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Synthesis of CH_2-Linked α(2,3)Sialylgalactose Analogue: On the Stereoselectivity of the Key Ireland-Claisen Rearrangement

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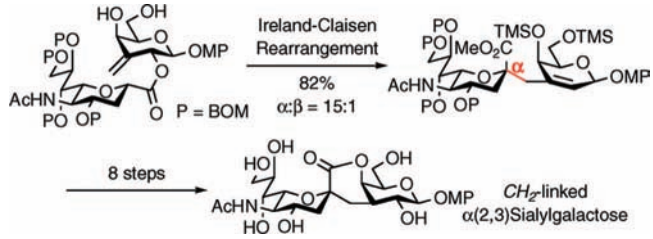
ABSTRACT



A CH_2-linked α(2,3)sialylgalactose analogue was efficiently synthesized using an Ireland-Claisen rearrangement, which was developed recently by our group for constructing a CF_2-sialoside. The reaction conditions of the rearrangement were optimized for α-stereoselective formation of the CH_2-sialoside. On the basis of the observed temperature effects, the origin of the stereoselectivity of the Ireland-Claisen rearrangement is discussed. Moreover, reconstruction of the 2α-hydroxyl group on the galactose unit of the rearrangement product was achieved by means of stereoselective dihydroxylation and deoxygenation.

The α(2,3)sialylgalactose structure (**1**, Figure 1A) is widely found at the nonreducing end of glycoproteins and glycolipids and is recognized as one of the most important units in carbohydrate molecules. For example, sialyl Lewis^x and sialyl Lewis^a, which are ligands of L-, E-, and P-selectin, are composed of **1**.[1] Gangliosides also contain the same structure, and are thought to make important contributions[2] to cell signaling and cell surface interactions. But, the physiological roles of **1** are still not fully clarified. Dynamic metabolism of α-sialosides in living cells, involving hydrolysis of α-sialoside linkages by sialidases and their formation by sialyltransferases, is associated with complex signalling networks. Biologically stable analogues could serve as useful chemical probes for clarifying the biological functions of these molecules.

C-Glycoside analogues of α(2,3)sialylgalactose structure (*C*-sialoside), in which the anomeric oxygen atom of sialic acid is replaced by a carbon atom, are particularly attractive candidate molecules as mimics of native *O*-sialosides. Recently, we reported the synthesis of the CF_2-linked α(2,3)sialylgalactose **2** (Figure 1A), because the difluoromethylene group is expected to be a good bioisostere of the oxygen atom.[3] Indeed, CF_2-linked ganglioside GM4 showed

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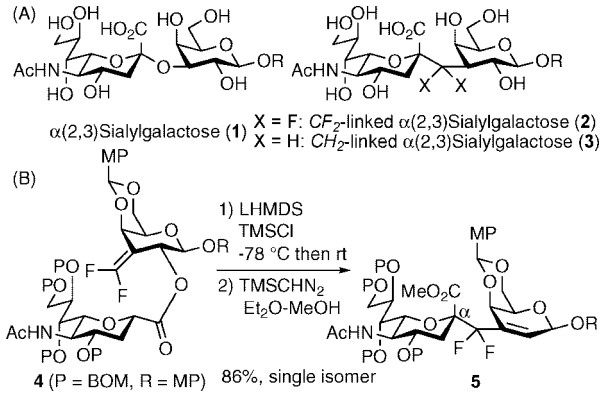
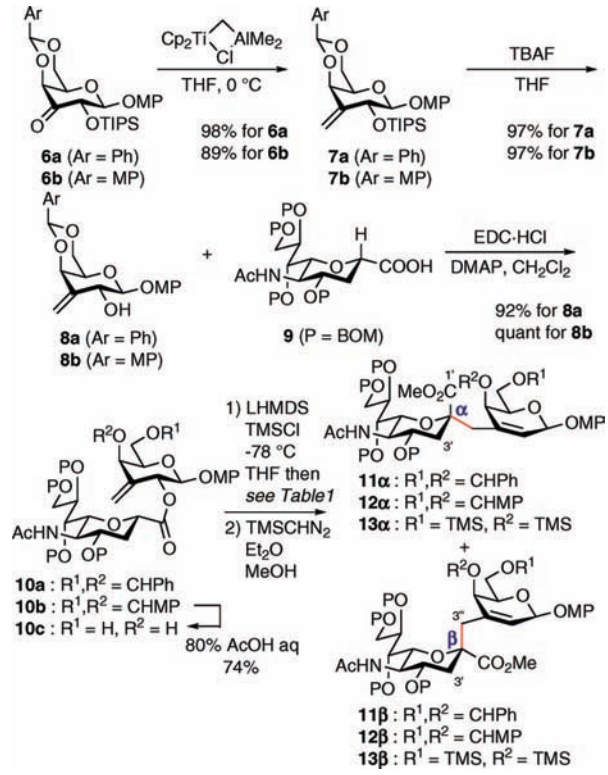


