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Oxidatively generated electrophiles as initiators of epoxide cascade cyclization processes

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Abstract—Oxidatively generated oxocarbenium ions are shown to be effective promoters of polyepoxide cascade cyclization reactions to form polyether compounds. The reaction conditions are neutral, ensuring that background acid-mediated processes are not operative and that other acid-sensitive functional groups, such as acetals, can be incorporated into cyclization substrates. While 5-*exo* pathways are more common that 6-*endo* pathways, a rational design has been employed to access tetrahydropyranyl ethers.

1. Introduction

Cascade reactions, in which the formation of a single reactive intermediate leads to multiple bond forming events provide significant increases in molecular complexity, making them quite useful for applications in organic synthesis. Numerous reports of cation, anion, and radical mediated cascade processes have appeared in the literature,[1] with alkenes or other π-bonds serving to propagate the reactive intermediate, leading to the construction of carbocyclic structures. Transition metal alkene and alkyne complexation is also emerging as an intriguing method for initiating cascade processes.[2] Cyclic ethers have been prepared through the use of epoxides in cascade processes under either acidic or basic conditions (Fig. 1).

Acid-mediated intramolecular additions into epoxides have attracted considerable attention in polyether synthesis, because of their capacity to alter the regiochemical outcome from the stereoelectronically preferred[5] *exo*-pathway to the *endo*-pathway through substitution.[6] In the context of cascade cyclizations, however, treating a polyepoxide with an acid can result in non-selective acid–base interactions, leading to potential undesired pathways and to ambiguous mechanistic interpretations. An approach to alleviating these problems is to use an intramolecular acid–base interaction to promote the reaction. In this approach, a single epoxide reacts with an electrophile to form an epoxonium ion,[7] with selectivity arising from simple cyclization kinetics. This epoxonium ion can then react with another epoxide to continue the cascade. To ensure selectivity in such reactions, a non-acidic method for forming the initial electrophile is desirable. Oxidative electrophile formation (Fig. 2) is well suited for this purpose, although only limited examples of this strategy have been reported. In a recent synthesis of hemibrevetoxin, Holton utilized selenonium ion formation as a method for intramolecular epoxide activation,[8] while Martín[9] and McDonald[10] have used halonium ions in intramolecular Lewis acid activation.[11] An alternative approach to non-acidic polyether synthesis involves sequential olefin oxidation with metal oxides.[12]

We have developed a method for converting homobenzylic ethers and amides to oxocarbenium and acyliminium ions, respectively, through single electron oxidation (Fig. 3).[13] This method of carbon–carbon bond activation proceeds under non-acidic conditions, making chemoselectivity for electrophile formation exceptionally high, even in the presence of functional groups which are readily activated under conventional acidic conditions. Therefore, oxidatively formed oxocarbenium ions should function as excellent initiators for polyepoxide cascade cyclization reactions. The products of these reactions would contain a latent aldehyde group, creating additional benefit to this process. Herein, we report our studies on oxidatively initiated polyepoxide cascade reactions to form tetrahydrofurans

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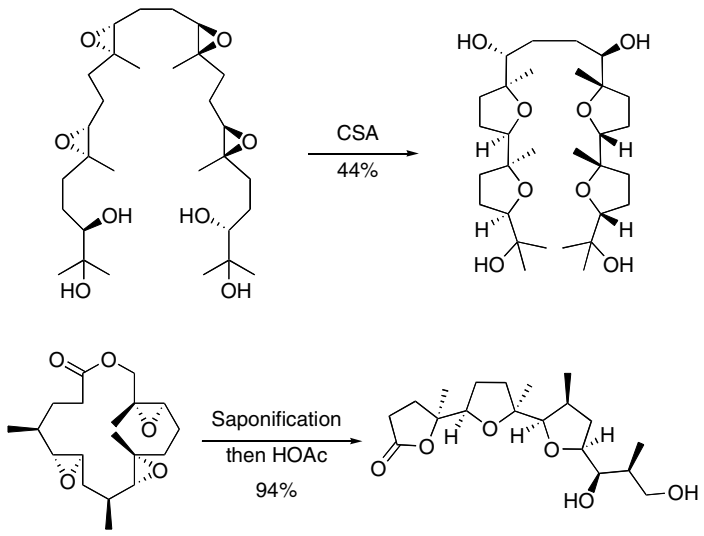


Figure 1. Literature examples of epoxide cascade cyclizations.[3,4]

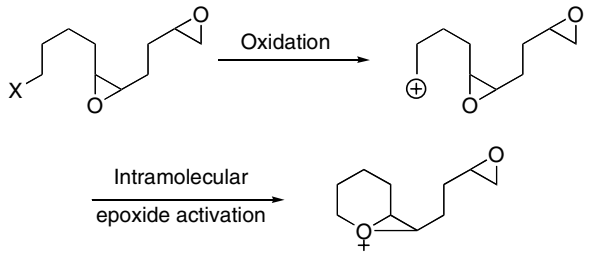


Figure 2. Oxidatively-initiated intramolecular epoxide activation.

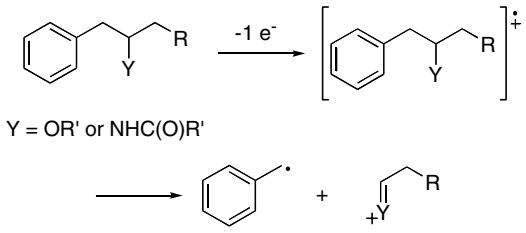


Figure 3. Electrophile formation through carbon–carbon bond activation.

