

A concise approach to (+)-1-*epi*-castanospermine

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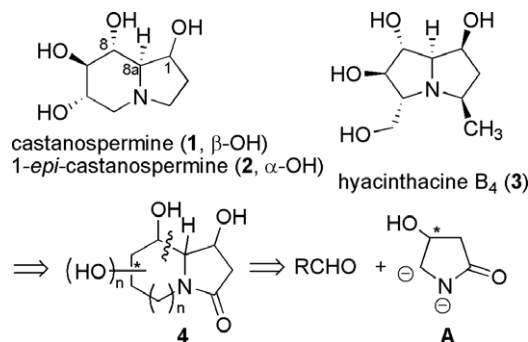
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Abstract—A concise enantioselective synthesis of (+)-1-*epi*-castanospermine (**2**) is described, which featured the use of chiral non-racemic tetramic acid derivative **5** as a synthetic equivalent of the challenging synthon **A** through a highly diastereoselective vinylogous Mukaiyama type reaction.

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Sugar mimetics, such as polyhydroxylated pyrrolidine, piperidine, pyrrolizidine, and indolizidine alkaloids, known as azasugars, show important bioactivities.¹ Among them, castanospermine (**1**), an alkaloid first isolated² from the seeds of *Castanospermum australe* and then from the dried pod of *Alexa leiopetala*, has attracted considerable attention. Because of its powerful inhibitory activities toward α - and β -glucosidases,³ castanospermine (**1**) shows considerable potential as an antiviral agent in the treatment of HIV,⁴ hepatitis C,⁵ and HSV-1⁶ infections. Castanospermine and its stereomers also have potential use in the inhibition of progression of multiple sclerosis,⁷ angiogenesis, cancer,⁸ and diabetes.⁹ Several stereomers of castanospermine have also been isolated from natural sources.¹⁰ The synthetic 1-*epi*-castanospermine (**2**)¹¹ was suggested to possess anti-HIV activity, and thus constitutes a valuable synthetic target for biological activities evaluation.

In addition, these alkaloids also provide a natural platform for exploring new synthetic methodologies. So far numerous strategies have been developed for the enantioselective synthesis of castanospermine and other polyhydroxylated alkaloids as well as their stereomers.^{11,12} However, novel, efficient, and flexible methods are still highly demanding. That the carbanionic synthon **A**-based strategy as illustrated retrosynthetically in Scheme 1^{13,14} is conceptually attractive for a general



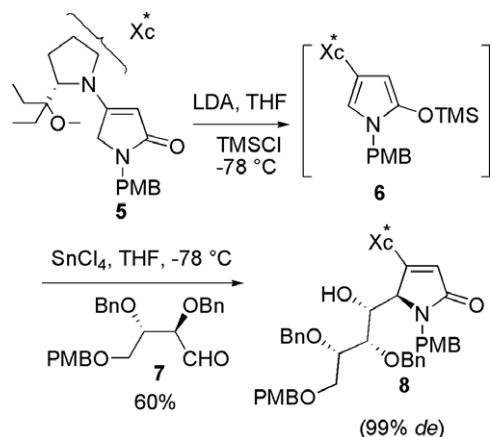
Scheme 1. Retrosynthetic analysis of polyhydroxylated alkaloids (azasugars).

approach to the azasugars such as castanospermine (**1**) and hyacinthacine B₄ (**3**).¹⁵

Although a number of unpoled methods have been developed,¹⁶ and the generation of chiral non-racemic *N*- α -carbanion of 4-hydroxy-2-pyrrolidinone **A** has been reported,^{13,17} the C–C bond formation based on synthon **A** remains a challenging problem in carbanion chemistry due to quick proton exchange¹⁷ or β -elimination if the hydroxyl group is protected.^{13,18} Recently, we reported a flexible approach to 5-alkyl tetramic acid derivatives based on the C-5 alkylation of tetramic acid derivative **5**, which was used as a synthetic equivalent of 4-hydroxy-2-pyrrolidinone 5-carbanionic synthon **A**.^{19,20} With the aim to develop a general asymmetric approach to polyhydroxylated alkaloids, we now describe the extension of this method from alkylation to α -hydroxyalkylation and the asymmetric synthesis of 1-*epi*-castanospermine (**2**).

