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Nat Chem Biol. Author manuscript; available in PMC 2013 July 01.

Published in final edited form as:

Nat Chem Biol. 2013 January ; 9(1): 21–29. doi:10.1038/nchembio.1130.

Biomimetic diversity-oriented synthesis of benzannulated medium rings via ring expansion

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Abstract

Nature has exploited medium-sized 8- to 11-membered rings in a variety of natural products to address diverse and challenging biological targets. However, due to the limitations of conventional cyclization-based approaches to medium-ring synthesis, these structures remain severely underrepresented in current probe and drug discovery efforts. To address this problem, we have established an alternative, biomimetic ring expansion approach to the diversity-oriented synthesis of medium-ring libraries. Oxidative dearomatization of bicyclic phenols affords polycyclic cyclohexadienones that undergo efficient ring expansion to form benzannulated medium-ring scaffolds found in natural products. The ring expansion reaction can be induced using three complementary reagents that avoid competing dienone–phenol rearrangements and is driven by rearomatization of a phenol ring adjacent to the scissile bond. Cheminformatic analysis of the resulting first-generation library confirms that these molecules occupy chemical space overlapping with medium-ring natural products and distinct from that of synthetic drugs and drug-like libraries.

Medium-ring structures (8–11 atoms) are found in a variety of natural products with diverse biological activities. Of particular interest are benzannulated medium rings, which include aryl ethers such as the heliannuols[1] (allelopathic) and brazilone[2] (anticoagulant), diaryl ethers such as aspercyclide A[3] (IgE receptor inhibitor), aryl esters such as puerol A[4] (Chinese traditional medicine component) and kurzichalcolactone[5] (anticancer), and biaryls

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AUTHOR CONTRIBUTIONS

R.A.B, T.A.W., and D.S.T designed the experiments, analyzed the data, and wrote the manuscript. R.A.B. and T.A.W. performed the synthesis and characterization. T.A.W. performed the molecular modeling studies. R.A.B. performed the PCA analysis.

COMPETING FINANCIAL INTERESTS STATEMENT

The authors declare no competing financial interests.

ADDITIONAL INFORMATION

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such as pterocaryanin C[6] (anticancer, antiviral), steganacin[7] (antileukemic), and rhazinilam[8] (anticancer) (**Supplementary Results, Supplementary Fig. 1a**).

These cyclic frameworks are useful for organizing the overall presentation of functional groups to biological targets.[9] Furthermore, the conformational constraint provided by cyclic scaffolds can afford enhanced binding affinity compared to corresponding linear structures[10] (although not necessarily due to reduced entropic costs[11,12]). Conformational restriction has also been correlated with improved bioavailability[13] and, in some cases, enhanced cell permeability[14,15].

However, despite their occurrence in many important natural products, medium rings are absent among the current top 200 brand name and top 200 generic drugs (http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster)[16] (**Supplementary Fig. 1b**). In contrast, aliphatic 5- and 6-membered rings occur widely in these drugs, along with lower incidences of other small rings (3, 4, or 7 atoms) and macrocyclic rings (≥12 atoms). While numerous compounding factors influence the progression of molecules that ultimately become commercially successful approved drugs, synthetic accessibility plays an important role at multiple stages of drug discovery and development. Thus, the absence of medium rings in current drugs may be attributed to challenges associated with their synthesis[17] that lead to their scarcity in commercial and proprietary small-molecule screening collections. Analogous academic efforts to discover biological probes are likewise dependent on the composition of screening collections[18], and a recent PubChem substructure search of the >360,000-membered US National Institutes of Health (NIH) Molecular Libraries Small Molecule Repository identified only 10 benzannulated medium-ring molecules of the types targeted herein (**Supplementary Figs. 2** and **3**).

Indeed, the synthesis of medium rings is a long-standing challenge in organic synthesis[17]. Classical cyclization-based approaches are subject to both entropic effects (frequency of encounters of reactive groups at chain ends and additional losses in torsional degrees of freedom) and enthalpic effects (ring strain due to unfavorable bond angles and torsion). Moreover, medium rings suffer from unfavorable transannular steric interactions that are not present in smaller and larger rings. As a result, the efficiency of medium-ring cyclizations can be highly variable and subject to unpredictable substrate effects. For example, although ring-closing metathesis was used in the total synthesis of aspercyclide C, it proved ineffective for accessing the closely related aspercyclides A and B[19,20]. Variable, substrate-dependent yields (30–94%) have been reported in ring-closing metathesis approaches to heliannuol A and related helianane congeners[21,22,23,24,25,26]. In the sphere of library synthesis, elegant cyclization-based approaches to medium rings have been reported[27,28,29,30,31], but are generally limited in their ability to accommodate diverse backbone substituents, ring sizes, and other structural factors that affect cyclization efficiency.

An alternative, potentially more flexible approach to the synthesis of medium rings involves ring expansion of polycyclic substrates[32,33]. Indeed, such ring expansion reactions have been proposed in biosynthetic pathways to various medium-ring natural products. For example, ring-expanding rearomatization of a polycyclic cyclohexadienone intermediate,

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formed via an earlier oxidative dearomatization reaction, was proposed in a biosynthetic route to the alkaloid protostephanine in 1964[34], and the chemical feasibility of this route was demonstrated shortly thereafter (**Fig. 1a**)[35]. Related oxidative dearomatization–ring-expanding rearomatization sequences have also been invoked in biosynthetic proposals and biomimetic syntheses of erythrina and homoerythrina alkaloids (**Fig. 1b**)[36,37,38,39,40]. Notably, in all of these cases, the ring expansion reaction is aided by a strategically placed nitrogen atom that drives electron flow toward the developing aromatic ring.

Thus, we envisioned that a biomimetic ring expansion approach might provide efficient and flexible access to a variety of benzannulated medium-ring scaffolds found in natural products (**Fig. 1c**). This ring expansion approach would circumvent the challenges associated with cyclization-based approaches, particularly in the context of diversity-oriented synthesis[41], where diverse linear substrates would otherwise need to cyclize efficiently to access these scaffolds[31]. Key linkages found in medium-ring natural products (for example, aryl ethers, diaryl ethers, lactones, biaryl linkages) would be installed via initial oxidative dearomatization of simple bicyclic phenols, and a subsequent aromatization-driven ring expansion of the intermediate polycyclic cyclohexadienones would provide a variety of medium-ring scaffolds. Modular synthetic access to the bicyclic phenol precursors would be readily achieved in 3–5 steps from simple starting materials.

At the outset, we noted that other acid-catalyzed reactions that convert cyclohexadienenones to phenols, such as dienone–phenol (1,2-alkyl shift) and Cope rearrangements[42], are well-known and that our synthetic approach would need to avoid these competing pathways leading to other undesired products. Indeed, the alternative dienone–phenol rearrangement was observed during early studies of related biomimetic ring expansions (**Fig. 1b**)[43]. In the context of a diversity-oriented synthesis, our overall goals were to establish ring expansion conditions that (i) provide access to a wide variety of medium-ring sizes and linkages, (ii) do not require a backbone nitrogen for ring expansion, (iii) are tolerant of diverse functional groups, and (iv) avoid competing pathways such as dienone–phenol rearrangements.

We describe herein the development of this biomimetic strategy, termed oxidative dearomatization–ring-expanding rearomatization (ODRE), resulting in the synthesis of a first-generation library of diverse benzannulated medium rings. Three complementary reagent classes have been discovered that induce this relatively neglected mode of cyclohexadienone reactivity while avoiding competing dienone–phenol rearrangements for a wide variety of polycyclic cyclohexadienone substrates. The products are amenable to further downstream modifications and cheminformatic analysis confirms that they occupy regions of chemical space that overlap with medium-ring natural products and are distinct from current, high-profile synthetic drugs and related libraries.

