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Diastereoselective reduction of β-ketophosphonates derived from amino acids. A new entry to enantiopure β-hydroxy-γ-aminophosphonate derivatives

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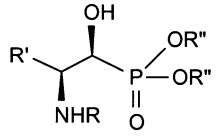
Abstract—The reduction of γ-*N*,*N*-dibenzylamino-β-ketophosphonates **4** derived from readily available (*S*)-tribenzylated amino acids was achieved with catecholborane at –20°C affording γ-amino-β-hydroxyphosphonates **5** in high diastereoselectivity and good chemical yield. These reactions provide a new entry to enantiomerically pure γ-amino-β-hydroxyphosphonates.

1. Introduction

Phosphonates and phosphinates functionalized with amino and hydroxy groups have attracted considerable attention in recent years for their role in biologically relevant processes such as inhibition of rennin and HIV protease and human calpain I, and as a result of their use as haptens in the development of catalytic antibodies.[1] In particular, β-amino-α-hydroxyphosphonates of the type **1** and γ-amino-β-hydroxyphosphonates of the type **2** have resulted in unique phosphate mimics with resistance to phosphatase hydrolysis.[2]



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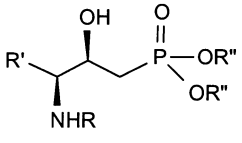

2

As a result, numerous synthetic methods for β-amino-α-hydroxyphosphonates have been developed.[1,3] However, to the best of our knowledge, only a few synthetic approaches to obtain optically active γ-amino-β-hydroxyphosphonates **2** have been reported in the literature. These involve the reaction of the anion of methylphosphonate with α-aminopropanal,[4] or the catalytic asymmetric aminohydroxylation of unsaturated phosphonates.[3d] Both approaches afford the γ-amino-β-hydroxyphosphonates with low enantioselectivity.

As part of our ongoing program directed towards the design of chiral γ-amino-β-hydroxyphosphonates we report herein a simple entry to these compounds that takes advantage of the diastereoselective reduction of the ketone group of γ-*N*,*N*-dibenzylamino-β-ketophosphonates **4a**–**d**,[5] derived from readily available tribenzylated amino acids[6] and catecholborane as the reducing agent.

2. Results and discussion

The starting protected amino acids **3** were prepared in 74–80% yield by treatment of the corresponding amino acids with K_2CO_3 and benzyl bromide under reflux.[7] The reaction of benzyl esters **3** with 4 equiv. of the lithiated dimethyl methylphosphonate at –78°C in THF gave the corresponding β-ketophosphonates **4** in excellent yield (Scheme 1).[8]

From the γ-*N*,*N*-dibenzylamino-β-ketophosphonates **4a**–**d** we selected the isopropyl analog **4b** (R = *i*-Pr) to evaluate diastereoselective reduction using several hydrides (Table 1). As shown in Table 1, the yields and stereoselectivities (entries 1–4) were higher when catecholborane was used and,[9] therefore, catecholborane

