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Pharmacophore-Directed Retrosynthesis Applied to Rameswaralide: Synthesis and Bioactivity of *Sinularia* Natural Product Tricyclic Cores

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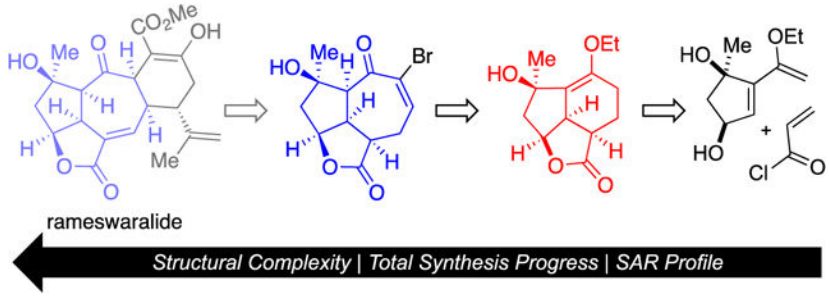
Abstract

A Pharmacophore-Directed Retrosynthesis (PDR) strategy applied to rameswaralide provided simplified precursors bearing the common 5,5,6 (red) and 5,5,7 (blue) skeleton present in several cembranoid and norcembranoids from *Sinularia* soft corals. Key steps include a Diels-Alder lactonization organocascade delivering the common 5,5,6 core and a subsequent ring expansion affording a 5,5,7 core serviceable for the synthesis of rameswaralide. Initial structure-activity relationships of intermediates *en route* to the natural product has revealed interesting differential and selective cytotoxicity.

Graphical Abstract



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Author Contributions

N.J.T. and K.N.V. synthesized and characterized all new compounds reported toward rameswaralide. S.A and J.O.L designed and preformed the biological assays. D.R. and N.J.T. wrote the manuscript with input from all other authors.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Procedures for all synthetic transformations and characterization data for all new compounds including $_1$H and 13C NMR, IR, HRMS, and crystallographic data for compounds **15**, **20**, **29**, **30** (PDF). Materials and methods for biological assays.

Crystallographic data contained in this article have been deposited at the Cambridge Crystallograpic Data Centre under deposition number CCDC 1937890 (**15**), 1937891 (**20**), 1937892 (**29**), 1937893 (**30**). The data can be accessed free of charge at https://www.ccdc.cam.ac.uk/structures/.

The authors declare no competing financial interest.

Soft corals belonging to the genus *Sinularia* produce a number of cembranoid and norcembranoid diterpenes bearing a complex, caged, highly oxygenated tri- or tetracyclic skeleton as seen in several representative members **1–6** (Figure 1).[1–6] However, the limited availability of these natural products from corals has hindered a broader understanding of their bioactivity. To date, moderate cytotoxicity of ineleganolide (**5**) toward the P388 leukemia cell line (11.6 μM ED_{50})[5] was reported. The potential anti-inflammatory activity[7] and cytotoxicity toward A549 human lung carcinoma epithelial cells (IC_{50} 67 ± 3.7 μM)[8] of rameswaralide (**6**) was also reported. Furthermore, with the exception of rameswaralide,[8] the absolute stereochemistry of these diterpenoids has not yet been confirmed; however it was indirectly assigned based on the established absolute stereochemistry of a probable biosynthetic precursor.[3,9] While several groups have pursued the synthesis of rameswaralide (**6**)[10–14] and ineleganolide (**5**)[15–21] which bear the 5,5,7 core (blue, Figure 1), to our knowledge, there are no reported total syntheses. Less synthetic work has been directed to members possessing the 5,5,6 core (red) such as that found in yonarolide, scabrolides, dissectolides, and sinulochmodin C (**1**-**4**).[22–25]

