the case of substrate 7c and when tetrahydrofuran (THF)/MeOH was used as solvent (Table I, entries 1 and 10). Saponification of 16 with 6 N HCl furnished a 90–100% yield of crude phosphinothricin hydrochloride (1a), the ee of which was determined by HPLC.[28]

Recrystallization of 1a from ethanol/water gave a final yield of 75–80% and usually led to an increase of the ee value by 3–5%. Treatment of the hydrochlorides 1a with propene oxide furnished 1 in 90–96% yield.

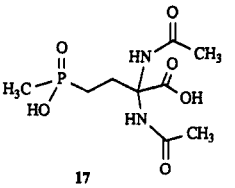
The results of the hydrogenation experiments are compiled in Table I.

N-Formyldehydroamino acid ester 7c was hydrogenated very slowly and proved to be a poor substrate for asymmetric hydrogenation with the (*S,S*)-DIOP-derived catalyst (Table I, entry 1). The reason for this behavior remains unclear, but we think it can neither be attributed to the carboxylic ester function nor the *N*-formyl substituent, since the esterified *N*-acetyl substrates 7b react at a higher rate than their carboxylic acid counterparts 7a (vide infra) and asymmetric hydrogenation of *N*-formyltryptophan precursors proceeds with enantioselectivities comparable to those obtained with *N*-acetyl subtrates.[29] However, hydrogenation of dehydro(*N*-formyl)aminophosphonic acid derivatives has been reported to take place very sluggishly.[30]

In contrast, hydrogenation of the *N*-acetyl substrate 7a with catalysts derived from (*S,S*)-DIOP, (*R*)-PROPHOS, (*R,R*)-NORPHOS, and (*S,S*)-CHIRAPHOS proceeded with the same magnitude of enantioselectivity as has been observed in the hydrogenation of the corresponding *N*-acetamidocinnamates.[21-24]

This applies only for the use of pure crystalline 7a, since the employment of crude 7a reduced the ee from 69.5% to 60% in the (*S,S*)-DIOP-catalyzed hydrogenation (Table I, entry 2). We attribute this to the presence of 17, which is a byproduct[31] in the synthesis of 7a that even at low concentrations poisons the catalyst.

In case of (*S,S*)-DIOP- and (*R*)-PROPHOS-catalyzed hydrogenations, enantioselectivity was markedly influenced by the solvent polarity. By using a water/methanol mixture instead of pure methanol to create a more polar reaction medium, ee could be increased about 2% (Table I, entries 4 and 8). The adverse effect was observed when hydrogenations were performed in a THF/methanol mixture (Table I, entry 10).



17

Catalysts derived from (*R,R*)-NORPHOS seemed to be less sensitive to the nature of the solvent, since hydrogenations in methanol proceeded with the same ee as in water/methanol mixtures (Table I, entries 14 and 15).[32]

Raising the reaction temperature to 50 °C increased the ee about 2% when (*S,S*)-DIOP- and (*R*)-PROPHOS-derived catalysts were employed (Table I, entries 5 and 9).[33]

No difference in enantioselectivity could be established between hydrogenations performed with (*R*)-PROPHOS catalyst prepared in situ and reactions in which crystalline catalyst 15 was used (Table I, entries 6 and 7).[34,35] In contrast to hydrogenations performed with phosphinite ligands,[36] the question as to whether the counterion of the rhodium(I) species is capable of binding coordinatively to the metal center or not seems to be of less importance.

The addition of 1 equiv of base led to a slight increase of enantioselectivity, whereas upon addition of 2 equiv of triethylamine no reaction occurred at all (Table I, entries 11 and 12). These results are in compliance with the assumption that the carboxylate anion is no longer a good substrate for the catalyst, since because of its acidity (pK_a 1.8)[37] the phosphinic acid moiety must be deprotonated first.[38]

The most significant increase of enantioselectivity was achieved with the (*R,R*)-NORPHOS catalyst system when the concentration of the substrate was decreased 20-fold to 0.0125 M, which resulted in an ee of nearly 91% (Table I, entry 17). This behavior resembles the BINAP-catalyzed hydrogenations[39] that appear to be very sensitive toward the concentration of the substrate.

Only one experiment was conducted with (*S,S*)-CHIRAPHOS, a catalyst system for the production of D-amino acids. The ee of 91% compares well with the results obtained in the *N*-acetamidocinnamic acid series.[24]

The hydrogenations of the esterified substrate 7b with (*R*)-PROPHOS- and (*R,R*)-NORPHOS-derived catalysts proceeded at a higher reaction rate but with a 1–3% lower ee in comparison to the free acid derivative 7a (Table I, entries 13 and 18). Thus, as in the case of many pheny-

(25) Prepared in analogy to Schrock et al. (Schrock, R. R.; Osborn, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 3089).

