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Aliphatic C−H to C−C Conversion: Synthesis of (−)-Cameroonan-7α-ol

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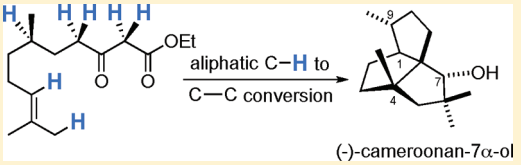
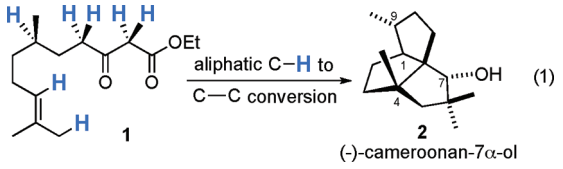
Supporting Information

ABSTRACT: In the course of a synthesis of the tricyclic sesquiterpene (−)-cameroonan-7α-ol from the acyclic (+)-citronellal, seven aliphatic C−H bonds were converted to C−C bonds, and three rings and four new stereogenic centers were established.



INTRODUCTION

Cameroonan-7α-ol (**2**), a sesquiterpene from the essential oil of the rhizome *Echinops giganteus* var. *lelyi*, was originally described by Weyerstahl in 1997.[1] While the essential oil is a complex mixture of several sesquiterpenes, (−)-**2** is believed to be the major contributor to its strong woody, patchouli-like fragrance. The tricyclic skeleton of (−)-cameroonanol (**2**) is biogenetically derived from farnesyl pyrophosphate, through polyene cyclization and carbocationic rearrangements.[2] Composed of three *cis*-fused five-membered rings and five contiguous stereogenic centers in a dense configuration, (−)-**2** offers significant synthetic challenges.



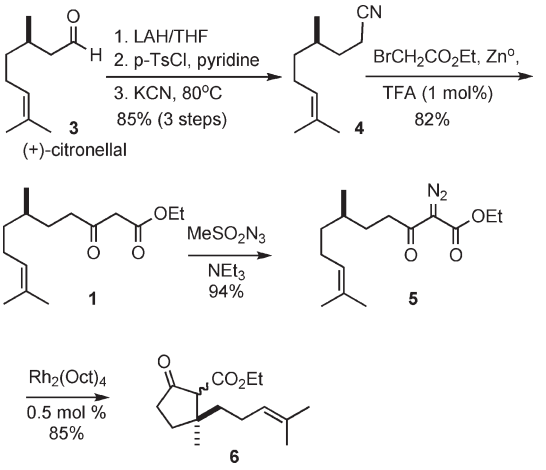
(1)

Previous syntheses of (±)-**2** focused on dipolar cycloaddition to a racemic bicyclooctenone.[3] We sought an alternative approach, based on ring construction by C−H to C−C bond functionalization (eq 1). There has been a great deal of attention paid recently to the selective oxidation of aliphatic C−H bonds to C−O bonds.[4] The direct conversion of aliphatic C−H bonds to C−C bonds is strategically at least as important.[5,6] Herein, we report the first synthesis of enantiopure (−)-cameroonan-7α-ol (**2**), starting (Scheme 1) from the acyclic (+)-citronellal (**3**). We envisioned that, by the judicious conversion of seven aliphatic C−H bonds to C−C bonds, it could be possible to incorporate the *complete* carbon skeleton of **1** into (−)-cameroonan-7α-ol (**2**). Of particular note is a sequence of Rh^{II}-catalyzed C−H functionalization followed by Mn^{III}-mediated oxidative radical cyclization for the stereocontrolled construction of [3.3.0]-fused bicyclooctanes in enantiomerically pure form.

RESULTS AND DISCUSSION

Cyclization by Rh−Carbenoid C−H Functionalization. We planned to establish the absolute configuration of (−)-**2** via enantioretentive C−H functionalization[7] of the C-4 methine of (+)-citronellal **3**. To that end, the α-diazo-β-ketoester **5** was constructed (Scheme 1). The synthesis commenced with a three-step sequence of $LiAlH_4$ reduction, tosylation, and nucleophilic displacement of (+)-**3** to provide the known nitrile **4**.[8] Homologation to the β-ketoester **1** was accomplished via Blaise reaction[9] of the nitrile **4** with $BrCH_2CO_2Et$. We found that reproducibly high yields in this reaction could be achieved using activated Zn^0 metal[10] and in situ activation with a catalytic amount of TFA.[11] Diazo transfer using MsN_3[12] then provided the requisite α-diazo-β-ketoester **5** for C−H functionalization. Using catalytic $Rh_2(Oct)_4$, **5** readily cyclized to **6**.

Scheme 1



Mn^{III} Oxidative Radical Cyclization. We planned next to cyclize the β-ketoester **6** with $Mn(OAc)_3$. As described by Snider,[13] oxidative radical generation, followed by subsequent cyclization, further oxidation and deprotonation, would provide the second ring of **2** (Scheme 2). Its application to the synthesis

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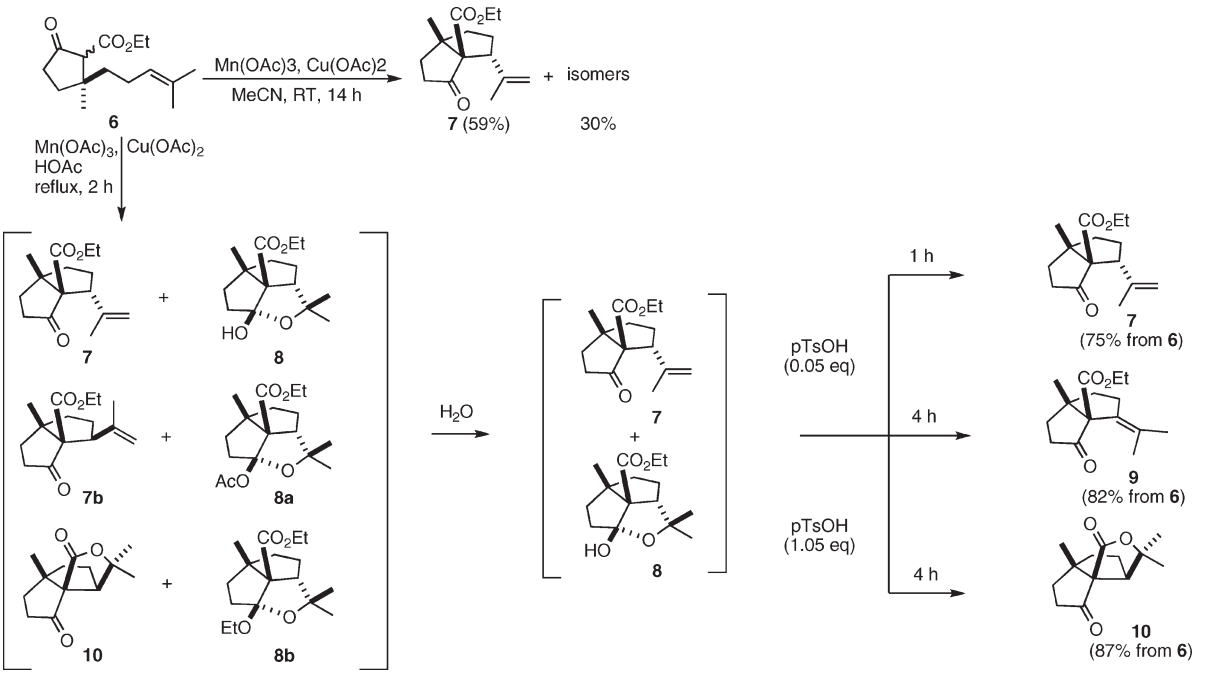
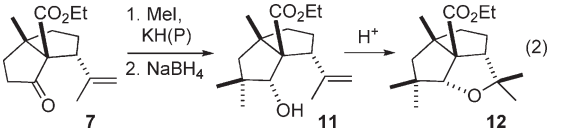
Scheme 2

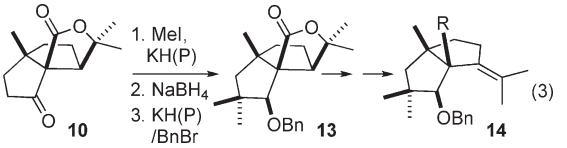


of (−)-cameroonanol (**2**) immediately raised a question of selectivity, as one ring and at least one additional stereogenic center are formed in the cyclization. We expected preference for the formation of the *cis*-5/5-fused versus the corresponding *trans*-5/5 or 6/5 bicyclic products. The relative stereochemical orientation of the pendant alkyl side chain (i.e., *endo* vs *exo* selectivity) in the product had yet to be investigated using this method, although radical cyclizations in general proceed with *endo* selectivity.[14]

In the event (Scheme 2), we observed that the cyclization did proceed with high preference for the *cis*-5/5-fused products, as expected. Initially, the use of anhydrous acetonitrile solvent led to the *endo*-alkene **7** as the dominant product. The use of acetic acid as a solvent shortened the reaction time considerably but also delivered a more complex mixture of products.[15] Conveniently, after treatment of that crude reaction material with water, the hemiketal **8** and the *endo*-alkene **7** emerged as the major products. Furthermore, products **7**, **9**, or **10** could *each* be selectively obtained from the crude reaction mixture in high overall yield depending upon the dehydration conditions. This iterative protocol of cyclization followed by dehydration allowed *endo* or *exo* cyclization products to be selectively obtained.

