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Synthesis of Benzannulated Medium-ring Lactams via a Tandem Oxidative Dearomatization–Ring Expansion Reaction

Tezcan Guney,[a,†] Todd A. Wenderski,[a,†] Matthew W. Boudreau,[b] and Derek S. Tan*[a,c]

Abstract: Medium-ring natural products exhibit diverse biological activities but such scaffolds are underrepresented in probe and drug discovery efforts due to the limitations of classical macrocyclization reactions. We report herein a tandem oxidative dearomatization–ring-expanding rearomatization (ODRE) reaction that generates benzannulated medium-ring lactams directly from simple bicyclic substrates. The reaction accommodates diverse aryl substrates (haloarenes, aryl ethers, aryl amides, heterocycles) and strategic incorporation of a bridgehead alcohol generates a versatile ketone moiety in the products amenable to downstream modifications. Cheminformatic analysis indicates that these medium rings access regions of chemical space that overlap with related natural products and are distinct from synthetic drugs, setting the stage for their use in discovery screening against novel biological targets.

Introduction

Medium-ring structures (8–11-membered rings)[1] are found in diverse biologically-active natural products[2] and are attractive scaffolds for use in discovery libraries.[3-16] Such scaffolds have also been leveraged in structure-based drug design.[17-19] The cyclic constraint imparts conformational restriction that is associated with favorable pharmacological properties, including increased binding affinity,[20] cell permeability,[21,22] and oral bioavailability.[23] However, medium rings remain severely underrepresented in screening collections and approved drugs,[24] likely due to the well-known synthetic challenges in accessing these structures.[25] Conventional cyclization-based approaches to medium rings are highly substrate-dependent[26-29] and suffer from the lowest cyclization rates among all ring sizes due to unfavorable transannular interactions.[25] To address this synthetic challenge, we have been developing alternative synthetic approaches based on ring expansion to access medium-ring and macrocyclic structures.[15,16] Herein, we report a new tandem oxidative dearomatization–ring expansion (ODRE) reaction that provides efficient access to a wide range of medium-ring lactams in a single step from readily available bicyclic substrates (**Fig. 1a**). We demonstrate the scope of this tandem ODRE across 31 substrates, and downstream reactions of the resulting scaffolds to introduce additional functionalities. Cheminformatic analysis confirms that the resulting medium-ring compounds access regions of chemical space that overlap with related natural products and are distinct from synthetic drugs and conventional drug-like libraries.

In recent years, there has been growing interest in developing creative synthetic strategies to access medium-ring compounds.[30-33] Tandem cyclization/ring expansion approaches[34-40] are particularly useful as they offer greater

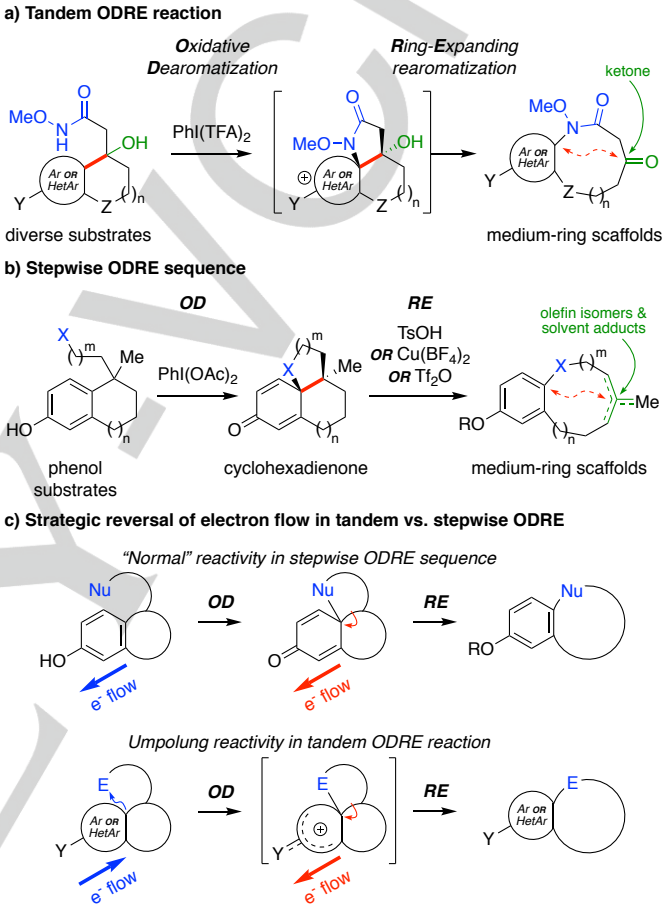

Figure 1. Oxidative dearomatization–ring-expanding rearomatization (ODRE) approaches to medium ring synthesis. (a) Tandem ODRE provides medium-ring scaffolds from bicyclic substrates having an electron-rich aromatic ring. (b) Stepwise ODRE sequence is limited to phenol substrates and provides mixtures of products. (c) Umpolung reversal of electron flow enables new tandem ODRE reaction.