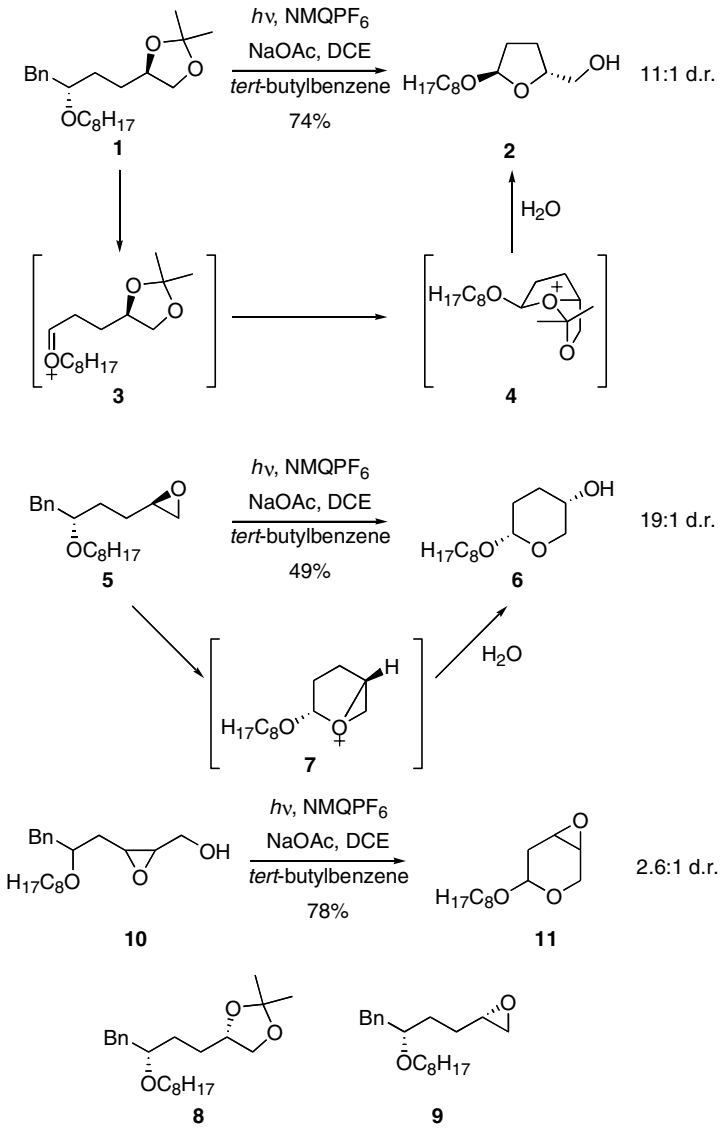
and tetrahydropyrans, in which relative and, in some cases, absolute stereochemistry in the products is controlled by the stereochemistry of the epoxides. In addition to epoxides, we also highlight the utility of acid-sensitive acetals as nucleophiles under oxidative conditions.[14]

2. Results and discussion

Our initial efforts[13a] in this project (Scheme 1) arose from our observation that acetonide **1**, when exposed to photoinitiated single electron oxidation conditions (*hv*, Pyrex filtration, *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$), NaOAc, 1,2-dichloroethane, *tert*-butylbenzene), yielded tetrahydrofuran **2** in good yield with high stereocontrol. This process proceeds through benzylic carbon–carbon bond cleavage to form oxocarbenium ion **3**. Cyclization of the proximal oxygen of the acetonide provided bicyclic oxonium ion **4**, in which the alkoxy group is preferentially oriented on the convex face. Hydrolytic breakdown of **4** yields **2**.

The success of this reaction led us to consider the possibility of using other cyclic ethers as nucleophiles in these reactions. Epoxides were particularly desirable in this regard due to their expected capacity to serve as potent electrophiles and engage in further bond formation upon intramolecular reaction with the oxocarbenium ion. Indeed, single electron oxidation of epoxide **5** provided hydroxytetrahydropyranyl ether **6** in moderate yield, but with high stereocontrol through the formation of epoxonium ion **7**, which reacted with adventitious water at the secondary carbon. In both of these examples, the intermediacy of the oxocarbenium ion was inferred from the observation that cyclization reactions of **8** and **9** yielded identical diastereomer ratios to the cyclizations of **1** and **5**. The efficient cyclization of epoxy alcohol **10** to yield **11** provided further evidence that epoxides do not undergo rapid decomposition under the oxidative conditions.

While not proceeding in exceptional yield, the cyclization of **5** led us to consider the viability of incorporating an additional nucleophile into the substrate in order to trap the intermediate epoxonium ion and form a second ring. Of additional interest herein was the effect of activating the epoxide through complexation with an oxocarbenium ion on cyclization regiochemistry (*exo* vs *endo*) and stereochemistry (S_N1 vs S_N2). Thus, racemic epoxy alcohol **15a** was prepared through a straightforward sequence (Scheme 2) and subjected to the aerobic variant[15] of our oxidative cyclization conditions to provide **16** and **17** in a 3:1 ratio in 51% overall yield, indicating that *exo*- and *endo*-pathways are competitive for this substrate. The relationship between the regiochemistry and



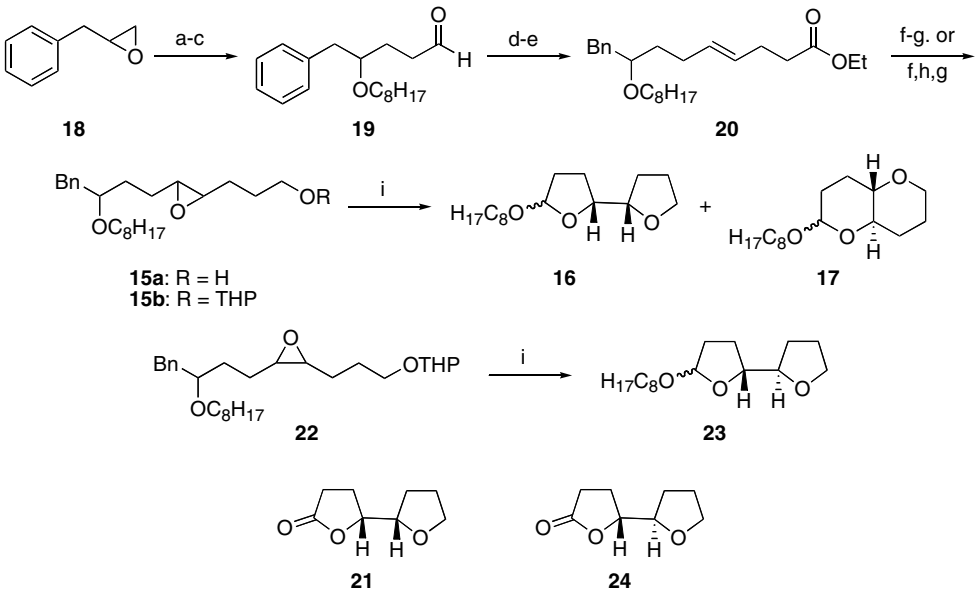
Scheme 1. Cyclic ethers as nucleophiles in oxidative cyclizations.

