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First resolution of (*R*,*R*)- and (*S*,*S*)-bis(1-hydroxyphenylmethyl)phosphinic acids via diastereomeric salt formation with enantiopure 1-phenylethylamines

Babak Kaboudin,[a,*] Hamideh Haghighat[a] and Tsutomu Yokomatsu[b]

[a]*Department of Chemistry, Institute for Advanced Studies in Basic Sciences (IASBS), Gava Zang, Zanjan 45195-1159, Iran*
[b]*School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan*

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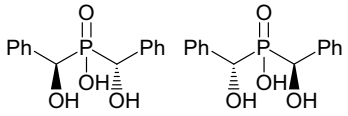
Abstract—The resolution of racemic bis(1-hydroxyphenylmethyl)phosphinic acid with enantiopure 1-phenylethylamines via diastereomeric salt formation was investigated. X-ray crystallographic analysis of the salt clearly revealed that (*S*)-1-phenylethylamine was an efficient resolving agent for obtaining the single enantiomer (*R*,*R*)-bis(1-hydroxyphenylmethyl)phosphinic acid. Resolving racemic bis(1-hydroxyphenylmethyl)phosphinic acid with (*R*)-2-phenylethylamine gave access to (*S*,*S*)-bis(1-hydroxyphenylmethyl)phosphinic acid in good yield.

1. Introduction

α-Functionalized phosphinic acid derivatives have attracted significant attention due to their usefulness both in medicinal chemistry and materials chemistry.[1–7] Among the α-functional phosphinic acids, α-hydroxyphosphinic acids are chiral organic molecules involved in a wide variety of biological processes.[8–10] Some chiral α-hydroxyphosphinic acids are useful intermediates for α-hydroxyphosphinyl peptides showing good inhibitory activity against renin.[11] Symmetric or pseudo-symmetric chiral bis(α-hydroxyalkyl)phosphinic acid derivatives have also attracted attention in the design of HIV protease inhibitors.[12] In addition, the structure of the phosphinic functional group mimics the transition state of peptide hydrolysis, while the symmetric nature of the phosphinic acid derivatives is expected to help in their binding to the homodimer of HIV-protease with a C_2-axis of symmetry.[13] Moreover, α-hydroxyphosphinic acid derivatives are useful intermediates in the synthesis of other phosphorus chiral organic compounds of material interest.[14] In contrast to the widely studied separation of 1-hydroxyalkylphosphonic acid derivatives,[15] there is no report for the resolution bis(α-hydroxyalkyl)phosphinic acid derivatives, although there is evidence that bis(α-hydroxyalkyl)phosphinic acids are pharmaceutically active.[13] As part of our efforts for the synthesis of organophosphorus compounds,[16] we have recently described a new method for the synthesis[17] and separation of diastereoisomeric bis(α-hydroxyalkyl)phosphinic acids[18] from the reactions of hypophosphorous acid with aldehydes. Herein, we report the first resolution of (±)-bis(1-hydroxyphenylmethyl)phosphinic acid **1** via diastereomeric salt formation with enantiopure 1-phenylethylamines.



(*R*,*R*) **1** (*S*,*S*) **1**

2. Results and discussion

A diastereomeric mixture of bis(α-hydroxyphenylmethyl)phosphinic acid derivatives *rac*-**1** and **2** was obtained in multi-gram quantities (82% yield in a 56:45 ratio of diastereoisomers, Scheme 1) by microwave-assisted reaction or by heating with benzaldehyde and hypophosphorus acid as previously described (Scheme 1).[19] It has previously

* Corresponding author. Tel.: +98 241 415 3220; fax: +98 241 421 4949; e-mail: kaboudin@iasbs.ac.ir