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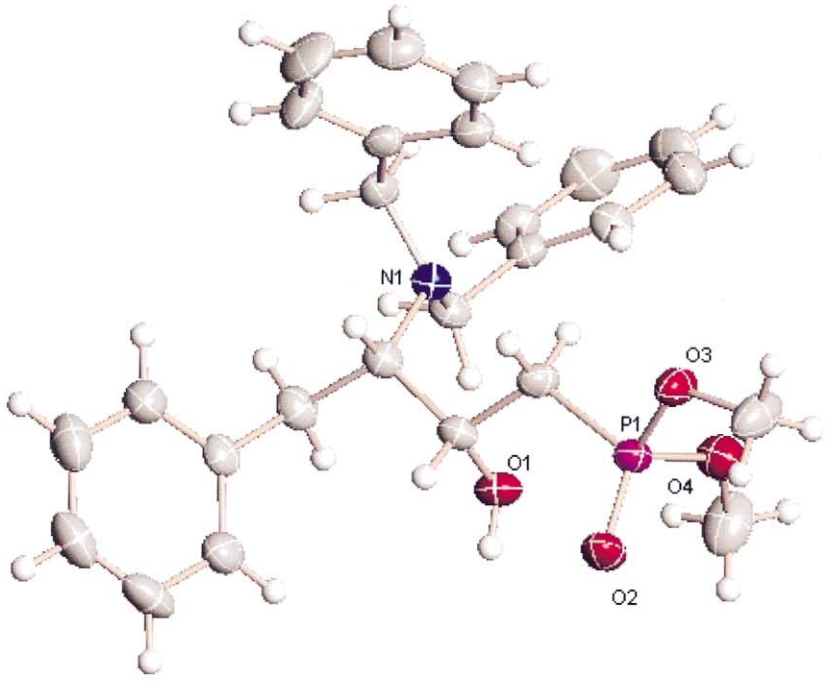
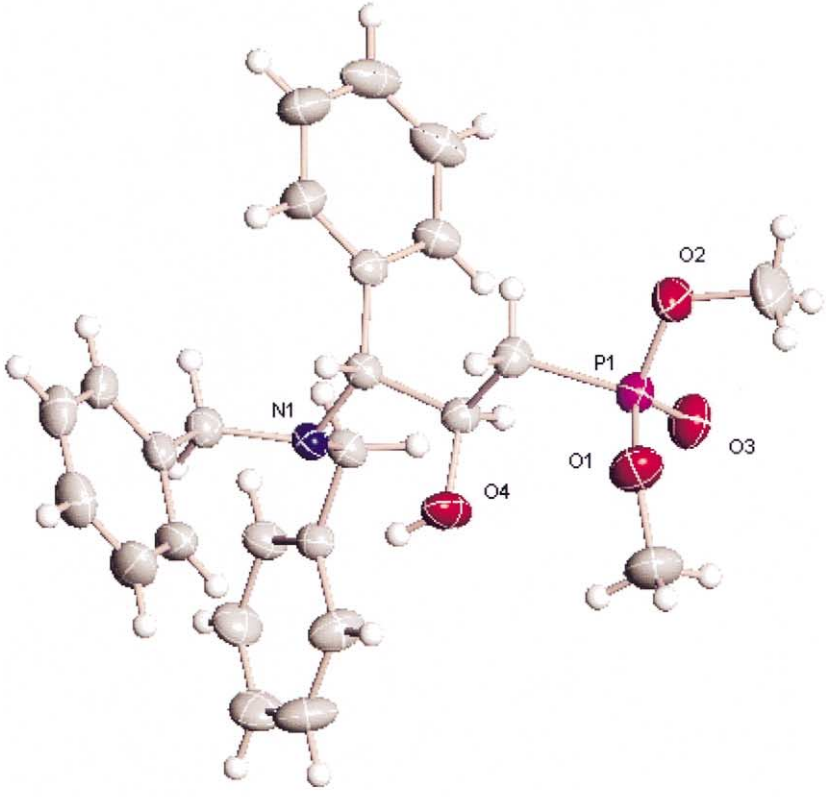
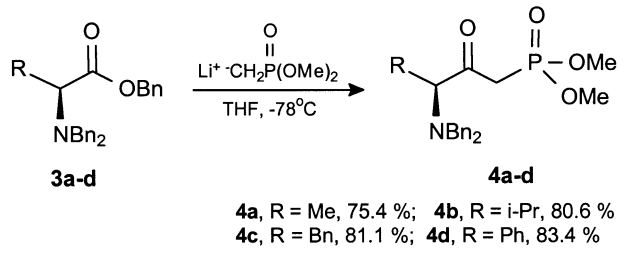


syn **5c**



syn **5d**

Figure 1. X-Ray crystal structure of *syn*-**5c** and *syn*-**5d**.



Scheme 1.

was the reducing agent used for the other β-ketophosphonates **4a**–**d**.[10]

From the results summarized in Table 1, it should be pointed out that the diastereoselectivity of the reduction of γ-*N*,*N*-dibenzylamino-β-ketophosphonates **4a**–**d** is independent of the steric demands placed upon increasing size of the R group at C(3). The diastereomeric excesses for *syn*-**5** and *anti*-**5** were determined by ^{1}H NMR at 400 MHz. The configuration at the carbinol center was assigned by analogy of other phosphonates reported in the literature[3d] and confirmed by the X-ray crystal structures of diastereomeric pure **5c** and **5d** (Fig. 1).[13]

In summary, ready access to γ-*N*,*N*-dibenzylamino-β-ketophosphonates **4** in conjunction with the reduction of a ketone group using catecholborane with very high diastereoselectivity and good chemical yield as described in this paper make this experimental operation a good, simple and general method to obtain enantiomerically pure γ-*N*,*N*-dibenzylamino-β-hydroxy-phosphonates **5**.

