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A Concise Synthesis of (–)-Aplyviolene Facilitated by a Strategic Tertiary Radical Conjugate Addition**

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Aplyviolene (**1**) and macfarlandin E (**2**, Figure 1A) are representative of the more complex members of the rearranged spongian diterpene class of natural products.^[1,2] These diterpenes are structurally defined by attached *cis*-perhydroazulene and 6-acetoxy-2,7-dioxabicyclo[3.2.1]octan-3-one fragments. The substantial challenge in assembling these structures centers on the construction of the sensitive bicyclic lactone subunit and the formation of the C8–C14 σ -bond joining the two ring systems, a challenge augmented by the quaternary nature of C8.^[3] We previously reported preparation of the lactone subunits of **1** and **2** by the synthesis of truncated congeners **3** and **4** (Figure 1A),^[4] as well as the first total synthesis of aplyviolene (outlined in Figure 1B).^[5] In this latter effort, the key C8–C14 σ -bond was formed by Michael addition of tertiary enolate **5** to enone **6**.^[6] Subsequent elaboration of product **7** provided intermediate **8**, which was converted to (–)-aplyviolene along the lines of our earlier synthesis of **3**. Undesirable aspects of this first-generation synthesis are the lengthy preparation of the *cis*-perhydroazulene unit and the need to remove the extraneous ketone carbonyl group from the product of the fragment-coupling step.

As described in the accompanying communication,^[7] our initial attempt to streamline the synthesis by using a tertiary organocuprate derived from *cis*-perhydroazulene nitrile **9** in the key fragment coupling was prevented by exclusive formation of adduct **11**, which is epimeric to aplyviolene at the critical quaternary carbon stereocenter (Figure 1C). This unexpected stereochemical outcome of the organocuprate conjugate addition reaction provoked consideration of an alternative strategy in which the C8–C14 σ -bond would be formed by the union of the tertiary radical **12** and enone **13** (Figure 1D, X = leaving group). Reductive silylation of the coupled product **14** would then provide enoxy silane **8**, an advanced intermediate in the synthesis of (–)-aplyviolene. Despite the many advances in stereoselective radical chemistry,^[8] bimolecular reactions that transform trialkyl-substituted tertiary radicals to stereogenic quaternary carbons are extremely rare.^[9]

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Moreover, the use of tertiary radicals to couple two complex fragments in the context of target-oriented synthesis is also uncommon.^[10] Encouraged by reports that achiral tertiary radicals undergo particularly diastereoselective additions to chiral alkenes, we chose to pursue this strategy.^[11] Reported herein is a much-improved second-generation total synthesis of (-)-aplyviolene (**1**) that features the stereoselective coupling of a tertiary carbon radical and a carbon electrophile to combine chiral fragments with formation of a new quaternary carbon stereocenter.

A critical consideration was the identity of the radical precursor. The common option of employing a bromide or iodide precursor was not viable, as preliminary studies showed that these tertiary halide intermediates were not accessible in satisfactory yield.^[8] Barton esters were also unsuited for this application.^[12] The use of such radical precursors would entail the coupling of **12** and enone **13** (X = H) to provide product **14** (X = 2-thiopyridine), whose reductive silylation to form enoxy silane **8** was expected to be unsuccessful.^[13] By contrast, an (*N*-acyloxy)phthalimide precursor appeared distinctly advantageous. Over 20 years ago Okada demonstrated that, when exposed to visible light, Ru(bpy)₃Cl₂ (bpy = 2, 2'-bipyridine), and the hydrogen-donor 1-benzyl-1,4-dihydronicotinamide, such compounds are transformed in the presence of α,β -unsaturated ketones to products of conjugate addition in excellent yield.^[14] We noted that in a single instance a tertiary radical (1-admantanyl) had been coupled effectively. Surprisingly, the use of (*N*-acyloxy)phthalimides as radical precursors in conjugate addition reactions has not been described since this initial disclosure, and their photosensitized cleavage has only rarely been reported in any form.^[15] We hoped that realizing the proposed demanding application of the Okada chemistry would be assisted by insight gained from recent advances in photoredox catalysis.^[16,17]

