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Scalable, Divergent Synthesis of Meroterpenoids via "Borono-sclareolide"

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Supporting Information

ABSTRACT: A scalable, divergent synthesis of bioactive meroterpenoids has been developed. A key component of this work is the invention of "borono-sclareolide", a terpenyl radical precursor that enables gram-scale preparation of (+)-chromazonarol. Subsequent synthetic operations on this key intermediate permit rapid access to a variety of related meroterpenoids, many of which possess important biological activity.

Meroterpenoids are broadly defined as compounds of mixed polyketide-terpenoid origin.[1] Quinone/hydroquinone sesquiterpenoids[2] are chiefly found in marine organisms, with both antipodes occurring naturally.[3] These meroterpenoids have attracted attention due to their structural diversity and biological activity ranging from anti-fungal to anti-cancer and anti-HIV.[4] This class of natural products generally consists of a drimane or rearranged drimane sesquiterpenoid attached to a quinone or hydroquinone moiety, exemplified by the natural product (+)-yahazunol (**1**), discovered by Zubia and co-workers from a sponge of the genus *Dysidea*.[5] Hundreds of meroterpenoids with related structures are known, and synthetic pathways to these molecules have been investigated extensively. This Communication describes the design and execution of the first scalable, divergent approach to this natural product family and analogues thereof.

Previous approaches to this class of natural products have relied on the addition of a suitably protected arene nucleophile to a terpene electrophile.[6] Major drawbacks to this approach are the use of protecting groups and subsequent redox manipulations. Most of these syntheses consist of more than 12 steps and, in some cases, as many as 18 steps. Trammell and Yamamoto, however, have utilized elegant biomimetic cyclizations of polyprenoids to prepare a small set of meroterpenoids efficiently.[7] Strategies to divergently access this entire natural product family from a single building block are still absent.[8]

With the above precedent in mind, the direct coupling of a terpenoid donor with a non-terpenoid acceptor was envisioned, as outlined in Figure 1A. It was reasoned that such a direct coupling would minimize reliance on concession steps.[9] Whereas the coupling of simple aryl- and alkylboronic acids or trifluoroborates with electron-deficient heterocycle[10] and quinone[11] radicophiles is known, the direct coupling of a drimane skeleton and quinone has been less fruitful. Theodorakis has employed a conceptually similar radical-based strategy toward rearranged drimane sesquiterpenoids via

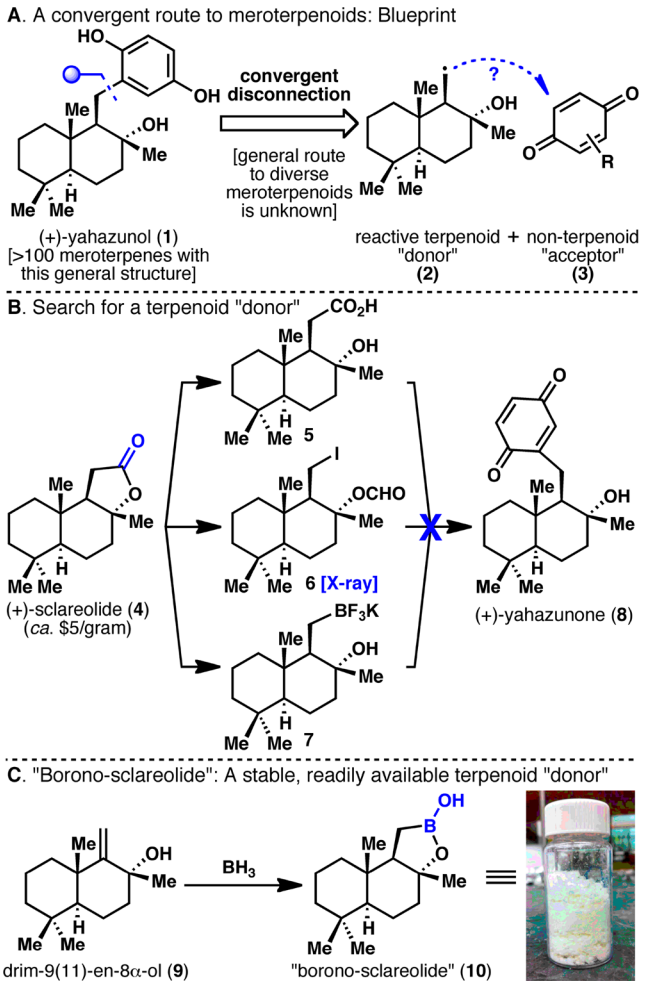

Figure 1. A global approach to meroterpenoids utilizing borono-sclareolide (**10**).

