

UC Irvine

UC Irvine Previously Published Works

Title

Short Enantioselective Total Syntheses of trans-Clerodane Diterpenoids: Convergent Fragment Coupling Using a trans-Decalin Tertiary Radical Generated from a Tertiary Alcohol Precursor

Permalink

<https://escholarship.org/uc/item/4z3976wg>

Journal

The Journal of Organic Chemistry, 81(16)

ISSN

0022-3263

Authors

Slutskyy, Yuriy
Jamison, Christopher R
Lackner, Gregory L
et al.

Publication Date

2016-08-19

DOI

10.1021/acs.joc.6b00697

Peer reviewed

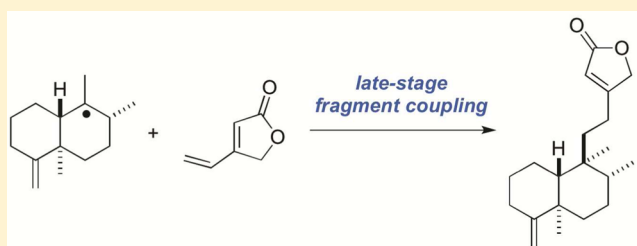
Short Enantioselective Total Syntheses of *trans*-Clerodane Diterpenoids: Convergent Fragment Coupling Using a *trans*-Decalin Tertiary Radical Generated from a Tertiary Alcohol Precursor

Yuriy Slutskey,[†] Christopher R. Jamison,[†] Gregory L. Lackner,[†] Daniel S. Müller, André P. Dieskau, Nicholas L. Untiedt, and Larry E. Overman*

Department of Chemistry, University of California, 1102 Natural Sciences II, Irvine, California 92697-2025, United States

S Supporting Information

ABSTRACT: The evolution of a convergent fragment-coupling strategy for the enantioselective total synthesis of *trans*-clerodane diterpenoids is described. The key bond construction is accomplished by 1,6-addition of a *trans*-decalin tertiary radical with 4-vinylfuran-2-one. The tertiary radical is optimally generated from the hemioxalate salt of the corresponding tertiary alcohol upon activation by visible light and an Ir(III) photoredox catalyst. The enantioselective total synthesis of *trans*-clerodane diterpenoid **1** reported here was accomplished in seven steps from 3-methyl-2-cyclohexenone. The synthetic strategy described in this report allows a number of *trans*-clerodane diterpenoids to be synthesized in enantioselective fashion by synthetic sequences of 10 steps or less. This study illustrates a powerful tactic in organic synthesis in which a structurally complex target structure is disconnected at a quaternary carbon stereocenter to fragments of comparable complexity, which are united in the synthetic pathway by conjugate addition of a nucleophilic tertiary radical to a fragment harboring an electron-deficient C=C double bond.



INTRODUCTION

The clerodane family of diterpenoid natural products is composed of more than 650 secondary metabolites isolated from various plant sources.¹ Many clerodane diterpenoids are known to exhibit antifeedant activity,¹ whereas the biological activity reported for certain members is much more extensive.² The *trans*-clerodane subset of this family of natural products, represented by **1**,³ solidagolactone (**2**),³ 16-hydroxycleroda-3,13-dien-15,16-olide (**3**, referred to as PL3 or HCD),^{2,4} and annonene (**4**)⁵ (Figure 1), is structurally characterized by a *trans*-decalin core harboring four contiguous stereocenters, two of which are 1,3-related quaternary carbons. As a result of this structural complexity, early total syntheses of *trans*-clerodanes, including those of **3**⁶ and **4**,⁷ required lengthy sequences to install the contiguous stereocenters and fashion the C-9 quaternary stereocenter.⁸

We recently reported that 1,6-addition of a *trans*-decalin cuprate or nucleophilic tertiary radical intermediates **5** to 4-vinylfuran-2-one (**6**) could be employed to join the decalin and side-chain fragments and fashion the C-9 quaternary stereocenters of *trans*-clerodane diterpenoids **1** and **2**.⁹ Straightforward manipulation of **1** then secured the total syntheses of diterpenoids **2**–**4**. The recent development of alcohol-derived hemioxalate salts as convenient precursors of tertiary radicals upon activation by visible light and a photoredox catalyst¹⁰ allowed us to considerably streamline the radical-based approach. Detailed herein is the development of this optimized fragment-coupling strategy, which led to extremely short

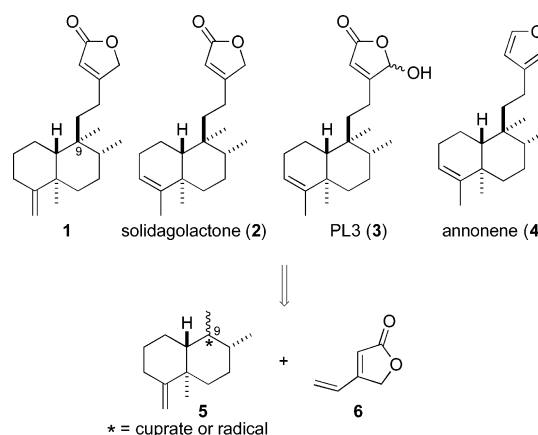


Figure 1. Four representative *trans*-clerodane diterpenoids and a fragment-coupling strategy for their synthesis.

enantioselective total syntheses of *trans*-clerodane diterpenoids **1**–**4**.

RESULTS AND DISCUSSION

Initial Exploration of the Fragment-Coupling Strategy. Our preliminary investigations focused on identifying

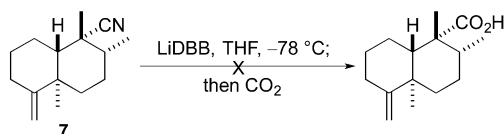
Special Issue: Photocatalysis

Received: March 31, 2016

Published: June 2, 2016

viable precursors for generating either the tertiary organocuprate or tertiary radical intermediates **5**. We postulated that a tertiary organometallic reagent could be most easily formed by reductive lithiation of a tertiary nitrile¹¹ or phenyl thioether,¹² followed by transmetalation to copper. We elected to compare the reductive lithiation of the tertiary nitrile **7** and thioether **8**,⁹ which were prepared readily as racemates using chemistry largely developed by Piers (Figure 2).¹³ We were surprised to

A. Attempted generation of an organolithium from nitrile



B. Forming a thioether-derived cuprate and its reaction with 6

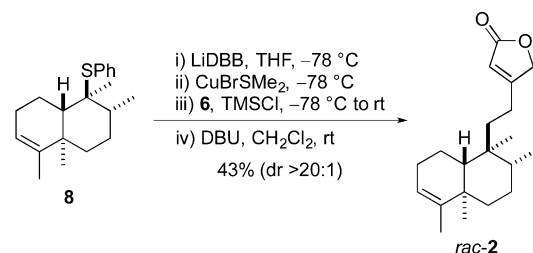
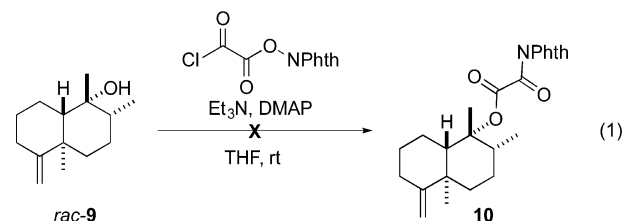


