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Generation and Fate of Regioisomeric Side-Chain Impurities in the Preparation of Fosinopril Sodium

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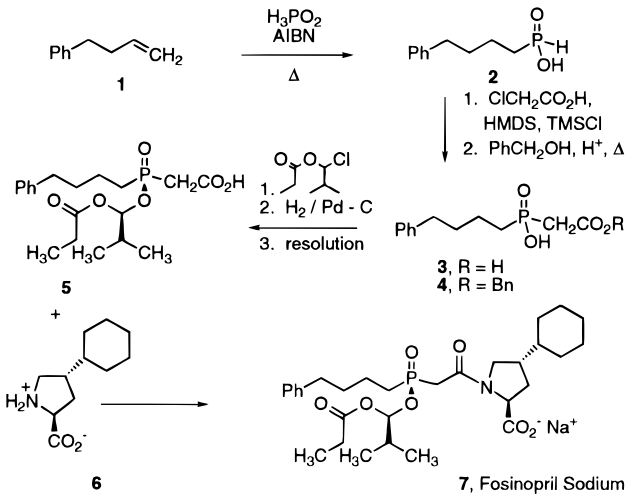
Abstract:

A regioisomeric impurity is routinely formed during preparation of the first intermediate of the fosinopril sodium side chain. This first step, the radical-initiated condensation of 4-phenyl-1-butene (1) and aqueous hypophosphorous acid, provides low levels of the phosphinic acid (8) resulting from carbon−phosphorus bond formation to the internal olefin carbon. This impurity was isolated by preparative chromatography, and its structure was proven by independent synthesis. Subsequent reactions of 8 in the two following steps produce the corresponding regioisomeric impurities. Pure samples of these impurities were prepared for HPLC analysis to determine potential impact on the quality of intermediates downstream. The initial regioisomer averages 2 area % in manufacturing batches, and the levels of regioisomeric impurities diminish sharply with sequential conversion to further side-chain intermediates. After two steps, the levels of the regioisomeric impurities have been less than 0.08 area % in production batches; therefore, no significant amount of side-chain regioisomeric impurities (i.e., <0.1%) is expected to be found in production batches of fosinopril sodium side chain.

Introduction. Detailed HPLC investigations into the quality of **2**, the first side-chain intermediate in the preparation of fosinopril sodium[1,2] (Scheme 1), revealed the presence of low levels of an impurity eluting just after **2**. This impurity was isolated and identified as compound **8**, the regioisomer of **2**, from addition of hypophosphorous acid to the internal olefinic carbon of **1** (Scheme 2). Impurity **8** was expected to be converted to the analogous regioisomeric impurities **9**, **10**, and **12**, with the possibility of generating **12** as four enantiomeric pairs. Such contamination could cause processing and purification to be difficult in these and downstream steps. Although it was anticipated that these early intermediates would not be carried along to isolated fosinopril sodium, it was necessary to assess the impact of **8** to ensure that no isomeric impurities would be found in fosinopril sodium at the level of 0.1% or more.[3]

Scheme 1. **Preparation of fosinopril sodium**



Identification of 8 in Batches of 2. Condensation of 4-phenyl-1-butene (**1**) and aqueous hypophosphorous acid in methanol in the presence of the radical initiator AIBN [2,2′-azobis(2-methylpropionitrile)] produced **2**, the first side-chain intermediate in the preparation of fosinopril sodium. After the methanol was removed under vacuum, **2** was purified by extraction into methylene chloride. The rich methylene chloride extract was dried azeotropically and concentrated, to afford **2** as a viscous yellow fluid, which often crystallized with time, to afford a solid with a melting point as high as 38 °C. Since this low-melting solid was inconvenient for analytical purposes, the dicyclohexylamine salt of **2** had been prepared as a reference standard (mp 98−100 °C, from EtOAc/heptane). Very little purification in the routine isolation of **2** was expected, as **2** was carried on as a residue into the preparation of **3**.

The quality of **2** was suitably high, as demonstrated by acceptable analyses and subsequent conversion to **3**.[2a] Initial HPLC investigations did not imply that any regioisomeric impurity was present in preparations of **2**; however, a late-eluting shoulder on the main peak of a manufacturing batch of **2** prompted inquiry into the presence of an impurity structurally similar to **2**. The dicyclohexylamine salt was prepared from a sample of **2**, enriching the impurity in the

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(1) Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; DeForrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rovnyak, G.; Schwartz, J.; Natarajan, S.; Godfrey, J. D.; Ryono, D. E.; Neubeck, R.; Atwal, K. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1988**, *31*, 1148.