light-induced decarboxylation, but this approach is less direct due to ensuing functional group manipulations.[12]

In the initial plan (Figure 1A), the non-terpenoid unit found in these natural products would be derived from 1,4-benzoquinone, and the terpenoid unit would arise from a radical precursor such as an alkylcarboxylic acid or alkyl halide. Thus, a Minisci reaction with **5** as the terpenoid "donor" was investigated (Figure 1B). Compound **5** is readily available via

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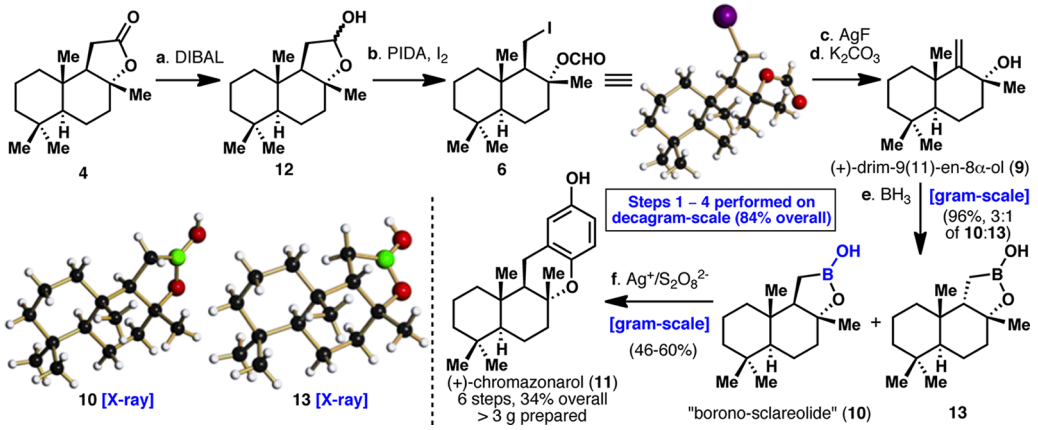
Scheme 1. Brief, Scalable Synthesis of "Borono-sclareolide" (10) and (+)-Chromazonarol (11)[a]



[a]Reagents and conditions: (a) DIBAL, CH_2Cl_2, −78 °C, 1 h; (b) PIDA, I_2, PhH, *hν*, 70 °C, 1 h; (c) AgF, py, rt, 12 h; (d) K_2CO_3, MeOH, 0 °C to rt, 2 h; 84% yield from **4**; (e) THF, BH_3·THF, 0 °C to rt, 12 h; 96% combined yield (3:1 dr of **10**:**13**); (f) **10**, 1,4-benzoquinone (2 equiv), $AgNO_3$ (0.2 equiv), $K_2S_2O_8$ (5.0 equiv), $PhCF_3/H_2O$, 60 °C, 2.5 h; 60% yield, 46% yield on 1.34 g scale.

hydrolysis[13] of (+)-sclareolide (**4**), a common feedstock in the perfume industry that can be purchased in kilogram quantities. Carboxylic acid **5** has been previously reported in a Minisci reaction with naphthoquinone, resulting in a 20% yield of the desired adduct.[14] Exposure of **5** to $Ag^+/S_2O_8^{2-}$ and 1,4-benzoquinone in various solvents failed to yield any of the desired terpene-quinone product **8**. Radical initiation or Pd-based methods on iodide **6** were also investigated in a union with 1,4-benzoquinone, and this also failed to yield yahazunone (**8**). Trifluoroborate **7** (*vide infra*) also failed to react in the expected manner with $Mn(OAc)_3$[10b] or $Ag^+/S_2O_8^{2-}$.[11] In striking contrast, the newly invented chemical entity "borono-sclareolide" (**10**, Figure 1C) merged smoothly with 1,4-benzoquinone, providing (+)-chromazonarol (**11**).[7b,15]