Stereoselective Reduction. Each of the three bicycles (**7**, **9**, and **10**) from Mn^{III}-mediated cyclization could potentially be useful for the synthesis of (−)-cameroonanol (**2**). Each was independently investigated, beginning with the *endo*-alkene **7**. Installation of the *gem*-dimethyl moiety was accomplished using methyl iodide and potassium hydride in paraffin [KH(P)].[16a] Chemoselective ketone reduction of **7** with $NaBH_4$ provided the secondary alcohol **11** as a single diastereomer (eq 2). However, alcohol **11** was prone to undesired cyclization to the cyclic ether **12** under mildly acidic conditions. Conversely, when the *cis*-fused lactone **10** was subjected to identical $NaBH_4$ reduction, the opposite stereoselectivity was observed (eq 3). Attempts to fragment the protected lactone **13** ultimately resulted in the formation of tetrasubstituted alkenes of type **14**. As these derivatives were more directly accessible from **9**, we turned our attention to that intermediate.





We were pleased to observe that reduction of the ketone **9** delivered the desired alcohol **15** with high diastereocontrol (Scheme 3). Before manipulation of the alkyl side chain, we sought to protect the potentially sensitive β-hydroxy ester **15**. Benzyl ether formation under Williamson etherification conditions[16b] provided **16** with complete inversion of the secondary carbinol center, presumably by a retro-aldol/aldol process. After screening a variety of benzylation procedures, we found that the protocol developed by Dudley[17] delivered the benzyl ether **17** cleanly and with retention of relative configuration.

Alkyl Side Chain Functionalization. Attempts to cyclize **17** (Scheme 4) by direct allylic deprotonation were unsuccessful. We therefore functionalized the allylic C−H of **17** to set the stage for the construction of final ring of (−)-**2**. Exposure of the alkene **17** to singlet oxygen regioselectively formed the alcohol **18**. Optimized dehydration conditions suppressed formation of the undesired **20**, giving clean conversion to the diene **19**. Initial attempts to functionalize the diene **19** as the thioether under standard radical conditions were low yielding and proceeded with poor regiocontrol. However, the use of Lewis acidic silica

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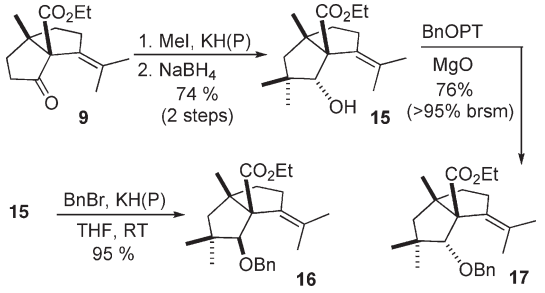
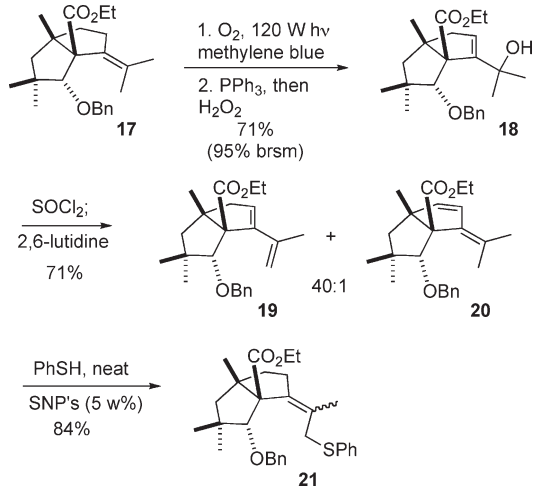
Scheme 3



Scheme 4

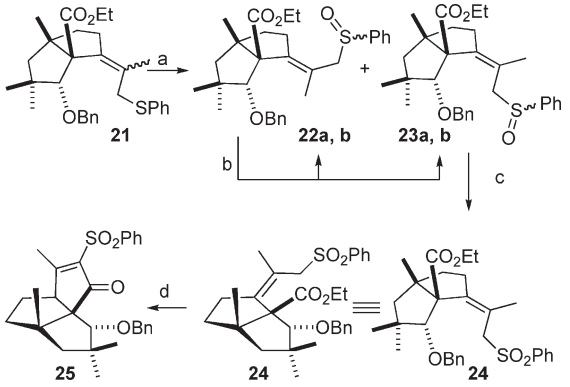


nanoparticles (SNPs)[18] allowed the selective functionalization of the terminal alkene. Concomitant (and desired) alkene isomerization provided an inseparable mixture of *E*/*Z*-allylic thioethers **21** in good yield.

Completion of the Synthesis. Formation of the final ring of (−)-**2** was accomplished by cyclization of the *Z*-allylic sulfone **24** derived from the thioether **21** (Scheme 5). While direct oxidation of the thioether **21** to the sulfone **24** was possible, an iterative oxidation sequence by way of the sulfoxides **22** and **23** proved useful for two reasons. First, the intermediate *Z*- and *E*-allylic sulfoxide isomers could be chromatographically resolved. Further, we found that the *E*-allylic sulfoxides **22a,b** could be equilibrated to a 3:1 mixture of *E*:*Z*-allylic sulfoxides under microwave conditions.[19] This allowed for increased throughput to the *Z*-allylic sulfoxides **23a,b** that were oxidized to the sulfone **24**. On exposure to LDA,[20] **24** smoothly cyclized to the enone **25**. The corresponding *E*-allylic sulfone did not cyclize.

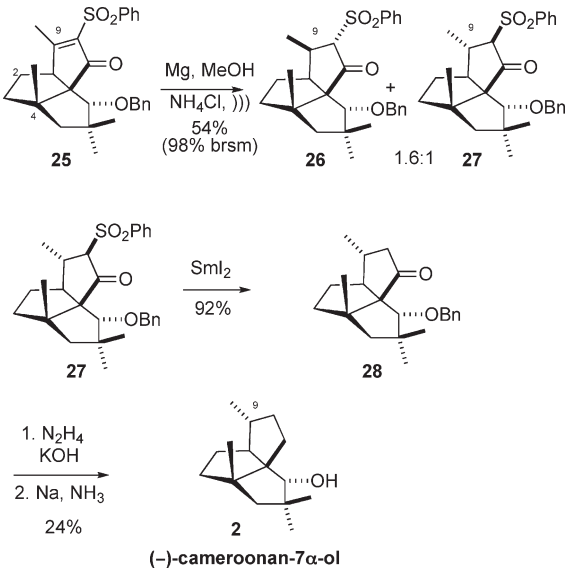
Having successfully installed the all-*cis*-5/5 ring fusions, we next turned our attention to the final stereocenter of **2**. Specifically, we required a method for introducing hydrogen to the *more* congested face of enone **25** to establish the C_9 stereocenter (Scheme 6). Among the various known protocols for enone reduction, methods based on hydrogenation or nucleophilic hydride delivery were anticipated to deliver the wrong diastereomer (i.e., product **27**) via approach from the more sterically accessible face of the enone **25**. However, dissolving metal reduction had been shown to deliver the thermodynamically more stable products from β-substituted cyclic enones.[21]

Scheme 5[a]



[a] Reagents and conditions: (a) *m*CPBA, CH_2Cl_2, −78 °C, 61% **23a,b**, 37% **24**; (b) PhMe, microwave, 120 °C, **23a,b**/**24** = 3:1; (c) H_2WO_4 (0.1 equiv), H_2O_2, RT, 24 h, 76%; (d) LDA, −40 °C, 90%.

Scheme 6



SmI_2/HMPA/NH_4Cl[22] proved to be an efficient system for the reduction of the enone **25**, providing a 1:1 mixture of desulfonylated C-9 methyl diastereomers (that is, **28** and *epi*-**28**, Scheme 6). However, the two ketone diastereomers were not separable. Mg/MeOH effected the chemoselective reduction of the enone **25** to a separable mixture of **26** and **27**. The relative configuration of the secondary methyl group was confirmed by the conversion of **26** to C-9-*epi*-cameroonanol (*epi*-**2**).[23] It seemed that the combined steric effect of the C-4 methyl group and developing C-2 to C-9 *syn*-pentane interaction slow protonation from the desired face during the reduction, even when using a small proton source such as NH_4Cl.

The ketone **27** was subject to SmI_2-mediated desulfonylation to deliver the ketone **28**. Wolff−Kishner reduction was followed by deprotection to complete the synthesis of the volatile (−)-cameroonan-7α-ol (**2**). The spectroscopic data (IR, MS, ^1H, and ^{13}C NMR) for synthetic (−)-**2** fully agreed with those previously reported [α_D ref 1 = (−) 34°; obs = (−) 37°].

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CONCLUSION

The first total synthesis of enantiomerically pure (−)-cameroonan-7α-ol (**2**) has been accomplished. Central to the synthesis is the specific conversion of aliphatic C−H bonds to C−C bonds. The procedure presented for the stereoselective two-stage construction of the first two rings of (−)-cameroonanol (**2**) from the acyclic ester **1** exemplifies the strategic efficiency of C−H bond functionalization in natural product synthesis. We anticipate that the sequence of Rh^{II}-mediated C−H functionalization followed directly by Mn^{III} oxidative radical cyclization developed here will become a general method for the construction of bicyclic intermediates with the control of both relative and absolute configuration. In the application described here, this two-step strategy enabled the controlled installation of the two contiguous cyclic quaternary centers of (−)-cameroonan-7α-ol (**2**).