(26) No efforts were made to determine the stereochemistry of the chiral phosphorus centers in 16b and 16c. Since starting materials 7b and 7c are racemic, we assume the phosphorus in 16b and 16c to be racemic too. For a general discussion of asymmetric pentacovalent phosphorus compounds, see: Hall, C. R.; Inch, T. D. *Phosphorus Sulfur* **1979**, *7*, 171. We thank a referee for bringing this reference to our attention.

(27) *N*-Acetyl-L-1 (L-16a) can be obtained as a solid compound, mp 145 °C, after multistep ion-exchange chromatography: Imai, S.; Seto, H.; Sasaki, T.; Tsuruoka, T.; Ogawa, H.; Satoh, A.; Inouye, S.; Niida, T.; Otake, N. *J. Antibiot.* **1985**, *38*, 687.

(28) Lam, S.; Malikin, G. *J. Chromatogr.* **1986**, *368*, 413.

(29) Hengartner, U.; Valentine, D.; Johnson, K. K.; Larscheid, M. E.; Pigott, F.; Scheidl, F.; Scott, J. W.; Sun, R. C.; Townsend, J. M.; Williams, T. H. *J. Org. Chem.* **1979**, *44*, 3741.

(30) Schoellkopf, U.; Hoppe, I.; Thiele, A. *Liebigs Ann. Chem.* **1985**, 555.

(31) The formation of an analogous byproduct has been observed upon condensation of 2-oxo-4-(4-methoxyphenyl)butanoic acid with methyl carbamate: Melillo, D. G.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5143.

(32) An extreme solvent dependence of enantioselectivity has been observed in hydrogenations conducted with (*S*)-(*R*)-BPPFA-derived catalysts: Hayashi, T.; Mise, T.; Mitachi, S.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1976**, 1133.

(33) For the temperature and pressure dependence of the enantioselectivity, cf.: (a) Ojima, I.; Kogure T.; Yoda, N. *J. Org. Chem.* **1980**, *45*, 4728. (b) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746.

(34) (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567. (b) King, R. B.; Bakos, J.; Hoff, C. D.; Marko, L. *J. Org. Chem.* **1979**, *44*, 1729.

(35) An increase of catalytic activity but not of ee is observed in some cases: (a) Sinou, D.; Kagan, H. B. *J. Organomet. Chem.* **1976**, *114*, 325. (b) Halpern, J. *Phosphorus Sulfur* **1983**, *18*, 307.

(36) Selke, R.; Pracejus, H. *J. Mol. Catal.* **1986**, *37*, 213.

(37) Ogawa, Y.; Tsuruoka, T.; Inouye, S.; Niida, T. *Sci. Rep. Meiji Seika Kaisha* **1973**, *13*, 42.

(38) Similar effects have been observed in the asymmetric hydrogenations of methylsuccinic acid precursors, cf. ref 33a.

(39) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

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lalanine precursors, the free carboxylic acid function seems to be crucial for achieving a high ee and a higher reaction rate is not necessarily related to a higher enantioselectivity.[35a,40]

Summary

Both enantiomers of phosphinothricin (1) have been prepared in 75–80% yield by asymmetric hydrogenation of dehydroamino acid precursors 7 with chiral rhodium(I) catalysts. The enantioselectivity of the reaction is most significantly influenced by the solvent polarity of the reaction medium and the concentration of the substrate. Highest enrichment of L-1 was achieved with the (*R,R*)-NORPHOS catalyst system (90.8% ee), while the (*S,S*)-CHIRAPHOS-derived catalyst afforded D-1 with an ee of 91%.

Experimental Section

General. Melting points are not corrected. Concentrations for specific rotations are g/100 mL. Preparative liquid chromatography (PLC) was performed with Merck Lichrosorb columns (25 × 310 mm). Enantiomeric excess (ee) was determined by analytical high-performance liquid chromatography (HPLC), after derivatization with *o*-phthaldialdehyde and *N*-acetyl-L-cysteine,[28] on a RP 18 column (Hypersil ODS, Shandon).

