

# Divergent Synthesis of Pyrone Diterpenes via Radical Cross Coupling

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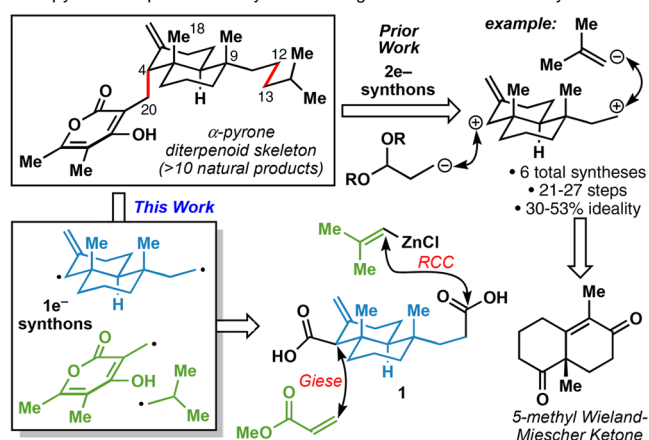
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## Supporting Information

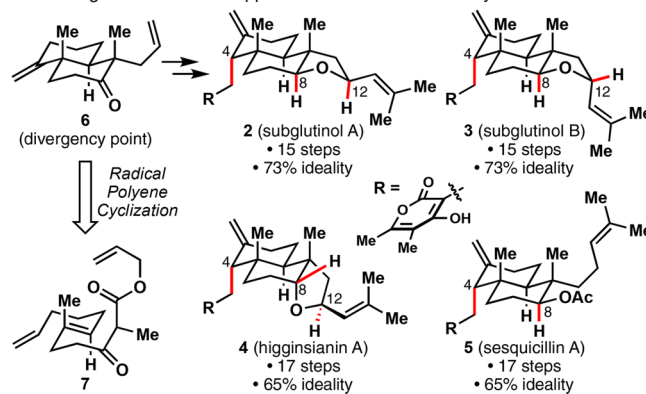
**ABSTRACT:** A divergent strategy for assembling pyrone diterpenes is presented. Capitalizing on the unique stereo- and chemoselectivity features of radical-based chemistry, the core decalin of these structures is efficiently forged using an electrochemically assisted oxidative radical polycyclization while key peripheral substituents are appended using decarboxylative radical cross couplings. In this way, access to four natural products (subglutinols A/B, higginsianin A, and sesquicillin A) is achieved in a concise and stereocontrolled fashion that is modular and amenable to future medicinal chemistry explorations.

The structural idiosyncrasies and promising biological effects of pyrone diterpenes render them exciting targets for total synthesis.<sup>1</sup> This modestly sized family of natural products,<sup>2</sup> so far only found in fungal strains, exhibits a wide range of bioactivities from immunosuppressive<sup>2a,c</sup> to anti-hypertensive<sup>3</sup> yet differ in only subtle ways on the periphery of a decalin core. From a medicinal chemistry perspective, a convergent approach to rapidly assemble this core and install the side-chains in a divergent and modular fashion would be preferable. Prior approaches to this family (Figure 1A) have demonstrated the feasibility of accessing selected  $\alpha$ -pyrone diterpenes in 21–27 steps via 5-methyl Wieland–Miescher ketone (prepared in 2 steps).<sup>4</sup> The main drawback of such approaches stems from a reliance on polar 2-electron disconnections that complicate stereoselective C–C bond formation and necessitate excessive functional group manipulations, protecting group interchanges, and unnecessary redox fluctuations.<sup>5</sup> Such a design makes it challenging to utilize one divergent route to access multiple family members. In stark contrast, single electron radical chemistry disconnections can unlock strategically powerful alternatives.<sup>6</sup> The 1-electron synthons generated through such an analysis of pyrone diterpenoids are easily traced back to diacid **1**. In the forward direction, key C–C bonds can be formed through decarboxylative Giese (C4–C20),<sup>7</sup> and alkenylation cross couplings (C12–C13).<sup>8</sup> A radical-based approach also allows multiple stereochemical challenges posed by this scaffold to be addressed in a simple way. As described in this Communication, sequential C–C bond forming radical cross-couplings (RCC) dramatically simplify access to this diterpenoid family as exemplified by improved syntheses of natural products **2**, **3**, and **5**. This short divergent path also enables the first total synthesis of **4** (Figure 1B).

