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Stereoselective nucleophilic substitution of 6-(*tert*-butyldimethylsilyloxy)-3,6-dihydro-2*H*-pyran-3-yl acetate: application to the synthesis of a NK_1 receptor antagonist☆

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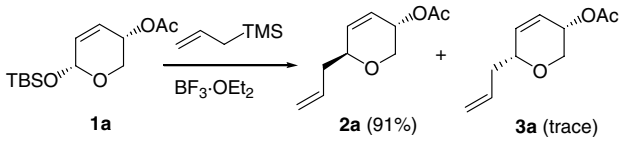
Abstract—Reaction of chiral *cis*- and *trans*-6-(*tert*-butyldimethylsilyloxy)-3,6-dihydro-2*H*-pyran-3-yl acetates with various nucleophiles (allyltrimethylsilane, bistrimethylsilylacetylene, benzyl alcohol, benzyl carbamate etc.) in the presence of a Lewis acid gave the corresponding 2,3-unsaturated pyran derivatives in good to excellent yield with trans selectivity. Application to the synthesis of NK_1 antagonist is also described.

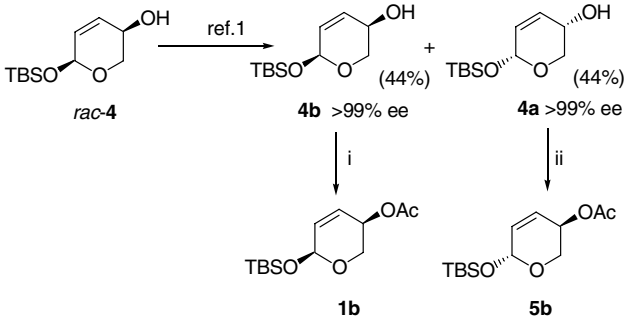
In our previous paper,[1] we have reported that the reaction of *cis*-(3*S*,6*S*)-6-(*tert*-butyldimethylsilyloxy)-3,6-dihydro-2*H*-pyran-3-yl acetate (**1a**) with allyltrimethylsilane in the presence of a Lewis acid gave a 6-allyl substituted pyran derivative (**2a**) in a highly trans selective manner (Scheme 1). In this reaction, the *tert*-butyldimethylsilyloxy group works as a good leaving group. The remarkable stereoselectivity observed in this reaction prompted us to investigate the reactivity and stereoselectivity with various nuculeophiles, including C-Nucleophiles, O-Nucleophiles, and N-Nucleophiles, in the presence of a Lewis acid.

As substrates, (3*R*,6*R*)-*cis* (**1b**) and (3*R*,6*S*)-*trans* (**5b**) were employed in order to investigate the influence of the stereochemistry at C-6; they were synthesized from *rac*-**4** in a multi-gram scale through a Lipase-catalyzed kinetic resolution method, followed by the Mitsunobu reaction (Scheme 2).



Scheme 1. Nucleophilic substitution reaction reported.[1]

Lewis-acid-promoted nucleophilic substitution of **1b** or **5b** with various nucleophiles is summarized in Table 1. The use of catalytic amounts of $Sc(OTf)_3$[2] showed comparable yield and selectivity to the stoichiometric use of $BF_3{\cdot}OEt_2$ (entry 1 vs 2). When allylsilane or bistrimethylsilyl acetylene was used as a nucleophile, the Lewis-acid-promoted reaction proceeded with high trans selectivity in good to excellent yields irrespective of the stereochemistry of C-6 (entry 1 vs 3, 4 vs 5).[3] The stereochemistry observed in these reactions can be explained by a common oxo-carbeniumion intermediate (Fig. 1). In the intermediate, the acetoxy substituent preferentially adopts a pseudo axial conformation (Aax) over



Scheme 2. Reagents and conditions: (i) Ac_2O, NEt_3, CH_2Cl_2, quant.; (ii) diisopropylazodicarboxylate, PPh_3, AcOH, THF, rt, 80%.

☆ Numbering of the products follows pyranone numbering.

