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Graphical Abstract

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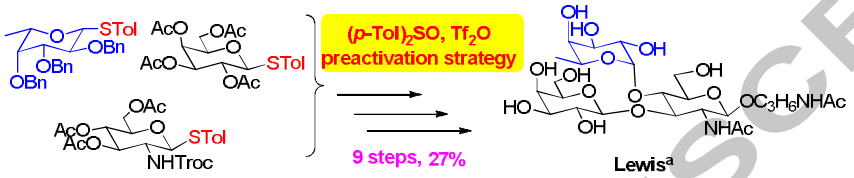

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A novel *O*-fucosylation strategy preactivated by $(p\text{-Tol})_2SO/Tf_2O$ and its application for the synthesis of Lewis blood group antigen Lewis[a]

Cui-yun Li[a] , Guang-jian Liu[a], Wei Du[a], Yuan Zhang[a,b] and Guo-wen Xing[a]*

[a] *College of Chemistry, Beijing Normal University, Beijing 100875, China*
[b] *Key Laboratory of Theoretical and Computational Photochemistry, Ministry of Education, College of Chemistry, Beijing Normal University, Beijing 100875, China*

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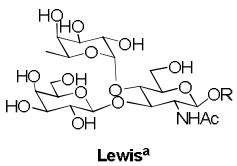
ABSTRACT

Based on a preactivation strategy using $(p\text{-Tol})_2SO/Tf_2O$, a new *O*-fucosylation method with thioglycoside as donor under mild conditions was reported. High yields and excellent α-stereoselectivities of the fucosylation were obtained with secondary sugar alcohol as acceptors. Moreover, the novel fucosylation strategy was successfully applied to the synthesis of an important Lewis blood group antigen Lewis[a], which was obtained in nine linear steps with 27% overall yield.

Blood group determinants are a class of cell surface glycoconjugates involving in a variety of biological events such as cell-cell adhesion, control of cell growth and differentiation, and immune response *etc.*[1] Besides the most familiar ABH(O) blood group system, Lewis system was also one of the important blood group antigen systems. Lewis antigens exist not only in the membrane of red blood cell, but also in epithelial tissue and its secretions, which was known as histo-blood group antigen.[2] Lewis histo-blood group determinants can be categorized into four types by their fucosylation states and the arrangement of the core glycosidic linkages, including Lewis[a] (Le^a), Le^x (mono-fucosylated), and Le^b, Le^y (di-fucosylated). Notably, L-fucose residue can be found in all of these Lewis antigens. In recent years, great attention has been paid to the findings that the abnormal expression of Lewis antigens was closely related to the occurrence and development of many cancers.[3] Determining the content and distribution of different Lewis antigens in tumor cells was critical in prevention, diagnosis and treatment of cancers, and helpful to explore the molecular mechanism of cancer inductions.



Lewis[a]

Figure 1. Chemical structure of Lewis[a] trisaccharide.

Up to date, a lot of carbohydrate antigens of the Lewis families have been synthesized, however the synthetic routes have often been laborious and time-consuming.[4-8] Based on our previous studies on high efficient glycosylations,[9-10] herein, we reported a novel fucosylation strategy preactivated by $(p\text{-Tol})_2SO/Tf_2O$, and its application for the synthesis of Lewis[a] (Fig. 1), one of the important Lewis blood group antigens.

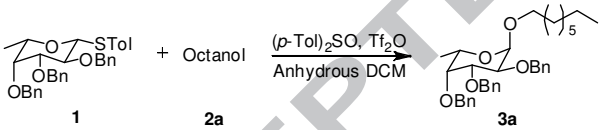
O-Fucosylation is the key reaction in the synthesis of various Lewis antigens. Up to now, several synthetic strategies have been developed to obtain fucosides. These methods employed different glycosyl donors, such as halide,[4,11] trichloroacetimidate,[5,12] acetate,[13] sulfoxide,[6] phosphate,[7,14] and thioglycoside.[8,15] However, it is still challenging to achieve the fucosylation with high yields and excellent α-stereoselectivities. Among these donors, thioglycoside was the most frequently used one, since thioglycoside was convenient to prepare and stable under many reaction conditions.[16] Preactivation is an important strategy for glycosylation, and many complex oligosaccharides were successfully synthesized.[17] In recent years, the $(p\text{-Tol})_2SO/Tf_2O$ preactivation system, which was derived from the traditional Ph_2SO/Tf_2O pair,[17d] has been confirmed to be a practical, straightforward, and high stereoselectivity protocol for *O*- and *C*-glycosylations when employing *N*-acetyl-5-*N*,4-*O*-oxazolidione protected thiosialoside as donor.[9] Meanwhile, above-mentioned protocol can also be used to prepare a series of nucleosides efficiently by coupling available thioglycosides with pyrimidine and purine nucleobases under mild conditions.[10] In continuation of our studies on the glycosylation strategy with $(p\text{-Tol})_2SO/Tf_2O$

