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Pestalotiopsin A. Side Chain Installation and Exhaustive Probing of Olefin Metathesis as a Possible Tool for Elaborating the Cyclononene Ring

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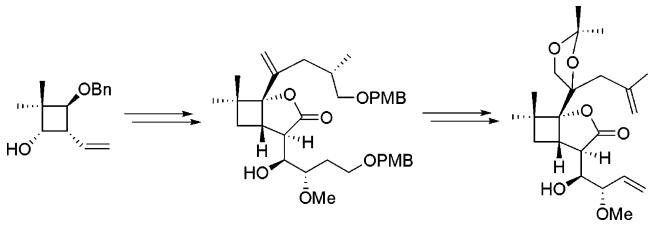
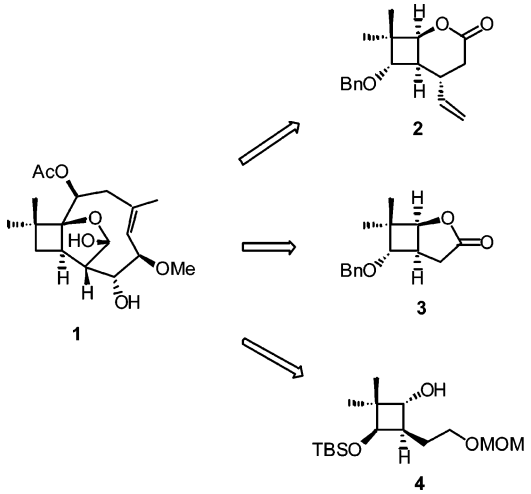


A program directed toward an asymmetric synthesis of pestalotiopsin A is described. The routing begins with the dextrorotatory cyclobutanol **37**, which is combined with the enantiomerically defined building blocks *ent*-**15** and **16**. These units are incorporated via stereocontrolled 1,2-nucleophilic addition and anti-aldol coupling, respectively. With these straightforward reactions accomplished, the sequel involved the introduction of terminal double bonds in anticipation of the fact that the (*E*)-cyclononene substructure could be realized by ring-closing metathesis. This central issue was evaluated with several diene substrates and catalysts, all to no avail. Cross-metathesis experiments involving **59** and **65** with the functionalized heptene **60** revealed a marked difference in the inability to engage interaction with the ruthenium catalyst. This awkwardness could not be skirted.

Introduction

The previous report in this issue outlines three strategies potentially suited to an asymmetric synthesis of the immunosuppressant known as pestalotiopsin A (**1**).[1] Either **2**, **3**, or **4** (Scheme 1) was considered to be a potential precursor of **1**. Should a workable pathway to **1** be developed from any one of these building blocks, the road would be opened to access the enantiomer as well, with the ultimate goals being determination of the absolute configuration of the target via synthesis and broader-based pharmacologic evaluation. As matters have turned out, a successful preparative route to **1** has so far proven elusive. Details of the reaction sequences that have nevertheless advanced our quest are presented herein.

SCHEME 1. Retrosynthetic Analysis



Results and Discussion

Demise of the [4.2.0] Bicyclic Lactone Approach. The first avenue to be pursued involved lactone **2** where the need existed to invert configuration at the vinyl substituted carbon. This objective was initially pursued by cleaving the unsaturated substituent in **2** via ozonolysis to arrive at aldehyde **5** (Scheme 2). We soon came to recognize that **5** is a very labile substance.

(1) Paquette, L. A.; Parker, G. D.; Tei, T.; Dong, S. *J. Org. Chem.* **2007**, *72*, 7125.

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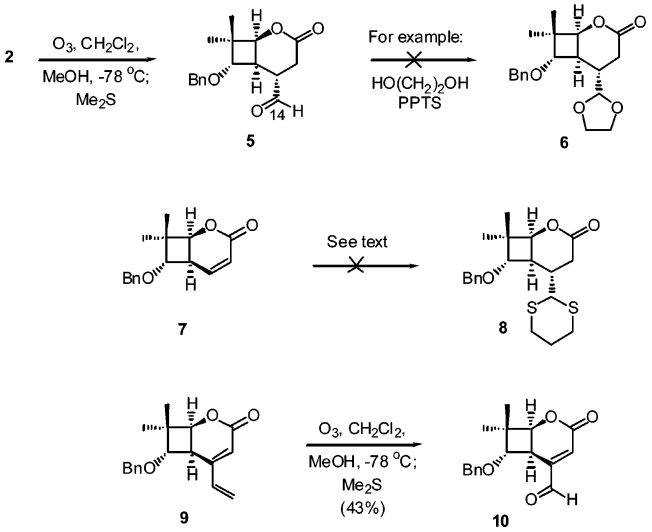
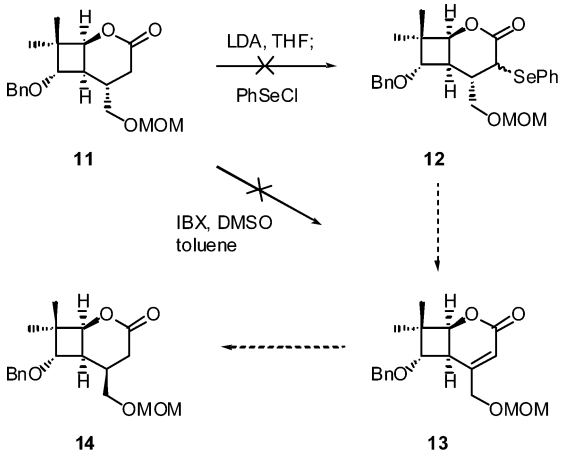
SCHEME 2. Assessment of C-14 Installation



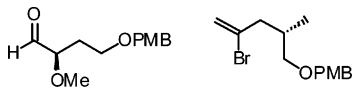
SCHEME 3. Issue of Ring Unsaturation



While NMR spectroscopy of the crude product indicated the transformation to have been successful, the material decomposes when absorbed on silica gel or when subjected to the mildest reagent combination for generating a cyclic acetal such as **6**. In an effort to reach comparable advancement in fewer steps, 1,4-addition[2] of the 1,3-dithianyl anion to enone **7** was also investigated. Unfortunately, C−C bond formation proved not to be effective under a variety of conditions. Another possible solution that was entertained involved the regioselective ozonolysis of **9**. In fact, the nonequivalence of its two olefinic sites can be relied upon to produce **10** following exposure to ozone. However, yields in excess of 43% could not be realized and lability issues persisted.

As a consequence, attention was redirected to lactone **11**. Initially, we sought to introduce an intracyclic double bond patterned after the organoselenium approach applied earlier.[1] In light of this analogy, it was disappointing to learn that treatment of **11** with LDA and phenylselenenyl chloride at −78 °C gave no reaction, while the corresponding reaction at −20 °C led to decomposition (Scheme 3). When alternate recourse was made to activation of the system as the silyl ketene acetal in advance of quenching with PhSeCl, the MOM protecting group did not survive. An alternative one-pot procedure involving IBX and DMSO in toluene[3] did not lead to incorporation of a double bond as in **13**, whose fate was to serve as the precursor to **14** via catalytic hydrogenation. The developments summarized above prompted us to consider the utilization of intermediates **3** and **4**, the availability of which offered the prospect of reasonable convergency.

Preliminary Assessment of the Core Buildup. To realize these sub-goals, suitable side chain fragments were required. From among several options, we came to favor **15** and **16**. Following their proper incorporation, medium-ring formation was envisioned to be realizable.



Our approach to **15** and its aldol coupling to **3** are detailed in Scheme 4. The known allylic alcohol **17**[4] was arrived at by sequential *O*-benzylation of 3-butyn-1-ol,[5] hydroxymethylation with paraformaldehyde and *n*-butyllithium,[6] and reduction with Red-Al.[7] The key Sharpless asymmetric epoxidation was accomplished with (−)-diisopropyl tartrate under standard conditions at −20 °C.[8] Conversion of **18** to the corresponding Mosher ester confirmed by ^{1}H NMR that a single enantiomer had been formed.[9] The subsequent acquisition of iodo epoxide **19** was cleanly realized through the agency of triphenylphosphine and iodine in the presence of imidazole.[10] To position ourselves to produce **15**, **19** was subjected to the action of *n*-butyllithium in THF,[11] and the resulting vinyl carbinol **20** was treated with potassium hydride in the presence of dimethyl sulfate. Dihydroxylation of **21** followed by diol cleavage delivered the lower side chain smoothly.

Installation of the lower side chain in **3** was initiated by deprotonation with sodium hexamethyldisilazide in THF at −78 °C. Capture of the resulting enolate anion with aldehyde **15** proceeded stereoselectively to deliver anti-aldol **23** as the major characterizable product. The stereochemical assignment to **23** was established by sodium borohydride reduction to give triol **24** (alongside a lesser amount of the elimination product **25**) and subsequent conversion of **24** into the corresponding cyclic acetal **26** (Scheme 5).[12] A vicinal coupling constant of 12.3 Hz for the 1,3-dioxanyl ring protons confirmed the trans disposition of its pendant groups. Consequently, the stereocontrol operating

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(3) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245.

(4) (a) Dias, L. C.; DeOliveira, L. G. *Org. Lett.* **2004**, *6*, 2587. (b) Deba, T.; Yakushiji, F.; Shindo, M.; Shishido, K. *Synlett* **2003**, 1500.

(5) (a) Yadav, J. S.; Srihari, P. *Tetrahedron: Asymmetry* **2004**, *15*, 81. (b) Giessert, A. J.; Brazis, N. J.; Diver, S. T. *Org. Lett.* **2003**, *5*, 3819.

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(8) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S.-Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

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(10) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.

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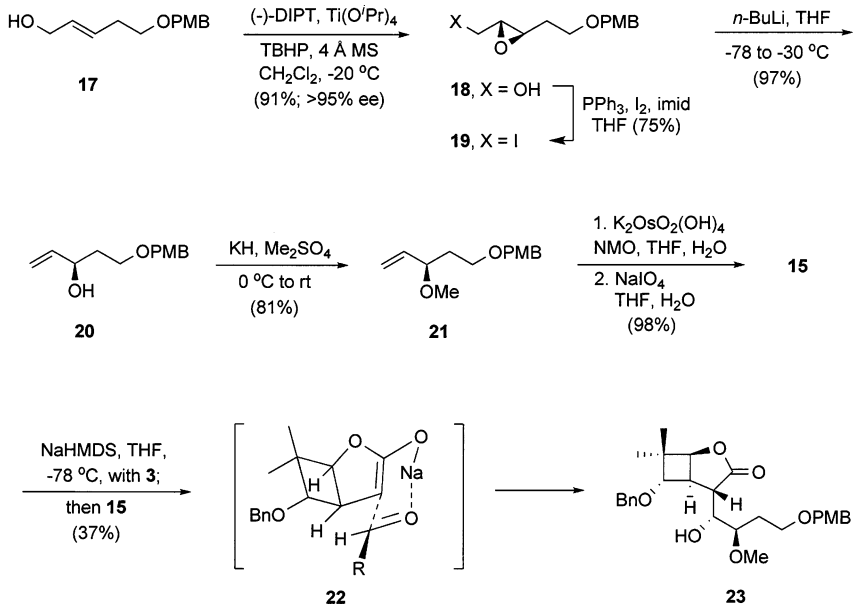
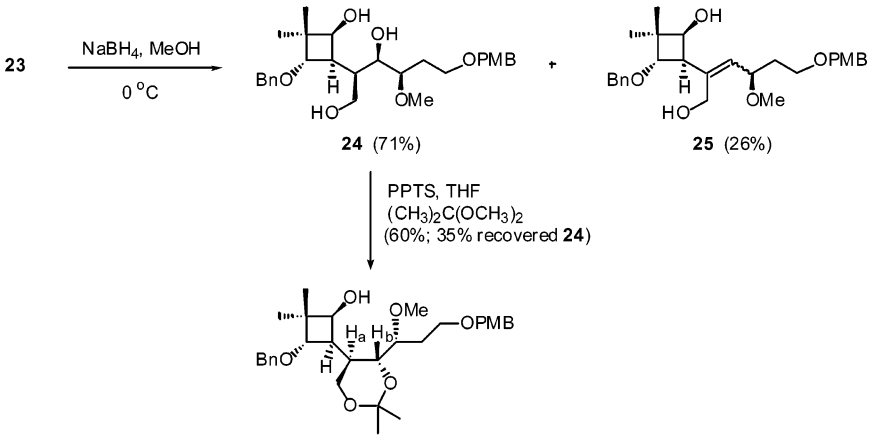
(12) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9.

SCHEME 4. Enantioselective Aldol Coupling of 15 to Bicyclic Lactone 3



SCHEME 5. Proof of Stereochemistry of 23



during the formation of **23** likely results from convex-face approach to the bicyclo[3.2.0]heptane framework with adoption of a chelated chairlike transition state as depicted in **22**.