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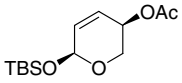
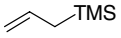
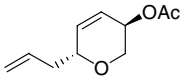
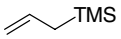
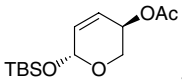
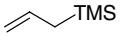
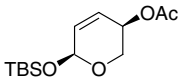
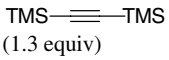
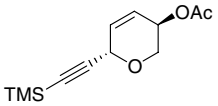
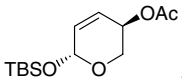
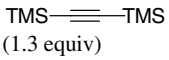
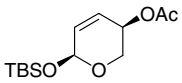
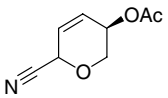
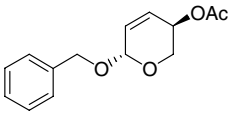
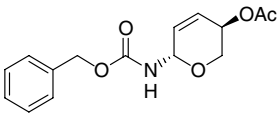
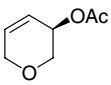
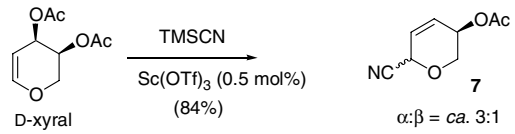
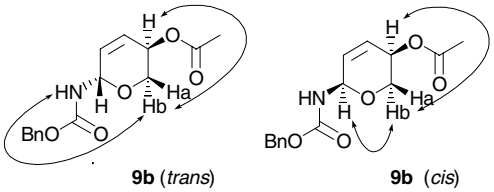
Table 1. Nucleophilic substitution reaction of **1b** or **5b**[a]

Run	Substrates	Nucleophiles	Conditions	Major products[b] (trans:cis)	Yield[c] (%)	Reference
1	 **1b**	 (2.0 equiv)	$BF_3{\cdot}OEt_2$ (1.3 equiv) CH_2Cl_2, −40 °C	 **2b** (95:5>)	91	1,3
2	**1b**	 (2.0 equiv)	$Sc(OTf)_3$ (0.5 mol %) CH_2Cl_2, −40 to 0 °C	**2b** (92:8)	85	3
3	 **5b**	 (2.0 equiv)	$BF_3{\cdot}OEt_2$ (1.3 equiv) CH_2Cl_2, −40 °C	**2b** (95:5>)	91	1,3
4	 **1b**	 (1.3 equiv)	$TiCl_4$ (1.3 equiv) CH_2Cl_2, −40 °C	 **6b** (95:5>)	66	3
5	 **5b**	 (1.3 equiv)	$TiCl_4$ (1.3 equiv) CH_2Cl_2, −40 °C	**6b** (95:5>)	72	3
6[d]	 **1b**	TMSCN (5.0 equiv)	$BF_3{\cdot}OEt_2$ (1.5 equiv) CH_2Cl_2, −40 to 0 °C or $Sc(OTf)_3$ (0.5 mol %), CH_2Cl_2, rt	 **7**	Trace	
7	**1b**	BnOH (1.2 equiv)	$BF_3{\cdot}OEt_2$ (20 mol %) CH_2Cl_2, −40 °C	 **8b** (82:18)	88	5
8[e]	**1b**	$BnOCONH_2$ (1.0 equiv)	$BF_3{\cdot}OEt_2$ (1.0 equiv) CH_2Cl_2, −40 to 0 °C	 **9b** (79:21)	71	12
9	**1b**		Et_3SiH (2.0 equiv) $BF_3{\cdot}OEt_2$ (1.2 equiv) CH_2Cl_2, −30 to 0 °C	 **10**	75	12

[a] All reactions were performed in 0.22 M substrate concentration.
[b] Product ratio was estimated by using ^1H NMR (300 MHz) analysis of the crude material.
[c] Isolated yield.
[d] When D-xyral was used as a substrate instead of **1b**, **7** was obtained in 84% yield as shown below.



[e] Structures of **9** were elucidated by using NOE analysis shown below.



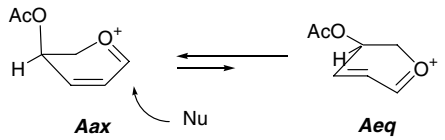
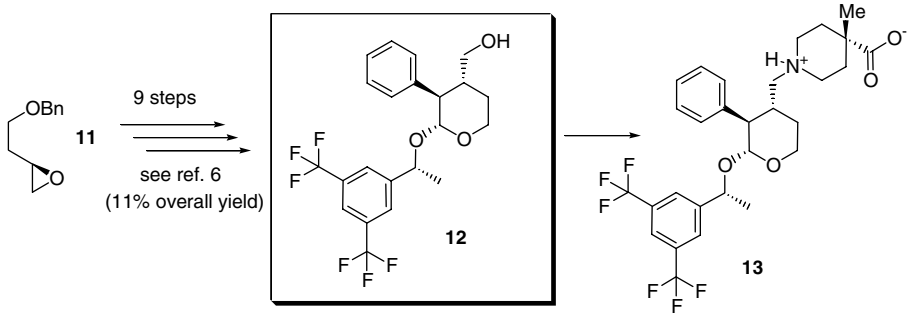


Figure 1. Oxocarbenium intermediate.

