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A Highly Stereoselective Synthesis of α-Linked *C*-Glycopyranosides Using 2,2'-Azobis-(2,4-dimethyl-4-methoxyvaleronitrile) (V-70)

Yasuyuki Kita*[a], Kentoku Gotanda[a], Atsunori Sano[b], Masahisa Oka[b], Kenji Murata[a],
Miki Suemura[a] and Masato Matsugi[a]

[a]Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565, Japan
[b]Tokyo Research Laboratories, Wako Pure Chemical Industries, Ltd., 1633, Matoba, Kawagoe, Saitama 350-11, Japan

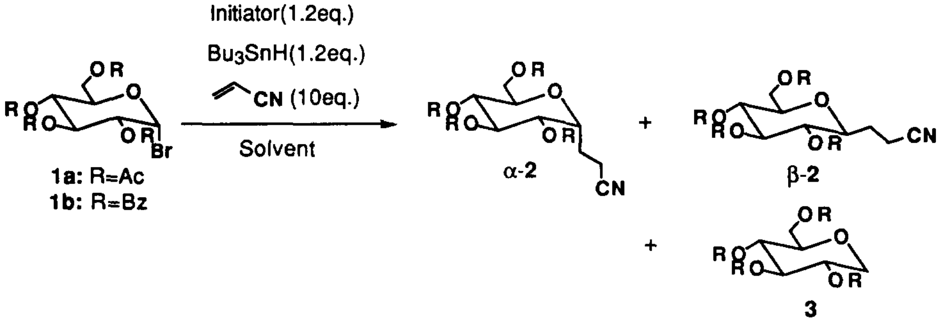
Abstract: α-Linked *C*-glycopyranosides were obtained effectively by the radical addition reaction using V-70, an effective radical initiator under mild conditions. © 1997 Elsevier Science Ltd.

C-Glycosides in which the anomeric oxygen of the glycoside is replaced by a carbon atom occur in several physiologically active natural products and act as subunits of natural products and as enzyme inhibitors.[1] Because several *C*-glycosides linked by *axial* carbon-carbon bonds are involved in interesting natural products such as Palytoxin,[2] it is important to control the selectivity at the anomeric position in the synthesis of these compounds. Many methods to control the stereo center at the anomeric position have been reported,[3] and it has been known that a diastereoselective synthesis of the *axial* *C*-glycopyranosides *via* anomeric radical additions to alkenes using tributyltinhydride under light conditions is one of the most effective methods.[4] The selectivity of this photo-induced radical reaction is, however, 10 / 1 (α / β), and a completely stereo-controlled and simpler reaction is desired.

We have already reported that 2,2'-Azobis-(2,4-dimethyl-4-methoxyvaleronitrile) (V-70)[5] acts as an effective radical initiator at low temperature instead of 2,2'-azobis-iso-butyronitrile (AIBN),[6] and we now report a V-70-induced highly stereoselective carbon-carbon bond formation at the anomeric position to give the α-linked *C*-glycopyranoside.

To a solution of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **1a**, V-70 (1.2 molar quantity vs. **1a**) and acrylonitrile (10 molar quantity vs. **1a**) in various solvents, a solution of tributyltinhydride (1.2 molar quantity vs. **1a**) was slowly added in each corresponding solvent by a syringe pump technique at room temperature with stirring. Consequently, we obtained the α-derivative **2a** with almost complete stereo-control at the anomeric position in high yield (Table 1, Entries 1-3). The β-anomer was not detected on thin layer chromatography in these reactions of entries 1-3. Although the α-derivative (α-**2a**) was obtained with heating in the case of using AIBN,[7] the β-derivative (β-**2a**) and reductive adduct **3** were also formed (Table 1, Entry 5). In the case of using Et_3B as an initiator, the yield of α-**2a** was low (Table 1, Entry 6). Thus we found that the radical addition reactions using V-70 as an initiator at room temperature were excellent methods for α-linked *C*-glycopyranoside synthesis. An effective α-stereoselective radical addition in *C*-glycosidation of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide **1b** and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl bromide **4** was also achieved using V-70 (Table 1, Entry 8; Scheme 1).

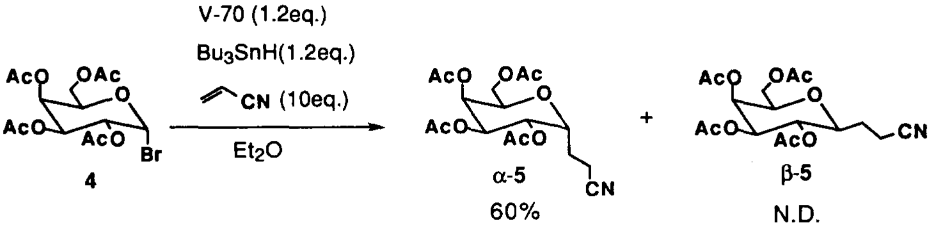
Table 1: Diastereoselective radical reaction by various initiators



