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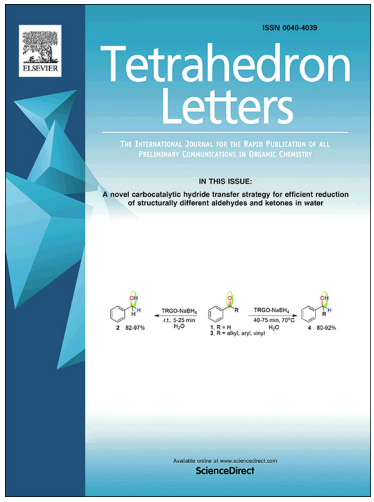

Total synthesis of natural (-)- and unnatural (+)-Melearoride A

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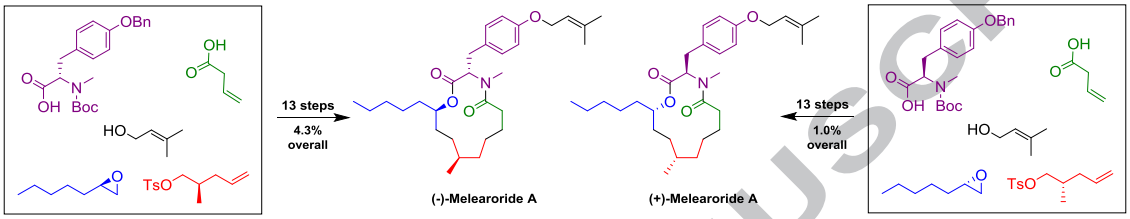

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Total synthesis of natural (-)- and unnatural (+)-Melearoride A

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ABSTRACT

This communication details the first total synthesis of the 13-membered macrolide, (-)-Melearoride A, as well as unnatural (+)-Melearoride A. The synthesis features a concise 13 step synthesis (11 steps longest linear sequence) that offers flexible stereo-control and multiple opportunities for unnatural analog synthesis to delve into antifungal SAR. The route features a cuprate addition, an Evans asymmetric alkylation, and a ring-closing metathesis (RCM) to close the 13-membered macrocyclic core.

Natural products can serve as novel chemical entities to initiate highly productive tool compound and lead optimization campaigns. Recently, total synthesis campaigns in our lab have led to the discovery of novel biological activity for a variety of natural products, and in instances, unnatural analogs displayed superior bioactivity.[1] (-)-Melearoride A (**1a**) (Figure 1) was first isolated in 2016 from a fermentation broth of *Penicillum meleagrinum* var. *viridiflavum* and shown to have synergistic activity with fluconazole against azole-resistant *Candida albicans*.[2] This 13-membered macrocyclic natural product belongs to a family of related natural products **3**-**7** (exemplified by PF1163A (**3**) and PF1163B (**4**)), whose syntheses have been previously reported.[3-7] These first-generation synthetic approaches rely heavily on the use of diastereoselective additions into functionalized aldehydes[3-4] or lactals,[5] or Sharpless kinetic resolution techniques[6] to set the stereochemistry at the C9 position and, with the exception of Bouazza,[4] involve lengthy synthetic routes. Given both that the synthesis of (-)-Melearoride A (**1a**) has yet to be accomplished and our desire to merge total synthesis with opportunities for medicinal chemistry optimization, our goal was to develop a concise, modular synthetic route that would be amenable for analog development. Ideally, we sought a route that would enable control of the substituents and stereochemistry of the alkyl groups on C6 and C9, the size of the macrocycle, and with late stage diversity opportunities for the phenolic alkyl group. The key features of this synthesis include Evans asymmetric alkylation, chiral epoxide opening using functionalized higher order cyanocuprates, ring-closing metathesis to form the 13-membered macrocycle, and late stage *O*-alkylation utilizing Mitsunobu conditions. In order to show the utility of this method for analog development, we synthesized not only natural (-)-Melearoride A (**1a**), but also unnatural (+)-Melearoride A (**1b**) in 13 steps and with 11 step Longest Linear Sequence (LLS) in good overall yields.