Keywords: Castanospermine; Tetramic acid; Synthon; Mukaiyama type reaction.

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Scheme 2.

Our initial efforts have been devoted to explore the use of the vinylogous enolate derived from tetramic acid derivative **5**. Unfortunately, although the alkylation of this enolate shows excellent diastereoselectivities,¹⁹ its reaction with *iso*-butanal gave four diastereomers with a modest ratio of 2:4:27:67.

In the light of the high diastereoselectivities observed in the vinylogous aldol reaction of heterocyclic silyloxy dienes,^{21,22} extensively studied by Casiraghi and co-workers, we turned our attention to explore the use of the vinylogous silyl enol ether²³ **6**, easily derived from the tetramic acid derivative **5** (Scheme 2). Accordingly, compound **5** was treated with LDA in THF at $-78\text{ }^{\circ}\text{C}$ for 1 h. The resulted vinylogous enolate was quenched with trimethylsilyl chloride and allowed to warm up to $-10\text{ }^{\circ}\text{C}$, and then stirred for 2 h. The in situ generated vinylogous silyl enol ether **6** was reacted, in the presence of tin tetrachloride at $-78\text{ }^{\circ}\text{C}$, with 4-*O*-(4-methoxybenzyl)-2,3-bis-(*O*-benzyl)-L-threose (**7**)²⁴ for 3.5 h. To our delight, the desired hydroxyalkylated product **8** was obtained as the sole product in 60% yield. Both the ^1H and ^{13}C NMR spectra of the product are quite complex, a 2.2:1 ratio of mixture was observed. The fact that the HPLC analysis showed only one product in 99% de allowed us to assume that the complex peaks which appeared in both the ^1H and ^{13}C NMR spectra of **8** are rotameric in nature, which is due to the slow rotation around the C–N bond.¹⁸ To confirm this assumption, both the ^1H and ^{13}C NMR spectra of **8** were recorded in $\text{DMSO}-d_6$ at $20\text{ }^{\circ}\text{C}$ and $95\text{ }^{\circ}\text{C}$, respectively. The peaks of the minor isomer disappeared at $95\text{ }^{\circ}\text{C}$

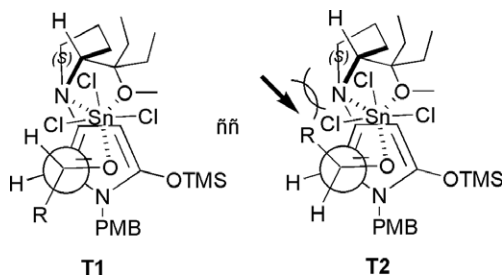
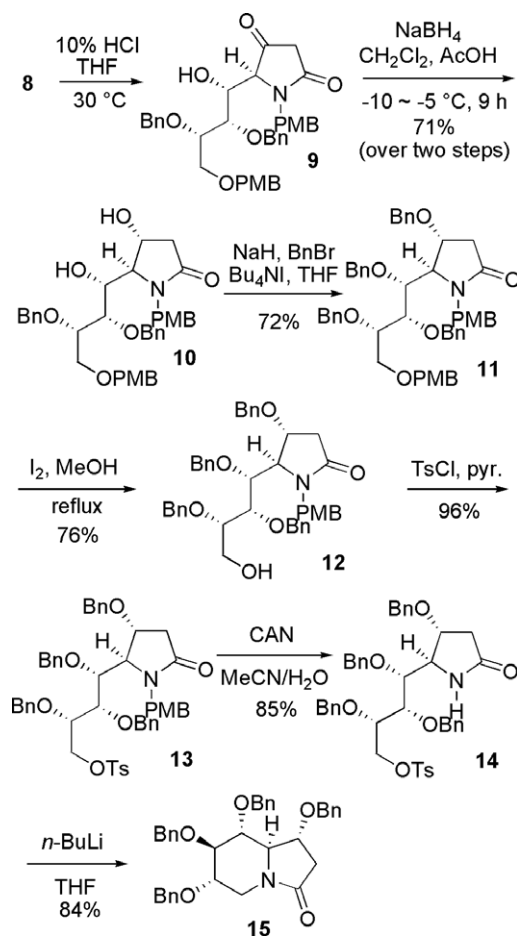


