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# 5- and 6-Exocyclic Products, *cis*-2,3,5-Trisubstituted Tetrahydrofurans, and *cis*-2,3,6-Trisubstituted Tetrahydropyrans via Prins-Type Cyclization

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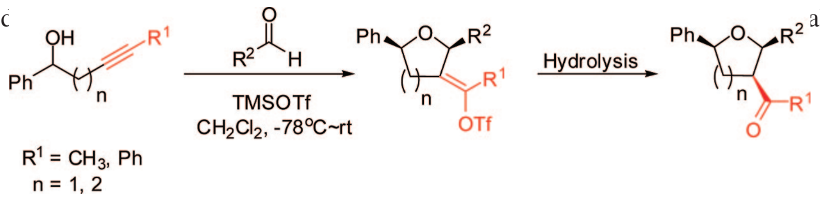

Exocyclic proc ally substituted alkynyl alcohols with various aldehydes via Prins-type cyclization in good yields. It is of interest that synthesized 5- and 6-exocyclic vinyl cations generated as a result of Prins-type cyclization could be trapped as a vinyl triflate in $CH_2Cl_2$ to give 3-furanylidenes and 3-pyranylidenes. Those 3-furanylidenes and 3-pyranylidenes underwent hydrolysis to give the corresponding 3-acyl-substituted products having *all-cis*-configured isomers, such as 2,3,5-trisubstituted tetrahydrofurans and 2,3,6-trisubstituted tetrahydropyrans.

## Introduction

Tetrahydropyrans and tetrahydrofurans are important compounds that occur as building blocks in many biologically active natural products such as polyether antibiotics, marine toxins, and pheromones.[1] Versatile syntheses of tetrahydrofurans and tetrahydropyrans represent an important challenge because of the presence of this structural unit in ployoxygenated terpenes such as eurylene,[2] polyether antibiotic ionophores such as ionomycins 1 and 3, and other natural products. Methods which allow the stereoselective introduction of functionality contiguous to C-2, C-5, and C-6 are particularly attractive because such fragments are potentially useful building blocks in natural product synthesis.[3] Although structurally complex tetrahydropyrans are most often assembled by cyclization that forms a C−O bond, the preparation of these heterocycles through C−C bond-forming Prins cyclization is becoming increasingly important.[4−6] The Prins cyclization reaction has been shown to be a very useful procedure for the construction of oxygen-containing heterocyclic units that appear in many natural products. This reaction typically involves a reaction between an aldehyde and a homoallylic alcohol promoted by acid. The relevance of this reaction as a carbon−carbon bond forming reaction has led to the study and application of many variations.

*cis*-2,5-Disubstituted tetrahydrofurans and *cis*-2,6-disubstituted tetrahydropyrans are also ubiquitous in nature, occurring in a wide range of biologically active substances. Therefore, there has been much interest in the development of methods for the stereoselective synthesis of these subunits.[7,8] Prins-type cyclization from homoallylic alcohols and aldehydes is a

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(6) (a) Overman, L. E. *Lect. Heterocycl. Chem.* **1985**, *8*, 59. (b) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352.

10.1021/jo800967p CCC: $40.75

**SCHEME 1. Synthesis of *all-cis*Ttrisubstituted Tetrahydrofurans and Tetrahydropyrans**

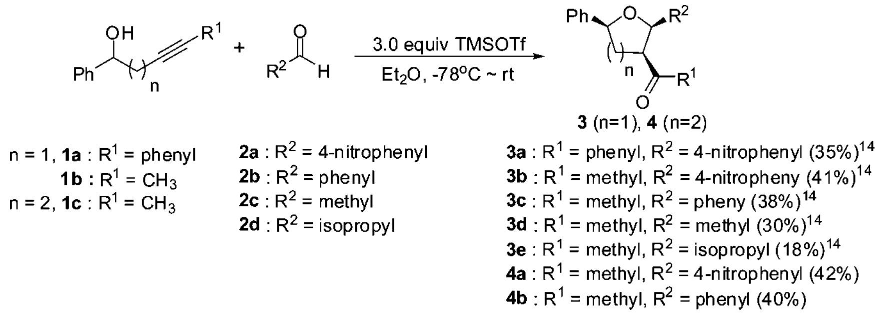
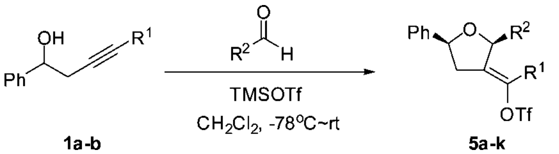