Prior to exploring the union of the complex fragments depicted in Figure 1D, we examined the addition of the tertiary radical generated from a simpler (*N*-acyloxy)phthalimide to methyl vinyl ketone. Using a slight modification of Okada's conditions, a THF/H₂O solution of (*N*-acyloxy)phthalimide **15** [**18**] and methyl vinyl ketone (1.5 equiv) were coupled using 1 mol % of Ru(bpy)₃Cl₂, excess 1,4-dihydronicotinamide **17**, and 1.5 h irradiation with blue light to give adduct **18** in 70% yield (Scheme 1).^[19] We were gratified to observe that this coupling took place with high selectivity from the convex face (dr >20:1). This finding was particularly promising because the corresponding addition of an organocuprate intermediate provided **18** as the minor component of a mixture of epimeric adducts.^[7]

Encouraged by these initial studies, we developed a synthesis of the *cis*-perhydroazulene *N*-(acyloxy)phthalimide **27** (Scheme 2). The synthesis began with inexpensive (+)-fenchone (**19**), which was readily transformed by Beckmann fragmentation to tertiary nitrile **20**.^[20] We were pleased to find that heating the oxime intermediate in 4 M H₂SO₄ for 8 h provided **20** in 83% yield as a 2:1 mixture of alkene regioisomers favoring the desired $\Delta^{1,2}$ isomer, whereas halting the reaction after 30 min gave **20** as the 1:1 mixture of double bond isomers described by Kreiser in the original description of this transformation.^[20] Reduction of nitrile **20** with diisobutylaluminum hydride and *Z*-selective Wittig reaction of the resulting crude aldehyde products with 3-hydroxypropyltriphenyl-phosphonium bromide yielded a 2:1 mixture of (*Z*)-allylic alcohol **21** and its $\Delta^{1,5}$ isomer.^[21] Separation of the alkene isomers was possible at this stage by column chromatography on silver nitrate-embedded silica gel, which could be carried out on large scale to give pure **21** in 55% overall yield (up to 25 g of **21** isolated per batch) from the Beckman fragmentation product **20**. Homoallylic alcohol **21** was converted to the corresponding nitro compound **22** by way of the primary iodide in 67% yield.^[22] Intramolecular nitrile oxide cycloaddition of **22** proceeded efficiently at 90 °C under Mukaiyama conditions to provide the desired isoxazoline product, which did not require purification prior to further use.^[23,24] After some experimentation, we found the most effective way to process the crude oxazoline intermediate to enone **24** was

by initial hydrogenation using a mixture of 10% palladium on carbon and Raney-nickel in the presence of boric acid to provide the β -hydroxy ketone product **23**.^[25,26] Acid-catalyzed dehydration of **23** in toluene at elevated temperature provided enone **24** in 61% overall yield from nitro diene **22**.^[27]

The conversion of enone **24** to the *N*-(acyloxy)phthalimide coupling partner **27** was ultimately achieved by way of only two isolated intermediates. Addition of the cuprate derived from copper cyanide and 2 equiv of vinylmagnesium bromide in THF containing hexamethylphosphoramide at 0 °C afforded vinyl addition product **25** as a 4.8:1 mixture of *cis*-perhydroazulene epimers in 77% yield.^[28,29] Attempted elaboration of alkenyl ketone **25** to carboxylic acid **26** by initial methylenation of the ketone, followed by selective oxidative cleavage of the terminal vinyl group was prevented by competitive oxidation of the exomethylene functionality. As an alternative, slow addition of **25** to a mixture of (trimethylsilyl)methylolithium in pentane at -78 °C provided the β -silyl alcohol adduct. Without purification, this intermediate was exposed sequentially to ozone in CH₂Cl₂ at -78 °C, triphenylphosphine and HF-pyridine to cleanly generate the exomethylene aldehyde product. Sodium chlorite oxidation of this unpurified intermediate delivered carboxylic acid **26** in 74% overall yield from **25**. The desired radical-coupling partner **27** was then secured in 84% yield by carbodiimide coupling of carboxylic acid **26** with *N*-hydroxyphthalimide.