RESULTS

Development of biomimetic ring expansion reactions

To test the feasibility of ring expansion of non-nitrogen-containing polycyclic cyclohexadienones, tricycle **5** was synthesized in five steps on gram scale from 6-hydroxytetralone via a modular route involving oxidative dearomatization of bicyclic phenol

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4 (**Supplementary Fig. 4**). The C1-methyl substituent blocked benzylic oxidation during the oxidative dearomatization step (**Supplementary Fig. 5**) and was also envisioned to facilitate the desired ring expansion by formation of a stable tertiary carbocation intermediate (*vide infra*). Cyclohexadienone **5** was then exposed to a variety of reaction conditions aimed at inducing ring expansion (**Table 1**). Treatment with mild Lewis acids, including MgI_2, which was used in the biomimetic synthesis of protostephanine[35], led to no reaction even at elevated temperatures (entries 1,2), highlighting the importance of the backbone nitrogen in the protostephanine system. Meanwhile, stronger Lewis acids caused decomposition of the starting material (entries 3,4). In contrast, treatment with $Me_3O{\cdot}BF_4$, $MeAlCl_2$, or $TiCl_4$ led to the formation of alternate tricycles **9** or **10** (entries 5–7), presumably via the undesired dienone–phenol rearrangement followed by a subsequent, second 1,2-alkyl shift (*vide infra*)[42]. Exposure to methanolic hydroxide, which was used in previous biomimetic syntheses of homoerythrina and erythrina alkaloids[38,39,40] led to no reaction at 25 °C, again emphasizing the importance of a backbone nitrogen in those systems, which was released by hydrolysis of a corresponding amide. At 80 °C, a distinct bicycle product **11** was formed (entries 8 and 9), presumably by γ-enolization and solvolytic S_N2' displacement of the alkoxyethyl side chain.

Gratifyingly, however, several conditions were found to effect the desired ring expansion of **5**. While TsOH did not induce ring expansion in aprotic solvents (entries 10–13), the reaction did proceed in alcoholic solvents such as MeOH (entry 14), and was further accelerated by the inclusion of $MeNO_2$ (entry 15). When the amount of MeOH was decreased to 10 equiv, the reaction proceeded more slowly and afforded a lower yield (entry 16). The ring expansion also proceeded in other alcohols such as EtOH, *i*-PrOH, and ethylene glycol, albeit with decreased efficiency (10–40% yields). Moreover, the reaction did not proceed in aqueous media (entries 17,18). A complementary Lewis acid-promoted ring expansion was also identified using $Cu(BF_4)_2$ in MeOH (entry 19). The TsOH and $Cu(BF_4)_2$-induced ring expansion reactions both led to a 3:1 mixture of olefin **6** and methanol adduct **8** (entries 14,15,19). Notably, these processes yielded anisoles rather than the corresponding phenols, providing a key mechanistic insight (*vide infra*). A third ring expansion using Tf_2O was also discovered, and provided triflate **7** as a mixture of three olefin regioisomers in excellent overall yield (entry 20). While ring expansion of this particular substrate led to a mixture of olefin regioisomers, we envisioned that increased regiocontrol might be possible using other functionalized substrates (*vide infra*).

Modular synthesis of cyclohexadienone substrates

With three complementary reaction conditions for ring expansion in hand, we sought to evaluate the scope of the ODRE sequence across a range of additional substrates. Thus, a variety of polycyclic cyclohexadienones were synthesized via the same modular synthetic approach used for **5**, starting from simple precursors (**Fig. 1c**; full details are in **Supplementary Note 1**).

Ketone alkylation or arylation of silyl protected bicyclic ketophenols with commercially available Grignard reagents, or dihydroxylation of 6-hydroxy-1-methyl-3,4-dihydronaphthalene, afforded intermediate benzylic alcohols. Convenient introduction of

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various sidechains was then achieved via addition of allyl trimethylsilanes or trialkylsilyl ketene acetals under Sakurai conditions ($TiCl_4$ or $ZnCl_2$)[44]. The resulting ester or olefin side chains were tailored using a variety of straightforward transformations to provide tethered acid, aryl, phenol, and primary and tertiary alcohol nucleophiles. Optional bromination at C5 provided a handle for subsequent introduction of other functional groups in the western half of the scaffold.

The key oxidative dearomatization of phenols **12**–**30** with $PhI(OAc)_2$ then provided efficient access to polycyclic cyclohexadienone substrates that could be further modified as desired to provide **31**–**50** (**Table 2**). O verall, the substrate syntheses are straightforward, scalable, and operationally simple, an several steps can be carried out without purification of the intermediates.

Scope of ring-expanding rearomatization reaction

We were pleased to find that polycyclic cyclohexadienones **31**–**50** all underwent effective ring expansion under one or more of our three reaction conditions, generating 8- to 12-membered rings **52**–**81** (**Table 2**; full details are in **Supplementary Note 1**). The larger [6,6,6]-tricycle **31** reacted efficiently under all three conditions to give 10-membered ring products **52** or **53** after extended treatment with TsOH to converge olefin isomers. Incorporation of an olefin in substrate **32** led to MeOH adduct **54**, presumably by S_N1' addition of MeOH during the ring expansion reaction. The [6,5,5]-tricyclic cyclohexadienone **33** led to 8-membered ring product **55**, comprising the core benzooxocane scaffold of heliannuol A. The Tf_2O ring expansion was most effective for this acid-labile tertiary ether system, with the TsOH and $Cu(BF_4)_2$ ring expansions affording low yields (<25%). Methyl, bromo, and aryl substituents on the cyclohexadienone ring (**34**–**36**) were well-tolerated under all three ring expansion conditions to provide aryl-substituted medium rings **56**–**61**, although increased reaction temperatures were required to induce ring expansion of the bromide **34**.

In contrast to C1-methyl cyclohexadienone **5**, TsOH- and $Cu(BF_4)_2$-induced ring expansions of the corresponding C1-phenyl cyclohexadienone **37** afforded not only the expected anisole products, but also the free phenol **62**, and could also be carried out under “MeOH-free” conditions to the phenol **62** exclusively, providing important mechanistic insights (*vide infra*). Moreover, the [6,7,5]-tricyclic cyclohexadienone **38** also yielded the corresponding free phenol **63** under the standard TsOH-induced ring expansion, and all of the cyclohexadienone substrates having larger 7- and 8-membered rings (**38**–**41**) were competent to undergo “MeOH-free” TsOH-induced ring expansions to 10- to 12-membered rings **63, 65, 67**, and **69**.

Importantly, carboxylate, phenol, and C-aryl sidechain nucleophiles in **21**–**26** afforded polycyclic cyclohexadienones **42–47** that also underwent efficient ring expansion reactions to afford aryl lactone (**71–76**), diaryl ether (**77**), and biaryl (**78**) scaffolds related to those found in natural products. In the lactone series (**71**–**76**), Tf_2O proved most generally effective for ring expansion. The position of the double bond in the ring expansion product could be modulated predictably by incorporation of an additional olefin in the substrate (**71**

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versus **72**). Notably, the same trend in ring size effects observed in the aryl ether series above (**5, 31** versus **38**–**41**) was also observed in the lactone series, with the 7- and 8-membered ring substrates **44** and **45** able to undergo "MeOH-free" TsOH-induced ring expansion directly to phenols **73** and **75**. Phenol and C-aryl sidechain nucleophiles in **25** and **26** afforded polycyclic cyclohexadienones **46** and **47**, which also underwent efficient ring expansion reactions to afford diaryl ether (**77**) and biaryl (**78**) scaffolds, and both of these processes were readily performed on gram scale. As expected, the Tf_2O ring expansion was incompatible with the enolizable ketone in **46**, resulting in a complex mixture.

