Establishment of the Structure of Pinpollitol by Total Synthesis of the Proposed Putative Structures

Kana M. Sureshan,* Tomohiro Murakami, Yutaka Watanabe*

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama 790-8577, Japan
Fax +81(89)9279944; E-mail: wyutaka@dpc.ehime-u.ac.jp; E-mail: sureshankm@yahoo.co.in

Received 2 January 2005

Abstract: Proposed structures of pinpollitol, namely 1,4-di-*O*-methyl-*chiro*-inositol and 1,3-di-*O*-methyl-*chiro*-inositol, have been synthesized from *myo*-inositol. Racemic 1,4-di-*O*-methyl-*chiro*-inositol has been synthesized from the readily available 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol, in five steps while DL-1,3-di-*O*-methyl-*chiro*-inositol from *myo*-inositol 1,3,5-orthoformate in nine steps. A comparison of the reported NMR data of pinpollitol with those of synthetic dimethyl ethers revealed that pinpollitol is D-1,4-di-*O*-methyl-*chiro*-inositol. Thus we have not only confirmed the structure of pinpollitol unambiguously but also achieved a rapid total synthesis of it from a cheaply available starting material, *myo*-inositol, in just six steps.

Key words: natural product, total synthesis, inositol, cyclitol, regioselectivity

A great deal of attention has been paid to the inositol chemistry since many of the family members are proved to possess interesting biological significance.[1] Of the nine possible isomers, *myo*-, D-*chiro*-, L-*chiro*-, *scyllo*-, *neo*- and *muco*-inositols are naturally occurring, *myo*-inositol being the abundant. In animals these inositols occur in the phosphorylated form while in plants they occur in phosphorylated, methylated or in free forms. One or more methyl ethers of each of these naturally occurring inositols have been isolated from plants. Most of these methyl ethers have been synthesized[2] owing to the impractical isolation of these natural products.

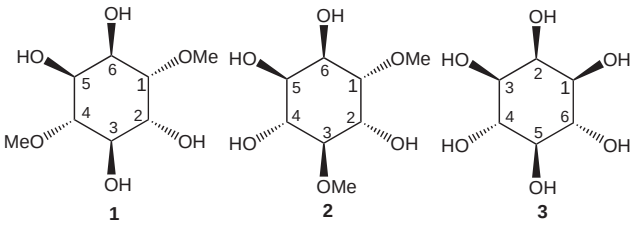


Figure 1

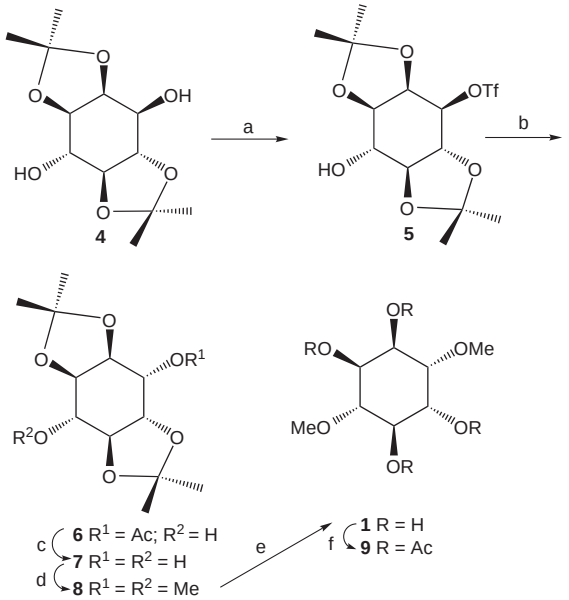
(+)-Pinpollitol, a dimethyl ether of *chiro*-inositol was isolated from the pollen and needles of the plant *Pinus radiata* by Gallagher.[3] (+)-Pinpollitol is the first di-*O*-methyl inositol to be found in a gymnosperm and is the third di-*O*-methyl inositols found in nature after dambonitol and liriodendritol. Since demethylation of pinpollitol provided D-*chiro*-inositol, it was concluded that (+)-pinpollitol is a dimethyl ether of D-*chiro*-inositol. Of the possible nine structures for the dimethyl ether of *chiro*-inositol, based on the lack of symmetry in the NMR spectrum and correlation of chemical shifts of both pinpollitol and its tetraacetyl derivative with similar type of compounds, the authors have tentatively proposed two probable structures for pinpollitol; 1D-1,4-di-*O*-methyl-*chiro*-inositol (**1**) and 1D-1,3-di-*O*-methyl-*chiro*-inositol (**2**). We herein report the establishment of the absolute structure of pinpollitol by total syntheses of both **1** and **2** (Figure 1).

