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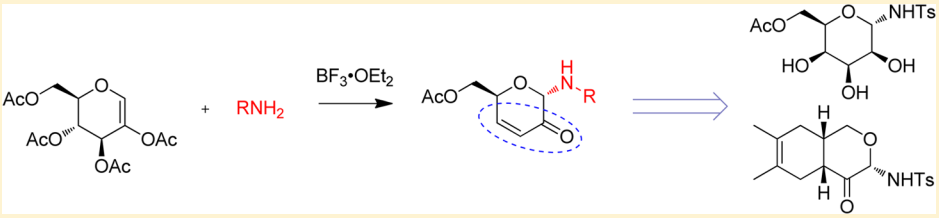
Ferrier-Type *N*-Glycosylation: Synthesis of *N*-Glycosides of Enone Sugars

Feiqing Ding, Ronny William, and Xue-Wei Liu*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

Supporting Information



ABSTRACT: A mild and efficient protocol for the stereoselective synthesis of *N*-glycosides of enone sugars has been developed. The reaction proceeds to provide *N*-glycosides of enone sugars in moderate to good yields with preferential α-anomeric selectivity. Additionally, applications of the *N*-glycosides of enone sugar derivatives as precursor to assemble some biochemically functional derivatives have also been explored. This includes the use of *N*-glycosides of enone sugars as reactive dienophile in asymmetric synthesis of bicyclic adduct through Diels–Alder cycloaddition reaction.

Structurally defined nucleosides with *N*-glycosidic linkage have attracted a great deal of interest academically in view of their extensive applicability as pharmacological agents including antibiotic, antineoplastic, and antiviral compounds.[1] Specifically, *N*-glycosides of enone sugars have emerged with potential applications in the development of antitumor-cancer oriented ketonucleosides[2] and optically active bicyclic lactams (Figure.1).[3] It is well established that oligosaccharides and

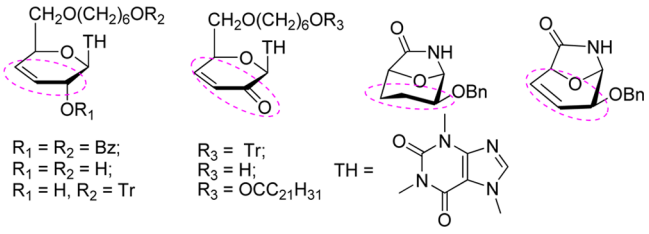


Figure 1. Structures of cancer oriented ketonucleosides and optically active bicyclic lactams.

glycoconjugates containing *O*-glycosidic bonds are prone to chemical or enzymatic hydrolysis leading to cleavage of glycosyl linkage and degradation. To address this issue, tremendous efforts have been directed toward structural modification of naturally occurring carbohydrates over the past few decades.[4] Needless to say, the development of more convenient methods to access structurally modified *N*-glycosides of enone sugars that are more biologically stable is highly desirable. Although 2,3-unsaturated glycals, which are traditionally obtained by Ferrier rearrangement,[5] have inspired many studies, the structural diversity of and approaches toward *N*-pseudoglycals remain limited.[6] Moreover, there are only few methods available for the synthesis of enoside *O*-glycosides or *N*-glycosides of enone sugars.[7] Nevertheless, the stereoselective synthesis of *N*-glycosides of enone sugars is still inadequate by virtue of the lack of advancement in methodological development for *N*-glycosides. Recently, we derived a strategy for ready access to 3-arylsulphonamino-2,3-dideoxysugars *via* regio- and stereoselective tandem hydroamination/glycosylation of a glycal (Figure 2, eq 1).[8] During our efforts to extend the method to include 2-OAc-substituted glycal, serendipitious formation of *N*-glycosides of enone sugars instead of the anticipated 3-arylsulphonamino-2,3-dideoxy product was observed. In conjunction with our previous work, herein we report a novel design for the stereoselective synthesis of *N*-glycosides of enone sugars through $BF_3{\cdot}Et_2O$-promoted glycal rearrangement (Figure 2, eq 2).

Initially, a systematic screening was executed using **1a** and *p*-toluenesulfonamide **2a** ($TsNH_2$) in the presence of $BF_3{\cdot}Et_2O$ to establish the ideal reaction conditions (Table 1). The first evaluation was conducted with different concentrations of $BF_3{\cdot}Et_2O$ as promoter at room temperature, whereby DCM was employed as reaction solvent. We found that 4.4 equiv of $BF_3{\cdot}Et_2O$ was required to promote the reaction and achieve excellent selectivity for the formation of *N*-glycoside of enone sugar **3ab** with 89% yield (Table 1, entry 5). It is notable that when promoter loading as low as 0.5–2.2 equiv was used, the reaction favored the Ferrier rearranged 2,3-unsaturated glycosides **4** as the major product (Table 1, entries 1–3).

