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Total Synthesis of the Protein Phosphatase 2A Inhibitor Lactodehydrothyrsiferol**

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Keywords

domino reactions; natural products; oxidation; oxygen heterocycles; total synthesis

Red algae are a prolific source of squalene-derived poly-ethers[1] that show moderate to high levels of cytotoxicity[2] and very selective protein phosphatase 2A (PP2A) inhibition. [3] These unique structures (see Figure 1 for examples) have inspired total syntheses of the family members venus-atriol, [4] thyrsiferol and its esters, [4b,5] pseudodehydrothyrsiferol, [6] and dioxepanedehydrothyrsiferol, [7] in addition to subunit and analogue syntheses. [8] Our interest in this molecule class arose from our work[9] on the construction of cyclic ethers through epoxide-opening cascade reactions. [10] Lactodehydrothyrsiferol (**1**), isolated from the red seaweed *Laurencia viridis* found near the Canary Islands, [11] attracted our attention because of its unique butyrolactone group and the challenges associated with applying an epoxide-opening cascade to construct the tetrahydropyran subunits. Herein, we report the first total synthesis of **1**. The sequence features an oxidatively initiated cascade reaction, a stereodivergent diene double epoxidation reaction, a diastereoselective fragment coupling through a Nozaki–Hiyama–Kishi reaction, and a selective monodeoxygenation of a triol.

We envisioned the construction of the polycyclic subunit of **1** through a cascade reaction that would be initiated by epoxide alkylation by an oxidatively generated oxocarbenium ion. [12] The resulting epoxonium ion can be opened by an appended nucleophile, such as an epoxide (to continue the cascade) or an alkyl carbonate (to terminate the cascade). Implementation of this strategy is complicated by the kinetic regioselectivity of intramolecular nucleophilic epoxoniumion-opening reactions. We have shown[9c] that intramolecular additions to bicyclo [3.1.0] epoxonium ions proceed preferentially through an *exo* pathway to provide tetrahydrofurans, while bicyclo [4.1.0] epoxonium ions react through an *endo* pathway to yield oxepanes (Scheme 1). Our solution to the tetrahydropyran synthesis was based on the work of McDonald and co-workers, in which spirocyclization reactions are used to dictate the regioselectivity of the epoxonium-ion opening. [13] We tested this strategy under oxidative conditions by irradiating (medium pressure mercury lamp, Pyrex filter) homobenzylic ether **4** in the presence of the single-electron oxidant *N*-methylquinolinium hexafluorophosphate and air. [14] This led to the oxidative cleavage of the benzylic carbon–carbon bond, thus forming an oxocarbenium ion that reacts with the

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epoxide group to yield epoxonium ion **5**. Nucleophilic addition by the carbonate group with subsequent loss of the *tert*-butyl cation provided spirocycle **6** in 79% yield. [15]

This result allowed us to propose that the synthesis of **1** could proceed through **7** (Scheme 2). This precursor will be derived from fragments **8** and **9**. Fragment **8** can be accessed through a cascade of epoxide-opening reactions involving diepoxide **10**, which can be prepared from a metal-mediated coupling of alkenes **11** and **12**. Subunit **9** can be prepared through oxidative transformations on geranylpropyne **13**.

