

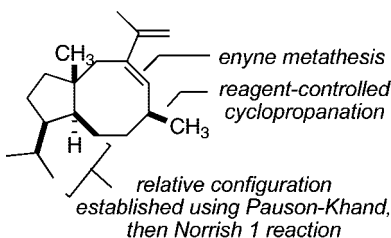
A Synthetic Approach to the Fusicoccane A–B Ring Fragment Based on a Pauson–Khand Cycloaddition/Norrish Type 1 Fragmentation

Gregory R. Dake,* Erik E. Fenster, and Brian O. Patrick†

Department of Chemistry, 2036 Main Mall, University of British Columbia, Vancouver, B.C., Canada, V6T 1Z1

gdake@chem.ubc.ca

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A synthetic approach to the A–B ring system within the fusicoccane family of diterpenes is presented. Key steps in this approach are a diastereoselective Pauson–Khand reaction, a Norrish 1 photofragmentation, a Charette cyclopropanation, and a ring-closing metathesis process.

Introduction

The fusicoccane family of diterpenes are characterized by a fused 5–8–5 carbocyclic skeleton (Figure 1). Members of this family class have been isolated and characterized from a number of natural sources, including fungi, liverworts, and higher plants.¹ The fusicoccane diterpenoids, with the structurally related classes typified by the cotylenins, fusicoplugins, ophiobolines, and plagiospirolides, exhibit interesting phytohormonal activities.² In the case of the fusicoccanes, this activity results from the interaction with 14–3–3 proteins in the plant's

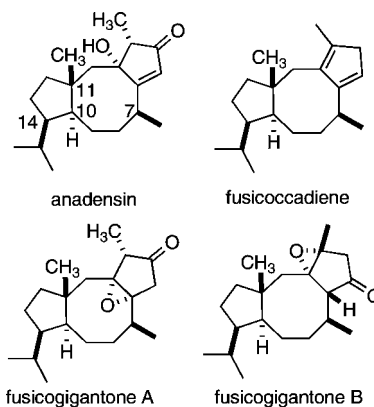


FIGURE 1. Prototypical fusicoccane diterpenes.

membranes, causing membrane hyperpolarization and activation of plasma membrane H⁺-ATP-ase.³

We became intrigued with the liverwort fusicoccane family of natural products after we recognized structural similarities between members of this family and that of nitiol, a sesterterpene natural product. Specifically, the *cis*-relationship between the methyl group and the isopropyl group appended on a five-

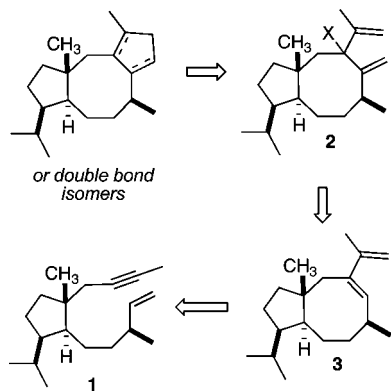
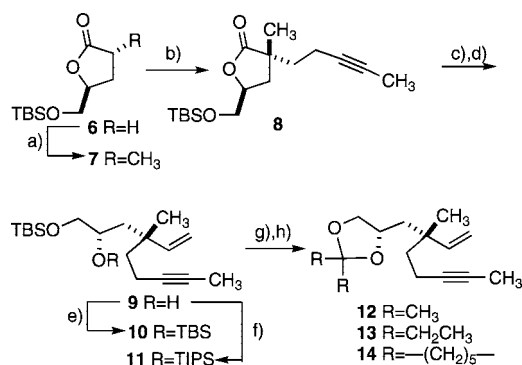
† Manager, University of British Columbia X-Ray Analysis Facility.

