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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 ?-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 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 α-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.

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.[1] We identified the eminently cytotoxic isomalabaricane triterpenoids as promising anticancer leads particularly well-suited for synthetic efforts (Figure 1a).[2,3] 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.[2-4] 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.[2,4c–d, 4f–g] 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_{50} value of 0.22 nM.[2,3b]

Despite these exciting preliminary reports of potent antitumor activity, the isomalabaricane scaffold remains largely unexplored as a potential anticancer lead.[2a,2c] 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.[5] 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,[6,7] 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.[8] This motif would be affixed to elementary *trans*-decalin **8**, reminiscent of the venerable Wieland–Miescher ketone,[10] which we speculated could be more rapidly and efficiently synthesized from simple and readily available precursors through a polyene cyclization.

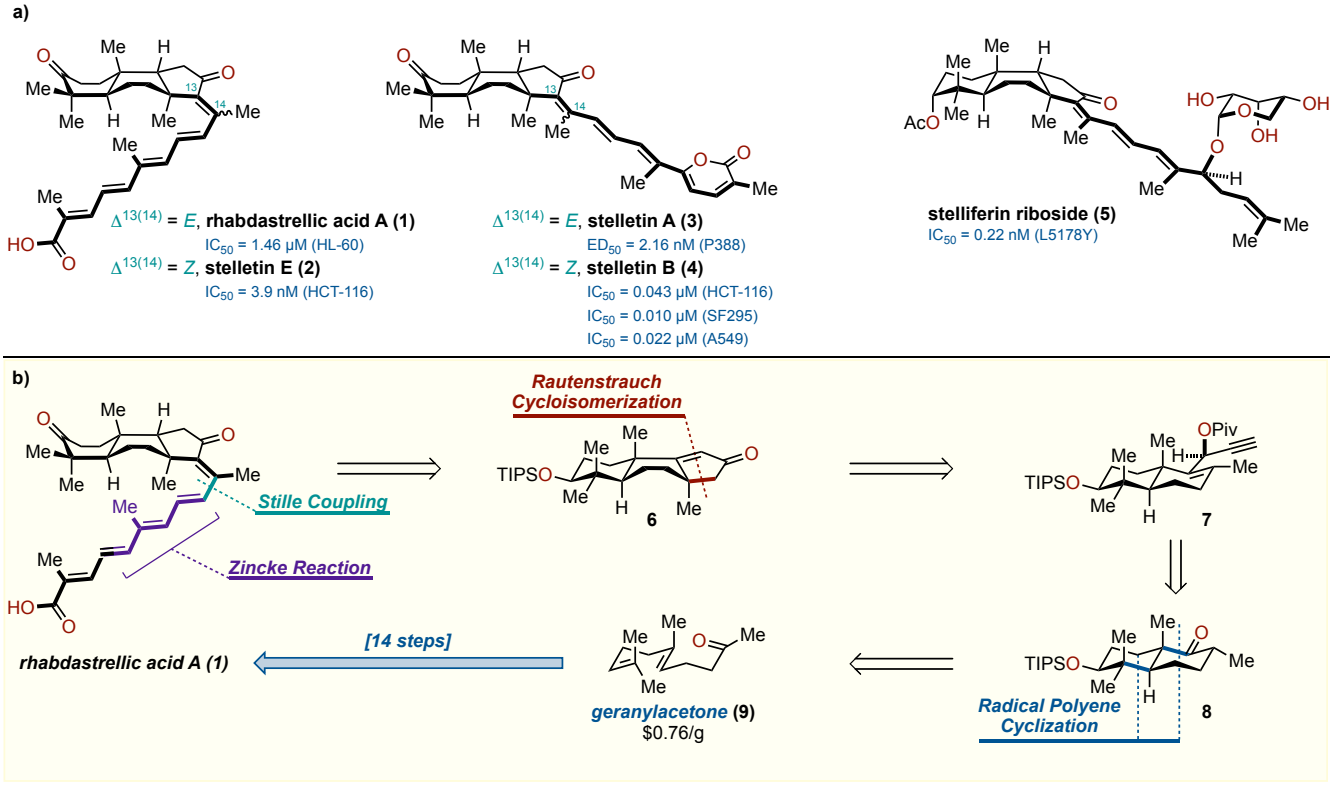

Figure 1. a) Selected isomalabaricane triterpenoids. b) Key retrosynthetic disconnections.

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[10] of the ketone with *p*-toluenesulfonylmethylisocyanide, followed by selective epoxidation of the terminal olefin with *N*-bromosuccinimide in water under standard conditions.[11] 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[12] 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,[13] 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 α,β–unsaturated aldehyde **11** was achieved on decagram scale in 80% yield through alkylation with dichloromethyllithium and Lewis-acid promoted elimination of the intermediate α–chloro aldehyde following a modified protocol from Nozaki and Yamamoto.[14] Due to the inherent allylic strain within the *trans*-decalin framework and in accordance with previous studies in analogous bicyclic systems,[15] 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 γ–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,[8] 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, $Ph_3PAuOTf$, could be formed *in situ* from commercial components through salt metathesis of Ph_3PAuCl and AgOTf. A protic additive was found to be essential for hydrolysis of the intermediate enol ester.[16] 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 bisneopentylic 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 α,β–unsaturated *p*-toluenesulfonylhydrazone with catecholborane, using the Kabalka modification of the Caglioti reaction.[17] In order to provide a functional handle with which to bring in the side chain after reduction, we explored the effect of α–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 α–functionalized cyclopentenones. With no synthetically useful electrophilic alkoxylating agents available to produce the requisite alkyl ether, we strove to construct this motif through an umpolung α–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 α–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 α–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.[18] 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.[18c] 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.[19] Stannanedienal **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**.[20] 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.[21]

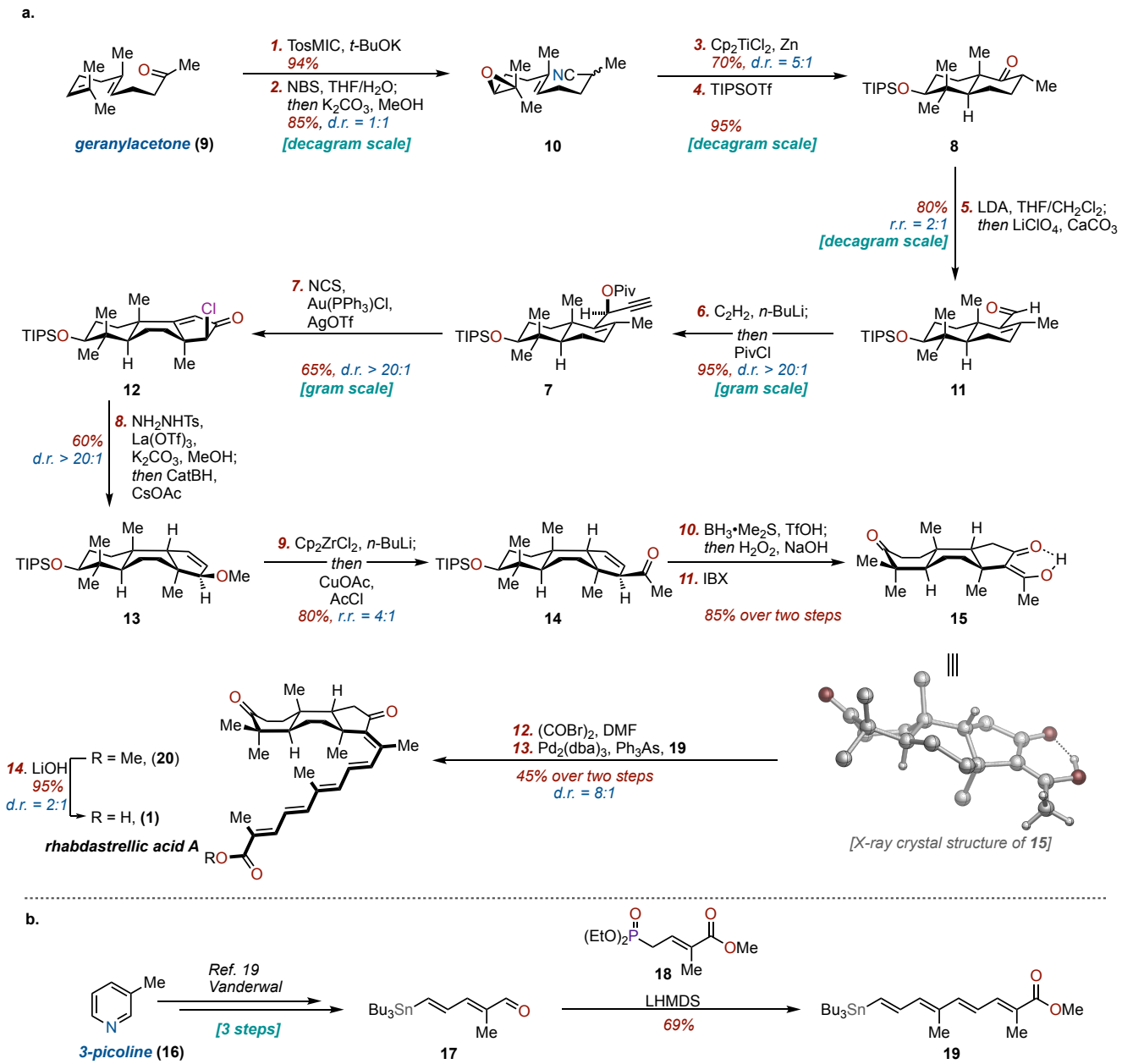

Figure 2. a) The total synthesis of rhabdastrellic acid A (**1**). Reagents and conditions: 1. **9**, TosMIC, *t*-BuOK, Et_2O, EtOH, 0 °C to 25 °C, 94%; 2. NBS, THF/H_2O 2:1, 0 °C; then K_2CO_3, MeOH, 25 °C, 85%; 3. Cp_2TiCl_2, Zn, THF, 25 °C; then NaH_2PO_4, 70%; 4. TIPSOTf, 2,6-lutidine, DCM, 0 °C to 25 °C, 95%; 5. LDA, DCM, THF, –100 °C to 60 °C; then $LiClO_4$, $CaCO_3$, DMPU, 80% (2:1 *r.r.*); 6. *n*-BuLi, C_2H_2, THF, –78 °C to –40 °C; then PivCl, 25 °C, 95%; 7. NCS, $Au(PPh_3)Cl$ (2.5 mol%), AgOTf (2.5 mol%), DCM, 25 °C, 65%; 8. $TsNHNH_2$, $La(OTf)_3$ (15 mol%), MeOH, 60 °C; then K_2CO_3, 25 °C; then CatBH, CsOAc, $CHCl_3$, 0 °C to 65 °C, 60%; 9. Cp_2ZrCl_2, *n*-BuLi, THF, 0 °C to 25 °C; then CuOAc (20 mol%), AcCl, 55 °C, 70%; 10-11. BH_3•DMS, THF, –78 °C to 25 °C; then TfOH, 0 °C to 25 °C; then IBX, EtOAc, reflux, 85%; 12-13. $(COBr)_2$, DMF, DCM, 0 °C to 25 °C; then $Pd_2(dba)_3$ (10 mol%), Ph_3As (30 mol%), **19**, NMP, 70 °C, 45%; 14. LiOH, THF/H_2O/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[22] 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;[2,3] 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.[3d,3g] 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.[23] 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 α–substitution sequence that dramatically improves step economy. This work adheres closely to recently articulated guidelines for efficiency and ideality in total synthesis,[24] 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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REFERENCES

(1) Newman, D. J.; Cragg, G. M. Natural Products as Sources of New Drugs from 1981 to 2014. *J. Nat. Prod.,* **2016***, 79*, 629–661l.

(2) For reviews, see: (a) Essack, M.; Bajic, V. B.; Archer, J. C. Recently Confirmed Apoptosis-Inducing Lead Compounds Isolated from Marine Sponge of Potential Relevance in Cancer Treatment. *Mar. Drugs* **2011***, 9*, 1580–1606; (b) Calcabrini, C; Catanzaro, E.; Bishayee, A.; Turrini, E.; Fimognari, C. Marine Sponge Natural Products with Anticancer Potential: An Updated Review. *Mar. Drugs* **2017***, 15*, 310–343; (c) Gomes, N. G. M.; Dasari, R.; Chandra, S.; Kiss, R.; Kornienko, A. Marine Invertebrate Metabolites with Anticancer Activities: Solutions to the "Supply Problem". *Mar. Drugs* **2016***, 14*, 98–136; (d) Ebada, S. S.; Lin, W.; Proksch, P. Bioactive Sesterterpenes and Triterpenes from Marine Sponges: Occurrence and Pharmacological Significance. *Mar. Drugs* **2010***, 8*, 313–346; (e) Domingo, V.; Arteaga, J. F.; del Moral, J. F.; Barrero, A. F. Unusually cyclized triterpenes: occurrence, biosynthesis and chemical synthesis. *Nat. Prod. Rep.,* **2009***, 26*, 115–134.

(3) Selected original isolation reports: (a) Fouad, M.; Edrada, R. A.; Ebel, R.; Wray, V.; Müller, W. E. G.; Lin, W.; Proksch, P. Cytotoxic Isomalabaricane Triterpenes from the Marine Sponge Rhabdastrella globostellata. *J. Nat. Prod.* **2006***, 69*, 211–218; (b) Tabudravu, J. N.; Jaspars, M. Stelliferin Riboside, a Triterpene Monosaccharide Isolated from the Fijian Sponge Geodia globostellifera. *J. Nat. Prod.* **2001***, 64*, 813–815; (c) Su, J. Y.; Meng, Y. H.; Zen, L. M.; Fu, X.; Schmitz, F. J. Stelletin A, A New Triterpenoid Pigment from The Marine Sponge Stelletta Tenuis. *J. Nat. Prod.* **1994***, 57*, 1450–1451; (d) Tasdemir, D.; Mangalindan, G. C.; Concepción, G. P.; Verbitski, S. M.; Rabindran, S.; Miranda, M.; Greenstein, M.; Hooper, J. N. A.; Harper, M. K.; Ireland, C. M. Bioactive Isomalabaricane Triterpenes from the Marine Sponge Rhabdastrella globostellata. *J. Nat. Prod.* **2002***, 65*, 210–214; (e) Lv, F.; Deng, Z.; Li, J.; Fu, H.; van Soest, R. W. M.; Proksch, P.; Lin, W. Isomalabaricane-Type Compounds from the Marine Sponge Rhabdastrella aff. distincta. *J. Nat. Prod.* **2004***, 67*, 2033–2036; (f) Lv, F.; Xu, M.; Deng, Z.; de Voogd, N. J.; van Soest, R. W. M.; Proksch, P.; Lin, W. Rhabdastrellins A-F, Isomalabaricane Triterpenes from the Marine Sponge Rhabdastrella aff. distincta.

J. Nat. Prod. **2008**, *71*, 1738–1741; (g) Rao, Z.; Deng, S.; Wu, H.; Jiang, S. Rhabdastrellic Acid-A, a Novel Triterpenoid from the Marine Sponge Rhabdastrella globostellata. *J. Nat. Prod.* **1997**, *60*, 1163-1164; (h) McKee, T. C.; Bokesch, H. R.; McCormick, J. L.; Rashid, M. A.; Spielvogel, D.; Gustafson, K. R.; Alavanja, M. M.; Cardellina, II, J. H.; Boyd, M. R. Isolation and Characterization of New Anti-HIV and Cytotoxic Leads from Plants, Marine, and Microbial Organisms. *J. Nat. Prod.* **1997**, *60*, 431–438.

(4) Biological studies: (a) Liu, W. K.; Cheung, F. W. K.; Che, C-T. Stellettin A Induces Oxidative Stress and Apoptosis in HL-60 Human Leukemia and LNCaP Prostate Cancer Cell Lines. *J. Nat. Prod.* **2006**, *69*, 934–937; (b) Clement, J. A.; Li, M.; Hecht, S. M.; Kingston, D. G. I. Bioactive Isomalabaricane Triterpenoids from Rhabdastrella globostellata that Stabilize the Binding of DNA Polymerase β to DNA. *J. Nat. Prod.* **2006**, *69*, 373–376; (c) Tang, S.-A.; Zhou, Q.; Guo, W.-Z.; Qiu, Y.; Wang, R.; Jin, M.; Zhang, W.; Li, K.; Yamori, T.; Dan, S.; Kong, D. In Vitro Antitumor Activity of Stellettin B, a Triterpene from Marine Sponge Jaspis stellifera, on Human Glioblastoma Cancer SF295 Cells. *Mar. Drugs* **2014**, *12*, 4200–4213; (d) Wang, R.; Zhang, Q.; Peng, X.; Zhou, C.; Zhong, Y.; Chen, X.; Qiu, Y.; Jin, M.; Gong, M.; Kong, D. Stellettin B Induces G1 Arrest, Apoptosis and Autophagy in Human Non-small Cell Lung Cancer A549 Cells via Blocking PI3K/Akt/ mTOR Pathway. *Scientific Reports* **2016**, *6*, 27071; (e) Liu, W. K.; Ho, J. C. K.; Che, C-T. Apoptotic activity of isomalabaricane triterpenes on human promyelocytic leukemia HL60 cells. *Cancer Letters* **2005**, *230*, 102–110; (f) Li D-D; Guo J-F; Huang J-J; Wang L-L; Deng R; Liu J-N; et al. Rhabdastrellic Acid-A Induced Autophagy-Associated Cell Death through Blocking Akt Pathway in Human Cancer Cells. *PLoS ONE* **2010**, *5*: e12176; (g) Guo, J.; Zhou, J.; Zhang, Y.; Deng, R.; Liu, J.; Feng, G.; Liu, Z.; Xiao, D.; Deng, S. and Zhu, X. Rhabdastrellic acid-A inhibited PI3K/Akt pathway and induced apoptosis in human leukemia HL-60 cells. *Cell Biology International* **2008**, *32*, 48-54.