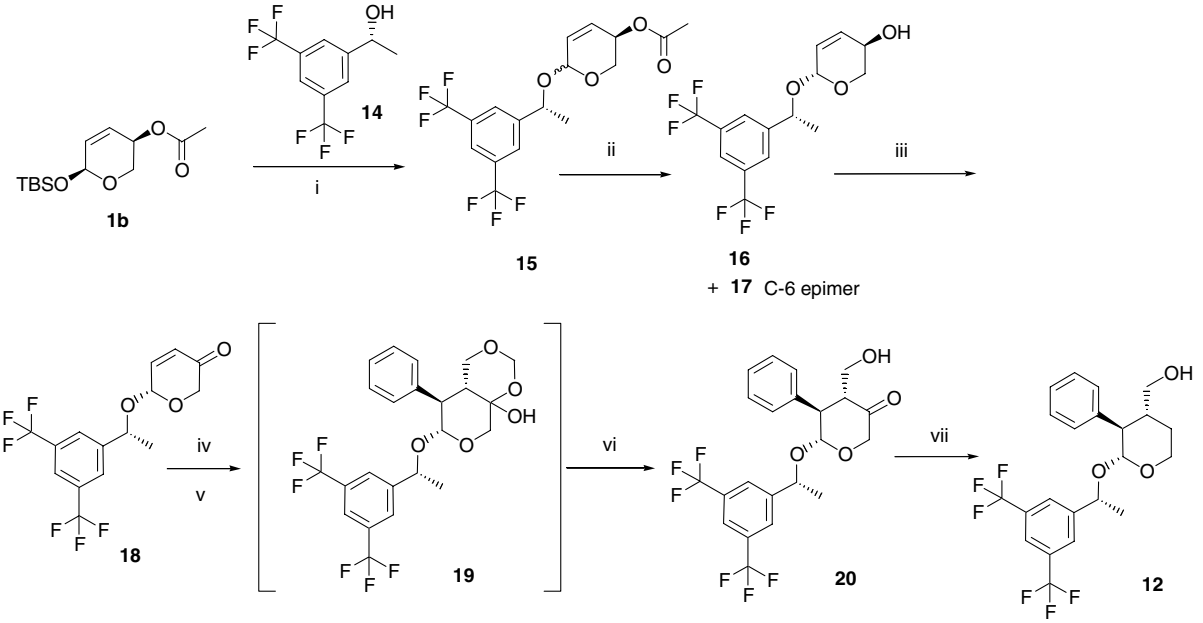
an equatorial one (Aeq) due to the stabilization of the electrostatic interactions between the partially negatively charged oxygen of the substituent and the positively charged carbon of the oxocarbenium ion. Therefore, the nucleophiles can attack the C-6 carbon anti to the acetoxy group.[4]

It is noteworthy that the reaction with TMSCN gave only trace amount of the desired product, in contrast to the same reaction with D-xyral (footnote d and entry 6). When benzyl alcohol or benzylcarbamate was used as a nucleophile, the reaction proceeded smoothly in the presence of a catalytic amount of Lewis acid, although with moderate selectivity (entry 7 and 8). These results suggest that an equilibrium between the *cis*- and *trans*-isomers exists under these conditions.[6] The OTBS group can be easily removed by Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ (entry 9).