EXPERIMENTAL SECTION

General Procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded, as solutions in deuteriochloroform ($CDCl_3$) unless otherwise indicated, at 400 and 100 MHz, respectively. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u". The infrared (IR) spectra were determined as neat oils. R_f values indicated refer to thin-layer chromatography (TLC) on 2.5 × 10 cm, 250 mm analytical plates coated with silica gel GF, unless otherwise noted, and developed in the solvent system indicated. Microwave reactions were performed using a CEM Discover Labmate microwave reactor with vertically focused IR temperature sensor. All glassware was oven-dried and rinsed with dry solvent before use. THF and diethyl ether were distilled from sodium metal/benzophenone ketyl under dry nitrogen. Toluene, dichloromethane, and acetonitrile were distilled from calcium hydride under dry nitrogen. CH_2Cl_2 is dichloromethane, MTBE is methyl-*tert*-butyl ether, and PE is petroleum ether. All reactions were conducted under N_2 and stirred magnetically.

*(4R)-4,8-Dimethylnon-7-enenitrile (**4**).* To a slurry of $LiAlH_4$ (11.81 g, 311 mmol, 1.2 equiv) in 450 mL of THF, in a 2 L multineck round-bottom flask (equipped with a reflux condenser, addition funnel and N_2 inlet adapter) submerged in a 0 °C ice bath, was added a solution of (*R*)-citronellal **3** (39.95 g, 259 mmol) in 70 mL of THF dropwise via addition funnel over 30 min. Upon complete addition, the ice bath was removed and the reaction was stirred at room temperature for 1 h. The reaction was quenched according to the method of Micovic.[23] After stirring at room temperature overnight, 20 g of Na_2SO_4 was added and the mixture was filtered through Celite to remove the white precipitate. The filter cake was thoroughly washed with Et_2O and concentrated in vacuo.

The residue was diluted with 108 mL of anhydrous pyridine and cooled to 0 °C under an N_2 atmosphere. *p*-Toluenesulfonyl chloride (76.52 g, 401.5 mmol, 1.55 equiv) was added in three equal portions over 15 min intervals. The reaction was gradually stirred to room temperature with the ice bath. After 4 h at room temperature, the reaction material was partitioned between Et_2O and, sequentially, 1 N aqueous HCl and saturated aqueous $NaHCO_3$. The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo.

The residue was diluted with 860 mL of 2:1 EtOH/H_2O, and KCN (50.5 g, 777 mmol, 3.0 equiv) was added. The temperature was increased to 70 °C, and the mixture was stirred overnight (16 h). After cooling to room temperature, the reaction mixture was concentrated in vacuo (to remove the bulk of the EtOH) and extracted with CH_2Cl_2. Combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was distilled bulb-to-bulb (bath = 100−105 °C, 0.05 Torr) to afford the known nitrile **4** as a pale yellow oil (36.32 g, 220 mmol, 85% yield from citronellal). The analytical data for nitrile **4** match those previously reported:[8] TLC R_f (PE/MTBE = 20:1) = 0.39; $[\alpha]^{20}_D$ = (+) 3.7 (*c* 2.15 $CHCl_3$); ^{1}H NMR δ 5.10 (1H, m), 2.01 (2H, m), 1.76−1.68 (1H, m), 1.70 (3H, s), 1.62 (3H, s), 1.61−1.56 (1H, m), 1.50 (1H, m), 1.36 (1H, m), 1.21 (1H, m), 0.94 (3H, d, *J* = 6.5 Hz); ^{13}C NMR[24] δ 131.7, 120.0, 36.3, 32.2, 25.2, 14.9; d 124.1, 31.6, 25.68, 18.7, 17.6; IR (film, cm^{-1}) 1672, 2247, 2359, 2921; HRMS calcd for $C_{11}H_{20}N$ (M + H) 166.1596, obsd 166.1598.

*Ethyl (6R)-6,10-Dimethyl-3-oxoundec-9-enoate (**1**).* Zn metal (Zn dust, 17.8 g, 271.9 mmol, 3.1 equiv) was washed successively with 3 N aqueous HCl, H_2O, EtOH, and anhydrous Et_2O. After removal of all solvent under high vacuum, the activated Zn metal was added to 50 mL of THF and the slurry was brought to reflux. Trifluoroacetic acid (65 μL, 0.88 mmol, 0.01 equiv) was added, followed by a minor amount of $BrCH_2CO_2Et$ (ca. 0.5 mL) until the reaction mixture became green. Nitrile **4** (14.47 g, 87.7 mmol) was then added in one portion. After stirring for 20 min, a solution of $BrCH_2CO_2Et$ (21.4 mL, 193 mmol, 2.2 equiv) in 21 mL of THF was added dropwise via addition funnel over 1 h. Upon complete addition, the reaction was stirred at reflux for 0.5 h. After cooling to room temperature, 100 mL of 3 N aqueous HCl was added and the reaction stirred for 2 h at room temperature. The reaction material was partitioned between EtOAc and, sequentially, saturated aqueous $NaHCO_3$ and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford β-ketoester **1** as a colorless oil (18.34 g, 72.2 mmol, 82% yield): TLC R_f (PE/MTBE = 20:1) = 0.15; $[\alpha]^{20}_D$ = (−) 3 (*c* 2.7 $CHCl_3$); ^{1}H NMR δ 5.08 (1H, m), 4.20 (2H, q, *J* = 7.1 Hz), 3.44 (2H, s), 2.54 (2H, m), 1.97 (2H, m), 1.68 (3H, s), 1.60 (3H, s), 1.65−1.58 (1H, m), 1.42 (2H, m), 1.28 (1H, m), 1.28 (3H, t, *J* = 7.1 Hz), 1.17 (1H, m), 0.89 (3H, d, *J* = 6.3 Hz); ^{13}C NMR δ u 203.1, 167.3, 131.3, 61.3, 49.3, 40.8, 36.8, 30.3, 25.4; d 124.6, 31.9, 25.7, 19.2, 17.6, 14.1; IR (film, cm^{-1}) 1643, 1743, 2921; HRMS calcd for $C_{15}H_{26}O_3$ (M + Na) 277.1780, obsd 277.1771.

*Ethyl (6R)-2-Diazo-6,10-dimethyl-3-oxoundec-9-enoate (**5**).* To a solution of β-ketoester **1** (10.0 g, 39.37 mmol) and $MeSO_2N_3$ (7.15 g, 59.06 mmol, 1.5 equiv) in 79 mL of acetonitrile at room temperature was added NEt_3 (11.05 mL, 78.74 mmol, 2.0 equiv) dropwise via syringe. Stirring was continued for 3.5 h at room temperature. The reaction material was diluted with 10% aqueous NaOH and extracted with Et_2O. Combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford α-diazo-β-ketoester **5** as a colorless oil (10.21 g, 36.5 mmol, 93% yield): TLC R_f (PE/MTBE = 20:1) = 0.46; $[\alpha]^{20}_D$ = (−) 6.1 (*c* 3.0 $CHCl_3$); ^{1}H NMR δ 5.09 (1H, m), 4.30 (2H, q, *J* = 7.1 Hz), 2.86 (2H, m), 1.98 (2H, m), 1.68 (1H, m), 1.68 (3H, s), 1.60 (3H, s), 1.46 (2H, m), 1.33 (1H, m), 1.33 (3H, t, *J* = 7.1 Hz), 1.18 (1H, m), 0.90 (3H, d, *J* = 6.4 Hz); ^{13}C NMR δ u 193.4, 161.4, 131.2, 75.8, 61.3, 38.0, 36.8, 31.3, 25.5; d 124.7, 32.2, 25.7, 19.3, 17.6, 14.3; IR (film, cm^{-1}) 1658, 1720, 2135, 2921; HRMS calcd for $C_{15}H_{24}N_2O_3$ (M + Na) 303.1685, obsd 303.1689.

*Ethyl (2R)-2-Methyl-2-(4-methylpent-3-en-1-yl)-5-oxocyclopentanecarboxylate (**6**).* $Rh_2(Oct)_4$ (142 mg, 0.182 mmol, 0.005 equiv) was added to 530 mL of CH_2Cl_2, and the mixture was sonicated to homogeneity over 10 min. To the resultant pale green homogeneous solution was added a solution of diazo compound **5** (10.2 g, 36.4 mmol) in 200 mL of CH_2Cl_2 dropwise via addition funnel over 1 h. The reaction was stirred for 1 h at room temperature and then concentrated in vacuo. The residue was chromatographed to afford a mixture β-ketoesters **6** (both α-epimers and enol) as a colorless oil (7.85 g, 31.14 mmol, 85% yield): TLC R_f (PE/MTBE = 20:1) = 0.40; ^{1}H NMR δ 10.98 (0.15H, br s, OH), 5.07 (1H, m), 4.24−4.11 (2H, m), 2.98 (0.52H, s), 2.89 (0.30H, s), 2.51−2.29 (2H, m), 2.20−1.74 (4H, m), 1.67 (3H, m), 1.60−1.40 (5H, m), 1.31−1.23 (3H, m), 1.12 (0.46H, s), 1.10 (0.90H, s), 1.09 (1.54H, s); ^{13}C NMR δ u 213.5, 212.8, 168.8, 168.6, 132.0, 131.7, 60.9, 60.8, 59.6, 45.0, 44.0, 43.8, 41.7, 40.3, 37.5, 36.2, 36.1, 33.9, 33.4, 33.2,

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30.9, 23.8, 23.1, 22.9; d 124.9, 124.0, 123.8, 65.8, 64.8, 27.4, 25.7, 25.6, 25.4, 21.2, 17.6, 17.5, 14.2, 14.2, 14.1; IR (film, cm^{-1}) 1649, 1726, 2968; HRMS calcd for $C_{15}H_{25}O_3$ (M + H) 253.1804, obsd 253.1807.

