Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# A Novel Asymmetric Synthesis of S-(+)-2-Amino-4-Phosphonobutanoic Acid

Xian-Yun Jiao [a], Wan-Yi Chen [a] & Bing-Fang Hu [a]
[a] Institute of Applied Chemistry. Beijing Agricultural University, Beijing, 100094, People's Republic of China
Published online: 23 Sep 2006.

To cite this article: Xian-Yun Jiao, Wan-Yi Chen & Bing-Fang Hu (1992) A Novel Asymmetric Synthesis of S-(+)-2-Amino-4-Phosphonobutanoic Acid, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:8, 1179-1186, DOI: 10.1080/00397919208021103

To link to this article: http://dx.doi.org/10.1080/00397919208021103

SYNTHETIC COMMUNICATIONS, 22(8), 1179-1186 (1992)

# A NOVEL ASYMMETRIC SYNTHESIS OF S-(+)-2-AMINO-4-PHOSPHONOBUTANOIC ACID

Xian-Yun Jiao Wan-Yi Chen Bing-Fang Hu*
Institute of Applied Chemistry. Beijing Agricultural University, Beijing 100094, People's Republic of China



**ABSTRACT:A novel asymmetric synthetic route to S(+)-2-amino-4-phosphonobutanoic acid through the cyclic condensation of ethyl-4-diethoxyphosphonyl-2-oxo-butanoate with L-erythro-(+)-1,2-diphenyl-2-hydroxyethylamine, followed by reduction and hydrolysis is described.**

Phosphorus analogues of glutamic acid are interesting as biologically active substances and S(+)-2-amino-4-phosphonobutanoic acid has been reported competing with glutamate for receptors in nerve cells and to have antiviral activity.[1] Recently, its asymmetric synthesis has been achieved by the Michael addition of a chiral glycine Schiff's base to a vinyl phosphonate. but the optical purity of the product is only moderate (ee 50%).[2] U.

* To whom correspondence should be addressed.

Scholkopf succeeded in the asymmetric synthesis of R(-)-2-amino-4-phorphonobutanoic acid by the hydrolysis of the alkylated bislactim ether of an diketopiperazine with a high degree of asymmetric induction up to ee > 95% [3]. It has been mentioned by J.P. Vigneron [4, 5] regarding the formation of 3-substituted-5, 6-diphenyl-5, 6-dihydro-2H-1, 4-oxazin-2-one, as a condensation product of an α-ketoesters with erythro-1, 2-diphenyl-2-hydroxyethylamine, which in turn, upon catalytic hydrogenation, gave a quantitative yield of 3, 5, 6-triphenyl-2, 3, 5, 6-tetrahydro-4H-1, 4-oxazin-2-one in a unique form. Accordingly, the hydrogenation is apparently totally stereospecific. Based upon this finding, they successfully achieved the addition of erythro-(+)-1, 2-diphenyl-2-hydroxyethylamine to dimethyl acetylenedicarboxylate, when the product, a substituted-5, 6-dihydro-2H-1, 4-oxazin-2-one, was hydrogenated catalytically, a nearly quantitative yield of S(+)-methyl aspartate was obtained with at least 98% enantiomeric purity.

