Total Synthesis

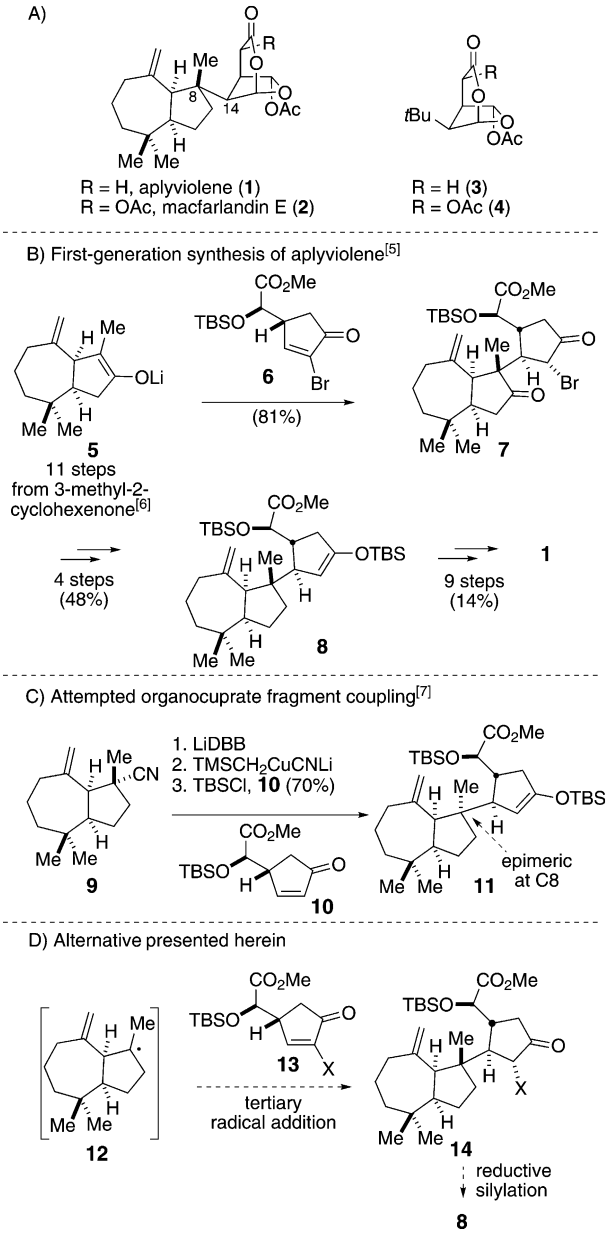
DOI: 10.1002/anie.201204977

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

*Martin J. Schnermann and Larry E. Overman**

Aplyviolene (**1**) and macfarlandin E (**2**, Scheme 1 A) 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** (Scheme 1 A),[4] as well as the first total synthesis of aplyviolene (outlined in Scheme 1 B).[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 (Scheme 1 C). 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**



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

(Scheme 1 D, 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

[*] Dr. M. J. Schnermann, Prof. L. E. Overman
Department of Chemistry, University of California Irvine
1102 Natural Sciences II, Irvine, CA 92697-2025 (USA)
E-mail: leoverma@uci.edu
Homepage: http://faculty.sites.uci.edu/overman/

[**] We thank Dr. Joe Ziller, University of California, Irvine, for the single-crystal X-ray analyses and Dr. John Greaves, University of California, Irvine, for mass spectrometric analyses. This research was supported by the NIH Neurological Disorders & Stroke Institute (Grant R01-NS12389), the NIH National Institutes of General Medical Sciences (Grant R01-GM098601), and by an NIH postdoctoral fellowship for M.J.S. (CA138084). NMR spectra, mass spectra, and the X-ray analyses were obtained at UC Irvine using instrumentation acquired with the assistance of NSF and NIH Shared Instrumentation grants. Unrestricted funds from Amgen and Merck are also gratefully acknowledged.

