ELSEVIER

www.elsevier.nl/locate/carres

Carbohydrate Research 325 (2000) 68–71

CARBOHYDRATE RESEARCH

Note

Thermal C-glycosylation of D-glucal with trimethylsilyl cyanide

Masahiko Hayashi *, Hirotoshi Kawabata, Kazutoshi Inoue

Department of Chemistry, Faculty of Science, Yamaguchi University, Yamaguchi 753-8512, Japan

Received 14 July 1999; revised 11 November 1999; accepted 14 November 1999

Abstract

The treatment of 3,4,6-tri-*O*-acetyl-D-glucal and unprotected D-glucal with trimethylsilyl cyanide, under thermal conditions in the absence of catalyst, afforded the corresponding 2,3-unsaturated glycosyl cyanides in high yield.

Keywords: C-Glycosylation; Glucal; Trimethylsilyl cyanide; Glycosyl cyanide

Glycosyl cyanides are versatile intermediates for the synthesis of *C*-glycosyl derivatives, because the cyano group can be readily transformed into a variety of other functional groups. In fact, glycosyl cyanides have been used as starting compounds for the synthesis of naturally occurring *C*-nucleoside antibiotics and many analogues [1]. In consequence, there have been some reports on the synthesis of *C*-glycosyl cyanides [2,3]; however, all reported procedures so far have used Lewis-acidic promoters such as $TiCl_4$, $BF_3{\cdot}OEt_2$ and Me_3SiOTf.

Here we report the first example of C-glycosylation of O-acetylated and unprotected glucals with trimethylsilyl cyanide under thermal conditions, in the absence of a catalyst, which affords a simple and convenient synthesis of glycosyl cyanides (in 1973, Evans and coworkers reported the reaction of aldehydes and ketones with trimethylsilyl cyanide under thermal conditions in the absence of solvent and catalyst, see Ref. [4]). During the course of our study on the synthesis of glycosyl cyanides, we previously reported that the reaction of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) with trimethylsilyl cyanide was complete within 1 h at room temperature in the presence of 1 mol% of $Pd(OAc)_2$ in acetonitrile [5], whereas the reaction of **1** with trimethylsilyl cyanide in the absence of $Pd(OAc)_2$ did not give the product at room temperature, even after 135 h. However, we found that when the reaction was carried out at 80 °C, it proceeded effectively to afford the corresponding 2,3-unsaturated glycosyl cyanides **5a** and **5b** in 95% yield in the α:β ratio of 58:42 (Entry 2 in Table 1). (Lindhorst and Kieburg reported thermal- and solvent-free preparation of glycosyl isothiocyanates [6].) Furthermore, unprotected glucal **2** was also coupled with trimethylsilyl cyanide under thermal conditions in the absence of catalyst and solvent to give the products **6a** and **6b** in 84% yield

* Corresponding author. Fax: +81-83-933-5727.
E-mail address: hayashi@po.cc.yamaguchi-u.ac.jp (M. Hayashi)

0008-6215/00/$ - see front matter
PII: S0008-6215(99)00302-X

(α:β = 74:26). The cyanation reaction of unprotected glucals evidently proceeds via the silylated glucal. The reaction in the absence of solvent proceeded faster than that in acetonitrile (Entry 2 versus 4). In the case of the unprotected glucal in acetonitrile, the reaction did not take place. As for the stereochemistry of the reaction, the α:β ratio of the product was higher for unprotected glucal **2** as compared with acetylated glucal **1**, a phenomenon similar to the reaction promoted by $Pd(OAc)_2$ [5]. Isomerization was not observed under the reaction conditions, indicating that the observed α:β selectivity resulted from kinetic control. The present thermal glycosylation evidently proceeds via a Ferrier type of reaction [7]. Trimethylsilyl cyanide itself might serve as a Lewis acid to help in the removal of an acetoxy or siloxy group at the 3-position.