(2) For the preparation of other fosinopril sodium intermediates, cf.: (a) Anderson, N. G.; Ciaramella, B. M.; Feldman, A. F.; Lust, D. A.; Moniot, J. L.; Moran, L.; Polomski, R. E.; Wang, S. S. Y. *Org. Process Res. Dev.* **1997**, *1*, 211. (b) Anderson, N. G.; Lust, D. A.; Colapret, K. A.; Simpson, J. H.; Malley, M. F.; Gougoutas, J. Z. *J. Org. Chem.* **1996**, *61*, 7955. (c) Kronenthal, D. R.; Mueller, R. H.; Kuester, P. L.; Kissick, T. P.; Johnson, E. J. *Tetrahedron Lett.* **1990**, *31*, 1241.

(3) These guidelines were later formalized as cGMP mandates by the International Conference on Harmonization; see: *Fed. Regis.* **1996**, *61* (3) (Jan 4), 372.

Scheme 2. **Generation of side-chain intermediates and regioisomeric impurities**

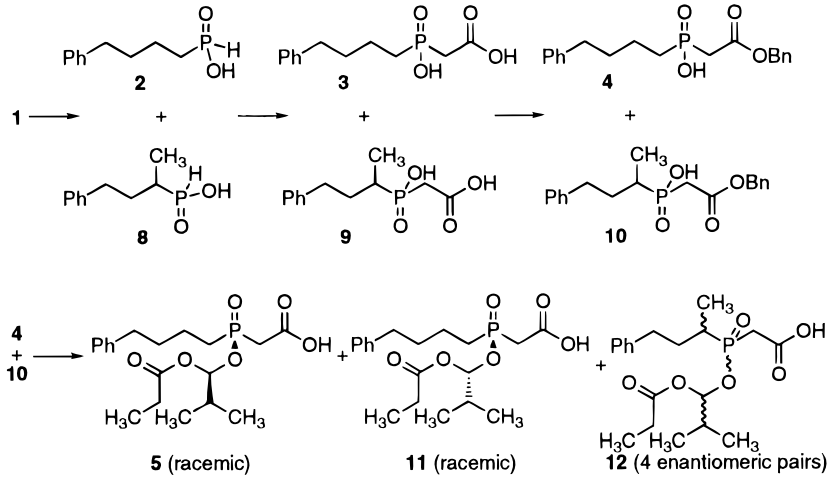


Table 1. **Regioisomer levels in production batches of fosinopril sodium side-chain intermediates**

compd prepared	regioisomer generated	concn of regioisomer		no. of batches
		average	range	
2	**8**	2.0 area %	0.4−2.8 area %	30
3[a]	**9**	<0.1 area %	0.15, 0.32 area %; 3 batches nd[b]	5
4	**10**	nd[b]	1 batch at <0.08 area %; 10 batches nd[b]	11

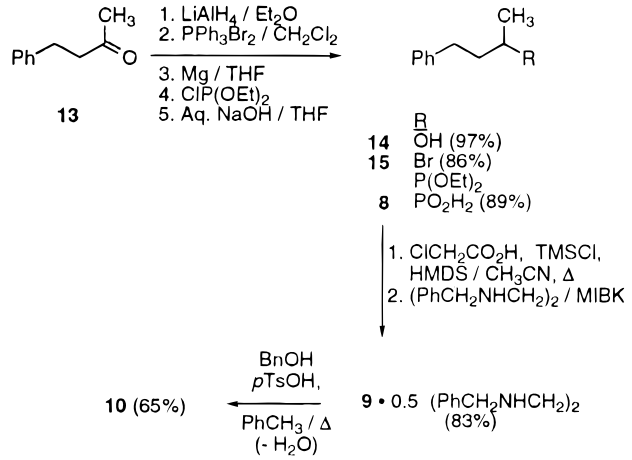
[a] Process E. [b] Not detected; limit of detection 0.02 area %.

mother liquor to 10%. Isolation and analyses indicated that this impurity was the regioisomer **8**: the doublet of doublets centered at 1.15 ppm (J = 20.0, 7.1 Hz) is consistent with the resonance for the methyl group attached to a methine carbon, which is adjacent to the phosphorus atom. Mass spectral data (chemical ionization and both positive and negative FAB) showed the molecular weight to be 198 daltons. The structure of **8** as the regioisomer of **2** was confirmed by synthesis (see below).

