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Electrophilic aromatic prenylation via cascade cyclization

John G. Kodet, Joseph J. Topczewski, Kevyn D. Gardner, and David F. Wiemer*

Department of Chemistry, University of Iowa, Iowa City, Iowa 52242-1294 USA

Abstract

To gain access to prenylated hexahydroxanthenes, tandem cascade cyclization-electrophilic aromatic substitution reactions have been studied on substrates bearing allylic and propargylic substituents. Both $\text{BF}_3 \cdot \text{OEt}_2$ and TMSOTf can be used to initiate this reaction sequence, resulting in different ratios of the C-2 and C-6 substitution products. Even though allylic transposition is observed in some cases, the results of a crossover experiment are consistent with an intramolecular reaction sequence. Taken together, these studies now allow preparation of either the C-2 or C-6 prenylated hexahydroxanthene products.

Keywords

Cationic; Cyclization; Electrophilic aromatic substitution; Prenylation; Tandem reactions

1. Introduction

Prenylated aromatic compounds are common natural products and individual examples are known to possess a wide variety of biological properties. Various compounds in the broad family display activity as anti-proliferative,^{1,2} anti-oxidant,³⁻⁵ chemopreventative,⁶ CNS modulating,^{7,8} or immunosuppressant agents,⁹ and as insect repellents.^{10,11} Common methods for incorporation of a prenyl moiety into an aromatic system include the use of lithiated intermediates,¹²⁻¹⁵ an approach which displays limited functional group tolerance, Friedel-Crafts alkylation,^{12,16-18} which often proceeds in modest yield even with an excess of the arene, or Claisen rearrangements,¹⁹⁻²² where the regiochemistry both about the allylic system and in the arene can be difficult to control. Our preliminary account²³ of a new reaction sequence based on cascade cyclization with tandem electrophilic aromatic substitution (Figure 1) suggested a route to prenylated aromatic compounds with the potential to overcome at least some of these limitations. Furthermore, cascade cyclization via an epoxide intermediate allows formation of several new bonds in a single reaction,²⁴ with the A- and B-ring absolute stereochemistry ultimately derived from the reagents employed for epoxide formation. The value of this approach is only enhanced to the extent that it can be coupled with a regioselective electrophilic aromatic substitution reaction,²⁵ because different isoprenoid substituents often are found at specific positions on the

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*Corresponding author. Tel.: +1 319 335 1365; fax: +1 319 335 1270. david-wiemer@uiowa.edu (D.F. Wiemer).

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Supplementary Material

The ¹H and/or ¹³C NMR spectra for compounds 9–11, 13, 15, 16, 18, 20–25, 27, and 28. This material is available free of charge via the Internet at:

aromatic ring.²⁶⁻³⁰ This report describes efforts to bring about cascade cyclization with electrophilic aromatic substitution on resorcinols bearing allylic and propargylic substituents, some of which are isoprenoid and others that might be viewed as precursors to isoprenoid groups, and delineates strategies that allow preparation of different prenylated regioisomers.

In the initial description of this sequence,²³ epoxide **1** was converted to the tricyclic compound **2** through a process initiated by treatment with $\text{BF}_3 \cdot \text{OEt}_2$. The product was elaborated to the natural product (+)-angelichalcone (**3**).²³ A subsequent effort employed the aromatic system **4**, demonstrated transformation of the tandem reaction product **5** to a phenol, and ultimately to (+)-schweinfurthin A (**6**).²⁵ Those results suggested that the ability of the phenolic substituent to stabilize at least a partial positive charge was central to its participation in the tandem sequence. Given the delocalization available in a prenyl cation,³¹ and the roles that such cations play in biosynthesis,³² there was reason to believe that a parallel process might be observed with a prenyl ether. However, nothing was known about the regiochemistry of the process either with respect to the site of EAS or that within a resulting prenyl substituent. Our studies of these questions are the subject of this report.

2. Results and Discussion

To this point only one allylic substituent has been examined for participation in this tandem reaction sequence, the diallyl ether **7** (Scheme 1).²⁵ Brief treatment of epoxide **7** with $\text{BF}_3 \cdot \text{OEt}_2$ gave the tandem product **8** in low yield (8%) along with a significant amount of the cyclic ether **9** (32%).²⁵ Because the C-allyl substituent can be viewed as a precursor to a prenyl group (*vide infra*), our interest was drawn to procedures that might optimize the formation of compound **8**. One strategy for increasing the yield of the desired hexahydroxanthene products would be to diminish formation of the bridged A-ring ether by-products. Because these side products presumably are formed from attack of the A-ring oxygen on a tertiary carbocation, we hypothesized that opening the epoxide with a Lewis acid that hindered this capture might increase the formation of hexahydroxanthene products. While some Lewis acids other than $\text{BF}_3 \cdot \text{OEt}_2$ have been studied with limited success,³³ one which fit this new hypothesis and had not been studied was TMSOTf .³⁴

To this end, the allyl epoxide **7** was treated with TMSOTf and four major products were isolated (Scheme 1). As one might anticipate, formation of the A-ring ether was affected, and it was impacted in several ways. First of all, under the TMSOTf conditions the A-ring ether **9** was isolated as a 3:2 mixture of diastereomers. This partial epimerization may indicate an appreciably long-lived carbocation or some degree of reversibility in the cascade.³⁵ Furthermore, the elimination product **11** also became significant which may support the concept of a long-lived carbocation. Finally, in striking contrast to the $\text{BF}_3 \cdot \text{OEt}_2$ mediated reactions of compound **7**, upon treatment with TMSOTf the regiochemistry of the product hexahydroxanthene varied and the distal isomer **10** now was found as the major product. Unfortunately, further efforts to optimize use of TMSOTf went unrewarded.

