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Letter

A Modular, Enantioselective Synthesis of Resolvins D3, E1, and Hybrids

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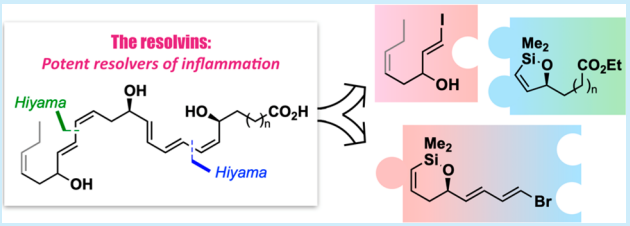
ABSTRACT: Resolvins D3 and E1 are important signaling molecules in the resolution of inflammation. Here, we report a convergent and flexible strategy to prepare these natural products using Hiyama–Denmark coupling of five- and six-membered cyclic alkenylsiloxanes to connect three resolvin fragments, and control the stereochemistry of the natural product (*Z*)-alkenes. The modular nature of this approach enables the synthesis of novel resolvin hybrids, opening up opportunities for more-extensive investigations of resolvin biology.



The resolution of inflammation is a complex process regulated by a host of different signaling molecules, including the resolvin, protectin, and maresin pro-resolving mediators (e.g., **1**–**4**, Figure 1).[1] These polyunsaturated fatty acids, which display nanomolar to picomolar bioactivity, stimulate a cascade of cellular resolution events involving the reduction of polymorphonuclear neutrophil infiltration and the initiation of macrophage clearance of apoptotic cells. Since numerous diseases are associated with chronic or excessive inflammation (such as cardiovascular diseases, asthma, diabetes, and neurodegenerative diseases),[2] there is great interest in the synthesis of these natural products in order to develop a deeper understanding of their individual roles.,[1b3] Resolvins D3 (RvD3, **1**) and E1 (RvE1, **2**) are typical examples of these polyhydroxylated lipid mediators, with the former being the most potent member of the family.[4]

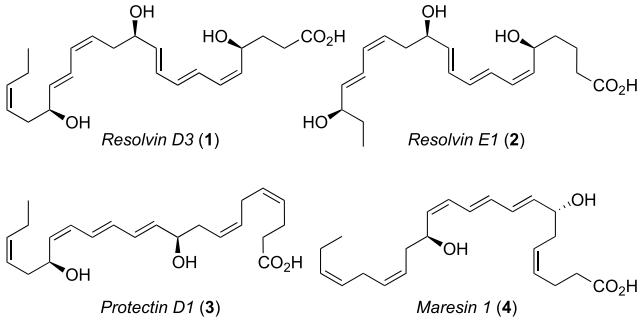


Figure 1. Pro-resolving natural products: Resolvin D3 (RvD3) (**1**), resolvin E1 (RvE1) (**2**), protectin D1 (**3**), and maresin 1 (**4**).

Subsequent to their initial discovery and isolation by Serhan et al.,[5] the structures and stereochemistry of RvD3 and RvE1 were confirmed by Petasis and Serhan via total synthesis.[6] Both contain a (*Z*,*E*)-diene and a (*Z*,*E*,*E*)-triene motif; in these previous approaches, the isomerization-prone (*Z*)-alkene of the triene unit was revealed in the final step via semireduction of the corresponding enynes with Zn/Ag/Cu. This tactic has been adopted by others for related resolvins,[7] and has enabled the in vivo testing of the natural products. A further synthesis of resolvin E1 was disclosed in which the (*Z*)-configured double bonds were introduced from a (*Z*)-alkenyl bromide via Suzuki coupling, and from a Wittig reaction.[8]