Thirty production batches of **2** were assayed at 0.4−2.8 area % of **8**, with 24 of them at 1.6−2.4 area % (see Table 1). Owing to the fact that **2** was isolated as a residue, regioisomer **8** was expected to be carried along in batches of **2** at the level with which it had been formed. This placed the burden of removing regioisomers upon the crystallization of subsequent intermediates.

Preparation of Side-Chain Regioisomers. In order to examine the burden of the regioisomeric impurities, standards of these regioisomers were prepared expeditiously in the laboratory. Impurity **8** was synthesized unambiguously from 4-phenyl-2-butanone (**13**, Scheme 3). Reduction of **13** with lithium aluminum hydride[4] afforded the alcohol **14**, which was readily converted to the bromide **15** by treatment with Ph_3PBr_2.[5] This bromination was superior to treatment of **14** with PBr_3 and pyridine in Et_2O, which gave a mixture of

Scheme 3. **Preparation of regioisomeric impurities 8, 9, and 10**



products, or treatment of **14** with LiBr/TMSCl in acetonitrile, which gave no reaction. Grignard formation from **15**, reaction with diethyl chlorophosphite,[6] and hydrolysis produced **8**. Modified Arbuzov reaction of **8** with chloroacetic acid[2a] produced **9**. Regioisomer **9** was isolated as the dibenzylethylenediamine salt (2:1), as **9** could not be crystallized from methyl isobutyl ketone (MIBK, see below). Treatment of **9** with benzyl alcohol and catalytic *p*-TsOH with azeotropic removal of water afforded the benzyl ester **10**, analogously to the preparation of **4**. Elaboration to the O-alkylated phosphinic acid **12** was not examined, as preparation of these compounds did not prove to be necessary (see below).

The Fate of Regioisomers in Preparation of 3 and 4. With the regioisomers **9** and **10** available, HPLC systems were developed to ensure that these impurities could be detected and quantitated in streams of **3** and **4**, respectively. In these systems, the minimum quantifiable levels (MQL) were 0.08 area % and the limits of detection (LD) were 0.02 area %.

Reduction of the regioisomeric burden could first be effected with the isolation of the Arbuzov product **3**, which

(4) Reduction with $NaBH_4$ or other agents was not examined.
(5) Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964. See also: Schmidt, S. P.; Brooks, D. W. *Tetrahedron Lett.* **1987**, *28*, 767.
(6) See: Engel, R. *The Synthesis of Carbon-Phosphorus Bonds*; CRC Press, Inc.: Boca Raton, FL, 1988; 169; Karanewsky, D. S.; Petrillo, E. W., Jr. U.S. Patent 4,432,972, 1984. Karanewsky, D. S.; Petrillo, E. W., Jr. U.S. Patent 4,432,971, 1984. Rovynak, G. C. U.S. Patent 4,371,526, 1983.

was optimally crystallized from MIBK (process E[2a]). Attempted crystallization of **9** from MIBK had been unsuccessful, indicating that crystallization of **3** from MIBK should provide considerable reduction in the level of **9**.

Thirteen production batches of **3** were analyzed with the improved HPLC method. The level of **9** averaged 0.9 area % (range 0.8−1.2 area %) in four batches of **3** crystallized from water. Four batches of **3** isolated from water and recrystallized from MIBK were assayed at a level averaging ca. 0.1 area % (range: trace−0.1 area %). For five batches of **3** crystallized from MIBK the level of **9** averaged <0.1 area % (range: none detected−0.3 area %). This comparison showed that crystallization of **3** from MIBK was superior to crystallization from water for lowering the level of the regioisomeric impurity **8**. There was a small amount of variability in the effectiveness of crystallizing **3**: when a batch of **2** containing 1.8 area % of **8** was converted in two runs to **3**, MIBK crystallization produced batches of **3** with 0.32 area % of **9** in one batch and no detected **9** in the other batch. The MIBK crystallization removed at least 80% of the regioisomeric burden from the side-chain intermediates (Table 1).

Given the low levels of **9** in **3**, no significant levels of **10** were expected in production batches of **4**. Eleven production batches of **4** were assayed, and **10** was found in only one, at <0.1 area % (Table 1). Even at this highest level, **5** was produced in 99.6% purity. The impact of the regioisomers on downstream intermediates was expected to be insignificant, and no regioisomeric impurities corresponding to **5** or other downstream intermediates were prepared.