reaction conditions was studied by changing the base from NaOAc to soluble, oxidatively stable 2,6-dichloropyridine. In this case, the observed ratio of **16/17** was 1:1 and the overall yield was 64%. Additionally, THP/ether **15b**, prepared in accord with our observations that acetals can be surrogates of hydroxyl groups in these processes, was subjected to the standard oxidation conditions to provide **16** in 83% yield with no detectable *endo*-product. Therefore, while the effect of changing the nucleophile on the regiochemistry of the cyclization is not understood, these results clearly indicate that the nucleophile's identity does impact the reaction outcome.

Bis-tetrahydrofuran **16** was isolated as a 1:1 mixture of stereoisomers. To determine whether the lack of stereocontrol resulted from a lack of anomeric control or from non-stereoselective epoxonium ion opening, both isomers were oxidized with Jones reagent to provide lactone **21**. Therefore, while anomeric stereocontrol was not controlled at the high level that was observed in the cyclization of **5**, opening the epoxonium ion proceeds stereoselectively. Evidence for stereospecificity in the cyclization was provided through the oxidation of *cis*-epoxide **22**. This reaction provided **23** as a diastereomeric mixture again with no detectable *endo*-cyclization. Oxidation of **23** provided lactone **24**, which was clearly spectroscopically distinct from **21**.

With the basic pathway established, we turned our attention to incorporate an additional epoxide into the substrate to create the possibility for an additional ring forming event and to determine whether epoxonium ions that form from the coupling of epoxides to secondary carbocations differ in reactivity from those formed from the addition of epoxides into oxocarbenium ions (Fig. 4). As an additional exploratory element, we wanted to examine the possibility of using mixed acetals to open epoxonium ions,[16] thereby delivering an alkoxy group with high regiocontrol.

Ester **20**, an intermediate in the synthesis of **15**, was converted to diene **25**, in which the ethoxyethyl ether was



Scheme 2. Prototype oxidative cascade cyclizations. Reagents and conditions: (a) allylmagnesium bromide, Et_2O, −78 °C, 80%; (b) NaH, DMF, then *n*-$C_8H_{17}I$, 60%; (c) O_3, CH_2Cl_2, −78 °C, then Ph_3P; (d) vinylmagnesium bromide, THF, −78 °C, 71% for two steps, (e) $(EtO)_3CCH_3$, propionic acid, xylenes, reflux, 75%; (f) $LiAlH_4$, Et_2O, 96%; (g) *m*-CPBA, NaOAc, CH_2Cl_2, 83%; (h) dihydropyran, PPTs, CH_2Cl_2, 76%; (i) see text.

Figure 4. Epoxonium ions formed from additions to oxocarbenium and secondary carbenium ions.

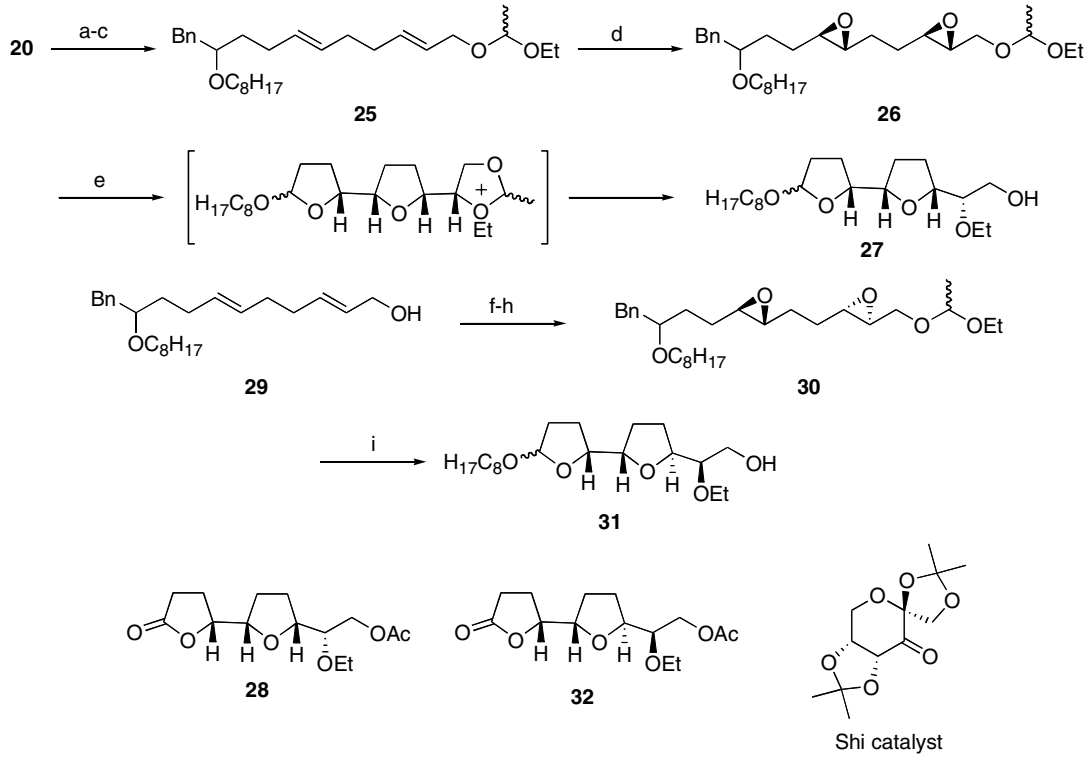
incorporated to be the terminal nucleophile in the cascade process. In order to avoid the formation of diastereomeric bis-epoxides, **25** was exposed to Shi's conditions[17,18] to yield **26** (Scheme 3).[19]

