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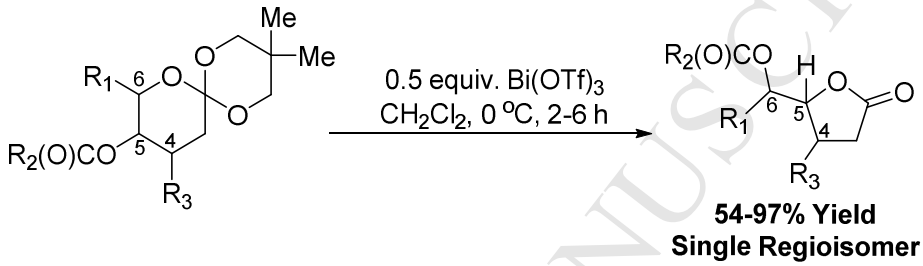

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A Highly Selective $Bi(OTf)_3$ Mediated Fragmentation-Contraction of δ-Ortholactones. A Facile Route to Functionalized γ-Lactones.

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ABSTRACT

A very selective method for the formation of γ-lactones from pyranyl ortholactones has been developed which occurs *via* a fragmentation-acetate migration-ring contraction process. The reaction is very functional group tolerant, providing functionalized γ-lactones as a single isomeric product following the ring contraction. Mechanistic studies indicate the reaction is mediated by triflic acid liberated from $Bi(OTf)_3$ in a slow and controlled manner providing excellent chemo and regioselectivity. We propose the triflic acid acts as both a proton and a nucleophile source with triflate anion mediating the fragmentation process.

1. Introduction

γ-Lactones are ubiquitous in nature appearing as a key feature in many complex molecules.[1] These structures range from simple alkyl substituted compounds, found in many food and beverage sources, to carbohydrate based furanosyl lactones and complex sesquiterpene structures (Figure 1). Alongside their prevalence in nature, they have been used as intermediates in many total syntheses, especially those derived from chiral pool material, and can be used to form nucleosides and nucleoside analogs for the treatment of various viral infections. As such, new methods for their synthesis that are highly chemo, regio and stereoselective are required for the synthetic and medicinal chemistry community.

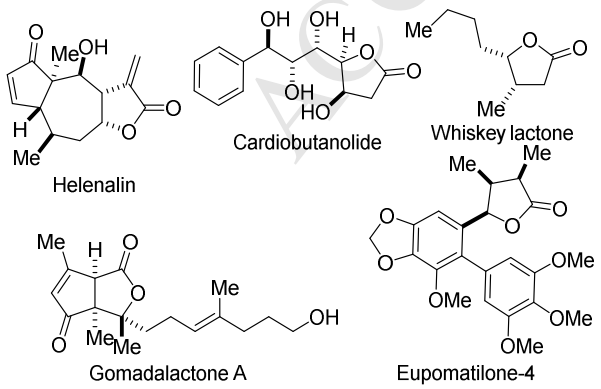
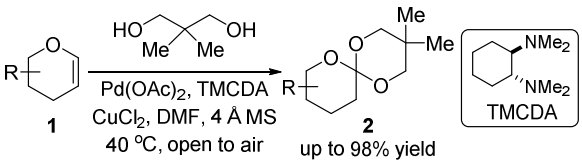


Figure 1: Examples of naturally occurring γ-lactones

We recently reported a new oxidative approach to ortholactones, a cyclic class of orthoester, utilizing a palladium/copper co-catalytic system with atmospheric air as the terminal oxidant (Scheme 1).[2] This Wacker-type approach allowed us to access highly functionalized ortholactones and is especially efficient at forming the spirocyclic variant due to its enhanced stability. The facile synthesis piqued our interest in to these unique compounds and we began to investigate their chemistry. Our initial aim was to utilize the ortholactonization as both an oxidation and protection step, allowing us to perform a wide range of chemistry prior to the deprotection step. Herein, we report the utilization of these ortholactones in multistep synthetic pathways and their subsequent reactions with Lewis and Brønsted acids.

Scheme 1: Formation of Ortholactones

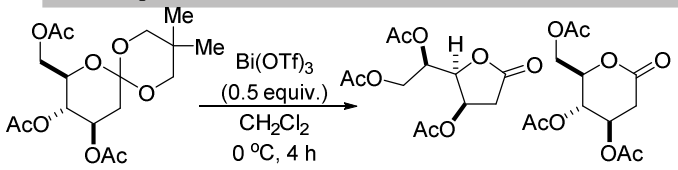
Previous work: Oxidative synthesis of ortholactones (Ref. 2)



2. Results and Discussion

We began examining the reactivity of ortholactone **2a** towards Lewis acids and discovered a facile fragmentation-acetate migration-ring contraction reaction occurs to form γ-lactone **3a** with $Bi(OTf)_3$ (Table 1).[3] The ring contraction of δ-lactones to γ-lactones is known to occur with unprotected alcohols under acidic conditions.[4] This process can also occur during protecting group manipulations including: silyl deprotections,[5] silylations utilizing silyl triflates,[6] and with concomitant migration of ketal

Table 1: Optimization Studies



2a **3a**, 80% **4a**, n.d.

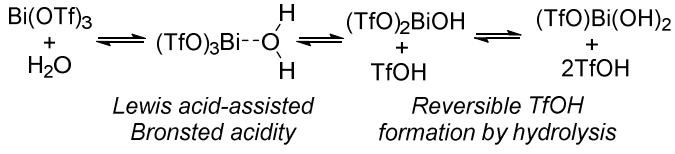
entry[a]	difference from optimized conditions	**3a**:**4a**[b]	total yield[c]
1	No Change	100:0	80%
2	$BF_3.OEt_2$ (1 equiv.) instead of $Bi(OTf)_3$	-	n.r.
3	1.0 equiv. $Bi(OTf)_3$	100:0	80%
4	0.25 equiv. $Bi(OTf)_3$	100:0	40%
5	$Sc(OTf)_3$ (1 equiv.) instead of $Bi(OTf)_3$	-	n.r.
6	$In(OTf)_3$ (1 equiv.) instead of $Bi(OTf)_3$	100:0	40%
7	DTBM-Py (1 equiv) added	-	n.r.
8	DTBM-Py (0.25 equiv) added, 18 h	100:0	26%
9	$BiBr_3$ (0.5 equiv.) instead of $Bi(OTf)_3$	-	n.r.
10	Run in glovebox	-	n.r.
11	TfOH (0.5 equiv.) instead of $Bi(OTf)_3$	-	n.r.
12	TfOH (1.5 equiv.) instead of $Bi(OTf)_3$	-	Complex
13	CSA (1 equiv.) instead of $Bi(OTf)_3$	100:0	55%
14	CSA (0.5 equiv.) instead of $Bi(OTf)_3$	100:0	33%
15	MeCN instead of CH_2Cl_2 as solvent	0:100	50%
16	Reaction run on 1.34 mmol scale	100:0	55%

[a] Typical reaction conditions: **1a** (0.05 mmol), $Bi(OTf)_3$ (0.025 mmol), anhydrous CH_2Cl_2, 0 °C; [b] **3a**:**4a** ratio determined by ^1H NMR of the crude reaction; [c] Isolated yield of lactone products.

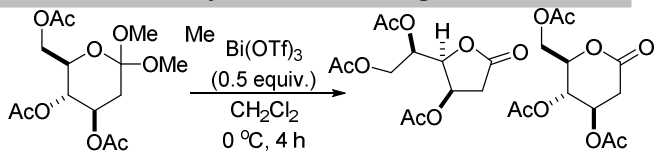
groups.[7] To our knowledge, there are no reports of a fragmentation-acetate migration-ring contraction strategy.

Our optimized conditions used 0.5 equivalents of $Bi(OTf)_3$ in freshly distilled methylene chloride at 0 °C to provide **3a** in 80% yield with no δ-lactone isomer **4a** observed after 4 hours (entry 1). We examined a range of Lewis acids and discovered that spirocyclic ortholactone **2a** is stable to a number of Lewis acids, such as $BF_3.OEt_2$ (entry 2) with no reaction observed and complete recovery of **2a**. We investigated the stoichiometry of $Bi(OTf)_3$ used and found that with 0.25 equivalents the reaction became very sluggish and with one equivalent the reaction occurs with equal efficiency (entries 3 & 4). We next examined alternative triflate Lewis acids with $Sc(OTf)_3$ providing no reaction, whereas, $In(OTf)_3$ afforded 40% yield, exclusively as the γ-lactone **3a**. Many triflate salt catalyzed and mediated processes have been shown to be Brønsted acid promoted reactions through the formation of TfOH from the Lewis acid with adventitious water in the reaction. This can occur in one of two modes: hydrolysis of the metal salt producing a small and controlled amount of TfOH;[8] or through a Lewis acid mediated acidification of the water molecule in a process termed "Lewis acid assisted Brønsted acidity" (LBA) (Scheme 2).[9] A clear reactivity profile observed between different triflate salts: Bi>In>Sc (entries 1, 5 & 6) which also corresponds to the hydrolysis constants (pK_h). Bismuth (1.09) hydrolyzes far faster

Scheme 2: Acidic Pathways for $Bi(OTf)_3$ with H_2O



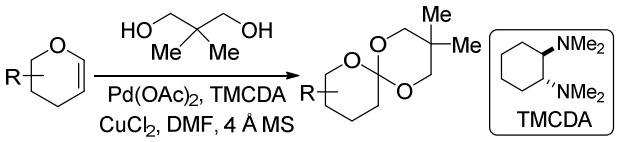
Scheme 3: Dimethyl Ortholactone Fragmentation



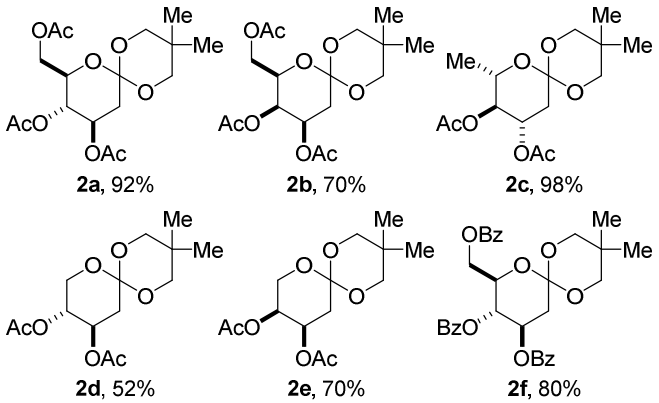
5 **3a**, 50% **4a**, n.d.

than indium (4.00) and scandium (4.30) therefore any adventitious water would provide triflic acid at a much higher active concentration.[10] To confirm that the reaction was Brønsted acid mediated, we added 2,6-di-tert-butyl-4-methylpyridine(DTBM-Py) as a proton sink. When one equivalent was added, the reaction was completely inhibited, however when 0.25 equivalents were used, an initiation period was seen with no reaction observed for several hours,followed by the formation of product **3a** (entries 8 & 9). To examine whether this reaction was a purely protic acid mediated process, we examined the use of $BiBr_3$. Evans and Hinkle demonstrated that $BiBr_3$ (and $Bi(NO_3)_3 \cdot 5H_2O$) were mild and controlled sources of protic acid to promote a variety of reactions.[11] The pK_a's of these two acids are very similar (0.3 [TfOH] and 0.9 [HBr] in DMSO),[12] therefore, if the BiX_3 salt was only acting as a proton source, or a Lewis acid, similar results should be observed regardless of the counterion. When $BiBr_3$ was used (entry 9), no reaction was observed, suggesting the triflate anion plays a key role. All of these reactions were conducted using oven dried glassware under an argon atmosphere with $Bi(OTf)_3$ stored in a desiccator. When the reaction was performed in a glovebox with freshly purchased $Bi(OTf)_3$ no reaction was observed (entry 10). This indicates that exogenous water is required above the levels present in commercially available sources of $Bi(OTf)_3$.[13] Neat triflic acid was also used in stoichiometric and substoichiometric quantities (entries 11 & 12). No reaction was observed when 0.5 equivalents of TfOH was used, whereas, 1.5 equivalents provided trace amounts of **3a** as part of an intractable mixture of degradation products. Replacing $Bi(OTf)_3$ with camphorsulfonic acid (CSA) also provided **3a** selectively, albeit in reduced yield (entries 13 & 14). CSA (pK_a 5.6)[14] is over 10^5-fold less acidic than TfOH suggesting the reactivity is a function of the sulfonic acid group rather than a unique property of $Bi(OTf)_3$/TfOH.[15] Finally, when the reaction was run in more Lewis basic solvent, such as MeCN, the fragmentation occurred, however, no ring contraction was observed with δ-lactone **4a** being formed in