Myo-inositol (**3**) was chosen as the synthon for the synthesis of **1** and **2** for the following reasons: (a) *myo*-inositol is inexpensive starting material compared to the *chiro*-inositol; (b) since the selective protection–deprotection strategies for *myo*-inositol is well explored,[4] access to the required hydroxyl group(s) can be easily achieved by adopting the known methodologies; (c) since pinpollitol is a derivative of D-*chiro*-inositol, determination of relative position of two methyl ethers on racemic *chiro*-inositol skeleton is sufficient enough to establish the absolute structure of pinpollitol.

For the synthesis of **1** from **3**, inversion of configuration at C-3 and methylation of 3-OH and 6-OH are the essential steps required. Inversion can be achieved by substitution of a sulfonate moiety with an oxygen nucleophile. Since no manipulation is required at 1-, 2-, 4- and 5-positions of *myo*-inositol, readily available 1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (**4**)[5] was chosen as the ideally protected starting material (Scheme 1). Use of diketal **4** as synthon allows syntheses of optically active derivatives as efficient methods are known[6] for the optical resolution of this diol. Enhanced reactivity of 3-OH in **4** towards electrophilic reagents is an additional advantage for selective introduction of a sulfonate group (for subsequent inversion) at this position. It has been reported[4] that 3-OH of diol **4** is more reactive than 6-OH towards acylation, alkylation, sulfonylation, etc. Regioselective sulfonylation of racemic diol **4** with 1.1 equivalents of triflic anhydride provided the monotriflate **5** (90%) as expected with minor amounts of ditriflate, which could be removed by washing with hexane. Nucleophilic substitution of triflate **5** with KOAc in *N*,*N*-dimethylacetamide (DMA) gave the racemic 1-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-*chiro*-inositol (**6**) in quantitative yield. The most downfield signal appeared as a triplet with a coupling

SYNLETT 2005, No. 5, pp 0769–0772
Advanced online publication: 09.03.2005
DOI: 10.1055/s-2005-863752; Art ID: U00105ST

constant of 2.4 Hz confirming the *chiro*-configuration (ae and ee coupling). Later, this structural assignment was confirmed by solving the single crystal X-ray structure of (–)-**6** (Figure 2).[7] No product with retention of configuration has been identified. The acetate **6** on methanolysis provided the racemic 1,2:4,5-di-*O*-isopropylidene-*chiro*-inositol (**7**) in 94% yield. Diol **7** on methylation provided (±)-1,2:4,5-di-*O*-isopropylidene-3,6-di-*O*-methyl-*chiro*-inositol (**8**)[8] in good (99%) yield. The isopropylidene groups were removed by acid hydrolysis to provide (±)-1,4-di-*O*-methyl-*chiro*-inositol (**1**, 73%),[9] which was acetylated to get the tetraacetate **9** (93%).[10]



Scheme 1 (a) Tf_2O (1.1 equiv), pyridine, CH_2Cl_2, –20 °C; (b) KOAc, DMA, 70 °C; (c) NaOMe, MeOH, reflux; (d) MeI, NaH, DMF, r.t.; (e) TFA, H_2O, r.t.; (f) Ac_2O, pyridine, r.t.