Mn^{III} Oxidative Radical Cyclization Method A. *(1R,5S,8R)-1-Ethoxycarbonyl-5-methyl-8-(prop-1-en-2-yl)bicyclo[3.3.0]octan-2-one (**7**).* A dry mixture of $Mn(OAc)_3 \cdot 2H_2O$ (12.92 g, 48.20 mmol, 2.0 equiv) and $Cu(OAc)_2 \cdot H_2O$ (4.82 g, 24.10 mmol, 1.0 equiv) was purged with argon for 10 min and diluted with 240 mL of acetonitrile. β-Ketoester **6** (6.08 g, 24.10 mmol) was added, and the reaction was stirred at room temperature overnight (16 h) under an atmosphere of argon. The reaction mixture was filtered through Celite, diluted with saturated aqueous $NaHCO_3$, and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford *endo*-alkene **7** as a colorless oil (3.57 g, 14.30 mmol, 59% yield) accompanied by a complex mixture of other isomers (1.81 g, ca. 7 mmol). For **7**: TLC R_f (PE/MTBE = 10:1) = 0.31; $[\alpha]^{20}_D$ = (+) 61.4 (*c* 1.52, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.78 (2H, d, *J* = 48 Hz), 4.20 (2H, m), 3.43 (1H, dd, 11.8, *J* = 12.0 Hz), 2.50 (1H, ddd, *J* = 6.1, 8.7, 18.1 Hz), 2.28 (1H, m), 1.79 (3H, s), 1.64−1.91 (6H, m), 1.27 (3H, t, *J* = 7.1 Hz), 1.17 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 214.1, 171.7, 144.8, 111.4, 71.2, 61.1, 53.6, 40.5, 39.7, 35.1, 29.1; d 52.6, 26.1, 23.7, 14.2; IR (film, cm^{-1}), 1643, 1732, 2958, 3086; HRMS calcd for $C_{15}H_{22}O_3$ (M + Na) 273.1467, obsd 273.1459.

Mn^{III} Oxidative Radical Cyclization Method B. To a mixture of $Mn(OAc)_3 \cdot 2H_2O$ (14.63 g, 54.6 mmol, 2.0 equiv) and $Cu(OAc)_2 \cdot H_2O$ (5.46 g, 27.3 mmol, 1.0 equiv) in 136 mL glacial acetic acid was added β-ketoester **6** (6.88 g, 27.3 mmol), and the reaction mixture was purged with argon while stirring rapidly. The heterogeneous solution was stirred at 80 °C under an argon atmosphere. Upon complete consumption of β-ketoester **6**, 20 mL of H_2O was added and the reaction gradually cooled to room temperature. The reaction mixture was filtered through Celite and concentrated in vacuo to remove the bulk of the acetic acid. The residue was diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford 6.9 g of crude product consisting mainly of hemiketal **8** and *endo* product **7**. This crude mixture was used in smaller portions as needed (and purified when required) to develop and optimize the procedures described below.

Analysis of Product Mixture. A small portion of the crude reaction material (235 mg), *prior to treatment with H_2O*, was chromatographed to afford the following pure materials along an additional amount of unresolved material (45 mg).

*(1R,5S,8R)-1-Ethoxycarbonyl-5-methyl-8-(prop-1-en-2-yl)bicyclo-[3.3.0]octan-2-one (**7**).* 34.5 mg.

*(1R,5S,8S)-1-Ethoxycarbonyl-5-methyl-8-(prop-1-en-2-yl)bicyclo-[3.3.0]octan-2-one(**7b**).* 7 mg, TLC R_f (PE/MTBE = 6.5:1) = 0.39; ^1H NMR (400 MHz, $CDCl_3$) δ 4.88 (2H, m), 4.14 (2H, m), 2.78 (1H, m), 2.52 (2H, m), 2.17 (1H, m), 1.79 (3H, s), 1.98−1.67 (5H, m), 1.25 (3H, t, *J* = 7.2 Hz), 1.17 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 214.9, 169.4, 144.4, 111.6, 71.0, 60.4, 54.8, 38.4, 36.6, 31.2, 30.0; d 53.0, 24.3, 23.4, 14.1; HRMS calcd for $C_{15}H_{22}O_3$ (M + Na) 273.1467, obsd 273.1459.

*(1R,4S,7S,10R)-10-Ethoxycarbonyl-1-hydroxy-3,3,7-trimethyl-2-oxatricyclo[2.2.2.1]decane (**8**).* 54 mg; TLC R_f (PE/MTBE = 4:1) = 0.32; $[\alpha]^{20}_D$ = (−) 18.5 (*c* 0.61 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.08 (OH, s), 4.25 (2H, m), 3.04 (1H, t, *J* = 9.3 Hz), 2.15 (1H, dd, *J* = 6.0, 12.8), 1.90−1.54 (7H, m), 1.34 (3H, t, *J* = 7.1 Hz), 1.33 (3H, s), 1.27 (3H, s), 1.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 176.0, 114.5, 83.9, 74.9, 61.1, 56.9, 40.6, 40.3, 34.6, 26.4; d 59.3, 30.1, 23.9, 23.4, 14.3; IR (film, cm^{-1}) 1724, 2967, 3456; HRMS calcd for $C_{15}H_{24}O_4$ (M − OH) 251.1647, obsd 251.1644.

*(1S,4S,7S,10R)-10-Ethoxycarbonyl-1-acetoxy-3,3,7-trimethyl-2-oxatricyclo[2.2.2.1]decane (**8a**).* 11 mg; TLC R_f (PE/MTBE = 6.5:1) = 0.26; ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (2H, m), 3.15 (1H, dd, *J* = 1.6, 6.0 Hz), 2.76 (1H, ddd, *J* = 4.5, 7.5, 12.0), 2.25 (1H, dt, *J* = 9.0, 14.3 Hz), 1.97 (3H, s), 1.89−1.67 (6H, m), 1.47 (1H, m), 1.33 (3H, t, *J* = 7.1 Hz), 1.30 (6H, br s), 1.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 171.6, 168.9, 119.3, 87.5, 80.1, 60.5, 54.7, 40.6, 37.0, 36.9, 26.9; d 55.3, 29.7, 24.4, 24.3, 22.1, 14.3; HRMS calcd for $C_{17}H_{26}O_5$ (M + Na) 333.1678, obsd 333.1674.

*(1R,4S,7S,10R)-1-Ethoxy-10-ethoxycarbonyl-3,3,7-trimethyl-2-oxatricyclo[2.2.2.1]decane (**8b**).* 42 mg, TLC R_f (PE/MTBE = 6.5:1) = 0.61; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (2H, m), 3.62 (1H, dq, *J* = 7.1, 8.9 Hz), 3.38 (1H, dq, *J* = 7.1, 8.9 Hz), 3.10 (1H, dd, *J* = 5.8, 7.7 Hz), 2.11−1.97 (2H, m), 1.83−1.64 (5H, m), 1.40 (1H, m), 1.33 (3H, s), 1.28 (3H, t, *J* = 7.1 Hz), 1.24 (3H, s), 1.11 (3H, s), 1.08 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 172.4, 119.2, 85.4, 79.1, 60.1, 58.0, 54.9, 41.0, 36.8, 34.5, 26.9; d 55.7, 29.6, 24.7, 15.3, 14.2; HRMS calcd for $C_{17}H_{28}O_4$ (M + Na) 319.1885, obsd 319.1880.

*(1R,5R,8S)-4,4,8-Trimethyl-3-oxatricyclo[6.3.0.0^{1,5}]undecan-2,11-dione (**10**).* 6.5 mg; TLC R_f (PE/MTBE = 4:1) = 0.22; mp = 102 °C; $[\alpha]^{20}_D$ = (+) 119.1 (*c* 1.33 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.76 (1H, t, *J* = 8.1 Hz), 2.57 (2H, m), 1.91 (4H, m), 1.75 (2H, m), 1.53 (3H, s), 1.39 (3H, s), 1.32 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 214.8, 173.0, 84.4, 73.8, 53.8, 41.2, 37.9, 32.6, 28.0; d 56.9, 31.2, 24.3, 23.1; IR (film, cm^{-1}) 1313, 1462, 1729 (br), 2939; HRMS calcd for $C_{13}H_{19}O_3$ (M + H) 223.1334, obsd 223.1332.

Selective Product Formation. The following is the optimized procedure for the selective formation of the *endo* alkene product **7** from the β-ketoester **6**.

*(1R,5S,8R)-1-Ethoxycarbonyl-5-methyl-8-(prop-1-en-2-yl)bicyclo-[3.3.0]octan-2-one (**7**).* A mixture of $Mn(OAc)_3 \cdot 2H_2O$ (268 mg, 1.0 mmol, 2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (100 mg, 0.5 mmol, 1.0 equiv), and β-ketoester **6** (126 mg, 0.5 mmol) was subject to the conditions described in Method B above. The residue was chromatographed to afford *endo*-alkene product **7** (47 mg, 0.19 mmol, 38% yield) along with a mixture of isomers (61 mg). This mixture of isomers was diluted with dry toluene (2.5 mL), and *p*-toluenesulfonic acid monohydrate (9 mg, 0.05 mmol, 0.05 equiv) was added. The reaction mixture was stirred at reflux for 1 h. After cooling to room temperature, the reaction material was diluted with 5% aqueous NaOH and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford *endo*-alkene **7** (47 mg, 0.19 mmol, 37% yield, 75% overall yield from β-ketoester **6**) as a viscous yellow oil and lactone **10** (12 mg, 0.05 mmol, 11% yield). The data for **7** prepared by Method B was identical to the data for **7** prepared by Method A.