As hoped, installation of an additional alcohol sidechain in cyclohexadienone **48** allowed ring expansion with concurrent cyclization of the alcohol to afford spiroether **79**. In contrast, placing an additional alcohol on the sidechain in **49** led to olefin **80** rather than the corresponding bridged ether product, presumably due to unfavorable ring strain in the latter. Meanwhile, incorporation of an alcohol functionality vicinal to the scissile bond in cyclohexadienone **50** afforded ketone **81**, presumably via 1,2-hydride shift after ring expansion. These ring expansion reactions were carried out with TsOH or $Cu(BF_4)_2$, avoiding undesired side reactions of the alcohol functionalities with Tf_2O. Finally, consistent with this general reactivity of polycyclic cyclohexadienones, we observed direct formation of spiroketal **82** during the oxidative dearomatization of bicyclic phenol **30**. This transformation can be envisioned to occur via an intermediate Adler–Becker oxidation[45] product **51**, followed by a surprising, but precedented, spontaneous C–C bond cleavage of the epoxide moiety[46].

Mechanistic analysis of ring expansion reactions

We next set out to determine whether the TsOH- and $Cu(BF_4)_2$-mediated ring expansion reactions produce kinetic or thermodynamic mixtures of medium-ring products in the parent system (**Table 1**). Separation and re-exposure of olefin **6** and methanol adduct **8** to the reaction conditions confirmed that they are kinetic products of the ring expansion reaction (**Supplementary Fig. 6**). However, methanol adduct **8** could be converted to olefin **6** by treatment with a stronger Lewis acid, $MeAlCl_2$. In contrast, treatment of **6** or **8** with $TiCl_4$ led unexpectedly to the alternate tricycle **9**. This ring contraction reaction is envisioned to involve initial formation of a tertiary carbocation, which then undergoes transannular Friedel–Crafts alkylation and subsequent 1,2-alkyl shift to form **9** (**Supplementary Fig. 7**), intercepting the same undesired dienone–phenol rearrangement pathway discussed earlier.

Interestingly, $TiCl_4$ was the only reagent observed to drive ring contraction of **6** and **8**. $MeAlCl_2$ induced MeOH elimination in **8** to form **6** without any observed ring contraction, and **6** and **8** were completely unreactive to TsOH, $Me_3O{\cdot}BF_4$, $ZnCl_2$, and MgI_2 at room temperature, suggesting that the $TiCl_4$-mediated pathway may not involve simple Lewis or Brønsted acid catalysis (**Supplementary Fig. 7**). Indeed, treatment of **6** and **8** with anhydrous HCl (CH_2Cl_2, 0 °C) did not induce this ring contraction to **9**, instead resulting in eliminative cleavage of the cyclic aryl ether bond followed by reclosure to a distinct vinyl benzooxepane rearrangement (1,3-phenoxide shift) product.

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Notably, in the aryl ether series above, we observed that substrates in which the cyclohexadienone is fused to a 6-membered ring (**5, 31**) require MeOH for both the TsOH and $Cu(BF_4)_2$-induced ring expansion reactions and incorporate MeOH to afford anisole products (**6, 52**). In contrast, analogous substrates with a fused 7- or 8-membered ring (**38–41**) do not require MeOH for ring expansion and proceed directly to the corresponding phenols (**63, 65, 67, 69**). Similar trends were observed in the aryl lactone series, where 7- and 8-membered ring substrates (**44, 45**) underwent effective "MeOH-free" TsOH-induced ring expansions to phenol products (**73, 75**).

To investigate the underlying mechanistic basis for these ring size effects, we carried out molecular modeling of cyclohexadienone ethers **5, 31, 38**–**41** and cyclohexadienone lactones **42, 44, 45** (**Supplementary Fig. 8**). Within each substrate series, calculated strain energies increased as the ring fused to the cyclohexadienone ring increased in size from 6- to 7- to 8-membered. Moreover, the scissile bond aligned more favorably with the π-system of the cyclohexadienone ring as ring size increased. This stereoelectronic effect has been used to rationalize ring size effects upon cyclohexadienone reactivity in duocarmycin analogues.[47] These results suggest that the increased reactivity of 7- and 8-membered ring substrates compared to the corresponding 6-membered rings arises from a combination of inherent ring strain and stereoelectronic alignment.

Having investigated the various competing reaction manifolds, substrate scope, and kinetic nature of the desired ring expansion, a mechanism for ring expansion that takes into account all the current data is proposed (**Fig. 2**). Initial activation of the cyclohexadienone carbonyl in **5** is followed by an aromatization-driven cationic ring expansion to form medium rings **6**–**8**. An obligate *O*-methyl oxocarbenium intermediate **83a** is proposed for the TsOH- and $Cu(BF_4)_2$-induced ring expansion reactions of **5**, consistent with the inability to induce ring expansion of **5** in aprotic solvents or aqueous mixtures (**Table 1**, entries 10–13,17,18) and with the formation of anisole (*O*-methylated) products in all cases in which MeOH is required for these ring expansions (**Table 2**). The enhanced reactivity of *O*-alkyl oxocarbenium intermediates compared to their *O*-proteo congeners has been highlighted previously[48,49]. The analogous *O*-triflyl oxocarbenium intermediate **83b** is proposed for Tf_2O-induced ring expansion reactions.

Notably, the carbonyl group can be activated by two distinct mechanisms, in which it acts as either an electrophile (TsOH- or $Cu[BF_4]_2$-catalyzed MeOH addition) or a nucleophile (Tf_2O sulfonylation). This characteristic provides useful flexibility when working with electron-rich or -deficient cyclohexadienone substrates. The *O*-methyl and *O*-triflyl oxocarbenium intermediates **83a,b** then undergo the desired ring expansions to the tertiary carbocations **84a,b**, which are quenched by either addition of a MeOH nucleophile or elimination to form the kinetic ring expansion products **6**–**8**.

The proposed cationic manifold is supported by observation that the TsOH-induced ring expansion reaction is accelerated by the addition of the charge-stabilizing solvent $MeNO_2$ (ε = 36) (**Table 1**, entries 14,15). Additional support for a cationic pathway is provided by the ability of C1-phenyl-substituted cyclohexadienone **37** to undergo ring expansion using TsOH or $Cu(BF_4)_2$ in the absence of MeOH (**Table 2**). Presumably, stabilization of the

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corresponding tertiary cation intermediate by the C1-phenyl substituent (*cf.* **84**) allows ring expansion to occur directly from the *O*-proteo and *O*-cupric oxocarbenium intermediates, without requiring formation of a more reactive *O*-methyl oxocarbenium intermediate (*cf.* **83a**). Similarly, other larger-ring substrates that accommodate "MeOH-free" TsOH-induced ring expansions (**38**–**41, 44, 45**) directly to phenol products (**63, 65, 67, 69, 73, 75**) are thought to proceed via *O*-proteo oxocarbenium intermediates that are sufficiently reactive to undergo ring expansion due to increased ring strain and improved stereoelectronic overlap of the scissile bond with the nascent aromatic ring in these systems (**Supplementary Fig. 8**)[47]. The undesired dienone–phenol rearrangement of cyclohexadienone **5** to form tricycles **9** and **10** using $Me_3O{\cdot}BF_4$, $MeAlCl_2$, or $TiCl_4$ in CH_2Cl_2 (**Table 1**, entries 5–7) indicates that alternative rearrangement pathways can, indeed, compete with the desired ring expansion reactivity under some conditions. Moreover, the $TiCl_4$-catalyzed ring contraction of medium ring products **6** and **8** to tricycle **9** (**Supplementary Fig. 6**) suggests that tertiary carbocations **84** are competent to undergo an alternative transannular Friedel–Crafts reaction to form cations **85**, leading to the same undesired rearrangement products **9** or **10** (**Fig. 2**). Thus, one reason for the success of TsOH, $Cu(BF_4)_2$, and Tf_2O in inducing the desired ring expansion pathway is likely the ability of these reagents to generate *kinetic* ring expansion products that do not react further (reversibly) under these reaction conditions, in contrast to reactions with $TiCl_4$.