Here, we describe an alternative strategy in which late-stage Hiyama–Denmark cross-coupling[9] of cyclic alkenylsiloxanes is used to specifically control the stereochemistry of the (*Z*)-alkenes in the resolvin polyene motifs.[10] Disconnection at these alkenes (Scheme 1a) reveals five- and six-membered cyclic alkenylsiloxanes (**5**/**6** and **7**/**8**, respectively), along with two alkenyl iodide resolvin "tails" (**9** and **10**). RvD3 and RvE1 are ideal candidates for this approach, as in previous work (Scheme 1b),[10a] we established that five-membered cyclic diethyl alkenylsiloxanes, prepared by Lindlar hydrogenation of the corresponding alkynylsiloxanes, undergo Hiyama coupling more rapidly and under distinct conditions (i.e., KOTMS as activator), compared to six-membered siloxanes (which require fluoride as the coupling promoter). We subsequently found that the more reactive cyclic dimethyl alkenylsiloxanes can be accessed using benzyldimethylsilanes as latent silanols (Scheme 1c), with the cyclic siloxane revealed through fluoride- or (for five-membered rings) base-mediated debenzylation.[11]

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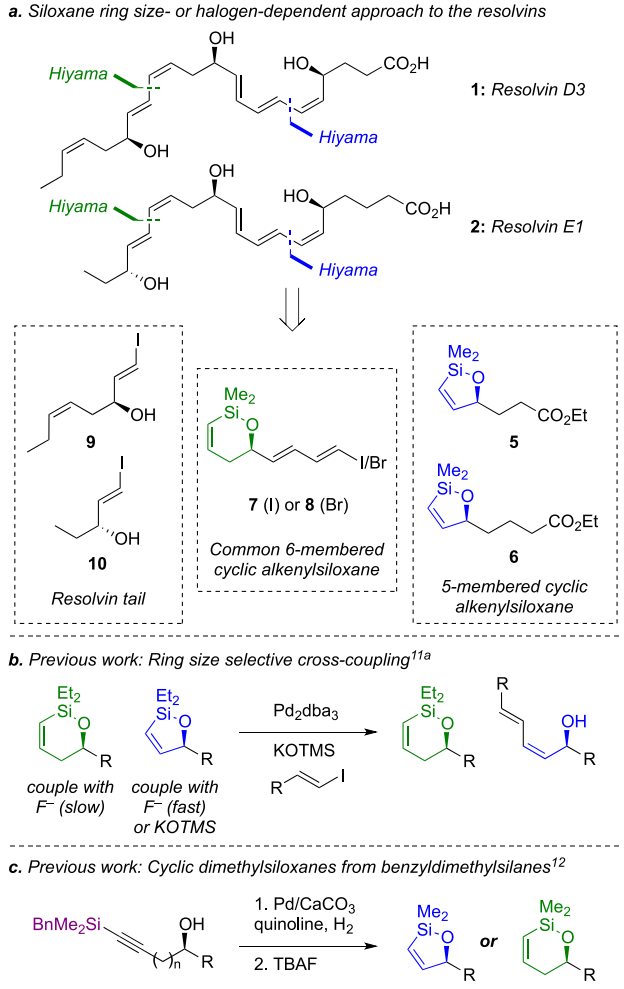
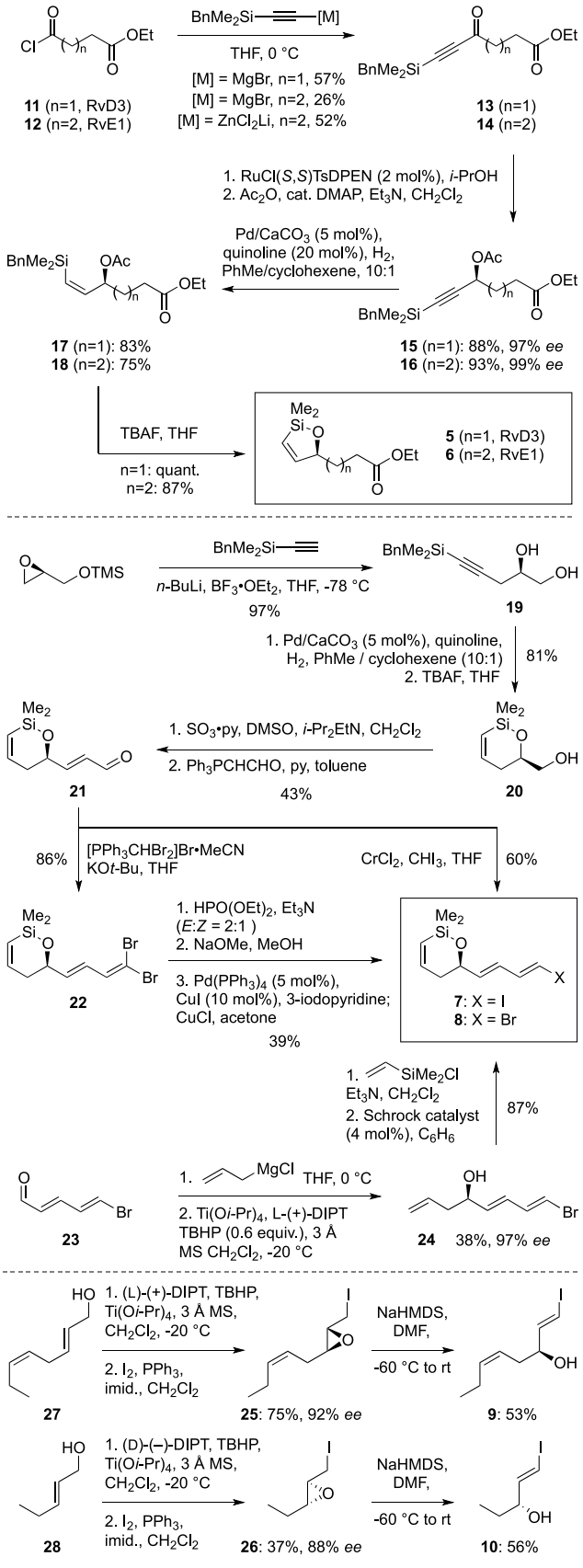
Scheme 1. (a) A Modular Strategy toward Resolvins D3 and E1; (b) Selectivity in the Cross-Coupling of Cyclic Diethylalkenylsiloxanes; (c) Synthesis of Cyclic Dimethylalkenylsiloxanes from Benzyldimethylsilanes