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SCHEME 1. An Analysis of the Fusicoccane Skeleton

SCHEME 2. Stereoselective Preparation of Pauson–Khand Substrates^a

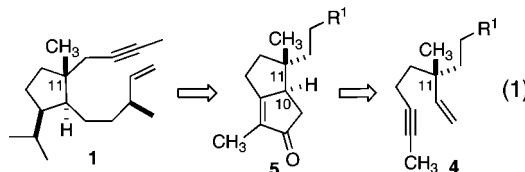
^a Reagents and conditions: (a) LDA, THF, $-78\text{ }^{\circ}\text{C}$, 30 min, then CH_3I , $-78\text{ }^{\circ}\text{C}$ (93%); (b) LDA, HMPA, THF, $-78\text{ }^{\circ}\text{C}$, 1 h, then 5-iodopent-2-yne, $-78\text{ }^{\circ}\text{C}$ to rt (54%, 80% based on conversion); (c) DIBAL-H, CH_2Cl_2 , $-78\text{ }^{\circ}\text{C}$ (92%); (d) KHMDS, $\text{CH}_3\text{PPh}_3\text{Br}$, THF, $0\text{ }^{\circ}\text{C}$ to rt, (99%); (e) TBSCl, imidazole, DMF, $50\text{ }^{\circ}\text{C}$ (95%); (f) TIPSCl, imidazole, DMF, $70\text{ }^{\circ}\text{C}$ (56%); (g) TBAF, THF (99%); (h) for **12**: 2,2-dimethoxypropane, *p*-TsOH, CH_2Cl_2 (87%); for **13**: 3,3-dimethoxypropane, *p*-TsOH, CH_2Cl_2 (91%); for **14**: cyclohexanone (neat), CuSO_4 , *p*-TsOH (96%).

membered ring in each of these natural products suggested that a related synthetic approach that we had applied to the construction of the nitiane A-ring system could be utilized within an approach to the fusicoccane ring system.⁴

As expected, a significant amount of attention by synthetic chemists has been brought to bear on the tricyclic ring system typified by the fusicoccane diterpenes and its structural relatives. A number of total syntheses and synthetic approaches to these and structurally related natural products have been disclosed.⁵ The specific problem in establishing the cis-relationship of the methyl and isopropyl groups on the five-membered ring has been dealt with by using a number of creative solutions, including a doubly diastereoselective addition of an allylstannane or allylchromium reagent to an aldehyde.⁶ Our analysis of the fusicoccane ring system is presented in Scheme 1. In a linear fashion, the target tricyclic ring would be envisioned to arise from three successive ring-forming events. We planned to annulate the final five-membered carbocycle onto the central eight-membered ring in **2** using Nazarov methodology.^{7,8}

The construction of eight-membered rings is recognized to be challenging, often requiring the development of new synthetic methodology.⁹ In this instance, the central eight-membered ring in **3** was envisioned to arise from an enyne or diene ring-closing metathesis reaction of a substrate related to **1**, based on the

precedent within Fürstner's dactylo synthesis.^{10,11} We thus intended to use a synthetic approach formatted on our previous work on the nitianes to produce the requisite metathesis substrate (eq 1). The key sequences in this route would involve a Pauson–Khand reaction to establish the stereogenic center at C10 (fusicoccane numbering), followed by a photochemical ring cleavage reaction.¹² A key question in this approach was one of diastereoselectivity: Would there be enough steric differentiation at C11 in enyne **4** to produce **5** with reasonable diastereoselectivity at C10? With this problem in mind, a synthetic route to a surrogate of **4** was developed.



Known lactone (*S*)-(+)-**6** was readily constructed from L-glutamic acid in three steps by using a literature procedure

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that was modified somewhat to improve both material throughput and reaction yields on multigram scales.¹³ A two-step alkylation sequence was used to establish the stereogenic quaternary carbon center of the enyne substrate (Scheme 2). Treatment of lactone **6** with LDA and methyl iodide generated a monomethylated lactone **7** as a ~9:1 mixture of diastereomers. This mixture was inconsequential as its deprotonation using LDA (1.1 equiv) in THF with HMPA (2.2 equiv) followed by the addition of 5-iodopent-2-yne produced the desired compound **8** in 40–50% yield (depending on reaction scale) with ~5% of the undesired diastereomer and ~30% of unalkylated lactone as the major byproducts. The use of LDA with HMPA was uniquely effective—in the absence of the HMPA additive the major reaction was an E₂ process on the electrophile. This sequence, while not optimal, could be performed on 35–80 g scales and the unalkylated lactone starting material was easily separable for recycling of material. The lactone was subsequently processed in a straightforward manner to the enyne **9** by using a DIBAL-H reduction followed by a Wittig reaction.