In addition, polar solvent effects in the ring expansion reactions using TsOH in 1:1 MeOH/$MeNO_2$ and $Cu(BF_4)_2$ in MeOH appear to play a role in directing the key oxocarbenium intermediate **83a** toward a desired ring-expanded tertiary carbocation **84a** rather than an undesired cation **85a**. In the $Me_3O{\cdot}BF_4$, $MeAlCl_2$, or $TiCl_4$ reactions carried out in CH_2Cl_2, the latter cation is likely favored since its charge is internally stabilized by delocalization, leading to alternative tricycles **9** and **10**. Ring expansion of the C1-phenyl-substituted cyclohexadienone **37** is feasible in CH_2Cl_2 due to the additional stabilization of the tertiary carbocation provided by the phenyl substituent. The Tf_2O-induced ring expansion can also be carried out in CH_2Cl_2, and we postulate that oxocarbenium intermediate **83b** favors ring expansion to tertiary carbocation **84b** rather than the alternative cation **85b** due to the instability of the latter caused by the electron-withdrawing triflyl group. Overall, it is apparent that reagent selection ($Me_3O{\cdot}BF_4$ in CH_2Cl_2 versus Tf_2O in CH_2Cl_2), solvent polarity (CH_2Cl_2 versus $MeNO_2$), and substrate structure (C1-methyl in **5** versus C1-phenyl in **37**) all play complementary roles in promoting ring expansion and in avoiding undesired alternative rearrangement reactions.

Downstream transformations of medium ring scaffolds

To establish the ability of the ring expansion products to undergo further functionalizations that might be useful in library synthesis, benzannulated medium ring scaffolds **77** and **78** were synthesized on gram scale and a variety of downstream transformations were investigated. The diaryl ether **77** underwent effective cyclopropanation (**88**), epoxidation (**89**), and dihydroxylation (**90**) of the olefin functionality, as well as Luche reduction of the ketone (**91**) (**Fig. 3a**). The methyl ether capping group could also be removed to afford free phenol **92**, which then allowed Mitsunobu alkylation to lactate derivative **93**. The biaryl scaffold **78** also underwent selective dihydroxylation on the trisubstituted olefin to afford

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diol **94** (**Fig. 3b**). The triflate capping group could again be removed under mild conditions to afford free phenol **95**, poised for further modifications. Several other benzannulated medium ring products also underwent efficient dihydroxylation reactions to afford diols **96–101** (**Fig. 3c**).

Cheminformatic analysis of ODRE-derived library

To evaluate the effectiveness of the biomimetic ODRE methodology in providing libraries that access regions of chemical space targeted by natural products, we used a cheminformatic approach involving principal component analysis (PCA; full details are in **Supplementary Note 2**) to compare the structural and physicochemical properties of the 47 benzannulated medium ring scaffolds and 25 polycyclic cyclohexadienones synthesized herein (**Supplementary Fig. 9**) with a collection of benzannulated medium ring natural products (**Supplementary Fig. 10**) and our established reference sets of brand-name drugs, natural products, and commercial drug-like library members[18,41,50] (**Supplementary Figs. 11–13**). Gratifyingly, the benzannulated medium ring scaffolds synthesized herein overlapped with the benzannulated medium ring natural products in this analysis (**Supplementary Fig. 14** and **Supplementary Data Set 1**), while the corresponding polycyclic cyclohexadienones were even more distinct from the narrow range of drug and drug-like structures currently targeted by the pharmacetical industry, due to increased ring system size and complexity (**Supplementary Fig. 15**).

DISCUSSION

Although Nature has successfully exploited medium-ring natural products to address diverse biological targets, such structures remain underrepresented in current probe and drug discovery efforts. Synthetic challenges in accessing these molecules, relating to slow cyclization kinetics and transannular ring strain, have presented obstacles to making natural product-inspired medium rings available for biological evaluation. The ring expansion approach to medium-ring synthesis developed herein, inspired by biosynthetic proposals for alkaloid natural products, is designed to avoid the drawbacks associated with conventional cyclization-based approaches.

The identification of three distinct reagent classes (Brønsted acid, Lewis acid, and sulfonyl anhydride) that induce this ring expansion allows selection amongst three complementary reaction conditions based on the functional groups present in a given substrate. Notably, these reactions access a relatively neglected mode of cyclohexadienone reactivity while avoiding undesired competing dienone–phenol rearrangement pathways. Moreover, they do not require embedded backbone nitrogen functionalities that appear to be essential for previously reported biomimetic variants of this transformation. Taken together, the reactions showed excellent functional group tolerance and were compatible with various cyclohexadienone substituents (**34–36**) in the substrates and with alcohol (**80**), ketone (**77, 81**), Michael acceptor (**72, 77**), ester (**71–74**), and acid-sensitive skipped diene (**78**) and tertiary ether (**55**) functionalities in the products.

Cheminformatic analysis using PCA demonstrated that molecules derived from medium-ring scaffolds **6**, **7**, and **52**–**82** possess structural and physicochemical properties that

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recapitulate those found in naturally-occurring benzannulated medium rings. Indeed, the scaffolds obtained by ODRE display key structural features found in natural products, such as the benzooxocane framework of heliannuol A[1] (**55**), the aryl ether linkage in brazilone[2] (**6**–**8**), the diaryl ether linkage in the aspercyclides[3] (**77**), the aryl lactones in kurzichalcolactone[5] and puerol A[4] (**71–76**), and the biaryl linkages in steganacin[7], rhazinilam[8], and various ellagitannins[6] (**78**). Downstream modifications of ODRE products such as olefin dihydroxylation provide additional structures that present the polar and stereochemically rich motifs found in benzannulated medium-ring natural products. Thus, these scaffolds probe attractive areas of chemical space that are not currently targeted by high-profile synthetic drugs and related libraries. Biological evaluation of the resulting libraries is ongoing and will be reported in due course.

ONLINE METHODS

The following general procedures were used for the ring expansion of polycyclic cyclohexadienones as described in **Tables 1** and **2**. All ring expansions were run on a scale of 30–60 mg, with the exception of **46**→**77** (TsOH and $CuBF_4$) and **47**→**78** (Tf_2O), which were run on a 1-g scale. Full details on synthetic methods are in **Supplementary Note 1**. Full details on principal component analysis are in **Supplementary Note 2**. NMR spectra are shown in **Supplementary Note 3**.

TsOH-Mediated Ring Expansion

To a solution of cyclohexadienone in 1:1 MeOH/$MeNO_2$ or $MeNO_2$ for “MeOH-free” ring expansions (0.1 M) was added TsOH·H_2O (2.0 equiv). The solution was stirred at 25 °C for 5–20 h. Once complete, the reaction was quenched with satd aq $NaHCO_3$ and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The product(s) was purified by silica gel chromatography (hexanes/EtOAc).