Based on this ring size-dependent reactivity, we planned a "head-to-tail" coupling strategy involving initial selective coupling of five-membered siloxanes **5**/**6** with dienyl halides **7** or **8**, followed by coupling of the residual six-membered siloxane with iodides **9** or **10**. Alternatively, we envisaged a "tail-to-head" approach, in which control would be achieved through differentiated rates of oxidative addition (I vs Br) in the initial coupling of iodides **9** or **10** with the central bromodiene siloxane **8**. The modular nature of the synthesis would allow access to both the natural products and to novel resolvin analogues by mixing components from the different synthesis streams. As very few unnatural resolvins have been studied, this route could open up opportunities for a wider exploration of the effects of chain length, stereochemistry, and the nature of the head/tail functionality on resolvin biology.[12]

The synthesis of the C1−C6 and C1−C7 "head" fragments **5** and **6** (Scheme 2, required for RvD3 and RvE1, respectively) began with the addition of benzyl(ethynyl)dimethylsilane to the commercially available acid chlorides **11** and **12**. The yields of these reactions proved quite dependent on chain length, with **13** formed in 64% yield, but homologue **14** in just 26% yield; fortunately, the latter could be improved to 52% by use of an alkynylzinc.[13] The resulting ketones were converted to

Scheme 2. Synthesis of Resolvin Building Blocks 5−10



the enantioenriched propargylic acetates **15** and **16** through Noyori asymmetric transfer hydrogenation (97%−99% enan-

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tiomeric excess (ee)),[14] followed by esterification.[15] Semihydrogenation to the (*Z*)-benzyldimethyl alkenylsilanes **17** and **18** proceeded with high yield and selectivity (75%−83%, *Z*:*E* > 20:1). These products were treated with TBAF, which effected debenzylation, in situ deacetylation, and cyclization to give the cyclic five-membered siloxanes **5** and **6** in excellent yields.