The preparation of borono-sclareolide (**10**) requires the excision of carbon monoxide from **4** and incorporation of B-OH in its place. Thus, DIBAL-mediated reduction of **4** resulted in sclaral[16] (**12**; Scheme 1), which upon exposure to the hypoiodite-mediated C−C bond cleavage conditions of Suárez ($PIDA/I_2/h\nu$) delivered iodoformate **6** (characterized by X-ray crystallographic analysis). A two-step dehydroiodination/hydrolysis procedure (AgF in pyridine followed by K_2CO_3 in methanol) afforded the sponge metabolite (+)-drim-9(11)-en-8*α*-ol (**9**)[17] in 84% overall yield from **4**, without the use of chromatographic separation and on decagram scale for each transformation. This route constitutes the highest yielding and most efficient synthesis of **9** to date. Hydroboration of **9** resulted in a 3:1 mixture of diastereomers[6c] **10** and **13** in 96% combined yield, which were readily separated by column chromatography and characterized by X-ray crystallographic analysis.

Borono-sclareolide (**10**) was converted into trifluoroborate **7** (Figure 1B) since some alkylboronic acids are prone to undergo oxidation.[18] When **7** was treated with a slight excess of 1,4-benzoquinone in the presence of $AgNO_3$ and $K_2S_2O_8$ in $PhCF_3/H_2O$ at 60 °C, the expected product **8** was not observed. Instead, (+)-chromazonarol (**11**) was obtained in ∼10−20% yield. This transformation is surprising, as this constitutes an overall redox-neutral process with respect to both benzoquinone and **10** under strongly oxidizing conditions. Remarkably, the use of borono-sclareolide (**10**) instead of **7**, 2 equiv of 1,4-benzoquinone, 5 equiv of oxidant (less oxidant led to lower yield), and degassing of the reaction mixture led to an improved yield of 60%.

Utilizing this route, more than 3 g of **11** has been prepared to date. The originally expected (+)-yahazunone (**8**) is not observed in the crude reaction mixture and does not appear to be an intermediate in the formation of **11**. This result is very unusual and suggests that a different mechanism may be operable than originally envisioned. The presence of the cyclic boronic acid has a drastic effect on the outcome of this reaction, and the mechanism of this transformation is currently under investigation.

With a highly efficient, scalable route to (+)-chromazonarol (**11**), this key intermediate was enlisted in the preparation of other related drimane meroterpenoid natural products (Scheme 2). Zonarol (**14**),[19] isozonarol (**15**),[20] zonarone (**17**),[21] and isozonarone (**18**)[22] were isolated by Fenical and co-workers in 1973 from the brown seaweed *Dictyopteris zonarioides*. Treatment of **11** with BCl_3[23] in the presence of 2,6-di-*tert*-butyl-4-methylpyridine at −78 °C afforded a 2.5:1.0:0.3 mixture of (−)-isozonarol (**15**), (−)-zonarol (**14**), and tetrasubstituted olefin **16**[24] in a combined 80% yield. After extensive screening, treatment of **11** with silica gel-supported sodium periodate yielded yahazunone (**8**)[25,26] in 84% yield. Other oxidants predominantly yielded *o*-quinone products (**20** and **21**, see structures in Scheme 3) and only trace amounts of the oxidized ring-opened product **8**.

(+)-Yahazunol (**1**) can be obtained readily from crude **8** via Pd-catalyzed hydrogenation in 76% yield over two steps from **11**, which can then be purified via trituration with CH_2Cl_2. This synthesis offers a drastic improvement over the previously reported synthesis[27] of **1** (18 steps from *β*-ionone, 3% overall vs 8 steps from (+)-sclareolide (**4**), 26% overall). Exposure of crude **8** to $SOCl_2$ in the presence of Et_3N at −78 °C yielded a 9:1 mixture of (−)-zonarone (**17**) and (−)-isozonarone (**18**) in a combined yield of 71% over two steps.