Conclusions. A regioisomeric impurity was detected in the preparation of fosinopril sodium side-chain intermediates, and the structure of this impurity was confirmed by independent synthesis. Subsequent reactions of this impurity in the two following steps produced the corresponding regioisomeric impurities. These impurities were synthesized to determine potential impact on the quality of intermediates downstream from **2**.

Batches of **2**−**4** were tracked to determine the effect of regioisomer burden for the preparation of fosinopril sodium. Results are summarized in Table 1. In the production of **2**, the level of the regioisomeric impurity **8** averaged 2.0 area %. Conversion of **2** to **3** reduced the level of regiosomeric impurity **9** in isolated **3** to ≤0.32 area %, using **2** with a regioisomer level as high as 1.8 area %. The reduction of the regioisomer by at least 80% was effected by the MIBK crystallization of **3**. Esterification of **3** to **4** produced a detectable amount (<0.1 area %) of the regioisomeric impurity **10** in only one of 11 batches. No regioisomer carryover to fosinopril sodium is expected, considering that the level of regioisomers in **4** averages <0.1 area %, and there are four crystallizations and isolations in converting **4** to fosinopril sodium. These investigations completed the process qualification of the side-chain sequence for the preparation of fosinopril sodium intermediates. Suitably low levels of regioisomeric impurities were demonstrated, indicating that the processes were properly controlled, with no significant risk of decreasing the quality of the active pharmaceutical ingredient. The quality of Fosinopril sodium has remained high.

Experimental Section

General Procedures. ^{1}H NMR data were generated at 300 and 400 MHz; ^{13}C NMR data were generated at 75 and 100 MHz. All reactions were conducted under a nitrogen atmosphere.

(4-Phenylbutyl)phosphinic Acid (2). A mixture of **1** (150 g, 1.135 mol), hypophosphorous acid (50% aqueous, 749 g, 5.675 mol), and AIBN (9.3 g, 56.6 mmol) in methanol (455 mL) was held at reflux (79−82 °C) until residual **1** was no greater than 1 area % by HPLC analysis (4−6 h). Volatiles were removed by distillation under reduced pressure until the specific gravity of the distillate reached 0.92. The pot residue was cooled to 20−25 °C, and water (227 mL) was added. As necessary, water was added (45 mL portions) to reach a specific gravity of no greater than 1.2. The resulting solution was extracted with dichloromethane (2 × 227 mL), and the combined organic extracts were diluted with 726 mL of water. The mixture was basified at 20−25 °C to pH 4.8−5.2 with aqueous NaOH (50%, 70−80 mL),[7] and the rich aqueous phase was extracted with dichloromethane (2 × 227 mL). The combined organic extracts were mixed with water (92 mL) and basified to pH 5.6 ± 0.15 with aqueous NaOH (50%, ca. 1 mL). The latter aqueous phase was combined with the rich aqueous phase, dichloromethane (227 mL) was added, and at 20−25 °C the mixture was acidified to pH 1.0−1.5 with concentrated H_2SO_4 (55−60 mL). The aqueous phase was extracted with dichloromethane (227 mL), and the latter two organic phases were combined and polish-filtered. Water was removed by atmospheric concentration, with return of the organic phase of the condensate, until the condensate was one phase. Further concentration under reduced pressure to a pot temperature of 60 °C returned **2** (208 g, 92.5%) as a viscous yellow oil, which crystallized upon standing to a solid with mp ca. 36.5−38 °C. Typical batches contained 1.6 wt % dichloromethane and less than 1 wt % water. ^{1}H NMR ($CDCl_3$): δ 12.76 (s, 1H), 7.28−7.13 (m, 5H), 7.02 (d, J = 536 Hz, 1H), 2.60 (pseudo t, J = 7.3 Hz, 2H), 1.77−1.52 (m, 6H), 1.1 (trace, methyl signals). ^{13}C NMR ($CDCl_3$): δ 141.7, 128.3 (2 signals), 125.8, 35.4, 32.1 (d, J_{CP} = 16.0 Hz), 29.4 (d, J_{CP} = 93.4 Hz), 20.4. IR (film) 2933, 1496, 1453, 1175, 973 cm^{-1}.