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efficiency and flexibility compared to conventional direct cyclization methods. However, despite these advances, several limitations are commonly observed, such as tedious multistep substrate preparation and narrow tolerance of functional groups and ring sizes found in natural products and bioactive pharmacophores.[41-43]

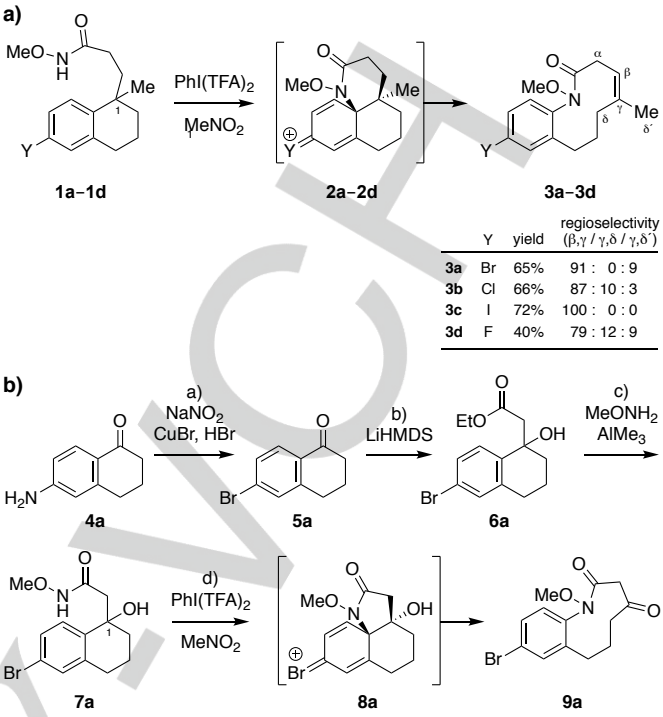
We recently reported a biomimetic, stepwise ODRE sequence to access diverse, natural product-based benzannulated medium rings (**Fig. 1b**).[16] This synthetic approach was inspired by Barton's seminal proposal for the biosynthesis of the alkaloid protostephanine,[44] which was later reduced to practice in several biomimetic syntheses.[45-49] Initial oxidative dearomative of a bicyclic phenol substrate forms an electrophilic cyclohexadienyl cation intermediate, which is then attacked by a side chain nucleophile to generate a tricyclic cyclohexadienone. This intermediate is then activated with a Brønsted acid, Lewis acid, or triflic anhydride to induce ring expansion with rearomatization of the phenol ring. While this stepwise ODRE sequence provided a variety of ring linkages found in medium-ring natural products, including aryl ethers, diaryl ethers, lactones, and biaryls, it was restricted to phenolic substrates and often led to mixtures of olefin isomers and solvent adducts, arising from various termination reactions of a penultimate tertiary carbocation intermediate.

To overcome these limitations, we envisioned a new umpolung approach in which the initial oxidative dearomatization step would instead proceed via attack of an electron-rich aromatic ring on an electrophilic side chain (**Fig. 1c**).[50-56] This would allow a wider range of non-phenolic substrates to be used and might also allow direct ring expansion from the nascent reactive intermediate in a tandem reaction (**Fig. 1a**). This umpolung ODRE strategy would also allow installation of a tertiary alcohol in the substrate to terminate the cationic cascade via formation of a ketone product, avoiding various other termination pathways as well as providing a versatile handle for further functionalization. Notably, Kikugawa has leveraged hypervalent iodine activation of *N*-methoxyamides as nitrenium electrophiles in such umpolung reactivity,[54] which was used by Wardrop in *ipso*-cyclization reactions to synthesize spirolactams.[57-59] Thus, we set out to investigate the utility of such *N*-methoxyamide side chains in an ODRE approach to medium-ring synthesis.