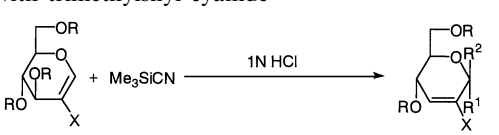
Next we examined the reaction of 3,4,6-tri-*O*-acetyl-2-bromo-D-glucal (**3**) [8] (for the use of branched-chain sugar synthesis, see [8b,c]) with trimethylsilyl cyanide under the same reaction conditions (without solvent, 80 °C). The corresponding glycosyl cyanide was obtained in 72% yield (α:β = 4:1). However the attempted reaction of 3,4-diacetoxy-5-vinyl-3,4-dihydro-2*H*-pyran-2-yl-methyl acetate (**4**) with trimethylsilyl cyanide did not proceed.

In conclusion, the present thermal C-glycosylation of D-glucal with trimethylsilyl cyanide to afford glycosyl cyanides has the characteristic feature of the reaction conditions being neutral, in contrast to the conventional Lewis-acid catalysis.

1. Experimental

General methods.—All melting points were uncorrected. ^1H and ^{13}C NMR were recorded on a Bruker Avance 400S instrument (400 and 100.6 MHz, respectively) using Me_3Si as the internal standard in $CDCl_3$. For compounds **6a** and **6b**, ^1H and ^{13}C NMR spectra were measured in CD_3CN using this solvent as standard (1.93 ppm for ^1H NMR and 1.2 ppm for ^{13}C NMR). IR spectra were measured on a Nicolet Impact 410 instrument. Optical rotations were measured with a SEPA-300 (Horiba) polarimeter for solutions in a 1-dm cell. Elemental analyses were performed on a Perkin–Elmer 2400II CHNS/O. Preparative column chromatography was carried out on a Fuji–Davison BW-820 or Daisogel IR-60-W (40/63 μm) system. Thin-layer chromatogra-

Table 1
Thermal C-glycosylation of D-glycals with trimethylsilyl cyanide



1; R = Ac, X = H
2; R = X = H
3; R = Ac, X = Br
4; R = Ac, X = $CH=CH_2$

5a; R = Ac, X = H, R^1 = CN, R^2 = H
5b; R = Ac, X = H, R^1 = H, R^2 = CN
6a; R = X = H, R^1 = CN, R^2 = H
6b; R = X = H, R^1 = H, R^2 = CN
7a; R = Ac, X = Br, R^1 = H, R^2 = CN
7b; R = Ac, X = Br, R^1 = CN, R^2 = H

Entry	Substrate	Equivalent of Me_3SiCN	Solvent	Conditions		Product	
				T (°C)	*t* (h)	% yield [a]	α:β [b]
1	**1**	1.2	none	80	98	67	3:2
2	**1**	2	none	80	13	95	29:21
3	**1**	2	none	22	135	0	
4	**1**	2	CH_3CN	80	66	82	29:21
5	**2**	5	none	80	84	84	37:13
6	**3**	5	none	80	181	72	4:1

[a] Isolated yield after silica-gel column chromatography.
[b] Determined by ^1H NMR analyses.

phy (TLC) employed: foil plates of Silica Gel 60 F254 (Merck; layer thickness 0.2 mm). Acetonitrile was distilled from P_4O_{10}.

*Thermal reaction of 3,4,6-tri-*O*-acetyl-*D*-glucal with trimethylsilyl cyanide.*—A mixture of 3,4,6-tri-*O*-acetyl-D-glucal (**1**) (1.0 g, 3.68 mmol) and Me_3SiCN (0.98 mL, 7.35 mmol) was stirred for 13 h at 80 °C. After confirmation of the completion of the reaction by TLC, the mixture was diluted with diethyl ether (5 mL) and poured into a mixture of 1 M HCI soln (20 mL) and diethyl ether (30 mL). Extractive work-up with EtOAc followed by silica-gel column chromatography afforded 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl cyanide (**5**) (836 mg, 95%) as a pale-yellow oil, a mixture of the α anomer **5a** and β anomer **5b** (**5a**:**5b** = 29:21).