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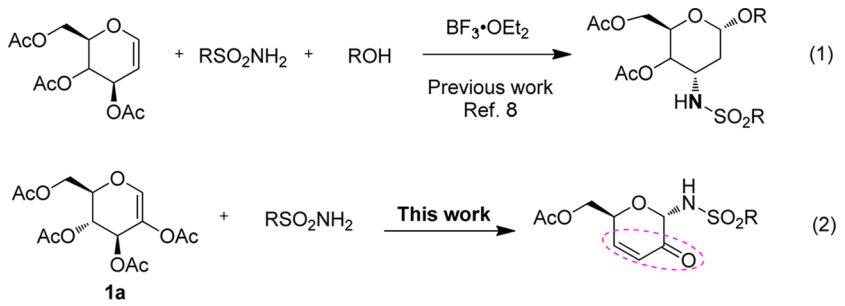
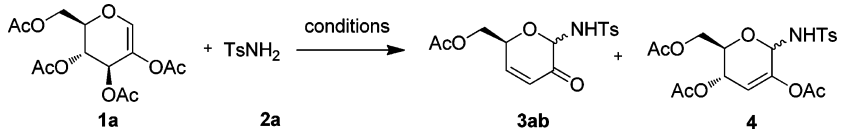


Figure 2. Our previous work and new design of quick access to *N*-glycosides of enone sugars.

Table 1. Optimization of the Synthesis of *N*-Glycosides of Enone Sugars



			yield[a] (%)		
entry	promoter (equiv)	solvent	**3ab**	**4**	α/β[b] (**3ab**)
1	$BF_3{\cdot}OEt_2$ (0.5)	DCM	20	63	ND[c]
2	$BF_3{\cdot}OEt_2$ (1.1)	DCM	26	55	ND[c]
3	$BF_3{\cdot}OEt_2$ (2.2)	DCM	31	48	ND[c]
4	$BF_3{\cdot}OEt_2$ (3.3)	DCM	57	24	ND[c]
5	**$BF_3{\cdot}OEt_2$ (4.4)**	**DCM**	**89**	**trace**	**84:16**
6	TMSOTf (4.4)	DCM	44	ND[c]	60:40
7	TESOTf (4.4)	DCM	55	ND[c]	56:44
8	$SnCl_4$ (4.4)	DCM	52	ND[c]	58:42
9	$TiCl_4$ (4.4)	DCM	trace	83	ND[c]
10	$Cu(OTf)_2$ (4.4)	DCM	NR[d]		
11	$Sc(OTf)_3$ (4.4)	DCM	72	ND[c]	72:28
12	TfOH (4.4)	DCM	complex		
13	$BF_3{\cdot}OEt_2$ (4.4)	THF	NR[d]		
14	$BF_3{\cdot}OEt_2$ (4.4)	CH_3CN	78	ND[c]	75:25
15	$BF_3{\cdot}OEt_2$ (4.4)	toluene	67	ND[c]	78:22
16	$BF_3{\cdot}OEt_2$ (4.4)	DMF	complex		

[a]Isolated yield of anomeric mixtures after purification. [b]The anomeric ratio was determined on the crude ^{1}H NMR spectra. [c]ND = no data. [d]NR = no reaction.

Furthermore, 4.4 equiv of $BF_3{\cdot}Et_2O$ led to a promising anomeric selectivity with α:β ratio of 84:16. Subsequently, the use of other Lewis acids as promoter (TMSOTf, TESOTf, $SnCl_4$, $TiCl_4$, and $Sc(OTf)_3$) also afforded the desired products of *N*-glycosides of enone sugars **3ab** and 2,3-unsaturated glycosides **4**, albeit with incomplete conversion and poor selectivity (Table 1, entries 6–9, 11). In contrast, treatment of the reaction with $Cu(OTf)_2$ exhibited no reaction, whereas with TfOH a complex mixture of products was obtained (Table 1, entries 10, 12). Next, screening was performed in various solvents, namely, THF, toluene, CH_3CN, and DMF. It is found that when DCM was used as solvent, the desired product was produced in the highest yield and selectivity (Table 1, entries 13–16). A decrement in reaction temperature adversely affected the yield and selectivity after prolonged reaction time. Thus, the optimized conditions were found to include the employment of 4.4 equiv of $BF_3{\cdot}Et_2O$ with DCM as the solvent and stirring at room temperature under nitrogen atmosphere for 20 min.

Under the optimized conditions obtained, the scope and generality of stereoselective synthesis of *N*-glycosides of enone sugars **3a**–**3m** promoted by $BF_3{\cdot}Et_2O$ was examined extensively. A range of nitrogen-derived nucleophiles with various substituent (R) groups was screened, and the results are summarized in Table 2. To our delight, the pure α isomer can be easily separated by purification with flash column chromatography, and the isolated yields of the pure isomer ranged from moderate to good. In general, aromatic sulfonamides (**2a**, **2c**–**2f**) afforded the corresponding *N*-glycosides of enone sugars (**3a**, **3c**–**3f**) in moderate yield and good anomeric selectivity (Table 2, entries 1 and 2). The only exception is aromatic sulfonamides bearing a nitro group (**2b** and **2g**), which have shown relatively lower reactivity with moderate α to β anomeric selectivity. Interestingly, halogen bearing aromatic sulfonamides (**2c** and **2d**) provided good yield and superior anomeric selectivity with α to β ratio of ~90:10. Subsequently, methanesulfonamide **2h** ($MsNH_2$) and trichloromethane-sulfonamide **2i** ($TecNH_2$) were also exploited as viable nucleophiles. Reaction of 2-acyloxy glycols with alkylsulfonamide, which provides the desired glycoside with moderate yield and high anomeric selectivity, illustrated the extended feasibility of our reaction (Table 2, entries 3 and 4). Encouraged by the results, we further investigated the scope of carbamates (**2j** to **2l**) that can serve as efficient nucleophiles