In accord with the retrosynthetic plan, we next set for ourselves the task of attaching a suitable upper chain segment stereoselectively onto an intermediate cyclobutane derivable from **4**.[1] To this end, advantage was taken of two relevant aspects of strategy level design. It was reasoned that cyclobutanol **4** would be straightforwardly amenable to oxidation to give **28** and that the ketone carbonyl so introduced would experience nucleophilic attack from the α-face to avoid encounter with the bulky OTBS substituent (Scheme 6). At the experimental level, the hydrogenolysis step to provide alcohol **4** and perruthenate oxidation of the latter to generate **28** proceeded quantitatively. Advantage was subsequently taken of the ready availability of highly enantioenriched (*S*)-4-bromo-2-methylpent-4-en-1-ol.[13] Following conversion to the PMB ether **16** and metalation with *tert*-butyllithium, coupling to provide **29** proceeded well. The successful testing of this critical reaction conformed nicely to the expected stereoselectivity as deduced by COSY/NOESY correlations between H-3 and H-4, in addition to a NOESY interaction involving H-4 and a vinyl proton.

Advanced Side-Chain Construction. Following arrival at **29**, the plan entailed subsequent elaboration of the bicyclic lactone core. However, selective deprotection of a MOM ether in the presence of an acid labile PMB ether can be challenging. For example, *B*-bromocatecholborane, which has been reported to allow the survival of a primary PMB ether while unmasking a secondary MOM substituent,[14] proved sufficiently reactive to remove both groups in **29** within 5 min at −100 °C to generate a triol. In contrast, conditions involving pyridinium tosylate in *tert*-butyl alcohol at reflux[15] proved mild enough for our purposes. Possible dehydration of the allylic tertiary alcohol[16] in **30** was largely suppressed by making recourse to this solvent (Scheme 7). Oxidation of **30** with TPAP and NMO resulted in the smooth generation of lactone **31**.

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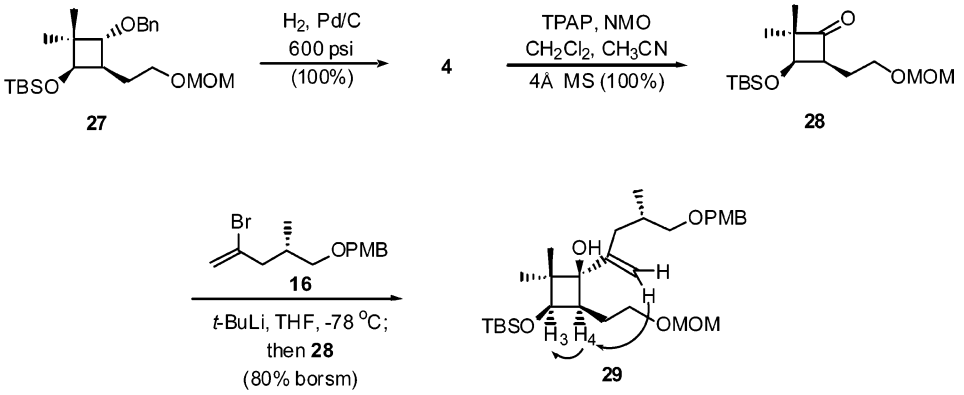
(14) Paquette, L. A.; Gao, Z.; Ni, Z.; Smith, G. F. *J. Am. Chem. Soc.* **1998**, *120*, 2543.

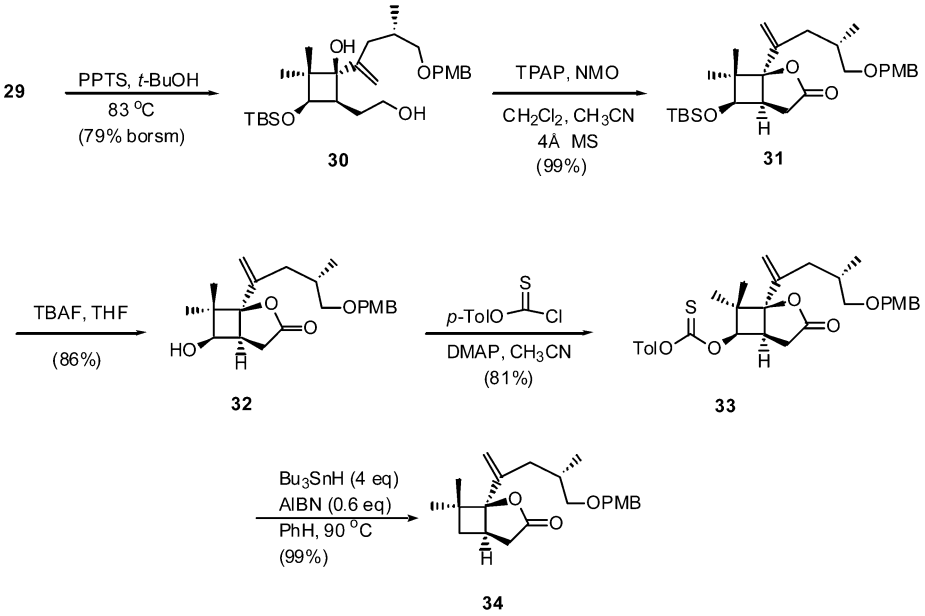
(15) Ghosh, A. K.; Wang, Y.; Kim, J. T. *J. Org. Chem.* **2001**, *66*, 8973.

(16) Chang, N.-C.; Chang, C.-K. *J. Org. Chem.* **1996**, *61*, 4967.

SCHEME 6. Upper Side Chain Incorporation



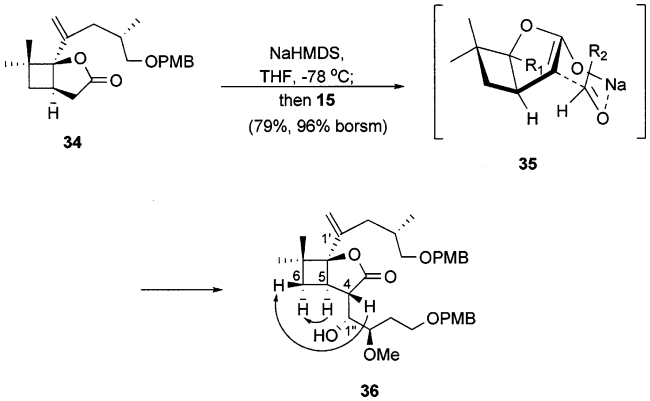
SCHEME 7. Pathway to Deoxygenated Lactone 34



At this point, the OTBS substituent in **31** was expected to contribute little to the diastereoselectivity of the pending aldol reaction. Consequently, deoxygenation was undertaken by sequential desilylation, thiocarbonate formation,[17] and tin hydride reduction. The notably crowded environment of the hydroxyl group in **32** required the adoption of forcing conditions to form *O*,*O*-thiocarbonate **33** (alongside a trace amount of the isomeric *O*,*S*-thiocarbonate) and to bring about the targeted delivery of **34**. Initial attempts to bring about reductive removal of the thiocarbonate functionality resulted in reversion to starting alcohol **32** (use of less than 0.1 equiv AIBN) or formation of an unknown side product (use of more than 1 equiv AIBN). After extensive optimization studies, it was uncovered that the heating of **33** with Bu_3SnH (4 equiv) and AIBN (0.6 equiv) in benzene at reflux generated **34** in essentially quantitative yield.

When **34** was next treated with NaHMDS followed by aldehyde **15**, **36** was obtained efficiently (Scheme 8). In its ^1H NMR spectrum, no coupling was observed between H-4 and H-5, thereby indicating the dihedral angle to approximate 90°. Added confirmation of this anti relationship was derived from NOESY correlations involving H-4/H-6β and H-5/H-6α. The configuration of C-1″ was deduced by comparison with **23** and

SCHEME 8. Attachment of the Lower Side Chain



the work of Tadano.[18] As in the earlier examples, the stereoselectivity of this aldol coupling can be attributed to consequences brought on by the bicyclo[3.2.0]heptane core that forces aldehyde **15** to approach from the convex face and C−C bond formation to proceed via the sodium enolate-chelated chairlike transition state **35** with the lower side chain (R_2) pointing away from the upper side chain (R_1).

(17) Drescher, M.; Ohler, E.; Zbiral, E. *Synthesis* **1991**, 362.

(18) Takao, K.; Saegusa, H.; Tsujita, T.; Washizawa, T.; Tadano, K. *Tetrahedron Lett.* **2005**, *46*, 5815.

SCHEME 9. Preparation of Aldol Diastereomer 38

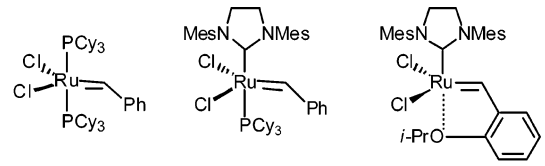
Synthesis of RCM Precursors. Concurrent with the work reported above, significant quantities of (+)-**37** were prepared in parallel fashion[1] and transformed as well into the diastereomeric aldol **38**[19] (Scheme 9). With the availability of this material in quantity, our synthesis was redirected to accommodate this modification which shares the same stereogenic center on the upper side chain, but demands a change to *ent*-**15**. Since the absolute configuration of **1** remains unknown, acquisition of its enantiomer via **38** would be equally revealing and diagnostic.

The greatly diminished reactivity of the hydroxyl functionality in **38** was soon recognized.[20] This inertness caused us not to be concerned with a protection strategy en route to **40** (Scheme 10). The first and shorter of two pathways from **38** entailed initial removal of the pair of PMB groups and subsequent ozonolytic cleavage of the double bond to afford the triol in high yield. Alternatively, application of the Johnson-Lemieux protocol[21] resulted in arrival at keto lactone **42** in advance of the dual deprotection step with TFA.[22] The employment of standard dihydroxylation conditions involving a catalytic amount of OsO_4 in the presence of NMO suffered from a quite slow reaction rate (>7 days) as a direct result of steric crowding in the vicinity of the vinyl group. The process was appreciably accelerated upon use of 2 equiv of pyridine[23] but never proceeded to completion unless recourse was made to stoichiometric levels of OsO_4. Gratifyingly, these complications were resolved when the Sharpless dihydroxylation protocol, with DABCO as promoter, was resorted to.[24] Under biphasic conditions with $K_3Fe(CN)_6$ as the reoxidant, only one stereoisomer of **41** was isolated quantitatively.

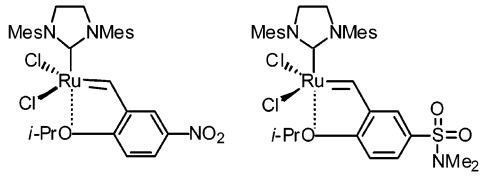
The availability of **40**, whose complex ^{1}H NMR spectrum indicated the existence of an equilibrium with **40′**, was projected to allow serial application of the Mitsunobu-type aryl selenylation with *o*-nitrophenyl selenocyanate and tributylphosphine (Scheme 11) followed by Grieco olefination upon exposure to hydrogen peroxide.[25] However, the predominant formation of the 2-cyanotetrahydrofuran **44** demonstrated that prior formation of acetonide **46** was warranted in order to bypass oxonium ion generation.[20] Subsequent to 2-fold PMB deprotection to generate **47**, its exposure to ArSeCN (3.6 equiv) and Bu_3P (3.6 equiv) resulted only in partial conversion to **48** (Scheme 12). This observation provided indication that the terminal hydroxyl group in the upper side chain is more crowded than its counterpart in the lower side chain. While the coformation of **48** and **49** could not be remedied by the incremental addition of excess reagents because of competing dehydration of the secondary carbinol, the problem was rectified by the chromatographic separation of **49** and its resubmission to the original selenylation conditions. Diene **50** was subsequently generated efficiently (90%) by reaction of **48** with 30% hydrogen peroxide and pyridine in THF at −40 °C to room temperature.[26]

Exploration of RCM Reactions. The availability of **50** set the stage for exploring the feasibility of ring closing metathesis (RCM) to construct the unsaturated nine-membered ring. The development of catalysts that combine high activity with excellent functional group tolerance has been key to the widespread application of olefin metathesis in organic synthesis.[27] In spite of the generally superb application profile of the ruthenium carbene **51**, its limited thermal stability and low activity toward substituted double bonds are major drawbacks.[28] Exchange of one PCy_3 in **51** with a sterically demanding *N*-heterocyclic carbene leads to the second generation metathesis catalyst **52**, which displays increased stability and superior reactivity toward polysubstituted and electron-deficient olefins.[29]

The phosphine-free catalyst **53**, which has been developed by the Hoveyda group, is a remarkably robust complex that promotes olefin metathesis by a "release-return" mechanism.[30] Its lower initiation activity compared to **52** renders **53** less advantageous for more challenging metatheses involving the formation of a trisubstituted double bond.[31] However, its robustness is beneficial for extended reaction times at elevated temperatures. Follow-up studies aimed at improving this state of affairs have been undertaken by several research groups. For example, Grela and co-workers introduced an electron-withdrawing nitro group para to the 2-isopropoxybenzylidene unit for the purpose of destabilizing the oxygen−metal interaction, thereby facilitating access to the propagating 14-electron



Grubbs I catalyst **51** | Grubbs II catalyst **52** | Hoveyda catalyst **53**



Grela catalyst **54** | Zhan catalyst **55**

(19) Dong, S. Ph.D. Dissertation, The Ohio State University, 2007.