Scheme 4: Carbohydrate Derived Ortholactones



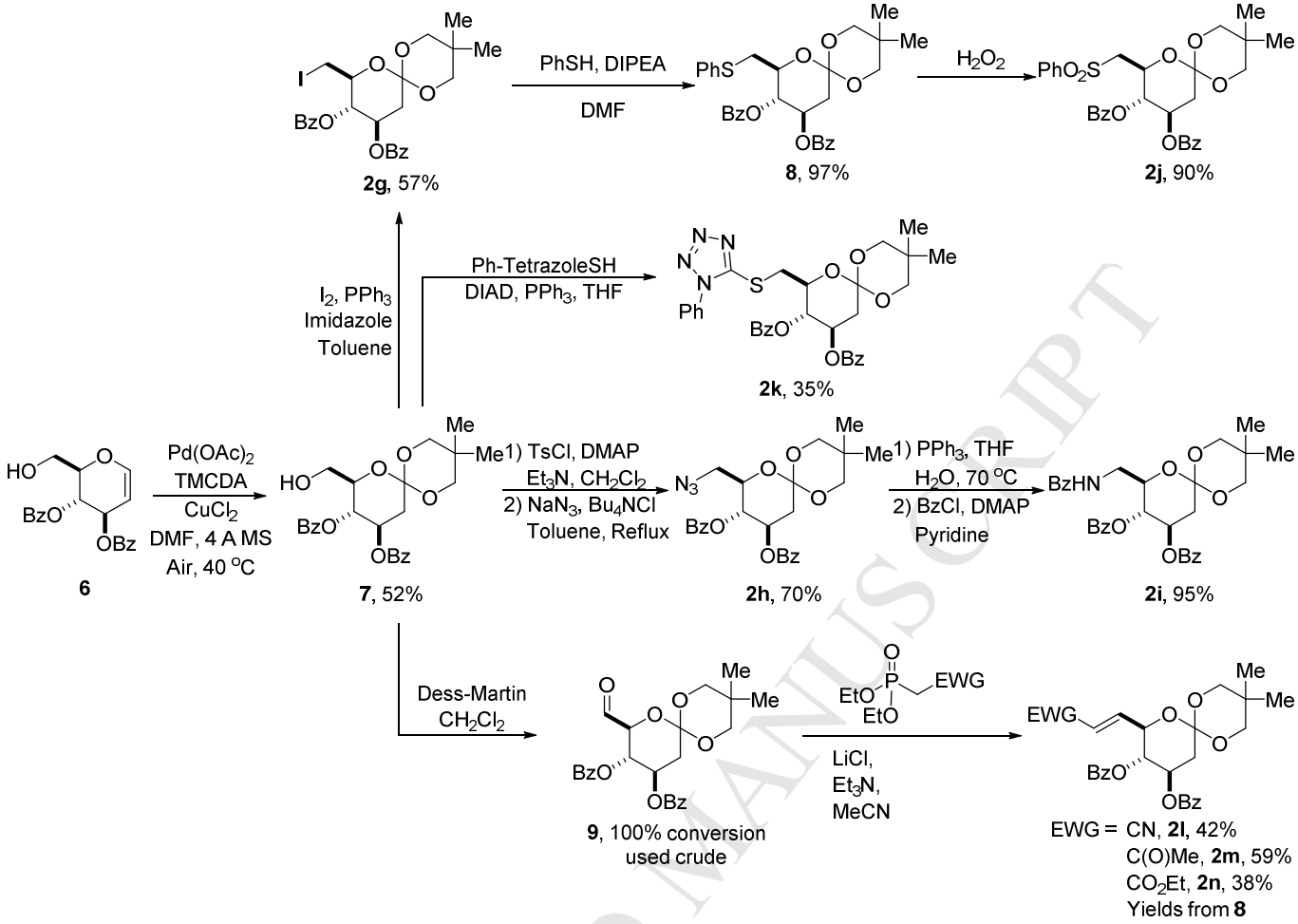
1 **2**



2a, 92% **2b**, 70% **2c**, 98%

2d, 52% **2e**, 70% **2f**, 80%

Scheme 5: Ortholactone derivatization

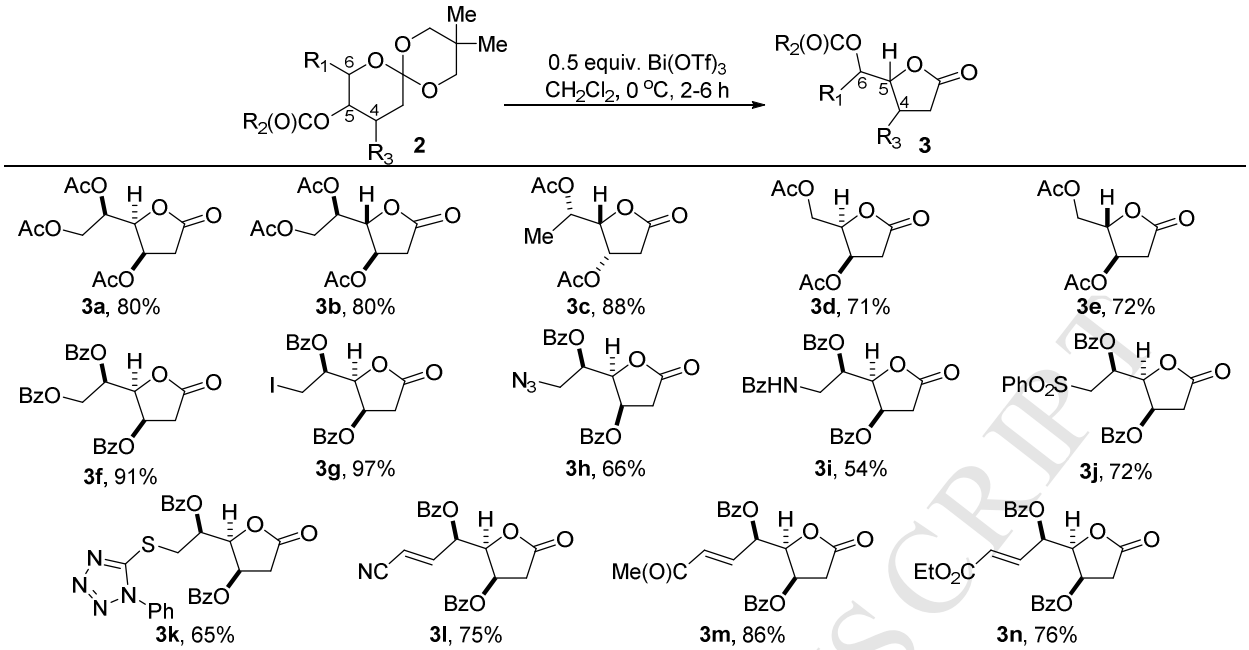


moderate yield (entry 16). These reactions could also be performed on larger, more synthetically useful scale, albeit with slightly reduced yield (entry 17). When ortholactone **2a** was replaced with its dimethoxy analog (**5**), **3a** was formed with complete selectivity, albeit in reduced yield demonstrating that the selectivity was not a function of the spirocyclic ortholactone (Scheme 3).

To further explore this reaction, we examined other ortholactone structures. Several were readily synthesized in a single step from commercially available or readily available carbohydrate glycal units. These dihydropyran structures could undergo an oxidative difunctionalization reaction using our previously disclosed palladium catalyzed aerobic oxidation reaction (Scheme 4). In this series, ortholactones derived from D-glucose (**2a**), D-galactose (**2b**), L-rhamnose (**2c**), D-xylose (**2d**) and L-arabinose (**2e**) could be formed in good to excellent yields. To explore the functional group tolerance further, we synthesized a series of substrates which included a range of functionality not present in simple carbohydrate derivatives (Scheme 5). We had previous reported the ortholactonization of primary alcohol **6**, which provided hydroxyl ortholactone **7** in 52% yield. Utilizing the versatility of this substrate, we derivatized **7** in to a wide array of ortholactone compounds which contained a myriad of functionality (Scheme 5). This included: iodination, using standard conditions, to provide iodide **2g**, which could in turn be converted to the corresponding sulfone **2j** through a substitution and subsequent oxidation of the corresponding sulfide **7**. The 5-phenyl tetrazole sulfide **2k**, was also synthesized from alcohol **7** through a Mitsubobu protocol. Nitrogen can be installed into the framework *via* tosylation of the alcohol followed by substitution with NaN_3 to afford azide **2h**. This azide (**2h**) can undergo a Staudinger reaction with PPh_3, with hydrolysis of the aza-phosphorane to afford the amine product. During the course of this reaction, partial benzoate migration occurs from the *C*-4 hydroxyl group to provide a mixture of benzoyl isomers. As a result, the crude mixture of isomers was treated with benzoyl chloride to provide the per-benzoylated amide **2i**. Alcohol **7** was also oxidized to the corresponding aldehyde **9**, which was used immediately in the subsequent Horner-Wadsworth-Emmons reaction to ensure no degradation or epimerization occurred. This aldehyde **9** was used to install a variety of α,β-unsaturated groups including nitrile **2l**, ketone **2m** and ethyl ester **2n** in good to moderate yields from **9**.

With a large number of substrates in hand (**2a-n**), we began subjecting them to the optimized reaction conditions outlined in Table 1 (Scheme 6). The reaction appears to be insensitive to the *C*-5 stereochemistry as both the glucose **2a** and galactose **2b** derived substrates reacted with equal efficiencies. Other carbohydrate derivatives also performed well with both 6-deoxyhexose **2c** and pentopyranose **2d-e** derivatives, derived from L-rhamnose, D-xylose and L-arabinose respectively, providing good to excellent yields. Replacing the acetate protecting groups with benzoate **2f** led to an even more efficient reaction with 91% isolated yield of γ-lactone **3f** obtained. We were able to introduce a wide range of functional groups into this scaffold at the *C*-6 position, all of which provided good to excellent yields of the corresponding γ-lactone products **3g-n**. These included: iodides **3g**; azides **23h**; amides **3i**; sulfones **3j** and tetrazole substituted sulfides **3k**. We also installed extended carbon chains at the *C*-6 with additional

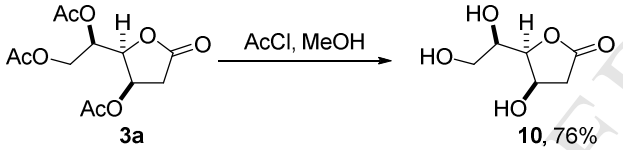
Scheme 6: Substrate Scope



Typical reaction conditions: Ortholactone (0.1 M in freshly distilled CH_2Cl_2), 0.5 equiv. of $Bi(OTf)_3$, under an argon atmosphere at 0 °C for 2-6 hours (see experimental section for specific details of each substrate).

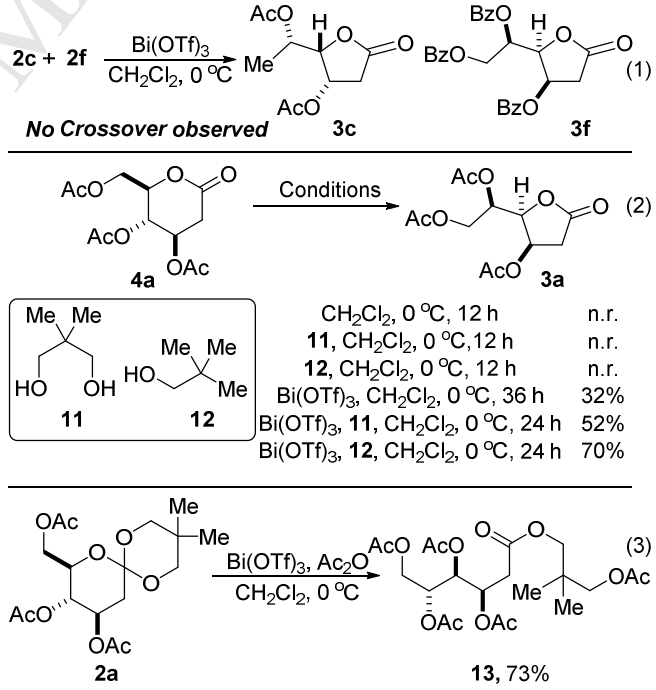
unsaturation forming nitrile **3l**, ketone **3m** and ester **3n** in good to excellent yields. All of these products were isolated as a single γ-lactone isomer with virtually no byproducts in a very efficient manner. The acetate protecting groups could be easily removed from **3a** using acidic methanol conditions providing 2-deoxy-D-gluclonic acid γ-lactone **10** in excellent yield (Scheme 7).

