16-Step Synthesis of the Isoryanodane Diterpene (+)-Perseanol

Arthur Han, Yujia Tao, Sarah E. Reisman*

Affiliations:

Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, CA 91125, USA.

* To whom correspondence should be addressed: reisman@caltech.edu

Summary:

(+)-Perseanol is an isoryanodane diterpene with potent antifeedant and insecticidal properties isolated from the tropical shrub *Persea indica*. It is structurally related to (+)-ryanodine, a high affinity ligand and modulator of ryanodine receptors (RyRs)—ligand-gated ion channels critical for intracellular Ca^{2+} signaling in vertebrates and invertebrates. Whereas ryanodine modulates RyR-dependent Ca^{2+} release across many organisms, including mammals, preliminary data indicate that ryanodane and isoryanodane congeners that lack the pyrrole-2-carboxylate ester, such as perseanol, may have selective activity in insects. Here we report the first chemical synthesis of (+)-perseanol, which proceeds in 16 steps from commercially available (*R*)-pulegone. The synthesis features a two-step annulation process that rapidly assembles the tetracyclic core from readily accessible cyclopentyl building blocks. This work demonstrates how convergent fragment coupling, when combined with strategic oxidation tactics, can enable the concise synthesis of complex and highly oxidized diterpene natural products.

Main Text:

The ryanodane and isoryanodane natural products are structurally related families of oxidized diterpenes with antifeedant and insecticidal activities against insects of the Hemiptera and Lepidoptera orders. Ryanodine (**1**, Figure 1a), isolated from *Ryania speciosa* Vahl, was the first of these natural products to be characterized, and powdered *R. speciosa* wood was marketed as a botanical insecticide with peak annual production reaching 200 metric tons.[1] The insecticidal properties of **1** result from its modulation of Ca^{2+} release by the ligand-gated calcium ion channel now known as the ryanodine receptor (RyR).[2] In the early 2000s, renewed interest in the insect RyR as a biological target for pest control agents resulted in the discovery and development of the phthalic acid diamide and anthranilic diamide insecticides—which bind at an allosteric site in the transmembrane domain of the insect RyR[3-4]—with

sales of these products exceeding 1 billion USD.[5] In addition, the discovery of **1** led to the purification and characterization of mammalian RyRs, and **1** continues to be used as a probe to assess the functional state of these important mediators of Ca^{2+} signaling.

Decades after the discovery of **1**, Fraga and coworkers isolated the natural product (+)-perseanol (**3**, Figure 1b) and related congeners from the shrub *Persea indica* found in the Canarian Archipelago. Perseanol (**3**) features an isomeric carbon framework to **1** but bears a similar oxidation pattern and likely results from a shared biosynthetic pathway.[6] A key difference between the structures of **3** and **1**, in addition to their carbon skeletons, is that **3** lacks the pyrrole-2-carboxylate ester at C3, a functional group that is required for high affinity binding of **1** to mammalian isoforms of the RyR.[2] Indeed, in preliminary assays, **3**, **4**, and related metabolites[7-15] were found to exhibit potent antifeedant activity for lepidopteran pests with minimal toxicity toward mammalian cell lines (in contrast to **1**) although the mode-of-action of **3** has not been confirmed to be modulation of the insect RyR.[16-17] Synthetic access to **3** could enable the elucidation of its mode-of-action and aid the identification of new approaches to target insect RyRs that have evolved resistance to the phthalic acid diamide and anthranilic diamide pesticides.[18] Here we report the first chemical synthesis of (+)-perseanol (**3**), which proceeds in 16 steps from commercially available (*R*)-pulegone. The concise synthesis is enabled by a convergent fragment coupling approach that rapidly builds the anhydroperseanol tetracycle and uses strategic C–O bond constructions to minimize unnecessary functional group interconversions.

The structure of perseanol presents several synthetic challenges, including the central bridging 7-membered lactol and the two *syn*-diol motifs at the A–B and B–C ring fusions. A critical aspect of our synthetic design was the strategic introduction of the six hydroxyl groups in order to minimize extraneous protecting group and oxidation state manipulations (Figure 1, b). With this in mind, we envisioned initially targeting the synthesis of anhydroperseanol (**5**), in which the C6–C10 diol would be introduced early in the synthetic sequence and the C4–C12 diol would be installed at a late stage (Figure 1, c). Although the conversion of anhydroperseanol to perseanol had not previously been validated experimentally, this disconnection was guided by Deslongchamps'[19-23] synthesis of (+)-ryanodol (**2**),[24] as well as our own synthesis of (+)-ryanodine.[25] Having simplified our target to **5**, we sought to identify a convergent fragment coupling that would rapidly assemble the tetracyclic lactone from two building blocks of similar size and complexity. Ultimately, lactone **6** was recognized as a strategic intermediate that could be accessed from simple cyclopentyl fragments by an annulation process involving two C–C bond forming steps: 1) the 1,2-addition of an organometallic species, such as **9**, to aldehyde **10** to initially join the A and

C rings, and 2) an intramolecular carbopalladation/carbonylation cascade reaction of **8** to close the B and D rings. In the key Pd-catalyzed cascade, it was envisioned that oxidative addition of alkenyl halide **8** to Pd^0 followed by 6-*exo*-trig migratory insertion of the pendant 1,1-disubstituted alkene would give rise to σ-alkylpalladium species **7**, which would be incapable of β-hydride elimination. Subsequent CO insertion of **7** and intramolecular capture by the C11 secondary alcohol would deliver **6**, bearing the tetracyclic ring system of anhydroperseanol.[26-29] In practice, this would require a bifunctional cyclopentene, **9**, which we anticipated accessing via the selective lithiation of the corresponding iodide following precedent established by Vidari and coworkers.[30] The second fragment, aldehyde **10**, would be prepared from commercially available (*R*)-pulegone via the methyl pulegenate.[31] The successful realization of this fragment coupling strategy would provide a modular route to **3** that we anticipated could ultimately give rise to additional designed and natural isoryanodanes.