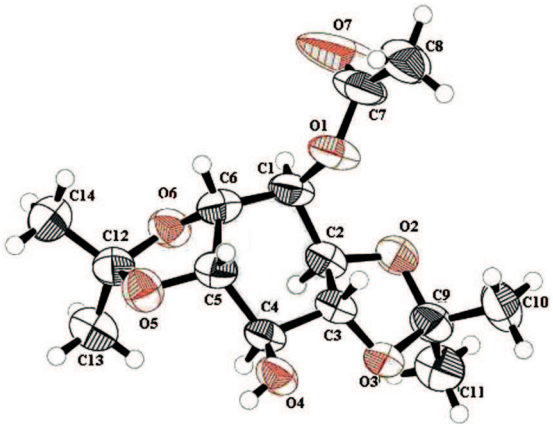


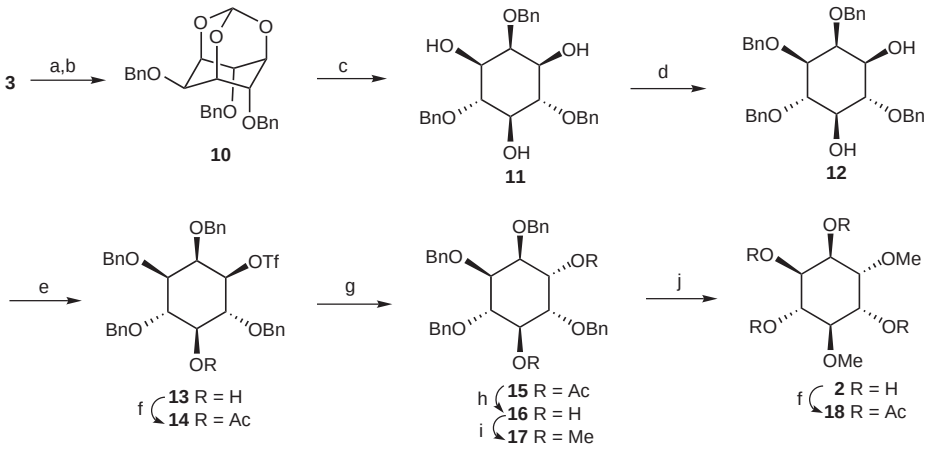
Figure 2 ORTEP diagram of **6**.

For the synthesis of **2** from *myo*-inositol (**3**), inversion at C-3 and methylation at 3-OH and 5-OH groups are the important steps to be considered. Since diketal derivatives of *myo*-inositols have protected 5-OH, they are not ideal intermediates for the synthesis of **2**. Access to 1-, 3- and 5-hydroxyl groups of *myo*-inositol can be achieved by temporary protection of these hydroxyls as orthoester followed by protection of 2-, 4- and 6-hydroxyl groups and acid hydrolysis of the orthoester functionality. Also it is known that 1- and 3-hydroxyl groups are more reactive than 5-OH. Hence initial protection of one of the two equivalent hydroxyl groups (1-OH or 3-OH) provides 1(3),5-diol. It is known that 1(3)-OH is relatively more reactive than 5-OH towards various electrophilic reagents. Since an inversion is inevitable at C-3 before methylation, 3-OH can be sulfonylated selectively and inverted by S_N2 substitution to have access to 1,3-diol with *chiro*-inositol configuration.

Myo-inositol 1,3,5-orthoformate[11] was converted to the fully protected tribenzyl ether **10**. Acid hydrolysis of **10** provided the meso triol **11**. Regioselective benzylation of triol **11** gave the known[12] tetrabenzyl ether **12**. In triol **11**, 1-OH and 3-OH are identical due to the symmetry of the molecule. Benzylation at 1(3)-OH give a dissymmetric molecule while benzylation at 5-OH give another *meso*-compound. Thus, the position of benzylation can easily be understood based on the presence or lack of symmetry in the NMR spectrum. Between the two hydroxyl groups of **12**, the more reactive 3-OH was sulfonylated with triflic anhydride to provide the triflate **13** (81%). The most deshielded proton appeared as a dd with coupling constants 7.6 and 2.0 Hz, which confirm the triflylation at O-3. Also the remaining hydroxyl group showed coupling (J = 2.4 Hz) with H-5. The triflate **13** was acetylated to give the monoacetate **14** (98%). The triflate **14** on nucleophilic substitution with KOAc in DMA provided racemic 1,2,3,5-tetra-*O*-benzyl-4,6-di-*O*-acetyl-*chiro*-inositol (**15**, 30%)[13] as a gum along with an unidentified product. Methanolysis of the diacetate **15** provided the diol **16** in 83% yield. Diol **16** on methylation formed the dimethyl ether **17** (63%) as expected. Finally, the hydrogenolysis of the benzyl ether moieties provided racemic 1,3-di-*O*-methyl-*chiro*-inositol (**2**, 89%),[14] which was acetylated to the tetraacetate **18**[15] in 93% yield (Scheme 2).