With convenient access to *cis*-perhydroazulene *N*-(acyloxy)phthalimide **27** in hand, we investigated the pivotal fragment-coupling reaction. To our delight, initial efforts to implement the radical coupling of *N*-(acyloxy)phthalimide **27** and α -chlorocyclopentenone **28**^[30,31] using only a minor modification (Scheme 2) of the conditions of Okada provided the crystalline addition product **30** as a single diastereomer, albeit in low and variable yields (20–40%).^[32] The low yield is best attributed to the sensitivity of **30**, as chloride reduction and hydrolysis byproducts were observed.^[33] Seeking to minimize the latter, we were attracted to a recent report by Gangé disclosing the photoredox-mediated reaction of glycosyl halides and electron-deficient alkenes under anhydrous conditions.^[34] In this way, irradiation of a 1.5:1 mixture of enone **28** and *N*-(acyloxy)phthalimide **27**, Ru(bpy)₃(BF₄)₂, Hantzsch ester **29**, *N,N*-diisopropylethylamine and dichloromethane with blue light provided coupled product **30**, containing <5% of the reductively dechlorinated analogue as an inseparable byproduct, in a 61% yield.^[35] Reductive enol silylation of **30** using dilithium-dimethyl(cyano)cuprate in the presence of *tert*-butyldimethylsilyl chloride at -20 °C delivered tricyclic enoxysilane **8**, which we had previously carried on to (-)-aplyviolene.^[5]

In summary, we report an improved second-generation total synthesis of aplyviolene (**1**) that is more efficient and proceeds by way of five fewer isolated intermediates than our original synthesis. The defining feature of this synthesis is the addition of the tertiary radical generated by photoredox-mediated fragmentation of *N*-(acyloxy)phthalimide **27** to α -chlorocyclopentenone **28**, a reaction that combines two fragments of significant complexity and fashions adjacent quaternary and tertiary carbon stereocenters with high stereoselectivity. This transformation highlights the largely untapped utility of addition reactions of tertiary carbon radicals in the construction of quaternary carbon stereocenters and in stereoselectively fashioning demanding σ -bonds that join two rings. Furthermore, the results of this study, and those reported in the accompanying communication,^[7] show that the creation of quaternary carbon stereocenters by the union of trialkyl-tertiary carbon radicals and related organometallic intermediates with carbon electrophiles can take place with complimentary stereoselection (Scheme 3). The generality of this observation and its exploitation in fragment coupling steps in stereoselective synthesis are under active investigation in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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26. We found that Raney-nickel was most effective for cleaving the N-O bond and Pd/C for hydrogenation of the alkene. Elevated temperature with either catalyst delivered the β-hydroxy ketone, albeit in reduced yield.
27. This sequence was readily scaled; more than 25 g of **24** has been prepared by this method.
28. This mixture of isomers is inconsequential; it can be carried forward to the coupling reaction or separated at this stage.
29. The use of HMPA is required in this reaction; in its absence **25** was not observed and only complex mixtures of products were obtained.
30. Available in 83% yield by chlorination of the corresponding enone^[4] with the Mioskowski reagent (Et₄NCl₃), at 0 °C.^[31]
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35. In line with previous observations,^[34] we found that the use of **29** in conjunction with *N,N*-disopropylethylamine was essential for realizing high yields and short reaction times.