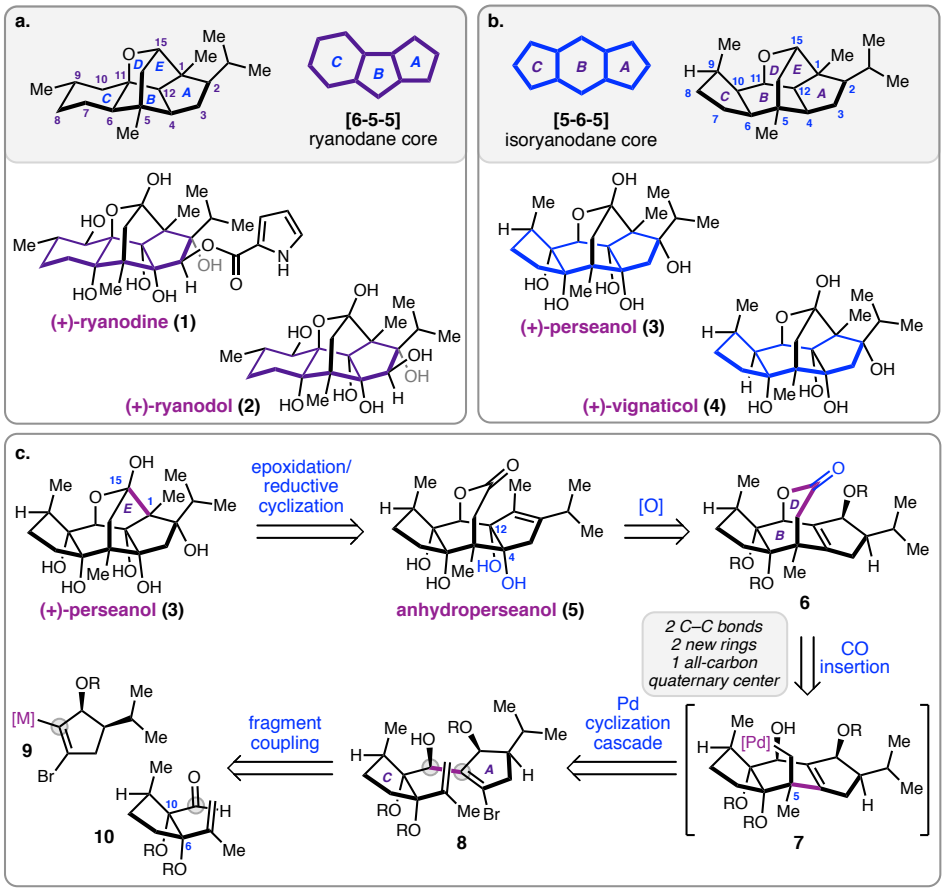


Figure 1. The ryanodane and isoryanodane diterpenes. (**a**) Chemical structure, carbon numbering, and ring system letter assignment for the ryanodane diterpenes. (**b**) Chemical structure, carbon numbering, and ring system letter assignment for the isoryanodane diterpenes. (**c**) Retrosynthetic analysis of the isoryanodane diterpene (+)-perseanol.

Our investigations began with the preparation of C-ring aldehyde **10**. Starting with (*R*)-(+)-pulegone (**11**), a known one-step oxidative ring contraction was performed to give methyl pulegenate (**12**) as an inconsequential mixture of diastereomers (Figure 2).[31-32] Enolization of methyl ester **12** with KHMDS followed by exposure to O_2 then $P(OMe)_3$ resulted in diastereoconvergent α-hydroxylation to furnish α-hydroxyester **13** (9:1 dr). Hydroxyl-directed epoxidation[33] with *m*-CPBA provided epoxide **14** as a single diastereomer, and subsequent treatment of **14** with $Et_2Al(TMP)$[34] induced epoxide isomerization to reveal *syn*-diol **15**, bearing the requisite oxidation at C6 and C10 for elaboration to **3**. Protection of the diol as the benzylidene acetal (**16**) followed by *in situ* DIBAL reduction of the ester provided alcohol **17** as a single diastereomer in 87% yield. Alcohol **17** was oxidized to aldehyde **18** via Stahl's Cu-catalyzed aerobic conditions.[35] This 6-step sequence provided gram scale access to a fully-elaborated C-ring precursor of (+)-perseanol (**3**).