Figure 1.

and reappeared when the temperature returned to $20\text{ }^{\circ}\text{C}$. These NMR experiments show that the aldol products observed in the NMR spectra are rotamers instead of diastereomers, as observed previously.¹⁹ This was confirmed at a later stage (**8**→**10**). The stereochemical assignment was also carried out at a later stage (vide infra), which revealed that the newly formed stereocenters are *erythro* (*anti*), and the relationship with the adjacent stereocenter is *threo* (*syn*).

Thus the vinylogous Mukaiyama type reaction between **6** and **7** established the correct configurations required for the synthesis of castanospermine and its C-1 epimer. This stereoselection can be rationalized by transition state^{21,22} **T1**, which is favored over **T2** (Fig. 1). The reaction of **6** with aldehyde **7** is distinct from those reported by Casiraghi not only in the stereoselection, but also in the reaction conditions used for their formations (in THF at $-78\text{ }^{\circ}\text{C}$ versus in diethyl ether at $-85\text{ }^{\circ}\text{C}$).

Now the stage was set for the synthesis of 1-*epi*-castanospermine (**2**) (Scheme 3). To this end, compound **8** was treated with a 10% HCl solution in THF at $30\text{ }^{\circ}\text{C}$ to give the desired tetramic acid **9**, and then compound **9** was treated with NaBH_4 ²⁵ in the presence of HOAc at -10 to $-5\text{ }^{\circ}\text{C}$ for 9 h to give **10** as the sole diastereomer judged by the NMR analysis. The two hydroxyl groups



Scheme 3.

were protected (NaH, BnBr, *n*-Bu₄NI) to afford the desired di-benzylated product **11** in 72% yield. Treatment of compound **11** with I₂ in refluxing methanol²⁶ resulted in the selective cleavage of the *O*-PMB group, which furnished alcohol **12** in 76% yield.

Tosylation of alcohol **12** (*p*-TsCl/pyr.) led to tosylate **13** in 96% yield. Cleavage of the *N*-PMB group under Yoshimura's conditions²⁷ (CAN, MeCN/H₂O = 9:1) for 5 h at rt gave the desired lactam **14** in 85% yield. The key cyclization of **14** was undertaken by treating with *n*-BuLi in THF at –78 °C for 0.5 h, then allowed to warm up and stir overnight. The desired indolizidone **15** was obtained in 84% yield. The relative stereochemistry of **15** was determined, first by ¹H–¹H COSY and ¹H–¹³C HMQC experiments to make the proton assignments, and then by NOESY experiment. These experiments not only allowed determining the *erythro* (*anti*)/*threo* (*syn*) relationship of the stereocenters formed by the vinylogous Mukaiyama type reaction (6→8), but also determined the stereochemistry of the reduction (9→10), which indicated a 1,3-*syn* relationship between the C-3 and C-5.

The stereochemistry of the reduction (NaBH₄ in HOAc/CH₂Cl₂) can be understood by Evan's directed reduction model²⁵ (Fig. 2). In this singular situation merging an alicyclic-cyclic β-hydroxy ketone system, the formation of the 1,3-*syn*-diol can be explained by the Evans' model (intramolecular hydride delivery).