Results and Discussion

Development of tandem ODRE with haloaromatic substrates

In initial studies, we investigated the reactivity of bromotetralin **1a** to access medium-ring lactam **3a** (**Fig. 2a**). The phenol in the original substrate system (**Fig. 1b**) was replaced with an aryl bromide[60,61] to avoid competing oxidative activation of the phenol. Indeed, Ciufolini has reported extensive studies of such oxidative dearomatization reactions of phenols in the presence of nitrogen nucleophiles under the 'normal' polarity reaction manifold.[62-65] We postulated that umpolung oxidative dearomatization would provide a cyclohexadienyl bromonium intermediate **2a** *in situ*,[60] which could then undergo spontaneous ring-expanding rearomatization to form a C1 tertiary carbocation, providing the olefin **3a** after E1 elimination.[16] We recognized that a potential undesired pathway could involve solvolysis of the bromonium intermediate **2a** to form a stable cyclohexadienone intermediate that would not be expected to undergo spontaneous ring expansion.[16,60] Moreover, the penultimate C1 tertiary carbocation could also form other endo- and exocyclic olefin regioisomers or solvent adducts.[16]



	Y	yield	regioselectivity (β,γ / γ,δ / γ,δ´)
3a	Br	65%	91 : 0 : 9
3b	Cl	66%	87 : 10 : 3
3c	I	72%	100 : 0 : 0
3d	F	40%	79 : 12 : 9

Figure 2. Tandem ODRE reactions of haloaromatic substrates to form medium-ring lactam products. (a) Synthesis of 10-membered ring haloaromatics **3a–3d** (major isomer shown). Reagents and conditions: $PhI(TFA)_2$ (2.0 equiv), $MeNO_2$, 0 ºC to 24 ºC, 14 h. (b) Synthesis of 9-membered ketolactam **9a**. Reagents and conditions: a) $NaNO_2$ (1.1 equiv), CuBr (2.2 equiv), HBr (aq), 85%. b) LiHMDS (3.0 equiv), EtOAc (3.0 equiv), THF, –78 ºC, 3 h, 93%. c) $AlMe_3$ (3.0 equiv), $NH_2(OMe)\cdot HCl$ (3.0 equiv), THF, 0 ºC to 24 ºC, 16 h, 96%. d) $PhI(TFA)_2$ (1.5 equiv), $MeNO_2$, 0 ºC to 24 ºC, 1 h, 73%. HMDS = hexamethyldisilazide; TFA = trifluoroacetate; THF = tetrahydrofuran.

Treatment of bromotetralin **1a** with (diacetoxyiodo)benzene in trifluoroethanol led to a mixture of olefin regioisomers (70 : 28 : 2 β,γ / γ,δ / γ,δ´) for the desired medium-ring lactam product **3a**. Use of $PhI(TFA)_2$ in trifluoroethanol improved the ratio of olefin isomers (75 : 18 : 7). Moreover, changing the solvent to nitromethane provided **3a** in 65% yield as a 91:9 mixture of β,γ and γ,δ´ olefin regioisomers, without formation of the γ,δ isomer. Similarly, $PhI(TFA)_2$-mediated tandem ODRE of chlorotetralin **1b**, iodotetralin **1c**, and fluorotetralin **1d** afforded the corresponding medium-ring lactams **3b**, **3c**, and **3d** in modest to good yields, with varying regioselectivity favoring endocyclic β,γ olefins.

