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# Efficient Stereoselective Synthesis of α-*C*-Glycopyranosides Using 2,2'-Azobis(2,4-dimethyl-4-methoxyvaleronitrile) [V-70]

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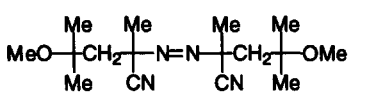
***Abstract:*** Efficient synthesis of α-*C*-glycopyranosides through a radical addition reaction using 2,2'-azobis(2,4-dimethyl-4-methoxyvaleronitrile) [V-70] as an initiator under mild condition was developed. This method made it possible to completely control the stereocenter at the anomeric position and obtain only the α-anomer in high yield compared with AIBN, $Et_3B$, and photo irradiation methods. 

Keywords: Glycosidation, Glycosides, Radical reactions, Stereocontrol

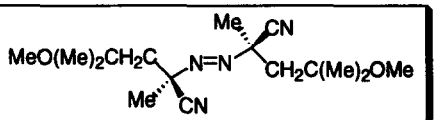
## INTRODUCTION

*C*-Glycopyranosides occur as subunits of a variety of physiologically active natural products and have attracted significant attention as enzyme inhibitors.[1] Furthermore, they have widespread utilities as chiral building blocks for organic synthesis.[2] In this research field, stereoselective construction of the carbon-carbon bonds at the anomeric center is a very important factor. Many useful methods to control the stereocenter at the anomeric position have been developed,[3] and it has been known that the diastereoselective synthesis of α-*C*-glycopyranosides *via* anomeric radical addition to alkenes is one of the most effective methods.[4-6] The radical addition reaction is one of the most powerful methods for the construction of the carbon-carbon bond in organic synthesis and many excellent radical reactions have been developed in the past two decades.[7] The remarkable features of these reactions are mild conditions and high functional group tolerance, thus various substrates can be used for the reaction.

We have already reported that 2,2'-azobis(2,4-dimethyl-4-methoxyvaleronitrile) [V-70][8] acts as an effective radical initiator at low temperature instead of AIBN, that is, radical addition reactions of bromomalononitrile to various alkenes induced by V-70 were described.[9] We then established the practical synthetic method of pyrrolo[2,3-*d*]pyrimidine antifolate TNP-351 from the key intermediate which was prepared by radical addition using V-70.[10]




2,2'-azobis(2,4-dimethyl-4-methoxyvaleronitrile)
[V-70]




V-70L
(*racemic* form)

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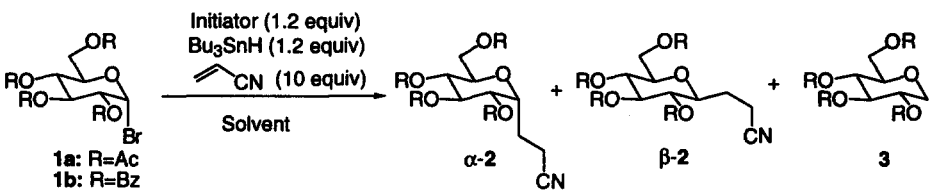
In our recent work, we applied V-70 to the stereoselective radical *C*-glycosylation and revealed that V-70 has a good ability to completely control the stereocenter at the anomeric position, and obtained only the desired α-anomer in higher yield than when using AIBN, $Et_3B$, and photo irradiation methods.[11] In this paper, we report the full details of the stereoselective radical *C*-glycosylation induced by V-70 as an initiator.

## RESULTS AND DISCUSSION

At first, the radical addition reactions of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **1a** with acrylonitrile using various initiators and solvents were examined (Table 1). The photo irradiation induced reaction was reported by Giese who obtained the α-anomer (α-**2a**) as well as the β-anomer (β-**2a**), together with a significant amount of the reduced deoxy-D-glucose derivative (**3a**) (Entry 8).[6] The *C*-glycosylation of **1a** using V-70 (1.2 equiv), $Bu_3SnH$ (1.2 equiv, syringe pump technique was used) and acrylonitrile (10 equiv) in various solvents at room temperature gave only the desired α-**2a** in good yield (Entries 1-3). The stereoselectivity at the anomeric position was completely controlled and β-**2a** was not detected by thin layer chromatography and $^1H$-NMR in these reactions. The best result was obtained using $Et_2O$ as the solvent (Entry 1). When the reaction was performed in the presence of a catalytic amount of V-70 (10 mol% against **1a**), the reaction rate decreased and **3a** was also

**Table 1.** Diastereoselective radical *C*-glycosylation by various initiators



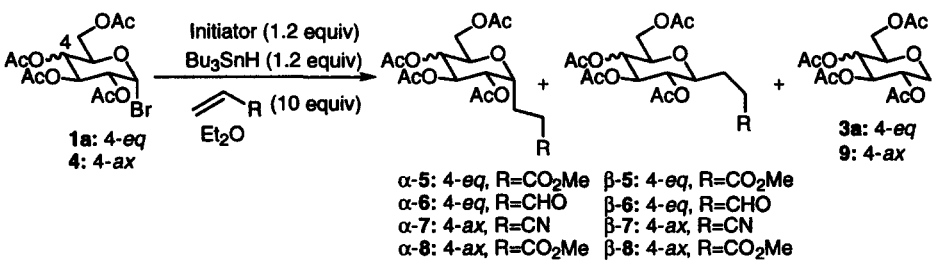

| Entry | 1 | Initiator | Solvent | Temp. | Time (h) | Yield (%)[a] | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | α-2 | β-2 | 3 |
| 1 | **1a** | **V-70** | $Et_2O$ | rt | 12 | 68 | 0[b] | trace[c] |
| 2 | // | // | TBME | // | 18 | 70 | // | // |
| 3 | // | // | $CH_2Cl_2$ | // | 48 | 58 | // | // |
| 4[e] | // | // | $Et_2O$ | // | 90 | 41 | // | 27 |
| 5 | // | **V-70L** | // | // | 12 | 71 | // | trace[c] |
| 6 | // | AIBN | $C_6H_6$ | reflux | 3 | 32 | 2 | 18 |
| 7 | // | $Et_3B$ | $Et_2O$ | -78 °C-rt | 10 | 18 | 0[b] | trace[c] |
| 8[f] | // | hυ | // | reflux | 8 | 53-55 | 5 | 21 |
| 9 | **1b** | **V-70** | $Et_2O$ | rt | 2 | 69 | 0[b] | 27 |
| 10 | // | **V-70L** | $Et_2O$ | // | 2 | 71 | // | 20 |
| 11 | // | AIBN | $C_6H_6$ | reflux | 0.25 | 36 | // | 52 |
| 12 | // | // | $Et_2O$ | // | 1 | 16 | // | 75 |
| 13 | // | hν | $Et_2O$ | // | 7 | 28 | // | 63 |

