

# The Total Synthesis of Rhabdastrellic Acid A

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**ABSTRACT:** The first total synthesis of rhabdastrellic acid A, a highly cytotoxic isomalabaricane triterpenoid, has been accomplished in a linear sequence of 14 steps from commercial geranylacetone. The prominently strained *trans-syn-trans*-perhydrobenz[e]indene core characteristic of the isomalabaricanes is efficiently accessed in a selective manner for the first time through a rapid, complexity-generating sequence incorporating a reductive radical polyene cyclization, an unprecedented oxidative Rautenstrauch cycloisomerization, and umpolung  $\alpha$ -substitution of a *p*-toluenesulfonylhydrazone with *in situ* reductive transposition. A late-stage cross-coupling in concert with a modular approach to polyunsaturated side chains renders this a general strategy for the synthesis of numerous family members of these synthetically challenging and hitherto inaccessible marine triterpenoids.

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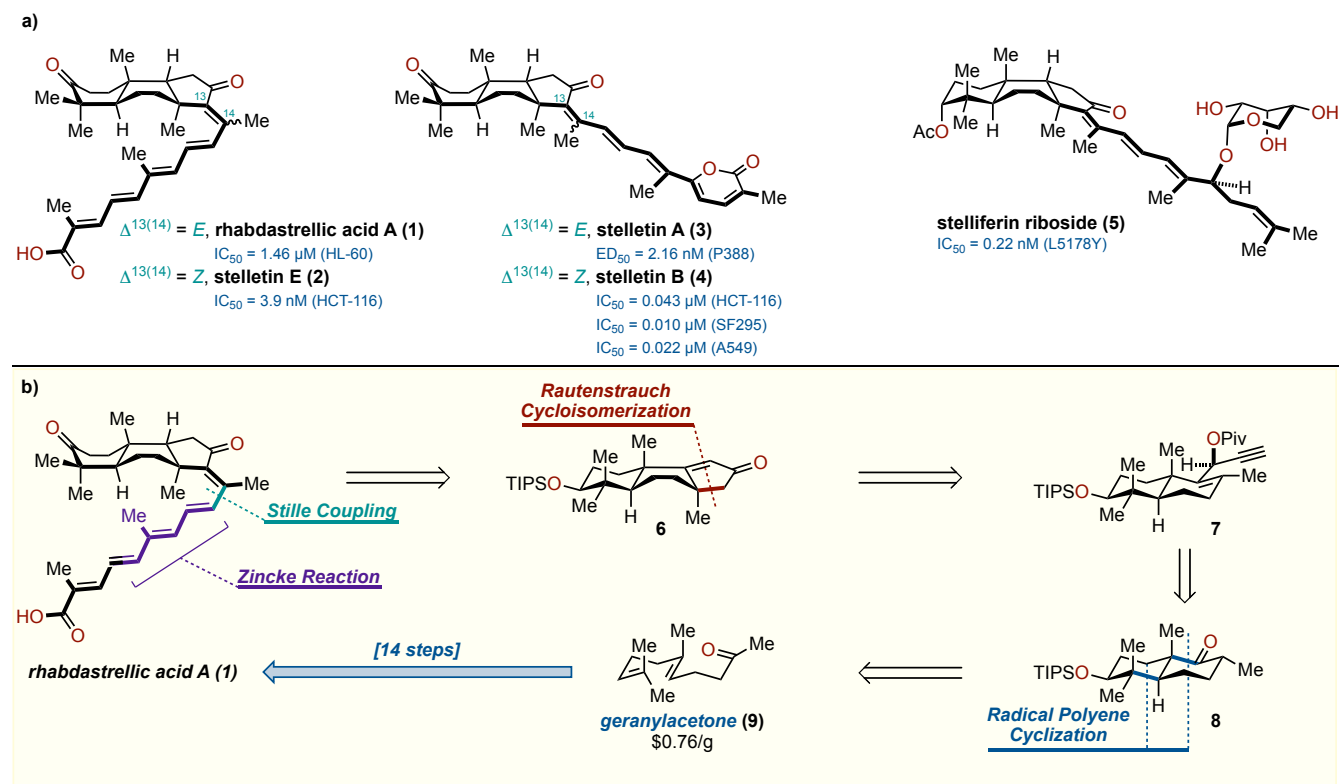
The intricate molecular architectures of natural products have inspired and informed medicinal chemists for decades, and their vast span of biological activities has accelerated the discovery of novel chemotypes with applications in medicine. Accordingly, the total synthesis of complex natural products continues to be one of the most fruitful strategies for obtaining new molecular scaffolds for drug development, providing solutions to supply problems as well as opportunities for analogue synthesis and medicinal chemistry.<sup>1</sup> We identified the eminently cytotoxic isomalabaricane triterpenoids as promising anticancer leads particularly well-suited for synthetic efforts (Figure 1a).<sup>2,3</sup> These apoptosis-inducing marine tricyclic triterpenoids have demonstrated low nanomolar cytotoxicity coupled with high specificity for certain cancer cell lines, along with a range of other antineoplastic effects including microtubule disassembly and disruption of DNA Damage Response mechanisms.<sup>2-4</sup> Among several isomalabaricanes with promising antiproliferative activities, rhabdastrellic acid A (**1**) and stelletin B (**4**) stand out as potent apoptosis inducers in the nanomolar range within human colon, leukemia, glioblastoma and non-small cell lung cancer cell lines, interfering with PI3K/Akt/mTOR growth factor signaling and inducing G1 arrest and autophagic cell death.<sup>2,4c-d, 4f-g</sup> Stelletin B has demonstrated remarkable selectivity for cancer cells over normal healthy tissue. An unusual glycosylated isomalabaricane, stelliferin riboside (**5**), was quite toxic to the L5178Y mouse lymphoma cell line, with an IC<sub>50</sub> value of 0.22 nM.<sup>2,3b</sup>