Ethyl 3-(Ethoxymethylphosphinyl)propionate (5). To a stirred mixture of 216.20 g (2.10 mol) of ethyl methylphosphinate[41] and a few drops of phenolphthalein was added under argon at 40 °C 202.20 g (2.00 mol) of ethyl acrylate. During the addition of ethyl acrylate a 5% solution of sodium ethoxide in ethanol was added to the reaction mixture from a second dropping funnel to ensure that the reaction mixture always remained alkaline. Consumption of sodium ethoxide solution totaled 25 mL. After the addition, the reaction mixture was stirred for 2 h at 65 °C and 24 h at room temperature. Distillation through a 10-cm Vigreux column yielded 338.9 g (81.4%) of 5 as a colorless liquid: bp 97 °C (0.7 Pa); n_D^{30} = 1.4430 [lit.[14] bp 92–93 °C (0.5 Pa); n_D^{20} = 1.4470]; ^{1}H NMR (100 MHz, $CDCl_3$) δ 4.00 (q, 2, *J* = 7.3 Hz, $COOCH_2CH_3$), 3.89 (quintet, 2, *J* = 7.3 Hz, $POCH_2CH_3$), 2.60–2.23 (m, 2, PCH_2CH_2COO), 2.10–1.68 (m, 2, PCH_2CH_2COO), 1.32 (d, 3, *J* = 14.1 Hz, PCH_3), 1.15 (t, 3, *J* = 7.3 Hz, $COOCH_2CH_3$), 1.10 (t, 3, *J* = 7.3 Hz, $POCH_2CH_3$); ^{31}P NMR (121 MHz, DMSO-d_6) δ 52.856.

4-(Hydroxymethylphosphinyl)-2-oxobutanoic Acid (6). To a stirred suspension of 11.50 g (0.50 mol) of sodium in toluene (prepared with a turbo stirrer at 95 °C) was added under argon at 50 °C 25.00 g (0.54 mol) of dry ethanol. After being refluxed for 1 h, the reaction mixture was cooled to −50 °C. To this sodium ethoxide suspension were added a mixture of 80.00 g (0.55 mol) of diethyl oxalate and 104.10 g (0.50 mol) of 5 at such a rate that the reaction temperature remained below −30 °C. After addition was complete (2 h), the reaction mixture was warmed to room temperature and stirred for 18 h. The solution was extracted with water (3 × 250 mL), and the combined water phases were washed with dichloromethane (100 mL) and diethyl ether (100 mL). The organic phases were discarded. The water phase was acidified to pH 4–5 by addition of concentrated HCl, warmed to 70 °C, and saturated with HCl gas. After being stirred at 70 °C for 16 h, the mixture was concentrated in vacuo and the remaining syrup was dissolved in acetone and filtered. The filtrate was concentrated to half of its volume and methyl isobutyl ketone was added to the stirred solution until it became turbid and crystallization was completed by stirring the suspension for 2 days to afford 42.40 g of 6 as a white solid, mp 105 °C [lit.[15] mp 105–107 °C]. From the mother liquors a second crop of 8.00 g, mp 104–106 °C, could be obtained to render a combined yield of 50.4 g (56%): ^{1}H NMR (100 MHz, DMSO-d_6) keto form δ 10.3 (s, br, O*H*), 3.21–2.82 (m, 2, PCH_2CH_2CO), 2.00–1.60 (m, 2, PCH_2CH_2CO), 1.33 (d, 3, *J* = 14.1 Hz, PCH_3); enol form δ 10.3 (s, br, O*H*), 5.52 (dt, 1, *J* = 8, 7.3 Hz, $PCH_2CH{=}C$), 2.54 (dd, 2, *J* = 18.7, 8 Hz, $PCH_2CH{=}$), 1.27 (d, 3, *J* = 14.1 Hz, PCH_3); ^{13}C NMR (90 MHz, DMSO-d_6) keto form δ 195.173, 195.022, 162.587, 162.577, 32.076, 32.063, 24.358, 23.310, 15.624, 15.366; enol form 165.651, 165.620, 144.386, 144.255, 103.508, 103.404, 29.257, 28.252, 15.366, 14.337; ^{31}P NMR (121 MHz, DMSO-d_6) keto form δ 48.082, enol form δ 45.942.

(*Z*)-2-Acetamido-4-(hydroxymethylphosphinyl)but-2-enoic Acid ((*Z*)-7a). A suspension of 18.00 g (0.10 mol) of 6 and 11.80 g (0.20 mol) of acetamide in 50 mL of acetic acid was stirred at room temperature for 4 h. After the addition of 100 mL of dry toluene and 0.5 g (0.003 mol) of *p*-toluenesulfonic acid, the vigorously stirred heterogeneous mixture was heated under argon at reflux for 5 h while the water formed was separated by means of a Dean–Stark trap. To the hot reaction mixture was added acetic acid until it became homogeneous. Upon cooling 13.10 g (59%) of (*Z*)-7a separated as a white solid: mp 186–189 °C; ^{1}H NMR (300 MHz, D_2O) δ 6.84 (dt, 1, *J* = 6.6, 8.1 Hz, $PCH_2CH{=}C$), 2.85 (dd, *J* = 18.9, 8.1 Hz, $PCH_2CH{=}$), 2.15 (s, 3, $NHCOCH_3$), 1.52 (d, 3, *J* = 14.1 Hz, PCH_3); ^{13}C NMR (75 MHz, D_2O) δ 176.478, 176.458, 169.148, 169.110, 133.691, 133.584, 131.690, 131,525, 34.142, 32.992, 24.386, 17.274, 16.027; ^{31}P NMR (121 MHz, D_2O) δ 50.188. Anal. Calcd for $C_7H_{12}NO_5P$: C, 38.02; H, 5.47; N, 6.33; P, 14.01. Found: C, 38.4; H, 5.5; N, 6.2; P, 13.9.

