

## A VERSATILE ASYMMETRIC SYNTHESIS OF $\alpha$ -AMINO $\alpha$ -ALKYL-PHOSPHONIC ACIDS OF HIGH ENANTIOMERIC PURITY

Stephen Hanessian \* and Youssef L. Bennani  
 Department of Chemistry, Université de Montréal  
 C.P. 6128, Succ. A, Montréal, QC, CANADA, H3C 3J7

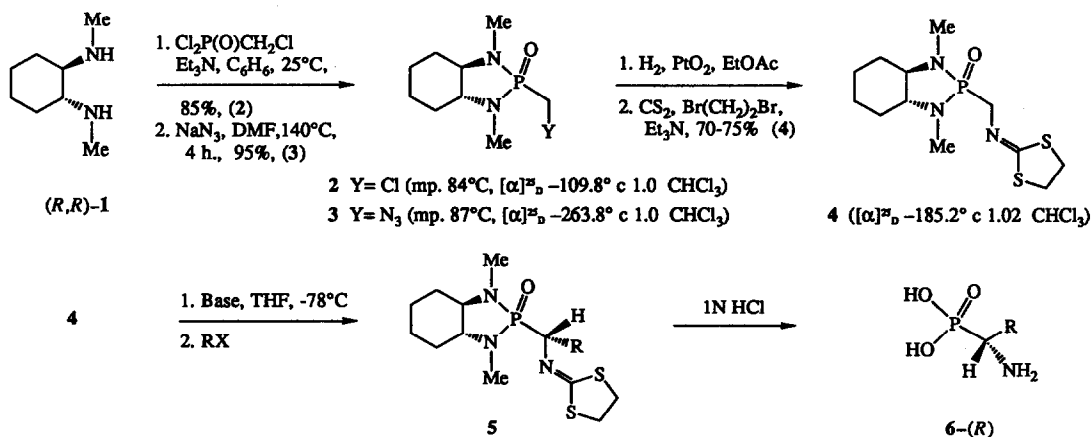
**Abstract:** A general protocol for the synthesis of  $\alpha$ -amino- $\alpha$ -alkyl phosphonic acids in either enantiomeric form is described based on the alkylation of chiral bicyclic phosphonamides derived from (*R,R*)- and (*S,S*)-1,2-diaminocyclohexane.

The  $\alpha$ -aminophosphonic acids are probably the most important substitutes for the corresponding  $\alpha$ -amino acids in biological systems.<sup>1</sup> Indeed a number of potent antibiotics,<sup>2</sup> enzyme inhibitors,<sup>3</sup> and pharmacological agents<sup>4</sup> are  $\alpha$ -aminophosphonic acids as well as their derivatives, notably peptides. These important compounds have also been used in ingenious ways as peptidomimetics<sup>5</sup> and their properties have been evaluated in a variety of enzymatic test systems.<sup>6</sup> Aminophosphonic acids are also found as constituents of natural products.<sup>7</sup>

Since a number of years, the major source of optically active (even pure)  $\alpha$ -aminophosphonic acids was, based on the resolution of racemic mixtures<sup>8</sup> or the utilization of enzymatic methods such as with aminoacylases.<sup>9</sup> More recently, a number of procedures have been reported that rely on asymmetric processes.<sup>10-12</sup> In spite of their individual merits, the levels of asymmetric induction have been variable or the methods have lacked generality.

We wish to report on a general method for the synthesis of  $\alpha$ -aminophosphonic acids of high optical purity in either enantiomeric series. The process consists in the highly stereoselective alkylation of the anion derived from the iminomethyldithiolane<sup>13</sup> bicyclic phosphonamide of type 4 which is easily prepared from (*R,R*)-1,2-bis-N-methylamino cyclohexane 1, a readily available  $C_2$  symmetrical template,<sup>14</sup> via the chloromethyl derivative 2, (Scheme 1).<sup>15</sup>

Scheme 1.