**TABLE 1. Synthesis of 3-Furanylidene Derivatives**[14]



| entry | $R^1$ | $R^2$ | no. | yield[a] (%) |
|---|---|---|---|---|
| 1 | methyl | 4-nitrophenyl | **5a** | 77 |
| 2 | methyl | phenyl | **5b** | 68 |
| 3 | methyl | 2-naphthyl | **5c** | 68 |
| 4 | methyl | 4-chlorophenyl | **5d** | 76[b] |
| 5 | methyl | 2-nitrophenyl | **5e** | 35 |
| 6 | methyl | methyl | **5f** | 68 |
| 7 | methyl | ethyl | **5g** | 69[c] |
| 8 | methyl | isopropyl | **5h** | 60 |
| 9 | methyl | *n*-pentyl | **5i** | 65 |
| 10 | methyl | 2-phenylethyl | **5j** | 61[c] |
| 11 | phenyl | 4-nitrophenyl | **5k** | 64 |

[a] Isolated yields. [b] Stereoisomers (cis/trans) were obtained in a ratio of 8:1, which was determined by $^1H$ NMR spectroscopy. [c] Stereoisomers (cis/trans) were obtained in a ratio of 5:1, which was determined by $^1H$ NMR spectroscopy.

powerful method of preparing *cis*-2,6-disubstituted tetrahydropyrans.[9,10] Prins-type cyclization of homoallylic alcohols gives 6-endocyclic products (tetrahydropyrans) rather than 5-exocyclic products (tetrahydrofurans).[11] Pure Prins-type cyclization has been rarely used for the synthesis of tetrahydrofurans, though pinacol rearrangement after Prins-type cyclization gives tetrahydrofurans.[12] Lewis acid catalyzed Prins-type cyclization[13] of a homopropargylic alcohol with a trimethylsilylmethyl group and aldehydes induces 5-exo cyclization to give *cis*-2,5-disubstituted 3-allenyltetrahydrofurans.[13a]

Methodology recently developed in our group has shown a convenient and highly stereoselective synthetic method of 5-exocyclization to give *cis*-2,3,5-trisubstituted tetrahydrofurans by the Lewis acid-assisted Prins-type cyclization of a homopropargylic alcohol with terminally substituted alkynes.[14] To expand the scope of this useful Prins-type cyclization, we set out to devise a novel cyclization methodology for the synthesis of 6-exocyclization to give *cis*-2,3,6-trisubstituted tetrahydropyrans. In this paper, we report Prins-type cyclization and the stereochemistry of terminally substituted alkynyl alcohols.

## Results and Discussion

Homopropargylic alcohols (2-alkynylethan-1-ol derivatives) **1a**,**b** and 3-alkynylpropan-1-ol derivative **1c** underwent Prins-type cyclization with substituted benzaldehydes and alkanals **2** (1.1 equiv, −78 °C, $Et_2O$) in the presence of TMSOTf (3.0 equiv) to give *all-cis*-configured products **3a**−**e** and **4a**,**b** in 18−42% yields (Scheme 1). Generally, a homoallylic alcohol undergoes Prins-type cyclization to give a tetrahydropyran in a 6-endocyclic manner.[9f] However, this Prins-type cyclization with alkynyl alcohols provided 5-exocyclic and 6-exocyclic products. Only one single stereoisomer was obtained, which was confirmed to be an *all-cis*-configured isomer by single-crystal X-ray crystallography.[15] As with other Prins-type cyclization,[13,15] the *all-cis* stereoselectivity between the C2, C3, and C5 or C6 positions must be the results of a cyclic transition state and the protonation from the α-face during the hydrolysis.

