Resolution of Enantiomers of Novel C_2-Symmetric Aminobisphosphinic Acids via Diastereomeric Salt Formation With Quinine

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ABSTRACT C_2-symmetric *N,N*-bis(phosphinomethyl)amines were prepared by the thermal reaction of aromatic aldehydes with ammonia and hypophosphorus acid as previously described. Both enantiomers of C_2-symmetric *N,N*-bis(phosphinomethyl)amine were obtained in a high enantiomeric purity through the diastereomeric salt formation with (–)-quinine, and subsequent fractional crystallization. X-ray crystallographic analysis of one of the diastereomeric salts clearly revealed that (–)-quinine could be an efficient resolving agent for obtaining the single enantiomer (*R,R*)-*N,N*-bis(phosphinomethyl)amine. *Chirality 27:71–74, 2015.* © 2014 Wiley Periodicals, Inc.

KEY WORDS: C_2-symmetric; α-aminophosphinic acids; thermal reaction

INTRODUCTION

α-Aminoalkylphosphinic acids are considered structural analogs of α-amino acids and possess potential biological activities applicable to antibiotics, enzyme inhibitors, pharmacological agents, antiviral agents, and herbicides (Figure 1).[1–14] Since the structure of the phosphinic functional group mimics the unstable tetrahedral intermediates formed in enzyme-mediated peptide bond cleavage, some pseudo-peptides derived from α-aminophosphinic acids are known to act as inhibitors of proteolytic enzymes such as metallo- and serine-proteases.[15–36]

In our continuous efforts to introduce novel methods for the synthesis of α-aminophosphinic derivatives, we recently found a new method for the synthesis of homodimeric α-aminophosphinic acid derivatives (HODAPAs) **2** (Scheme 1).[37–40] HODAPAs **2** were obtained as a diastereomeric mixture of (±)-**2** and *meso*-**2** from readily available diimines and hypophosphorus acid. Diastereomerically pure (±)-**2** and *meso*-**2** were readily isolated by washing with polar solvents, as described in our previous article.[37–40] The symmetric features of **2** would be applied to an important component of phosphinic pseudo-peptides, which are expected to be of benefit in their binding to the homodimeric proteases, having C_2-axis symmetry such as HIV-protease.[15] To incorporate HODAPAs **2** to pseudo-peptides, it is necessary to obtain them in high enantiomeric purities. In this article, we disclose that racemic HODAPAs can be resolved to their individual enantiomers by application of diastereomeric salt formation with (–)-quinine. Now we describe the results of our resolutions.

EXPERIMENTAL

Materials and Methods

All chemicals were commercial products and distilled or recrystallized before use. All melting points were obtained by a Yanagimoto micro-melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer (Norwalk, CT) 341 with a pathlength 0.1 dm using the 589.3 nm D-line of sodium. Solutions were prepared using spectroscopic-grade solvents and concentrations (*c*) are quoted in g/100 mL. NMR spectra were taken with a 400 Bruker (Billerica, MA) Avance III instrument with the chemical shifts being reported as δ ppm and couplings expressed in Hertz. Thin-layer chromatography (TLC) was carried out with Merck (Darmstadt, Germany) plates precoated with silica gel 60 F_{254} (0.25 mm thick).

X-ray crystal data of (–)-quinine salt of **3** were collected by a Bruker SMART APEX II diffractometer. The structure was solved by a direct method using SHLEXS-97 (Scheldrik, 1997) and refined with a full matrix laser-squares method. Molecular formula = $2(C_{20}H_{25}N_2O_2) \cdot C_{14}H_{15}NO_4P_2 \cdot C_3H_6O$ (including: 2 quinine + 1 molecule of compound (*R, R*)-**2a** + 1 acetone), MW = 1032.13, monoclinic, space group = *C 1 2 1*, a = 16.1193(19) Å, b = 103736(12) Å, c = 17.060(2) Å, V = 2622.6(5) Å^3, T = 90 K, Z = 2, D_x = 1.307 Mg/m^3, (Mo-Kα) = 0.71073 Å, R = 0.0247 over independent reflections. Crystallographic data (excluding structure factors) for the X-ray crystal structure analysis reported in this article have been deposited with the Cambridge Crystallographic Data Center (CCDC) as supplementary publication No. CCDC 986045. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