Reasonable diastereoselection in the Pauson–Khand reaction was needed for a useful synthesis of the A-ring fragment.¹⁴ A number of protecting group patterns were evaluated to determine the best choice. It was reasoned that the protecting group on the secondary alcohol of enyne **9** should be as large as possible. To that end a number of enynes **10–14** were synthesized by using standard procedures (silylation and ketalization).

These enyne substrates were then individually subjected to Pauson–Khand conditions (Co₂(CO)₈, 4Å molecular sieves, CH₂Cl₂; NMO, rt).¹⁵ The results are summarized in eq 2 and Table 1.

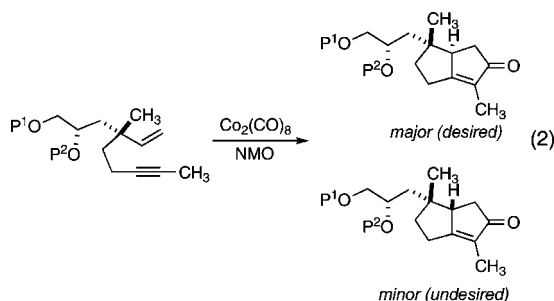


TABLE 1. Evaluation of Protecting Group Modifications on the Pauson–Khand Reaction

entry	substrate	P ¹	P ²	yield ^a (%)	dr ^b (major/minor)	pdts (major/minor)
1	10	TBS	TBS	83	2.4:1	15a/15b
2	11	TBS	TIPS	86	2.8:1	16a/16b
3	12	–C(Me) ₂ –		89	6.1:1	17a/17b
4	13	–C(Et) ₂ –		84	1.3:1	18a/18b
5	14	–C(C ₅ H ₁₀)–		79	2.2:1	19a/19b

^a Combined isolated yield. ^b dr = diastereomeric ratio; determined by GC analysis.

The results within Table 1 show that one protecting group strategy for the diol, the isopropyl acetonide, was obviously superior to other alternatives (entry 3). This empirical result is somewhat unexpected, especially in light of the results in entries 4 and 5. The result in entry 3 was welcome and useful for our purposes, but no mechanistic underpinning can be presented to rationalize it at the present time. The Pauson–Khand reaction of **12** was highly reproducible on several scales.

The structural constitution and relative stereochemistry of the products was established by NMR methods. Specifically, NOE

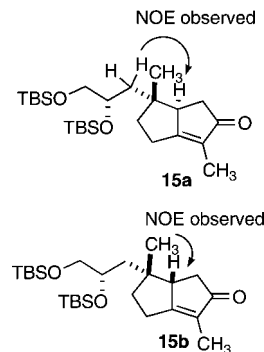
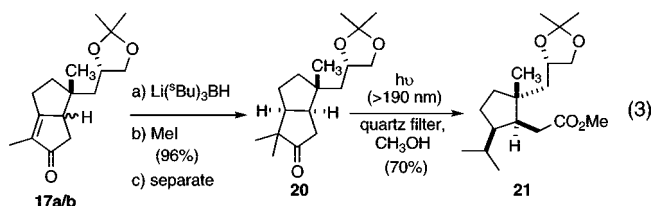


FIGURE 2. NOE experiments on **15a** and **15b**.

experiments were used to establish the relative stereochemistry of **15a** and **15b** (Figure 2). Deprotection of each of the product mixtures (**15–19a/b**) generated diols whose spectral data could be directly compared.