(20) Dong, S.; Paquette, L. A. *Heterocycles* **2007**, *72*, 111.

(21) Pappo, R.; Alen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.

(22) Yan, L.; Kahne, D. *Synlett* **1995**, 523.

(23) (a) Criegee, R.; Marchand, B.; Wannowlus, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99. (b) Schroder, M. *Chem. Rev.* **1980**, *80*, 187 and references therein.

(24) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Dong, S.; Paquette, L. A. *J. Org. Chem.* **2005**, *70*, 1580.

(25) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

(26) Pyridine was applied to avoid epoxidation of the resulting 2,2-disubstituted olefin. See: (a) Grieco, P. A.; Yokoyama, Y.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1977. (b) Clayden, J.; Knowles, F. E.; Baldwin, I. R. *J. Am. Chem. Soc.* **2005**, *127*, 2412.

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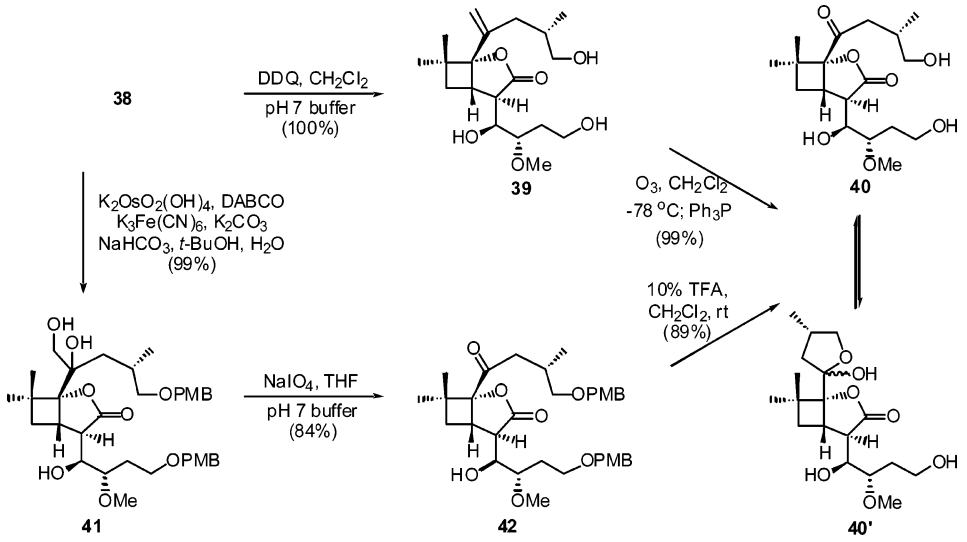
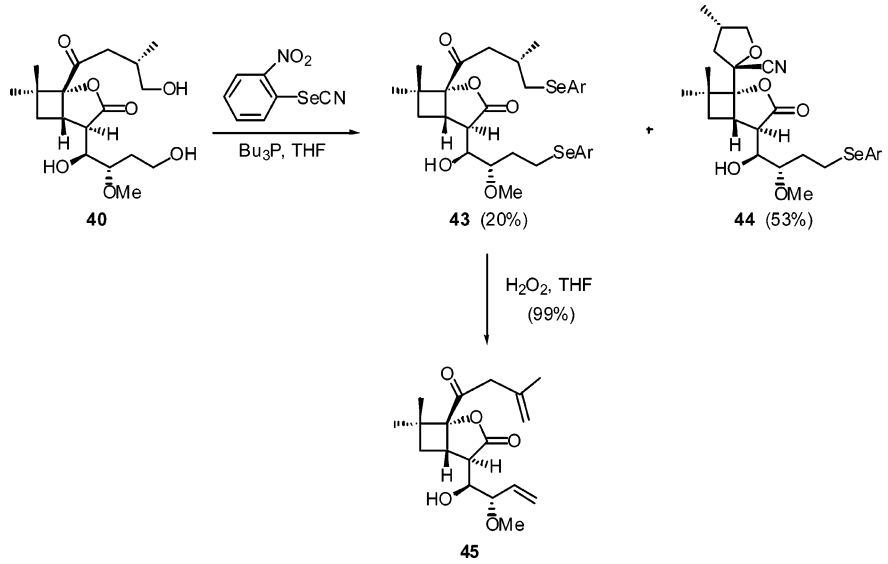
(29) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

SCHEME 10. Availability of Triol 40



SCHEME 11. Phenylselenylation of Triol 40



species.[32] The faster catalytic cycle initiation exhibited by **54** causes this catalyst to exhibit much improved capacity in ring-closing, cross, and enyne metathesis while retaining excellent air and thermal stability. More recently, Zhan and co-workers adopted a similar strategy and introduced the sulfonamide **55**, which displays even higher reactivity than the Grela catalyst.[33]

To avail ourselves of several RCM substrates, **50** was transformed via **56** into keto diene **45** as well as to the MOM-protected lactone **57** (Scheme 13). The initial ring closure trials involved **45** and **50** (0.002 or 0.01 M) with **52**, **53**, and **55** as the catalyst at 20 °C or more elevated temperatures (40 and 80 °C). In each example, the diene was fully recovered without any evidence of competing dimerization. Recourse to toluene at reflux for several hours resulted in substrate decomposition, but permitted recovery of the Hoveyda catalyst **53**. The co-addition of titanium isopropoxide[15] to prevent chelation of the catalyst with reactants bearing a homoallylic alcohol, if operative, offered no improvement. Subsequently, the secondary hydroxyl in **50** was protected as its MOM ether, a small, robust substituent that was not expected to impede close approach of the olefinic termini. The exposure of **57** to **55** in toluene (0.01 M) at 80 °C did result in the generation of a new substance, but it proved to be the isomer **58** and not a product of metathesis. The *Z*-configuration of this product follows from its ^{1}H NMR features.

Although the desired RCM product was not obtained, the formation of **58** clearly demonstrated involvement of the metathesis catalyst.[34,35] Interestingly, when monolefin **59**, which was derived from monoselenide **49**, was treated with alkene **60**[36] and the Zhan catalyst under cross metathesis conditions, the coupling product **61** was obtained (Scheme 14). Accordingly,

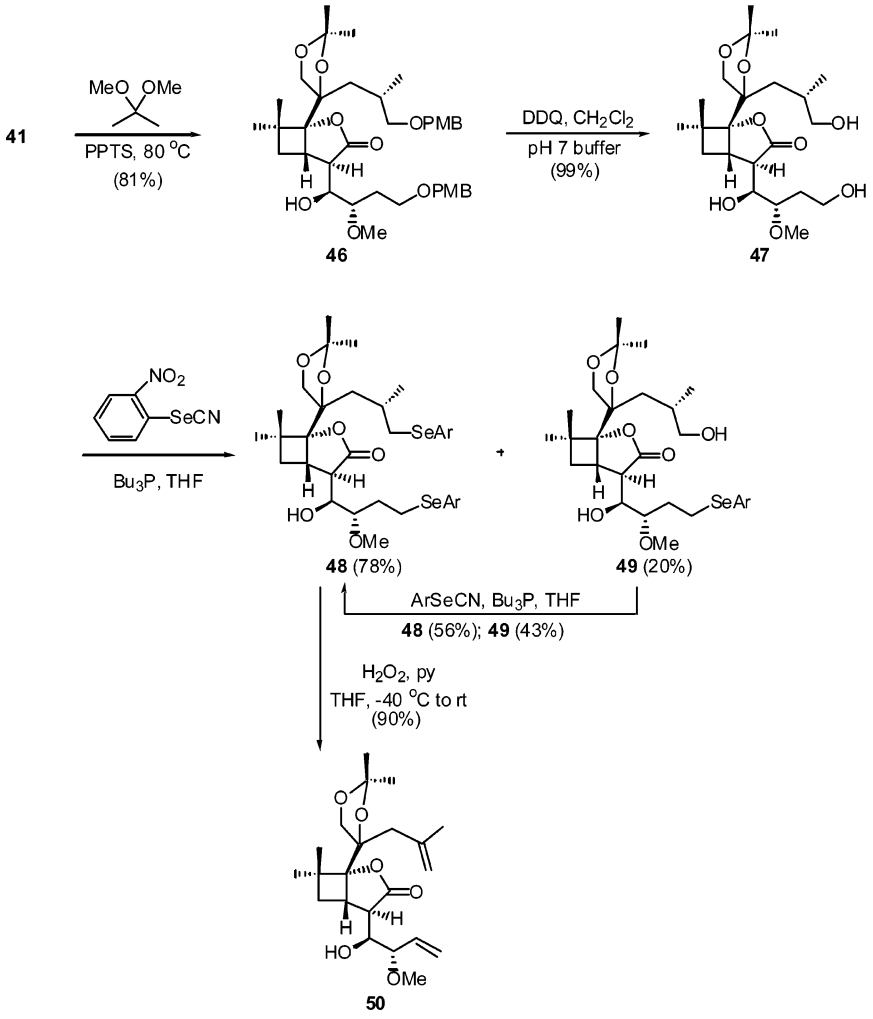
(30) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(31) (a) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 794. (b) Wakamatsu, H.; Blechert, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 2403.

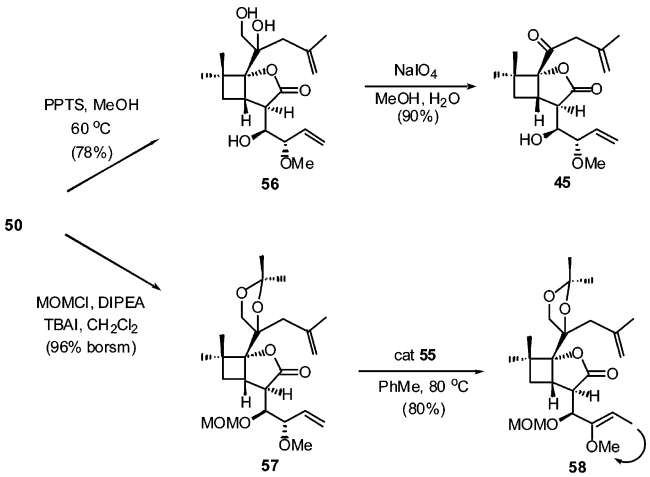
(32) (a) Grela, K.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038. (b) Grela, K.; Kim, M. *Eur. J. Org. Chem.* **2003**, 963. (c) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Dolgonos, G.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318. (d) Bieniek, M.; Bujok, R.; Cabaj, M.; Lugan, N.; Lavigne, G.; Arlt, D.; Grela, K. *J. Am. Chem. Soc.* **2006**, *128*, 13652.

(33) Zhan, Z. J. US Patent No. US20070043180A1.

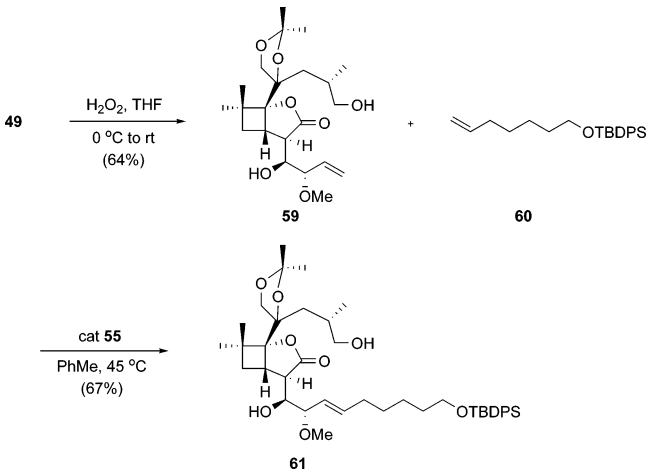
SCHEME 12. Arrival at Diene 50



SCHEME 13. Preparation of Additional RCM Substrates



SCHEME 14. Cross-Metathesis Involving 59 and 60

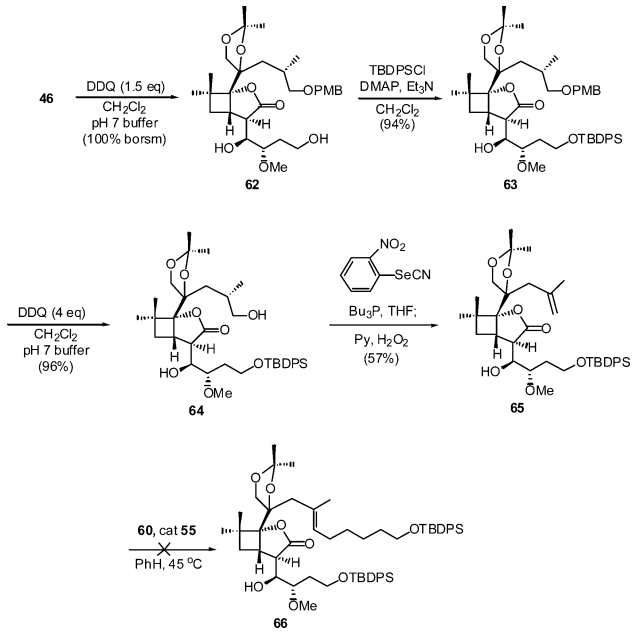


the olefinic center of the lower side chain, when bearing a homoallylic alcohol, is capable of participation in Ru-promoted metathesis as long as propagation is initiated in the other reaction partner. We do not imply that the secondary OH group is responsible for the formation of **61**, but only that it does not suppress the process.