Our interest in ineleganolide (**5**) and rameswaralide (**6**) stems from their structural complexity and the lack of information regarding structure and activity relationships (SAR) for these diterpenoids. Toward the latter goal, herein we apply our recently disclosed Pharmacophore-Directed Retrosynthesis (PDR)[26] strategy, to enable simultaneous collection of SAR for rameswaralide and congeners *en route* to a total synthesis. An initial hypothesis to guide our PDR approach is premised on the noted similarities in the common 5,5,7-core (blue, Figure 1) which we propose may encompass the pharmacophore of ineleganolide (**5**) and rameswaralide (**6**). Variations in this core structures derive from points of attachment of the fused 6-membered D ring to the C rings and a bridging ether in ineleganolide derived from a presumed oxa-Michael addition.[9] Furthermore, sinulochmodin C (**4**) and scabrolides A&B (**2**) are constitutional isomers of ineleganolide (**5**), yet in cell lines tested, have shown moderate to no bioactivity.[27,28] We propose that the 5,5,7 core structure imparts the greatest bioactivity to this class of diterpenoids. We therefore devised a retrosynthesis that would allow access to the 5,5,7 core through a ring expansion proceeding via a 5,5,6 core intermediate. This strategy would enable a systematic study of the impact of core ring size and location of attachment of the D-ring to the 5,5,7-core on bioactivity. Thus, annulation of various D-rings to these core structures and attendant functionality would provide valuable SAR information *en route* to members of this family. It is certainly possible that in these highly functionalized caged natural products, the entire molecule is required for bioactivity, nevertheless application of PDR facilitates and opens the possibility of identifying equipotent, simplified derivatives and also potential new bioactivities not previously observed with this class of diterpenoids.

We decided to set rameswaralide (**6**) as our initial target since it displays some of the most compelling bioactivity in this class of tetracyclic diterpenoids.[6] Based on previous work by both Mehta[10] and Trost,[11] who independently synthesized a similar 5,5,7 core of rameswaralide, we anticipated that annulation of the D-ring would be challenging given the lack of further efforts toward this end. With this in mind, we proposed that α-halo enones like enone **7**, could serve as highly versatile intermediates for several D-ring annulation

strategies toward rameswaralide (**6**). The α-bromo enone **7** could be accessed via a cyclopropanation ring expansion strategy from 5,5,6 tricycle **8**. Early access to both tricyclic intermediates **7** and **8** provides a divergence point towards several members of this natural product family and would enable a systematic study of potential varying bioactivity between 5,5,6 and 5,5,7 cores. We envisioned access to tricycle **8** through our recently described Diels-Alder Lactonization (DAL) organocascade process of diene **9** and acryloyl chloride.[29,30] Diene **9** is available through a Stille cross-coupling and 1,2 addition to cyclopentenone **10**, in turn available through a known Piancatelli rearrangement[31] of furfuryl alcohol (**11**).

Our synthetic studies began with the preparation of diol **9** employing known iodide **12**.[32–34] The latter was subjected to a Stille coupling with ethoxy vinyl stannane **13** to afford racemic diene **14**. Subsequent 1,2 addition with MeLi proceeded with high diastereoselectivity (>19:1 dr) and deprotection provided diol **9** in 45% yield over 2 steps. With the requisite diene in hand, we attempted the key DAL reaction initially employing racemic benzotetramisole, however, typical DAL conditions provided only enone **15** corresponding to the core of yonarolide (**1**). This product presumably results from elimination of the tertiary alcohol catalyzed by trace HCl; this same enone was recently obtained by Deng and co-workers through a different synthetic strategy.[23] Extensive optimization to identify acid scavenging conditions that did not interfere with the DAL process ultimately led to replacement of the previously reported biphasic proton shuttle base system[29,30] with only Hunig's base (*i*-Pr_2NEt). These conditions reliably provided the desired tertiary alcohol **8** in 77% yield with high diastereoselectivity (>19:1, $_1H$ NMR). An optimized route to obtain enone **15** was also identified involving direct workup with 1 M HCl. The relative stereochemistry of this product was confirmed by X-ray crystallography (Scheme 2, inset). While the current route provides racemic material, our previous studies suggest the potential for an asymmetric variant of the key DAL process.[29,30]