Despite these exciting preliminary reports of potent antitumor activity, the isomalabaricane scaffold remains largely unexplored as a potential anticancer lead.<sup>2a,2c</sup> To date no complete biochemical mechanism of action has been proposed, no specific molecular targets have been identified, no pharmacophore has been elucidated for this molecular framework, and further biological studies have been hampered by the extreme scarcity of these compounds. The need for foundational biochemical investigations, bolstered by the possibility for analogue synthesis and drug development, lends a distinct urgency to the creation of an efficient, scalable, and highly general synthetic strategy to synthesize the isomalabaricane triterpenoids.

Nonetheless, the isomalabaricanes have resisted the efforts of synthetic chemists, and have stood unconquered in the 37 years since their first isolation.<sup>5</sup> The extreme difficulty in preparing the *trans-syn-trans*-perhydrobenz[e]indene tricyclic core can be readily seen through simple conformational analysis, demanding both A- and B-rings be held rigidly in their high-energy twist-boat conformations. This formidable strain energy and unorthodox conformation stymies many of the traditional techniques for constructing polycyclic terpene systems, and helps to rationalize the complete void in the literature for any successful total syntheses of *trans-syn-trans*-perhydrobenz[e]indene natural products. With a keen interest in furthering the biological evaluation of the isomalabaricanes, we set out to provide a general, modular, and scalable solution to this tenacious problem in terpene synthesis. Herein we report the successful implementation of a catalytic enyne cycloisomerization with subsequent retro-ene transpositive reduction to gain access to the *trans-syn-trans*-perhydrobenz[e]indene core of the isomalabaricane triterpenoids in only eight steps from commercial geranylacetone, as well as the completion of the first total synthesis of rhabdastrellic acid A (**1**).

In the early stages of strategic design, we endeavored to develop a general blueprint for isomalabaricane triterpenoid synthesis that was amenable to diversification and analogue generation (Figure 1b). To provide modular access to the numerous isomalabaricanes that differ only in the structure of their pendant side chain, we planned for a late-stage Stille cross-coupling of linear tributylvinylstannanes with an exocyclic vinyl electrophile on the tricyclic core. This coupling partner could be synthesized through careful functional group and redox manipulations on the C-ring cyclopentanone after the key stereochemistry had been established at the BC-ring junction. The highly strained boat conformation in the B-ring severely circumscribes the methods available for its construction. To avert the considerable

challenges associated with the creation of such strained polycyclic systems *via* biomimetic cationic cyclization, which have been well documented,<sup>6,7</sup> we opted instead for a stepwise process involving a cyclopentannulation of a much simpler bicyclic framework. In order to set the all-carbon quaternary center at C-8 with a large concomitant increase in ring strain, we envisioned the use of a stereospecific, gold-catalyzed Rautenstrauch cycloisomerization of enyne **7**, which has been hypothesized to proceed through a helical transition state with complete transfer of chirality from the propargylic pivalate ester.<sup>8</sup> This motif would be affixed to elementary *trans*-decalin **8**, reminiscent of the venerable Wieland–Miescher ketone,<sup>10</sup> which we speculated could be more rapidly and efficiently synthesized from simple and readily available precursors through a polyene cyclization.