Scheme 7: Acetate Deprotection



We conducted several experiments to try and elucide the mechanistic pathways occurring (Scheme 8). To investigate whether the acetate migration was occurring *via* an inter or intramolecular process, we performed a crossover experiment (Eq. 1). The reaction of acetate **2c** and benzoate **2f** ortholactones was performed in the same reaction vessel and no crossover of acetate (or benzoate) groups to the alternate scaffold was observed suggesting the migration is intramolecular and not mediated by an exogenous acetate shuttle. When the reaction was followed by NMR, the ortholactone **2a** quickly fragments to the δ-lactone **4a** which then isomerizes to the γ-lactone product **3a**. As we identified the δ-lactone **4a** as an intermediate, we examined whether the ortholactone group, lost during the initial fragmentation, was mediating the ring contraction. (Eq. 2). δ-Lactone **4a** was found to be stable as a CH_2Cl_2 solution and in the presence of one equivalent of both diol **11** or *tert*-amyl alcohol **12**, with no ring contraction observed. When **4a** was subjected to 0.5 equivalents of $Bi(OTf)_3$ in the absence of alcohol **11** or **12**, ring contraction was observed, however, this occurred at a significantly slower rate than in the conversion of **2a** to **3a**. When diol **11** was introduced, isomerization did occur, however, this was also accompanied by significant acetate transfer to the diol alongside multiple other by-products. When *tert*-amyl alcohol **12** was utilized alongside $Bi(OTf)_3$, the efficiency of the reaction was increased compared to diol **11**. Finally, we attempted to trap any alcohol derived ester intermediate and performed the reaction in the presence of acetic anhydride which provided peracetylated ester **13** following triflate-acetate exchange. This strongly suggests the ring contraction is mediated by nucleophilic addition of an alcohol derived from the initial ortholactone fragmentation.

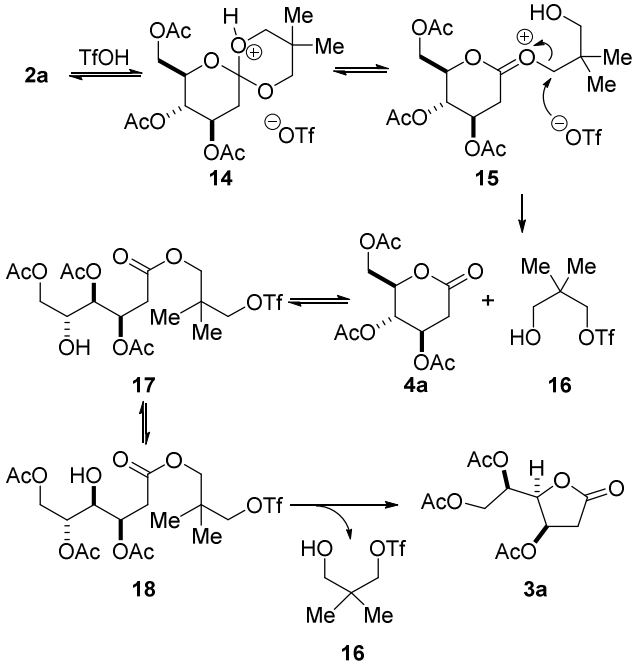
Scheme 8: Mechanistic Probes



By combining the data in Table 1 with the additional studies (Scheme 8), we can propose a plausible mechanism (Scheme 9). Initial protonation of the ortholactone **2a** is followed by ring opening to provide oxocarbenium ion **14**. The triflate anion can then act as a nucleophile to form δ-lactone **4a** and mono-triflated diol **16**. Although not generally regarded as a competent nucleophile, triflate has been shown to act as a nucleophile in many reactions.[16] The ring contraction proceeds by nucleophilic attack of **16** to provide ring opened ester **17** which undergoes acetate migration (**18**) and ring

closure to provide γ-lactone **3a**. Our mechanism also accounts for the stoichiometry of $Bi(OTf)_3$ required as one equivalent of triflic acid is consumed during the reaction. We therefore envisage that each $Bi(OTf)_3$ molecule provides two equivalents of TfOH.

Scheme 9: Proposed Mechanism



3. Conclusions

In conclusion, we have developed a new method for the selective formation of functionalized γ-lactones from easily synthesized ortholactones. Our studies have identified key mechanistic details of the reaction including: that $Bi(OTf)_3$ is a source of TfOH; the triflate anion acts as a nucleophile to facilitate fragmentation; the mono-triflated diol facilitates the ring contraction and that the acetate migration is an intramolecular event with no crossover seen in competition experiments. This report highlights the stability and synthetic utility of ortholactones alongside their highly chemoselective reactivity towards sulfonic acids.

4. Experimental section

4.1. General Information

All reactions were carried out in oven-dried glassware with magnetic stirring. All reactions were monitored by thin layer chromatography (TLC) using Merck TLC silica gel 60 sheets, which were visualized with ultraviolet light and then developed with iodine and basic potassium permanganate solution. Flash chromatography was performed on Sigma-Aldrich silica gel 60 as the stationary phase and the solvents employed were of analytical grade. ^{1}H NMR spectra were recorded on a Bruker AVX400 (400 MHz) spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$) taken as 7.26 ppm, integration, multiplicity (s = singlet; d = doublet; t = triplet; dd = double doublets m = multiplet), and coupling constant (Hz). ^{13}C NMR spectra were recorded on a Bruker AVX400 (100 MHz) spectrometer. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Infrared spectra were recorded on a Perkin Elmer RX I FT-IR spectrometer as liquid films or as dilute solutions between two KBr discs. Mass spectra were recorded on either a Micromass GCT Premier or a Waters Micromass LCT Premier spectrometer using electron ionization (EI) at 70 eV or electrospray (ES) techniques, respectively. Unless stated otherwise, all commercially available reagents were used as received.

*4.2. General procedure for the formation of **2a-e** and **6**.*[2]

To a 10 mL flask containing a stirrer bar was added dihydropyran (1 equiv), $Pd(OAc)_2$ (8 mol%), *N,N,N',N'*-tetramethylcyclohexyl-1,2-amine (TMCDA) (8 mol%), $CuCl_2$ (20 mol%), 5Å molecular sieves, 2,2-dimethyl-propan-1,3-diol (10 equiv.) and anhydrous DMF (0.367M). The flask was fitted with a reflux condenser fitted with a drying tube ($CaCl_2$) and heated to 40 °C open to the atmosphere with vigorous stirring until complete as monitored by TLC. The suspension was then cooled to rt., diluted with Et_2O, washed with H_2O, dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography on Et_3N treated SiO_2. Compounds **2a-f** and **6** were synthesized *via* this procedure and full characterization of ortholactones **2a-d**, **2f** and **6** has been previously reported.[2a]

*4.2.1. (9S,10R)-Acetic acid 10-acetoxy-3,3-dimethyl-1,5,7-trioxa-spiro[5.5]undec-9-yl ester **2e***

Compound **2e** was prepared according to *general procedure 4.2* from acetic acid (3*R*,4*S*)-3-acetoxy-3,4-dihydro-2H-pyran-4-yl ester **1e** (100 mg, 0.500 mmol), $Pd(OAc)_2$ (8.9 mg, 0.040 mmol, 8 mol%), TMCDA (6.8 mg, 0.040 mmol 8 mol%), $CuCl_2$ (13.5 mg, 0.100 mmol, 20 mol%), 5Å molecular sieves (100 mg), 2,2-dimethylpropan-1,3-diol (520 mg, 5.00 mmol, 10 equiv.) and DMF (1.4 mL, 0.37 M). After 18 hours the reaction mixture was diluted with Et_2O (50 mL), washed with $NaHCO_3$ (100 mL), Brine (100 mL), dried over $MgSO_4$, concentrated *in vacuo.* The crude product was purified by column chromatography on deactivated SiO_2 (EtOAc-Hexane 1:7) to afford the title compound **2e** (105 mg, 70%) as a colorless oil.

R_f = 0.51 (5:1/ Hexane: EtOAc). ^{1}H NMR (400 NMR, $CDCl_3$) δ 5.24 (1H, ddd, *J* = 9.6, 7.8, 3.0 Hz), 5.20-5.17 (1H, m), 4.02 (1H, dd, *J* = 10.8, 0.5 Hz), 3.89 (1H, dd, *J* = 12.8, 2.0 Hz), 3.76 (1H, dd, *J* = 13.0, 1.5 Hz), 3.64 (1H, dd, *J* = 10.6, 0.5 Hz), 2.14 (3H, s), 2.11-2.09 (1H, m), 2.09-2.07 (1H, m), 2.01 (3H, s), 1.19 (3H, s), 0.77 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.0, 109.3, 70.2, 69.1, 67.3, 66.8, 63.2, 34.6, 29.4, 22.7, 21.9, 21.0, 20.9. IR ν_{max} (Thin film) 3434, 3319, 2950, 2912, 1745, 1665, 1619, 1471, 1369, 1235, 1210, 1065. HRMS (ES^+) Calc. for $C_{14}H_{22}O_7Na$ $[M+Na]^+$ 325.1263; Found 325.1268.

*4.3. Synthesis of Functionalized Non-carbohydrate Ortholactone substrates **2f-n***

*4.3.1. (8S,9S,10R)- Benzoic acid 10-benzoyloxy-8-iodomethyl-3,3-dimethyl-1,5,7-trioxa-spiro[5.5] undec-9-yl ester **2g***

To a stirred solution of **6** (30.0 mg, 65.8 mmol) in toluene (0.54 mL, 0.12 M), at room temperature under argon was added successively Imidazole (13.4 mg, 197 mmol, 3 equiv.), Triphenylphosphine (25.9 mg, 98.7 mmol, 1.5 equiv.) and iodine (23.4, 92.1 mmol, 1.4 equiv.), and the resulting solution stirred in the absence of light for 24 hours, diluted with EtOAc (50 mL), washed successively with H_2O (50 mL), $NaHCO_3$ (50 mL) and Brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash column chromatography elution 20:1/ hexane EtOAc to yield the title compound **2g** as a pale yellow oil (26.0 mg, 57 %).[17]

R_f = 0.25 (10:1/ Hexane: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.88 (4H, m), 7.63-7.32 (6H, m), 5.65 (1H, ddd, *J* = 11.8, 9.6, 5.3 Hz), 5.27 (1H, dd, *J* = 9.5, 9.5 Hz), 4.19 (1H, d, *J* = 11.0 Hz), 4.04 (1H, d, *J* = 11.0 Hz), 3.93 (1H, ddd, *J* = 10.3,

10.3, 2.5 Hz), 3.43-3.35 (3H, m), 3.31 (1H, dd, *J* = 10.5, 10.5 Hz), 2.66 (1H, dd, *J* = 12.5, 5.5 Hz), 2.01 (1H, dd, *J* = 12.6, 11.8 Hz), 1.24 (3H, s), 0.83 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.5, 133.5, 133.1, 129.8, 129.7, 129.4, 128.9, 128.5, 128.3, 109.1, 73.8, 71.8, 70.5, 70.2, 69.1, 38.9, 29.4, 22.0, 22.0, 4.4. IR ν_{max} (thin film) 3434, 2912, 1717, 1624, 1276, 1065, 708. HRMS (ES^+) $C_{25}H_{28}O_7I$ $[M+H]^+$ 567.0880; Found 567.0868.