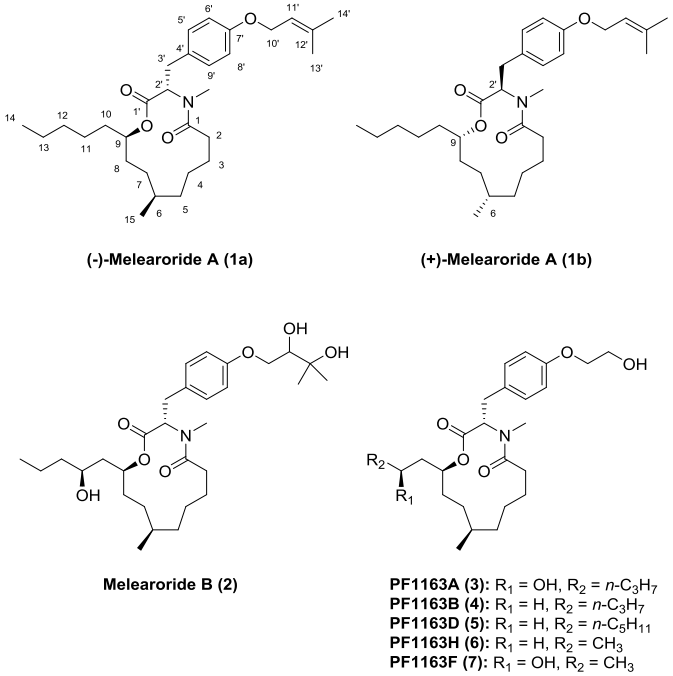


Figure 1. Structures of natural (-)-Melearoride A (**1a**), unnatural (+)-Melearoride A (**1b**), Melearoride B (**2**) and early members of this family of macrolide natural products PF1163A (**3**), PF1163B (**4**), PF1163D (**5**), PF1163H (**6**) and PF1163F (**7**).[2]

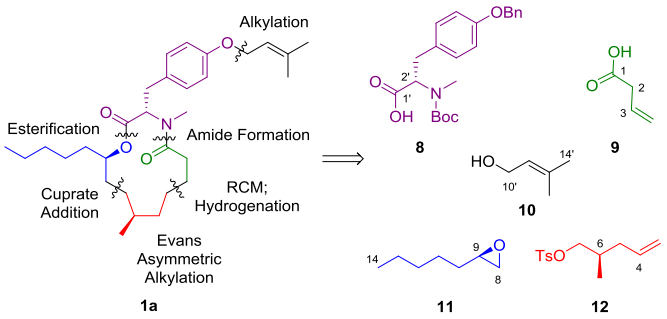
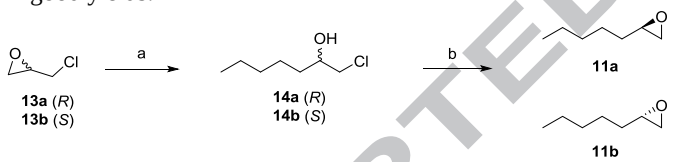


Figure 2. Retrosynthesis of (-)-**1a**. Five key bond disconnections lead to readily available intermediates **8**-**12**, with chirality derived from chiral pool molecules.

Figure 2 highlights our retrosynthetic analysis for **1a**, with five key bond disconnects leading to five simple intermediates **8**-**12**, all of which are commercial (eg., **8**, **9**, **10**) and/or readily derived from chiral pool molecules (eg., **11** and **12**). Based on this strategy, the ability to readily access unnatural (+)-**1b** by virtue of employing the opposite stereochemistry of intermediates **8**, **11**, and **12** was clear, and thus, two parallel synthesis campaigns were initiated.