(5) Previously reported attempts: (a) Raeppel, F.; Weibel, J-M.; Heissler, D. Synthesis of the trans-syn-trans perhydrobenz[e]indene moiety of the stellettins and of the stelliferins. *Tetrahedron Letters* **1999**, *40*, 6377–6381; (b) Raeppel, F.; Heissler, D. Conversion of a trans–syn–trans to a cis–syn–trans perhydrobenz[e]indenone triggered by intramolecular 1,5-hydrogen transfer. *Tetrahedron Letters* **2003**, *44*, 3487–3488; (c) Rosner, K. E. Approaches to the Synthesis of Stelliferin, a Marine Isomalabaricane Triterpene. PhD Dissertation, MIT, **1996**.

(6) Access to *trans-syn-trans*-perhydrobenz[*e*]indene via polyene cyclization has been reported as a very minor side product with only one substrate: Fish, V. P.; Sudhakar, A. R.; Johnson, W. S. Epoxide-Initiated Cationic Polyene Cyclizations. *Tetrahedron Letters* **1993**, *34*, 7849.

(7) Yee, N. K. N.; Coates, R. M. Total Synthesis of (+)-9,10-syn- and (+)-9,10-anti-Copalol via Epoxy Trienylsilane Cyclizations. *J. Org. Chem.* **1992**, *57*, 4598-4608.

(8) Shi, X.; Gorin, D. J.; Toste, D. F. Synthesis of 2-Cyclopentenones by Gold(I)-Catalyzed Rautenstrauch Rearrangement. *J. Am. Chem. Soc.* **2005**, *127*, 5802–5803.

(9) Wieland, P.; Miescher, K. Über die Herstellung mehrkerniger Ketone. *Helv. Chim. Acta* **1950**, *33*, 2215–2228.

(10) Oldenziel, O. H.; Van Leusen, D.; Van Leusen, A. M. Chemistry of sulfonylmethyl isocyanides. 13. A general one-step synthesis of nitriles from ketones using tosylmethyl isocyanide. Introduction of a one-carbon unit. *J. Org. Chem.* **1977**, *42*, 3114–3118.

(11) (a) Ting, C. P.; Xu, G.; Zeng, X.; Maimone, T. J. *J. Am. Chem. Soc.* **2016**, *138*, 14868–14871; (b) van Tamelen, E. E.; Curphey, T. J. The Selective In Vitro Oxidation of the Terminal Double Bonds in Squalene. *Tetrahedron Letters* **1962**, *3*, 121-124.

(12) Fernández-Mateos, A.; Teijón, H. P.; Clemente, R. R.; González, R. R.; González, F. S. Stereoselective Radical Cascade Cyclizations of Unsaturated Epoxynitriles: Quadruple Radical Cyclization Terminated by a 4-exo Process onto Nitrile. *Synlett* **2007**, *17*, 2718–2722.

(13) (a) Xing, X.; Demuth, M. Application of Photoinduced Biomimetic Cascade Cyclizations of Terpenoid Polyalkenes for the Synthesis of (6)-Stypoldione. *Eur. J. Org. Chem.* **2001**, 537–544; (b) Falck, J. R.; Chandrasekhar, S.; Manna, S.; Chiu, C. C. S.; Mioskowski, C.; Wetzel, I. Total synthesis of the spiro-o-benzoquinonefuran (-)-stypoldione. *J. Am. Chem. Soc.,* **1993**, *115*, 11606–11607; (c) Dethe, D. H.; Murhade, G. M.; Dherange, B. D.; Sau, S. K. Enantiospecific Syntheses of Hongoquercins A and B and Chromazonarol. *Eur. J. Org. Chem.* **2017**, 1143–1150; (d) Dhiman, S.; Ramasastry, S. S. V. One-Pot Relay Gold(I) and Brønsted Acid Catalysis: Cyclopenta[b]annulation of Indoles via Hydroamination/Nazarov-Type Cyclization Cascade of Enynols. *Org. Lett.,* **2015,** *17*, 5116–5119; (e) Jung, M. E.; Duclos, B. A. Synthetic approach to analogues of betulinic acid. *Tetrahedron* **2006**, *62*, 9321–9334; (f) Hagiwara, H.; Uda, H. Optically pure (4aS)-(+)- or (4aR)-(-)-1,4a-dimethyl-4,4a,7,8-tetrahydronaphthalene-2,5(3H,6H)-dione and its use in the synthesis of an inhibitor of steroid biosynthesis. *J. Org. Chem.* **1988**, *53*, 2308–2311.

(14) (a) Taguchi, H.; Tanaka, S.; Yamamoto, H.; Nozaki, H. A new synthesis of α,β-unsaturated aldehydes including (e)2-methyl-2-alkenal. *Tetrahedron Lett.* **1973**, *14*, 2465–2468; (b) Dethe, D. H.; Sau, S. K.; Mahapatra, S. Biomimetic Enantioselective Total Synthesis of (−)-Mycoleptodiscin A. *Org. Lett.* **2016**, *18*, 6392–6395.

(15) van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. A. Cyclization Studies with (±)-10,11-Oxidofarnesyl Acetate, Methyl Farnesate, and Methyl (±)-10,11-Oxidofarnesate. *Bioorganic Chemistry* **1982**, *11*, 133-170.

(16) Bürki, C.; Whyte, A.; Arndt, S.; Hashmi, A. S. K.; Lautens, M. Expanding the Scope of the Gold(I)-Catalyzed Rautenstrauch Rearrangement: Protic Additives. *Org. Lett.,* **2016**, *18*, 5058–5061.

(17) Kabalka, G. W.; Yang, D. T. C.; Baker, J. D. Deoxygenation of α,β-unsaturated aldehydes and ketones via the catecholborane reduction of the corresponding tosylhydrazones. *J. Org. Chem.* **1976**, *41*, 574–575.

(18) (a) Wipf, P.; Smitrovich, J. H. Transmetalation reactions of alkylzirconocenes: copper-catalyzed conjugate addition to enones. *J. Org. Chem.* **1991**, *56*, 6494–6496; (b) Ito, H.; Taguchi, T.; Hanzawa, Yu. Preparation and regio- and diastereoselective reactions of allylic zirconium reagents from allylic ether derivatives. *Tetrahedron Lett.* **1992**, *33*, 1295–1298; (c) Coffinet, M.; Jaroschik, F.; Vasse, J. Zirconocenes vs. Alanes: a Crucial Choice of the Allyl Source for Highly Diastereoselective Allylzincation of Nonracemic Chiral Imines. *Eur. J. Org. Chem*., **2016**, 2319-2327.

(19) Michels, T. D.; Rhee, J. U.; Vanderwal, C. D. Synthesis of δ-Tributylstannyl-α,β,γ,δ-Unsaturated Aldehydes from Pyridines. *Org. Lett.* **2008**, *10*, 4787–4790.

(20) Wang, J.; Boyarskih, V.; Rainier, J.D. Vinyl Diazophosphonates as Precursors to Quaternary Substituted Indolines and Cyclopentenes. *Org. Lett.* **2011,** *13*, 700–702.

(21) Mewshaw, R. E. Vilsmeier reagents: Preparation of β-halo-α,β-unsaturated ketones. *Tetrahedron Letters* **1989**, *30*, 3753-3756.

(22) Domíngez, B.; Iglesias, B.; de Lera, A. R. Tetraenylstannanes in the Synthesis of Retinoic Acid and Its Ring-Modified Analogues. *J. Org. Chem.* **1998**, *63*, 4135–4139.

(23) To the best of our knowledge, the *trans-syn-trans* perhydrobenz[*e*]indene has been accessed by three non-enzymatic chemical strategies prior to our work: (a) as a very minor component of a mixture of products via polyene cyclization, see ref 6; (b) as a component of a 2:1 mixture of tricyclic products formed *via* transannular Diels–Alder reaction of 13-membered macrocycles, see Bérubé, G. Deslongchamps, P. Synthesis and transannular diels-alder reaction of a 13-membered macrocyclic triene having a tetrasubstituted enol ether as a dienophile. *Tetrahedron Letters*

1987*, 28*, 5255-5258; (c) as one component of a 3:2 mixture of 5- and 6-membered rings obtained by cyclopropane ring opening of a substrate obtained through total synthesis, see ref 5.

(24) (a) Schwan, J.; Christmann, M. Enabling strategies for step efficient syntheses. *Chem. Soc. Rev.,* **2018***, 47*, 7985; (b) Gaich, T.; Baran, P. Aiming for the Ideal Synthesis. *J. Org. Chem.,* **2010***, 75*, 4657–4673; (c) Newhouse, T.; Baran, P.; Hoffmann, R. W. The economies of synthesis. *Chem. Soc. Rev.* **2009***, 38*, 3010-3021.

Supplementary Information

The Total Synthesis of Rhabdastrellic Acid A

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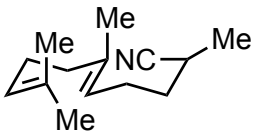
I. General Experimental

All reactions were performed under nitrogen atmosphere in oven or flame-dried glassware unless otherwise indicated. All chemicals were purchased from commercial suppliers and used as received, unless otherwise noted. *N*-bromosuccinimide was recrystallized from water prior to use. Diethyl ether (ACS grade), dichloromethane (ACS grade), tetrahydrofuran (HPLC grade), and toluene (ACS grade) were dried for reactions using the MB-SPS solvent purification system containing activated alumina manufactured by MBRAUN. Reaction temperatures correspond to the external temperature of the reaction vessel. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Macherey-Nagel silica gel plates (SIL G-25 UV254). Plates were visualized by UV and $KMnO_4$. Silicycle SiliaFlash® P60 (SiO2, 40–63 μm particle size, 230–400 mesh) was used for flash column chromatography. ^1H NMR spectra were obtained at 500 MHz and ^{13}C NMR were obtained at 126 MHz. NMR spectra were recorded using a Bruker Advance III 500 MHz spectrometer and were referenced to residual chloroform (7.26 ppm, ^1H) or solvent chloroform-*d* (77.0, ^{13}C). Chemical shifts are reported in parts per million (ppm) and multiplicities are indicated as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in Hertz. Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electron Impact (EI+) spectra were performed at 70 eV using methane as the carrier gas, with time-of-flight (TOF) mass analyzer. Electrospray ionization (ESI+) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100). For some compounds, an Agilent 6230 ESI TOF LC/MS spectrometer was used to obtain the high-resolution mass spectra. Infrared (IR) spectra were measured neat on a Perkin-Elmer Spectrum Two FT-IR ATR spectrometer. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad). Melting points were measured on a Buchi B-540 melting point apparatus and are uncorrected.

II. Total Synthesis of Rhabdastrellic Acid A– Synthesis and Characterization of products:

(*E*)-2,6,10-trimethylundeca-5,9-dienenitrile (21):



Geranylacetone (**9**) (52.4 g, 269.7 mmol, 1.00 equiv.) was dissolved in a mixture of Et_2O/THF (2.80 L, 13:1 v:v, 0.1 M). TosMIC (68.46 g, 350.6 mmol, 1.30 equiv.) was added in one portion under inert atmosphere and the resulting white suspension was cooled to 0 ºC. Potassium *tert*-butoxide (72.6 g, 647.3 mmol, 2.40 equiv.) was added in one portion as a solid. The mixture turned orange and all solids dissolved within 2 minutes, but precipitated out again after an additional 2 minutes. The resulting suspension was treated with EtOH (31 mL, 539.4 mmol, 2.00 equiv.) and the ice bath was removed. After 4 hours the reaction was quenched with water (500 mL), the organic layer was separated, and the aqueous portion was washed with Et_2O (3 × 300 mL). The combined organic extracts were washed with brine (1000 mL), dried over $MgSO_4$, and concentrated at 20 ºC at 120 mbar. The resulting crude oil was run through a short plug (SiO_2, 60% Et_2O in hexanes), concentrated, and dried *in vacuo*. Clean nitrile **21** was obtained (52.0 g, 250 mmol, 94%) as a colorless oil that was used for the next step without additional purification. A sample of high purity could be obtained by flash column chromatography (SiO_2, 25:1, hexanes/Et_2O) or by vacuum distillation (300 mtorr, 115 °C).

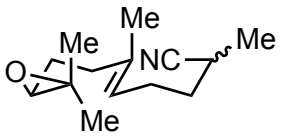
R_f 0.25 (SiO_2, hexanes/EtOAc = 25:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.10 – 5.04 (m, 2H), 2.61 (dtd, J = 7.2, 6.8, 6.2 Hz, 1H), 2.18 (ddd, J = 7.7, 7.7, 7.2 Hz, 2H), 2.08 (ddd, J = 7.0, 7.0, 6.8 Hz, 2H), 2.00 (dd, J = 7.0, 7.0 Hz, 2H), 1.70 (dtd, J = 16.0, 7.2, 6.2 Hz, 1H), 1.68 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 1.55 (dtd, J = 16.0, 7.7, 6.0, 1H), 1.31 (d, J = 6.8 Hz, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 137.4, 131.7, 124.3, 123.3, 122.2, 39.8, 34.3, 26.7, 25.8, 25.5, 24.9, 18.1, 17.8, 16.2

HRMS (EI+, *m/z*) calcd. for $C_{14}H_{23}N$ $[M]^+$ calcd.: 205.1831; found: 205.1840.

IR (ATR, neat, cm^{-1}): 2974 (m), 2923 (s), 2239 (w), 1733 (s),1379 (s)



(*E*)-8-((S)-3,3-dimethyloxiran-2-yl)-2,6-dimethyloct-5-enenitrile (10): To a cooled solution (0 °C) of the nitrile **21** (30.00 g, 146.1 mmol, 1.0 equiv) in THF/H_2O (10.1 L, 2:1 v:v, 0.0145 M) was added NBS (28.6 g, 160.7 mmol, 1.1 equiv) in 12 portions over a period of 2 hours. The reaction mixture was stirred at this temperature for an additional 1 hour and then a solution $Na_2S_2O_3$ (sat. aq. 200 mL) was added. K_2CO_3 (100.9 g, 730.5 mmol, 5.0 equiv) and MeOH (1000 mL) were added and the resulting mixture was warmed to room temperature and stirred overnight (about six hours). The reaction volume was reduced by removing methanol and THF at 20 ºC under reduced pressure. The residue was extracted with hexane/Et_2O (1:1 v:v, 3 x 1000 mL). The combined organic layers were washed with brine (1000 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was passed through a short plug (SiO_2, 3:1 hexane/Et_2O) and concentrated. Clean epoxynitrile **10** was obtained (26.30 g, 118.8 mmol, 82%) as a colorless oil that was could be used in the next step without further purification. A sample of high purity could be obtained by flash column chromatography (SiO_2, 5:1 → 4:1 hexanes/Et_2O) or vacuum distillation (300 mtorr, 130 °C).

R_f 0.18 (SiO_2, hexanes/EtOAc = 10:1)

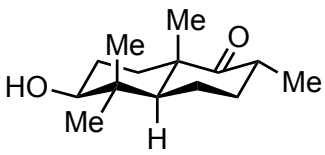
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.13 (t, J = 7.0 Hz, 1H), 2.69 (t, J = 6.2 Hz, 1H), 2.61 (dqd, J = 9.2, 7.1, 5.6 Hz, 1H), 2.22 – 2.07 (m, 4H), 1.73 – 1.53 (m, 4H), 1.66 (s, 3H), 1.31 (d, J = 7.1, 3H), 1.30 (s, 3H), 1.26 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 136.5, 123.2, 122.8, 64.2, 58.4, 36.5, 34.2, 27.5, 25.6, 25.1, 25.0, 18.9, 18.2, 16.2

HRMS (ES+, *m/z*) calcd. for $C_{14}H_{23}NO$ $[M]^+$ calcd.: 222.1858; found: 222.1863

IR (ATR, neat, cm^{-1}): 2925 (s), 2239 (w), 1667 (w), 1455 (s), 1378 (s), 1250 (m), 899 (w), 796 (w)

(2*R*,4a*S*,6*S*,8a*S*)-6-hydroxy-2,5,5,8a-tetramethyloctahydronaphthalen-1(2*H*)-one (22):



In an oven-dried 500 mL round-bottom flask, titanocene dichloride (5.42 g, 21.8 mmol, 3.3 equiv.) and zinc (activated by treatment with HCl) (2.85 g, 43.5 mmol, 6.6 equiv.) were vigorously stirred in degassed THF (200 mL) under nitrogen for 20 minutes. The appearance of a dark-green color indicates the formation of Cp_2TiCl, which was transferred to the solution of epoxynitrile **10** (1.46 g, 6.60 mmol) in degassed THF (500 mL) dropwise over the course of 8 hours via cannula under an atmosphere of nitrogen. Once the addition is done, the reaction was quenched with NaH_2PO_4 (sat. aq. solution 300 mL) and left to stir overnight at ambient temperature. The resulting mixture was filtered, concentrated to remove THF, and partitioned between EtOAc (300 mL) and water (100 mL). The organic phase was separated and the aqueous portion was extracted with EtOAc (2 × 150 mL). The combined organic extracts were washed with brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 12:1 → 10:1 hexanes/EtOAc) to give the title compound (1.03 g, 4.59 mmol, 70%, *d.r.* = 5:1) as a colorless oil that solidifies upon storage.

R_f 0.23 (SiO_2, hexanes/EtOAc = 3:1)

m.p. 79.7 – 80.9 ºC

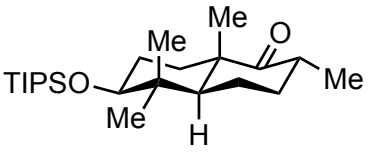
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.20 (dt, J = 10.1, 4.5 Hz, 1H), 2.67 (dp, J = 12.8, 6.4 Hz, 1H),2.12 (ddt, J = 13.2, 6.5, 3.2 Hz, 1H), 1.80 – 1.73 (m, 3H), 1.69 (dd, J = 14.2, 3.7 Hz, 1H), 1.62 – 1.57 (m, 2H), 1.35 (d, J = 5.3 Hz, 1H), 1.21 (ddt, J = 15.1, 8.3, 5.3 Hz, 1H), 1.14 (s, 3H), 1.10 (dd, J = 8.5, 6.9 Hz, 1H), 1.00 (s, 3H), 0.98 (d, J = 6.4 Hz, 3H), 0.90 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 216.2, 78.3, 54.3, 48.5, 40.0, 39.9, 35.7, 31.5, 28.1, 27.2, 21.2, 19.0, 15.9, 15.1

HRMS (EI+, *m/z*) calcd. for $C_{14}H_{24}O_2[M]^+$ calcd.: 224.1776; found: 224.1780.