As with our previous results,[14] the solvent was changed from $Et_2O$ to $CH_2Cl_2$ resulting in significant improvement in yield (Table 1). The reaction was greatly affected by the solvent. However, the obtained tetrahydrofuran analogues were proven to have an exocyclic vinyl triflate moiety instead of the desired 3-acyl moiety by single-crystal X-ray crystallography.[15] As in the synthesis of tetrahydrofurans, the 3-alkynylpropan-1-ol derivative **1c** ($n = 2$) proceeded in $CH_2Cl_2$ in good yields to give the corresponding pyranylidene derivatives with an exocyclic vinyl triflate moiety (Table 2).

Prins-type cyclization of a homopropargylic alcohol **1a** with 4-nitrobenzaldehyde (1.0 equiv, $CH_2Cl_2$) in the presence of TMSOTf (3.0 equiv) gave *all-cis*-configured product **5a** in 77% yield (Table 1). The obtained tetrahydrofuran analogue was

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(15) See the ORTEP drawings in the Supporting Information.

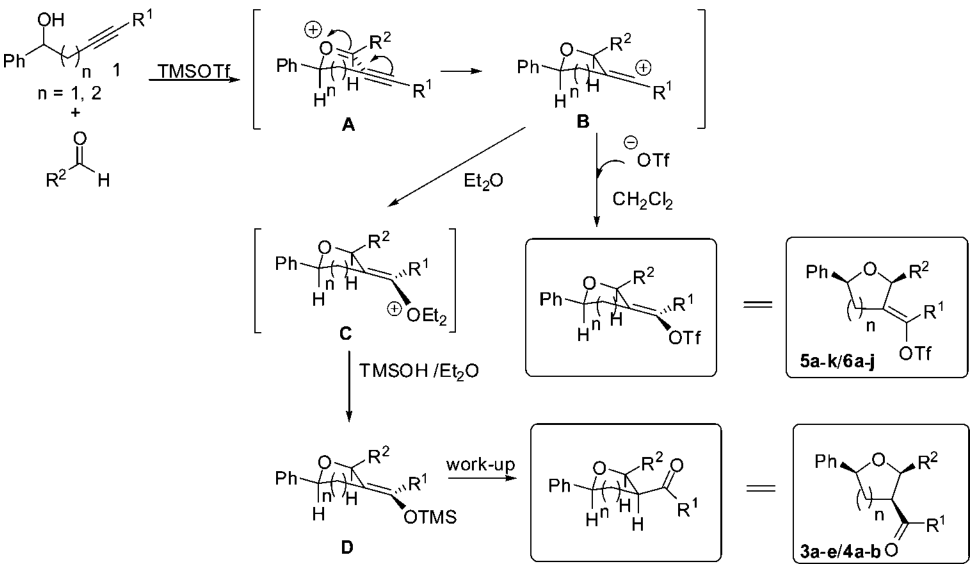
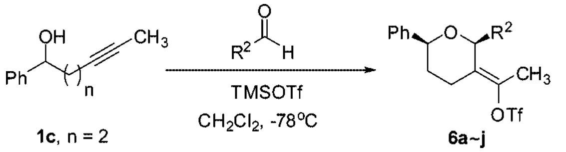


**FIGURE 1.** Proposed mechanism for the two different solvent systems.

**TABLE 2. Synthesis of 3-Pyranylidene Derivatives**



| entry | R$^2$ | no. | yield[a] (%) |
|---|---|---|---|
| 1 | 4-nitrophenyl | **6a** | 82 |
| 2 | phenyl | **6b** | 79 |
| 3 | 2-naphthyl | **6c** | 81 |
| 4 | 4-chlorophenyl | **6d** | 78 |
| 5 | 2-nitrophenyl | **6e** | 79 |
| 6 | methyl | **6f** | 76 |
| 7 | ethyl | **6g** | 77 |
| 8 | isopropyl | **6h** | 75 |
| 9 | *n*-pentyl | **6i** | 76 |
| 10 | 2-phenylethyl | **6j** | 69 |