The following are the optimized procedures for the selective formation of the lactone **10** or the tetrasubstituted alkene **9** directly from the β-ketoester **6**.

*(1R,5R,8S)-4,4,8-Trimethyl-3-oxatricyclo[6.3.0.0^{1,5}]undecan-2,11-dione (**10**).* A mixture of $Mn(OAc)_3 \cdot 2H_2O$ (268 mg, 1.0 mmol, 2.0 equiv), $Cu(OAc)_2 \bullet H_2O$ (100 mg, 0.5 mmol, 1.0 equiv), and β-ketoester **6** (126 mg, 0.5 mmol) was subject to the conditions described in Method B above.

The resultant crude mixture was then diluted with dry toluene (2.5 mL), and *p*-toluenesulfonic acid monohydrate (100 mg, 1.05 mmol, 1.05 equiv) was added. The reaction was stirred at reflux for 4 h. After cooling to room temperature, the reaction material was diluted with 5% aqueous NaOH and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford lactone **10** (97 mg, 0.44 mmol, 87% yield) as a viscous clear oil which crystallized upon standing.

*(1S,5S)-1-Ethoxycarbonyl-5-methyl-8-(propan-2-ylidene)bicyclo-[3.3.0]octan-2-one (**9**).* A mixture of $Mn(OAc)_3 \cdot 2H_2O$ (268 mg, 1.0 mmol, 2.0 equiv), $Cu(OAc)_2 \cdot H_2O$ (100 mg, 0.5 mmol, 1.0 equiv), and β-ketoester **6** (126 mg, 0.5 mmol) was subject to the conditions described in Method B above. The resultant crude mixture was then diluted with dry toluene (2.5 mL), and *p*-toluenesulfonic acid

monohydrate (9 mg, 0.05 mmol, 0.05 equiv) was added. The reaction was stirred at reflux for 4 h. After cooling to room temperature, the reaction material was diluted with 5% aqueous NaOH and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford tetrasubstituted alkene **9** (103 mg, 0.44 mmol, 82% yield) as a viscous yellow oil along with lactone **10** (20 mg, 0.09 mmol, 18%). For **9**: TLC R_f (PE/MTBE = 6.5:1) = 0.42; $[\alpha]^{20}_D = (-)$ 147 (*c* 1.9 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24−4.10 (2H, m), 2.60−2.50 (1H, m), 2.49−2.30 (3H, m), 1.89−1.79 (2H, m), 1.71 (3H, s), 1.68 (3H, s), 1.65−1.55 (2H, m), 1.25 (3H, 7, *J* = 7.1 Hz), 1.18 (3H, s), 1.01 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 213.9, 170.6, 131.8, 131.3, 72.4, 60.8, 55.4, 37.1, 37.0, 31.2, 30.3; d 23.2, 22.9, 22.5, 14.3; IR (film, cm^{-1}) 1033, 1257, 1378, 1453, 2939; HRMS calcd for $C_{15}H_{22}O_3$ (M + Na) 273.1467, obsd 273.1461.

*(1S,2R,5S)-1-Ethoxycarbonyl-3,3,5-trimethyl-8-(propan-2-ylidene)bicyclo[3.3.0]octan-2-ol (**15**).* To a slurry of KH(P) [2.63 g KH(P), 50 wt % KH, 32.88 mmol KH, 3.0 equiv] in 27 mL toluene was added tetrasubstituted alkene **9** (2.74 g, 10.96 mmol) dropwise over 10 min. After stirring for 5 min, CH_3I (6.83 mL, 110 mmol, 10 equiv) was added followed by a small amount of non-anhydrous Et_2O to initiate the reaction. The reactor was equipped with a condenser and stirred at room temperature for 3 h. The reaction material was cooled to 0 °C, diluted with Et_2O, and then quenched by slow addition of saturated aqueous NH_4Cl. After extraction with Et_2O, the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford the *gem*-dimethyl ketone as a colorless oil (2.54 g, 10.16 mmol, 83% yield): TLC R_f (PE/MTBE = 10:1) = 0.46; $[\alpha]^{20}_D = (-)$ 140 (*c* 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (2H, m), 2.50 (1H, m), 2.37 (1H, m), 1.82 (1H, d, *J* = 13.5 Hz), 1.75 (1H, d, *J* = 13.5 Hz), 1.74−1.62 (2H, m), 1.71 (3H, s), 1.69 (3H, s), 1.26 (3H, t, *J* = 7.0 Hz), 1.22 (3H, s), 1.15 (3H, s), 1.11 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 217.5, 171.1, 132.9, 131.4, 73.3, 60.7, 52.6, 47.9, 46.5, 38.7, 30.1; d 28.8, 27.9, 24.8, 22.7, 22.4, 14.3; IR (film, cm^{-1}) 1031, 1731, 2936; HRMS calcd for $C_{17}H_{26}O_3$ (M + H) 279.1960, obsd 279.1967.

To a solution of ketone (2.29 g, 8.24 mmol) in 36 mL 1:1 v/v MeOH/EtOH at 0 °C was added $NaBH_4$ (2.73 g, 71.9 mmol, 8.7 equiv) in small portions over 1 h. The reaction was stirred to room temperature over 2 h, diluted with 15 mL of 15% aqueous NaOH, and stirred for 3 h at room temperature. The reaction mixture was diluted with H_2O and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford alcohol **15** (2.04 g, 7.29 mmol, 74% yield from **9**) as a colorless oil which solidified upon standing (mp = 38−39 °C): TLC R_f (PE/MTBE = 10:1) = 0.38, $[\alpha]^{20}_D = (-)$ 28.2 (*c* 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47 (1H, d, *J* = 7.3 Hz), 4.15 (2H, m), 2.52 (1H, dd, *J* = 6.6, 14.7 Hz), 2.37 (1H, m), 1.80 (OH, d, *J* = 7.3 Hz), 1.71 (3H, s), 1.66−1.51 (7H, m), 1.24 (3H, t, *J* = 7.1 Hz), 1.13 (3H, s), 1.02 (3H, s), 0.93 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 175.4, 135.7, 128.5, 69.5, 60.4, 53.3, 52.9, 40.3, 39.5, 31.3; d 83.5, 31.3, 26.4, 24.2, 22.8, 22.7, 14.38; IR (film, cm^{-1}) 1206, 1453, 1712, 2942, 3519; HRMS calcd for $C_{17}H_{28}O_3$ (M + H) 281.2117, obsd 281.2121.

*(1S,2R,5S)-2-Benzyloxy-1-ethoxycarbonyl-3,3,5-trimethyl-8-(propan-2-ylidene)bicyclo[3.3.0]octane (**17**).* A mixture of alcohol **15** (2.02 g, 7.20 mmol), benzyloxypyridinium triflate (BnOPT, 3.65 g, 10.44 mmol, 1.45 equiv), and MgO (421 mg, 10.44 mmol, 1.45 equiv) in 14.5 mL anhydrous dichloroethane (freshly distilled from CaH_2) was stirred at 80 °C for 8 h. Additional BnOPT (1.26 g, 3.6 mmol, 0.5 equiv) and MgO (145 mg, 3.6 mmol, 0.5 equiv) were added, and the mixture was stirred at 80 °C for an additional 8 h. After cooling to room temperature, the reaction mixture was filtered through Celite to remove precipitates, and the filter cake was washed thoroughly with Et_2O. The filtrate was concentrated in vacuo and the residue chromatographed to afford benzyl ether **17** (2.02 g, 5.47 mmol, 76% yield) as an inseparable mixture with Bn_2O (607 mg, 3.06 mmol) and residual alcohol **12** (470 mg, 1.68 mmol, 23% recovered). For **17**: TLC R_f (PE/MTBE = 20:1) = 0.63; $[\alpha]^{20}_D = (-)$ 12.2 (*c* 2.3 $CHCl_3$; material is 84 wt % benzyl ether **17** and 16 wt % Bn_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.23 (10H, m), 4.88 (1H, d, *J* = 11.8 Hz), 4.68 (1H, d, *J* = 11.8 Hz), 4.56 (1.76H, s, Bn_2O), 4.40 (1H, s), 4.15 (2H, dq, *J* = 1.1, 7.3 Hz), 2.49 (1H, dd, *J* = 7.5, 15.5 Hz), 2.38 (1H, m), 1.56−1.63 (5H, m), 1.50−1.44 (5H, m), 1.25 (3H, t, *J* = 7.1 Hz), 1.03 (3H, s), 1.00 (3H, s), 0.95 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 176.3, 139.8, 138.3, 135.0, 127.9, 74.6, 72.1 (Bn_2O), 68.1, 60.2, 52.9, 52.2, 39.8, 39.1, 31.2; d 128.4, 128.0, 127.8, 127.7, 127.6, 127.0, 91.8, 32.3, 26.5, 24.9, 23.3, 22.8, 14.4; IR (film, cm^{-1}) 1114, 1207, 1364, 1453, 2361, 2936; HRMS calcd for $C_{24}H_{34}O_3$ (M + H) 371.2586, obsd 371.2600.