IR (ATR, neat, cm^{-1}): 3452 (br), 2968 (s), 2933(s), 1702 (s), 1141 (m)

(2*R*,4a*S*,6*S*,8a*S*)-2,5,5,8a-tetramethyl-6-((triisopropylsilyl)oxy)octahydronaphthalen-1(2*H*)-one (8):



To a stirred solution of decalone **22** (6.00 g, 26.7 mmol, 1.0 equiv.) in dry CH_2Cl_2 (110 mL, 0.2 M) at 0 ºC under a nitrogen atmosphere, 2,6-lutidine (7.17 mL, 61.5 mmol, 2.3 equiv.) was added followed by triisopropylsilyl trifluoromethanesulfonate (11.6 mL, 42.8 mmol, 1.6 equiv.). The reaction was warmed up to room temperature and stirred for 7 hours. Upon completion (TLC monitoring), the reaction was quenched with NH_4Cl (sat. aq. 100 mL). The organic phase was separated, and the aqueous layer was washed with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (SiO_2, 1% of Et_2O in hexanes) provided the desired compound as a white solid (9.7 g, 25.0 mmol, 95%)

R_f 0.15 (SiO_2, hexanes/EtOAc = 99:1)

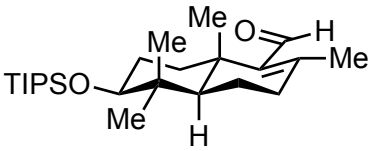
m.p. 98.9 ºC

^{1}H NMR (500 MHz, $CDCl_3$): δ 3.37 – 3.34 (m, 1H), 2.67 (dp, J = 12.8, 6.4 Hz, 1H), 2.10 (ddt, J = 13.0, 6.4, 3.3 Hz, 1H), 1.79 – 1.70 (m, 3H), 1.65 – 1.61 (m, 2H), 1.23 – 1.15 (m, 1H), 1.14 (s, 3H), 1.10 – 1.07 (m, 1H), 1.06 (s, 21H), 0.99 (s, 3H), 0.97 (d, J = 6.4 Hz, 3H), 0.89 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 216.7, 79.4, 53.7, 48.5, 41.0, 40.0, 35.9, 31.5, 28.5, 27.5, 21.4, 19.0, 18.5, 18.4, 16.3, 15.1, 13.2

HRMS (CI+, *m/z*) calcd. for $C_{23}H_{45}O_2Si$ $[M+H]^+$ calcd.: 381.3189; found: 381.3175.

IR (ATR, neat, cm^{-1}): 2942 (m), 2865 (s), 1699 (s), 1457 (w), 1115 (s), 881 (m), 667 (s)



(4a*R*,6*S*,8a*S*)-2,5,5,8a-tetramethyl-6-((triisopropylsilyl)oxy)-3,4,4a,5,6,7,8,8a-octahydronaphthalene-1-carbaldehyde (11):

In an oven-dried round-bottom flask LDA (85 mL, 0.6 M in THF, 51.1 mmol, 1.8 equiv.) was prepared *in situ* and cooled down to –100 ºC under nitrogen atmosphere. After 20 minutes, a solution of decalone **8** (10.92 g, 28.7 mmol, 1.0 equiv.) in CH_2Cl_2 (28 mL) was added dropwise, over the course of 10 minutes, with careful monitoring of the low temperature in an EtOH/liq. N_2 bath. The mixture was allowed to warm up to –20 ºC over 2 hours and then followed by a gentle reflux at 60 °C for an additional 1 hour. The resulting black solution was cooled down to room temperature, concentrated under reduced pressure, and redissolved in DMPU (50 mL). $LiClO_4$ (3.05 g, 28.7 mmol, 1.0 equiv.) and $CaCO_3$ (2.87 g, 28.7 mmol, 1.0 equiv.) were added sequentially with vigorous stirring, and the suspension was brought up to 140 ºC for 1.5 hour. Finally, the reaction was cooled down to room temperature, carefully quenched with aqueous HCl (1 M, 30 mL), and partitioned between Et_2O (200 mL) and water (100 mL). The organic phase was separated and the aqueous layer was washed with Et_2O (2 × 100 mL). The combined organic fractions were washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (SiO_2, 1% of Et_2O in hexanes) furnished **11** (5.9 g, 15.0 mmol, 52%) and olefin isomer **11′** (3.2 g, 8.0 mmol, 28%, *d.r.* = 4.5 : 1) in 1.9:1 ratio.

R_f 0.30 (SiO_2, hexanes/EtOAc = 25:1)

m.p. 75.7 – 76.8 ºC

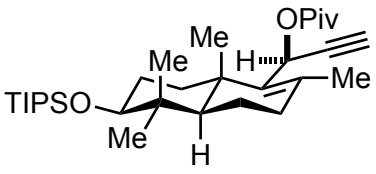
^{1}H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1H), 3.41 (dd, *J* = 11.0, 5.1 Hz, 1H), 2.59 (dt, 13.4, 3.6 Hz, 1H), 2.28 (m, 2H), 2.03 (s, 3H), 1.75 – 1.64 (m, 3H), 1.50 (tdd, *J* = 13.1, 10.1, 7.2 Hz, 1H),1.17 (s, 3H), 1.09 – 1.03 (m, 23H), 1.02 (s, 3H), 0.82 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 192.4, 154.4, 143.5, 79.9, 51.3, 40.2, 37.4, 37.0, 34.5, 28.8, 28.3, 20.3, 19.2, 18.5, 18.4, 18.4, 16.2, 13.2

HRMS (ES+, *m/z*) calcd. for $C_{24}H_{45}O_2Si$ $[M+H]^+$ calcd.: 393.3189; found: 393.3208.

IR (ATR, neat, cm^{-1}): 2939 (m), 2864 (s), 1669 (s), 1612 (w), 1111 (s), 882 (m), 679(s)

(*S*)-1-((4a*R*,6*S*,8a*S*)-2,5,5,8a-tetramethyl-6-((triisopropylsilyl)oxy)-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)prop-2-yn-1-yl pivalate (7):



To a solution of freshly prepared lithium acetylide in THF (153 mL, 0.1 M, 15.4 mmol, 2.0 equiv.) at –78 ºC, a solution of the aldehyde **11** (3.02 g, 7.69 mmol) in THF (30 mL) was added dropwise over the course of 5 min. The reaction mixture was slowly warmed up over 6 hours to 0 ºC. Upon completion (TLC monitoring), pivaloyl chloride (2.2 mL, 17.7 mmol, 2.3 equiv.) was added and the resulting solution was stirred for additional 4 hours at room temperature. The reaction was quenched with NH_4Cl (sat. aq. 50 mL) and partitioned between Et_2O (300 mL) and water (200 mL). Organic layer was separated and aqueous phase was washed with Et_2O (2 × 100 mL). Combined organic fractions were vigorously washed with 2 M NH_4OH (2 × 200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated. Crude material was passed through short pad of SiO_2 (3% of Et_2O in hexanes, 400 mL), which afforded of yellow oil (3.73 g, 7.3 mmol, 95%, *d.r.* > 20:1), which was used for the next step without further purification

R_f 0.68 (SiO_2, hexanes/EtOAc = 25:1)

m.p. 97.4 – 98.9 ºC

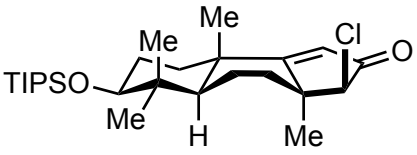
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.01 (d, J = 2.4 Hz, 1H), 3.38 (m, 1H), 2.44 (d, J = 2.4 Hz, 1H), 2.12–2.09 (m, 2H), 1.89 (s, 3H), 1.83 (dt, J = 13.0, 3.6 Hz, 1H), 1.71–1.64 (m, 3H), 1.46 (tdd, J = 13.0, 10.2, 7.7 Hz, 1H), 1.21 (s, 9H), 1.15 (dd, J = 11.2, 5.2 Hz, 1H), 1.06 (m, 22H), 1.03 (s, 3H), 1.00 (s, 3H), 0.79 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 177.3, 136.7, 136.4, 82.5, 79.8, 72.7, 60.1, 51.4, 40.0, 38.9, 38.8, 35.2, 34.4, 28.7, 28.2, 27.2, 21.1, 20.1, 18.8, 18.5, 18.4, 16.2, 13.2

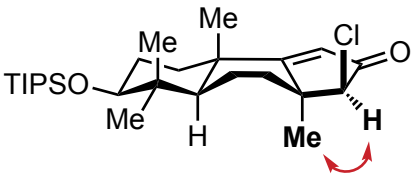
HRMS (EI+, *m/z*) calcd. for $C_{31}H_{54}O_3Si$ $[M]^+$ calcd.: 502.3842; found: 502.3855.

IR (ATR, neat, cm^{-1}): 3311 (w), 2942 (s), 2866 (m), 1736 (s), 1141 (s)

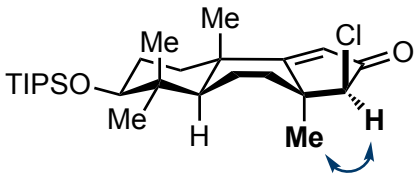
(3*S*,3a*S*,5a*R*,7*S*,9a*S*)-3-chloro-3a,6,6,9a-tetramethyl-7-((triisopropylsilyl)oxy)-3,3a,4,5,5a,6,7,8,9,9a-decahydro-2*H*-cyclopenta[a]naphthalen-2-one (12):



Enyne **7** (500 mg, 0.995 mmol, 1.0 equiv.) was dissolved in dry CH_2Cl_2 (4.0 mL). *N*-chlorosuccinimide (146 mg, 1.09 mmol, 1.1 equiv.) was added and the resulting solution was protected from light. A separate 4 mL vial was charged with [Au(PPh$_3$)Cl] (12 mg, 0.025 mmol, 2.5 mol %) and AgOTf (6.4 mg, 0.025 mmol, 2.5 mol%) inside of a nitrogen-filled glovebox. Dry CH_2Cl_2 (1.0 mL) was added under inert atmosphere and stirred at room temperature with protection from light. After 10 minutes, precipitated AgCl was visible and the suspension was transferred into the reaction mixture. Conversion was monitored by TLC. Once full conversion was achieved (about 1-2 hours), the reaction was quenched with $NH_4OH_{aq.}$ (3 mL, 2.0 M). The organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (3 × 4 mL). Combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Ketone **12** (290 mg, 0.65 mmol, 65%, *d.r.* > 20:1) was isolated by flash chromatography (SiO_2, 2% of Et_2O in hexanes) as a white solid.



NOESY-Correlation



HMBC-Correlation

R$_f$ 0.18 (SiO_2, hexanes/EtOAc = 20:1)

m.p. 83.3 – 84.7 °C

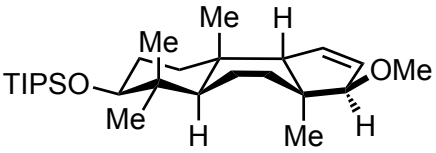
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (s, 1H), 3.89 (s, 1H), 3.42 (dd, *J* = 10.7, 5.0 Hz, 1H), 2.18 (dt, *J* = 13.9, 9.6 Hz, 1H), 1.94 (dt, J = 13.3, 3.5 Hz, 1H), 1.88 (tdd, *J* = 9.3, 8.6, 6.1 Hz, 1H), 1.82 (m, 1H), 1.77 (m, 2H), 1.67 (d, *J* = 7.9 Hz, 1H), 1.64 (m, 1H), 1.45 (td, *J* = 13.2, 4.7 Hz, 1H), 1.40 (s, 3H), 1.18 (s, 3H), 1.08 (s, 21H), 1.01 (s, 3H), 0.94 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 202.8, 197.6, 120.3, 79.9, 67.4, 47.4, 42.7, 40.7, 39.3, 36.5, 30.6, 28.5, 28.1, 25.4, 24.6, 18.5, 18.4, 16.9, 15.9, 13.2

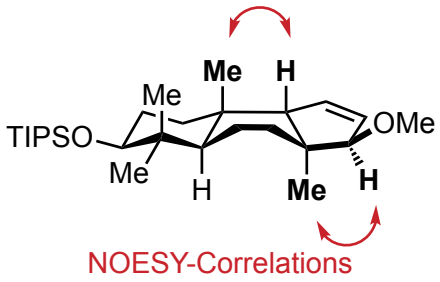
HRMS (ES+, *m/z*) calcd. for $C_{26}H_{46}O_2{}^{35}ClSi$ $[M+H]^+$ calcd.: 453.2950; found: 453.2953.

IR (ATR, neat, cm^{-1}): 2942 (br), 2866 (s), 1720 (s), 1600 (w), 1462 (w), 1113 (m)

triisopropyl(((3*R*,3a*S*,5a*R*,7*S*,9a*S*,9b*S*)-3-methoxy-3a,6,6,9a-tetramethyl-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-3*H*-cyclopenta[a]naphthalen-7-yl)oxy)silane (13):



The α-Chloroketone **12** (20 mg, 0.044 mmol, 1.0 equiv.) was mixed with tosylhydrazone (10 mg, 0.055 mmol, 1.25 equiv.) in pressure-tube and dissolved in MeOH (0.44 mL, 0.1 M). The solution was heated at 60 ºC for 12 h, then cooled down to room temperature. A white precipitate was observed. The suspension was treated with potassium carbonate (6.1 mg, 0.044 mmol, 1.0 equiv.) and MeOH (0.44 mL) and stirred at room temperature for 30 minutes. The solvent was removed *in vacuo* and residual water was removed by azeotrope distillation with benzene (2 × 0.1 mL). The residue was redissolved in dry $CHCl_3$ (0.44 mL, 0.1 M) under nitrogen atmosphere, cooled down to 0 ºC, and treated with catechol borane (7.1 µL, 0.066 mmol, 1.5 equiv.) in a dropwise manner. After 5 min, the yellow suspension was warmed up to room temperature and stirred for additional 1.5 h. Solid CsOAc (21 mg, 0.11 mmol, 2.5 equiv.) was added and mixture was brought to reflux for another 1.5 h. The thick white suspension was cooled down to ambient temperature and filtered through celite. The filtrate was concentrated and subjected to purification by flash chromatography (SiO_2, 1% of Et_2O in hexanes). Allyl ether **13** (11.5 mg, 0.0265 mmol, 60%, *d.r.* > 20:1) was isolated as a colorless oil.



R_f 0.42 (SiO_2, hexanes/EtOAc = 20:1)

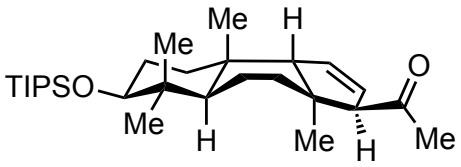
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.14 (dd, J = 6.0, 1.8 Hz, 1H), 6.05 (ddd, J = 6.0, 3.6, 2.4 Hz, 1H), 3.42 (dd, J = 10.6, 5.8 Hz, 1H), 3.36 (d, J = 2.4 Hz, 1H), 3.29 (s, 3H), 2.76 (dd, J = 3.6, 1.8 Hz, 1H), 2.19 (dd, J = 12.9, 8.7 Hz, 1H), 1.76–1.70 (m, 3H), 1.67 (dd, J = 13.5, 9.0 Hz, 1H), 1.48 (dt, J = 13.0, 3.7 Hz, 1H), 1.42 (dt, J = 12.3, 9.0 Hz, 1H), 1.37 – 1.29 (m, 2H), 1.14 (s, 3H), 1.07 (s, 21H), 1.02 (s, 3H), 1.00 (s, 3H), 0.79 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 136.9, 131.5, 91.3, 80.8, 57.7, 57.6, 47.1, 46.5, 40.4, 35.1, 33.7, 29.9, 29.8, 28.5, 27.0, 23.9, 18.8, 18.6, 18.5, 16.6, 13.3

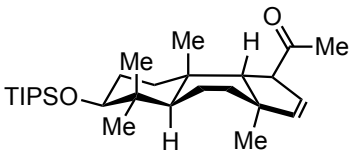
HRMS (ES+, *m/z*) calcd. for $C_{26}H_{47}OSi$ $[M–OCH_3]^+$ calcd.: 403.3396; found: 403.3403.

IR (ATR, neat, cm^{-1}): 2940 (br), 2866 (s), 1463 (w), 1106 (m), 1057 (w

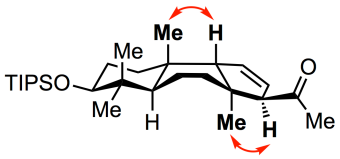
1-((3*R*,3a*S*,5a*R*,7*S*,9a*S*,9b*S*)-3a,6,6,9a-tetramethyl-7-((triisopropylsilyl)oxy)-3a,4,5,5a,6,7,8,9,9a,9b-decahydro-3*H*-cyclopenta[a]naphthalen-3-yl)ethan-1-one (14):



To a solution of **13** (75 mg, 0.17 mmol, 1.0 equiv.) and Cp_2ZrCl_2 (55 mg, 0.19 mmol, 1.10 equiv.) in THF (0.4 mL, 0.3 M) was added dropwise a solution of *n*-BuLi (0.23 mL, 1.6 M, 0.36 mmol, 2.1 equiv.) under a nitrogen atmosphere at 0 ºC. The yellow reaction mixture underwent a color change to brown. The ice bath was removed after 10 minutes and the mixture was stirred at ambient temperature for 24 hours. Acetyl chloride (0.050 mL, 0.69 mmol, 4.0 equiv.) was added to the bright-orange suspension at 24 ºC. Another 4-mL drum vial was charged with CuOAc (4.2 mg, 0.035 mmol, 0.20 equiv.) inside of the glovebox, which was dissolved in THF (0.8 mL) and resulting suspension heated to 55 ºC. Mixture of allylzirconium and acetyl chloride was cannulated to the copper-catalyst and additional portion of THF (0.3 mL) was used for washing. After 3 hours at above temperature reaction was quenched with 1 M HCl (1 mL) and partitioned between EtOAc (7 mL) and water (5 mL). Organic layer was separated and aqueous phase was washed with EtOAc (2 × 5 mL). Combined organic fractions were washed with brine (10 mL), dried over $MgSO_4$, filtered and concentrated. Material was purified via flash chromatography (1% EtOAc in hexanes) to give skipped enone **14** (38 mg, 0.085 mmol, 50%) and its constitutional isomer **14′** (9 mg, 0.020 mmol, 12%) as crystalline solids in a ratio of 4:1.