In runs where water was not separated efficiently (low temperature, incomplete reflux) reasonable amounts of byproduct 17 could be isolated by taking up the mother liquor in isobutyl alcohol from which 17 separated as a white solid: mp 188–190 °C; ^{1}H NMR (100 MHz, DMSO-d_6) δ 8.27 (s, 2, $NHCOCH_3$), 2.54–2.20 (m, 2, $PCH_2CH_2C(NHCOCH_3)_2$), 1.84 (s, 6, $NHCOCH_3$), 1.58–1.20 (m, 2, $PCH_2CH_2C(NHCOCH_3)_2$), 1.25 (d, 3, *J* = 14.1 Hz, PCH_3); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.520, 168.178, 68.953, 68.711, 26.933, 25.750, 24.577, 22.541, 15.532, 14.285; ^{31}P NMR (121 MHz, DMSO-d_6) δ 46.503. Anal. Calcd for $C_9H_{17}N_2O_2P$: C, 38.57; H, 6.12; N, 10.00. Found: C, 38.5; H, 6.0; N, 10.0.

Methyl (*Z*)-2-Acetamido-4-(methoxymethylphosphinyl)-but-2-enoate ((*Z*)-7b). A suspension of 4.90 g (0.022 mol) of (*Z*)-7a in a mixture of 25 mL of acetic acid and 50 mL of 1,1,1-trimethoxyethane was heated at reflux for 5 min. The resulting clear solution was concentrated in vacuo (0.1 Pa, temperature < 75 °C) to yield (*Z*)-7b as a viscous colorless oil (5.50 g, 100%), which was used for hydrogenation without further purification. An analytical sample was prepared by Kugelrohr distillation: bp 212–215 °C (0.1 Pa); ^{1}H NMR (100 MHz, $CDCl_3$) δ 8.40 (s, br, 1, N*H*), 6.44 (q, 1, *J* = 8 Hz, $PCH_2CH{=}$), 3.79 (s, 3, $COOCH_3$), 3.74 (d, 3, *J* = 10.5 Hz, $POCH_3$), 2.77 (dd, 2, *J* = 18, 8 Hz, $PCH_2CH{=}$), 2.13 (s, 3, $NHCOCH_3$), 1.53 (d, 3, *J* = 14.1 Hz, PCH_3); ^{13}C NMR (75 MHz, D_2O) δ 176.542, 168.070, 168.031, 132.117, 132.035, 132.012, 131.963, 55.809, 54.883, 54.792, 31.988, 30.821, 24.424, 15.106, 13.857; ^{31}P NMR (121 MHz, D_2O) δ 59.318. Anal. Calcd for $C_9H_{16}NO_5P$: C, 43.37; H, 6.47; N, 5.62; P, 12.43. Found: C, 43.0; H, 6.5; N, 5.6; P, 11.8.

Heating a sample of crude (*Z*)-7b to 100 °C for 3 h produced an 88:12 mixture of (*Z*)-7b and (*E*)-7b. (*E*)-7b: ^{1}H NMR (100 MHz, $CDCl_3$) δ 8.04 (s, br, 1, N*H*), 6.80 (q, 1, *J* = 8 Hz, $PCH_2CH{=}$), 3.83 (s, 3, $COOCH_3$), 3.71 (d, 3, *J* = 10.5 Hz, $POCH_3$), 3.20 (dd, 2, *J* = 18, 8 Hz, $PCH_2CH{=}$), 2.08 (s, 3, $NHCOCH_3$), 1.50 (d, 3, *J* = 14.1 Hz, PCH_3). In DMSO-d_6 the resonances of the olefinic protons ($PCH_2CH{=}$) in the ^{1}H NMR spectrum (100 MHz) appear in an inverse order: (*Z*)-7b δ 6.22 (q, 1, *J* = 8 Hz); (*E*)-7b δ 5.76 (q, 1, *J* = 8 Hz).