Compounds **17a/b** were not easily separable, and so this mixture was typically taken directly into the next reaction sequence (eq 3). Conjugate reduction of the enone function in **17a/b** with L-Selectride followed by a methyl iodide quench produced readily separable ketones in 96% combined yield. At this point a straightforward separation provided the desired diastereomer **20**.



Ketone **20** was subjected to photolytic Norrish 1 fragmentation conditions (UV light, $\lambda > 190$ nm, methanol).¹⁶ Gratifyingly, the functionalized cyclopentane derivative **21** could be produced in 41–70% yield, depending on the reaction conditions. Running the reactions at higher dilutions (0.015 M) for ~5 h consistently resulted in useful yields of 70%. Prolonged reaction times resulted in lowered yields.

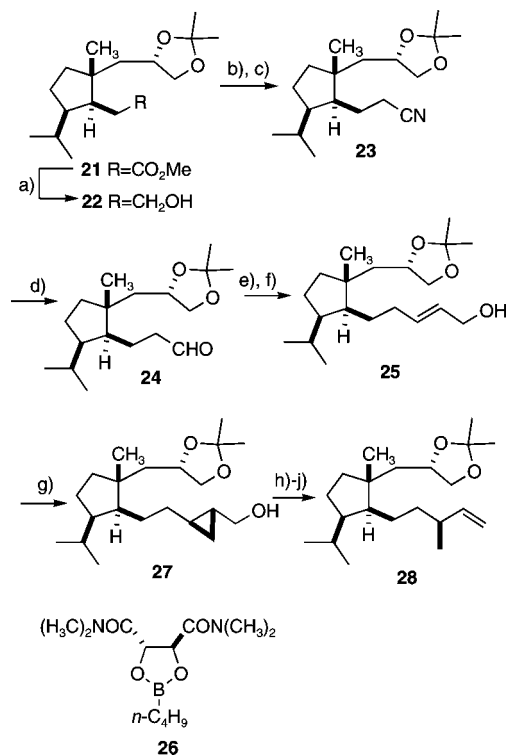
At this stage, ester **21** was processed to allylic alcohol **25** by using standard synthetic procedures (Scheme 3). An important intermediate along this route was the nitrile **23**, as its crystals

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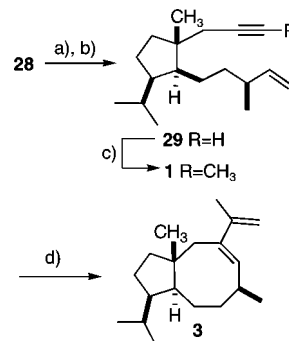
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SCHEME 3. Installation of the C7 Stereocenter^a

were amenable to X-ray analysis, allowing for verification of its constitution and relative stereochemistry. Using this sequence, alcohol **25** could be produced in an efficient manner.

The elegant and useful protocols of Charette and his group were then used to establish the necessary pendant methyl group substitution on C-7 of the eight-membered B-ring.^{17,18} Treatment of **25** with di(iodomethylene)zinc in the presence of 1.1 equiv of the chiral organoboron promoter (*S,S*)-**26** led to formation of cyclopropane **27** in >90% yield with >95:5 diastereoselectivity. We encountered reduced diastereoselectivity in this cyclopropanation reaction when the reaction was scaled up, perhaps because of its exothermicity. For consistent results, synthetic material was processed in parallel batches on ~250 mg scales. Conversion of **27** to alkene **28** was performed by (a) conversion of the hydroxyl function to an iodide followed by (b) lithium–halogen exchange followed by cyclopropane ring opening.

