# Stereoinversion of Stereocongested Carbocyclic Alcohols via Triflylation and Subsequent Treatment with Aqueous N,N-Dimethylformamide

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S Supporting Information

ABSTRACT: A convenient method for the stereoinversion of secondary alcohols, applicable to stereocongested carbocyclic substrates, is reported. A simple three-step procedure, including triflylation of the hydroxy group, nucleophilic oxygenative displacement by the treatment with aqueous N,N-dimethylformamide (DMF), and methanolysis, allowed for efficient stereoinversion of various substrates, including sugar derivatives, in one pot.
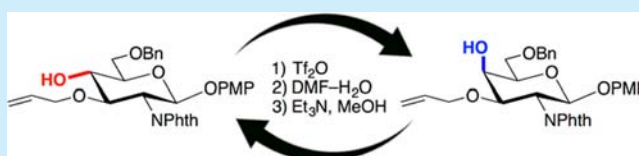
Stereoinversion of secondary alcohols is a fundamental and important transformation in organic synthesis. The Mitsunobu reaction is the most widely used method for this purpose.[1] This method has been successfully applied for the stereoinversion of alcohols bearing a broad range of functional groups, including intermediates for the synthesis of complex molecules. Another occasionally used approach is the S_N2 displacement by oxygen nucleophiles, performed after converting the hydroxy group to a good leaving group such as a sulfonyloxy group.[2–4] For some substrates, stereoinversion of alcohols has been achieved through a sequence of reactions comprising oxidation of the starting alcohols to ketones followed by their stereoselective reduction.[5]

These conventional methods, however, have substrate limitations; in particular, they are often inapplicable to stereocongested carbocyclic alcohols.[2d,f,5i,6] Indeed, some of our trials to invert the stereochemistry of the hydroxy group in ribose derivative **1a** with two neighboring *cis*-benzoyloxy groups were unsuccessful (Scheme 1). For example, under typical Mitsunobu conditions,[7] a stereoretained *O*-acylated product **3** was obtained in low yield instead of the desired stereoinverted arabinose derivative **2** (Scheme 1A). Furthermore, tosylation of the hydroxy

group in **1a** did not proceed even under reflux conditions in 1,2-dichloroethane, indicating severe steric congestion around the hydroxy group (Scheme 1B). These results demonstrated the difficulty of achieving stereoinversion of sterically congested alcohols. Herein, we report a convenient method that increases options for stereoinversion of stereocongested secondary alcohols.

To achieve stereoinversion of stereocongested alcohols, we revisited the S_N2 displacement approach. We assumed that using small-sized reagents for both hydroxy group activation and nucleophilic displacement would be advantageous to achieve the desired transformation. More specifically, we considered that triflylation of the hydroxy group followed by stereoinvertive formyloxylation of the resulting triflate **6** with DMF via iminium salt **7**[8] would be a promising approach (Scheme 2). We expected that the undesired β-elimination
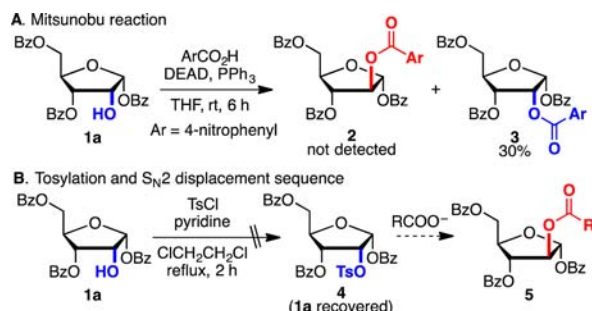
Scheme 1. Initial Attempts

Scheme 2. Working Hypothesis

reaction in **6** to form the corresponding alkene,[9] which often competes with the intended nucleophilic displacement, would be avoidable because of the superior leaving group ability of the triflyloxy group and low Brønsted basicity of DMF. If the S_N2 displacement with DMF can be conducted in an acidic aqueous solution, the iminium intermediate **7** can be hydrolyzed in situ to furnish the desired stereoinverted formate **8**.