Syringe pump technique was used in Entries 1-7 and 9-13; [a] Isolated yield; [b] β-Anomer was not detected by thin layer chromatography and $^1H$-NMR; [c] Trace of **3a**, unreacted **1a** and unidentified products were obtained; [d] TBME = *t*-butylmethylether; [e] 10 mol% against **1a** was used; [f] Reported method and value.[6a]

formed, however, we could confirm that V-70 acts as an initiator (Entry 4). On the other hand, we previously reported that V-70 is a mixture of diastereomers which is composed by *meso* V-70H (high melting point) and *racemic* V-70L (low melting point) and V-70L has a good ability to generate radical species compared with V-70H.[9b,12] The radical *C*-glycosylation induced by V-70L was then examined and only α-**2a** was obtained in high yield as expected (Table 1, Entry 5). Although α-**2a** was obtained with heating in the case of using AIBN, β-**2a** and **3a** were also formed (Entry 6). For the reaction using $Et_3B$ as an initiator, the yield of α-**2a** was low and starting **1a** was recovered (Entry 7). Similarly, the effective α-stereoselective radical addition during the *C*-glycosylation of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide **1b** was also achieved using V-70L (Table 1, Entry 10).[13]

Additionally, the *C*-glycosylation reactions of **1a** with other olefins using V-70 and V-70L were examined compared with the photo-induced radical reaction (Table 2).[13] The yields of the α-anomers (α-**5** and α-**6**) using V-70 and V-70L were higher than those of the photo irradiation method and similar complete stereocontrol was observed as shown in the reaction of **1a** and acrylonitrile (Entries 1 and 2 vs 3, Entries 4 and 5 vs 6). It is noteworthy that the reaction with an unstable olefin such as acrolein was also successful to give the desired α-anomer in moderate yields using V-70 and V-70L (Entries 4 and 5). Using the photo-induced method, the reaction produced a complex mixture probably due to the polymerization of acrolein (Entry 6). On the other hand, in the reactions of each olefin, V-70L smoothly gave the desired α-anomer with high yield compared with that of V-70 (Entry 1 vs 2, Entry 4 vs 5). Similarly, the reactions of 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide **4** were examined and only the α-anomers (α-**7** and α-**8**) were obtained.[13] Thus, it was revealed that V-70L has good utility particularly for unstable substrates and/or reagents because of the quick generation of radicals at room temperature.

**Table 2.** Radical *C*-glycosylation of glycosyl bromides (**1a** and **4**) with various olefins



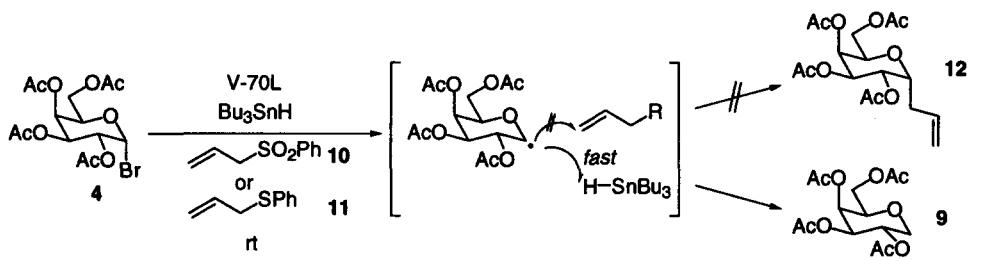

α-**5**: 4-*eq*, R=$CO_2Me$ β-**5**: 4-*eq*, R=$CO_2Me$
α-**6**: 4-*eq*, R=CHO β-**6**: 4-*eq*, R=CHO
α-**7**: 4-*ax*, R=CN β-**7**: 4-*ax*, R=CN
α-**8**: 4-*ax*, R=$CO_2Me$ β-**8**: 4-*ax*, R=$CO_2Me$

| Entry | Substrate 1a or 4 | Olefin R | Initiator | Temp. | Time (h) | | Product Yield (%)[a] α | β | 3a or 9 |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | $CO_2Me$ | **V-70** | rt | 24 | 5 | 59 | 0[b] | trace[c] |
| 2 | // | // | **V-70L** | // | 17 | // | 66 | // | // |
| 3 | // | // | hυ | reflux | 11 | // | 41 | 4 | 41 |
| 4 | // | CHO | **V-70** | rt | 18 | 6 | 30 | 0[b] | trace[c] |
| 5 | // | // | **V-70L** | // | 22 | // | 50 | // | // |
| 6 | // | // | hυ | reflux | 24 | // | complex mixture | | |
| 7 | **4** | CN | **V-70L** | rt | 3 | 7 | 67 | 0[b] | 14 |
| 8 | // | $CO_2Me$ | **V-70L** | // | 17 | 8 | 36 | // | 5 |

*a*, *b* and *c*; see Table 1

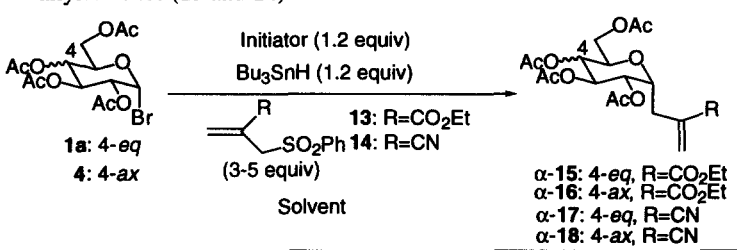
Based on these results, we applied V-70L to the unimolecular chain transfer (UMCT) reaction.[14] Recently, the radical addition reactions of **4** to allylic sulfides and sulfones *via* the UMCT process using the photo irradiation method were reported by Magnusson *et al.*[15] However, attempted *C*-glycosylation of **4** with allyl phenyl sulfone **10** or sulfide **11** induced by V-70L was not successful and gave only the reduced product **9** (Scheme 1). It is presumably because the reduction of the generated anomeric radical by $Bu_3SnH$ is much faster than the addition reaction to the olefin because of the low electrophilicity of these allyl compounds.