Figure 1. (A) Structure of *O*-, CF_2-, and CH_2-sialoside (**1**−**3**). (B) Ireland-Claisen strategy for the synthesis of CF_2-sialoside.

similar biological profiles to native GM4 and inhibitory activity toward human sialidase NEU2 and NEU4. Recently CF_2-glycosides have attracted attention as nonhydrolyzable glycoside mimics, but systematic studies on the effects of fluorine on the biological activity and conformational properties of the *C*-glycosides are still limited.[4] Thus, we envisioned the synthesis of the simple CH_2-linked α(2,3)sialylgalactose (CH_2-sialoside **3**, Figure 1A) for a comparison of its biological activity and chemical properties with those of the CF_2-sialoside. Stereoselective syntheses of the *C*-linked α(2,3)-sialylgalactose unit have been reported by two groups.[5−7] Linhardt reported a convergent synthesis of *CH(OH)*-linked α(2,3)sialylgalactose via SmI_2-mediated coupling reaction,[5a] but they noted that all attempts to remove the pseudoanomeric hydroxyl group were unsuccessful.[8] Schmidt reported a synthesis of **3** via a long linear sequence.[6] Although various synthetic methods for *C*-glycosides have already been reported,[9] few are applicable to the synthesis of both CH_2- and CF_2-glycoside.[10,11] Among them, our synthesis of CF_2-sialoside based on Ireland-Claisen rearrangement using ester **4** having a one-carbon-elongated galactose unit was convergent, and the key rearrangement proceeded smoothly at room temperature with complete α-stereoselectivity (Figure 1B).[3] Thus, we planned to extend our Ireland-Claisen strategy to the synthesis of the CH_2-linked α(2,3)-sialylgalactose unit. Herein we report an efficient synthesis of the CH_2-linked α(2,3)-sialylgalactose lactone unit **21** using this approach.

Rearrangement precursor **10a** was prepared via a three-step sequence from **6**[3] in good yield, as shown in Scheme 1. Ireland-Claisen rearrangement of **10a** proceeded at ambient temperature on treatment with LHMDS and TMSCl in THF (−78 °C, then rt). The desired product **11α** was obtained as the major product, but a significant amount of the undesired isomer **11*β*** was also formed (**11α**:**11*β*** = 5:1, Table 1, entry 2). Thus, we examined the reaction temperature for rearrangement after formation of the silyl ketene acetal of **10a**, which should be generated by the treatment with LHMDS and TMSCl at −78 °C for 30 min. To increase the selectivity, the reaction temperature was lowered to −20 °C (entry 1). Rearrangement proceeded slowly even at this temperature, but the selectivity was further decreased (1.8:1). Interestingly,

Scheme 1. Synthesis of CH_2-Sialoside



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(7) *CH(OH)*-linked and CH_2-linked Siaα(2,6)-GalNAc derivatives: (a) Kuberan, B.; Sikkander, S. A.; Tomiyama, H.; Linhardt, R. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2073. (b) Abdallah, Z.; Doisneau, G.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5209.

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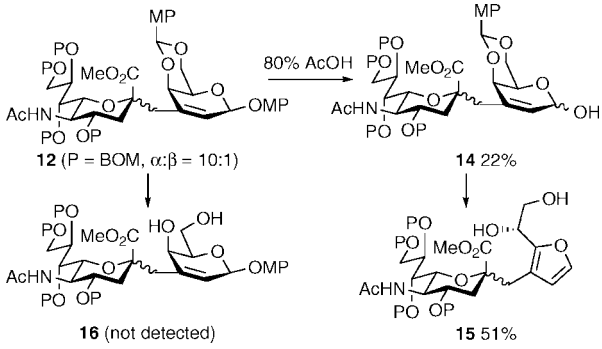
Table 1. Ireland-Claisen Rearrangement of **10**

entry	allylester	product	temp [°C]	t [min]	ratio (α:β)	yield (2 steps)
1	**10a**	**11**	−20	840	1.8:1[a]	25%
2	**10a**	**11**	25	40	5:1[b]	73%
3	**10a**	**11**	reflux	15	10:1[a]	66%
4	**10b**	**12**	reflux	10	10:1[b]	86%
5	**10c**	**13**	reflux	10	15:1[b]	82%