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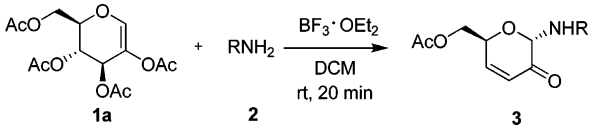
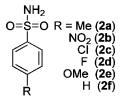
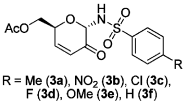
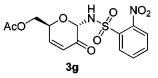
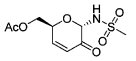
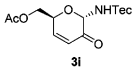
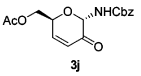
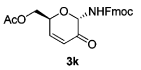
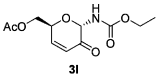
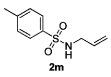
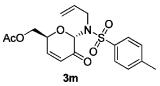
Table 2. Scope of the Synthesis of *N*-Glycosides of Enone Sugars



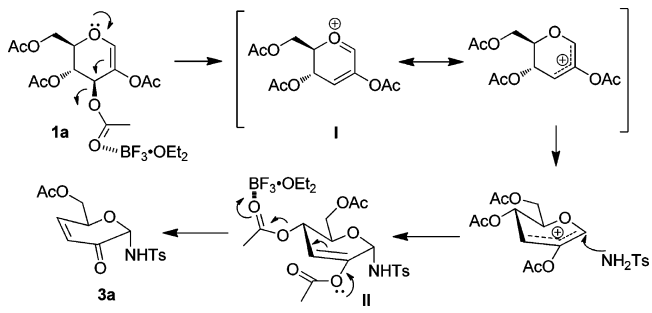
entry	RNH_2	product[b]	yield[c] (%)	α/β[d]
1			75 (**3a**) 56 (**3b**) 83 (**3c**) 86 (**3d**) 76 (**3e**) 73 (**3f**)	84/16 (**3a**) 86/14 (**3b**) 89/11 (**3c**) 91/9 (**3d**) 81/19 (**3e**) 84/16 (**3f**)
2			44	74/26
3			68	90/10
4			71	78/22
5	$CbzNH_2$ **2j**		54	77/23
6	$FmocNH_2$ **2k**		46	75/25
7			55	89/11
8			42	68/32

[a]All products were characterized by IR, HRMS, ^{1}H NMR, and ^{13}C NMR. [b]Isolated yields of pure isomer after purification. [c]The anomeric ratio was determined on the crude ^{1}H NMR spectra.

(Table 2, entries 5−7). The enone *N*-glycoside **3j** represents a crucial example as the benzyloxycarbonyl (Cbz) group could be transformed into amines easily following simple protective group chemistry.[8a] Likewise, we have attempted the reaction with allyl-substituted aromatic sulfonamide **2m**, which furnished the corresponding *N*-glycoside of enone sugar **3m** with moderate yield and selectivity (Table 2, entry 8). The presence of easily functionalized allyl group allows promising application of the resulting *N*-glycosides as precursor in asymmetric synthesis. Overall, this novel synthetic method provides a straightforward access to a wide range of *N*-glycosides of enone sugar derivatives, with potential biochemical applications.

In our initial attempt to probe the reaction mechanism, we found that when the C-4 epimer of 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-galactal (from the corresponding D-galactal) was reacted under the same reaction conditions, the *N*-glycoside of the enone sugar formed was of the similar result as that obtained from the corresponding D-glucal. This observation implies that both acetyl-protected D-glucal and D-galactal led to a common reactive intermediate that eventually converged to the resulting *N*-glycoside of enone sugar. Additionally, in the reaction with *p*-toluenesulfonamide **2a** and 2,3-unsaturated glycosides **4**, a similar α/β ratio of **3ab** was observed. A plausible mechanism for the formation of *N*-glycosides of enone sugars **3** is depicted in Scheme 1.[9] The selectivity for the

Scheme 1. Proposed Mechanism



α isomer in the formation of **3** can be explained by taking into account the steric course of the glycosylation of **1a** combined with anomeric effect. Our proposed mechanism involves formation of intermediary allyloxocarbenium ion **I** as a result of expulsion of acetoxy group. Assuming that **1a** reacts in the preferred $^4H_1$ conformation, the quasiaxial allylic acetoxy group can be readily eliminated by coordinating with the Lewis acid. Simultaneous migration of the double bond (Ferrier's rearrangement) generates a cation at C-1 that can be stabilized by participation of the oxygen-ring lone pair. The quasiaxially oriented alkoxy group at C-4 should induce the attack of the sulfonamide from the opposite face to give the 2-enopyranoside