It is possible that a more highly substituted allylic system would afford the tandem product in better yield than the allyl case, especially if the substituent(s) would provide more stabilization to a cationic intermediate. However, incorporation of substituents that would afford unsymmetrical allyl cations also would present issues of regiochemistry and/or stereochemistry that do not trouble the parent allyl ether, and may afford still more complex product mixtures. The crotyl derivative was examined based on the hypothesis that the added methyl group would stabilize the putative cationic intermediate relative to the parent allyl group. After preparation of the epoxide **12** through standard methods,^{25,36} exposure of this epoxide to $\text{BF}_3 \cdot \text{OEt}_2$ resulted in facile cyclization (Scheme 2). In this case, the

predominant product had undergone hexahydroxanthene formation with concurrent aromatic substitution, and it had done so in a reasonably attractive yield (58%). This reaction furnished the substitution product **13** as a mixture of diastereomers (~2:1) at the new benzylic position. The observed regiochemistry of the substituent can be explained through electrophilic aromatic substitution via the more substituted allylic terminus, and the linear isomer was not detected in any measureable amount. To determine if the olefin stereochemistry was involved in the transfer of stereochemical information to the new benzylic position, commercial crotyl chloride also was employed to prepare the substrate **12** as a ~3:1 mixture of olefin isomers. When this material was treated with $\text{BF}_3 \cdot \text{OEt}_2$ under standard conditions, the only product observed was the C-2 substituted hexahydroxanthene, and it was isolated as a ~2.5:1 mixture of the branched diastereomers. Because both the pure *E*-olefin **12** and the mixed *E/Z* material gave the branched product as a mixture of diastereomers in a similar ratio, it appears likely that formation of this center is not determined directly by the olefin stereochemistry of the starting material.

Several related systems also were examined in an effort to gauge the scope of this process. A known two-step method was used to introduce the propargyl groups of the bis ethers **14** and **17**.^{37,38} When epoxide **14** was subjected to the standard cascade conditions (Scheme 3), the major product was the bridged A-ring ether **15** (47%) although it was accompanied by the hexahydroxanthene **16** in low yield (14%). The parallel reaction of the propargyl ether **17** gave only the bridged A-ring ether **18** (47%), and the hexahydroxanthene **19** was not detected in this reaction mixture. A standard reduction of compound **14** over Lindlar's catalyst gave the corresponding "reversed" prenyl compound **20**. When epoxide **20** was subjected to cascade conditions, the bridged A-ring ether **21** was isolated in low yield (12%) as the only identifiable product from a very complicated mixture.

To extend this study further in the prenyl series, epoxide **22** was prepared from epoxide **7** through a metathesis reaction with 2-methyl-2-butene and Grubbs' 2nd generation catalyst under Lipshutz's conditions (Scheme 4).^{39,40} Cyclization of the resulting prenyl epoxide **22** upon treatment with $\text{BF}_3 \cdot \text{OEt}_2$ provided three hexahydroxanthene products, and all of those had undergone aromatic substitution. Based on the ^1H NMR spectrum, it was clear that the major product **23** bears a "normal" prenyl substituent at the C-2 position. The other two compounds had undergone substitution at the C-6 position, which might be expected from a more stabilized cation,²⁵ and were obtained as an inseparable mixture of allylic isomers with the reversed prenyl compound **24** dominating over the normal prenyl isomer **25** (18% and 11% respectively, by ^1H NMR). While prenylation at either C-2 or C-6 could be useful, formation of a mixture of the two regioisomeric products, with one product further complicated as a mixture of olefin isomers, was less attractive. However, compound **10** undergoes cross-metathesis with 2-methyl-2-butene in 83% yield to give the prenyl derivative **25**, a product that was not available as a pure isomer by direct cyclization of the prenyl epoxide **22**. Thus, both the C-2 and C-6 prenyl arenes **23** and **25** can be obtained selectively by this general methodology, although different reaction sequences appear to be required.

In contrast to the reaction with $\text{BF}_3 \cdot \text{OEt}_2$, treatment of compound **22** with one equivalent of TMSOTf resulted in a 20% yield of a mixture of compounds **24** and **25** in a ratio of 5 to 2 respectively. Although compound **23** was not observed under these conditions, it was obtained when the TMSOTf was used in excess (2.6 eq gave a 14% yield of **23**) while amounts of compounds **24** and **25** decreased and more undesired side products were observed.

The various allylic and propargylic systems examined yield a number of different product types, and they also lead to increased understanding of this complicated reaction sequence.

One might consider two explanations for the absence of the linear isomer from the crotyl epoxide **12**. The more straightforward one is that the branched product is the result of enhanced cationic character at the more substituted terminus of the allylic system. A second potential explanation would be that the mechanism of this process with allylic substrates is based upon a Claisen rearrangement pathway.^{41,42} However, if the Claisen mechanism were operative in all cases, then one would expect a reversed prenyl group at the C-2 position in the product obtained from compound **22**, and that was not observed.