**Scheme 1**




Thus we attempted the reaction with more electron deficient allylic sulfones which were substituted by an ester or nitrile at the 2-position such as **13**[16] or **14**[17]. These results are summarized in Table 3.[13] The reaction of **4** with **13** was examined using various initiators (Entries 1-4). The best result was obtained in the case of V-70L, that is, the reaction was finished within 2 h and the desired product, α-**16** was obtained in high yield (77%, Entry 1). With heating using AIBN as an initiator, α-**16** was obtained in 67% yield (Entry 3). The result using V-70L was superior to that of the photo irradiation method (12 h, 61%) or that of the AIBN method (Entry 1 vs 3, 4). Other α-allylated sugars α-**15**, α-**17**, and α-**18**, were also obtained in satisfactory yields using V-70L as an initiator at room temperature (Entries 5-7).

**Table 3.** Radical *C*-allylation reaction of glycosyl bromides (**1a** and **4**) with α-substituted allylsulfones (**13** and **14**)




| Entry | Substrate 1a or 4 | Olefin 13 or 14 | Initiator | Solvent | Temp. | Time (h) | Product | Yield[a] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | **4** | **13** | V-70L | $Et_2O$ | rt | 2 | α-**16** | 77 |
| 2 | // | // | none | // | // | 6 | no reaction | |
| 3 | // | // | AIBN | $C_6H_6$ | reflux | 3 | α-**16** | 67 |
| 4[b] | // | // | hυ | // | rt | 12 | // | 61 |
| 5 | **1a** | // | V-70L | $Et_2O$ | // | 3 | α-**15** | 70 |
| 6 | **4** | **14** | // | $CH_2Cl_2$ | // | 5 | α-**18** | 88 |
| 7 | **1a** | // | // | // | // | 4 | α-**17** | 81 |

[a] Isolated yield; [b] Reported method and value.[15]

## CONCLUSION

Various types of α-*C*-glycopyranosides were readily obtained from glycosyl bromides through the radical *C*-glycosylation reactions using V-70 and V70L as initiators at room temperature in high yield and high stereoselectivity at the anomeric position compared to other commonly used initiators such as photo irradiation, AIBN, and $Et_3B$. Both V-70L and V-70 do not require elevated temperature to generate radical species, and are applicable to large-scale production, not like in the case of photo irradiated reactions. It is expected that this method improve the efficiencies and/or stereoselectivities of other types of radical reactions.

## EXPERIMENTAL SECTION

All melting points are uncorrected. $^1$H-NMR spectra were measured in $CDCl_3$ using 200, 300, and 500 MHz spectrometers with $SiMe_4$ as the internal standard. Infrared (IR) absorption spectra were recorded as a KBr pellet. E. Merck silica gel 60 (70-230 mesh ASTM) for column chromatography was used. V-70 is commercially available from Wako Pure Chemical Ind., Ltd., Japan. 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide **1a** was obtained from the Sigma Chemical Company and was recrystallized from $Et_2O$/pentane before use.[6a] α-D-Glucopyranosyl bromide tetrabenzoate **1b** was commercially available from the Aldrich Chemical Company and acetobromo-α-D-galactose **4** was from Lancaster Synthesis, Ltd. Olefins **13**[16] and **14**[17] were prepared according to the published procedures. Unless otherwise noted, all experiments were carried out under an atmosphere of dry nitrogen using anhydrous solvents which were distilled and dried according to standard procedures.

**Separation of the diastereomers of V-70.** Typical procedure. V-70 (5.00 g) in $Et_2O$ (25 ml) was stirred at 10 °C for 30 min to precipitate only V-70H (2.46 g; content of 100% from $^1$H-NMR). On the other hand, the filtrate, upon cooling at -10 °C for 2 days, gave crystallized V-70L (1.05 g; content of 100% from $^1$H-NMR). **V-70L**: colorless crystal; mp 58 °C (dec.); $^1$H-NMR ($CDCl_3$) δ 1.29 (s, 6 H), 1.64 (s, 6 H), 2.26 (d, 2 H, *J*=11.0 Hz), 2.42 (d, 2 H, *J*=11.0 Hz), 3.21 (s, 6 H). **V-70H**: colorless crystal; mp 107 °C (dec.); $^1$H-NMR ($CDCl_3$) δ 1.20 (s, 6 H), 1.27 (s, 6 H), 1.69 (s, 6 H), 2.19 (d, 2 H, *J*=11.0 Hz), 2.59 (d, 2 H, *J*=11.0 Hz), 3.19 (s, 6 H).