Figure 2. Comparison of a nitrile and a phenyl sulfide as precursors of a tertiary cuprate intermediate.

observe that the reductive lithiation of tertiary nitrile **7** at $-78\text{ }^{\circ}\text{C}$ was inefficient, as subjection of **7** to 2.2 equiv of lithium 4,4'-(di-*tert*-butyl)biphenylide (LiDBB) in THF at $-78\text{ }^{\circ}\text{C}$, followed by attempted trapping of the organolithium with CO_2 , resulted in nearly quantitative recovery of the tertiary nitrile. In contrast, reductive lithiation of tertiary thioether **8** took place readily under identical conditions. Thus, treatment of **8** with 2.2 equiv of LiDBB in THF at $-78\text{ }^{\circ}\text{C}$, followed successively by transmetalation with 1 equiv of $\text{CuBr}\cdot\text{SMe}_2$ and addition to 4-vinylfuran-2-one (**6**) in the presence of TMSCl, gave exclusively the product of 1,6-addition as a mixture of double-bond isomers. By exposing this crude mixture to DBU in dichloromethane, the isomeric products converged to form racemic (\pm)-solidagolactone (*rac*-**2**) in 43% overall yield from thioether **8**.⁹ The coupling of the tertiary organocuprate with the conjugate acceptor **6** occurred with high stereoselectivity exclusively from the less hindered β -face of the *trans*-octahydronaphthalene nucleophile. This outcome contrasts with the coupling reactions of *cis*-perhydropentalene and *cis*-perhydroazulene cuprates that we had studied previously, which took place preferentially from the more hindered concave face.^{11a} We attribute the stereoselection observed in forming

rac-**2** as arising from the severe steric impediment for the coupling to take place from the face proximal to the α -oriented angular methyl group. The coupling partner, 4-vinylfuran-2-one (**6**), is commercially available on scale^{14a} or prepared in two steps from tetrone acid following a literature procedure.^{14b}

We next examined potential precursors from which the alternative tertiary radical intermediate could be generated and coupled with 4-vinylfuran-2-one (**6**). Our recent introduction of *tert*-alkyl-(*N*-phthalimidyl)oxalates as precursors of tertiary carbon radicals suggested that the radical coupling might be accomplished using such a precursor.¹⁵ However, we found that attempted acylation of tertiary alcohol *rac*-**9** with (*N*-phthalimidyl)chlorooxalate in the presence of Et_3N and catalytic DMAP returned only the starting alcohol (eq 1). A brief survey of more forcing conditions, including preformation of various tertiary alkoxide intermediates from alcohols and their reaction with (*N*-phthalimidyl)chlorooxalate, resulted in substantial decomposition of the sensitive (*N*-phthalimidyl)-oxalate products. We then elected to perform the fragment coupling using the visible-light photoredox catalyzed method pioneered by Okada for generating tertiary radicals from carboxylic acid-derived (*N*-acyloxy)phthalimides,¹⁶ since recent studies from our laboratory had shown that the reductive coupling of these substrates with electron-deficient alkenes is especially robust.¹⁷



High-yielding 1,6-addition of carbon radicals to electron-deficient 1,3-dienes appears to be extremely rare,^{18,19} in contrast to the well-established 1,6-addition of organocuprate intermediates.^{19,20} We chose to initially explore this approach using the simpler (*N*-acyloxy)phthalimide **11** derived from trimethylacetic acid. Salient results of our optimization of the 1,6-coupling of the *tert*-butyl radical generated from **11** with 4-vinylfuran-2-one (**6**) are summarized in Table 1. Using conditions that we had optimized for the 1,4-addition of tertiary radicals to electron-deficient alkenes,^{17b} **11** did provide the coupled product **12** accompanied by trace amounts of β,γ -unsaturated lactones **13** (entry 1). This product distribution would be inconsequential, as treatment with base had been shown previously to converge regioisomeric products of this type. More problematic was the formation of a significant amount of a product **14** containing two *tert*-butyl butenolide fragments. Such a product would arise from dimerization of the delocalized allylic radical intermediate **A** at the carbon adjacent

Scheme 1. Synthesis of Cesium Oxalate *rac*-**20** and Its Photoredox Coupling with 4-Vinylfuran-2-one (**6**)

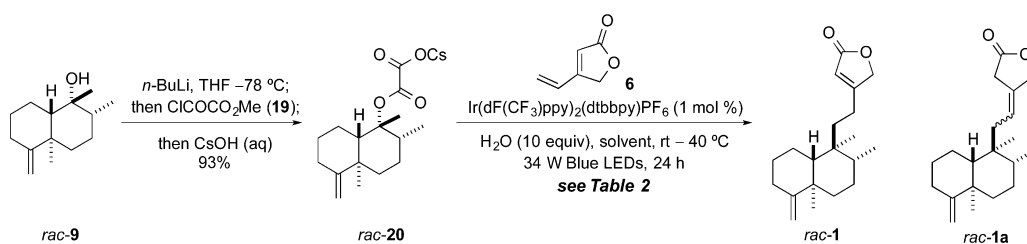


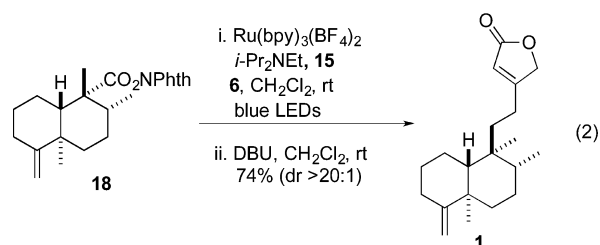
Table 1. Optimizing the 1,6-Addition of the *tert*-Butyl Radical Generated from *N*-(Acyloxy)phthalimide Precursor 11 with 4-Vinylfuran-2-one (6)^a

| entry | photocatalyst | reductant (equiv) | yield 12 ^b (%) | yield 13 ^b (%) | yield 14 ^b (%) |
|----------------|--|-------------------|---------------------------|---------------------------|---------------------------|
| 1 | Ru(bpy) ₃ (BF ₄) ₂ | 15 (1.5) | 36 | <5 | 30 |
| 2 ^c | Ir(ppy) ₃ | 15 (1.5) | 0 | 0 | 0 |
| 3 | Ir(dF(CF ₃)ppy) ₂ (dtbbpy)PF ₆ | 15 (1.5) | 24 | 0 | 42 |
| 4 ^c | Ir(dtbbpy)ppy ₂ PF ₆ | 15 (1.5) | 25 | 0 | 33 |
| 5 | Ru(bpz) ₃ (PF ₆) ₂ | 15 (1.5) | 0 | 0 | 0 |
| 6 | Ru(bpy) ₃ (BF ₄) ₂ | 16 (1.5) | 27 | 20 | 9 |
| 7 | Ru(bpy) ₃ (BF ₄) ₂ | 17 (1.5) | 66 | 9 | <5 |
| 8 | Ru(bpy) ₃ (BF ₄) ₂ | 15 (5) | 46 | <5 | 34 |
| 9 ^d | Ru(bpy) ₃ (BF ₄) ₂ | 15 (5) | 25 | 75 | 0 |