### A. $\alpha$ -pyrone diterpenoid retrosynthesis: Single-electron based retrosynthesis



### B. A divergent and modular approach with increased ideality



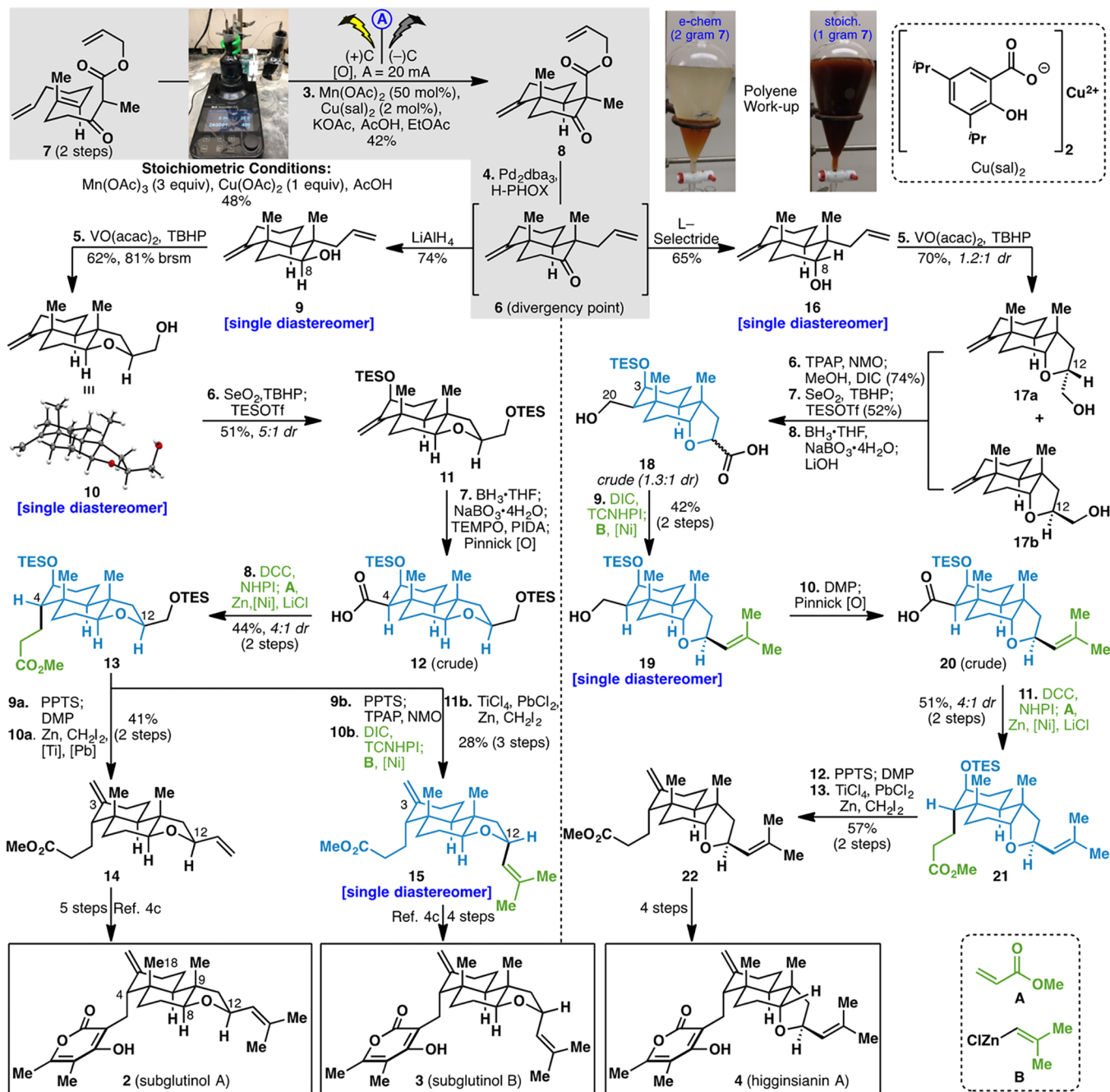
**Figure 1.** (A) 1-electron vs 2-electron based retrosynthetic analyses for pyrone diterpenoid synthesis; (B) divergent access to natural products 2–5 through a modular approach.