A comparison of ^{1}H NMR of pinpollitol and its tetraacetate with that of dimethyl ethers (**1** and **2**) and their tetraacetates (**9** and **18**) revealed that pinpollitol is 1,4-di-*O*-methyl-*chiro*-inositol. Since pinpollitol is known to be a dimethyl ether of D-*chiro*-inositol, the absolute configuration of pinpollitol is 1D-1,4-di-*O*-methyl-*chiro*-inositol.

In conclusion, we have reported efficient routes for the syntheses of proposed structures of pinpollitol. This has established the structure of pinpollitol unambiguously. We hope the chemistry explored here will be of interest to a wider cross section of organic chemists as inositol and other cyclitols are increasingly being used as synthons for many natural products,[16] metal complexing agents,[17] gelators,[18] catalysts,[19] supramolecular assemblies,[20] chiral auxiliary,[21] etc.



Scheme 2 (a) $CH(OEt)_3$, *p*TSA, DMF, 100 °C, 2 h; (b) BnBr, NaH, DMF, r.t.; (c) 1 M HCl, MeOH, reflux, 1 h; (d) BnBr, NaH, DMF, r.t., 10 min; (e) Tf_2O, pyridine, 0 °C; (f) Ac_2O, pyridine, 0 °C; (g) KOAc, DMA, 70 °C; (h) Et_3N, MeOH, reflux, 1 h; (i) MeI, NaH, DMF, 0 °C; (j) Pd/C, H_2, MeOH, EtOAc, r.t.

Acknowledgment

We thank JSPS for a postdoctoral fellowship (KMS) and Grant-in-aid (No. 02170). Also we thank Venture Business Laboratory and Advanced Instrumentation Center for Chemical Analysis, Ehime University for NMR and elemental analysis, respectively.

References

(1) (a) Hinchliffe, K.; Irvine, R. *Nature* **1997**, *390*, 123. (b) *Phosphoinositides: Chemistry, Biochemistry and Biomedical Applications*; Bruzik, K. S., Ed.; ACS Symposium Series 718, Oxford University Press: Oxford, **1999**. (c) Ferguson, M. A. J.; Williams, A. F. *Annu. Rev. Biochem.* **1988**, *57*, 285.

(2) **Pinitol:** (a) Hudlicky, T.; Price, J. D.; Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439. (b) Ley, S. V.; Sternfeld, F.; Taylor, S. *Tetrahedron Lett.* **1987**, *28*, 225. (c) Ley, S. V.; Sternfeld, F. *Tetrahedron* **1989**, *45*, 3463. (d) Jung, P. M. J.; Motherwell, W. B.; Williams, A. S. *Chem. Commun.* **1997**, 1283. **Ononitol:** (e) Pietrusiewicz, K. M.; Salamonczyk, G. M. *Synth. Commun.* **1995**, *25*, 1863. **Quebrachitol:** (f) Carless, H. A. J.; Busia, K.; Oak, O. Z. *Synlett* **1993**, 672.

(3) Gallagher, R. T. *Phytochemistry* **1975**, *14*, 755.

(4) Sureshan, K. M.; Shashidhar, M. S.; Praveen, T.; Das, T. *Chem. Rev.* **2003**, *103*, 4477.

(5) Diketal **4** can be synthesized from *myo*-inositol in one step. See: Gigg, J.; Gigg, R.; Payne, S.; Conant, R. *Carbohydr. Res.* **1985**, *142*, 132.

(6) Sureshan, K. M.; Yamasaki, T.; Hayashi, M.; Watanabe, Y. *Tetrahedron: Asymmetry* **2003**, *14*, 1771; and references cited therein.

(7) Crystallographic data are deposited as CCDC 236206. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033, e-mail: deposit@ccdc.cam.ac.uk].

(8) Analytical data: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 3 H, CH_3), 1.48 (s, 6 H, 2 × CH_3), 1.50 (s, 3 H, CH_3), 3.44 (dd, 1 H, *J* = 10.3, 5.9 Hz, H-3), 3.560 (s, 3 H, OCH_3), 3.564 (s, 3 H, OCH_3), 3.79 (dd, 1 H, *J* = 10.3, 2.4 Hz, H-5), 3.96 (t, 1 H, *J* = 10.3 Hz, H-4), 4.02 (t, 1 H, *J* = 2.4, 2.0 Hz, H-6), 4.14 (t, 1 H, *J* = 5.9 Hz, H-2), 4.30 (dd, 1 H, *J* = 5.9, 2.0 Hz, H-1). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 25.60 (CH_3), 26.50 (CH_3), 27.10 (CH_3), 27.80 (CH_3), 58.50 (OCH_3), 60.00 (OCH_3), 74.70, 74.73, 77.26, 78.01, 80.64 (C-3 or C-6), 84.78 (C-6 or C-3), 109.24 (O-*C*-O), 111.34 (O-*C*-O).