Treatment of **4** with 2.1 equivalents of KHMDS at  $-78^{\circ}$  in THF followed by addition of the desired alkyl halide led to the formation of the corresponding  $\alpha$ -alkylated phosphonamides of general structure **5** in high yield and excellent diastereomeric purity (Table 1).<sup>16</sup> The structure and absolute configuration at the newly formed stereogenic center was unequivocally substantiated by a single crystal X-ray analysis of the  $\alpha$ -allyl derivative (entry 4).<sup>17</sup> Mild acid hydrolysis of the products of alkylation led to the free  $\alpha$ -aminophosphonic acids shown in Table 1 whose optical rotations were in excellent agreement with the values reported for the resolved acids.<sup>8</sup> Using the phosphonamide of type **4** derived from the (*S,S*)-diamine, led to the enantiomeric series of  $\alpha$ -alkylated phosphonic acids (entries 8,9).

Table 1 ALKYLATION of **4** and HYDROLYSIS of the  $\alpha$ -SUBSTITUTED IMINOMETHYL PHOSPHONAMIDES

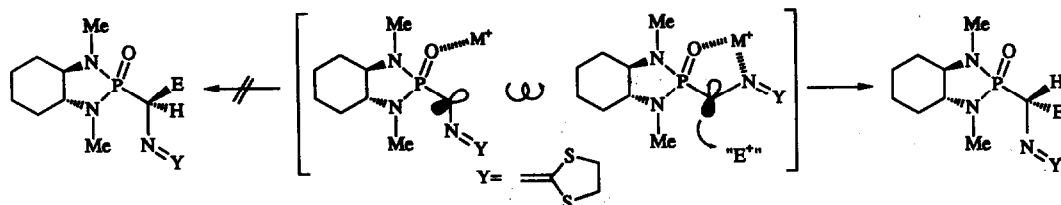
| ENTRY                      | RX  | ALKYLATION( $-78^{\circ}\text{C}$ ) |                    |                           |   | HYDROLYSIS          |  |                             |                   |                      |
|----------------------------|---|-------------------------------------|--------------------|---------------------------|---|---------------------|--|-----------------------------|-------------------|----------------------|
|                            |   | Yield% <sup>a</sup>                 | Ratio <sup>b</sup> | mp.( $^{\circ}\text{C}$ ) | $[\alpha]_{\text{D}}^{25}$ <sup>c</sup> | Yield% <sup>d</sup> | mp.( $^{\circ}\text{C}$ ) <sup>e</sup> | $[\alpha]_{578}^{\text{f}}$ | e.e. <sup>g</sup> | Config. <sup>h</sup> |
| <b>(<i>R,R</i>) Series</b> |   |                                     |                    |                           |   |                     |  |                             |                   |                      |
| 1.                         | CH <sub>3</sub> I                                     | 74                                  | 90:10              | 134 $^{\circ}$            | -183.6 $^{\circ}$ (c 0.6)               | 82                  | 278                                    | -12.9 $^{\circ}$            | 81%               | <i>R</i>             |
| 2.                         | CH <sub>3</sub> CH <sub>2</sub> I                     | 73                                  | 95:5               | 137 $^{\circ}$            | -189.0 $^{\circ}$ (c 0.9)               | 84                  | 277                                    | -19.2 $^{\circ}$            | 91%               | <i>R</i>             |
| 3.                         | CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> I     | 76                                  | >99:1              | 129 $^{\circ}$            | -178.0 $^{\circ}$ (c 0.7)               | 86                  | 272                                    | +8.5 $^{\circ}$             | 98%               | <i>R</i>             |
| 4.                         | CH <sub>2</sub> =CHCH <sub>2</sub> Br                 | 82                                  | >99:1              | 123 $^{\circ}$            | -163.2 $^{\circ}$ (c 1.0) <sup>l</sup>  | 88                  | 272                                    | -8.9 $^{\circ}$             | (-) <sup>j</sup>  | <i>R</i>             |
| 5.                         | (CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> OTf | 77                                  | 95:5               | 136 $^{\circ}$            | -183.0 $^{\circ}$ (c 1.0)               | 81                  | 288                                    | -21.6 $^{\circ}$            | 90%               | <i>R</i>             |
| 6.                         | PhCH <sub>2</sub> Br                                  | 78                                  | >99:1              | 140 $^{\circ}$            | -148.6 $^{\circ}$ (c 0.5)               | 87                  | 268                                    | -47.6 $^{\circ}$            | 97%               | <i>R</i>             |
| 7.                         | HC $\equiv$ C-CH <sub>2</sub> Br                      | 78                                  | >99:1              | 125 $^{\circ}$            | -137.2 $^{\circ}$ (c 0.8)               | -                   | -                                      | -                           | -                 | -                    |
| <b>(<i>S,S</i>) Series</b> |   |                                     |                    |                           |   |                     |  |                             |                   |                      |
| 8.                         | CH <sub>3</sub> I                                     | 75                                  | 8:92               | 139 $^{\circ}$            | +187.0 $^{\circ}$ (c 1.0)               | 84                  | 278                                    | +14.3 $^{\circ}$            | 84%               | <i>S</i>             |
| 9.                         | PhCH <sub>2</sub> Br                                  | 81                                  | >1:99              | 142 $^{\circ}$            | +148.0 $^{\circ}$ (c 0.75)              | 86                  | 270                                    | +50.9 $^{\circ}$            | 98%               | <i>S</i>             |

