Asymmetric Hydrogenation of β-Keto Phosphonates: A Practical Way to Fosfomycin

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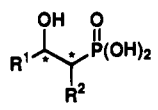
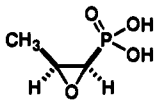
Chiral β-hydroxy phosphonic acids of type **1** have received significant attention recently because of their unique physiological activities as well as their ability to mimic the corresponding hydroxy carboxylic acids or amino acids.[1,2] They are intermediates in the syntheses of potentially significant peptide analogues, haptens of catalytic antibodies, and phosphonic acid-based antibiotics.[3] This paper discloses a general,



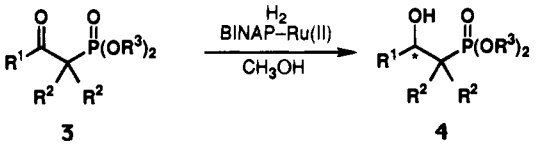
1, R^1 = alkyl, aryl; R^2 = H, NH_2, OH, halogen



2, fosfomycin

catalytic asymmetric synthesis of β-hydroxy phosphonic acids and its application to the practical synthesis of fosfomycin (**2**),[4] a clinically used antibiotic which was originally isolated from the fermentation broth of *Streptomyces fradiae*.[5] The development of a practical synthesis of **2** required (1) efficient synthesis of the β-keto phosphonic esters, (2) easy synthesis of the chiral catalyst, (3) enantioselective hydrogenation of the β-keto phosphonates, and (4) development of suitable conditions for efficient dynamic kinetic resolution via hydrogenation. All these requirements have been satisfied.

Synthesis of the β-keto phosphonates **3** by the existing methods was not very practical.[6] We found that the modified Arbuzov reaction using a chloromethyl ketone, potassium iodide, and trimethyl phosphite in an acetone−acetonitrile mixture gave the desired phosphonates **3** in a high yield and at a low cost.[7,8] We also found that the BINAP−Ru(II) complex[9] formed in situ by simple heating of a mixture of $[RuCl_2(benzene)]_2$ and (*R*)- or (*S*)-BINAP in DMF[10] acted as an excellent catalyst for the enantioselective hydrogenation of prochiral β-keto phosphonates **3**, leading to β-hydroxy phosphonates **4** with high enantiomeric excess (ee) in high yield. The reaction took place smoothly



3 **4**

a: $R^1 = R^3 = CH_3$; R^2 = H
b: $R^1 = CH_3$; R^2 = H; $R^3 = C_2H_5$
c: $R^1 = R^2 = R^3 = CH_3$
d: $R^1 = n\text{-}C_5H_{11}$; R^2 = H; $R^3 = CH_3$
e: $R^1 = (CH_3)_2CH$; R^2 = H; $R^3 = CH_3$
f: $R^1 = C_6H_5$; R^2 = H; $R^3 = CH_3$

with 0.5−50 g of **3** in methanol under 4 atm of hydrogen gas. Enantioselection was not affected by hydrogen pressure ranging from 4 to 100 atm, as shown in Table 1. The absolute configurations of non-phenylated **4** were determined by NMR analysis of the Mosher esters. Owing to the diamagnetic shielding effect of the benzene ring, the R^1 proton signals in (*R*)-**4**[11] and the ^{31}P signal in (*S*)-**4**[12] appear upfield in the (*R*)-MTPA ester relative to the (*S*)-MTPA ester, as substantiated with stereoauthentic **4a**. The sense of asymmetric induction is consistent with that observed in the BINAP−Ru-catalyzed hydrogenation of other functionalized ketones.[13,14] The reaction of the α,α-dimethylated β-keto phosphonate **3c** proceeded equally well, indicating that the hydrogenation is occurring in the keto rather than the enol form.