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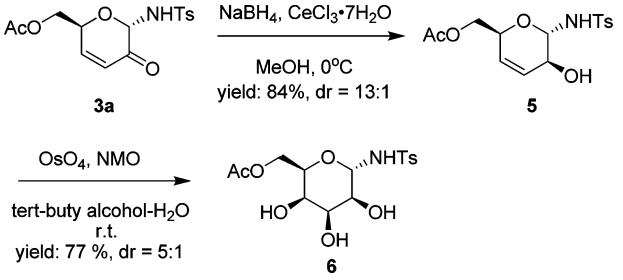
with the α-anomeric configuration. This intermediate **II** undergoes a β-elimination affording the dihydropyranones **3a**.

To demonstrate the application of *N*-glycosides of enone sugars **3** as precursor to potentially biological active derivatives, compound **3** was subjected to a sequence of reactions that consisted of the reduction of ketone functionality followed by dihydroxylation of the unsaturated double bond (Scheme 2).[10]

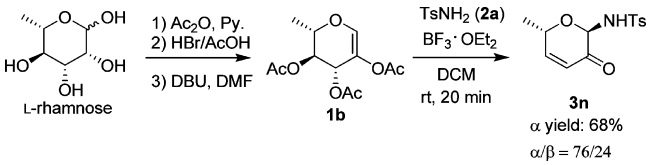
Scheme 2. Synthesis of *N*-Sulfonamidotalose 6



It is noteworthy that there was a remarkable diastereoselectivity in the reduction of **3a** to **5**, probably due to steric hindrance imposed by anomeric substituent adjacent to the carbonyl group.[11] Chemical structure determination and stereochemical characterization of **5a** were achieved by extensive and detailed 1D and 2D NMR studies.[12] The subsequent dihydroxylation[13] of **5** occurred smoothly by diastereofacial selective addition of osmium tetroxide to the double bond from the same side of the ring as the existing allylic hydroxy group to afford *N*-sulfonamidotalose **6**.[14]

In similar manner, we have prepared the 6-deoxy enone *N*-glycoside derivative **3n**, which has various possible synthetic and biochemical applications. The starting 2,3,4-tri-*O*-acetyl-6-deoxy-L-rhamnal **1b** was synthesized from L-rhamnose according to a literature reported procedure (Scheme 3).[12,15]

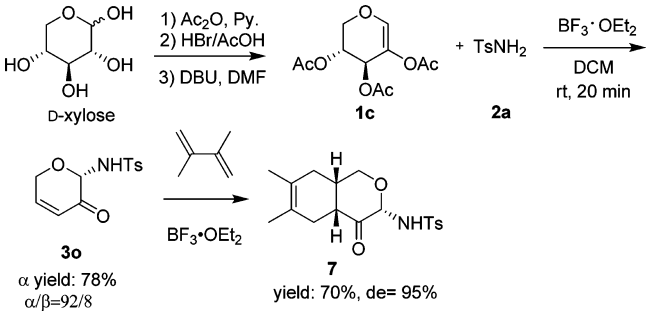
Scheme 3. Synthesis of 6-Deoxy Enone *N*-Glycoside 3n



Optically active dihydropyranones derived from common sugars are useful chiral templates for the synthesis of natural products and their analogues.[16] To explore the reactivity of *N*-glycoside of enone sugar derivative **3o** as dienophile, optically active pure 2,6-dihydropyran-3-one **7** has been prepared through Diels–Alder cycloaddition with 2,3-dimethylbutadiene (Scheme 4).[9,17] As expected, the presence of chiral center at the anomeric position that induces asymmetry during the cycloaddition reaction led to preponderant formation of a diastereomer. The high diastereofacial selectivity in the cycloaddition provides reliable entry to optically active tetrahydrobenzopyranones possessing a number of contiguous stereogenic centers established in a desired manner. However, in the Diels–Alder cycloaddition with C5-substituted *N*-glycosides of enone sugars **3a** and **3n**, no desired cycloproducts were obtained.

In conclusion, we have developed a new protocol for stereoselective synthesis of *N*-glycosides of enone sugars with a

Scheme 4. Synthesis of 2,6-Dihydropyran-3-one 7



wide range of nitrogen nucleophiles utilizing $BF_3{\cdot}Et_2O$ as promoter. This method would allow the application of *N*-glycosides of enone sugar derivatives to expeditiously assemble a wide pool of biologically active derivatives through a straightforward manner. *N*-Glycosides of enone sugar derivatives also served as dienophiles that underwent Diels–Alder cycloaddition with excellent diastereofacial selectivity providing a landmark access to optically active bicyclic adducts, where the multiple stereogenic centered compound could serve as chiral building block for potential synthesis of complex natural products.

