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ASYMMETRIC SYNTHESIS OF α-AMINO β-HYDROXY PHOSPHONIC ACIDS VIA BINAP–RUTHENIUM CATALYZED HYDROGENATION

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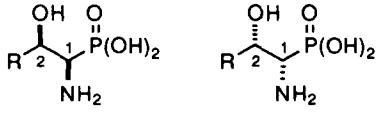
Abstract: BINAP–Ru catalyzed hydrogenation of configurationally labile α-amido β-keto phosphonic esters gives the (*R*,*R*)- or (*S*,*S*)-α-amido β-hydroxy phosphonic esters in a highly enantio- and diastereoselective manner.

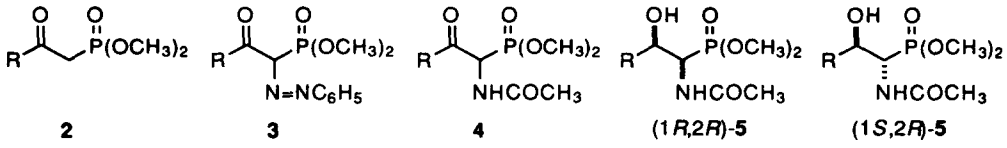
Phosphonate analogs of α-amino acids have received considerable attention in the past decade in bioorganic and medicinal chemistry because of their unique biological activities as well as their potential uses as peptide mimics and haptens of catalytic antibodies.[1] Although a variety of approaches to optically active phosphonates have been developed,[2] few reports have been made on the stereoselective synthesis of threonine-type compounds with two consecutive stereogenic centers.[3] We here disclose a second-order asymmetric synthesis of α-amino β-hydroxy phosphonic acids of type **1** based on the BINAP–Ru(II) catalyzed hydrogenation[4] of racemic α-acetamido β-keto phosphonic esters via dynamic kinetic resolution.[5]



(1*R*,2*R*)-**1** (1*S*,2*S*)-**1**

The substrate (±)-**4a** was prepared in 76% overall yield in two steps from dimethyl 2-oxopropylphosphonate (**2a**). First, **2a** (0.10 mol) was treated with a mixture of benzenediazonium chloride [prepared from aniline (0.11 mol) and sodium nitrite (0.11 mol) in 5.3 M HCl at 0 °C for 20 min] and sodium acetate (0.67 mol) in a 2:5 water–methanol mixture at 0 °C for 5 min, at 20 °C for 30 min, and at 40 °C for 30 min to form the α-benzenediazo phosphonate **3a**. The crude product was reductively acetylated to **4a** by treatment with zinc powder in a 5:2 acetic acid–acetic anhydride mixture at room temperature for 2 h. Pure **4a**, mp 85 °C, was obtained by column chromatography on silica gel using a 19:1 ethyl acetate–ethanol eluent followed by recrystallization from a 1:10 ethanol–ether mixture.[6] Similarly, (±)-**4b** was synthesized in 54% yield, mp 98–99 °C.[6] Hydrogenation of (±)-**4a** (1.0 g) was carried out in a 0.91 M methanol solution containing 0.17 mol % of $RuCl_2$[(*R*)-binap](dmf)$_n$[7] under 4 atm of hydrogen gas at 25 °C for 65 h, affording quantitatively (1*R*,2*R*)-**5a** in >98% ee and (1*S*,2*R*)-**5a** in >90% ee in a 97:3 ratio.[8,9] This mixture was treated with 6 M HCl at 95 °C for 12 h to give, after recrystallization from a 1:1:5 water–ethanol–ether mixture, (1*R*,2*R*)-phosphothreonine [(1*R*,2*R*)-**1** (R = CH_3)] in 92% yield, mp 216 °C; $[\alpha]_D^{25}$ –9.38 (*c* 1.06, H_2O).[3c] The 2-phenyl substrate (±)-**4b** was hydrogenated under similar conditions ([**4b**] = 0.89 M in methanol, 1 mol % $RuCl_2$[(*R*)-binap](dmf)$_n$, 4 atm of H_2, 45 °C, 120 h) to give (1*R*,2*R*)-**5b** in 95% ee[8,9] and in a 98:2 syn:anti selectivity.[10] The absolute configurations of the products **5** were ascertained using Mosher's method.[11] In the spectra of the corresponding

MTPA esters, the diamagnetic shielding effect of the benzene ring causes the ^1H signal of C(3)H_3 in (1*R*,2*R*)-**5a** and the ^{31}P signal from (1*S*,2*S*)-**5a** to appear further upfield for the (*R*)-MTPA ester relative to those of the *S* ester.[11] This was authenticated by using (1*R*,2*R*)-**5a** of known configuration.

