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Synthesis of novel (*R*)- and (*S*)-piperidazine-3-phosphonic acids and transformation into (*R*)- and (*S*)-pyrrolidine-2-phosphonic acids

Mamoru Kaname, Yasushi Arakawa and Shigeyuki Yoshifuji*

Faculty of Pharmaceutical Sciences, Hokuriku University, Kanazawa 920-1181, Japan

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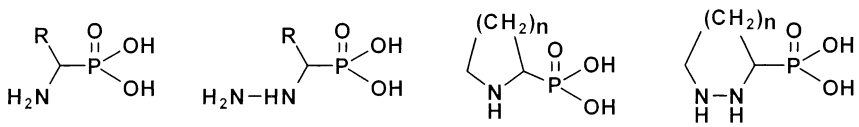
Abstract—The first synthesis of a pair of (*R*)- and (*S*)-piperidazine-3-phosphonic acids was performed via a one-pot process of hetero Diels–Alder reaction and Lewis acid-catalyzed phosphonylation. The absolute configuration of the target compounds was established by a novel transformation into known (*R*)- and (*S*)-pyrrolidine-2-phosphonic acids. © 2001 Elsevier Science Ltd. All rights reserved.

α-Aminophosphonic acids **1** and α-hydrazinophosphonic acids **2** (Fig. 1) are considered as analogues of naturally occurring α-amino acids and have received considerable attention over the past two decades in the areas of medicinal and agricultural chemistry on account of their potential biological activities.[1,2] Therefore, these compounds, especially α-aminophosphonic acids and their derivatives, have been synthesized by various methods.[3,4] However, a simple and general synthetic method for the cyclic amino-type of compounds such as **3** and **4** is relatively unknown. Recently, as the first example of cyclic α-hydrazinophosphonic acid, we reported the synthesis of racemic piperidazine-3-phosphonic acid **4** ($n=2$) employing the hetero Diels–Alder (D–A) reaction and subsequent phosphonylation of the D–A adduct in the presence of a Lewis acid.[5] Herein, we report the successful application of this methodology to an asymmetric synthesis of (*R*)- and (*S*)-piperidazine-3-phosphonic acids and a novel transformation of these piperidazine derivatives into the corresponding pyrrolidine-2-phosphonic acids **3** ($n=2$).

In the initial stage of the synthesis, a two-step procedure of the hetero D–A reaction and subsequent phosphonylation, previously adopted for the racemic compounds,[5] was improved to a one-pot reaction, as illustrated in Scheme 1. Thus, di-(−)-menthyl azodicarboxylate[6] was reacted in CH_2Cl_2 at room temperature with 1-trimethylsilyloxybutadiene (or 1-methoxybutadiene) in the presence of trimethyl phosphite and TMSOTf (trimethylsilyl triflate) as a Lewis acid to afford an inseparable mixture of two diastereoisomers **5** in 100% (or 78% from 1-methoxybutadiene) yield.[7] Catalytic hydrogenation of **5** using Pd on charcoal in methanol at 4 atm of H_2 gave a mixture of the saturated derivatives **6a** and **6b** in a ratio of 66:34 and 99% yield, which could be easily separated by column chromatography on silica gel using AcOEt and hexane (1:1) to provide **6a** (yield 65%, $[\alpha]_D^{27}$ −71.7° ($c=0.93$, $CHCl_3$)) and **6b** (yield 34%, $[\alpha]_D^{24}$ −39.9° ($c=1.23$, $CHCl_3$)). The ratio of **6a**:**6b** is a reflection of the stereoselectivity in the phosphonylation to the acyliminium intermediate generated from the hetero D–A



1 2 3 4

Figure 1.

Keywords: hexahydropyridazine-3-phosphonic acid; hetero Diels–Alder reaction; ruthenium tetroxide oxidation.