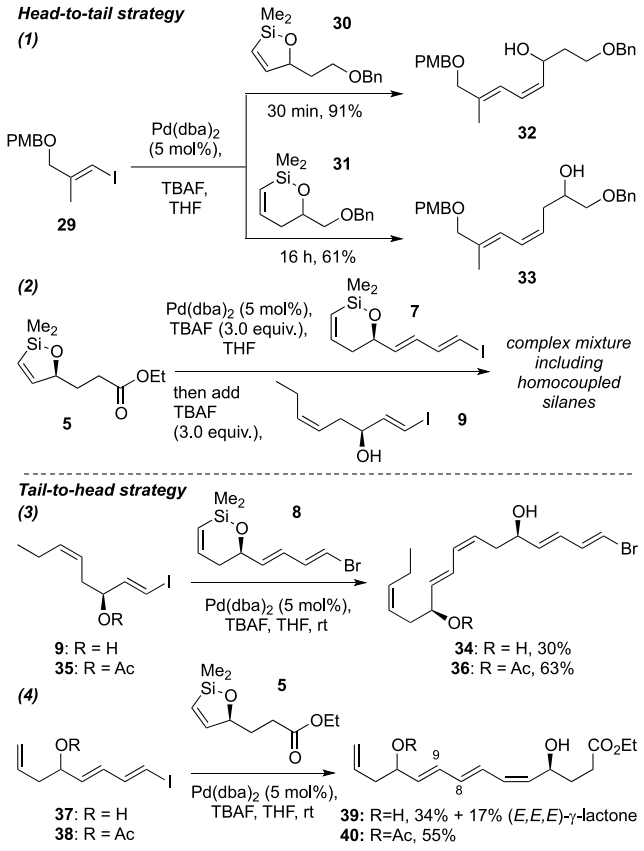
Synthesis of the "middle" fragments **7** and **8** (Scheme 2, common to both RvD3 and RvE1) initially utilized a chiral pool strategy. The addition of lithium benzyldimethylsilylacetylide to TMS-protected (*S*)-glycidol afforded diol **19** in 98% yield, which was carried through the Lindlar hydrogenation/cyclization sequence[10a] to give the six-membered cyclic alkenylsiloxane **20** (81%). Parikh−Doering oxidation afforded an unstable aldehyde, which was used directly in a Wittig olefination to give enal **21**, which displayed greater stability and could be purified by chromatography. Here, a serendipitous discovery was made: residual pyridine from the Parikh−Doering oxidation improved the yield of the olefination from 32% to 52% (43% overall). **21** was converted to dienyl iodide **7** via Takai iodoolefination (60%, *E*:*Z* = 5:1). Synthesis of the equivalent bromide **8** was achieved in two steps, consisting of Ramirez olefination (**22**, 86%), followed by Hirao monodebromination using dimethyl phosphite.[16] This latter reaction is known to exhibit variable selectivity for conjugated systems,[17] and indeed the product bromodiene was obtained as a 2:1 (*E*,*E*):(*E*,*Z*) mixture. Variation of solvent or temperature did not affect this ratio, and while the bulkier diisopropyl phosphite offered a modest improvement (*E*:*Z* = 2.5:1), the conversion decreased significantly. Fortunately, the undesired (*E*,*Z*)-dienyl bromide could be removed by elimination of HBr (refluxing NaOMe),[18] followed by Sonogashira coupling of the resulting enyne with 2-iodopyridine. Despite the obstacles encountered, this sequence does illustrate the capacity of the six-membered cyclic dimethylsiloxane to survive a range of reaction conditions.

To overcome the limitations of this route, a shorter synthesis was developed, exploiting the Denmark ring-closing metathesis approach to cyclic dimethylsiloxanes.[10b−f] (*E*,*E*)-5-bromopentadienal **23** was readily accessed from SO_3·py by alkaline hydrolysis and bromination.[19] The addition of allylmagnesium bromide, followed by Sharpless resolution (98% ee),[20] afforded enantio-enriched alcohol **24**. Formation of an intermediate vinyldimethylsilyl ether set the stage for ring-closing metathesis mediated by the Schrock catalyst,[10b−f] which proceeded in excellent yield (87% over two steps).