4.3.2. (8S,9S,10R)- Benzoic acid 9-benzoyloxy-8-azidomethyl-3,3-dimethyl-1,5,7-trioxa-spiro[5.5] undec-10-yl ester ***2h***

To a stirred solution of **6** (200 mg, 0.439 mmol), in CH_2Cl_2 (2.2 mL, 0.2 M) under an atmosphere of Argon at room temperature was added DMAP (10.0 mg, 87.8 μmol, 20 mol %), and Et_3N (0.25 mL, 1.75 mmol, 4 equiv.). The resulting solution was cooled to 0°C and *p*-toluenesulfonyl chloride (100 mg, 0.527 mmol, 1.2 equiv.) added in one portion. The solution was stirred for a further 3 hours, diluted with EtOAc (50 mL), washed successively with saturated aqueous NH_4Cl (50 mL), $NaHCO_3$ (50 mL), Brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography elution 10:1 - 5:1 hexane: EtOAc to yield benzoic acid 9-benzoyloxy-3,3-dimethyl-8-(toluene-4-sulfonyloxymethyl)-1,5,7-trioxa-spiro[5.5]undec-10-yl ester as a yellow oil. The resulting oil (40.0 mg, 67.7 mmol) was dissolved in toluene (0.7 mL, 0.1 M) under an atmosphere of Argon at room temperature. Bu_4NCl (56.4 mg, 0.203 mmol, 3 equiv.) and NaN_3 (15.4 mg, 0.237 mmol, 3.5 equiv. were subsequently added and the resulting solution heated to reflux for 18 hours whereupon it was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was then extracted with Et_2O (50 mL x 3) and combined organic layers dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography elution 30:1 hexane: EtOAc to yield the title compound **2h** as a colorless oil (26 mg, 79 %).[18]

R_f = 0.44 (2:1/ Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.90 (4H, m), 7.56-7.46 (2H, m), 7.42-7.32 (4H, m), 5.66 (1H, ddd, *J* = 11.8, 9.5, 5.5 Hz), 5.35 (1H, dd, *J* = 9.8, 9.8 Hz), 4.09 (1H, d, *J* = 11.0 Hz), 4.05 (1H, ddd, *J* = 10.0, 8.8, 2.2 Hz), 3.77 (1H, d, *J* = 11.0 Hz), 3.59 (1H, dd, *J* = 13.3, 8.8 Hz), 3.42 (1H, dd, *J* = 7.5, 2.5 Hz), 3.39 (1H, dd, *J* = 7.5, 2.2 Hz), 3.19 (1H, dd, *J* = 13.2, 2.2 Hz), 2.69 (1H, dd, *J* = 12.6, 5.5 Hz), 2.03 (1H, dd, *J* = 12.5, 11.8 Hz), 1.25 (3H, s), 0.3 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 165.6, 133.5, 133.1, 129.8, 129.7, 129.5, 128.9, 128.5, 128.3, 109.1, 72.6, 71.0, 70.4, 70.1, 69.2, 51.8, 38.8, 29.3, 22.8, 21.9. IR ν_{max} (thin film) 2958, 2870, 2099, 1727, 1453, 1279, 1247, 1069, 962, 708 cm^{-1}. HRMS (ES^+) Calc. for $C_{25}H_{28}N_3O_7$ $[M+H]^+$ 482.1927; Found 482.1941.

4.3.3. *(8S,9S,10R)- Benzoic acid 10-benzoyloxy-8-(benzoylamino-methyl)-3,3-dimethyl-1,5,7-trioxa-spiro[5.5]undec-9-yl ester* **2i**

To a stirred solution of **2h** (54.0 mg, 0.112 mmol) in 10:1 THF: H_2O (2.3: 0.23 mL, 0.4 M) was added under Argon at room temperature Triphenylphosphine (90.7 mg, 0.337 mmol, 3 equiv.) and the resulting suspension heated to 70°C and stirred for 5 hours whereupon it was cooled to room temperature and concentrated *in vacuo*. The crude amine was then dissolved in pyridine (1.1 mL, 0.1 M), and cooled to 0°C under an atmosphere of Argon. DMAP (2 mg, cat.) and BzCl (14.3 μL, 0.123 mmol, 1.1 equiv.) were then added and the resulting solution stirred for 14 hours, quenched with saturated aqueous $NaHCO_3$ (50 mL), extracted with Et_2O (50 mL x 3), combined organic layers wahed succesively with aqueous $CuSO_4$ (50 mL x 2) brine (50 mL), dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography elution 15:1 Hexane: EtOAc to yield the title compound **2i** as a yellow oil (60 mg, 95% over 2 steps). [19]

R_f = 0.62 (2:1/ Hexanes: EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (2H, dd, *J* = 8.4, 1.5 Hz), 7.93 (2H, dd, *J* = 8.4, 1.1 Hz), 7.81 (2H, dd, *J* = 8.5, 1.5 Hz), 7.55-7.34 (9H, m), 6.76-6.71 (1H, m), 5.69 (1H, ddd, *J* = 11.4, 7.6, 5.2 Hz), 5.39 (1H, dd, *J* = 9.6, 9.6 Hz), 4.16-4.05 (2H, m), 4.01 (1H, d, *J* = 10.1 Hz), 3.60 (1H, d, *J* = 10.7 Hz), 3.46 (1H, ddd, *J* = 14.3, 6.3, 5.2 Hz), 3.34 (2H, ddd, *J* = 12.5, 9.9, 2.6 Hz), 2.67 (1H, dd, *J* = 12.9,5.5 Hz), 1.99 (1H, dd, *J* = 19.3, 19.3 Hz), 1.21 (3H, s), 0.68 (3H, s). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2, 166.3, 166.2, 133.5, 133.1, 131.6, 129.8, 129.7, 129.0, 128.6, 128.4, 128.3, 128.2, 126.9, 109.0, 71.5, 70.5, 70.3, 70.1, 69.0, 40.3, 38.9, 29.3, 27.5, 22.7, 21.9 ppm. IR ν_{max} (thin film) 3434, 2956, 2912, 2857, 1723, 1646, 1457, 1372, 1276, 1243, 1067, 749, 708. HRMS (ES^+) Calc. for $C_{32}H_{34}NO_8$ $[M+H]^+$ 560.2284; Found 560.2263.

4.3.4. *(8S,9S,10R)- Benzoic acid 10-benzoyloxy-3,3-dimethyl-8-phenylsulfanylmethyl-1,5,7-trioxa-spiro[5.5]undec-9-yl ester* **7**

To a stirred solution of **2g** (85.0 mg, 0.150 mmol) in DMF (1.5 mL, 0.1 M), under an atmosphere of Argon at room temperature was added DIPEA (31.4 μL, 0.180 mmol, 1.2 equiv.) and Thiophenol (18.4 μL, 0.180 mmol, 1.2 equiv.) and the resulting solution stirred for 18 hours, diluted with Et_2O (30 mL), washed with 1M HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and Brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo* and purified by flash chromatography elution 30: 1 Hexane: EtOAc to yield **7** (80.0 mg, 97 %) as a pale yellow oil.[20]

R_f = 0.53 (2:1/ Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.90 (4H, m), 7.57-7.31 (8H, m), 7.27-7.21 (2H, m), 7.18-7.13 (1H, m) 5.60 (1H, ddd, *J* = 11.8, 9.5, 5.5 Hz), 5.38 (1H, dd, *J* = 9.8, 9.8 Hz), 4.00 (1H, ddd, *J* = 9.8, 8.6, 3.3 Hz), 3.83 (1H, d, *J* = 11.0 Hz), 3.81 (1H, d, *J* = 11.0 Hz), 3.29-3.15 (4H, m), 2.64 (1H, dd, *J* = 12.5, 5.5 Hz), 1.99 (1H, dd, *J* = 12.6, 11.8 Hz), 1.19 (3H, s), 0.73 (3H, s). ^{13} C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.6, 136.4, 133.4, 133.1, 129.8, 129.7, 129.6, 129.1, 128.9, 128.6, 128.4, 128.3, 125.9, 108.9, 73.1, 72.1, 70.5, 70.4, 68.9, 38.8, 35.4, 29.2, 21.9, 21.4. IR ν_{max} (thin film) 3440, 2918, 1723, 1377, 1279, 1067, 708. HRMS (ES^+) Calc. for $C_{31}H_{33}O_7S$ $[M+H]^+$ 549.1947; Found 549.1928.

4.3.5. (8S,9S,10R)- Benzoic acid 10-benzoyloxy-8-benzenesulfonylmethyl-3,3-dimethyl-1,5,7-trioxa-spiro[5.5]undec-9-yl ester 2j

7 (75.0 mg, 0.137 mmol) was dissolved in CH_2Cl_2 (7 mL, 0.02 M), at 0°C under an atmosphere of Argon and *m*-CPBA (118 mg, 0.684 mmol, 5 equiv.) added in one portion. The suspension was stirred for 4 hours whereupon it was quenched with saturated aqueous $NaHCO_3$ (50 mL), extracted with CH_2Cl_2 (50 mL x 2), combined organic layers dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography elution 7: 1 Hexane: EtOAc to yield the title compound **1j** as a pale-yellow oil (72.0 mg, 90 %).[21]

R_f = 0.62 (2:1/ Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.83 (6H, m), 7.66-7.57 (1H, m), 7.56-7.44 (4H, m), 7.41-7.30 (4H, m), 5.65 (1H, ddd, *J* = 11.8, 9.6, 5.5 Hz), 5.23 (1H, dd, *J* = 9.8, 9.8 Hz), 4.55 (1H, ddd, *J* = 9.6, 9.6, 1.8 Hz), 4.10 (1H, d, *J* = 10.8 Hz), 3.94 (1H, d, *J* = 10.5 Hz), 3.61 (1H, dd, *J* = 14.6, 9.5 Hz), 3.41 (1H, dd, *J* = 10.8, 2.8 Hz), 3.34-3.30 (1H, m), 3.30-3.28 (1H, m), 2.65 (1H, dd, *J* = 12.5, 5.3 Hz), 1.98 (1H, dd, *J* = 11.8, 11.8 Hz), 1.22 (3H, s), 0.83 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 165.4, 140.3, 133.8, 133.6, 133.1, 129.9, 129.6, 129.4, 129.4, 128.6, 128.5, 128.3, 127.5, 109.1, 72.0, 70.4, 70.1, 69.2, 66.8, 57.4, 38.7, 29.3, 22.8, 21.9. IR ν_{max} (thin film) 3434, 2918, 2247, 1723, 1446, 1276, 1067, 746. HRMS (ES^+) Calc. for $C_{31}H_{33}O_9S$ $[M+H]^+$ 581.1845 Found 581.1870.

4.3.6. *(8S,9S,10R)- Benzoic acid 10-benzoyloxy-3,3-dimethyl-8-(1-phenyl-1H-tetrazol-5-ylsulfanylmethyl)-1,5,7-trioxa-spiro[5.5]undec-9-yl ester* **2k**

To a stirred solution of **6** (132 mg, 0.289 mmol) in THF (2.6 mL, 0.11 M) under an atmosphere of Argon at 0°C was added successively PPh_3 (152 mg, 0.579 mmol, 2 equiv.), phenyltetrazole thiol (72.1 mg, 0.405 mmol, 1.4 equiv.) and DIAD (85.5 µL, 0.434 mmol, 1.5 equiv.) in one portion respectively and the resulting solution stirred for a further 18 hours with warming to room temperature. The solution was then concentrated *in vacuo* and purified by flash chromatography elution 10:1 Hexane: EtOAc to yield the title compound **2k** as a colourless oil (62 mg, 35 %).[22]

R_f = 0.60 (2:1/ Hexane: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (2H, d, *J* = 8.1 Hz), 7.96 (1H, s), 7.93 (2H, d, *J* = 7.8 Hz), 7.82 (2H, d, *J* = 7.8 Hz), 7.56 (1H, t, *J* = 7.3 Hz), 7.50 (1H, t, *J* = 7.8 Hz), 7.46-7.31 (7H, m), 5.71 (1H, ddd, *J* = 12.2, 11.0, 6.6 Hz), 5.41 (1H, dd, *J* = 10.0, 10.0 Hz), 4.81 (1H, d, *J* = 13.7 Hz), 4.50 (1H, dd, *J* = 14.0, 10.3 Hz), 4.27 (1H, dd, *J* = 10.0, 10.0 Hz), 3.69 (1H, d, *J* = 10.5 Hz), 3.27 (1H, d, *J* = 10.5 Hz), 3.12 (1H, d, *J* = 10.8 Hz), 2.79 (1H, d, *J* = 11.0 Hz), 2.67 (1H, dd, *J* = 12.7, 5.4 Hz), 2.03 (1H, dd, *J* = 22.8, 10.8 Hz), 1.10 (3H, s), 0.38 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 147.6, 133.7, 133.2, 130.4, 130.0, 129.7, 129.4, 128.9, 128.7, 128.6, 128.4, 128.2, 125.6, 121.7, 109.0, 71.8, 70.8, 70.6, 70.1, 68.8, 51.6, 38.8, 28.9, 22.6, 21.5. IR ν_{max} (thin film) 3351, 3064, 2981, 2954, 2875, 2359, 2343, 1735, 1732, 1694, 1653, 1506, 1272, 1245, 1106 cm^{-1}. HRMS (ES^+) Calc. for $C_{32}H_{33}N_4O_7S$ $[M+H]^+$ Calc. 617.2064; Found 617.2064.