The selectivity observed for the normal prenylated product **23** at the C-2 position (Scheme 4), and the observed mixture of isomers found in the C-6 substituted product (**24** and **25**), suggested that the C-6 products might arise from an intermolecular process while the C-2 product might result from an intramolecular process. Previous studies have shown that another C-2 substituted hexahydroxanthene results from an intramolecular transfer,²³ but the nature of substitution at the C-6 position has not yet been examined. To explore the process leading to formation of the C-6 product, a new type of crossover experiment was conducted (Scheme 5). Highly deuterated isoprenoids have been employed in a variety of studies of terpene biosynthesis,⁴³ and they commonly have been prepared through Wittig chemistry.⁴⁴⁻⁴⁶ To begin this study, the deuterium labeled prenyl epoxide **28** was synthesized through a metathesis strategy. Hexadeutero-2-methyl-2-butene (**27**)^{47,48} was prepared by Wittig condensation of *d*₆-acetone (**26**) with ethylidene triphenylphosphorane prepared in situ from the corresponding phosphonium bromide. Due to the volatility of the deuterated olefin **27**, it was prepared as a solution in THF and then used directly in the cross metathesis reaction to provide labeled epoxide **28**. After a ~60:40 mixture of epoxides **28** and **22** was subjected to standard cyclization conditions, the hexahydroxanthene products were isolated and analyzed by GC-MS in comparison to authentic samples. This analysis revealed that D₀ and D₁₂ compounds were present, but little D₆ product was observed (Table 1). The near absence of any cross-over products suggested that both the C-2 and C-6 substituted compounds arise from an intramolecular process (or processes), despite the loss of selectivity about the allylic system.

A single mechanism that would unify these data is difficult to envision. With phenolic substituents that contain an allylic system, for example compound **22** (Scheme 6), an initial cyclization might afford the oxonium ion **29** where [3,3] rearrangements clearly would be possible. However, in the prenyl system found in compound **22**, such a rearrangement of intermediate **29** to provide the C-2 product would be expected to occur with allylic transposition, contrary to the retention of the olefinic position that is observed. At the same time, rearrangement to the C-6 substituted product would require two allylic transpositions, or net retention,⁴⁹ which is contrary to the mixture of compounds **24** and **25** that is formed. Thus it may be more likely that dissociation of intermediate **29** to an allylic cation and compound **30** is followed by electrophilic aromatic substitution to afford the observed mixture of products **23** to **25**, and the lack of significant crossover products suggests that the substitution would have to be fast.

3. Conclusion

In conclusion, these studies have expanded the scope of cascade cyclizations terminated by electrophilic aromatic substitution in several ways. For the first time TMSOTf has been shown to serve as a Lewis acid able to bring about the tandem cascade cyclization-electrophilic aromatic substitution sequence, and its use has provided a unique product distribution. Through variations of these procedures, it now is possible to obtain the regioisomeric prenyl-substituted hexahydroxanthenes **23** and **25**. During the course of this work, a cross-over experiment established that both the C-2 and the C-6 substitution products are formed at least predominantly through an intramolecular process, which

increases the mechanistic understanding of this tandem sequence. Thus it appears likely that further studies of this reaction sequence will unveil additional applications.

4. Experimental

4.1 General Experimental

Tetrahydrofuran and ether were freshly distilled from sodium/benzophenone. Methylene chloride and triethylamine were distilled from calcium hydride prior to use. All other reagents and solvents were purchased from commercial sources and used without further purification. All reactions in nonaqueous solvents were conducted in flame dried glassware under a positive pressure of argon and with magnetic stirring. NMR spectra were obtained at 300–500 MHz for ^1H , and 75–125 MHz for ^{13}C with CDCl_3 or CD_3OD as solvent, and $(\text{CH}_3)_4\text{Si}$ (^1H , 0.00 ppm) or CDCl_3 (^{13}C , 77.0 ppm or 49.0 ppm) as internal standards unless otherwise noted. High resolution mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. Silica gel (60 Å, 0.040–0.063 mm) was used for flash chromatography.

4.2 General Procedure for Cascade Cyclizations with $\text{BF}_3\cdot\text{OEt}_2$

To a solution of the epoxide (~0.20 mmol) in CH_2Cl_2 (25 mL) at -78°C was added $\text{BF}_3\cdot\text{OEt}_2$ (0.20 mL, 1.6 mmol). After 10 min, the reaction was quenched by addition of triethylamine (0.5 mL), diluted with HCl, and extracted with CH_2Cl_2 . The organic phase was washed with water followed by brine, dried (MgSO_4), filtered, and concentrated in vacuo. Final purification by column chromatography (ethyl acetate in hexanes) afforded products as indicated below, generally as colorless oils.