To facilitate quantitations, the dicyclohexylamine (DCHA) salt of **2** was prepared: Dicyclohexylamine (25.1 mL, 126 mol) was added to a solution of **2** (25.00 g, 126 mmol) in EtOAc (25 mL), and heptane (100 mL) was added. Solids were dissolved by heating to 67−70 °C, and the solution was cooled gradually to room temperature. Crystallization occurred at 52−53 °C. The suspension was cooled and stirred at 2−5 °C for 2 h, and the solids were washed with heptane−EtOAc (2:1, 2 × 25 mL). Drying at ambient conditions returned the DCHA salt of **2**, 40.49 g (84.7%), mp 98−100 °C. ^{1}H NMR ($CDCl_3$): δ 10.0 (br s, 1H), 7.28−7.13 (m, 5H), 7.09 (d, J = 476 Hz, 1H), 2.90 (pseudo t, J = 11.4 Hz, 2H), 2.62 (pseudo t, J = 7.6 Hz, 2H), 2.05 (pseudo d, J = 11.9 Hz, 4H), 1.80−1.45 (m, 16H), 1.28−1.13 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 142.4, 128.3, 128.1, 125.5, 52.1,

(7) At pH 5, **2** was extracted into the aqueous phase, while the organic phase contained primarily bis(4-phenylbutyl)phosphinic acid, a byproduct formed during the reaction.

35.8, 33.2 (d, J_{CP} = 90.8 Hz), 32.9 (d, J_{CP} = 15.3 Hz), 28.9, 25.2, 24.8, 22.3. IR (KBr) 3421, 2940, 1452, 1170 cm^{-1}. Anal. Calcd for $C_{22}H_{38}NO_2P$: C, 69.62; H, 10.09; N, 3.69; P, 8.16. Found: C, 69.61; H, 10.28; N, 3.62; P, 7.90.

Isolation and Identification of 8. To obtain a sample of **2** enriched in the impurity, a batch of **2** was purified in the laboratory by the preparation of the DCHA salt (see above). The mother liquor contained ca. 10 area % of the unknown by HPLC. After concentration to a residue, 100 mg was dissolved in 10 mL of mobile phase (CH_3CN−0.005 M KH_2PO_4−2-propanol, 30:65:5). The solution was injected (500 μL, 20 injections) onto a semipreparative Phenomenex Ultramex NH_2 column (5 μm, 22.5 × 250 mm). Enriched fractions containing ca. 80% of **8** and 20% of **2** were combined and concentrated via rotary evaporation to remove CH_3CN and 2-propanol. The aqueous solution was frozen and lyophilized to afford a white solid, which was not soluble in mobile phase or in methanol. The white solids were dissolved in ca. 200 mL of water and injected onto the semipreparative HPLC column (100 mL, two injections). Fractions containing **8** were collected, combined, concentrated, and lyophilized as described above. The isolate was dissolved in water (100 mL) and desalted using a semipreparative C18 column (Regis HiChrom Prep 20 ODS, 15−25 mm, 25 mm i.d. × 25 cm). Water was used to elute **8**. The fraction containing **8** (98 area %) was frozen and lyophilized, returning ca. 2 mg of residue. ^{1}H NMR ($CDCl_3$): δ 1.15 (dd, J = 20.0, 7.1 Hz, 3H), other resonances consistent with the proposed structure of **8** (see below). Mass spectral data showed fw 198 (positive and negative FAB, as well as CI). Fragmentation pattern observed in the mass analyzed ion kinetic energy spectroscopy (MIKES) scans of $(M + H)^+$: 121, 105, 91, 65.

(1-Methyl-3-phenylpropyl)phosphinic Acid (8). A solution of **13** (15.0 g, 101.4 mmol) in diethyl ether (650 mL) was cooled to 0−5 °C, and lithium aluminum hydride (4.2 g, 110.6 mmol) was added in portions over 30 min. After stirring at 0−5 °C for 30 min, TLC indicated consumption of **13**. Excess lithium aluminum hydride was destroyed by adding water (4.2 mL), aqueous NaOH (15%, 4.2 mL), and water (12.6 mL), and the suspension was stirred for 30 min. Solids were removed by filtration through a pad of anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give 14.77 g (97.5%) of **14** as an oil. NMR data agreed with those reported in the literature.[8] Without further purification this material was used for the preparation of **15**.