(34) (a) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865. (b) Schmidt, B. *J. Mol. Catal. A* **2006**, *254*, 53.

The metathesis reactivity of the olefinic functionality in the upper side chain was probed in similar fashion. The preparation of **65** originated with the regioselective removal of the less hindered PMB ether by the treatment of **46** with 1.5 equiv of DDQ (Scheme 15). Masking of the primary hydroxyl in **62** as the TBDPS ether **63** was followed by treatment with excess DDQ to generate **64**. Subsequent Grieco olefination produced monoalkene **65** efficiently. However, attempts to apply the same

SCHEME 15. Attempted Cross-Metathesis Involving 59 and 60

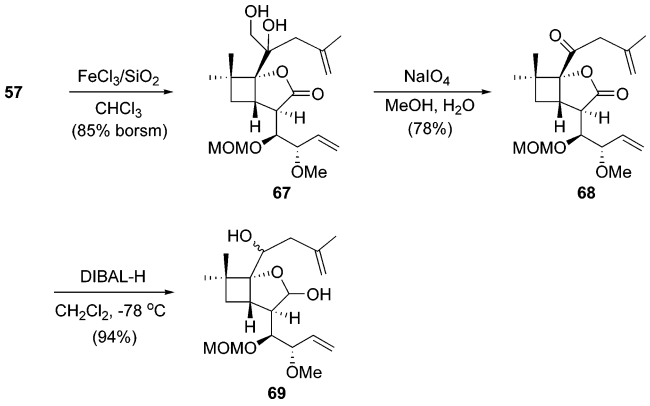


cross metathesis conditions described above to generate **66** failed. The efficient recovery of **65** from all of the runs clearly reflected its lack of reactivity, which in turn impeded us from exploring relay ring-closing metathesis (RRCM) strategies for elaboration of the cyclononene ring.[37]

To lessen the conformational constraints introduced by the acetonide functionality, it was necessary to generate the diol without perturbing the MOM ether. Heating **57** with PPTS in methanol induced the concomitant deprotection of both sites; nor did the use of triflic acid in trifluoroethanol and THF at 0 °C[38] exhibit reasonable chemoselectivity. The most well-suited conditions were identified to be ferric chloride on silica gel with $CHCl_3$ as reaction medium[39] (Scheme 16). Nevertheless, special care had to be exercised as too little reagent was ineffective, while too much resulted in dual cleavage and double bond migration. Cleavage of the 1,2-diol was successfully accomplished with $NaIO_4$ in aqueous methanol, and the resulting keto lactone **68** was reduced with excess Dibal-H to produce **69**. Neither of these advanced intermediates gave evidence of entering into RCM.

In summary, the upper and lower side chains have been incorporated via stereo-controlled nucleophilic addition and anti-aldol reactions, respectively. Several of these potential precursors to pestalotiopsin A possessing all of the framework carbons were

SCHEME 16. Recourse to Lactol Functionality



transformed into a series of dienes by Grieco olefination. Construction of the (*E*)-cyclononene ring via RCM proved to be challenging, although not entirely without analogy,[40] leading to the conclusion that a different ring-closing strategy must be adopted in the future.[41]

Experimental Section

(1*S*,6*S*,7*S*)-7-Benzyloxy-8,8-dimethyl-3-oxo-2-oxabicyclo[4.2.0]-oct-4-ene-5-carbaldehyde (10). A stirred solution of **9** (7 mg, 25 μmol) in methanol/CH_2Cl_2 (1:1) (0.5 mL) was cooled to −78 °C and treated with ozone for 2 min. N_2 gas was bubbled through the reaction mixture until the blue color had completely dispersed, and dimethyl sulfide (25 μL) was added. The reaction mixture was warmed to rt, stirred for 4 h, and partitioned between CH_2Cl_2 (10 mL) and water (5 mL). The combined organic extracts were washed with brine (2 mL), and dried. The solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (eluting with an increasing proportion of ethyl acetate in hexanes from 20 to 30%) to give **10** (3 mg, 43%) as a colorless oil: IR (film, cm^{-1}) 1726, 1697, 1607; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.41−7.27 (m, 5H), 6.51 (d, J = 0.8 Hz, 1H), 4.77 (d, J = 8.2 Hz, 1H), 4.67 (d, J = 12.1 Hz, 1H), 4.43 (d, J = 12.1 Hz, 1H), 3.65 (d, J = 5.4 Hz, 1H), 3.43 (m, 1H), 1.26 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 162.2, 149.9, 137.7, 129.6, 128.4, 127.8, 127.4, 85.2, 79.5, 71.5, 47.2, 34.3, 21.8, 21.1; HRMS (ES) m/z $(M + Na)^+$ calcd 286.1200, obsd 286.1220; $[\alpha]_D^{20}$ +69.7 (*c* 0.3, $CHCl_3$).

{(2*R*,3*R*)-3-[2′-(4′′-Methoxybenzyloxy)ethyl]oxiranyl}-methanol (18). A stirred solution of D-(−)-diisopropyl tartrate (0.96 g, 4.10 mmol) in anhydrous CH_2Cl_2 (40 mL) was treated with 4 Å molecular sieves (1 g) under nitrogen. After 10 min, the reaction mixture was cooled to −20 °C and treated with titanium isopropoxide (0.99 g, 3.47 mmol). After 30 min, a solution of **17** (700 mg, 3.15 mmol) in anhydrous CH_2Cl_2 (10 mL) was added, and the reaction mixture was stirred for a further 90 min. TBHP (5.56 mL, 9.46 mmol) was added, and the resultant mixture was stirred for 12 h at −20 °C, quenched with dimethyl sulfide (0.67 mL), and warmed to 0 °C. After 1 h, the reaction mixture was filtered through Celite, which was rinsed with CH_2Cl_2 (50 mL). The filtrate was treated with 10% aqueous tartaric acid solution (10 mL), stirred for 30 min, and separated into layers. The aqueous phase was

(35) The observation of isomerization products does not necessarily mean that the metathesis catalyst interacts directly with the alkene. Impurities in the metathesis catalyst (Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236) or decomposition products thereof (Hong, S. H.; Day, M. W.; Grubbs. R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414) might be responsible. Attempts to suppress this side reaction with additives have been probed (Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160).

(36) Clive, D. L. J.; Yeh, V. S. C. *Synth. Commun.* **2000**, *320*, 3267.

(37) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210.

(38) (a) Kobayashi, S.; Reddy, R. S.; Sugiura, Y.; Sasaki, D.; Miyagawa, N.; Hirama, M. *J. Am. Chem. Soc.* **2001**, *123*, 2887. (b) Holcombe, J. L.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 111.

(39) Kim, K. S.; Song, Y. H.; Lee, B. H.; Hahn, C. S. *J. Org. Chem.* **1986**, *51*, 404.

(40) (a) Nickel, A.; Maruyama, T.; Tang, H.; Murphy, P. D.; Greene, B.; Yusuff, N.; Wood, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16300. (b) Li, Y.; Hale, K. J. *Org. Lett.* **2007**, *9*, 1267.

(41) For an example of an alternative tactic as applied to a synthesis of punctaporonin B, consult: Kende, A. S.; Kaldor, I.; Aslanian, R. *J. Am. Chem. Soc.* **1988**, *110*, 6265.

extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were dried. The solvent was evaporated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel (eluting with 20−30% ethyl acetate in hexanes) to provide **18** (683 mg, 91%) as a colorless oil: IR (film, cm^{-1}) 3430, 1613, 1586; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.45 (s, 2H), 3.90-(ddd, J = 12.5, 5.5, 2.7 Hz, 1H), 3.81 (s, 3H), 3.62 (m, 1H), 3.58 (t, J = 5.9 Hz, 2H), 3.09 (ddd, J = 6.7, 5.5, 2.7 Hz, 1H), 2.97 (dt, J = 6.7, 2.5 Hz, 1H), 1.99−1.65 (m, 2H), 1.62 (dd, J = 7.3, 5.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2, 130.3, 129.3 (2 C), 113.8 (2 C), 72.8, 66.5, 61.7, 58.4, 55.3, 53.7, 32.0; $[\alpha]_D^{19}$ +27.0 (*c* 1.5, $CHCl_3$) (lit. $[\alpha]_D^{19}$ +27.7 (*c* 0.9, $CHCl_3$)).

(2*S*,3*R*)-2-Iodomethyl-3-[2′-(4″-methoxybenzyloxy)ethyl]oxirane (19). A solution of **18** (500 mg, 2.1 mmol) in anhydrous THF (20 mL) was cooled to 0 °C under N_2 in the dark and treated with triphenylphosphine (716 mg, 2.73 mmol) and imidazole (429 mg, 6.30 mmol). A solution of iodine (693 mg, 2.73 mmol) in anhydrous THF (5 mL) was added over 1 h, and the reaction mixture was allowed to warm slowly to rt over a further 1 h, quenched with saturated $Na_2S_2O_3$ solution (25 mL), and extracted with ether (3 × 30 mL). The combined organic extracts were washed with brine (20 mL) and then dried. The solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (eluting with 0−10% ethyl acetate in hexanes) to give **19** (550 mg, 75%) as a colorless oil: IR (film, cm^{-1}) 1613, 1586, 1514; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 4.50 (s, 2H), 3.89 (s, 3H), 3.57 (m, 2H), 3.24 (m, 1H), 3.10−3.02 (m, 2H), 2.98 (ddd, J = 6.5, 5.1, 1.7 Hz, 1H), 1.87 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 130.3, 129.3 (2 C), 113.8 (2 C), 72.8, 66.4, 60.4, 58.3, 55.3, 32.2, 4.9; $[\alpha]_D^{19}$ −4.3 (*c* 1.1, $CHCl_3$) (lit. $[\alpha]_D^{19}$ −4.3 (*c* 1.04, $CHCl_3$)).

(*R*)-5-(4-Methoxybenzyloxy)pent-1-en-3-ol (20). A stirred solution of **19** (8.3 g, 23.9 mmol) in anhydrous THF (300 mL) was cooled to −78 °C under N_2 and treated with *n*-butyllithium (19.6 mL, 31.0 mmol, 1.58 M in hexanes). After 2 h, the reaction mixture was warmed to −30 °C over 1 h and treated with water (150 mL). The aqueous layer was extracted with ether (3 × 500 mL), and the combined organic extracts were washed with brine (200 mL) and then dried. The solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (eluting with 10−20% ethyl acetate in hexanes) to give 20 (5.14 g, 97%) as a colorless oil: IR (film, cm^{-1}) 3414, 1613, 1586; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 5.87 (ddd, J = 17.3, 10.3, 5.5 Hz, 1H), 5.27 (dd, J = 17.3, 1.4 Hz, 1H), 5.10 (dd, J = 10.3, 1.4 Hz, 1H), 4.45 (s, 2H), 4.33 (s, 1H), 3.81 (s, 3H), 3.81−3.56 (m, 2H), 2.88 (d, J = 3.1 Hz, 1H), 1.92−1.73 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 140.5, 130.0, 129.3 (2 C), 114.3, 113.8 (2 C), 73.0, 72.0, 68.1, 55.3, 36.3; $[\alpha]_D^{19}$ −9.2 (*c* 1.0, $CHCl_3$) (lit. $[\alpha]_D^{19}$ −8.5 (*c* 0.98, $CHCl_3$)).