* Corresponding author. e-mail: gwxing@bnu.edu.cn (G.W. Xing)

as preactivation reagent, we have investigated whether this method was suitable for *O*-fucosylation, and further synthesized the important fucosyl glycoconjugates.

Previous literatures have reported some methods about the *O*-fucosylations between L-fucosyl donors and primary alcohol acceptors, while most of them had low α-selectivities.[18-19] We initially chose a perbenzylated fucosyl thioglycoside **1**[20] as donor and octanol (**2a**) as acceptor for the model fucosylation reaction using $(p\text{-Tol})_2SO/Tf_2O$ as promoter. Detailedly, a solution of **1** and $(p\text{-Tol})_2SO$ (1.2 eq.) was preactivated by Tf_2O (1.2 eq.) in dichloromethane at -70°C for 0.5 h, followed by the addition of **2a** (1.2 eq.). The resulting mixture was stirred for 2 h, and then warmed up to -50°C for another 2 h. The coupling product **3a** (Table 1, entry 1) was obtained in 75% yield with inferior α-stereoselectivity. The structure of **3a** was confirmed by ^{1}H NMR spectrum determination, which was consistent with the reported data.[19] According to our previous findings,[9-10] an excessive amount of $(p\text{-Tol})_2SO$ could raise the glycosylation yields by stabilizing the active intermediates derived from donors. Then, we increased the amount of $(p\text{-Tol})_2SO$ from 1.2 eq. to 6.0 eq., and it was found that the corresponding proportion of α-configuration products was increased visibly from 0.3:1 to 1.1:1 (Table 1, entries 2-4). However, the reactions yields hardly showed big changes. These unsatisfactory results prompted us to further optimize the reaction conditions by modulating both the temperature of preactivation and the amount of $(p\text{-Tol})_2SO$ at the same time. To our delight, when the preactivation temperature was increased to -60°C, the isolated product yield jumped significantly from 65% to 99%. At the same time, the α-selectivity of the glycosylation was maintained, which produced a 1.1:1 α/β-anomeric ratio (Table 1, entries 4, 5). In addition, a contrasting experiment was performed using ether instead of dichloromethane as solvent. The proportion of α isomer product decreased dramatically in the ether media (Table 1, entry 6).

Table 1. Effect of the $(p\text{-Tol})_2SO$ amount, preactivation temperature and solvent on fucosylation with **1** as the donor.



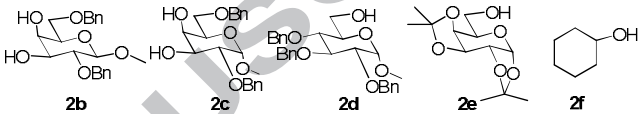
1 **2a** **3a**

Entry	Solvent	$(p\text{-Tol})_2SO$	T(°C)	Yield (%)[a]	α:β[b]
1	DCM	1.2 eq.	-70	75	0.4:1
2	DCM	2.0 eq.	-70	70	0.3:1
3	DCM	4.0 eq.	-70	70	1.1:1
4	DCM	6.0 eq.	-70	65	1.1:1
5	DCM	6.0 eq.	-60	99	1.1:1
6	Et_2O	6.0 eq.	-60	98	0.4:1

[a]Isolated yields.
[b]Determined by ^{1}H NMR analysis.

The above optimization showed that the decisive factors of fucosylation were the preactivation temperature and the $(p\text{-Tol})_2SO$ amount, which was similar to the observations in our previous studies.[9-10] We speculated that unreactive donors could need higher preactivation temperature, and unstable glycosylation intermediates should need larger $(p\text{-Tol})_2SO$ amount to be trapped and stabilized in the reaction. Based on these results, several other glycosyl acceptors including primary alcohols and secondary alcohols **2b–f**[21-22] (Fig. 2) were used to explore the substrate scope of the fucosylation promoted by $(p\text{-Tol})_2SO/Tf_2O$, still with thioglycoside **1** as donor.