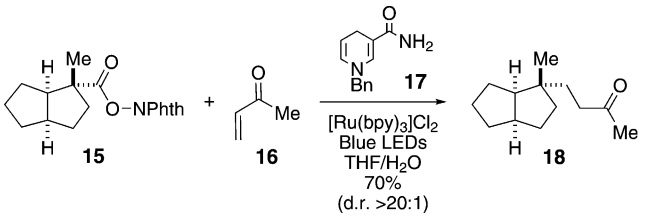
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201204977.

tertiary radicals to stereogenic quaternary carbons are extremely rare.[9] 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, $[Ru(bpy)_3]Cl_2$ (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-adamantanyl) 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 Scheme 1 D, 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/H_2O solution of (*N*-acyloxy)-phthalimide **15**[18] and methyl vinyl ketone (1.5 equiv) was coupled using 1 mol% of $[Ru(bpy)_3]Cl_2$, excess 1,4-dihydronicotinamide **17**, and 1.5 h irradiation with blue light to give adduct **18** in 70% yield (Scheme 2).[19] The coupling took place with high selectivity from the convex face (d.r. > 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 3). The synthesis began with inexpensive (+)-fenchone (**19**), which was readily transformed by Beckmann fragmentation to tertiary nitrile **20**.[20] Heating the oxime intermediate in 4 M H_2SO_4 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] Reduc-

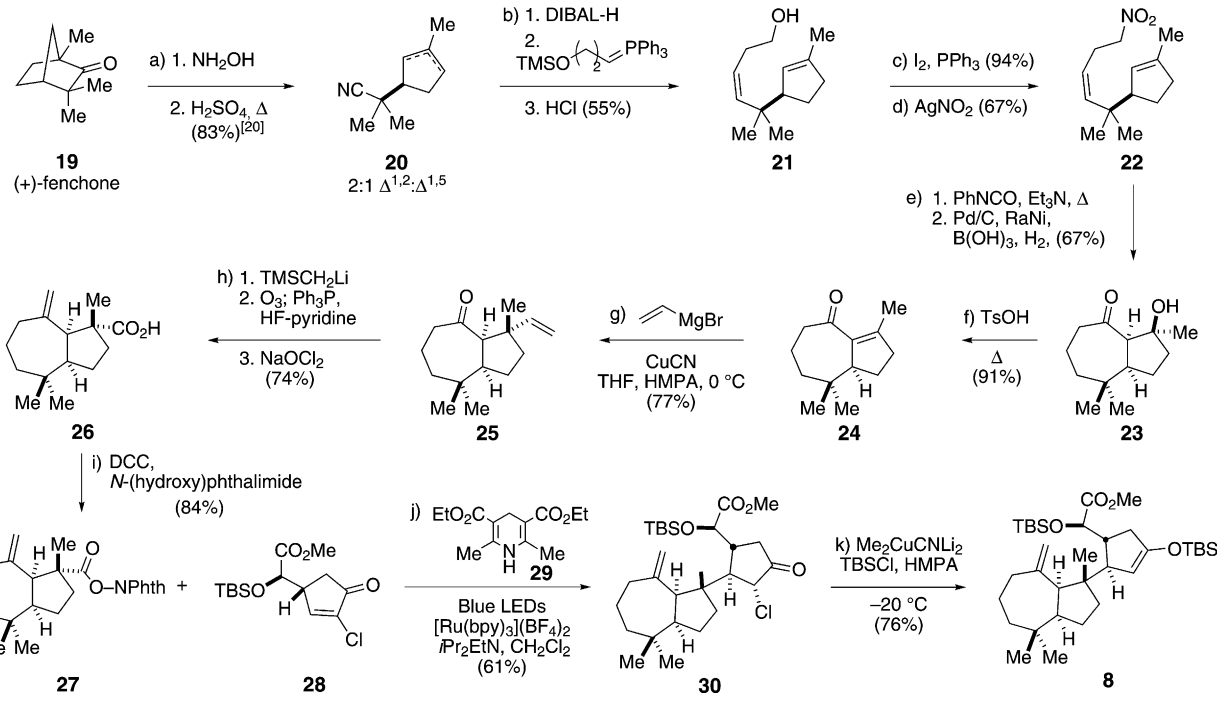


Scheme 2. Synthesis of **18**: a) **15**, **16** (1.5 equiv), **17** (1.5 equiv), $Ru(bpy)_3Cl_2$ (0.01 equiv), THF/H_2O (2:1), blue LEDs, RT, 90 min, 70%. NPhth = *N*-phthalimido; bpy = 2,2′-bipyridine.

tion of nitrile **20** with diisobutylaluminum hydride and *Z*-selective Wittig reaction of the resulting crude aldehyde products with 3-hydroxypropyltriphenylphosphonium 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)methyllithium in pentane at −78 °C provided the β-silyl alcohol adduct. Without purification, this intermediate was exposed sequentially to ozone in CH_2Cl_2 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.

