Pergamon

Tetrahedron Letters, Vol. 38, No. 20, pp. 3495-3498, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00705-3

Enantioselective Synthesis of α-Hydroxy Phosphonates via Oxidation with (Camphorsulfonyl)oxaziridines

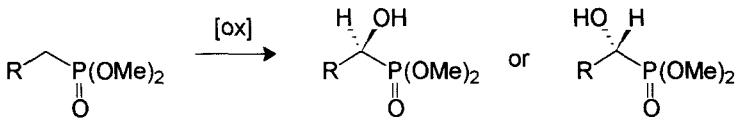
Diana M. Pogatchnik and David F. Wiemer*

Department of Chemistry
University of Iowa
Iowa City, Iowa 52245

Abstract: Reaction of phosphonate anions with enantiomerically pure (camphorsulfonyl)oxaziridines results in formation of nonracemic α-hydroxy phosphonates. This enantioselective hydroxylation methodology provides convenient access to optically active α-hydroxy phosphonates and their corresponding phosphonic acids. © 1997 Elsevier Science Ltd.

α-Hydroxy phosphonates and phosphonic acids demonstrate important biological activity through inhibition of a number of enzymes,[1-4] and the absolute configuration at the α-position of substituted phosphonic acids has been shown to influence their biological properties significantly.[5] Although synthesis of nonracemic α-amino phosphonic acids has been studied extensively,[6] the synthesis of nonracemic α-hydroxy phosphonates has only recently begun to receive more attention. Currently available routes to these compounds include addition of nonracemic phosphorus reagents to aldehydes[7] and use of chiral catalysts[8] to control stereochemistry when achiral reagents are used. Enantioselective reductions of α-keto phosphonates[9] and enzymatic resolution of racemic mixtures of α-hydroxy phosphonates also have been reported.[10] While these methods provide access to many nonracemic α-hydroxy phosphonates, synthesis of the chiral reagents and/or catalysts may be required and stereoselectivity is not always high. A method for stereoselective introduction of the hydroxyl group to prochiral phosphonates would be desirable (Eq. 1), particularly if it could be done with a readily available oxidant.

Eq. 1

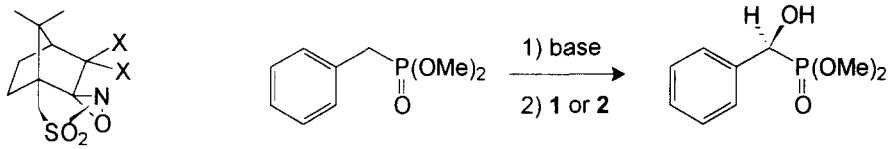


A well-known method for introduction of the hydroxyl group at an activated methylene position is based on oxidation using an aprotic oxidizing agent. Although not previously employed with phosphorus-containing compounds, chiral oxaziridines have been used extensively for stereoselective hydroxylation of carbonyl compounds.[11] Davis and coworkers have demonstrated that (+)- and (-)-(camphorsulfonyl)oxaziridines (**1**)[12]

are useful asymmetric reagents because they provide good stereocontrol, are easily prepared in large quantities[13] and are stable to storage.[14] A modified reagent, ((8,8-dichlorocamphoryl)sulfonyl)oxaziridine (**2**),[15] subsequently was reported to afford improved enantioselectivity for asymmetric oxidation of ketones, with ee's often exceeding 95%. Oxaziridine **2** is also a commercial product at this time,[14] or can be prepared easily in multi-gram quantities from (camphorsulfonyl)imine.[16]

To test the feasibility of obtaining enantioselective oxidation of phosphonate-stabilized anions with oxaziridines, phosphonate **3** was treated with base and then with oxaziridine **1** or **2** under conditions chosen to parallel those reported for oxidation of various carbonyl compounds (Table 1). The product **4** is a known compound, allowing configuration and ee to be established by comparison with literature values for the optical rotation.[8] In all cases, (+)-reagents **1** and **2** favored formation of the *S* product as would be expected if these oxidations proceed via transition states parallel to those advanced to explain the stereoselectivity observed with ketones.[11] However, the stereoselectivity was greatest when sodium counterions were employed with the halogenated reagent **2**.

Table 1. Oxidation of Dimethyl Benzylphosphonate.



(+)-**1** X = H
(+)-**2** X = Cl

3

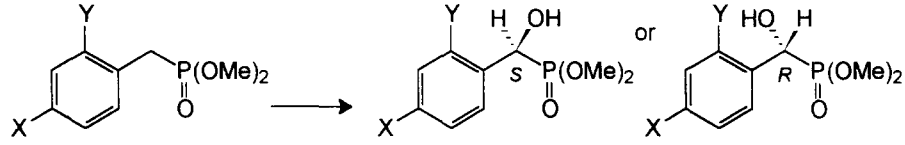
4

trial	base	reagent	°C	% yield	$[\alpha]_D$	% ee
1	n-BuLi	**1**	-65	51	-23.0	50
2	LDA	**1**	-75	75	-28.9	63
3	LDA/HMPA	**1**	-75 to 0 to -75	62	-13.0	29
4	NaHMDS	**1**	-95	70	-31.9	69
5	NaHMDS	**2**	-95	50	-43.6	95
6	NaHMDS	**2**	-78	51	-42.5	92
7	NaHMDS	**2**	-90 to -40 to -90	70	-43.0	93

To gauge the generality of this procedure, the most favorable conditions (Table 1, Entry 7) were used to prepare several known α-hydroxy phosphonates from the readily available parent phosphonates (Table 2).[17] Each of the five benzyl phosphonates undergoes hydroxylation with good stereocontrol, as measured by comparison of the optical rotation of the observed products with literature values.[8] Reasonable chemical

yields are observed throughout this short series, with relatively little variation noted as a function of electron withdrawing or donating substituents. Finally, dimethyl benzylphosphonate (**3**) also was treated with the (-)-enantiomer of reagent **2** (Entry 6), resulting in formation of the *R* α-hydroxy phosphonate in essentially the same yield and ee that was obtained with the (+)-oxaziridine enantiomer (Entry 1).