Subjecting **26** to single electron oxidation conditions resulted in the smooth formation of bis-tetrahydrofuran **27** as a mixture of two diastereomers. Again the anomeric position was identified as the site of stereochemical ambiguity through acylation the primary hydroxyl group followed by oxidation of with the Jones reagent, thus forming lactone **28** as a single stereoisomer. This reaction demonstrated that the epoxonium ion opening proceeds stereoselectively with epoxide nucleophiles, that no compelling reactivity difference in reactivity between epoxonium ions, that were formed from reaction with oxocarbenium ions relative to non-stabilized carbenium ions could be determined, and that mixed acetals are effective at delivering alkoxy groups to electrophilic carbons. To further demonstrate the stereoselectivity of the process, we converted diene **29** to diastereomeric bis-epoxide **30** through sequential Sharpless[20] and Shi epoxidations. This substrate proceeded efficiently through cyclization to provide **31** as a mixture of anomers. Acylation and oxidation yielded lactone **32** as a single isomer.

Based on substitution patterns, both carbons of the epoxonium ions herein should be equally electrophilic. The cascades that have been described show a preference for tetrahydrofuran formation over tetrahydropyran formation because of the stereoelectronic preference for *exo*-attack on the epoxonium ion relative to *endo*-addition. Based on these considerations, we postulated that tetrahydropyran formation would be possible through changing the topography of the substrate by placing the terminal nucleophile between the homobenzylic ether and the epoxide. Therefore, upon epoxonium ion formation, the nucleophile would be constrained to react through a fused bicyclic transition state rather than a bridged transition state, leading to tetrahydropyran formation (Fig. 5).

Methyl olivoside **33** was selected as a synthetic target to test this hypothesis. In our approach (Scheme 4) **33** arises from deprotection of the C5 ether group of **34**. The ether can be installed through the delivery of an alkoxy group to an oxidatively generated epoxonium ion through a mixed acetal that is present in cyclization substrate **35**. Phenylacetaldehyde was seen as a suitable precursor for the stereoselective synthesis of **35**.

Thus, commercially available phenylacetaldehyde was subjected to a Brown allylation reaction[21] to provide the expected homoallylic alcohol, which was converted to methyl ether **36**. Ozonolysis followed in the same flask by the addition of propynylmagnesium bromide yielded a 3:1 mixture of propargylic alcohols favoring the *syn*-isomer, as determined by subsequent transformations, in 68% yield (unoptimized). Reduction of the major product with $LiAlH_4$ gave allylic alcohol **37** in 85% yield. Diastereocontrolled epoxide formation was best achieved using Sharpless' conditions.[20] It is worthy of note that this reaction never proceeded to completion, most likely due to the epoxidation performing a kinetic resolution[22] concurrent with the diastereoselective oxidation. In consideration of our objective of delivering



Scheme 3. Cascade cyclizations of di-epoxides with excellent stereocontrol. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C, then Ph_3PCHCO_2Et, rt, 87%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 81%; (c) Shi catalyst, oxone, K_2CO_3, Bu_4NHSO_4, EDTA, H_2O, CH_3CN, 85%; (d) *hv*, $NMQPF_6$, O_2, NaOAc, $Na_2S_2O_3$, PhMe, DCE, 66%; (f) (+)-diisopropyl tartrate, *t*-BuOOH, $Ti(Oi\text{-}Pr)_4$, 4 Å MS, CH_2Cl_2, 93%; (g) 1-chloroethyl ethyl ether, *N*,*N*-dimethylaniline, CH_2Cl_2, 94%; (h) Shi catalyst, oxone, K_2CO_3, Bu_4NHSO_4, EDTA, H_2O, CH_3CN, 64%; (i) *hv*, $NMQPF_6$, O_2, NaOAc, $Na_2S_2O_3$, PhMe, DCE, 69%.

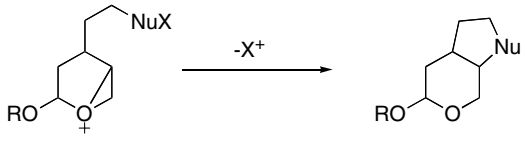
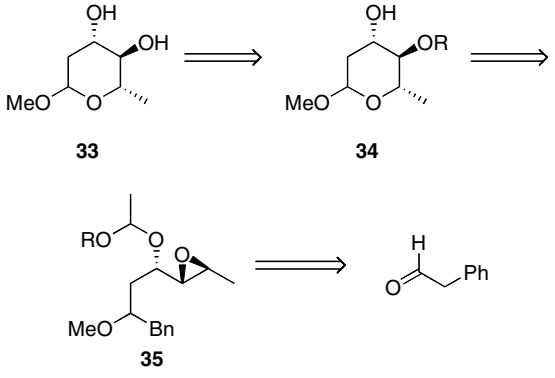


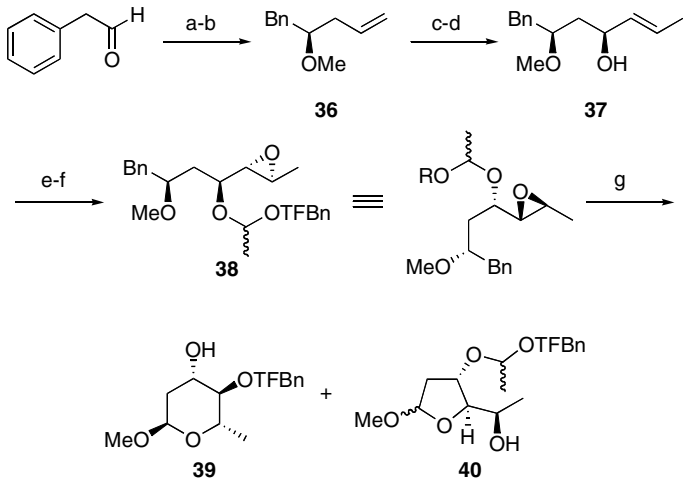
Figure 5. Strategy for tetrahydropyran formation.



