COMMUNICATION

ChemComm
www.rsc.org/chemcomm

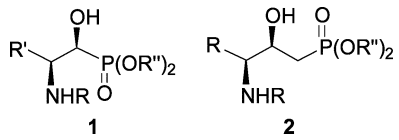
Highly diastereoselective synthesis of *anti*-γ-*N*-benzylamino-β-hydroxyphosphonates

Mario Ordóñez,* Ricardo de la Cruz-Cordero, Citlali Quiñónes and Angelina González-Morales
Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, 62210 Cuernavaca, Mor, Mexico. E-mail: palacios@buzon.uaem.mx; Fax: 52(777)3297997; Tel: 52(777)3297997

Received (in Corvallis, OR, USA) 12th December 2003, Accepted 14th January 2004
First published as an Advance Article on the web 10th February 2004

The reduction of γ-*N*-benzylamino-β-ketophosphonates 7 derived from readily available amino acids can be carried out stereoselectively with $Zn(BH_4)_2$ at −78 °C to produce the *anti*-γ-amino-β-hydroxyphosphonates 8.

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 renin and HIV protease, human calpain I and for their use as haptens in the development of catalytic antibodies.[1] In particular, β-amino-α-hydroxyphosphonates **1** and γ-amino-β-hydroxyphosphonates **2** have resulted in unique phosphate mimics with resistance to phosphatase hydrolysis.[2]

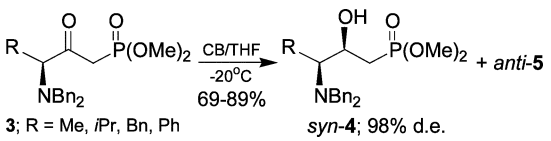


As a result, numerous synthetic methods for chiral non-racemic β-amino-α-hydroxyphosphonates have been developed.[3] However, to the best of our knowledge, only a few synthetic approaches to obtain optically active γ-amino-β-hydroxyphosphonates **2** are reported in the literature, which involve the reaction of the anion of methylphosphonate with α-amino-aldehydes,[4] or the catalytic asymmetric aminohydroxylation of unsaturated phosphonates,[4] but both synthetic approaches yield the γ-amino-β-hydroxyphosphonates with low enantioselectivity.

Recently we described the reduction of dimethyl γ-*N*,*N*-dibenzylamino-β-ketophosphonates **3** with catecholborane, obtaining the dimethyl γ-*N*,*N*-dibenzylamino-β-hydroxyphosphonates *syn*-**4** with high diastereoselectivity and good chemical yield (Scheme 1).[5]

The absolute configuration of the new stereogenic centre in **4c** and **4d** (R = Bn and Ph, respectively) was established by single-crystal X-ray crystal analysis. The absolute configuration of the other γ-*N*,*N*-dibenzylamino-β-hydroxyphosphonates *syn*-**4** was assigned by analogy. Therefore, the reduction of **3** took place under nonchelation control or the Felkin–Anh model,[6] based on steric constraints imparted by the bulky *N*,*N*-dibenzyl protecting group, and is independent of the steric demand placed upon the increasing size of the R group at C-3. This diastereofacial preference is in agreement with that reported previously for the reduction of 1-aminoalkylchloromethyl ketones,[7] for the reductive amination of α-amino ketones,[8] and reduction of 1-aminoalkyl-chloromethyl ketimines.[9]

In order to induce the formation of *anti*-γ-amino-β-hydroxyphosphonates, we choose now only one benzyl as protecting group. Thus, the starting *N*-benzyl methyl esters **6a–e** (R = Me **a**, *i*Pr **b**, *i*Bu **c**, Bn **d**, Ph **e**) were prepared by treatment of corresponding amino methyl ester hydrochloride with K_2CO_3 and benzyl bromide

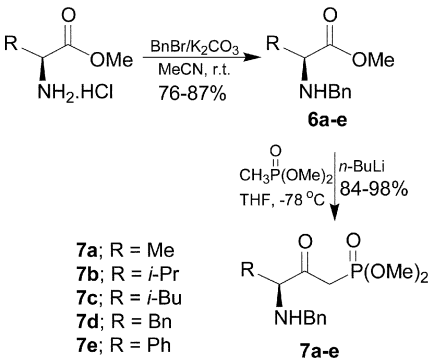


Scheme 1

in acetonitrile at room temperature. Then, the methyl esters **6a–e** were treated with three equivalents of the lithium salt of dimethyl methylphosphonate at −78 °C in THF to afford the corresponding *N*-benzylamino-β-ketophosphonates **7a–e** in excellent yield (Scheme 2).

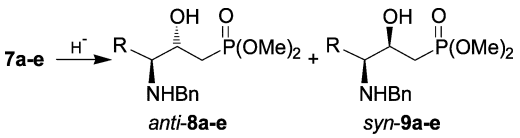
Having efficiently prepared the β-ketophosphonates **7a–e**, we turned our attention to the diastereoselective reduction to obtain the γ-*N*-benzylamino-β-hydroxyphosphonates **8** and **9**. The reduction was carried out with a variety of reducing agents and conditions. Yields and diastereomeric excess are summarized in Table 1.