[a] Isolated yields.

proven to be a furanylidene derivative by single-crystal X-ray crystallography.[15] A series of aliphatic or aromatic aldehydes with homopropargylic alcohols **1a**,**b** were tested under the Prins-type cyclization conditions to give the corresponding 3-furanylidene derivatives (Table 1). In addition, Prins-type cyclization of 3-alkynylpropan-1-ol derivative **1c** ($n = 2$) with 4-nitrobenzaldehyde gave a 6-exocyclic product having *cis*-2,6 configured products in 82% yield (Table 2), whereas a series of aliphatic or aromatic aldehydes with a 3-alkynylpropan-1-ol derivative **1c** ($n = 2$) underwent the Prins-type cyclization conditions to give the corresponding pyranylidene derivatives **6a**−**j** (Table 2).

All reactions proceeded smoothly to afford various five- and six-membered exocyclic products. Adjustment of the chain length ($n = 1$ and 2) gave rise to different ring sizes of cyclic ethers. In addition, the method exhibits excellent functional tolerance, and a great variety of aldehydes can be employed to furnish the ring backbone with different substituents.

Aromatic aldehydes gave the cyclization products in higher yields than aliphatic aldehydes except 2-nitrobenzenaldehyde (entry 5 in Table 1) in cases of 3-furanylidene derivatives and 3-pyranylidene derivatives. In case of 3-furanylidene derivatives, two diastereomers (*cis*/*trans*) were obtained in a ratio of 8:1 (**5d**) to 5:1 (**5g** and **5j**). Besides **5d**, **5g**, and **5j**, all other compounds in Table 1 have a single *cis*-stereoismer. In the case of 3-pyranylidene derivatives, only *cis* forms were obtained. When an alkyl substituent at the terminal carbon of a homoallylic alcohol was replaced with an aromatic substituent (phenyl), the cyclized product **5k** was obtained in a good yield (entry 11 in Table 1).

On the basis of all the above experiments and our previous works,[13,14] the possible mechanisms for the formation of 5- and 6-exocyclic derivatives are proposed as shown in Figure 1. It is of interest that the same conditions except for the solvent (Et$_2$O or CH$_2$Cl$_2$) gave totally different products. An alkynyl alcohol **1a** and an aldehyde would make an oxocarbenium ion **A**. The *cis*-configuration between the phenyl group of **1a** and R$^2$ group of the aldehyde was obtained to avoid steric hindrance between the two groups (Figure 1). The vinyl cation **B** would be transiently formed after Prins-type cyclization. In CH$_2$Cl$_2$ solution, trapping the exocyclic vinyl cation **B** by the triflate anion afforded exocyclic vinyl triflates **5a**−**k** and **6a**−**j**. The triflate anion attacked the vinyl cation **B** from the front rather than from the back because of steric hindrance with the R$^2$ group of the aldehyde. There are some examples where a carbocation or a vinyl cation was captured by counteranion such as halide ion, acetate anion, or trfliate anion.[16] On the other hand, 3-acetyl-substituted products (**3a**−**e** and **4a**,**b**) in Et$_2$O suggest that the exocyclic vinyl cation **B** would be stabilized by ether solvent itself (refer **C**) and trapped by TMSOH to give the TMS-enol **D** which is hydrolyzed during workup to the corresponding products (**3a**−**e** and **4a**,**b**). During the tautomerization, the attack of hydrogen from the α-face gave *all-cis* trisubstituted products (**3a**−**e** and **4a**,**b**).