The racemic α-bromo β-keto phosphonate, (±)-**5**, a precursor for the synthesis of **2**, was most conveniently prepared by the reaction of dimethyl 2-oxopropylphosphonate (**3a**) with 8.8 M hydrogen bromide and 30% hydrogen peroxide in THF at 25 °C.[15] Hydrogenation of a racemic α-substituted β-keto phosphonate usually gives a mixture of four possible stereoisomers. The lability of the α-stereogenic center, however, allows for the stereoselective synthesis of a single isomer via dynamic kinetic resolution utilizing in situ stereoinversion.[16] Here, optimized reaction conditions are crucial for maximizing the

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(6) The standard alkyllithium-aided condensation of dialkyl methylphosphonates and carboxylic esters is not economical for a large-scale preparation. Dimethyl 2-oxopropylphosphonate costs $16.25/g and $160.35/25 g (Aldrich, 1994−1995 catalog prices).

(7) Stirring of a mixture of chloroacetone (99.9 g), KI (179.2 g), and $P(OCH_3)_3$ (134.7 g) in acetone (300 mL) and acetonitrile (250 mL) for 6 h at 20 °C and for 4 h at 50 °C in the air followed by simple filtration and distillation (81−85 °C/0.02−0.05 mmHg) gave **3a** (127.5 g, 71% yield) contaminated with <1% of dimethyl 2-propenyl phosphate. Use of $P(OC_2H_5)_3$ afforded **3b** in 83% yield.

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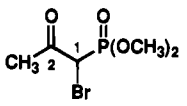
Table 1. BINAP–Ru(II)-Catalyzed Asymmetric Hydrogenation of β-Keto Phosphonic Esters[a]

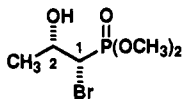
substrate	BINAP config in catalyst	conditions: H_2, atm	conditions: temp, °C	conditions: time, h	product: no.[b]	product: yield,[c] %	product: ee,[d] %
3a[e]	*R*	4	25	72	(*R*)-**4a**	99	98
3a	*R*	4	80	37	(*R*)-**4a**	97	97
3a	*R*	100	25	38	(*R*)-**4a**	96	98
3b	*R*	4	50	50	(*R*)-**4b**	98	96
3c	*R*	4	50	60	(*R*)-**4c**	97	98
3d	*S*	4	50	80	(*S*)-**4d**	98	94
3e	*S*	4	80	16	(*S*)-**4e**	96	96
3f	*R*	4	60	160	(*R*)-**4f**[f]	96	95
5[g]	S	4	25	100	(1*R*,2*S*)-**6**[h]	95[i]	98

[a] Reaction was carried out in methanol containing $RuCl_2(binap)(dmf)_n$ (1.6–3.6 mM) and the substrate (0.4–1.3 g, 0.6–1.9 M). [b] Absolute configuration was determined by the improved Mosher method (ref 11). For details, see supplementary material. [c] Isolated yield. [d] HPLC analysis of the product or the corresponding *N*-[(*S*)-(1-naphthyl)ethyl] carbamates. [e] A 50-g scale reaction; [substrate] = 3.3 M, [catalyst] = 2.7 mM. [f] Determined by comparison of the retention time of HPLC sample prepared from (*R*)-styrene oxide and dimethyl phosphite (Azuhata, T.; Okamoto, Y. *Synthesis* **1983**, 916). [g] A 20-g scale reaction; [substrate] = 338 mM, [catalyst] = 0.18 mM. [h] The minor isomer was (1*S*,2*S*)-**6** in 94% ee. [i] An 85:15 mixture of **6** and **4a**.

efficiency of the second-order stereoselective reaction, particularly, to secure a high relative rate of the stereoinversion to hydrogenation. Experimentation coupled with computer-aided quantitative analysis of the stereochemical and kinetic parameters[17] was used to determine suitable conditions for hydrogenation in methanol: [substrate **5**] = 338 mM; [(*S*)-BINAP–Ru catalyst] = 0.18 mM; H_2 pressure, 4 atm; reaction temperature, 25 °C; reaction time, 100 h. The (*S*)-BINAP–Ru-catalyzed