((1*R,1'*R**)-Azanediylbis(phenylmethylene))bis(phosphinic acid) ((±)-2a).** This compound (0.8 g) was obtained as a white solid (mp: 222–224 °C) from benzaldehyde (3 mL), ammonium hydroxide (15 mL of 30% aqueous solution), and anhydrous hypophosphorus acid (3.3 g) in an analogous manner to those described in our previous article.[37–40] The physical data were identical to those described previously.[37–40]

Preparation of (+)-(*R,R*)-2a. Racemic bisphosphinic acid (±)-**2a** (0.650 g, 2 mmol) was dissolved in refluxing ethanol (10 mL) to give a milky suspension. A solution of (–)-quinine (4 mmol, 1.3 g) in ethanol (2 mL) was added dropwise to the milky suspension. The reaction was terminated after being stirred at reflux for 5 h. The solvent was removed from the reaction mixture by evaporation and acetone (10 mL) was added to the reaction mixture. The flask was left to gradually cool and kept for 1 d at an ambient temperature. The resulting white solid was collected by filtration and the mother liquor kept for the separation of other diastereomeric salts. The white solids were recrystallized from acetone to yield quinine salt **5** (0.3 g, 32% yield) as white crystals: mp: decomposed at 210 °C; $[\alpha]_D^{20} = -3.3$ (c 0.6, MeOH); ^{1}H NMR (CD_3SOCD_3,

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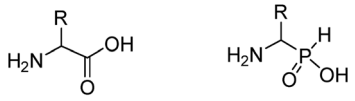
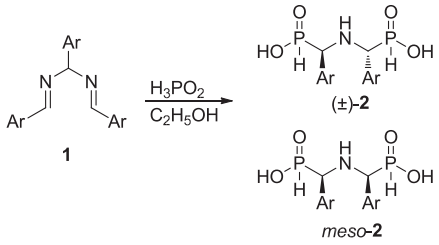


Fig. 1. Structures of α-amino acids and α-aminophosphinic acids.



Scheme 1. Synthesis of HODAPAs **2**.

400 MHz): 1.19 (1H, t, J = 7.2 Hz), 1.40 (2H, m), 1.83 (2H, m), 1.94-2.10 (12H, m), 2.69 (2H, broad), 3.09-3.18 (4H, m), 3.56 (2H, broad), 3.91 (6H, S), 4.02-4.12(2H, m), 4.98 (2H, d, J = 10.4 Hz), 5.08 (2H, d, J = 17.2 Hz), 5.76-5.85 (2H, m), 5.93 (1H, S), 6.42 (2H, broad), 6.65 (2H, S), 6.91-6.93 (6H, m), 7.18 (2H, S), 7.48 (2H, dd, J = 2.0 Hz, J = 9.2 Hz), 7.67 (4H, S), 8.03 (2H, d, J = 9.2 Hz), 8.76 (2H, d, J = 4.4 Hz); ^{31}P NMR (CD_3SOCD_3-H_3PO_4, 162.0 MHz): 20.94 ppm. The compound **5** (0.24 g, 0.25 mmol) was suspended in ethyl acetate (50 mL) and 5% aqueous HCl (50 mL) was added. The biphasic mixture was stirred rapidly until all the solid had dissolved. The organic layer was separated and the aqueous layer was re-extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water (100 mL), dried over $MgSO_4$, and concentrated to give (*R,R*)-**2a** (0.076 g, quantitative) as a white crystalline solid: mp: 222–224 °C; $[\alpha]_D^{20}$ = +56.6 (c 0.73, MeOH). Other spectral data are identical to those of (±)-**2a**.

Preparation of (–)-(*S,S*)-2a. The crude **6** was isolated by fractional crystallization from the mother liquor as described in the previous section. The solvent was removed from the mother liquor by evaporation and acetone (10 mL) was added to the crude **6** and the solution was allowed to warm to ~60 °C. The flask was left to gradually cool and kept for 1 d at an ambient temperature. The white solids were recrystallized from acetone and gave diastereomerically pure **6** (purity of the salt **6** was checked by ^{31}P NMR) in 30% yield (0.28 g) as a white crystalline solid: mp: decomposed at 210 °C; $[\alpha]_D^{20}$ = –80.0 (c 0.1, MeOH); ^{31}P NMR (CD_3SOCD_3-H_3PO_4, 162.0 MHz): 21.26 ppm. ^{1}H NMR (D_2O, 400 MHz): 1.36-1.40 (2H, m), 1.80-2.07 (14H, m), 2.63 (2H, broad), 3.06-3.43 (4H, m), 3.54 (2H, broad), 3.88 (6H, S), 4-4.15 (2H, m), 4.95 (2H, d, J = 10.4 Hz), 5.04 (2H, d, J = 17.2 Hz), 5.68-5.83 (4H, m), 6.40-6.50 (2H, m), 6.57-6.59 (2H, m), 6.85-6.87 (5H, m), 7.15 (1H, S), 7.35 (1H, S), 7.44 (2H, d, J = 9.2 Hz), 7.6-7.7 (5H, m), 8.00 (2H, d, J = 9.2 Hz), 8.70 (2H, d, J = 4.4 Hz).

