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Electron Transfer Initiated Heterogenerative Cascade Cyclizations: Polyether Synthesis under Nonacidic Conditions

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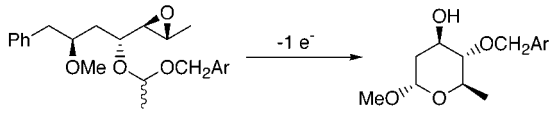
ABSTRACT



Single-electron oxidation has been employed to initiate heterogenerative cascade cyclization reactions that form polyether compounds under essentially neutral conditions. The reactions proceed through mesolytic benzylic carbon–carbon bond cleavages of homobenzylic ether-derived radical cations followed by intramolecular epoxonium ion formation, leading to further cyclizations. Both oligotetrahydrofuran and tetrahydropyran structures can be prepared by altering substrate topography.

Cascade reactions, in which multiple bond forming events ensue from the generation of a single reactive intermediate, can expedite synthetic sequences by effecting rapid increases in molecular complexity. The utility of these reactions has been validated through numerous applications to the synthesis of polycyclic structures and natural products.[1] Acid-initiated cationic cascade cyclization reactions have proven to be particularly efficacious in the synthesis of carbocyclic structures through cation−olefin cyclizations[2] and polyether compounds through epoxide-opening sequences.[3] The need for strong Lewis or protic acids in the initiation steps of these reactions, however, can prohibit the inclusion of acid-sensitive functional groups into cyclization substrates and products. This limitation can be circumvented by initiating these processes with a heterogenerative reaction[4] in which a reactive intermediate is formed under nonacidic conditions and subsequently disproportionates into a potent electrophile.[5] In this communication we report that radical cations of homobenzylic ethers undergo mesolytic carbon−carbon σ-bond cleavage reactions to form oxonium ions that react with pendent epoxides, resulting in an effective method to provide bicyclic epoxonium ions. When appropriately functionalized these intermediates undergo further cyclization reactions, providing efficient syntheses of polyether ring systems. In addition to reporting several synthetic applications of this process, we also discuss mechanistic issues concerning the regiochemistry of intramolecular nucleophilic additions into bicyclic epoxonium ions.

We recently reported[6] that, when irradiated (medium-pressure mercury lamp, Pyrex filtration) in the presence of the photooxidant *N*-methylquinolinium hexafluorophosphate ($NMQPF_6$), homobenzylic ethers that contain pendent nucleophilic groups undergo intramolecular benzyl group displacement reactions to provide cyclic acetals. These

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(2) (a) Johnson, W. S. *Tetrahedron* **1991**, *47*, R11. (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647. (c) Huang, A. X.; Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 9999 and references therein.
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(4) Wender, P. A.; Miller, B. L. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 27−66.
(5) For an excellent illustration of this strategy, see: Khan, N.; Xiao, H.; Zhang, B.; Cheng, X.; Mootoo, D. R. *Tetrahedron* **1999**, *55*, 8303.
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electron transfer initiated cyclization reactions are practicable because of the significant and selective benzylic carbon−carbon σ-bond weakening that results from radical cation formation.[7] During the course of this study we demonstrated that exposing epoxide **1** to our standard cyclization conditions (*hν*, 2 equiv of $NMQPF_6$, NaOAc, dichloroethane, *tert*-butylbenzene) provides hydroxy-tetrahydropyranyl ether **3** in moderate yield (Figure 1). This result is consistent with

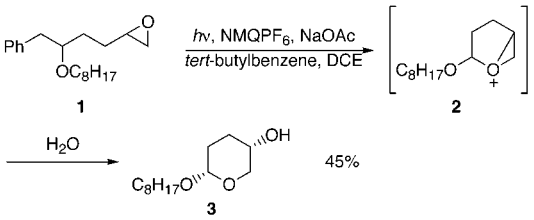

Figure 1. Epoxonium ion formation and hydration under oxidative conditions.

the intermediacy of epoxonium ion **2**, which upon reaction with adventitious water provides **3**. We believed that the mild conditions employed for these reactions and the intramolecular epoxide activation portended well for the use of this method to initiate cascade cyclization processes that lead to polyether structures related to biologically active natural products such as the Annonaceous acetogenins[8] and other marine toxins.[9]