(*R*)-2-Methoxy-4-(4′-methoxybenzyloxy)butyraldehyde (15). A stirred solution of **21** (500 mg, 2.12 mmol) in 1:1 THF/pH 7 buffer (30 mL) was treated with NMO·H_2O (573 mg, 4.24 mmol) and potassium osmate (78 mg, 0.21 mmol). After 24 h, sodium bisulfite (2.2 g, 21.2 mmol) was added, and the reaction mixture was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (20 mL) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the crude diols. A stirred solution of these diols (2.12 mmol) in 5:1 THF/pH 7 buffer (30 mL) was treated with $NaIO_4$ (906 mg, 4.24 mmol) and stirred for 24 h. The reaction mixture was diluted with brine (25 mL) and extracted with 10% Et_2O/hexanes (3 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried, and freed of solvent under reduced pressure to provide **15** (492 mg, 98%) as a colorless oil: IR (film, cm^{-1}) 1733, 1612, 1586; ^1H NMR (300 MHz, $CDCl_3$) δ 9.66 (d, J = 1.5 Hz, 1H), 7.24 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.47−4.36 (m, 2H), 3.80 (s, 3H), 3.78 (m, 1H), 3.60−3.53 (m, 2H), 3.44 (s, 3H), 2.08−1.83 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 159.2, 130.2, 129.3 (2 C), 113.8 (2 C), 83.0, 72.6, 64.7, 58.3, 55.3, 30.6; HRMS (ES) m/z $(M + Na)^+$ calcd 261.1103, obsd, 261.1107;$[\alpha]_D^{19}$ +20.4 (*c* 1.0, $CHCl_3$).

(1*S*,4*S*,5*S*,6*S*)-6-Benzyloxy-4-[(2*R*,3*R*)-1-hydroxy-2-methoxy-4-(4-methoxybenzyloxy)butyl]-7,7-dimethyl-2-oxabicyclo[3.2.0]-heptan-3-one (23). A stirred solution of **3** (100 mg, 0.41 mmol) in anhydrous THF (8 mL) was cooled to −78 °C under N_2 and treated with NaHMDS (0.49 mL, 1.0 M in THF, 0.49 mmol). After 2 h, a solution of **15** (193 mg, 0.81 mmol) in THF (2 mL) was added. The reaction mixture was warmed to rt over 4 h, treated with saturated NH_4Cl solution (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried, and evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (eluting with an increasing proportion of ethyl acetate in hexanes from 0 to 50%) to give **23** (72 mg, 37%) as a colorless oil: IR (film, cm^{-1}) 3432, 1767, 1612; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 7.22 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 4.48 (d, J = 11.5 Hz, 1H), 4.45 (s, 2H), 4.44 (d, J = 11.5 Hz, 1H), 4.34 (d, J = 6.5 Hz, 1H), 3.99 (dd, J = 3.0, 1.0 Hz, 1H), 3.80 (s, 3H), 3.70−3.64 (m, 2H), 3.61 (dt, J = 9.0, 2.5 Hz, 1H), 3.55 (d, J = 5.5 Hz, 1H), 3.48 (ddd, J = 9.5, 6.5, 3.0 Hz, 1H), 3.37 (s, 3H), 2.88 (s, 1H), 2.87 (t, J = 6.0 Hz, 1H), 2.00−1.88 (m, 2H), 1.20 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.5, 159.5, 137.9, 129.5, 129.3, 128.5, 127.8, 127.6, 113.9, 84.4, 82.0, 79.1, 74.6, 73.1, 71.7, 65.6, 56.8, 55.2, 47.9, 44.4, 43.9, 29.3, 21.6, 19.9; HRMS (ES) m/z $(M + Na)^+$ calcd 507.2359, obsd, 507.2373; $[\alpha]_D^{19}$ −98.5 (*c* 0.2, $CHCl_3$).

(3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-4-(2-(methoxymethoxy)-ethyl)-2,2-dimethylcyclobutanone (28). A stirred solution of **4** (70 mg, 0.22 mmol) and *N*-methylmorpholine *N*-oxide monohydrate (44 mg, 0.33 mmol) in 10% $MeCN/CH_2Cl_2$ (10 mL) was treated with 4 Å molecular sieves (110 mg) under N_2. After 5 min, TPAP (4 mg, 0.011 mmol) was added, and the reaction mixture was stirred for a further 30 min and passed through a pad of silica gel which was rinsed with ethyl acetate (20 mL). The solvent was evaporated under reduced pressure to yield the crude product, which was purified by column chromatography on silica gel (elution with 5−10% ethyl acetate in hexanes) to yield **28** (69.5 mg, 100%) as a colorless oil: IR (film, cm^{-1}) 1777, 1462, 1111, 1043; ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (s, 2H), 4.18 (d, J = 7.7 Hz, 1H), 3.62−3.51 (m, 3H), 3.34 (s, 3H), 1.93−1.83 (m, 2H), 1.20 (s, 3H), 1.03 (s, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.2, 96.4, 70.1, 65.8, 62.6, 57.2, 55.2, 25.8 (3 C), 24.0, 22.8, 18.2, 16.1, −4.7, −5.1; HRMS (ES) m/z $(M + Na)^+$ calcd 339.1968, obsd 339.1967; $[\alpha]_D^{21}$ −1.7 (*c* 1.57, $CHCl_3$).

(1*R*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-((*S*)-5-(4-methoxybenzyloxy)-4-methylpent-1-en-2-yl)-4-(2-(methoxymethoxy)ethyl)-2,2-dimethylcyclobutanol (29). To a stirred solution of (*S*)-1-(4-methoxybenzyloxy)-2-methyl-4-bromopent-4-ene (**16**) (0.61 g, 2.05 mmol) in THF (10 mL) at −78 °C was added *tert*-butyllithium (2.25 mL, 1.75 M in pentane, 3.93 mmol) slowly. After 15 min, a solution of **28** (0.54 g, 1.71 mmol) in THF (13 mL) was added slowly against the wall of the reaction flask. After 3 h at −78 °C, saturated NH_4Cl solution (10 mL) was added. The aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried and concentrated in vacuo. Purification of the residue by column chromatography (elution with 5−20% EtOAc in hexanes) gave **29** (0.65 mg, 71%, 80% borsm) as a colorless oil, along with starting material **28** (0.060 g, 11%), and the epimer of **28** (0.083 g, 16%): IR (film, cm^{-1}) 3450, 1614, 1513, 1462; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2 H), 6.86 (d, J = 8.5 Hz, 2 H), 4.96 (s, 1 H), 4.89 (s, 1 H), 4.59 (ABq, J = 6.5 Hz, $\Delta\nu$ = 9.3 Hz, 2 H), 4.43 (s, 2 H), 3.80 (s, 3 H), 3.74 (d, J = 5.5 Hz, 1 H), 3.49 (dt, J = 6.4, 1.3 Hz, 2 H), 3.36−3.33

(m, 1 H), 3.35 (s, 3 H), 3.22 (dd, J = 9.1, 6.9 Hz, 1 H), 2.97 (dd, J = 14.0, 6.4 Hz, 1 H), 2.78 (s, 1 H), 2.25 (dd, J = 15.2, 5.2 Hz, 1 H), 2.17−2.11 (m, 1 H), 1.88−1.82 (m, 1 H), 1.69−1.56 (m, 2 H), 0.99 (s, 3 H), 0.94 (d, J = 6.6 Hz, 3 H), 0.93 (s, 3 H), 0.92 (s, 9 H), 0.04 (s, 3 H), 0.03 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 147.6, 131.0, 129.1 (2 C), 113.7 (2 C), 111.1, 96.5, 84.1, 76.1, 75.9, 72.5, 66.4, 55.3 (2 C), 46.4, 39.6, 36.0, 31.8, 25.9 (3 C), 24.2, 23.0, 18.3, 17.4, 16.9, −4.6, −5.0; HRMS (ES) m/z (M + Na)$^+$ calcd 559.3431, obsd 559.3445; $[\alpha]_D^{21}$ −21.2 (c 0.52, $CHCl_3$).

(1*R*,5*S*,6*R*)-6-(*tert*-Butyldimethylsilyloxy)-1-((*S*)-5-(4-methoxybenzyloxy)-4-methylpent-1-en-2-yl)-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one (31). A stirred solution of **30** (16.5 mg, 0.034 mmol) and *N*-methylmorpholine *N*-oxide monohydrate (13.6 mg, 0.10 mmol) in 10% $MeCN/CH_2Cl_2$ (2 mL) was treated with 4 Å molecular sieves (20 mg) under N_2. After 5 min, TPAP (0.6 mg, 1.7 μmol) was added, and the reaction mixture was stirred for a further 90 min and passed through a pad of silica gel which was rinsed with ethyl acetate (10 mL). The solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with 5−20% ethyl acetate in hexanes) to yield **31** (16.1 mg, 99%) as a colorless oil: IR (film, cm^{-1}) 1778, 1611, 1461, 1250, 1122; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2 H), 6.87 (d, J = 8.5 Hz, 2 H), 5.02 (s, 1 H), 4.97 (s, 1 H), 4.42 (ABq, J = 11.7 Hz, $\Delta\nu$ = 14.0 Hz, 2 H), 3.80 (s, 3 H), 3.74 (d, J = 6.9 Hz, 1 H), 3.36 (t, J = 7.3 Hz, 1 H), 3.30 (dd, J = 9.2, 5.8 Hz, 1 H), 3.23 (dd, J = 9.2, 6.6 Hz, 1 H), 2.64 (dd, J = 17.7, 1.0 Hz, 1 H), 2.43 (dd, J = 17.7, 8.8 Hz, 1 H), 2.29 (dd, J = 15.9, 5.0 Hz, 1 H), 2.13−2.08 (m, 1 H), 1.72 (dd, J = 15.6, 9.0 Hz, 1 H), 1.04 (s, 3 H), 0.98 (s, 3 H), 0.92 (d, J = 6.7 Hz, 3 H), 0.91 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 159.0, 143.9, 130.8, 129.2 (2 C), 113.7 (2 C), 112.6, 94.9, 75.4, 72.5, 72.2, 55.3, 47.4, 38.3, 36.4, 31.5, 28.6, 25.8 (3 C), 24.0, 18.3, 17.1, 16.8, −4.8, −5.1; HRMS (ES) m/z (M + Na)$^+$ calcd 511.2856, obsd 511.2856; $[\alpha]_D^{25}$ −12.0 (c 0.25, $CHCl_3$).

***O*-(1*R*,5*S*,6*R*)-1-((*S*)-5-(4-Methoxybenzyloxy)-4-methylpent-1-en-2-yl)-7,7-dimethyl-3-oxo-2-oxabicyclo[3.2.0]heptan-6-yl *O*-*p*-Tolyl Carbonothioate (33).** A stirred solution of **32** (24 mg, 0.064 mmol) in anhydrous CH_3CN (1 mL) was treated with DMAP (23 mg, 0.19 mmol) and *O*-*p*-tolyl chlorothionoformate (29 μL, 0.19 mmol) under N_2. The cloudy reaction mixture was vigorously stirred for 24 h, and more DMAP (23 mg, 0.19 mmol) and *O*-*p*-tolyl chlorothionoformate (29 μL, 0.19 mmol) were added. After a further day, the reaction mixture was quenched with water (5 mL), and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), then dried. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (elution with 5−30% ethyl acetate in hexanes) to afford **33** (27 mg, 81%) as a pale yellow oil: IR (film, cm^{-1}) 1778, 1611, 1506, 1267, 1194; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2 H), 7.21 (d, J = 8.3 Hz, 2 H), 6.97 (d, J = 8.3 Hz, 2 H), 6.88 (d, J = 8.5 Hz, 2 H), 5.12 (d, J = 9.6 Hz, 1 H), 5.11 (s, 1 H), 5.05 (s, 1 H), 4.43 (ABq, J = 11.8 Hz, $\Delta\nu$ = 13.7 Hz, 2 H), 3.81 (s, 3 H), 3.67 (dt, J = 7.3, 2.1 Hz, 1 H), 3.33−3.23 (m, 2 H), 2.71−2.57 (m, 2 H), 2.37 (s, 3 H), 2.33 (dd, J = 15.7, 4.7 Hz, 1 H), 2.15−2.09 (m, 1 H), 1.75 (dd, J = 15.6, 9.1 Hz, 1 H), 1.19 (s, 3 H), 1.17 (s, 3 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.0, 175.9, 159.1, 151.1, 143.1, 130.2 (2 C), 129.7, 129.2 (2 C), 128.3, 121.2 (2 C), 113.7 (2 C), 113.5, 94.0, 81.8, 75.3, 72.6, 55.3 (2 C), 47.7, 37.3, 36.4, 31.6, 29.7, 23.9, 17.0, 16.8; HRMS (ES) m/z (M + Na)$^+$ calcd 547.2130, obsd 547.2127; $[\alpha]_D^{20}$ −3.0 (c 0.30, $CHCl_3$).