To obtain the 3-acetyl-substituted tetrahydrofurans and tetrahydropyrans from the furanylidenes and pyranylidenes, the exocyclic vinyl triflates **5a** and **6a** could be readily converted to the 3-acetyl-substituted products **3b** and **4a**, respectively, by treatment with aqueous NaOH (1%) in a 2:1 mixture of 1,4-

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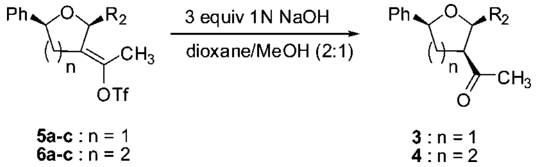
[16] (a) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2002**, *4*, 3407. (b) Barry, C. St. J.; Crosby, S. T.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett.* **2003**, *5*, 2429. (c) Dobbs, A. P.; Livnevi, L.; Penny, M. J.; Marinovic, S.; Iley, J. N.; Stephenson, P. T. *ChemComm* **2006**, 3134. (d) Miranda, P. O.; Ramirez, M. A.; Martin, V. S.; Pardron, J. I. *Org. Lett.* **2006**, *8*, 1633.

**TABLE 3. Synthesis of 2,3,5-Trisubstituted Tetrahydrofurans and 2,3,6-Trisubstituted Tetrahydropyrans**



| entry | R$^2$ | *n* | compd | yield (%) |
|---|---|---|---|---|
| 1 | 4-nitrophenyl | 1 | **3b** | 98[14] |
| 2 | | 2 | **4a** | 75 |
| 3 | phenyl | 1 | **3c** | 97[14] |
| 4 | | 2 | **4c** | 80 |
| 5 | 2-naphthyl | 1 | **3f** | 98[14] |
| 6 | | 2 | **4d** | 70 |

**SCHEME 2. Application to Chiral Synthesis[14]**

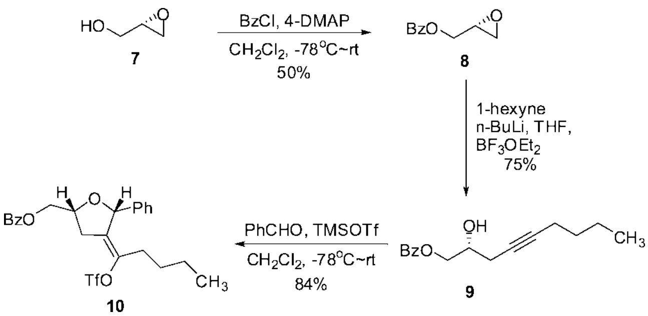
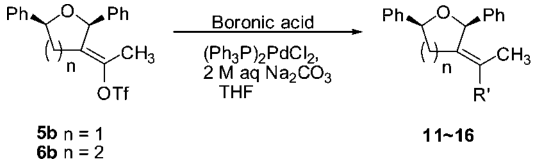


**TABLE 4. Application to Suzuki Coupling**



| entry | triflate | boronic acid (R′) | product | yield[a] (%) |
|---|---|---|---|---|
| 1 | **5b** | phenyl | **11** | 96 |
| 2 | | *trans*-2-phenylvinyl | **12** | 94 |
| 3 | | 4-fluorophenyl | **13** | 94 |
| 4 | **6b** | phenyl | **14** | 89 |
| 5 | | *trans*-2-phenylvinyl | **15** | 83[b] |
| 6 | | 4-fluorophenyl | **16** | 90 |

[a] Isolated yields. [b] Stereoisomers (*cis/trans*) at the 2,6-positions were obtained in a ratio of 3:1 (ref 20), which was determined by $^1$H NMR spectroscopy.

dioxane and methanol at room temperature in 98% and 75% yields, respectively (Table 3).[14] Interestingly, in the case of 5-exocyclic vinyl triflates, the use of saturated NaOH solution led a fast reaction to give desired products, while in case of 6-exocyclic vinyl triflates, saturated NaOH solution gave the starting material, i.e., the alkynyl alcohol **1c**.