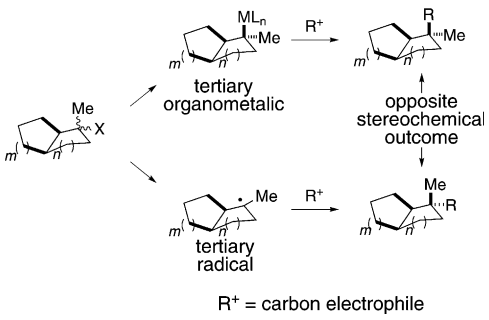
With convenient access to *cis*-perhydroazulene *N*-(acyloxy)phthalimide **27** in hand, we investigated the pivotal fragment-coupling reaction. To our delight, initial efforts to



Scheme 3. Formal total synthesis of (−)-aplyviolene: Synthesis of enoxysilane **8**: a) 1. **19**, sodium acetate (2 equiv), $NH_2OH{\cdot}HCl$ (1.75 equiv), EtOH, reflux, 36 h; 2. 4 M H_2SO_4, reflux, 8 h, 83% as a 2:1 mixture of $\Delta^{1,2}$:$\Delta^{1,5}$ isomers. b) 1. **20**, DIBAL-H (1.2 equiv), CH_2Cl_2, −78 °C, 1 h; 2. 3-hydroxypropyltriphenylphosphonium bromide (2 equiv), *n*BuLi (4 equiv), TMSCl (2 equiv), THF, 0 °C, 20 min; + aldehyde from step 1, −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) 1. **22**, PhNCO (3 equiv), Et_3N (0.5 equiv), toluene, 18 h, 90 °C; 2. H_2, 10% Pd/C (5 wt%), Raney-Ni (5 wt%), $B(OH)_3$ (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) 1. $TMSCH_2Li$ (5 equiv), pentane, −78 °C; + **25**; 2. O_3, CH_2Cl_2, −78 °C; Ph_3P (1.5 equiv), HF-pyridine, 1 h, 0 °C; 3. $NaClO_2$ (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*Pr_2EtN (2.25 equiv), $[Ru(bpy)_3](BF_4)_2$ (0.01 equiv), CH_2Cl_2, blue LEDs, 2.5 h, RT, 61%. k) **31**, $Me_2CuCNLi_2$ (2.0 equiv), TBSCl (5 equiv), Et_2O/THF/HMPA (4:2:1), 1 h, −20 °C, 76%. DIBAL-H = Diisobutylaluminum hydride; TsOH = *p*-toluenesulfonic acid; DCC = *N*,*N*′-dicyclohexylcarbodiimide; DMAP = 4-dimethylaminopyridine; HMPA = hexamethylphosphoramide.

implement the radical coupling of *N*-(acyloxy)phthalimide **27** and α-chlorocyclopentenone **28**[30,31] using only a minor modification (Scheme 3) 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 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**, $[Ru(bpy)_3](BF_4)_2$, 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



Scheme 4. Complimentary stereoselection in forming quaternary carbon stereocenters by the reaction of tertiary carbon radicals and tertiary organometallic intermediates with carbon electrophiles.

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 4). The generality of this observation and its exploitation in fragment coupling steps in stereoselective synthesis are under active investigation in our laboratories.

Received: June 25, 2012
Published online: August 24, 2012

Keywords: fragment-coupling · fused-ring systems · photoredox chemistry · terpenoids · total synthesis

[1] a) R. A. Keyzers, P. T. Northcote, M. T. Davies-Coleman, *Nat. Prod. Rep.* **2006**, *23*, 321; b) M. Gonzalez, *Curr. Bioact. Compd.* **2007**, *3*, 1.

[2] a) T. W. Hambley, A. Poiner, W. C. Taylor, *Tetrahedron Lett.* **1986**, *27*, 3281; b) J. S. Buckleton, P. R. Bergquist, R. C. Cambie, G. R. Clark, P. Karuso, C. E. F. Rickard, *Acta Crystallogr. Sect. C* **1986**, *42*, 1846; c) T. F. Molinski, D. J. Faulkner, C. H. He, G. D. Van Duyne, J. J. Clardy, *J. Org. Chem.* **1986**, *51*, 4564.