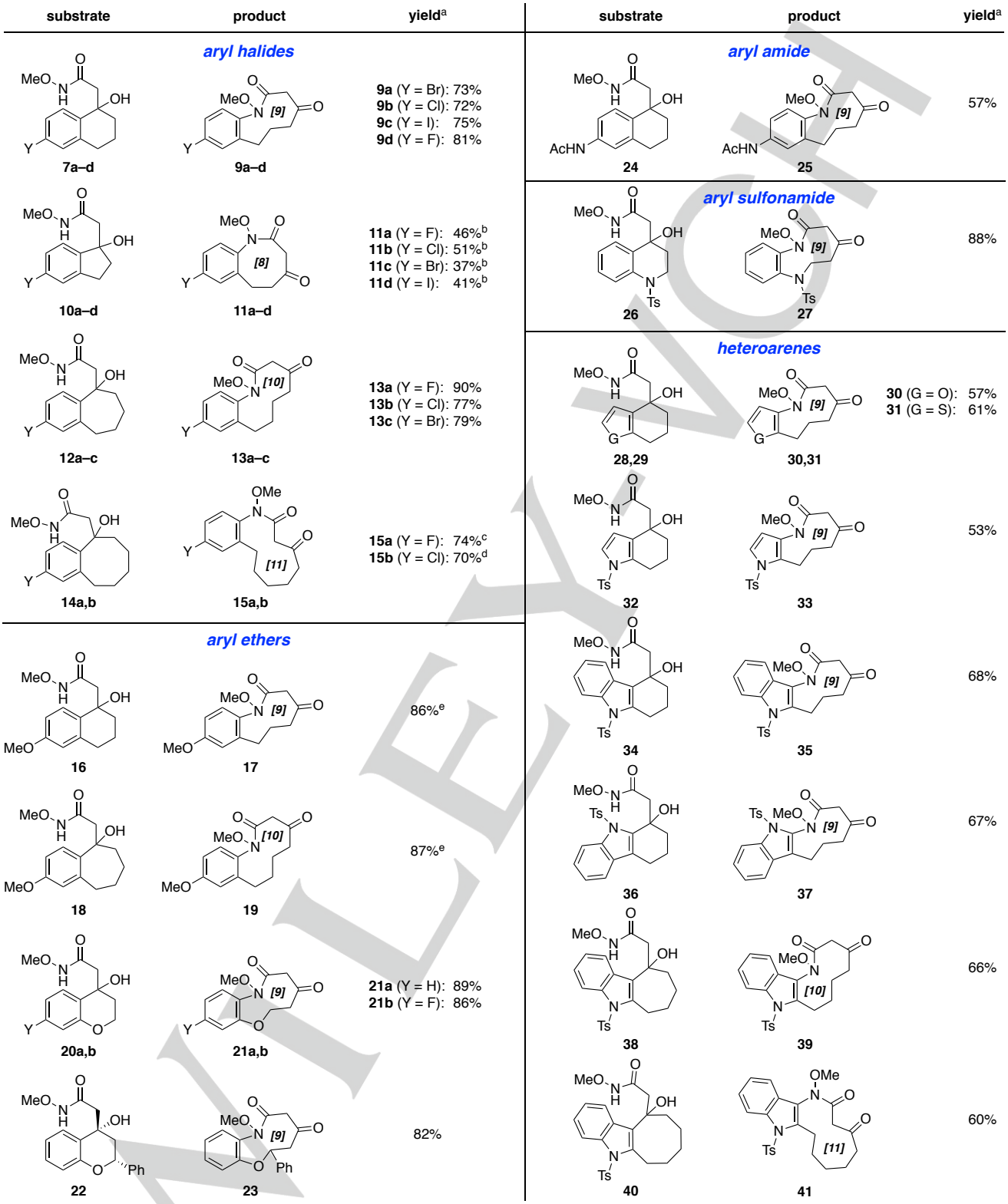


Figure 3. Scope of tandem ODRE reaction. [a]Reagents and conditions: $PhI(TFA)_2$ (1.0–1.5 equiv), $MeNO_2$, 0 ºC to 24 ºC, 0.5–2 h. [b]Remainder indene byproducts resulting from dehydration of **10a–d** and unidentified side products, based on ^{1}H-NMR analysis of crude product. [c]Isolated as a mixture of amide rotamers (3:2 *E*/*Z*). [d]Isolated as a mixture of amide rotamers (2:1 *E*/*Z*). [e]Reaction performed in MeOH at 0 °C.

Strategic installation of tertiary alcohol to generate ketone products

Next, to avoid formation of mixtures of olefin regioisomers, we replaced the C1-methyl group in the tetralin substrate with a hydroxyl group, that would lead to a single ketone product (**Fig. 2b**). We reasoned that the lone-pair electrons of the hydroxyl group would also potentiate the ring-expanding rearomatization step, by analogy to previous biomimetic syntheses of protostephanine and related alkaloids, in which an endocyclic amine nitrogen likely plays a similar role in driving ring-expanding rearomatization.[45-49] Moreover, the resulting ketone motif would serve as a versatile handle for further chemical diversification of the medium-ring scaffolds. Notably, this approach was not feasible in the original stepwise ODRE sequence with phenolic substrates[16] due to competing Adler–Becker oxidation.[66,67] Thus, reversing the electron flow in the oxidative dearomatization step of this umpolung tandem ODRE reaction was critical to this approach.

Accordingly, bromotetralol **7a** was prepared from commercially available 6-amino-1-tetralone (**4a**) in 3 steps and 76% overall yield. Treatment of **7a** with $PhI(TFA)_2$ in nitromethane then afforded the desired β-ketolactam **9a** in 73% yield. The corresponding chloro-, iodo-, and fluorotetralol substrates **7b**-**d** were also obtained using the same scalable, efficient synthetic sequence and converted via tandem ODRE to medium rings **9b-d** in good yields (**Fig. 3**). The aryl fluoride product **9d** was obtained in the highest yield in this series (81%), consistent with improved "back-donation" of the fluorine lone pairs into the cyclohexadienyl halonium intermediate.[60,68]

Scope of the tandem ODRE reaction

We next investigated the effects of varying ring size in the substrates (**Fig. 3**). In tandem ODRE reactions of haloindanol substrates **10a–d**, the corresponding 8-membered ring lactam products **11a–d** were recovered in moderate 37–51% yields. This decreased efficiency may be attributed to competing formation of indene side products via dehydration of the indanol substrates, or poor orbital overlap of the scissile bond with the nascent aromatic p-system in the rearomatization reaction.[16] In contrast, the corresponding halobenzosuberanols **12a-c** and halobenzocyclooctanols **14a,b** afforded 10- and 11-membered benzannulated lactams **13a-c** and **15a,b**, respectively, in 70–90% yields.