^aConditions unless otherwise noted: 11 (1 equiv), 6 (1.3 equiv), photocatalyst (0.01 equiv), *i*-Pr₂NEt (2.2 equiv), reductant (1.5 or 5 equiv), 0.15 M (with respect to 11) in CH₂Cl₂, rt, 18 h, blue LEDs. ^bDetermined by ¹H NMR integration relative to an internal standard (1,4-dimethoxybenzene). ^cA compact fluorescent light was used in place of blue LEDs. ^dThe concentration of 11 was 0.02 M.

to the carbonyl group, followed by isomerization of the double bonds into conjugation with the lactone carbonyl group. Speculating that the reduction potential of the catalyst might affect the termination sequence,²¹ we screened several common visible-light photoredox catalysts in an attempt to minimize the formation of 14. Of the iridium photocatalysts examined, Ir(ppy)₃ did not promote the reaction, whereas Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ provided primarily radical dimer 14 (entries 2–4). Ru(bpz)₃(BF₄)₂, whose +1 oxidation state is a much poorer reductant than Ru(bpy)₃¹⁺, also promoted no reactivity (entry 5). We also examined in addition to Hantzsch ester 15 the use of two other reductive quenchers, 16²² and 17,²³ with Ru(bpy)₃(BF₄)₂. Both reduced the formation of product 14 (entries 6 and 7), with 17 delivering a 75% overall yield of 1,6-addition products. Ultimately, we found that the highest yields of adducts 12 and 13 were obtained, while the formation of radical dimer 14 was avoided by conducting the reaction at higher dilution (0.02 M) using an excess of the dihydropyridine reductant 15 (entry 9).²⁴

Fortunately, the direct application of these conditions to the coupling of decalin tertiary radical formed from enantioenriched (*N*-acyloxy)phthalimide 18 gave in high yield the desired 1,6-adducts as a mixture of double-bond isomers (eq 2).⁹ Equilibration of these crude products with DBU afforded the *trans*-clerodane diterpenoid 1 as a single stereoisomer at the newly formed C-9 quaternary carbon stereocenter. As expected,¹⁷ this coupling took place exclusively from the less hindered β-face of the *trans*-decalin tertiary radical intermediate. In addition, the yield of the coupled product 1 was significantly higher than that realized in the related coupling of an organocuprate intermediate (Figure 2B).



Fragment Coupling Using a Hemioxalate Salt as the Precursor of the Tertiary Radical. The enantioselective total synthesis of 1 and the derived *trans*-clerodanes 2–4 that we reported earlier⁹ suffered from the extra steps involved in introducing the carboxyl functionality in precursor of (*N*-acyloxy)phthalimide 18, steps made necessary by our inability to form (*N*-phthalimidoyl)oxalate 10 from the readily available tertiary alcohol *rac*-9 (eq 1). As a result of the relative stability of cesium salts of tertiary hemioxalates, it seemed likely that the method recently introduced from our and the MacMillan laboratories for generating tertiary radicals from cesium oxalate derivatives of tertiary alcohols under visible-light photoredox conditions might be successful with *trans*-decalin alcohol 9.¹⁰

This possibility was initially pursued in the racemic series (Scheme 1). Although the highly hindered, axial tertiary alcohol *rac*-9¹⁰ did not react with methyl chlorooxacetate (19) in the presence of DMAP and triethylamine, initial deprotonation of *rac*-9 in THF with *n*-BuLi at −78 °C, followed by the addition of 1.5 equiv of 19 and allowing the reaction to warm to room temperature, generated the mixed oxalate diester in nearly quantitative yield. Exposure of a THF solution of this crude intermediate to just less than 1 equiv of aqueous CsOH provided cesium salt *rac*-20 in 93% yield upon concentration of the aqueous layer.

Optimization of the 1,6-conjugate addition of the tertiary carbon radical, generated from alkyl cesium oxalate *rac*-20, to 4-

vinylfuran-2-one (**6**) was explored next (Table 2). Guided by the results from our previous studies with (*N*-acyloxy)-

Table 2. Optimization of the 1,6-Addition of the *trans*-Decalin Radical Generated from Alkylcesium Oxalate *rac*-20 with 4-Vinylfuran-2-one (6**)**

| entry | solvent ^a (M) | <i>rac</i> -20 (equiv) | 6 (equiv) | yield ^b (%) |
|-------|-------------------------------------|------------------------|------------------|---|
| 1 | 3:1 DME/DMF (0.05 M) | 1.1 | 1 | 63, <i>rac</i> -1 (57) ^c |
| 2 | 3:1 DME/DMF (0.05 M) | 1.5 | 1 | 98, <i>rac</i> -1 (65) ^c |
| 3 | 3:1 DMF/CH ₃ CN (0.05 M) | 1 | 1 | 48, <i>rac</i> -1 |
| 4 | 3:1 DMF/THF (0.05 M) | 1 | 1 | 52, <i>rac</i> -1 |
| 5 | 3:1 DME/CH ₃ CN (0.05 M) | 1 | 1 | 66, <i>rac</i> -1 |
| 6 | 3:1 DME/THF (0.05 M) | 1 | 1 | 70, <i>rac</i> -1 10, <i>rac</i> -1a |
| 7 | 3:1 THF/DME (0.05 M) | 1 | 1 | 47, <i>rac</i> -1 10, <i>rac</i> -1a |
| 8 | 3:1 DME/THF (0.01 M) | 1 | 1 | 65, <i>rac</i> -1 11, <i>rac</i> -1a |
| 9 | 3:1 DME/THF (0.2 M) | 1 | 1 | 41, <i>rac</i> -1 8, <i>rac</i> -1a |
| 10 | 3:1 DME/THF (0.2 M) | 1 | 2 | 66, <i>rac</i> -1 8, <i>rac</i> -1a |