The subsequent reduction of **15** with borane dimethyl sulfide complex (BH₃·SMe₂) proceeded smoothly to give indolizidine **16** in 92% yield (Scheme 4). Finally, cleavage of the four benzyl groups in **16** was achieved by Pd/C-catalyzed transfer hydrogenolysis, which gave 1-*epi*-castanospermine (**2**) {[α]_D²² +3.8 (*c* 0.54, MeOH); lit.¹¹ [α]_D²⁵ +6 (*c* 0.45, H₂O); [α]_D²⁵ +3.8 (*c* 0.5, MeOH); [α]_D²² +6.2 (*c* 0.15, MeOH); for the antipode: [α]_D²² –4 (*c* 1.2, MeOH); [α]_D²² –3.1 (*c* 1.86, MeOH)} in quantitative yield. The ¹H and ¹³C NMR spectral data of the synthetic material are in consistent with those reported.¹¹

In summary, chiral non-racemic tetramic acid derivative **5** is demonstrated to be a good synthetic equivalent to synthon **A**, via highly diastereoselective vinylogous Mukaiyama type reaction with an aldehyde. An application of the present method to the asymmetric synthesis of (+)-1-*epi*-castanospermine (**2**) was achieved in 10 steps and 14.8% overall yield from **5**. Further application of synthon **A**-based method in the asymmetric synthesis of castanospermine and other azasugars using

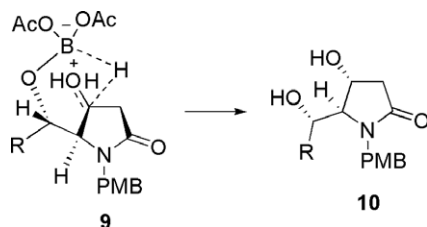
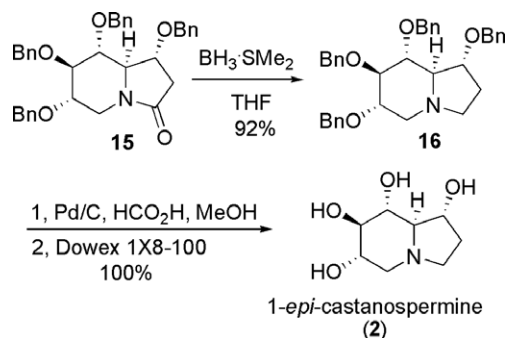


Figure 2.



Scheme 4.

achiral aldehydes is in progress in these laboratories and will be reported in due course.

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References and notes

- For recent reviews on the synthesis and biological activities, see: (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645; (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265; (c) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300; (d) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 625; (e) Michael, J. P. *Nat. Prod. Rep.* **1999**, *16*, 675; (f) Elbein, A. D.; Molyneux, R. J. In *Iminosugars as Glycosidase Inhibitors*; Stutz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999; p 216; (g) Michael, J. P. *Nat. Prod. Rep.* **1997**, *14*, 619.
- (a) Hohenschutz, L. D.; Bell, E. A.; Jewess, P. J.; Leworthy, D. P.; Pryce, R. J.; Arnold, E.; Clardy, J. *Phytochemistry* **1981**, *20*, 811; (b) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Stirton, C. H.; Carter, D.; Hegarty, M. P.; Bell, E. A. *Phytochemistry* **1988**, *27*, 1403.
- For two reviews, see: (a) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 751; (b) Winchester, B. *Biochem. Soc. Trans.* **1992**, *20*, 699.
- De Clercq, E. *Med. Res. Rev.* **2000**, *20*, 323.
- Whitby, K.; Taylor, D.; Patel, D.; Ahmed, P.; Tyms, A. S. *Antiviral Chem. Chemother.* **2004**, *15*, 141.
- Bridges, C. G.; Ahmed, S. P.; Kang, M. S.; Nash, R. J.; Porter, E. A.; Tyms, A. S. *Glycobiology* **1995**, *5*, 249.
- Walter, S.; Fassbender, K.; Gulbins, E.; Liu, Y.; Rieschel, M.; Herten, M.; Bertsch, T.; Engelhardt, B. *J. Neuroimmunol.* **2002**, *132*, 1.
- Pili, R.; Chang, J.; Partis, R. A.; Mueller, R. A.; Chrest, F. J.; Passaniti, A. *Cancer Res.* **1995**, *55*, 2920.
- Nojima, H.; Kimura, I.; Chen, F.-J.; Sugihara, Y.; Haruno, M.; Kato, A.; Asano, N. *J. Nat. Prod.* **1998**, *61*, 397.
- (a) Molyneux, R. J.; Roitman, J. N.; Dunnheim, G.; Szumilo, T.; Elbein, A. D. *Arch. Biochem. Biophys.* **1986**,