(1*S*,5*R*)-1-((*S*)-5-(4-Methoxybenzyloxy)-4-methylpent-1-en-2-yl)-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one (34). A solution of **33** (18 mg, 0.034 mmol), tributyltin hydride (38 μL, 0.14 mmol), and AIBN (3.4 mg, 0.021 mmol) in freshly distilled benzene (6 mL) was degassed thoroughly with argon. The reaction mixture was heated at 90 °C for 5 h, cooled, and purified by column chromatography on silica gel (elution with an increasing proportion of ethyl acetate in hexanes from 0 to 20%) to furnish **34** (12 mg, 99%) as a colorless oil: IR (film, cm^{-1}) 1777, 1613, 1248, 1097; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.5 Hz, 2 H), 6.87 (d, J = 8.5 Hz, 2 H), 5.03 (s, 1 H), 4.97 (s, 1 H), 4.43 (ABq, J = 11.9 Hz, $\Delta\nu$ = 13.3 Hz, 2 H), 3.80 (s, 3 H), 3.30 (dd, J = 9.2, 5.9 Hz, 1 H), 3.24 (dd, J = 9.2, 6.5 Hz, 1 H), 3.15 (dd, J = 16.0, 7.6 Hz, 1 H), 2.60 (dd, J = 17.8, 7.6 Hz, 1 H), 2.38 (d, J = 17.8 Hz, 1 H), 2.30 (dd, J = 15.6, 4.7 Hz, 1 H), 2.17−2.10 (m, 1 H), 1.87 (dd, J = 11.8, 8.8 Hz, 1 H), 1.72 (dd, J = 15.6, 9.0 Hz, 1 H), 1.48 (dd, J = 11.8, 7.6 Hz, 1 H), 1.15 (s, 3 H), 1.03 (s, 3 H), 0.92 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 159.0, 143.8, 129.7, 129.2 (2 C), 113.7 (2 C), 112.9, 97.2, 75.4, 72.6, 55.3, 41.7, 36.1, 35.3, 31.5, 31.4, 29.7, 25.0, 22.9, 17.0; HRMS (ES) m/z (M + Na)$^+$ calcd 381.2042, obsd 381.2030; $[\alpha]_D^{24}$ −33.3 (c 0.64, $CHCl_3$).

(1*S*,4*S*,5*R*)-4-((1*R*,2*R*)-1-Hydroxy-2-methoxy-4-(4-methoxybenzyloxy)butyl)-1-((*S*)-5-(4-methoxybenzyloxy)-4-methylpent-1-en-2-yl)-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one (36). To a stirred solution of NaHMDS (0.19 mL, 0.85 M in toluene, 0.16 mmol) in THF (0.8 mL) at −78 °C under N_2 was slowly added lactone **34** (53.2 mg, 0.15 mmol) in THF (0.4 mL). After 20 min, a solution of aldehyde **15** (39 mg, 0.16 mmol) in THF (0.2 mL) was added. The reaction mixture was stirred at −78 °C for 2 h, quenched with a saturated NH_4Cl solution (10 mL), and extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), then dried. The solvent was evaporated under reduced pressure to leave a residue that was purified by column chromatography on silica gel (elution with an increasing proportion of ethyl acetate in hexanes from 5 to 40%) to yield **36** (70 mg, 79%, 96% borsm) as a colorless oil, along with recovered **34** (9.6 mg, 18%): IR (film, cm^{-1}) 1760, 1613, 1514, 1248, 1094; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.21 (m, 4 H), 6.88−6.85 (m, 4 H), 5.01 (s, 1 H), 4.96 (s, 1 H), 4.44−4.39 (m, 4 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.67−3.60 (m, 3 H), 3.56−3.50 (m, 1 H), 3.35 (s, 3 H), 3.32 (dd, J = 9.2, 5.7 Hz, 1 H), 3.22 (dd, J = 9.2, 6.7 Hz, 1 H), 3.01 (t, J = 7.9 Hz, 1 H), 2.79 (d, J = 3.8 Hz, 1 H), 2.26 (dd, J = 15.7, 4.6 Hz, 1 H), 2.14−2.09 (m, 1 H), 1.96−1.88 (m, 3 H), 1.72 (dd, J = 15.7, 9.0 Hz, 1 H), 1.49 (dd, J = 12.2, 6.8 Hz, 1 H), 1.13 (s, 3 H), 0.99 (s, 3 H), 0.91 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 159.3, 159.0, 144.1, 130.9, 129.9, 129.4 (2 C), 129.2 (2 C), 113.9 (2 C), 113.7 (2 C), 112.7, 96.0, 79.2, 75.6, 73.2, 72.9, 72.5, 65.8, 57.2, 55.3, 51.1, 41.7, 37.7, 36.2, 36.0, 31.3 (2 C), 28.9, 25.7, 23.4, 17.1; HRMS (ES) m/z (M + Na)$^+$ calcd 619.3247, obsd 619.3280; $[\alpha]_D^{23}$ −46.6 (c 0.38, $CHCl_3$).

(1*R*,4*R*,5*S*)-4-((1*S*,2*S*)-1,4-Dihydroxy-2-methoxybutyl)-1-((*S*)-5-hydroxy-4-methylpent-1-en-2-yl)-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one (39). To a solution of aldol adduct **38** (30 mg, 0.05 mmol) in CH_2Cl_2 (6 mL) and pH 7 buffer (0.3 mL) was added DDQ (69 mg, 0.30 mmol). The green mixture was stirred at 0 °C for 30 min and at rt for 4 h. The resulting orange suspension was washed with saturated NaHCO3 solution (10 mL). The aqueous phase was extracted with CH2Cl2 (5 × 10 mL), and the combined organic extracts were dried and evaporated. The residue was chromatographed over silica gel eluting with 2−7% $MeOH/CH_2Cl_2$ to give triol **39** (17 mg, 100%) as a colorless oil: IR (film, cm-1) 3404, 1747, 1454, 1077; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.13 (s, 1 H), 5.08 (s, 1 H), 3.82−3.62 (series of m, 4 H), 3.53−3.41 (series of m, 2 H), 3.42 (s, 3 H), 3.08 (t, J = 8.0 Hz, 1 H), 2.86 (d, J = 3.8 Hz, 1 H), 2.10 (dd, J = 13.8, 6.4 Hz, 1 H), 2.01−1.87 (series of m, 5 H), 1.53 (dd, J = 12.1 7.0 Hz, 1 H), 1.14 (s, 3 H), 1.01 (s, 3 H), 0.92 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 144.7, 113.7, 96.1, 80.2, 73.4, 67.5, 59.1, 57.4, 51.1, 41.8, 37.5, 36.5, 36.2, 34.2, 31.7, 25.7, 23.2, 17.5; HRMS (ES) m/z (M + Na)$^+$ calcd 379.2097, obsd 379.2111; $[\alpha]_D^{23}$ +98.5 (c 0.41, $CHCl_3$).

(1*R*,4*R*,5*S*)-4-((1*S*,2*S*)-1,4-Dihydroxy-2-methoxybutyl)-1-((*S*)-4-hydroxy-3-methylbutanoyl)-7,7-dimethyl-2-oxabicyclo[3.2.0]-

heptan-3-one (40). Triol **39** (17 mg, 0.048 mmol) was dissolved in CH2Cl2 (2 mL) and cooled to −78 °C. Ozone was bubbled into the reaction mixture until a pale blue color persisted, followed by O_2 for 10 min. The reaction mixture was quenched with PPh_3 (63, 0.24 mmol), allowed to warm to rt, and stirred overnight. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel (eluting with 2−7% MeOH/CH2Cl2) to give **40** (16.9 mg, 99%) as a pale oil. Compound **40** is characterized by complex ^{1}H and ^{13}C NMR spectra indicating the existence of lactols and keto alcohol. Therefore the NMR data are not reported: IR (film, cm^{-1}) 3404, 1770, 1712, 1087; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 381.1889, obsd 381.1893.

(1*R*,4*R*,5*S*)-1-((2*S*,4*S*)-1,2-Dihydroxy-5-(4-methoxybenzyloxy)-4-methylpentan-2-yl)-4-((1*S*,2*S*)-1-hydroxy-2-methoxy-4-(4-methoxybenzyloxy)butyl)-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one (41). To a solution of **38** (30 mg, 0.05 mmol) in 1 mL of *t*-BuOH−H_2O (l:l, 0.5 mL of each) was added DABCO (6 mg, 0.05 mmol), $K_2OsO_2(OH)_4$ (4 mg, 0.01 mmol), $K_3Fe(CN)_6$ (50 mg, 0.15 mmol), K_2CO_3 (21 mg, 0.15 mmol), and $NaHCO_3$ (13 mg, 0.15 mmol). After vigorous stirring at rt for 1 day, Na_2SO_3 (71 mg, 0.5 mmol) was added and stirring was maintained overnight. The reaction mixture was extracted with EtOAc. The combined organic extracts were dried and evaporated to give the crude product, which was purified by flash chromatography on silica gel (1−3% MeOH/CH_2Cl_2) to afford **41** (31 mg, 99%) as a colorless oil: IR (film, cm^{-1}) 3363, 1760, 1514, 1248, 1089; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 4 H), 6.87 (d, J = 8.6 Hz, 4 H), 4.53 (d, J = 11.6 Hz, 1 H), 4.43 (s, 4 H), 4.40 (d, J = 11.6 Hz, 1 H), 3.79 (s, 6 H), 3.70−3.53 (series of m, 5 H), 3.44 (dd, J = 9.2, 4 Hz, 1 H), 3.39 (s, 3 H), 3.13−3.06 (m, 1 H), 2.82 (s, 1 H), 1.98 (dd, J = 11.8, 9.4 Hz, 1 H), 1.92−1.86 (m, 1 H), 1.72 (dd, J = 15.0, 7.8 Hz, 1 H), 1.61−1.56 (m, 3 H), 1.45 (dd, J = 11.8, 6.6 Hz, 1 H), 1.23 (s, 3 H), 1.12 (s, 3 H), 0.89 (d, J = 6.8 Hz, 3 H; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 159.4, 159.2, 130.2, 129.8, 129.6, 129.5, 129.4, 129.3, 129.2, 127.8, 113.9, 113.7, 96.1, 78.8, 76.8, 75.5, 73.2, 73.1, 72.8, 67.2, 66.1, 57.5, 55.3, 55.2, 50.4, 43.3, 41.9, 40.6, 39.6, 36.4, 29.7, 28.8, 26.5, 19.6; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 653.3302, obsd 653.3306; $[\alpha]_D^{23}$ +13.6 (*c* 1.73, $CHCl_3$).

(1*R*,4*R*,5*S*)-4-((1*S*,2*S*)-1-Hydroxy-2-methoxy-4-(4-methoxybenzyloxy)butyl)-1-((*S*)-4-(4-methoxybenzyloxy)-3-methylbutanoyl)-7,7-dimethyl-2-oxabicyclo[3.2.0]heptan-3-one (42). A stirred solution of **41** (20 mg, 0.032 mmol) in 5:1 THF/pH 7 buffer (1.8 mL) was treated with $NaIO_4$ (30 mg, 0.14 mmol) and stirred for 48 h. The reaction mixture was diluted with brine (5 mL) and extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), then dried. The solvent was evaporated under reduced pressure to give a residue, which was purified by flash chromatography on silica gel (10−40% EtOAc/hexanes) to afford **42** (16 mg, 84%) as a colorless oil: IR (film, cm^{-1}) 3443, 1775, 1712, 1613; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 8.6 Hz, 2 H), 7.18 (d, J = 8.6 Hz, 2 H), 6.93 (d, J = 8.6 Hz, 2 H), 6.86 (d, J = 8.6 Hz, 2 H), 4.38 (s, 4 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.73 (dd, J = 3.4, 1.4 Hz, 1 H), 3.66−3.57 (m, 2 H), 3.46−3.41 (m, 2 H), 3.34 (s, 3 H), 3.27 (dd, J = 9.1, 5.8 Hz, 1 H), 3.22−3.18 (m, 2 H), 2.80 (s, 1 H), 2.53−2.42 (m, 2 H), 2.33−2.29 (m, 1 H), 1.98 (dd, J = 12.1, 9.2 Hz, 1 H), 1.90−1.87 (m, 2 H), 1.54 (dd, J = 12.1, 7.6 Hz, 1 H), 1.12 (s, 3 H), 1.07 (s, 3 H), 0.83 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.4, 177.7, 159.5, 159.1, 153.6, 130.7, 129.5 (2 C), 129.3, 129.2 (2 C), 114.1 (2 C), 113.7 (2 C), 94.9, 78.7, 74.7, 74.5, 73.1, 72.5, 65.2, 56.9, 55.3 (2 C), 49.2, 43.3, 42.5, 37.0, 36.7, 28.8, 28.3, 24.6, 23.1, 17.2; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 621.3040, obsd 621.3031; $[\alpha]_D^{23}$ +21.5 (*c* 0.62, $CHCl_3$).