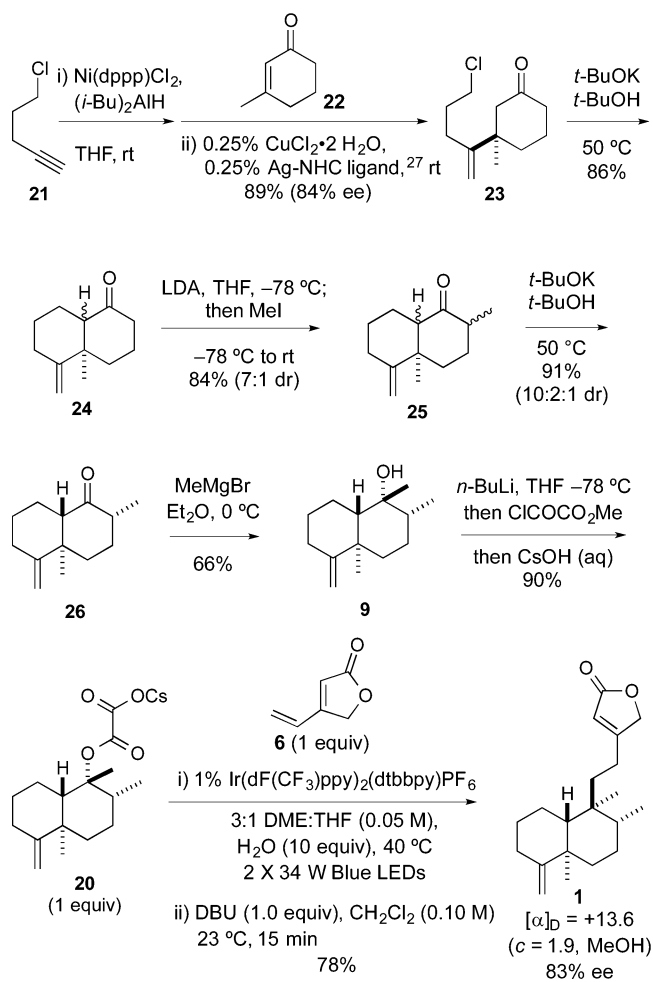
^aConcentration is reported with respect to cesium oxalate *rac*-20.

^bDetermined by ¹H NMR integration relative to an internal standard (1,2-dibromo-4,5-methylenedioxybenzene). ^cYield with respect to cesium oxalate *rac*-20.

phthalimide **18**, the coupling of *rac*-20 with **6** was performed under high dilution to avoid dimerization of the intermediate allylic radical, providing the desired coupling product *rac*-1 in 63% yield (entry 1). Utilization of an excess of the radical precursor *rac*-20 had a minor effect on the efficiency of the reaction with respect to the more valuable coupling partner (entry 2). Solvent combinations that proved to be advantageous in other reactions utilizing *tert*-alkylcesium oxalates were investigated next (entries 3–7), identifying a 3:1 mixture of DME/THF to be optimal for this transformation. Under these reaction conditions, the double-bond regioisomers, *rac*-1 and *rac*-1a,²⁵ were formed and subsequently equilibrated with DBU in the final step of the synthesis (vide infra). Attempts to further increase the efficiency of the coupling via changes in concentration of the reaction mixture (entries 8 and 9) or employing an excess of 4-vinylfuran-2-one (**6**) (entry 10) were unsuccessful.

Scheme 2 summarizes the use of the visible-light photoredox reaction of a *trans*-decalin cesium hemioxalate **20** with 4-vinylfuran-2-one (**6**) to achieve a short enantioselective total synthesis of *trans*-clerodane diterpenoid **1**. The synthesis begins with the enantioselective construction of *trans*-decalone **26** following the general lines outlined much earlier by Piers in the racemic series.¹³ To render this sequence enantioselective, the first intermediate, 3,3-disubstituted (*R*)-cyclohexanone **23**, was prepared by catalytic enantioselective conjugate addition of a vinyl cuprate to 3-methyl-2-cyclohexenone (**22**).²⁶ Specifically, two methods pioneered by Hoveyda were utilized: Ni-catalyzed regioselective hydroalumination of chloroalkyne **21**²⁷ and Cu–NHC-catalyzed 1,4-addition of the internal vinylallene intermediate to 3-methyl-2-cyclohexenone (**22**)²⁸ to furnish (*R*)-cyclohexanone **23** in 89% yield and 84% ee. Cyclization of **23** with *t*-BuOK provided decalone **24**, a 2.8:1 mixture of *trans*/*cis*

Scheme 2. Seven-Step Enantioselective Total Synthesis of *trans*-Clerodane Diterpenoid **1**



stereoisomers, in 77% overall yield from enone **22**. Methylation of decalone **24**, followed by *t*-BuOK-catalyzed equilibration provided **26** as a 10:2:1 mixture of diastereomers. Reaction of **26** with methylmagnesium bromide delivered *trans*-decalin alcohol **9**, which could be isolated in diastereomeric purity in 66% yield from **26**. Next, the one-pot acylation/saponification procedure described previously provided oxalate salt **20** in 90% yield. The pivotal coupling of *trans*-decalin cesium oxalate **20** and butenolide **6** was carried out with equimolar amounts of the two coupling partners using the optimized visible-light photoredox conditions identified in our exploratory study (Table 2) to give **1** and its β,γ-unsaturated isomer as single epimers at the newly formed C-9 quaternary carbon stereocenter. Exposure of the crude product mixture to DBU at room temperature furnished *trans*-clerodane **1**, [α]_D +12.9 (c = 0.43, CHCl₃) and +13.6 (c = 1.9, MeOH), in 78% yield.²⁹ NMR data of synthetic (+)-**1** were identical to those observed previously by us⁹ and fully consistent with data described for natural **1**, whose rotation at the sodium D line was reported to be +15.2 (c = 1.9, MeOH).³

CONCLUSION

The enantioselective total synthesis of (+)-*trans*-clerodane diterpenoid **1** described in detail herein and our previous synthesis of (+)-**1** and congeners **2–4** illustrate a powerful tactic in organic synthesis in which a target structure is

disconnected at a quaternary carbon stereocenter to yield fragments of comparable complexity, which are united in the synthesis by conjugate addition of a tertiary radical to a fragment harboring alkene, or in this case diene, functionality.³⁰ The selection of the precursor for generating the tertiary carbon radical intermediate is an important consideration. The short enantioselective total synthesis of (+)-clerodane diterpenoid **1** summarized in Scheme 2 exploits the use of tertiary alcohols as convenient precursors of tertiary carbon radicals upon activation by visible light and photoredox catalyst.¹⁰ Of critical importance, the coupling of *trans*-decalin cesium oxalate **20** and vinyl butenolide **6** was carried out in 78% yield using equimolar amounts of the two coupling partners. This enantioselective total synthesis of (+)-**1** was accomplished in seven steps from 3-methyl-2-cyclohexenone. As the *trans*-clerodane diterpenoids (–)-solidagolactone (**2**), (–)-PL3 (**3**), and (–)-annonene (**4**) have previously been prepared from (+)-**1** in one to three additional steps,⁹ the synthetic strategy described in this report provides enantioselective access to a number of *trans*-clerodane diterpenoids by short sequences of 10 steps or less. We anticipate that convergent synthetic strategies that unite complex fragments by the reaction of structurally elaborate tertiary carbon radicals with radical acceptors will find many future applications in the construction of complex molecules.