**Figure 1.** a) Selected isomalabaricane triterpenoids. b) Key retrosynthetic disconnections.

The synthesis begins with two chemoselective modifications of a basic linear terpene to activate it for cyclization (Figure 2a). Commencing with the commercially available terpene geranylacetone (**9**), epoxynitrile **10** was synthesized on a decagram scale by a modified Van Leusen reductive cyanation<sup>10</sup> of the ketone with *p*-toluenesulfonylmethylisocyanide, followed by selective epoxidation of the terminal olefin with *N*-bromosuccinimide in water under standard conditions.<sup>11</sup> With all requisite carbons and reactive handles now in place, construction of the bicyclic ketone **8** was accomplished with an efficient Ti(III)-mediated reductive radical polyene cyclization<sup>12</sup> and subsequent silylation of the resulting C-3 alcohol, generating an inconsequential 5:1 mixture of diastereomers on the C-8 methyl group. We find it worth noting that protected decalones of type **8**, widely-used synthetic intermediates traditionally accessed in nine steps *via* Robinson annulation of 1,3-cyclohexanedione,<sup>13</sup> can be easily prepared on decagram scale using this method in only four steps and >50% overall yield. One-carbon homologation of the ketone to  $\alpha,\beta$ -unsaturated aldehyde **11** was achieved on decagram scale in 80% yield through alkylation with dichloromethyl lithium and Lewis-acid promoted elimination of the intermediate  $\alpha$ -chloro aldehyde following a modified protocol from Nozaki and Yamamoto.<sup>14</sup> Due to the inherent allylic strain within the *trans*-decalin framework and in accordance with previous studies in analogous bicyclic systems,<sup>15</sup> we found that competing olefin isomerization to the thermodynamically preferred deconjugated aldehyde was unavoidable under the conditions necessary to effect dehydrohalogenation. However, this byproduct was minor, and could readily be converted to the desired conjugated aldehyde **11** through kinetic  $\gamma$ -protonation of its *tert*-butyl metallodienamine in quantitative yield, and thus all aldehydic material could be progressed beyond this stage. Finally, a highly diastereoselective addition of freshly prepared lithium acetylide with *in situ* pivalate protection completed the synthesis of key cycloisomerization precursor **7** in 90% yield. Gratifyingly, in one pass this six-step sequence could produce more than five grams of enyne **7** as a single diastereomer, and provided rapid entry into our cyclization studies aimed towards the construction of the C-ring.