*(1S,5S,8R)-8-Benzyloxy-1-ethoxycarbonyl-5,7,7-trimethyl-2-(2-hydroxyprop-2-yl)bicyclo[3.3.0]oct-2-ene (**18**).* A solution of benzyl ether **17** (1.07 g, 2.88 mmol) and methylene blue (photosensitizer, 11 mg, 0.03 mmol, 0.01 equiv) in 7.2 mL of MeOH was prepared in a 100 mL Pyrex glass test tube. A smaller diameter test tube was then submerged into the solution to create a thin film annular reactor. The reactor was capped and irradiated with a flood lamp (120 W, 12 in. from reactor) as O_2 was bubbled through the solution. A water bath was used to thermostat the reaction at 20−25 °C as it was irradiated. After 9 h, the reaction was diluted with 10 mL of Et_2O, PPh_3 (755 mg, 2.88 mmol, 1.0 equiv) was added, and the reaction was stirred overnight (12 h). Aqueous H_2O_2 (30 wt %, 1.5 mL, 5.0 equiv) was added and the reaction stirred 1.5 h at room temperature. The reaction mixture was partitioned between Et_2O and, sequentially, saturated aqueous $Na_2S_2O_3$ and brine. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford alcohol **18** (780 mg, 2.02 mmol, 70% yield) as a colorless oil and residual alkene starting material (298 mg, 0.81 mmol, 28% recovered). For **18**: TLC R_f (PE/MTBE = 20:1) = 0.22; $[\alpha]^{20}_D = (-)$ 4.78 (*c* 1.0 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.28 (5H, m), 5.55 (1H, t, *J* = 2.4 Hz), 4.68 (1H, d, *J* = 10.8 Hz), 4.63 (1H, d, *J* = 10.8 Hz), 4.59 (1H, s), 4.50 (OH, s), 4.18 (2H, m), 2.41 (2H, d, *J* = 2.4 Hz), 1.71 (1H, d, *J* = 13.6 Hz), 1.54 (1H, d, *J* = 13.6 Hz), 1.30 (3H, s), 1.29 (3H, s), 1.27 (3H, t, *J* = 7.2 Hz), 1.15 (3H, s), 1.09 (3H, s), 1.04 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 174.6, 153.3, 137.3, 75.4, 73.8, 70.3, 60.7, 55.5, 50.2, 49.2, 40.4; d 128.5, 128.5, 128.4, 128.0, 90.9, 32.0, 31.9, 31.5, 27.2, 22.7, 14.2; IR (film, cm^{-1}) 1227, 1366, 1366, 1455, 1718, 2930, 3456; HRMS calcd for $C_{24}H_{34}O_4$ (M + Na) 409.2355, obsd 409.2351.

*(1S,5S,8R)-8-Benzyloxy-1-ethoxycarbonyl-5,7,7-trimethyl-2-(propan-2-ylidene)bicyclo[3.3.0]oct-2-ene (**19**).* To a solution of alcohol **18** (386 mg; 1.0 mmol) and anhydrous DMF (233 μL, 3.0 mmol, 3.0 equiv) in 10 mL of CH_2Cl_2 at −78 °C was added $SOCl_2$ (183 μL, 2.5 mmol, 2.5 equiv) dropwise. After 10 min at −78 °C, 2,6-lutidine (582 μL, 5.0 mmol, 5.0 equiv) was added dropwise over 10 min. The reaction was gradually stirred to −40 °C over 20 min, and additional $SOCl_2$ (183 μL, 2.5 mmol, 2.5 equiv) was added. The reaction was warmed to −20 °C and quenched with 1 N aqueous HCl. The reaction material was partitioned between CH_2Cl_2 and, sequentially, H_2O and saturated aqueous $NaHCO_3$. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford diene **19** (276 mg, 0.75 mmol, 79% yield) as a yellow oil and residual alcohol starting material (47 mg, 0.12 mmol, 12% recovered). For **19**: TLC R_f (PE/MTBE = 10:1) = 0.66, $[\alpha]^{20}_D = (+)$ 81.6 (*c* 1.84 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.20 (5H, m), 5.84 (1H, t, *J* = 2.4 Hz), 4.78 (2H, d, *J* = 12.5 Hz), 4.70 (1H, d, *J* = 11.6 Hz), 4.60 (1H, d, *J* = 11.6 Hz), 4.41 (1H, s), 4.17 (2H, m), 2.46 (1H, d, *J* = 17.6 Hz), 2.40 (1H, d, *J* = 17.6 Hz), 1.83 (3H, s), 1.72 (1H, d, *J* = 13.4 Hz), 1.52 (1H, d, *J* = 13.4 Hz), 1.25 (3H, t, *J* = 7.0 Hz), 1.08 (3H, s), 1.00 (3H, s), 0.99 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 175.3, 146.0, 140.6, 139.5, 112.1, 74.3, 73.3, 60.6, 55.4, 51.5, 49.7, 41.6; d 130.8, 128.0, 127.5, 127.0, 90.2, 30.7, 27.3, 23.2, 22.5, 14.2; IR (film, cm^{-1}) 1718,

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2928, 3418; HRMS calcd for $C_{24}H_{32}O_3$ (M + H) 368.2351, obsd 368.2341.

*(1S,2R,5S)-E and Z-2-Benzyloxy-1-ethoxycarbonyl-3,3,5-trimethyl-8-[1-(phenylthio)propan-2-ylidene]bicyclo[3.3.0]octane (**21**).* A mixture of diene **19** (380 mg, 1.03 mmol), thiophenol (115 μL, 1.13 mmol, 1.1 equiv), and silica nanoparticles (SNPs, 19 mg, 5 wt %) in a small vial was stirred vigorously at room temperature for 18 h. The reaction mixture was filtered through Celite and concentrated in vacuo. The residue was chromatographed to afford a 1:1.5 *Z*:*E* mixure of allylic thioethers **21** (412 mg, 0.86 mmol, 84% yield) as a colorless oil: TLC R_f (PE/MTBE = 100:1) = 0.22; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−6.90 (10H, m), 4.95 (0.4H, d, *J* = 11.5 Hz, *Z*-isomer), 4.88 (0.6H, d, *J* = 11.7 Hz, *E*-isomer), 4.77 (0.4H, d, *J* = 11.7 Hz, *E*-isomer), 4.69 (0.7H, d, *J* = 11.7 Hz, *Z*-isomer), 4.43 (1H, m), 4.24−4.09 (2H, m), 3.98 (0.4H, d, *J* = 11.5 Hz, *Z*-isomer), 3.66 (0.6H, d, *J* = 11.1 Hz, *E*-isomer), 3.44 (0.6H, d, *J* = 11.1 Hz, *E*-isomer), 3.18 (0.4H, d, *J* = 11.5 Hz, *Z*-isomer), 2.59−2.37 (2H, m), 1.78 (1.1H, s), 1.64 (1.8H, s), 1.61−1.45 (4H, m), 1.23−1.30 (3H, m), 1.09 (1H, s), 1.04 (3H, s), 1.00 (2H, s), 0.96 (1H, s), 0.94 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 175.7, 175.5, 140.7, 139.7, 139.6, 140.0, 139.0, 137.9, 127.3, 126.6, 74.6, 74.6, 68.6, 68.0, 60.8, 60.5, 53.0, 52.9, 52.1, 51.8, 49.7, 49.5, 41.0, 40.9, 40.4, 40.3, 39.9, 39.4, 39.0, 38.8, 31.8, 31.0; d 129.4, 128.6, 128.5, 128.1, 128.0, 127.6, 127.8, 127.5, 127.1, 127.0, 125.7, 124.7, 91.8, 91.3, 32.5, 32.2, 26.5, 26.4, 25.0, 24.7, 20.8, 20.4, 14.4, 14.2; IR (film, cm^{-1}) 1218, 1452, 1582, 1714, 2945; HRMS calcd for $C_{30}H_{38}O_3S$ (M + H) 479.2620, obsd 479.2612.

*(1S,2R,5S)-E-2-Benzyloxy-1-ethoxycarbonyl-3,3,5-trimethyl-8-[1-(phenylsulfinyl)propan-2-ylidene]bicyclo[3.3.0]octane (**22a,b**) and (1S,2R,5S)-Z-2-Benzyloxy-1- ethoxycarbonyl-3,3,5-trimethyl-8-[1-(phenylsulfinyl)propan-2-ylidene]bicyclo[3.3.0]octane (**23a,b**).* To a solution of allylic thioethers **22** (410 mg, 0.86 mmol) in 4.0 mL of CH_2Cl_2 at −78 °C was added a solution of *m*-CPBA (148 mg, 0.86 mmol, 1.0 equiv) in 4.6 mL of CH_2Cl_2 dropwise via syringe over 10 min. The reaction material was stirred at −78 °C for 30 min and diluted with 5 mL of saturated aqueous $Na_2S_2O_3$. The reaction material was diluted with H_2O and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford a mixture of *E*-allylic sulfoxides **22a,b** (260 mg, 0.526 mmol, 61% yield) and *Z*-allylic sulfoxides **23a,b** (155 mg, 0.314 mmol, 37% yield, dr = 1.5:1).

*E-Allylic Sulfoxide **22a** (major).* TLC R_f (PE/EtOAc = 5:1) = 0.13; $[\alpha]^{20}_D$ = (−) 24.6 (*c* 1.79 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (2H, d, *J* = 7.6 Hz), 7.40−7.24 (8H, m), 4.80 (1H, d, *J* = 11.2 Hz), 4.67 (1H, d, *J* = 11.2 Hz), 4.47 (1H, s), 4.20 (2H, dq, *J* = 1.7, 7.0 Hz), 3.81 (1H, d, *J* = 12.2 Hz), 3.43 (1H, d, *J* = 12.2 Hz), 2.52 (1H, m), 2.25 (1H, dd, *J* = 6.8, 16.0), 1.63−1.45 (7H, m), 1.30 (3H, t, *J* = 7.0 Hz), 1.09 (3H, s), 1.04 (3H, s), 1.00 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 175.2, 145.3, 144.4, 139.2, 121.5, 75.1, 69.1, 66.8, 60.7, 53.0, 52.2, 40.1, 39.0, 31.6; d 130.8, 128.9, 128.2, 128.0, 127.3, 92.3, 32.3, 26.4, 25.4, 22.5, 14.4; IR (film, cm^{-1}) 1040, 1724, 2936; HRMS calcd for $C_{30}H_{38}O_4S$ (M + H) 495.2569, obsd 495.2564.