Scheme 4. Retrosynthesis of methyl olivoside.

an ether group that would provide a hydroxyl group upon exposure to mild cleavage conditions while not being cleaved in the oxidative cyclization. A *p*-trifluoromethylbenzyloxyethyl ether appeared to be well suited for this purpose since the trifluoromethyl group was expected to inhibit arene oxidation and trifluoromethylbenzyl (TFBn) ethers have been shown to be cleaved through hydrogenolysis.[23] Thus, $TFBnOCH(CH_3)Cl$, which was prepared from TFBnOH and acetaldehyde in the presence of HCl, was coupled with the epoxide of **37** in the presence of *N*,*N*-dimethylaniline to provide cyclization substrate **38**. Exposure of **38** to our standard oxidative cyclization resulted in the formation of **39** in 48% yield. Variable amounts of tetrahydrofuran **40** were also observed if the reaction was not conducted under anhydrous conditions. Stereochemical confirmation of the final product was obtained through cleaving the TFBn ether to yield **33**, which showed identical NMR spectra to a literature report (Scheme 5).[24]

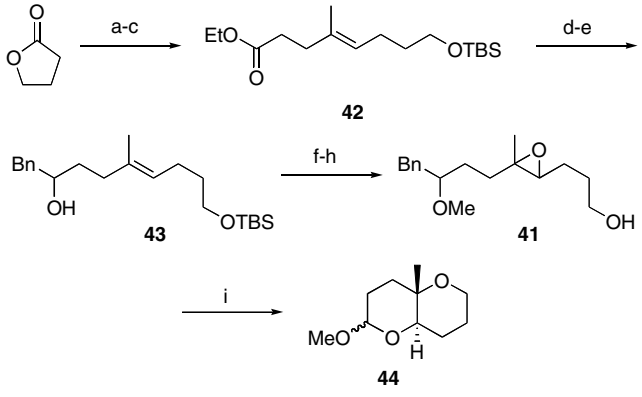
It is noteworthy that in the cyclization of **38** to **39**, no direct delivery of the TFBnO-group to the initially formed oxocarbenium ion was observed, even though the formation of this product would proceed through a favorable 6-*exo* cyclization pathway. Two explanations for this are possible. The geometrical constraints of the epoxide could make the lone pairs on the oxygen more kinetically accessible even though, from a thermodynamic perspective, they should be less reactive than standard ethers due to the higher s-character of their orbitals. Alternatively, the trifluoromethylbenzyloxy group could serve as the initial nucleophile into the epoxonium ion to form an oxonium ion intermediate. If the alkoxy group transfer is slow relative to the reformation of the oxocarbenium ion, then the epoxide could



Scheme 5. Oxidative carbohydrate synthesis. Reagents and conditions: (a) (+)-$Ipc_2BCH_2CH{=}CH_2$, CH_2Cl_2, −78 °C; (b) NaH, DMF, then MeI, 82%; (c) O_3, CH_2Cl_2, −78 °C, then Ph_3P, then propynylmagnesium bromide, 51% + 17% *anti*-diastereomer; (d) $LiAlH_4$, Et_2O, reflux, 85%; (e) Ti(O*i*-Pr)$_4$, (+)-diisopropyl tartrate, *t*-BuOOH, CH_2Cl_2, −20 °C, 91%; (f) TFBnOCH(Cl)CH_3, *N*,*N*-dimethylaniline, CH_2Cl_2, 93%; (g) *hv*, NMQPF_6, O_2, NaOAc, $Na_2S_2O_3$, PhMe, DCE, 46%.

eventually react to form the epoxonium ion. Due to the strain of the epoxonium ion, rapid and essentially irreversible opening by the trifluoromethylbenzyloxy group occurs (Fig. 6).

Another strategy for promoting tetrahydropyran formation is to disrupt the degenerate reactivity of the carbons in the epoxonium ion through substitution. Towards this goal, trisubstituted epoxide substrate **41** was prepared from butyrolactone as shown in Scheme 6, with the expectation that the increased cationic character at the tertiary center, that would be realized during epoxonium ion formation, would promote *endo*-cyclization. Indeed, exposing **41** to our standard cyclization conditions resulted in the formation of **44**, albeit in ⩽20% yield. The structural assignment for this compound was based on the chemical shift of the hydrogen on the anomeric carbon at 4.65 ppm,[25] characteristic of tetrahydropyranyl ethers. Interestingly, the THP ether of **44** was a poor cyclization substrate, showing evidence of an epoxide rearrangement to form a ketone. This product is likely to result from the intermediate epoxonium ion undergoing a rearrangement faster than nucleophilic addition. Therefore, while trisubstituted epoxonium ions show a greater tendency to react through the *endo*-pathway, a sufficiently reactive nucleophile must be employed to avoid competitive isomerization. We are currently pursuing this strategy.