$Cu(BF_4)_2$-Mediated Ring Expansion

To a solution of cyclohexadienone in MeOH (0.1 M) was added $Cu(BF_4)_2$·xH_2O (20 mol%) and trimethyl orthoformate (3 equiv). The solution was warmed to 50 °C and stirred for 5–16 h. The reaction could be accelerated by adding more $Cu(BF_4)_2$ with no deterioration in yield (for example, 50 or 100 mol% catalyst). Once complete, the reaction was quenched with satd aq NH_4Cl and extracted with EtOAc (2×). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The product(s) was purified by silica gel chromatography (hexanes/EtOAc).

Tf_2O-Mediated Ring Expansion

To a solution of cyclohexadienone and 2,6-di-*tert*-butyl-4-methylpyridine (1.5 equiv) in CH_2Cl_2 (0.1 M) at 0 °C was added triflic anhydride (1 M in CH_2Cl_2, 1.3 equiv). The reaction was allowed to stir for 0.25–6 h. An extra 0.5 equiv of triflic anhydride could be added to accelerate sluggish ring expansions. The reaction was quenched at 0 °C with satd aq $NaHCO_3$, warmed to rt, and extracted with EtOAc (2×). The combined organic extracts

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were washed with brine, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation. The product(s) was purified by silica gel chromatography (hexanes/EtOAc).

Supplementary Material

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ACKNOWLEDGMENTS

Dedicated to the memory of our colleague and mentor, Prof. David Y. Gin (1967–2011). We thank D. Boger (Scripps) for helpful discussions, C. Stratton (MSKCC) for assistance with PCA calculations, J. Njarðarson (University of Arizona) for providing drug structures, and G. Sukenick, H. Liu, H. Fang, and S. Rusli (MSKCC Analytical Core Facility) for expert mass spectral analyses. Instant JChem was generously provided by ChemAxon. Financial support from the NIH (P41 GM076267 to D.S.T.; P41 GM076267-03S1 to R.A.B.; T32 CA062948-Gudas to T.A.W.), MSKCC Experimental Therapeutics Center, and Tri-Institutional Stem Cell Initiative is gratefully acknowledged.

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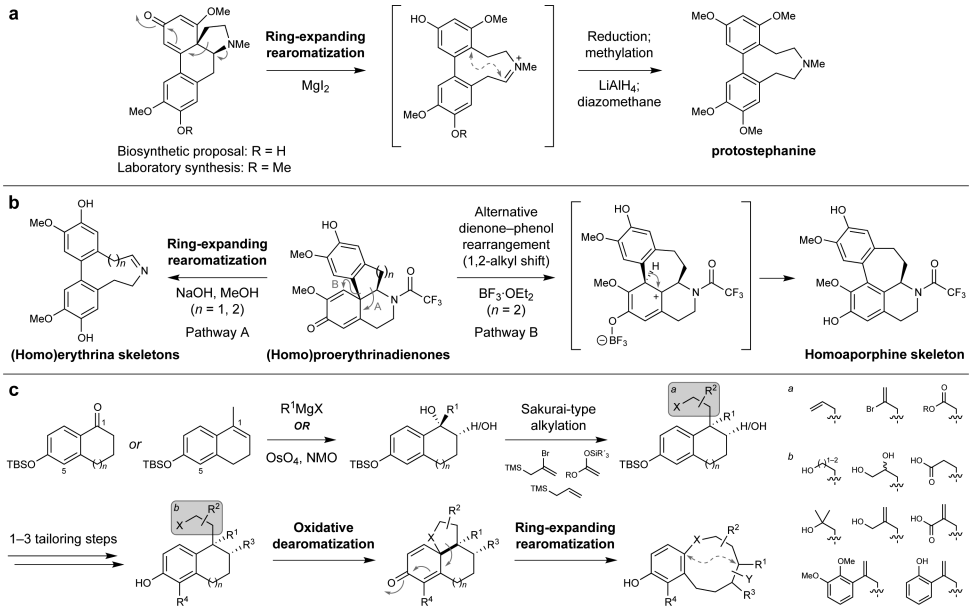

Figure 1. Overall strategy and precedents for the synthesis of benzannulated medium rings

(**a**) Proposed biosynthetic route[34] and biomimetic synthesis[35] of protostephanine. (**b**) Biomimetic syntheses of (homo)erythrina alkaloids[38,39] (pathway A) and alternative dienone–phenol rearrangement (1,2-alkyl shift) pathway leading to a homoaporphine scaffold[43] (pathway B). (**c**) Biomimetic oxidative dearomatization–ring-expanding rearomatization (ODRE) approach to benzannulated medium ring synthesis. NMO, *N*-methyl morpholine, *N*-oxide; TBS, *tert*-butyldimethylsilyl.

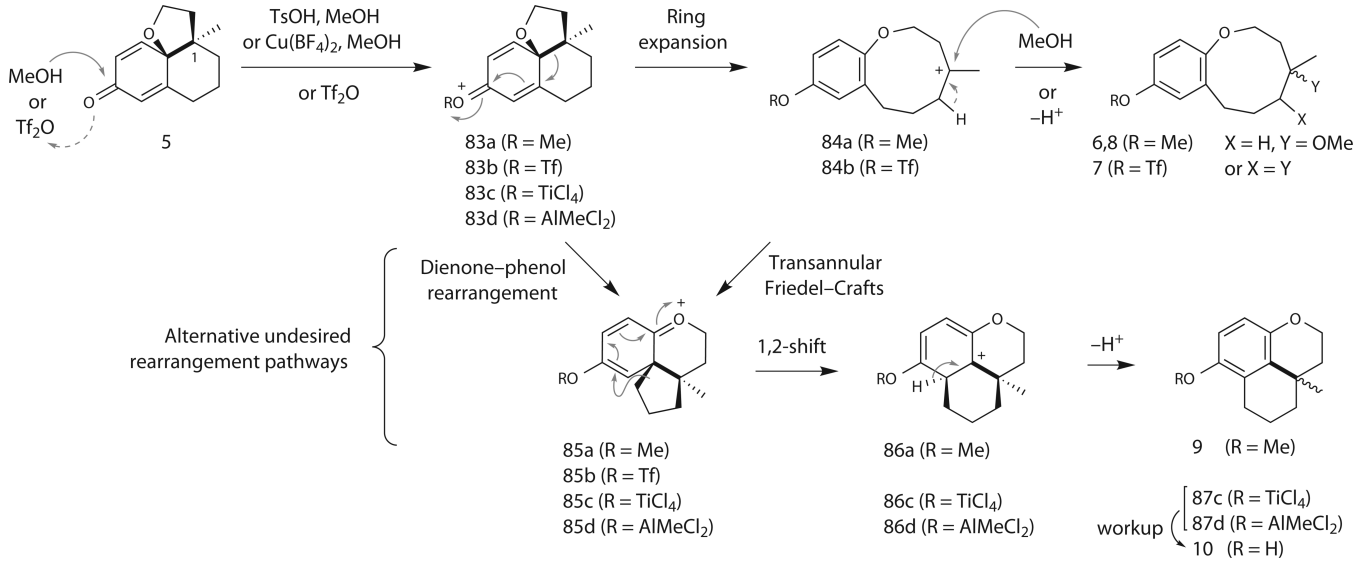

Figure 2. Proposed mechanisms for aromatization-driven ring expansion of 5 to benzannulated medium rings 6–8 and for formation of alternate tricycles 9 and 10

In the desired pathway, polarization of the cyclohexadienone carbonyl in oxocarbenium intermediates **83** induces bond scission to form tertiary carbocations **84**, leading to ring expansion products **6**–**8**. In alternative undesired pathways, dienone–phenol rearrangement of **83** or transannular Friedel–Crafts alkylation of **84** affords **85**, which then undergoes 1,2-alkyl shift to **86** leading to tricycles **9** and **10**.