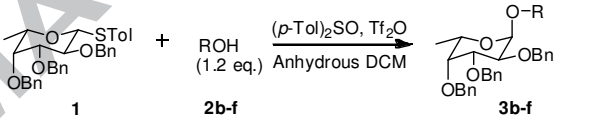
Under the optimized reaction conditions (-60 °C → -40 °C, $(p\text{-Tol})_2SO$ (6.0 eq.)), the coupling reactions of **1** with secondary sugar alcohols **2b/2c** provided 3-*O*-fucosyl galacopyranoside **3b/3c**[23] in high yields and excellent α-stereoselectivities (Table 2, entries 1 and 2). With primary glucosyl-sugar alcohol **2d** as acceptor, the reaction yield and α-stereoselectivity were still satisfactory (Table 2, entry 3). As a comparison, the primary galacosyl-sugar alcohol **2e** gave a poor α-selectivity (α:β = 0.4:1, Table 2, entry 4). In the case of cyclohexanol (**2f**), low α-selectivity (α:β = 1.3:1, Table 2, entry 5) was obtained. The structural assignment of **3b-f** and the α/β ratio of products were determined unambiguously by ^{1}H NMR.[23-26] The results indicated that the α-selectivity of the fucosylation was highly dependent on the acceptor structures. High α-selectivity could be obtained with secondary sugar alcohol as acceptor, and low α-selectivity was observed with simple non-sugar alcohol as acceptors. Therefore, the current protocol we proposed for the fucosylation should be feasible for the synthesis of Le[a] oligosaccharide, which contains secondary sugar alcohol unit as acceptor during the fucosylation reactions.



2b **2c** **2d** **2e** **2f**

Figure 2. Structures of glycosyl acceptors for fucosylations.

Table 2. Fucosylation of **2b–f** with **1** as glycosyl donor (the optimized reaction conditions: 6.0 eq. $(p\text{-Tol})_2SO$, -60°C → -40°C).



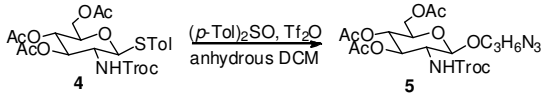
1 **2b-f** **3b-f**

Entry	Acceptor	Product	Yield (%)[a]	α:β[b]
1	**2b**	**3b**	86	α only
2	**2c**	**3c**	84	7.0:1
3	**2d**	**3d**	93	3.1:1
4	**2e**	**3e**	88	0.4:1
5	**2f**	**3f**	93	1.3:1

[a]Isolated yields.
[b]Determined by ^{1}H NMR analysis.

Then, we focused our attention on the synthesis of the complex Le[a] trisaccharide. Scheme 1 shows the synthetic route for Le[a], all the glycosylations employed $(p\text{-Tol})_2SO/Tf_2O$ preactivation strategy. The starting building block **4** was prepared according to the previous literature.[27] Firstly, **4** was converted to its β-glycoside **5** in 91% yield. The optimum reaction conditions (Table 3) for this reaction was obtained through changing the equivalent amounts of $(p\text{-Tol})_2SO$ and acceptor (3-azido-1-propanol). The chemical structures of **5** has been determined by

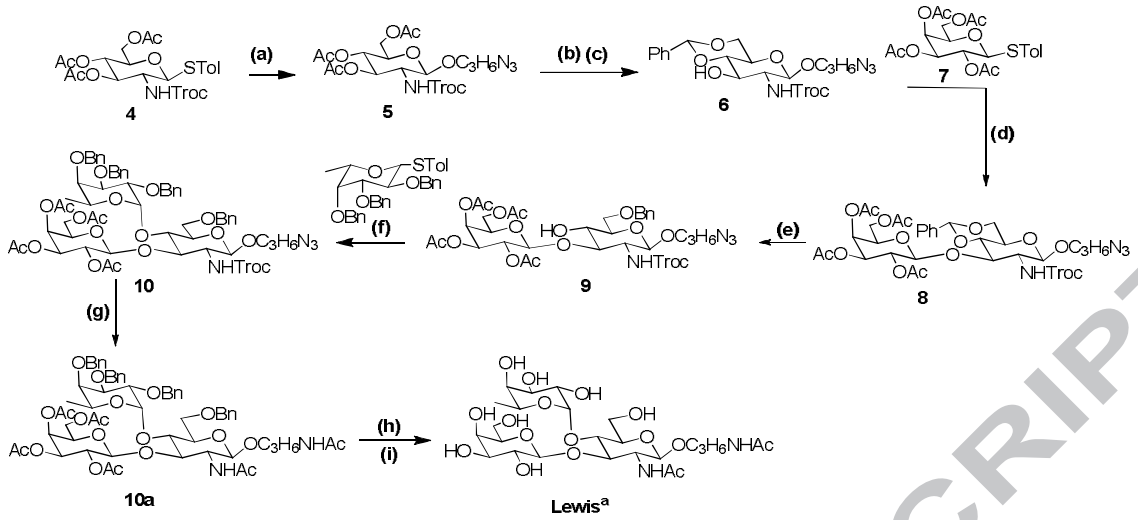
Table 3. Effect of the $(p\text{-Tol})_2SO$ amount and acceptor amount on glycosylation with **4** as the donor.