(1*R*,4*R*,5*S*)-4-((1*S*,2*S*)-1,4-Dihydroxy-2-methoxybutyl)-1-((*S*)-4-hydroxy-3-methylbutanoyl)-7,7-dimethyl-2-oxabicyclo[3.2.0]-heptan-3-one (40). Compound **42** (16 mg, 0.027 mmol) was treated with TFA (0.05 mL) in CH_2Cl_2 (0.5 mL) at rt. After 5 min, the reaction mixture was quenched with saturated $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with EtOAc (10 × 5 mL). The combined organic extracts were washed with brine (5 mL) and then dried. The solvent was removed to leave a residue, which was purified by flash chromatography on silica gel (eluting with 2−7% MeOH/CH_2Cl_2) to yield **40** (16.9 mg, 99%) as a pale oil.

Selenylation of 40. To a stirring solution of **40** (10.3 mg, 0.029 mmol) and *o*-nitrophenyl selenocyanate (33 mg, 0.14 mmol) in THF (0.3 mL) under N_2 at rt was added tri-*n*-butylphosphine (36 μL, 0.14 mmol). After being stirred for 3 h, the solvent was removed in vacuo. The crude product was purified by column chromatography on silica gel (eluting with 10−40% EtOAc/hexanes) to give **43** (4 mg, 20%) and **44** (8 mg, 53%) as yellow oils. Compound **43** was used directly and not characterized.

For **44**: IR (film, cm^{-1}) 3456, 1777, 1511, 1332, 1097; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J = 8.0 Hz, 1 H), 7.64 (d, J = 8.0 Hz, 1 H), 7.55 (t, J = 8.0 Hz, 1 H), 7.33 (t, J = 8.0 Hz, 1 H), 4.12 (dd, J = 8.0, 6.5 Hz, 1 H), 3.87 (d, J = 7.5, 4.5 Hz, 1 H), 3.69−3.66 (m, 2 H), 3.50 (s, 3 H), 3.16−2.97 (series of m, 4 H), 2.59−2.54 (m, 1 H), 2.45 (dd, J = 12.5, 8.0 Hz, 1 H), 2.30 (dd, J = 12.5, 10.0 Hz, 1 H), 2.17−2.07 (series of m, 3 H), 1.64−1.58 (m, 1 H), 1.26 (s, 3 H), 1.18−1.14 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 156.3, 143.7, 133.7, 129.1, 126.5, 125.3, 120.3, 90.5, 80.7, 79.5, 77.2, 76.7, 72.7, 68.6, 57.8, 50.8, 41.8, 40.9, 38.8, 36.7, 34.3, 29.7, 25.5, 25.2, 22.7, 20.6, 17.4; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 575.1272, obsd 575.1258; $[\alpha]_D^{23}$ +31.9 (*c* 0.16, $CHCl_3$).

Selenoxide Elimination within 43. To a solution of **43** (4 mg, 0.0055 mmol) in THF (0.5 mL) was added 30% aqueous hydrogen peroxide (4 μL) at 0 °C. Stirring was maintained for 1 d at rt. The reaction mixture was diluted with H_2O (1 mL) and extracted with ether (3 × 2 mL). The combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography on silica gel (eluting with 10−30% EtOAc/hexanes) to give **45** (2 mg, 99%) as a colorless oil: IR (film, cm^{-1}) 3496, 1780, 1716, 1651, 1121, 1089; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60−5.56 (m, 1 H), 5.44 (d, J = 10.0 Hz, 1 H), 5.41 (d, J = 16.8 Hz, 1 H), 4.94 (s, 1 H), 4.77 (s, 1 H), 3.77 (t, J = 8.4 Hz, 1 H), 3.54 (d, J = 8.4 Hz, 1 H), 3.30−3.24 (m, 5 H), 3.16 (d, J = 16.4 Hz, 1 H), 2.98 (s, 1 H), 2.03 (dd, J = 12.0, 9.2 Hz, 1 H), 1.74 (s, 3 H), 1.58 (dd, J = 12.0, 7.2 Hz, 1 H), 1.15 (s, 3 H), 1.10 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.8, 176.8, 137.9, 135.7, 122.5, 115.5, 94.8, 82.4, 77.2, 74.0, 56.4, 49.0, 48.2, 42.3, 37.0, 35.3, 29.7, 24.5, 22.9, 22.8; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 345.1678, obsd 345.1677; $[\alpha]_D^{23}$ +84.3 (*c* 0.07, $CHCl_3$).

Acetonide 46. A solution of **41** (50 mg, 0.079 mmol) in 2,2-dimethoxypropane (3 mL) was treated with PPTS (2 mg, 0.008 mmol) and stirred for 1 h at 80 °C. The solvent was removed, and the crude product was purified by column chromatography on silica gel (eluting with 20−40% EtOAc/hexanes) to give **46** (43 mg, 81%) as a colorless oil: IR (film, cm^{-1}) 3395, 1766, 1613, 1513, 1248, 1094; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24−7.22 (m, 4 H), 6.87−6.84 (m, 4 H), 4.41 (s, 2 H), 4.40 (s, 2 H), 4.34 (s, 1 H), 4.01 (d, J = 8.8 Hz, 1 H), 3.92 (d, J = 8.8 Hz, 1 H), 3.79 (s, 6 H), 3.60−3.52 (m, 4 H), 3.39 (s, 3 H), 3.30 (d, J = 6.2 Hz, 2 H), 2.82 (s, 1 H), 2.79−2.76 (m, 1 H), 2.29−2.25 (m, 1 H), 2.00−1.94 (m, 2 H), 1.88−1.85 (m, 1 H), 1.79 (dd, J = 15.0, 5.2 Hz, 1 H), 1.67 (dd, J = 15.0, 5.4 Hz, 1 H), 1.45 (dd, J = 12.6, 5.2 Hz, 1 H), 1.42 (s, 3 H), 1.36 (s, 3 H), 1.12 (s, 3 H), 1.10 (s, 3 H), 1.00 (d, J = 6.7 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.1, 159.2, 159.0, 130.9, 130.3, 129.4 (2 C), 129.2 (2 C), 113.8 (2 C), 113.6 (2 C), 109.2, 94.8, 86.3, 79.3, 75.8, 73.8, 72.7, 72.5, 70.9, 66.1, 57.9, 55.3 (2 C), 51.6, 42.4, 40.2, 39.1, 36.6, 29.8, 28.8, 27.1, 26.8, 26.3, 25.8, 19.9; HRMS (ES) *m*/*z* (M + Na)$^+$ calcd 693.3615, obsd 693.3637; $[\alpha]_D^{23}$ +25.9 (*c* 0.83, $CHCl_3$).

Removal of PMB Groups from 46. The reaction was carried out according to the procedure described for the preparation of **39** starting with **46** (35 mg, 0.052 mmol) and DDQ (71 mg, 0.31 mmol). The usual workup and silica gel chromatography (2−7%

MeOH/CH_2Cl_2) gave **47** (22.2 mg, 99%) as a colorless oil: IR (film, cm^{-1}) 3400, 1758, 1238, 1060; ^1H NMR (400 MHz, $CDCl_3$) δ 4.05 (d, $J = 9.0$ Hz, 1 H), 3.95 (d, $J = 9.0$ Hz, 1 H), 3.79−3.73 (m, 3 H), 3.61−3.56 (m, 2 H), 3.47 (dd, $J = 10.4$, 5.6 Hz, 1 H), 3.43 (s, 3 H), 3.92−3.85 (m, 2 H), 2.21−2.16 (m, 1 H), 2.08 (dd, $J = 12.6$, 9.6 Hz, 1 H), 1.93−1.88 (m, 2 H), 1.83 (dd, $J = 15.2$, 7.2 Hz, 1 H), 1.66 (dd, $J = 15.2$, 4.8 Hz, 1 H), 1.52 (dd, $J = 12.6$, 5.6 Hz, 1 H), 1.50 (s, 3 H), 1.49 (s, 3 H), 1.16 (s, 3 H), 1.13 (s, 3 H), 0.98 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 109.5, 94.8, 86.1, 81.0, 73.3, 71.5, 68.2, 59.3, 57.7, 51.8, 42.2, 41.1, 39.1, 36.3, 31.9, 31.8, 27.2, 26.7, 26.3, 25.7, 19.6; HRMS (ES) *m/z* (M + Na)$^+$ calcd 453.2464, obsd 453.2476; $[\alpha]_D^{23}$ +22.3 (*c* 1.31, $CHCl_3$).

Selenylation of 47. The reaction was carried out according to the procedure described for the preparation of **43** starting with **47** (22.2 mg, 0.052 mmol), ArSeCN (42 mg, 0.186 mmol), and Bu_3P (46 μL, 0.186 mmol). The usual workup and silica gel chromatography (10−50% EtOAc/ hexanes) gave **48** (32 mg, 78%) and **49** (6.3 mg, 20%) as yellow oils.

For **48**: IR (film, cm^{-1}) 3379, 1770, 1513; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, $J = 8.0$, 1.2 Hz, 1 H), 8.24 (dd, $J = 8.0$, 1.2 Hz, 1 H), 7.67 (dd, $J = 8.0$, 1.2 Hz, 1 H), 7.61 (dd, $J = 8.0$, 1.2 1 H), 7.56 (dt, $J = 8.0$, 1.2 Hz, 1 H), 7.48 (dt, $J = 8.0$, 1.2 Hz, 1 H), 7.32−7.26 (m, 2 H), 4.57 (s, 1 H), 4.04 (d, $J = 8.8$ Hz, 1 H), 3.96 (d, $J = 8.8$ Hz, 1 H), 3.74 (dd, $J = 7.6$, 4.0 Hz, 1 H), 3.60−3.55 (m, 1 H), 3.49 (s, 3 H), 3.35−3.31 (m, 1 H), 3.03−2.86 (series of m, 4 H), 2.78 (dd, $J = 12.0$, 8.0 Hz, 1 H), 2.52−2.47 (m, 1 H), 2.17−2.04 (m, 3 H), 1.90−1.88 (m, 2 H), 1.51 (s, 3 H), 1.45 (s, 3 H), 1.44−1.38 (m, 1 H), 1.19−1.08 (m, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.5, 147.1, 146.9, 133.9, 133.6, 133.3, 129.9, 129.0, 126.5, 126.3, 125.4, 125.3, 109.6, 94.6, 86.2, 81.2, 73.0, 71.6, 58.0, 52.1, 44.2, 42.3, 39.0, 36.3, 35.3, 28.8, 28.2, 27.4, 26.7, 26.3, 25.7, 23.3, 20.6; HRMS (ES) *m/z* (M + Na)$^+$ calcd 821.1243, obsd 821.1235; $[\alpha]_D^{23}$ +24.8 (*c* 0.50, $CHCl_3$).

For **49**: IR (film, cm^{-1}) 3376, 1761, 1513; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (dd, $J = 8.0$, 1.2 Hz, 1 H), 7.62 (d, $J = 8.0$ Hz, 1 H), 7.51 (dt, $J = 8.0$, 1.2 Hz, 1 H), 7.31 (dt, $J = 8.0$, 1.2 Hz, 1 H), 4.54 (s, 1 H), 4.02 (s, 2 H), 3.76−3.49 (series of m, 4 H), 3.48 (s, 3 H), 3.04−2.82 (series of m, 4 H), 2.24−2.04 (series of m, 3 H), 1.84 (dd, $J = 15.2$, 7.6 Hz, 1 H), 1.66 (dd, $J = 15.2$, 4.4 Hz, 1 H), 1.52 (s, 3 H), 1.51−1.46 (m, 1 H), 1.42 (s, 3 H), 1.12 (s, 6 H), 0.99 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.8, 151.0, 133.6, 129.0, 126.5, 125.3, 115.1, 109.4, 94.7, 86.2, 81.5, 77.2, 72.7, 71.5, 68.3, 58.0, 52.2, 42.1, 41.1, 39.1, 36.2, 31.7, 28.0, 27.3, 26.8, 26.2, 25.7, 19.7; HRMS (ES) *m/z* (M + Na)$^+$ calcd 638.1844, obsd 638.1851; $[\alpha]_D^{23}$ +47.9 (*c* 0.14, $CHCl_3$).