Next, we explored the use of aryl ether substrates in the tandem ODRE. Anisoles have been used previously in such umpolung oxidative dearomatization spirocyclization reactions of *N*-methoxyamides.[57-59] However, reaction of the anisole **16** led to only a 15% yield of the desired medium-ring lactam **17**. From this complex mixture, we also recovered a cyclohexadienone byproduct (≈20%), presumably resulting from hydrolysis or demethylation of the corresponding *O*-methyl oxocarbenium intermediate (**Supplementary Fig. 1a**). We posited that this unproductive pathway could be avoided by stabilizing the *O*-methyloxocarbenium intermediate with a temporary nucleophile. Thus, when the reactions were conducted in methanol instead of nitromethane, the 9- and 10-membered medium-ring products **17** and **19** were obtained in 86% and 87% yields, respectively. Notably, subjecting **16** to the same conditions in CD_3OD did not result in deuterium incorporation in the methyl ether moiety of the product **17**, suggesting that methanol may undergo a 1,4-addition to the *O*-methyloxocarbenium intermediate, followed by elimination during, or en route to, anisole rearomatization (**Supplementary Fig. 1b**).

In contrast, chromanone-derived substrates **20a,b** and flavanone derivative **22**, both having an endocyclic ether moiety, did not suffer from the dealkylation pathway in nitromethane, and proceeded to the medium-ring products **21a,b** and **23**, respectively, in excellent yields (82–89%). Similarly, acetanilide substrate **24** and quinolone derivative **26** provided the corresponding acetamidoaryl lactam and sulfonamidoaryl lactam products **25** and **27** respectively**,** under the standard reaction conditions. Sulfanilides have been used previously in hypervalent iodine-induced oxidative dearomatization spirocyclization reactions under the 'normal' polarity reaction manifold.[69]

We next sought to extend the tandem ODRE reaction to heteroaromatic ring systems found in natural products and drug pharmacophores. Commercially available furano-, thiopheno-, and pyrrolocyclohexanones were transformed into the corresponding b-hydroxy-*N*-methoxyamide substrates **28**, **29**, and **32**, respectively, then converted via tandem ODRE to 9-membered ring lactam products **30**, **31**, and **33** in serviceable yields. Hypervalent iodine-induced oxidative dearomatization reactions have been reported under the 'normal' polarity reaction manifold for furans[70,71] and under the umpolung reaction manifold for thiophenes and pyrroles.[72,73] Further, indoles **34** and **36** proved to be reactive as nucleophiles at both the C3- and C2-positions, respectively, providing the corresponding regioisomeric indole products **35** and **37**. Hypervalent iodine-induced oxidative dearomatization reactions of indoles with nitrogen nucleophiles or electrophiles have been reported under the 'normal'[74,75] and umpolung[76-78] reaction manifolds, respectively. The larger indole-fused 7- and 8-membered ring substrates **38** and **40**, readily accessed from the corresponding cyclic ketones via Fischer indole synthesis followed by a DDQ oxidation sequence, were also converted to the corresponding 10- and 11-membered lactam products **39** and **41** in good yields. Taken together, these results demonstrate the excellent scope of the tandem ODRE reaction in providing access to a wide variety of benzannulated medium-ring lactam products.

Mechanistic proposal

A proposed mechanism for the tandem ODRE reaction involves initial $PhI(TFA)_2$ activation of the *N*-methoxyamide side chain in **42**, in the presence of the charge-stabilizing solvent nitromethane, to form a nitrenium ion intermediate[57,79-81] **44** (**Fig. 4**). Ensuing intramolecular electrophilic substitution through *ipso*-attack of the tethered arene generates a cationic tricyclic intermediate **45** poised for ring expansion. Rearomatization of the arene then drives spontaneous C–C bond cleavage, facilitated by the lone-pair electrons on the C1-hydroxyl group, to afford the benzannulated medium ring-lactam product **46**.