14′



NOESY-Correlation

R_f 0.48 (SiO_2, hexanes/EtOAc = 40:1)

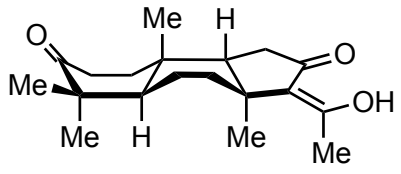
^{1}H NMR (500 MHz, $CDCl_3$): δ 6.11 (d, J = 5.7 Hz, 1H), 5.76 (dt, J = 6.1, 3.2 Hz, 1H), 3.42 (dd, J = 9.7, 6.8 Hz, 1H), 3.06 (d, J = 2.7 Hz, 1H), 2.77 (d, J = 3.6 Hz, 1H), 2.11 (s, 3H), 1.83 (dd, J = 13.4, 8.9 Hz, 1H), 1.77–1.71 (m, 2H), 1.68 (m, 1H), 1.64 (dd, J = 13.1, 8.9 Hz, 1H), 1.56–1.50 (m, 2H), 1.44 – 1.35 (m, 2H), 1.32 (s, 3H), 1.08 (s, 21H), 1.03 (s, 3H), 0.98 (s, 3H), 0.78 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 209.5, 134.6, 130.6, 80.7, 70.3, 58.7, 49.4, 45.7, 40.4, 35.6, 33.6, 32.1, 31.1, 30.3, 29.9, 29.8, 24.1, 18.8, 18.6, 18.5, 16.6, 13.2

HRMS (ES+, *m/z*) calcd. for $C_{28}H_{51}O_2Si$ $[M+H]^+$ calcd.: 447.3658; found: 447.3662.

IR (ATR, neat, cm^{-1}): 2942 (br), 2865 (s), 1708 (m), 1463 (w), 1111 (m)

(3a*S*,5a*R*,9a*R*,9b*S*,*Z*)-3-(1-hydroxyethylidene)-3a,6,6,9a-tetramethyldecahydro-1*H*-cyclopenta[a]naphthalene-2,7-dione (15):



The skipped enone **14** (48 mg, 0.11 mmol, 1.0 equiv.) was dissolved in dry THF (1.1 mL, 0.1 M) under a nitrogen atmosphere and cooled down to –78 ºC. The substrate was treated with BH_3•Me_2S (12 µl, 0.13 mmol, 1.2 equiv.) and slowly warmed up to room temperature. After stirring for 8 hours, the solution was cooled down to 0 ºC, triflic acid (19 µl, 0.21 mmol, 2.0 equiv.) was added, the reaction was allowed to warm to room temperature again. After 3 hours at ambient temperature, the reaction mixture was cooled down to 0 ºC again and treated with NaOH (0.2 mL, 10% in MeOH) followed by H_2O_2 (0.2 mL, $30\%_{aq}$). The resulting solution was aged for an additional 6 hours and then partitioned between EtOAc and water (20 mL, 1:1). The aqueous layer was separated and extracted with EtOAc (2 × 5 mL). The combined organic portions were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated.

The resultant material from the first stage was redissolved in EtOAc (1.1 mL, 0.1 M). IBX (210 mg, 0.74 mmol, 7.0 equiv.) was added and the suspension was refluxed for 3 hours until conversion was observed (monitoring by TLC). Then the solution was cooled down to room temperature, filtered through a short pad of SiO_2, and concentrated. The residue was purified by flash chromatography (SiO_2, 10:1 hexanes/EtOAc) and desired triketone **15** (16 mg, 0.053 mmol, 50%) was isolated as a white crystalline solid.

R_f 0.33 (SiO_2, hexanes/EtOAc = 3:1)

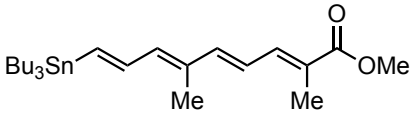
^{1}H NMR (500 MHz, $CDCl_3$) δ 13.66 (s, 1H), 2.72 (ddd, J = 16.1, 12.0, 5.8 Hz, 1H), 2.43 (dd, *J* = 13.1, 2.6 Hz, 1H), 2.37 (ddd, *J* = 16.1, 9.8, 3.1 Hz, 1H), 2.31–2.22 (m, 2H), 2.16 (ddd, *J* = 12.5, 12.3, 3.1 Hz, 1H), 2.04 (dd, *J* = 13.3, 8.7 Hz, 1H), 1.99 (s, 3H), 1.93 (t, *J* = 9.3 Hz, 1H), 1.89 (ddd, *J* = 14.1, 13.4, 8.7 Hz, 1H), 1.63–1.57 (m, 1H), 1.55–1.48 (m, 2H), 1.34 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H), 0.85 (s, 3H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 219.2, 207.3, 172.5, 123.7, 50.7, 47.1, 45.3, 41.3, 36.0, 34.7, 34.6, 33.6, 31.4, 29.3, 26.4, 23.7, 19.5, 19.4, 19.0

HRMS (ES+, *m/z*) calcd. for $C_{19}H_{29}O_3$ $[M+H]^+$ calcd.: 305.2117; found: 305.2118.

IR (ATR, neat, cm^{-1}): 2935 (br), 1704 (s), 1650 (m), 1615 (m), 1382 (w), 1230 (w)

methyl (2*E*,4*E*,6*E*,8*E*)-2,6-dimethyl-9-(tributylstannyl)nona-2,4,6,8-tetraenoate (19):



To a solution of phosphonate **18**[2] (195 mg,0.779 mmol, 1.5 equiv.) in THF (24 mL, 0.033M) under nitrogen was added a 1.0 M THF solution of LHMDS (143mg, 0.857 mmol, 0.860 mL, 1.65 equiv.) dropwise at –10 °C. After ten minutes, the reaction was cooled to –60 °C and HMPA (0.271 mL, 1.56 mmol, 3.0 equiv.) was added dropwise. After ten minutes, the reaction was cooled to –78 °C, and a solution of stannanedienal **17**[1] (200 mg, 0.519 mmol, 0.55mL, 0.95 M) was added dropwise. The reaction was held at –78 °C for 1.5 hours and then warmed up to room temperature. After stirring for 30 minutes at room temperature, the reaction was quenched with saturated aqueous ammonium chloride, and extracted with ether (3 × 15 mL), washed with brine, and dried with $MgSO_4$. Solvent was removed *in vacuo*. The product was unstable on silica, and thus was purified simply by passing through a thin plug of silica gel with 10% EtOAc/hexanes, to remove excess phosphonate. Stannane **19** was obtained as a bright yellow oil (173 mg, 0.519 mmol, 68% yield), which was clean enough to use in cross-coupling without further purifications

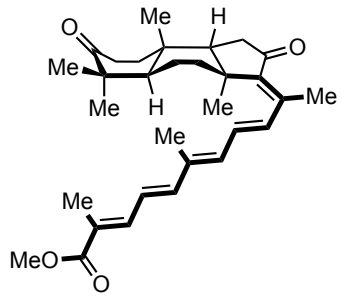
R_f 0.24 (SiO_2, hexanes/EtOAc = 99:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, J = 11.0 Hz, 1H), 6.92 (dd, J = 18.5, 10.6 Hz, 1H), 6.53 (m, 3H), 6.19 (d, J = 10.7 Hz, 1H), 3.76 (s, 3H), 1.99 (s, 3H), 1.97 (s, 3H), 1.52 (p, J = 8.1, 8.1, 7.6, 7.6 Hz, 6H), 1.32 (h, J = 7.3, 7.3, 7.3, 7.3, 7.3 Hz, 6H), 0.93 (m, 6H), 0.90 (t, J = 7.5, 7.5 Hz, 9H)

^{13}C NMR (126 MHz, $CDCl_3$): δ 169.1, 144.6, 142.8, 139.6, 139.1, 137.6, 133.7, 126.0, 123.6, 51.9, 29.3, 27.4, 13.8, 13.0, 12.8, 9.8

HRMS (ES+, *m/z*) calcd. for $C_{24}H_{42}NaO_2Sn$ $[M+H]^+$ calcd.: 505.2104; found: 505.2125.

IR (ATR, neat, cm^{-1}): 2923 (br), 1705 (s), 1618 (w), 1582 (m), 1284 (m), 1227 (s)



Synthesis of rhabdastrellic acid A methyl ester (20):

A mixture of triketone **15** (5.80 mg, 19.1 μmol, 1.0 equiv.), DMF (1.9 μL, 24.8 μmol, 1.30 equiv.), and DCM (100 μL) was cooled to 0 °C, and to it was added dropwise oxalyl bromide (2.15 μL, 22.9 μmol, 1.20 equiv.), with concurrent gas evolution. The reaction was allowed to warm to ambient temperature while stirring for approximately 2 hours, and then poured into ether and a cold solution of $NaHCO_3$. The organic layer was separated, dried over anhydrous sodium sulfate and filtered. Quantitative conversion to a single isomer of vinyl bromide was observed, and this crude vinyl bromide was used in the next stage directly without additional purification due to instability of the compound on silica gel.

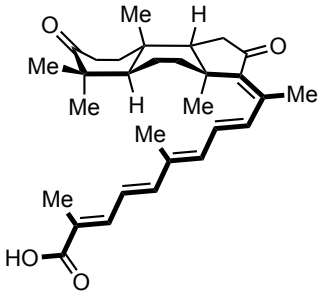
In a nitrogen-filled glovebox, a vial was charged with $Pd_2(dba)_3$ (1.7 mg, 1.9 μmol, 10 mol%), and Ph_3As (1.8 mg, 5.7 μmol, 30 mol%). To it was added 100 μL of NMP (degassed by 5 freeze-pump-thaw cycles) under an atmosphere of argon, and the solution was stirred for 5 minutes at room temperature. A solution of crude vinyl bromide (7.0 mg, 19 μmol, 1.0 equiv.) in 100 μL of NMP was added at room temperature, and stirred for ten minutes. After this time, the vessel was shielded from all possible sources of light, and a solution of stannane **19** (14 mg, 29 μmol, 1.5 equiv.) in 100 μL of NMP was added, and the reaction was heated to 70 °C. After two hours, the reaction was cooled to room temperature, 300 μL of saturated KF solution was added. The reaction was stirred at room temperature for 30 minutes, after which it was extracted three times with diethyl ether. The combined organic extracts were washed with water, washed with saturated KF, dried with $MgSO_4$, and concentrated *in vacuo*. *All workup and purification procedures were performed with rigorous protection from light*, working in a dark room with foil-wrapped, amberized glassware. The methyl ester **20** was purified by preparatory TLC, with two developments in a 2:1 hexanes/EtOAc solvent system, the desired compound eluting as the bottom of four bright yellow bands easily visible to the eye. After scraping the silica, stirring in EtOAc for 40 minutes, filtering, rinsing again with EtOAc, and concentrating in vacuo, methyl ester **20** was obtained as an 8:1 mixture with stelletin E methyl ester as a bright yellow oil (4.0 mg, 45%)

R_f 0.40 (SiO_2, hexanes/EtOAc = 2:1)

^{1}H NMR (500 MHz, C_6D_6): δ 7.59 (dd, J = 10.7, 1.6 Hz, 1H), 6.99 (dd, J = 14.9, 11.5 Hz, 1H), 6.74 (d, J = 14.9 Hz, 1H), 6.54 (m, 2H), 6.33 (d, J = 11.6 Hz, 1H), 3.49 (s, 3H), 2.60 (s, 3H), 2.30 (ddd, J = 15.7, 11.7, 5.8 Hz, 1H), 2.18 (ddd, J = 15.8, 9.7, 3.2 Hz, 1H), 2.04 (m, 2H), 2.01 (s, 3H), 1.91 (m, 2H), 1.72, (s, 3H), 1.55 (td, J = 12.6, 12.6, 3.2 Hz, 1H), 1.38 (dd, J = 15.2, 7.3 Hz, 1H), 1.31 (m, 1H), 1.24, (ddd, J

= 13.8, 8.0, 2.0 HZ, 1H), 1.12 (s, 3H), 1.06 (s, 3H), 0.95 (s, 3H), 0.92 (m, 2H), 0.51 (s, 3H)

^{13}C NMR (126 MHz, C_6D_6): δ 216.2, 205.6, 168.2, 147.3, 143.3, 140.4, 138.6, 135.2, 134.9, 131.6, 128.3, 125.2, 51.5, 47.6, 46.6, 45.6, 45.0, 38.8, 36.7, 34.7, 33.41, 31.3, 29.1, 26.0, 23.3, 19.9, 19.6, 14.6, 13.2, 12.8



Synthesis of rhabdastrellic acid A (1):

A mixture of methyl ester **20** (4.0 mg, 8.36 μmol, 1.0 equiv.), lithium hydroxide monohydrate (1.05 mg, 25.1 μmol, 3.0 equiv.), MeOH (5 μL), water (75 μL), and THF (75 μL) was heated to 50 °C for two hours. Upon cooling to room temperature, the reaction was acidified to pH = 4 with 10% aqueous citric acid, extracted with EtOAc, and concentrated. The residue was purified by preparatory TLC in a 1:1 hexane/EtOAc solvent system to reveal rhabdastrellic acid A (3.7 mg, 95%).

R_f 0.27 (SiO_2, hexanes/EtOAc = 1:1)

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (dt, J = 9.0, 1.6, 1.6 Hz, 1H), 7.05 (dd, J = 14.8, 11.6 Hz, 1H), 6.75 (d, J = 14.9 Hz, 1H), 6.66 (m, 2H), 6.42 (d, J = 11.5 Hz, 1H), 2.73 (ddt, J = 16.5, 10.9, 5.2, 5.2 Hz, 1H), 2.40 (m, 1H), 2.35 (s, 3H), 2.24 (m, 2H), 2.20 (m, 2H), 2.05 (s, 3H), 2.03 (s, 3H), 1.88 (dd, J = 11.9, 10.2 Hz, 1H), 1.63 (dt, J = 14.0, 6.6, 6.6 Hz, 1H), 1.52 (m, 2H), 1.44 (s, 3H), 1.13 (s, 3H), 1.06, (s, 3H), 0.86 (s, 3H)

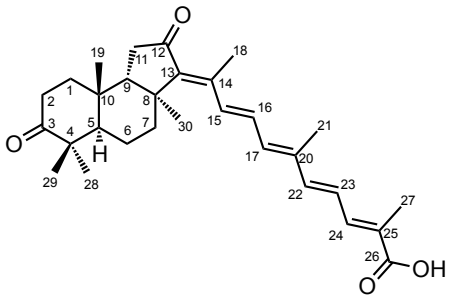
^{13}C NMR (126 MHz, $CDCl_3$): δ 219.3, 207.2, 171.8, 146.9, 144.4, 141.8, 140.6, 138.6, 135.7, 134.8, 132.0, 126.3, 124.8, 48.0, 47.0, 45.6, 45.2, 38.7, 36.9, 34.9, 33.6, 31.5, 29.4, 26.1, 23.6, 19.9, 19.6, 14.7, 13.2, 12.9

HRMS (ES+, *m/z*) calcd. for $C_{30}H_{41}O_4$ $[M+H]^+$ calcd.: 465.3005; found: 465.3012.

Table 1. ^{1}H NMR ($CDCl_3$) spectroscopic data comparison of natural[5] and synthetic rhabdastrellic acid A (**1**).

Natural	Synthetic
δ ^{1}H [ppm, int, mult, J (Hz)] 600 MHz	δ ^{1}H [ppm, int, mult, J (Hz)] 500 MHz
7.42, 1H, d, 9.3	7.40, 1H, dt, 9.0, 1.6, 1.6
7.06, 1H, dd, 14.5, 11.8	7.05, 1H, dd, 14.8, 11.6
6.76, 1H, d, 15.0	6.75, 1H, d, 14.9
6.676 (1H), 6.659 (1H)	6.66, 2H, m
6.44, 1H, d, 11.4	6.42, 1H, d, 11.5
2.76, 1H, m	2.73, 1H, ddt, 16.5, 10.9, 5.2, 5.2
2.44, 1H, m	2.40, 1H, m
2.37, 3H, s	2.35, 3H, s
2.25, 2H, dd, 12.1, 10	2.24, 2H, m
2.21, 2H, m	2.20, 2H, m
2.07, 3H, s	2.05, 3H, s
2.05, 3H, s	2.03, 3H, s
1.90, 1H, dd, 12.1, 10	1.88, 1H, dd, 11.9, 10.2
1.64, 1H, m	1.63, 1H, dt, 14.0, 6.6, 6.6
1.54, 2H, m	1.52, 2H, m
1.46, 3H, s	1.44, 3H, s
1.15, 3H, s	1.13, 3H, s
1.08, 3H, s	1.06, 3H, s
0.88, 3H, s	0.86, 3H, s

Table 2. ^{13}C NMR ($CDCl_3$) spectroscopic data comparison of natural[5] and synthetic rhabdastrellic acid A (**1**).