*4,6-Di-*O*-acetyl-2,3-dideoxy-α-*D*-erythro-hex-2-enopyranosyl cyanide* (**5a**).—$R_f = 0.29$ (2:1 hexane–EtOAc); $[\alpha]_D - 13.6°$ (*c* 1.0, $CHCl_3$) (lit. [2] $-14.6°$ (*c* 1, $CHCl_3$)); IR (neat): ν_{max} (cm^{-1}) 2949, 1751, 1747, 1651, 1435, 1372, 1227, 1110, 1041, 1012, 981, 917; ^1H NMR ($CDCl_3$): δ 2.11, 2.12 (each s, 6 H, $COCH_3 \times 2$), 4.03 (dt, 1 H, $J_{5,4}$ 9.1, $J_{5,6}$ 3.9 Hz, H-5), 4.26 (d, 2 H, $J_{6,5}$ 3.9 Hz, H-6), 5.10 (ddd, 1 H, $J_{1,2}$ 3.5, $J_{1,3}$ 1.9, $J_{1,4}$ 2.0 Hz, H-1), 5.34 (dddd, 1 H, $J_{4,1}$ 2.0, $J_{4,2}$ 2.0, $J_{4,3}$ 2.0, $J_{4,5}$ 9.1 Hz, H-4), 5.91 (ddd, 1 H, $J_{2,1}$ 3.5, $J_{2,4}$ 2.0, $J_{2,3}$ 10.2 Hz, H-2), 6.03 (ddd, 1 H, $J_{3,2}$ 10.2, $J_{3,1}$ 1.9, $J_{3,4}$ 2.0 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 21.1, 21.3 ($COCH_3 \times 2$), 62.6 (C-6), 63.0 (C-1), 64.1 (C-4), 72.4 (C-5), 116.0 (CN), 124.0 (C-2), 130.0 (C-3), 170.4, 171.0 ($COCH_3 \times 2$).

*4,6-Di-*O*-acetyl-2,3-dideoxy-β-*D*-erythro-hex-2-enopyranosyl cyanide* (**5b**).—$R_f = 0.19$ (2:1 hexane–EtOAc); $[\alpha]_D + 214.7°$ (*c* 1.0, $CHCl_3$) (lit. [2] $+197.5°$ (*c* 1, $CHCl_3$)); IR (neat): ν_{max} (cm^{-1}) 3082, 3042, 2968, 2903, 2868, 1753, 1747, 1469, 1371, 1231, 1149, 1087, 1053, 1027, 990, 956, 914, 875; ^1H NMR ($CDCl_3$): δ 2.10, 2.11 (each s, 6 H, $COCH_3 \times 2$), 3.83 (ddd, 1 H, $J_{5,4}$ 8.2, $J_{5,6}$ 2.9, $J_{5,6'}$ 6.0 Hz, H-5), 4.20 (dd, 1 H, $J_{6,6'}$ 12.4, $J_{6,5}$ 6.0 Hz, H-6), 4.27 (dd, 1 H, $J_{6,6'}$ 12.4, $J_{6',5}$ 2.9 Hz, H-6′), 5.15 (ddd, 1 H, $J_{1,2}$ 1.8, $J_{1,3}$ 2.5, $J_{1,4}$ 2.2 Hz, H-1) 5.30 (dddd, 1 H, $J_{4,1}$ 2.2, $J_{4,2}$ 1.8, $J_{4,3}$ 2.5, $J_{4,5}$ 8.2 Hz, H-4), 5.94 (ddd, 1 H, $J_{2,1}$ 1.8, $J_{2,3}$ 10.3, $J_{2,4}$ 1.8 Hz, H-2), 6.05 (ddd, 1 H, $J_{3,1}$ 2.5, $J_{3,2}$ 10.3, $J_{3,4}$ 2.5 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 21.1, 21.2 ($COCH_3 \times 2$), 62.9 (C-6), 63.3 (C-1), 63.9 (C-4), 74.8 (C-5), 116.2 (CN), 124.6 (C-2), 129.1 (C-3), 170.3, 171.0 ($COCH_3 \times 2$).

Thermal reaction of D*-glucal with trimethylsilyl cyanide.*—A mixture of D-glucal (**2**) (442 mg, 3.02 mmol) and Me_3SiCN (2.0 mL, 15.1 mmol) was stirred for 84 h at 80 °C. After confirmation of the completion of the reaction by TLC, the mixture was diluted with diethyl ether (5 mL) and poured into a mixture of 1 M HCl soln (20 mL) and diethyl ether (30 mL). Extractive work-up with EtOAc followed by silica-gel column chromatography afforded 2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl cyanide (**6**) (394 mg, 84%) as a mixture of the α anomer **6a** and β anomer **6b** (**6a**:**6b** = 37:13).