4.2.1. (E)-6-(But-2-enyloxy)-5-(but-3-en-2-yl)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (13)—According to the general procedure, a solution of epoxide **12**³⁶ (114 mg, 0.31 mmol) in CH_2Cl_2 (60 mL) at -78°C was treated with $\text{BF}_3\cdot\text{OEt}_2$ (0.20 mL, 1.6 mmol). After 10 min, the reaction was quenched, and standard work-up gave compound **13** as a 2.1:1 mixture of diastereomers (66 mg, 58%). For the major component: ^1H NMR (CDCl_3) δ 6.83 (dd, $J = 8.5, 0.9$ Hz, 1H), 6.43 (d, $J = 8.4$ Hz, 1H), 6.25 (ddd, $J = 17.2, 10.1, 6.9$ Hz, 1H), 5.85–5.76 (m, 1H), 5.74–5.66 (m, 1H), 4.99 (ddd, $J = 17.3, 2.0, 1.6$ Hz, 1H), 4.87 (ddd, $J = 10.2, 2.1, 1.4$ Hz, 1H), 4.41–4.39 (m, 2H), 4.16–4.08 (m, 1H), 3.42 (dd, $J = 11.6, 4.1$ Hz, 1H), 2.67–2.62 (m, 2H), 2.01 (dt, $J = 12.6, 3.2$ Hz, 1H), 1.87–1.58 (m, 7H), 1.53 (br s, 1H), 1.34 (d, $J = 7.2$ Hz, 3H), 1.17 (s, 3H), 1.07 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (CDCl_3) δ 155.3, 151.6, 143.4, 129.0, 127.1, 126.8, 121.8, 114.9, 111.8, 105.3, 78.1, 75.9, 69.7, 46.7, 38.2, 37.7, 33.5, 28.2, 27.2, 22.8, 19.8, 18.4, 17.9, 14.2. For the minor diastereomer: ^1H NMR (CDCl_3) δ 6.83 (dd, $J = 8.5, 0.9$ Hz, 1H), 6.43 (d, $J = 8.4$ Hz, 1H), 6.26 (ddd, $J = 17.1, 10.1, 7.4$ Hz, 1H), 5.85–5.76 (m, 1H), 5.74–5.66 (m, 1H), 4.98 (ddd, $J = 17.2, 2.1, 1.4$ Hz, 1H), 4.85 (ddd, $J = 10.1, 2.1, 1.1$ Hz, 1H), 4.41–4.39 (m, 2H), 4.16–4.08 (m, 1H), 3.42 (dd, $J = 11.6, 4.1$ Hz, 1H), 2.67–2.62 (m, 2H), 2.01 (dt, $J = 12.6, 3.2$ Hz, 1H), 1.87–1.58 (m, 7H), 1.53 (br s, 1H), 1.36 (d, $J = 7.2$ Hz, 3H), 1.19 (s, 3H), 1.07 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (CDCl_3) δ 155.3, 151.4, 143.2, 129.0, 127.1, 126.8, 121.7, 114.9, 111.9, 105.4, 78.1, 75.9, 69.7, 46.7, 38.2, 37.8, 33.8, 28.2, 27.2, 22.8, 19.6, 18.7, 17.9, 14.2; HRMS (EI) m/z calcd for $\text{C}_{24}\text{H}_{34}\text{O}_3$ (M^+) 370.2508, found 370.2504.

4.2.2. 2-(2,4-bis(2-Methylbut-3-yn-2-yloxy)benzyl)-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptanes and 1,1,4a-trimethyl-6-(2-methylbut-3-yn-2-yloxy)-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (15 and 16)—According to the general procedure, epoxide **14**³⁶ (51 mg, 0.13 mmol) in CH_2Cl_2 (26 mL) was treated with $\text{BF}_3\cdot\text{OEt}_2$ (0.08 mL, 0.65 mmol). After 10 min, standard work-up and purification by column chromatography gave compound **15** (24 mg, 47%) and compound **16** (6 mg, 14%),

both as colorless oils. For compound **15**: ^1H NMR (CDCl_3) δ 7.46 (d, $J = 2.4$ Hz, 1H), 7.06 (d, $J = 8.4$ Hz, 1H), 6.74 (dd, $J = 8.4, 2.4$ Hz, 1H), 3.73 (d, $J = 5.3$ Hz, 1H), 2.59–2.55 (m, 2H), 2.56 (s, 1H), 2.54 (s, 1H), 1.95–1.90 (m, 2H), 1.72–1.65 (m, 1H), 1.68 (s, 6H), 1.63 (s, 6H), 1.58–1.51 (m, 1H), 1.47–1.42 (m, 1H), 1.28 (s, 3H), 1.00 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (CDCl_3) δ 153.7, 153.5, 129.5, 127.7, 114.9, 112.0, 89.9, 86.4, 86.2, 86.1, 73.5, 73.4, 72.3, 71.7, 54.0, 45.6, 39.0, 29.7, 29.6, 29.5, 27.5, 25.9, 25.8, 23.8, 19.1; HRMS (EI) m/z calcd for $\text{C}_{26}\text{H}_{34}\text{O}_3$ (M^+) 394.2508, found 394.2504. For compound **16**: ^1H NMR (CDCl_3) δ 6.95 (d, $J = 8.3$ Hz, 1H), 6.70 (dd, $J = 8.3, 2.5$ Hz, 1H), 6.66 (d, $J = 2.4$ Hz, 1H), 3.42 (dd, $J = 11.5, 4.2$ Hz, 1H), 2.67–2.63 (m, 2H), 2.55 (s, 1H), 2.01–1.97 (m, 1H), 1.87–1.82 (m, 1H), 1.78–1.60 (m, 4H), 1.62 (s, 3H), 1.61 (s, 3H), 1.27 (s, 3H), 1.09 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (CDCl_3) δ 154.7, 153.2, 129.5, 116.5, 113.7, 110.0, 86.3, 78.1, 76.3, 73.6, 72.2, 47.0, 38.4, 37.8, 29.6, 29.6, 28.3, 27.3, 22.6, 19.9, 14.3; HRMS (EI) m/z calcd for $\text{C}_{21}\text{H}_{28}\text{O}_3$ (M^+) 328.2038, found 328.2034.