(9) Analytical data: mp 189–192 °C. ^{1}H NMR (400 MHz, D_2O): δ = 3.33 (t, 1 H, *J* = 9.6 Hz, H-4), 3.43 (s, 3 H, CH_3), 3.60 (t, 1 H, *J* = 9.6 Hz, H-3), 3.60 (s, 3 H, CH_3), 3.64 (t, 1 H, *J* = 3.6 Hz, H-1), 3.74 (dd, 1 H, *J* = 9.6, 3.6 Hz, H-5), 3.81 (dd, 1 H, *J* = 10.0, 3.6 Hz, H-2), 4.22 (t, 1 H, *J* = 3.6 Hz, H-6). (^{13}C NMR (100.4 MHz, D_2O, dioxane reference at 66.5 ppm): δ = 58.5, 59.6, 68.0, 69.8, 70.2, 72.3, 81.2, 82.5. Anal. Calcd for $C_8H_{16}O_6$ (%): C, 46.15; H, 7.75. Found: C, 46.09; H, 7.59.

(10) Analytical data: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3 H, $COCH_3$), 2.08 (s, 6 H, 2 × $COCH_3$), 2.13 (s, 3 H, $COCH_3$), 3.44 (s, 3 H, O-CH_3), 3.50 (s, 3 H, O-CH_3), 3.62 (t, 1 H, *J* = 10.3 Hz, H-4), 3.64 (t, 1 H, *J* = 3.4 Hz, H-1), 5.14 (dd, 1 H, *J* = 10.3, 3.4 Hz, H-2), 5.21 (dd, 1 H, *J* = 10.3, 3.4 Hz, H-5), 5.43 (t, 1 H, *J* = 10.3 Hz, H-3), 5.51 (t, 1 H, *J* = 3.4 Hz, H-6). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 20.8 ($COCH_3$), 59.4 (O-CH_3), 59.8 (O-CH_3), 67.6, 70.5, 71.1, 76.6, 78.5, 169.5 (O-$COCH_3$), 169.6 (O-$COCH_3$), 169.8 (O-$COCH_3$), 170.3 (O-$COCH_3$).

(11) Lee, H. W.; Kishi, Y. *J. Org. Chem.* **1985**, *69*, 4402.

(12) Westerduin, P.; Willems, H. A. M.; van Boeckel, C. A. A. *Tetrahedron Lett.* **1990**, *31*, 6915.

(13) Analytical data: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.93 (s, 3 H, $COCH_3$), 2.01 (s, 3 H, $COCH_3$), 3.71 (t, 1 H, *J* = 3.9 Hz, H-1), 3.74–3.80 (2 × dd, 2 H, H-2 and H-5), 3.88 (t, 1 H, *J* = 9.8 Hz, H-3), 4.31–4.89 (m, 8 H, 4 × CH_2), 5.31 (t, 1 H, *J* = 9.8 Hz, H-4), 5.35 (t, 1 H, *J* = 3.9 Hz, H-6), 7.20–7.40 (m, 20 H, Ph). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 20.90 ($COCH_3$), 20.95 ($COCH_3$), 67.3, 71.9, 73.1, 73.3, 73.6, 74.6, 74.7, 75.5, 77.2, 79.4, 79.4, 127.5, 127.6, 127.7, 127.8, 127.83, 127.9, 127.90, 127.92, 128.3, 128.4, 128.43, 137.8, 137.9, 138.1, 138.6, 169.8 ($OCOCH_3$), 170.02 ($OCOCH_3$). Anal. Calcd for $C_{38}H_{40}O_8 \cdot 0.5H_2O$ (%): C, 72.02; H, 6.52. Found C, 72.01; H, 6.89.