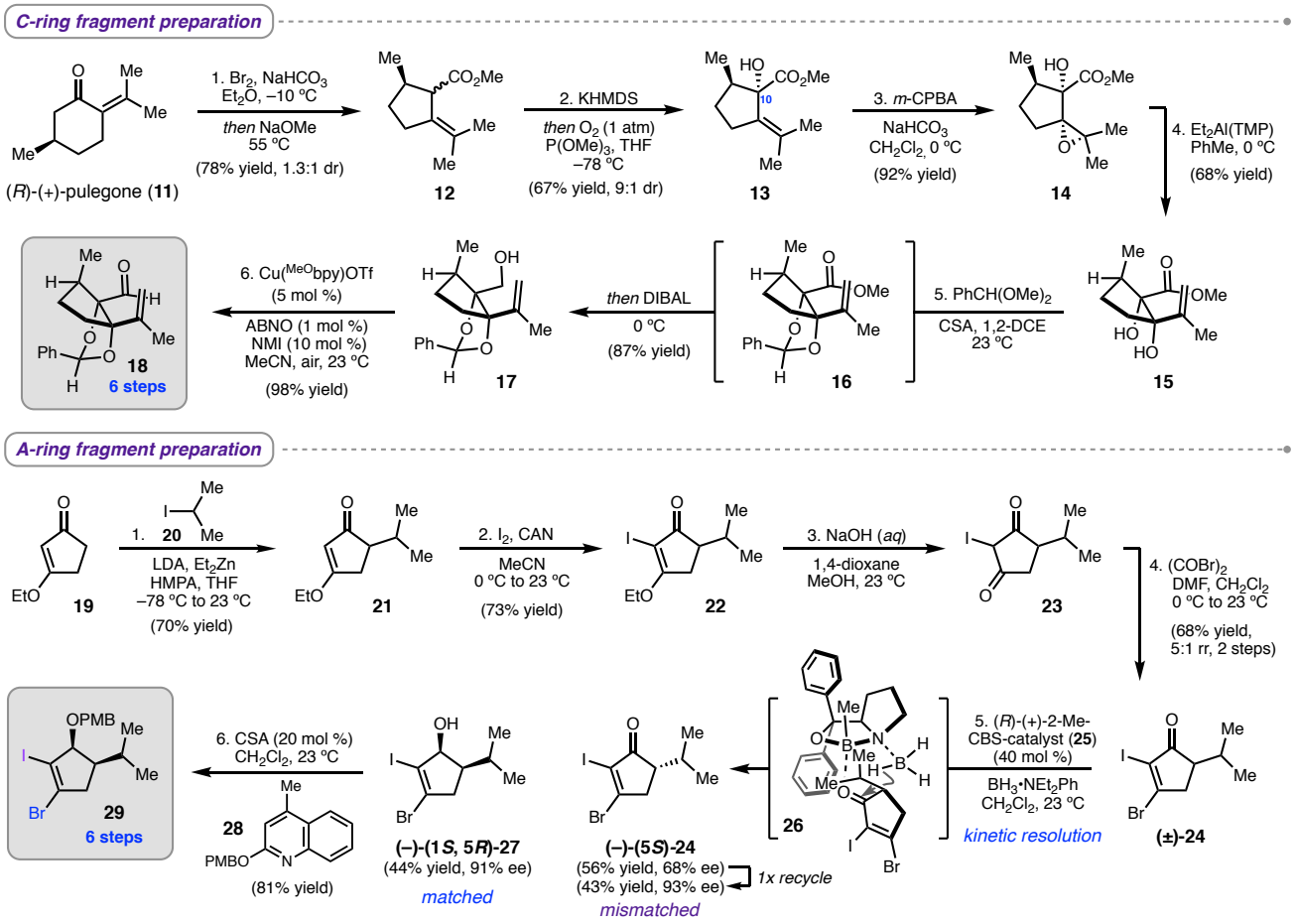


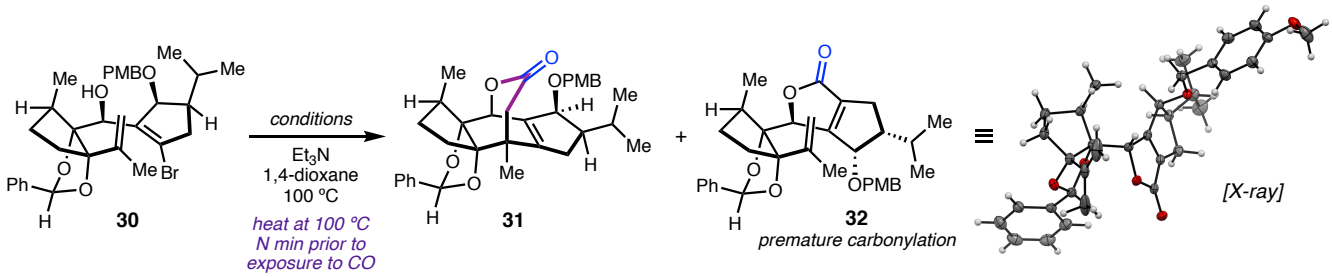
Figure 2. Fragment preparation for the synthesis of (+)-perseanol. Reagents and conditions as follows for C-ring fragment preparation: (1) Br_2 (1.1 equiv), $NaHCO_3$ (0.3 equiv), Et_2O, –10 ºC then NaOMe (2.2 equiv), MeOH, 55 ºC, 78% yield. (2)

KHMDS (2.0 equiv), THF then O_2 (1 atm), $P(OMe)_3$ (2.0 equiv), –78 ºC, 67% yield. (3) *m*-CPBA (2.0 equiv), $NaHCO_3$ (4.0 equiv), CH_2Cl_2, 0 ºC, 92% yield. (4) $Et_2Al(TMP)$ (2.4 equiv), PhMe, 0 ºC, 68% yield. (5) benzaldehyde dimethyl acetal (5.0 equiv), (±)-10-camphorsulfonic acid (1.0 equiv), 1,2-dichloroethane, 23 ºC then DIBAL (9.0 equiv), 0 ºC, 87% yield. (6) $Cu(MeCN)_4OTf$ (5 mol %), 4,4'-dimethoxy-2,3'-bipyridine (5 mol %), ABNO (1 mol %), NMI (10 mol %), air, MeCN, 23 ºC, 98% yield. Reagents and conditions as follows for A-ring fragment preparation: (1) **20** (5.0 equiv), LDA (1.1 equiv), Et_2Zn (1.05 equiv), HMPA (4.5 equiv), THF, –78 ºC to 23 ºC, 70% yield. (2) I_2 (1.05 equiv), ceric ammonium nitrate (1.05 equiv), MeCN, 0 ºC to 23 ºC, 73% yield. (3) 1.0 M NaOH (*aq*) (10 equiv), 1,4-dioxane/MeOH (1:1), 23 ºC. (4) oxalyl bromide (1.5 equiv), DMF (3.0 equiv), CH_2Cl_2, 0 ºC to 23 ºC, 68% yield, 2 steps. (5) **25** (0.4 equiv), BH_3•NEt_2Ph (0.7 equiv), CH_2Cl_2, 23 ºC, 44% yield **(–)-27**, 91% ee. (6) **28** (2.0 equiv), (±)-10-camphorsulfonic acid (0.2 equiv), CH_2Cl_2, 23 ºC, 81% yield.

Preparation of the A-ring fragment commenced with commercially available vinylogous ester **19** (Figure 2). Due to concerns about potential racemization under the conditions required to install the vicinal dihalide, we elected to prepare **24** first as a racemate, and then resolve the enantiomers in a subsequent asymmetric reduction step. To this end, the zinc enolate of 3-ethoxy-2-cyclopentenone (**19**) was alkylated under conditions reported by Overman and coworkers[36] to generate *rac*-**21**. Iodination of the vinylogous ester with I_2 and ammonium cerium(IV) nitrate (CAN) afforded iodide **22**, which was hydrolyzed with aqueous sodium hydroxide. Diketone **23** was converted to *rac*-bromoiodocyclopentenone **24** upon treatment with a mixture of oxalyl bromide and DMF.[37] The reaction proceeds with 5:1 regioselectivity, favoring bromination of the enol tautomer distal to the *i*-propyl group. Corey-Bakshi-Shibata (CBS) reduction of *rac*-**24** using catalyst (*R*)-**25**[38] resulted in a kinetic resolution to deliver alcohol (–)-(1*S*, 5*R*)-**27** in 44% yield and 91% ee ($S = 44$, see Supplemental Information for details). The kinetic resolution is consistent with the stereochemical model developed by Corey (see **26**),[39-41] wherein the *i*-propyl substituent of (*R*)-**24** projects away from the coordinated borane, resulting in reduction of (*R*)-**24** at a faster rate than (*S*)-**24**. Unreacted enone (*S*)-**24** could be recovered in 56% yield and 68% ee; resubjection of (*R*)-**24** to (*R*)-**25** allows it to be further enriched to 95% ee (79% recovery). Protection of alcohol **27** using Dudley's conditions[42-43] provided the C-ring fragment, PMB ether **29**.

