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SYNTHESIS OF *C*-GLYCOSYL COMPOUNDS FROM 3,4,6-TRI-*O*-ACETYL-1,5-ANHYDRO-D-*arabino*-HEX-1-ENITOL AND ALLYLTRIMETHYLSILANE AND BIS(TRIMETHYLSILYL)ACETYLENE

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ABSTRACT

C-Glycosyl derivatives of compounds bearing two, three, or four carbon atoms were obtained from 3,4,6-tri-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol (**1**) *via* a deacetoxylated oxonium ion generated by treatment with a Lewis acid. The nucleophilic reagents with this cation were bis(trimethylsilyl)acetylene, allyltrimethylsilane, and furan, which were found to exhibit a higher reaction velocity than **1** itself, a potential nucleophile leading to polymerization.

INTRODUCTION

Carbohydrate compounds have frequently been used as chiral starting materials for the synthesis of natural products by utilizing the chiral center existing in the original skeleton[1], and for asymmetric induction in the side-chain linked to the cycle. Thus, we have demonstrated the use of carbohydrate starting materials in the syntheses of the Prelog–Djerassi lactonic acid[2], of an ansamacrolactam, maytansine[3], and of a marine polyether, namely, okadaic acid[4]. We describe herein the preparation of the key intermediates (**3**, **7**, and **10**) for the synthesis of polyethers by *C*-glycosyl intermediates of 3,4,6-tri-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol[5] (**1**).

RESULTS AND DISCUSSION

In our synthetic studies on okadaic acid[5], compound **1** was chosen as the starting material for *C*-glycosyl formation, since its cation (**2**) is readily generated under mild conditions by treatment with Lewis acids, such as boron trifluoride etherate, titanium tetrachloride, etc. Generation of **2** in the presence of a nucleophile would produce adduct(s) if the nucleophile attacks **2** much faster than does the starting vinyl ether **1** (ref. 6). Danishefsky *et al.*[7] reported that **1** when treated

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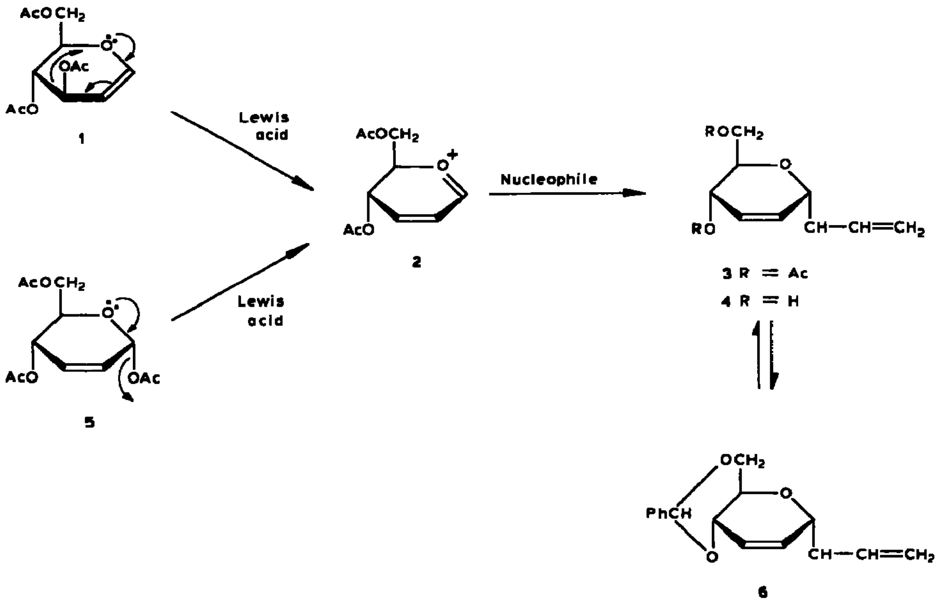