4 **5**

Entry	Acceptor	$(p\text{-Tol})_2SO$	T(°C)	Yield (%)[a]
1	1.2 eq.	4.0 eq.	-60	68
2	1.2 eq.	6.0 eq.		47
3	2.4 eq.	4.0 eq.		88
4	2.4 eq.	3.0 eq.		91

[a]Isolated yields.



Scheme 1. Synthetic route of Lewis[a]. (a) 3eq. $(p\text{-Tol})_2SO$, Tf_2O, 3-azido-1-propanol, anhydrous CH_2Cl_2, -60°C → 40°C, 91%. (b) MeONa/MeOH, r.t.. (c) benzaldehyde dimethyl acetal, CSA, CH_3CN, r.t., 81% (two steps). (d) 3eq. $(p\text{-Tol})_2SO$, Tf_2O, anhydrous CH_2Cl_2, -60°C → -40°C, 70%. (e) $NaCNBH_3$, THF, $HCl{\cdot}Et_2O$, quant. (f) 6eq. $(p\text{-Tol})_2SO$, Tf_2O, anhydrous CH_2Cl_2, -60°C → -40°C → r.t., 81%. (g) Ac_2O/HOAc/THF (2:1:3, v:v:v), Zn, r.t.. (h) NaOMe/ MeOH, r.t.. (i) 20% $Pd(OH)_2$, MeOH, H_2 , r.t..65% (three steps).

the analyses of 1D and 2D NMR (^1H, ^{13}C, H-H COSY) as well as HRMS experiments, in which the anomeric proton resonated as a doublet at 4.62 ppm with a coupling constant of 8.3 Hz and MS peak at *m/z* 585.0526 (calc. *m/z* 585.0528, $[M+H]^+$) (*see* ESI). After two steps of protective group manipulations, the free 3-OH secondary sugar alcohol **6** was obtained in 81% yield. [28]

Then, a solution of **7** and $(p\text{-Tol})_2SO$ (1.2 eq.) was preactivated by Tf_2O (1.2 eq.) in dichloromethane at -60°C for 0.5 h, followed by the addition of **6** (1.2 eq.).[10,29] The resulting mixture was stirred for 2 h, and warmed up to -40°C for another 2 h. The disaccharide **8** was given in 70% yield, in which all hydroxyls were fully protected. During the selective deprotection process, phenylmethylene group of **8** was reduced to give the free 4-OH secondary sugar alcohol **9** quantitively. Since alcohol **9** had low reaction activity, the fucosylation reaction time was prolonged to overnight and the reaction temperature was slowly returned to room temperature. Coupling of fucosyl donor **1** with acceptor **9** in the presence of $(p\text{-Tol})_2SO/Tf_2O$ as promoter afforded the desired trisaccharide **10** in 81% yield. The configuration of the newly formed fucosidic linkage was determined to be exclusively α, since the anomeric proton of the fucose moiety in **10** appeared as doublets at 5.09 ppm (^3J = 3.1 Hz). The HRMS spectrum showed peak at *m/z* 1295.3607 (calc. *m/z* 1295.3619, $[M+H]^+$), indicating that the desired trisaccharide derivative **10** was produced. In addition, the ^1H NMR spectrum of **10** indicated the anomeric protons of the galactose and glucosamine units as a doublet at 4.86 ppm (^3J = 11.5 Hz) and doublet at 4.49 ppm (^3J = 10.4 Hz), respectively, suggesting the β glycosidic linkages existed in the trisaccharide **10** (*see* ESI).