To test this proposal we subjected unstable hydroxy epoxide **4a** (Figure 2) to our standard cyclization conditions. This procedure resulted in the isolation of a 1:3 mixture of bistetrahydrofurans **6** and **7** in 51% combined yield as the result of a competition between *endo*- and *exo*-cyclization pathways from epoxonium ion **5** (pathways *a* and *b*, respectively, Figure 2). Replacing NaOAc with the soluble, oxidatively inert base 2,6-dichloropyridine provided a 1:1 mixture of **6** and **7** in 64% combined yield. We hypothesized that the regioselectivity of the process would be affected by changing the nucleophilic group. Thus, stable tetrahydropyranyl ether **4b** was subjected to standard cyclization conditions to form **7** in 83% yield as a 1:1 mixture of epimers at the anomeric center. No trace of **6** could be detected in this reaction. Oxidation of each epimer of the product with Jones' reagent provided a single lactone **8**, confirming that the stereochemical difference between the products results from the initial reaction between the epoxide group and the oxidatively generated oxonium ion and not from solvolysis of the intermediate epoxonium ion. Application of our

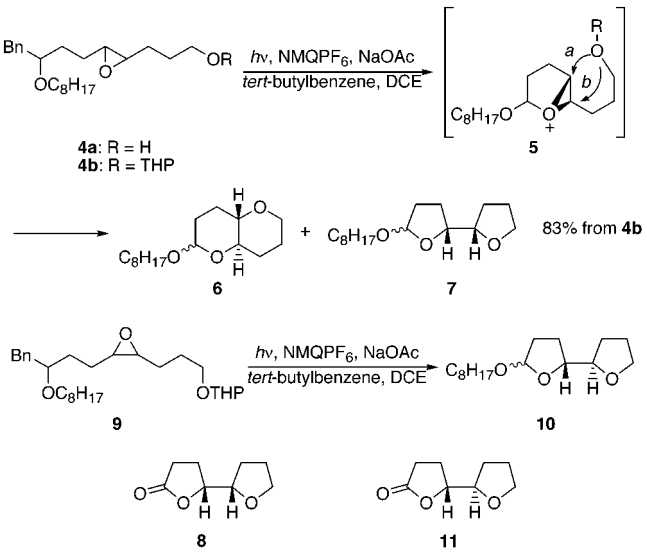

Figure 2. Heterogenerative cascade cyclization reactions.

catalytic aerobic procedure[10] to this reaction (*hν*, 0.025 equiv of $NMQPF_6$, gentle aeration, NaOAc, $Na_2S_2O_3$, dichloroethane, toluene) provided **7** in 73% yield, again as a 1:1 mixture at the anomeric center. Isomeric epoxide **9** underwent cyclization with comparable efficiency to provide **10** as a 1:1 mixture of anomers in 78% yield under stoichiometric conditions and in 80% yield under catalytic conditions, demonstrating that *cis*- and *trans*-epoxides react with comparable efficiency. Lactone **11** was formed by oxidizing each anomer of **10** with Jones reagent, again confirming the stereospecificity of epoxonium ion opening.

The successful utilization of the THP-ether as a nucleophile in opening epoxonium ions suggested that other ethers, including epoxides, could serve in the same capacity. To test this proposal we prepared **12**, in which the absolute stereochemistry of the two epoxide groups was established through the use of a double Shi epoxidation[11] on the diene precursor,[12] and subjected it to our standard cyclization conditions (Figure 3). This reaction provided bistetrahydrofuran **16** in 64% isolated yield (82% at 78% conversion) as a 3:2 ratio of anomers under stoichiometric conditions and in 66% yield under catalytic conditions. We propose that the conversion of **12** to **16** proceeds through initial formation of epoxonium ion **13** followed by reaction with the distal epoxide group to provide epoxonium ion **14**. In contrast to termination through tetrahydrofuran formation, we chose to open this epoxonium ion with an alkoxy group transfer process[13] that proceeds through nucleophilic attack by the distal oxygen of the mixed acetal group to produce oxonium ion **15**. Hydrolysis of **15**

(7) For discussions of the reactivity patterns of radical cations, see: (a) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2551. (b) Baciocchi, E.; Bietti, M.; Lanzalunga, O. *Acc. Chem. Res.* **2000**, *33*, 243. (c) Schmittel, M.; Ghorai, M. K. In *Electron Transfer in Chemistry*; Balzani, V., Ed.; Wiley-VCH: Weinheim, 2001; Vol. 2, Organic Molecules, pp 5−54. (d) Mella, M.; Fagnoni, M.; Freccero, M.; Fasani, E.; Albini, A. *Chem. Soc. Rev.* **1998**, *27*, 81.

(8) (a) Alali, F. Q.; Liu, X.-X.; McLaughlin, J. L. *J. Nat. Prod.* **1999**, *62*, 504. (b) Hoppe, R.; Scharf, H.-D. *Synthesis* **1995**, 1447.

(9) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897.

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(11) (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.