a. Isolated yields. b. Diastereomeric ratios (*R*:*S*) evaluated by <sup>1</sup>H and <sup>31</sup>P NMR recorded at 121.42 MHz on a Varian VXR-300 using 85% H<sub>3</sub>PO<sub>4</sub> solution as an external reference. When the ratio is indicated as >99:1, only one diastereomer was detected by <sup>1</sup>H and <sup>31</sup>P NMR. c. Optical rotations measured on a Perkin-Elmer-281 polarimeter in CHCl<sub>3</sub>. d. Isolated yields after 1 N HCl, then H<sub>2</sub>O<sub>2</sub>, neutralization with NaHCO<sub>3</sub>, Dowex $\text{C}$ -1-OH<sup>-</sup>-form and Dowex $\text{C}$ -50H<sup>+</sup>-form chromatography. e. Compounds usually decompose at these temperatures. f. Optical rotations measured in 1N NaOH, at c=1.0 except entry 4, c=0.9. g. Enantiomeric excess based on the values reported for the resolved  $\alpha$ -aminophosphonic acids (ref. 8). h. Configuration established based on the absolute configuration of the precursor alkylated phosphonamide as determined by X-ray crystallography (ref.17) and on literature data (refs. 1 and 8). i. With n-BuLi (2.1 eq., 63%), LDA (2.1 eq., 57%), LiHMDS (2.1 eq., 53%), NaHMDS (2.1 eq., 34%). j. The rotation value is not reported in the literature.

Three features of the alkylation of the iminomethyldithiolane derivative **4** are worthy of note. Firstly, although several bases were tried, (Table 1, entry 4i), the ultimate choice of KHMDS was based on the combination of efficiency and high diastereoselectivity. Secondly, it is important to utilize slightly over 2 equivalents of base, even when n-BuLi is used where proton exchange with the anion is not possible. Thirdly, it may not have eluded the reader that unlike other cases of alkylation of chloromethyl or ethyl, phosphonamides in the same (*R,R*)-series,<sup>15</sup> alkylation of **4** gives products with the *opposite orientation* of the alkyl chain which is normally expected from the enantiomeric (*S,S*)-series.<sup>17,18</sup> A plausible explanation for this intriguing and unexpected behavior is that a chelated entity is produced prior to the alkylation reaction. As a consequence, the "opposite" face of the anion is now exposed for alkylation as illustrated in scheme 2. A similar chelate for a potassium enolate prepared from