Alkene **28** was subjected to periodate cleavage (Scheme 4). This process was followed by reaction between the resulting aldehyde and the Ohira–Bestmann phosphonate (a modified Gilbert–Seyferth process) to produce terminal alkyne **29**.¹⁹ In our hands, the enyne metathesis of compound **1** did furnish the

SCHEME 4. Elaboration to the A–B Ring System^a

^a Reagents and conditions: (a) H₅IO₆, EtOAc (85%); (b) Ohira–Bestmann phosphonate, K₂CO₃, MeOH (70%); (c) *n*-BuLi, THF, -78 °C, then CH₃I, -78 °C to rt; (d) (IMes)Cl₂Ru=CHPh (30 mol %), CH₂Cl₂, 40 °C (53 %).

desired eight-membered ring, but only when catalyzed by a Grubbs “Type 2” *N*-heterocyclic carbene containing ruthenium catalyst²⁰ at high loadings (30 mol %) in dichloromethane (40 °C). Major side products included compounds resulting from cross-metathesis of (a) 2 equiv of **1** and (b) **1** and styrene (originating from the catalyst).²¹ Alkene ring-closing metathesis did not proceed on a related substrate to **1** with use of either a Grubbs “Type 2” catalyst or a Schrock catalyst.

The successful construction of **3** has provided significant information regarding this strategy for a fusicoccane synthesis. The relative stereochemistry of the A-ring fragment of the fusicoccane ring system was established by application of our diastereoselective Pauson–Khand–Norrish 1 ring-opening process. Reagent-controlled cyclopropanation followed by ring opening was used to install the methyl group at C(7) of the fusicoccanes with the appropriate stereochemical configuration. The eight-membered ring of the fusicoccane skeleton was constructed by using a metathesis strategy. Our aim is to utilize **3** as a common intermediate for the installation of differently functionalized five-membered C ring equivalents to access a number of fusicoccane natural products.²² A second generation approach may utilize a more convergent strategy for the natural product skeleton while maintaining the specific tactics described in this paper to establish crucial relative stereochemical configurations. Our laboratory is continuing work toward the solution of these problems.

Experimental Section

[3.3.0]-(5*R*,6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**17a**) and [3.3.0]-(5*S*,6*R*)-6-((2*S*)-2,3-*O*-Isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**17b**). A solution of (2*S*,4*R*)-1,2-*O*-isopropylidene-4-methyl-4-vinyl-7-nonyne-1,2-diol (**12**) (5.10 g, 21.6 mmol, 1 equiv) in methylene chloride (430 mL) was added to 4 Å molecular sieves (51.0 g) followed by dicobalt octacarbonyl (8.12 g, 23.7 mmol, 1.10 equiv) in 1 portion and the reaction mixture was stirred at rt for 1 h. 4-Methylmorpholine *N*-oxide (22.8 g, 0.194 mol, 9.0 equiv) was added in 3 portions to the reaction

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(21) Attempting the enyne metathesis ring closure under an ethylene atmosphere led to formation of a 1,3-diene from the alkyne function in the starting material. See: Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082–6083.

(22) Preliminary model studies investigating the installation of the fusicoccane “C-ring” have been conducted. Please refer to the Supporting Information.

mixture at 0 °C and the reaction mixture was stirred at rt overnight. The reaction mixture was filtered through a plug of silica gel, the silica gel was washed with ether (500 mL), and the filtrate was concentrated to yield a clear brown liquid. The crude liquid was purified by column chromatography (1/9 ethyl acetate–hexanes) to yield 5.09 g (89%) of a 86:14 mixture of the two diastereomers **17a** and **17b** (gas chromatography analysis) as a clear colorless liquid. Further purification of an analytical sample by column chromatography (1/19 ethyl acetate–hexanes) was performed to yield an analytically pure sample of **17a** as a clear colorless liquid.

IR (neat): 2985, 2933, 1706, 1668 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 4.18–3.93 (m, 2H), 3.42 (t, $J = 7.6$ Hz, 0.84H), 3.35 (t, $J = 7.7$ Hz, 0.16H), 2.75–2.25 (4H), 2.10–1.55 (m, 8H), 1.35 (s, 5.03H), 1.29 (s, 2.52H), 1.10 (s, 0.48H), 0.65 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 210.7, 210.5, 183.0, 182.6, 132.5, 132.0, 108.8, 108.6, 73.6, 73.1, 70.5, 70.3, 56.3, 53.5, 45.1, 41.1, 40.7, 39.9, 37.4, 36.7, 35.5, 35.0, 26.9, 26.8, 25.8, 25.4, 24.4, 24.0, 18.1, 8.2. LRMS (EI) m/z (rel intensity): 264 (M^+ , 27).