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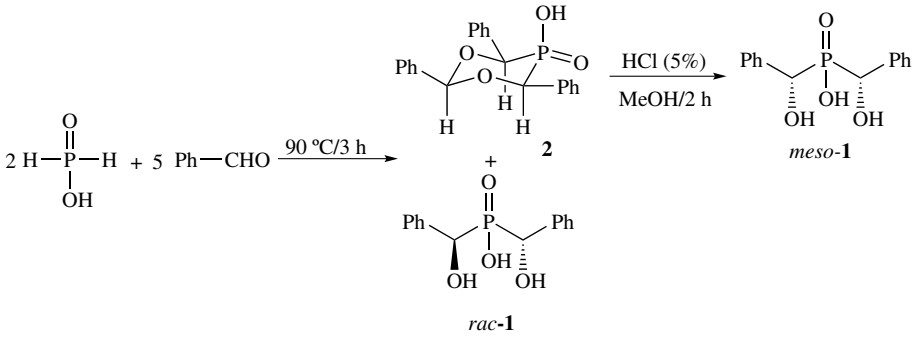
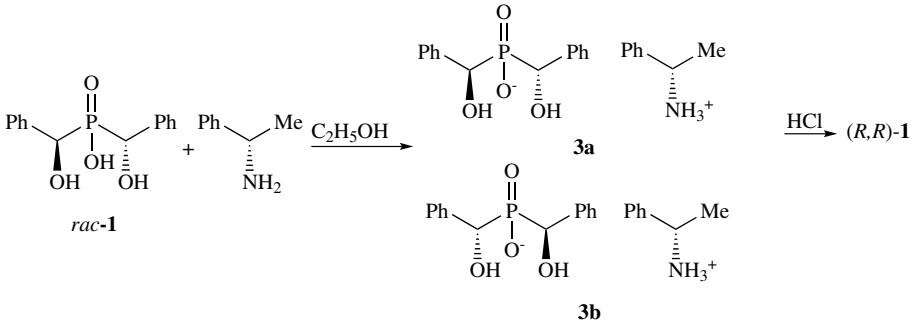


Scheme 1.

been noted that when the reaction mixture was subjected to washing with successively non-polar and polar solvents, relatively non-polar phosphinic acid **2** was extracted with chloroform and only *rac*-**1** was extracted with methanol. Compound **2** was readily converted to phosphinic acid *meso*-**1** of *meso*-stereochemistry. The stereochemistry of *rac*-**1** was confirmed after the conversion to the corresponding methyl ester using trimethyl orthoformate.[18] The methyl ester of *rac*-**1** was produced as a single diastereomer. However, under the same conditions, *meso*-**1** was converted to the corresponding methyl ester as a mixture of two diastereoisomers, due to the new stereogenic centre formed.[18]

In an effort to resolve *rac*-**1**, we examined the diastereomeric salt formation with 1 equiv of (*S*)-2-phenylethylamine in a variety of solvents, expecting that one of diastereomeric salts **3a** and **3b** would be preferably crystal-



Scheme 2.

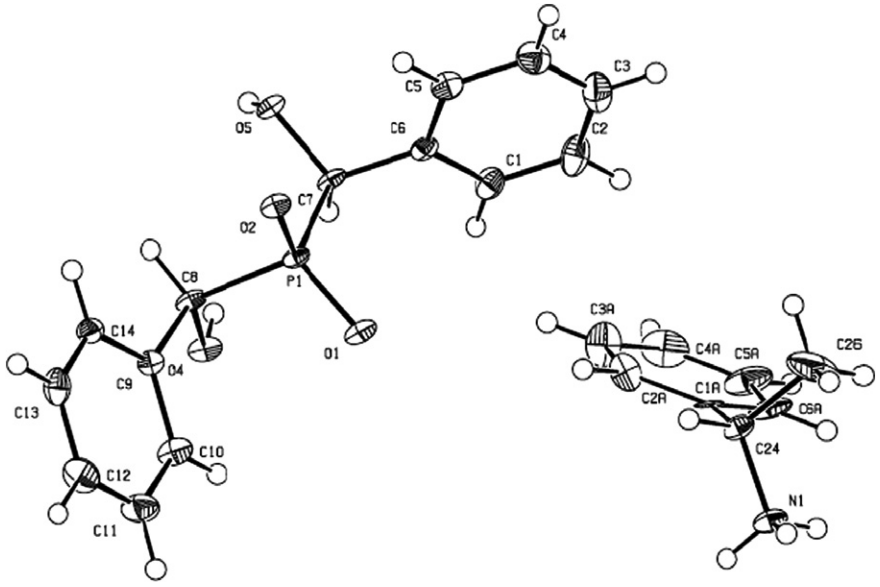
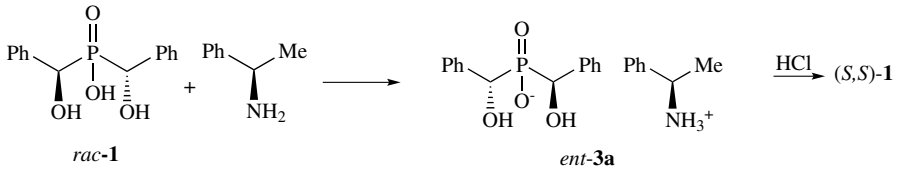