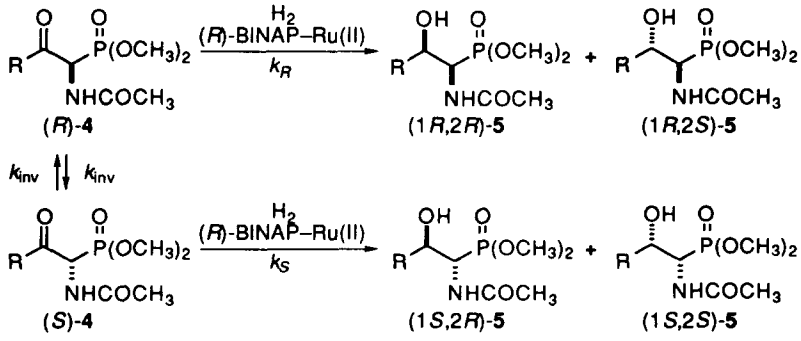


2 **3** **4** (1*R*,2*R*)-**5** (1*S*,2*R*)-**5**

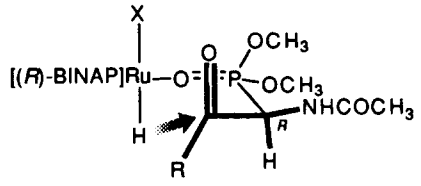
a: R = CH_3 **b**: R = C_6H_5

The predominant formation of (1*R*,2*R*)-**5** among four possible stereoisomers is ascribed to the excellent combination of stereochemical and kinetic factors. The sense of asymmetric induction at the C(2) position is consistent with that observed in the BINAP–Ru catalyzed hydrogenation of achiral 2-keto phosphonates.[12] Furthermore, the reaction proceeds in a highly syn-selective manner. In the presence of the (*R*)-BINAP catalyst, the *R* substrate is more reactive than the *S* enantiomer ($k_R > k_S$), while the stereoinversion of the slow-reacting (*S*)-**4** occurs more efficiently than hydrogenation ($k_{inv} > k_S$). The overall stereochemical outcome of the second-order asymmetric reaction is explained by the Felkin-Anh working model.[13] The structure **6** (X = anionic or neutral ligand)[14] presents the most stable transition geometry leading to (1*R*,2*R*)-**5**, among the four possibilities. The unique chiral environment of the (*R*)-BINAP–Ru template[15] induces stereoselective hydride transfer from Ru to the *si*-face of the carbonyl carbon anti to the electronegative acetamide group at C(1). The catalyst/substrate combined stereochemical factors facilitate the hydrogenation of (*R*)-**4** resulting in a 1*R*,2*R* configuration. Quantitative analysis[5] of experiments using (±)-**4a** and enantiomerically pure (*R*)-BINAP–Ru complex or the racemic catalyst indicates that, when (*R*)-**4a** and (*S*)-**4a** are present in equal amounts ($t = 0$), the four possible stereoisomers, (1*R*,2*R*)-**5a**, (1*S*,2*S*)-**5a**, (1*S*,2*R*)-**5a**, and (1*R*,2*S*)-**5a**, are formed in a 97.4:0.6:1.9:0.1 ratio. This inherent stereoselectivity is close to the observed ratio, >96:1:3:<1. The k_R/k_S and k_{inv}/k_S values attained in the given reaction system are estimated to be 39 and 31, respectively.[16]

Thus the combination of the configurational lability of the α-substituted β-keto phosphonate, the electronegative nature of the α-amido group, and the chiral discriminating properties of (*R*)-BINAP as well as the appropriate reaction conditions leads to the formation of (*R*,*R*)-α-amido β-hydroxy phosphonate of high enantiomeric and high diastereomeric purity in excellent yield.