[3.3.0]-(5*R*,6*R*)-6-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**17a**): $[\alpha]_{\text{D}}^{20.7} -48.47 \pm 0.08$ (c 0.303, CHCl_3). IR (neat): 2985, 2933, 1706, 1668 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 4.18–4.10 (m, 1H), 4.01 (dd, $J = 7.8, 5.9$ Hz, 1H), 3.42 (t, $J = 7.6$ Hz, 1H), 2.70 (m, 1H), 2.59–2.29 (m, 3H), 2.04 (dd, $J = 18.1, 2.9$ Hz, 1H), 1.97–1.78 (m, 2H), 1.74–1.57 (m, 2H), 1.64 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H), 0.64 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 210.6, 182.4, 132.6, 108.8, 73.6, 70.3, 53.5, 45.1, 41.1, 40.0, 36.8, 27.0, 25.8, 24.0, 18.1, 8.2. LRMS (EI) m/z (rel intensity): 264 (M^+ , 5). Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{O}_3$: C, 72.69; H, 9.15. Found: C, 72.52; H, 9.28.

[3.3.0]-(1*R*,5*S*,6*R*)-6-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-2,2,6-trimethylbicyclonon-3-one (**20**). L-Selectride (16.0 mL of a 1.0 M solution in THF, 16.0 mmol, 1.05 equiv) was added dropwise to a solution of a 5.2:1 mixture of [3.3.0]-(5*R*,6*R*)-6-(2',3'-*O*-isopropylidene-2',3'-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**17a**) and [3.3.0]-(5*S*,6*R*)-6-(2',3'-*O*-isopropylidene-2',3'-dihydroxypropyl)-2,6-dimethylbicyclonon-1-en-3-one (**17b**) (4.03 g, 15.2 mmol, 1 equiv) in THF (150 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 30 min. Iodomethane (0.996 mL, 16.0 mmol, 1.05 equiv) was added dropwise and the reaction mixture was warmed to rt over 30 min, followed by stirring at rt overnight. Water (100 mL) was added and the mixture was extracted with ether (3×50 mL). The ether extracts were combined, washed with a 2 N aqueous solution of sodium hydroxide (50 mL) and a saturated aqueous solution of sodium chloride (50 mL), dried over magnesium sulfate, and concentrated in vacuo to yield a clear colorless liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate–hexanes) to yield 3.45 g (81%) of **20** as a clear colorless liquid and 0.639 g (15%) of [3.3.0]-(1*S*,5*R*,6*R*)-6-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-2,2,6-trimethylbicyclonon-3-one as a white solid.

20: $[\alpha]_{\text{D}}^{22.4} +58.15 \pm 0.09$ (c 0.367, CHCl_3). IR (neat): 2932, 1737 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 4.19–4.11 (m, 1H), 4.04 (dd, $J = 7.92, 5.79$ Hz, 1H), 3.44 (t, $J = 7.92$ Hz, 1H), 2.47–2.24 (m, 3H), 2.06–1.98 (m, 1H), 1.82–1.64 (m, 3H), 1.52–1.33 (m, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.02 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 222.9, 108.4,

73.7, 70.7, 52.8, 49.7, 46.9, 45.5, 43.3, 37.6, 37.4, 26.9, 25.9, 25.5, 23.2, 19.7. Anal. Calcd for $\text{C}_{17}\text{H}_{28}\text{O}_3$: C, 72.82; H, 10.06. Found: C, 72.42; H, 10.19.