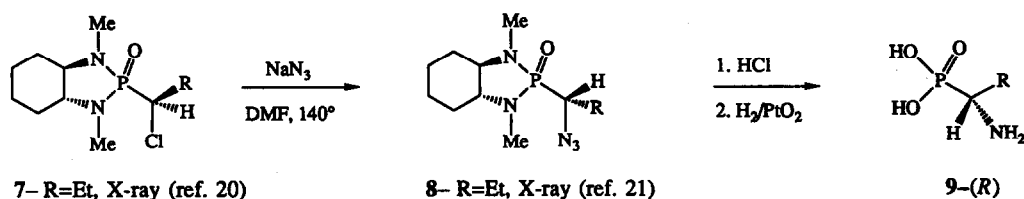
N-(1,3-dithiolan-2-ylidene) glycine ethyl ester has been proposed by Hoppe.<sup>13, 19</sup>

Scheme 2.



Another route to  $\alpha$ -aminophosphonic acids is possible from the  $\alpha$ -chloro- $\alpha$ -alkylphosphonamides of general structure 7 which are easily obtained by the asymmetric alkylation of chloromethylphosphonamide 2.<sup>15</sup> Nucleophilic displacement with azide ion gives the corresponding  $\alpha$ -azido derivatives of type 8. Mild acid hydrolysis followed by hydrogenation of the azido group led in almost quantitative yields to the corresponding  $\alpha$ -amino phosphonic acids 9, (Scheme 3).

Scheme 3.



Unfortunately due to the relatively harsh conditions of the displacement reactions, this method could not be adapted for the synthesis of the  $\alpha$ -azido- $\alpha$ -alkyl phosphonamides having a potentially acidic proton such as the  $\alpha$ -benzyl or the  $\alpha$ -allyl analog. In these cases elimination rather than substitution was the main event, Table 2.<sup>22</sup>

Table 2                       $\alpha$ -AZIDO and  $\alpha$ -AMINO- $\alpha$ -ALKYL PHOSPHONIC ACIDS FROM  $\alpha$ -CHLORO- $\alpha$ -ALKYL PHOSPHONAMIDES

| ENTRY               | R   | AZIDES              |                    |         |                    | HYDROLYSIS and REDUCTION |                      |                    |                   |                      |
|---------------------|---|---------------------|--------------------|---------|--------------------|--------------------------|----------------------|--------------------|-------------------|----------------------|
|                     |   | Yield% <sup>a</sup> | Ratio <sup>b</sup> | mp.(°C) | $[\alpha]_D^{25c}$ | Yield% <sup>d</sup>      | mp.(°C) <sup>e</sup> | $[\alpha]_{578}^f$ | e.e. <sup>g</sup> | Config. <sup>h</sup> |
| <b>(R,R) Series</b> |   |                     |                    |         |                    |                          |                      |                    |                   |                      |
| 1.                  | CH <sub>3</sub> -                                   | 62                  | 90:10              | 39°     | -99.8° (c 1.23)    | 95                       | 278                  | -12.5°             | 78%               | R                    |
| 2.                  | CH <sub>3</sub> CH <sub>2</sub> -                   | 65                  | >99:1              | 86°     | -186.0°(c 1.03)    | 98                       | 276                  | -21.6°             | 98%               | R                    |
| 3.                  | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> -   | 65                  | >99:1              | oil     | -166.4°(c 2.20)    | 96                       | 272                  | +8.5°              | 98%               | R                    |
| 4.                  | (CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> - | 66                  | 89:11 <sup>i</sup> | oil     | -100.0°(c 2.25)    | 95                       | 288                  | -18.8°             | 78%               | R                    |
| <b>(S,S) Series</b> |   |                     |                    |         |                    |                          |                      |                    |                   |                      |
| 5.                  | CH <sub>3</sub> CH <sub>2</sub> -                   | 64                  | >1:99              | 84°     | +187.1°(c 1.02)    | 96                       | 277                  | +20.8°             | 98%               | S                    |
| 6.                  | CH <sub>3</sub> (CH <sub>2</sub> ) <sub>2</sub> -   | 67                  | >1:99              | oil     | +167.3°(c 3.29)    | 97                       | 269                  | -8.4°              | 97%               | S                    |