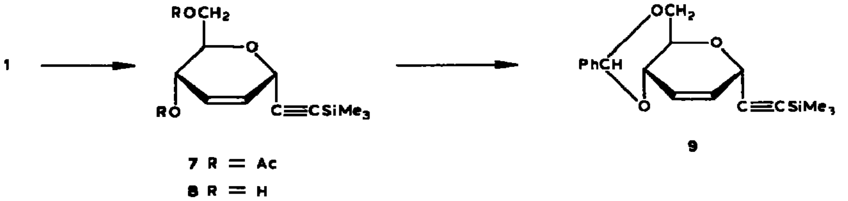

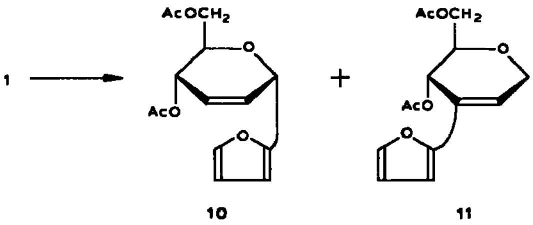

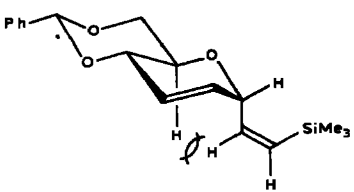

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with allyltrimethylsilane [(3-propenyl)trimethylsilane][8] in the presence of titanium tetrachloride gives 3 in 85% yield as a mixture of α- and β-D anomers in a 16:1 ratio. These authors did not report experimental details nor physical data, such as optical rotation. We have reproduced the same experiment[5], but under a nitrogen atmosphere, to obtain a similar result. The ratio of α- to β-D anomer of 3 was 94:6 when the reaction was catalyzed by boron trifluoride etherate. Essentially no condition afforded exclusively the pure α anomer without chromatographic separation, even in the presence of other Lewis acids such as titanium or tin tetrafluoride. This mixture of anomers was not pure enough as starting material for the synthesis of okadaic acid[5]. An attempt to separate, by l.c. on silica gel, this mixture, only afforded less than one gram of the α and 30 mg of the β anomer. The latter was used for stereochemical studies *(vide infra)*[8]. It was evident that the l.c. technique was inconvenient for the molar-scale purification required for the synthesis of okadaic acid[5]. The pure α anomer **3** was eventually prepared without chromatographic separation, as it was found to be convertible into a crystalline benzylidene derivative **6** by hydrolysis of the mixture of anomers with triethylamine in methanol, and benzylidenation with benzaldehyde dimethyl acetal in the presence of camphorsulfonic acid[9]. Pure **6** was hydrolyzed with acetic acid to give **4**, further acetylated into pure **3**. In this synthesis, participation of the cation **2** was demonstrated by the observation that a similar, unsaturated compound, 1,4,6-tri-*O*-acetyl-α-D-*erythro*-hex-2-enopyranose (**5**), when subjected to the same conditions, afforded **3** in the same ratio of α to β anomer (94:16). The same ratio of products was also observed when the reaction was carried out on a 1:1 mixture of the α and β anomers of **5** (in 80% yield).

Bis(trimethylsilyl)acetylene reacted, as nucleophile, with the cation **2**, which was generated by titanium tetrachloride, to afford an α anomer of **7** in 75% yield. This compound was only obtained when **1** was introduced into the mixture of bis(trimethylsilyl)acetylene and titanium tetrachloride at temperatures <0°. Another Lewis acid, boron trifluoride etherate, afforded only a small proportion of **7** as polymerization of **1** was rapid. Compound **7** was also converted into the crystalline benzylidene derivative **9** by deacetylation with lithium aluminium hydride to give **8**, followed by treatment with benzaldehyde dimethyl acetal[9].