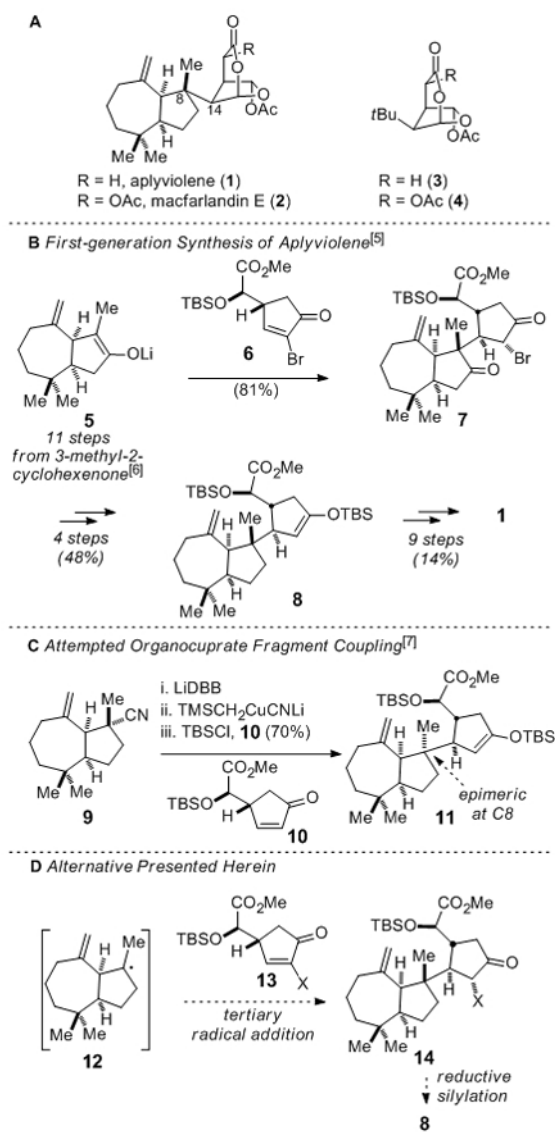
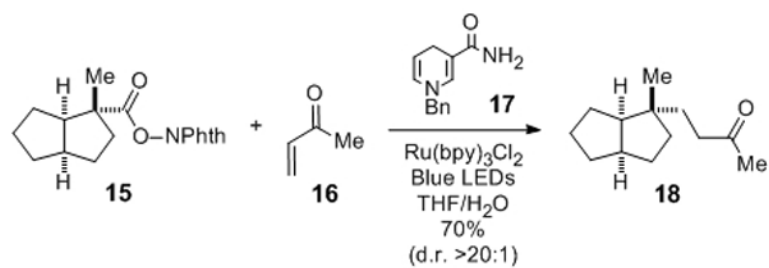
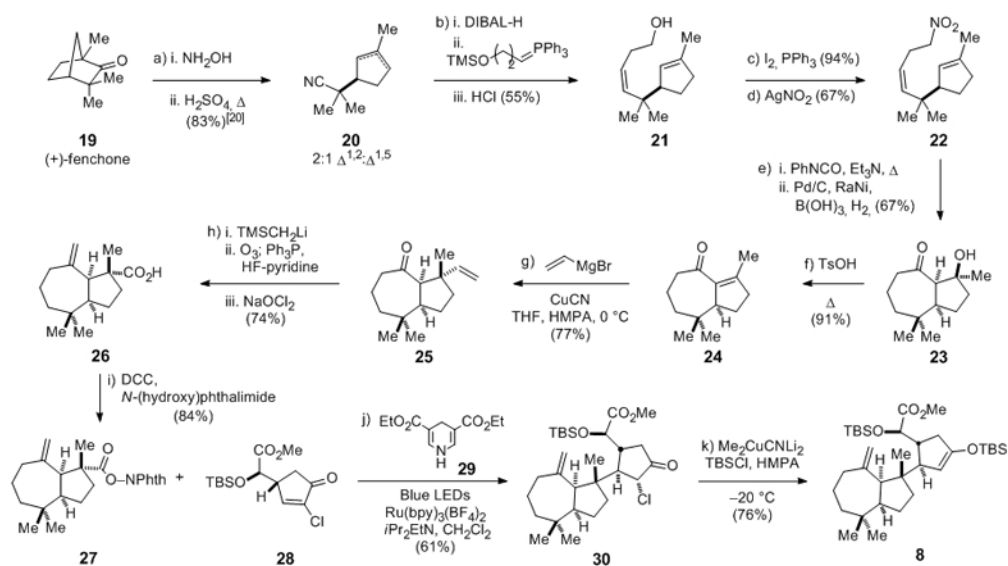


Figure 1. Structurally complex rearranged spongian diterpenes (A), previous synthetic efforts (B and C), and current synthetic approach (D). TMS = trimethylsilyl. TBS = *tert*-butyldimethylsilyl.