Based on these considerations, we examined the reaction conditions for stereoinversion of alcohol **1a** (Table 1). Triflylation of **1a** with triflic anhydride (Tf_2O) proceeded smoothly at a low

Table 1. Screening of Reaction Conditions

entry	aq acid or water	temp (°C)	time (h)	yield (%)[a]		
				8a	9a	total[b]
1	10 wt % aq HBr	100	5	nd	nd	—
2	10 wt % aq HCl	100	5	nd	nd	—
3	10 wt % aq HF	100	5	45	44	89
4	10 wt % aq HOTf	100	5	51	39	90
5	water	100	5	50	41	91
6	water	100	24	nd	85	85
7	water	60	120	47	52	99

[a]Isolated yields are shown. nd = not detected. [b]Total yields of stereoinverted products (8a + 9a).

temperature to afford triflate 6a almost quantitatively. Triflate 6a was sufficiently stable to be purified using silica-gel column chromatography and could be stored at room temperature under open-air conditions for more than a month without any decomposition. We then aimed for the realization of stereo-invertive formyloxylation of the triflyloxy group in 6a by performing the reaction in a 10:1 (v/v) mixture of DMF and an acidic aqueous solution with heating at 100 °C (Table 1). Neither the desired stereoinverted formate 8a nor alcohol 9a was obtained on using aqueous hydrobromic acid or hydro-chloric acid; however, 6a was consumed completely and a mixture of unidentified compounds was obtained (entries 1 and 2). Efficient results were obtained on using aqueous hydro-fluoric acid or trifluoromethanesulfonic acid (HOTf), both of which afforded oxygenated products 8a and 9a in high com-bined yields (entries 3 and 4).[10] Treatment of formate 8a with triethylamine in methanol at room temperature afforded the corresponding alcohol 9a in high yield, leaving the benzoyl groups intact. Further examination revealed that the reaction proceeded efficiently even without adding an acid (entries 5 and 6) and may have been promoted by triflic acid, which generated gradually in situ as the S$_N$2 displacement progressed. The reaction also proceeded efficiently at a lower temperature of 60 °C; however, a significant prolongation of the reaction time was required to obtain the desired oxygenated products with high yield (entry 7).[11]

Supportive experiments suggested that alcohol 9a was generated mainly through deformylation of 8a.[12] For example, heating 8a at 100 °C for 9 h in a mixture of DMF and aqueous HOTf or water afforded 9a (Scheme S3).

From the mechanistic viewpoint, there was a possibility that dimethylammonium formate, which could be generated in situ via the decomposition of DMF, served as an oxygen nucleo-phile in this transformation. Thus, to trace the origin of oxygen incorporated in the oxygenated products, we conducted the inversion reaction using [^{18}O]H$_2$O (≥98 atom%^{18}O) as the water source (Schemes 3 and S4).[13] Theoretically, if the in situ generated formate serves as an oxygen nucleophile, the ^{18}O atom in 8a is introduced randomly in the formyloxy group and