4.3.7. *(8S,9S,10R)- vBenzoic acid 10-benzoyloxy-8-formyl-3,3-dimethyl-1,5,7-trioxa-spiro[5.5]undec-9-yl ester* **8**

To a stirred solution of **6** (100 mg, 0.219 mmol) in CH_2Cl_2 (1 mL, 0.25 M) at room temperature under an atmosphere of Argon was added DMP (140 mg, 0.329 mmol, 1.5 equiv.) and the resulting suspension stirred for 2 hours, whereupon it was poured into a saturated solution of $Na_2S_2O_3$ (25 mL and saturated aqueous $NaHCO_3$ (25 mL), stirred for a further hour whereupon the organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (40 mL x 3). Combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to afford **8** which used without further purification.[23]

R_f = 0.24 (2:1/ Hexanes: EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.72 (1H, d, *J* = 2.3 Hz), 8.01-7.87 (4H, m), 7.58-7.44 (2H, m), 7.43-7.33 (4H, m), 5.73 (1H, ddd, *J* = 11.5, 9.4, 5.3 Hz), 5.55 (1H, dd, *J* = 9.8, 9.8 Hz), 4.15 (1H, dd, *J* = 10.0, 2.3 Hz), 4.05 (1H, d, *J* = 10.9 Hz), 3.68 (1H, d, *J* = 10.9 Hz), 3.45-3.36 (2H, m), 2.69 (1H, dd, *J* = 12.6, 5.3 Hz), 2.06 (1H, dd, *J* = 12.6, 11.7 Hz), 1.23 (3H, s), 0.81 (3H, s).

4.3.8. *(8S,9S,10R)- Benzoic acid 10-benzoyloxy-8-(2-cyano-vinyl)-3,3-dimethyl-1,5,7-trioxa-spiro[5.5]undec-9-yl ester* **2l**

To a stirred solution of diethyl cyanomethyl phosphonate (30.4 µL, 0.188 mmol, 1.2 equiv.) in acetonitrile (1.3 mL, 0.1 M) was added LiCl (8.0 mg, 0.188 mmol 1.2 equiv.), Et_3N (17.6 µL, 0.126 mmol, 1 equiv.) and crude **8** (57.0 mg, 0.126 mmol) in MeCN (0.4 mL). The resulting orange solution was stirred for 3 hours, diluted with EtOAc (50 mL), washed with brine (40 mL), dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography elution 15: 1 Hexane: EtOAc to yield the title compound **2l** as a pale yellow oil (25.0 mg, 42 % from **6**).

R_f = 0.69 (2:1/ Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (2H, d, *J* = 7.8 Hz), 7.92 (2H, d, *J* = 7.8 Hz), 7.55 (1H, t, *J* = 7.6 Hz), 7.50 (1H, t, *J* = 7.8 Hz), 7.41 (2H, t, *J* = 7.6 Hz), 7.37 (2H, t, *J* = 8.0 Hz), 6.73 (1H, dd, *J* = 15.9, 4.2 Hz), 5.79 (1H, d, *J* = 16.4 Hz), 5.67 (1H, ddd, *J* = 10.3, 10.3, 5.4 Hz), 5.30 (1H, dd, *J* = 9.8, 9.8 Hz), 4.42 (1H, ddd, *J* = 9.8, 4.6, 2.0 Hz), 4.00 (1H, d, *J* = 10.8 Hz), 3.59 (1H, d, *J* = 10.8 Hz), 3.41 (1H, d, *J* = 8.3 Hz), 3.39 (1H, d, *J* = 8.0 Hz), 2.68 (1H, dd, *J* = 13.0, 5.2 Hz), 2.02 (1H, dd, *J* = 12.5, 12.5 Hz), 1.24 (3H, s), 0.80 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 165.3, 148.3, 133.6, 133.2, 129.8, 129.7, 129.3, 128.5, 128.4, 116.5, 109.3, 101.8, 72.3, 70.6, 70.6, 70.1, 69.3, 38.7, 31.9, 29.3, 22.6, 21.9IR ν_{max} (thin film) 3445, 2918, 2247, 1652, 1460, 1388, 1366, 752. HRMS (ES^+) Calc. for $C_{27}H_{28}NO_7$ $[M+H]^+$ 478.1866; Found 478.1856.

4.3.9. *(8S,9S,10R)- Benzoic acid 9-benzoyloxy-3,3-dimethyl-8-(3-oxo-but-1-enyl)-1,5,7-trioxa-spiro[5.5]undec-10-yl ester* **2m**

To a stirred solution of dimethyl 2-oxopropylphosphonate (8.0 µL, 58.1 µmol, 1.2 equiv.) in MeCN (0.5 mL, 0.1 M) under an atmosphere of Argon at room temperature was added LiCl (2.5 mg, 58.1 µmol, 1.2 equiv.), Et_3N (6.8 µL, 48.5 µmol, 1 equiv.) and **8** (22.0 mg, 48.5 µmol) in MeCN (0.2 mL) and the resulting solution stirred for 6 hours whereupon it was diluted with EtOAc (30 mL) washed with Brine (20 mL), dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography elution 10: 1 Hexane: EtOAc to yield the title compound **2m** as a pale yellow oil (14.2 mg, 59 % from **6**).[24]

R_f = 0.54 (2:1/ Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (4H, t, *J* = 7.8 Hz), 7.57-7.44 (2H, m), 7.37 (4H, q, *J* = 7.6 Hz), 6.72 (1H, dd, *J* = 16.2, 5.6 Hz), 6.34 (1H, d, *J* = 15.9 Hz), 5.71 (1H, ddd, *J* = 11.0, 10.2, 5.4 Hz), 5.35 (1H, dd, *J* = 10.0, 10.0 Hz), 4.42 (1H, dd, *J* = 9.8, 5.6 Hz), 4.03 (1H, d, *J* = 11.0 Hz), 3.63 (1H, d, *J* = 11.2 Hz), 3.39 (1H, d, *J* = 9.3 Hz), 3.38 (1H, d, *J* = 10.8 Hz), 2.69 (1H, dd, *J* = 12.7, 5.1 Hz), 2.40 (3H, s), 2.04 (1H, dd, *J* = 12.2, 12.2 Hz), 1.24 (3H, s), 0.80 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 165.6, 140.5, 133.4, 133.1, 132.2, 129.7, 129.5, 128.5, 128.3, 109.2, 72.6, 71.3, 70.5, 70.2, 69.2, 38.8, 29.7, 29.4, 27.0, 22.6, 21.9, 14.1. IR ν_{max} (thin film) 3064, 2958, 2925, 2875, 2362, 2343, 1728, 1683, 1653, 1554, 1457, 1366, 1313, 1279, 1120, 1071, 958, 714 cm^{-1}. HRMS (ES^+) Calc. for $C_{28}H_{31}O_8$ $[M+H]^+$ 495.2019; Found 495.2012.

4.3.10. *(8*S*,9*S*,10*R*)- 3-(9,10-Dibenzoyloxy-3,3-dimethyl-1,5,7-trioxa-spiro[5.5]undec-8-yl)-acrylic acid ethyl ester* **2n**

To a stirred solution of Triethyl phosphonacetate (37.4 µL, 0.188 mmol, 1.2 equiv.) in MeCN (1.3 mL, 0.1 M) under an atmosphere of Argon at room temperature was added LiCl (8.0 mg, 0.188 mmol, 1.2 equiv.) and Et_3N (17.6 µL, 0.126 mmol, 1 equiv.) and **8** (57.0 mg, 0.126 mmol) and the resulting solution stirred for a further 3 hours whereupon it was diluted with EtOAc (50 mL), washed with Brine (40 mL), dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography elution 20:1 Hexane: EtOAc to yield the title compound **2n** as a pale yellow oil (25.0 mg, 38 %).

R_f = 0.71 (2:1/ Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (2H, d, *J* = 8.0 Hz), 7.93 (2H, d, *J* = 8.1 Hz), 7.51 (2H, q, *J* = 7.8 Hz), 7.37 (4H, q, *J* = 7.4 Hz), 6.92 (1H, dd, *J* = 15.4, 5.2 Hz), 6.19 (1H, d, *J* = 15.6 Hz), 5.66 (1H, ddd, *J* = 12.2, 10.5, 5.8 Hz), 5.34 (1H, dd, *J* = 9.8, 9.8 Hz), 4.44 (1H, dd, *J* = 10.0, 5.2 Hz), 4.20 (1H, d, *J* = 7.3 Hz), 4.16 (1H, d, *J* = 6.8 Hz), 4.06 (1H, d, *J* = 10.8 Hz), 3.63 (1H, d, *J* = 10.8), 3.39 (1H, d, *J* = 9.0 Hz), 3.37 (1H, d, *J* = 10.0 Hz), 2.68 (1H, dd, *J* = 12.7, 5.4 Hz), 2.03 (1H, dd, *J* = 12.0, 12.0 Hz), 1.30-1.26 (3H, m), 1.24 (3H, s), 0.80 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 165.6, 165.4, 141.5, 133.3, 133.1, 129.7, 129.7, 129.5, 129.2, 128.4, 128.3, 123.3, 109.1, 72.5, 70.7, 70.5, 70.5, 69.2, 60.6, 38.7, 29.4, 22.7, 22.0, 14.1. IR ν_{max} (thin film) 3065, 2958, 2924, 2871, 1727, 1602, 1453, 1308, 1274, 1179, 1122, 1069, 712 cm^{-1}. HRMS (ES^+) $C_{29}H_{33}O_9$ $[M+H]^+$ 525.2125; Found 525.2135.

4.4. General procedure for the Bi(OTf)3 Mediated Fragmentation-Ring Contration of ortholactones ***2a-n.*** *The formation of γ-lactones* ***3a-n****.*

To a stirred solution of ortholactone (1 equiv.) in CH_2Cl_2 (0.1 M) under an atmosphere of Argon at 0 °C was added in one portion $Bi(OTf)_3$ (0.5 equiv.) and the resulting suspension stirred until complete by TLC (2-6 hours). The suspension is then quenched by pouring into a saturated aqueous solution of $NaHCO_3$ and extracted three times with CH_2Cl_2. The resulting organic layer is washed with saturated aqueous brine, dried over $MgSO_4$, concentrated in vacuo and purified by flash column chromatograpy.

4.4.1. 3,5,6-Tri-O-acetyl-D-glucono-1,4-lactone **3a**

The title compound **3a** was prepared according to *general procedure 4.4* from **2a** (20.0 mg, 53.4 μmol), $Bi(OTf)_3$ (17.5 mg, 26.8 μmol, 0.5 equiv.) for 4 hours to afford the title compound **3a** as a colorless oil (12 mg, 80 %).

R_f = 0.20 (2:1 Hexane: EtOAc). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.65 (1H, dd, *J* = 5.8, 4.2 Hz), 5.36 (1H, dd, *J* = 9.5, 4.5, 2.5 Hz), 4.69 (1H, dd, *J* = 12.6, 4.3 Hz), 4.64 (1H, dd, *J* = 12.6, 2.2 Hz), 4.16 (1H, dd, *J* = 12.6, 4.3 Hz), 2.91 (1H, dd, *J* = 18.1, 5.5 Hz), 2.61 (1H, d, *J* = 18.3 Hz), 3.09 (3H, s), 2.07 (3H, s), 2.04 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 170.4, 169.6, 169.4, 78.2, 68.4, 67.1, 62.5, 36.6, 20.7, 20.7, 20.6. IR ν_{max} (thin film) 3462, 2929, 1801, 1747, 1432, 1374, 1228, 1141, 1040 cm^{-1}. HRMS (ES^+) Calc. for $C_{12}H_{16}O_8Na$ [M+Na] 311.0743, Found 311.0735.