The salt **6** (0.24 g, 0.25 mmol) was suspended in ethyl acetate (50 mL) and 5% aqueous HCl (50 mL) was added. The biphasic mixture was stirred rapidly until all the solid had dissolved. The organic layer was separated and aqueous layer was re-extracted with ethyl acetate (3x30 mL). The combined organic layers were washed with water (100 mL), dried over $MgSO_4$ and concentrated to give (*S,S*)-**2a** (0.069 g, quantitative) as a white crystalline solid: mp: 222–224 °C; $[\alpha]_D^{20}$ = –57.1 (c 0.45, MeOH). Other spectral data are identical to those of (±)-**2a**.

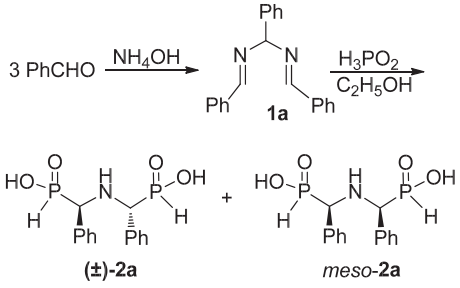
RESULTS AND DISCUSSION

Among HODAPAs previously synthesized, we focused on (±)-**2a** having two phenyl groups as substituents. Compound (±)-**2a** was prepared in a diastereomerically pure state according to the protocols described in our previous article (Scheme 2).[37–40]

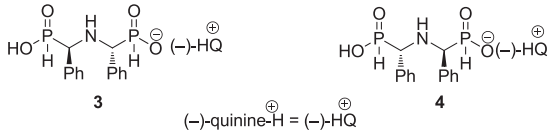
After synthesis of diastereomerically pure (±)-**2a,** first its resolution with (*R*)-2-phenylethylamine was examined. However, all of our efforts to prepare the crystalline diastereomeric salts failed using a variety of reaction media (EtOH, MeOH, *i*-PrOH, and these solvents containing water).

In an effort to resolve (±)-**2a**, we next examined the diastereomeric salts formation with one equivalent of (–)-quinine in a variety of solvents, as it was expected that one of the diastereomeric salts **3** and **4** would be preferably crystallized (Scheme 3). However, due to their high polarity, salts obtained under the conditions were found to be not soluble in any representative organic solvents and inconvenient for the purpose of our fractional recrystallization.

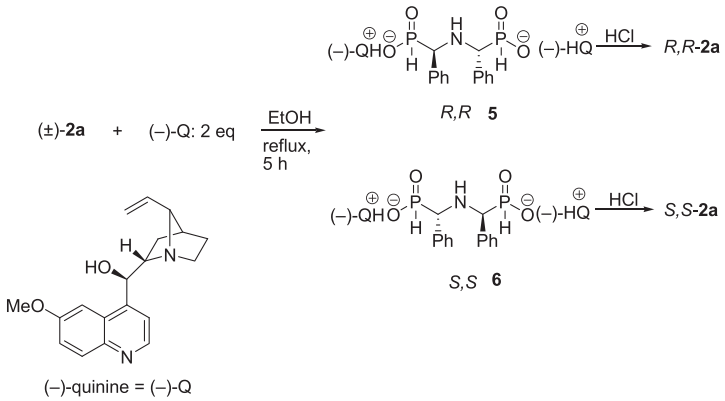
To increase the lipophilicity of the diastereomeric salts, (±)-**2a** was reacted with two equivalents of (–)-quinine in refluxing ethanol for 5 h to give a 1:1 mixture of **5** and **6** in quantitative yield (Scheme 4). As expected, the salts obtained by this method were found to be soluble to a representative organic solvent and suitable for fractional recrystallization. The ^{31}P-NMR spectrum for the mixture of **5** and **6** in DMSO-d_6 exhibited two singlet peaks at 20.94 and 21.21 ppm, respectively. We were pleased to find solubility of the diastereomeric salts in acetone, which is desirable for the fractional recrystallization. When the mixture of **5** and **6** was dissolved in acetone, only diastereomeric salt **5** was preferably crystallized from the solvent in 32% yield at an ambient temperature. The mother liquor was kept to isolate another diastereomeric salt **6**. The ^{31}P-NMR spectrum of crystallized salt **5** exhibited a singlet at δ 20.94 ppm. The diastereomeric purity of salt **5** can be readily assessed by ^{31}P-NMR spectroscopy. In this case, the salt **5** is produced in >98% purity. The



Scheme 2. Preparation of racemic and meso HODAPAs **2a**.