Scheme 6. Regiochemical reversal through substitution. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, −78 °C, then isopropenylmagnesium bromide, 61%; (b) TBSCl, imidazole, DMF, 82%; (c) $(EtO)_3CCH_3$, propionic acid, 140 °C, 88%; (d) DIBAL-H, CH_2Cl_2, −78 °C; (e) BnMgCl, CuCN, $BF_3{\cdot}OEt_2$, LiCl, THF, −78 °C, 68% for two steps; (f) NaH, DMF, then MeI; (g) Bu_4NF, THF, 95% for two steps; (h) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 85%; (i) *hv*, NMQPF_6, O_2, NaOAc, $Na_2S_2O_3$, PhMe, DCE, <20%.

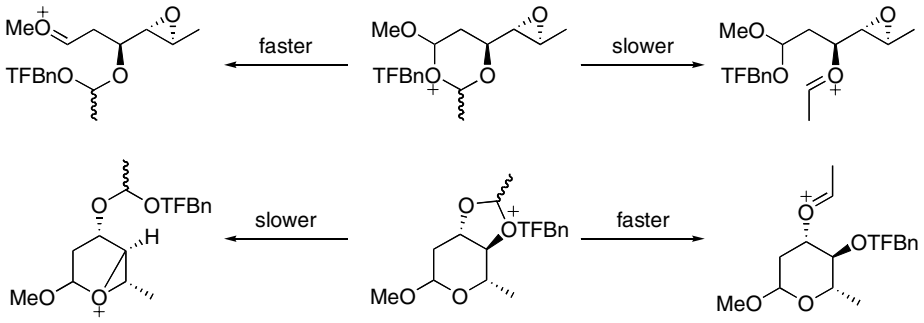


Figure 6. Fates of oxonium ion intermediates in the cyclization.

3. Conclusion

Oxidatively generated electrophiles have been effectively utilized for intramolecular epoxide activation. This method employs essentially neutral conditions and offers the desirable attribute of controlling the sequence of functional group activation when several acid-sensitive groups are present. Cascade reactions to form oligotetrahydrofuran products that demonstrated a strong preference for the *exo*-cylization pathway were achieved in good yields when disubstituted epoxides were used as substrates. High stereoselectivity was observed in these reactions, with complementary diastereomers being formed from diastereomeric epoxides. Mixed acetals were also shown to be suitable nucleophiles for opening epoxonium ions, resulting in a stereoselective alkoxy group delivery. Two strategies for tetrahydropyran formation using this strategy have been devised. Installing the terminal mixed acetal nucleophile between the oxocarbenium ion and the epoxide was used in the enantioselective synthesis of methyl olivoside. Trisubstituted epoxides have been employed in these reactions to promote the *endo*-cyclization pathway relative to the *exo*-pathway. In these reactions, the intermediate epoxonium ions are prone to isomerization, requiring that nucleophiles are sufficiently reactive to engage in cyclization faster than the undesired side reaction.

4. Experimental

4.1. General procedures

THF and Et_2O were dried by distillation over Na/benzophenone under N_2. Toluene, 1,2-dichloroethane, and CH_2Cl_2 were dried by distillation over CaH_2. Photoirradiations were performed with a Hanovia 450 W medium pressure mercury lamp through Pyrex filtration. Reagents were used, as purchased, without further purification unless otherwise noted. Chemical shifts (δ) are reported in parts per million.

4.2. Bis-furan 16

To epoxy-ether **15b** (90 mg, 0.20 mmol) in dichloroethane (12 mL) in a borosilicate flask at room temperature were added *N*-methylquinolinium hexafluorophosphate (1.4 mg, 0.005 mmol), sodium acetate (180 mg, 2.19 mmol), anhydrous $Na_2S_2O_3$ (180 mg, 1.13 mmol), and toluene (2 mL). The mixture was photoirradiated with gentle air bubbling for 2 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the filtrate concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to provide the desired compound as two diastereomers. Faster eluting compound (21 mg, 37.6%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.14 (dd, $J = 4.9$, 1.7 Hz, 1H), 4.03 (td, $J = 12.9$, 4.5 Hz, 1H), 3.91–3.82 (m, 2H), 3.76 (td, $J = 8.2$, 6.5 Hz, 1H), 3.66 (td, $J = 9.6$, 6.9 Hz, 1H), 3.36 (td, $J = 9.6$, 6.7 Hz, 1H), 2.19–1.84 (m, 6H), 1.74–1.62 (m, 2H), 1.52 (quintet, $J = 6.9$ Hz, 2H), 1.38–1.21 (m, 10H), 0.88 (t, $J = 6.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.1, 80.5, 79.7, 68.5, 67.3, 31.9, 31.8, 29.7, 29.2, 28.1, 26.1, 25.6, 25.4, 22.6, 14.1; IR (neat) 2965, 2856, 1454, 1329, 1193, 1079 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{23}O_2$ (M−71) 199.1698, found 199.1695. Slower eluting compound (19 mg, 35.4%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.06 (dd, $J = 3.8$, 2.7 Hz, 1H), 3.98 (td, $J = 7.8$, 6.4, 1H), 3.92–3.79 (m, 2H), 3.78–3.71 (m, 1H), 3.64 (td, 9.5, 6.9 Hz, 1H), 3.33 (td, $J = 9.5$, 6.6 Hz, 1H), 2.04–1.81 (m, 8H), 1.55 (quintet, $J = 7.4$ Hz, 2H), 1.38–1.21 (m, 10H), 0.88 (t, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.9, 82.2, 82.0, 68.4, 67.2, 32.9, 31.8, 29.6, 29.4, 29.2, 27.9, 27.3, 26.2, 25.8, 22.6, 14.0; IR (neat) 2965, 2856, 1454, 1329, 1193, 1079 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{23}O_2$ (M−71) 199.1698, found 199.1695.

