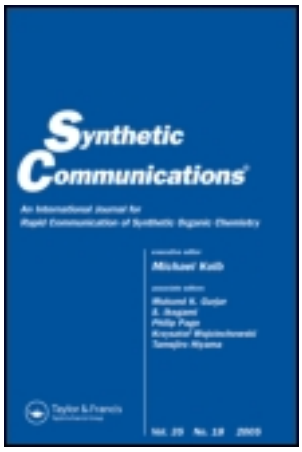


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

# First Synthesis of a Trisaccharide of Glycosylkaemferide: A Resistance Factor in Carnations

Mamoru Koketsu [a], Motoaki Kuwahara [a], Hisako Sakurai [a] & Hideharu Ishihara [a]

[a] Department of Chemistry, Faculty of Engineering, Gifu University, Gifu, 501-1193, Japan

Published online: 18 Oct 2011.

To cite this article: Mamoru Koketsu , Motoaki Kuwahara , Hisako Sakurai & Hideharu Ishihara (2004): First Synthesis of a Trisaccharide of Glycosylkaemferide: A Resistance Factor in Carnations, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 34:2, 239-245

To link to this article: http://dx.doi.org/10.1081/SCC-120027259

SYNTHETIC COMMUNICATIONS®
Vol. 34, No. 2, pp. 239–245, 2004

# First Synthesis of a Trisaccharide of Glycosylkaemferide: A Resistance Factor in Carnations

**Mamoru Koketsu,* Motoaki Kuwahara, Hisako Sakurai, and Hideharu Ishihara***

Department of Chemistry, Faculty of Engineering, Gifu University, Gifu, Japan

## ABSTRACT

A trisaccharide, phenyl $\beta$-D-glucopyranosyl-(1 $\rightarrow$ 2)-[$\alpha$-L-rhamnopyranosyl-(1 $\rightarrow$ 6)]-1-thio-$\beta$-D-glucopyranoside, of glycosylkaemferide, a resistance factor in carnations, was synthesized in a practical way.

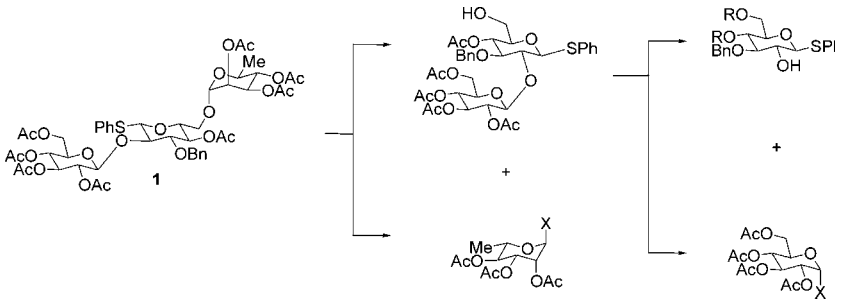
*Key Words:* Trisaccharide; Carnation; Flavonol; Antifungal compound.

Many carnations (*Dianthus caryophyllus*) suffer from a fungal parasite, *Fusarium oxysporum* f. sp. *Dianthi*, which causes severe crop losses worldwide.[1] Carnations of the cultivar Novada bearing a high resistance to this

*Correspondence: Mamoru Koketsu and Hideharu Ishihara, Department of Chemistry, Faculty of Engineering, Gifu University, Gifu 501-1193, Japan.



DOI: 10.1081/SCC-120027259 0039-7911 (Print); 1532-2432 (Online)



***Scheme 1.*** Retrosynthetic analysis.

parasite are of commercial interest.[2] Recently, kaempferide triglycoside has been reported, for the first time, to be one of the most important resistance factors in the carnation.[3] The total synthesis of the kaempferide triglycoside is required for the detailed elucidation of its antifungal mechanism. In this paper, we describe the first preparative synthesis of the trisaccharide, phenyl 2,3,4,6-tetra-*O*-acetyl-$\beta$-D-glucopyranosyl-(1 $\rightarrow$ 2)-[2,3,4-tri-*O*-acetyl-$\alpha$-L-rhamnopyranosyl-(1 $\rightarrow$ 6)]-4-*O*-acetyl-3-*O*-benzyl-1-thio-$\beta$-D-glucopyranoside **1**, a critical portion of this antifungal compound (Sch. 1).