To expand the scope of our synthetic method, the Prins-type cyclization was applied to a chiral nonracemic starting material, (*S*)-glycidol **7** (Scheme 2).[14] The treatment of (*S*)-glycidol **7** with benzoyl chloride and 4-DMAP in CH$_2$Cl$_2$ afforded benzoylated glycidol **8** in 50% yield. The compound **8** was converted under the known conditions to compound **9**.[17] Compound **9** underwent Prins-type cyclization to give a furanylidene derivative **10** in 84% yield. The diasteromeric ratio of compound **10** was over 99:1, which was detected by HPLC.[18]

In addition, to prove synthetic uses of our furanylidene and pyranylidene triflates, we have run the Suzuki cross-coupling of the vinyl triflates with boronic acids using (Ph$_3$P)$_2$PdCl$_2$. The results are shown in Table 4.[19] The treatment of 3-furanylidene and 3-pyranylidene derivatives **5b** and **6b** with boronic acids under the basic conditions afforded the corresponding products in good yields.

## Conclusion

In conclusion, we have discovered a novel, facile, and efficient methodology for the synthesis of new tetrahydrofurans and tetrahydropyrans, and the key features of this new synthesis are that all *cis*-configured 2,3,5-trisubstituted tetrahydrofurans and 2,3,6-trisubstituted tetrahydropyrans were synthesized via Prins-type cyclization and that the exocyclic vinyl triflates generated as a result of Prins-type cyclization underwent hydrolysis to give the corresponding 3-acyl-substituted product, which can be applied for the preparation of various synthetically useful intermediates as a new scaffold. It is also of great interest to note that the exocyclic vinyl cation generated as a result of Prins-type cyclization could be trapped as a vinyl triflate when CH$_2$Cl$_2$ was used as a solvent, whereas in ethereal solution the same intermediate underwent hydrolysis to give the corresponding 3-acyl-substituted product. We conceived that this novel methodology opens the access to interesting functionalized heterocyclic frameworks that are useful as building blocks in total syntheses of natural products as well as in the exploration of some novel bioactive molecules.

## Experimental Section

**General Procedure for Synthesis of 3-Furanylidene Derivatives.** To a stirred solution of substrates **1b** (0.31 mmol) and the aldehyde (0.37 mmol) in dry dichloromethane (3.0 mL) was added TMSOTf (0.93 mmol) for 1 h at −78 °C. The mixture was allowed to warm to room temperature slowly for 3 h and stirred at room temperature for an additional 1−2 h until completion of reaction. The reaction mixture was quenched with NaHCO$_3$ and diluted with 10 mL of diethyl ether. The organic solution was washed with water and brine and the organic layer was dried over MgSO$_4$, filtered, and concentrated. Purification by flash column chromatography using Hex/EtOAc (20:1) as eluent afforded the desired products **5a−k** (Table 1).

**Selected data for 5a:** mp 76−78 °C; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.30 (d, 2H, $J = 8.8$ Hz), 7.61 (d, 2H, $J = 8.7$ Hz) 7.38−7.32 (m, 5H), 5.61 (s, 1H), 5.07 (dd, 1H, $J = 10.8$, 5.1 Hz), 3.41 (dd, 1H, $J = 16.0$, 5.1 Hz), 2.92−2.81 (m, 1H), 1.77 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 148.2, 146.0, 139.9, 139.0, 135.4, 129.0, 128.7, 126.0, 124.3, 118.2 (q, $J = 320$ Hz), 81.2, 80.4, 40.2, 17.6; IR (neat) 2862, 1607, 1524, 1415, 1348, 1351, 1214, 1139, 1107, 1035 cm$^{-1}$; HRMS-CI (*m*/*z*) $[M + H]^+$ calcd for $C_{19}H_{17}F_3O_6NS$ 444.0729, found 444.0727.

**General Procedure for Synthesis of 3-Pyranylidene Derivatives.** To a stirred solution of substrate **1c** (0.31 mmol) and the aldehyde (0.37 mmol) in dry dichloromethane (3.0 mL) was added TMSOTf (0.93 mmol) for 1 h at −78 °C. The mixture was allowed to stir at −78 °C for 3 h, and the reaction was monitored by TLC. Upon disappearance of alcohol (typically 2 h), the reaction mixture

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(17) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391.