EXPERIMENTAL SECTION

Materials and Methods. Experimental procedures and characterization data for **1–4**, **7**, **8**, *rac*-**9**, **18**, and **22–25** have been reported previously.⁹ The synthesis of *rac*-**20** and its characterization data have also been reported.¹⁰ A procedure for the radical addition reported in Table 2 has also been described previously in the racemic series.¹⁰ Unless stated otherwise, reactions were conducted in oven-dried glassware under an atmosphere of argon using anhydrous solvents (either freshly distilled or passed through activated alumina columns). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde, ceric ammonium molybdate, or potassium permanganate. Flash chromatography was performed using 40–63 μ m EMD Chemicals silica gel 60 Å geduran silica gel. ¹H NMR spectra were recorded at 500 or 600 MHz, and chemical shifts are reported relative to deuterated solvent signals. Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. ¹³C NMR spectra were recorded at 125 or 150 MHz. Data for ¹³C NMR spectra are reported in terms of chemical shift. IR spectra were recorded on an FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{–1}). High-resolution mass spectra were obtained using a conventional instrument having a TOF analyzer, and Blue LEDs (30 cm, 1 W) were purchased from <http://www.creativelightings.com> (product code CL-FRS5050-12WP-12 V) and were powered by 8 AA batteries. Kessil KSH150B LED Grow Light 150, Blue LEDs, used in cesium oxalate couplings, were purchased from <http://www.amazon.com>.

1,3-Dioxoisindolin-2-yl Pivalate (11). Pivalic acid (2.00 g, 19.6 mmol, 1 equiv) and *N*-hydroxyphthalimide (4.80 g, 29.4 mmol, 1.5 equiv) were dissolved in THF (200 mL) under an argon atmosphere. After sequential addition of dicyclohexylcarbodiimide (6.07 g, 29.4 mmol, 1.5 equiv) and DMAP (120 mg, 0.98 mmol, 0.05 equiv), the reaction mixture was stirred for 18 h at rt. The mixture was concentrated under reduced pressure, and the resulting residue was suspended in Et₂O (200 mL) and transferred to a separatory funnel. The organic layer was washed with saturated aqueous NH₄Cl solution (3 \times 150 mL) and brine (2 \times 150 mL) and was dried over MgSO₄. The drying agent was removed by filtration, and the filtrate was concentrated under reduced pressure. The crude residue obtained was purified by silica gel chromatography (7% EtOAc/hexanes) to provide

the (*N*-acyloxy)phthalimide **11** (3.68 g, 14.9 mmol, 76%) as a colorless solid. Characterization data matched that previously reported.³¹

4-(3,3-Dimethylbutyl)furan-2(5H)-one (12), (E)- and (Z)-4-(3,3-Dimethylbutylidene)dihydrofuran-2(3H)-one (13), and 4,4'-Bis(3,3-dimethylbutyl)[3,3'-bifuran]-2,2'(5H,5'H)-dione (14): General Procedure for 1,6-Radical Addition Optimization Reported in Table 1. (Table 1, entry 1 is described.) A solution of 4-vinylfuran-2-one³² in Et₂O (0.53 M, 610 μ L, 0.34 mmol, 1.3 equiv) was added to a 1-dram vial, and the solution was concentrated under reduced pressure. The residue was immediately dissolved in CH₂Cl₂ (1.5 mL, previously sparged with Ar for 5 min) under an argon atmosphere. After sequential addition of (*N*-acyloxy)phthalimide **11** (64 mg, 0.26 mmol, 1 equiv), Hantzsch ester **15**³³ (100 mg, 0.39 mmol, 1.5 equiv), *i*-Pr₂NEt (100 μ L, 0.57 mmol, 2.2 equiv), and a solution¹⁷ of Ru(bpy)₃(BF₄)₂ in CH₂Cl₂ (0.01 M, 260 μ L, 0.003 mmol, 0.01 equiv) under Ar, the 1-dram vial was capped and placed in the center of a 30 cm loop of blue LEDs. The reaction mixture was stirred at rt under visible light irradiation for 18 h, after which time a solution of 1,4-dimethoxybenzene (36 mg, 0.26 mmol, 1 equiv) in CH₂Cl₂ (1 mL) was added. The reaction mixture was stirred for 1 min, and a small aliquot was removed and concentrated under reduced pressure. ¹H NMR analysis of the residue and comparison of relative peak integrations using 1,4-dimethoxybenzene as an internal standard was used to determine the yield of products obtained. Silica gel chromatography (10% acetone/hexanes) of the crude mixture provided analytically pure samples of **12–14**.

4-(3,3-Dimethylbutyl)furan-2(5H)-one (12): R_f = 0.16 (10% acetone/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 5.80–5.83 (m, 1H), 4.74 (s, 2H), 2.32–2.38 (m, 2H), 1.43–1.48 (m, 2H), 0.93 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 174.3, 171.4, 115.1, 73.2, 41.2, 30.4, 29.2, 24.2; IR (thin film) 2955, 2868, 1781, 1748, 1638, 1027 cm^{–1}; HRMS (ESI-TOF) m/z calcd for C₁₀H₁₆O₂Na (M + Na⁺) 191.1048, found 191.1054.

(E)- and (Z)-4-(3,3-Dimethylbutylidene)dihydrofuran-2(3H)-one (13), a 2.6:1 mixture of double-bond isomers: R_f = 0.3 (10% acetone/hexanes); ¹H NMR (500 MHz, CDCl₃, mixture of isomers) δ 5.50–5.60 (m, 1H, major and minor isomers), 4.85–4.88 (m, 2H, major and minor isomers), 3.22–3.25 (m, 2H, major isomer), 3.13–3.15 (m, 2H, minor isomer), 1.90 (d, J = 7.5 Hz, 2H, minor isomer), 1.82 (d, J = 7.5 Hz, 2H, major isomer), 0.91 (s, 9H, major and minor isomers); ¹³C NMR (125 MHz, CDCl₃, mixture of isomers) δ 175.9, 175.8, 130.1, 129.6, 122.7, 122.2, 72.5, 70.7, 43.9, 42.6, 34.0, 31.9, 31.73, 31.68, 29.34, 29.29; IR (thin film) 2955, 1785, 1364, 1163, 1028 cm^{–1}; HRMS (ESI-TOF) m/z calcd for C₁₀H₁₆O₂Na (M + Na⁺) 191.1048, found 191.1057.

4,4'-Bis(3,3-dimethylbutyl)[3,3'-bifuran]-2,2'(5H,5'H)-dione (14): R_f = 0.12 (10% acetone/hexanes); ¹H NMR (500 MHz, CDCl₃) δ 4.87 (s, 4H), 2.45–2.50 (m, 4H), 1.38–1.44 (m, 4H), 0.91 (s, 18H); ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 169.7, 117.3, 72.2, 41.6, 30.7, 29.1, 24.4; IR (thin film) 2955, 1756, 1620, 1157, 1030 cm^{–1}; HRMS (ESI-TOF) m/z calcd for C₂₀H₃₀O₄Na (M + Na⁺) 357.2042, found 357.2043.