## RESULTS AND DISCUSSION

Retrosynthetic analysis indicates that the trisaccharide can be obtained by condensation of a rhamnose donor and a glucose dimer acceptor. The disaccharide could be constructed from a glucose donor and a 2-hydroxy-glucose acceptor (Sch. 1).

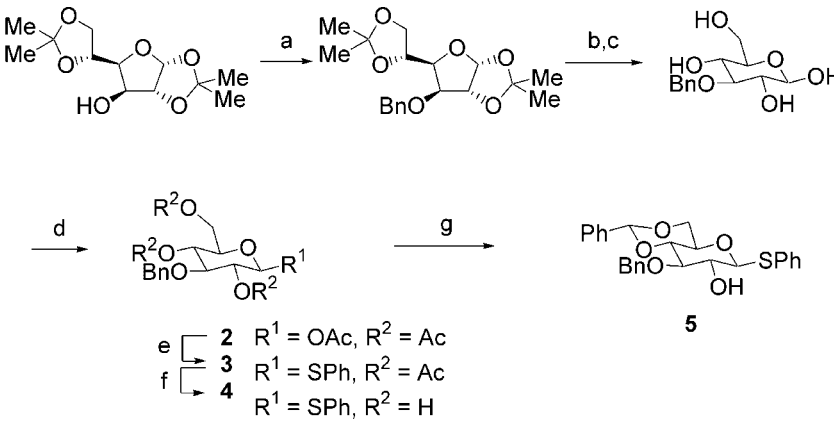
2-Hydroxy-glucose acceptor **5** was prepared from 1,2:5,6-di-*O*-isopropylidene-$\alpha$-D-glucofuranose in seven steps as shown in Sch. 2. 1,2:5,6-di-*O*-isopropylidene-$\alpha$-D-glucofuranose was benzylated, hydrolyzed with acid, and treated with acetic anhydride-sodium acetate. 1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl-$\beta$-D-glucopyranose **2** was obtained in four steps in a satisfactory yield (overall 80%).[4] A thiophenyl group was chosen as both the leaving and protecting group at the reducing end of the glucose **3**.[5] 2-Hydroxy-glucose acceptor **5** was prepared from **3** through selective deacetylation **4** and 4,6-*O*-benzylidenation of glucose.[6]

Synthesis of glucose donor **7** was achieved by peracetylation (quantitative yield), followed by a regioselective hydrazinolysis[7] of the 1-*O*-acetyl group of peracetylated glucose to afford **6** (87%). Subsequent treatment of **6** with trichloroacetonitrile afforded trichloroacetimidate **7** (59%) (Sch. 3).





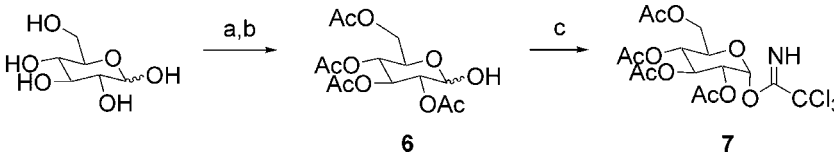
Marcel Dekker, Inc.
270 Madison Avenue, New York, New York 10016