**General procedure for *C*-glycosylation using V-70L (V-70) as the initiator. Preparation of 3-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl) propionitrile (α-2a)[6] (Table 1, entry 5).** To a stirred solution of 2,3,4,6-tetra-*O*-acethyl-α-D-glucopyranosyl bromide **1a** (46.1 mg, 0.112 mmol), acrylonitrile (0.07 ml, 1.123 mmol), and V-70L (41.2 mg, 0.134 mmol) in dry $Et_2O$ (5 ml) was added $Bu_3SnH$ (0.04 ml, 0.134 mmol) *via* a syringe pump over 4 h, and the mixture was further stirred for 8 h at room temperature. 15 % aqueous KF (2 ml) was then added, and the mixture was stirred vigorously at room temperature for 2 h. The organic layer was separated and the aqueous layer was extracted with AcOEt. Combined organic layers were dried over with $MgSO_4$, and concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane/AcOEt, 2:1) to give the α-anomer, **α-2a** (30.5 mg, 71%), and unreacted starting material **1a** (4.5 mg, 10%). **α-2a:** colorless crystal; mp. 120-121 °C (hexane-$Et_2O$) (lit.[6] 121-122 °C). $[\alpha]_D^{19}$ +67° (*c* 1.0, $CHCl_3$) {lit.[6] $[\alpha]_D^{25}$ +66.2° (*c* 0.7, $CHCl_3$)}. IR 2249, 1755, 1747 cm$^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.89 (1H, ddt, *J* = 14.4, 3.6, 8.1 Hz), 2.01 (3H, s), 2.06 (6H, s), 2.11 (3H, s), 2.06-2.19 (1H, m), 2.46 (2H, m), 3.88 (1H, ddd, *J* = 8.4, 5.7, 3.0 Hz), 4.12 (1H, dd, *J* = 12.3, 3.0 Hz), 4.23 (1H, ddd, *J* = 12.3, 5.1, 3.0 Hz), 4.32 (1H, dd, *J* = 12.3, 5.7 Hz), 4.98 (1H, t, *J* = 8.4 Hz), 5.09 (1H, dd, *J* = 8.4, 5.1 Hz), 5.24 (1H, t, *J* = 8.4 Hz).

**3-(2,3,4,6-Tetra-*O*-benzoyl-α-D-glucopyranosyl) propionitrile (α-2b) and 2,3,4,6-tetra-*O*-benzoyl-D-glucitol (3b)[18] (Table 1, entry 10).** Following the general procedure, α-**2b** (78.3 mg, 71%) and **3b** (20.3 mg, 20%) were obtained from **1b** (115,1 mg, 0.175 mmol), acrylonitrile (0.12 ml, 1.745 mmol), V-70L (64.6 mg, 0.209 mmol), and $Bu_3SnH$ (0.06 ml, 0.209 mmol, syringe pump, 2 h) after purification by column chromatography on silica gel (hexane/AcOEt, 3:1). α-**2b:** colorless crystal; mp. 121-123 °C (hexane-$Et_2O$). $[\alpha]_D^{19}$ +50° (*c* 0.6, $CHCl_3$). IR 2249, 1726 $cm^{-1}$. $^1H$- NMR ($CDCl_3$) δ: 1.98-2.07 (1H, m), 2.29-2.42 (1H, m), 2.46-2.53 (2H, m), 4.38 (1H, dt, *J*= 3.3, 6.9 Hz), 4.52-4.58 (1H, m), 4.53 (1H, dd, *J* = 12.0, 3.3 Hz), 4.80 (1H, dd, *J* = 12.0, 6.9 Hz), 5.49 (1H, dd, *J* = 7.5, 5.4 Hz), 5.51 (1H, t, *J* = 7.5 Hz), 5.88 (1H, t, *J* = 7.5 Hz), 7.28-7.60 (12H, m), 7.90-8.05 (8H, m). *Anal.* Calcd for $C_{37}H_{31}NO_9$: C, 70.13; H, 4.93; N, 2.21. Found: C, 69.88; H, 4.92; N, 2.16. FAB-HRMS. Calcd for $C_{37}H_{32}NO_9$ ($M^+$+H) 634.2077. Found 634.2069. **3b:** colorless crystal; mp 47-49 °C (hexane-$Et_2O$). $[\alpha]_D^{20}$ +40° (*c* 1.0, $CHCl_3$). IR 1738, 1732 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ: 3.60 (1H, t, *J* = 10.5 Hz), 4.04 (1H, ddd, *J* = 9.9, 5.1, 2.4 Hz), 4.41-4.49 (2H, m), 4.63 (1H, dd, *J* = 12.3, 2.4 Hz), 5.44 (1H, dt, *J* = 5.4, 9.9 Hz), 5.66 (1H, t, *J* = 9.6 Hz), 5.92 (1H, t, *J* = 9.6 Hz), 7.28-7.58 (12H, m), 7.87-8.07 (8H, m). *Anal.* Calcd for $C_{34}H_{28}O_9$: C, 70.34; H, 4.86. Found: C, 70.30; H, 4.78.

**Methyl 3-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl) propionate (α-5)[19] (Table 2, entry 2).** Following the general procedure, α-**5** (33.8 mg, 66%) was obtained from **1a** (50.0 mg, 0.122 mmol), methyl acrylate (0.11 ml, 1.216 mmol), V-70L (45.0 mg, 0.146 mmol), and $Bu_3SnH$ (0.04 ml, 0.146 mmol, syringe pump, 4 h) after purification by column chromatography on silica gel (hexane/AcOEt, 2:1). α-**5:** colorless oil; $[\alpha]_D^{19}$ +58° (*c* 1.3, $CHCl_3$). IR 1755, 1747, 1738, 1732 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ: 1.85-1.93 (1H, m), 2.03 (3H, s), 2.04 (3H, s), 2.07 (3H, s), 2.10 (3H, s), 2.14 (1H, m), 2.34-2.45 (2H, m), 3.69 (3H, s), 3.85 (1H, ddd, *J* = 9.3, 5.1, 2.4 Hz), 4.04 (1H, dd, *J* = 12.3, 2.4 Hz), 4.18 (1H, ddd, *J* = 12.0, 5.1, 2.4 Hz), 4.25 (1H, dd, *J* = 12.0, 5.1 Hz), 5.00 (1H, t, *J* = 9.3 Hz), 5.10 (1H, dd, *J* = 9.3, 5.7 Hz), 5.32 (1H, t, *J* = 9.3 Hz). FAB-HRMS. Calcd for $C_{18}H_{28}NO_{11}$ ($M^+$+H) 419.1553. Found 419.1535.