4.3. Bis-furan 23

To epoxy-ether **22** (50 mg, 0.11 mmol) in dichloroethane (6 mL) in a borosilicate flask at room temperature were added *N*-methylquinolinium hexafluorophosphate (0.8 mg, 0.003 mmol), sodium acetate (100 mg, 1.21 mmol), anhydrous $Na_2S_2O_3$ (100 mg, 0.63 mmol), and toluene (1 mL). The mixture was photoirradiated with gentle air bubbling for 1.5 h, while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and then concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to provide the desired compound as two diastereomers. Faster eluting compound (12.5 mg, 41.3%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.17 (dd, $J = 4.8$, 1.4 Hz, 1H), 4.26 (dd, $J = 13.4$, 6.9 Hz, 1H), 3.95–3.88 (m, 1H), 3.82–3.75 (m, 2H), 3.72 (td, $J = 9.5$, 6.9 Hz, 1H), 3.37 (td, $J = 9.5$, 6.9 Hz, 1H), 2.10–1.81 (m, 5H), 1.62–1.53 (m, 5H), 1.38–1.19 (10H), 0.88 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 81.4, 80.1, 68.1, 67.4, 32.1, 31.8, 29.7, 29.4, 29.2, 28.1, 26.1, 25.7, 22.6, 14.1; IR (neat) 2926, 2856, 1730, 1459, 1347, 1318, 1197, 1078, 1038, 990, 856 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{29}O_3$ (M−1) 269.2117, found 269.2125. Slower eluting compound (11.8 g, 39.0%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23 (d, $J = 3.8$ Hz, 1H), 4.12–3.92 (m, 4H), 3.88 (td, $J = 9.6$, 6.9 Hz, 1H), 3.49 (td, $J = 9.6$, 6.7 Hz, 1H), 2.14–1.96 (m, 5H), 1.95–1.80 (m, 1H), 1.70–1.58 (m, 4H), 1.50–1.36 (m, 10H), 1.02 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.9, 83.1, 82.8, 68.3, 67.3, 33.1, 31.8, 29.6, 29.4, 29.2, 27.9, 26.2, 25.8, 22.6, 14.1; IR (neat) 3026, 2928, 2855, 1602, 1495, 1454, 1378, 1346, 1136, 1098, 1057, 1134, 1098, 1057, 943, 930, 894, 870 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{29}O_3$ (M−1) 269.2117, found 269.2117.

4.4. Bis-furan 27

To diepoxide **26** (50 mg, 0.10 mmol) in dichloroethane (6 mL) in a borosilicate flask at room temperature were added *N*-methylquinolinium hexafluorophosphate (0.7 mg, 0.0026 mmol), sodium acetate (100 mg, 1.21 mmol), anhydrous $Na_2S_2O_3$ (10 mg, 0.63 mmol), and toluene (1 mL). The mixture was photoirradiated with gentle air bubbling for 1.5 h while stirring at room temperature. The reaction mixture was filtered through

a small plug of silica gel and the filtrate was concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to provide the desired compound as a mixture of two diastereomers (28 mg, 66.4%): $[\alpha]_D^{25} = -3.8$ (c −0.45, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (dd, $J = 4.9$, 1.4 Hz, 0.5H), 5.05 (d, $J = 4.8$ Hz, 0.5H), 4.05–3.88 (m, 2.5H), 3.78–3.59 (m, 5.5H), 3.37–3.29 (m, 2H), 2.12–1.84 (m, 7H), 1.82–1.65 (m, 1H), 1.58–2.50 (m, 2H), 1.39–1.23 (m, 10H), 1.21 (t, $J = 7.0$ Hz, 3H), 0.88 (t, $J = 6.7$ Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 82.5, 82.2, 81.5, 81.4, 81.3, 81.0, 79.6, 67.5, 67.4, 66.2, 66.1, 62.9, 62.8, 32.9, 31.9, 31.8, 29.8, 29.7, 29.4, 29.4, 28.4, 28.1, 27.5, 27.4, 26.9, 26.3, 26.2, 25.8, 22.6, 15.6, 13.9; IR (neat) 3459, 2974, 2962, 2927, 2875, 2857, 1766, 1730, 1459, 1376, 1347, 1197, 1097, 1077, 1041, 935, 852 cm^{-1} HRMS (EI) calcd for $C_{12}H_{21}O_4$ (M−129) 229.1439, found 229.1439.

4.5. Bis-furan 31

To diepoxide **30** (50 mg, 0.10 mmol) in dichloroethane (6 mL) in a borosilicate flask at room temperature were added *N*-methylquinolinium hexafluorophosphate (1.5 mg, 0.0052 mmol), sodium acetate (100 mg, 1.21 mmol), anhydrous $Na_2S_2O_3$ (100 mg, 0.63 mmol), and toluene (1 mL). The mixture was photoirradiated with gentle air bubbling for 1.5 h, while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the filtrate concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to provide the desired compound as a mixture of two diastereomers. Faster eluting compound (14 mg, 37.2%): $[\alpha]_D^{25} = -8.5$ (c 0.30, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (dd, $J = 5.1$, 1.6 Hz, 1H), 4.01 (dd, $J = 13.2$, 6.0 Hz, 2H), 3.93 (dt, $J = 13.2$, 5.8 Hz, 1H), 3.73–3.58 (m, 5H), 3.39–3.30 (m, 2H), 2.10–1.67 (m, 8H), 1.59–1.51 (m, 2H), 1.32–1.24 (m, 10H), 1.20 (t, $J = 7.0$ Hz, 3H), 0.88 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2, 81.1, 81.0, 80.7, 79.8, 67.4, 66.3, 66.1, 32.8, 31.9, 31.8, 29.8, 29.7, 29.4, 29.2, 26.2, 25.7, 22.6, 15.7, 14.0; IR (neat) 3456, 2927, 2857, 1459, 1376, 1347, 1197, 1097, 1041, 936, 852 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{21}O_4$ (M−129) 229.1439, found 229.1430. Slower eluting compound (12 mg, 31.9%): $[\alpha]_D^{25} = -1.5$ (c 0.15, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (dd, $J = 3.3$, 1.2 Hz, 1H), 4.15–4.05 (m, 3H), 3.88–3.73 (m, 5H), 3.49–3.43 (m, 2H), 2.27–1.92 (m, 6H), 1.73–1.63 (m, 2H), 1.32–1.24 (m, 7H), 1.35 (t, $J = 7.0$ Hz, 3H), 1.04 (t, $J = 7.0$ Hz, 3H), 0.88 (t, $J = 6.8$ Hz, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.1, 82.2, 82.2, 80.9, 80.6, 67.4, 66.3, 62.9, 32.9, 31.8, 29.7, 29.4, 29.3, 28.7, 28.1, 27.1, 26.3, 22.7, 15.7, 14.1; IR (neat) 3456, 2927, 2857, 1459, 1376, 1347, 1197, 1097, 1041, 936, 852 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{21}O_4$ (M−129) 229.1439, found 229.1440.