Scheme 3. Stereoinvertive Oxygenation Using [^{18}O]H$_2$O
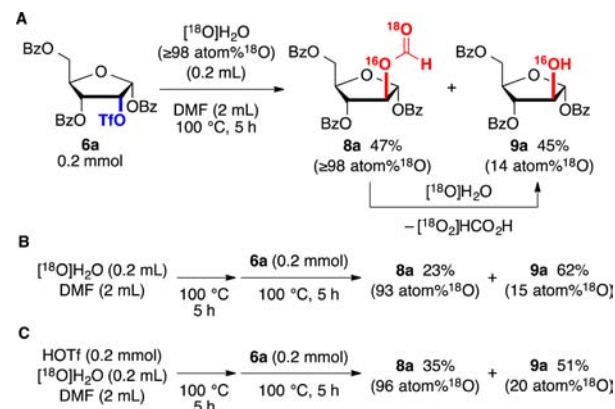
subsequent hydrolysis provides 9a with 50 atom%^{18}O incor-poration (Scheme S5A). However, ESI-MS analyses of the oxygenated products showed that the content ratios of ^{18}O in 8a and 9a were ≥98% and 14%, respectively (Scheme 3A). Considering that nucleophilic substitution with DMF provides 9a without incorporation of the ^{18}O atom (Scheme S5B), this result indicated that the reaction proceeded mainly based on our scenario (Scheme 2).[14] Furthermore, performing the reaction using a preheated mixture of DMF and [^{18}O]H$_2$O (10/1, v/v) without or with HOTf (1 equiv) at 100 °C for 5 h also afforded 9a that contained a small amount of ^{18}O (Scheme 3B and 3C), suggesting that involvement of formate as a nucleophile is a minor pathway in this reaction.

Using the additive-free conditions (Table 1, entry 5), the stereochemistry of a hydroxy group in various sugar derivatives was invertible via the corresponding triflates 6 (Table 2).[15] A commercial tetraacetyl mannose triflate 6b, which has been utilized as a radiolabeling precursor of ^{18}F-fluorodeoxyglucose ([^{18}F]FDG),[16] was successfully converted to glucose formate 8b. In this case, selective methanolysis of the formate moiety proceeded in the absence of triethylamine to afford 9b. In addition to benzoyl and acetyl protecting groups, a wide variety of functional groups such as an imide and ethers bearing benzyl, methyl, 4-methoxyphenyl, and allyl moieties tolerated this trans-formation, considerably expanding the scope of this method. Not only 2,3,6-tri-O-benzoyl-D-galactoside triflate 6c but also 2,3,6-tri-O-benzyl-D-galactoside triflate 6d was converted efficiently to its corresponding glucosides 9c and 9d, respectively.[17] Protected glucosamine triflate 6e was also efficiently transformed to a galactosamine derivative 9e.[17] Notably, the interconversion between the glucosamine derivative and the galactosamine deriv-ative was successfully conducted by using this method; 1f (= 9g) was converted into 9f (= 1g) and vice versa with high yields. The method was also applied to a disaccharide; cellobiose deriv-ative 9h was obtained in high yield from a protected lactose triflate 6h. Through these stereoinversion sequences, neither epimerized nor hydrolyzed products with the functional groups at the anomeric position were detected, despite the likely gen-eration of triflic acid.[18]

A sequence of reactions for the stereoinversion could be simply performed in a one-pot procedure, as demonstrated by an efficient gram-scale transformation of 1a to 9a (Scheme 4), demonstrating the practicality of the method.[13]

The one-pot procedure was particularly effective for the stereoinversion of sterically less-hindered alcohols for which the corresponding triflates were too labile to be isolated.

Table 2. Substrate Scope[a]

entry	1 (R = H)	t[1] (h)	6 (R = Tf)	t[2] (h)	8 (R' = CHO)	9 (R' = H)	t[3] (h)	yield (%) of 9 from 8
1	–		6b[b]	4	8b 65	nd	2	47[c]
2	1c	12	6c 83	3	8c 71	nd	1	90[d]
3	1d	24	6d 97	1.5 (120)[e]	8d 51 (62)[e]	9d 24 (25)[e]	3	98[d]
4	1e	4.5	6e 66	1.5	8e 88	9e 11	13	95
5	1f (= 9g)	9	6f 87	1.5	8f 56	9f 21	1	92
6	1g (= 9f)	5	6g 85	3	8g 65	9g 11	3	90
7[f]	1h	4	6h 51[g]	2	8h 39	9h 33	7	77

[a]Isolated yields are shown. See Supporting Information for details of reaction conditions. [b]Commercial. [c]Methanolysis was performed under reflux conditions without using triethylamine. [d]The reaction was performed using MeOH−CH$_2$Cl$_2$ as a solvent. [e]Reaction time or yields when the reaction was performed at 60 °C are shown in the parentheses. [f]PMP = p-methoxyphenyl. [g]46% of 1h was recovered.