With the requisite fragments in hand, a two-step annulation to forge the anhydroperseanol tetracyclic ring system was investigated (Figure 3). First, the A and C ring fragments were joined by addition of aldehyde **18** to the alkenyllithium generated by selective lithium–iodide exchange of **29**, which provided secondary alcohol **30** in 75% yield (3.2:1 dr, major diastereomer drawn). However, preliminary attempts to induce the subsequent carbopalladation/carbonylation cascade under canonical conditions, which involved exposure of the substrate to a Pd catalyst and base under a CO atmosphere, resulted in the clean recovery of alkenyl bromide **30** (Table 1, entry 1). A control experiment demonstrated that bromide

30 can undergo oxidative addition to Pd(P(*o*-Tol)$_3$)$_2$ in the absence of CO, which led to the hypothesis that coordination of CO to Pd was inhibiting the rate of oxidative addition.[44-47] To investigate the feasibility of the carbonylation step, bromide **30** was heated with stoichiometric Pd(P(*o*-Tol)$_3$)$_2$ to induce oxidative addition and alkene insertion, and upon consumption of starting material, CO was introduced. Gratifyingly, the desired tetracyclic lactone **31** was isolated in 52% yield under these stoichiometric conditions (entry 3). An extensive investigation of different Pd sources and ligands did not improve the yield further (entries 4 and 5, see Supplementary Information for further details). The major side product observed under these conditions was direct carbonylation of the bromide of **30** to give butyrolactone **32**. Having validated that the cascade could be effected under stoichiometric conditions, we reasoned that *in situ* generation of CO, to maintain low concentrations of CO in solution,[48-52] might enable the reaction to proceed with catalytic Pd. Ultimately, it was determined that the combination of 1.2 equiv *N*-formylsaccharin (**36**) and KF, in the presence of 50 mol % Pd(PPh$_3$)$_4$ and Et$_3$N provided the tetracyclic lactone **31** in 57% yield, as a single diastereomer at the newly formed quaternary carbon (entry 10). In contrast to the Manabe's original report[51] of Pd-catalyzed carbonylation with *N*-formylsaccharin, bisphosphine-ligated Pd complexes performed poorly (entries 12 and 13). This key transformation forges two C–C bonds, with perfect control over the C5 quaternary center, while forming the central 7-membered lactone of anhydroperseanol.



entry[a]	[M]	mol %	CO source	additive	*N* (min)	30 (%)[b]	31 (%)[b]	32 (%)[b]
1	Pd(P(*o*-Tol)$_3$)$_2$	50	CO (1 atm)	–	0	92	1	5
2	Pd(P(*o*-Tol)$_3$)$_2$	50	CO (1 atm)	–	20	67	11	15
3	Pd(P(*o*-Tol)$_3$)$_2$	120	CO (1 atm)	–	90	0	52	0
4	Pd(P(*o*-Tol)$_3$)$_2$	120	CO (10 atm)	–	90	0	53	0
5	Pd(PPh$_3$)$_4$	120	CO (1 atm)	–	90	23	48	13
6	Pd(PPh$_3$)$_4$	50	**33**	DBU	–	85	0	8
7	Pd(PPh$_3$)$_4$	50	**34**	–	–	90	0	0
8	Pd(PPh$_3$)$_4$	50	**35**	–	–	14	7	4
9	Pd(PPh$_3$)$_4$	50	**36**	–	–	22	31	10
10	Pd(PPh$_3$)$_4$	50	**36**	KF	–	1	57	14
11	Pd(P(*o*-Tol)$_3$)$_2$	50	**36**	KF	–	60	0	0
12	PdCl$_2$(dppf)	50	**36**	KF	–	80	0	0
13	PdCl$_2$(Xantphos)	50	**36**	KF	–	55	1	4

Mo(CO)$_6$ **33** *t*-BuNC **34**

35

36

[a]Reactions performed on 0.01 mmol scale at 100 °C (0.01M).
[b]Yields determined by ^{1}H NMR versus pyrazine as an added internal standard.

Table 1. Evaluation of conditions for a Pd-catalyzed carbopalladation/carbonylation cascade.

With the tetracyclic framework of anhydroperseanol (**5**) in place, our focus transitioned to the final adjustments of the A-ring oxidation pattern (Figure 3). To this end, PMB ether **31** was first subjected to DDQ to reveal C1 secondary alcohol **37**, which was oxidized with DMDO to the corresponding enone. In the presence of excess DMDO, the benzylidene acetal was unexpectedly oxidized[53] to deliver hydroxybenzoate **38** (3:1 rr, major isomer drawn). Treatment of **38** with MeMgCl in the presence of $CeCl_3$•2LiCl[54] effected 1,2-addition to generate diol **39** (55% isolated yield of single isomer, over two steps), an intermediate that now harbors all of the carbons present in the isoryanodane framework. Serendipitously, it was discovered that exposure of allylic alcohol **39** to TFA at 0 °C gives rise to orthobenzoate **41** in excellent yield.[55] This 1,3-allylic transposition presumably proceeded by solvolysis under anchimeric assistance to generate dioxolenium ion **40**, which is followed by intramolecular trapping with the C10 alcohol. Thus, over the course of these four steps, the benzylidene acetal protecting group was transiently repurposed as a directing group to guide the installation of the C4 tertiary alcohol and then reinstated as an orthobenzoate protecting group to mask the resulting triol for the rest of the synthesis.