4.4.2. 3,5,6-Tri-O-acetoxy-D-galactono-1,4-lactone **3b**

The title compound was prepared according to *general procedure 4.4* from **2b** (20 mg, 53.4 μmol), $Bi(OTf)_3$ (17.5 mg, 26.8 μmol, 0.5 equiv.) for 4 hours to afford the title compound **3b** as a colourless oil (12 mg, 80 %).

R_f = 0.20 (2:1 Hexane: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (1H, ddd, *J* = 8.3, 5.5, 3.0 Hz), 5.18 (1H, ddd, *J* = 7.6, 2.3, 2.3 Hz), 4.68 (1H, ddd, *J* = 9.3, 6.5, 1.8 Hz), 4.32 (1H, dd, *J* = 11.6, 5.5 Hz), 4.22 (1H, dd, *J* = 11.6, 6.6 Hz), 2.91 (1H, dd, *J* = 19.1, 7.5 Hz), 2.58 (1H, dd, *J* = 18.6, 2.0 Hz), 2.12 (3H, s), 2.12 (3H, s), 2.08 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 170.3, 170.1, 169.5, 82.5, 71.1, 70.0, 61.6, 34.7, 20.7, 20.6. IR ν_{max} (thin film) 3440, 2918, 2099, 1734, 1649, 1375, 1243, 752, 711. HRMS (ES^+) Calc. for $C_{12}H_{16}O_8Na$ $[M+Na]^+$ 311.0743, found 311.0736. Data is consistent with literature values.[25]

4.4.3. 3,5-Di-O-acetoxy-L-rhamnono-1,4-lactone **3c**

Title compound prepared according to *general procedure 4.4* from **2c** (45.0 mg, 142 μmol), $Bi(OTf)_3$ (46.7 mg, 71.2 μmol, 0.5 equiv.) for 4 hours to afford the title compound **3c** as a colourless oil (32.6 mg, 88 %).

R_f = 0.33 (2:1 Hexane: EtOAc). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.64 (1H, ddd, *J* = 5.9, 3.9, 0.7 Hz), 5.21 (1H, ddd, *J* = 12.5, 8.8, 6.1 Hz), 4.43 (1H, dd, *J* = 8.8, 3.9 Hz), 2.89 (1H, 18.4, 5.9 Hz), 2.59 (1H, dd, *J* = 18.1, 0.5 Hz), 2.07 (3H, s), 2.02 (3H, s), 1.41 (3H, d, *J* = 6.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 169.6, 169.6, 83.0, 68.5, 66.4, 36.7, 21.5, 20.7, 17.8. IR ν_{max} (thin film) 3396, 2928, 1789, 1744, 1432, 1375, 1243, 1144, 1089, 1054, 952 cm^{-1}. HRMS (ES^+) Calc. for $C_{10}H_{14}O_6Na$ $[M+Na]^+$ 253.0688, Found 253.0682.

4.4.4. 3,5-Di-O-acetoxy-D-xylono-1,4-lactone **3d**

Title compound was prepared according to *general procedure 4.4* from **2d** (30 mg, 99.3 μmol), $Bi(OTf)_3$ (32.6 mg, 49.7 μmol, 0.5 equiv.) for 6 hours to afford the title compound **3d** as a colorless oil (15 mg, 71 %).

R_f = 0.16 (2:1 Hexane: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24-5.19 (1H, m), 5.10-5.05 (1H, m), 4.62 (1H, dd, *J* = 13.0, 3.0 Hz), 4.42 (1H, ddd, *J* = 13.0, 2.8, 1.2 Hz), 3.02 (1H, dd, *J* = 18.0, 5.0 Hz), 2.75 (1H, ddd, *J* = 18.0, 3.5, 0.8 Hz), 2.15 (3H, s), 2.12 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 169.2, 167.1, 67.7, 66.1, 65.8, 32.8, 20.8, 20.8. IR ν_{max} (thin film) 3396, 2918, 1792, 1743, 1383, 1232, 1163, 1048 cm^{-1}. HRMS (ES^+) Calc. for $C_9H_{12}O_6Na$ $[M+Na]^+$ 239.0532, Found 239.0525

4.4.5. 3,5-Di-O-acetoxy-L-Arabinono-1,4-lactone **3e**

Title compound was prepared according to the *general procedure 4.4* from **2e** (90.0 mg, 0.298 mmol), $Bi(OTf)_3$ (97.8 mg, 0.149 mmol, 0.5 equiv.) for 6 hours to afford the title compound **3e** as a colorless oil (46.3 mg, 72 %).

R_f = 0.24 (2:1 Hexane: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (1H, ddd, *J* = 7.4, 1.7, 1.7 Hz), 4.68 (1H, ddd, *J* = 3.4, 3.4, 1.7 Hz), 4.39 (1H, dd, 12.2, 3.4 Hz), 4.29 (1H, dd, *J* = 12.5, 3.6 Hz), 3.00 (1H, dd, *J* = 18.8, 7.6 Hz), 2.63 (1H, dd, *J* = 18.6, 2.0 Hz), 2.13 (3H, s), 2.10 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 173.2, 170.3, 82.0, 71.1, 63.3, 34.8, 20.8, 20.6. IR ν_{max} (thin film) 3439, 2925, 2851, 1788, 1742, 1374, 1228, 1160, 1047, 938 cm^{-1}. HRMS (ES^+) Calc. for $C_9H_{12}O_6Na$ $[M+Na]^+$ 239.0532, Found 239.0532. Characterisation was in correspondence with literature values.[26]

4.4.6. 3,5,6-Tri-O-benzoyloxy-D-glucono-1,4-lactone **3f**

Compound was prepared according to *general procedure 4.4* from **2f** (30.0 mg, 53.6 μmol), $Bi(OTf)_3$ (17.6 mg, 26.8 μmol, 0.5 equiv.) for 4 hours to afford the title compound **3f** as a colorless oil (23.0 mg, 91 %).

R_f = 0.47 (2:1 Hexane: EtOAc). ^{1}H NMR (400MHz, $CDCl_3$) δ 8.16-7.95 (6H, m), 7.65-7.32 (9H, m), 5.77-5.65 (2H, m), 4.95-4.86 (1H, m), 4.75 (1H, dd, *J* = 12.3, 3.5 Hz), 4.65 (1H, dd, *J* = 12.3, 5.3 Hz), 3.33 (1H, dd, *J* = 17.3, 4.8 Hz), 3.02 (1H, dd, *J* = 17.0, 4.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 165.9, 165.1, 164.9, 134.0, 133.8, 133.4, 129.9, 129.9, 129.8, 129.2, 128.6, 128.6, 128.4, 76.5, 69.2, 68.5, 63.1, 34.1. IR ν_{max} (thin film) 3060, 2925, 1764 1725, 1601, 1452,1315, 1267, 1177, 1107, 1070, 1027 cm^{-1}. HRMS (ES^+) Calc. for $C_{27}H_{23}O_8$ $[M+H]^+$ 475.1393, Found 475.1396.

4.4.7. 6-Iodo-3,5-Di-O-benzoyloxy-D-glucono-1,4-lactone **3g**

The title compound 2g was prepared according to *general procedure 4.4* from **2g** (25.0 mg, 44.1 μmol), $Bi(OTf)_3$ (14.5 mg, 22.1 μmol, 0.5 equiv.) for 5 hours to afford the title compound **3g** as a pale yellow oil (20.6 mg, 97 %).

R_f = 0.37 (2:1 Hexane: EtOAc). ^{1}H NMR (400MHz, $CDCl_3$) δ 8.07-7.98 (4H, m), 7.66-7.55 (2H, m), 7.51-7.41 (4H, m), 5.66 (1H, dd, *J* = 10.3, 5.2 Hz), 5.59 (1H, ddd, *J* = 7.6, 5.3, 0.7 Hz), 4.51 (1H, ddd, *J* = 7.5, 5.5, 4.5 Hz), 3.61 (1H, dd, *J* = 11.3, 4.5 Hz), 3.50 (1H, dd, *J* = 11.3, 5.5 Hz), 3.28 (1H, dd, *J* = 17.0, 5.0 Hz), 3.00 (1H, ddd, *J* = 17.3, 5.3, 0.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.7, 165.1, 164.9, 134.0, 133.8, 129.9, 129.9, 128.7, 128.6, 128.6, 128.4, 77.3, 71.7, 68.9, 34.1, 3.6. IR ν_{max} (thin film) 3429, 3055, 2925, 1726, 1601, 1451, 1264, 1095, 1070, 1027, 709 cm^{-1}. HRMS (ES^+) Calc. for $C_{20}H_{18}O_6I$ $[M+H]^+$ 481.0148, Found 481.0137.

4.4.8. 6-azido-3,5-Di-O-benzoyloxy-D-glucono-1,4-lactone **3h**

The title compound **3h** was prepared according to the *general procedure 4.4* from **2h** (21.0 mg, 43.7 μmol), $Bi(OTf)_3$ (14.3 mg, 21.8 μmol, 0.5 equiv) for 3 hours to afford the title compound **3h** as a pale yellow oil (11.3 mg, 66 %).

R_f = 0.33 (2:1 Hexane: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12-8.05 (4H, m), 7.68-7.58 (2H, m), 7.54-7.42 (4H, m), 5.61

(1H, ddd, *J* = 10.5, 7.0, 2.8 Hz), 4.77 (1H, ddd, *J* = 6.8, 6.3, 2.0 Hz), 4.66 (1H, dd, *J* = 11.6, 6.0 Hz), 4.63 (1H, dd, *J* = 11.6, 6.8 Hz), 4.45 (1H, ddd, *J* = 2.8, 1.7, 0.7 Hz), 3.22 (1H, ddd, *J* = 18.0, 7.0, 0.8 Hz), 3.06 (1H, dd, *J* = 17.8, 10.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 166.0, 165.3, 134.1, 133.6, 130.0. 129.8, 129.0, 128.7, 128.6, 128.4, 74.8, 68.7, 63.0, 57.8, 32.2. IR ν_{max} (thin film) 3445, 2923, 2104, 1720, 1597, 1449, 1268, 1108, 711. HRMS (ES^+) Calc. for $C_{20}H_{18}N_3O_6$ $[M+H]^+$ 396.1190; Found 396.1203.

4.4.9. 6-Benzamido-3,5-Di-O-benzoyloxy-glucono-1,4-lactone **2i**

Title compound was prepared according to *general procedure 4.4* from **2i** (14.0 mg, 25.0 μmol), $Bi(OTf)_3$ (8.2 mg, 12.5 μmol, 0.5 equiv.) and CH_2Cl_2 (0.3 mL, 0.1 M) for 3 hours to afford the title compound **3i** as a pale yellow oil (6.5 mg, 54 %)

R_f = 0.22 (2:1/ Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.05 (2H, m), 8.01-7.96 (2H, m), 7.81-7.76 (2H, m), 7.65-7.39 (9H, m), 6.70 (1H, bdd, *J* = 6.5, 5.5 Hz), 5.66 (1H, ddd, *J* = 5.5, 4.8, 4.8 Hz), 5.50 (1H, ddd, *J* = 8.5, 5.0, 0.8 Hz), 4.77 (1H, ddd, *J* = 8.5, 7.5, 3.2 Hz), 4.21 (1H, ddd, *J* = 14.3, 7.0, 3.2 Hz), 3.76-3.58 (1H, m) 3.31 (1H, dd, *J* = 17.1, 5.5 Hz), 2.98 (1H, ddd, *J* = 17.3, 4.8, 0.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.9, 133.7, 131.9, 130.0, 129.9, 128.7, 128.6, 127.0, 69.9, 69.6, 41.2, 34.3, 29.7, 27.5, 24.9. IR ν_{max} (thin film) 3396, 2917, 1731, 1451, 1380, 1095 cm^{-1}. HRMS (ES^+) Calc. for $C_{27}H_{24}NO_7$ $[M+H]^+$ 474.1553 found 474.1549.