The anti-tumor and highly potent angiogenesis inhibitor, (+)-8-*epi*-puupehedione (**19**), a synthetic analogue of puupehedione, was also targeted (Scheme 3). The sequence of Alvarez-Manzaneda to synthesize **19** was first explored.[6b,15b,28] It was reported that treatment of **11** with Fremy's salt ($K_2NO(SO_3)_2$) affords a single *o*-quinone product **20** in 85% yield. When **11** was subjected to the published conditions, a 3:2

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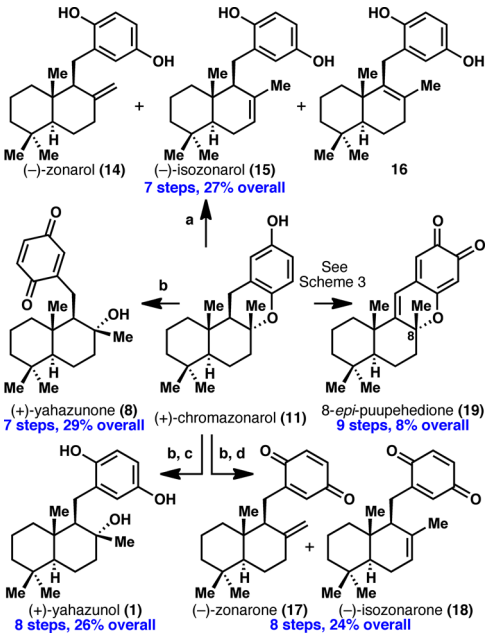
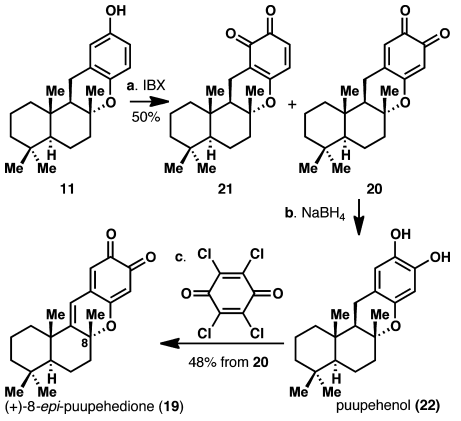
Scheme 2. Divergent Synthesis of Meroterpenoids via 11[a]



[a]Reagents and conditions: (a) 2,6-di-*tert*-butyl-4-methylpyridine, BCl_3, CH_2Cl_2, −78 °C, 1 h; 80% combined yield (2.5:1.0:0.3 mixture of **15**:**14**:**16**); (b) $NaIO_4/SiO_2$, CH_2Cl_2, rt, 30 min; 84% yield; (c) Pd/C, H_2, CH_2Cl_2, rt, 45 min; 76% yield from **11**; (d) Et_3N, $SOCl_2$, CH_2Cl_2, −78 °C, 1 h; 71% combined yield (9:1 mixture of **17**:**18**) from **11**.

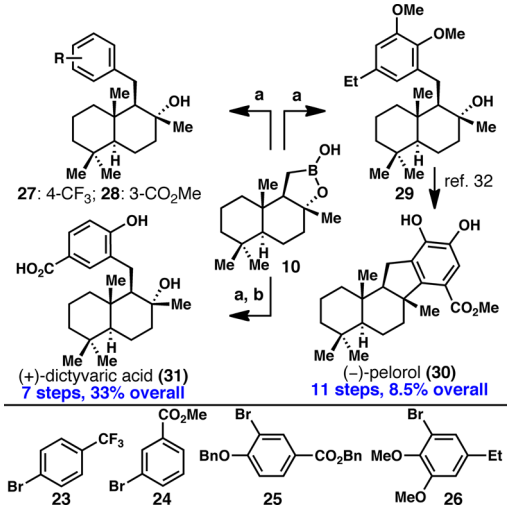
Scheme 3. 8-*epi*-Puupehedione (19) from 11[a]