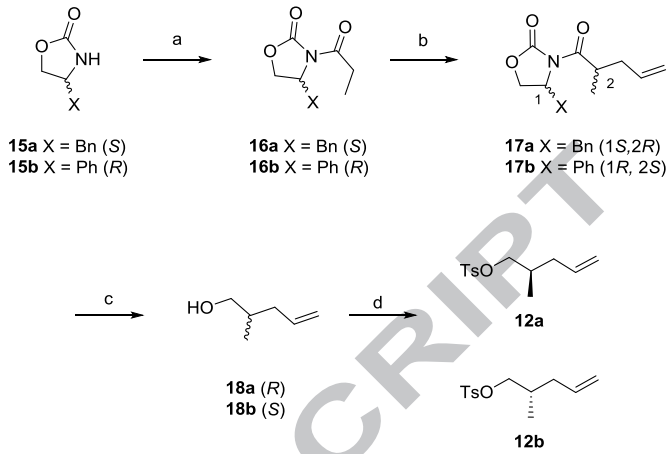
The key C8-C14 epoxide intermediate **11** was readily prepared in two steps (Scheme 1). Following the precedent of Moriarty and Kulkarni,[8-9] commercial chiral pool (*R*)- and (*S*)-epichlorohydrin **13a** and **13b**, respectively, were treated with *n*-butyl magnesium chloride and catalytic copper iodide to afford the α-chloro alcohols (*R*)-**14a** and (*S*)-**14b** in yields ranging from 66-77%. Treatment with NaOH in Et_2O provides the requisite chiral epoxides **11a** (to access (-)-**1a**) and **11b** (to access (+)-**1b**) in good yields.



Scheme 1. Synthesis of chiral expoxides **11a-b**. Reagents and conditions: (a) *n*-BuMgCl, cat. CuI, THF, -78 °C to 0 °C, 3h, 66-77%; (b) NaOH, Et_2O, rt, 3h, 70-86%.

Chiral tosylates **12a** and **12b** were synthesized per the methods of Jouillié and Molander (Scheme 2).[10-11] Upon acylation of commercial oxazolidinones (*S*)-**15a** and (*R*)-**15b** under standard conditions,[12-13] an Evans asymmetric allylation was utilized to synthesize oxazolidinones **17a** and **17b** in good yields with ~20:1 d.r. Reduction with lithium borohydride provided alcohols (*R*)-**18a** and (*S*)-**18b** in yields ranging from 54-72%. Subsequent treatment with *p*-toluenesulfonyl chloride and pyridine afforded (*R*)-**12a** (en route to **1a**) and (*S*)-**12b** (en route to **1b**) in good yields (69-80%).

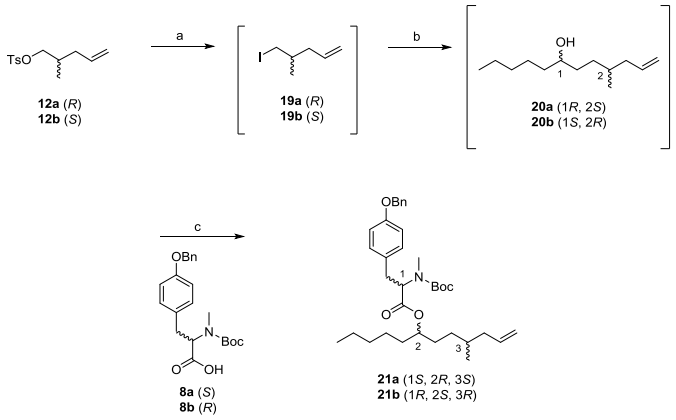
With requisite fragments **11a-b** and **12a-b** in hand, a method was needed to unite both fragments and form the crucial C7-C8 bond. To achieve this synthetic transformation, we envisioned that organocuprate reagents derived from **12a-b** would be satisfactory in opening epoxides **11a-b** to form the required C7-C8 bond (Scheme 3). S_N2 displacement of tosylates **12a-b** with lithium iodide in DMA afforded alkyl iodides **19a-b** which underwent lithium-halogen exchange with *t*-BuLi smoothly.



Scheme 2. Synthesis of chiral tosylates **12a-b**. Reagents and conditions: (a) *n*-BuLi, propionic anhydride, THF, -78 °C to rt, 1h, 89-94%; (b) NaHMDS, allyl iodide, THF, -78 °C, 6h, 58-61%; (c) $LiBH_4$, EtOH, 0 °C to rt, 16h, 54-72%; (d) TsCl, pyr., $CHCl_3$, 0 °C to rt, 16h, 69-80%.