The following nucleophiles were unable to produce *C*-glycosyl compounds owing to rapid polymerization of **1**: trimethylphenylsilane, trimethylvinylsilane, ethynyltrimethylsilane, and dihydropyran. However, furan was found to react with **2** more rapidly than **1**, when treated with boron trifluoride etherate for 2 h at −40°, to give a 1:1 mixture of the 2-(α-D-glycosyl)- (**10**) and 2-(D-glycit-3-yl)-furan (**11**) derivatives, respectively, in 54% yield. The configuration at C-1 of the *C*-glycosyl compounds was found to be mostly in axial orientation, which resulted in the formation of an α-D, axial substituent. The α-D configuration of the propene derivative **3** was proven by comparison of the ^{13}C-n.m.r. spectrum with that of the minor β anomer; the former exhibited chemical shifts at δ 37.8 and 69.7 as compared to the latter at δ 39.4 and 74.2 for C-3 and C-8. These assignments were based on the γ effect in ^{13}C-n.m.r. spectroscopy, which has been often used for distinguishing between epimers[10]. The minor product in the formation of **3** was also shown to have the β configuration by Danishefsky *et al.*[8], by means of a n.O.e. study of the H-1 and H-5 signals in the ^{1}H-n.m.r. spectrum. The configuration of the ethynyl compounds **7**–**9** was proved also to be α by ^{1}H-n.m.r. spectrometry, as follows. Compound **9** having a fixed configuration was partially reduced into the corresponding dihydro derivative **12**. A clear n.O.e. effect was observed with ~3.5% enhancement between the H signal appearing at δ 6.47 (dd, *J* 14.2, 9.1 Hz) and the

H-5′ signal at δ 3.70 (ddd, *J* 10.4, 8.2, 4.4 Hz). This result indicated that the vinyl substituent in **12** is located in α-axial orientation and that the initial reaction with trimethylsilylacetylene had given an α anomer.

Linkage of two, three, or four carbon atom fragments to **1** afforded new possibilities of using this sugar as a chiral starting material for various synthetic targets. The propenyl derivative **3** has been used for the synthesis of okadaic acid[5] and other polyethers[11], and the ethynyl derivative **7** may also be utilized as a precursor of olefins or long carbon-chain molecules.

EXPERIMENTAL

General methods. — Melting points were determined with a Mitamura Giken apparatus and are uncorrected. Optical rotations were measured in 1-dm cells of 2- or 8-mL capacity with a JASCO Model DIP-4 polarimeter. I.r. spectra were recorded with a JASCO A-3 spectrometer. ^{1}H-N.m.r. spectra were recorded at 200 or 500 MHz with JEOL FX200 or GX500 spectrometers for solutions in (^{2}H)chloroform and are reported from the signal of internal tetramethylsilane. 3,4,6-Tri-*O*-acetyl-1,5-anhydro-D-*arabino*-hex-1-enitol (**1**) was prepared from D-glucose[12], and all silicon reagents were purchased from Shin-etsu Chem. Co. Ltd., Niigata, Japan. Elemental analyses were performed by Mr. S. Kitamura of the Analytical Laboratory of this department.

*3-(4,6-Di-O-acetyl-2,3-dideoxy-α-*D-erythro-*hex-2-enopyranosyl)-1-propene* (**3**). — *From* **1**. A solution of **1** (400 g) and allyltrimethylsilane (370 mL) in dichloromethane (4.5 L) was cooled to −50°. It was stirred and BF_3 etherate was added dropwise over 30 min. The stirring was continued for 1 h at −50°, and for 2.5 h at 0°. The mixture was poured into aqueous $NaHCO_3$ with vigorous stirring and the product extracted with dichloromethane. The extracts were dried (Na_2SO_4) and evaporated under reduced pressure to afford **3** and its isomer in quantitative yield (475.2 g, ratio 94:16) as an oil, and this material was used without further purification; ^{13}C-n.m.r. (**3**): δ 20.7, 20.9, 37.8, 62.8, 64.9, 69.7, 71.2, 117.2, 123.7, 132.5, 133.9, 169.8, and 170.1; (minor β-D anomer) 20.7, 20.9, 39.4, 63.6, 65.5, 74.2 (2 C), 117.4, 125.0, 132.0, 133.1, 169.8, and 170.4.

From **6**. Recrystallized **6** (0.25 g) was dissolved in acetic acid (3 mL) and water (1 mL), and heated for 24 h at 55°. The mixture was evaporated to dryness, the residue treated overnight at room temperature with acetic anhydride (1.5 mL) and pyridine (3 mL), and the mixture evaporated *in vacuo* and separated by silica gel t.l.c. to afford pure **3** (85% overall yield); $[\alpha]_D^{20}$ +62.3° (*c* 1.03, chloroform); $\nu_{max}^{CHCl_3}$ 1740 cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 2.09 (3 s, H_2), 2.2–2.6 (H_2-3), 3.95 (td, *J* 6, 4 Hz, H-5′), 4.1–4.25 (H-6′), 4.29 (m, H-1), 5.05–5.2 (H-1,1,4′), and 5.75–6.0 (H-2,2′,3′).