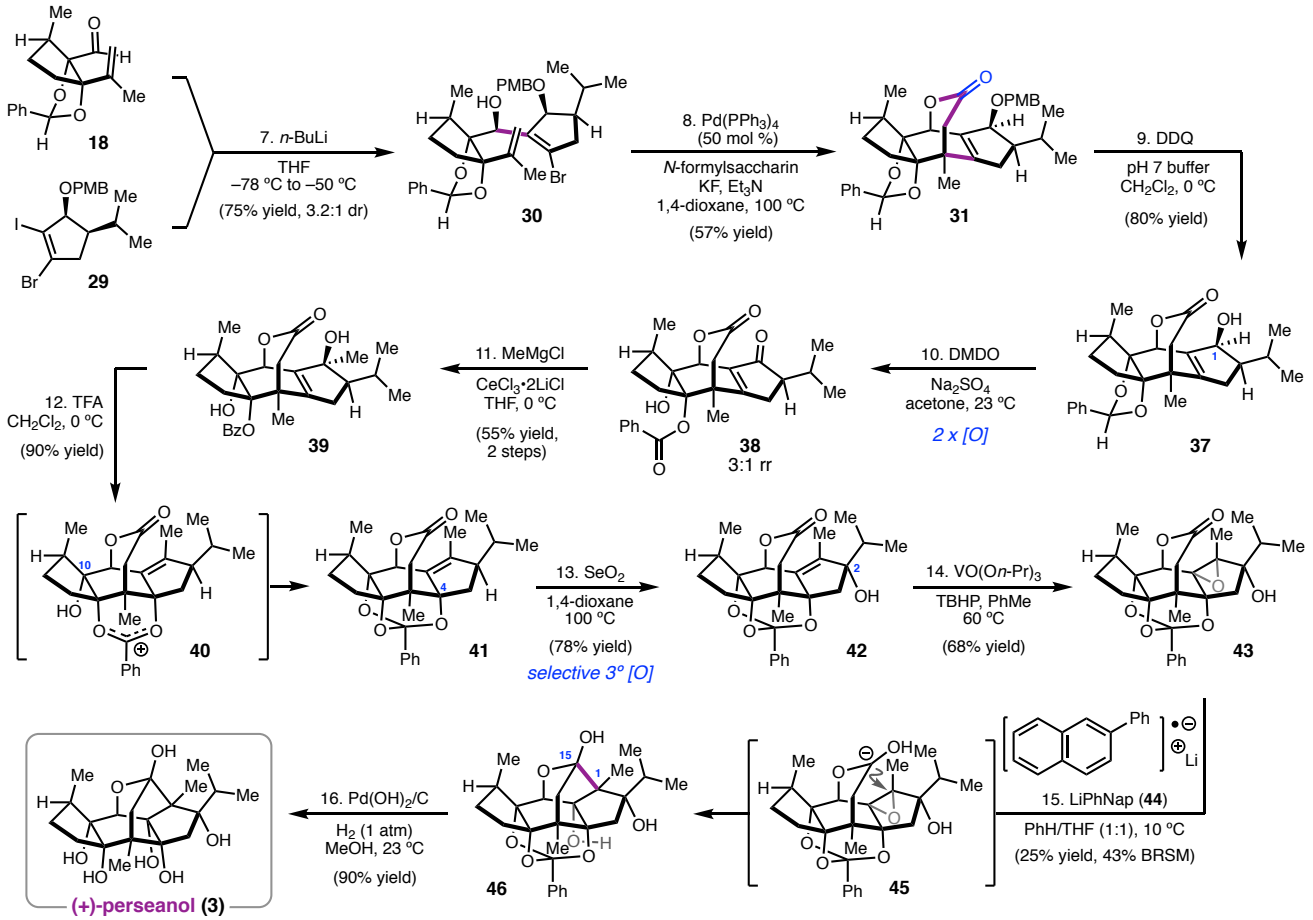


Figure 3. 16-step synthesis of (+)-perseanol. Reagents and conditions as follows: (7) **29** (1.25 equiv), *n*-butyllithium (1.25 equiv), THF, –78 ºC to –50 ºC, 75% yield. (8) $Pd(PPh_3)_4$ (50 mol %), *N*-formylsaccharin (1.2 equiv), KF (2.5 equiv), Et_3N (4.0 equiv), 1,4-dioxane, 100 ºC, 57% yield. (9) DDQ (1.8 equiv), CH_2Cl_2/pH 7 buffer (5:1), 0 ºC, 80% yield. (10) DMDO (3.0 equiv), Na_2SO_4 (200% w/w), acetone, 23 ºC. (11) MeMgCl (2.0 equiv), $CeCl_3$•2LiCl (2.0 equiv), THF, 0 ºC, 55% yield, 2 steps. (12) TFA (5.0 equiv), CH_2Cl_2, 0 ºC, 90% yield. (13) SeO_2 (5.0 equiv), 1,4-dioxane, 100 ºC, 78% yield. (14) VO(O*n*-Pr)$_3$ (1.0 equiv), TBHP (6.0 equiv), PhMe, 60 ºC, 68% yield. (15) **44** (4.5 equiv), PhH/THF (1:1), 10 ºC, 25% yield, 43% BRSM. (16) $Pd(OH)_2$/C (200% w/w), H_2 (1 atm), MeOH, 90% yield.

With this fortuitous discovery, we were left to reconsider the final sequence of steps to prepare perseanol. Although we had initially targeted the preparation of anhydroperseanol (see Figure 1), the ability to prepare **41** led us to consider whether epoxide **43**—potentially accessible from **41** by allylic C–H oxidation and hydroxyl-directed epoxidation—could undergo reductive cyclization. It was recognized that this cyclization might be challenging, given that formation of the C1–C15 bond via epoxylactone isomer **43** would require a Baldwin disfavored[56-59] 5-*endo*-tet epoxide ring opening, when viewed from the formation of the THF ring. Successful *endo*-ring openings of epoxides have been reported in the literature, but they generally rely on directing groups to stabilize the epoxonium intermediate under Brønsted or Lewis acidic conditions; the related *endo*-cyclizations of epoxides under neutral or basic conditions are less common. Nevertheless, given the strategic advantage of this approach, we elected to investigate it.

To this end, exposure of **41** to SeO_2 in 1,4-dioxane at 100 °C resulted in site-selective and stereospecific oxidation at C2 to give tertiary allylic alcohol **42** in 78% yield (Figure 3).[60] Vanadium-mediated hydroxyl-directed epoxidation of **42** then provided epoxyalcohol **43** as a single diastereomer. The use of VO(O*n*-Pr)$_3$[61] proved essential to obtain full conversion of alkene **42**; the more routinely used $VO(acac)_2$ gave only 5–10% conversion under otherwise identical conditions. Treatment of epoxylactone **43** with LiDBB,[62] the optimal conditions from our (+)-ryanodine synthesis,[25] did produce small quantities of the desired pentacycle **46**; however, significant decomposition was observed. Analysis of the side products revealed that reduction of the orthobenzoate was a competing process, prompting a screen of different reductants in order to prevent this undesired reactivity. Use of lithium naphthalenide (LiNap) provided the desired pentacycle in 17% isolated yield. Weaker reductants, like lithium anthracenide (LiAnth), gave rise to epoxide isomerization products instead of reductive cyclization. A further screen of modified naphthalenes revealed that use of lithium 2-phenylnaphthalenide (LiPhNap) effects cyclization to give the desired pentacycle **46** in 25% yield (43% yield based on recovered starting material). The use