- 251, 450; (b) Chen, T. M.; George, R. C.; Weir, J. L.; Leapheart, T. *J. Nat. Prod.* **1990**, 53, 359; (c) Molyneux, R. J.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1990**, 53, 609; (d) Molyneux, R. J.; Pan, Y. T.; Tropea, J. E.; Benson, M.; Kaushal, G. P.; Elbein, A. D. *Biochemistry* **1991**, 30, 9981; (e) Winchester, B. G.; Cenci di Bello, I.; Richardson, A. C.; Nash, R. J.; Fellows, L. E.; Ramsden, N. G.; Fleet, G. W. *J. Biochem. J.* **1990**, 269, 227.
11. (a) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, 25, 165; (b) Setoi, H.; Takeno, H.; Hashimoto, M. *Tetrahedron Lett.* **1985**, 26, 4617; (c) Mulzer, J.; Dehmlow, H.; Buschmann, J.; Luger, P. *J. Org. Chem.* **1992**, 57, 3194; (d) Ina, H.; Kibayashi, C. *J. Org. Chem.* **1993**, 58, 52; (e) Denmark, S. E.; Herbert, B. *J. Org. Chem.* **2000**, 65, 2887; (f) Cronin, L.; Murphy, P. V. *Org. Lett.* **2005**, 7, 2691.
12. (a) Leeper, F. J.; Howard, S. *Tetrahedron Lett.* **1995**, 36, 2335; (b) Martin, S. F.; Chen, H. J.; Lynch, V. M. *J. Org. Chem.* **1995**, 60, 276; (c) Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, 37, 547; (d) Zhang, H. X.; Xia, P.; Zhou, W. S. *Tetrahedron* **2003**, 59, 2015; (e) Zhao, Z. M.; Song, L.; Mariano, P. S. *Tetrahedron* **2005**, 61, 8888; (f) Sletten, E. M.; Liotta, L. J. *J. Org. Chem.* **2006**, 71, 1335.
13. For brief discussions on this strategy, see: (a) Huang, P.-Q. Recent Advances on the Asymmetric Synthesis of Bioactive 2-Pyrrolidinone-Related Compounds Starting from Enantiomeric Malic Acid. In *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles*; Vicario, J. L.; Badia, D.; Carrillo, L., Eds.; Research Signpost: Kerala, 2005; p 197; (b) Huang, P.-Q. *Synlett* **2006**, 1133.
14. For similar approaches based on the corresponding pyrrolidine synthons, see: (a) Gallagher, T.; Giles, M.; Subramanian, R. S.; Hadley, M. S. *J. Chem. Soc., Chem. Commun.* **1992**, 166; (b) Thompson, S. H. J.; Subramanian, R. S.; Roberts, J. K.; Hadley, M. S. *J. Chem. Soc., Chem. Commun.* **1994**, 933; (c) Zheng, X.; Feng, C.-G.; Ye, J.-L.; Huang, P.-Q. *Org. Lett.* **2005**, 7, 553.
15. Yamashita, T.; Yasuda, K.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. *J. Nat. Prod.* **2002**, 65, 1875.
16. For recent reviews involving the generation and application of α -lithioamines, see: (a) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, 29, 552; (b) Yus, M. *Chem. Soc. Rev.* **1996**, 25, 155; (c) Cohen, T. *Pure Appl. Chem.* **1996**, 68, 913; (d) Gawley, R. E. *Curr. Org. Chem.* **1997**, 1, 71; (e) Kessar, S. V.; Singh, P. *Chem. Rev.* **1997**, 97, 721; (f) Katritzky, A.; Qi, M. *Tetrahedron* **1998**, 54, 2647; (g) Husson, H. P.; Royer, J. *Chem. Soc. Rev.* **1999**, 28, 383.