Anal. Calc. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.40; H, 7.21.

*3-(2,3-Dideoxy-α-*D-erythro-*hex-2-enopyranosyl)-1-propene* (**4**). — *From* **3**. To a solution of **3** (475.2 g) in methanol (3.2 L) were added triethylamine (650 mL) and water (550 mL). The solution was stirred at room temperature for two days and the solvent removed under reduced pressure to give crude **4** (22.54 g, yield 89%, in 2 steps from **1**) which was used directly without further purification.

From **6**. Hydrolysis of pure **6** afforded an analytically pure sample of **4**, $[\alpha]_D^{20}$ $-35.1°$ (c 0.85, chloroform); ^{1}H-n.m.r. (200 MHz): δ 2.2–2.55 (m, 2 H), 2.8 (br, 1 H, OH), 3.1 (br, 1 H, OH), 3.5 (m, 1 H), 3.7–3.9 (m, 2 H), 4.10 (br. d, 1 H, J 8 Hz), 4.23 (br. t, 1 H, J 7 Hz), 5.05–5.2 (m, 2 H), and 5.7–5.95 (m, 3 H).

Anal. Calc. for $C_9h_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.49; H, 8.33.

*3-(4,6-O-Benzylidene-2,3-dideoxy-α-*D-erythro*-hex-2-enopyranosyl)-1-propene* (**6**). — To a solution of **4** (99.6 g, 0.585 mol) and dicamphorsulfonic acid (10 g) in dichloromethane (1.2 L) was added benzaldehyde dimethyl acetal[9] (170 mL, 1.01 mmol) dropwise and the mixture stirred at room temperature overnight. The solvent (120 mL) was removed by heating until t.l.c. analysis showed the absence of the starting material. The mixture was cooled to room temperature and then poured into sat. $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), and passed through a short column of silica gel. Evaporation under reduced pressure afforded crude crystals (251.1 g) and recrystallization from ether and hexane gave **6** (121 g, yield 80%), white needles, m.p. 63.0°, $[\alpha]_D^{20}$ $+26.7°$ (c 1.25, chloroform); ^{1}H-n.m.r. (200 MHz): δ 2.25–2.60 (m, H_2-3), 3.62 (ddd, J 10, 8, 4 Hz, H-5′), 3.77 (t, J 10 Hz, H-6′), 4.14 (dq, J 8, 2 Hz, H-1′), 4.23–4.38 (m, H-4′,6′), 5.09 (br.s, H-1), 5.16 (dq, J 8, 1 Hz, H-1), 5.59 (s, PhCH), 5.76 (dt, J 10, 2 Hz, H-2′), 5.75–5.94 (m, H-2), 6.01 (br.d, J 10 Hz, H-3′), and 7.3–7.6 (5 H, Ar).

Anal. Calc. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.37; H, 7.03.

*1-(4,6-Di-O-acetyl-2,3-dideoxy-α-*D-erythro*-hex-2-enopyranosyl)-3,3-dimethyl-3-sila-1-butyne* (**7**). — To a solution of bis(trimethyl)acetylene (1.26 g, 7.4 mmol) and $TiCl_4$ (0.4 mL, 3.7 mmol) in dichloromethane (10 mL), cooled to $-20°$ under N_2 atmosphere, was slowly added, overnight with stirring, a solution of **1** (1.0 g, 3.7 mmol) in dichloromethane (30 mL). The mixture was stirred for an additional 2 h at $-20°$ and then poured into 10% potassium sodium tartrate (40 mL), stirred for 3 h, and extracted dichloromethane (3 ×). The combined organic layers, washed with aq. $NaHCO_3$ and sat. NaCl, dried (Na_2SO_4), and evaporated under reduced pressure, gave a crude oil (1.65 g). Purification by silica gel column chromatography afforded **7** (0.85 g, 75% yield) as an oil, which became crystalline in a freezer, m.p. 43°, $[\alpha]_D^{20}$ $-82.0°$ (c 1.00, chloroform); ν_{max}^{film} 3000, 2200, 1740, 1730 cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 0.20 (s, 9 H), 2.10 (s, 6 H), 4.12 (m, 1 H), 4.24 (m, 2 H), 4.96 (m, 1 H), 5.3 (ddd, 1 H, J 10, 4, 2 Hz), 5.77 (dt, 1 H, J 10, 2 Hz), and 5.90 (ddd, 1 H, J 10, 3, 2 Hz); ^{13}C-n.m.r.: δ 0.24, 21.0, 21.2, 63.2, 64.6, 64.9, 70.2, 91.8, 101.1, 125.7, 129.2, 170.3, and 170.8; m.s.; m/z 250 (M^+ − AcOH) and 209 (M^+ − 101).