Enol ether **8** is a regioisomer of an ideal alkene substrate for the planned ring expansion to the desired cycloheptanone ring. This realization coupled with the propensity for elimination of the tertiary alcohol leading to enone **15**, under even mild acidic conditions, led us to consider strategies for direct transposition of the alkene through an electrophilic addition/alkene transposition pathway. Davies reported a similar alkene transposition utilizing *N*-bromosuccinimide (NBS) presumably driven by release of strain.[35] Indeed, the desired transposition of the less stable ring-fused alkene was achieved under mild conditions with NBS providing the brominated, regioisomeric enol ether **16**.

With an initial substrate for cyclopropanation in hand, we studied the Furukawa-modified, Simmons-Smith cyclopropanation (Scheme 3).[36–38] However, not surprisingly, treatment of alcohol **16** to cyclopropanation conditions initially generates the tertiary alkoxide which cyclized to epoxide **21** as the sole product. Unfortunately, the instability of epoxide **21** precluded its use as a cyclopropanation substrate. Protection of the tertiary alcohol as a triethylsilyl (TES) ether **17** precluded epoxide formation, however the cyclopropanation still did not proceed and only starting material was recovered. We considered that the tertiary bromide may be preventing approach of the Zn-carbenoid to the more accessible convex face. Therefore, standard radical dehalogenation conditions provided enol ether **18**.

However, attempted cyclopropanation again led only to recovered starting material. We next considered removal of the TES protecting group which, based on models, may be forcing the ethyl group of the enol ether into the more accessible convex face through a gearing effect. The net result would be steric blocking of both faces of the enol ether. Furthermore, deprotection of the alcohol would enable a complex-induced proximity effect through formation of a pendant carbenoid proximal to the enol ether thereby increasing the rate of cyclopropanation through intramolecularity.[39,40] Use of allylic alcohols in this manner through directed Furukawa-modified, Simmons-Smith cyclopropanation is precedented.[41–45] Indeed, after removal of the TES protecting group, enol ether **19** participated in the desired cyclopropanation employing diiodomethane delivering cyclopropane **20** as a single diastereomer (>19:1 by 1H NMR, 600 MHz) in 38% yield, (unoptimized) sufficient for our initial studies of the ring expansion. The relative stereochemistry was confirmed by X-ray analysis and verifies that methylene transfer occurred exclusively on the sterically less accessible, concave face and that delivery of the zinc carbenoid is likely directed by the ideally situated, *in situ* generated tertiary alkoxide.

With cyclopropane **20** in hand, we attempted radical mediated, oxidative ring expansions (Scheme 4). Under FeCl3 conditions reported by Seagusa for cyclopropyl TMS ethers,[38] no reaction was observed. Use of ceric ammonium nitrate (CAN) with NaI,[46,47] which presumably generates iodine radicals, led to cleavage of the cyclopropane providing primary iodide **22** which proved to be highly unstable. This suggest that the ethyl ether is not being oxidized directly but rather iodine radical is formed and attacks the least hindered carbon of the cyclopropane as proposed in Scheme 4.[48]

To direct the cyclopropane ring expansion, we targeted the monobromocyclopropane **24** (Scheme 5). We anticipated that the bromide would enable ring expansion via an ionic mechanism or, alternatively, it could block addition of a radical to the undesired cyclopropyl carbon. The same cyclopropanation conditions employed previously were performed with tribromomethane and led to a very sluggish conversion to the desired cyclopropane. The presence of oxygen has been reported to increase the rate of cyclopropanation by aiding in the formation of the bromozinc carbenoid.[49,50] Thus, addition of a balloon of O_2 after alkoxide formation and addition of tribromomethane greatly enhanced the reaction rate and led to reproducible yields of cyclopropane **24** with high diastereoselectivity (>19:1, $_1$H NMR). The relative stereochemistry of the cyclopropane ring was assigned by analogy to cyclopropane **20** and coupling constant analysis of the cyclopropane protons.