4.4.10. 6-Benzenesulfonyl-3,5-Di-O-benzoyloxy-D-glucono-1,4-lactone **3j**

Title compound prepared according to *general procedure 4.4* **2j** (35.0 mg, 60.3 μmol), $Bi(OTf)_3$ (19.8 mg, 30.2 μmol, 0.5 equiv.) for 4 hours to afford the title compound **3j** pale yellow oil (21 mg, 72 %).

R_f = 0.34 (2:1/ Hexane: EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06-7.91 (6H, m), 7.69 (1H, dd, *J* = 7.4, 7.4 Hz), 7.64 (1H, ddd, *J* = 7.4, 7.4, 2.2 Hz), 7.58 (3H, dd, *J* = 8.1, 8.1 Hz), 7.48 (2H, dd, *J* = 8.5, 8.5 Hz), 7.42 (2H, dd, *J* = 8.1, 8.1 Hz), 5.63 (1H, dd, *J* = 8.8, 4.1 Hz), 5.45 (1H, dd, *J* = 8.5, 4.4 Hz), 5.11 (1H, dd, *J* = 1H, ddd, *J* = 8.5, 8.5, 3.0 Hz), 3.71 (1H, dd, *J* = 15.0, 8.4 Hz), 3.59 (1H, dd, *J* = 15.0, 2.9 Hz), 3.28 (1H, dd, *J* = 17.3, 5.5 Hz), 2.92 (1H, dd, *J* = 17.3, 4.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 164.9, 134.3, 134.2, 133.8, 130.0, 129.8, 128.3, 73.3, 70.4, 69.4, 58.3, 33.9. IR ν_{max} (thin film) 3434, 2923, 2868, 1726, 1443, 1305, 1260, 1147, 1108, 712 cm^{-1}. HRMS (ES^+) Calc. for $C_{26}H_{22}O_8Na$ $[M+Na]^+$ 517.0933 found 517.0926.

4.4.11. 6-(sulphanyl-9-phenyl-9H-tetrazole)-3,5-Di-O-benzoyloxy-D-glucono-1,4-lactone **3k**

Title compound was prepared according to *general procedure 4.4* from **2k** (37.0 mg, 60.1 μmol), $Bi(OTf)_3$ (19.7 mg, 30.0 μmol, 0.5 equiv.) for 5 hours to afford the title compound **3k** as a colorless oil (20.0 mg, 65 %).

R_f = 0.26 (2:1 Hexane: EtOAc). ^{1}H NMR (400MHz, $CDCl_3$) δ .13-8.08 (2H, m), 8.03-7.98 (2H, m), 7.66-7.42 (11H, m), 5.67 (1H, ddd, *J* = 5.4, 4.6, 4.6 Hz), 5.54 (1H, ddd, *J* = 8.6, 4.9, 0.7 Hz), 5.05 (1H, ddd, *J* = 8.3, 8.3, 3.4 Hz), 4.05 (1H, dd, *J* = 14.4, 3.4 Hz), 3.70 (1H, dd, *J* = 14.4, 8.3 Hz), 3.30 (1H, dd, *J* = 17.4, 5.6 Hz), 2.98 (1H, ddd, *J* = 17.1, 4.4, 0.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 165.5, 165.2, 165.0, 134.0, 133.8, 133.3, 130.4, 130.1, 129.9, 129.9, 128.7, 128.7, 128.6, 128.4, 123.8, 76.2, 71.1, 69.6, 35.1, 34.3. HRMS (ES^+) Calc. for $C_{27}H_{23}N_4O_6S$ $[M+H]^+$ 531.1333; Found 531.1331. IR ν_{max} (thin film) 2916, 2362, 2339, 1727, 1075, 709 cm^{-1}.

4.4.12. (4R, 5S)-4-Benzoyloxy-5-[(1S,E)-1-Benzoyloxy-3-cyano-prop-2-ene]dihydrofuran-2(3H)one **3l**

Title compound was prepared according to *general procedure 4.4* from **2l** (25.0 mg, 52.4 μmol), $Bi(OTf)_3$ (17.2 mg, 26.2 μmol, 0.5 equiv.) for 4 hours to afford the title compound **3l** as a colorless oil (15.4 mg, 75 %).

R_f = 0.29 (2:1 Hexane: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (2H, d, *J* = 7.8 Hz), 7.97 (2H, d, *J* = 7.6 Hz), 7.66 (1H, t, *J* = 7.8 Hz), 7.63 (1H, t, *J* = 6.1 Hz), 7.51 (2H, t, *J* = 6.4 Hz), 7.49 (2H, t, *J* = 6.6 Hz), 6.84 (1H, dd, *J* = 16.4, 3.9 Hz), 5.90 (1H, d, *J* = 16.2 Hz), 5.67 (1H, dd, *J* = 9.3, 4.4 Hz), 5.48 (1H, dd, *J* = 4.9, 4.9 Hz), 5.33-5.26 (1H, m), 3.31 (1H, dd, *J* = 17.6, 5.2 Hz), 3.03 (1H, dd, *J* = 17.6, 4.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 164.9, 164.9, 146.7, 134.3, 134.1, 129.9, 129.8, 128.8, 128.8, 128.2, 115.7, 102.8, 77.6, 69.1, 68.1, 33.2.IR ν_{max} (thin film) 3407, 3049, 2923, 2225, 1725, 1597, 1454, 1317, 1260, 1177, 1093, 710 cm^{-1}. HRMS (ES^+) Calc. for $C_{22}H_{18}NO_6$ $[M+H]^+$ 292.1134; Found 292.1134.

4.4.13. (4R, 5S)-4-Benzoyloxy-5-[(1S,E)-1-Benzoyloxy-4-oxo-but-2-ene]-dihydrofuran-2(3H)-one **3m**

Title compound was prepared according to *general procedure 4.4* from **2m** (14.2 mg, 28.7 μmol), $Bi(OTf)_3$ (9.4 mg, 14.4 μmol, 0.5 equiv.) and CH_2Cl_2 (0.6 mL, 0.1 M) for 2 hours to afford the title compound **3m** as a colorless oil (10.1 mg, 86 %).

R_f = 0.24 (2:1 Hexane: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (2H, d, *J* = 7.8 Hz), 7.96 (2H, d, *J* = 7.8 Hz), 7.64 (1H, t, *J* = 7.1 Hz), 7.60 (1H, t, *J* = 8.6 Hz), 7.49 (2H, t, *J* = 7.6 Hz), 7.45 (2H, t, *J* = 7.3 Hz), 6.84 (1H, dd, *J* = 15.2, 4.2 Hz), 6.50 (1H, d, *J* = 15.9 Hz), 5.66 (1H, ddd, *J* = 8.8, 8.8, 4.4 Hz), 5.55 (1H, dd, *J* = 1.9, 1.9 Hz), 5.32 (1H, dd, *J* = 4.9, 4.9 Hz), 3.33 (1H, dd, *J* = 17.9, 4.4 Hz), 3.02 (1H, dd, *J* = 17.8, 3.7 Hz), 2.16 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 166.2, 165.0, 138.7, 134.2, 133.9, 131.5, 129.9, 128.8, 128.7, 78.4, 69.5, 68.3, 33.3, 29.7, 29.6, 27.9, 22.7. IR ν_{max} (thin film) 3396, 2923, 1726, 1451, 1383, 1262, 1095, 711 cm^{-1}. HRMS (ES^+) Calc. for $C_{23}H_{21}O_7$ $[M+H]^+$ 409.1287, Found 409.1283.

4.4.14. (4R, 5S)-4Benzoyloxy-5-[(1S, E)-1-Benzoyloxy-4-oxo-4ethoxyprop-2-ene]-dihydrofuran-2(3H)-one. **3n**

Title compound was prepared according to *general procedure 4.4* from **2n** (25.0 mg, 47.7 μmol), $Bi(OTf)_3$ (15.6 mg, 23.8 μmol, 0.5 equiv.) for 3 hours to afford the title compound **3n** as a colorless oil (15.8 mg, 76 %).

R_f = 0.39 (2:1 Hexane: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (2H, d, *J* = 7.6 Hz), 7.97 (2H, d, *J* = 7.8 Hz), 7.64 (1H, t, *J* = 7.4 Hz), 7.59 (1H, t, *J* = 7.8 Hz), 7.49 (2H, t, *J* = 7.3 Hz), 7.44 (2H, t, *J* = 7.3 Hz) 7.05 (1H, dd, *J* = 15.6, 4.4 Hz), 6.28 (1H, d, *J* = 15.6 Hz), 5.64 (1H, dd, *J* = 8.6, 4.2 Hz), 5.54 (1H, dd, *J* = 4.4, 4.4 Hz), 5.34 (1H, dd, *J* = 4.4, 4.4 Hz), 4.15 (2H, q, *J* = 6.8 Hz), 3.31 (1H, dd, *J* = 17.6, 4.9 Hz), 3.00 (1H, dd, *J* = 17.8, 3.4 Hz), 1.24 (3H, t, *J* = 7.1 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.1, 165.0, 164.9, 140.4, 134.1, 133.8, 130.0, 129.9, 128.7, 128.6, 128.5, 128.4, 123.9, 78.3, 69.4, 68.3, 60.8, 33.2, 14.1. IR ν_{max} (thin film) 3434, 2918, 1723, 1599, 1454, 1317, 1262, 1174, 1094, 710 cm^{-1}. HRMS (ES^+) Calc. for $C_{24}H_{22}O_8Na$ $[M+Na^+]$ 461.1212, Found 461.1211.

4.5. *3,4,6-Tri*-O-*acetoxy-D-glucono-1,5-lactone* **4a**

To a stirred solution of **2a** (50.0 mg, 0.134 mmol) in MeCN (1.3 mL, 0.1 M), under argon at 0°C was added $Bi(OTf)_3$ (43.0 mg, 66.8 μL, 0.5 equiv) and the resulting solution stirred for 4 hours whereupon it was quenched with $NaHCO_3$, extracted with CH_2Cl_2, combined organic layers dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash chromatography on

SiO_2 elution 3:1 Hexanes: EtOAc to yield the title compound **4a** as a colorless oil (15.0 mg, 50 %) .

R_f = 0.40 (1:1 Hexane: EtOAc). ^{1}H NMR (400MHz, $CDCl_3$) δ 5.26 (1H, ddd, *J* = 5.2, 4.6, 4.6 Hz), 5.14 (1H, ddd, *J* = 8.1, 4.9, 0.7 Hz), 4.49 (1H, ddd, *J* = 8.3, 4.7, 3.7 Hz), 4.34 (1H, dd, *J* = 12.5, 4.9 Hz), 4.30 (1H, dd, *J* = 12.5, 3.9 Hz), 3.05 (1H, dd, *J* = 17.1, 5.4 Hz), 2.77 (1H, ddd, *J* = 17.1, 4.7, 0.8 Hz), 2.13 (3H, s), 2.12 (3H, s), 2.10 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.5, 169.2, 167.0, 76.2, 68.6, 67.8, 62.1, 33.7, 20.8, 20.7. IR ν_{max} (thin film) 2955, 2360, 2338, 1733, 1558, 1278, 1047 cm^{-1}. HRMS (ES^+) Calc. for $C_{12}H_{16}O_8Na$ $[M+Na]^+$ Calc. 311.0737; Found 311.0737.

4.6. 3,5,6-Trihydroxy-D-glucono-1,4-lactone **9**

To a stirred solution of **3a** (111 mg, 0.385 mmol) in MeOH (2.4 mL, 0.16 M) under an atmosphere of Argon at room temperature was added AcCl (48.2 µL, 2% v/v) and the resulting solution stirred for 20 hours whereupon it was concentrated *in vacuo* and purified by flash chromatography elution 10: 1 CH_2Cl_2: MeOH to yield the title compound **4a** as a colorless oil (47.0 mg, 76 %).