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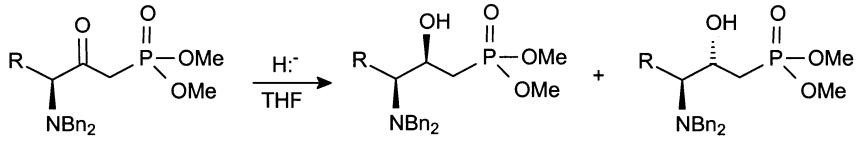
References

1. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P.; Hudson, H. R., Eds.; John Wiley: New York, 2000 and references cited therein.
2. (a) Nieschalk, J.; Batsanov, A. S.; O'Hagan, D.; Howard, J. A. K. *Tetrahedron* **1996**, *52*, 165; (b) Burke, T. R., Jr.; Smyth, M. S.; Nomizu, M.; Otaka, A.; Roller, P. P. *J. Org. Chem.* **1993**, *58*, 1336.
3. (a) Yamagishi, T.; Suemune, K.; Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **2001**, *42*, 5033; (b) Hammerschmidt, F.; Lindner, W.; Wuggenig, F.; Zarbl, E. *Tetrahedron: Asymmetry* **2000**, *11*, 2955; (c) Barco, A.; Benetti, S.; Bergamini, P.; De Risi, C.; Marchetti, P.; Pollini, G. P.; Zanirato, V. *Tetrahedron Lett.* **1999**, *40*, 7705; (d) Thomas, A. A.; Sharpless, K. B. *J. Org. Chem.* **1999**, *64*, 8379; (e) Wróblewski, A. E.; Piotrowska, D. G. *Tetrahedron* **1998**, *54*, 8123; (f) Gravotto, G.; Giovenzana, G. B.; Pagliarin, R.; Palmisano, G.; Sisti, M. *Tetrahedron: Asymmetry* **1998**, *9*, 745.
4. (a) O'Brien, P.; Powell, H. R.; Raithby, P. R.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1031; (b) O'Brien, P.; Warren, S. *Tetrahedron Lett.* **1996**, *37*, 4271; (c) Froestl, W.; Mickel, S. J.; Hall, R. G.; Sprecher, G. V.; Strub, D.; Baumann, P. A.; Brugger, F.; Gentsch, C.; Jaekel, J.; Olpe, H.-R.; Rihhs, G.; Vassout, A.; Valdmeier, P. C.; Bittiger, H. *J. Med. Chem.* **1995**, *38*, 3297; (d) Dellaria, J. F., Jr.; Maki, R. G.; Stein, H. H.; Cohen, J.; Whittern, D.; Marsh, K.; Hoffman, D. J.; Plattner, J. J.; Perum, T. J. *J. Med. Chem.* **1990**, *33*, 534; (e) Chakravarty, P. K.; Greenlee, W. J.; Parsons, W. H.; Patchett, A. A.; Combs, P.; Roth, A.; Busch, R. D.; Mellin, T. N. *J. Med. Chem.* **1986**, *32*, 1886.
5. Chung, S.-K.; Kang, D.-H. *Tetrahedron: Asymmetry* **1997**, *8*, 3027.
6. (a) Hungerhoff, B.; Samanta, S. S.; Roels, J.; Metz, P. *Synlett* **2000**, 77; (b) Lagu, B. R.; Crane, H. M.; Liotta, D. C. *J. Org. Chem.* **1993**, *58*, 4191.

Table 1. Diastereoselective reduction of γ-*N*,*N*-dibenzylamino-β-ketophosphonates **4a**–**d**



Entry	R	H:$^-$	Temp. (°C)	Yield (%), **5**[a]	*syn*:*anti*[b]
1	*i*-Pr, **5b**	$BH_3{\cdot}SMe_2$	−20	[c]	[c]
2	*i*-Pr, **5b**	DIBAL-H	−78	50	82:18
3	*i*-Pr, **5b**	$NaBH_4$	−20	44	85:15[12]
4	*i*-Pr, **5b**	CB[d]	−20	69	>98:2
5	Me, **5a**	CB[d]	−20	85	>98:2
6	Bn, **5c**	CB[d]	−20	89	>98:2
7	Ph, **5d**[e]	CB[d]	−20	82	90:10

[a] Chemical yield after purification by column chromatography.[11]
[b] Determined by ^{1}H NMR at 400 MHz.
[c] The reaction did not proceed.
[d] Catecholborane.
[e] The configuration of the amino acid used was (*R*).