a-c and e-g (same as in Table 1) d. Isolated yields after cat. hydrogenation (PtO<sub>2</sub>/H<sub>2</sub>O), Dowex®-H<sup>+</sup> chromatography. Recrystallization lowers the yields by 5-10%. i. The precursor 1-(R)-1-chloro-3-methyl butyl phosphonamide was obtained in 78% yield and 89:11 diastereomeric ratio using (CH<sub>3</sub>)<sub>2</sub>CHCH<sub>2</sub>-OTf. Using iso-butyl iodide, the reaction was much less efficient (2 h, -78°C, 15% yield, 95:5 ratio).

### Acknowledgments

We wish to thank NSERCC, FCAR and the Killam Foundation for generous financial assistance. We greatly acknowledge the collaboration of the X-ray laboratory at l'Université de Montréal.

### References

1. Dhawan, B. and Redmore, D., *Phosphorus and Sulfur*, **1987**, *32*, 119.; Neuzil, E., Cassaigne, A.; *Exp. Ann. Biochim. Med.*, **1980**, *34*, 165.
2. Atherton, F. R., Hassall, C. H., Lambert, R. W.; *J. Med. Chem.*, **1986**, *29*, 29.
3. a) Giannousis, P. P., Bartlett, P. A.; *J. Med. Chem.*, **1987**, *30*, 1603; b) Logusch, E. W., Walker, D.M., McDonald J. F., Leo, G. C. and Franz, J. E.; *J. Org. Chem.*, **1988**, *53*, 4069; c) Allen, M. C., Fuhrer, W., Tuck, B., Wade, R. and Wood, J. M.; *J. Med. Chem.*, **1989**, *32*, 1652.
4. a) Kupczyk-Subotkowska, L. and Mastalertz, P.; *Int. J. Peptide Protein Res.*, **1983**, *21*, 485. b) Hassall, C. H., in "Antibiotics"; ed. F. E. Hahn, Springer-Verlag, Berlin, **1983**, *Vol. VI*, 1-11.
5. a) Jacobsen, N. E. and Bartlett, P. A.; *J. Am. Chem. Soc.*, **1981**, *103*, 654; b) Bartlett, P. A. and Kezer, W. B.; *J. Am. Chem. Soc.*, **1984**, *106*, 4282.; c) Hassall, C. H., Atherton, F. R., Hall, M. J., Lambert, R. W., Llyod, W. J., Ringrose, P. S.; *Peptides, Proc. Eur. Pept. Sym.*, **17th**, **1982** (Pub. **1983**); Blaha, K. and Malon, P. G., ed. Walter de Gruyter Co., Berlin, New York.
6. Bartlett, P. A. and Marlowe C. K.; *Biochemistry*, **1983**, *22*, 4618, see also refs. 5 and 3a.
7. a) Kase, K., Yamamoto, M., Kogushi, T. Okashi, R., Kasai, M., Shirahata, K., Kawamoto I., Shuto, K., Karasawa A.; *Eur. Pat. App. EP* 61,172, *US Patent* 4,522,812; *Chem. Abst.*, **1983**, *98*, 107793; b) Horigushi, M., Kandatsu, M.; *Nature*, **1959**, *184*, 901., c) Park, B. K., Hirota, A., Sakai, H.; *Agr. Biol. Chem.*, **1977**, *41*, 161.
8. Kafarski, P. Lejczak, B.; *Can. J. Chem.*, **1983**, *61*, 2425.
9. Telegdi, J., Morovcsik, E., Otvos, L.; *Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod (proc)*, **1981**, *Ist. 3*, 221; *Chem. Abst.*, **1981**, *97*, 87977y.