Next, we tried to apply this chemistry to the synthesis of a selective human neurokin-1 (hNK_1) receptor antagonist, which has been reported by a group at Merck[7] (Scheme 3). In the synthetic scheme, **12** is a key intermediate in their synthetic array for tetrahydropyran NK_1 antagonists, including **13**.[8] Thus, we chose this compound as a synthetic target. Staring from **1b**, treatment with the known phenethyl alcohol **14**[9] in the presence of a catalytic amount of $BF_3{\cdot}OEt_2$ afforded **15** as an inseparable mixture of epimers (8:1). After hydrolysis of the acetate group, these epimers were readily separated by SiO_2 chromatography to give **16**. The allyl alcohol moiety of **16** was then oxidized with *O*-iodoxybenzoic acid (IBX)[10] to give enone **18**, which was then subjected to phenylcuprate-mediated 1,4-addition in the presence of TMSCl. Crude silyl enol ether was then treated with an aqueous solution of formaldehyde in the presence



Scheme 3. Synthesis of NK_1 antagonists reported by a group at Merck.



Scheme 4. Reagents and conditions: (i) $BF_3{\cdot}OEt_2$ (20 mol %), CH_2Cl_2, −30 °C, 93%; (ii) K_2CO_3, MeOH, rt, **16**: 82%, **17**: 10%; (iii) IBX, DMSO, rt, 91%; (iv) PhMgBr, HMPA, $CuBr{\cdot}SMe_2$, THF, −78 °C, then TMSCl; (v) 37% HCHO, $Yb(OTf)_3$ (10 mol %), THF, rt; (vi) MS4A, toluene reflux, 72% from **18**; (vii) NH_2NHTs, TsOH, MeOH, then $NaBH_3(CN)$, MS4A, THF, 50%.

of $Yb(OTf)_3$ as a catalyst.[11] Under these conditions, hemiacetal **19** was obtained as an inseparable mixture with the desired **20**. Fortunately, **19** was readily converted to the desired alcohol **20** by simply heating it in toluene in the presence of MS4A. Finally, modified Wolff–Kishner procedure, involving the formation of tosylhydrazone, followed by its reduction with $NaBH_3CN$, afforded **12** (Scheme 4). As a result, we synthesized **12** via a seven-step sequence with a 25% overall yield from **1b**.

In conclusion, we investigated the reactivity and stereoselectivity of the nucleophilic substitution reaction of **1b** and **5b** in the presence of a Lewis acid. Furthermore, we showed the utility of this chemistry by the short stereocontrolled synthesis of a NK_1 antagonist. The chemistry developed during the course of this study should allow access to a range of highly substituted tetrahydropyran derivatives, as well as hNK_1 antagonists.

References and notes

1. Sugawara, K.; Imanishi, Y.; Hashiyama, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4529.
2. Aggarwal, V. K.; Vennall, G. P. *Tetrahedron Lett.* **1996**, *37*, 3745.
3. Synthesis of **7a** and **7b** from Pentose glycals see: Hosokawa, S.; Kirschbaum, B.; Isobe, M. *Tetrahedron Lett.* **1998**, *39*, 1917, and reference cited therein.
4. Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322, and reference cited therein.
5. Synthesis of the enantiomers of **8b** from 3,4-di-*O*-acetyl-D-xylal, see: Cristina, F.; Roberta, G.; Giovanna, M.; Matio, O. T. *Tetrahedron: Asymmetry* **2001**, *12*, 2731, and reference cited therein.
6. When **8b** was treated with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −40 °C, formation of *cis*-**8b** was detected by HPLC analysis (ca. 15%). In the case of **9b,** cis-isomer was detected in $CDCl_3$ medium after allowing to stand at room temperature for 1 week.
7. Nelson, T. D.; Rosen, J. D.; Smitrovich, J. H.; Payack, J.; Craig, B.; Matty, L.; Huffman, M. A.; McNamara, J. *Org. Lett.* **2005**, *7*, 55, and reference cited therein.
8. Owen, S. N.; Seward, E. M.; Swain, C. J.; Williams, B. J. U.S. Patent 6,458,830 B1, 2001.
9. Brands, K. M. J.; Payack, J. F.; Rosen, J. D.; Nelson, T. D.; Candelario, A.; Huffman, M. A.; Zhao, M.; Li, J.; Craig, B.; Song, Z.; Tschaen, D. M.; Hansen, K.; Devine, P. N.; Pye, P. J.; Rossen, K.; Dormer, P.; Reamer, R. A.; Welch, C. J.; Mathre, D.; Tsou, N. N.; McNamara, J. M.; Reider, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 2129.
10. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
11. Kobayashi, S. *Chem. Lett.* **1991**, *12*, 2187.
12. All new compounds were fully characterized.