Figure 1. ORTEP drawing of **3a**.



Scheme 3.

lized (Scheme 2). We were pleased to find that when *rac*-**1** was treated with (*S*)-2-phenylethylamine in EtOH at 30–33 °C, only diastereomeric salt **3a** was preferably crystallized. Salt **3a** was found to precipitate from ethanol in 24% yield at 30–33 °C. The ^{31}P NMR spectrum of crystallized salt **3a** exhibited a singlet at δ 27.51 ppm, while that of oily residue composed with salts **3a** and **3b** showed two singlets at 27.51 ppm and 27.42 ppm, respectively (Scheme 2). The ^{1}H NMR spectrum exhibited two doublets at δ 4.75 and 4.74 ppm indicative of CH–P coupling ($J_{HP} = 9.2$ Hz for **3a** and 8.0 Hz for **3b**). The diastereomeric purity of salt **3a** can be readily assessed by a combination with ^{31}P NMR and ^{1}H NMR spectroscopy. In this case, salt **3a** is produced in >98% purity. The selection of the (*R*,*R*)-hand of *rac*-**1** with (*S*)-1-phenylethylamine was confirmed by X-ray crystallography (Fig. 1) after recrystallization. Since it is difficult to determine precisely the absolute structure by purely crystallographic methods, the known chirality of the (*S*)-1-phenylethylamine moiety was used as an internal reference. The treatment of salt **3a** with concd HCl gave enantiopure (*R*,*R*)-**1** in quantitative yield (Scheme 2).

Resolving *rac*-**1** with (*R*)-1-phenylethylamine by the same procedure descried above as in EtOH gave access to (*S*,*S*)-**1** in 21.6% yield (Scheme 3).

It is noteworthy that while other solvents, such as methanol and its mixtures with water, were not suitable for obtaining good crystals due to the excessive solubility of the intended salt in the solvents, diastereomeric salts **3a** prepared in 2-propanol are good crystals to be isolated in higher yield (35.3%). Using 2-propanol as a solvent, we were able to efficiently resolve *rac*-**1** with (*R*)-1-phenylethylamine and (*S*)-1-phenylethylamine to give (*S*,*S*)-**1** and (*R*,*R*)-**1** in 35.3% and 31.4% yield, respectively.

Since 1-phenylethylamine is readily available in both enantiomeric forms, the resolution procedure above therefore gives access to both enantiomers of bis(1-hydroxyphenylmethyl)phosphinic acid **1**.

3. Conclusion

We have shown that enantiomerically pure bis(1-hydroxyphenylmethyl)phosphinic acid can be accessed by the fractional crystallization of salts formed from racemic bis(1-hydroxyphenylmethyl)phosphinic acid and enantiopure 1-phenylethylamine. Since we have developed a method for obtaining a series of racemic bis(1-hydroxyarylmethyl)phosphinic acid derivatives,[19] a combination with the present resolution method would open up the possibility to prepare optically active bis(1-hydroxyarylmethyl)phosphinic acid derivatives with biological activity.

4. Experimental

4.1. Materials and methods

All chemicals were commercial products and distilled or recrystallized before use. All melting points obtained by a Buchi 510 and are uncorrected. Optical rotations were recorded on a CETI Polaris polarimeter with a path length 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. The infrared (IR) spectra were determined using a FT-IR Brucker-Vector 22. NMR spectra were taken with a 250 and 500 Brucker Avance instrument with the chemical shifts being reported as δ ppm and couplings expressed in Hertz. Silica gel column chromatography was carried out with Silica Gel 100 (Merck No. 10184).