of PhH as a co-solvent, which had previously been reported by Carreira and coworkers to improve ketyl anion chemistry, was critical for the improved yield.[63] We note that a similar substrate, lacking the C2 *i*-propyl substituent, undergoes the reductive cyclization mediated by LiDBB in 50% yield, demonstrating that the position of the epoxide itself is not chiefly responsible for the reduced efficiency in the cyclization. Deprotection of **46** with $Pd(OH)_2/C$ under an atmosphere of H_2 afforded (+)-perseanol (**3**) in 90% yield. This approach provides (+)-perseanol (**3**) in 16 steps (longest linear sequence) from (*R*)-pulegone (**11**), and is the first total synthesis of an isoryanodane diterpene.[64] The concision of the synthesis derives from the convergent union of two cyclopentyl fragments of comparable complexity, followed by a carbopalladation/carbonylation cascade to form two C–C bonds and rapidly constructs the tetracyclic lactone framework of anhydroperseanol. Strategic late-stage introduction of the A-ring oxidation pattern minimized lateral redox and protecting group manipulations. This synthetic framework should provide a versatile platform for the preparation of designed isoryanodanes and further studies of their mode-of-action.

Acknowledgments. Dr. Scott Virgil and the Caltech Center for Catalysis and Chemical Synthesis are gratefully acknowledged for access to analytical equipment. We thank Mr. Larry Henling (Caltech) and Dr. Julie Hofstra (Caltech) for X-ray data collection and data refinement, respectively, for the structure of **32** and **S21**. Prof. Yonghui Zhang (Huanzhong University of Science and Technology) is acknowledged for providing original spectral data of perseanol. Dr. Kangway Chuang (Caltech) is gratefully acknowledged for insightful contributions to the synthetic design. Fellowship support was provided by the NIH (A.H., Nos. 5T32GM007616-37 and 1F31GM120821). S.E.R. is a Heritage Medical Research Investigator. Financial support from the NIH (Nos. NIGMS RGM097582-01 and R35GM118191-01), Eli Lilly, and Novartis is gratefully acknowledged.

Author Contributions. A.H. and S.E.R. conceived this work; A.H., Y.T., and S.E.R. designed the experiments and analyzed the data; A.H. and Y.T. conducted the experiments; A.H. and S.E.R. wrote the manuscript.

Author Information. Metrical parameters for the structure of **32** and **S21** are available free of charge from the Cambridge Crystallographic Data Centre (CCDC) under reference number 1909375 and 1914686, respectively.

References

1. United States Environmental Protection Agency R.E.D. Facts Ryanodine. https://archive.epa.gov/pesticides/reregistration/web/pdf/2595fact.pdf (accessed Oct 2018).

2. Sutko, J. L.; Airey, J. A.; Welch, W.; Ruest, L. The pharmacology of ryanodine and related compounds. *Pharmacol. Rev.* **1997**, *49*, 53.

3. Lahm, G. P.; Stevenson, T. M.; Selby, T. P.; Freudenberger, J. H.; Dubas, C. M.; Smith, B. K.; Cordova, D.; Flexner, L.; Clark, C. E.; Bellin, C. A.; Hollinghaus, G. Rynaxypyr™: a new anthranilic diamide insecticide acting at the Ryanodine receptor. In *Pesticide Chemistry: Crop Protection, Public Health, Environmental Safety*, Ohkawa, H.; Miyagawa, H.; Lee, P. W., Eds. Wiley-VCH: Weinheim, 2007; p 111.

4. Cordova, D.; Benner, E. A.; Sacher, M. D.; Rauh, J. J.; Sopa, J. S.; Lahm, G. P.; Selby, T. P.; Stevenson, T. M.; Flexner, L.; Caspar, T.; Ragghianti, J. J.; Gutteridge, S.; Rhoades, D. F.; Wu, L.; Smith, R. M.; Tao, Y. Elucidation of the mode of action of Rynaxypyr™, a selective Ryanodine receptor activator. In *Pesticide Chemistry: Crop Protection, Public Health, Environmental Safety*, Ohkawa, H.; Miyagawa, H.; Lee, P. W., Eds. Wiley-VCH: Weinheim, 2007; pp 121.

5. Selby, T. P.; Lahm, G. P.; Stevenson, T. M. A retrospective look at anthranilic diamide insecticides: discovery and lead optimization to Chlorantraniliprole and Cyantraniliprole. *Pest Manag. Sci.* **2017**, *73*, 658.

6. Gonzalez-Coloma, A.; Terrero, D.; Perales, A.; Escoubas, P.; Fraga, B. M. Insect antifeedant ryanodane diterpenes from *Persea indica*. *J. Agric. Food. Chem.* **1996**, *44*, 296.

7. Nohara, T.; Kashiwada, Y.; Tomimatsu, T.; Kido, M.; Tokubuchi, N.; Nishioka, I. Cinncassiol D_1 and its Glucoside, novel pentacyclic diterpenes from *Cinnamomi cortex*. *Tetrahedron Lett.* **1980**, *21*, 2647.

8. Nohara, T.; Kashiwada, Y.; Murakami, K.; Tomimatsu, T.; Kido, M.; Yagi, A.; Nishioka, I. Constituents of *Cinnamomi Cortex*. 5. Structures of five novel diterpenes, Cinncassiols D_1, D_1 Glucoside, D_2, D_2 Glucoside and D_3. *Chem. Pharm. Bull.* **1981**, *29*, 2451.

9. Nohara, T.; Kashiwada, Y.; Tomimatsu, T.; Nishioka, I. Two novel diterpenes of *Cinnamomum cassia*. *Phytochemistry* **1982**, *21*, 2130.

10. Chai, X. Y.; Bai, C. C.; Shi, H. M.; Xu, Z. R.; Ren, H. Y.; Li, F. F.; Lu, Y. N.; Song, Y. L.; Tu, P. F. Six insecticidal isoryanodane diterpenoids from the bark and twigs of *Itoa orientalis*. *Tetrahedron* **2008**, *64*, 5743.

11. Tang, W. W.; Wei, X. Y.; Xu, H. H.; Zeng, D. Q.; Long, L. P. 13-Deoxyitol A, a new insecticidal isoryanodane diterpene from the seeds of *Itoa orientalis*. *Fitoterapia* **2009**, *80*, 286.