Anal. Calc. for $C_{15}H_{22}O_5Si$: C, 58.06; H, 7.10. Found: C, 58.04; H, 7.16.

*1-(2,3-Dideoxy-α-*D-erythro*-hex-2-enopyranosyl)-3,3-dimethyl-3-sila-1-butyne* (**8**). — A solution of **7** (300 mg) in tetrahydrofuran (10 mL) was cooled in an ice bath and mixed with M $LiAlH_4$ in tetrahydrofuran (~1.5 mL). After being stirred for 0.5 h at this temperature, the mixture was poured into 10% tartaric acid (10 mL), extracted with dichloromethane, (3 ×), and the extract washed with water half-saturated with NaCl, dried (Na_2SO_4), and evaporated to give crystals (177 mg, 94% yield), m.p. 90°, $[\alpha]_D^{20}$ −191.7° (*c* 1.00, chloroform); ν_{max}^{film} 3600 and 3400 cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 0.18 (s, 9 H), 2.15 (br., H-3, OH), 3.75 (m, H-5′), 3.88 (m, H-6′), 4.20 (d, H-4′, *J* 9 Hz), 4.92 (m, H-1′), and 5.84 (m, H-2′,3′).

Anal. Calc. for $C_{11}H_{18}O_3Si$: C, 58.41; H, 7.96. Found: C, 58.39; H, 7.97.

*1-(4,6-O-Benzylidene-2,3-dideoxy-α-*D-erythro*-hex-2-enopyranosyl)-3,3-dimethyl-3-sila-1-butyne* (**9**). — A solution of **8** (1.0 g) in *N,N*-dimethylformamide (30 mL) was stirred with benzaldehyde dimethyl acetal (1.0 mL) in the presence of camphorsulfonic acid (0.10 g) for 6 h at 100°. The mixture was poured into a mixture of $NaHCO_3$ (sat., 30 mL) and ice with stirring, and extracted with ether (3 ×). The combined extracts were washed twice with water and sat. NaCl, and dried (Na_2SO_4). Evaporation of the solvent afforded a crude oil which was separated on a silica gel column (~50 g) with 1:2 ether–hexane as eluant to afford pure **9** (1.24 g, 89% yield), which crystallized on storage in a refrigerator; m.p. 68°, $[\alpha]_D^{20}$ −56.3° (*c* 1.00, chloroform); ν_{max}^{film} 2850 cm^{-1}; ^{1}H-n.m.r. (200 MHz): δ 0.20 (s, $SiMe_3$), 3.76 (m, H-5′), 3.90 (m, H-6′b), 4.18 (m, H-4′), 4.40 (dd, *J* 10, 4 Hz, H-6′a), 4.98 (m, H-1′), 5.62 (s, PhCH), 5.76 (dt, *J* 10, 3 Hz, H-2′), and 6.02 (m, H-3′).

Anal. Calc. for $C_{18}H_{22}O_3Si$: C, 68.79; H, 7.01. Found: C, 68.80; H, 7.17.

*2-(4,6-Di-O-acetyl-2,3-dideoxy-α-*D-erythro*-hex-2-enopyranosyl)furan* (**10**). — ^{1}H-N.m.r. (200 MHz): δ 2.06 (s, 3 H), 2.09 (s, 3 H), 3.35 (s, 1 H), 3.55–3.8 (3 H), 5.3–5.4 (2 H), 5.9–6.1 (2 H, AB), 6.3–6.4 (2 H), and 7.45 (dd, 1 H, *J* 2.1 Hz).