* Corresponding author. E-mail: s-yoshifuji@hokuriku-u.ac.jp

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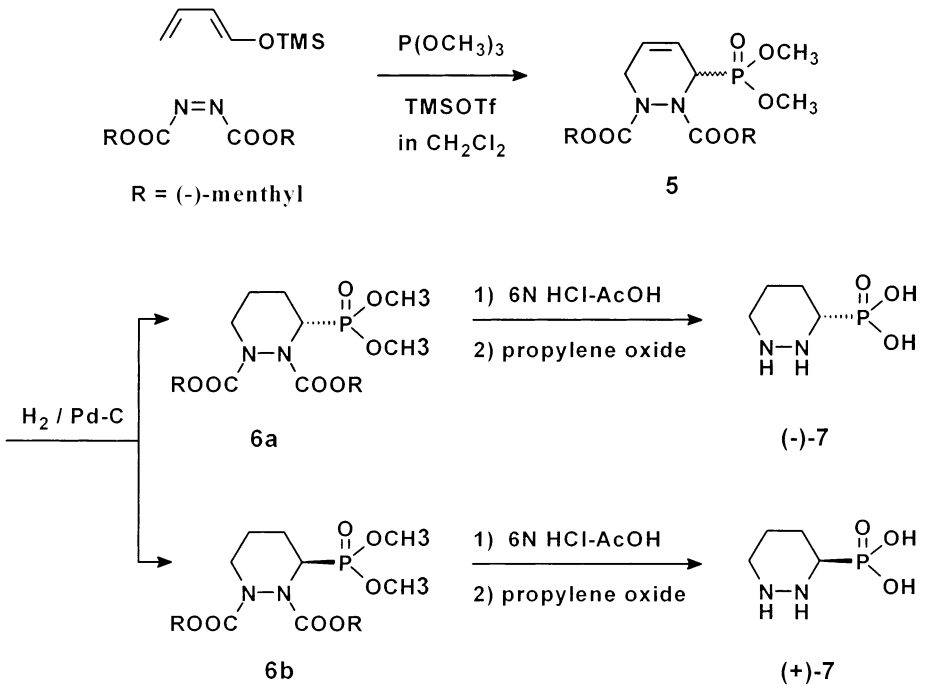
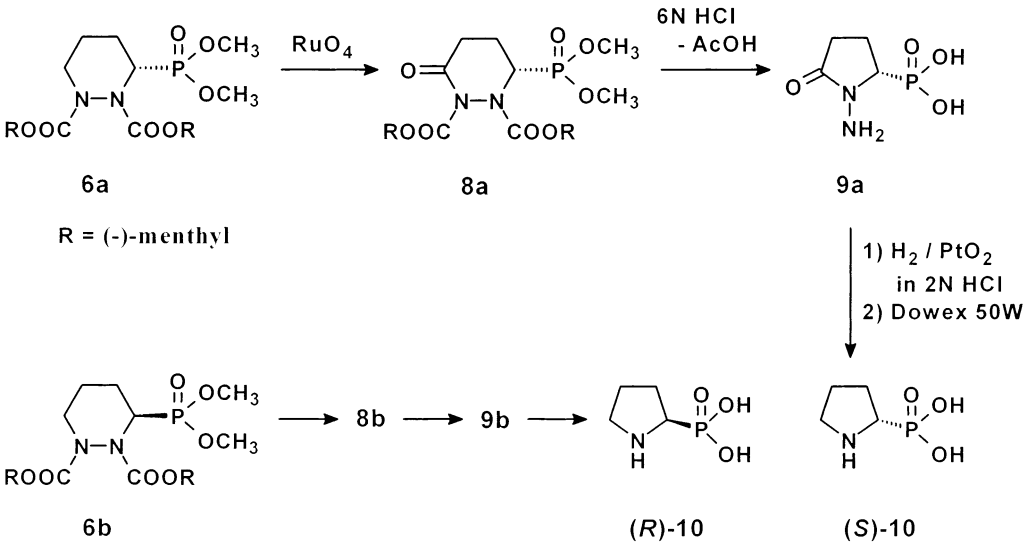


Scheme 1.

adduct by TMSOTf. Finally, each of the diastereoisomers **6a** and **6b** was hydrolyzed in boiling 6N HCl–AcOH (1:1) and subsequently treated with propylene oxide[5] in methanol to give optically active piperidazine-3-phosphonic acids (–)-**7**, mp 163–165°C, $[\alpha]_D^{25}$ −16.0° ($c=0.70$, 2N HCl) and (+)-**7**, mp 161–163°C, $[\alpha]_D^{26}$ +13.7° ($c=0.67$, 2N HCl), in 64 and 67% yield, respectively. The structures of (–)-**7** and (+)-**7** were separately confirmed by comparison of spectral data with those of racemic piperidazine-3-phosphonic acid,[5] except with regard to the optical rotation.