4-(Ethoxycarbonyl)-5-[(ethoxymethylphosphinyl)-methyl]-2-oxazolin (9). A solution of 13.37 g (0.089 mol) of 2-(ethoxymethylphosphinyl)acetaldehyde (8)[18] in 30 mL of dry ethanol was added under nitrogen to a solution of 9.76 g (0.086 mol) of ethyl isocyanoacetate and 0.5 g (0.010 mol) of sodium cyanide in 100 mL of dry ethanol at a rate such that the reaction temperature remained below 25 °C. The solution was stirred for 90 h at room temperature. The solvent was distilled off in vacuo and the residue taken up in CCl_4 and filtered over a short path of silica gel. Evaporation of the filtrate afforded 18.15 g (79.5%) of 9 as a yellow oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 6.87 (s, br, 1, O*H*C=N), 5.30–4.65 (m, 1, $PCH_2CHOCHN{=}$), 4.50 (m, 1, $CHOCHNCH_2COOCH_2CH_3$), 4.16 (q, 2, *J* = 7 Hz, $COOCH_2CH_3$), 4.00 (quintet, 2, *J* = 7 Hz, $POCH_2CH_3$), 2.45–1.85 (m, 2, PCH_2CH),

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PGR2026-00026
PETITIONER EX1032

1.48 (d, 3, J = 14.1 Hz, PCH_3), 1.29 (t, 3, J = 7 Hz, $COOCH_2CH_3$), 1.25 (t, 3, J = 7 Hz, $POCH_2CH_3$). Anal. Calcd for $C_{10}H_{18}NO_5P$: C, 45.63; H, 6.89; N, 5.32. Found: C, 45.6; H, 7.0; N, 5.3.

Ethyl (*Z*)-2-Formamido-4-(ethoxymethylphosphinyl)-but-2-enoate ((*Z*)-7c). A solution of 4.83 g (0.018 mol) of **9** in 10 mL of THF was added under argon at −70 °C to a suspension of 2.26 g (0.020 mol) of potassium *tert*-butoxide. After being stirred for 30 min, the reaction mixture was warmed to room temperature. The solvent was evaporated and the residue dissolved in 20 mL of water containing 1.25 g (0.020 mol) of acetic acid. The mixture was stirred for 30 min and then extracted with CH_2Cl_2 (4 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and filtered over a short path of silica gel. Evaporation of the filtrate afforded a brown oil, which was purified by PLC (CH_2Cl_2/CH_3OH/EtOAc 6:1:1) to yield 3.20 g (66%) of (*Z*)-**7c** as a pale yellow oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.83 (s, br, 1, NHCHO), 8.20 (s, 1, NHCHO), 6.55 (q, 1, J = 8 Hz, PCH_2CH=), 4.22 (q, 2, J = 7 Hz, $COOCH_2CH_3$), 4.05 (quintet, 2, J = 7 Hz, $POCH_2CH_3$), 2.78 (dd, 2, J = 18, 8 Hz, PCH_2CH=), 1.53 (d, 3, J = 14.1 Hz, PCH_3), 1.36 (t, 3, J = 7 Hz, $COOCH_2CH_3$), 1.34 (t, s, J = 7 Hz, $POCH_2CH_3$); ^{13}C NMR (25 MHz, $CDCl_3$) δ 163.368, 163.256, 159.697, 129.378, 128.888, 124.804, 124.456, 61.646, 61.068, 60.804, 32.703, 29.201, 16.648, 16.413, 16.062, 14.106, 12.302. Anal. Calcd for $C_{10}H_{18}NO_5P$: C, 45.63; H, 6.89; N, 5.32; P, 11.77. Found: C, 45.3; H, 7.1; N, 5.3; P, 11.4.

(Norbornadiene)[(*R*)-(+)-1,2-bis(diphenylphosphino)-propane]rhodium Tetrafluoroborate (15). Silver tetrafluoroborate (77.87 mg, 0.4 mmol) and 92.20 mg (0.2 mmol) of chloro–norbornadiene–rhodium dimer (**14**) were dissolved under argon in 10 mL of degassed acetone. After stirring for 2 h at room temperature, the precipitated AgCl was filtered off and washed with 4 mL of acetone. To the orange filtrate was added under argon 166.7 mg (0.4 mmol) of (*R*)-(+)-1,2-bis(diphenylphosphino)propane (**11**). The mixture was stirred for 30 min at room temperature, concentrated to half of its volume, and treated with 15 mL of ether whereupon 270.5 mg (97.4%) of **15** precipitated as an orange solid. This product was used for hydrogenations without further purification: ^{1}H NMR (80 MHz, DMSO-d_6) δ 4.11 (s, 2), 3.93 (s, 1) [lit.[25] δ 4.02 (s, 2), 3.96 (s, 1)].

General Procedure for Asymmetric Hydrogenations. Hydrogenations were carried out in a glass autoclave with 0.125–0.25 M solutions of the substrates at ambient temperature or 50 °C and an initial hydrogen pressure of 0.25–0.30 MPa. Concentrations of the substrate solutions were chosen so that the reaction mixture remained homogeneous during the entire hydrogenation. The substrate/catalyst ratio was 300:1 or as specified in Table I. In most cases hydrogenations were complete after 45 min as indicated by the hydrogen uptake, but the reaction vessel was kept pressurized for 22 h to establish identical conditions for every run. Turnovers of individual runs can be easily estimated from the ^{1}H NMR spectra of the reaction mixtures. Catalysts were removed from the reaction mixtures by stirring in the presence of an ion exchange resin (H^+ form). Before every experiment the glass surface on the reaction vessel was rinsed with a 2.5% solution of HF in THF to avoid any contamination with catalysts from foregoing experiments. The following procedures are representative.

