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Progress toward the Total Synthesis of (±)-Havellockate

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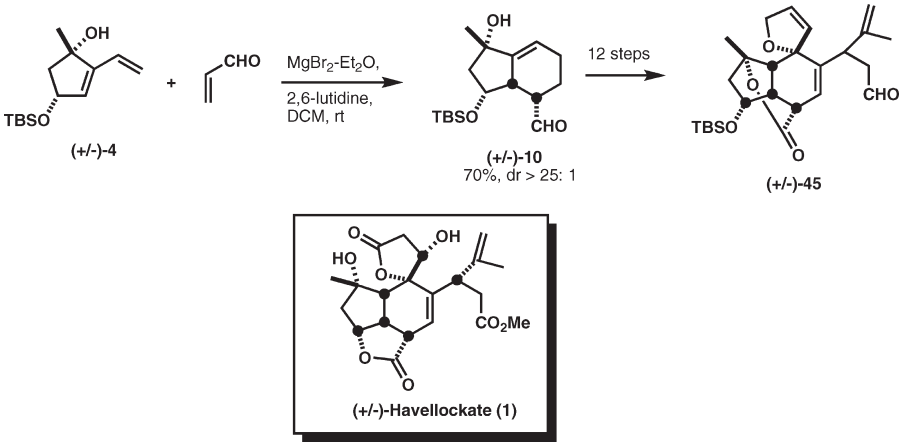

Havellockate (**1**) was isolated from the soft coral *Sinularia granosa* located on the Havellock island in the Indian Ocean. This highly compact and polyoxygenated marine diterpene bears a *cis*-fused hydrindane core that contains eight stereogenic centers as well as a spiro-lactone. To the best of our knowledge, no syntheses of **1** have been reported yet. Herein, we describe the synthesis of the all-carbon framework of havellockate (**1**) in 18 chemical operations. Our approach highlights the efficiency and utility of the hydroxy-directed Diels−Alder (HDDA) reaction to quickly access the cis-fused hydrindane core and securing the correct stereochemistry at C6 and C7. Moreover, six of the eight stereogenic centers have been installed in the correct stereochemistry.

Introduction

Marine organisms provide a seemingly continual supply of novel compounds often containing complex carbocyclic frameworks.[1] Soft corals, for example, produce large quantities of structurally diverse secondary metabolites that are thought to have roles in defense, competition, and reproduction of the organism.[2] During their quest for bioactive secondary metabolites, Anjaneyulu and coworkers discovered a novel diterpenoid from the soft coral *Sinularia granosa* located on the Havellock Island in the Indian Ocean.[3] The structure of this compound later named havellockate (**1**) was established without ambiguity by NMR spectroscopy and X-ray analysis (Figure 1). A cursory inspection of this molecule unveils a *cis*-fused hydrindane core bearing eight stereogenic centers and the presence of a spiro-lactone. As with the other known diterpenoids isolated from the *Sinularia* genus, havellockate (**1**) is believed to arise from furanocembrane diterpene.[4] To the best of our knowledge, the total synthesis of havellockate (**1**) has not yet been described.[5] In this paper, recent advances in the synthesis of this natural product are presented.

(1) Faulkner, D. *J. Nat. Prod. Rep.* **2000**, *17*, 7 and references therein.
(2) Faulkner, D. *J. Nat. Prod. Rep.* **1995**, *2*, 223.
(3) Anjaneyulu, A. S. R.; Venugopal, M. J. R. V.; Sarada, P.; Clardy, J.; Lobkovsky, E. *Tetrahedron Lett.* **1998**, *39*, 139.
(4) (a) Roethle, P. A.; Trauner, D. *Nat. Prod. Rep.* **2008**, *25*, 298. (b) Anjaneyulu, A. S. R.; Venugopal, M. J. R. V.; Sarada, P. *Indian J. Chem.* **2000**, *39B*, 530.
(5) For a previous synthetic study on havellockate, see: Mehta, G.; Senthil Kumaran, R. *Tetrahedron Lett.* **2001**, *42*, 8097.