The synthesis of the diepoxide precursor **20** for the cyclization reaction is shown in Scheme 3. Methylalumination and iodination of 4-pentyn-1-ol according to the Wipf variant[16] of Negishi3s protocol[17] with subsequent palladium-mediated coupling using vinylmagnesium bromide[18] provided diene **14**. While **14** could be prepared in a single operation by coupling the vinylalane intermediate directly with vinyl bromide, the two-step protocol proved to be substantially more efficient. Oxidation, diphenylmethyl-lithium addition, and methylation provided fragment **15**. The diphenylmethyl group was selected because of its accessibility and high reactivity[19] in oxidative cleavage reactions. Fragment **16** was prepared through a straightforward sequence from 4-pentyn-1-ol, and a palladium-mediated hydrostannylation/iodination[20] served as the key step. Coupling the fragments through a Suzuki reaction[21] proved to be quite challenging. Hydroboration of **15** required the use of the 9-BBN dimer to form an alkylborane that showed reproducible reactivity. Catalyzing the coupling reaction with [Pd-(PPh_3)$_4$] at room temperature resulted in a slow reaction, in which **16** decomposed by the loss of the carbonate, and **15** was regenerated, presumably through a β-hydride elimination. Elevating the temperature caused alkene isomerization. Success was finally achieved by using [Pd(P*t*Bu_3)$_2$], a catalyst that was shown by Fu and co-workers to be effective for Suzuki reactions with aryl boronic acids, [22] to yield **17** in 74% yield with no carbonate loss or β-hydride elimination. The double epoxidation reaction of **17** was complicated by the need to oxidize each alkene with opposite stereochemical control. We solved this problem by exploiting the differential reactivity of the two alkenes that arises from the inductive deactivation by the allylic carbonate group. This allowed us to use the less-reactive, first-generation, sorbose-derived Shi catalyst **18**[23] to effect the epoxidation of the more reactive alkene. Upon completion of this reaction the more-reactive pseudoenantiomeric fructose-derived second-generation Shi catalyst **19**[24] was added to promote the oxidation of the allylic carbonate. This sequence resulted in the isolation of diepoxide **20** in 82% yield. Although we were unable to determine the diastereoselectivity of this reaction precisely, we saw only two diastereomers by ^{13}C NMR spectroscopy (no attempt was made to control the stereochemical orientation at the homobenzylic site). Through the synthesis of a derivative[25] we showed that the product was a single enantiomer, within the limits of NMR detection.

The key cascade cyclization of **20** (Scheme 4) proceeded under the standard reaction conditions that were described in Scheme 1 to provide **21** in 45% yield upon isolation (75% yield based on recovered starting material). This reaction stalled prior to the complete consumption of the starting material and did not proceed further even after the addition of more catalyst. The reason for this is not clear, but control reactions show that benzophenone, a triplet-sensitizing product that is formed in the oxidative cleavage reaction, does not inhibit the reaction. However, the unreacted diepoxide can be resubjected to the reaction conditions to access gram quantities of **21**. The synthesis of **8** was completed by a one-pot lactone formation/silyl ether cleavage using *m*CPBA and $Sc(OTf)_3$, [26] with subsequent alcohol oxidation using IBX. [27] No diastereomers were isolated in this sequence, thus indicating that diastereocontrol in the diepoxidation reaction was high.

The right-hand fragment of **1** was prepared (Scheme 5) through the addition of lithiated trimethylsilylpropyne[28] to geranyl chloride with a subsequent desilylative work-up to yield **13**. Sharpless asymmetric dihydroxylation[29] of the dimethyl-substituted alkene was highly enantioselective[25] and moderately regioselective, and provided **22** in 53% yield. A Shi epoxidation using catalyst **18** and subsequent treatment with pyridinium camphorsulfonate provided tetrahydrofuran **23** as a 13:1 mixture of diastereomers. [25] The diastereomers were readily separated by MPLC methods and the minor stereoisomer was shown to arise from imperfect stereocontrol in the epoxidation step. [25] Silyl ether formation proceeded under standard reaction conditions, and then hydrosilylation under Trost3s protocol[30] with subsequent iodination resulted in the formation of vinyl iodide **24** in 82% yield for the one-pot process.

The completion of the synthesis (Scheme 6) commenced with the union of **8** and **24** through a reagent-controlled diastereoselective Nozaki–Hiyama–Kishi coupling[31] using ligand **25**, to form allylic alcohol **26** in 84% yield as an 8:1 mixture of diastereomers. [25] The cyclic carbonate was converted into diol **27** through methanolysis, selective tosylation of the primary alcohol of the resulting triol by the Lilly protocol[32] (at which point a single diastereomer could be isolated), and reduction with $NaBH_4$ in warm HMPA. [33] The final ring closure was conducted by exposing **27** to the Tsunoda dehydration reagent ($Me_3P{=}C(H)CN$), [34] a step that is analogous to the endgame of the synthesis of pseudodehydrothyrsiferol reported by Hioki et al. [6] This led to the formation of **28** in 40% yield. Silyl ether cleavage by Bu_4NF resulted in the isolation of **1**. All spectral data for synthetic **1** matched the values that were reported for the natural product. [11]