*2,3-Dideoxy-α-*D*-erythro-hex-2-enopyranosyl cyanide* (**6a**).—$R_f = 0.53$ (EtOAc); $[\alpha]_D - 73.6$ (*c* 1.0, EtOH); IR (neat): ν_{max} (cm^{-1}) 3416, 2933, 2883, 2246, 1713, 1654, 1414, 1377, 1275, 1127, 1098, 1032, 970, 900, 828, 720; ^1H NMR (CD_3CN): δ 2.97 (dd, 1 H, $J_{6,-CH_2OH}$ 6.0, $J_{6',-CH_2OH}$ 6.0 Hz, $-CH_2OH$), 3.40 (d, 1 H, $J_{4,-CHOH}$ 7.1 Hz, $-CHOH$), 3.51 (ddd, 1 H, $J_{5,4}$ 8.6, $J_{5,6}$ 5.9, $J_{5,6}$ 2.6 Hz, H-5), 3.64 (ddd, 1 H, $J_{6,6'}$ 12.1, $J_{6,5}$ 5.9, $J_{6,-CH_2OH}$ 6.0 Hz H-6), 3.80 (ddd, 1 H, $J_{6,6'}$ 12.1, $J_{6',5}$ 2.6, $J_{6',-CH_2OH}$ 6.0 Hz, H-6′), 4.04 (ddddd, 1 H, $J_{4,1}$ 1.9, $J_{4,2}$ 2.0, $J_{4,3}$ 2.0, $J_{4,5}$ 8.6, $J_{4,-CHOH}$ 7.1 Hz, H-4), 5.12 (ddd, 1 H, $J_{1,2}$ 3.6, $J_{1,3}$ 2.0, $J_{1,4}$ 1.9 Hz, H-1), 5.82 (ddd, 1 H, $J_{2,1}$ 3.6, $J_{2,3}$ 10.1, $J_{2,4}$ 2.0 Hz, H-2), 6.01 (ddd, 1 H, $J_{3,1}$ 2.0, $J_{3,2}$ 10.1, $J_{3,4}$ 2.0 Hz, H-3); ^{13}C NMR (CD_3CN): δ 62.1 (C-6), 62.7 (C-4), 63.2 (C-1), 78.3 (C-5), 118.3 (CN), 122.7 (C-2), 134.6 (C-3). Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.14; H, 6.11; N, 8.69.

*2,3-Dideoxy-β-*D*-erythro-hex-2-enopyranosyl cyanide* (**6b**).—$R_f = 0.49$ (EtOAc); mp 120–122 °C, $[\alpha]_D + 219.0°$ (*c* 1.0, EtOH); IR (neat): ν_{max} (cm^{-1}) 3406, 3274, 2983, 2953, 2920, 2891, 2850, 2358, 2249, 1413, 1372, 1289, 1231, 1180, 1137, 1088, 1051, 1003, 963, 874, 807; ^1H NMR (CD_3CN): δ 2.95 (dd, 1 H, $J_{6,-CH_2OH}$ 6.0, $J_{6,-CH_2OH}$ 6.0 Hz, $-CH_2OH$), 3.32 (ddd, 1 H, $J_{5,4}$ 8.6, $J_{5,6}$ 5.8, $J_{5,6}$ 2.8 Hz, H-5), 3.37 (d, 1 H, $J_{4,-CHOH}$ 6.6 Hz, $-CHOH$), 3.63 (ddd, 1 H, $J_{6,6'}$ 12.1, $J_{6,5}$ 5.8, $J_{6,-CH_2OH}$ 6.0 Hz, H-6), 3.76 (ddd, 1 H, $J_{6,6'}$ 12.1, $J_{6',5}$ 2.8,