We next attempted the ring expansion utilizing various silver salts but were unsuccessful in obtaining the desired enone **27** (Scheme 5) but instead obtained pyranone **25**, derived from ring expansion followed by oxa-Michael, and enone **26** derived from elimination. Since an ionic mechanism failed, we again turned to addition of a halo radical and in particular, a bromide radical through oxidation of Br- with CAN. This reaction afforded the desired ring expanded product **28** along with significant quantities of tribromide **29** (relative stereochemistry assigned by X-Ray, see SI). The latter product presumably results from the desired ring expansion followed by α-bromination. While this α-bromination was not expected, it proved extremely useful. Treatment of dibromo ketone **28** under several basic conditions to give the α-bromo enone **7** led to complex mixtures. However, treatment of

tribromo ketone **29** with DBU provides the epoxy, α-bromo enone **30** in which the tertiary alkoxide again cyclizes to form an epoxide and serves to prevent elimination of the tertiary alcohol.

Our described PDR strategy toward rameswaralide (**6**) provided access to both 5,5,6- and 5,5,7-tricyclic intermediates, bearing resemblance to *Sinularia* natural products, that were assayed for bioactivity. Furthermore, intermediates **15** and **19** were readily transformed into three additional analogs **31**-**33** providing additional SAR data (see SI for synthetic details).[51] In collaboration with Prof. Brian Stoltz's group (Caltech), three additional tricyclic analogs **34**-**36** were assayed to widen the SAR profile.[52]

Cell viability assays (alamar blue viability assay, 72 h incubation) employing three cancer cell lines were performed with the described simplified *Sinularia* natural product derivatives (Table 1). Rameswaralide previously showed cytotoxicity against the A549 (human lung epithelial carcinoma) cell line with an IC_{50} of 67 ± 3.7 μM.[8] We therefore assayed this cell line along with triple-negative breast cancer (MDA-MB-231) and colorectal carcinoma (HCT116) cell lines along with primary Human Umbilical Vein Endothelial cells (HUVEC) to obtain information regarding selective cytotoxicity. The presence of α,β-enones, as a result of our synthetic strategy and also present in some *Sinularia* family members opens the possibility of covalent modifying compounds via thio-Michael additions. However, when selectivity can be achieved with these Michael acceptors, they have found utility for drug design and identification of novel cellular targets.[53]

While a complete SAR profile is not yet available, several interesting observations can be made from initial assays performed on the described tricyclic intermediates. Not surprisingly, the presence of α,β-enones on both the 5,5,6 and 5,5,7 core structures (*i.e.* **26**, **30**, **31**) led to the greatest cytotoxicity toward all cancer cell lines however with some interesting and unexpected selectivities observed. A notable example involves the most potent analog tested, our key synthetic intermediate α-bromo enone **30**, which uniquely displays nanomolar activity (0.39 ± 0.03 μM) against the HCT116 cell line with 8–27X greater potency over other cancer cell lines and also primary HUVEC. In addition, the cross-conjugated dienone **31**, which displays micromolar activity against HCT116 cells (28.90 ± 6.36 μM) but is inactive up to 100 μM toward other cancer cell lines tested including primary HUVEC. Furthermore, it appears that α,β-enones present in the cyclopentane ring (C ring) do not inherently result in cytotoxicity given that enone **15**, possessing a β-disubstituted enone, is inactive (up to 100 μM) toward all cell lines tested while dienone **31**, possessing a β-monosubstituted cyclohexanone, displays cytotoxicity toward HCT116 cells. However, the tertiary alcohol in enone **33** appears to reduce toxicity compared to dienone **31**. Overall, it is interesting to note that the 5,5,6-tricyclic cores are generally less cytotoxic to all cell lines tested compared to the 5,5,7-variants (*cf.* dienones **31** and **26**). However, the α,β-unsaturated lactones **35** and **36** display selective cytotoxicity toward MDA-MB-231 cells but comparable cytotoxicity to HUVEC cells. The SAR gathered to date provides preliminary validation for our initial hypothesis that the 5,5,7-tricyclic core present in some of the most cytotoxic members of this family may be important for activity. However, further support for this hypothesis and the relevance of the observed bioactivities to the natural

products themselves must await further studies including eventual proteomics studies to identify cellular targets.