[3] For a discussion on the challenge of assembling attached-ring stereocenters and examples, see: L. E. Overman, E. J. Velthuisen, *J. Org. Chem.* **2006**, *71*, 1581.

[4] a) M. J. Schnermann, C. M. Beaudry, A. V. Egorova, R. S. Polishchuk, C. Sutterlin, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 6158; b) M. J. Schnermann, C. M. Beaudry, N. E. Genung, S. M. Canham, N. L. Untiedt, B. D. W. Karanikolas, C. Sutterlin, L. E. Overman, *J. Am. Chem. Soc.* **2011**, *133*, 17494.

[5] M. J. Schnermann, L. E. Overman, *J. Am. Chem. Soc.* **2011**, *133*, 16425.

[6] For the initial development of this strategy in the context of a total synthesis of a structurally less complex spongian diterpene, see: A. D. Lebsack, L. E. Overman, R. J. Valentekovich, *J. Am. Chem. Soc.* **2001**, *123*, 4851.

[7] M. J. Schnermann, N. L. Untiedt, G. Jiménez-Osés, K. N. Houk, L. E. Overman, *Angew. Chem.* **2012**, *124*, 9719; *Angew. Chem. Int. Ed.* **2012**, *51*, 9581.

[8] For select recent reviews, see: a) G. Bar, A. F. Parsons, *Chem. Soc. Rev.* **2003**, *32*, 251; b) G. S. C. Srikanth, S. L. Castle, *Tetrahedron* **2005**, *61*, 10377.

[9] No examples of the stereoselective formation of quaternary carbon stereocenters from intermolecular additions of alkyl-substituted tertiary radicals to alkenes are mentioned in a recent comprehensive treatise, see a) *Quaternary Stereocenters-Challenges and Solutions for Organic Synthesis* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**, pp. 287–314. We are aware of only one report of such reactions occurring with high stereoselectivity, see: b) A. Gansäuer, H. Bluhm, B. Rinker, S. Narayan, M. Schick, T. Lauterbach, M. Pierobon, *Chem. Eur. J.* **2003**, *9*, 531. For examples of such reactions that take place with poor to moderate diastereoselectivity, see: c) W. Damm, B. Giese, J. Hartung, T. Hasskerl, K. N. Houk, H. Zipse, *J. Am. Chem. Soc.* **1992**, *114*, 4067; and d) A. Srikrishna, P. Hemamalini, G. V. R. Sharma, *J. Org. Chem.* **1993**, *58*, 2509.

[10] For one example, see; J. Cossy, S. Bouzbouza, A. Hakiki, *Tetrahedron* **1999**, *55*, 11289.

[11] The addition of achiral tertiary radicals to chiral alkenes often take place with higher diastereoselectivity than the corresponding reactions of secondary and primary radicals; see, for example: a) B. Giese, T. Witzel, *Tetrahedron Lett.* **1987**, *28*, 2571; b) T. Toru, Y. Watanabe, M. Tsusaka, Y. Ueno, *J. Am. Chem. Soc.* **1993**, *115*, 10464; c) A. Hayen, R. Koch, W. Saak, D. Haase, J. O. Metzger, *J. Am. Chem. Soc.* **2000**, *122*, 12458.

[12] There are many examples of the use of tertiary radicals generated from Barton esters to form achiral quaternary carbons, see: a) D. H. R. Barton, D. Crich, G. Kretzschmar, *Tetrahedron Lett.* **1984**, *25*, 1055; b) D. H. R. Barton, D. Crich, G. Kretzschmar, *J. Chem. Soc. Perkin Trans. 1* **1986**, 39.

[13] A. Lebsack, Ph.D. Dissertation, University of California, Irvine (USA), **2002**.

[14] K. Okada, K. Okamoto, N. Morita, K. Okubo, M. Oda, *J. Am. Chem. Soc.* **1991**, *113*, 9401.