We have reported the first total synthesis of lactodehydrothyrsiferol, the longest linear sequence of which is a 16 step route. This is the shortest route that has yet been reported for any member of this molecule class. The route featured an epoxide-opening cascade cyclization to prepare the tetrahydrofuran subunit and one tetrahydropyran ring. Other notable transformations include a Suzuki coupling that employed an iodinated allylic carbonate, a diepoxidation reaction that exploited the differential reactivities of the alkenes and two pseudoenantiomeric catalysts to achieve the desired stereochemical outcome, an efficient and mild one-pot transformation of an alkyne to a vinyl iodide through hydrosilylation chemistry, a diastereoselective Nozaki–Hiyama–Kishi reaction for complex fragment coupling, and a selective sequence for the deoxygenation of a single hydroxy group from a triol. The modular nature of the synthesis and the reliance upon reagent control to establish the stereocenters makes this sequence well suited for the construction of analogues that can be used to test hypotheses regarding the structure–activity relationships of this interesting class of PP2A inhibitors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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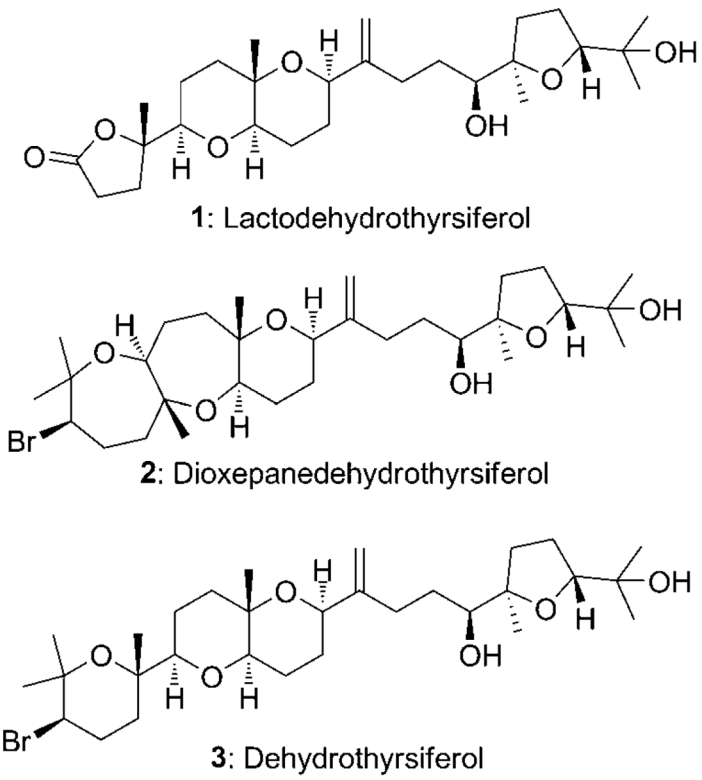
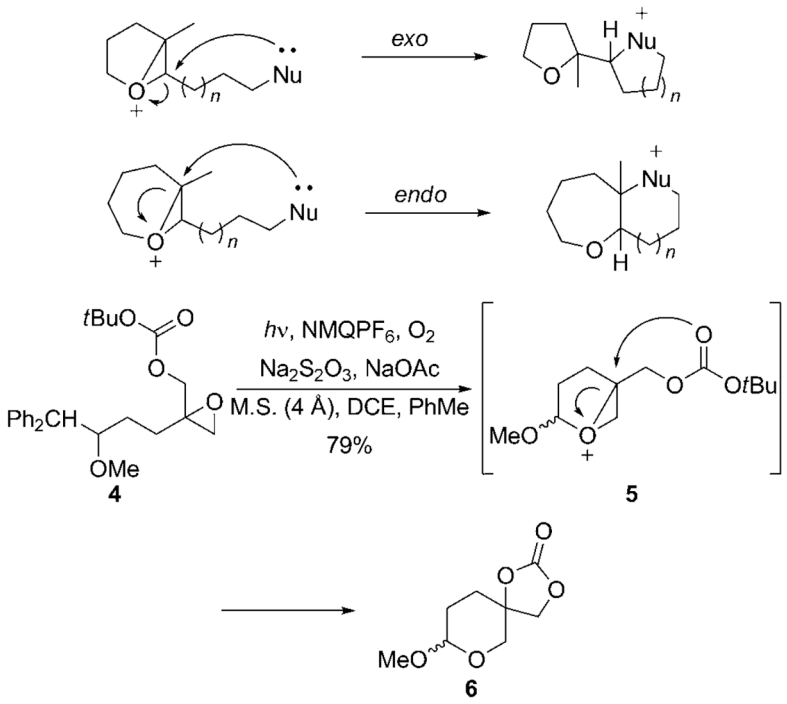
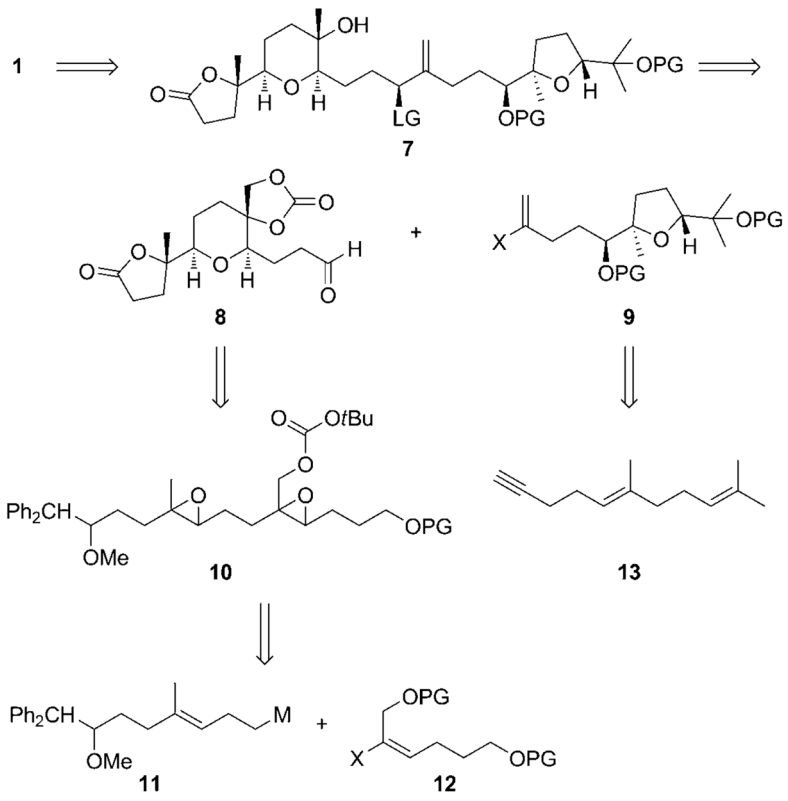