EXPERIMENTAL SECTION

General Methods. All solvents were distilled under nitrogen from the following drying agents immediately before use: tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl; dichloromethane and 1,2-dichloroethane were distilled from calcium hydride. $BF_3{\cdot}OEt_2$ was distilled from calcium hydride before use. 2,3,4,6-Tetra-*O*-acetyl-2-hydroxy-D-glucal (**1a**), 2,3,4-tri-*O*-acetyl-2-hydroxy-L-rhamnal (**1b**), and 2,3,4-tri-*O*-acetyl-2-hydroxy-D-xylal (**1c**) were prepared from L-fucose according to literature reported procedure.[18] The promoters were purchased from commercial suppliers and used without further purification. High resolution mass spectra (HRMS) were recorded on a Q-Tof premier mass spectrometer.

General Procedure for the Synthesis of *N*-Glycisides of Enone Sugars 3a–3o. To a solution of 2,3,4,6-tetra-*O*-acetyl-2-hydroxy-D-glucal **1a** (40 mg, 0.12 mmol) and nitrogen nucleophiles **2** (0.132 mmol, 1.1 equiv) in DCM (4.0 mL) was added $BF_3{\cdot}OEt_2$ (62 μL, 0.53 mmol, 4.4 equiv) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 20 min, subsequently quenched with saturated $NaHCO_3$ (3 mL), and extracted with DCM (3 × 10 mL). The extract was then washed with brine (2 × 20 mL), dried over Na_2SO_4, and concentrated. The residue was separated using column chromatography (silica gel, hexane/EtOAc system) to obtain pure *N*-glycosides of enone sugars **3a–3o**.

Spectroscopic Data for 3a–3o. *N-(p-Methylphenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3a**).* Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 30 mg, 75% yield: $[\alpha]^D_{21} = -9.16$ (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 6.95 (dd, *J* = 10.4, 2.0 Hz, 1H), 6.17 (dd, *J* = 10.8, 2.4 Hz, 1H), 5.46 (d, *J* = 7.2 Hz, 1H), 4.45–4.48 (m, 1H), 4.27 (dd, *J* = 11.6, 5.2 Hz, 1H), 4.05 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.43 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.8, 170.6, 148.2, 144.1, 137.4, 129.7, 126.6, 80.7, 68.4, 63.8, 21.6, 20.7; IR ($CHCl_3$) 3429, 1739, 1701, 1327, 1153, 1041, 976 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{17}NO_6SNa$ 362.0674, found 362.0681.

*N-(p-Nitrophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3b**).* Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 25 mg, 56% yield: $[\alpha]^D_{21} = -7.80$ (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.39 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 2H), 6.99 (dd, *J*

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= 10.4, 2.8 Hz, 1H), 6.24 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.80 (br, 1H), 5.65 (s, 1H), 4.56−4.60 (m, 1H), 4.41 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.22 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.2, 170.4, 147.7, 145.4, 128.5, 126.6, 124.4, 80.0, 70.0, 63.3, 30.9, 20.7; IR ($CHCl_3$) 3422, 1643, 1350, 1169, 1042, 945 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{14}N_2O_8SNa$ 393.0369, found 393.0370.

N-(o-Nitrophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3c**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 37 mg, 83% yield: $[\alpha]^D_{21}$ = −6.35 (*c* 0.4 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.21 (d, *J* = 10.0 Hz, 1H), 7.91 (d, *J* = 10.0 Hz, 1H), 7.78−7.82 (m, 2H), 7.00 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.44 (d, *J* = 7.2 Hz, 1H), 6.24 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.58 (d, *J* = 8.4 Hz, 1H), 4.55−4.58 (m, 1H), 4.25 (dd, *J* = 12.0, 5.2 Hz, 1H), 4.05 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.7, 170.5, 163.3, 147.9, 131.8, 129.5, 126.6, 114.3, 80.6, 68.7, 63.8, 55.7, 20.7; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_8S$ 371.0549, found 371.0529.

N-(p-Chlorophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3d**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 37 mg, 86% yield: $[\alpha]^D_{21}$ = −45.0 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 6.97 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.21 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.53 (d, *J* = 7.2 Hz, 1H), 4.52−4.55 (m, 1H), 4.34 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.16 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.5, 170.5, 147.8, 139.7, 139.0, 129.4, 128.7, 126.7, 80.3, 69.2, 63.6, 20.7; IR ($CHCl_3$) 3020, 1744, 1701, 1215, 1088 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{14}NO_6SClNa$ 382.0128, found 382.0125.

N-(p-Fluorophenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3e**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 31 mg, 76% yield: $[\alpha]^D_{21}$ = −17.0 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94−7.97 (m, 2H), 7.21 (t, *J* = 8.4 Hz, 2H), 6.97 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.20 (dd, *J* = 10.4, 2.4 Hz, 1H), 5.52 (d, *J* = 7.2 Hz, 1H), 4.50−4.54 (m, 1H), 4.33 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.14 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.6, 170.5, 147.9, 140.4, 130.1, 130.0, 126.6, 116.8, 116.3, 80.4, 69.0, 63.6, 20.7; IR ($CHCl_3$) 3429, 1740, 1697, 1339, 1157, 1042, 841 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{14}NO_6SFNa$ 366.0424, found 366.0415.