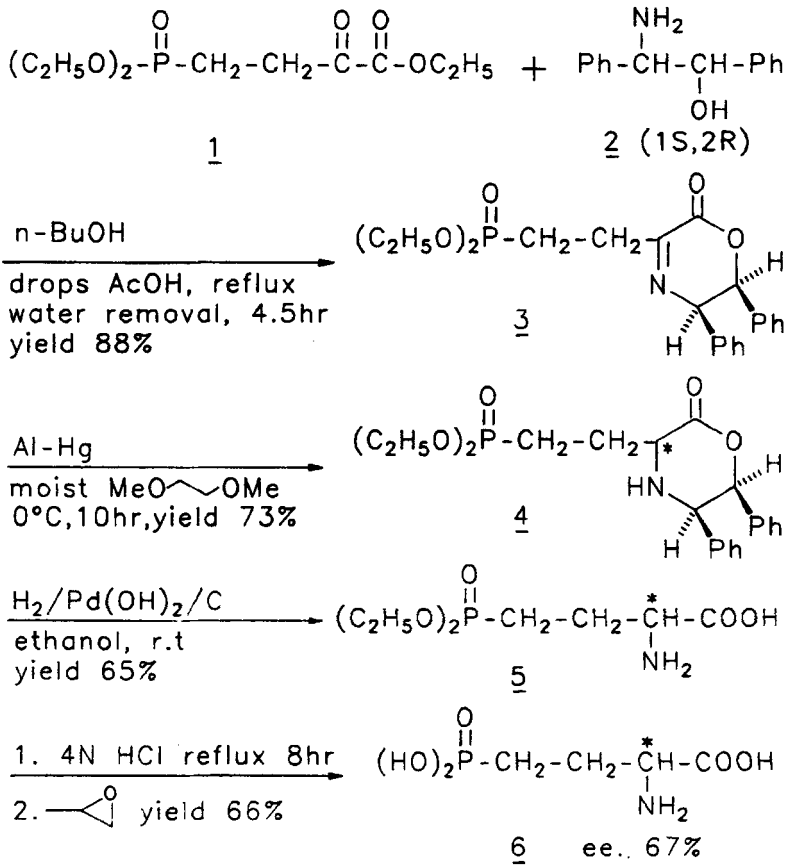
Encouraged and intrigued by these findings, we sought to develope a new route for the asymmetric synthesis of S(+)-2-amino-4-phosphonobutanoic acid, using L-erythro-(1S, 2R)-1, 2-diphenyl-2-hydroxyethylamine as chiral source in the condensation with ethyl-4-(diethoxyphosphonyl)-2-oxo-butanoate. Taking advantages of the fact that the optically active erythro-1, 2-diphenyl-2-hydroxyethylamine is derived from inexpensive benzoin and resolved on large scale by L-(+)-glutamic acid [6], and the various α-ketoesters can be successfully purchased through a facile and general route from acetoacetic ester [7], the whole process, therefore, would be resonably expected to be useful as an asymmetric synthetic

method for various α-aminoacids of either antipode. The synthetic pathway is depicted in following scheme.

The cyclization step 1, consisting of formation of Schiff's base and acid catalyzed transesterification, can only be successfully performed in a protic solvent, viz, n-butanol which permits satisfactory azeotropic removal of



SCHEME



water at a higher reaction temperature. The value of $^{2}J$ ($H_1$, $H_2$) in the compound (2) is 8.5Hz, while the value of $^{2}J$ ($H_5$, $H_6$) in the compound (3) is 2.2 Hz, which accords with Karplus-formula[8] for a structure of cyclic vicinal syn hydrogen. The value of $\nu_{C=N}$ in the compound (3) is 1647cm$^{-1}$. The Al-Hg reduction step 2 is critical to the asymmetric reduction. According to E. J. Corey[9], the Al-Hg is prepared by treating the clean aluminium foil in 2% $HgCl_2$ strictly for 10 sec. The 2 min submersion as described in lit[ 10] results in agglomeration of the aluminium amalgam particles which in turn results an inactive reagent. The imino linkage is saturated by Al-Hg reduction. The $\nu_{N-H}$ in the compound (4) is formed, the $\nu_{C=N}$ in the compound (3) is disappeared. Hydrogenation catalysed by such as Raney Ni, Pt or Pd/C is much more effective than Al-Hg, but the reduction of imino linkage always suffered from the simultaneous destruction of the oxazine ring which functions the chiral induction. Consequently, the racemic product is formed.

## EXPERIMENTAL

The values of specific rotation were measured on a polartronic D Schmidt+Haensch polarimeter. Melting points were determined on a Yanoco apparatus. $^{1}H$ NMR data were recorded with a JEOL FX-90Q or Varian XL-400, Using TMS as an internal standard, $^{31}P$ NMR data were recorded using 85% $H_3PO_4$ as external standard. Mass spectra were taken on a FINNIGAN MAT 4510 mass spectrometer. IR Spectra were recorded on a FT-Nicolet-5DX spectrophotometer.