[a] Ratio was determined by HPLC. [b] Ratio was determined by ^{1}H NMR.

when the reaction was conducted at the reflux temperature of THF, we found that the selectivity was greatly improved (10:1, entry 3). Isomers **11α** and **11*β*** were separated by PTLC, and their stereochemistries were confirmed by examination of the HMBC spectra, in which a strong correlation between α-H3′ and C1′ in **11α** or between α-H3′ and C3″ in **11*β*** was observed. Similarly, reaction of **10b** also proceeded to give **12α** and **12*β*** in a ratio of 10:1 (entry 4). Next, we tried to remove the 4-methoxybenzylidene group of **12**, but this was unsuccessful. As shown in Scheme 2,

Scheme 2. Attempts at Deprotection of 4,6-Benzylideneacetal



treatment of **12** with 80% acetic acid gave a mixture of **14** and **15**, and none of the desired product **16** was obtained, indicating that the allylic and anomeric OMP group was hydrolyzed much faster than methoxybenzylidene acetal. Moreover, the furan derivative was easily formed after removal of the 4,6-protecting group from **14**.[12] This was unexpected, because deprotection reaction of the difluoro derivative **5** proceeded without difficulty under the same conditions.[3] This fact indicated that the strongly electron-withdrawing fluorine atoms stabilize the anomeric OMP group. To solve this problem, we decided to remove the 4,6-benzylidene moiety before the Ireland-Claisen rearrangement. The desired diol **10c** was obtained without difficulty by acid hydrolysis of **10b**. To our delight, reaction of **10c** at the reflux temperature in THF proceeded smoothly to give the desired product **13α** with much better selectivity and chemical yield (**13α**:**13*β*** = 15:1, Table 1, entry 5).

To understand the interesting stereoselectivity of the Ireland-Claisen rearrangement, we considered the transition state (TS) models shown in Figure 2. Ireland-Claisen

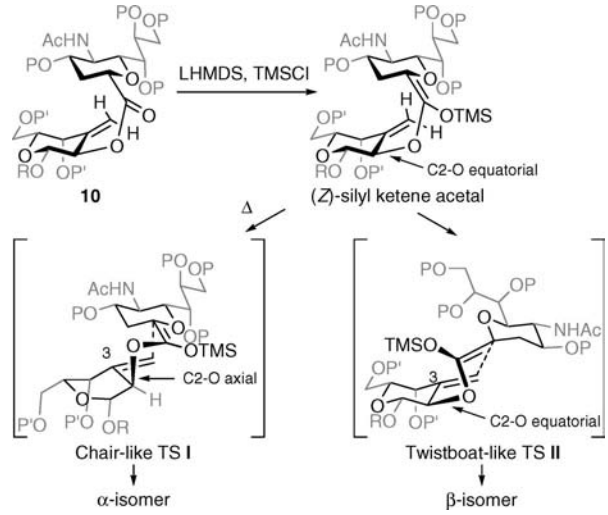


Figure 2. Plausible TS for constructing *CH*$_2$-sialoside.

rearrangement is known to prefer a chairlike transition state. Therefore, it is reasonable that this rearrangement proceeds via chairlike TS **I** to give the major isomer **11α**−**13α** after formation of the expected (*Z*)-silyl ketene acetal from **10a**−**10c**.[13] But, to form this favorable chairlike TS **I** giving the desired α-isomer, in which the C2−O bond has peudo-axial configuration, the conformation of the galactose unit must be changed from chair to boat. The undesired *β*-isomer would be formed via the boat-like TS **II**, in which the conformational change of the galactose unit is not required. It is likely that **10a** and **10b**, having the rigid 4,6-acetal group, strongly favor the chair conformation of the galactose unit, whereas the 4,6-non- protected **10c** would be more flexible. As a result, conformational change of the galactose unit of **10c** is expected to be easier than in the cases of **10a**/**10b**, and this may be the reason why higher α-selectivity was achieved with **10c**. In the case of the previously reported difluoro-olefin **4**, the chair conformation of the galactose unit seems to be destabilized due to the allylic strain between the fluorine atom and the C2-oxygen atom, even though **4** has a 4,6-acetal group. As a result, the α-isomer was obtained exclusively from **4**. The observed unique temperature dependency would also be explained by the conformational change of the galactose unit. As higher temperature favors this conformational change of the galactose unit of **10a**, even

(12) A similar transformation was reported in the case of glycal derivatives: (a) Gonzalez, F.; Lesage, S.; Perlin, A. S. *Carbohydr. Res.* **1975**, *42*, 267. (b) Agarwal, A.; Rani, S.; Vankar, Y. D *J. Org. Chem.* **2004**, *69*, 6137, and references therein.