17. (a) Huang, P.-Q.; Zheng, X.; Wang, S.-L.; Ye, J.-L.; Jin, L.-R.; Chen, Z. *Tetrahedron: Asymmetry* **1999**, 10, 3309. See also: (b) Iula, D. M.; Gawley, R. E. *J. Org. Chem.* **2000**, 65, 6169.
18. Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, 58, 1109.
19. (a) Huang, P.-Q.; Wu, T.-J.; Ruan, Y.-P. *Org. Lett.* **2003**, 5, 4341; (b) Huang, P.-Q.; Deng, J. *Synlett* **2004**, 247.
20. For an indirect method, see: (a) Zhou, X.; Huang, P.-Q. *Synlett* **2006**, 1235; (b) Zhou, X.; Liu, W.-J.; Ye, J.-L.; Huang, P.-Q. *J. Org. Chem.* **2007**, 72, 8904.
21. For a recent review dealing with the silyloxy diene chemistry, see: Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, 100, 1929.
22. For selected examples, see: (a) Fiorenza, M.; Reginato, G.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1984**, 49, 551; (b) Casiraghi, G.; Rassu, G.; Spanu, P.; Pinna, L.; Ulgheri, F. *J. Org. Chem.* **1993**, 58, 3397; (c) Soro, P.; Rassu, G.; Spaun, P.; Pinna, L.; Zanardi, F.; Casiraghi, G. *J. Org. Chem.* **1996**, 61, 5172; (d) Bqussqnnne, I.; Schwardt, O.; Royer, J.; Pichon, M.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1997**, 38, 2259; (e) Poli, G.; Baffoni, S. C.; Giambastiani, G.; Reginato, G. *Tetrahedron* **1998**, 54, 10403; (f) Barnes, D. M.; McLaughlin, M. A.; Oie, T.; Rasmussen, M. W.; Stewart, K. D.; Wittenberger, S. J. *Org. Lett.* **2002**, 4, 1427; (g) DeGoey, D. A.; Chen, H.-J.; Flosi, W. J.; Grampovnik, D. J.; Yeung, C. M.; Klein, L. L.; Kempf, D. J. *J. Org. Chem.* **2002**, 67, 5445; (h) Brimble, M. A.; Burgess, C.; Halim, R.; Petersson, M.; Ray, J. *Tetrahedron* **2004**, 60, 5751. See also: (i) Schlesinger, R. H.; Pettus, T. R. R. *J. Org. Chem.* **1994**, 59, 3246, and the references cited therein.
23. (a) Jones, R. C. F.; Bates, A. D. *Tetrahedron Lett.* **1986**, 27, 5285. While this manuscript was in preparation, Hunter and co-workers communicated another vinylogous Mukaiyama type reaction: (b) Hunter, R.; Rees-Jones, S. C. M.; Su, H. *Tetrahedron Lett.* **2007**, 48, 2819.
24. Compound **7** was prepared in a similar way as described in the following references: (a) Nemoto, H.; Takamatsu, S.; Yamamoto, Y. *J. Org. Chem.* **1991**, 56, 1321; (b) Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, 46, 265.
25. (a) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, 24, 4287; (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, 110, 3560; (c) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, 24, 273.
26. Vaino, A. R.; Szarek, W. A. *Synlett* **1995**, 1157.
27. (a) Yamaura, M.; Suzuki, T.; Hashimoto, H.; Yoshimura, J.; Okamoto, T.; Shin, C. *Bull. Chem. Soc. Jpn.* **1985**, 58, 1413; (b) Yoshimura, J.; Yamaura, M.; Suzuki, T.; Hashimoto, H. *Chem. Lett.* **1983**, 1001.