(5R, 6S)-3-[2'-(Diethoxyphosphonyl)-ethyl]-5, 6-diphenyl-5, 6-dihydro-2H-1, 4-oxazin-2-one. (3)

L-erythro-(+)-1, 2-diphenyl-2-hydroxyethylamine, m. p. 148℃, $[\alpha]_D^{20}$=6.5° (c, 0.615, ethanol) [lit (4) m. p. 148℃, $[\alpha]_D^{20}$=-6.8° (c, 0.6 ethanol)] (1.6g, 7.5 mmol) is dissolved in dry n-butanol (45ml), glacial acetic acid (0.45ml) is added to maintain it at pH5, Ethyl-4-diethoxyphosphonyl-2-oxo-butanoate [colorless liquid $n_D^{20}$=1.4441, MS, $M^+$, m/z 267 lit (7)] (2g, 7.50 mmol) is added dropwise. The reaction mixture is refluxed for 40 minutes and then the condensed azeotropic mixture is slowly removed (about 10mL). After further 2hr reflux and the azeotropic mixture is slowly removed, the n-butanol is removed under reduced pressure, toluene (30ml) is added. After 1hr reflux and removal of azeotropic mixture, the residue is finally obtained under reduced pressure. The product, a reddish brown oily liquid, is chromatographed on alumina (150g, 45cm×2.5cm, 200-300 mesh) and is eluted with a mixture of $CH_2Cl_2$, cyclohexane, isopropanol (in ratio 1.8:1.2:0.3), yield, 2.7g, (88%), $n_D^{20}$=1.536, $[\alpha]_D^{20}$=+5.71° (c, 0.70, $CHCl_3$), IR, 3350, 3033, 2935, 1729, 1647, 1450, 1393, 1145, 1032, 988, 753, 695; $^1$H NMR, $\delta_H$, 1.31 (6H, t, $CH_3$), 1.40-2.40 (4H, m, $CH_2$), 3.98-4.33 (5H, m, $CH_2$, CH-N), 4.88 (1H, d, $J_{H-C-C-H}$ 2.2Hz, CH-O), 7.20-7.96 (10H, m, $C_6H_5$); $\delta_P$, 30.8; MS, $M^+$, m/z 414, m/z 182 basic peak; Using D-erythro-(-)-1.2-diphenyl-2-hydroxyethylamine, (5S, 6R)-3-[2'-(diethoxy-phosphonyl)-ethyl]-5, 6-diphenyl-5, 6-dihydro-2H-1, 4-oxazin-2-one is prepared likewisely. Yield 83.3% $n_D^{20}$=1.5360, $[\alpha]_D^{21}$=-5.79° (c, 0.69, $CHCl_3$).

(3S, 5R, 6S)-3-[2'-(Diethoxyphosphonyl)-ethyl]-5, 6-diphenyl-2, 3, 5, 6-tetrahydro-4H-1, 4-oxazin-2-one. (4)

To a solution of freshly distilled dimethoxyethane (30mL) containing distilled water (4.2mL) and compound (3) (0.77g).

Al-Hg (0.3g) is added and at 0℃ stirred for 10hr. Filter and the aluminium foil is washed with dimethoxyethane (2×15mL). The combined washing and filtrate is evaporated under redueed pressure. The liquid obtained (0.88g) is chromatographed on alumina column (45cm×2.5cm, 150g, 200-300 mesh) and is eluted with a mixture of $CH_2Cl_2$, cyclohexane (1:1). This affords a semi-solid (0.55g), yield 78.3%. $[\alpha]_D^{20}$=-5.57° (c, 0.71, $CHCl_3$); IR, 3320, 3068, 2984, 1729, 1672, 1602, 1491, 1450, 1393, 1229, 1155, 1032, 704; $^1H$ NMR δ ppm 1.35 (6H, t, $CH_3$), 1.44-2.07 (4H, m, Ax-Bx, $CH_2$), 3.6-3.9 (1H, m, CH), 4.01-4.38 (5H, m, $2CH_2$-O, CH-N), 4.95 (1H, d, $J_{H-C-C-H}$, 2.5Hz, CH-O) 5.45 (1H, b, NH), 7.20-8.90 (10H, m, $C_6H_5$); δ p, 30.83; MS, $M^+$, m/z 417, main, 253 basic peak, 91. The (3R, 5S, 6R)-3-[2'-(diethoxyphosphonyl)-ethyl]-5,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one is prepared with same procedure. $[\alpha]_D^{20}$=+5.57° (c, 0.71. $CHCl_3$).