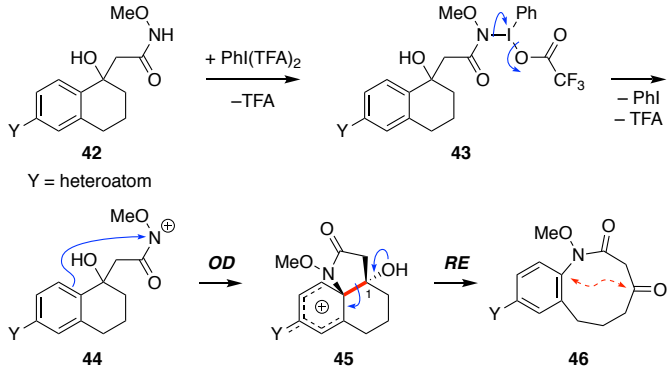


Figure 4. Proposed mechanism of tandem ODRE reaction.

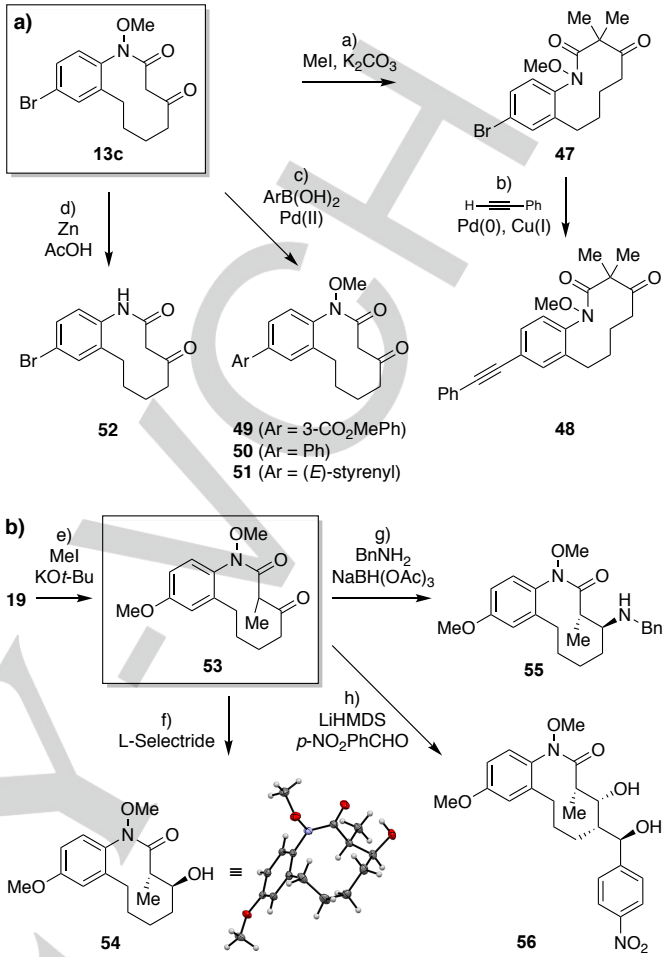


Figure 5. Downstream modification reactions of medium-ring scaffolds 13c and 53. Reagents and conditions: a) MeI (4.0 equiv), K_2CO_3 (4.0 equiv), DMF, 24 °C, 48 h, 68%. b) phenylacetylene (10.0 equiv), $Pd(PPh_3)_4$ (20 mol%), CuI (25 mol%), Et_3N, DMF, 60 °C, 16 h, 65%. c) $ArB(OH)_2$ (1.1 equiv), $Pd(OAc)_2$ (20 mol%), K_2CO_3 (2.5 equiv), TBAB (1.1 equiv), H_2O, 70 °C, 2 h, 65–77%. d) Zn (40.0 equiv), AcOH/H_2O (1:1), 24 °C, 24 h, 85%. e) MeI (3.0 equiv), KO*t*-Bu (1.05 equiv), THF, 0 °C, 4 h, 72%. f) L-Selectride (2.0 equiv), THF, 0 °C to 24 °C, 3 h. 94%, >99:1 dr *anti*/syn. g) $BnNH_2$ (1.1 equiv), AcOH (1.0 equiv), 4Å MS, toluene, 90 °C, 2 h, then $NaBH(OAc)_3$ (4.0 equiv), DCE, 24 °C, 16 h, 76%, 94:6 dr *anti/syn*. h) LiHMDS (3.0 equiv), THF, –78 °C, 1 h; then *p*-NO_2PhCHO (2.5 equiv), –78 °C to 24 °C, 16 h, 59%, 99:1 dr. DCE = dichloroethane; DMF = *N*,*N*-dimethylformamide; L-Selectride = lithium tri-*s*-butylborohydride; TBAB = tetrabutylammonium bromide.