In summary, application of a PDR strategy that employed the use of a Diels-Alder lactonization organocascade has enabled rapid access to both 5,5,6 and 5,5,7 tricyclic cores present in several *Sinularia* soft coral-derived natural products including rameswaralide. Preliminary cytotoxicity studies revealed some interesting cytotoxicities and selectivities that will be further verified and elaborated upon throughout our total synthesis efforts and subsequent in-depth biological studies. We anticipate that the versatile intermediate, α-bromo enone **30**, will serve as a useful springboard toward several members of the *Sinularia* class of natural products bearing the 5,5,7-tricyclic core.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(53). Jackson PA; Widen JC; Harki DA; Brummond KM Covalent Modifiers: A Chemical Perspective on the Reactivity of α,β-Unsaturated Carbonyls with Thiols via Hetero-Michael Addition Reactions. J. Med. Chem 2017, 60, 839–885. [PubMed: 27996267]

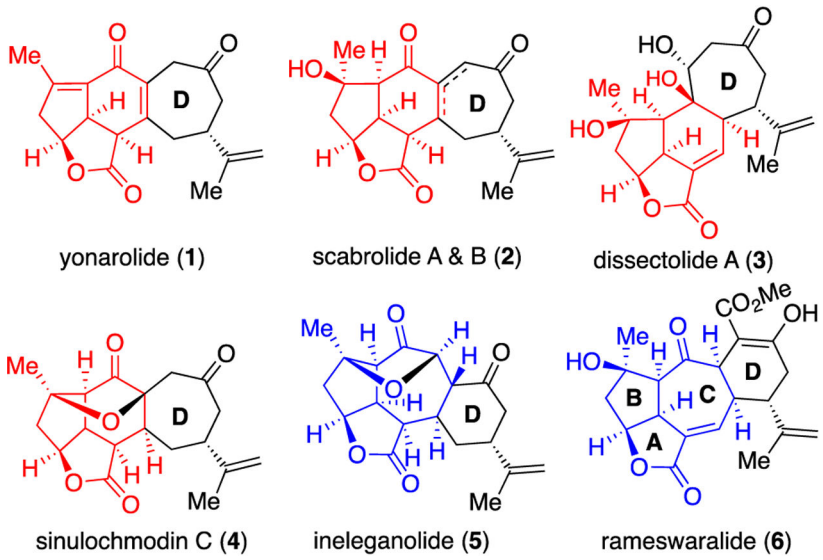
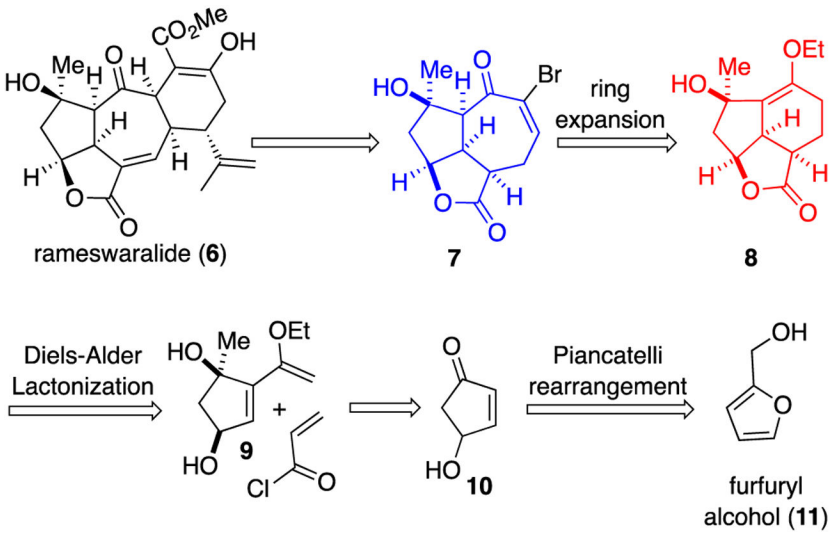
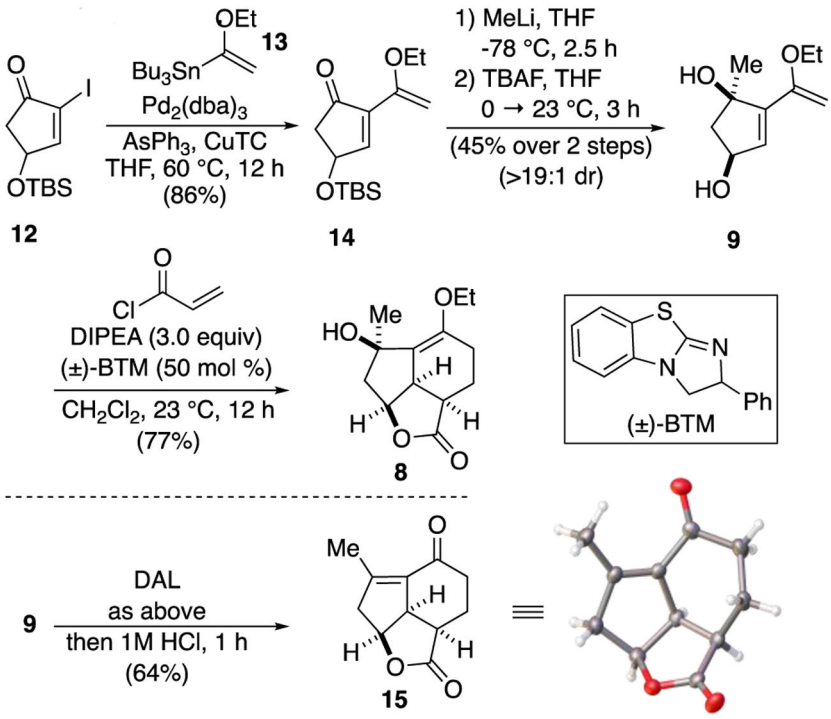