X-ray crystal data of **3a** 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 = $C_{22}H_{26}NO_4P$, MW = 399.41, orthorhombic, space group = $P2_12_12_1$, $a = 6.4432(19)$ Å, $b = 11.049(3)$ Å, $c = 28.968(8)$ Å, $V = 2062.3(11)$ Å^3, $T = 90$ K, $Z = 4$, $D_x = 1.286$ Mg/m^3, (Mo-Kα) = 0.71073 Å, $R = 0.0401$ over independent reflections. Crystallographic data (excluding structure factors) for the X-ray crystal structure analysis reported in this paper have been deposited with the Cambridge Crystallographic Data Center (CCDC) as Supplementary Publication No. CCDC 675456, copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2. (+)-(*R*)-Hydroxy(phenyl)methyl[(*R*)-hydroxy(phenyl)-methyl]phosphinic acid (*R*,*R*)-1

Racemic bis(1-hydroxyphenylmethyl)phosphinic acid **1** (1.0 g, 3.6 mmol) and (*S*)-1-phenylethylamine (0.46 mL, 3.6 mmol) were dissolved in refluxing ethanol (24 mL). After refluxing for 1 h, heating was stopped, and the flask was left to gradually cool and kept for 6 h at 30–33 °C (corresponding to crystallization temperature). The resulting white solid was collected by filtration, washed with ethanol (2 mL in total) and dried in vacuo. The materials were recrystallized from ethanol to yield (*S*)-1-phenylethan-

aminium (*R*)-hydroxy(phenyl)methyl[(*R*) hydroxy(phenyl)-methyl]phosphinate **3a** in 24% yield as a white crystalline solid: mp 212–214 °C (ethanol); $[\alpha]_D^{20} = +47.2$ (*c* 2.50, CH_3OH); FT-IR (KBr) ν_{max}: 3347, 3300–2200, 1621, 1150 (P=O), 1018; ^1H NMR (CD_3SOCD_3/TMS-500 MHz): 1.27 (3H, d, $J = 6.6$ Hz), 3.20–3.60 (1H, br, –OH), 3.84 (1H, q, $J = 6.4$ Hz), 4.74 (2H, d, $J = 9.2$ Hz), 5.10–5.30 (1H, br, OH), 7.1–7.45 (15H, m); ^{31}P NMR (CD_3SOCD_3/H_3PO_4—202.4 MHz): 27.77; ^{13}C NMR (CD_3SOCD_3/TMS—125.8 MHz): 22.1, 50.7, 68.8 (d, $J_{PC} = 97.4$ Hz), 126.4, 127.5, 127.9, 128.0 (d, $J_{PC} = 3.4$ Hz), 128.7, 129.3, 141.5, 142.6. Anal. Calcd for $C_{22}H_{26}NO_4P$: C, 66.1; H, 6.6; N, 3.5. Found: C, 65.9; H, 6.8; N, 3.3. Salt **3a** (0.4 g, 1 mmol) was suspended in ethyl acetate (100 mL) and 5% aqueous HCl (100 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 (100 mL). The combined organic layers were washed with water (100 mL), dried over $MgSO_4$ and concentrated to give (*R*,*R*)-**1** (0.26 g, quantitative) as a white crystalline solid: mp 201–203 °C (ethanol); $[\alpha]_D^{20} = +62.5$ (*c* 1.80, CH_3OH). Other spectral data are identical to those of *rac*-**1**. ^1H NMR (CD_3SOCD_3/TMS—250 MHz): 5.14 (2H, d, $J = 7.4$ Hz), 4.93 (2H, br, OH), 5.99 (1H, br, OH), 7.2–7.45 (10H, m); ^{31}P NMR (CD_3SOCD_3/H_3PO_4): 38.74; ^{13}C NMR (CD_3SOCD_3/TMS—62.9 MHz): 68.8 (d, $J_{PC} = 106.7$ Hz), 127.3, 127.9, 128.0, 138.9 (d, $J_{PC} = 2.5$ Hz). Anal. Calcd for $C_{14}H_{15}O_4P$. C, 60.4; H, 5.4. Found: C, 60.3; H, 5.3.