[a]Reagents and conditions: (a) DMF, IBX, rt, 30 min (1:1 mixture of **20**:**21**); (b) **20**, EtOH, $NaBH_4$, rt, 15 min; (c) **22**, chloranil, *t*-BuOH, 100 °C, 16 h; 24% from **11**.

ratio of *o*-quinone products **20** and **21** was observed, slightly favoring **20** along with unreacted **11**. Even with a large excess of Fremy's salt, the oxidation did not go to completion and always resulted in a mixture of *o*-quinone products. After screening various oxidants, it was found that the conditions reported by Pettus[29] (IBX in DMF) resulted in a very rapid and reproducible reaction giving a ∼1:1 mixture of **20** and **21** that was readily separable by column chromatography. Reduction of **21** with $NaBH_4$ and subsequent oxidation of crude puupehenol[15b] (**22**) with chloranil in refluxing *tert*-butanol afforded **19** in 24% from **11**.[30] The direct oxidation of **20** under various conditions failed to produce **19** in appreciable amounts.

Scheme 4. (–)-Pelorol (30) and (+)-Dictyvaric Acid (31) from 10[a]



[a]Reagents and conditions: (a) 1,4-dioxane, ArBr (**23**–**26**), 10 mol% $Pd(OAc)_2$, 15 mol% S-Phos, CsF, 50 °C, 12 h [**23**, 95% yield; **24**, 84% yield; **25**, 72% yield; **26**, 87% yield]; (b) EtOAc, 10% Pd/C, 200 psi H_2, rt, 12 h; 77% yield.

To further establish the utility of borono-sclareolide (**10**) as a versatile terpene donor, it was exposed to a variety of aryl bromides (**23**–**26**) under Suzuki conditions developed by Buchwald,[31] resulting in excellent yields of the coupled product (Scheme 4). The formal synthesis of the potent SHIP2 inhibitor (−)-pelorol (**30**) was accomplished by intercepting Andersen's intermediate **29** in 87% yield.[32] Coupling between **10** and benzyl ester **25** followed by hydrogenation with 10% Pd/C under 200 psi H_2 yielded the previously unprepared meroterpenoid (+)-dictyvaric acid (**31**) in 55% yield from **10**.[33]

In summary, the power of borono-sclareolide (**10**) to divergently and scalably access meroterpenoid natural products has been demonstrated with the synthesis of 10 different meroterpenoids: (+)-chromazonarol (**11**, 6 steps, 34% overall yield), (−)-isozonarol (**15**) and (−)-zonarol (**14**, 7 steps, 25% overall yield), (−)-yahazunone (**8**, 7 steps, 29% overall yield), (+)-yahazunol (**1**, 8 steps, 26% overall yield), (−)-zonarone (**17**) and (−)-isozonarone (**18**, 8 steps, 24% overall yield), (+)-8-*epi*-puupehedione (**19**, 9 steps, 8% overall yield), the formal synthesis of (−)-pelorol (**30**, 11 steps, 8.5% overall), and synthesis of (+)-dictyvaric acid (**31**, 7 steps, 33% overall yield). Notable elements of the syntheses include the following: (1) expedient, scalable, four-step synthesis of (+)-drim-9(11)-en-8α-ol (**9**); (2) invention of borono-sclareolide (**10**), a privileged terpenoid donor fragment; (3) unprecedented reactivity of **10** with 1,4-benzoquinone resulting in a redox-neutral convergent union and annulation process; and (4) the use of (+)-chromazonarol (**11**) as a divergent intermediate to rapidly access meroterpenoid natural products.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data (^1H and ^{13}C NMR, CIF) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(25) Since the majority of hydroquinone natural products are isolated along with their quinone counterparts, **8** is assumed to be an as-yet unisolated natural product.

(26) Using other solvents (EtOAc or THF) or solid support (Florisil) for the oxidation greatly decreased the rate of reaction (days vs 30 min).

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