10. a) Vasella, A., Voeffray, R.; *Helv. Chim. Acta*, **1982**, *Vol. 65*, 1953; b) Huber, R., Knierzinger, A., Obrecht, J. P. and Vasella, A.; *Helv. Chim. Acta*, **1982**, *Vol. 68*, 1730; c) Hoppe, I., Schöllkopf, U., Nieger, M. and Egert, E.; *Angew. Chem. Int. Ed. Engl.*, **1985**, *24*, 1067; d) Schöllkopf, U. and Schütze, R., *Liebigs Ann. Chem*, **1987**, *45*; e) Bartlett, P. A. and McLaren K.; *Phosphorus and Sulfur*, **1987**, *Vol. 33*, 1; f) Jacquier, R., Ouazzani, F., Roumestant, M-L. and Viallefont, P.; *Phosphorus and Sulfur*, **1988**, *Vol.36*, 73; g) Sting, M. and Steglich, W.; *Synthesis*, **1990**, 132.
11. a) Schöllkopf, U., Hoppe, I. and Thiele, A.; *Liebigs Ann. Chem*, **1985**, 555; b) Sawamura, M., Ito, Y., Hayashi, T.; *Tetrahedron Letters*, **1989**, *17*, 2247.
12. Denmark, S. E., Dorow, R. L., *J. Am. Chem. Soc.*, **1990**, *112*, 864; the asymmetric synthesis of  $\alpha$ -azido- $\alpha$ -benzylphosphonic acids by treatment of phosphorus stabilized carbanions with tripsyl azide has been achieved in the Denmark laboratories, private communication, Nov., 1989.
13. a) Hoppe, D. and Beckmann, L.; *Liebigs Ann. Chem*, **1979**, 2066; b) Hoppe, D.; *Angew. Chem., Int. Ed. Engl*, **1975**, *14*, 424.
14. a) Galsbol, F., Steenbol, P. and Sorensen, S. B.; *Acta Chem. Scand.*; **1972**, *26*, 3605; b) Onuma, K., Ito, T., Nakamura, A.; *Bull. Chem. Soc. Jpn.*, **1980**, *53*, 2012.
15. Hanessian, S., Bennani, Y. L. and Delorme, D.; *Tetrahedron Letters*, **1990**, preceding paper.
16. In a typical procedure, a solution of **4** (0.166 g, 0.52 mmoles) in 5.0 mL of dry THF is cooled at -78°C and treated with KHMDS (0.5 M in Toluene, 1.04 mmoles). After 10 min., benzyl bromide (0.2 g, 1.18 mmoles) is added to the yellow lime solution. After 15 min., the mixture is quenched with excess KH<sub>2</sub>PO<sub>4</sub> at -78°C, then allowed to warm at room temp. Usual work up, followed by chromatography affords 0.152 g (82% yield) of the  $\alpha$ -benzylated product, (Table 1, Entry 6).
17. Hanessian, S., Bennani, Y. L.; *Acta Cryst.*, **1990**; in press.
18. When 0.1-5 eq. of HMPA were used during the alkylation with allyl bromide, neither the yield nor the diastereoselectivity were affected.
19. For the crystal structure of a phosphorus stabilized  $\alpha$ -benzylcarbanion, see ref. 12.
20. Bélanger-Gariépy, F., Bennani, Y. L., Hanessian, S. and Brisse, F.; *Acta Cryst.*, **1989**, *C45*, 289.
21. Bennani, Y. L., Bélanger-Gariépy, F. and Hanessian, S.; *Acta Cryst.*, **1990**, *C46*, 653.
22. The chiral diamine could be recovered after Dowex®-H<sup>+</sup> chromatography. All new compounds showed satisfactory spectroscopic and analytical results by <sup>1</sup>H, <sup>13</sup>C, <sup>31</sup>P, NMR, IR and HRMS.