With the above considerations in mind, the minimally oxidized decalin **6** was chosen as an equivalent to **1** and the point of divergency to access natural products **2**–**5**. It was envisaged that such a construct could be easily accessed via a Snider-type radical polyene cyclization<sup>9</sup> of **7** followed by a Tsuji allylation.<sup>10</sup>

Scheme 1 outlines the divergent synthesis of **2**–**4**, in which the majority of C–C bonds are forged by radical-based methods. Commencing with polyene **7** (prepared in 2 steps,

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Scheme 1. Syntheses of Subglutinols A (2), B (3), and Higginsianin A (4)<sup>a</sup>

<sup>a</sup>See Supporting Information for reagents and conditions; Cu(sal)<sub>2</sub> = copper(II) 3,5-diisopropylsalicylate, dba = dibenzylideneacetone, PHOX = phosphinooxazolines, TBHP = *tert*-butyl hydroperoxide, TES = triethylsilyl, THF = tetrahydrofuran, PIDA = (diacetoxyiodo)benzene, TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl, DCC = *N,N'*-dicyclohexylcarbodiimide, NHPI = *N*-hydroxyphthalimide, PPTS = pyridinium *p*-toluenesulfonate, DMP = Dess–Martin periodinane, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide, DIC = *N,N'*-diisopropylcarbodiimide, TCNHPI = *N*-hydroxytetrachlorophthalimide, 2,2'-BiPy = 2,2'-bipyridine.

see SI), Mn-mediated radical polycyclization was initially employed. This powerful method, employed in dozens of natural product syntheses,<sup>9c,11</sup> historically utilizes an excess of Mn(III) salts (2–3 equiv) and varying levels of Cu(II)-based (0.1–1 equiv) salts, complicating reaction work up and making scale-up challenging and cumbersome. It was reasoned that this powerful redox cyclization could be rendered catalytic in both metals using electrochemistry. After extensive optimization (see SI), it was discovered that using a divided cell with substoichiometric amounts of Mn(II)-acetate (0.5 equiv) and

catalytic Cu(II) 3,5-diisopropylsalicylate (0.02 equiv) resulted in a comparable isolated yield of 8 relative to classic stoichiometric conditions (42% vs 48%). Several points are notable in this improved Snider cyclization: (1) Mn(OAc)<sub>2</sub> (ca. 7 cents/gram) is significantly less expensive than the Mn(III) salts [Mn(OAc)<sub>3</sub> costs ca. \$6/gram] typically employed;<sup>12</sup> (2) the original conditions required rigorous solvent degassing and inert atmosphere while electrochemical conditions are conducted open to the air; (3) the use of Cu(sal)<sub>2</sub> in this reaction is new and proved superior to other Cu-based salts presumably

due to the enhanced chelation of the ligand; and (4) the significant reduction of metal-based waste also simplifies and accelerates the workup of these reactions (see inset graphic) on gram-scale. To our knowledge, this is the first nonstoichiometric implementation of this transformation.<sup>13</sup>