Functionalization of medium-ring scaffolds

With access to a variety of medium-ring scaffolds established, we next investigated downstream synthetic modifications to introduce additional structural diversity. Thus, bromoaryllactam **13c** and methoxyaryllactam **53** were scaled up to explore these transformations (**Fig. 5a**). The acidity of the 1,3-dicarbonyl methylene protons in **13c** enabled conversion to α,α-dimethylketone **47** in a one-pot geminal dimethylation.[82] Sonogashira coupling of the aryl bromide moiety in **47** with phenyl acetylene then afforded aryl alkyne **48** in 65% yield.[83] From the parent aryl bromide **13c**, several boronic acids were also coupled under standard Suzuki–Miyaura conditions[84] to provide cross-coupling products **49–51** in good yields. Reductive cleavage of the *N–O* bond in **13c** with zinc metal afforded corresponding secondary lactam **52** without affecting the bromide.[85]

In a second series, β-ketolactam **19** (**Fig. 5b**) was first converted to α-methyl-β-ketolactam **53** using potassium *tert*-butoxide and methyl iodide. The ketone moiety of **53** was then reduced to afford *anti*-α-methyl-β-hydroxylactam **54** in 94% yield and >99:1 dr.[86] The stereochemical configuration of **54** was assigned based on X-ray crystallographic analysis (see Electronic Supplementary Information). Analogously, reductive amination of the ketone in scaffold **53** with benzyl amine provided β-aminolactam **55** in 76% yield and 94:6 dr, favoring the *anti* diastereomer, assigned based on extensive 2D NMR studies.[87] Finally, a one-pot aldol–Tishchenko reaction generated *anti*-1,3-diol **56** in good yield as a single diastereomer with four contiguous stereocenters.[88] Relative stereochemistry was assigned via conversion to the corresponding acetonide and 1D and 2D NMR studies (see Electronic Supplementary Information).

Cheminformatic analysis of medium-ring scaffolds

To assess the structural features of the tandem ODRE products, we carried out a cheminformatic analysis of these 41 compounds in comparison to 47 accessed by the original stepwise ODRE sequence, 20 benzannulated medium-ring natural products, and our previously established reference sets of 60 diverse natural products, 40 top-selling brand-name drugs, and 20 commercial drug-like library compounds.[15,16,89,90] We analyzed each compound based on our established set of 20 structural and physicochemical parameters, then used principal component analysis (PCA) to identify correlations between parameters, reducing the dimensionality of the complete 20-dimensional dataset to enable convenient visualization (**Supplementary Fig. 2**).[89] The first three principal components (PC1–PC3) accounted for 75% of the variance represented in the complete 20-dimensional dataset.

In this analysis, visualization of the first two principal components (PC1, PC2) was insufficient to differentiate the medium-ring ODRE libraries and natural products clearly from the synthetic drugs and drug-like libraries. In contrast, the

reference set of 60 diverse natural products occupied a larger, distinct region of the plot. Examination of component loadings (**Supplementary Fig. 3**) indicated that positioning along PC1 was dominated by parameters that correlate with molecular size (*e.g.*, molecular weight, van der Waals surface area). Along PC2, parameters that correlate with hydrophobicity (logP, logD) shifted molecules down (negative) while those that correlate with polarity (logS, relative polar surface area) shift molecules up (positive). Thus, the overlap of the medium-ring and drug/drug-like sets is likely due to their relatively small and hydrophobic nature. Further, the broader range of this plot covered by the diverse natural product reference set is primarily due to the larger size of these molecules and, in some cases, high polarity.

In contrast, when PC3 was plotted, the medium-ring libraries and natural products diverged from the synthetic drugs and drug-like libraries. Along PC3, parameters that correlate with three-dimensional structure (stereochemical density, sp^3 content) shifted molecules positively while aromatic ring content shifted molecules negatively. Thus, the relatively three-dimensional structures of the medium-ring compounds effectively differentiated them from the relatively flat, highly aromatic structures of the drugs and drug-like molecules. Notably, the former parameters have been associated with increased target specificity[91] and progression through preclinical and clincial development[92,93] while the latter has been associated with preclinical toxicity.[94,95] Moreover, both of the ODRE libraries overlapped well with bonafide medium-ring natural products across all three principal components.