(12) For a related approach to the enantioselective synthesis of bisepoxides, see ref 3b.

(13) Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376.

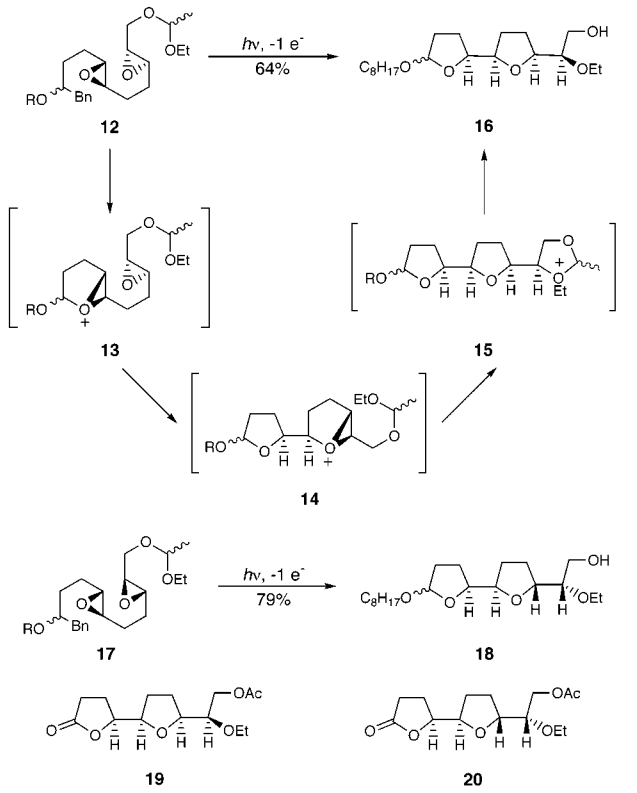


Figure 3. Cascade cyclizations followed by alkoxy-group transfer.

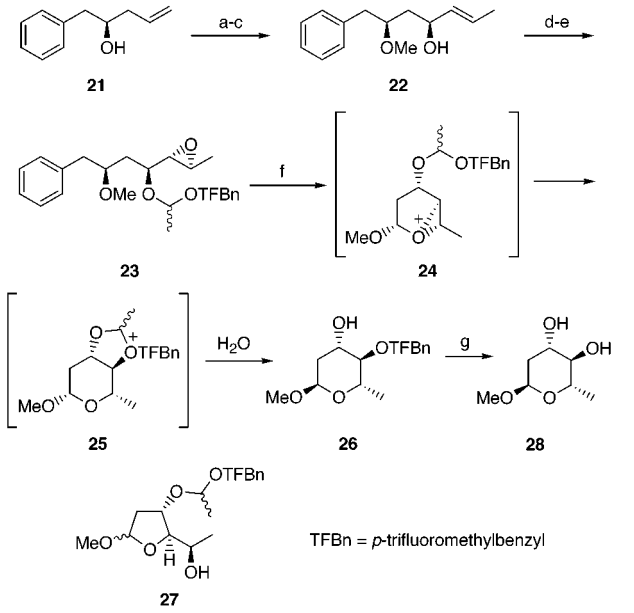
forms **16**. The anomeric mixture of **16** was converted to a single lactone (**19**) by acetylation followed by oxidation with Jones' reagent. To obtain additional evidence for the stereospecificity of epoxonium ion opening in this series, we prepared bisepoxide **17**, in which the absolute stereochemistry of the epoxide groups was set by sequential Sharpless[14] and Shi epoxidations on the dienyl alcohol precursor.[9] Oxidative cyclization of **17** provided **18** in 79% yield as a 1:1 mixture of anomers under stoichiometric conditions and in 69% yield under catalytic conditions. Conversion of **18** to lactone **20** proceeded as before.

Epoxonium ion **13** opens exclusively through a 5-*exo*-pathway. This result contrasts with McDonald's observation[3b] that the 6-*endo*-pathway is kinetically preferred over the 5-*exo*-pathway for intramolecular reactions between epoxides and epoxonium ions. Although our photoinitiated reaction conditions differ substantially from McDonald's Lewis acid mediated processes, we postulate that this discrepancy can largely be ascribed to the different substitution patterns of the epoxonium ions in each study. The 6-*endo*-ring-opening reactions of trisubstituted epoxonium ions reported by McDonald can be explained by nucleophilic attack at the carbon that is better disposed to tolerate cationic character due to increased alkyl substitution.[15] Our results indicate that, in the absence of a substitution-induced bias, 5-*exo*-cyclizations proceed in preference to 6-*endo*-cyclizations.