a: R = CH_3 **b**: R = C_6H_5



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References and Notes

1. Hirschmann, R.; Smith, A. B., III; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234. Kukhar', V. P.; Svistunova, N. Y.; Solodenko, V. A.; Soloshonok, V. A. *Russ. Chem. Rev.* **1993**, *62*, 261. Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. Dhawan, B.; Redmore, D. *Phosphorus and Sulfur* **1987**, *32*, 119.
2. Yager, K. M.; Taylor, C. M.; Smith, A. B., III *J. Am. Chem. Soc.* **1994**, *116*, 9377. Rath, N. P.; Spilling, C. D. *Tetrahedron Lett.* **1994**, *35*, 227. Li, Y.-F.; Hammerschmidt, F. *Tetrahedron: Asymmetry* **1993**, *4*, 109. Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1783. Groth, U.; Richter, L.; Schöllkopf, U. *Tetrahedron* **1992**, *48*, 117. Laschat, S.; Kunz, H. *Synthesis* **1992**, 90. Hanessian, S.; Bennani, Y. L.; Delorme, D. *Tetrahedron Lett.* **1990**, *45*, 6461. Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465. Schöllkopf, U.; Schütze, R. *Liebigs Ann. Chem.* **1987**, 45. Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730. Schöllkopf, U.; Hoppe, I.; Thiele, A. *Liebigs Ann. Chem.* **1985**, 555. Wynberg, H.; Smaardijk, A. A. *Tetrahedron Lett.* **1983**, *24*, 5899.
3. (a) Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 7930. (b) Bongini, A.; Camerini, R.; Hofman, S.; Panunzio, M. *Tetrahedron Lett.* **1994**, *35*, 8045. (c) Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401. (d) Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247.
4. BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl. Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth.* **1989**, *67*, 20.
5. Review: Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. For the dynamic kinetic resolution of the racemic α-substituted β-keto esters, see: Kitamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron: Asymmetry* **1990**, *1*, 1. Noyori, R.; Ikeda,T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134.
6. **4a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (d, 3, J = 0.8 Hz, $CHCOCH_3$), 2.45 (s, 3, $NHCOCH_3$), 3.77 (d, 3, J = 11.6 Hz, OCH_3), 3.85 (d, 3, J = 11.2 Hz, OCH_3), 5.33 (dd, 1, J = 8.4 and 23.6 Hz, CH), 6.41 (brs, 1, NH). Anal. Calcd for $C_7H_{14}NO_5P$: C, 37.67; H, 6.32; N, 6.28. Found: C, 37.69; H, 6.44; N 6.16. **4b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3, $COCH_3$), 3.70 (d, 3, J = 11.2 Hz, OCH_3), 3.74 (d, 3, J = 11.2 Hz, OCH_3), 6.25 (dd, 1, J = 8.8 and 21.2 Hz, CH), 6.77 (d, 1, J = 8.4 Hz, NH), 7.48–7.66 and 8.05–8.09 (5, aromatic). Anal. Calcd for $C_{12}H_{17}NO_5P$: C, 50.35; H, 5.99; N, 4.89. Found: C, 50.56; H, 5.73; N 4.78. The reductive acetylation of **3b** was carried out at 0 °C.
7. Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1.
8. The ee's were determined by ^{31}P NMR analysis of the (*S*)-MTPA esters of **5a** and (*R*)-MTPA esters of **5b**. (1*S*,2*S*)-**5a**, δ 23.22; (1*R*,2*R*)-**5a**, δ 23.15; (1*R*,2*S*)-**5a**, δ 22.96; (1*S*,2*R*)-**5a**, 22.89 in a 3:7 $CDCl_3$–CCl_4

mixture. (1*R*,2*R*)-**5b**, δ 22.55; (1*S*,2*S*)-**5b**, δ 22.52; (1*S*,2*R*)-**5b**, δ 22.71; (1*R*,2*S*)-**5b**, 22.62 in $CDCl_3$. HPLC analysis using the silica-gel based stationary phase could not be used because of the instability of the MTPA esters.