(1*R*,2*S*,3*R*)-3-isopropyl-1-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-1-methyl-2-methylethanoatecyclopentane (**21**). A solution of [3.3.0]-(1*R*,5*S*,6*R*)-6-((2*S*)-2,3-*O*-isopropylidene-2,3-dihydroxypropyl)-2,2,6-trimethylbicyclonon-3-one (**20**) (1.48 g, 5.28 mmol, 1 equiv) in methanol (350 mL) in a quartz reaction vessel was irradiated with light from a 450-W Hanovia medium pressure mercury lamp for 5.5 h, after which the reaction mixture was concentrated in vacuo to yield a clear colorless liquid. The crude liquid was purified by column chromatography (1/19 ethyl acetate–hexanes) to yield 1.15 g (70%) of **21** as a clear colorless liquid, and 0.133 g (9%) of **20** as a clear colorless liquid.

$[\alpha]_{\text{D}}^{25.1} +22.20 \pm 0.02$ (0.645, CHCl_3). IR (neat): 2953, 2872, 1740 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 4.17–4.06 (m, 2H), 3.65 (s, 3H), 3.42 (t, $J = 7.16$ Hz, 1H), 2.27–2.04 (m, 3H), 1.81–1.69 (m, 3H), 1.65–1.54 (m, 2H), 1.47–1.29 (m, 2H), 1.37 (s, 3H), 1.33 (s, 3H), 1.25–1.12 (m, 1H), 0.89 (s, 3H), 0.86 (d, $J = 5.82$ Hz, 3H), 0.84 (d, $J = 5.82$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 174.8, 108.0, 73.9, 70.8, 51.6, 49.7, 45.8, 45.2, 44.2, 36.9, 30.5, 29.7, 27.5, 26.9, 25.9, 22.7, 22.0, 21.7. Anal. Calcd for $\text{C}_{18}\text{H}_{32}\text{O}_4$: C, 69.19; H, 10.32. Found: C, 69.09; H, 10.34.

[6.3.0]-(1*R*,5*S*,8*S*,9*R*)-1,5-Dimethyl-9-isopropyl-3-(prop-1-en-2-yl)bicycloundec-2-ene (**3**). Ruthenium [1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolinyldene]dichloro(phenylmethylene)(tricyclohexylphosphine) (68 mg, 0.08 mmol, 30 mol %) was added in 1 portion to a solution of (1*R*,2*S*,3*R*)-1-(2-but-2-ynyl)-3-isopropyl-1-methyl-2-((3*S*)-3-methylpent-4-enyl)cyclopentane (**1**) (70 mg, 0.27 mmol, 1 equiv) in methylene chloride (5 mL) and the reaction mixture was heated to reflux for 18 h. Triethylamine (0.5 mL) was added, and the reaction mixture was concentrated in vacuo to yield a dark red liquid. Purification by column chromatography (hexanes) yielded 37 mg (53%) of the title compound as a clear, colorless liquid.

$[\alpha]_{\text{D}}^{20.0} +8.87 \pm 0.15$ (c 0.100, CHCl_3). IR (neat): 3089, 2926, 2854, 1637 cm^{-1} . ^1H NMR (300 MHz, CDCl_3): δ 5.40 (d, $J = 9.4$ Hz, 1H), 5.01 (s, 1H), 4.87 (s, 1H), 2.57 (d, $J = 13$ Hz, 1H), 2.12 (d, $J = 13$ Hz, 1H), 1.90 (s, 3H), 1.85–1.00 (m, 12H), 1.01 (d, $J = 6.2$ Hz, 3H), 0.85 (d, $J = 6.9$ Hz, 3H), 0.70 (d, $J = 6.9$ Hz, 3H), 0.63 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 145.0, 144.4, 113.8, 112.4, 50.4, 50.3, 48.0, 45.7, 38.8, 38.1, 38.0, 32.1, 29.7, 27.3, 25.3, 22.4, 22.0, 14.2, 14.1. LRMS (EI) m/z (rel intensity): 260 (M^+ , 1).

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Supporting Information Available: Experimental procedures and characterization data for compounds **1–31**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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