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Novel galactosyl donor with 2-naphthylmethyl (NAP) as the non-participating group at C-2 position: efficient synthesis of α-galactosyl ceramide

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ABSTRACT

Predominant α-linked products can be generated in glycosylation involving galactosyl trichloroacetimidate donors with 2-naphthylmethyl (NAP) as the non-participating group at C-2 position. The above-mentioned donor was successfully utilized for the synthesis of α-galactosyl ceramide.

1. Introduction

Glycans, the vital endogenous biomolecules, found mostly in conjugation with lipids (to form glycolipids) and proteins (to form glycoproteins), are composed of various monosaccharide units linked together through O-glycosidic linkages. They are crucially engaged in various biochemical pathways and biological processes viz., cell-cell communication, cell adhesion, immune response, molecular recognition, tissue repair, and microbial and viral pathogenesis.[1] Therefore, practical and stereocontrolled synthesis of glycans occupies great importance in carbohydrate chemistry where a glycosylation reaction involving a donor and an acceptor can yield α- as well as β-isomers during the glycosidic bond formation.[2] Despite the enormous efforts put in by various groups for the development of efficient and stereoselective glycosylation methodologies, not all problems are completely answered.[3] In carbohydrate chemistry, generally it is believed that the glycosylation with glycosyl donors possessing an *O*-acyloxyl group at C-2 usually afford 1,2-*trans* glycoside with quite high stereoselectivity by virtue of its neighboring group participation.[2k,n,4] But, some reports revealed unusual 1,2-*cis*-glycosylation,[5] α-(1→3)-glycosylations,[6] and 1,2-*cis*-galactosylations[7] with glycosyl donors having a C-2 ester capable of neighboring group participation.

Stereoselective synthesis of 1,2-*cis* glycosides is usually a more difficult issue where no assistance by neighboring group participation is available.[2f] For instance, the stereoselective construction of certain 1,2-*cis* glycosyl linkages such as α-glucopyranosyl,[8] α-galactopyranosyl,[9] α-arabinofuranosyl,[10] α-sialyl linkages,[11] and β-mannopyranosyl[12] still presents significant challenge as each case requires a special strategy when applied to construct a complex carbohydrate structure.

In general, a non-assisting functionality at C-2 position of glycosyl donors in most cases is a benzyl, a substituted benzyl or allyl group for the introduction of 1,2-*cis*-glycosidic linkages. Invariably, the use of these glycosyl donors leads to the formation of mixtures of anomers.[2f] Time-consuming purification protocols are required for the separation of these anomers which also results in the loss of material. In order to find a better stereoselective glycosylation methodology, we became interested in checking the influence of 2-naphthylmethyl (NAP) group as a non-participating group in 1,2-*cis* α-galactosyl bond formation as it is endowed with versatile properties such as stability to variety of acidic and basic conditions, selective introduction, and chemoselective removal.[13] With the intention of studying the stereoselectivity–structure relationship, a variety of donors (with *O*-NAP group at C-2) and acceptors were used for coupling together (Table 1). Herein, we describe the results for the above-described coupling reactions and successful application of our findings to the synthesis of biologically important α-galactosyl ceramide **24**.[14] The synthesis of modified analogs of this molecule is the focus of attention in numerous laboratories.[14]

2. Results and discussion

Galactosyl imidates used for 1,2-*cis* galactosylations suffer from certain drawbacks. For example, 2,3,4,6-tetra-*O*-benzyl-galactosyl donor generates anomeric mixtures which are difficult to purify

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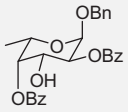
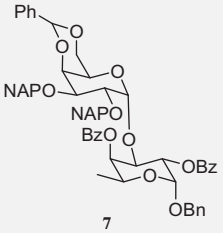
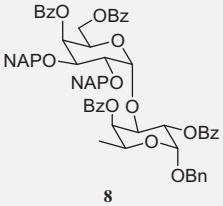
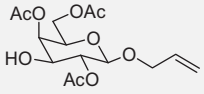
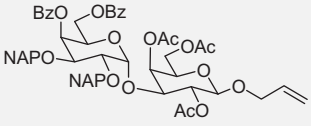
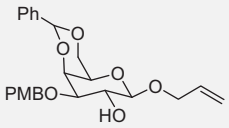
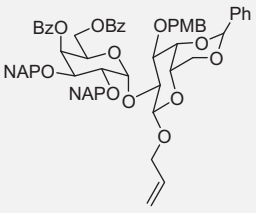
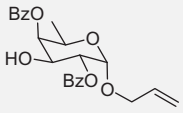
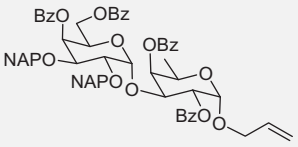
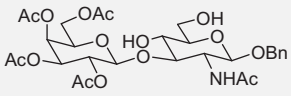
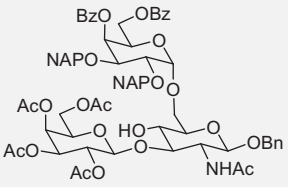
Table 1
Coupling results with different donors and acceptors[a]

Entry	Donor (1.2 equiv)	Acceptor (1 equiv)	Product	Yield (%)	Ratio (α/β)
1	**4**	 **6**	 **7**	68	9:1
2	**5**	**6**	 **8**	88	Only α
3	**5**	 **9**	 **10**	82	Only α
4	**5**	 **11**	 **12**	68	6.2:1
5	**5**	 **13**	 **14**	78	Only α
6	**5**	 **15**	 **16**	74	Only α

[a] All the reactions were conducted using TMSOTf (0.2 equiv) in CH_2Cl_2 and at −15 °C. The reactions were completed within 3–4 h.

after glycosylation.[9c] Furthermore, its 4,6-benzylidene derivative is highly unstable and difficult to isolate and store.[9c] Inspired by the past success of NAP group in glycosylation, we became interested in exploring the applicability of NAP group being utilized as a non-participating group in α-glycosylations.[15]

We designed the synthesis of galactosyl donor **4** starting from D-galactose pentaacetate (**1**). Treatment of **1** with ethanethiol and BF_3–OEt_2 at 0 °C gave β-ethylthio galactoside,[16] which on Zemplén deacetylation[17] provided crystalline β-thioethyl galactoside **2** in 92% yield over two steps. Benzylidene protection of β-galactoside **2** with benzaldehyde dimethylacetal and PTSA followed by naphthylmethylation[13] of 2,3-hydroxyl groups provided compound **3** as a white solid in 78 % yield (for two steps). The removal of anomeric ethylthio group of **3** was accomplished using NBS,[18] followed by activation of the resultant hemiacetal with trichloroacetonitrile in the presence of DBU as a base,[9c] to afford the imidate **4** in 74% yield over two steps (Scheme 1).

We first examined the use of compound **4** as a galactosyl donor using benzyl 2,4-dibenzoyl-α-L-fucoside **6** as an acceptor, the reaction gave a moderate yield of dissacharide **7** with low α-selectivity (Table 1, entry 1). The ^1H NMR spectra of compound **7** showed a doublet at δ 5.63 for anomeric proton with $J_{1,2}$ = 3.7 Hz which confirm the α-stereochemistry in the dissacharide **7**. It was found (also reported for similar imidate in the literature) that the imidate **4** is very unstable and difficult to store.[9c] In order to increase the stability and α-selectivity of the donor **4**, the benzylidene protection was replaced with dibenzoyl ester protection. The dibenzoyl ester protection at C-4 and C-6 makes donor **5** less reactive than donor **4**