Selenoxide Elimination within 48. A solution of **48** (42 mg, 0.052 mmol) in THF (1.7 mL) was cooled to −40 °C and then treated with pyridine (9 μL, 0.11 mmol) and 30% hydrogen peroxide (33 μL, 0.32 mmol). The reaction mixture was allowed to warm to rt, stirred for 12 h, and quenched with saturated $NaHSO_3$ solution (2 mL). The aqueous layer was extracted with ether (3 × 5 mL), and the combined organic extracts were washed with brine, dried, and evaporated. The residue was purified by column chromatography on silica gel (eluting with 10−20% EtOAc/hexanes) to give **50** (18.6 mg, 90%) as a colorless oil: IR (film, cm^{-1}) 3434, 1746, 1463; ^1H NMR (500 MHz, $CDCl_3$) δ 5.83−5.76 (m, 1 H), 5.37 (d, $J = 10.3$ Hz, 1 H), 5.29 (d, $J = 17.3$ Hz, 1 H), 4.87 (s, 1 H), 4.78 (s, 1 H), 4.08 (s, 1 H), 4.03 (ABq, $J = 9.0$ Hz, $\Delta\nu = 19.9$ Hz, 2 H), 3.79 (t, $J = 5.8$ Hz, 1 H), 3.74−3.71 (m, 1 H), 3.33 (s, 3 H), 2.85−2.79 (m, 2 H), 2.57 (d, $J = 14.2$ Hz, 1 H), 2.44 (d, $J = 14.2$ Hz, 1 H), 2.03 (dd, $J = 12.6$, 9.6 Hz, 1 H), 1.88 (s, 3 H), 1.50 (dd, $J = 12.6$, 4.6 Hz, 1 H), 1.47 (s, 3 H), 1.40 (s, 3 H), 1.15 (s, 3 H), 1.12 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 142.3, 135.0, 120.0, 115.6, 109.3, 94.3, 86.6, 83.8, 74.0, 70.1, 56.7, 51.5, 43.8, 42.0, 38.9, 35.3, 27.2, 26.9, 26.3, 26.0, 24.3; HRMS (ES) *m/z* (M + Na)$^+$ calcd 417.2253, obsd 417.2250; $[\alpha]_D^{23}$ +15.2 (*c* 0.23, $CHCl_3$).

Attempted RCM Reaction of 57. To a solution of **57** (5 mg, 0.011 mmol) in degassed PhMe (1.0 mL, 0.01 M) at 80 °C was added **55** (1.7 mg, 0.0023 mmol) in PhMe (0.2 mL). The stirred reaction mixture was heated for 2 days before being cooled to rt. Concentration in vacuo gave a dark oily residue which was purified by column chromatography on silica gel (10−20% EtOAc in hexanes) to afford **58** (4 mg, 80%) as a tan oil: IR (film, cm^{-1}) 1773, 1645, 1456; ^1H NMR (500 MHz, $CDCl_3$) δ 5.00 (q, $J = 6.9$ Hz, 1 H), 4.88 (s, 1 H), 4.77 (d, $J = 6.8$ Hz, 1 H), 4.74 (s, 1 H), 4.60 (d, $J = 6.8$ Hz, 1 H), 4.25 (d, $J = 9.3$ Hz, 1 H), 3.94 (ABq, $J = 8.7$ Hz, $\Delta\nu = 14.6$ Hz, 2 H), 3.65 (s, 3 H), 3.40 (s, 3 H), 2.95 (dd, $J = 9.3$, 3.2 Hz, 1 H), 2.69−2.65 (m, 1 H), 2.59 (d, $J = 14.2$ Hz, 1 H), 2.39 (d, $J = 14.2$ Hz, 1 H), 2.02 (dd, $J = 12.4$, 9.7 Hz, 1 H), 1.90 (s, 3 H), 1.67 (d, $J = 6.9$ Hz, 3 H), 1.49 (dd, $J = 12.4$, 4.9 Hz, 1 H), 1.42 (s, 3 H), 1.40 (s, 3 H), 1.21(s, 3 H), 1.13 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9, 151.6, 142.9, 129.7, 128.3, 115.3, 113.6, 109.3, 93.4, 85.9, 77.2, 75.9, 69.9, 60.3, 55.7, 51.4, 42.5, 39.4, 34.6, 29.7, 27.7, 27.2, 26.5, 25.9, 24.5; HRMS (ES) *m/z* (M + Na)$^+$ calcd 461.2515, obsd 461.2520; $[\alpha]_D^{23}$ +25.4 (*c* 0.13, $CHCl_3$).

Grieco Olefination of 49. To a solution of **49** (17 mg, 0.028 mmol) in THF (2 mL) was added 30% hydrogen peroxide (70 μL) at 0 °C. Stirring was maintained for 1 day at rt. The reaction mixture was diluted with H_2O (2 mL) and extracted with ether (3 × 5 mL). The combined organic extracts were washed with brine, then dried and concentrated. The residue was purified by column chromatography on silica gel (eluting with 30−70% EtOAc/hexanes) to give **59** (7 mg, 64%) as a colorless oil: IR (film, cm^{-1}) 3390, 1755, 1644; ^1H NMR (400 MHz, $CDCl_3$) δ 5.84−5.74 (m, 1 H), 5.37 (dd, $J = 10.0$, 1.2 Hz, 1 H), 5.29 (d, $J = 17.6$ Hz, 1 H), 4.05 (d, $J = 8.8$ Hz, 1 H), 4.03 (s, 1 H), 3.92 (d, $J = 8.8$ Hz, 1 H), 3.79 (t, $J = 5.6$ Hz, 1 H), 3.70 (t, $J = 6.8$ Hz, 1 H), 3.60 (dd, $J = 10.4$, 5.6 Hz, 1 H), 3.49 (dd, $J = 10.4$, 5.6 Hz, 1 H), 3.32 (s, 3 H), 2.88−2.80 (m, 2 H), 2.24−2.18 (m, 1 H), 2.04 (dd, $J = 12.4$, 9.6 Hz, 1 H), 1.82 (dd, $J = 15.2$, 7.6 Hz, 1 H), 1.67 (dd, $J = 10.8$, 6.0 Hz, 1 H), 1.53−1.49 (m, 4 H), 1.39 (s, 3 H), 1.14 (s, 3 H), 1.12 (s, 3 H), 0.98 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 135.0, 120.1, 109.5, 94.7, 85.7, 83.9, 77.2, 73.7, 71.6, 68.3, 56.7, 51.4, 41.9, 41.5, 39.0, 35.5, 31.9, 27.2, 26.9, 26.2, 25.7, 19.6; HRMS (ES) *m/z* (M + Na)$^+$ calcd 435.2359, obsd 435.2359; $[\alpha]_D^{23}$ +30.0 (*c* 0.34, $CHCl_3$).

Cross-Metathesis between 59 and 60. To a solution of **59** (5 mg, 0.012 mmol) and **60** (11.1 mg, 0.032 mmol) in degassed PhMe (0.2 mL) was added **55** (1.8 mg, 0.0024 mmol). The reaction mixture was heated at 45 °C for 2 d before being cooled to rt. Concentration in vacuo gave a dark oily residue which was purified by column chromatography on silica gel (1−3% MeOH in CH_2Cl_2) to afford **61** (6 mg, 67%) as a tan oil: IR (film, cm^{-1}) 3451, 1762, 1653; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4 H), 7.43−7.35 (m, 6 H), 5.70−5.64 (m, 1 H), 5.40 (dd, $J = 15.5$, 8.5 Hz, 1 H), 4.04 (d, $J = 8.9$ Hz, 1 H), 3.89 (d, $J = 8.9$ Hz, 1 H), 3.82−3.79 (m, 2 H), 3.70−3.58 (m, 3 H), 3.52−3.48 (m, 1 H), 3.27 (s, 3 H), 2.84−2.80 (m, 1 H), 2.73 (dd, $J = 7.1$, 2.9 Hz, 1 H), 2.21−2.17 (m, 1 H), 2.09−2.04 (m, 2 H), 2.01 (dd, $J = 12.5$, 9.7 Hz, 1 H), 1.82 (dd, $J = 15.2$, 7.7 Hz, 1 H), 1.68−1.51 (m, 3 H), 1.47 (s, 3 H), 1.46−1.34 (m, 8 H), 1.14 (s, 3 H), 1.12 (s, 3 H), 1.04 (s, 9 H), 0.97 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 137.7, 135.6 (4 C), 134.1 (2 C), 129.5 (2 C), 127.6 (4 C), 126.1, 109.5, 94.6, 85.6, 83.5, 77.2, 73.5, 71.7, 68.3, 63.9, 56.3, 51.5, 41.9, 39.0, 35.2, 32.4, 32.0, 29.0, 27.2, 27.0, 26.9 (3 C), 26.2, 25.7, 25.4, 19.7, 19.2, 11.2; HRMS (ES) *m/z* (M + Na)$^+$ calcd 759.4268, obsd 759.4263; $[\alpha]_D^{23}$ +21.1 (*c* 0.18, $CHCl_3$).

Regioselective Removal of PMB Group in 46. The reaction was carried out according to the procedure described for the preparation of **39** starting with **46** (32 mg, 0.048 mmol) and DDQ (16 mg, 0.072 mmol). The usual workup and silica gel chromatography (1−5% MeOH/CH_2Cl_2) gave **62** (16 mg, 62%; 100% borsm) as a colorless oil, along with recovered **46** (12 mg, 38%):

IR (film, cm^{-1}) 3382, 1762, 1514; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, $J = 8.6$ Hz, 2 H), 6.87 (d, $J = 8.6$ Hz, 2 H), 4.42 (s, 2 H), 4.26 (s, 1 H), 4.09−4.05 (m, 2 H), 3.80 (s, 3 H), 3.65−3.42 (series of m, 6 H), 3.39 (s, 3 H), 2.83−2.77 (m, 2 H), 2.14−2.10 (m, 1 H), 1.99 (dd, $J = 12.5$, 9.7 Hz, 1 H), 1.94−1.84 (m, 2 H), 1.77 (dd, $J = 15.0$, 6.4 Hz, 1 H), 1.67 (dd, $J = 15.0$, 5.2 H, 1 H), 1.50−1.47 (m, 4 H), 1.37 (s, 3 H), 1.18 (s, 3 H), 1.12 (s, 3 H), 0.99 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 159.2, 130.3, 129.4 (2 C), 113.8 (2 C), 109.4, 94.6, 85.9, 79.5, 73.6, 72.8, 71.6, 68.4, 66.2, 57.8, 55.3, 51.4, 42.4, 41.0, 39.2, 36.5, 31.8, 29.9, 27.1, 26.8, 26.5, 25.7, 19.6; HRMS (ES) *m*/*z* $(M + Na)^+$ calcd 573.3040, obsd 573.3036; $[\alpha]_D^{23}$ +25.9 (*c* 0.76, $CHCl_3$).

TBDPS Protection of 62. A solution of **62** (20 mg, 0.036 mmol) in CH_2Cl_2 (0.4 mL) was charged with Et_3N (7 μL, 0.047 mmol) and DMAP (0.5 mg, 0.004 mmol) at rt. TBDPSCl (12 μL, 0.044 mmol) was added dropwise into the reaction mixture under Ar. The reaction mixture was stirred at rt for 1 d and quenched with water (2 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic extracts was washed with brine, dried, and evaporated. The residue was purified by column chromatography on silica gel (10−30% EtOAc in hexanes) to afford **63** (27 mg, 94%) as a colorless oil: IR (film, cm^{-1}) 3394, 1766, 1513, 1464, 1249, 1112; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4 H), 7.43−7.34 (m, 6 H), 7.22 (d, $J = 8.6$ Hz, 2 H), 6.85 (d, $J = 8.6$ Hz, 2 H), 4.40 (s, 2 H), 4.31 (s, 1 H), 4.05 (d, $J = 8.9$ Hz, 1 H), 3.87 (d, $J = 8.9$ Hz, 1 H), 3.79 (s, 3 H), 3.62−3.47 (series of m, 6 H), 3.40 (s, 3 H), 2.84 (s, 1 H), 2.80−2.76 (m, 1 H), 2.19−2.15 (m, 1 H), 2.02−1.56 (series of m, 5 H), 1.46 (dd, $J = 12.3$, 5.2 Hz, 1 H), 1.36 (s, 3 H), 1.35 (s, 3 H), 1.14 (s, 3 H), 1.11 (s, 3 H), 1.05 (s, 9 H), 1.00 (d, $J = 6.7$ Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.0, 159.2, 135.6 (4 C), 133.9 (2 C), 130.3, 129.5 (2 C), 129.3 (2 C), 127.6 (4 C), 113.8 (2 C), 109.3, 94.6, 86.3, 79.3, 77.2, 74.0, 72.6, 71.0, 69.5, 66.1, 57.8, 55.2, 51.7, 42.6, 39.2, 36.5, 31.1, 29.9, 29.7, 27.0 (3 C), 26.9, 26.8, 26.5, 26.0, 22.7, 19.5, 19.3; HRMS (ES) *m*/*z* $(M + Na)^+$ calcd 811.4217, obsd 811.4221; $[\alpha]_D^{23}$ +14.7 (*c* 0.81, $CHCl_3$).

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

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