S(+)-2-Amino-4-diethoxyphosphenobutanoic acid. (5)

Compound (4) (2.2g, 5.3mmol) in absolute ethanol (45mL) containing 10% $Pd(OH)_2/C$ (3.5 g) is hydrogenated under atmospheric pressure. After 14 mmol of $H_2$ is absorbed, the reaction mixture is filtered and the catalyst is washed by boiling in ethanol for 5 min (2×20mL), The filtrate, combined with washings, is concentrated. The viscous product is then chromatographed on silicagel (45cm×2.5cm, 200-300 mesh) and is eluted with ethyl acetate and finally with ethanol. After removal of solvent under reduced pressure, a colorless viscous liquid is obtained, 0.77g. yield 85%, $[\alpha]_D^{20}$=+8.6° (0.93g, $CHCl_3$); IR, 3400-3100, 2994, 2810, 1715, 1450, 1390, 1225, 1025, 984, 695; δ p, 30.99.

S(+)-2-Amino-4-phosphonobutanoic acid. (8)

When the product, compound (5), (0.39) is refluxed in 4N HCl (10mL) for 8hr, then evaporated to dryness, the residue obtained is dissolved in absolute ethanol (40mL) and is agitated with propyloxide (5mL). After filtration, final product (8), (0.15g) is obtained, yield 88%, m.p. 230-240℃ (dec), $[\alpha]_D^{20}$=+19.5° (c, 0.44, aqueous 8NHCl), ee, 87%. $^1$H NMR, $\delta_H$, 1.10-2.10 (4H, m, $CH_2$), 3.6-3.8 (1H, m, CH), ($D_2O$). According to lit (3) for R-(-)-2-amino-4-phosphonobutanoic acid, m.p. 215-218 ℃ (dec), $[\alpha]_D^{20}$=-26.9°, $^1$H NMR, $\delta_H$ 1.25-2.24 (4H, m, $CH_2CH_2$-P) $D_2O$, 3.86 ($J_{A-X}$=8Hz, $J_{B-X}$=8Hz, 1H).

## REFERENCE


1. Koerner, J.F. and Cotman, C.W., Brain Research, 1981, 214, 192,
2. Minowa, N.; Hirayama, M. and Fukatsu, S., Tetrahedron Lett., 1984, 25, 1147-1150.
3. Schollkopf, U.; Busse, U.; Lonsky, R. and Hinrichs, R., Liebigs Ann. Chem., 1986, 2150-2163.
4. Vigneron, J.P.; Kagan, H. and Horeau, A., Tetrahedron Lett. 1968, 5681.
5. Vigneron, J.P.; Kagan, H.; B. and Horeau, A., Bull. Soc. Chim. Fr., 1972, 3836.
6. Weijlard, P.K.; Swaneey, E.F.; Robinson, C.A. and Tishler, M., J. Am. Chem. Soc., 1951, 73, 1216.
7. Si, Zong-Xing; Jiao, Xian-Yun; Hu, Bing-Fang; Synthesis, 1990, 509-510.
8. M. Karplus, J.Am. Chem. Soc. 1963, 85, 2870. C. Benezra, ibid, 1973, 95, 6890.
9. Corey, E.J.; McCaully, R.J. and Sachdev, H.S., J.Am. Chem. Soc. 1970 92, 2476-2488.

**10. Vogel's Textbook of Practical Organic Chemistry, 1978, 4th Edn, 281. Langman Group Ltd.**

(Accepted in The Netherlands 22 November, 1991)