9. (1*R*,2*R*)-**5a**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (dd, 3, J = 2.0 and 6.4 Hz, CH(OH)CH_3), 2.08 (d, 3, J = 1.6 Hz, $COCH_3$), 3.41 (brs, 1, OH), 3.77 (d, 3, J = 10.8 Hz, OCH_3), 3.81 (d, 3, J = 10.8 Hz, OCH_3), 4.35 (ddq, 1, J = 1.6, 5.2, and 6.4 Hz, C*H*OH), 4.41 (ddd, 1, J = 1.6, 10.0, and 17.2 Hz, CHPO), 6.53 (brs, 1, NH). ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.7. mp 113 °C. $[\alpha]_D^{25}$ –37.6 (*c* 1.02, CH_3OH). Anal. Calcd for $C_7H_{16}NO_5P$: C, 37.34; H, 7.16; N, 6.22. Found: C, 37.23; H, 7.18; N 6.16. (1*S*,2*R*)-**5a**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, 3, J = 6.8 Hz, CH(OH)CH_3), 2.06 (d, 3, J = 0.8 Hz $COCH_3$), 1.90 (brs, 1, OH), 3.77 (d, 3, J = 10.4 Hz, OCH_3), 3.80 (d, 3, J = 10.8 Hz, OCH_3), 4.02 (ddq, 1, J = 4.8, 6.8, and 21.6 Hz, C*H*OH), 4.49 (ddd, 1, J = 4.8, 10.0, and 17.2 Hz, CHPO), 6.74 (brs, 1, NH). ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.4. (1*R*,2*R*)-**5b**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.87 (d, 3, J = 1.6 Hz, $COCH_3$), 3.80 (d, 3, J = 10.4 Hz, OCH_3), 3.86 (d, 3, J = 10.8 Hz, OCH_3), 4.05 (d, 1, J = 4.0 Hz, OH), 4.75 (ddd, 1, J = 2.0, 10.0, and 16.0 Hz, CHPO), 5.31 (dd, 1, J = 2.0 and 4.4 Hz, C*H*OH), 6.49 (d, 1, J = 10.0 Hz, NH), 7.25–7.37 (5, aromatic). ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.3. $[\alpha]_D^{25}$ –46.4 (*c* 1.15, CH_3OH). (1*S*,2*R*)-**5b**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.5 (brs, 1, OH), 1.97 (d, 3, J = 1.6 Hz, $COCH_3$), 3.41 (d, 3, J = 10.8 Hz, OCH_3), 3.66 (d, 3, J = 10.8 Hz, OCH_3), 4.90 (ddd, 1, J = 4.8, 9.6, and 16.4 Hz, CHPO), 6.56 (d, 1, J = 9.6 Hz, NH), 5.04 (dd, 1, J = 4.8 and 22.0 Hz, C*H*OH), 7.25–7.43 (5, aromatic). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.8.
10. The relative configuration of **5b** was assigned by comparison of the ^1H NMR coupling constants of stereo-defined **5a**. $J_{C(1)H-C(2)H}$, $J_{C(1)H-P}$, and $J_{C(2)H-P}$ values are as follows. *syn*-**5a**: 1.6, 17.2, and 5.2 Hz. *anti*-**5a**: 4.8, 17.2, and 21.6 Hz. *syn*-**5b**: 2.0, 16.0, and 4.4 Hz. *anti*-**5b**: 4.8, 16.4, and 22.0 Hz.
11. Ohtani, I., Kusumi, T.; Kashmam, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092. Typical Δδ ($\delta_S - \delta_R$) values in Hz obtained for (*R*)- and (*S*)-MTPA esters of **5** are as follows. (1*R*,2*R*)-**5a**: C(3)H_3, +0.09; C(1)H, –0.10; $PO(OCH_3)_2$, –0.06 and –0.11; $COCH_3$, –0.03; P, –0.069. (1*S*,2*R*)-**5a**: C(1)H, –0.087; P, –0.076. (1*R*,2*R*)-**5b**: C(1)H, –0.04; $PO(OCH_3)_2$, –0.02 and –0.06; $COCH_3$, –0.07; P, –0.028. (1*S*,2*R*)-**5b**: C(1)H, –0.048; P, –0.095. See also, Hammerschmidt, F.; Li, Y.-F. *Tetrahedron* **1994**, *50*, 10253.
12. Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931.
13. Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D. ; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Yi; Loncharich, R. J. *Science* **1986**, *231*, 1108. Anh, N. T. *Topics in Current Chemistry*, **1980**, *88*, 145.
14. The carbonyl oxygen atom may interact with the Ru atom or methanol.
15. Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994, Chapter 2. Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.
16. Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144. Kitamura, M.; Tokunaga, M.; Noyori, R. *Tetrahedron* **1993**, *49*, 1853. The calculation was made based on the assumption that the ratio of (1*R*,2*R*)-**5a**:(1*S*,2*S*)-**5a**:(1*S*,2*R*)-**5a**:(1*R*,2*S*)-**5a** is 96:1:3:0.1. The minor stereoisomer (1*R*,2*S*)-**5a** could not be detected by the ^{31}P NMR analysis of the MTPA esters of the hydrogenation product. The limit of the detection is at least 1%, as confirmed by using the (*R*)-MTPA esters of authentic (*R*)-dimethyl 2-hydroxypropylphosphonate in 98% ee [HPLC analysis of the *N*-[(*S*)-1-(1-naphthyl)ethyl] carbamates (column, Develosil ODS-5; eluent, 3:2 water–acetonitrile mixture; flow rate, 1 mL/min; detection, 254-nm light; t_R of *R,S* isomer, 14.3 min; t_R of *S,S* isomer, 15.3 min)].

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