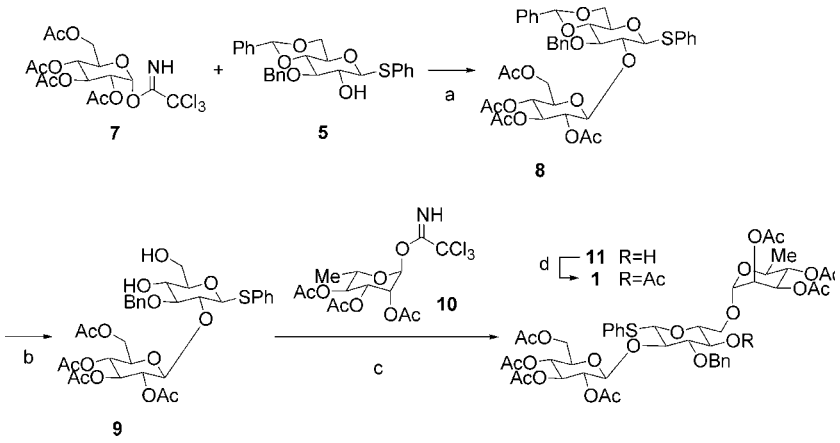

***Scheme 2.*** Synthesis of glucose acceptor **5**. Reagents and conditions: (a) BnBr, NaH, DMF, 90°C, 2 h; (b) 60% $AcOH/H_2O$, 90°C, 2 h; (c) 0.1 M $H_2SO_4/H_2O$, 90°C, 2 h; (d) $Ac_2O$, NaOAc, 110°C, 6 h, 80% (overall yield for 4 steps); (e) PhSH, $Et_2O \cdot BF_3$, $CH_2Cl_2$, rt, overnight, 63%; (f) NaOEt, MeOH, rt, overnight, quant.; (g) $PhCH(OMe)_2$, *p*-$MeC_6H_4SO_3H$, $CH_3CN$, rt, 3 h, 82%.

The 2-hydroxy-D-glucose acceptor **5** was glycosylated with **7** in the presence of $Et_2O \cdot BF_3$ to give (1 → 2)-linked disaccharide **8**. Removal of the 4,6-*O*-benzylidene group of **8** by acid hydrolysis[8] afforded **9** (58%, 2 steps overall yield). The $^1H$ and $^{13}C$ NMR spectra of **9** showed that the reaction gave exclusively the $\beta$-glycoside.

Rhamnose trichloroacetimidate donor **10**[9] was prepared from L-rhamnopyranose by the same procedures shown in Sch. 3 (3 steps in 70% overall yield). Selective glycosylation of the 6-OH in **9** with 2,3,4-tri-*O*-acetyl-$\alpha$-L-rhamnopyranosyl trichloroacetimidate (**10**) gave the trisaccharide derivative **11** in 54% yield. Total synthesis of the target trisaccharide moiety **1** was achieved by quantitative acetylation of **11** (Sch. 4).




***Scheme 3.*** Synthesis of glucose donor **7**. Reagents and conditions: (a) $Ac_2O$, pyridine, rt, overnight, quant.; (b) $H_2NNH_2/AcOH$, DMF, 50°C, 2 h, 87% (2 steps); (c) $CCl_3CN$, DBU, $CH_2Cl_2$, 0°C, 2 h, 59%.




***Scheme 4.*** Synthesis of target trisaccharide **1**. Reagents and conditions: (a) $Et_2O \cdot BF_3$, $CH_2Cl_2$, 0°C, 2 h; (b) 70% $AcOH/H_2O$, 70°C, 4 h, 58% (2 steps overall); (c) $Et_2O \cdot BF_3$, $CH_2Cl_2$, −20°C, 5 h, 54%; (d) $Ac_2O$, pyridine, rt, 12 h, quant.

## EXPERIMENTAL

### General Procedures

Melting points were determined by use of a Yanagimoto micromelting point apparatus and are uncorrected. $^1H$ and $^{13}C$ spectra were recorded on a JEOL JNM-$\alpha$400 spectrometer. Mass spectra were obtained on Shimadzu 9020-DF mass spectrometer.

**1,2,4,6-Tetra-*O*-acetyl-3-*O*-benzyl-β-D-glucopyranose[4] 2**. M.p.: 106.2–107.2°C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.98 (6H, s, $2CH_3$), 1.98 (3H, s, $CH_3$), 2.08 (3H, s, $CH_3$), 2.10 (3H, s, $CH_3$), 3.75 (1H, m, H5), 3.78 (1H, t, $J = 9.2$ Hz, H3), 4.09 (1H, dd, $J = 12.0$, 2.4 Hz, H6a), 4.23 (1H, dd, $J = 12.0$, 4.8 Hz, H6b), 4.62 (2H, s, $CH_2$Ph), 5.15 (1H, t, $J$ 9.2 Hz, H4), 5.16 (1H, t, $J = 8.4$ Hz, H2), 5.66 (1H, d, $J = 8.4$ Hz, H1), 7.23–7.35 (5H, m, Ph); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.3, 20.4, 20.6, 21.9, 61.7, 69.0, 71.5, 73.0, 74.2, 79.9, 91.9, 127.5–137.5, 169.0, 169.19, 169.22, 170.7; CIMS: $m/z$ 439 [$M^+ + 1$].