**3-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl) propanal (α-6) (Table 2, entry 5).** Following the general procedure, α-**5** (50.0 mg, 50%) and unreacted starting material **1a** (40.1 mg, 38%) were obtained from **1a** (105.4 mg, 0.256 mmol), acrolein (0.17 ml, 2.563 mmol), V-70L (94.7 mg, 0.307 mmol), and $Bu_3SnH$ (0.08 ml, 0.308 mmol, syringe pump, 4 h) after purification by column chromatography on silica gel (hexane/AcOEt, 1:1). α-**6:** pale yellow gummy; $[\alpha]_D^{20}$ +47° (*c* 1.4, $CHCl_3$). IR 1747 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ: 1.82-1.95 (1H, m), 2.038 (3H, s), 2.042 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 2.15 (1H, m), 2.59 (2H, brdd, *J* = 9.6, 6.0 Hz), 3.84 (1H, ddd, *J* = 9.0, 6.0, 3.0 Hz), 4.04 (1H, dd, *J* = 12.0, 2.4 Hz), 4.09-4.19 (1H, m), 4.25 (1H, dd, *J* = 12.0, 5.4 Hz), 4.98 (1H, t, *J* = 9.0 Hz), 5.08 (1H, dd, *J* = 9.0, 5.4 Hz), 5.31 (1H, t, *J* = 9.0 Hz), 9.83 (1H, s). FAB-HRMS. Calcd for $C_{17}H_{25}O_{10}$ ($M^+$ +H) 389.1447. Found 389.1449.

**3-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosyl) propionitrile (α-7)[5c] and 2,3,4,6-tetra-*O*-acetyl-D-galactitol (9)[20] (Table 2, entry 7).** Following the general procedure, α-**7** (124.9 mg, 67%) and **9** (22.5 mg, 14%) was obtained from **4** (200.0 mg, 0.486 mmol), acrylonitrile (0.44 ml, 4.886 mmol), V-70L (180.0 mg, 0.583 mmol), and $Bu_3SnH$ (0.16 ml, 0.594 mmol, syringe pump, 2.5 h) after purification by column chromatography on silica gel (hexane/AcOEt, 1:1). α-**7:** colorless gummy; $[\alpha]_D^{19}$ +77° (*c* 0.7, $CHCl_3$). IR 2249, 1755, 1747 $cm^{-1}$. $^1H$-NMR ($CDCl_3$) δ: 1.82 (1H, ddt, *J* = 14.4, 3.0, 7.8 Hz), 2.00 (1H, m), 2.07 (3H, s), 2.08 (3H, s), 2.11 (6H, s), 2.45 (1H, dd,

$J$ = 8.1, 2.7 Hz), 2.47 (1H, dd, $J$ = 8.1, 2.1 Hz), 4.04-4.12 (2H, m), 4.26 (1H, dt, $J$ = 11.4, 3.9 Hz), 4.43 (1H, dd, $J$= 13.2, 9.3 Hz), 5.17 (1H, dd, $J$ = 7.8, 3.3 Hz), 5.23 (1H, dd, $J$ = 7.8, 3.9 Hz), 5.41 (1H, t, $J$ = 3.3 Hz). FAB-HRMS. Calcd for $C_{17}H_{24}NO_9$ ($M^+$ +H) 386.1451. Found 386.1452. **9**: mp 74-75, 106-108 °C (lit.[20] 75-77, 105-106 °C). $[\alpha]_D^{19}$ +49° (*c* 1.1, $CHCl_3$) {lit.[20] $[\alpha]_D^{17}$ +49° (*c* 1, $CHCl_3$)}. IR 1755, 1747, 1732 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.00 (3H, s), 2.04 (3H, s), 2.05 (3H, s), 2.15 (3H, s), 3.29 (1H, dd, $J$ = 11.2, 10.2 Hz), 3.82 (1H, dt, $J$ = 1.2, 6.6 Hz), 4.09 (2H, d, $J$ = 6.6 Hz), 4.19 (1H, dd, $J$ = 11.2, 5.6 Hz), 5.04 (1H, dd, $J$ = 10.2, 3.3 Hz), 5.22 (1H, dt, $J$ = 5.6, 10.2 Hz), 5.44 (1H, dd, $J$ = 3.3, 1.2 Hz).

**Methyl 3-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl) propionate (α-8) (Table 2, entry 8).** Following the general procedure, **α-8** (72.7 mg, 36%) and **9** (9.3 mg, 5%) was obtained from **4** (200.0 mg, 0.486 mmol), methyl acrylate (0.11 ml, 1.216 mmol), V-70L (45.0 mg, 0.146 mmol), and $Bu_3SnH$ (0.04 ml, 0.146 mmol, syringe pump, 2.5 h) after purification by column chromatography on silica gel (hexane/AcOEt, 2:1). **α-8:** colorless oil; $[\alpha]_D^{19}$ +71° (*c* 0.55, $CHCl_3$). IR 1755, 1747 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.77-1.88 (1H, m), 1.96-2.06 (1H, m), 2.03 (3H, s), 2.06 (3H, s), 2.09 (3H, s), 2.13 (3H, s), 2.35-2.45 (2H, m), 3.69 (3H, s), 4.05 (1H, dd, $J$ = 12.6, 5.7 Hz), 4.06 (1H, dd, $J$ = 9.0, 5.7 Hz), 4.22 (1H, dd, $J$ = 12.6, 9.0 Hz), 4.23 (1H, dd, $J$ = 11.4, 1.2 Hz), 5.20 (1H, dd, $J$ = 9.3, 3.0 Hz), 5.29 (1H, dd, $J$ = 9.3, 5.1 Hz), 5.41 (1H, dd, $J$ = 5.1, 2.7 Hz). *Anal.* Calcd for $C_{18}H_{26}O_{11}$: C, 51.67; H, 6.26. Found: C, 51.37; H, 6.17. FAB-HRMS. Calcd for $C_{18}H_{27}O_{11}$ ($M^+$ +H) 419.1554. Found 419.1561.