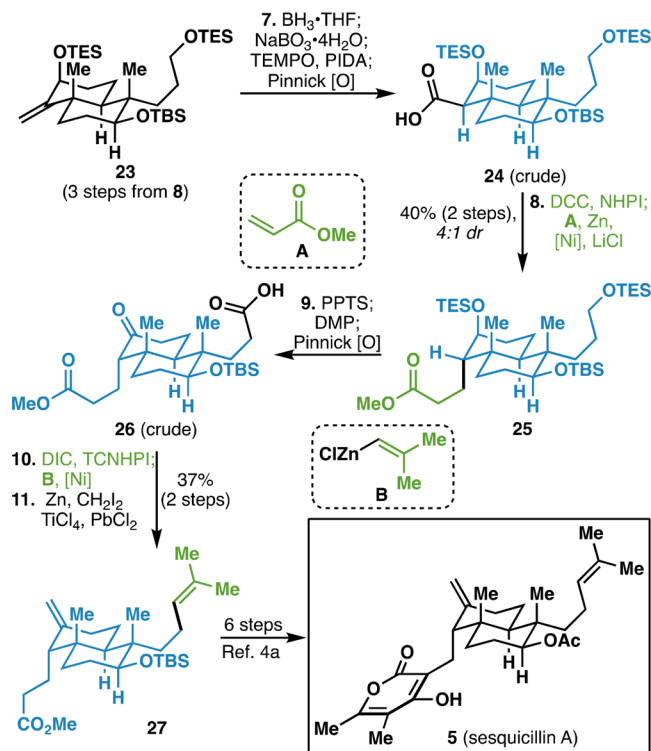
The electrochemically assisted polycyclization solved a key bottleneck in the scale-up of **8**, which could then be subjected to a diastereoselective Tsuji-allylation using achiral H-PHOX<sup>14</sup> to access **6** (not isolated). In order to access the subglutinols (**2–3**), the reaction was quenched with LiAlH<sub>4</sub> to deliver alcohol **9** as a single diastereomer (74% yield).<sup>15</sup> Subglutinols A (**2**) and B (**3**), two immunosuppressive members of the natural product family, are epimeric about C12.<sup>2c</sup> As described below, the strategic application of RCC enables late-stage diversification to access both natural products with complete stereocontrol. Sharpless's V-directed epoxidation<sup>16</sup> of **9** and *in situ* cyclization furnished a single THF diastereomer **10** as verified by X-ray crystallography (62% isolated yield). SeO<sub>2</sub>-mediated allylic oxidation followed by quenching with TESOTf provided allylic ether **11** in 51% yield (5:1 dr). Subsequent hydroboration/oxidation to form **12** set the stage for a key decarboxylative RCC with methyl acrylate (**A**).<sup>7</sup> Acid **12**, used directly from **11** without purification, was subjected to Giese-type RCC to access **13** (44% yield over 2 steps, 4:1 dr). This radical-based method, which essentially inverts the stereochemistry at C4, allows smooth access to a configuration was shown to be difficult to install in all prior approaches. With **13** in hand, the syntheses of **2** and **3** could be completed by installing the C-3 methylene, an isopropenyl group with the correct THF-stereochemistry at C12, and the hallmark pyrone moiety. Thus, conversion of **13** to the keto-aldehyde using PPTS and DMP followed by simple Takai–Lombardo olefination<sup>17</sup> afforded **14** (41% yield over 2 steps), completing the formal total synthesis of **2**.<sup>4c</sup> In the case of **3**, RCC proved crucial to invert C12 and install the isopropenyl unit with complete stereocontrol.<sup>8</sup> To that end, **13** was instead converted to a keto-acid using PPTS and TPAP/NMO.<sup>18</sup> Ni-catalyzed RCC with alkenyl zinc reagent **B** cleanly delivered **15**, after olefination, as a single diastereomer in 28% yield over 3 steps thereby completing the formal synthesis of **3**.<sup>4c</sup> RCC is a uniquely powerful tactic in this context as common radical precursors such as  $\alpha$ -oxy halides would likely not be stable. This radical chemistry approach also represents a complete strategic departure for installing substituents and controlling the THF stereochemistry of the subglutinols at a late-stage (see SI for comparison to prior routes).