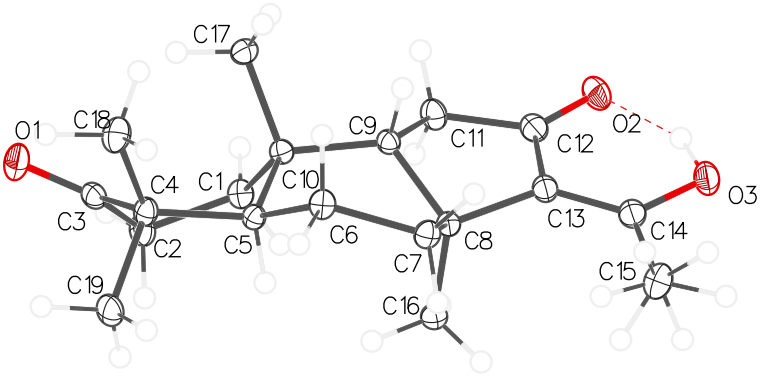


Position	Natural	Synthetic	$\Delta\delta$
	δ ^{13}C (ppm) 150 MHz	δ ^{13}C (ppm) 126 MHz	ppm
1	31.4	31.5	–0.1
2	33.5	33.6	–0.1
3	219.2	219.3	–0.1
4	46.9	47.0	–0.1
5	45.6	45.6	–0.1
6	19.8	19.9	–0.1
7	38.6	38.7	–0.1
8	45.1	45.2	–0.1
9	47.9	48.0	–0.1
10	34.9	34.9	0.0
11	36.7	36.9	–0.2
12	207.2	207.2	0.0
13	146.8	146.9	–0.1
14	141.8	141.8	–0.1
15	134.7	134.8	–0.1
16	131.9	132.0	–0.1
17	135.6	135.7	–0.1
18	23.5	23.6	–0.1
19	14.6	14.7	–0.1
20	138.6	138.6	0.0
21	12.7	12.9	–0.3
22	144.4	144.4	0.0
23	124.8	124.8	0.0
24	140.6	140.6	0.0
25	126.6	126.3	0.3
26	173.8	171.8	2.0

27	13.1	13.2	–0.1
28	29.3	29.4	–0.1
29	19.5	19.6	–0.2
30	26.0	26.1	–0.1

III. Crystallographic Data:

Single crystals of **15** $C_{19}H_{28}O_3$ were crystallized by slow evaporation of dichloromethane from a solution in dichloromethane + isopropanol. A suitable crystal was selected and mounted on a cryoloop (Hampton research) using Paratone oil (Exxon) with (–1 0 –1) face roughly perpendicular to the spindle axis on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 100 K during data collection. Data was acquired using Mo Kα radiation (λ = 0.71073 Å). Using Olex2[3] the structure was solved with the XS[4] structure solution program using Direct Methods and refined with the XL[4] refinement package using Least Squares minimization. Methyl group was disordered due to free rotation with corresponding chemical occupancies of 0.65 and 0.35.



Empirical formula	$C_{19}H_{28}O_3$
Formula weight	304.41
Temperature	99.99 K
Crystal system	Triclinic
Space group	P –1
a, b, c	6.6780(3), 9.4722(4), 13.5770(6) Å
α, β, γ	72.958(2), 83.610(2), 77.293(2) °
V	799.99(6) Å^3
Z	2
ϱ_{calc}	1.264 g cm^{-3}
μ	0.083 mm^{-1}
F(000)	332.0
Crystal size	0.525 × 0.223 × 0.124 mm^3
Radiation	Mo Kα (λ = 0.71073 Å)
2Θ range	4.788° to 56.74°
Index ranges	$-8 \le h \le 8, -12 \le k \le 12, -18 \le l \le 18$
Reflections collected	31524
Independent reflections	3984 [R_{int} = 0.0438, R_{sigma} = 0.0226]
Data / restraints / parameters	3984 / 0 / 209
Goodness-of-fit on F^2	1.035
Final R indexes $I \ge \sigma(I)$	R_1 = 0.0427, wR_2 = 0.1018

Final *R* indexes [all data]	$R_1 = 0.0507$, $wR_2 = 0.1074$
Max diff. peak / hole	0.39 / –0.27 e Å^{-3}

Fractional Atomic Coordinates (×10^4) and Equivalent Isotropic Displacement Parameters (Å^2×10^3)

U_{eq} is defined as 1/3 of the trace of the orthogonalized U_{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}
O1	6454.5(15)	6931.7(10)	4571.7(7)	21.5(2)
O2	7140.1(14)	11643.1(10)	9111.1(7)	20.2(2)
O3	7714.1(14)	9803.3(11)	10912.1(7)	20.5(2)
C1	8478.9(18)	8778.9(13)	6067.2(9)	14.5(2)
C2	8885.3(19)	7769.1(14)	5322.7(9)	16.8(2)
C3	7199.5(18)	6912.0(13)	5353.0(9)	14.8(2)
C4	6598.7(18)	5937.5(13)	6418.4(9)	14.2(2)
C5	7098.1(17)	6612.3(12)	7255.3(9)	11.8(2)
C6	6052.9(18)	6068.2(13)	8323.9(9)	14.6(2)
C7	6985.9(18)	6464.5(13)	9181.9(9)	14.6(2)
C8	7956.8(17)	7882.5(13)	8777.1(9)	12.6(2)
C9	6722.0(17)	8939.6(12)	7844.1(9)	12.1(2)
C10	6762.3(17)	8362.7(12)	6891.5(9)	11.8(2)
C11	7187.6(19)	10505.0(13)	7701.9(9)	16.5(2)
C12	7314.8(18)	10495.7(14)	8809.5(10)	16.4(2)
C13	7671.7(18)	8958.4(14)	9454.8(9)	14.7(2)
C14	7894.5(18)	8667.2(14)	10482.7(10)	16.8(2)
C15	8343(2)	7160.3(16)	11243.8(10)	22.5(3)
C16	10292.8(18)	7455.8(14)	8549.5(9)	15.4(2)
C17	4674.0(18)	9117.8(13)	6408.7(9)	15.2(2)
C18	4367(2)	5744.4(15)	6461.9(10)	20.0(3)
C19	8000(2)	4372.1(14)	6520.6(10)	20.2(3)
H3	7420(30)	10700(20)	10348(14)	31

Anisotropic Displacement Parameters (Å^2×10^3).

The Anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2a^{*2}U_{11} + 2hka^*b^*U_{12}+\ldots]$.

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O1	31.2(5)	20.3(5)	15.7(4)	–5.8(4)	–5.5(4)	–7.5(4)
O2	23.0(5)	17.6(4)	23.5(5)	–11.0(4)	1.0(4)	–5.3(3)
O3	22.3(5)	24.3(5)	18.5(4)	–11.5(4)	–0.1(3)	–4.8(4)
C1	16.0(5)	14.3(5)	14.1(5)	–4.1(4)	0.4(4)	–5.6(4)
C2	17.9(6)	19.7(6)	14.2(5)	–6.2(4)	2.5(4)	–6.5(5)
C3	17.4(5)	12.2(5)	15.3(5)	–5.6(4)	–0.9(4)	–1.1(4)
C4	17.7(5)	12.5(5)	13.8(5)	–4.1(4)	–2.0(4)	–4.3(4)
C5	13.4(5)	10.7(5)	12.1(5)	–3.2(4)	–1.3(4)	–3.1(4)
C6	17.4(5)	13.7(5)	13.2(5)	–2.6(4)	0.3(4)	–6.3(4)
C7	17.2(5)	13.6(5)	12.3(5)	–1.4(4)	–0.9(4)	–4.1(4)
C8	13.2(5)	12.8(5)	12.2(5)	–4.0(4)	–0.9(4)	–2.0(4)
C9	13.3(5)	10.9(5)	12.5(5)	–4.0(4)	–0.7(4)	–2.3(4)
C10	12.6(5)	10.8(5)	12.1(5)	–3.0(4)	–0.4(4)	–2.8(4)
C11	21.8(6)	12.3(5)	17.0(6)	–5.5(4)	–0.4(4)	–4.9(4)
C12	13.9(5)	17.8(6)	19.7(6)	–8.4(5)	0.5(4)	–4.2(4)
C13	13.6(5)	16.8(6)	15.1(5)	–6.6(4)	0.1(4)	–3.5(4)
C14	13.2(5)	21.2(6)	18.4(6)	–8.7(5)	0.3(4)	–4.7(4)
C15	26.4(7)	25.5(7)	16.3(6)	–4.6(5)	–3.4(5)	–6.7(5)
C16	13.0(5)	17.3(6)	16.8(6)	–6.5(4)	–1.2(4)	–2.0(4)
C17	15.0(5)	14.8(5)	15.1(5)	–3.4(4)	–3.0(4)	–1.2(4)
C18	21.2(6)	22.8(6)	20.2(6)	–7.4(5)	–1.3(5)	–11.0(5)
C19	29.5(7)	12.6(6)	19.3(6)	–6.4(5)	–4.2(5)	–1.4(5)

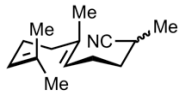
Bond Lengths

Atom	Atom	Length / Å	Atom	Atom	Length / Å
O1	C3	1.2145(15)	C6	C7	1.5514(16)
O2	C12	1.2477(15)	C7	C8	1.5484(16)
O3	C14	1.3444(15)	C8	C9	1.5533(15)
C1	C2	1.5497(16)	C8	C13	1.5320(16)
C1	C10	1.5417(16)	C8	C16	1.5430(16)
C2	C3	1.5167(17)	C9	C10	1.5401(15)
C3	C4	1.5350(16)	C9	C11	1.5343(16)
C4	C5	1.5541(15)	C10	C17	1.5414(16)
C4	C18	1.5339(17)	C11	C12	1.5129(17)
C4	C19	1.5463(17)	C12	C13	1.4460(17)
C5	C6	1.5337(15)	C13	C14	1.3595(17)
C5	C10	1.5570(15)	C14	C15	1.4869(18)

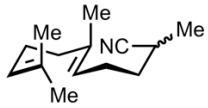
Bond Angles

Atom	Atom	Atom	Angle / °	Atom	Atom	Atom	Angle / °
C10	C1	C2	111.66(9)	C16	C8	C9	115.05(9)
C3	C2	C1	114.50(10)	C10	C9	C8	117.70(9)
O1	C3	C2	121.73(11)	C11	C9	C8	105.56(9)
O1	C3	C4	122.09(11)	C11	C9	C10	119.32(9)
C2	C3	C4	116.05(10)	C1	C10	C5	107.25(9)
C3	C4	C5	108.63(9)	C9	C10	C1	114.61(9)
C3	C4	C19	104.98(10)	C9	C10	C5	108.35(9)
C18	C4	C3	110.77(10)	C9	C10	C17	105.24(9)
C18	C4	C5	114.97(10)	C17	C10	C1	108.24(9)
C18	C4	C19	107.58(10)	C17	C10	C5	113.30(9)
C19	C4	C5	109.44(9)	C12	C11	C9	101.29(9)
C4	C5	C10	112.52(9)	O2	C12	C11	124.86(11)
C6	C5	C4	115.23(9)	O2	C12	C13	125.72(11)
C6	C5	C10	111.16(9)	C13	C12	C11	109.41(10)
C5	C6	C7	112.93(9)	C12	C13	C8	109.35(10)
C8	C7	C6	113.29(9)	C14	C13	C8	130.32(11)
C7	C8	C9	107.04(9)	C14	C13	C12	120.00(11)
C13	C8	C7	117.76(10)	O3	C14	C13	120.41(12)
C13	C8	C9	99.21(9)	O3	C14	C15	112.76(11)
C13	C8	C16	106.25(9)	C13	C14	C15	126.83(11)
C16	C8	C7	111.29(9)				

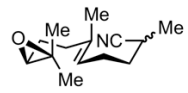
IV. Spectroscopic Data:



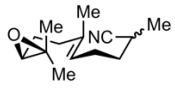
(^{1}H NMR, $CDCl_3$, 500 MHz)



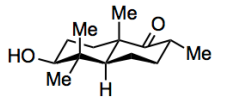
(^{13}C NMR, $CDCl_3$, 126 MHz)



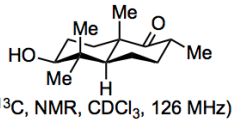
(^{1}H NMR, $CDCl_3$, 500 MHz)



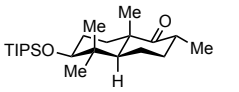
(^{13}C NMR, $CDCl_3$, 126 MHz)



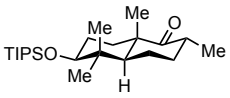
(^{1}H, NMR, $CDCl_3$, 500 MHz)



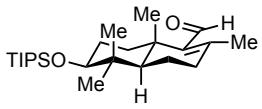
(^{13}C, NMR, $CDCl_3$, 126 MHz)



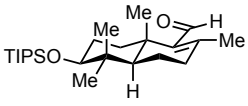
(^{1}H NMR, $CDCl_3$, 500 MHz)



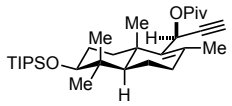
(^{13}C NMR, $CDCl_3$, 126 MHz)



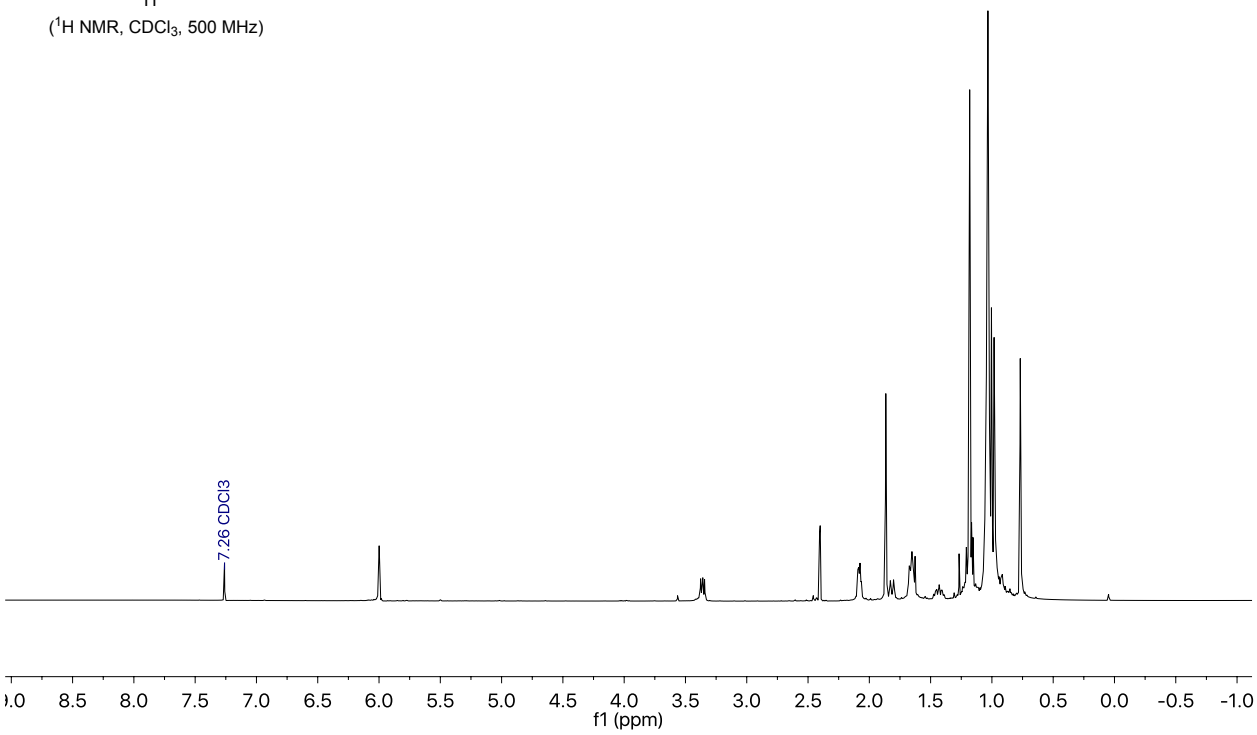
(^{1}H NMR, $CDCl_3$, 500 MHz)

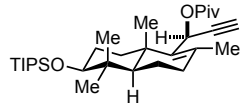


(^{13}C NMR, $CDCl_3$, 126 MHz)

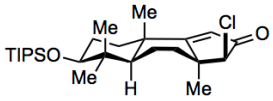


(^{1}H NMR, $CDCl_3$, 500 MHz)

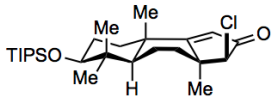




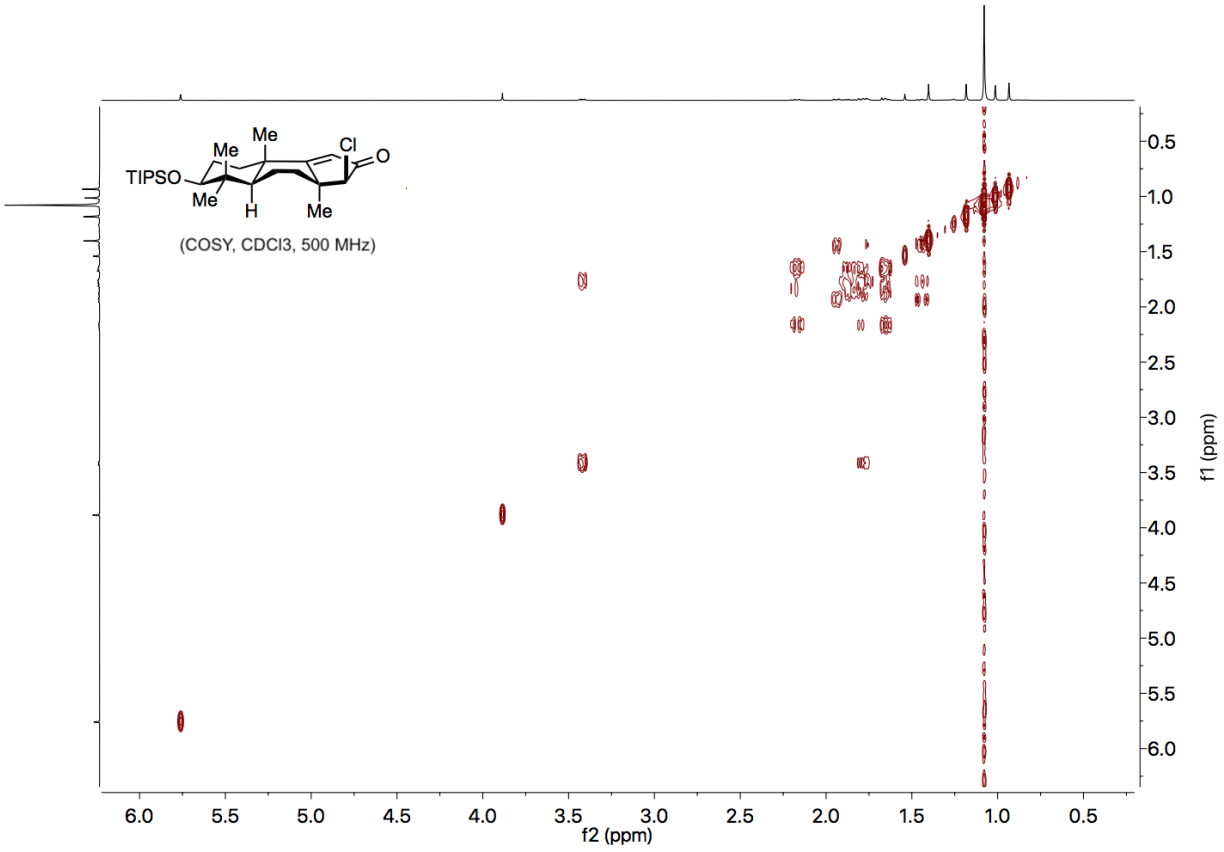
(^{13}C NMR, $CDCl_3$, 126 MHz)