**General procedure for *C*-glycosylation using AIBN as an initiator. Preparation of α-2a, 3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) propionitrile (β-2a)[6], and 2,3,4,6-tetra-*O*-acetyl-D-glucitol (3a)[6,20] (Table 1, entry 6).** To a stirred solution of **1a** (30.0 mg, 0.073 mmol), acrylonitrile (0.04 ml, 0.577 mmol), and AIBN (12.0 mg, 0.073 mmol) in refluxed dry benzene (4 ml) was added $Bu_3SnH$ (0.04 ml, 0.134 mmol) *via* a syringe pump over 3 h, and the mixture was further stirred for 1 h, then 15% aqueous KF (2 ml) was added, and the mixture was stirred vigorously at room temperature for 2 h. The organic layer was separated and extracted with AcOEt, dried over with $MgSO_4$, and concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane/AcOEt, 1:1) to give the α-anomer, **α-2a** (9.0 mg, 32%), β-anomer, **β-2a** (0.5 mg, 2%), **3a** (4.3 mg, 18%), and unreacted starting material **1a** (9.0 mg, 30%). **β-2a:** colorless crystal; mp 90-91, 115-117 °C (lit.[6a] 91-93, 117-119 °C). $[\alpha]_D^{19}$ -21° (*c* 0.8, $CHCl_3$) {lit.[6a] $[\alpha]_D^{25}$ -19.6° (*c* 1.01, $CHCl_3$)}. IR 2240, 1750, 1745 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.79 (1H, m), 1.95 (1H, m), 2.01 (3H, s), 2.03 (3H, s), 2.08 (3H, s), 2.10 (3H, s), 2.53 (2H, m), 3.56 (1H, dt, $J$ = 9.5, 2.6 Hz), 3.69 (1H, ddd, $J$ = 9.9, 5.1, 2.0 Hz), 4.12 (1H, dd, $J$ = 12.3, 2.0 Hz), 4.23 (1H, dd, $J$ = 12.3, 5.1 Hz), 4.88 (1H, t, $J$= 9.6 Hz), 5.05 (1H, t, $J$ = 9.3 Hz), 5.21 (1H, t, $J$ = 9.6 Hz). **3a:** colorless crystal; mp 72-73 °C (hexane-$Et_2O$) (lit.[20] 71-73 °C). $[\alpha]_D^{19}$ +41° (*c* 1.1, $CHCl_3$) {lit.[20] $[\alpha]_D^{18}$ +42° (*c* 1.4, $CHCl_3$)}. IR 1767, 1732 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 2.03 (3H, s), 2.04 (6H, s), 2.10 (3H, s), 3.31 (1H, t, $J$ = 11.1 Hz), 3.60 (1H, ddd, $J$ = 9.9, 4.8, 2.4 Hz), 4.10-4.24 (3H, m), 5.00 (1H, t, $J$ = 9.6 Hz), 5.03 (1H, dd, $J$ = 12.9, 9.6 H), 5.21 (1H, t, $J$ = 9.6 Hz).

**General procedure for *C*-glycosylation using $Et_3B$ as an initiator. Preparation of α-2a (Table 1, entry 7).** To a stirred solution of **1a** (57.1 mg, 0.139 mmol), acrylonitrile (0.05 ml, 0.699 mmol), and $Et_3B$ (1.0 M solution in hexane, 0.16 ml, 0.160 mmol) in dry $Et_2O$ (3.75 ml) was added $Bu_3SnH$ (0.05 ml, 0.186 mmol) *via* a syringe pump over 5 h at -78 °C, and the reaction mixture was warmed to room temperature and further stirred for 5 h, then 15% aqueous KF (2 ml) was added, and the mixture was stirred vigorously at room temperature for 2 h. The organic layer was separated and extracted with AcOEt, dried over with $MgSO_4$, and concentrated *in vacuo*, and

the residue was chromatographed on silica gel (hexane/AcOEt, 3:2) to give the α-anomer, α-**2a** (9.8 mg, 18%), and unreacted starting material **1a** (39.3 mg, 69%).

**General procedure for *C*-glycosylation using photo irradiation method. Preparation of 3-(2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl) propionitrile (α-2b) and 3b (Table 1, entry 13).** A stirred solution of **1b** (100.0 mg, 0.152 mmol) and acrylonitrile (0.05 ml, 0.758 mmol) in dry $Et_2O$ (14 ml) was irradiated with a sunlamp. The heat from the sunlump maintains a reflux and $Bu_3SnH$ (0.05 ml, 0.182 mmol) was added *via* a syringe pump over 2 h, then 15% aqueous KF (4 ml) was added, and the mixture was stirred vigorously at room temperature for 2 h. The organic layer was separated and extracted with AcOEt, dried over with $MgSO_4$, and concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane/AcOEt, 3:1) to give the α-anomer, α-**2b** (9.8 mg, 28%), and **3b** (39.3 mg, 63%).

**General procedure for *C*-allylated glycopyranosides using V-70L as an initiator. Preparation of ethyl 2-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosylmethyl) acrylate (α-16)[15] (Table 3, entry 1).** To a stirred solution of acetobromogalactose **4** (100.0 mg, 0.243 mmol), sulfone **13** (309.2 mg, 1,216 mmol) and V-70L (90.0 mg, 0.292 mmol) in dry $Et_2O$ (10 ml) was added $Bu_3SnH$ (0.08 ml, 0.292 mmol) *via* a syringe pump over 2 h at room temperature, then 15% aqueous KF (2 ml) was added, and the mixture was stirred vigorously at room temperature for 2 h. The organic layer was separated and extracted with AcOEt, dried over with $MgSO_4$, and concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane/AcOEt, 3:1) to give α-**16** (83.4 mg, 77%). α-**16:** colorless oil; $[\alpha]_D^{21}$ +69° (*c* 0.5, $CHCl_3$) {lit.[15] $[\alpha]_D^{23}$ +71° (*c* 1.3, $CHCl_3$)}. $^1$H-NMR ($CDCl_3$) δ: 1.28 (3H, t, *J*= 7.2 H), 2.00 (3H, s), 2.01 (3H, s), 2.07 (3H, s), 2.11 (3H, s), 2.58 (1H, dd, *J* = 10.4, 4.8 Hz), 2.64 (1H, dd, *J* = 10.4, 5.2 Hz), 4.03 (1H, dd, *J* = 13.8, 8.4 Hz), 4.08-4.14 (2H, m), 4.19 (2H, qd, *J* = 7.2, 0.9 Hz), 4.46 (1H, ddd, *J* = 10.2, 5.1, 4.5 Hz), 5.20 (1H, dd, *J* = 9.6, 3.3 Hz), 5.30 (1H, dd, *J* = 9.6, 5.1 Hz), 5.40 (1H, dd, *J* = 3.0, 0.9 Hz), 5.65 (1H, s), 6.28 (1H, s).