7. **General procedure for the preparation of benzyl γ-*N*,*N*-dibenzylamino acids 3a–d**. A solution of benzyl bromide (170.7 mmol) in ethanol (40 mL) was slowly added to solution of the amino acid (42.68 mmol) and K_2CO_3 (170.7 mmol) in a 5:1 mixture of ethanol–water (250 mL). The reaction mixture was heated under reflux for 14 h. The solvent was removed under reduced pressure. Water was added to the residue and the resulting slurry extracted with ethyl acetate (3×150 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude products were purified by flash chromatography.
8. **General procedure for the preparation of γ-*N*,*N*-dibenzylamino-β-ketophosphonates γ-substituted 4a–d**. A solution of dimethylmethylphosphonate (18.97 mmol) in anhydrous THF (45 mL) was cooled at –78°C before the slow addition of a solution of *n*-BuLi in hexanes (1.5 M, 12.4 mL, 19.45 mmol). The resulting solution was stirred at –50°C for 1 h. The solution was cooled to –78°C and slowly added to a solution of the benzyl ester (18.97 mmol) in THF (45 mL). The reaction mixture was stirred at –78°C for 3 h before the addition of a saturated solution of NH_4Cl. The organic phase was separated and the aqueous layer was extracted with ethyl acetate (3×40 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude ketophosphonates were purified by flash chromatography.
9. High diastereoselectivity was also found in the reduction of β-amino-α-ketophosphonates with catecholborane in the presence of a catalytic amount of oxazaborolidine, see Ref. 3c.
10. **General procedure for the diastereoselective reduction of β-ketophosphonates γ-substituted 4a–d**. A solution of β-ketophosphonate **4** (0.57 mmol) in anhydrous THF (7 mL) was cooled at –78°C before the slow addition of a solution of chatecolborane in THF (1 M, 0.28 mL, 28 mmol) The reaction mixture was stirred at –20°C for 4 h and at room temperature for 3 h then quenched by the addition of a saturated aqueous solution of NH_4Cl. The organic phase was separated and the aqueous layer was extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude β-hydroxyphosphonate was analyzed by ^1H NMR at 400 MHz and purified by flash chromatography.
11. All compounds were fully characterized by ^{13}C, ^1H and ^{31}P NMR at 400 MHz.
12. Similar relations have been reported by related compounds, see Refs. 4a,b.
13. X-Ray crystal data of *syn*-**5c** and *syn*-**5d** were collected at 293 K using a Bruker APEX instrument (Mo Kα radiation, $\lambda = 0.71073$ Å). The SHELXTL v. 6.1 program package was used for structures solution and refinement. An absorption correction was applied using SADABS in both cases. The structures were solved by direct methods and refined by full-matrix least square procedures. All non-hydrogen atoms were refined anisotropically. *syn*-**5c**: $C_{24}H_{32}NO_4P$, $M = 453.49$, monoclinic space group $P2_1/c$, $a = 10.144(1)$, $b = 17.122(1)$, $c = 14.425(1)$ Å, $\beta = 90.77(1)^\circ$, $V = 2505.3$ (2) Å^3, $Z = 4$, $D_c = 1.202$ g cm^{-1}, 12013 reflections measured, 4213 unique ($R_{int} = 0.0205$) wich were used in all calculations, final R values were 0.0616 [$F > 4\sigma(F)$] and 0.0647 (all data). *syn*-**5d**: $C_{25}H_{30}NO_4P$, $M = 439.47$, monoclinic space group $C2/c$, $a = 16.533(1)$, $b = 15.774(1)$, $c = 19.369(2)$ Å, $\beta = 108.01(1)^\circ$, $V = 4803.72$ (6) Å^3, $Z = 8$, $D_c = 1.215$ g cm^{-1}, 29233 reflections measured, 7869 unique ($R_{int} = 0.0269$) which were used in all calculations, final R values were 0.0574 [$F > 4\sigma(F)$] and 0.0679 (all data).