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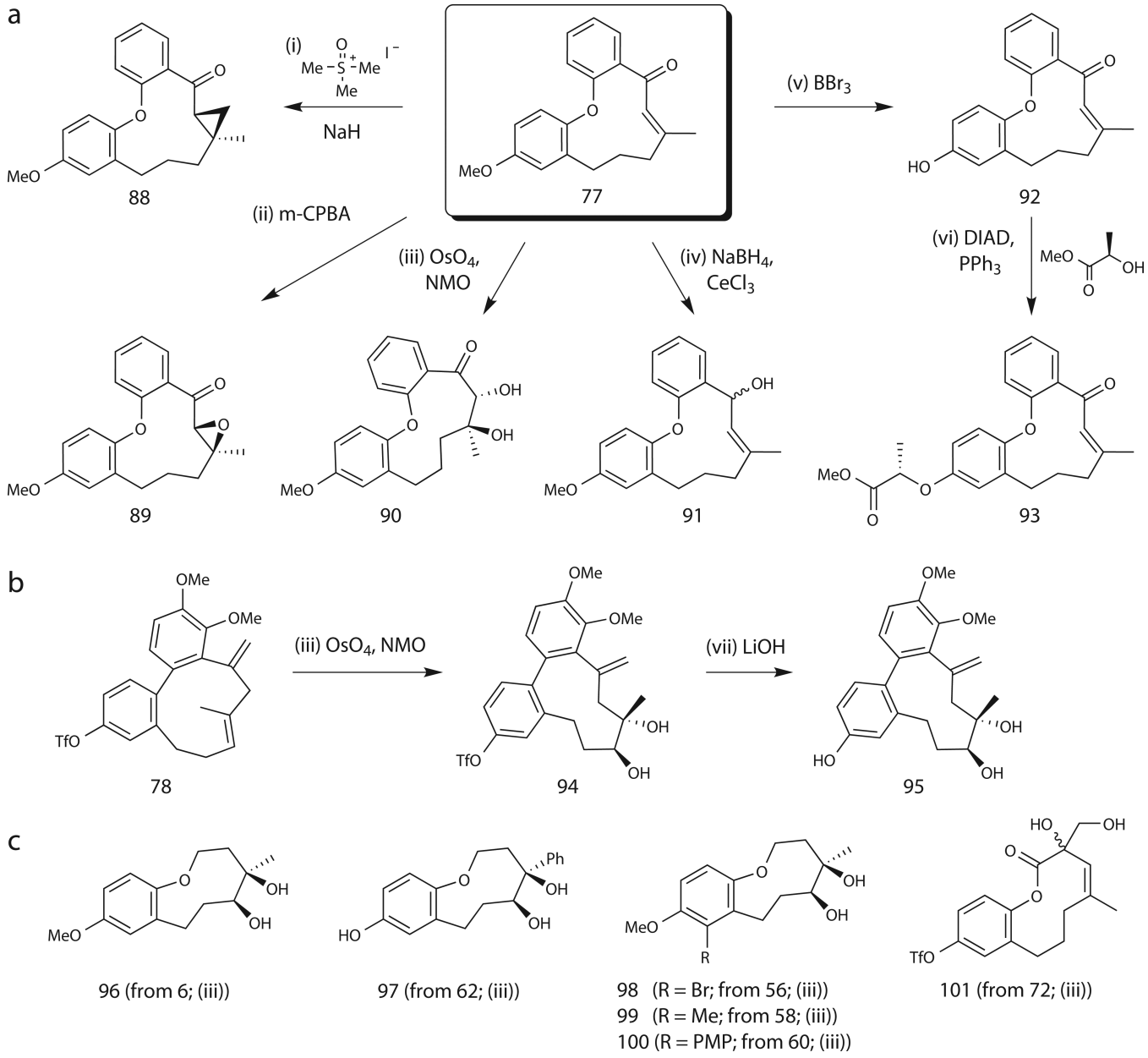

Figure 3. Downstream modifications of ODRE-derived benzannulated medium ring scaffolds

(**a**) Diversification reactions of diaryl ether **77**. (**b**) Dihydroxylation and detriflation of biaryl **78**. (**c**) Additional dihydroxylated products synthesized from ODRE-derived benzannulated medium ring scaffolds. (i) trimethylsulfoxonium iodide, NaH, DMSO, 25 °C, 20 h, 80%. (ii) *m*-CPBA, CH_2Cl_2, 0 → 25 °C, 14 h, 61%. (iii) OsO_4, NMO, 3:1 acetone/H_2O, 0 °C, 15 min; **90**: 82%; **94**: 97%; **96**: 50%; **97**: 62%; **98**: 80%; **99**: 83%; **100**: 77%; **101**: 66%. (iv) $NaBH_4$, $CeCl_3$, MeOH, 0 → 15 °C, 3 h, 77%. (v) BBr_3, CH_2Cl_2, 0 → 25 °C, 2 h, 85%. (vi) methyl (2*R*)-lactate, DIAD, PPh_3, THF, 0 → 25 °C, 12 h, 84%. (vii) LiOH, MeOH, 0 → 25 °C, 30 min, 100%. DIAD, diisopropyl azodicarboxylate; DMSO, dimethylsulfoxide; *m*-CPBA, 3-

chloroperoxybenzoic acid; NMO, *N*-methylmorpholine-*N*-oxide; Ph, phenyl; PMP, p-methoxyphenyl; THF, tetrahydrofuran.

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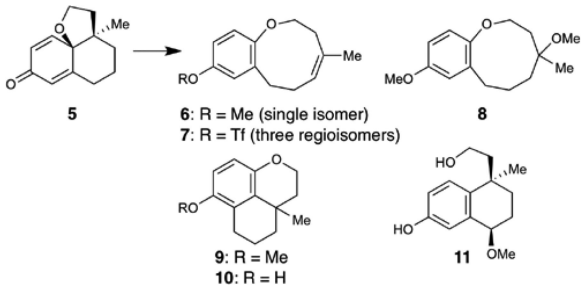
Table 1

Reactivity of a tricyclic cyclohexadienone substrate.



Entry	Conditions[a]	T (°C)	Product	Yield (%)
1	$ZnCl_2$, 1,2-DCE	84	no rxn	–
2	MgI_2, C_6H_6	80	no rxn	–
3	$BF_3{\cdot}OEt_2$, CH_2Cl_2	0 → 25	decomp	–
4	$InBr_3$, CH_2Cl_2	0 → 25	decomp	–
5	$Me_3O{\cdot}BF_4$, Proton-sponge, CH_2Cl_2	40	**9**	60
6	$TiCl_4$, CH_2Cl_2	25	**10**	90
7	$MeAlCl_2$, CH_2Cl_2	25	**10**	65
8	NaOH, MeOH	80[b]	**11**	20[c]
9	NaOMe, MeOH	80[b]	**11**	79[c]
10	TsOH, CH_2Cl_2	25	no rxn	–
11	TsOH, CH_3CN	80	no rxn	–
12	TsOH, DMF	80	no rxn	–
13	TsOH, $MeNO_2$	70	no rxn	–
14	TsOH, MeOH	25 (32 h)	**6 + 8**	81[d]
15	**TsOH, 1:1 MeOH/$MeNO_2$**	**25 (12 h)**	**6 + 8**	**86**[d]
16	TsOH, 10 equiv MeOH, $MeNO_2$	25 (24 h)	**6 + 8**	30[e]
17	TsOH, 1:1 H_2O/THF	100	no rxn	–
18	TsOH, 1:1 H_2O/MeOH	60	no rxn	–
19	**$Cu(BF_4)_2$, TMOF, MeOH**[f]	**50**	**6 + 8**	**88**[d]
20	**Tf_2O, DTBMP, CH_2Cl_2**	**0**	**7**	**90**[g]

[a] 2 equiv of each reagent unless otherwise noted, 0.1 M substrate concentration.