N-(p-Methoxyphenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3f**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 31 mg, 73% yield: $[\alpha]^D_{21}$ = −28 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (d, *J* = 9.0 Hz, 2H), 6.90−7.02 (m, 3H), 6.21 (dd, *J* = 10.5, 2.4 Hz, 1H), 5.48−5.52 (m, 2H), 4.53−4.56 (m, 1H), 4.36 (dd, *J* = 11.7, 5.1 Hz, 1H), 4.14 (dd, *J* = 11.7, 4.5 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.2, 170.4, 147.7, 145.4, 128.5, 126.6, 124.4, 80.0, 70.0, 63.3, 30.9, 20.7; IR ($CHCl_3$) 3422, 1728, 1643, 1339, 1157, 1034 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{17}NO_7SNa$ 378.0623, found 378.0632.

N-(Phenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3g**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 17 mg, 44% yield: $[\alpha]^D_{21}$ = −9.16 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.94 (d, *J* = 4.0 Hz, 2H), 7.54−7.63 (m, 3H), 6.95 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.19 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.69 (d, *J* = 6.8 Hz, 1H), 4.47−4.49 (m, 1H), 4.31 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.09 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.6, 170.5, 147.9, 140.4, 133.2, 129.1, 127.2, 126.6, 80.5, 68.8, 63.7, 20.7; IR ($CHCl_3$) 3429, 1740, 1701, 1450, 1165, 1042 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{15}NO_6SNa$ 348.0518, found 348.0514.

N-(Methylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3h**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 21 mg, 68% yield: $[\alpha]^D_{21}$ = −11.0 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.02 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.27 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.63 (d, *J* = 6.8 Hz, 1H), 5.51 (d, *J* = 6.0 Hz, 1H), 4.80−4.84 (m, 1H), 4.49 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.35 (dd, *J* = 12.0, 4.4 Hz, 1H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.8, 170.5, 147.4, 126.8, 80.0, 70.1, 63.5, 43.3, 20.7; IR ($CHCl_3$) 3418, 1732, 1697, 1327, 1153, 1042, 976 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_9H_{13}NO_6SNa$ 286.0361, found 286.0360.

N-(2′,2′,2′-Trichloroethylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3i**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 32 mg, 71% yield: $[\alpha]^D_{21}$ = −27.7 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.05 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.29 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.66 (d, *J* = 6.8 Hz, 1H), 4.85−4.90 (m, 1H), 4.67−4.77 (m, 1H), 4.51 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.33 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 187.5, 170.5, 147.8, 126.6, 80.2, 78.8, 73.3, 70.5, 63.5, 20.8; IR ($CHCl_3$) 3163, 1732, 1701, 1377, 1188, 1045, 961 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_{12}NO_6SCl_3Na$ 401.9349, found 401.9350.

N-(Benzyloxycarbonylamino)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3j**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 21 mg, 54% yield: $[\alpha]^D_{21}$ = −37.0 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.37 (m, 5H), 6.99 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.25 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.71 (d, *J* = 8.0 Hz, 1H), 5.15 (s, 2H), 4.75−4.79 (m, 1H), 4.51 (dd, *J* = 12.0, 5.2 Hz, 1H), 4.27 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.2, 170.6, 147.5, 135.6, 128.6, 128.4, 128.3, 127.6, 127.1, 78.6, 70.1, 67.7, 63.9, 20.8; IR ($CHCl_3$) 3418, 1732, 1697, 1369, 1169, 1042, 988 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{17}NO_6Na$ 342.0954, found 342.0959.

N-(((9H-Fluoren-9-yl)methoxy)carbonylamino)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3k**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 22 mg, 46% yield: $[\alpha]^D_{21}$ = −9.56 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.59 (d, *J* = 4.4 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 6.99 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.25 (dd, *J* = 10.4, 2.0 Hz, 1H), 5.69 (d, *J* = 6.8 Hz, 1H), 4.75−4.82 (m, 1H), 4.47 (d, *J* = 6.8 Hz, 1H), 4.32 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.24 (dd, *J* = 12.0, 4.0 Hz, 1H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.2, 170.6, 147.5, 143.6, 141.3, 127.8, 127.1, 125.1, 125.0, 120.0, 78.6, 67.6, 63.9, 47.0, 20.8; IR ($CHCl_3$) 3418, 1694, 1636, 1450, 1161 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{21}NO_6Na$ 430.1267, found 430.1270.