L-2-Acetamido-4-(hydroxymethylphosphinyl)butanoic Acid (L-16a). A catalyst solution prepared by stirring under argon a mixture of 7.9 mg (0.017 mmol) of chloro–norbornadiene–rhodium dimer (**14**) and 15.3 mg (0.037 mmol) of (*R*)-(+)-1,2-bis(diphenylphosphino)propane (**11**) in 5 mL of methanol at room temperature for 15 min was added under argon to a solution of 2.21 g (10 mmol) of (*Z*)-**7a** in 65 mL of methanol. The reaction vessel was evacuated and flushed with argon. This measure was repeated twice; then the autoclave was evacuated and pressurized with H_2 (0.30 MPa). After 22 h the H_2 pressure was released, and the reaction mixture was treated with 300 mg of ion exchange resin (H^+ form) and stirred for 3 h. After filtering off the ion exchange resin, the filtrate was concentrated in vacuo to yield 2.20 g (98.7%) of L-**16a** as a colorless, glasslike substance: $[\alpha]_D^{22}$ = +5.74° (c = 1.00, H_2O) [lit.[27] $[\alpha]_D^{25}$ = +8.5° (c = 1.00, H_2O) for optically pure material]; ^{1}H NMR (100 MHz, D_2O) δ 4.43 (m, 1, CHNHCOCH$_3$), 2.36–1.64 (m, 4, $PCH_2CH_2CHCOOH$), 2.04 (s, 3, NHCOCH$_3$), 1.52 (d, 3, J = 14.1 Hz, PCH_3); ^{13}C NMR (75 MHz, D_2O) δ 177.104, 176.732, 55.683, 55.542, 29.053, 27.820, 26.125, 26.100, 24.378, 16.823, 15.605; ^{31}P NMR (121 MHz, D_2O) δ 55.925. Anal. Calcd for $C_7H_{14}NO_5P$: C, 37.67; H, 6.32; N, 6.28; P, 13.88. Found: C, 37.8; H, 6.5; N, 6.1; P, 13.6.

Methyl L-2-Acetamido-4-(methoxymethylphosphinyl)butanoate (L-16b). (*Z*)-**7b** (3.89 g, 15.6 mmol) furnished after hydrogenation with a (*R*,*R*)-NORPHOS-derived catalyst 3.90 g (99.5%) of L-**16b** as a colorless, viscous oil: ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.10 (br, 1, NHCOCH$_3$), 4.62 (m, 1 CHNHCOCH$_3$), 3.76 (s, 3, $COOCH_3$), 3.70 (d, 3, J = 11 Hz, $POCH_3$), 2.28–1.60 (m, 4, PCH_2CH_2CHCOO), 2.04 (s, 3, NHCOCH$_3$), 1.48 (d, 3, J = 14.1 Hz, PCH_3); ^{13}C NMR (75 MHz, D_2O) δ 176.775, 175.800, 55.766, 55.656, 55.435, 54.498, 54.413, 27.300, 26.055, 25.925, 25.866, 24.419, 14.577, 13.361; ^{31}P NMR (121 MHz, D_2O) δ 64.322, 64.287;

According to the ^{1}H NMR spectrum, this product contained 0.5 mol of H_2O, which could not be removed even after extended drying (14 days) over P_2O_5. Anal. Calcd for $C_9H_{18}NO_5P$·0.5H_2O: C, 41.54; H, 7.36; N, 5.38; P, 11.90. Found: C, 41.2; H, 7.0; N, 5.3; P, 12.3.

Ethyl L-2-Formamido-4-(ethoxymethylphosphinyl)butanoate (L-16c). (*Z*)-**7c** (2.10 g, 8 mmol) afforded after hydrogenation with a (*S*,*S*)-DIOP-derived catalyst and filtration over silica gel 1.80 g (84.9%) of L-**16c** as a brownish oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 8.20 (s, 1, NHCHO), 7.57 (d, br, 1, NHCHO), 4.66 (m, 1, CH(NHCHO)COO), 4.16 (q, 2, J = 7 Hz, $COOCH_2CH_3$), 4.00 (quintet, 2, J = 7 Hz, $POCH_2CH_3$), 2.50–1.60 (m, 4, PCH_2CH_2CH), 1.45 (d, 3, J = 14.1 Hz, PCH_3), 1.28 (t, 3, J = 7 Hz, $COOCH_2CH_3$), 1.24 (t, 3, J = 7 Hz, $POCH_2CH_3$).