4.3. (−)-(*S*)-Hydroxy(phenyl)methyl[(*S*)-hydroxy(phenyl)-methyl]phosphinic acid (*S*,*S*)-1

Following the above procedure resolving (±)-bis(1-hydroxyphenylmethyl)phosphinic acid *rac*-**1** with (*R*)-1-phenylethylamine, gave access to (*R*)-1-phenylethanaminium (*S*)-hydroxy (phenyl)methyl[(*S*)-hydroxy(phenyl)methyl]-phosphinate *ent*-**3a** in 21.6% yield as a white crystalline solid. Following the above procedure, (*S*,*S*)-**1** was obtained from *ent*-**3a** as a white solid in quantitatively yield: $[\alpha]_D^{20} = -62.5$ (*c* 1.80, CH_3OH). Other spectral data are identical to those of *rac*-**1**.

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References

1. (a) Martin, M. T.; Angeles, T. S.; Sugasawara, R.; Aman, N. I.; Napper, A. D.; Darsley, M. J.; Sanchez, R. I.; Booth, P.; Titmas, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 6508; (b) Li, T.; Janda, K. D. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2001.
2. Hiratake, J.; Oda, J. *Biosci., Biotechnol., Biochem.* **1997**, *61*, 211, and references cited therein.
3. (a) Yamagishi, T.; Yokomatsu, T.; Suemune, K.; Shibuya, S. *Tetrahedron* **1999**, *55*, 12125; (b) Yamagishi, T.; Kusano, T.; Kaboudin, B.; Yokomatsu, T.; Sakuma, C.; Shibuya, S. *Tetrahedron* **2003**, *59*, 767–772; (c) Yokomatsu, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1992**, *3*, 377–378; (d) Kaboudin, B.; Haruki, T.; Yamaghishi, T.; Yokomatsu, T. *Tetrahedron* **2007**, *63*, 8199–8205; (e) Kaboudin, B.; Haruki, T.; Yamagishi, T.; Yokomatsu, T. *Synthesis* **2007**, 3226–3232.
4. Engel, R. *Chem. Rev.* **1977**, *77*, 349–367.
5. Kafarski, P.; Lejczak, B.; Tyka, R.; Koba, L.; Pliszczak, E.; Wieczorek, P. *J. Plant Growth Regul.* **1995**, *14*, 199–203.
6. (a) Hilderbrand, R. L. In *The Role of Phosphonates in Living Systems*; CRC Press: Boca Raton, F1, 1982; (b) Redmore, D. In *Topics in Phosphorus Chemistry*; Griffith, E. J., Grayson, M., Eds.; Wiley: New York, 1976; Vol. 8.
7. (a) Pudovik, A. N.; Konovalova, I. V. *Synthesis* **1979**, 81–96; (b) Wynberg, H.; Smaardijk, Ab A. *Tetrahedron Lett.* **1983**, *24*, 5899–5900; (c) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *Tetrahedron: Asymmetry* **1994**, *5*, 499–502; (d) Rath, N. P.; Spilling, C. D. *Tetrahedron Lett.* **1994**, *35*, 227–230; (e) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *J. Org. Chem.* **1995**, *60*, 931–940.
8. Yamagishi, T.; Miyamae, T.; Yokomatsu, T.; Shibuya, S. *Tetrahedron Lett.* **2004**, *45*, 6616–6713.
9. Vayron, P.; Renard, P. Y.; Taran, F.; Creminon, C.; Frobert, Y.; Grassi, J.; Mioskowski, C. *PNAS* **2000**, *97*, 7058.
10. Yiotakis, A.; Georgiadis, D.; Matziari, M.; Makaritis, A.; Dive, V. *Curr. Org. Chem.* **2004**, *8*, 1135–1158.
11. Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Rogers, W. L.; Smith, S. A.; DeForrest, J. M.; Oehl, R. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1995**, *38*, 4557.
12. Peyman, A.; Budt, K.-H.; Spanig, J.; Stowasser, B.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 4549.
13. Brik, A.; Wong, Ch.-H. *Org. Biomol. Chem.* **2003**, *1*, 5–14.
14. (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5587–5590; (b) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E. *Tetrahedron Lett.* **1990**, *31*, 5591–5594; (c) Stowasser, B.; Budt, K. H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 1625–1628; (d) Peyman, A.; Budt, K. H.; Spanig, J.; Ruppert, D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1720–1722; (e) Black, R. M.; Harrison, J. M.. In *The Chemistry of Organophosphorus Compounds*; Hartley, F. R., Ed.; Wiley: New York, 1996; Vol. 4 p 781, and references cited therein; (f) Ruel, R.; Bouvier, J.-P.; Young, R. N. *J. Org. Chem.* **1995**, *60*, 5209–5213; (g) Page, P. C. B.; Moore, J. P. G.; Mansfield, I.; McKenzie, M. J.; Bowler, W. B.; Gallagher, J. A. *Tetrahedron* **2001**, *57*, 1837–1847; (h) Einhauser, Th. J.; Galanski, M.; Vogel, E.; Keppler, B. K. *Inorg. Chim. Acta* **1997**, *257*, 265–268; (i) Hudson, H. R.; Ismail, F.; Pianka, M. *Phosphorus, Sulfur Silicon Relat. Elem.* **2001**, *173*, 143–162; (j) Stowasser, B.; Budt, K.-H.; Jian-Qi, L.; Peyman, A.; Ruppert, D. *Tetrahedron Lett.* **1992**, *33*, 6625.
15. (a) Pirkle, W. H.; Brice, L. J. *Tetrahedron: Asymmetry* **1996**, *7*, 2173–2176; (b) Blakskjaer, P.; Wyatt, P. W. *Tetrahedron Lett.* **1999**, *40*, 6481–6483; (c) Drescher, M.; Li, Y.-F.; Hammerschmidt, F. *Tetrahedron* **1995**, *51*, 4933–4946; (d) Kozlowski, J. K.; Rath, N. P.; Spilling, C. D. *Tetrahedron* **1995**, *51*, 6385–6396.
16. (a) Sardarian, A. R.; Kaboudin, B. *Tetrahedron Lett.* **1997**, *38*, 2543–2546; (b) Kaboudin, B. *Chem. Lett.* **2001**, 880–881; (c) Kaboudin, B.; Nazari, R. *Tetrahedron Lett.* **2001**, *42*, 8211; (d) Kaboudin, B.; Nazari, R. *Synth. Commun.* **2001**, *31*, 2245–2250; (e) Kaboudin, B.; Balakrishna, M. S. *Synth. Commun.* **2001**, *31*, 2773–2776; (f) Kaboudin, B. *Tetrahedron Lett.* **2002**, *43*, 8713–8714; (g) Kaboudin, B. *Tetrahedron Lett.* **2003**, *44*, 1051–1053; (h) Kaboudin, B.; Rahmani, A.