$J_{6',-CH_2OH}$ 6.0 Hz, H-6′), 4.06 (ddddd, 1 H, $J_{4,1}$ 2.7, $J_{4,2}$ 1.9, $J_{4,3}$ 2.3, $J_{4,5}$ 8.6, $J_{4,-CHOH}$ 6.6 Hz, H-4), 5.16 (ddd, 1 H, $J_{1,2}$ 1.9, $J_{1,3}$ 2.3, $J_{1,4}$ 2.7 Hz, H-1), 5.80 (ddd, 1 H, $J_{2,1}$ 1.9, $J_{2,3}$ 10.2, $J_{2,4}$ 1.9 Hz, H-2), 6.00 (ddd, 1 H, $J_{3,1}$ 2.3, $J_{3,2}$ 10.2, $J_{3,4}$ 2.3 Hz, H-3); ^{13}C NMR (CD_3CN): δ 62.2 (C-6), 62.4 (C-4), 64.2 (C-1), 80.8 (C-5), 118.2 (CN), 122.9 (C-2), 134.3 (C-3). Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.51; H, 5.98; N, 8.85.

*Thermal reaction of 3,4,6-tri-*O*-acetyl-2-bromo-*D*-glucal with trimethylsilyl cyanide.*—A mixture of 3,4,6-tri-*O*-acetyl-2-bromo-D-glucal (**3**) (500 mg, 1.42 mmol) and Me_3SiCN (0.95 mL, 7.12 mmol) was stirred for 181 h at 80 °C. After confirmation of the completion of the reaction by TLC, the mixture was diluted with diethyl ether (5 mL) and poured into a mixture of 1 M HCl soln (20 mL) and diethyl ether (30 mL). Extractive work-up followed by silica-gel column chromatography afforded 4,6-di-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranosyl cyanide (**7**) (328 mg, 72%) as a mixture of the α anomer **7a** and β anomer **7b** (**7a**:**7b** = 4:1).

*4,6-Di-*O*-acetyl-2-bromo-3-deoxy-α-*D*-erythro-hex-2-enopyranosyl cyanide* (**7a**).—R_f = 0.28 (3:1 hexane–EtOAc); $[\alpha]_D$ + 59.0° (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} (cm^{-1}) 3008, 2971, 2935, 2892, 2386, 2353, 1748, 1442, 1415–6, 1375, 1221, 1144, 1095, 1070, 1046, 979, 903, 831; ^{1}H NMR ($CDCl_3$): δ 2.03, 2.05 (each s, 6 H, $COCH_3 \times 2$), 4.02 (ddd, 1 H, $J_{5,4}$ 9.2, $J_{5,6}$ 2.2, $J_{5,6'}$ 4.8 Hz, H-5), 4.16 (dd, 1 H, $J_{6,6'}$ 12.6, $J_{6,5}$ 4.8 Hz, H-6), 4.21 (dd, 1 H, $J_{6,6'}$ 12.6, $J_{6',5}$ 2.2 Hz, H-6′), 5.00 (d, 1 H, $J_{1,3}$ 1.2 Hz, H-1), 5.27 (dd, 1 H, $J_{4,3}$ 1.9, $J_{4,5}$ 9.2 Hz, H-4), 6.29 (br d, 1 H, *J* 1.2 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 20.4, 20.5 ($COCH_3 \times 2$), 61.5 (C-6), 65.1 (C-4), 67.7 (C-1), 71.6 (C-5), 116.0 (CN), 114.2 (C-2), 130.6 (C-3), 169.6, 170.3 ($COCH_3 \times 2$). Anal. Calcd for $C_{11}H_{12}NO_5Br$: C, 41.53; H, 3.80; N, 4.40. Found: C, 41.68; H, 3.92; N, 4.22.