Figure 1.
Squalene-derived ethers from red algae.

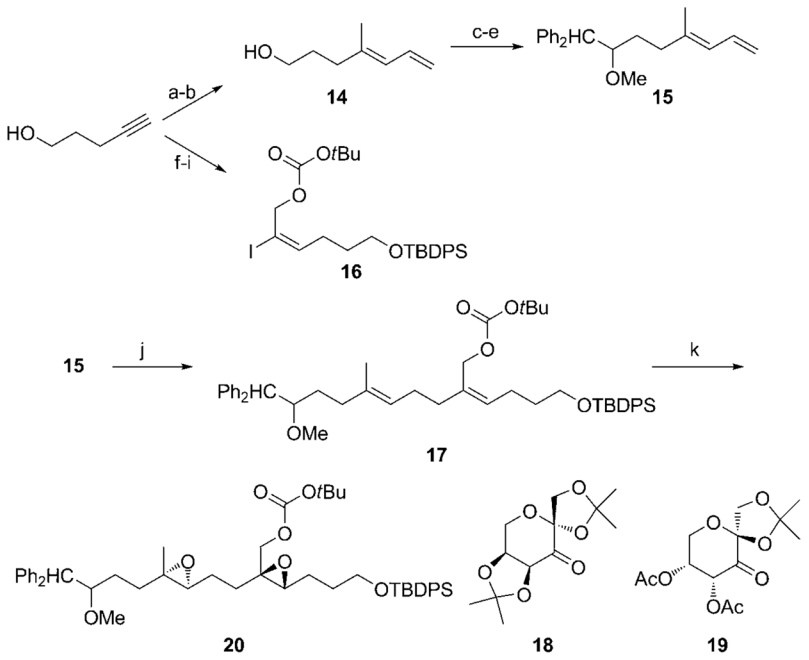


Scheme 1.

Synthesis of oxygen-containing heterocycles through epoxonium-ion opening. DCE =1,2-dichloroethane, M.S. =molecular sieves, $NMQPF_6$ = *N*-methylquinolinium hexafluorophosphate.

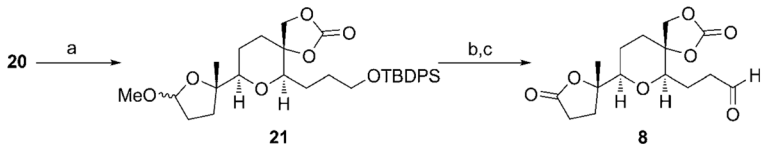


Scheme 2.
Retrosynthesis of **1**. LG =leaving group, M =metal, PG =protecting group.



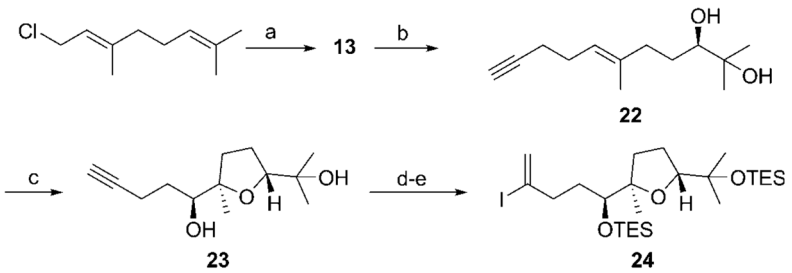
Scheme 3.

Synthesis of the cascade cyclization substrate. Reagents and conditions: a) Me_3Al, Cp_2ZrCl_2, H_2O, DCE, then I_2, 94%; b) CH_2=CHMgBr, [$Pd(PPh_3)_4$], PhMe, 91%; c) Oxalyl chloride, DMSO, CH_2Cl_2, Et_3N, −78 °C; d) Ph_2CH_2, *n*BuLi, THF, 82% (two steps); e) NaH, DMF, then MeI, 96%; f) TBDPSCl, imidazole, DMF, 100%; g) *n*BuLi, THF, then $(CH_2O)_n$, 94%; h) Bu_3SnH, [$Pd(PPh_3)_4$], C_6H_6, then I_2, CH_2Cl_2,83%; i) $(Boc)_2O$, *N*-methylimidazole, PhMe, 99%; j) 9-BBN dimer, THF, then **16**, [$Pd(PtBu_3)_2$], K_3PO_4, H_2O, PhMe, 74%; k) Oxone, **18**, K_2CO_3, Bu_4NHSO_4, CH_3CN, H_2O, then **19**, 82 %. 9-BBN = 9-borabicyclo[3.3.1] nonane, Boc =*tert*-butyloxycarbonyl, DMF =*N*,*N*′-dimethylformamide, DMSO=dimethyl sulfoxide, TBDPS =*tert*-butyldiphenylsilyl, THF =tetrahydrofuran.