N-(Ethoxycarbonylamino)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3l**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 17 mg, 55% yield: $[\alpha]^D_{21}$ = −20.0 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (dd, *J* = 10.4, 2. 4 Hz, 1H), 6.27 (dd, *J* = 10.4, 2.8 Hz, 1H), 5.68 (d, *J* = 8.0 Hz, 1H), 4.76−4.79 (m, 1H), 4.51 (dd, *J* = 12.0, 4.8 Hz, 1H), 4.34 (dd, *J* = 12.0, 4.0 Hz, 1H), 4.15−4.28 (m, 2H), 2.11 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.7, 170.6, 155.6, 147.5, 127.7, 127.1, 78.6, 73.1, 64.6, 63.9, 61.9, 20.8, 14.2; IR ($CHCl_3$) 2924, 1736, 1373, 1242, 1034 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{15}NO_6Na$ 280.0797, found 280.0798.

N-(N-Allyl-p-methylphenylsulfonamido)-6-O-acetyl-3,4-dideoxy-α-D-glycero-hex-3-eno-pyranoside-2-ulose (**3m**). Following the general procedure, the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 19 mg, 42% yield: $[\alpha]^D_{21}$ = −64.4 (*c* 0.5 $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 6.96 (dd, *J* = 10.4, 2.4 Hz, 1H), 6.29 (dd, *J* = 10.4, 2.0 Hz, 1H),

5.58−5.68 (m, 1H), 5.13 (dd, J = 17.2, 1.6 Hz, 1H), 5.05 (dd, J = 14.4, 1.6 Hz, 1H), 4.82−4.85 (m, 1H), 4.46 (dd, J = 12.0, 5.2 Hz, 1H), 4.25 (dd, J = 12.0, 4.0 Hz, 1H), 3.79−3.86 (m, 1H), 2.43 (s, 3H), 2.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.8, 170.3, 146.4, 143.9, 136.5, 133.2, 129.5, 128.3, 127.9, 118.8, 84.4, 70.4, 64.3, 49.1, 21.6, 20.8; IR ($CHCl_3$) 1730, 1705, 1311, 1183, 1045, 956 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{21}NO_6SNa$ 402.0987, found 402.0988.

*N-(p-Methylphenylsulfonamido)-6-methyl-3,4-dideoxy-D-rhamnal-hex-3-eno-pyranoside-2-ulose (**3n** and **3nb**).* Compounds **3n** (gummy liquid, 48 mg, 68% yield) and **3nb** (gummy liquid, 13 mg, 19% yield) were prepared according to the general procedure from 2,3,4-tri-*O*-acetyl-2-hydroxy-L-rhamnal **1b** (68 mg, 0.25 mmol), *p*-toluenesulfonamide **2a** (47 mg, 0.275 mmol, 1.1 equiv) and $BF_3{\cdot}OEt_2$ (138 μL, 1.1 mmol, 4.4 equiv), and the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1). **Data for 3n**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.91 (dd, J = 10.4, 1.6 Hz, 1H), 6.03 (d, J = 10.4 Hz, 1H), 5.90 (br, 1H), 5.36 (d, J = 8.0 Hz, 1H), 4.34−4.38 (m, 1H), 2.43 (s, 3H), 1.24 (d, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.3, 153.4, 143.9, 137.6, 129.6, 127.3, 124.3, 80.2, 65.8, 21.6, 18.6; IR ($CHCl_3$) 3023, 1746, 1715, 1334, 1176, 1042, 954 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{15}NO_4SNa$ 304.0619, found 304.0614. **Data for 3nb**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 6.90 (dd, J = 10.0, 1.6 Hz, 1H), 6.10 (dd, J = 10.0, 2.4 Hz, 1H), 5.92 (d, J = 6.0 Hz, 1H), 5.26 (dd, J = 6.0, 1.6 Hz, 1H), 4.63−4.69 (m, 1H), 2.41 (s, 3H), 1.32 (d, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 189.3, 153.4, 143.7, 138.1, 129.5, 127.2, 125.2, 82.1, 70.9, 21.5, 20.3; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{15}NO_4SNa$ 304.0619, found 304.0617.

*(S)-4-Methyl-N-(3-oxo-3,6-dihydro-2H-pyran-2-yl)-benzenesulfonamide (**3o**).* Compound **3o** was prepared according to the general procedure from 2,3,4-tri-*O*-acetyl-2-hydroxy-D-xylal **1c** (64.5 mg, 0.25 mmol), *p*-toluenesulfonamide **2a** (47 mg, 0.275 mmol, 1.1 equiv) and $BF_3{\cdot}OEt_2$ (138 μL, 1.1 mmol, 4.4 equiv), and the crude product was purified over a silica gel column using a hexane/EtOAc system (8:1 to 4:1) to give a gummy liquid, 54 mg, 78% yield: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.90 (dq, J = 10.4, 2.4 Hz, 1H), 6.10 (dq, J = 10.4, 1.6 Hz, 1H), 5.87 (d, J = 6.4 Hz, 1H), 5.27 (dd, J = 6.4, 1.6 Hz, 1H), 4.39−4.54 (m, 2H), 2.42 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 188.7, 149.2, 143.9, 137.8, 129.7, 127.1, 125.6, 82.3, 63.9, 21.6; IR ($CHCl_3$): 3033, 1748, 1356, 1201, 1056 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{13}H_{15}NO_4SNa$ 304.0619, found 304.0617.