*4,6-Di-*O*-acetyl-2-bromo-3-deoxy-β-*D*-erythro-hex-2-enopyranosyl cyanide* (**7b**).—R_f = 0.18 (3:1 hexane–EtOAc); $[\alpha]_D$ + 123.3° (*c* 1.0, $CHCl_3$); IR (neat): ν_{max} (cm^{-1}) 3064, 2956, 1751, 1736, 1650, 1434, 1372, 1236, 1110, 1089, 1040, 985, 936, 850, 807; ^{1}H NMR ($CDCl_3$): δ 2.03, 2.05 (each s, 6 H, $COCH_3 \times 2$), 3.94 (ddd, 1 H, $J_{5,4}$ 7.4, $J_{5,6}$ 3.1, $J_{5,6'}$ 5.9 Hz, H-5), 4.22 (dd, 1 H, $J_{6,6'}$ 12.5, $J_{6,5}$ 5.9 Hz, H-6′), 4.29 (dd, 1 H, $J_{6,6'}$ 12.5, $J_{6',5}$ 3.1 Hz, H-6), 5.16 (ddd, $J_{1,3}$ 2.4, $J_{1,4}$ 2.3, 1 H, H-1), 5.28 (dddd, 1 H, $J_{4,1}$ 2.3, $J_{4,3}$ 2.7, $J_{4,5}$ 7.4 Hz, H-4), 6.41 (dd, 1 H, $J_{3,1}$ 2.4, $J_{3,4}$ 2.7 Hz, H-3); ^{13}C NMR ($CDCl_3$): δ 20.6, 20.9 ($COCH_3 \times 2$), 61.9 (C-6), 65.0 (C-4), 67.4 (C-1), 74.0 (C-5), 114.2 (C-2), 116.2 (CN), 130.0 (C-3), 170.0, 170.4 ($COCH_3 \times 2$).

Anal. Calcd for $C_{11}H_{12}NO_5Br$: C, 41.53; H, 3.80; N, 4.40. Found: C, 41.78; H, 3.60; N, 4.32.

Acknowledgements

Financial support from Monbusho (Grant-in-Aid for Scientific Research on Priority Areas, no. 706: Dynamic Control of Stereochemistry) is gratefully acknowledged.

References

[1] D.E. Levy, C. Tang, *The Chemistry of C-Glycosides*, Pergamon, Oxford, 1995 (Chapter 2).
[2] F.G. De-Las Heras, A.S. Felix, P. Fernández-Resa, *Tetrahedron*, 39 (1983) 1617–1620.
[3] (a) A. de Raadt, H. Griengl, N. Klempie, A.E. Stütz, *J. Org. Chem.*, 58 (1993) 3179–3184. (b) K.N. Drew, P.H. Gross, *J. Org. Chem.*, 56 (1991) 509–513. (c) P. Pudlo, J. Thiem, V. Vill, *Chem. Ber.*, 123 (1990) 1129–135. (d) G.D. Kini, C.R. Petrie, W.J. Hennen, J. William, N.K. Dalley, B.E. Wilson, R.K. Robins, *Carbohydr. Res.*, 159 (1987) 81–94. (e) K.C. Nicolaou, C.K. Hwang, M.E. Duggan, *J. Chem. Soc., Chem. Commun.*, (1986) 925–926. (f) M.G. Hoffmann, R.R. Schmidt, *Justus Liebigs Ann. Chem.*, (1985) 2403–2419. (g) Y. Araki, N. Kobayashi, K. Watanabe, Y. Ishido, *J. Carbohydr. Chem.*, 4 (1985) 565–585. (h) G. Grynkiewicz, J.N. BeMiller, *Carbohydr. Res.*, 108 (1982) 229–235. (i) F.G. De-Las Heras, P. Fernández-Resa, *J. Chem. Soc., Perkin Trans. 1*, (1982) 903–907.
[4] D.A. Evans, L.K. Truesdale, G.L. Carroll, *J. Chem. Soc., Chem. Commun.*, (1973) 55–56.
[5] M. Hayashi, H. Kawabata, O. Arikita, *Tetrahedron Lett.*, 40 (1999) 1729–1730.
[6] T.K. Lindhorst, C. Kieburg, *Synthesis*, (1995) 1228–1230.
[7] R.J. Ferrier, *Adv. Carbohydr. Chem. Biochem.*, 20 (1965) 67–137; 24 (1969) 199–266.
[8] (a) A. Fogh, I. Lundt, C. Pedersen, P. Rasmussen, *Acta Chem. Scand. B*, 31 (1977) 768–770. (b) M. Hayashi, K. Amano, K. Tsukada, C. Lamberth, *J. Chem. Soc., Perkin Trans. 1*, (1999) 239–240. (c) M. Hayashi, K. Tsukada, H. Kawabata, C. Lamberth, *Tetrahedron*, 55 (1999) 12,287–12,294.