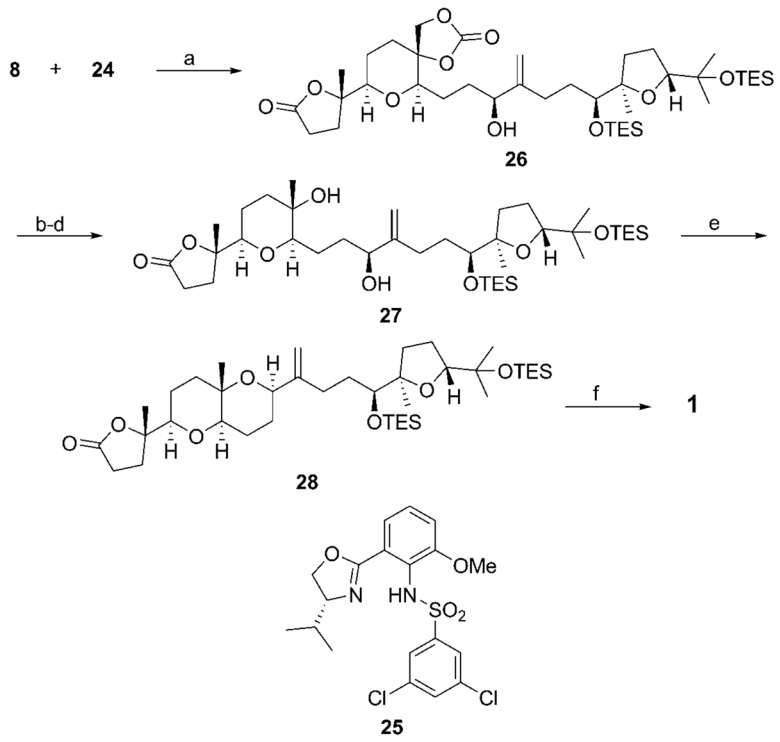
Scheme 4.

Completion of the left-hand fragment. Reagents and conditions: a) *hv*, $NMQPF_6$, O_2, $Na_2S_2O_3$, NaOAc, DCE, PhMe, 45% yield of isolated product (75% based on recovered starting material); b) *m*CPBA, $Sc(OTf)_3$, CH_2Cl_2, 68%; c) IBX, DMSO, 93%. IBX = 2-iodoxybenzoic acid, *m*CPBA=*meta*-chloroperoxybenzoic acid, Tf =tri-fluoromethanesulfonyl.



Scheme 5.

Synthesis of the right-hand fragment. Reagents and conditions: a) 1-Trimethylsilylpropyne, *n*BuLi, THF, −78°C, then Bu_4NF, 88%; b) AD-Mix β, $CH_3SO_2NH_2$, *t*BuOH, H_2O, 53 %; c) **18**, Oxone, K_2CO_3, Bu_4NHSO_4, CH_3CN, H_2O, then Py·CSA, 83%, d. r. = 13:1; d) TESCl, imidazole, DMAP, DMF, 89%; e) Et_3SiH, $[CpRu\text{-}(NCCH_3)_3]PF_6$, CH_2Cl_2, then I_2, 2,6-lutidine, 82%. Cp = cyclopentadienyl, DMAP =4-dimethylaminopyridine, Py·CSA=pyridinium camphorsulfonate, TES =triethylsilyl.



Scheme 6.

Completion of the synthesis. Reagents and conditions: a) $CrCl_2$, $NiCl_2$·DMP, **25**, Proton Sponge, Mn, Cp_2ZrCl_2, LiCl, CH_3CN, 84%, d. r. =8:1; b) K_2CO_3, MeOH, 91%; c) TsCl, Et_3N, Bu_2SnO, CH_2Cl_2, 92%; d) $NaBH_4$, HMPA, 50 °C, 76 %; e) $Me_3P{=}C(H)CN$, C_6H_6, 80 °C, 40%; f) Bu_4NF, THF, 77 %. DMP = 2,9-dimethylphenanthroline, HMPA =hexamethylphosphoramide.