(2R,4aR,8aS)-2,4a-Dimethyl-5-methyleneoctahydronaphthalen-1(2H)-one (26). A round-bottom flask was charged with ketone **25** (844 mg, 4.39 mmol, 1.0 equiv), ⁹*t*-BuOH (8.8 mL), and *t*-BuOK (985 mg, 8.78 mmol, 2.0 equiv). The resulting solution was maintained at 50 °C for 2 h. The vessel was allowed to cool to rt, and the reaction was quenched with saturated aqueous NH₄Cl (10 mL). The resulting mixture was transferred to a separatory funnel and extracted with Et₂O (3 \times 20 mL). The combined organic layers were dried over MgSO₄ and concentrated under reduced pressure to yield a colorless oil, which was purified by flash column chromatography on silica gel (98:2 hexanes/EtOAc) to yield **26** as a colorless oil (770 mg, 4.0 mmol, 91% yield, 10:2:1 dr); R_f = 0.37 (19:1 hexanes/ethyl acetate); ¹H NMR (500 MHz, CDCl₃) of the major diastereomer δ 4.71 (s, 2H), 2.41–2.22 (m, 3H), 2.18–2.09 (m, 2H), 1.98 (td, J = 13.5, 4.5 Hz, 1H), 1.91–1.84 (m, 2H), 1.67–1.56 (m, 3H), 1.30–1.21 (m, 1H), 1.03 (d, J = 6.5 Hz, 3H), 0.89 (s, 3H); ¹³C NMR (126 MHz, CDCl₃) of the major diastereomer δ 213.5, 156.1, 105.8, 58.2, 45.4, 44.8, 36.1, 32.4, 32.0, 26.8, 21.2, 19.2, 14.6; IR (thin film) 2931, 2865,

1710, 1639, 1240 cm^{-1} ; $[\alpha]_{\text{D}}^{19} + 63.2$, $[\alpha]_{577}^{19} + 63.3$; $[\alpha]_{546}^{19} + 74.1$, $[\alpha]_{435}^{19} + 148$, $[\alpha]_{405}^{19} + 194$ ($c = 0.6$, CH_2Cl_2); HRMS (ESI-TOF) m/z calcd for $\text{C}_{13}\text{H}_{20}\text{ONa}$ ($\text{M} + \text{Na}^+$) 215.1412, found 215.1403.

(1R,2R,4aR,8aS)-1,2,4a-Trimethyl-5-methylenedecahydronaphthalen-1-ol (9). A round-bottom flask was charged with 13 mL of Et_2O and a solution of MeMgBr (2.5 mL, 7.5 mmol, 2.0 equiv, 3.0 M solution in Et_2O) under an atmosphere of argon. The solution was stirred and cooled to 0°C before a solution of ketone **26** (730 mg, 3.8 mmol, 1.0 equiv 10:2:1 mixture of three stereoisomers from the previous step) and Et_2O (3.0 mL) was added over 3 min. The reaction mixture was stirred for another 15 min at 0°C and then was allowed to warm to rt. After 1 h at rt, the reaction mixture was poured into a saturated aqueous NH_4Cl solution (20 mL). The organic phase was separated, and the aqueous phase was extracted with Et_2O (2×15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (98:2 hexanes/ Et_2O) to yield, as the single stereoisomer, **9** (524 mg, 2.52 mmol, 66% yield, 86% yield based on major diastereomer of **26**) as a colorless oil that solidified to a colorless solid upon standing; $R_f = 0.40$ (10:1 hexanes/ethyl acetate, stained with KMnO_4); ^1H NMR (500 MHz, CDCl_3) δ 4.54–4.53 (m, 1H), 4.52 (s, 1H), 2.37 (td, $J = 13.7$, 5.2 Hz, 1H), 2.13–2.07 (m, 1H), 1.96–1.89 (m, 1H), 1.86–1.79 (m, 1H), 1.67–1.49 (m, 4H), 1.49–1.41 (m, 1H), 1.38–1.24 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H), 1.02 (dd, $J = 12.5$, 2.8 Hz, 1H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.89 (s, 1H); ^{13}C NMR (126 MHz, CDCl_3) δ 159.7, 103.3, 74.4, 53.3, 41.5, 40.0, 37.0, 32.7, 28.4, 27.3, 26.7, 21.3, 20.1, 15.7; IR (thin film) 3619, 2931, 2859, 1634, 1447, 1372, 1180, 895 cm^{-1} ; $[\alpha]_{\text{D}}^{21} + 79.3$, $[\alpha]_{577}^{21} + 82.8$, $[\alpha]_{546}^{21} + 93.6$, $[\alpha]_{435}^{21} + 156$, $[\alpha]_{405}^{21} + 187$ ($c = 1.2$, CHCl_3); HRMS (GC-ESI-TOF) m/z calcd for $\text{C}_{14}\text{H}_{24}\text{O}$ ($\text{M} + \text{NH}_4^+$) 226.2171, found 226.2173.

Cesium 2-Oxo-2-(((1R,2R,4aR,8aS)-1,2,4a-trimethyl-5-methylenedecahydronaphthalen-1-yl)oxy)acetate (20). A round-bottom flask was charged with alcohol **9** (478 mg, 2.30 mmol, 1.0 equiv) and THF (9.0 mL, 0.25 M) under an atmosphere of argon. The solution was cooled to -78°C before a 2.5 M solution of $n\text{-BuLi}$ in hexanes (930 μL , 2.3 mmol, 1.0 equiv) was added dropwise with stirring. The solution was stirred for an additional 15 min, and then methyl chlorooxoacetate (320 μL , 3.5 mmol, 1.5 equiv) was added dropwise. The reaction was stirred at -78°C for an additional 1 h, then was allowed to slowly warm to rt over 2–3 h as the dry ice/acetone bath slowly warmed to rt. The reaction was diluted with 20 mL of THF, and the organic phase was washed with saturated aqueous NaHCO_3 (2×10 mL), then with 50% satd brine (10 mL). Aqueous 0.5 M CsOH (4.2 mL, 2.1 mmol, 0.9 equiv) was added to the separatory funnel, and the mixture was shaken until the intermediate methyl oxalate was consumed as judged by TLC analysis (<5 min). Hexanes (30 mL) were added, and the aqueous phase was separated. The organic phase was washed with a second portion of water (10 mL), and the combined aqueous phases were concentrated under reduced pressure to give the product **20** as a colorless solid (849 mg, 2.06 mmol, 90% yield); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 4.52 (d, $J = 8.3$ Hz, 2H), 2.30 (td, $J = 13.5$, 4.8 Hz, 1H), 2.05 (app d, $J = 12.4$ Hz, 1H), 1.93–1.86 (m, 2H), 1.65 (qd, $J = 13.1$, 2.8 Hz, 1H), 1.60–1.49 (m, 6H), 1.39–1.31 (m, 2H), 1.19 (qt, $J = 13.3$, 4.0 Hz, 1H), 1.10 (s, 3H), 1.04 (dd, $J = 12.4$, 2.4 Hz, 1H), 0.88 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (126 MHz, $\text{DMSO}-d_6$) δ 167.6, 163.7, 158.8, 103.6, 83.9, 54.0, 43.2, 39.0, 36.7, 32.3, 27.9, 26.6, 22.8, 22.7, 20.2, 16.5; IR (thin film) 2832, 1715, 1635, 1218, 1163, 1038 cm^{-1} ; $[\alpha]_{\text{D}}^{22} + 43.5$, $[\alpha]_{577}^{22} + 44.7$, $[\alpha]_{546}^{22} + 51.0$, $[\alpha]_{435}^{22} + 85.8$, $[\alpha]_{405}^{22} + 101.6$ ($c = 1.0$, MeOH); HRMS (ESI-TOF) m/z calcd for $\text{C}_{16}\text{H}_{23}\text{O}_4$ ($\text{M} - \text{Cs}^+$) 279.1596, found 279.1588.