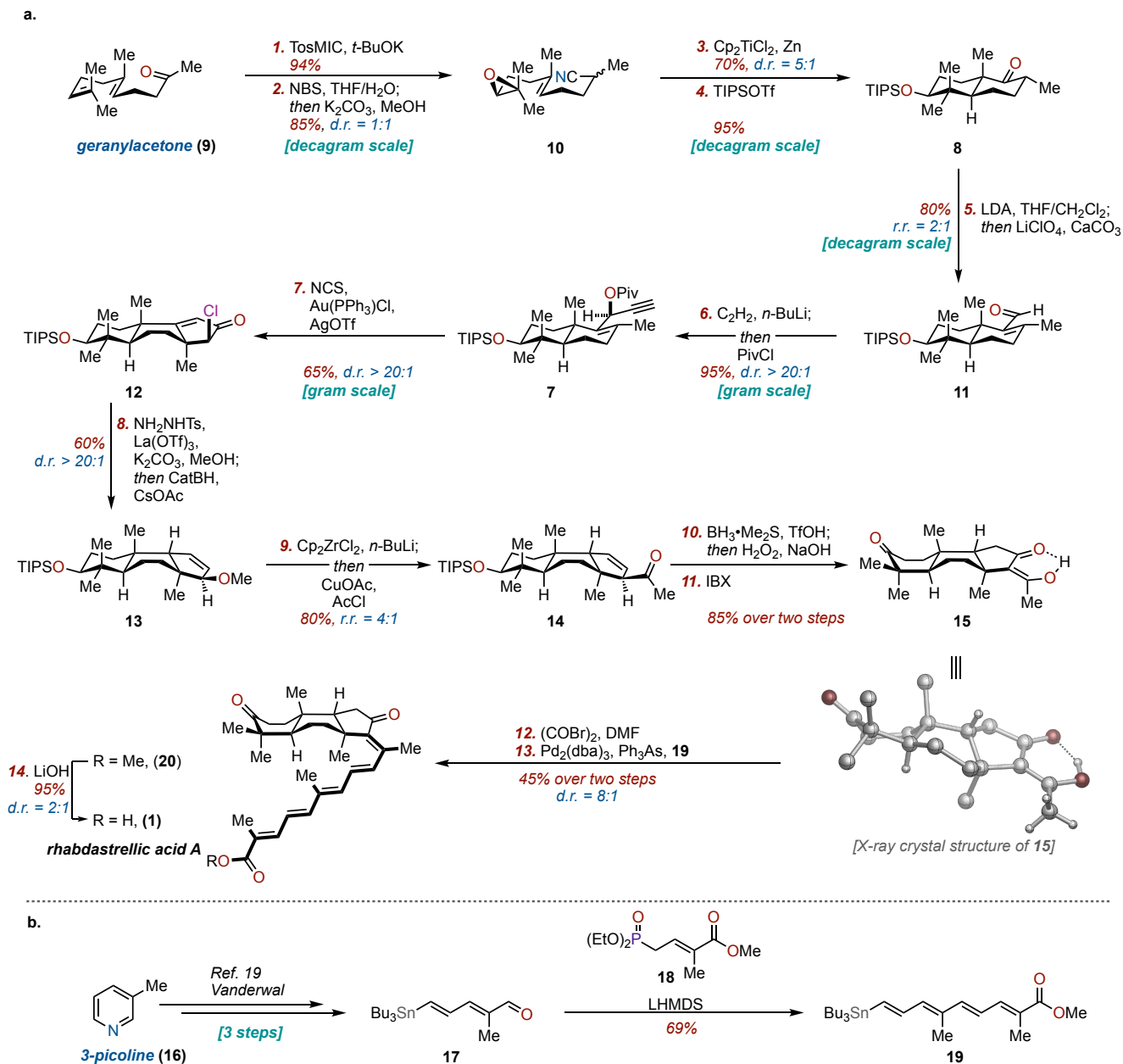
Using conditions first reported by Toste,<sup>8</sup> we were delighted to find that the envisaged Rautenstrauch rearrangement proceeded in high efficiency under cationic gold(I) catalysis to construct tricyclic enone **6** as a single diastereomer, the configuration of which was confirmed by single crystal X-ray analysis. The transformation proved to be robust and practical, and could be carried out on multi-gram scale under open-flask conditions. Only 2.5 mol% of the catalyst was needed to achieve full conversion within several hours. Furthermore, the active catalyst, Ph<sub>3</sub>PAuOTf, could be formed *in situ* from commercial components through salt metathesis of Ph<sub>3</sub>PAuCl and AgOTf. A protic additive was found to be essential for hydrolysis of the intermediate enol ester.<sup>16</sup> Finally, it is worthy of note that, to the best of our knowledge, this is the first example of the construction of a quaternary stereocenter using a gold-catalyzed Rautenstrauch cycloisomerization.

The kinetic and thermodynamic obstacles to reduce this enone from the desired face were substantial, requiring hydrogen delivery at the bisneopentyl site of a trisubstituted, electronically-deactivated olefin from the concave face to set the final stereocenter of the *trans-syn-trans* core, increasing its strain even further. After extensive experimentation, we found that the proper stereochemistry could only be established through a reductive transposition of the corresponding  $\alpha,\beta$ -unsaturated *p*-toluenesulfonylhydrazone with catecholborane, using the Kabalka modification of the Caglioti reaction.<sup>17</sup> In order to provide a functional handle with which to bring in the side chain after reduction, we explored the effect of  $\alpha$ -substitution on the transposition process and found simple alkyl and silyl ethers to be optimal for an efficient and selective sequence.