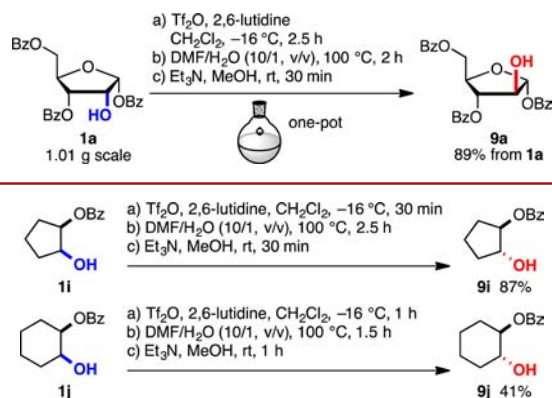## Scheme 4. One-Pot Procedure in Gram Scale

Figure 1. Stereoinversion of alcohols via labile triflates using a one-pot procedure.

For example, by using this method, monobenzoyl-protected 5- and 6-membered cycloalkane cis-1,2-diols **1i** and **1j** were successfully converted to trans-1,2-diols **9i** and **9j**, respectively (Figure 1).[13,19,20]

In summary, we have developed a simple method for the stereoinversion of carbocyclic alcohols applicable to stereocongested substrates. This method is unique in that the oxygenative displacement proceeds under acidic conditions, providing a new option for the stereoinversion of alcohols.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02675.

Experimental procedures, characterization for new compounds including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(9) For examples that afforded *β*-eliminated products under the conventional stereoinversion conditions, see refs 2d, 2f, 4c, 5i, and 6a.

(10) Stereoinversion of 6a with other nucleophiles such as carboxylates and nitrite also proceeded to afford the stereoinverted compounds (Schemes S1 and S2).

(11) In these experiments, even in the case when none of desired product was provided, we have not observed the formation of alcohol 1a, which might be generated via hydrolysis of triflate 6a.

(12) Formate 8a was gradually hydrolyzed to 9a under these reaction conditions (Table S1 and Scheme S3).

(13) See the Supporting Information for details.

(14) The small incorporation of ^{18}O in 9a indicated the involvement of direct S_N2 displacement with $[^{18}O]H_2O$ as a minor pathway.

(15) For less efficient and unsuccessful substrates for the stereoinversion, see Figure S3.

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(17) It was reported in ref 4d that the presence of an acyl protecting group adjacent to the hydroxy group was crucial to achieve an efficient stereoinversion of sugar derivatives using the Lattrel−Dax reaction. However, we have found that the Lattrel−Dax reaction of 6d and 6e without a neighboring acyl protecting group proceeded to give the stereoinverted alcohols 9d and 9e, respectively, in good yields (Scheme S2).

(18) For the stability of *p*-methoxyphenyl glycosides under various acidic conditions, see: Zhang, Z.; Magnusson, G. *Carbohydr. Res.* **1996**, *295*, 41.

(19) Stereoinversion of monobenzoyl-protected *trans*-diol 9j using the one-pot procedure afforded the corresponding *cis*-derivataive 1j in 91% yield. However, performing the stereoinversion step using $[^{18}O]$ H_2O afforded 1j with the ^{18}O atom highly incorporated at the carbonyl group, indicating that the transformation proceeded mainly via the anchimeric assistance by the benzoyl group (Scheme S6).

(20) The one-pot reaction for stereoinversion of monobenzyl-protected *cis*-1,2-cyclopentanediol 1k gave stereoinverted product 9k only in low yield, and benzyl alcohol was isolated in 42% yield. We also observed the formation of cyclopentene oxide by GC-MS analysis of the reaction mixture, indicating that gradually liberated acid triggered the debenzylation via an intramolecular S_N2 reaction.