4.2.3 (E)-3-(5-(2,4-bis(Prop-2-ynyloxy)phenyl)-3-methylpent-3-enyl)-2,2-dimethyloxirane (**18**)

—According to the general procedure, epoxide **17**³⁶ (89 mg, 0.26 mmol) in CH_2Cl_2 (53 mL) at -78°C was treated with $\text{BF}_3\cdot\text{OEt}_2$ (0.17 mmol, 1.3 mmol). After 10 min, standard work-up and purification by column chromatography gave ether **18** (42 mg, 47%) as a colorless oil: ^1H NMR (CDCl_3) δ 7.10 (d, $J = 8.4$ Hz, 1H), 6.60 (d, $J = 2.4$ Hz, 1H), 6.52 (dd, $J = 8.3, 2.5$ Hz, 1H), 4.68–4.66 (m, 4H), 3.74 (d, $J = 5.3$ Hz, 1H), 2.59–2.57 (m, 2H), 2.54 (t, $J = 2.3$ Hz, 1H), 2.50 (t, $J = 2.4$ Hz, 1H), 1.97–1.47 (m, 5H), 1.30 (s, 3H), 1.00 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (CDCl_3) δ 156.4, 156.1, 130.1, 124.1, 105.6, 100.6, 86.9, 86.0, 78.6, 78.5, 75.5, 75.4, 55.9, 55.8, 54.2, 45.6, 38.9, 36.6, 25.9, 25.7, 23.8, 19.0; HRMS (EI) m/z calcd for $\text{C}_{22}\text{H}_{26}\text{O}_3$ (M^+) 338.1882, found 338.1882.

4.2.4 2-(2,4-bis(2-Methylbut-3-en-2-yloxy)benzyl)-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane (**21**)

—According to the general procedure, epoxide **20** (65 mg, 0.16 mmol) in CH_2Cl_2 (32 mL) at -78°C was treated with $\text{BF}_3\cdot\text{OEt}_2$ (0.1 mL, 0.8 mmol). After 8 min, standard workup and purification by column chromatography gave ether **21** (8 mg, 12%): ^1H NMR (CDCl_3) δ 6.98 (d, $J = 8.5$ Hz, 1H), 6.69 (d, $J = 2.4$ Hz, 1H), 6.49 (dd, $J = 8.3, 2.5$ Hz, 1H), 6.12 (dd, $J = 10.9, 4.9$ Hz, 1H), 6.06 (dd, $J = 10.9, 4.9$ Hz, 1H), 5.20–5.07 (m, 4H), 3.72 (d, $J = 5.2$ Hz, 1H), 2.63–2.48 (m, 2H), 1.98–1.88 (m, 2H), 1.76–1.52 (m, 3H), 1.46 (s, 6H), 1.39 (s, 6H), 1.28 (s, 3H), 1.00 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (CDCl_3) δ 154.1, 153.6, 144.7, 144.5, 129.3, 126.9, 114.5, 113.0, 113.0, 112.5, 86.9, 86.1, 79.3, 79.2, 53.9, 45.6, 39.0, 27.7, 27.3, 27.2, 26.9, 26.8, 25.9, 25.8, 23.8, 19.1; HRMS (EI) m/z calcd for $\text{C}_{26}\text{H}_{38}\text{O}_3$ (M^+) 398.2821, found 398.2820.

4.2.5 1,1,4a-Trimethyl-5-(3-methylbut-2-enyl)-6-(3-methylbut-2-enyloxy)-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (**23**)

—According to the general procedure, a solution of epoxide **22** (81 mg, 0.20 mmol) in CH_2Cl_2 (25 mL) at -78°C was treated with $\text{BF}_3\cdot\text{OEt}_2$ (0.20 mL, 1.6 mmol). After 10 min, the reaction was quenched, and standard work-up gave compound **23** (25 mg, 31%) along with a mixture of compounds **24** and **25** (23 mg, 28% total, 3:2 **24**:**25**). For compound **23**: ^1H NMR (CDCl_3) δ 6.84 (d, $J = 8.4$ Hz, 1H), 6.44 (d, $J = 8.4$ Hz, 1H), 5.48 (t, $J = 6.4$ Hz, 1H), 5.20 (t, $J = 7.4$ Hz, 1H), 4.47 (d, $J = 6.5$ Hz, 2H), 3.42 (dd, $J = 11.5, 7.4$ Hz, 1H), 3.28 (d, $J = 7.4$ Hz, 2H), 2.65–2.62 (m, 2H), 2.00 (dt, $J = 12.2, 3.2$ Hz, 1H), 1.87–1.82 (m, 1H), 1.79–1.69 (m, 4H), 1.77 (s, 3H), 1.77 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H), 1.17 (s, 3H), 1.08 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (CDCl_3) δ 155.6, 151.2, 136.6, 130.3, 126.6, 123.1, 120.7, 118.1, 114.4, 104.4, 78.2, 75.8, 65.5, 46.9, 38.3, 37.9, 28.3, 27.3, 25.9, 25.7, 22.7, 22.4, 20.0, 18.2, 17.9, 14.2; HRMS (EI) m/z calcd for $\text{C}_{26}\text{H}_{38}\text{O}_3$ (M^+) 398.2821, found 398.2825.