In order to determine the absolute configurations of the target compounds (–)-**7** and (+)-**7**, we attempted a novel transformation of these piperidazine intermediates **6a** and **6b** by reducing one of the two nitrogen atoms into chiral pyrrolidine-2-phosphonic acids having known absolute stereochemistry. For this purpose, it was needed to cleave the C6–N1 bond in the piperidazine ring. One possible approach might be by an effective RuO_4 oxidation of the C6 methylene constructing a carbonyl function, followed by hydrolysis of the resultant amide bond. Such synthetic outline is shown in Scheme 2. RuO_4 oxidation of the piperidazine derivative **6a** was carried out using a catalytic amount of RuO_2 under a two-phase system of 10% aqueous $NaIO_4$ and AcOEt,[8] and the corresponding piperidazin-6-one **8a** was obtained in 57% yield as a single product. Hydrolysis of **8a** in boiling 6N HCl–AcOH (1:1) afforded not the expected ring-opened product but,



Scheme 2.

fortunately, the ring-contracted five-membered lactam **9a** in 77% yield. Lactam **9a** was smoothly hydrogenated in 2N HCl using PtO_2 at 4 atm of H_2 through a one-pot operation combined with hydrogenolysis of the N–N bond and reduction of the lactam C=O function, and then treated by ion-exchange chromatography (Dowex 50W) to furnish the desired pyrrolidine-2-phosphonic acid (–)-**10**, mp 275–276°C (lit.[9] mp 275–276°C) in 73% yield. The specific rotation of (–)-**10** ($[\alpha]_{578}^{20}$ −64.2° ($c=1.03$, 1N NaOH) was in accord with the reported value for (*S*)-pyrrolidine-2-phosphonic acid ($[\alpha]_{578}^{20}$ −60° ($c=1$, 1N NaOH)).[9]

In a similar way, piperidazine derivative **6b**, a precursor of (+)-**7**, was transformed into the pyrrolidine-2-phosphonic acid (+)-**10**, mp 276–277°C (lit.[9] mp 272–273°C), $[\alpha]_{578}^{22}$ +66.3° ($c=1.0$, 1N NaOH), the optical rotation of which was in good agreement with that of the known (*R*)-form, $[\alpha]_{578}^{20}$ +64° ($c=1$, 1N NaOH).[9]

Thus, the chemical conversion was successfully accomplished. The absolute configuration of the levorotatory piperidazine-3-phosphonic acid (–)-**7** and its precursor **6a** was assigned to be (*S*)-configuration, while that of the dextrorotatory compound (+)-**7** and its derivative **6b** to be (*R*)-configuration.

In summary, the first synthesis of (*R*)- and (*S*)-piperidazine-3-phosphonic acids and the related compounds[10] provides ready access to a new type of optically active cyclic α-hydrazinophosphonic acids. Furthermore, the transformation of the piperidazine derivatives into the pyrrolidine compounds, which was effectuated by RuO_4 oxidation, provides a new synthetic route to useful compounds having a pyrrolidine ring system.