Higginsianin A (**4**), a relatively new member of this natural product family with promising anticancer bioactivity,<sup>2e</sup> differs slightly from **2** (opposite stereochemistry at C8) and the lessons learned from the subglutinol synthesis could be easily translated to allow access to synthetic **4** for the first time. Thus, subsection of crude **6** to *L*-selectride delivers the epimeric alcohol **16** (C8) as a single diastereomer (65% yield). Under Sharpless's V-directed epoxidation conditions an inconsequential mixture of diastereomers **17a** and **17b** at the THF-stereocenter (C12, ca. 1:1 dr) were obtained. The alcohol was converted to methyl ester using TPAP/NMO and *in situ* Steglich esterification. Allylic oxidation followed by quenching with TESOTf provided an allylic ether (52%, 5:1 dr at C3) that was subjected to hydroboration/oxidation and hydrolysis of methyl ester to form acid **18**. The lack of stereocontrol at C12 was irrelevant as a decarboxylative RCC on the mixture of epimers (**18**) with alkenyl zinc reagent **B** delivered a single

diastereomer of **19** in 42% yield over two steps. Notably, the RCC proceeded uneventfully in the presence of the unprotected C20 primary alcohol. In a similar manner to the synthesis of **2** and **3**, the C4 stereocenter was also set using a radical coupling. Thus, sequential oxidation (DMP, followed by Pinnick oxidation) of **19** followed by a Giese RCC with **A** on crude **20** delivered **21** in 51% yield (4:1 dr). To complete the first total synthesis of **4**, a similar sequence of events was followed as with **2/3** involving olefination and pyrone installation (see SI for details).

Sesquicillin A (**5**),<sup>2a</sup> a natural product exhibiting a broad array of bioactivities, was also amenable to the same modular strategy as depicted in Scheme 2. Triether **23**, available through

Scheme 2. Synthesis of Sesquicillin A (**5**)<sup>a</sup>



<sup>a</sup>See Supporting Information for reagents and conditions.

a sequence analogous to that shown in Scheme 1 (see SI), was converted to acid **24** and directly subjected to Giese RCC with **A** to deliver homologated ester **25** in 40% yield (4:1 dr) over 2 steps. Removal of the TES-ethers and direct oxidation to keto-acid **26** set the stage for RCC with alkenyl zinc reagent **B**. Conversion to **27** as before completed the formal synthesis of sesquicillin A (**5**).<sup>4a</sup>

It is notable that ca. 70% of the stereodefining C–C bond forming steps in these syntheses were achieved using radical chemistry. In several instances, two-electron chemistry simply failed or delivered the wrong stereochemistry (see SI for extensive listing). For example, multiple attempts to employ a classic alkyl-Suzuki coupling after hydroboration of intermediates such as **11**, **17**, and **23** only delivered the wrong diastereomer at C4 due to steric shielding by the C18 methyl group. In those cases, simple electrophiles such as bromobenzene or vinyl bromide (see SI for complete listing) were the only viable coupling partner rather than the necessary pyrone or any synthetic equivalent thereof. The C12 stereochemistry of



2 and 3 also posed a challenge for classic polar disconnections since it was set early (step 5) either as a mixture (for 4) or as a single diastereomer (which would only allow access to 2). Reliance on Wittig or related olefination methods would require custom routes for each C12 isomer in the case of 2 and 3 (see SI for discussion) or isomer separation in the case of 5. By the strategic combination of one- and two-electron chemistry, four key stereocenters could be controlled through a simple relay wherein the C18 methyl group guided both C4 and C9, which consequently helped to set C8 and C12 stereocenters. Overall, the syntheses outlined above are a compelling demonstration of the power of both intramolecular<sup>6b,19</sup> and intermolecular radical-based chemistry to simplify access to a natural product family exhibiting a largely conserved core and differing peripheral substituents.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b04891.

Data for C<sub>16</sub>H<sub>26</sub>O<sub>2</sub> (CIF)

Experimental procedures, analytical data (<sup>1</sup>H and <sup>13</sup>C NMR, MS) for all new compounds as well as summaries of unsuccessful approaches (PDF)

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### Notes

The authors declare no competing financial interest.

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