L-Phosphinothricin Hydrochloride (L-1a). L-**16b** (2.67 g, 10.6 mmol) was dissolved in 100 mL of 6 N HCl and boiled at reflux for 15 h. Norite (0.3 g) was added, and the refluxing was continued for 30 min. The reaction mixture was filtered and the filtrate concentrated in vacuo to yield 2.30 g (99.5%) of crude L-**1a** as a white solid: mp 189–190 °C; $[\alpha]_D^{19}$ = +18.53° (c = 1.4, 1 N HCl); ee 84.4% (Table I, entry 18).

Recrystallization of 1.70 g of crude material from ethanol/H_2O afforded 1.30 g (76.5%) of pure L-**1a**: mp 194–196 °C; $[\alpha]_D^{22}$ = +21.4° (c = 2.02, 1 N HCl); ee 89.2%; ^{1}H NMR (100 MHz, D_2O) δ 4.13 (t 1, J = 5.5 Hz, $CH(NH_2)COOH$), 2.43–1.68 (m, 4, PCH_2CH_2CH), 1.47 (d, 3, J = 14.1 Hz, PCH_3); ^{13}C NMR (75 MHz, D_2O) δ 173.674, 55.701, 55.479, 28.579, 27.269, 25.460, 25.430, 16.980, 15.756; ^{31}P NMR (121 MHz, D_2O) δ 54.070. Anal. Calcd for $C_5H_{13}ClNO_4P$: C, 27.60; H, 6.02; N, 6.44; P, 14.24. Found: C, 27.6; H, 6.0; N, 6.4; P, 14.3.

L-Phosphinothricin (L-1). L-**1a** (0.50 g, 2.3 mmol) was dissolved in boiling ethanol containing a few drops of water. After the clear solution was cooled to 35 °C, 0.50 g (8.6 mmol) of propene oxide was added, whereupon the solution became turbid. Crystallization was completed by standing overnight to yield 0.40 g (96%) of L-**1**: mp 206–210 °C; $[\alpha]_D^{23}$ = +14.9° (c = 1.00, H_2O) [lit.[37] mp 214 °C; $[\alpha]_D^{23}$ = +17° (c = 1.00, H_2O) for optically pure material]; ee 90.4%; ^{1}H NMR (100 MHz, D_2O) δ 3.97 (t, 1, J = 5.5 Hz, $CH(NH_2)COOH$), 2.35–1.50 (m, 4, PCH_2CH_2), 1.37 (d, 3, J = 14.1 Hz, PCH_3). Anal. Calcd for $C_5H_{12}NO_4P$: C, 33.15; H, 6.68; N, 7.73. Found: C, 33.1; H, 6.8; N, 7.7.

D-2-Acetamido-4-(hydroxymethylphosphinyl)butanoic Acid (D-16a). Following the procedure for the synthesis of L-**16a**, 2.21 g (10 mmol) of (*Z*)-**7a** furnished after hydrogenation with a (*S*,*S*)-CHIRAPHOS-derived catalyst 2.23 g (100%) of D-**16a** as a colorless, glasslike substance: $[\alpha]_D^{22}$ = −3.66° (c = 1.01, H_2O); ^{1}H NMR (100 MHz, D_2O) δ 4.43 (m, 1, CHNHCOCH$_3$), 2.37–1.65 (m, 4, $PCH_2CH_2CHCOOH$), 2.07 (s, 3, NHCOCH$_3$), 1.50 (d, 3, J = 14.1 Hz, PCH_3).

D-Phosphinothricin Hydrochloride (D-1a). D-**16a** (2.23 g, 10 mmol) was dissolved in 100 mL of 6 N HCl and boiled at reflux for 15 h. Norite (0.3 g) was added and the refluxing continued for 60 min. The reaction mixture was filtered and the filtrate concentrated in vacuo to yield 2.13 g (99.3%) of crude D-**1a** as a white solid: mp 190–192 °C; $[\alpha]_D^{19}$ = −20.00° (c = 1.41, 1 N HCl); ee 91% (Table I, entry 19); ^{1}H NMR (100 MHz, D_2O) δ 4.18 (t, 1, J = 5.5 Hz, $CH(NH_2)COOH$), 2.44–1.72 (m, 4, PCH_2CH_2CH), 1.53 (d, 3, J = 14.1 Hz, PCH_3).