Figure 1.
Structurally related, polycyclic, *Sinularia* diterpenoid natural products.

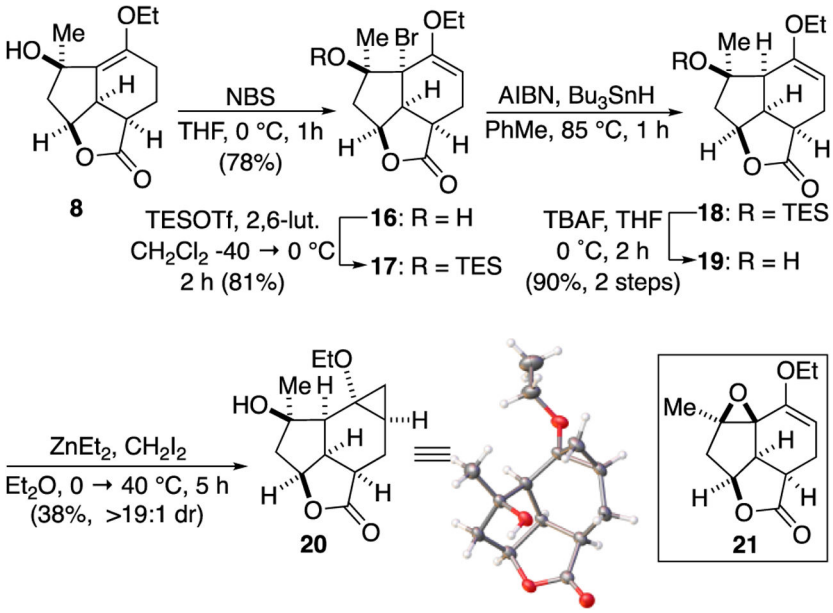


Scheme 1.
Pharmacophore Directed Retrosynthetic (PDR) approach toward rameswaralide