(14) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5675. (b) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

To expand the structural motifs that can be accessed through this method, we prepared cyclization substrate **23** according to the route shown in Scheme 1. Methylation of

Scheme 1. Cascade Approach to Methyl Olivoside[a]



[a] Reagents and conditions: (a) NaH, MeI, DMF, 82%. (b) O_3, CH_2Cl_2, −78 °C, then Ph_3P, rt, then propynylmagnesium bromide, 68%, 3:1 misture of diasteromers. (c) $LiAlH_4$, Et_2O, reflux 85%. (d) $Ti(O^iPr)_4$, (+)-diisopropyl tartrate, ^{t}BuOOH, 4 Å MS, CH_2Cl_2, −20 °C, 91%. (e) TFBnOCH(CH_3)Cl, *N*,*N*-dimethylaniline, CH_2Cl_2, 93%. (f) NMQPF$_6$, *hν*, 0_2, $Na_2S_2O_3$, NaOAc, 1,2-dichloroethane, toluene, 46%. (g) H_2, Pd/C, EtOAc, Et_3N.

the known[16] alcohol **21**, readily available in high enantiomeric excess from a Brown allylation,[17] followed by ozonolysis, propynylmagnesium bromide addition, and reduction of the resulting *anti*-isomer with $LiAlH_4$ in refluxing diethyl ether produced allylic alcohol **22**. Epoxidation of **22** under Sharpless' conditions[18] provided a single diastereomer that was converted to trifluoromethylbenzyloxyethyl acetal **23** under standard conditions.[19] The *p*-trifluoromethylbenzyl acetal was employed because, although cleavable by hydrogenolysis,[20] the trifluoromethylbenzyl group is stable under the standard oxidative reaction conditions. Subjecting **23** to catalytic cyclization conditions provided selectively protected olivose derivative **26** in 46% yield as a 4:1 mixture of

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(16) Koide, K.; Finkelstein, J. M.; Ball, Z.; Verdine, G. L. *J. Am. Chem. Soc.* **2001**, *123*, 398.

(17) (a) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432. (b) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092.

(18) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(19) The chloro-ether was prepared by bubbling anhydrous HCl gas through a solution of acetaldehyde and *p*-trifluoromethylbenzyl alcohol in benzene at 0 °C for 6 h.

(20) Liotta, L. J.; Dombi, K. L.; Kelley, S. A.; Targontsidis, S.; Morin, A. M. *Tetrahedron Lett.* **1997**, *38*, 7833.

anomers, with the α-isomer being the major product. This reaction proceeds initially through epoxonium ion **24**, which undergoes alkoxy group transfer through fused bicyclic intermediate **25**. Furanoside **27**, the product of bimolecular epoxonium ion opening with water, can be isolated in varying quantities if the reaction is not performed under anhydrous conditions, providing further support for the intermediacy of **24**. Structural confirmation of **26** was provided through hydrogenolysis to the known[21] olivose derivative **28**.

No evidence of direct trifluoromethylbenzyloxy group transfer to the initially formed oxonium was detected, even though this reaction would proceed through a kinetically favorable six-*exo*-*trig* pathway.[22] This indicates that either epoxides are superior nucleophiles relative to acyclic ethers (at least inductively deactivated *p*-trifluoromethylbenzyl ethers) or that acetal attack is reversible, whereas the strained epoxonium reacts rapidly and irreversibly with pendent nucleophiles.

In summary, we have demonstrated that single-electron oxidation is an effective method for initiating heterogenerative cascade reactions. Mesolytic benzylic carbon−carbon bond cleavages of the radical cations of homobenzylic ethers form oxonium ions, which react with pendent epoxide groups to form epoxonium ions that can undergo further cyclization reactions. Bistetrahydrofuran compounds are formed efficiently under both stoichiometric and catalytic aerobic conditions when ether groups are used as cascade-terminating nucleophiles. Alkoxy-group transfer from an acetal to an epoxonium ion is an effective method for installing a protected secondary alcohol with complete stereocontrol. In the absence of a substitution-induced bias, epoxonium ions were shown to undergo intramolecular reactions with epoxides through a 5-*exo* pathway in preference to a 6-*endo* pathway. Fused intermediates are accessible by altering the substrate structure, leading to stereoselective syntheses of highly substituted tetrahydropyran compounds. In addition to synthetic applications, activation of epoxide groups through intramolecular cyclization reactions is an excellent method for studying the preferred reaction pathways of intramolecular additions to synthetically useful epoxonium ions.

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Supporting Information Available: Synthetic schemes and characterizations for all cyclization products. This material is available free of charge via the Internet at http://pubs.acs.org.

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