**Phenyl 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-1-thio-β-D-glucopyranose[5] 3**. $[\alpha]^{24}D$ −7.5° (c, 0.05, $CHCl_3$); M.p.: 114.0–114.8°C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.96 (3H, s, $CH_3$), 2.04 (3H, s, $CH_3$), 2.07 (3H, s, $CH_3$), 3.61–3.66 (1H, m), 3.72 (1H, t, $J$ 9.2 Hz), 4.17 (2H, m), 4.58 (1H, d, $J = 11.0$ Hz), 4.61 (1H, d, $J = 11.0$ Hz), 4.64 (1H, d, $J = 10.0$ Hz), 5.03–5.10 (2H, m), 7.21–7.50 (10H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.69, 20.73, 20.9, 62.5, 69.6, 71.3, 74.2, 76.1, 81.5, 86.2, 169.2, 169.3, 170.6; CIMS: $m/z$ 489 [$M^+ + 1$].

**Phenyl 3-*O*-benzyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranose 5**. $[\alpha]^{25}_D$ −60.0° (c, 0.05, $CHCl_3$); M.p.: 127.5–128.0°C; $^1$H NMR ($CDCl_3$) $\delta$ 2.58 (1H, d, $J$ 2.4 Hz, OH), 3.47–3.71 (4H, m, H2–H5), 3.79 (1H, t, $J$ = 10.2 Hz, H6a), 4.38 (1H, dd, $J$ = 10.2, 5.0 Hz, H6b), 4.62 (1H, d, $J$ 9.2 Hz, H1), 4.78 (1H, d, $J$ = 11.4 Hz, $CH_2$Ph), 4.95 (1H, d, $J$ = 11.4 Hz, $CH_2$Ph), 5.56 (1H, s, CHPh), 7.24–7.54 (15H, m, 3Ph); $^{13}$C NMR ($CDCl_3$) $\delta$ 68.6, 70.7, 72.2, 74.8, 81.1, 81.6, 88.4, 101.2, 126.0–138.1; CIMS: $m/z$ 451 [$M^+$ + 1].

**2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate 7**. $[\alpha]^{27}_D$ +52.0° (c, 0.001, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 2.02 (3H, s, $CH_3$), 2.04 (3H, s, $CH_3$), 2.06 (3H, s, $CH_3$), 2.08 (3H, s, $CH_3$), 4.13 (1H, dd, $J$ = 12.8, 2.0 Hz, H6a), 4.20–4.24 (1H, m, H5), 4.28 (1H, dd, $J$ = 12.4, 4.0 Hz, H6b), 5.14 (1H, dd, $J$ = 10.0, 4.0 Hz, H2), 5.19 (1H, t, $J$ = 10.0 Hz, H3), 5.57 (1H, t, $J$ = 9.6 Hz, H-4), 6.57 (1H, d, $J$ = 4.0 Hz, H1), 8.71 (1H, s, NH); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.4, 20.5, 20.6, 61.3, 67.7, 69.6, 69.8, 69.9, 92.8, 160.7, 169.4, 169.8, 169.9, 170.5; CIMS: $m/z$ 492 [$M^+$ + 1].

**Phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1 → 2)-3-*O*-benzyl-1-thio-β-D-glucopyranoside 9**. $[\alpha]^{26}_D$ −20.0° (c, 0.001, $CHCl_3$); M.p.: 65.5–68.5°C; $^1$H NMR ($CDCl_3$) $\delta$ 2.01 (3H, s, $CH_3$), 2.02 (3H, s, $CH_3$), 3.29 (1H, m), 3.44 (1H, t, $J$ = 8.8 Hz,), 3.64 (1H, t, $J$ = 9.2 Hz,), 3.71–3.84 (3H, m), 4.09–4.14 (3H, m), 4.22 (1H, dd, $J$ = 12.4, 4.4 Hz), 4.67 (1H, d, $J$ = 9.6 Hz) 4.83 (2H, s, $CH_2$Ph), 5.10–5.18 (3H, m), 7.24–7.49 (10H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.5, 20.7, 21.0, 61.7, 62.2, 68.3, 70.8, 71.6, 71.9, 73.1, 75.6, 76.5, 79.0, 85.7, 86.7, 99.6, 127.4–137.9 (Ph), 169.1, 169.3, 170.2, 170.7; FABMS (pos.-ion): $m/z$ 693 [$M^+$ + 1].

**2,3,4-Tri-*O*-acetyl-α-L-rhamnopyranosyl trichloroacetimidate**[9] **10**. $[\alpha]^{27}_D$ −72.0° (c, 0.001, $CHCl_3$); $^1$H NMR ($CDCl_3$) $\delta$ 1.27 (3H, d, $J$ = 5.6 Hz, $CH_3$), 2.00 (3H, s, $CH_3$), 2.08 (3H, s, $CH_3$), 2.19 (3H, s, $CH_3$), 4.10 (1H, m, H5), 5.18 (1H, t, $J$ = 10.4 Hz, H4), 5.37 (1H, dd, $J$ = 10.4, 3.2 Hz, H3), 5.46 (1H, dd, $J$ = 3.2, 2.0 Hz, H2), 6.20 (1H, d, $J$ = 2.0 Hz, H1) 8.74 (1H, s, NH); $^{13}$C NMR ($CDCl_3$) $\delta$ 17.4, 20.6, 20.7, 68.0, 68.7, 69.2, 70.2, 90.6, 94.6, 159.9, 169.75, 169.82; CIMS: $m/z$ 435 [$M^+$ + 1].

**Phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1 → 2)-[2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1 → 6)]-3-*O*-benzyl-1-thio-β-D-glucopyranoside 11**. $[\alpha]^{26}_D$ −56.0° (c, 0.001, $CHCl_3$); M.p.: 80.2–81.0°C; $^1$H NMR ($CDCl_3$) $\delta$ 1.18 (3H, d, $J$ 6.0 Hz, $CH_3$), 2.01 (3H, s, $CH_3$), 2.02 (3H, s, $CH_3$), 2.03 (3H, s, $CH_3$), 2.04 (3H, s, $CH_3$), 2.06 (3H, s, $CH_3$), 2.09 (3H, s, $CH_3$), 2.14 (3H, s, $CH_3$), 3.40 (1H, m) 3.52 (1H, t, $J$ = 8.8 Hz), 3.60–3.70 (3H, m), 3.82 (1H, t, $J$ = 8.8 Hz) 3.89–3.95 (2H, m), 4.06 (1H, dd, $J$ = 12.4, 2.4 Hz) 4.12 (1H, dd, $J$ = 14.4, 7.2 Hz), 4.26 (1H, dd, $J$ = 12.0, 4.4 Hz) 4.62 (1H, d, $J$ = 9.2 Hz), 4.73 (1H, s) 4.77 (1H, d, $J$ = 10.4 Hz, $CH_2$Ph), 4.88 (1H, d, $J$ = 11.2 Hz, $CH_2$Ph) 5.01–5.20 (5H, m), 5.23–5.26 (2H, m) 7.22–7.52 (10H, m, Ph); $^{13}$C NMR ($CDCl_3$) $\delta$ 20.6, 20.8, 20.8, 20.9, 61.8, 66.5, 66.8,





MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

68.3, 69.2, 69.4, 70.1, 70.8, 71.7, 72.0, 73.2, 75.8, 76.5, 78.0, 85.8, 86.9, 97.7, 99.6, 127–137.8,169.2, 169.4, 167.0, 170.1, 107.1, 170.3, 170.7; FABMS (pos.-ion): $m/z$ 965 [$M^+ + 1$].

**Phenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-(1 → 2)-[2,3,4-tri-*O*-acetyl-α-L-rhamnopyranosyl-(1 → 6)]-4-*O*-acetyl-3-*O*-benzyl-1-thio-β-D-glucopyranoside 1**. $[\alpha]^{26}_D$ −49.0° (c, 0.001, $CHCl_3$); M.p.: 73.0–75.0°C; $^1$H NMR ($CDCl_3$) δ 1.19 (3H, d, $J$ = 6.4 Hz, $CH_3$), 1.97 (3H, s, $CH_3$), 1.99 (3H, s, $CH_3$), 2.01 (3H, s, $CH_3$), 2.02 (3H, s, $CH_3$), 2.04 (3H, s, $CH_3$), 2.06 (3H, s, $CH_3$), 2.09 (3H, s, $CH_3$), 2.12 (3H, s, $CH_3$) 3.53–3.61 (3H, m), 3.64–3.71 (2H, m), 3.81 (1H, dd, $J$ = 9.4, 6.2 Hz) 3.88 (1H, t, $J$ = 9.0 Hz), 4.06 (1H, dd, $J$ = 12.6, 2.2 Hz) 4.24 (1H, dd, $J$ = 12.6, 4.6 Hz), 4.60 (1H, d, $J$ = 11.2 Hz) 4.63 (1H, d, $J$ = 10.0 Hz), 4.72 (1H, s) 4.79 (1H, d, $J$ = 10.8 Hz,), 4.95–5.25 (8H, m) 7.22–7.51 (10H, m, Ph); $^{13}$C NMR ($CDCl_3$) δ 20.5–20.9, 61.8, 66.5, 67.1, 68.2, 69.0, 69.4, 70.8, 70.9, 71.8, 71.9, 73.2, 75.7, 76.2, 84.4, 85.7, 98.0, 99.5, 127.6–132.0, 169.1, 169.4, 169.7, 169.87, 169.90, 169.93, 170.3, 170.7; FABMS (pos.-ion): $m/z$ 1008 [$M^+ + 1$]; Anal. Calcd for $C_{47}H_{58}NOS$: C, 56.06; H, 5.81. found: C, 56.34; H, 5.76.

## ACKNOWLEDGMENTS

We thank Professors Makoto Kiso, Hideharu Ishida, and Robert J. Linhardt for critical discussion and helpful suggestions.

## REFERENCES

1. Garibaldi, A.; Gullino, M. Acta. Hort. **1987**, *216*, 45–54.
2. Baayen, R.P.; Niemann, G.J. J. Phytopathol. **1989**, *126*, 281–292.
3. Curir, P.; Dolci, M.; Lanzotti, V.; Taglialatela-Scafati, O. Phytochemistry **2001**, *56*, 717–721.
4. David, S.; Malleron, A.; Dini, C. Carbohydr. Res. **1989**, *188*, 193–200.
5. Khan, S.; Matta, K.L. Carbohydr. Res. **1995**, *278*, 351–362.
6. Pozsgay, V.; Dubois, E.P.; Pannell, L. J. Org. Chem. **1997**, *62*, 2832–2846.
7. Fairbanks, A.J.; Perrin, E.; Sinaÿ, P. Synlett. **1996**, 679–681.
8. Excoffier, G.; Gagnaire, G.; Utille, J.-P. Carbohydr. Res. **1975**, *39*, 368–373.
9. Nicholas, M.K.; Kund, J.J. J. Carbohydr. Chem. **2001**, 537–548.
10. Garegg, P.J.; Oscarson, S.; Tidén, A.-K. Carbohydr. Res. **1990**, *200*, 475–480.





MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016

11. Sakagami, M.; Hamana, H. Tetrahedron Lett. **2000**, *41*, 5547–5551.
12. Zhang, J.; Kong, F. J. Carbohydr. Chem. **2002**, *21*, 89–97.

Received in Japan June 9, 2003





MARCEL DEKKER, INC.
270 Madison Avenue, New York, New York 10016