(14) Analytical data: ^{1}H NMR (400 MHz, D_2O): δ = 3.28 (t, 1 H, *J* = 9.4 Hz, H-3), 3.48 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3), 3.63 (t, 1 H, *J* = 9.6 Hz, H-4), 3.64 (t, 1 H, *J* = 3.6 Hz, H-1), 3.69 (dd, 1 H, *J* = 9.6, 3.6 Hz, H-5), 3.86 (dd, 1 H, *J* = 10.2, 3.6 Hz, H-2), 4.22 (t, 1 H, *J* = 3.6 Hz, H-6). ^{13}C NMR (100.4 MHz, D_2O, dioxane reference at 66.5 ppm): δ = 58.5, 59.8, 67.8, 70.6, 71.9, 81.5, 83.0. Anal. Calcd for $C_8H_{16}O_6 \cdot 1.4H_2O$ (%): C, 41.16; H, 8.12. Found: C, 41.08; H, 7.86.

(15) Analytical data: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (s, 3 H, $COCH_3$), 2.08 (s, 3 H, $COCH_3$), 2.14 (s, 6 H, 2 × $COCH_3$), 3.47 (s, 3 H, OCH_3), 3.49 (s, 3 H, OCH_3), 3.68 (t, 1 H, *J* = 3.4 Hz, H-1), 3.68 (t, 1 H, *J* = 9.8 Hz, H-3), 5.12 (dd, 1 H, *J* = 10.3, 2.9 Hz, H-2), 5.20 (dd, 1 H, *J* = 10.3, 3.4 Hz, H-5), 5.34 (t, 1 H, *J* = 9.8 Hz, H-4), 5.49 (t, 1 H, *J* = 3.9 Hz, H-6). ^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 20.65 ($COCH_3$), 20.82 ($COCH_3$), 20.86 ($COCH_3$), 21.02 ($COCH_3$), 59.32 (OCH_3), 60.57 (OCH_3), 67.24, 69.23, 71.26, 72.62, 76.55, 78.66, 169.73 ($OCOCH_3$), 169.75 ($OCOCH_3$), 170.04 ($OCOCH_3$), 170.11 ($OCOCH_3$). Anal. Calcd for $C_{16}H_{26}O_{11}$ (%): C, 48.73; H, 6.65. Found: C, 48.46; H, 6.30.

(16) (a) Kwon, Y.-K.; Lee, C.; Chung, S.-K. *J. Org. Chem.* **2002**, *67*, 3327. (b) Suzuki, T.; Suzuki, S. T.; Yamada, I.; Koashi, Y.; Yamada, K.; Chida, N. *J. Org. Chem.* **2002**, *67*, 2874. (c) Chida, N.; Ogawa, S. *Chem. Commun.* **1997**, 807; and references cited therein. (d) Suzuki, T.; Tanaka, S.; Yamada, I.; Koashi, Y.; Yamada, K.; Chida, N. *Org. Lett.* **2000**, *2*, 1137. (e) Chida, N.; Yoshinaga, M.; Tobe, T.; Ogawa, S. *Chem. Commun.* **1997**, 1043. (f) Akiyama, T.; Ohnari, M.; Shima, H.; Ozaki, S. *Synlett* **1991**, 831.

(17) Sureshan, K. M.; Shashidhar, M. S.; Varma, A. J. *J. Org. Chem.* **2002**, *67*, 6884; and references cited therein.

(18) (a) Hosoda, A.; Miyake, Y.; Nomura, E.; Taniguchi, H. *Chem. Lett.* **2003**, *32*, 1042. (b) Watanabe, Y.; Miyasou, T.; Hayashi, M. *Org. Lett.* **2004**, *6*, 1547. (c) Sureshan, K. M.; Yamaguchi, K.; Sei, Y.; Watanabe, Y. *Eur. J. Org. Chem.* **2004**, 4703.

(19) Akiyama, T.; Hara, M.; Fuchibe, K.; Sakamoto, S.; Yamaguchi, K. *Chem. Commun.* **2003**, 1734.

(20) Sureshan, K. M.; Gonnade, R. G.; Shashidhar, M. S.; Puranik, V. G.; Bhadbhade, M. M. *Chem. Commun.* **2001**, 881.

(21) (a) Akiyama, T.; Nishimoto, H.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1992**, 447. (b) Akiyama, T.; Horiguchi, N.; Ida, T.; Ozaki, S. *Chem. Lett.* **1995**, 975.