Synthetic Procedure and Characterization for 5 and 6. To a solution of compound **3a** (50 mg, 0.15 mmol) in dry MeOH (1 mL) was added $CeCl_3{\cdot}7H_2O$ (15 mg, 0.04 mmol). After10 min of stirring at room temperature, the solution was cooled to 0 °C, and $NaBH_4$ (6 mg, 0.15 mmol) was added with stirring for 30 min. After the workup, the crude syrup, which showed a main product by TLC (R_f = 0.3, DCM/MeOH = 10:1), was purified by flash chromatography (DCM/MeOH = 10:1) to afford the corresponding alcohol **5** (40 mg, yield: 84%). Compound **5** (40 mg, 0.12 mmol) was dissolved in a mixture of *tert*-butyl alcohol (250 μL) and water (25 μL), and *N*-methylmorpholine *N*-oxide was added (12 mg, 0.12 mmol). The resulting solution, cooled to 0 °C, was treated with 2% (w/v) OsO_4 in *tert*-butyl alcohol (10 μL). After 16 h of stirring at room temperature, the mixture was diluted with *tert*-butyl alcohol and stirred with $NaHSO_3$. After filtration, the residue was washed with *tert*-butyl alcohol, and the filtrate was concentrated to give the 8:1 mixture of isomers, determined from the ^{1}H NMR spectrum. The crude syrup was purified by flash chromatography (DCM/MeOH = 10:1) to afford the pure major isomer **6** (14 mg, yield of pure **6**: 64%). **Data for 5**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 6.95 (dq, J = 10.4, 2.4 Hz, 1H), 6.17 (dq, J = 10.4, 0.8 Hz, 1H), 5.30−5.33 (m, 1H), 4.19−4.21 (m, 1H), 4.09−4.13 (m, 2H), 4.03 (dd, J = 12.0, 4.0 Hz, 1H), 2.42 (s, 3H), 2.08 (s, 3H), 1.67 (br, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 143.6, 138.5, 129.5, 128.8, 127.9, 127.2, 78.7, 70.6, 64.4, 63.0, 21.6, 20.8; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{19}NO_6SNa$ 364.0831, found 364.0833. **Data for 6**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.0 Hz, 2H), 6.78 (d, J = 9.2 Hz, 1H), 5.37 (t, J = 1.6 Hz, 1H), 4.33 (d, J = 11.6 Hz, 1H), 4.27 (d, J = 0.8 Hz, 1H), 3.76 (t, J = 2.4 Hz, 1H), 3.36−3.41 (m, 3H), 3.23 (br, 3H), 2.43 (s, 3H), 2.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 143.7, 138.5, 129.6, 129.5, 127.3, 127.2, 81.3, 72.0, 66.5, 65.8, 62.6, 29.7, 21.5, 20.8; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{15}H_{21}NO_8SNa$ 398.0886, found 398.0884.

Synthetic Procedure and Characterization for Cycloadducts 7. The compound **3o** (50 mg, 0.18 mmol) was weighed into a vial equipped with a magnetic stirrer and septum seal. The anhydrous solvent (0.5 mL) was added, and the vial was flushed with dry argon and sealed. The mixture was cooled to −18 °C, and $BF_3{\cdot}OEt_2$ (27 mg, 0.18 mmol) was added. The mixture was stirred at −18 °C for 5 min, and the flask was placed in a bath at the temperature desired for the cycloaddition. A solution of the 2,3-dimethyl-1,3-butadiene (26 mg, 0.32 mmol) in the dry solvent (0.6 mL) was then slowly injected, and the temperature was maintained for 20 min. The reaction mixture was diluted with ethyl ether (10 mL), except for the reaction in CH_2Cl_2 in which case the same solvent was used for the dilution. The resulting solution was washed with satd aq $NaHCO_3$ and satd aq NaCl, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (10−30% EtOAc in hexane) to afford the pure cycloadducts **7** (41 mg, yield of pure **7**, 67%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 5.97 (d, J = 8.0 Hz, 1H), 5.13 (d, J = 6.8 Hz, 1H), 4.10 (dd, J = 12.0, 2.4 Hz, 1H), 3.77 (d, J = 12.0 Hz, 1H), 2.97 (t, J = 6.4 Hz, 1H), 2.44−2.48 (m, 2H), 2.41 (s, 3H), 2.44−2.48 (m, 2H), 2.01−2.14 (m, 3H), 1.79 (dd, J = 12.8, 4.8 Hz, 1H), 1.64 (s, 3H), 1.55 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.2, 143.5, 138.3, 129.5, 127.0, 123.4, 122.3, 83.9, 69.4, 47.3, 39.3, 31.3, 29.0, 21.5, 19.1, 18.6; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{18}H_{23}NO_4SNa$ 372.1245, found 372.1241.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xuewei@ntu.edu.sg.

Notes

The authors declare no competing financial interest.

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