**Ethyl 2-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosylmethyl) acrylate (α-15)[21] (Table 3, entry 5).** Following the general procedure, α-**15** (76.0 mg, 70%) was obtained from **1a** (100.0 mg, 0.243 mmol), sulfone **13** (311.2 mg, 1.223 mmol), V-70L (90.0 mg, 0.292 mmol), and $Bu_3SnH$ (0.08 ml, 0.292 mmol, syringe pump, 2 h) after purification by column chromatography on silica gel (hexane/AcOEt, 2:1). α-**15:** colorless crystal; mp 45-46 °C (hexane-$Et_2O$). $[\alpha]_D^{19}$ +59° (*c* 0.6, $CHCl_3$) {lit. $[\alpha]_D^{20}$ +59.9° (*c* 1.1, $CHCl_3$)}. IR 2984, 1755, 1747, 1714 $cm^{-1}$. $^1$H-NMR ($CDCl_3$) δ: 1.30 (3H, t, *J* = 7.2 Hz), 2.04 (3H, s), 2.05 (3H, s), 2.08 (6H, s), 2.62 (1H, dd, *J* = 15.0, 3.3 Hz), 2.76 (1H, dd, *J* = 15.0, 11.4 Hz), 3.97 (1H, ddd, *J* = 9.3, 7.5, 2.7 Hz), 4.01 (1H, dd, *J* = 13.8, 2.7 Hz), 4.19 (1H, dd, *J* = 13.8, 7.5 Hz), 4.21 (2H, q, *J* = 7.2 Hz), 4.44 (1H, ddd, *J* = 11.4, 5.7, 3.3 Hz), 4.99 (1H, t, *J* = 9.3 Hz), 5.12 (1H, dd, *J* = 9.3, 5.7 Hz), 5.36 (1H, t, *J* = 9.3 Hz), 5.69 (1H, s), 6.31 (1H, s). FAB-HRMS. Calcd for $C_{20}H_{29}O_{11}$ ($M^+$+H) 445.1710. Found 445.1691.

**2-(2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosylmethyl) acrylonitrile (α-17) (Table 3, entry 6).** Following the general procedure, α-**17** (18.0 mg, 81%) was obtained from **1a** (23.2 mg, 0.056 mmol), sulfone **14** (33.6 mg, 0.162 mmol), V-70L (20.9 mg, 0.067 mmol), and $Bu_3SnH$ (0.02 ml, 0.067 mmol, syringe pump, 2 h) after purification by column chromatography on silica gel (hexane/AcOEt, 2:1). α-**17:** colorless crystal; mp 87-88 °C (hexane-$Et_2O$). $[\alpha]_D^{19}$ +55° (*c* 0.065, $CHCl_3$). IR 2224, 1767, 1755, 1747, 1732, 1714 $cm^{-1}$. $^1$H- NMR ($CDCl_3$) δ:

2.05 (6H, s), 2.09 (6H, s), 2.48 (1H, dd, $J$ = 15.3, 3.6 Hz), 2.76 (1H, dd, $J$ = 15.3, 11.4 Hz), 3.91 (1H, ddd, $J$ = 8.7, 5.1, 2.7 Hz), 4.11 (1H, dd, $J$ = 12.3, 2.7 Hz), 4.29 (1H, dd, $J$ = 12.3, 5.1 Hz), 4.42 (1H, ddd, $J$ = 11.4, 5.4, 3.6 Hz), 5.00 (1H, t, $J$ = 8.7 Hz), 5.14 (1H, dd, $J$ = 8.7, 5.4 Hz), 5.27 (1H, t, $J$ = 8.7 Hz), 5.88 (1H, s), 6.02 (1H, s). FAB-HRMS. Calcd for $C_{18}H_{24}NO_9$ ($M^+$ +H) 398.1451. Found 398.1437.

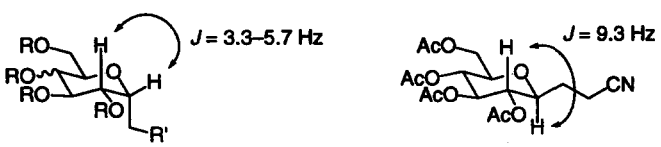
**2-(2,3,4,6-Tetra-*O*-acetyl-α-D-galactopyranosylmethyl) acrylonitrile (α-18) (Table 3, entry 7).** Following the general procedure, α-**18** (42.1 mg, 88%) was obtained from **4** (50.0 mg, 0.122 mmol), sulfone **14** (74.6 mg, 0.360 mmol), V-70L (45.0 mg, 0.146 mmol), and $Bu_3SnH$ (0.04 ml, 0.149 mmol, syringe pump, 2 h) after purification by column chromatography on silica gel (hexane/AcOEt, 2:1). α-**18:** colorless gummy; $[\alpha]_D^{19}$ +79° (*c* 0.43, $CHCl_3$). IR 2224, 1755, 1747 $cm^{-1}$. $^1H$- NMR ($CDCl_3$) δ: 2.05 (6H, s), 2.12 (3H, s), 2.13 (3H, s), 2.43 (1H, dd, $J$ = 15.0, 3.6 Hz), 2.65 (1H, dd, $J$ = 15.0, 11.1 Hz), 4.11 (1H, ddd, $J$ = 9.6, 9.0, 3.0 Hz), 4.12 (1H, dd, $J$ = 13.5, 9.0 Hz), 4.30 (1H, dd, $J$ = 13.5, 9.6 Hz), 4.45 (1H, ddd, $J$ = 11.1, 4.8, 3.6 Hz), 5.18 (1H, dd, $J$ = 8.7, 3.0 Hz), 5.30 (1H, dd, $J$ = 8.7, 4.8 Hz), 5.42 (1H, t, $J$ = 3.0 Hz), 5.83 (1H, s), 6.00 (1H, s). *Anal.* Calcd for $C_{18}H_{23}NO_9$: C, 54.40; H, 5.83; N, 3.52. Found: C, 54.11; H, 6.04; N, 3.35. FAB-HRMS. Calcd for $C_{18}H_{24}NO_9$ ($M^+$ +H) 398.1451. Found 398.1440.