12. Zeng, J. F.; Xue, Y. B.; Shu, P. H.; Qian, H. Q.; Sa, R. J.; Xiang, M.; Li, X. N.; Luo, Z. W.; Yao, G. M.; Zhang, Y. H. Diterpenoids with immunosuppressive activities from *Cinnamomum cassia*. *J. Nat. Prod.* **2014**, *77*, 1948.

13. Fraga, B. M.; Terrero, D.; Bolanos, P.; Diaz, C. E. Diterpenes with new isoryanodane derived skeletons from *Persea indica*. *Tetrahedron Lett.* **2017**, *58*, 2261.

14. Zhou, L.; Tuo, Y. L.; Hao, Y.; Guo, X. M.; Tang, W.; Xue, Y. B.; Zeng, J. F.; Zhou, Y.; Xiang, M.; Zuo, J. P.; Yao, G. M.; Zhang, Y. H. Cinnamomols A and B, immunostimulative diterpenoids with a new carbon skeleton from the leaves of *Cinnamomum cassia*. *Org. Lett.* **2017**, *19*, 3029.

15. Zhou, H. F.; Guoruoluo, Y.; Tuo, Y. L.; Zhou, J. F.; Zhang, H. Q.; Wang, W.; Xiang, M.; Aisa, H. A.; Yao, G. M. Cassiabudanols A and B, immunostimulative diterpenoids with a Cassiabudane carbon skeleton featuring a 3-oxatetracyclo[6.6.1.$0^{2,6}$.$0^{10,14}$]pentadecane scaffold from Cassia buds. *Org. Lett.* **2019**, *21*, 549.

16. Gonzalez-Coloma, A.; Reina, M.; Gutierrez, C.; Fraga, B. M. Natural insecticides: structure diversity, effects and structure-activity relationships. A case study. In *Studies in Natural Products Chemistry*, 2002; Vol. 26, pp 849.

17. Ling, S. Q.; Xu, Y. N.; Gu, Y. P.; Liu, S. Y.; Tang, W. W. Toxicity and biochemical effects of Itol A on the brown planthopper, *Nilaparvata lugens* (Stål) (Hemiptera: Delphacidae). *Pestic. Biochem. Physiol.* **2018**, *152*, 90.

18. Sattelle, D. B.; Cordova, D.; Cheek, T. R. Insect Ryanodine receptors: molecular targets for novel pest control chemicals. *Invert. Neurosi.* **2008**, *8*, 107.

19. Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; MacLachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. Total synthesis of Ryanodol. *Can. J. Chem.* **1979**, *57*, 3348.

20. Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. The total synthesis of (+)-Ryanodol. Part I. General strategy and search for a convenient diene for the construction of a key tricyclic intermediate. *Can. J. Chem.* **1990**, *68*, 115.

21. Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. The total synthesis of (+)-Ryanodol. Part II. Model studies for ring B and ring C of (+)-Anhydroryanodol. Preparation of a key pentacyclic intermediate. *Can. J. Chem.* **1990**, *68*, 127.

22. Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. The total synthesis of (+)-Ryanodol. Part III. Preparation of (+)-Anhydroryanodol from a key pentacyclic intermediate. *Can. J. Chem.* **1990**, *68*, 153.

23. Deslongchamps, P.; Bélanger, A.; Berney, D. J. F.; Borschberg, H. J.; Brousseau, R.; Doutheau, A.; Durand, R.; Katayama, H.; Lapalme, R.; Leturc, D. M.; Liao, C. C.; Maclachlan, F. N.; Maffrand, J. P.; Marazza, F.; Martino, R.; Moreau, C.; Ruest, L.; Saint-Laurent, L.; Saintonge, R.; Soucy, P. The total synthesis of (+)-Ryanodol. Part IV. Preparation of (+)-Ryanodol from (+)-Anhydroryanodol. *Can. J. Chem.* **1990**, *68*, 186.

24. Chuang, K. V.; Xu, C.; Reisman, S. E. A 15-step synthesis of (+)-Ryanodol. *Science* **2016**, *353*, 912.

25. Xu, C.; Han, A.; Virgil, S. C.; Reisman, S. E. Chemical synthesis of (+)-Ryanodine and (+)-20-Deoxyspiganthine. *ACS Cent. Sci.* **2017**, *3*, 278.

26. Artman, G. D.; Weinreb, S. M. An Approach to the Total synthesis of the marine ascidian metabolite perophoramidine via a halogen-selective tandem Heck/carbonylation strategy. *Org. Lett.* **2003**, *5*, 1523.

27. Aggarwal, V. K.; Davies, P. W.; Schmidt, A. T. Asymmetric synthesis of Avenaciolide via cascade palladium catalysed cyclisation-carbonylation of bromodienes. *Chem. Commun.* **2004**, 1232.

28. Bai, Y.; Shen, X. Y.; Li, Y.; Dai, M. J. Total synthesis of (–)-Spinosyn A via carbonylative macrolactonization. *J. Am. Chem. Soc.* **2016**, *138*, 10838.

29. Bai, Y.; Davis, D. C.; Dai, M. J. Natural product synthesis via palladium-catalyzed carbonylation. *J. Org. Chem.* **2017**, *82*, 2319.

30. Luparia, M.; Vadala, A.; Zanoni, G.; Vidari, G. 1,2-Bisanionic coupling approach to 2,3-disubstituted cyclopentenols and cyclopentenones. *Org. Lett.* **2006**, *8*, 2147.

31. Marx, J. N.; Norman, L. R. Synthesis of (–)-Acorone and related spirocyclic sesquiterpenes. *J. Org. Chem.* **1975**, *40*, 1602.

32. Shen, Y.; Li, L. B.; Pan, Z. S.; Wang, Y. L.; Li, J. D.; Wang, K. Y.; Wang, X. C.; Zhang, Y. Y.; Hu, T. H.; Zhang, Y. D. Protecting-group-free total synthesis of (–)-Jiadifenolide: development of a [4+1] annulation toward multisubstituted tetrahydrofurans. *Org. Lett.* **2015**, *17*, 5480.

33. Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Substrate-directable chemical reactions. *Chem. Rev.* **1993**, *93*, 1307.

34. Yasuda, A.; Yamamoto, H.; Nozaki, H. Highly Stereospecific isomerization of oxiranes into allylic alcohols by means of organoaluminum amides. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1705.

35. Steves, J. E.; Stahl, S. S. Copper(I)/ABNO-catalyzed aerobic alcohol oxidation: alleviating steric and electronic constraints of Cu/TEMPO catalyst systems. *J. Am. Chem. Soc.* **2013**, *135*, 15742.