4-(2-(((1S,2R,4R,8R)-1,2,4a-Trimethyl-5-methylenedecahydronaphthalen-1-yl)ethyl)furan-2(5H)-one (1). An 8 mL scintillation vial equipped with a Teflon septum and magnetic stir bar was charged with cesium oxalate salt **10** (106 mg, 0.300 mmol, 1.0 equiv) and $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbbpy})\text{PF}_6$ (3.4 mg, 0.0030 mmol, 0.01 equiv). A 3:1 mixture of DME/THF (6.0 mL, 0.05 M) was added, followed by water (54 μL , 3.0 mmol, 10 equiv) and 4-vinylfuran-2-one (**6**) (33 mg, 0.30 mmol, 1.0 equiv). The reaction mixture was degassed by sparging

with argon for 15 min, and the vial was sealed and irradiated (2×34 W blue LED lamps) for 24 h with the reaction temperature rising to 40°C because of heat given off from the LEDs. The reaction mixture was diluted with saturated aqueous LiCl (25 mL), and the aqueous phase was extracted with Et_2O (2×25 mL). The combined ethereal extracts were dried over Na_2SO_4 and concentrated. The crude material was filtered through silica gel (4:1 hexanes/ EtOAc) to give a 1.3:1 mixture of α,β : β,γ -double bond isomers³⁴ (71 mg, 0.23 mmol). The mixture was dissolved in CH_2Cl_2 (2.5 mL, 0.10 M), followed by the addition of DBU (15 mg, 0.10 mmol, 1.0 equiv with respect to β,γ -double bond isomer). The homogeneous solution was maintained at 23°C for 15 min and loaded directly onto a silica gel column, eluting with 4:1 hexanes/ EtOAc to yield (+)-**1** as a colorless solid (71 mg, 0.23 mmol, 78% yield); R_f 0.4 (4:1 hexanes/ EtOAc); visualized with KMnO_4 ; $[\alpha]_{\text{D}}^{21} + 12.9$, $[\alpha]_{546}^{21} + 12.6$, $[\alpha]_{435}^{21} + 17.9$, $[\alpha]_{405}^{21} + 13.1$ ($c = 0.43$, CHCl_3); $[\alpha]_{\text{D}}^{21} + 13.6$, $[\alpha]_{577}^{21} + 13.9$, $[\alpha]_{546}^{21} + 15.2$, $[\alpha]_{435}^{21} + 21.0$ ($c = 1.9$, MeOH). Other characterization data acquired for (+)-**1** matched that previously reported.^{3,9}

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00697.

^1H and ^{13}C NMR spectra of obtained compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: leoverma@uci.edu.

Author Contributions

[†]Y.S., C.R.J., and G.L.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the National Science Foundation (CHE1265964) and the National Institute of General Medical Sciences (R01-GM098601). We thank the ACS Organic Chemistry Division for partial support of G.L.L. by a Graduate Fellowship and NIGMS for partial fellowship support of Y.S. (1F31GM113494). NMR and mass spectra were determined at UC Irvine using instruments purchased with the assistance of NSF and NIH shared instrumentation grants.

■ REFERENCES

- (a) Merritt, A. T.; Ley, S. V. *Nat. Prod. Rep.* **1992**, 9, 243–287. (b) Tokoroyama, T. *Synthesis* **2000**, 611–633. (c) Hanson, J. R. *Nat. Prod. Rep.* **2013**, 30, 1346–1356.
- (2) For example, a broad spectrum of bioactivity has been reported for *trans*-clerodane diterpenoid **3**. See: (a) Habtemariam, S.; Gray, A. I.; Waterman, P. G. *Planta Med.* **1992**, 58, 109–110. (b) Gupta, V. K.; Verma, S.; Pal, A.; Srivastava, S. K.; Srivastava, P. K.; Darokar, M. P. *Appl. Microbiol. Biotechnol.* **2013**, 97, 9121–9131. (c) Misra, P.; Sashidhara, K. V.; Singh, S. P.; Kumar, A.; Gupta, R.; Chaudhaery, S. S.; Gupta, S. S.; Majumder, H. K.; Saxena, A. K.; Dube, A. B. *J. Pharmacol.* **2010**, 159, 1143–1150. (d) Sashidhara, K. V.; Singh, S. P.; Srivastava, A.; Puri, A.; Chhonker, Y. S.; Bhatta, R. S.; Shah, P.; Siddiqi, M. I. *Eur. J. Med. Chem.* **2011**, 46, S206–S211. (e) Chen, C.-Y.; Chang, F.-R.; Shih, Y.-C.; Hsieh, T.-J.; Chia, Y.-C.; Tseng, H.-Y.; Chen, H.-C.; Chen, S.-J.; Hsu, M.-C.; Wu, Y.-C. *J. Nat. Prod.* **2000**, 63, 1475–1478. (f) Chang, F.-R.; Hwang, T.-L.; Yang, Y.-L.; Li, C.-E.; Wu, C.-C.; Issa, H.-H.; Hsieh, W.-B.; Wu, Y.-C. *Planta Med.* **2006**, 72, 1344–1347. (g) Lin, Y.-H.; Lee, C.-C.; Chang, F.-R.; Chang, W.-H.; Wu, Y.-C.; Chang, J.-G. *Life Sci.* **2011**, 89, 886–895. (h) Lin, Y.-H.; Lee, C.-C.; Chan, W.-L.; Chang, W.-H.; Wu, Y.-C.; Chang, J.-G. *Toxicology* **2011**,