4.2.6 1,1,4a-Trimethyl-7-(3-methylbut-2-enyl)-6-(3-methylbut-2-enyloxy)-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol and 1,1,4a-trimethyl-6-(3-methylbut-2-enyloxy)-7-(2-methylbut-3-en-2-yl)-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (24 and 25)—¹H NMR (CDCl₃) δ 6.92 (s, 1H), 6.79 (s, 0.7H), 6.31 (s, 1H), 6.31 (s, 0.7H), 6.21 (dd, *J* = 14.8, 10.7 Hz, 1H), 5.50 (m, 1.7H), 5.29 (m, 0.7H), 4.96 (dd, *J* = 14.0 Hz, 1.6 Hz, 1H), 4.92 (dd, *J* = 7.0, 1.6 Hz, 1H), 4.42 (m, 3.4H), 3.41 (dd, *J* = 11.2, 4.2 Hz, 1.7H), 3.23 (d, *J* = 7.3 Hz, 1.4H), 2.61 (m, 3.4H), 1.99 (m, 1.7H), 1.84 (m, 1.7H), 1.75–1.65 (m, 6.8H), 1.78 (s, 5.1H), 1.74 (s, 2.1H), 1.70 (s, 5.1H), 1.68 (s, 2.1H), 1.43 (s, 6H), 1.22 (s, 3H), 1.21 (s, 2.1H), 1.09 (s, 3H), 1.08 (s, 2.1H), 0.87 (s, 3H), 0.86 (s, 2.1H); ¹³C NMR (CDCl₃) δ 156.7, 155.7, 151.7, 151.4, 148.5, 136.9, 136.4, 131.7, 129.6, 128.5, 127.8, 123.2, 122.1, 120.3, 112.8, 112.2, 109.4, 101.5, 100.6, 78.1, 78.1, 76.3, 76.2, 65.1, 65.0, 47.3, 47.2, 40.0, 38.4, 38.3, 37.8, 28.2, 27.7, 27.4, 27.4, 27.3, 27.2, 25.9, 25.7, 25.6, 22.5, 22.3, 20.0, 19.9, 18.1, 17.7, 14.3, 14.2; HRMS (EI) *m/z* calcd for C₂₆H₃₈O₃ (M⁺) 398.2821, found 398.2815.

4.3 Cyclization of epoxide 7 with TMSOTf

4.3.1. 7-Allyl-6-(allyloxy)-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (10)—To a solution of epoxide **7** (90 mg, 0.26 mmol) in CH₂Cl₂ (30 mL) at –78 °C was added TMSOTf (0.25 mL, 1.4 mmol). After 12 min, the reaction was quenched by addition of 1N HCl (10 mL), diluted with water, and extracted with CH₂Cl₂. The organic phase was washed brine, dried (MgSO₄), filtered, and the filtrate was concentrated in vacuo. Final purification by column chromatography (20% ethyl acetate in hexanes) afforded a mixture of compounds **9** (16 mg, 18%), **11** (15 mg, 17%), **10** (29 mg, 32%), and the known compound **8**²⁴ (9 mg, 10%) as yellow oils. For the title compound **10**: ¹H NMR (CDCl₃) δ 6.82 (s, 1H), 6.29 (s, 1H), 6.08–5.93 (m, 2H), 5.40 (m, 1H), 5.24 (m, 1H), 5.03 (m, 2H), 4.46 (m, 2H), 3.41 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.32 (d, *J* = 6.2 Hz, 2H), 2.62 (m, 2H), 1.98 (dt, *J* = 12.4, 3.3 Hz, 1H), 1.85 (dq, *J* = 12.8, 3.8 Hz, 1H), 1.73 (td, *J* = 13.6, 3.2 Hz, 1H), 1.67–1.58 (m, 2H), 1.48 (br, 1H), 1.21 (s, 3H), 1.08 (s, 3H), 0.87 (s, 3H); ¹³C NMR (CDCl₃) δ 155.4, 151.9, 137.6, 133.5, 130.2, 120.7, 116.7, 115.0, 113.3, 100.8, 78.1, 76.3, 68.7, 47.2, 38.4, 37.8, 33.8, 28.2, 27.4, 22.3, 19.8, 14.3; HRMS (EI) *m/z* calcd for C₂₂H₃₀O₃ (M⁺) 342.2195, found 342.2197.

4.3.2. 2-(2,4-bis(Allyloxy)benzyl)-1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptane (9)—Obtained as a 3:2 ratio of diastereomers. ¹H NMR (CDCl₃) δ 7.05 (d, *J* = 8.4 Hz, 1H), 7.01 (d, *J* = 8.2 Hz, 0.65H), 6.45–6.40 (m, 3.3H), 6.09–6.01 (m, 3.3H), 5.44–5.39 (m, 3.3H), 5.30–5.25 (m, 3.3H), 4.52 (m, 6.6H), 3.79 (d, *J* = 5.3 Hz, 0.65H), 3.73 (d, *J* = 5.4 Hz, 1H), 2.64 (dd, *J* = 14.2, 7.0 Hz, 0.65H), 2.60 (d, *J* = 7.6 Hz, 2H), 2.42 (dd, *J* = 14.2, 8.4 Hz, 0.65H), 1.95–1.42 (m, 8.5H), 1.30 (s, 3H), 1.09 (s, 2H), 1.02 (s, 2H), 1.01 (s, 3H), 0.94 (s, 3H), 0.90 (s, 2H).

4.3.3. 5-(2,4-bis(Allyloxy)benzyl)-4,6,6-trimethylcyclohex-3-enol (11)—¹H NMR (CDCl₃) δ 7.09 (d, *J* = 8.0 Hz, 1H), 6.45–6.43 (m, 2H), 6.10–6.02 (m, 2H), 5.44–5.38 (m, 2H), 5.30–5.23 (m, 3H), 4.56–4.49 (m, 4H), 3.52 (dd, *J* = 7.7, 5.6 Hz, 1H), 2.86 (dd, *J* = 14.8, 4.2 Hz, 1H), 2.73 (dd, *J* = 14.8, 8.2 Hz, 1H), 2.36 (m, 1H), 2.24 (m, 1H), 2.06–2.00 (m, 1H), 1.52 (br s, 1H), 1.49 (s, 3H), 0.99 (s, 3H), 0.92 (s, 3H); ¹³C NMR (CDCl₃) δ 157.7, 157.0, 137.5, 133.5, 133.4, 130.3, 124.4, 118.3, 117.6, 117.3, 105.2, 100.3, 75.1, 68.9, 68.9, 49.0, 38.3, 31.8, 28.4, 25.6, 23.1, 16.8; HRMS (EI) *m/z* calcd for C₂₂H₃₀O₃ (M⁺) 342.2195, found 342.2208.