Synthesis **2003**, 2705–2708; (i) Kaboudin, B.; Saadati, F. *Synthesis* **2004**, 1249–1252; (j) Kaboudin, B.; Rahmani, A. *Org. Prep. Proced. Int.* **2004**, *36*, 82–86; (k) Kaboudin, B.; Moradi, K. *Tetrahedron Lett.* **2005**, *46*, 2989–2991; (l) Kaboudin, B.; As-habei, N. *Tetrahedron Lett.* **2003**, *44*, 4243–4245; (m) Kaboudin, B.; Karimi, M. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5324–5327; (n) Kaboudin, B.; Farjadian, F. *Beilstein J. Org. Chem.* **2006**, *2*, 4; (o) Kaboudin, B.; Moradi, K. *Synthesis* **2006**, 2339–2342; (p) Kaboudin, B.; Jafari, E. *Synthesis* **2006**, 3063–3066; (q) Kaboudin, B.; Sorbiun, M. *Tetrahedron Lett.* **2007**, *48*, 9015–9017; (r) Kaboudin, B.; Jafari, E. *Synthesis* **2007**, 1823–1826.

17. Kaboudin, B.; As-habei, N. *Tetrahedron Lett.* **2004**, *45*, 9099–9101.
18. Kaboudin, B.; Haghighat, H. *Tetrahedron Lett.* **2005**, *46*, 7955–7957.
19. Kaboudin, B.; Haghighat, H.; Yokomatsu, T. *J. Org. Chem.* **2006**, *71*, 6604–6606.