[b] Sealed reaction vessel.

[c] Single diastereomer.

[d] 3:1 ratio of olefin **6** and methanol adduct **8**.

[e] 10:1 ratio of olefin **6** and methanol adduct **8**.

[f] 20 mol% $Cu(BF_4)_2$, 3 equiv TMOF.

[g] Mixture of three olefin regioisomers (major isomer **7** shown). no rxn, no reaction; decomp, decomposition of starting material; THF, tetrahydrofuran; TMOF, trimethyl orthoformate; TsOH, *p*-toluenesulfonic acid DTBMP, di-*tert*-butylmethyl-pyridine; Tf_2O, trifluoromethanesulfonic anhydride.

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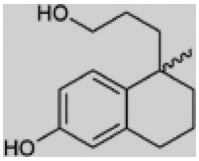
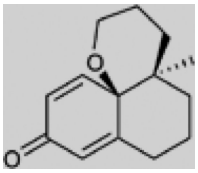
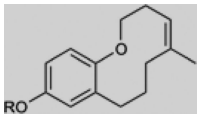
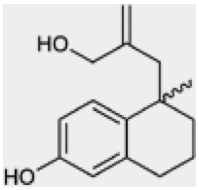
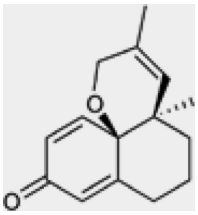
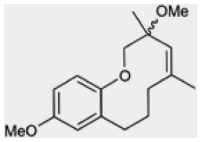
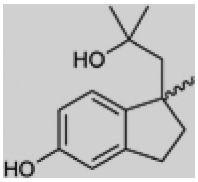
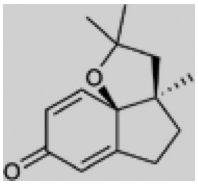
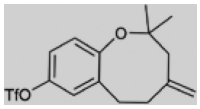
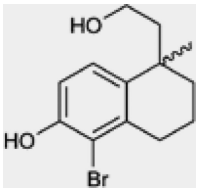
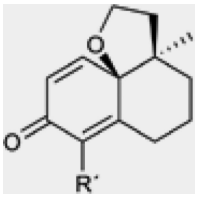
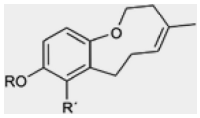
Table 2

Scope of the oxidative dearomatization–ring expansion sequence.

Phenol	Cyclohexa-dienone[a]	Medium ring	Expansion yield (%)[b]
			
12	**31** (45)	**52**(R = Me) **53**(R = Tf)	82[c] (TsOH) 86[c] ($Cu[BF_4]_2$) 91[c] (Tf_2O)
			
13	**32** (55[d])	**54**	90 (TsOH) 49 ($Cu[BF_4]_2$)
			
14	**33** (94)	**55**	75[e] (Tf_2O)
			
15	R′ = Br: **34** (74)	**56**(R = Me) **57**(R = Tf)	50 (TsOH[f]) 85[g] ($Cu[BF_4]_2$[h]) 96[i] (Tf_2O[j])
	R′ = Me: **35** (89[k])	**58**(R = Me) **59**(R = Tf)	85[g] (TsOH) 84[g] ($Cu[BF_4]_2$) 92[i] (Tf_2O)
	R′ = PMP: **36** (95[k])	**60**(R = Me) **61**(R = Tf)	89[g] (TsOH) 85[g] ($Cu[BF_4]_2$)

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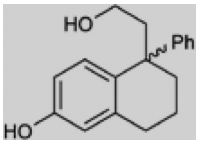
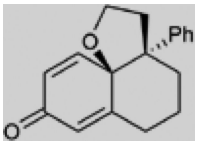
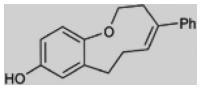
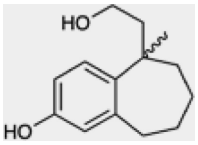
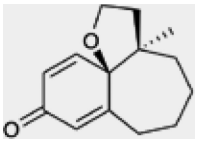
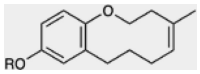
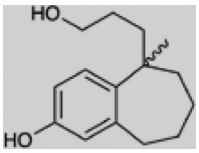
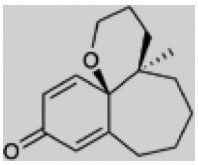
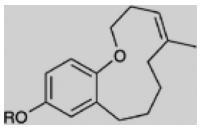
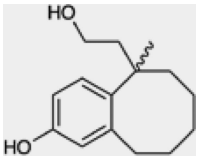
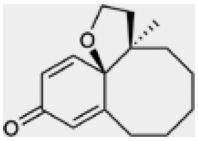
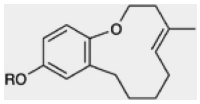
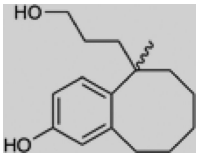
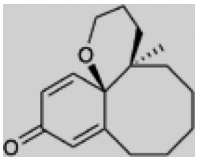
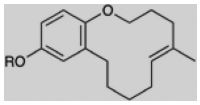
Phenol	Cyclohexa-dienone[a]	Medium ring	Expansion yield (%)[b]
			83[i] (Tf_2O)
			
16	**37** (86)	**62**	57[m] (TsOH) 54[n] (TsOH′) 67 (in CH_2Cl_2)[b] 77[o] ($Cu[BF_4]_2$) 88 (in CH_2Cl_2)[b]
			
17	**38** (96)	**63**(R = H) **64**(R = Tf)	95[g] (TsOH) 98 (TsOH′) 57[c] (Tf_2O)
			
18	**39** (39)	**65**(R = H) **66**(R = Tf)	63[i] (TsOH′) 52[i] (Tf_2O)
			
19	**40** (67)	**67**(R = H) **68**(R = Tf)	82[i] (TsOH′) 87[i] (Tf_2O)
			
20	**41** (26)	**69**(R = H) **70**(R = Tf)	90[n] (TsOH′) 59[p] (Tf_2O)

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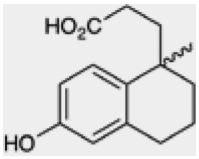
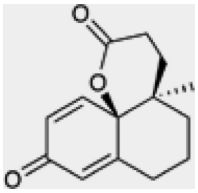
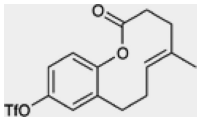
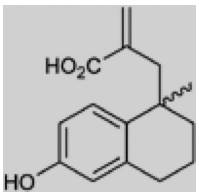
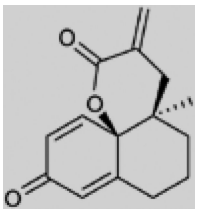
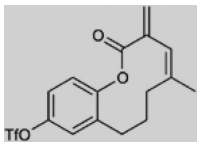
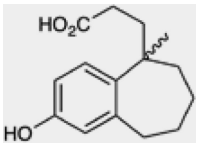
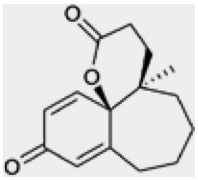
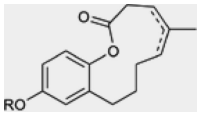
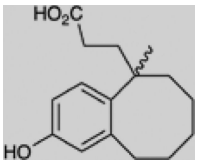
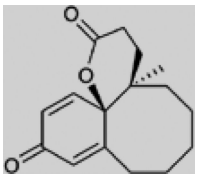
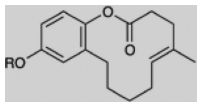
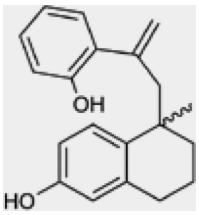
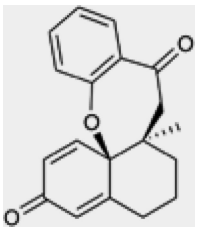
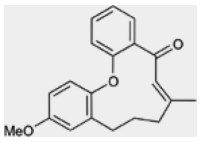
Phenol	Cyclohexa-dienone[a]	Medium ring	Expansion yield (%)[b]
			