36. Iimura, S.; Overman, L. E.; Paulini, R.; Zakarian, A. Enantioselective total synthesis of Guanacastepene N using an uncommon 7-*endo* Heck cyclization as a pivotal step. *J. Am. Chem. Soc.* **2006**, *128*, 13095.

37. Mewshaw, R. E. Vilsmeier reagents: preparation of β-halo-α,β-unsaturated ketones. *Tetrahedron Lett.* **1989**, *30*, 3753.

38. Helal, C. J.; Meyer, M. P. The Corey-Bakshi-Shibata reduction: mechanistic and synthetic considerations – bifuntional Lewis base catalysis and dual activation. In *Lewis Base Catalysis in Organic Synthesis*, 1st ed.; Vedejs, E.; Denmark, S. E., Eds. Wiley-VCH: Weinheim, Germany, 2016.

39. Corey, E. J.; Link, J. O. A new chiral catalyst for the enantioselective synthesis of secondary alcohols and deuterated primary alcohols by carbonyl reduction. *Tetrahedron Lett.* **1989**, *30*, 6275.

40. Evans, D. A. Stereoselective organic reactions: catalysts for carbonyl addition processes. *Science* **1988**, *240*, 420.

41. Jones, D. K.; Liotta, D. C.; Shinkai, I.; Mathre, D. J. Origins of enantioselectivity observed in oxazaborolidine-catalyzed reductions of ketones *J. Org. Chem.* **1993**, *58*, 799.

42. Nwoye, E. O.; Dudley, G. B. Synthesis of *para*-methoxybenzyl (PMB) ethers under neutral conditions. *Chem. Commun.* **2007**, 1436.

43. Stewart, C. A.; Peng, X. W.; Paquette, L. A. An efficient means for generating *p*-methoxybenzyl (PMB) ethers under mildly acidic conditions. *Synthesis* **2008**, 433.

44. Barnard, C. F. J. Palladium-catalyzed carbonylation–a reaction come of age. *Organometallics* **2008**, *27*, 5402.

45. Grigg, R.; Mutton, S. P. Pd-catalysed carbonylations: versatile technology for discovery and process chemists. *Tetrahedron* **2010**, *66*, 5515.

46. Wu, L. P.; Fang, X. J.; Liu, Q.; Jackstell, R.; Beller, M.; Wu, X. F. Palladium-catalyzed carbonylative transformation of C(sp^3)-X bonds. *ACS Catalysis* **2014**, *4*, 2977.

47. Labinger, J. A. Tutorial on oxidative addition. *Organometallics* **2015**, *34*, 4784.

48. Odell, L. R.; Russo, F.; Larhed, M. Molybdenum hexacarbonyl mediated CO gas-free carbonylative reactions. *Synlett* **2012**, 685.

49. Ueda, T.; Konishi, H.; Manabe, K. Palladium-catalyzed carbonylation of aryl, alkenyl, and allyl halides with phenyl formate. *Org. Lett.* **2012**, *14*, 3100.

50. Ueda, T.; Konishi, H.; Manabe, K. Trichlorophenyl formate: highly reactive and easily accessible crystalline CO surrogate for palladium-catalyzed carbonylation of aryl/alkenyl halides and triflates. *Org. Lett.* **2012**, *14*, 5370.

51. Ueda, T.; Konishi, H.; Manabe, K. Palladium-catalyzed fluorocarbonylation using *N*-formylsaccharin as CO source: general access to carboxylic acid derivatives. *Org. Lett.* **2013**, *15*, 5370.

52. Jiang, X.; Wang, J. M.; Zhang, Y.; Chen, Z.; Zhu, Y. M.; Ji, S. J. Palladium-catalyzed formylation of aryl halides with *tert*-butyl isocyanide. *Org. Lett.* **2014**, *16*, 3492.

53. Mycock, D. K.; Sherlock, A. E.; Glossop, P. A.; Hayes, C. J. Studies on DMDO-mediated benzylidene acetal oxidation. *Tetrahedron Lett.* **2008**, *49*, 6390.

54. Krasovskiy, A.; Kopp, F.; Knochel, P. Soluble Lanthanide salts $LnCl_3$•2LiCl for the improved addition of organomagnesium reagents to carbonyl compounds. *Angew. Chem. Int. Ed.* **2006**, *45*, 497.

55. Myers, A. G.; Glatthar, R.; Hammond, M.; Harrington, P. M.; Kuo, E. Y.; Liang, J.; Schaus, S. E.; Wu, Y. S.; Xiang, J. N. Development of an enantioselective synthetic route to Neocarzinostatin Chromophore and its use for multiple radioisotopic incorporation. *J. Am. Chem. Soc.* **2002**, *124*, 5380.

56. Baldwin, J. E. Rules for ring-closure. *J. C. S. Chem. Commun.* **1976**, 734.

57. Baldwin, J. E. Approach vector analysis: stereochemical approach to reactivity. *J. C. S. Chem. Commun.* **1976**, 738.

58. Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. 5-*endo*-trigonal reactions: disfavored ring-closure. *J. C. S. Chem. Commun.* **1976**, 736.

59. Stork, G.; Cohen, J. F. Ring size in epoxynitrile cyclization. General synthesis of functionally substituted cyclobutanes. Application to (±)-Grandisol. *J. Am. Chem. Soc.* **1974**, *96*, 5270.

60. Trachtenberg, E. N.; Nelson, C. H.; Carver, J. R. Mechanism of selenium dioxide oxidation of olefins. *J. Org. Chem.* **1970**, *35*, 1653.

61. Nicolaou, K. C.; Harrison, S. T. Total synthesis of Abyssomicin C, *atrop*-Abyssomicin C, and Abyssomicin D: implications for natural origins of *atrop*-Abyssomicin C. *J. Am. Chem. Soc.* **2007**, *129*, 429.

62. Hill, R. R.; Rychnovsky, S. D. Generation, stability, and utility of lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB). *J. Org. Chem.* **2016**, *81*, 10707.

63. Wolleb, H.; Carreira, E. M. Total synthesis of (+)-Dendrowardol C. *Angew. Chem. Int. Ed.* **2017**, *56*, 10890.

64. Inoue and coworkers have recently reported a 28-step approach to prepare a pentacyclic isoryanodane intermediate: Koshimizu, M.; Nagatomo, M.; Inoue, M. Construction of a pentacyclic ring system of isoryanodane diterpenoids by SmI_2-mediated transannular cyclization. *Tetrahedron* **2018**, *74*, 3384.