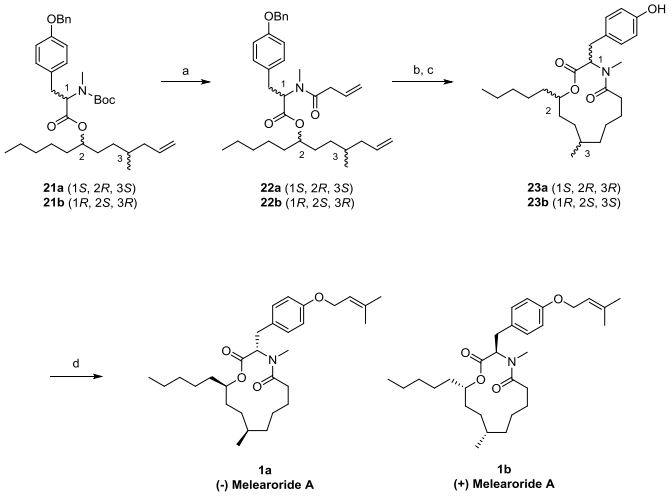
Following the method of Lipshutz,[14] transmetalation of the resulting alkyl lithium reagents with lithium 2-thienyl cyanocuprate afforded functionalized higher order cuprates, which were competent in opening epoxides **11a-b**. With the desired C7-C8 bond formed, esterification of alcohols **20a-b** with commercially available acids (*S*)-**8a** and (*R*)-**8b** was accomplished using Yamaguchi conditions. Overall, this three-step transformation afforded esters **21a** and **21b** in good yields (31-47% over three steps) and only required one formal chromatographic operation.

With all the stereocenters set, the final steps toward the synthesis of **1a** and **1b** could be accomplished. Boc-deprotection of **21a-b** using TFA in CH_2Cl_2 followed by PyBroP-mediated amide coupling with vinylacetic acid **9** led to the formation of amides **22a** and **22b** in 82-89% yield (Scheme 4). In order to avoid undesired chelation and catalyst sequestration due to the presence of the β-γ unsaturated amide in **22a-b**,[15] a Lewis acid assisted ring closing-metathesis (RCM) reaction was determined to be most suitable for forming the desired 13-membered macrocyclic core.[16] Indeed, the use of Grubbs II and Ti(O*i*Pr)$_4$ in the RCM followed by subsequent hydrogenation gave desired phenols **23a-b** in 60-65% yield over two steps.



Scheme 3. Synthesis of esters **21a-b**. Reagents and conditions: (a) LiI, DMA, 80 °C, 2h; (b) *t*-BuLi, lithium 2-thienylcyanocuprate, **11a** or **11b**,

Et_2O, THF, -78 °C to rt, 5h; (c) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, **8a** or **8b**, toluene, rt, 16h, (31-47% over three steps).



Scheme 4. Synthesis of natural (-)-Melearoride A **1a** and unnatural (+)-Melearoride A **1b**. Reagents and conditions: (a) i. TFA, CH_2Cl_2, 0 °C to rt, 1h, ii. PyBroP, vinylacetic acid (**9**), *N*,*N*-diisopropylethylamine, CH_2Cl_2, 0 °C to rt, 3h, 82-89%; (b) Grubbs Catalyst™ 2nd Generation, $Ti(OiPr)_4$, toluene, 90 °C, 7h; (c) H_2, Pd/C, EtOAc, rt, 16h, (60-65% over two steps); (d) DIAD, PPh_3, 3-methyl-2-buten-1-ol (**10**), THF, 0 °C to rt, 2h, 69-72%.

Lastly, *O*-alkylation of phenol **23a** and **23b** using alcohol **10** under Mitsunobu conditions yielded natural (-)-Melearoride A (**1a**) and unnatural (+)-Melearoride A (**1b**) in 69-72% (4.3% and 1.0% overall yields for **1a** and **1b**, respectively).

In conclusion, we have presented the first total synthesis of both (-)-Melearoride A (**1a**) and (+)-Melearoride A (**1b**) in good overall yields. In addition, our modular synthetic approach enables facile analog development, which will prove useful for the future exploration of antifungal SAR around related macrocyclic congeners.

Acknowledgments

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Highlights

- First total synthesis of (-)-melearoride A
- Total synthesis of (+)-melearoride A
- A concise 13 step synthesis from chiral pool starting materials
- High yielding RCM to close the 13-membered macrocycle