- 28S, 72–80. (i) Phadnis, A. P.; Patwardhan, S. A.; Dhaneshwar, N. N.; Tavale, S. S.; Row, T. N. G. *Phytochemistry* **1988**, *27*, 2899–2901.
- (3) Hara, N.; Asaki, H.; Fujimoto, Y.; Gupta, Y.; Singh, A.; Sahai, M. *Phytochemistry* **1995**, *38*, 189–194.
- (4) (a) Bohlmann, F.; Ahmed, M.; Jakupovic, J.; King, J. M.; Robinson, H. *Rev. Latinoamer. Quim* **1984**, *15*, 16–18. (b) Phadnis, A. P.; Patwardhan, S. A.; Dhaneshwar, N. N.; Tavale, S. S.; Row, T. N. G. *Phytochemistry* **1988**, *27*, 2899–2901. (c) Kijjoo, A.; Pinto, M. M. M.; Herz, W. *Planta Med.* **1989**, *55*, 205–206. (d) Hao, X.-J.; Yang, X.-S.; Zhang, Z.; Shang, L.-J. *Phytochemistry* **1995**, *39*, 447–448. (e) Depending upon the plant source, PL3 is isolated as largely the 16S or 16R diastereomer or as a mixture of hydroxy epimers.
- (5) Ferrari, M.; Pelizzoni, F.; Ferrari, G. *Phytochemistry* **1971**, *10*, 3267–3269.
- (6) Hagiwara, H.; Inome, K.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 757–764.
- (7) (a) Takahashi, S.; Kusumi, T.; Kakisawa, H. *Chem. Lett.* **1979**, 515–518. (b) Tokoroyama, T.; Fujimori, K.; Shimizu, T.; Yamagiwa, T.; Monden, M.; Iio, H. *J. Chem. Soc., Chem. Commun.* **1983**, 1516–1519. (c) Goldsmith, D. J.; Deshpande, R. *Synlett* **1995**, 1995, 495–497.
- (8) The total syntheses of **3** and **4** previously described required 19–27 steps; see refs **6** and **7**. More efficient routes to related diterpenoids or meroterpenoids have been described that potentially could be used to prepare the *trans*-clerodane diterpenoids that are subject to this account; see, for example: (a) Ling, T.; Poupon, E.; Rueden, E. J.; Kim, S. H.; Theodorakis, E. A. *J. Am. Chem. Soc.* **2002**, *124*, 12261–12267. (b) Stahl, P.; Kissau, L.; Mazitschek, R.; Huwe, A.; Furet, P.; Giannis, A.; Waldmann, H. *J. Am. Chem. Soc.* **2001**, *123*, 11586–11593.
- (9) Müller, D. S.; Untiedt, N. L.; Dieskau, A. P.; Lackner, G. L.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 660–663.
- (10) Nawrat, C. C.; Jamison, C. R.; Slutskyy, Y.; MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **2015**, *137*, 11270–11273.
- (11) (a) Schnermann, M. J.; Untiedt, N. L.; Jimenez-Oses, G.; Houk, K. N.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 9581–9586. (b) La Cruz, T. E.; Rychnovsky, S. D. *Chem. Commun.* **2004**, 168–169.
- (12) (a) Cherkaskas, J. P.; Cohen, T. J. *Org. Chem.* **1992**, *57*, 6–8. (b) Cohen, T.; Zhang, B.; Cherkaskas, J. P. *Tetrahedron* **1994**, *50*, 11569–11584.
- (13) (a) Piers, E.; Wai, J. S. M. *Can. J. Chem.* **1994**, *72*, 146–157. (b) Piers, E.; Yeung, B. W. A. *J. Org. Chem.* **1984**, *49*, 4567–4569. (c) Piers, E.; Yeung, B. W. A.; Fleming, F. F. *Can. J. Chem.* **1993**, *71*, 280–286.
- (14) (a) From Accel Pharmtech. (b) Cheval, N. P.; Dikova, A.; Blanc, A.; Weibel, J.-M.; Pale, P. *Chem.–Eur. J.* **2013**, *19*, 8765–8768.
- (15) Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 15342–15345.
- (16) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. *J. Am. Chem. Soc.* **1991**, *113*, 9401–9402.
- (17) (a) Schnermann, M. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 9576–9580. (b) Pratsch, G.; Lackner, G. L.; Overman, L. E. *J. Org. Chem.* **2015**, *80*, 6025–6036.
- (18) There is no discussion of radical 1,6-additions in a recent review of 1,6-additions of carbon nucleophiles; see ref **19**. For the examples that we are aware of, see: (a) Ohno, M.; Ishizaki, K.; Eguchi, S. *J. Org. Chem.* **1988**, *53*, 1285–1288. (b) Mao, S.; Fang, X.; Ba, L.; Wu, F. J. *Fluorine Chem.* **2007**, *128*, 5–11. (c) Gong, H.; Andrews, R. S.; Zuccarello, J. L.; Lee, S. J.; Gagné, M. R. *Org. Lett.* **2009**, *11*, 879–882. (d) Liu, X.-K.; Zheng, X.; Ruan, Y.-P.; Ma, J.; Huang, P.-Q. *Org. Biomol. Chem.* **2012**, *10*, 1275–1284.
- (19) Csáký, A. G.; de la Herrán, G.; Murcia, M. C. *Chem. Soc. Rev.* **2010**, *39*, 4080–4102.
- (20) For reviews, see: (a) Krause, N.; Thorand, S. *Inorg. Chim. Acta* **1999**, *296*, 1–11. (b) Tissot, M.; Li, H.; Alexakis, A. In *Copper-Catalyzed Asymmetric Synthesis*; Alexakis, A., Krause, N., Woodward, S., Eds.; Wiley-VCH: Weinheim, 2014; Chapter 3.
- (21) Termination by both hydrogen-atom transfer and single-electron reduction followed by protonation are possible; see: Lackner, G. L.; Quasdorf, K. W.; Pratsch, G.; Overman, L. E. *J. Org. Chem.* **2015**, *80*, 6012–6024. See also ref **17b**.
- (22) Tarantino, K. T.; Liu, P.; Knowles, R. R. *J. Am. Chem. Soc.* **2013**, *135*, 10022–10025.
- (23) Hasegawa, E.; Takizawa, S. *Aust. J. Chem.* **2015**, *68*, 1640–1647.
- (24) Hantzsch ester **15** was ultimately chosen as the reductant for these conditions as it is more easily prepared than **16** and **17**.
- (25) Compound *rac*-**1a** was not isolated in pure form. Upon exposure of the mixture of addition products to DBU in CH₂Cl₂, equilibration of *rac*-**1a** to *rac*-**1** was observed (see the [Experimental Section](#) for details).
- (26) For a recent review of catalytic enantioselective methods to prepare quaternary carbon stereocenters, see: Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181–194.
- (27) Gao, F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2010**, *132*, 10961–10963.
- (28) May, T. L.; Dabrowski, J. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 736–739.
- (29) Carrying out this coupling in a similar fashion in 3:1 DME/DMF (0.05 M) using 1.5 equiv of *trans*-decalin cesium oxalate **10** (160 mg) gave directly (+)-**1** in 98% yield (65% yield from **10**). Under these conditions, the β,γ -unsaturated lactone isomer of **1** was not detected.
- (30) For an early example of the use of this strategy, see ref **17a**.
- (31) Tan, B.; Toda, N.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2012**, *51*, 12538–12541.
- (32) This compound was prepared as previously reported and was stored as an approximately 0.5 M solution in Et₂O at –20 °C when not in use; see ref **14b**.
- (33) Eey, S. T. C.; Lear, M. J. *Org. Lett.* **2010**, *12*, 5510–5513.
- (34) The β,γ -unsaturated lactones exist as a 1:1 mixture of *cis*- and *trans*-double-bond isomers.