4.6. Lactone 28

To **27** (11 mg, 0.0275 mmol) in CH_2Cl_2 (2 mL) was added Et_3N, DMAP, and Ac_2O. The mixture was stirred for 3 h and then was partitioned between CH_2Cl_2 and H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude residue was dissolved in acetone (2 mL) and cooled to 0 °C. Jones reagent (four drops) was then added. The reaction mixture instantly turned from colorless to green and then stirred for an additional 10 min. The reaction mixture was concentrated and purified by flash chromatography to provide the desired product (5.5 mg, 70%): $[\alpha]_D^{25} = -8.3$ (c 0.40, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (dd, $J = 13.2$, 6.4 Hz, 1H), 4.32 (dd, $J = 11.8$, 3.7 Hz, 1H), 4.04 (dd, $J = 11.8$, 5.4 Hz, 1H), 4.01–3.95 (m, 2H), 3.72 (dq, $J = 9.2$, 7.0 Hz, 1H), 3.54 (dq, $J = 9.2$, 7.0 Hz, 1H), 3.48 (m, 1H), 2.58–2.50 (m, 2H), 2.32–2.26 (m, 1H), 2.14–1.93 (m, 4H), 2.08 (s, 3H), 1.85–1.75 (m, 1H), 1.92 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 170.9, 81.2, 80.3, 79.4, 78.9, 77.8, 77.2, 76.4, 66.5, 63.8, 29.7, 28.1, 27.5, 26.8, 24.0, 15.5; HRMS (EI) calcd for $C_{14}H_{23}O_6$ (M+1) 287.1495, found 287.1503.

4.7. Lactone 32

To **31** (11 mg, 0.0275 mmol) in CH_2Cl_2 (2 mL) was added Et_3N, DMAP, and Ac_2O. The mixture was stirred for 3 h and then partitioned between CH_2Cl_2 and H_2O. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude residue was dissolved in acetone (2 mL) and cooled to 0 °C. Jones reagent (four drops) was added. The reaction mixture was turned from colorless to green and then stirred for 10 min. The reaction mixture was concentrated and purified by flash chromatography to provide the desired product (5 mg, 63%): $[\alpha]_D^{25} = -7.8$ (c 0.45, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (dd, $J = 12.6$, 6.9 Hz, 1H), 4.27 (dd, $J = 10.2$, 3.9 Hz, 1H), 4.11–3.99 (m, 3H), 3.78–3.65 (m, 1H), 3.63–3.51 (m, 1H), 3.52–3.44 (m, 1H), 2.63–2.47 (m, 2H), 2.36–2.26 (m, 1H), 2.18–1.90 (m, 4H), 2.08 (s, 3H), 1.78–1.65 (m, 1H), 1.19 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 170.8, 81.6, 80.2, 79.6, 79.1, 66.7, 63.9, 28.1, 27.4, 23.8, 20.9, 15.6. HRMS (EI) calcd for $C_{14}H_{23}O_6$ (M+1) 287.1495, found 287.1505.

4.8. Protected methyl olivoside 39

To epoxide **38** (50 mg, 0.11 mmol) in dichloroethane (6 mL) in borosilicate flask at room temperature were added *N*-methylquinolinium hexafluorophosphate (1.6 mg, 0.0057 mmol), sodium acetate (100 mg, 1.21 mmol), anhydrous $Na_2S_2O_3$ (100 mg, 0.63 mmol), and toluene (1 mL). The mixture was photoirradiated with gentle air bubbling for 2.5 h while stirring at room temperature. The reaction mixture was filtered through a small plug of silica gel and the filtrate concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to provide the desired compound as a 10:1 mixture of two diastereomers (15 mg, 46%): $[\alpha]_D^{25} = -129.3$ (c 0.18, EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, $J = 8.1$ Hz, 2H), 7.48 (d, $J = 8.1$ Hz, 2H), 4.87 (d, $J = 12.1$ Hz, 1H), 4.81 (d, $J = 12.1$ Hz, 1H), 4.74 (d, $J = 3.3$ Hz, 0.9H), 4.42 (dd, $J = 9.4$, 2.0 Hz, 0.1H), 4.10–4.02 (m, 1H), 3.76–3.67 (m, 1H), 3.50 (s, 0.3H), 3.32 (s, 2.7H), 3.01 (t, $J = 9.1$ Hz, 1H), 2.25 (ddd, $J = 13.1$, 4.4, 0.9 Hz,

0.9H), 2.04 (br s, 1H), 1.71 (ddd, $J = 15.3$, 11.6, 3.7 Hz, 0.9H), 1.38 (d, $J = 6.2$ Hz, 0.3H), 1.33 (d, $J = 6.2$ Hz, 2.7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5, 127.7, 127.6, 125.5 (q), 100.5, 98.3, 86.7, 86.3, 74.3, 74.2, 71.1, 69.1, 66.7, 54.7, 37.9, 29.8, 18.4; IR (neat) 3200, 2934, 1616, 1327, 1211, 1168, 1109, 1067, 1051, 1018, 969, 821 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{19}O_4F_3$ (M+) 320.1235, found 320.1240.

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