Global deprotection of compound **10** was performed in three steps. Zinc dust in acetic anhydride removed the trichloroethyl carbamate protecting group (Troc) in **10** and re-acetylated the free amino group simultaneously. At the same time, the azido group of **10** was reduced by Zn/AcOH/Ac_2O to provide free amine which was directly transformed into acetamido group.[30] We successfully isolated compound **10a** during this process, which was confirmed by ^1H NMR and HRMS spectra. The remaining acetyl protecting groups of **10a** were further cleaved by deacylation with NaOMe in MeOH solution, and the final debenzylation was accomplished by hydrogenation in the presence of $Pd(OH)_2$ on activated carbon.[31] The expected **Le[a]** was obtained in 65% yield from **10** through three steps. The characterization of **Le[a]** was confirmed by HRMS and NMR analysis. The ^1H NMR spectra of Lewis[a] was shown in Fig. 3.

In summary, we reported a new strategy for fucosylation promoted by $(p\text{-Tol})_2SO/Tf_2O$ under mild conditons with high yields and stereoselectivities. The optimal reaction conditions were obtained *via* investigating the influence of crucial reaction factors such as preactivation temperature and the added amount of $(p\text{-Tol})_2SO$ in the reaction. Excellent α-stereoselectivities were obtained with secondary sugar alcohol as acceptors. Combined with our previous work,[9-10] the $(p\text{-Tol})_2SO/Tf_2O$ preactivation protocol discussed in this study has further exhibited its usefulness and generality for various efficient glycosylations, and the scope of its applicability was expanded to *O*-fucosylations. In addition, Le[a] containing L-fucose residue has been successfully synthesized with a total 27% yield via 9 linear steps. Current study provided a meaningful and powerful tool to facilely prepare other Lewis antigens, which could be further utilized for the cancer-related studies.

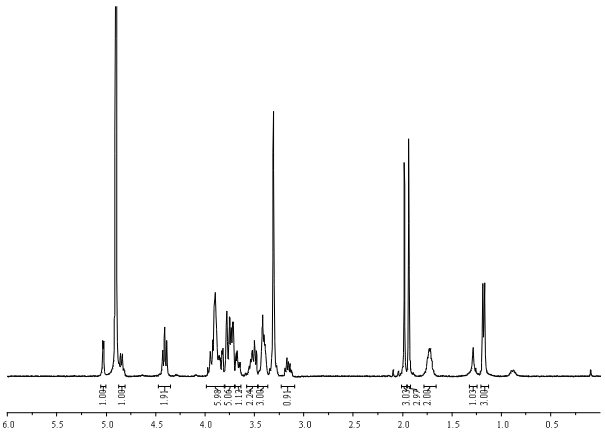


Figure 3. The ^1H NMR spectra of Lewis[a] in methanol-d_4.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.xxxx

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Graphical Abstract

A *O*-fucosylation strategy preactivated by $(p\text{-Tol})_2SO/Tf_2O$ was successfully applied to the synthesis of Lewis[a], which was obtained in nine linear steps with 27% overall yield.

A novel *O*-fucosylation strategy preactivated by $(p\text{-Tol})_2SO/Tf_2O$ and its application for the synthesis of Lewis blood group antigen Lewis[a]

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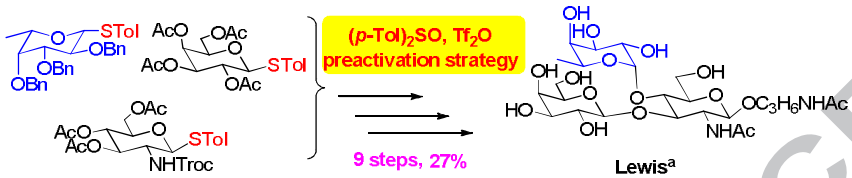
Cui-yun Li, Guang-jian Liu, Wei Du, Yuan Zhang and Guo-wen Xing*



- A new *O*-fucosylation method promoted by $(p\text{-Tol})_2SO/Tf_2O$ was reported.
- Secondary sugar alcohol acceptors gave high yields and α-stereoselectivities in the fucosylation.
- Lewis[a] was facilely synthesized in nine linear steps with 27% overall yield.