*E-Allylic Sulfoxide **22b** (minor).* TLC R_f (PE/EtOAc = 5:1) = 0.16; $[\alpha]^{20}_D$ = (−) 42.9 (*c* 0.96 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (2H, m), 7.45 (3H, m), 7.35−7.29 (4H, m), 7.25 (1H, m), 4.81 (1H, d, *J* = 11.5 Hz), 4.67 (1H, d, *J* = 11.5 Hz), 4.43 (1H, s), 4.19 (2H, m), 3.75 (1H, d, *J* = 12.8 Hz), 3.44 (1H, d, *J* = 12.8 Hz), 2.73 (1H, dd, *J* = 7.4, 15.7 Hz), 2.37 (1H, m), 1.65 (1H, td, *J* = 7.4, 11.7 Hz), 1.58−1.47 (6H, m), 1.31 (3H, t, *J* = 7.1 Hz), 1.06 (3H, s), 1.01 (3H, s), 0.90 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 175.2, 145.2, 144.5, 139.3, 121.9, 74.8, 69.1, 66.5, 60.7, 53.0, 52.4, 40.1, 38.9, 31.5; d 131.0, 129.0, 128.1, 127.7, 127.2, 124.4, 92.0, 32.3, 26.4, 25.2, 22.3, 14.4; IR (film, cm^{-1}) 1036, 1208, 1452, 1714, 2934; HRMS calcd for $C_{30}H_{38}O_4S$ (M + H) 495.2569, obsd 495.2567.

*Z-Allylic Sulfoxides **23a,b**.* TLC R_f (PE/EtOAc = 5:1) = 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−6.82 (10H, m), 4.70−4.06 (6H, m), 3.08 (0.6H, d, *J* = 13.8 Hz), 2.97 (0.4H, d, *J* = 13.5 Hz), 2.64 (1H, m), 2.50 (1H, m), 1.94 (1.8H, s), 1.88−1.78 (2.2H, m), 1.62−1.47 (3H, m), 1.32 (3H, m), 1.07 (6H, m), 0.87 (2H, s), 0.85 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 176.0, 176.0, 145.1, 144.9, 144.4, 142.9, 138.8, 138.3, 125.0, 122.4, 74.9, 74.7, 67.8, 67.8, 67.2, 66.0, 61.4, 60.9, 52.9, 52.6, 52.0, 51.9, 39.2, 39.1, 38.6, 38.5, 32.1, 32.1; d 130.7, 130.4, 129.1, 129.0, 128.0, 127.9, 127.7, 127.5, 127.1, 127.0, 124.2, 123.6, 91.6, 91.4, 32.4, 32.3, 26.2, 26.2, 24.9, 24.7, 22.4, 20.2, 14.2, 14.1; IR (film, cm^{-1}) 1242, 1381, 1451, 1713, 2932; HRMS calcd for $C_{30}H_{38}O_4S$ (M + H) 495.2569, obsd 495.2566.

*Isomerization of E-Allylic Sulfoxides (**22a,b**).* A solution of allylic sulfoxides **22a,b** (37 mg, 0.075 mmol) in 1.5 mL of toluene was irradiated in a microwave reactor (*P* = 150 W, T_{ramp} = 23−120 °C over 10 min, T_{hold} = 120 °C, 15 min). The reaction material was concentrated in vacuo and the residue chromatographed to afford *Z*-allylic sulfoxides **23a,b** (7.7 mg, 0.016 mmol, 21% yield) and *E*-allylic sulfoxides **22a,b** (25.8 mg, 0.052 mmol, 70% recovered yield).

*(1S,2R,5S)-Z-2-Benzyloxy-1-ethoxycarbonyl-3,3,5-trimethyl-8-[1-(phenylsulfonyl)propan-2-ylidene]bicyclo[3.3.0]octane (**24**).* A mixture of *Z*-allylic sulfoxides **23a,b** (70 mg, 0.142 mmol), aqueous H_2O_2 (30 wt %, 73 μL, 5.0 equiv), and H_2WO_4 (3.5 mg, 0.014 mmol, 0.1 equiv) in 700 μL of 1:1 of MeOH/THF was stirred vigorously at room temperature for 20 h. The reaction mixture was then diluted with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford *Z*-allylic sulfone **24** (55 mg, 0.108 mmol, 76% yield): TLC R_f (PE/EtOAc = 6.5:1) = 0.46; $[\alpha]^{20}_D$ = (−) 80.6 (*c* 1.35 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 7.6 Hz), 7.57 (1H, t, *J* = 7.4 Hz), 7.48 (2H, t, *J* = 7.6 Hz), 7.12 (1H, t, *J* = 7.3 Hz), 7.05 (2H, t, *J* = 7.3 Hz), 6.85 (2H, d, *J* = 7.5 Hz), 4.69 (1H, d, *J* = 10.8 Hz), 4.55−4.40 (3H, m), 4.25 (2H, m), 3.33 (1H, d, *J* = 14.5 Hz), 2.65 (1H, dd, *J* = 7.9, 16.7 Hz), 2.50 (1H, m), 1.92 (3H, s), 1.90 (1H, m), 1.59−1.48 (3H, m), 1.33 (3H, t, *J* = 7.0 Hz), 1.09 (3H, s), 1.08 (3H, s), 0.83 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 175.7, 145.8, 141.6, 138.4, 120.1, 74.8, 67.8, 63.5, 61.1, 52.6, 52.0, 39.0, 38.3, 32.2; d 133.0, 129.0, 128.0, 127.5, 127.5, 127.1, 91.4, 32.4, 26.0, 24.9, 20.9, 14.2; IR (film, cm^{-1}) 1366, 1452, 1730, 2360, 2949; HRMS calcd for $C_{30}H_{38}O_5S$ (M + Na) 533.2338, obsd 533.2332.

*(1R,5R,8S,11R)-11-Benzyloxy-4,8,10,10-tetramethyl-3-phenylsulfonyltricyclo[6.3.0.0^{1,5}]undec-3-en-2-one (**25**).* To a solution of Et_2NH (220 μL, 1.56 mmol, 14 equiv) in 200 μL of THF at −78 °C was added *n*-BuLi (2.09 M, 641 μL, 12.0 equiv). The solution was gradually stirred to −40 °C, and a solution of *Z*-allylic sulfone **25** (57 mg, 0.112 mmol) in 300 μL of THF was added dropwise. The reaction was stirred to −20 °C and quenched with saturated aqueous NH_4Cl. The reaction mixture was diluted with H_2O and extracted with Et_2O. The combined organic extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed to afford α-sulfonylenone **25** (47 mg, 0.101 mmol, 90% yield) as a viscous oil: TLC R_f (PE/EtOAc = 5:1) = 0.54; $[\alpha]^{20}_D$ = (−) 21.8 (*c* 0.55 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (2H, d, *J* = 7.5 Hz), 7.56 (1H, t, *J* = 7.4 Hz), 7.47 (2H, t, *J* = 7.4 Hz), 7.27 (3H, m), 6.93 (2H, m), 4.00 (1H, s), 3.98 (1H, d, *J* = 11.9 Hz), 3.83 (1H, d, *J* = 11.9 Hz), 3.49 (1H, d, *J* = 9.8 Hz), 2.62 (3H, s), 2.18 (1H, m), 1.81 (1H, dd, *J* = 6.7, 13.5 Hz), 1.64−1.54 (2H, m), 1.50 (1H, d, *J* = 14.0 Hz), 1.28 (1H, m), 1.05 (3H, s), 0.99 (3H, s), 0.92 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 202.3, 186.6, 140.5, 138.3, 138.3, 73.0, 71.5, 53.9, 50.2, 40.4, 40.1, 27.0; d 133.6, 128.8, 128.2, 128.1, 127.4, 127.1, 91.4, 53.8, 31.9, 26.4, 24.9, 17.6.; IR (film, cm^{-1}) 2957, 2361, 1707, 1604, 1453, 1320, 1154; HRMS calcd for $C_{28}H_{32}O_4S$ (M + H) 465.2100, obsd 465.2090.