A solution of triphenylphosphine dibromide (45.0 g, 106.6 mmol) in methylene chloride (350 mL) was cooled to 0 °C. A solution of **14** (14.77 g, 98.5 mmol) in methylene chloride (60 mL) was slowly added. The solution was stirred at 0 °C for 60 min, when TLC indicated complete conversion of alcohol to bromide. The byproduct triphenylphosphine oxide was precipitated by the addition of hexane (300 mL) and removed by filtration. The solvent was removed under reduced pressure to give 18.02 g (86.0%) of **15** as an oil. NMR data agreed with those reported in the literature.[9] Without further purification this material was used for the Grignard reaction.

A solution of **15** (16.0 g, 75.1 mmol) in THF (75 mL) was added to a slurry of magnesium turnings (2.42 g, 99.5 mmol) and several beads of iodine crystals in THF (25 mL). The reaction mixture was refluxed for 2 h, by which time TLC indicated complete disappearance of the bromide. Over 10 min the solution of Grignard reagent was added by cannula to a 0 °C solution of diethyl chlorophosphite (12.9 g, 82.9 mmol) in THF (50 mL). The transfer of the Grignard solution was completed by rinsing with THF (3 × 20 mL). The reaction mixture was stirred at 0 °C for 2 h and then overnight at ambient temperature. After quenching with distilled water (24 mL), the reaction mixture was diluted with diethyl ether (45 mL). The organic phase was washed with saturated brine solution (15 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give an oil, which was dissolved in THF (150 mL) and hydrolyzed with 5 N NaOH (22 mL) by stirring at room temperature for 3 h. The reaction mixture was acidified (1 N HCl) to pH <1, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with distilled water (25 mL) and saturated brine solution (35 mL) and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give 13.3 g (89.5%) of **8** as a viscous oil. Spectral data were identical to those of the isolated impurity. HPLC spiking experiments showed that the synthetic material coeluted with the isolated impurity. ^{1}H NMR ($CDCl_3$): δ 8.68 (br s, ca. 1.3H), 7.29−7.16 (m, 5H), 6.91 (d, J = 535 Hz, 1H), 2.81−2.77 (m, 1H), 2.67−2.63 (m, 1H), 2.09−2.00 (m, 1H), 1.74−1.64 (m, 2H), 1.18 (dd, J = 20.0, 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 141.9, 129.23, 129.17, 126.8, 33.8 (d, J_{CP} = 12.7 Hz), 32.7 (d, J_{CP} = 95.8 Hz), 30.8, 12.0. IR (CCl_4) 1456, 1179, 965 cm^{-1}. Anal. Calcd for $C_{10}H_{15}O_2P$·0.25 H_2O: C, 59.25; H, 7.71; P, 15.28. Found: C, 59.63; H, 7.68; P, 15.25.

[Hydroxy(1-methyl-3-phenylpropyl)phosphinyl]acetic Acid, *N*,*N*′-Bis(phenylmethyl)-1,2-ethanediamine Salt (2:1) (9). A solution of **8** (4.10 g, 20.7 mmol) and chloroacetic acid (2.55 g, 27.0 mmol) in acetonitrile (4 mL) was added at 10−20 °C to a mixture of hexamethyldisilazane (6.05 mL, 28.7 mmol) and chlorotrimethylsilane (3.65 mL, 28.7 mmol). The reaction mixture was heated to reflux (75−81 °C) and maintained at reflux for 6 h. The reaction was quenched into deionized water (18 mL), and volatiles were removed atmospherically until a pot temperature of 96 °C was reached. The reactor contents were cooled to ca. 45 °C and extracted with MIBK (3 × 12 mL). The combined organic phases were washed with water and concentrated under reduced pressure until the residual water level was <0.5 vol % by Karl Fischer titration. The salt was precipitated by the addition of *N*,*N*′-dibenzylethylenediamine (3.8 mL, 16.1 mmol), collected by filtration, and dried. The salt was purified by reslurrying in MIBK (3 × 50 mL). After filtration and vacuum drying, the return was 3.23 g of white solid (33%, unoptimized), mp 167.3 °C (differential thermal analysis). ^{1}H NMR (DMSO-d_6): δ 7.49 −7.13 (m, 10 H),

(8) Dragovich, P. S.; Prins, T. J.; Zhou, R. *J. Org. Chem.* **1995**, *60*, 4922.

(9) Anastasis, P.; Freer, I.; Overton, K. H.; Picken, D.; Rycroft, D. S.; Singh, S. B. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2427.