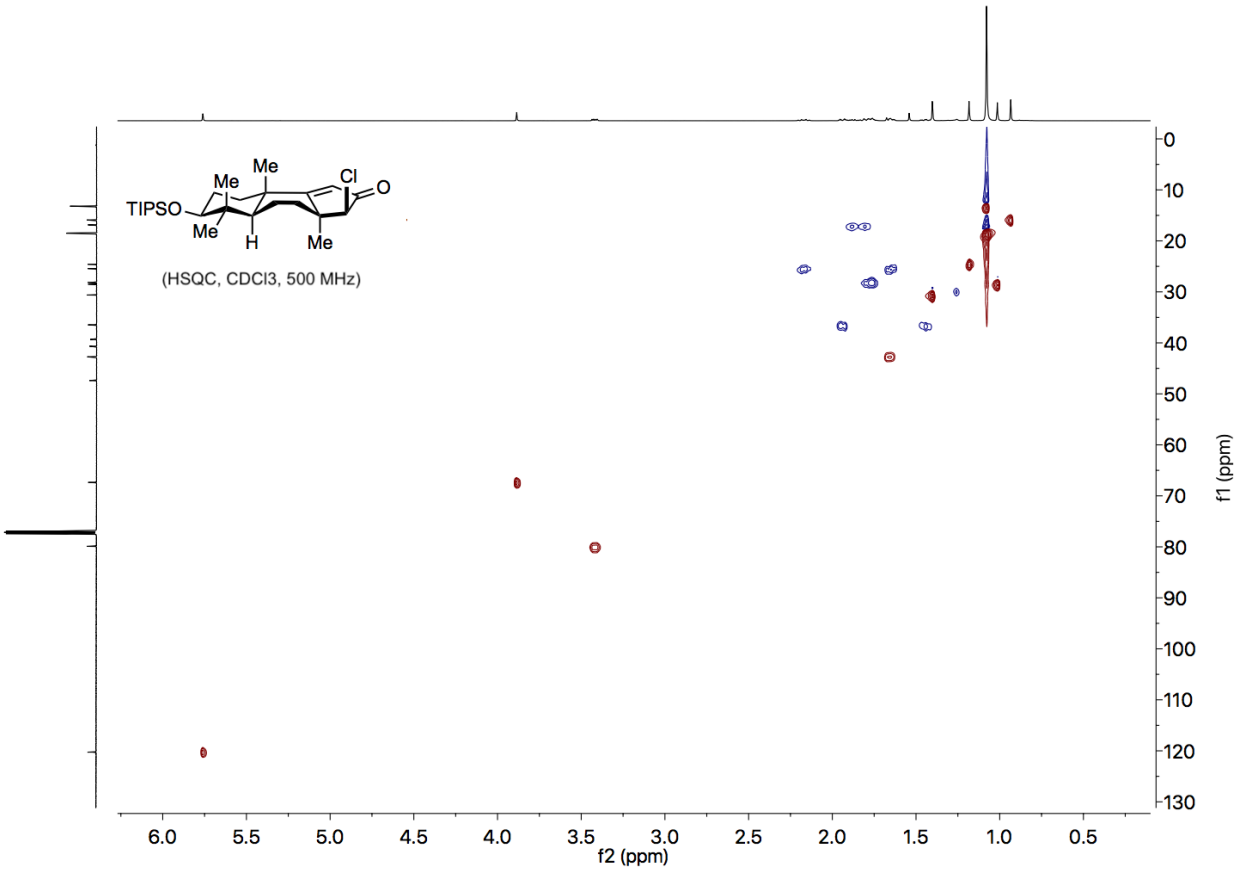


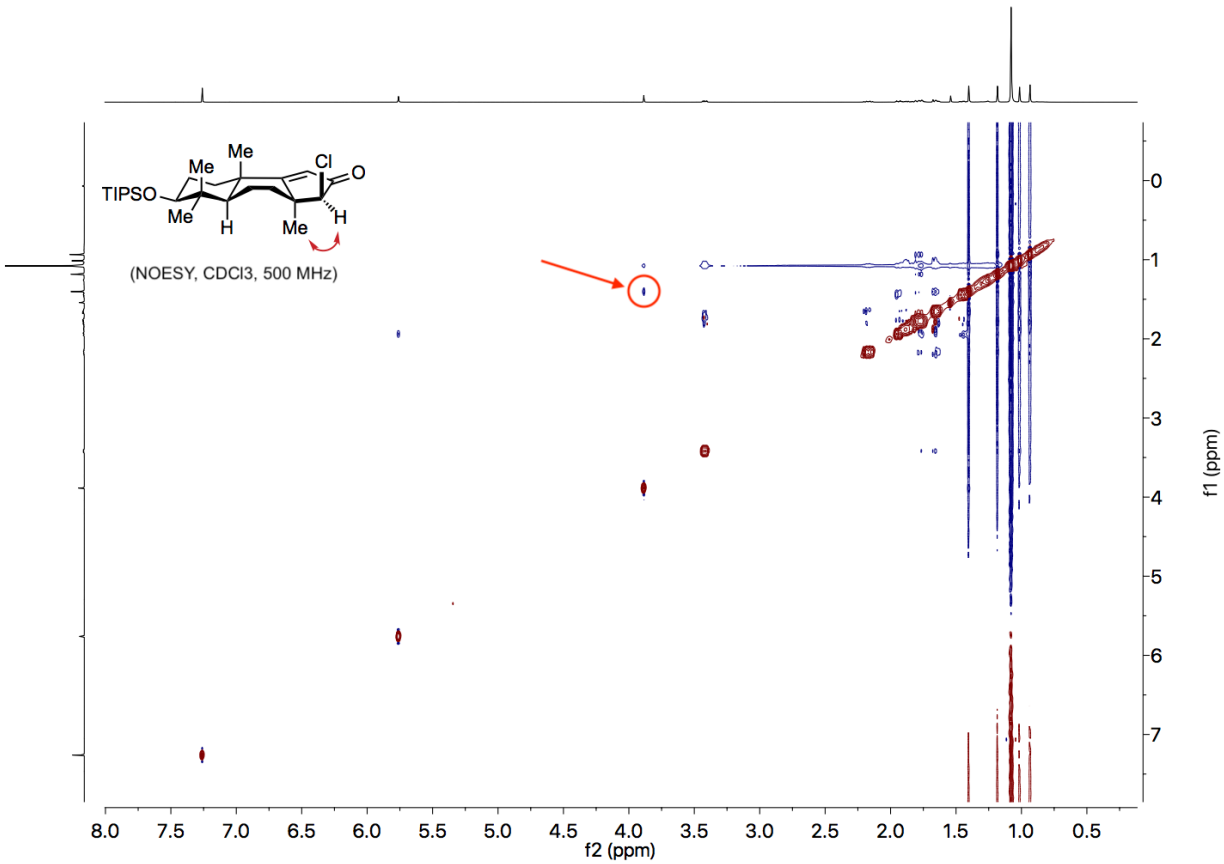
(^{1}H, NMR, $CDCl_3$, 500 MHz)

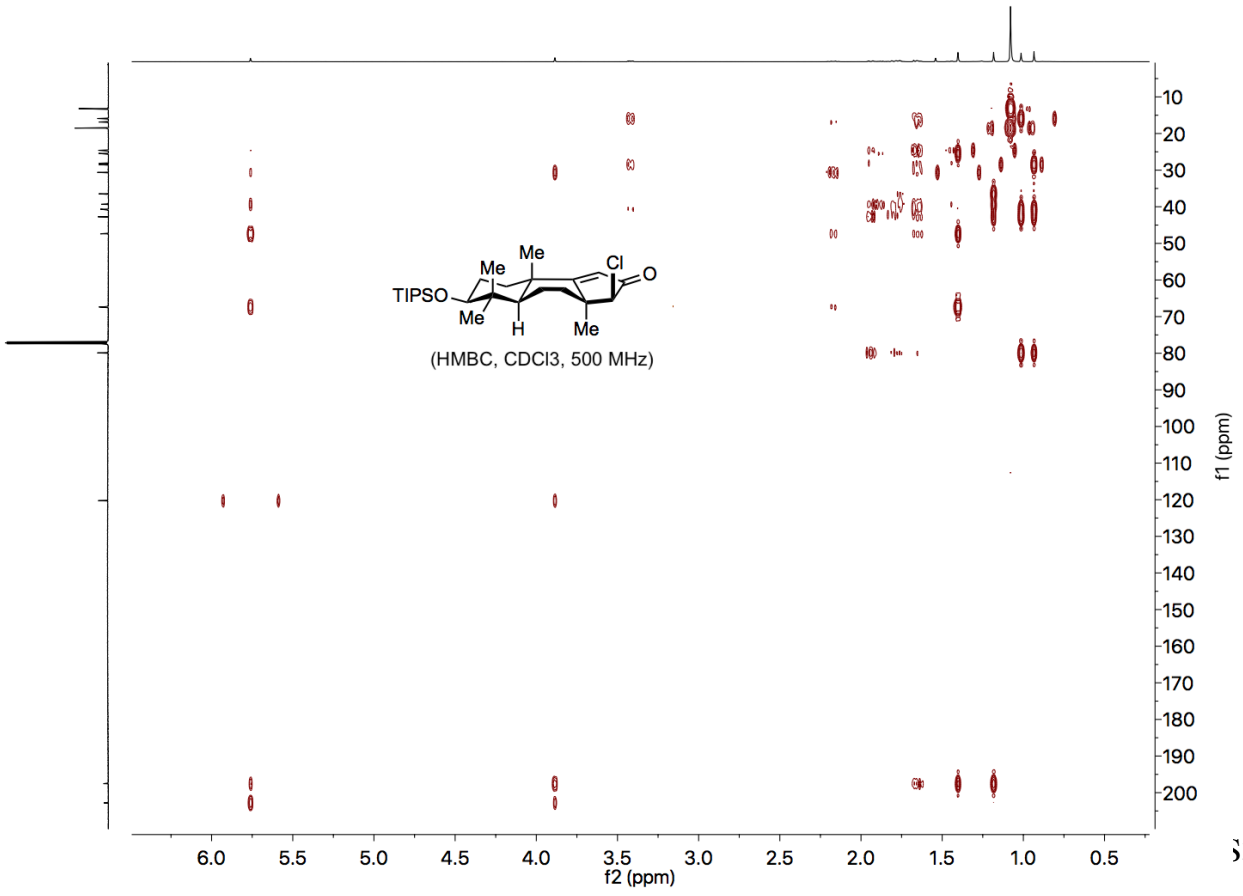


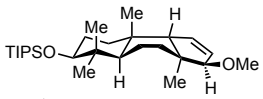
(^{13}C, NMR, $CDCl_3$, 126 MHz)


Me
Me
Cl
O
TIPSO
Me
H
Me
(COSY, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

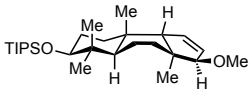

Me
Me
Cl
O
TIPSO
Me
H
Me
(HSQC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)


TIPSO
Me
Me
Me
Me
H
H
Cl
O
(NOESY, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

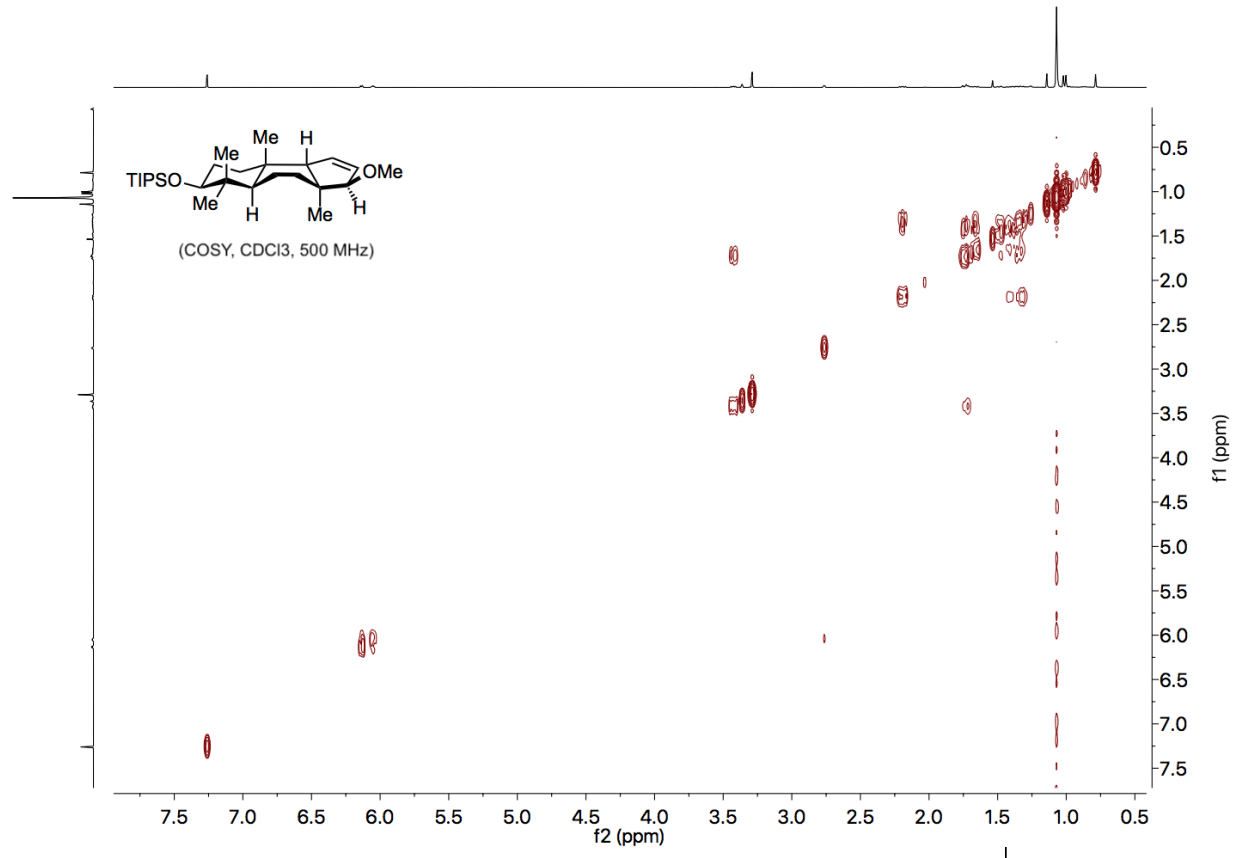

TIPSO
Me
Me
Me
Me
H
Cl
O
(HMBC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