## REFERENCES AND NOTES


1. (a) Connor, D. T.; Greenough, R. C.; von Strandtmann, M. J. *J. Org. Chem.* **1977**, *42*, 3664-3669. (b) Moore, R. E.; Bartoline, G. J. *J. Am. Chem. Soc.* **1981**, *103*, 2491-2494. (c) Shulmann, M. L.; Shilyan, S. D.; Khorlin, A. Y. *Carbohydr. Res.* **1974**, *33*, 229-235. (d) Chmielewski, M.; BeMiller, J. N.; Cerretti, D. P. *ibid.* **1981**, *97*, C1-C4.
2. Hanessian, S. *Total Synthesis of Natural Products. The Chiron Approach*; Pergamon Press: Oxford, **1983**.
3. For reviews see: (a) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913-9959. (b) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545-8599.
4. Togo, H.; He, W.; Waki, Y.; Yokoyama, M. *Synlett* **1998**, 700-717.
5. For recent examples, see: (a) Roe, B. A.; Boojamra, C. G.; Griggs, J. L.; Bertozzi, C. R. *J. Org. Chem.* **1996**, *61*, 6442-6445. (b) Hang, S.-C.; Wong, C.-H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2671-2674. (c) Spencer, R. P.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 4204-4205. (d) Gervay, J.; Flaherty, T. M.; Holms, D. *Tetrahedron* **1997**, *53*, 16355-16364. (e) Breithor, M.; Herden, U.; Hoffmann, H. M. R. *Tetrahedron* **1997**, *53*, 8401-8420.
6. (a) Giese, B.; Dupuis, J.; Nix, M. *Org. Synth.* **1987**, *65*, 236-239. (b) Giese, B.; Dupuis, J. *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 622-623.
7. For reviews see: (a) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969-1146. (b) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296-304. (c) RajanBabu, T. V. *Acc. Chem. Res.* **1991**, *24*, 139-145. (d) Smadja, W. *Synlett* **1994**, 1-26. (e) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, 1996. (f) Renaud, P.; Gerster, M. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2562-2579.
8. (a) Robertson, J. A. U. S. Patent 2,586,995 (1952) [Chem. Abstr. 1952, 46, 9579c]. (b) Lim, D. *Collect. Czechoslov. Chem. Commun.* **1968**, *33*, 1122-1130. (c) Shinohara, N.; Kudo, M.; Iwabuchi, M. Jpn. Kokai

Tokkyo Koho JP 04,66,588 [92,66,588] (Cl. C07F7/12), 02 Mar 1992, Appl. 90/172,449, 29 Jun 1990; 4pp. [Chem. Abstr. 1992, 117, 26799b] (d) Satsuka, H.; Takasu, Y. Jpn. Kokai Tokkyo Koho JP 06,172,232 [94,172,232] (Cl. C07C22/04), 21 Jun 1994, Appl. 92/329,416, 09 Dec 1992; 6pp. [Chem. Abstr. 1994, 121, 230457a] (e) Katsura, T.; Shiratani, H. Eur. Pat. Appl. EP 709,369 (Cl. C07C253/30),1 May 1996, JP Appl. 94/289,079, 27 Oct 1994; 7pp. [Chem. Abstr. 1996, 125, 58121f]. 2,2'-Azobis(2,4-dimethyl-4-methoxy-valeronitrile) is commercially available from Wako Pure Chemical Ind., Ltd., (Japan), and V-70 is its trade name. This compound should be stored below -10 °C to prevent any decomposition. V-70 is stable in a refrigerator for a few months, and the pure V-70 can be easily obtained by the following procedure: V-70 (10.0 g, ca. 90% content) was added to dry acetone (20 ml) at -10 °C with stirring. The heterogeneous solution was stirred for 30 min at -10 °C. Collecting the crystalline precipitates afforded 6.2g of pure V-70 (62%, >99% content).

9. (a) Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K.; Matsugi, M. *Tetrahedron Lett.* **1997**, *38*, 3549-3552. (b) Kita, Y,; Gotanda, K.; Murata, K.; Suemura, M.; Sano, A.; Yamaguchi, T.; Oka, M.; Matsugi, M. *Org. Process Res. Dev.* **1998**, *2*, 250-254.
10. Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K.; Matsugi, M. *J. Org. Chem.* **1999**, *64*, 675-678.
11. Kita, Y.; Gotanda, K.; Sano, A.; Oka, M.; Murata, K.; Suemura, M.; Matsugi, M. *Tetrahedron Lett.* **1997**, *38*, 8345-8348.
12. V-70L: low melting point diastereomer, mp. 58 °C.; V-70H: high melting point diastereomer, mp. 107 °C.
13. The stereochemistry of all new compounds were assigned on the basis of the coupling constant (*J*) of the anomeric proton and the adjacent axial proton of gulycopyranoside ring.




14. Curran, D. P.; Xu, J.; Lazzarini, E. *J. Chem. Soc., Perkin Trans. 1* **1995**, 3049-3059.
15. Ponten, F.; Magnusson, G. *J. Org. Chem.* **1996**, *61*, 7463-7466.
16. Baldwin, J. E.; Adlington, R. M.; Birch, D. J.; Crawford, J. A.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1986**, 1339-1340.
17. Baldwin, J. E.; Adlington, R. M.; Lowe, C.; O'Neil, I. A.; Sanders, G. L.; Schofield, C. J.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1030-1031.
18. Elvebak II, L. E.; Gray, G. R. *Carbohydr. Res.* **1995**, *274*, 85-97.
19. Adlington, R. M.; Baldwin J. E.; Basak, A.; Kozyrod, R. P. *J. Chem. Soc., Chem. Commun.* **1983**, 944-945.
20. Kocienski, P.; Pant, C. *Carbohydr. Res.* **1982**, *110*, 330-332.
21. Giese, B.; Linker, T.; Muhn, R. *Tetrahedron* **1989**, *45*, 935-940.