[15] a) Okada also reported light-promoted decarboxylative reduction, chlorination, and selenylation of *N*-(acyloxy)phthalimides, see: b) K. Okada, K. Okamoto, M. Oda, *J. Am. Chem. Soc.* **1988**, *110*, 8736; c) K. Okada, K. Okamoto, M. Oda, *J. Chem. Soc. Chem. Commun.* **1989**, 1636; d) K. Okada, K. Okubo, N. Morita, M. Oda, *Chem. Lett.* **1993**, 2021; e) K. Okada, K. Okubo, N. Morita, M. Oda, *Tetrahedron Lett.* **1992**, *33*, 7377; f) two other groups have used this decarboxylative reduction, see: g) M. J. Fisher, C. D. Myers, J. Joglar, S. H. Chen, S. J. Danishefsky, *J. Org. Chem.* **1991**, *56*, 5826; h) M. Cano, G. Fabrias, F. Camps, J. Joglar, *Tetrahedron Lett.* **1998**, *39*, 1079.

[16] For important recent contributions, see: a) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77; b) M. A. Ischay, M. E. Anzovino, J. Du, T. P. Yoon, *J. Am. Chem. Soc.* **2008**, *130*, 12886; c) D. A. Nagib, M. E. Scott, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 10875; d) J. M. R. Narayanam, J. W. Tucker, C. R. J. Stephenson, *J. Am. Chem. Soc.* **2009**, *131*, 8756.

[17] For recent reviews, see: a) K. Zeitler, *Angew. Chem.* **2009**, *121*, 9969; *Angew. Chem. Int. Ed.* **2009**, *48*, 9785; b) T. P. Yoon, M. A. Ischay, J. Du, *Nat. Chem.* **2010**, *2*, 527; c) J. M. R. Narayanam, C. R. J. Stephenson, *Chem. Soc. Rev.* **2011**, *40*, 102; d) F. Telpy, *Collect. Czech. Chem. Commun.* **2011**, *76*, 859; e) J. W. Tucker, C. R. J. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617.

[18] Available in five steps from cyclooctene oxide, see Supporting Information for details.

[19] An excess (1.5 equiv) of the hydrogen donor was required to suppress over-addition of methyl vinyl ketone. The use of blue LEDs strips was experimentally convenient; the reaction took place in similar yield using a compact fluorescent bulb.

[20] W. Kreiser, P. Below, *Liebigs Ann. Chem.* **1985**, 203.

[21] The hydroxy group of the ylide was protected in situ as a trimethylsilyl ether and then cleaved during workup using 2 N hydrochloric acid, see: M. Couturier, Y. L. Dory, F. Rouillard, P. Deslongchamps, *Tetrahedron* **1998**, *54*, 1529.

[22] a) The displacement of the primary iodide with silver nitrite was most effective in the absence of solvent, in which case only a slight excess of $AgNO_2$ was required; b) This reaction is typically carried out in ethereal solvents using 3–5 equiv of $AgNO_2$; see, for example: A. T. Hewson, D. T. Macpherson, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2625.

[23] For the use of this approach in forming a perhydroazulene ring system, see: A. P. Kozikowski, B. B. Mugrage, B. C. Wang, Z. B. Xu, *Tetrahedron Lett.* **1983**, *24*, 3705.

[24] T. Mukaiyama, T. Hoshino, *J. Am. Chem. Soc.* **1960**, *82*, 5339.

[25] D. P. Curran, *J. Am. Chem. Soc.* **1983**, *105*, 5826.

[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 **23** 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 (Et_4NCl_3), at 0°C.[31]
[31] T. Schlama, K. Gabriel, V. Gouverneur, C. Mioskowski, *Angew. Chem.* **1997**, *109*, 2440; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2342.
[32] The relative configuration of **30** was secured by crystallographic analysis: CCDC 885482 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[33] The use of the corresponding α-bromoenone (**13**, X = Br) in the radical coupling reaction resulted in extensive reductive debromination of coupled product.
[34] a) R. S. Andrews, J. J. Becker, M. R. Gagné, *Angew. Chem.* **2010**, *122*, 7432; *Angew. Chem. Int. Ed.* **2010**, *49*, 7274; b) R. S. Andrews, J. J. Becker, M. R. Gagné, *Org. Lett.* **2011**, *13*, 2406.
[35] In line with previous observations,[16d,34] we found that the use of **29** in conjunction with *N*,*N*-disopropylethylamine was essential for realizing high yields and short reaction times.