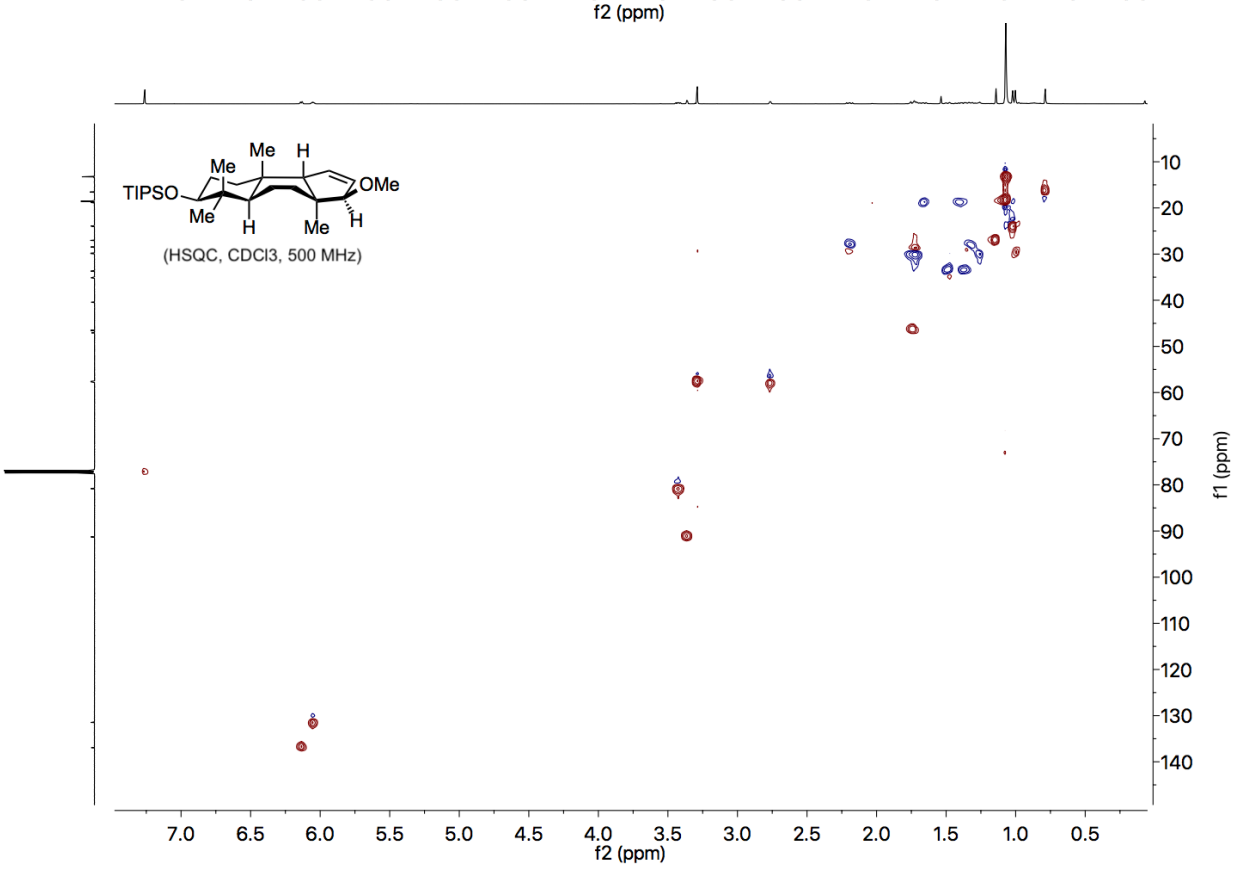


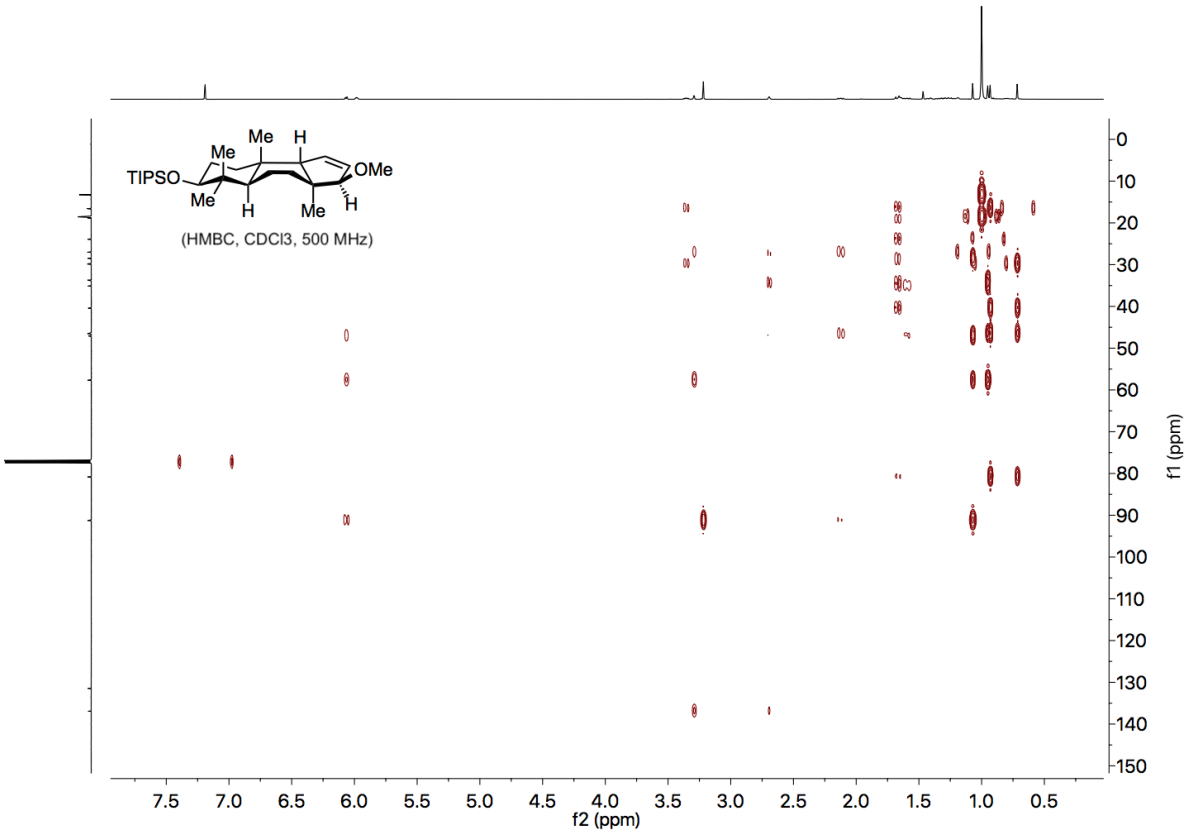
(^{1}H NMR, $CDCl_3$, 500 MHz)

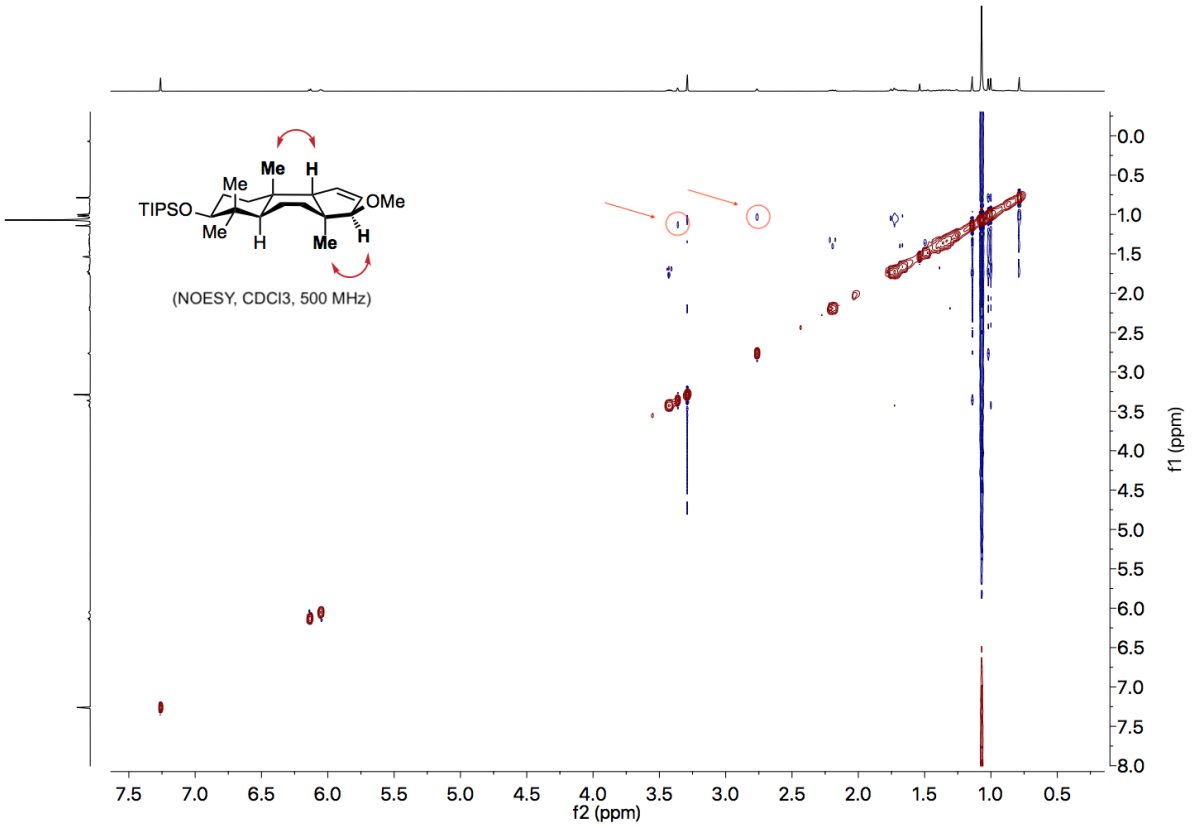


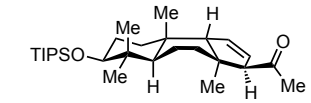
(^{13}C NMR, $CDCl_3$, 126 MHz)


Me
H
Me
TIPSO
OMe
Me
H
Me
H
(COSY, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

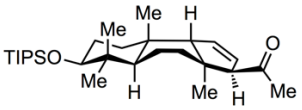

Me
H
Me
TIPSO
OMe
Me
H
Me
H
(HSQC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)


Me
H
Me
TIPSO
OMe
Me
H
Me
H
(HMBC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

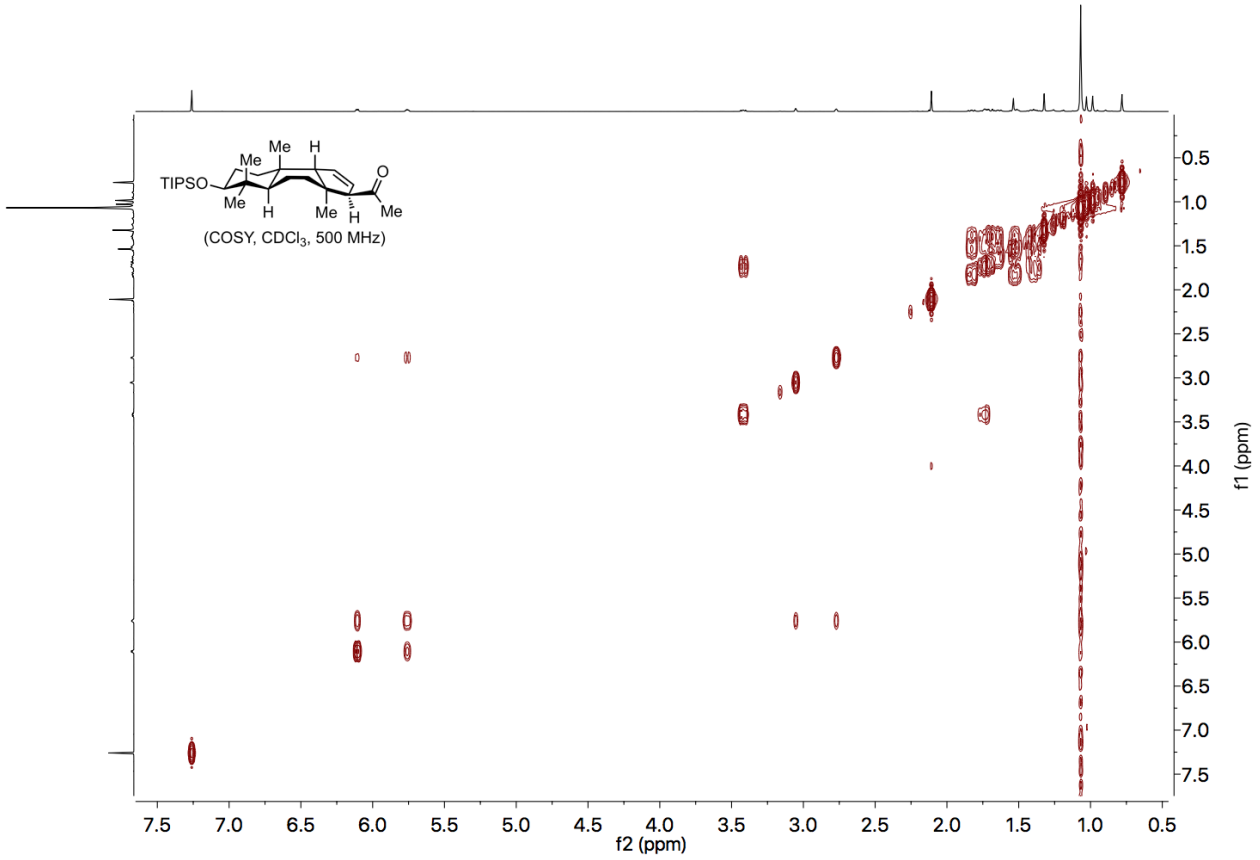

Me
H
Me
TIPSO
OMe
Me
H
Me
H
(NOESY, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

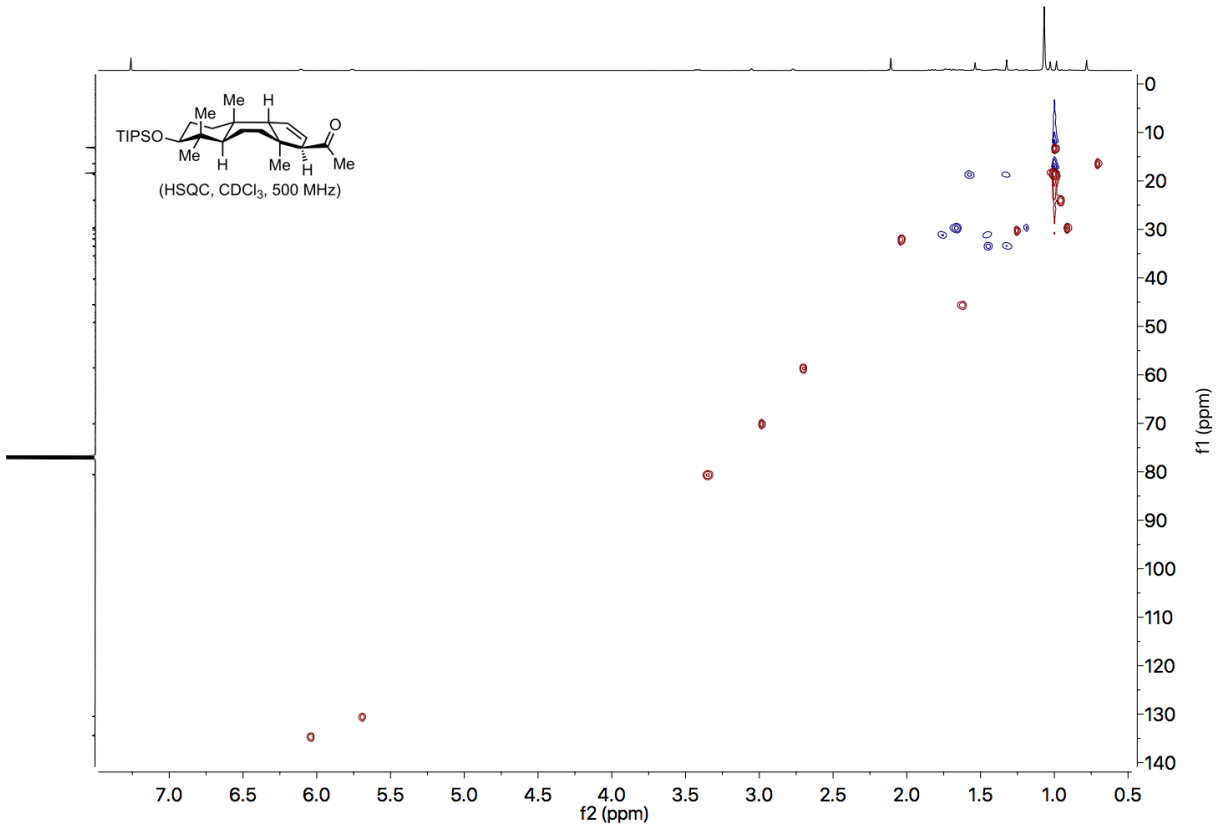


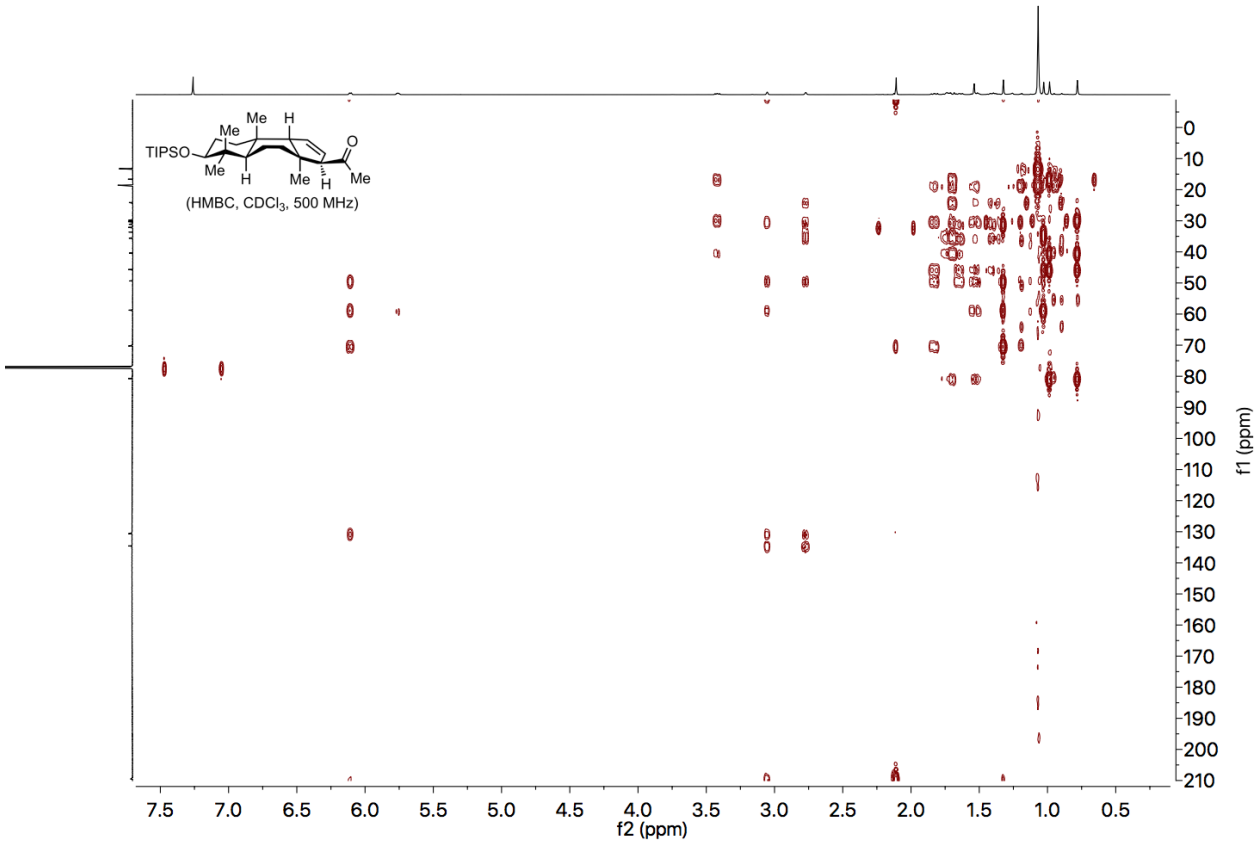
(^{1}H NMR, $CDCl_3$, 500 MHz)