3.98 (br s, 2H), 3.06 (br s, 2H), 2.73 (m, 1H), 2.54 (d, J = 14.3 Hz, 2H), 2.50 (m, 1H), 1.95 (m, 1H), 1.47 (m, 2H), 1.03 (dd, J = 17.0, 6.8 Hz, 3H). ^{13}C NMR (CD_3OD + $CDCl_3$): δ 172.7 (d, J_{CP} = 5.6 Hz), 142.7, 131.7, 130.5, 130.1, 129.7, 129.0, 128.9, 126.4, 51.8, 43.8, 43.4, 37.3 (d, J_{CP} = 70.7 Hz), 35.1 (d, J_{CP} = 85.5 Hz), 34.3, 32.4, 13.1. IR (KBr) 3440, 1670, 1633, 1154, 1031 cm^{-1}.

[Hydroxy(1-methyl-3-phenylpropyl)phosphinyl]acetic Acid, Phenylmethyl Ester (10). To a suspension of **9** (0.5 g, 1.3 mmol) in MIBK (15 mL) was added H_2SO_4 (1 N, ca. 8 mL), and the aqueous phase was extracted with MIBK (2 × 15 mL). The combined extracts were concentrated under reduced pressure to afford ca. 0.25 g of an oil, which was dissolved in toluene (1.5 mL). To this were added benzyl alcohol (0.11 g, 1.0 mmol) and a few crystals of *p*-toluenesulfonic acid, and the mixture was held at reflux with azeotropic water removal for 14 h. The solution was cooled to 50−60 °C, and heptane (1 mL) was added. The resulting suspension was stirred at 25 °C for ca. 2 h and at 0−5 °C for 2 h. The product was filtered off and dried with suction at room temperature to give 0.32 g of brown solid. This material was recrystallized from a minimum amount of MIBK to afford 0.18 g (65%, unoptimized) of a white solid, mp 106−107.5 °C. ^{1}H NMR ($CDCl_3$): δ 7.38−7.11 (m, 10H), 5.09 (s, 2H), 2.96 (d, 2H, J = 16.5 Hz), 2.81−2.71 (m, 1H), 2.56−2.46 (m, 1H), 2.12−2.06 (m, 1H), 1.93−1.85 (m, 1H), 1.66−1.57 (m, 1H), 1.18 (dd, J = 9.4, 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 166.2 (d, J_{CP} = 3.8 Hz), 141.2, 135.3, 128.5, 128.4, 126.0, 67.2, 35.4 (d, J_{CP} = 77.4 Hz), 33.4 (d, J_{CP} = 5.5 Hz), 32.3 (d, J_{CP} = 99.1 Hz), 30.4, 11.9. IR (KBr) 3440, 1728, 1275, 1190, 1125 cm^{-1}. Anal. Calcd for $C_{19}H_{23}O_4P$·0.6 H_2O: C, 63.88; H, 6.83; P, 8.67. Found: C, 64.08; H, 6.55; P, 8.29.

HPLC Methods for Resolution of Regioisomers. *Separation of **2** and **8**:* Ultramex NH_2 column, 5 μm, 4.6 mm i.d. × 25 cm (Phenomenex), eluted at 1.0 mL/min with 5 mM KH_2PO_4 (pH 4.5)−2-propanol−acetonitrile (50:5:45), with detection at 210 nm. Typical retention times: **2**, 10.0 min; **8**, 10.6 min. For the analysis of **8** in **2**, the MQL was 0.1 area %, and the LD was 0.02 area %.

*Separation of **3** and **9**:* Selectosil NH_2 column, 5 μm, 100 Å pore size, 4.6 mm i.d. × 25-cm (Phenomenex), eluted at 1.0 mL/min with 0.2% phosphoric acid−acetonitrile−methanol−2-propanol (41:29:9:21), with detection at 215 nm. Typical retention times: **9**, 12.6 min; **3**, 13.4 min. For the analysis of **9** in **3**, the MQL was 0.08 area %, and the LD was 0.02 area %.

*Separation of **4** and **10**:* Chromegabond AlkylPhenyl column, 5 μm, 60 Å pore size, 4.6 mm i.d. × 25 cm (ES Industries), eluted at 1.0 mL/min with 0.25 M NaH_2PO_4 (pH 2.8)−acetonitrile (73:27), with detection at 210 nm. Typical retention times: **10**, 25.5 min; **4**, 27.3 min. For the analysis of **10** in **4**, the MQL was 0.08 area %, and the LD was 0.02 area %.

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