*(1R,3S,4R,5R,8S,11R)-11-Benzyloxy-4,8,10,10-tetramethyl-3-phenylsulfonyltricyclo[6.3.0.0^{1,5}]undecan-2-one (**26**) and (1R,3R,4S,5R,8S,11R)-11-Benzyloxy-4,8,10,10-tetramethyl-3-phenylsulfonyltricyclo[6.3.0.0^{1,5}]-undecan-2-one (**27**).* A mixture of enone **26** (138 mg, 0.30 mmol,

1.0 equiv) and Mg turnings (154 mg, 6.34 mmol, 20 equiv) in 5 mL of a 1:1 v/v mixture of MeOH/THF was sonicated at room temperature until bubbling from the surface of the Mg turnings was visible and the mixture turned cloudy gray. Small portions of NH_4Cl (45 mg, 0.85 mmol, 2.8 equiv/portion) were introduced at 15 min intervals with continuous sonication until the reaction mixture became cloudy white (ca. 10 portions, 8.5 mmol NH_4Cl). The reaction was quenched with 3 N aqueous HCl (slow addition!) until clear and diluted with H_2O. The biphasic mixture was extracted with Et_2O, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed to afford ketones **26** (45.8 mg, 0.098 mmol, 33% yield), **27** (28.7 mg, 0.062 mmol, 21% yield), and residual enone **25** (60.7 mg, 0.131 mmol, 44% recovered). Ketone **26** (major diastereomer): TLC R_f (PE/EtOAc = 6.6:1) = 0.52; $[\alpha]^{20}_D$ = (+) 30 (*c* 0.4 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.57 (d, *J* = 7.4 Hz, 1H), 7.50 (dd, *J* = 8.1, 6.7 Hz, 2H), 7.36−7.28 (m, 5H), 4.21 (d, *J* = 11.6 Hz, 1H), 4.08 (d, *J* = 11.6 Hz, 1H), 3.82 (s, 1H), 3.72 (d, *J* = 13.0 Hz, 1H), 3.30−3.22 (m, 1H), 2.84−2.69 (m, 1H), 1.99−1.88 (m, 2H), 1.59−1.48 (m, 2H), 1.42 (dd, *J* = 11.6, 7.3 Hz, 1H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.30 (d, *J* = 13.5 Hz, 1H), 1.06 (s, 3H), 0.90 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 211.8, 138.9, 138.5, 73.8, 73.4, 54.4, 52.1, 42.8, 42.6, 27.6; d 133.8, 129.5, 128.8, 128.2, 127.8, 127.5, 92.7, 73.7, 49.0, 33.1, 30.6, 26.3, 22.9, 16.8; IR (film, cm^{-1}) 2931, 1729, 1455, 1312, 1149, 1084; HRMS calcd for $C_{28}H_{34}O_4S$ (M + Na) 489.2076, obsd 489.2054.

Ketone **27** (minor diastereomer): TLC R_f (PE/EtOAc = 6.6:1) = 0.56; $[\alpha]^{20}_D$ = (−) 45.5 (*c* 0.22 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.87 (m, 2H), 7.71−7.64 (m, 1H), 7.62−7.56 (m, 2H), 7.24 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.15 (dd, *J* = 6.8, 2.8 Hz, 2H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.14 (d, *J* = 11.8 Hz, 1H), 3.88 (s, 1H), 3.13 (d, *J* = 11.1 Hz, 1H), 2.60−2.54 (m, 1H), 2.45−2.33 (m, 1H), 2.14−2.01 (m, 1H), 1.74−1.66 (m, 1H), 1.62 (d, *J* = 14.1 Hz, 1H), 1.59−1.54 (m, 2H), 1.52 (d, *J* = 14.1 Hz, 1H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.10 (s, 3H), 0.99 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 212.2, 138.8, 138.4, 75.9, 74.2, 55.8, 54.7, 41.8, 41.5, 30.8; d 133.9, 129.4, 128.8, 128.3, 127.6, 127.5, 95.5, 77.2, 49.8, 36.7, 32.1, 27.2, 24.0, 20.9; IR (film, cm^{-1}) 2957, 1730, 1455, 1313, 1149, 1086; HRMS calcd for $C_{28}H_{34}O_4S$ (M + Na) 489.2076, obsd 489.2061.

*(1R,4S,5R,8S,11R)-11-Benzyloxy-4,8,10,10-tetramethyltricyclo-[6.3.0.0^{1,5}]undecan-2-one (**28**).* To a solution of α-sulfonyl ketone **27** (22 mg; 0.047 mmol) in 400 μL of dry THF at −78 °C (thoroughly purged with N_2) was added SmI_2 (2.35 mL of 0.1 M stock solution in THF, 0.235 mmol, 5.0 equiv) rapidly via syringe. The reaction material was stirred for 10 min at −78 °C and brought to room temperature in the presence of O_2. The reaction material was then concentrated in vacuo and chromatographed to afford ketone **28** (14.1 mg, 0.043 mmol, 92% yield): TLC R_f (PE/MTBE = 10:1) = 0.67; $[\alpha]^{20}_D$ = (+) 6.2 (*c* 0.65 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H), 4.46 (q, *J* = 11.7 Hz, 2H), 4.06 (s, 1H), 2.68 (ddd, *J* = 7.4, 5.2, 2.1 Hz, 1H), 2.42 (dd, *J* = 19.5, 10.5 Hz, 1H), 2.19−2.08 (m, 1H), 1.87 (dd, *J* = 19.1, 6.8 Hz, 1H), 1.88−1.83 (m, 1H), 1.61 (d, *J* = 13.9 Hz, 1H), 1.70−1.52 (m, 3H), 1.47 (d, *J* = 13.8 Hz, 1H), 1.10 (s, 3H), 1.03 (s, 3H), 0.99 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 222.7, 138.9, 73.8, 73.7, 54.9, 53.3, 47.6, 42.3, 41.2, 31.6; d 128.2, 127.5, 127.3, 92.3, 51.7, 34.3, 31.9, 27.1, 24.0, 21.2; IR (film, cm^{-1}) 2953, 1727, 1458, 1109; HRMS calcd for $C_{22}H_{30}O_2$ (M + Na) 349.2144, obsd 349.2149.

*(1S,2R,5S,8S,9S)-3,3,5,9-Tetramethyltricyclo[6.3.0.0^{1,5}]undecan-2-ol; C-9-epi-cameroonan-7α-ol (epi-**2**).* To a solution of α-sulfonyl ketone **26** (4 mg, 8.6 μmol) in 200 μL of dry THF at −78 °C was added SmI_2 (0.1 M stock solution in THF, 1.0 mL, 0.1 mmol) rapidly via syringe. The reaction solution was stirred at −78 °C for 10 min and brought to room temperature in the presence of O_2. The reaction material was concentrated in vacuo and filtered through a short plug of silica gel.

The crude filtrate was taken up in triethylene glycol (400 μL) and hydrazine monohydrate (100 μL, 0.1 mmol, 12 equiv). The reaction material was stirred at 130 °C for 2 h. KOH (2 mg, 0.04 mmol, 4 equiv) was added, and the reaction mixture was stirred at 140 °C for 6 h. After cooling to room temperature, the mixture was diluted with H_2O and extracted with Et_2O. The combined organic fractions were dried (Na_2SO_4) and concentrated in vacuo.

The crude concentrate was then diluted with 0.5 mL of EtOH, and 10% Pd/C (ca. 5 mg) was added. The reaction mixture was stirred vigorously under H_2 (balloon) for 2.5 h at room temperature. The reaction material was filtered through Celite and concentrated in vacuo to afford *epi*-**2** (0.5 mg, 26% yield from **26**): TLC R_f (PE/MTBE = 20:1) = 0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (br s, 1H), 2.51 (dd, *J* = 15.1, 7.4 Hz, 1H), 1.94−1.82 (m, 2H), 1.61 (m, 2H), 1.52−1.36 (m, 5H), 1.32 (m, 2H), 1.02 (s, 3H), 1.01 (s, 3H), 0.97 (s, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 66.7, 53.2, 49.1, 42.9, 39.6, 34.2, 32.6, 24.3; d 89.2, 49.7, 39.3, 31.6, 26.4, 23.3, 15.8. These data were congruent with those previously reported.[3b]

*(1S,2R,5S,8S,9R)-3,3,5,9-Tetramethyltricyclo[6.3.0.0^{1,5}]undecan-2-ol: (−)-cameroonan-7α-ol (**2**).* A mixture of ketone **28** (12 mg, 0.037 mmol), anhydrous N_2H_4 (38 μL, 1.22 mmol, 33 equiv), and KOH (34 mg, 0.61 mmol, 16 equiv) was stirred at 170−180 °C for 18 h in a sealed vial. The reaction material was diluted with 5% aqueous NaOH and extracted with Et_2O. The combined organic extracts were dried (Na_2SO_4), concentrated in vacuo, and filtered through a short plug of silica gel.

The crude material was diluted with 200 μL of dry THF and cooled to −78 °C. Liquid NH_3 (ca. 1 mL) was condensed into the reactor, and a single piece of Na (ca. 50 mg, 2.17 mmol) was added. The blue reaction solution with blue foam was stirred at −78 °C for 10 min, and MeOH was slowly added to dissipate the blue color. Excess NH_3 was removed by warming the reaction to room temperature. The reaction material was then concentrated in vacuo and chromatographed to afford (−)-cameroonan-7α-ol **2** (2.0 mg, 24% yield): TLC R_f (PE/MTBE = 20:1) = 0.35; $[\alpha]^{20}_D$ = (−) 37 (*c* 0.10 $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 1H), 1.90 (t, *J* = 8.0 Hz, 1H), 1.84−1.72 (m, 1H), 1.69−1.58 (m, 2H), 1.55 (d, *J* = 14.3 Hz, 1H), 1.52−1.47 (m, 1H), 1.44−1.38 (m, 3H), 1.41 (d, *J* = 14.2 Hz, 1H), 1.36−1.29 (m, 1H), 1.25 (t, *J* = 5.3 Hz, 1H), 1.04 (s, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.97 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ u 67.1, 52.6, 47.5, 39.9, 38.6, 36.1, 35.3, 29.0; d 89.7, 51.3, 43.8, 32.5, 25.7, 23.9, 19.4; IR (film, cm^{-1}) 3485, 2932, 2866, 1459; GC-MS (EI, 70 eV) *m*/*z* (rel. intensity %) 222 (2), 204 (18), 189 (14), 166 (25), 148 (32), 135 (100), 124 (33), 109 (24); HRMS calcd for $C_{15}H_{25}$ (M − OH) 205.1956, obsd 205.1955.

■ ASSOCIATED CONTENT

Supporting Information. General experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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