Scheme 3. Diastereomeric salts formation of (I)-**2a** with one equivalent of (-)-quinine.



Scheme 4. Diastereomeric salts formation of (±)-**2a** with two equivalent of (–)-quinine.

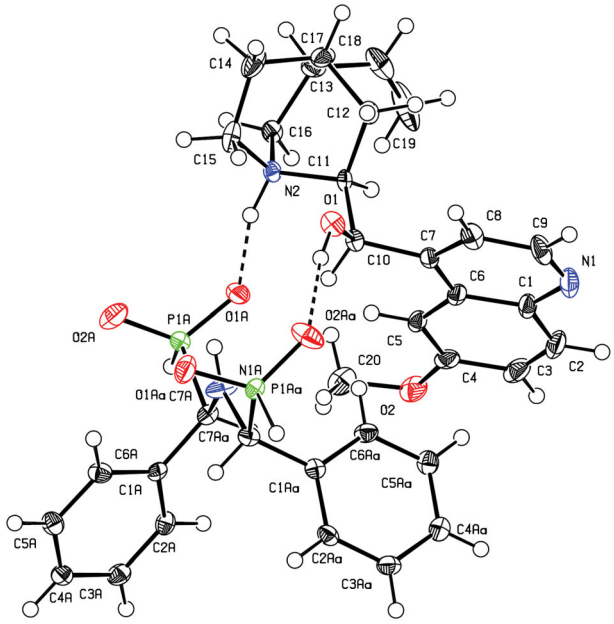


Fig. 2. ORTEP drawing of salt **5**: one of (–)-quinine is omitted due to the ORTEP drawing program.

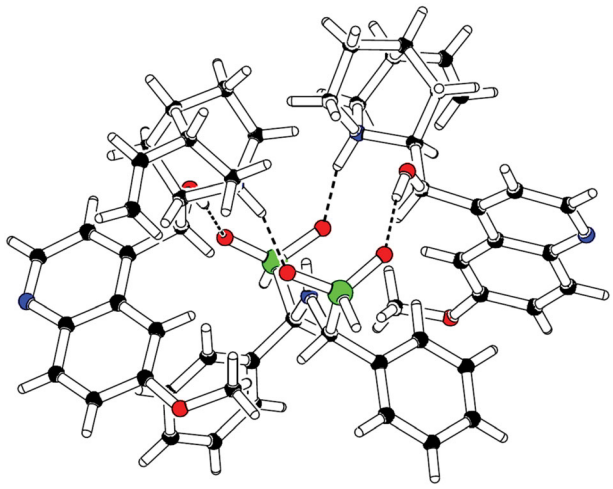


Fig. 3. The structure for crystalline structure unit of salt **5**.

stereostructure of salt **5** was confirmed by X-ray crystallography (Figures 2 and 3). In the crystalline structure unit, two molecules of (–)-quinine binds with one molecule of (*R,R*)-**2a** via hydrogen bond and ionic interactions as shown in Figure 3. Treatment of salt **5** with conc. HCl gave enantiopure (*R,R*)-**2a** in quantitative yield (Scheme 4).

Crystallization of the mother liquor from acetone at room temperature gave access to quinine salt **6** of (*S,S*)-**2a** in 30% yield (Scheme 4).

CONCLUSION

We have shown that both enantiomers of HODAPA **2a** can be accessed by resolution of the fractional crystallization of salts formed from the racemate **2a** and enantiopure (–)-quinine. The structure of one of the diastereomeric salts was determined by X-ray crystallographic analysis. Simple hydrolysis of the individual diastereomeric salts in the usual manner afforded (*R,R*)- and (*S,S*)-**2a**. The features of the present method are easy, rapid, and yield good preparation of both enantiomers of novel HODAPAs. The present resolution method would open up the possibility to prepare optically active HODAPAs of interest to their biological activity.

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