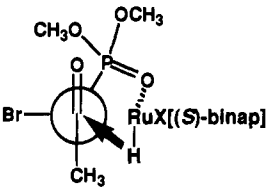
(±)-**5**



(1*R*,2*S*)-**6**

reaction afforded the desired stereoisomer, (1*R*,2*S*)-**6**, in 98% ee and 84% yield. There were no operational problems with the 20-g-scale reaction.[18] The ^1H NMR spectrum of the hydrogenation product was consistent with the reported values.[4] The chiral *cis*-epoxide **2** as the Na salt can be obtained by acid-catalyzed hydrolysis of this hydrogenation product, followed by treatment with sodium hydroxide.[19]

The stereochemical efficiency of the second-order stereoselective reaction relies on the asymmetric induction due to the catalyst and substrate as well as the kinetic parameters.[17] The phosphonate function in **5** clearly directs the asymmetric hydrogenation through interaction with the Ru center of the catalyst. The absolute configuration of the hydroxyl-bearing C(2) stereogenic center is determined by the intermolecular asymmetric induction from the BINAP–Ru catalyst, whereas the 1,2-threo relative configuration[20] results from intramolecular asymmetric induction based on the bromine-containing C(1) stereogenic carbon. The overall stereochemical outcome is reasonably explained by the Felkin–Anh working model.[21] Thus structure **7** (X = anionic or neutral ligand)[22] illustrates the most



7, X = halogen, H_2, solvent, etc.

stable transition geometry leading to (1*R*,2*S*)-**6**, among the four possibilities, in which the hydride approaches the *re*-face of the carbonyl carbon from the direction anti to the electronegative bromine atom. The threo/erythro ratio,[20] [(1*R*,2*S*)-**6** + (1*S*,2*R*)-**6**]:[(1*R*,2*R*)-**6** + (1*S*,2*S*)-**6**] = 90:10, obtained with the enantiomerically pure (*S*)-BINAP–Ru catalyst is close to the 93:7 attained by mutual kinetic resolution with the racemic BINAP–Ru catalyst, indicating that near optimum conditions had been achieved. Quantitative treatment of the selectivity profile[17] indicated that the inherent 1*R*,2*S*:1*R*,2*R*:1*S*,2*S*:1*S*,2*R* distribution, obtained when the *R* and *S* substrates are present in equal amounts (t = 0), is 92.6:0.32:6.68:0.43. Thus the intrinsic stereoselectivity for the most abundant stereoisomer (1*R*,2*S*)-**6**, 92.6%, is well maintained until the completion of the reaction, 89%. The *R* enantiomer of **5** is hydrogenated, giving mainly (1*R*,2*S*)-**6**, 13 times faster than the *S* isomer. However, the slow-reacting (*S*)-**5** also gives the same configuration of the product, because it undergoes stereoinversion 11.5 times faster than hydrogenation under such conditions. When the reaction was conducted with a higher substrate concentration or with an increased amount of the catalyst, the threo/erythro diastereoselectivity was considerably decreased, as expected.

Supplementary Material Available: Descriptions of the procedure for the catalytic hydrogenation, determination of the enantiomeric excesses and absolute configurations of the products, and synthesis of (±)-**5** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(18) The practical procedure uses (±)-**5** contaminated with some **3a** and the dibromo compound, which affords a similar stereoselectivity to the pure substrate. Thus the degassed methanol solution (235 mL) containing (±)-**5** (20.35 g, 91% purity) and $RuCl_2[(S)\text{-binap}](dmf)_n$ (35 mg) was stirred under 4 atm of H_2 at 25 °C for 100 h in a 420-mL glass autoclave.[10] Evaporation of the solvent and distillation (110–120 °C/0.1 mmHg) yielded 18.92 g of the product consisting of (1*R*,2*S*)-**6** in 98% ee (84% yield), (1*S*,2*S*)-**6** in 94% ee (9.3% yield), and (*S*)-**4a** in 98% ee in a 76.5:8.5:15 ratio.

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(22) The carbonyl oxygen atom may interact with the Ru atom or methanol.