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PGR2026-00026
PETITIONER EX1032

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Analogues of the Cyclic Hydroxamic Acid 2,4-Dihydroxy-7-methoxy-2*H*-1,4-benzoxazin-3-one: Decomposition to Benzoxazolinones and Reaction with β-Mercaptoethanol

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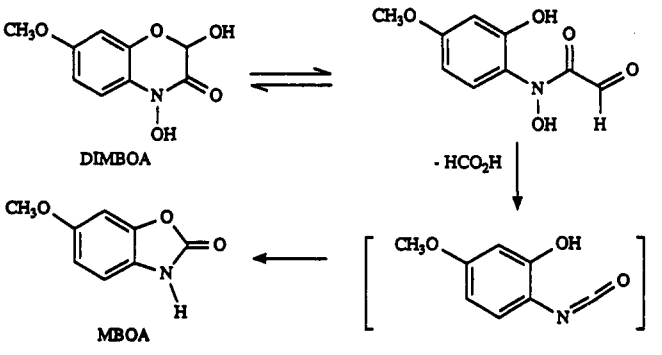
Analogues of the aglucones of naturally occurring cyclic hydroxamic acids (2,4-dihydroxy-1,4-benzoxazin-3-ones) from Gramineae (Poaceae) have been synthesized by the reductive cyclization of the ring-substituted methyl α-(*o*-nitrophenoxy)-α-methoxyacetates, followed by demethylation of the C-2 methoxy group with BBr_3 or BCl_3 to reveal the 2-hydroxy group. A structure–activity series was produced by varying the substituent at C-7 on the aromatic ring [R = MeO (1), *t*-Bu (6), Me (7), H (8), Cl (9), F (10), CO_2Me (11a)]. The pK_a values for the hydroxamic acid and the phenol moieties were determined for each member of the C-7 series. They correlated well with σ in a linear free energy relationship (LFER) yielding values of $\rho = 0.71$ (with σ_p) for pK_{a1} (the hydroxamic acid) and $\rho = 1.6$ (with σ_m) for pK_{a2} (the phenol). A LFER also existed between the rate constants for the unimolecular decomposition of these hydroxamic acids to benzoxazolinones and σ^+ ($\rho = -1.1$). The rates of hydroxamic acid reduction to lactams by β-mercaptoethanol were also investigated. It was found that only compounds with electron-rich aromatic rings and specifically an oxa functionality para to the hydroxamic acid nitrogen atom (compounds 1 and 3–5) had measurable rates of reduction. ^1H NMR spectra recorded during this reaction in D_2O buffers (pD 9), however, showed that compounds 1, 2, 6–9 (the only ones investigated) formed a hemithioacetal at C-2 even though only 1 has a measurable rate of reduction by the same thiol. The remarkable rate enhancement provided by an oxa functionality suggests that reduction occurs by direct attack of thiolate on the hydroxamic nitrogen of a resonance-stabilized ion pair.

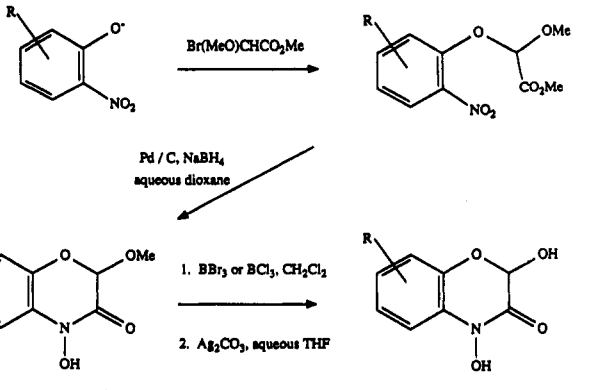
Over 400 species of insects are now known to be resistant to insecticides.[1,2] Because of the problems of resistance and environmental contamination, most researchers in the area of crop protection agree on the urgency of developing new pest management strategies that reduce our dependence on pesticides. One such important area of research is the development of plant varieties resistant to pest attack.[2,3] A plant may be resistant to attack for a number of reasons, including morphological characteristics such as shape, toughness of tissues, presence of trichomes (leaf hairs), or silica.[4] Much recent research[5-13] demonstrates that the presence of secondary chemicals has an important role in protecting the plant against pest attack.

Cyclic hydroxamic acids with the 1,4-benzoxazin-3-one skeleton are secondary metabolites found in several grasses (Gramineae) of which maize (corn), wheat, and rye are important crop plants. These hydroxamic acids exhibit a wide variety of biological activities and have recently been reviewed.[14] The most abundant hydroxamic acid in maize is 2,4-dihydroxy-7-methoxy-1,4-benzoxazin-3-one, DIMBOA.[15] The presence of this allelochemical in plant tissues has been correlated with resistance toward herbivory by the European corn borer (*Ostrinia nubilalis*, Lepidoptera: Pyralidae).[16-22] Our laboratories have investigated the toxicity and toxicokinetics of hydroxamic acids in corn borer larvae[23,24] and an endoparasitoid[25] of the larvae. In parallel with this work the chemistry of DIMBOA itself has also been investigated, including its reaction with thiols[26] and with amines[27] and its decomposition–rearrangement to MBOA in organic and aqueous solvents[28] (Scheme I). We report here the synthesis of

Scheme I



Scheme II



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