The resolvin "tail" fragments, destined for coupling with the central six-membered cyclic siloxane, were prepared via base mediated ring-opening of α-iodoepoxides **25** and **26** as developed by Spur[21] and Nakata (Scheme 2),[22] which selectively afforded the desired (*E*)-iodoalkenes **9** and **10** respectively. The configuration of these epoxides was set by Sharpless epoxidation of the corresponding allylic alcohols **27** and **28**.[23]

With all key fragments in hand, attention turned to assembly of the resolvin framework. We first studied the "head-to-tail" strategy which would rely on an enhanced rate of transmetalation for the five-membered siloxane over the six-membered siloxane in the initial cross-coupling, as had been observed in our earlier work with equivalent diethylsiloxanes (see Scheme 1, eq 1).[10a] Indeed, we were pleased to find that model fluoride-promoted couplings of iodoalkene **29** with substrates **30** and **31** (Scheme 3, eq 1) revealed significantly more rapid and higher yielding coupling of the five-membered

Scheme 3. Evaluation of Cross-Coupling Strategies



ring siloxane **30** (91%). However, attempts to translate this reactivity difference to selective coupling of **5** in the presence of the six-membered siloxane in **7** met with failure (Scheme 3, eq 2), whether using fluoride or KOTMS as the promoter, and with simultaneous or sequential addition of the reactants; side reactions including desilylation, homocoupling, and ester hydrolysis were observed in a variety of model studies. It appeared that while less reactive toward transmetalation, the six-membered ring was nonetheless susceptible to rapid ring opening under the reaction conditions, compromising the ability of the coupling promoter to mediate selective coupling of the five-membered ring.

Examination of the "tail-to-head" strategy proved more fruitful. This approach relies on selectivity in the oxidative addition of the resolvin vinyl iodide "tails" (**9**/**10**) over the dienyl bromide **8** in the central fragment. We first studied the coupling of RvD3 iodide **9** with **8** (Scheme 3, eq 3); this coupling proved sluggish and low yielding (30%), and resulted in the formation of a byproduct tentatively assigned as homocoupling of iodide **9**.[24] However, reaction of the acetate derivative of the allylic alcohol (**35**) proceeded at a significantly higher rate, and delivered product **36** in higher yield (63%) and without iodide dimerization. The benefit of acetylation was reinforced in an equivalent model coupling of dienyl iodide **37** with RvE1 "head" siloxane **5** (Scheme 3, eq 4). Reaction of the free alcohol **37** (to give **39**) led to competing formation of a byproduct assigned as an isomerized γ-lactone;[24] use of the acetate **38** derivative suppressed this side reaction and proceeded in higher yield (**38** → **40**, 55%). We suggest that the free allylic alcohols in **9** or **37** may