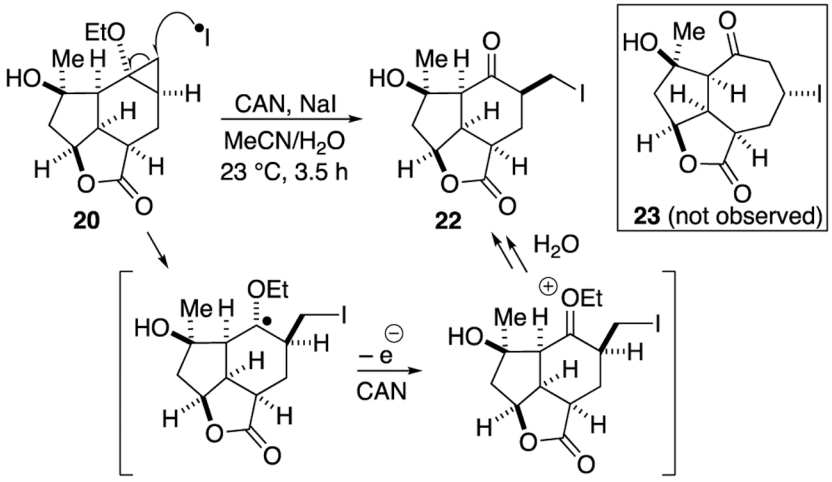
Scheme 2.

Synthesis of diene **9** and the 5,5,6 tricyclic cores **8** and **15** via the Diels-Alder Lactonization (DAL) organocascade.



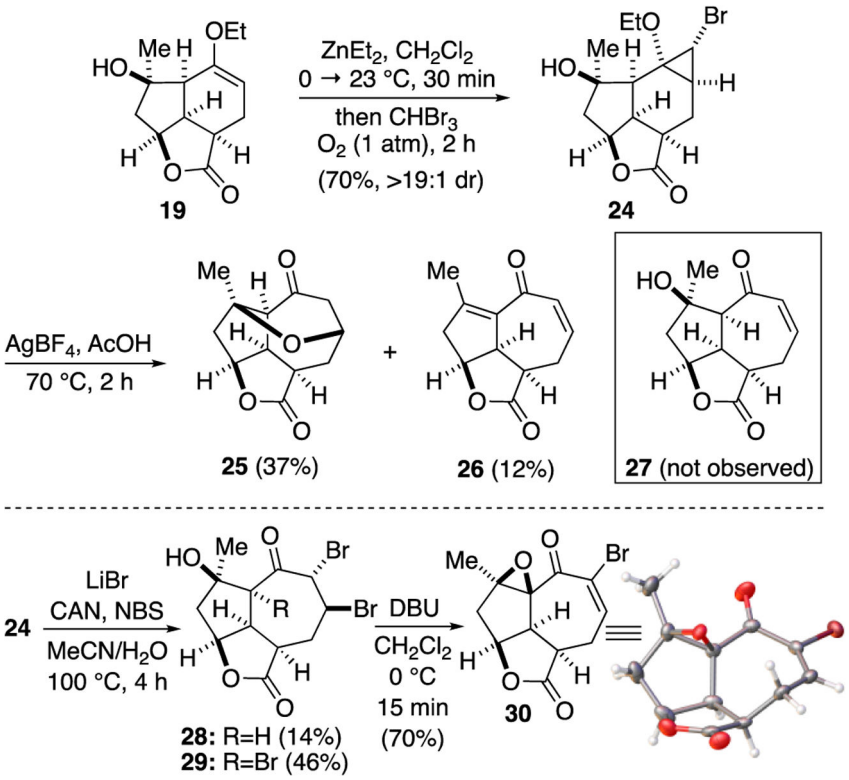
Scheme 3.