Reduction of **7a–e** was carried out using $NaBH_4$, catecholborane, $LiBH_4$ and $Zn(BH_4)_2$. Our first trials sought to determine the most suitable reducing agent. The reduction of **7a–e** with $NaBH_4$ at 0 °C in methanol (entries 1–5) afforded the γ-*N*-benzylamino-β-hydroxyphosphonates *anti*-**8** and *syn*-**9** with good chemical yields and moderate diastereoselectivity, in favour of diastereomer *anti*-**8**.



Scheme 2

Table 1 The reduction of **7a–e** with various reducing agents[10]



Entry	R	Hydride	Conditions	Yield[a] (%)	^{31}P NMR [b]*anti* : *syn*	*anti* : *syn*[b]
1	Me	$NaBH_4$	MeOH, 0 °C	86	34.94 : 34.68	46 : 54
2	*i*-Pr	$NaBH_4$	MeOH, 0 °C	70	35.65 : 33.44	85 : 15
3	*i*-Bu	$NaBH_4$	MeOH, 0 °C	88	34.84 : 34.71	46 : 54
4	Bn	$NaBH_4$	MeOH, 0 °C	65	34.56 : 34.80	55 : 45
5	Ph	$NaBH_4$	MeOH, 0 °C	75	35.22 : 34.16	63 : 37
6	*i*-Pr	CB	THF, −78 °C	70	35.65 : 33.44	79 : 21
7	*i*-Pr	$LiBH_4$	THF, −78 °C	78	35.65 : 33.44	79 : 21
8	*i*-Pr	$LiBH_4$[c]	THF, −78 °C	50	35.65 : 33.44	91 : 9
9	Me	$Zn(BH_4)_2$	THF, −78 °C	88	34.94 : 34.68	67 : 33
10	*i*-Pr	$Zn(BH_4)_2$	THF, −78 °C	85	35.65 : 33.44	96 : 4
11	*i*-Bu	$Zn(BH_4)_2$	THF, −78 °C	95	34.84 : 34.71	94 : 6
12	Bn	$Zn(BH_4)_2$	THF, −78 °C	70	34.56 : 34.80	96 : 4
13	Ph	$Zn(BH_4)_2$	THF, −78 °C	80	35.22 : 34.16	88 : 12

[a] Chemical yield after purification by column chromatography. [b] Determined by ^{1}H NMR at 400 MHz and ^{31}P NMR at 200 MHz in the crude reaction. [c] In presence of $ZnCl_2$ (1 equiv.).

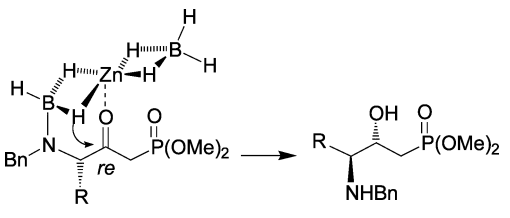
DOI: 10.1039/b316262a

The diastereomeric excess of the reduction of **7a–e** was determined by means of ^{1}H and ^{31}P NMR. In fact, the signals in ^{31}P NMR for the diastereomers *syn*-**9** were more shielded than for the diastereomers *anti*-**8** (Table 1). Assignment of the absolute configuration of the new stereogenic centre in the diastereomer *anti*-**8** was by chemical correlation. Thus, the mixture of the diastereomers *anti*-**8** and *syn*-**9** was treated with benzyl bromide in acetonitrile at room temperature to afford a mixture of the known γ-*N*,*N*-dibenzylamino-β-hydroxyphosphonates. The ^{31}P NMR signals for these β-hydroxyphosphonates were identical to those obtained for *anti*-**5** and *syn*-**4**.[5]

When the reduction of **7b** was carried out with catecholborane and $LiBH_4$ (entries 6–7), the diastereomers *anti*-**8b** and *syn*-**9b** were obtained in a ratio of 79 : 21; these last results were better than those obtained when the reduction was carried out with $NaBH_4$. The *syn*/*anti* relations obtained with $NaBH_4$, catecholborane and $LiBH_4$ in the reduction of **7** (entries 1–7) took place under chelation control, but the chelating atom is not the metal counterion, rather hydrogen bonding between the NH proton and the carbonyl oxygen significantly influences the diastereoselection. When $LiBH_4/ZnCl_2$ was used at −78 °C (entry 8) the corresponding β-hydroxyphosphonates were obtained with high diastereoselectivity and with a predominance of the desired *anti* product. However, under these conditions the reaction was not completed, in spite of using excess of $LiBH_4$ and a long reaction time.

Finally, with the reduction of **7a–e** with $Zn(BH_4)_2$ at −78 °C in THF (entries 9–13), the corresponding γ-*N*-benzylamino-β-hydroxyphosphonates were obtained in high diastereoselectivity and good chemical yield, with a predominance of the desired *anti* product. Therefore, the reduction of **7** takes place under chelation control predominantly, where an acid–base reaction between the NH proton and $Zn(BH_4)_2$ takes place, with molecular hydrogen evolution, while the zinc ion coordinates with the oxygen of the carbonyl group (Fig. 1). The reducing agent is more tightly bound to the substrate, so hydrogen transfer takes place intramolecularly in a more rigid structure, and is dependent on the steric demand placed upon the increasing size of the R group at C-3.