Table 2. Oxidation of Phosphonate Anions with Oxaziridine **2**.



entry			oxaziridine	% yield	$[\alpha]_D$	% ee	config.
1(**3**)	X = H	Y = H	(+)-**2**	70	-43.0	93[8a]	S
2	X = NO_2	Y = H	(+)-**2**	54	-54.2	80[8b]	S
3	X = Cl	Y = H	(+)-**2**	76	-51.4	87[8b]	S
4	X = CH_3O	Y = H	(+)-**2**	60	-40.0	81[8b]	S
5	X = H	Y = Cl	(+)-**2**	72	-68.1	93[8a]	S
6(**3**)	X = H	Y = H	(-)-**2**	65	+41.1	89[8a]	R

These studies demonstrate that stereocontrolled hydroxylation of phosphonate-stabilized anions can be achieved through reaction with nonracemic Davis reagents. While further work will be necessary to establish the complete range of this reaction, the chemical yields and high ee's observed thus far suggest that this strategy will compare favorably with other synthetic approaches to nonracemic α-hydroxy phosphonates.

ACKNOWLEDGMENTS

Financial support from the Leukemia Society of America and the National Institutes of Health (GM-44986) is gratefully acknowledged.

REFERENCES AND NOTES

1. a) Patella, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587. b) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591.
2. Sikorski, J. A.; Miller, M. J.; Braccolino, D. S.; Cleary, D. G.; Corey, S. D.; Font, J. L.; Gruys, K. J.; Han, C. Y.; Lin, K. C.; Pansegrau, P. D.; Ream, J. E.; Schnur, D.; Shah, A.; Walker, M. C. *Phosphorus, Sulfur, Silicon* **1993**, *76*, 115.

3. a) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625. b) Moore, M. L.; Dreyer, G. B. *Perspect. Drug Discovery Des.* **1993**, *1*, 85.

4. Pompliano, D. L.; Rands, E.; Schaber, M. D.; Mosser, S. D.; Anthony, N. J.; Gibbs, J. B. *Biochemistry* **1992**, *31*, 3800.

5. a) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wakisaka, K.; Haga, S.; Sugi, H.; Tanigawa, K.; Suzuki, Y.; Fukawa, K.; Irino, O.; Saita, O.; Yamabe, S. *Heterocycles* **1981**, *16*, 1205. b) Atherton, F. R.; Hall. M. J.; Hassall, C. H.; Lambert, R. W.; Lloyd, W. J.; Ringrose, P. S. *Antimicrob. Agents Chemother.* **1979**, *15*, 696.

6. a) Dhawan, B.; Redmore, D. *Phosphorus, Sulfur, Silicon* **1987**, *32*, 119. b) Denmark, S. E.; Chantani, N.; Pansare, S. V. *Tetrahedron* **1992**, *48*, 2191.

7. a) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *J. Org. Chem.* **1995**, *60*, 931.

8. a) Smaardijk, A. A.; Noorda, S.; van Bolhuis, F.; Wynberg, H. *Tetrahedron Lett.* **1985**, *26*, 493. b) Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 2926.

9. Gadja, T. *Tetrahedron: Asymmetry* **1994**, *5*, 1965.

10. a) Li, Y.-F.; Hammerschmidt, F. *Tetrahedron: Asymmetry* **1993**, *4*, 109. b) Drescher, M.; Hammerschmidt, F.; Kahlig, H. *Synthesis* **1995**, 1267.

11. Davis, F. A.; Chen, B.-C. *Chem. Rev.* **1992**, *92*, 919 and references cited within.

12. a) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679. b) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402.

13. Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.

14. Nonracemic (camphorsulfonyl)oxaziridines are commercially available both from Aldrich Chemical Company and from Fluka.

15. Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715.

16. a) Davis, F. A.; Weismiller, M. C.; Murphy, C. K.; Reddy, R. T.; Chen, B.-C. *J. Org. Chem.* **1992**, *57*, 7274. b) Mergelsberg, I.; Gala, D.; Scherer, D.; DiBenedetto, D.; Tanner, M. *Tetrahedron Lett.* **1992**, *33*, 161. c) Chen, B.-C.; Murphy, C. K.; Kumar, A.; Reddy, R. T.; Clark, C.; Zhou, P.; Lewis, B. M.; Gala, D.; Mergelsberg, I.; Scherer, D.; Buckley, J.; DiBenedetto, D.; Davis, F. A. *Org. Synth.* **1996**, *75*, 159.

17. Representative procedure: A 1 M solution of NaHMDS (1.5 eq) in THF was added to dimethyl benzylphosphonate (**3**, 0.75 mmol) in 12 mL THF at -90 °C. The resulting solution was allowed to warm to -40 °C for 20 min, then cooled back to -90 °C and finally added to oxaziridine **2** (2 eq in 12 mL THF). After 1-3 hrs at -90 °C, the reaction was quenched by addition of aqueous NH_4Cl. The reaction mixture was extracted with ethyl acetate, and the combined organic extracts were dried over $MgSO_4$, concentrated in vacuo, and the residue was purified by column chromatography to give the α-hydroxy phosphonate.

(*Received in USA* 17 *March* 1997; *accepted* 8 *April* 1997)