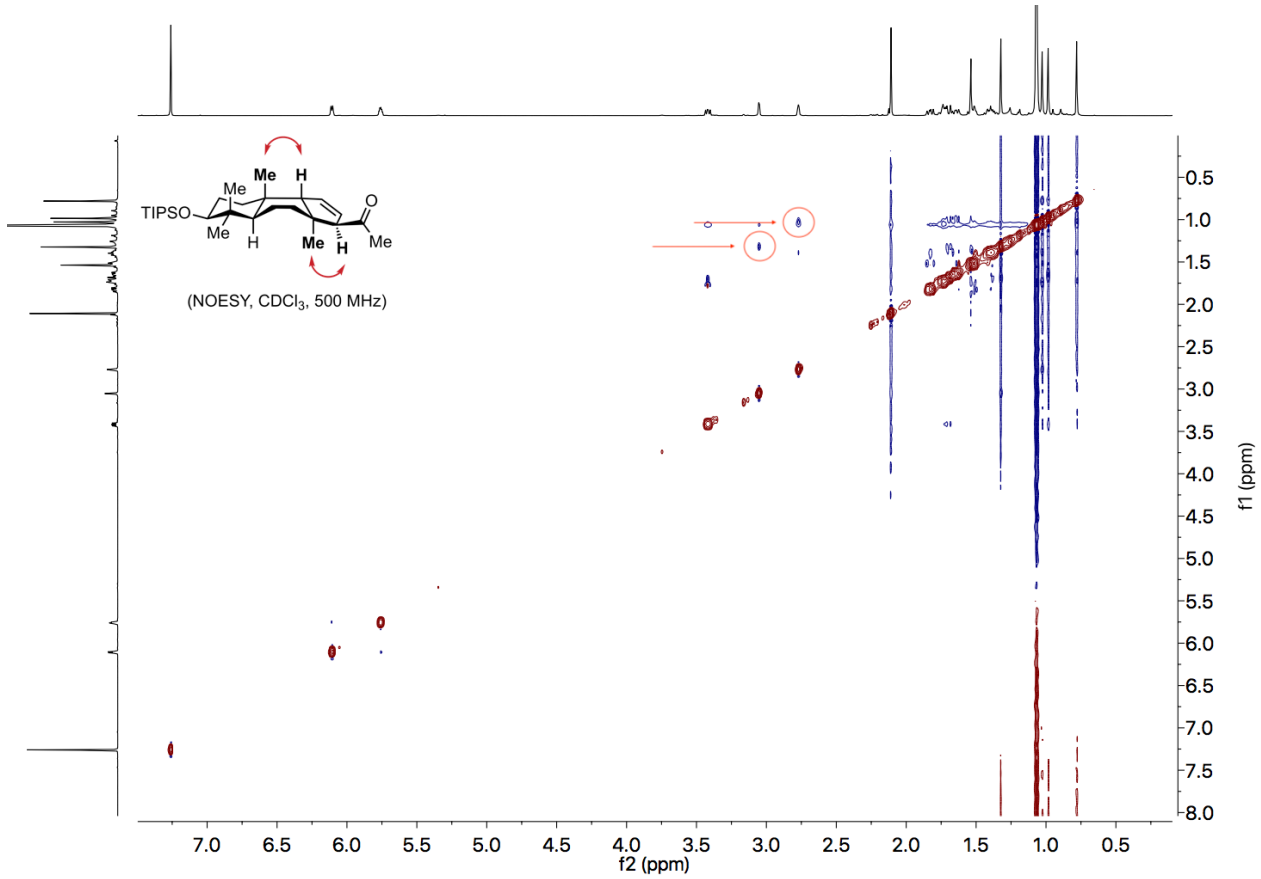


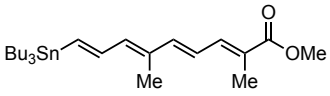
(^{13}C NMR, $CDCl_3$, 126 MHz)


TIPSO
Me
Me
H
Me
H
Me
H
O
Me
(COSY, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

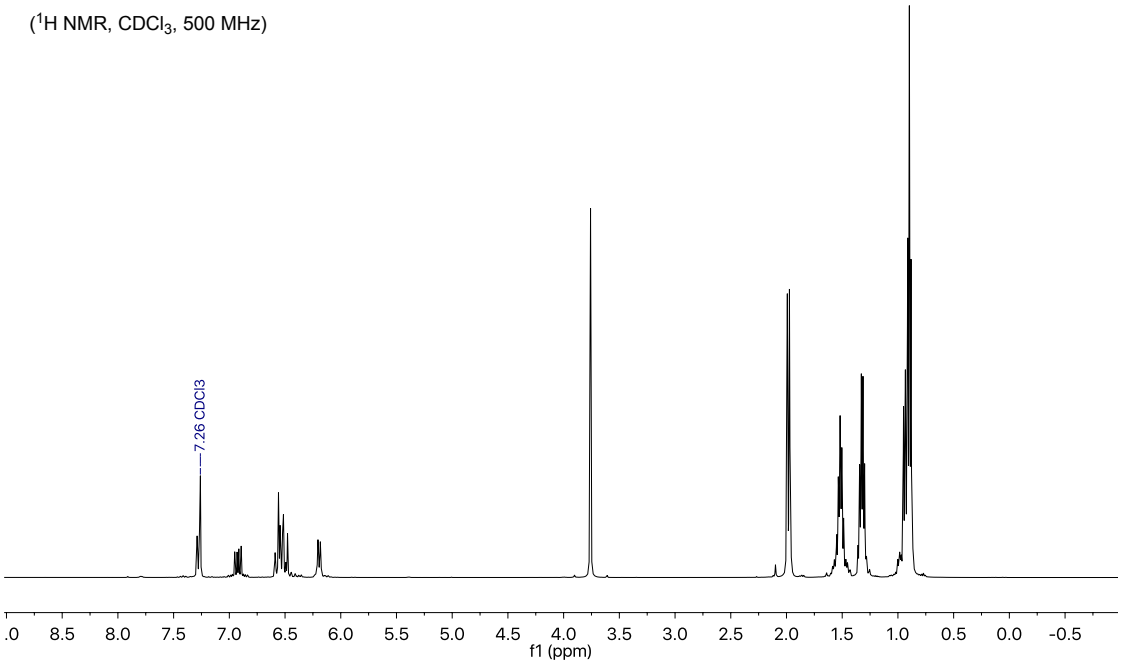

TIPSO
Me
Me
H
Me
H
Me
H
O
Me
(HSQC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

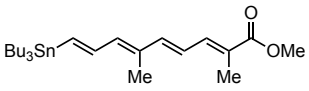

(HMBC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)


(NOESY, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

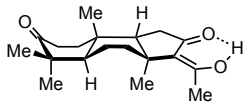


(^{1}H NMR, $CDCl_3$, 500 MHz)

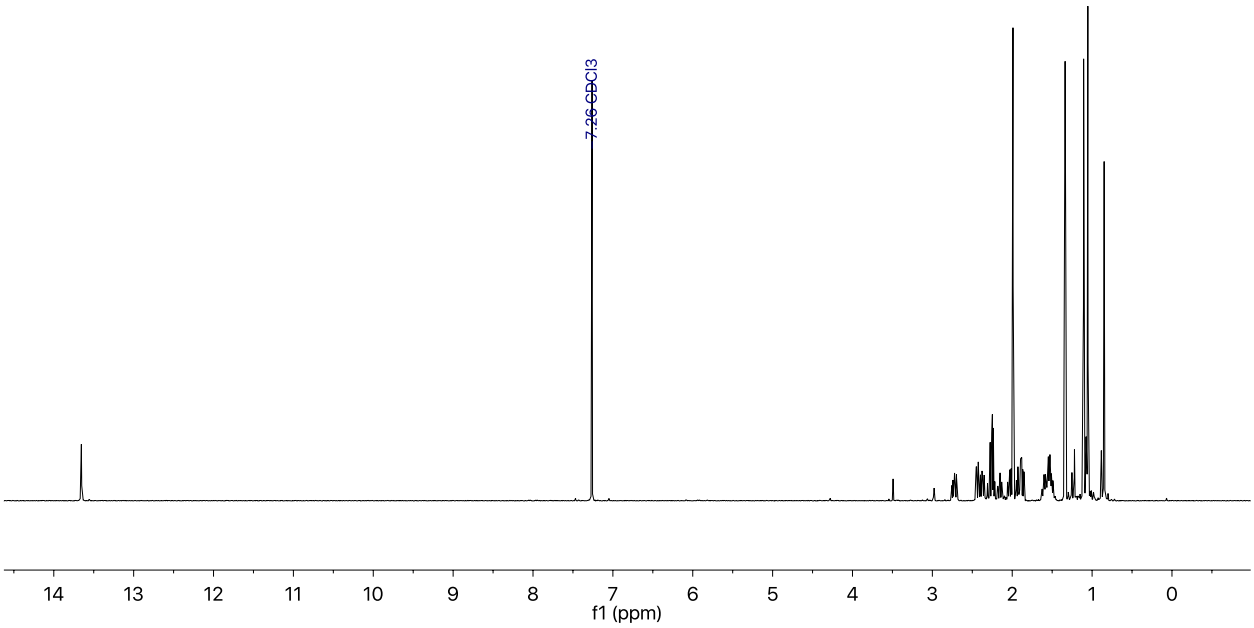


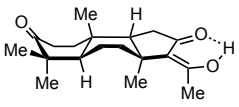


(^{13}C NMR, $CDCl_3$, 126 MHz)

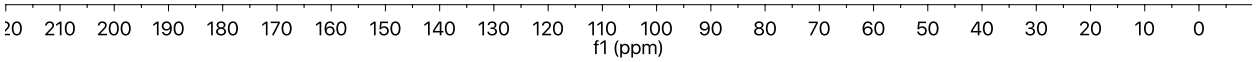


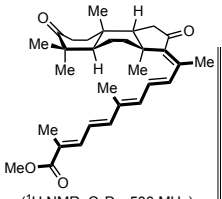
(^{1}H NMR, $CDCl_3$, 500 MHz)



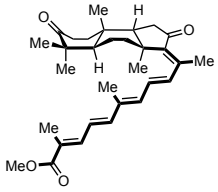


(^{13}C NMR, $CDCl_3$, 126 MHz)

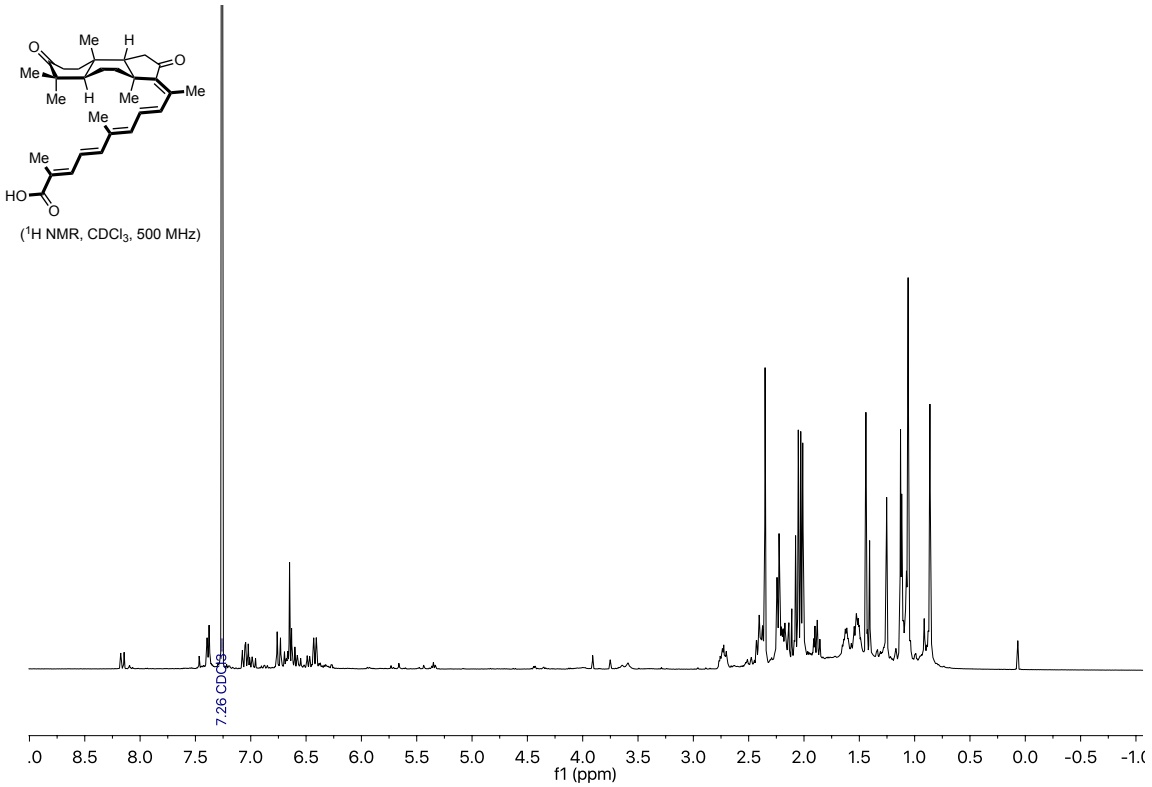




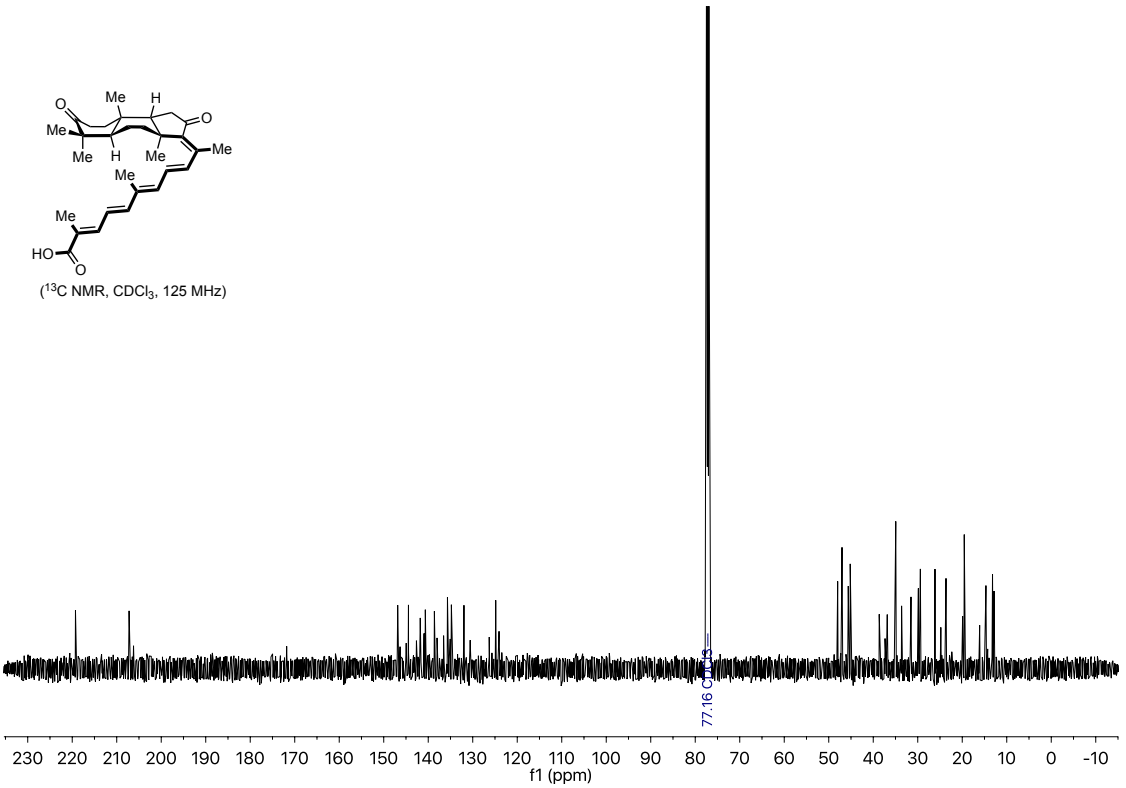
(^{1}H NMR, C_6D_6, 500 MHz)



(^{13}C NMR, C_6D_6, 126 MHz)



(^{1}H NMR, $CDCl_3$, 500 MHz)



(^{13}C NMR, $CDCl_3$, 125 MHz)

V. References:

(1) Michels, T. D.; Rhee, J. U.; Vanderwal, C. D. Synthesis of δ-Tributylstannyl-α,β,γ,δ-Unsaturated Aldehydes from Pyridines. *Org. Lett.* **2008***, 10*, 4787–4790.

(2) Wang, J.; Boyarskih, V.; Rainier, J.D. Vinyl Diazophosphonates as Precursors to Quaternary Substituted Indolines and Cyclopentenes. *Org. Lett.* **2011,** *13*, 700–702.

(3) Dolomanov, O.V., Bourhis, L.J., Gildea, R.J, Howard, J.A.K. & Puschmann, H. (2009), J. Appl. Cryst. 42, 339-341

(4) Sheldrick, G.M. (2008). Acta Cryst. A64, 112-122

(5) Rao, Z.; Deng, S.; Wu, H.; Jiang, S. Rhabdastrellic Acid-A, a Novel Triterpenoid from the Marine Sponge Rhabdastrella globostellata. *J. Nat. Prod.* **1997***, 60*, 1163-1164