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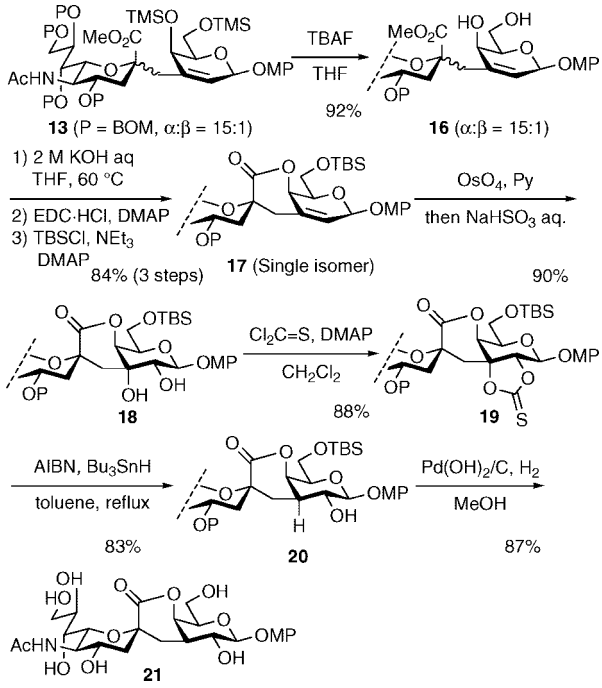
when a rigid 4,6-acetal group is present, the α-selectivity would increase temperature-dependently.[14]

Finally, the rearrangement product **13** was converted to the key CH_2-linked α(2,3)sialyl-galactose lactone unit **21** as shown in Scheme 3. First, the stereoisomeric mixture **13α,*β*** was converted to the conformationally fixed lactone **17** by removal of the TMS group, saponification of the methyl ester, selective *δ*-lactone formation, and protection of the primary alcohol with a TBS group. Since only the desired α-isomer provided a *δ*-lactone derivative, the undesired *β*-isomer was easily separated at this stage. Upon treatment of the lactone **17** with a stoichiometric amount of OsO_4, dihydroxylation proceeded in a completely stereoselective manner to afford the diol **18**.[15] Next, to remove the C3-hydroxyl group, diol **18** was converted into cyclic thiocarbonate **19**. Radical reduction proceeded in a regio- and stereoselective manner with freshly opened Bu_3SnH to give **20** in 83% yield. Finally, hydrogenolysis of four BOM groups, together with removal of the TBS group, gave the CH_2-linked α(2,3)sialylgalactose lactone unit **21**. The stereochemical assignment of newly formed chiral carbon centers (C2′, C2, C3) was confirmed by X-ray crystallographic analysis of **21** (Figure 3). The overall yield of this CH_2-linked sialoside unit **21** from **6b** was 23% (14 steps).

Scheme 3. Synthesis of CH_2-Linked α(2,3)Sialylgalactose



(14) For further discussion on the stereoselectivity, see Supporting Information.

(15) Transformation of 2,3-olefin in galactose by hydroboration or epoxidation failed due to the low reactivity of 2,3-olefin.

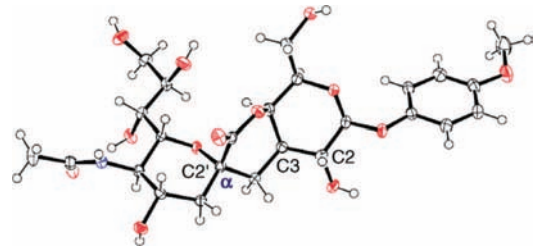


Figure 3. X-ray structure of **21**.

In conclusion, the CH_2-linked α(2,3)sialylgalactose unit was synthesized in a highly stereoselective manner. This synthesis is more efficient in terms of short and convergent reaction sequences and high overall yield compared to the reported synthesis of CH_2-linked α(2,3)sialylgalactose.[6] Moreover, we succeeded in synthesizing two electronically different types of *C*-linked α(2,3)sialylgalactose unit, CF_2- and CH_2-linked derivatives, by using the same strategy and the same starting materials, **6** and **9**.[3] This indicates that our Ireland-Claisen strategy would also be applicable to the synthesis of various other types of *C*-sialosides such as *CHF*-linked sialoside, which would be useful for further detailed study of the effect of the fluorine atom. Synthesis of oligosaccharide or glycoconjugate analogues such as GM3 and Sialyl-Lewis^x from **21**, and biological experiments using CH_2-linked ganglioside analogs are currently under way.

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Supporting Information Available: Experimental procedure, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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