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7. One-pot reaction (preparation of compound **5**): Trimethyl phosphite (8.85 ml, 75.0 mmol) was added slowly to a solution of di-(–)-menthyl azodicarboxylate (11.84 g, 30.0 mmol) and trimethylsilyloxy-1,3-butadiene (or 1-methoxy-1,3-butadiene) (60.0 mmol) in CH_2Cl_2 (40 ml) at room temperature. Then, TMSOTf (8.14 ml, 45.0 mmol) was dropped slowly in the reaction mixture at 0°C. The solution was allowed to warm to room temperature and was held there for 12 h. Water (30 ml) was added dropwise to the reaction solution at 0°C, and the mixture was vigorously stirred for 30 min. The mixture was diluted with saturated aq. $NaHCO_3$ (300 ml) and extracted with AcOEt (twice, total 800 ml). The AcOEt solution was washed with saturated aq. NaCl, dried over anhyd. Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt–hexane, 1:1 ~ 2:1 v/v) to give an inseparable mixture of (3*R*)- and (3*S*)-di-(–)-menthyl 3-dimethylphosphoryl-1,2,3,6-tetrahydropyridazine-1,2-dicarboxylate (**5**). Yield 100% (or 73% from 1-methoxy-1,3-butadiene), colorless oil. MS *m/z*: 556 (M^+). ^1H NMR ($CDCl_3$) δ: 0.64–1.18 (24H, m), 1.18–1.57 (4H, m), 1.57–1.83 (4H, m), 1.87–2.30 (4H, m), 3.73–3.92 (7H, m), 4.28–4.76 (3H, m), 4.91–5.33 (1H, m), 5.90–6.05 (2H, br).
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10. Data for new compounds are as follows:
Compound **6a**: Colorless oil. $[\alpha]_D^{27}$ −71.7° ($c=0.93$, $CHCl_3$). IR (film): 1732, 1712 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.67–1.14 (24H, m), 1.20–1.58 (5H, m), 1.61–1.74 (4H, m), 1.74–2.23 (7H, m), 2.94–3.17 (1H, br), 3.74–3.89 (6H, m), 3.99–4.22 (1H, m), 4.45–4.84 (3H, m). HRMS *m/z*: Calcd for $C_{28}H_{51}N_2O_7P$: 558.3434. Found: 558.3434.
Compound **6b**: Colorless oil. $[\alpha]_D^{24}$ −39.9° ($c=1.23$, $CHCl_3$). IR (film): 1732, 1705 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.72–1.17 (24H, m), 1.22–1.60 (5H, m), 1.60–1.75 (4H, m), 1.75–2.30 (7H, m), 2.81–3.08 (1H, m), 3.76–3.84 (6H, m), 4.05–4.25 (1H, m), 4.48–4.90 (3H, m). HRMS *m/z*: Calcd for $C_{28}H_{51}N_2O_7P$: 558.3434. Found 558.3430.
Compound (–)-**7**: White powder, mp 163–165°C. $[\alpha]_D^{25}$ −16.0° ($c=0.70$, 2N HCl). IR (KBr): 3433, 3278, 1157, 1084 cm^{-1}. ^1H NMR (D_2O) δ: 1.56–1.85 (2H, m), 1.90–2.05 (2H, m), 3.03–3.12 (1H, m), 3.16–3.26 (1H, m), 3.30–3.40 (1H, m). ^{13}C NMR (100 Mz, D_2O) δ: 21.30 (t), 23.72 (t), 46.04 (t), 54.88 (ddP, $^1J_{CP}=146.5$ Hz). HRMS *m/z*: Calcd for $C_4H_{12}N_2O_3P$: 167.0586. Found: 167.0586.
Compound (+)-**7**: White powder, mp 161–163°C. $[\alpha]_D^{26}$ +13.7° ($c=0.67$, 2N HCl). Other spectral data, identical with those of (–)-**7**.
Compound **8a**: Colorless oil. $[\alpha]_D^{22}$ −38.0° ($c=0.73$, $CHCl_3$). IR (film): 1790, 1755, 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.67–1.28 (24H, m), 1.28–1.62 (4H, br), 1.62–1.76 (4H, br), 1.84–2.27 (6H, m), 2.44–2.62 (2H, m),

3.75–3.88 (6H, m), 4.53–4.76 (2H, m), 4.84–5.00 (1H, br). ^{13}C NMR ($CDCl_3$) δ: 150.90 (s), 155.56 (s), 169.70 (s). HRMS m/z: Calcd for $C_{28}H_{50}N_2O_8P$: 573.3305. Found: 573.3310.

Compound **8b**: Yield 60% from **6b**. Colorless oil. $[\alpha]_D^{22}$ −78.9° ($c=1.18$, $CHCl_3$). IR (film): 1790, 1755, 1720 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 0.68–1.22 (24H, m), 1.25–1.59 (4H, m), 1.61–1.78 (4H, m), 1.83–2.27 (6H, m), 2.42–2.64 (2H, m), 3.74–3.89 (6H, m), 4.51–4.64 (1H, m), 4.64–4.85 (1H, m), 4.85–4.99 (1H, m). ^{13}C NMR ($CDCl_3$) δ: 150.65 (s), 155.43 (s), 169.72 (s). HRMS m/z: Calcd for $C_{28}H_{50}N_2O_8P$: 573.3305. Found: 573.3310.

Compound **9a**: Colorless prisms (H_2O), mp 225–226°C (dec.). $[\alpha]_D^{18}$ −11.7° ($c=0.90$, 2N HCl). MS (FAB) m/z: 181. IR (KBr): 3440, 3041, 1718, 1128, 1011, 989 cm^{-1}. ^{1}H NMR (2N DCl) δ: 2.18–2.33 (1H, m), 2.41–2.66 (3H, m), 4.08–4.20 (1H, m). ^{13}C NMR (2N DCl) δ: 19.48 (t), 27.47 (t), 55.26 (ddP, $^1J_{CP}=158.4$ Hz), 175.95 (s). Anal. calcd for $C_4H_9N_2O_4P$: C, 26.68; H, 5.04; N, 15.55. Found: C, 26.62; H, 4.80; N, 15.43.

Compound **9b**: Yield 68% from **8b**. Colorless prisms (H_2O), mp 225–226°C (dec.). $[\alpha]_D^{21}$ +12.4° ($c=0.73$, 2N HCl). Anal. calcd for $C_4H_9N_2O_4P$: C, 26.68; H, 5.04; N, 15.55. Found: C, 26.61; H, 4.80; N, 15.43.