21	**42** (53)	**71**	64[i] (Tf_2O)
			
22	**43** (84)	**72**	76 (Tf_2O[j])
			
23	**44** (95)	**73**(R = H, $\Delta^{\gamma,\delta}$) **74**(R = Tf, $\Delta^{\beta,\gamma}$)	56[n] (TsOH′) 56[i] (Tf_2O)
			
24	**45** (42)	**75**(R = H) **76**(R = Tf)	51[p] (TsOH′) 68[i] (Tf_2O)
			**(gram scale)**
25	**46** (50[q])	**77**	89 (TsOH) 74 ($Cu[BF_4]_2$)

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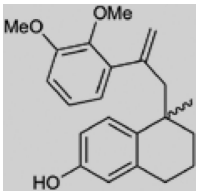
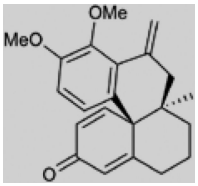
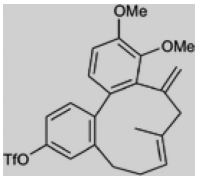
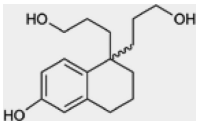
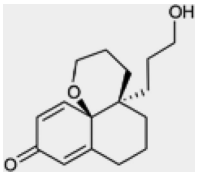
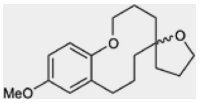
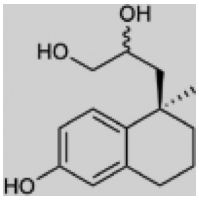
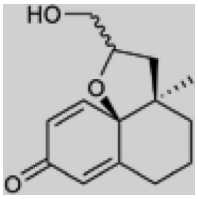
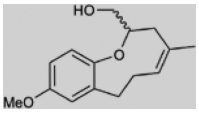
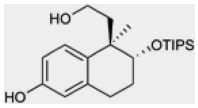
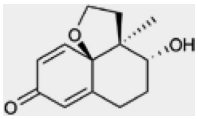
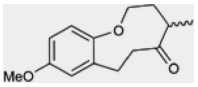
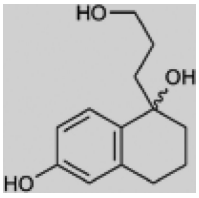
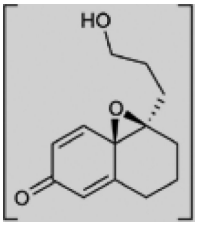
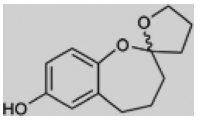
Phenol	Cyclohexa-dienone[a]	Medium ring	Expansion yield (%)[b]
			**(gram scale)**
26	**47** (72)	**78**	84 (Tf_2O)
			
27	**48** (55)	**79**	71 (TsOH) 74 ($Cu[BF_4]_2$)
			
28 (1.2:1 dr)	**49** (71, 1.2:1 dr)	**80**	73[e] (TsOH) 44[e] ($Cu[BF_4]_2$)
			
29	**50** (81[r])	**81**	0 (TsOH) 80 ($Cu[BF_4]_2$)
			**ODRE cascade**
30[s]	**51**	**82**	42 (from **30**[a])

[a] $PhI(OAc)_2$ (1–2 equiv), K_2CO_3 (2–3 equiv), CF_3CH_2OH, 0 → 25 °C; yields shown in parentheses.

[b] TsOH = 2 equiv TsOH, 1:1 MeOH/$MeNO_2$, 25 °C; TsOH′ = 2 equiv TsOH, $MeNO_2$, 25 °C; $Cu(BF_4)_2$ = 20 mol% $Cu(BF_4)_2$, 3 equiv TMOF, MeOH, 50 °C; 'in CH_2Cl_2' indicates the reaction in the preceding entry was performed again using methylene chloride as the solvent; Tf_2O = 1.1 equiv Tf_2O, 2 equiv DTBMP, CH_2Cl_2, 0 °C.

[c] Yield after subsequent treatment with TsOH to converge olefin regioisomers.

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[d] Overall two-step yield after treatment of initially formed exocyclic olefin with TsOH, CH_2Cl_2, 40 °C.

[e] Mixture of endocyclic and exocyclic olefin regioisomers (major isomer shown).

[f] 50 °C.

[g] 3:1 ratio of olefin to MeOH adduct (*cf.* **8**).

[h] 80 °C.

[i] Mixture of three olefin regioisomers (major isomer shown).

[j] 25 °C.

[k] Yield after treatment of **34** with Me_4Sn, $Pd(PPh_3)_4$, CuBr, DMF, 80 °C.

[l] Yield after treatment of **34** with PMP-$B(OH)_2$, $Pd(PPh_3)_4$, Na_2CO_3, 1:1 toluene/EtOH, 50 °C.

[m] 1:3 ratio of phenol **62** to corresponding anisole (*cf.* **6**).

[n] Mixture of two endocyclic olefin regioisomers (major isomer shown).

[o] 1.0:2.3:1.4 ratio of phenol olefin **62** to corresponding anisole olefin (*cf.* **6**) to anisole MeOH adduct (*cf.* **8**).

[p] >10:1 ratio of olefin regioisomers (major isomer shown).

[q] Overall three-step yield after treatment of initially formed exocyclic olefin with OsO_4, NMO, DABCO, 3:1 THF/H_2O, 45 °C, then $Pb(OAc)_4$, 1:1 EtOAc/CH_2Cl_2, 0 °C.

[r] Overall two-step yield after treatment of initially formed TIPS-protected tricyclic cyclohexadienone with TBAF, THF, 0 °C.

[s] Prepared by treatment of a silyl-protected precursor with TBAF, THF, 0 °C, and used immediately without further purification. See **Supplementary Note 1** for complete details. DABCO, 1,4-diazabicyclo[2.2.2]octane; DMF, *N*,*N*-dimethylformamide; DTBMP, 2,6-di-*t*-butyl-4-methylpyridine; EtOAc, ethyl acetate; Me_4Sn, tetramethylstannane; NMO, *N*-methylmorpholine *N*-oxide; $Pb(OAc)_4$, lead(IV) tetraacetate; $Pd(PPh_3)_4$, tetrakis(triphenylphosphine)palladium(0); $PhI(OAc)_2$, iodosobenzene diacetate; PMP, *p*-methoxyphenyl; PMP-$B(OH)_2$, *p*-methoxyphenylboronic acid; TBAF, tetrabutylammonium fluoride; Tf, trifluoromethanesulfonyl; Tf_2O, trifluoromethanesulfonic anhydride; THF, tetrahydrofuran; TMOF, trimethylorthoformate; TsOH, *p*-toluenesulfonic acid.