4.4. (E)-3-(5-(2,4-bis(2-Methylbut-3-en-2-yloxy)phenyl)-3-methylpent-3-enyl)-2,2-dimethyloxirane (20)

To epoxide **14** (95 mg, 0.24 mmol), in MeOH (3 mL) at 0 °C was added Lindlar catalyst (7 mg) and quinoline (2 drops) and the reaction mixture was allowed to stir under H₂ (1 atm). After 2 h, the reaction mixture was filtered through celite, the pad was washed with ethyl acetate, and the filtrate was concentrated in vacuo. Final purification of the residue by column chromatography (4% ethyl acetate in hexanes) afforded epoxide **20** (73 mg, 76%) as a colorless oil: ¹H NMR (CDCl₃) δ 6.92 (d, *J* = 8.3 Hz, 1H), 6.72 (d, *J* = 2.2 Hz, 1H), 6.51 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.17–6.03 (m, 2H), 5.36–5.31 (m, 1H), 5.21–5.07 (m, 4H), 3.26 (d, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.21–2.12 (m, 2H), 1.76–1.60 (m, 2H), 1.72 (s, 3H), 1.45 (s, 6H), 1.39 (s, 6H), 1.26 (s, 3H), 1.24 (s, 3H); ¹³C NMR (CDCl₃) δ 153.9 (2C), 144.7, 144.4, 134.2, 128.7, 126.8, 124.0, 114.9, 113.0, 112.9, 112.6, 79.3, 79.1, 64.1, 58.3, 36.3, 28.2, 27.3, 27.2, 27.1, 26.8, 26.8, 24.8, 18.7, 16.1; HRMS (EI) *m/z* calcd for C₂₆H₃₈O₃ (M⁺) 398.2821, found 398.2811.

4.5 (E)-3-(5-(2,4-bis(3-Methylbut-2-enyloxy)phenyl)-3-methylpent-3-enyl)-2,2-dimethyloxirane (22)

To suspension of epoxide **7**²⁵ (85 mg, 0.25 mmol) in PTS (0.6 mL, 2.5% w/v in water) in a screw-cap vial at rt was added 2-methyl-2-butene (0.16 mL, 1.5 mmol) followed by Grubb's 2nd generation catalyst (14 mg, 0.016 mmol). After 19 h, the reaction mixture was diluted with ethyl acetate and filtered through celite. The filtrate was concentrated in vacuo and final purification of the residue by column chromatography (12% ethyl acetate in hexanes) afforded epoxide **22** (52 mg, 53%) as a colorless oil: ¹H NMR (CDCl₃) δ 7.00 (d, *J* = 8.2 Hz, 1H), 6.47 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 8.2, 2.4 Hz, 1H), 5.47 (m, 2H), 5.33 (t, *J* = 7.2 Hz, 1H), 4.47 (d, *J* = 6.6 Hz, 4H), 3.26 (d, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.20–2.12 (m, 2H), 1.79 (s, 3H), 1.78 (s, 3H), 1.74 (s, 3H), 1.72 (s, 3H), 1.72 (s, 3H), 1.69–1.60 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H); ¹³C NMR (CDCl₃) δ 158.1, 157.3, 138.0, 137.1, 134.4, 129.3, 123.7, 122.4, 120.1, 119.7, 104.6, 100.2, 64.9, 64.7, 64.2, 58.3, 36.3, 27.8, 27.4, 25.8, 25.7, 24.8, 18.7, 18.2, 18.1, 16.0; HRMS (EI) *m/z* calcd for C₂₆H₃₈O₃ (M⁺) 398.2821, found 398.2816.

4.6 1,1,4a-Trimethyl-7-(3-methylbut-2-enyl)-6-(3-methylbut-2-enyloxy)-2,3,4,4a,9,9a-hexahydro-1H-xanthen-2-ol (25)

To suspension of compound **10** (28 mg, 0.082 mmol) in PTS (0.3 mL, 2.5% w/v in water) in a screw-cap vial at rt was added 2-methyl-2-butene (0.1 mL, 0.94 mmol) followed by Grubb's 2nd generation catalyst (10 mg, 0.012 mmol). After 2 h, the reaction mixture was diluted with ethyl acetate and filtered through celite. The filtrate was concentrated in vacuo and final purification by column chromatography (20% ethyl acetate in hexanes) to afford compound **25** (27 mg, 83%) as a colorless oil: ¹H NMR (CDCl₃) δ 6.79 (s, 1H), 6.30 (s, 1H), 5.48 (m, 1H), 5.28 (t, *J* = 7.4 Hz, 1H), 4.43 (m, 2H), 3.41 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.22 (d, *J* = 7.4 Hz, 2H), 2.65–2.59 (m, 2H), 1.98 (dt, *J* = 12.6, 3.5 Hz, 1H), 1.84 (dq, *J* = 12.6, 3.6 Hz, 1H), 1.78 (s, 3H), 1.73 (s, 3H), 1.70 (s, 6H), 1.68–1.62 (m, 4H), 1.21 (s, 3H), 1.08 (s, 3H), 0.86 (s, 3H); ¹³C NMR (CDCl₃) δ 155.8, 151.5, 137.0, 131.7, 129.7, 123.3, 122.1, 120.3, 112.9, 100.7, 78.2, 76.2, 65.1, 47.3, 38.4, 37.9, 28.3, 27.8, 27.4, 25.9, 25.7, 22.4, 19.9, 18.2, 17.7, 14.3; HRMS (EI) *m/z* calcd for C₂₆H₃₈O₃ (M⁺) 398.2821, found 398.2805.