Conclusions

Despite their prevalance in natural products and attractive pharmacological properties, medium-ring structures are underrepresented in current discovery libraries due to the challenges associated with classical cyclization-based synthetic approaches. To address this limitation, we have developed a novel tandem ODRE reaction that provides flexible, efficient access to diverse medium-ring scaffolds in 3 steps from readily available cyclic ketone precursors. In contrast to our previously reported stepwise ODRE sequence,[16] this tandem reaction provides medium-ring scaffolds directly from simple bicyclic precursors through an umpolung strategy. Conceptual reversal of electron flow in the initial oxidative dearomatization step leads to a cationic tricyclic intermediate that undergoes spontaneous ring-expanding rearomatization. Moreover, this umpolung strategy enables strategic installation of an adjacent hydroxyl group to prevent formation of olefin regioisomers and other cation termination products, while also providing a versatile ketone motif for further transformations. This was not feasible in the original stepwise ODRE sequence due to competing Adler–Becker reaction of phenolic substrates. Finally, the umpolung strategy enables use of a much wider array of arene substrates to provide haloaryl, aryl ether, acetanilide, aryl sulfonamide and heteroaromatic medium-ring products found in numerous natural and synthetic pharmacophores. The resulting natural product-based medium ring scaffolds are amenable to scale-up and a variety of downstream modifications. Cheminformatic analysis indicates that the tandem ODRE library overlaps with medium-ring natural products and is distinct from conventional synthetic drugs and drug-like libraries, accessing regions of chemical space that are underrepresented in probe and drug discovery. Notably, related benzannulated medium-ring lactam scaffolds have also been used in structure-based designed of angiotensin-converting enzyme inhibitors.[17-19] While the immediate applications of these molecules lie in efforts to discover novel biological probes, both β-ketolactam and *N*-alkoxyamide motifs are found in approved and investigational drugs, suggesting that these motifs are also compatible with eventual translational applications.[96-100] Biological evaluation of this tandem ODRE library is ongoing and will provide insights into its utility in identifying novel probes and therapeutic leads.

Experimental Section

See Supporting Information for complete experimental protocols and analytical data, as well as PCA and X-ray crystallographic datafiles.

General procedure for tandem ODRE reaction

The β-hydroxy-*N*-methoxyamide substrate (0.32 mmol, 1.0 equiv) was dissolved in nitromethane (3.2 mL) and cooled to 0 °C. [Bis(trifluoroacetoxy)iodo]benzene (0.48 mmol, 1.5 equiv) was added as a solid at 0 °C and the reaction was slowly warmed to 24 °C and stirred for 0.5–2 h and monitored by TLC until complete consumption of the starting material was observed. The reaction was then quenched with satd aq $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (4 ´ 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), filtered, and concentrated by rotary evaporation to afford the crude product. Purification by silica flash chromatography (0% → 5% MeOH in CH_2Cl_2) provided the corresponding medium-ring lactam. In the case of anisole-tethered β-hydroxy-*N*-methoxyamides, the general procedure was modified by using methanol instead of nitromethane as the solvent and keeping the reaction at 0 °C.

Principal component analysis

PCA of the 41 resulting benzannulated medium-ring lactams, 47 medium-ring products synthesized previously by the stepwise ODRE sequence,[16] and our previously established reference sets of 40 drugs, 20 commercial drug-like library members, and 60 natural products was conducted using R, an open-source statistical computing package.[89] A set of 20 physicochemical descriptors (**Supplementary Table 3**) for all compounds was obtained from PubChem and/or calculated using cheminformatics tools (Instant JChem and VCCLab[101]) or ChemDraw and uploaded to R for the study. The first three principal components (PC1–PC3) were obtained using R, which accounted for 74.6% of the cumulative variance in the complete data set. They were then plotted on newly generated, unitless, orthogonal axes (principal components) based on linear combinations of the original 20 parameters (**Supplementary Table 3** and **Supplementary Data Set 1**). The PCA graphs shown in **Supplementary Fig. 2** were generated using the data visualization software Prism.

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Keywords: medium ring, tandem reaction, oxidative dearomatization, ring expansion, umpolung

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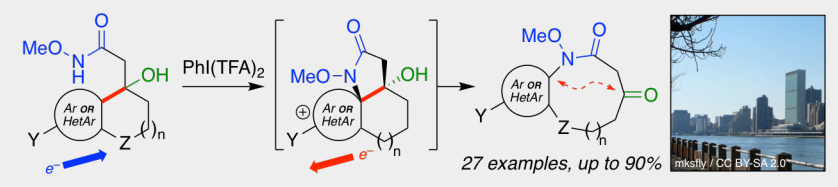

East River Reactivity: Reversal of electron flow during a tandem oxidative dearomatization–ring-expanding rearomatization reaction (left) was inspired by the East River in New York City, a tidal estuary that reverses direction with each tide (right). The tandem reaction provides rapid and efficient access to a wide range of medium-ring products that probe natural product-like regions of chemical space.

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Synthesis of Benzannulated Medium-ring Lactams via a Tandem Oxidative Dearomatization–Ring Expansion Reaction