Entry	1	Initiator	Solvent	Temp.	Time(hr)	Yield		
						α-**2** (%)	β-**2** (%)	**3** (%)
1	**1a**	**V-70**	Et_2O	r.t.	12	68	N.D.[a] (> 20 : 1)[b]	trace[c]
2	**1a**	**V-70**	TBME[d]	r.t.	18	70	N.D.[a]	trace[c]
3	**1a**	**V-70**	CH_2Cl_2	r.t.	48	58	N.D.[a]	trace[c]
4	**1a**	**V-70**[e]	Et_2O	r.t.	90	41	N.D.[a]	27[c]
5	**1a**	AIBN	C_6H_6	refl.	3	32	2	18[c]
6	**1a**	Et_3B	Et_2O	-78°C-r.t.	10	18	N.D.[a]	trace[c]
7	**1a**	hν[f]	Et_2O	refl.	8	53-55	5	21
8	**1b**	**V-70**	Et_2O	r.t.	2	69	N.D.[a]	27
9	**1b**	AIBN	C_6H_6	refl.	0.25	36	N.D.[a]	52
10	**1b**	AIBN	Et_2O	refl.	1	16	N.D.[a]	75
11	**1b**	hν	Et_2O	refl.	7	28	N.D.[a]	63

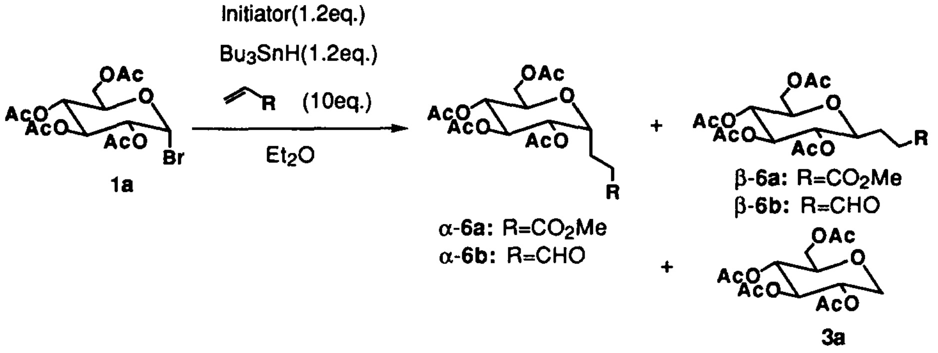
All yields were isolated yields; Syringe pump technique was used in Entry 1 - 6 and 8 - 11; [a]β-Anomer was not detected on thin layer chromatography; [b]Ratio was determined by ^1H NMR; [c]Unreacted **1a** and unidentified products were obtained; [d]TBME = ^{t}butylmethylether; [e]10mol % against **1a** was used; [f]Reported method and value.[4]

Scheme 1: Diastereoselective radical reaction using **4** as the substrate



Additionally, other α-linked *C*-glycopyranosides (α-**6a** and α-**6b**) were also obtained effectively by this V-70 radical generation method in contrast to the photo-induced radical generation method (Table 2).

Table 2: Diastereoselective radical reaction using other alkenes

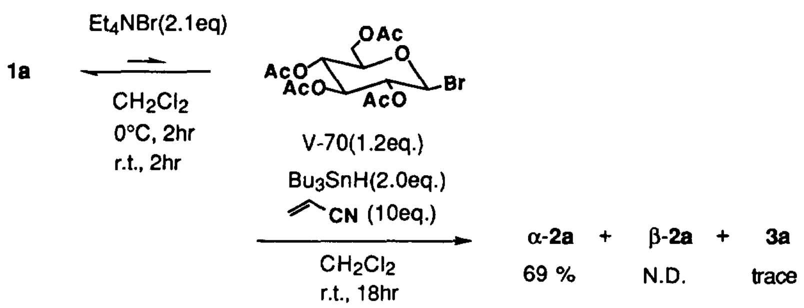


Entry	Initiator	R	Temp.	Time(hr)	Yield α-6(%)	β-6 (%)	3a (%)
1	V-70	CO_2Me	r.t.	24	**6a**: 59	N.D.[a]	trace[b]
2	hν	CO_2Me	refl.	11	**6a**: 41	4	41
3	V-70	CHO	r.t.	18	**6b**: 30	N.D.[a]	trace[b]
4	hν	CHO	refl.	24	complex mixture		

All yields were isolated yields; Syringe pump technique was used in all cases; [a]β-anomer was not detected on thin layer chromatography; [b]Unreacted **1a** and unidentified products were obtained.

Next, we examined a radical addition reaction in the presence of tetraethylammonium bromide (TEAB) to clarify the attribute of α-selectivity, that is, by anomeric effect[8] or by trapping of an α-radical by acrylonitrile before inversion at the anomeric position (Scheme 2). It is known that α-haloglycopyranoside is an equilibrium state between the α-bromide compound and the β-bromide compound in the presence of TEAB.[9] As a result, the β-adduct was not detected on thin layer chromatography under this condition. Therefore, it may be suggested that this α-selectivity is attributed mainly to the anomeric effect.

Scheme 2: Diastereoselective radical reaction by V-70 in the presence of TEAB



In conclusion, we achieved highly diastereoselective carbon-carbon bond formations to give α-glycopyranosides through the radical addition reaction using V-70 as the initiator. It is expected that this method will make possible to raising the selectivities in other stereoselective radical addition reactions.

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