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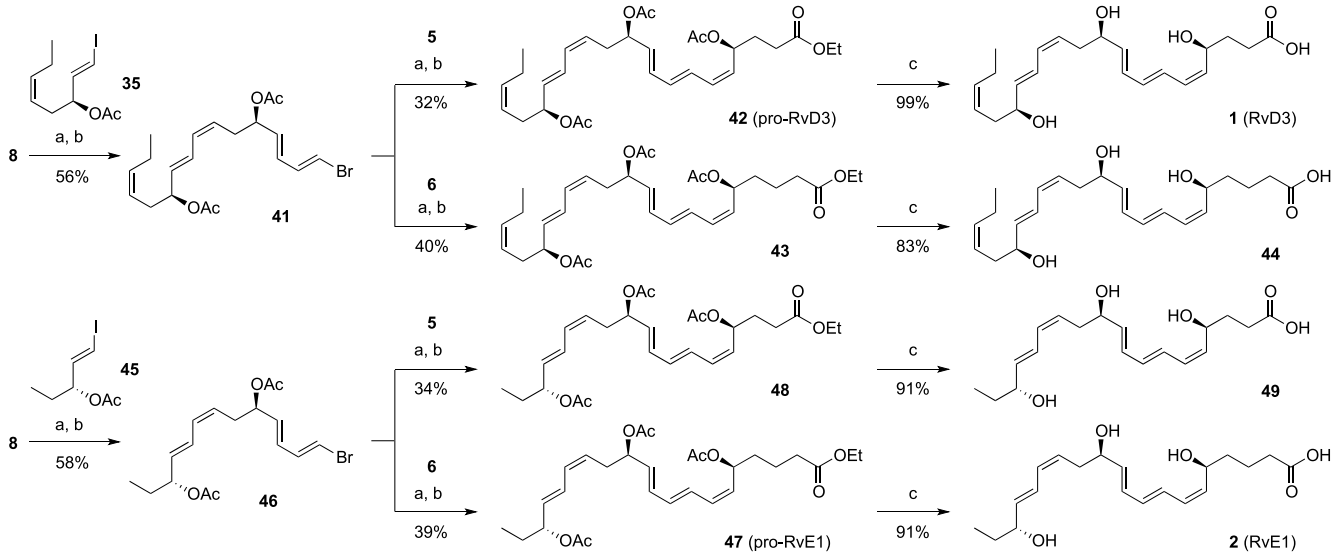
Scheme 4. Synthesis of Resolvins D3, E1, and Hybrids[a]



[a]Reagents and conditions: (a) $Pd(dba)_2$ (5 mol %), TBAF (3 equiv), THF, 16 h; (b) Ac_2O, py, CH_2Cl_2; (c) LiOH, THF/H_2O (1:1).

interfere with the efficiency of coupling by moderating the reactivity of the fluoride activator.

Irrespective of the basis of this beneficial effect, the Hiyama–Denmark coupling had now been validated for the formation of both C–C bonds, and our attention turned to completion not only of the natural resolvins **1** and **2**, but also resolvin hybrids by mixing different natural product building blocks. As such, coupling of **8** and **35** (Scheme 4), followed by acetylation, afforded dienyl bromide **41** (53%). This was coupled with siloxanes **5** and **6** to give product alcohols that were immediately acetylated (**42** and **43**, respectively; 32%–40%)—in part to aid purification from a γ-lactone formed from cyclization of the γ-hydroxyester headgroup,[25] but also to impart stability toward long-term storage of these "pro-resolvins", compared to the natural products. Resolvin D3 (**1**)[26] and the RvD3/E1 hybrid **44** were revealed in near quantitative yield upon treatment with lithium hydroxide. Similar coupling of **8** with iodoalkene acetate **45** gave the tetraene **46** after acetylation (58%). Coupling of **46** with the two headgroup siloxanes and acetylation now afforded triacetate pro-RvE1 **47** and hybrid **48**. Again, these could be saponified in high yield on treatment with aqueous lithium hydroxide to afford resolvin E1 (**2**)[27] and the RvE1/D3 hybrid **49**.

In conclusion, resolvins D3 and E1 were prepared in 12 steps in the longest linear sequence (~20 steps total), employing Hiyama cross-coupling of cyclic alkenylsiloxanes in key fragment union transformations. The modular and convergent nature of the route also enabled the synthesis of new resolvin analogues. These enantioselective syntheses open up opportunities for a wider study of the role of these (*Z*)-alkenyl polyene natural products in inflammatory response pathways; studies to this end are ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00089.

Experimental details and copies of ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(24) See the Supporting Information for details of structural assignment.
(25) This γ-lactone was isolated as a mixture of alkene stereoisomers, which may be due to a reversible intramolecular Tsuji−Trost reaction. This prevented productive hydrolysis/recycling of this compound. The formation of a γ-lactone accompanied the reaction under all conditions screened.
(26) Spectroscopic data for synthetic resolvin D3 was identical to that reported in ref 6a.
(27) Spectroscopic data for synthetic resolvin E1 was identical to that reported in ref 8d.

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