4.7 Crossover Experiment

4.7.1. Preparation of 1,1,1-Trideutero-2-(1,1,1-trideuteromethyl)-2-butene (27)

—To a suspension of EtP(Ph₃)₃Br (7.4 g, 20 mmol) in THF (30 mL) cooled in an ice bath was added PhLi (12 mL, 1.6 M in Et₂O, 19 mmol). The ice bath was removed for 5 min to

allow anion formation and then the reaction was cooled with an ice bath. After 5 min, (CD₃)₂CO (0.9 mL, 12 mmol) was added and the reaction flask was fitted with a distillation apparatus. After 5 min, the ice bath was removed and the reaction was slowly heated to 33 °C. This afforded 1.75 g of distillate in the receiving flask which was a 1:8 mixture of compound **27**^{46,47} (210 mg, 23%) and THF by ¹H NMR analysis. This mixture was used in the subsequent reaction without further purification: ¹H NMR (CDCl₃) δ 5.10 (q, *J* = 6.8 Hz, 1H), 1.47 (d, *J* = 6.8 Hz, 3H).

4.7.2 Preparation of Deuterium-Labeled Epoxide 28—To suspension of epoxide **7** (62 mg, 0.18 mmol) in PTS (0.5 mL, 2.5% w/v in water) in a screw-capped vial at rt was added labeled 2-methyl-2-butene (**27**, 690 mg of an 8:1 THF:**27** mixture, 83 mg) followed by Grubb's 2nd generation catalyst (11 mg, 0.013 mmol). After 19 h, the reaction mixture was diluted with ethyl acetate and filtered through celite. After the filtrate was concentrated in vacuo, final purification by column chromatography (8% ethyl acetate in hexanes) afforded epoxide **28** (39 mg, 53%) as a colorless oil: ¹H NMR (CDCl₃) δ 7.00 (d, *J* = 8.4 Hz, 1H), 6.48 (d, *J* = 2.4 Hz, 1H), 6.42 (dd, *J* = 8.0, 2.4 Hz, 1H), 5.52–5.46 (m, 2H), 5.34–5.32 (m, 1H), 4.47 (d, *J* = 6.4 Hz, 2H), 4.46 (d, *J* = 6.8 Hz, 2H), 3.26 (d, *J* = 7.2 Hz, 2H), 2.71 (t, *J* = 6.8 Hz, 1H), 2.22–2.08 (m, 2H), 1.71 (s, 3H), 1.74–1.62 (m, 2H), 1.27 (s, 3H), 1.25 (s, 3H); HRMS (EI) *m/z* calcd for C₂₆H₂₆D₁₂O₃ (M⁺) 410.3574, found 410.3578.

4.7.3. Crossover Experiment—To a solution of epoxide **22** (8 mg, 0.020 mmol) and deuterated epoxide **28** (12 mg, 0.029 mmol) in CH₂Cl₂ (40 mL) at –78 °C was added BF₃·OEt₂ (0.10 mL, 0.8 mmol). After 10 min, the reaction was quenched by addition of triethylamine (0.25 mL), diluted with HCl, and extracted with CH₂Cl₂. The organic phase was washed with water and brine, dried (MgSO₄), filtered, and concentrated in vacuo. Final purification by column chromatography (20% ethyl acetate in hexanes) afforded a mixture of deuterium labeled products. This separate compounds were analyzed by ¹H NMR and displayed a spectrum identical to that observed for compounds **23**, **24** and **25** except that it showed decreased intensity in the methyl region. This mixture was analyzed by GC-MS using authentic samples of compounds **23**, **24** and **25** as standards. For the mixture of compound **23** and its labeled analogue, GC-MS analysis showed 27% D₀, 8% D₆, and 65% D₁₂. For the mixture of compounds **24** and **25** and their labeled analogues, GC-MS analysis showed 29% D₀, 8% D₆, and 63% D₁₂, corresponding to an intramolecular process. This experiment was repeated with epoxide **22** (10 mg, 0.025 mmol) and labeled epoxide **28** (15 mg, 0.037 mmol) in a slightly different ratio. Analysis of the resulting mixtures by GC-MS indicated 27% D₀, 10% D₆, and 63% D₁₂ for compounds **23** and its labeled analogue, and 28% D₀, 7% D₆, and 65% D₁₂ for the mixture of compounds **24** and **25** with their deuterated analogues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Applications of cascade cyclizations with tandem electrophilic aromatic substitution.

Scheme 1.
Tandem reactions of allyl ether **7**.

Scheme 2.
Tandem reaction of crotyl ether **12**.

Scheme 3.
Reactions of propargyl ethers **14** and **17**.

Scheme 4.
Synthesis and tandem reaction of prenyl ether **22**.

Scheme 5.
A crossover experiment.

Scheme 6.
A possible mechanistic rationale.

Table 1

Distribution of deuterium in attempted crossover experiments.

Trial	Starting Material (%)		Product	Isotopic Distribution (%)		
	22 (D ₀)	28 (D ₁₂)		D ₀	D ₆	D ₁₂
1	41	59	23	27	8	65
			24/25	29	8	63
2	40	60	23	27	10	63
			24/25	28	7	65