To streamline this process, we developed a series of tandem reactions to achieve annulation and reduction in a rapid and economical fashion. We hypothesized that omission of the protic additive during cycloisomerization might render the intermediate enol pivaloate susceptible to electrophilic attack to generate  $\alpha$ -functionalized cyclopentenones. With no synthetically useful electrophilic alkoxyating agents available to produce the requisite alkyl ether, we strove to construct this motif through an umpolung  $\alpha$ -substitution of an appropriate *p*-toluenesulfonylhydrazone during the reductive transposition. Thus, simultaneous treatment of enyne **9** with the Au(I) catalyst and *N*-chlorosuccinimide delivered  $\alpha$ -chloro ketone **12** in 70% yield and as a single diastereomer. To our knowledge, this is the first example of an intercepted Rautenstrauch cycloisomerization with intermolecular electrophilic functionalization. The  $\alpha$ -chloro enone **12** was found to be an ideal substrate for a convenient one-pot protocol incorporating lanthanum(III) triflate-catalyzed hydrazone formation with subsequent exposure to potassium carbonate in methanol, promoting conjugate addition of the solvent into a transiently generated azoalkene, followed by reductive transposition under the standard conditions. This unconventional complexity-building annulation sequence from **7** to **13** rapidly constructs the C-ring, forges three contiguous stereocenters including both challenging bridgehead positions entrenched within the completed *trans-syn-trans*-perhydrobenz[e]indene tricyclic nucleus, and establishes an appropriate allylic electrophile for subsequent elaboration in only two steps.

With the nature of this electrophile restricted by the demands of the reductive transposition, we required a suitable method to activate the relatively unreactive methyl ether **13** for allylic substitution. After a brief exploration of transition-metal umpolung processes, we found that the desired transformation could be achieved through reductive zirconation and trapping with acetyl chloride under copper catalysis.<sup>18</sup> Although this somewhat rare transformation is reported in the literature to work quite poorly with 5-membered cyclic allylzirconocene species, we were able to obtain the desired deconjugated enone **14** in 70% yield after sufficient optimization.<sup>18c</sup> Relay hydroboration of this olefin from the ketone, followed by *in situ* deprotection of the silyl group with triflic acid and two-fold global oxidation furnished triketone **15** as a single constitutional isomer, the structure of which was confirmed by single crystal X-ray diffraction analysis.

With rapid access to the fully oxidized tricyclic core of the isomalabaricanes in hand, the stage was set for the synthesis of the polyene side chains and the final cross-coupling. We identified 3-picoline (**16**) as an ideal starting material for a divergent synthesis of numerous side chain coupling partners through Zincke reaction and 1,6-addition-elimination of tributylstannyl lithium, a sequence first disclosed by Vanderwal.<sup>19</sup> Stannanedial **17** should serve as a common intermediate to a variety of side chain coupling partners through olefination or allylation chemistries. To this end, the tetraenylstannane methyl ester **19**, a precursor of rhabdastrellic acid A (**1**) and stelletin E (**2**), was prepared in 69% yield through Horner–Wadsworth–Emmons olefination with known phosphonate ester **18**.<sup>20</sup> As we initiated studies into the formation of a suitable vinyl electrophile for cross-coupling, we found that, consistent with the preceding synthetic operations for these molecules, the triketone **15** exhibited a strong bias against the selectivity we required. Chemoselective functionalization of unsymmetrical 1,3-diketones seems to be a largely unaddressed problem in organic synthesis. Triflation under a wide variety of conditions delivered only the undesired endocyclic constitutional isomer. Gratifyingly, bromination with the Vilsmeier reagent proved uniquely capable of delivering the requisite vinyl bromide as a single constitutional and geometrical isomer.<sup>21</sup>