(18) Retention time: 3.63 min, HPLC conditions: column type. CHIRALPAK AD (Daicel Chemical Industries, LTD, Japan); column size, 4.6 mm i.d. × 250 mm; column temperature, rt; flow rate 1.0 mL min$^{-1}$; detection, 256 nm; eluent, 5% 2-propanol in hexane.

(19) Occhiato, E. G. *J. Org. Chem.* **2001**, *66*, 2459.

(20) (a) For a related epimerization, see: (b) Bower, J. F.; Williams, A. J.; Woodward, H. L.; Szeto, P.; Lawrence, R. M.; Gallagher, T. *Org. Biomol. Chem.* **2007**, *5*, 2636.

was quenched with $NaHCO_3$ and diluted with 10 mL of diethyl ether. The organic solution was washed with water and brine, the organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. Purification by flash column chromatography, using Hex/EtOAc (15:1) as eluent, afforded the desired products **6a−j** (Table 2).

**Selected data for 6a:** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.26 (d, 2H, $J$ = 4.3 Hz), 7.66 (d, 2H, $J$ = 4.3 Hz), 7.30−7.39 (m, 5H), 5.60 (s, 1H), 4.69 (dd, 1H, $J$ = 10.6, 5.2 Hz), 2.88−2.93 (m, 1H), 2.49−2.52 (m, 1H), 2.15−2.19 (m, 1H), 2.05−2.08 (m, 1H), 1.99 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 147.8, 146.3, 141.9, 141.76, 130.5, 128.6, 127.9, 125.7, 124.0, 123.1, 119.9, 116.8, 113.6, 77.4, 76.2, 31.5, 21.8, 17.3; IR (neat) 2864, 1694, 1607, 1523, 1413, 1349, 1212, 1140 cm$^{-1}$; HRMS-CI ($m/z$) $[M + H]^+$ calcd for $C_{20}H_{19}F_3O_6NS$ 458.0885, found 458.0885.

**General Procedure for Synthesis of 2,3,5-Trisubstituted Tetrahydrofuran and 2,3,6-Trisubstituted Tetrahydropyran Derivatives.** The 3-furanylidene or 3-pyranylidene derivative (0.11 mmol) was added to solvent system of dioxane/methanol (2:1), and then 3 mL of 1 N NaOH solution was added. The reaction was stirred at room temperature for 3 h. The reaction was quenched by adding aqueous sodium chloride. The organic materials were extracted with ethyl acetate, dried over $Na_2SO_4$, and concentrated in vacuo. Purification by flash column chromatography (neutral silica gel; EtOAc/Hex = 2:15) provided the corresponding 3-acyl-substituted products (Table 3).

**Selected data for 4a:** $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.18 (d, 2H, $J$ = 8.7 Hz), 7.58 (d, 2H, $J$ = 8.7 Hz), 7.27−7.43 (m, 7H), 4.84(d, 1H, $J$ = 9.9 Hz), 4.61 (d, 1H, $J$ = 11.2 Hz), 2.86−2.90 (m, 1H), 2.11−2.25 (m, 1H), 1.98−2.10 (m, 2H), 1.87 (s, 3H), 1.74−1.82 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 209.9, 148.0, 147.6, 141.9, 128.5, 128.1, 127.8, 126.2, 123.7, 80.4, 79.9, 56.3, 32.7, 31.1, 28.0; IR (neat) 2855, 1715, 1702, 1606, 1521, 1495, 1450, 1349, 1282, 1168, 1089, 1063, 1014 cm$^{-1}$; HRMS-Cl ($m/z$) $[M + H]^+$ calcd for $C_{19}H_{20}NO_4$ 326.1392, found 326.1392.

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**Supporting Information Available:** Experimental procedures and spectral data of all new compounds including ORTEP drawings of compounds **3a** and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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