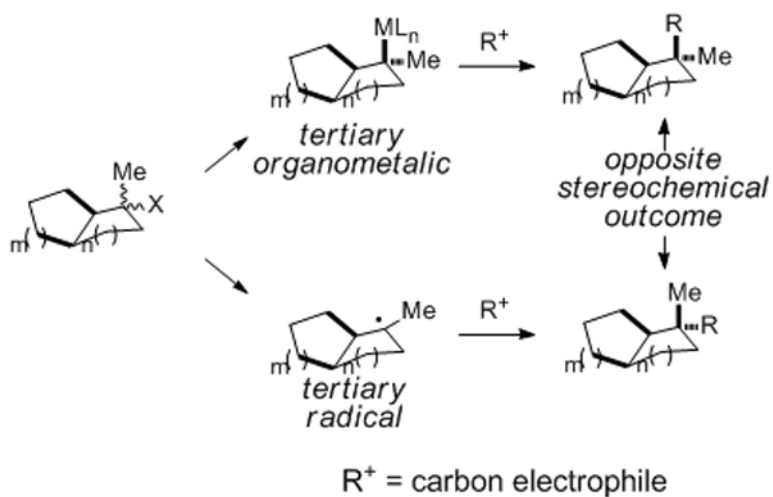
**Scheme 1.**

Synthesis of **18**: a) **15**, **16** (1.5 equiv), **17** (1.5 equiv), Ru(bpy)₃Cl₂ (0.01 equiv), THF/H₂O (2:1), blue LEDs, RT, 90 min, 70%. NPhth = *N*-phthalimido. bpy = 2,2'-bipyridine



Scheme 2.

Formal total synthesis of (-)-aplyviolene: Synthesis of enoxysilane **8**: a) i. **19**, sodium acetate (2 equiv), $\text{NH}_2\text{OH}\cdot\text{HCl}$ (1.75 equiv), EtOH, reflux, 36 h; ii. 4 M H_2SO_4 , reflux, 8 h, 83% as a 2:1 mixture of $\Delta^{1,2}:\Delta^{1,5}$ isomers. b) i. **20**, DIBAL-H (1.2 equiv), CH_2Cl_2 , -78°C , 1 h; ii. 3-hydroxypropyltriphenylphosphonium bromide (2 equiv), $n\text{-BuLi}$ (4 equiv), TMSCl (2 equiv), THF, 0°C , 20 min; + aldehyde from i., -78°C , 1 h; 2 N H_2SO_4 , RT, 18 h; 55%. c) **21**, I_2 (1.05 equiv), PPh_3 (1.05 equiv), imidazole (1.1 equiv), benzene, 18 h, RT, 94%. d) alkyl iodide from c), AgNO_2 (1.5 equiv), 18 h, RT, 67%. e) i. **22**, PhNCO (3 equiv), Et_3N (0.5 equiv), toluene, 18 h, 90°C ; ii. H_2 , 10% Pd/C (5 wt%), Raney-Ni (5 wt%), $\text{B}(\text{OH})_3$ (3 equiv), MeOH/ H_2O (5:1), 36 h, RT, 67%. f) **23**, TsOH (0.1 equiv), 5 h, 100°C , 91%. g) 1 M vinylmagnesium bromide (5 equiv), CuCN (2.5 equiv), THF/HMPA (5:1), 10 min, 0°C , + **24**, 7 h, 0°C , 77%. h) i. TMSCH_2Li (5 equiv), pentane, -78°C ; + **25**; ii. O_3 , CH_2Cl_2 , -78°C ; Ph_3P (1.5 equiv), HF-pyridine, 1 h, 0°C ; iii. NaClO_2 (3 equiv), 2-methyl-2-butene (3 equiv), NaH_2PO_4 (1 equiv), acetone/ H_2O (30:1), RT, 1 h, 74%. i) **26**, DCC (1.5 equiv), N -(hydroxy)phthalimide (1.7 equiv), DMAP (0.05 equiv), THF, 18 h, RT, 84%. j) **27**, **28** (1.5 equiv), **29** (1.5 equiv), $i\text{Pr}_2\text{EtN}$ (2.25 equiv), $\text{Ru}(\text{bpy})_3(\text{BF}_4)_2$ (0.01 equiv), CH_2Cl_2 , blue LEDs, 2.5 h, RT, 61%. k) **31**, $\text{Me}_2\text{CuCNLi}_2$ (2.0 equiv), TBSCl (5 equiv), Et₂O/THF/HMPA (4:2:1), 1 h, -20°C , 76%. DIBAL-H = Diisobutylaluminum hydride. TsOH = *p*-toulenesulfonic acid. DCC = N,N' -dicyclohexylcarbodiimide. DMAP = 4-dimethylaminopyridine. HMPA = hexamethylphosphoramide.

**Scheme 3.**

Complimentary stereoselection in forming quaternary carbon stereocenters by the reaction of tertiary carbon radicals and tertiary organometallic intermediates with carbon electrophiles.