In summary, ready access to γ-*N*-benzylamino-β-ketophosphonates **7** in conjunction with the reduction of the carbonyl group using $Zn(BH_4)_2$ with very high diastereoselectivity and good chemical yield under chelation control as described in this paper, make this experimental operation a good, simple and general method to obtain the *anti*-γ-*N*-benzylamino-β-hydroxyphosphonates with high diastereoselectivity, which could be used for the preparation of phosphostatine analogues.



7a-e *anti*-**8**

Fig. 1 Transition state for the intramolecular hydride transfer on the *re* face.

We gratefully acknowledge CONACYT, Mexico, for financial support *via* grant 41657-Q and graduate fellowships for R.C.C., C.Q. and A.G.M.

Notes and references

1 V. P. Kukhar and H. R. Hudson, Eds., *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; John Wiley: New York, 2000 and references therein.

2 J. Nieschalk, A. S. Batsanov, D. O'Hagan and J. A. K. Howard, *Tetrahedron*, 1996, **52**, 165; T. R. Burke, Jr., M. S. Smyth, M. Nomizu, A. Otaka and P. P. Roller, *J. Org. Chem.*, 1993, **58**, 1336.

3 M. Drag, R. Latjka, E. Gumienna-Kontecka, H. Kozlowski and P. Kafarski, *Tetrahedron: Asymmetry*, 2003, **14**, 1837; A. E. Wróblewski and D. G. Piotrowska, *Tetrahedron: Asymmetry*, 2002, **13**, 2509 and references therein; F. Hammerschmidt, W. Wolfgang, F. Wuggenig and E. Zarbl, *Tetrahedron: Asymmetry*, 2000, **11**, 2955; A. Barco, S. Benetti, P. Bergamini, C. De Risi, P. Marchetti, G. P. Pollini and V. Zanirato, *Tetrahedron Lett.*, 1999, **40**, 7705; G. Gravotto, G. B. Giovenzana, R. Pagliarin, G. Palmisano and M. Sisti, *Tetrahedron: Asymmetry*, 1998, **9**, 745; F. Hammerschmidt, W. Lindner, F. Wuggenig and E. Zarbl, *Tetrahedron: Asymmetry*, 2000, **11**, 2955.

4 A. A. Thomas and K. B. Sharpless, *J. Org. Chem.*, 1999, **64**, 8379; J. F. Dellaria, Jr., R. G. Maki, H. H. Stein, J. Cohen, D. Whittern, K. Marsh, D. J. Hoffman, J. J. Plattner and T. J. Perum, *J. Med. Chem.*, 1990, **33**, 534; P. K. Chakravarty, W. J. Greenlee, W. H. Parsons, A. A. Patchett, P. Combs, A. Roth, R. D. Busch and T. N. Mellin, *J. Med. Chem.*, 1989, **32**, 1886; J. F. Dellaria, Jr. and R. G. Maki, *Tetrahedron Lett.*, 1986, **27**, 2337; S. Chen and C. Yuan, *Phosphorus, Sulfur and Silicon*, 1993, **82**, 73.

5 M. Ordóñez, R. De la Cruz-Cordero, M. Fernández-Zertuche and M. A. Muñoz-Hernández, *Tetrahedron: Asymmetry*, 2002, **13**, 559.

6 M. Cherest and H. Felkin, *Tetrahedron Lett.*, 1968, **18**, 2199; M. Cherest and H. Felkin, *Tetrahedron Lett.*, 1968, **18**, 2205; N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, 1977, **1**, 61. For an excellent summary, see: E. L. Eliel, S. H. Wilen and L. N. Mander, *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994, p. 876.

7 J. Barluenga, B. Baragaña and J. M. Concellón, *J. Org. Chem.*, 1995, **60**, 6696.

8 R. V. Hoffman, N. Maslouh and F. Cervantes-Lee, *J. Org. Chem.*, 2002, **67**, 1045; M. T. Reetz and A. Schmitz, *Tetrahedron Lett.*, 1999, **40**, 2741.

9 J. M. Concellón, P. L. Bernard, E. Riego, S. García-Granda and A. Forcén-Acebal, *J. Org. Chem.*, 2001, **66**, 2764.

10 General procedure for the reduction of **7**: A solution of β-ketophosphonate **7** (1 equiv.) in anhydrous THF was cooled at −78 °C before the slow addition of a solution of $Zn(BH_4)_2$ in THF (0.2 M, 4 equiv.) which had been recently prepared.[11] The reaction mixture was stirred at −78 °C for 6 h and quenched at room temperature 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. The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude mixture of the β-hydroxyphosphonates *anti*-**8** and *syn*-**9** was analyzed by ^{1}H and ^{31}P NMR and purified by flash chromatography.

11 A. Pelter, K. Smith and H. Brown, *Borane Reagents*, Academic Press, London, 1988, p. 414.