Alkene transposition of enol ether **8** and a complex-induced, proximity effect driven cyclopropanation.



Scheme 4.

Attempted ring expansion of cyclopropane **20**.

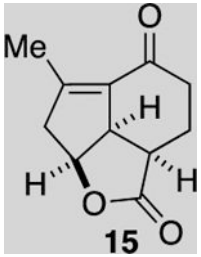
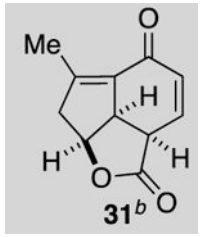
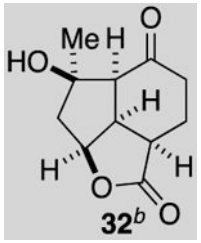
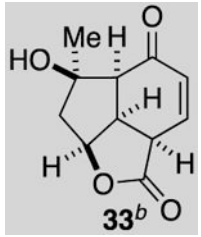
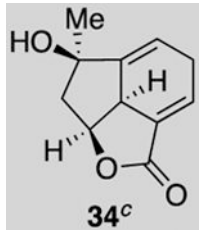
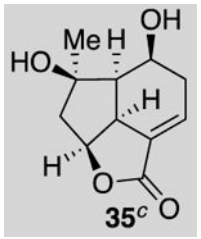
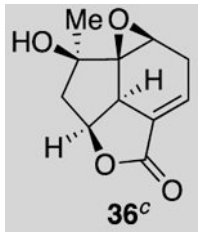
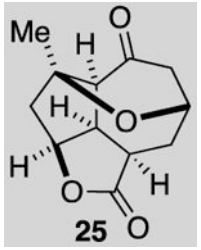
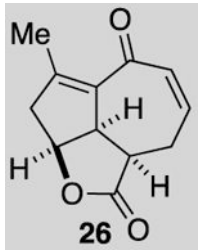
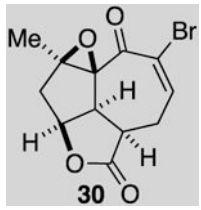


Scheme 5.

Synthesis of bromocyclopropane **24** and ring-expansions to functionalized 5,5,7 tricyclic ring systems.

Table 1.

Cell viability data (alamar blue assay, 72 h incubation) of select intermediates toward *Sinularia* natural products.[a]

	 **15**	 **31**[b]	 **32**[b]	 **33**[b]	 **34**[c]
MDA MB 231 (EC_{50}, μM)	>100	>100	>100	>100	>100
HCT 116 (EC_{50}, μM)	>100	28.90 ± 6.36	>100	>100	>100
A549 (EC_{50}, μM)	>100	>100	>100	>100	>100
HUVEC (EC_{50}, μM)	>100	>100	>100	>100	>100
	 **35**[c]	 **36**[c]	 **25**	 **26**	 **30**
MDA MB 231 (EC_{50}, μM)	77.70 ± 21.63	45.40 ± 7.97	>100	45.20 ± 10.19	10.52 ± 2.21
HCT 116 (EC_{50}, μM)	>100	>100	>100	2.97 ± 0.50	0.39 ± 0.03
A549 (EC_{50}, μM)	>100	>100	>100	5.69 ± 0.75	3.26 ± 0.35
HUVEC (EC_{50}, μM)	62.91 ± 6.32	48.66 ± 4.07	>100	6.88 ± 0.73	3.89 ± 0.33

[a] Rameswaralide was previously assayed only against the A549 cell line (IC50 of 67 ± 3.7 μM).[8]

[b] See SI for synthetic details.

[c] Analogs **34**-**36**, were kindly provided by Prof. Brian Stoltz (Caltech).[52]