*2-(4,6-Di-O-acetyl-1,5-anhydro-2,3-dideoxy-2-*D-ribo*-hex-1-enit-3-yl) furan* (**11**). — ^{1}H-N.m.r. (200 MHz): δ 1.98 (s, 3 H), 2.09 (s, 3 H), 4.02 (td, *J* 6, 2 Hz, H-3′), 4.14 (dt, *J* 10, 4 Hz, H-5′), 4.25–4.35 (m, H_2-6′), 4.80 (d, *J* 6 Hz, H-2′), 5.05 (dd, *J* 10, 6 Hz, H-4′), 6.13 (dd, *J* 3 Hz, H-3 or 4), 6.33 (dd, *J* 3.2 Hz, H-4 or 3), 6.52 (dd, *J* 6, 2 Hz, H-1), and 7.37 (dd, *J* 2 Hz, H-5).

*1-(4,6-O-Benzylidene-2,3-dideoxy-α-*D-erythro*-hexopyranosyl)-3,3-dimethyl-3-sila-1-butene* (**12**). — Compound **9** (18 mg) and dipotassium azodicarboxylate (100 mg) were dissolved in methanol (4 mL), and to this mixture acetic acid (0.05 mL) was added dropwise under a N_2 atmosphere. The mixture was stirred for 4 h at room temperature and, before workup, additional acetic acid (1 mL) was added. After 30 min, the mixture was poured into sat. $NaHCO_3$ solution and was extracted with dichloromethane (× 3). The combined organic layers were washed (NaCl), dried (Na_2SO_4), and evaporated to dryness, and the residual oil was purified by t.l.c. chromatography to afford **12** and its completely reduced derivative in 1:5 ratio in 50% yield; ^{1}H-n.m.r. (500 MHz): δ 0.17 ($SiMe_3$), 3.70 (ddd, *J* 10.3, 8.1, 4.2 Hz, H-5′), 3.77 (t, *J* 10.3 Hz, H-6′b), 4.15 (ddd, *J* 8.1, 4.0, 2.4 Hz, H-4′), 4.32 (dd, *J* 10.2, 4.2 Hz, H-2′), 4.85 (dddd, *J* 9.1, 2.4, 2.0, 0.9 Hz, H-1′), 5.61 (s, PhCH), 5.64 (dt, *J* 10.3, 2.6 Hz, H-2′), 5.76 (dd, *J* 14.2, 0.9 Hz, H-2), 6.04 (br.d, *J* 10.3 Hz, H-3′), 6.47 (dd, *J* 14.2, 9.1 Hz, H-1), 7.37 (m, 3 H, Ar), and 7.51 (m, 2 H, Ar).

REFERENCES

1 S. HANESSIAN, *Total Synthesis of Natural Products; The Chiron Approach*, Pergamon, Oxford, 1983.
2 M. ISOBE, Y. ICHIKAWA, AND T. GOTO, *Tetrahedron Lett.*, 22 (1981) 4287–4290.
3 M. KITAMURA, M. ISOBE, Y. ICHIKAWA, AND T. GOTO, *J. Am. Chem. Soc.*, 106 (1984) 3252–3257.
4 M. ISOBE, Y. ICHIKAWA, AND T. GOTO, *Tetrahedron Lett.*, 27 (1986) 963–966.
5 Y. ICHIKAWA, M. ISOBE, AND T. GOTO, *Tetrahedron Lett.*, 25 (1984) 5049–5052.
6 R. D. DAWE AND B. FRASER-REID, *J. Chem. Soc., Chem. Commun.*, (1981) 1180–1181.
7 A. HOSOMI AND H. SAKURAI, *Tetrahedron Lett.*, (1976) 1295–1298.
8 S. DANISHEFSKY AND J. F. KERWIN, JR., *J. Org. Chem.*, 47 (1982) 3803–3804, 5428.
9 M. E. EVANS, *Carbohydr. Res.*, 21 (1972) 473–475.
10 E. BREITMAIER AND W. VOELTER, *^{13}C NMR Spectroscopy*, Verlag Chemie, Weinheim, 1978 247–257.
11 K. C. NICOLAOU, M. E. DUGGAN, C.-K. HWANG, AND P. K. SOMERS, *J. Chem. Soc., Chem. Commun.*, (1985) 1359–1362.
12 W. ROTH AND W. PIGMAN, *Methods Carbohydr. Chem.*, 2 (1963) 405–408.