**Figure 2.** a) The total synthesis of rhabdastrellic acid A (**1**). Reagents and conditions: 1. **9**, TosMIC, *t*-BuOK, Et<sub>2</sub>O, EtOH, 0 °C to 25 °C, 94%; 2. NBS, THF/H<sub>2</sub>O 2:1, 0 °C; then K<sub>2</sub>CO<sub>3</sub>, MeOH, 25 °C, 85%; 3. Cp<sub>2</sub>TiCl<sub>2</sub>, Zn, THF, 25 °C; then NaH<sub>2</sub>PO<sub>4</sub>, 70%; 4. TIPSOTf, 2,6-lutidine, DCM, 0 °C to 25 °C, 95%; 5. LDA, DCM, THF, -100 °C to 60 °C; then LiClO<sub>4</sub>, CaCO<sub>3</sub>, DMPU, 80% (2:1 *r.r.*); 6. *n*-BuLi, C<sub>2</sub>H<sub>2</sub>, THF, -78 °C to -40 °C; then PivCl, 25 °C, 95%; 7. NCS, Au(PPh<sub>3</sub>)Cl (2.5 mol%), AgOTf (2.5 mol%), DCM, 25 °C, 65%; 8. TsNHNH<sub>2</sub>, La(OTf)<sub>3</sub> (15 mol%), MeOH, 60 °C; then K<sub>2</sub>CO<sub>3</sub>, 25 °C; then CatBH, CsOAc, CHCl<sub>3</sub>, 0 °C to 65 °C, 60%; 9. Cp<sub>2</sub>ZrCl<sub>2</sub>, *n*-BuLi, THF, 0 °C to 25 °C; then CuOAc (20 mol%), AcCl, 55 °C, 70%; 10-11. BH<sub>3</sub>•DMS, THF, -78 °C to 25 °C; then TfOH, 0 °C to 25 °C; then IBX, EtOAc, reflux, 85%; 12-13. (COBr)<sub>2</sub>, DMF, DCM, 0 °C to 25 °C; then Pd<sub>2</sub>(dba)<sub>3</sub> (10 mol%), Ph<sub>3</sub>As (30 mol%), **19**, NMP, 70 °C, 45%; 14. LiOH, THF/H<sub>2</sub>O/MeOH 2:2:1, 50 °C, 95%. b) Synthesis of coupling partner **19**. Reagents and conditions: LHMDS, **18**, THF, -10 °C; then HMPA, -60 °C; then **17**, -78 °C to 25 °C, 69%.

Stille coupling of this vinyl bromide with tetraenylstannane **19** under "soft" palladium conditions reported by De Lera<sup>22</sup> assembled the methyl ester of rhabdastrellic acid A (**20**) in 45% overall yield from triketone **15**, in an 8:1 ratio with the isomeric methyl ester of stelletin E. The isomalabaricanes have been widely reported to undergo facile C-13–C-14 olefin isomerization upon irradiation with visible light,<sup>2,3</sup> however, this mixture of isomers was consistently

observed even with rigorous exclusion of ambient illumination. Saponification of this ester with lithium hydroxide quantitatively delivered rhabdastrellic acid A (**1**) with stelletin E (**2**) in a 2:1 ratio, both spectroscopically identical to the naturally obtained materials.<sup>3d,3g</sup> Olefin isomerization under our current cross-coupling and hydrolysis conditions remains a limitation in this synthesis, and efforts to address these challenges are underway.

The synthesis of rhabdastrellic acid A (**1**) was accomplished in 14 steps with an average yield of 82% per step, representing the first total synthesis of an isomalabaricane triterpenoid as well as the only reported highly selective chemical approach for the synthesis of their remarkably strained *trans-syn-trans*-perhydrobenz[e]indene core.<sup>23</sup> Highlights of this strategy include the implementation of a rapid and scalable sequence to access synthetically useful Wieland–Miescher ketone derivatives, as well as development of a tandem oxidative cycloisomerization and reductive transposition with umpolung  $\alpha$ -substitution sequence that dramatically improves step economy. This work adheres closely to recently articulated guidelines for efficiency and ideality in total synthesis,<sup>24</sup> and all synthetic operations engage in requisite C–C bond formation or productive redox alteration, with the exception of a single protecting group manipulation. We believe this unconventional approach to the tricyclic core in concert with the generalizable Zincke aldehyde route for polyenylstannanes will serve as a universal strategy for the synthesis of isomalabaricane triterpenoids, providing material for comprehensive biological mode-of-action studies that has hitherto been near-inaccessible.

## ASSOCIATED CONTENT

### Supporting Information.

The Supporting Information is available free of charge via the internet at <http://chemrxiv.org>.

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### Notes

We declare no competing financial interests.

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