R_f = 0.10 (10:1 CH_2Cl_2: MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 4.59 (1H, dd, *J* = 5.4, 3.7 Hz), 4.33 (1H, dd, *J* = 8.8, 3.4 Hz), 3.98 (1H, ddd, 8.3, 5.1, 2.9 Hz), 3.8 (1H, dd, *J* = 11.7, 2.9 Hz), 3.66 (1H, dd, *J* = 11.7, 5.4 Hz), 2.90 (1H, dd, *J* = 17.4, 5.2 Hz), 2.42 (1H, d, *J* = 17.6 Hz). ^{13}C NMR (100 MHz, CD_3OD) δ 178.5, 84.3, 70.1, 69.1, 65.0, 40.2. HRMS (ES^-) Calc. for $C_6H_9O_5$ $[M-H^-]$ 161.0450, Found 161.0444 IR ν_{max} (thin film) 2962, 2928, 2569, 2362, 2339, 1653, 1558, 1457, 1079, 1026 cm^{-1}. Characterization was in correspondence to literature values.[27]

4.7. (3R,4S,5R,6)-Tetraacetoxy-hexanoic acid 3-acetoxy-2,2-dimethyl-propyl ester **12**

To a stirred solution of **2a** (20.5 mg, 54.9 µmol) in CH_2Cl_2 (0.6 mL, 0.1 M) under argon at rt was added $Bi(OTf)_3$ (18 mg, 27.4 µmol, 0.5 equiv.) and Ac_2O (10 µL, 0.109 mmol, 2 equiv.) and the resulting solution stirred for a further 24 hours whereupon it was quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 10 mL) combined organic layers dried over $MgSO_4$, concentrated *in vacuo*, and purified by flash column chromatography on SiO_2 elution 5:1, hexanes: EtOAc to yield the title compound **12** as a colourless oil (20.6 mg, 79 %).

R_f = 0.55 (2:1/ Hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, ddd, *J* = 7.6, 6.4, 2.4 Hz), 5.37 (1H, dd, *J* = 9.1, 2.2 Hz), 5.14 (1H, ddd, *J* = 9.0, 4.6, 2.7 Hz), 4.25 (1H, dd, *J* = 12.7, 2.7), 4.17 (1H, dd, *J* = 12.5, 4.6 Hz), 3.96-3.83 (4H, m), 2.59 (1H, dd, *J* = 15.9, 7.6 Hz), 2.53 (1H, dd, *J* = 16.1, 6.4 Hz), 2.15 (3H, s), 2.09 (3H, s), 2.07 (3H, s), 2.06 (3H, s), 2.05 (3H, s), 0.98 (3H, s), 0.97 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.6, 169.8, 169.8, 169.3, 69.9, 69.8, 69.0, 68.2, 67.1, 61.8, 35.8, 34.5, 21.7, 21.7, 20.8, 20.8, 20.7, 20.7, 20.6.

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References and notes

1. (a) Faul, M. M.; Huff, B. E., *Chem. Rev.* **2000,** *100*, 2407; (b) Kang, E. J.; Lee, E., *Chem. Rev.* **2005,** *105*, 4348; (c) Kitson, R. R. A.; Millemaggi, A.; Taylor, R. J. K., *Angew. Chem. Int. Ed.* **2009,** *48*, 9426; (d) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M., *Chem. Rev.* **2013,** *113*, 4567; (e) Kammerer, C.; Prestat, G.; Madec, D.; Poli, G. *Acc. Chem. Res.* **2014**, *47*, 3439.
2. (a) Baddeley, K. L.; Cao, Q.; Muldoon, M. J.; Cook, M. J., *Chem., Eur. J.* **2015,** *21*, 7726. For a review of ortholactones see: (b) Undheim, K., *Synthesis* **2017**, *49*, 705.
3. For review of Bi(III) mediated reactions, see: (a) Gaspard-Iloughmane, H.; Le Roux, C. In *Bismuth (III) Lewis acids* **2008** Wiley-VCH Verlag GmbH & Co. KGaA; pp 551-588; (b) Bothwell, J. M.; Krabbe, S. W.; Mohan, R. S., *Chem. Soc. Rev.* **2011,** *40*, 4649; (c) Salvador, J. A. R.; Silvestre, S. M.; Pinto, R. M. A.; Santos, R. C.; LeRoux, C., *Top. Curr. Chem.* **2012,** *311*, 143; (d) Ollevier, T., *Org. Biomol. Chem.* **2013,** *11*, 2740.
4. (a) Bardili, B.; Marschall-Weyerstahl, H.; Weyerstahl, P., *Liebigs Ann. Chem.* **1985,** *1985*, 275; (b) Lee, J.; Lewin, N. E.; Acs, P.; Blumberg, P. M.; Marquez, V. E., *J. Med. Chem.* **1996,** *39*, 4912; (c) Yang, W.-B.; Patil, S. S.; Tsai, C.-H.; Lin, C.-H.; Fang, J.-M., *Tetrahedron* **2002,** *58*, 253; (d) Paśniczek, K.; Socha, D.; Jurczak, M.; Solecka, J.; Chmielewski, M., *Can. J. Chem.* **2006,** *84*, 534; (e) Knijnenburg, A. D.; Spalburg, E.; de Neeling, A. J.; Mars-Groenendijk, R. H.; Noort, D.; Grotenbreg, G. M.; van der Marel, G. A.; Overkleeft, H. S.; Overhand, M., *Helv. Chim. Acta* **2012,** *95*, 2544; (f) Lin, T.-S.; Liw, Y.-W.; Song, J.-S.; Hsieh, T.-C.; Yeh, H.-W.; Hsu, L.-C.; Lin, C.-J.; Wu, S.-H.; Liang, P.-H., *Bioorg. Med. Chem.* **2013,** *21*, 6282; (g) Zhao, G.; He, M.; Li, H.; Duan, S.; Yuan, Z.; Xie, X.; She, X., *Chem. Commun.* **2015,** *51*, 17321; (h) Colomer, I.; Barcelos, R. C.; Christensen, K. E.; Donohoe, T. J., *Org. Lett.* **2016,** *18*, 5880; (i) Li, F. F.; Atkinson, D. J.; Furkert, D. P.; Brimble, M. A., *Eur. J. Org. Chem.* **2016,** *2016*, 1145; (j)Lin, R.; Cao, L.; West, F. G., *Org. Lett.* **2017,** *19*, 552.
5. (a) Shiozaki, M.; Kobayashi, Y.; Hata, T.; Furukawa, Y., *Tetrahedron* **1991,** *47*, 2785; (b) Knapp, S.; Amorelli, B.; A. Doss, G., *Tetrahedron Lett.* **2004,** *45*, 8507.
6. Scott, R. W.; Mazzetti, C.; Simpson, T. J.; Willis, C. L., *Chem. Commun.* **2012,** *48*, 2639.
7. (a) Takano, S.; Inomata, K.; Ogasawara, K., *Heterocycles* **1988,** *27*, 2413; (b) Wheatley, J. R.; Beacham, A. R.; de Q. Lilley, P. M.; Watkin, D. J.; Fleet, G. W. J., *Tetrahedron: Asymm.* **1994,** *5*, 2523; (c) Abdelkafi, H.; Herson, P.; Nay, B., *Org. Lett.* **2012,** *14*, 1270.
8. (a) Dumeunier, R.; Marko, I. E., *Tetrahedron Lett.* **2004,** *45*, 825; (b) Ollevier, T.; Nadeau, E., *Org. Biomol. Chem.* **2007,** *5*, 3126; (c) Kwie, F. H. A.; Baudoin-Dehoux, C.; Blonski, C.; Lherbet, C., *Synth. Commun.* **2010,** *40*, 1082.
9. (a) Yamamoto, H.; Futatsugi, K., *Angew. Chem., Int. Ed.* **2005,** *44*, 1924; (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F., *Org. Lett.* **2006,** *8*, 4179; (c) Williams, D. B. G.; Lawton, M., *J. Mol. Catal. A: Chem.* **2010,** *317*, 68; (d) Cheon, C. H.; Kanno, O.; Toste, F. D., *J. Am. Chem. Soc.* **2011,** *133*, 13248.
10. (a) Baes, C. F., Jr.; Mesmer, R. *The Hydrolysis of Cations*; Wiley: New York, **1976**. (b) Yatsimirksii, K. B.; Vasil'ev, V. P. *Instability Constants of Complex Compounds*; Pergamon: New York, **1960**. (c) Martell, A. E., Ed.; *Coordination Chemistry; ACS Monograph 168*; American Chemical Society: Washington, DC, **1978**; *Vol. 2*; (d) Kobayahi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.
11. (a) Evans, P. A.; Cui, J.; Gharpure, S. J.; Hinkle, R. J., *J. Am. Chem. Soc.* **2003,** *125*, 11456; (b) Evans, P. A.; Cui, J.; Gharpure, S. J., *Org. Lett.* **2003,** *5*, 3883; (c) Evans, P. A.; Andrews, W. J., *Tetrahedron Lett.* **2005,** *46*, 5625; (d) Hinkle, R. J.; Lian, Y.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C., *Tetrahedron* **2005,** *61*, 11679; (e) Evans, P. A.; Andrews, W. J., *Angew. Chem., Int. Ed.* **2008,** *47*, 5426; (f) Hinkle, R. J.; Lian, Y.; Speight, L. C.; Stevenson, H. E.; Sprachman, M. M.; Katkish, L. A.; Mattern, M. C., *Tetrahedron* **2009,** *65*, 6834; (g) Evans, P. A.; Grisin, A.; Lawler, M. J., *J. Am. Chem. Soc.* **2012,** *134*, 285.
12. Bordwell, F. G. *Bordwell pKa Table (Acidity in DMSO)*; Department of Chemistry, University of Wisconsin Website.
13. Commercially available $Bi(OTf)_3$ contains an unspecified amount of water. For example, the analytical specifications, based on elemental analysis, for 99% purity $Bi(OTf)_3$ purchased from Alfa Aesar (Prod. No.: L19687) allow for up to one equivalent of water. For further discussion, see: Mathia, F.; Szolcsányi, P., *Org. Biomol. Chem.* **2012,** *10*, 2830 and references therein.
14. Yang, C.; Xue, X. –S.; Li, X.; Cheng, J. –P. *J. Org. Chem.* **2014**, 79, 4340.
15. For recent examples of TfOH mediated reactions using $Bi(OTf)_3$, see: (a) Masahito, M.; Origuchi, K. Takai, K. *Org. Lett.* **2014**, *16*,

3828; (b) Schneider, A. E.; Manilokakes, G. *J. Org. Chem.* **2015**, *80*, 6193; (c) Metz, T. L.; Evans, J.; Stanley, L. M. *Org. Lett.* **2017**, *19*, 3442; (d) Metz, T. L.; Lutovsky, G.; A.; Stanley, L. *J. Org. Chem.* **2018**, *83*, 1643.
16. For a review of triflate anion nucleophilicity, see: Dhakal, B.; Bohé, L.; Crich, D. *J. Org. Chem.* **2017**, *82*, 9263.
17. Sasaki, M., Inoue, M., Takamatsu, K., Tachibana, K., *J. Org. Chem.*, **1999**, 64, 9399.
18. Squarcia, A., Vivolo, F., Weinig, H-G., Passacantilli, P., Piancatelli, G. *Tetrahedron Lett.* **2002**, *43*, 4653.
19. Zhong, M., Meng, X. -B., Zhong, J. -L., *Carbohydr. Res.* **2010**, *345*, 1099.
20. Christina, A. F., Van der Es, D., Dinkelaar, J., Overkleeft, H. S., Van der Marel, G., Codée, J. D. C., *Chem. Commun.*, **2012**, 48, 2868.
21. Fujita, M., Lainé, D., Ley, S. V., *J. Chem. Soc., Perkin Trans. 1*, **1999**, 1647.
22. Hubshwerlen, C. Surivet, J. –P.; Zumbrunn, A. C. *PCT Int. Appl.* 2007086016.
23. Peri, F., Jiménez-Barbero, J., García-Aparicio, V., Tvaroška, I., *Chem. Eur. J.*, **2004**, 10, 1433.
24. Blanchette, M. A., Choy, W., Davis, J. T., Essenfeld, A. P., Masamune, S., Roush, W. R., Sakai, T., *Tetrahedron Lett.* **1984**, 25, 2183.
25. Chiocconi, A.; Marino, C.; Otal, E. de Lederkremer, R. M. *Carbohydr. Res*. 337, **2002**, 2119.
26. Kita, Y.; Tamura, O.; Itoh, F.; Yasuda, H.; Kishino, H.; Ke, Y. Y.; Tamura, Y. *J. Org. Chem.* **1998**, 53, 554.
27. Overend, W. G.; Shafizadeh, F.; Stacey, M. *J. Chem. Soc*. **1950**, 671.

Supplementary Material

A supplementary file containing copies of all the ^{1}H and ^{13}C NMR spectra is included with this submission.