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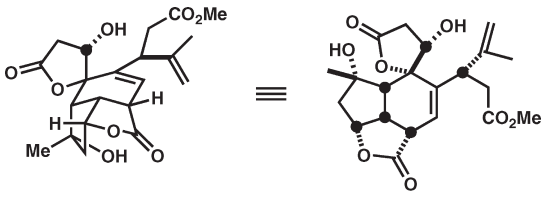
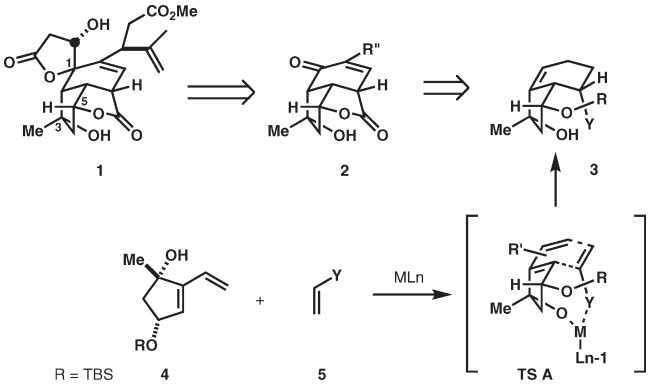


(+/-)-Havellockate (**1**)

FIGURE 1. Structure of (±)-havellockate (**1**).

SCHEME 1

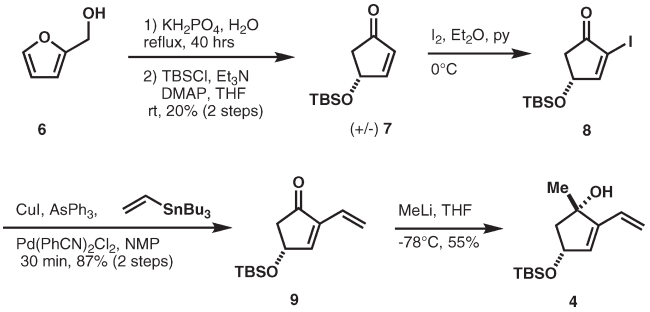


Results and Discussion

By examining **1**, one can imagine that the hydrindane core **2** could arise from a Diels−Alder reaction between diene **4** and dienophile **5** (Scheme 1). However, it is of paramount importance that the facial selectivity be controlled in such a way that all the hydrogens at the ring junction are placed *syn* to the methyl group at C3. Inspired by the work of Ward,[6] we recently demonstrated the use of temporary metal tethers to govern the facial selectivity in Diels−Alder reactions of various 2-vinylcycloalken-1-ols.[7] Using this approach, we envisioned that diene **4** and dienophile **5** would undergo a hydroxy-directed Diels−Alder reaction (HDDA) via transition state A (TS A) to provide the desired bicyclo[4.3.0]nonane framework **3**.

Our first objective was to develop a concise synthesis of diene **4**. This was achieved according to Scheme 2, whereby commerically available furfuryl alcohol **6** was refluxed in water in the presence of KH_2PO_4 (pH of 4.10) for 40 h to afford the corresponding 4-hydroxy-2-cyclopentanenone (Scheme 2).[8] The crude alcohol was then treated with TBSCl, Et_3N, and DMAP in THF to give **7** in 20% yield over two steps. Exposure of **7** to iodine[9] in a mixture of ether/pyridine

SCHEME 2



(1:1) gave the corresponding vinyl iodide **8**, which subsequently underwent a Stille cross-coupling reaction with tributyl(vinyl)tin in the presence of $AsPh_3$ (10 mol %), CuI (10 mol %), and $Pd(PhCN)_2Cl_2$ (5 mol %) to generate **9** in 87% yield over two steps.[10] Finally, alkylation with methyllithium in THF at −78 °C delivered diene **4** in 55% yield.

We were pleased to observe the HDDA reaction between **4** and acrolein in the presence of $MgBr_2 \cdot OEt_2$, and 2,6-lutidine in methylene chloride afforded the cycloadduct **10** in 70% yield as the sole diastereomer (Scheme 3). Treatment of **10** with fluoride ions afforded a mixture of the desired aldehyde in equilibrium with the lactol form. Subsequent oxidation using TPAP and NMO in methylene chloride provided lactone **11** in 73% yield. At this stage, a stereoselective hydroboration of **11** was envisioned to install the *cis*-hydrindane ring junction. Much to our surprise, the anti-Markovnikov addition of BH_3−DMS on **11** did not give the expected product **13** after an oxidative workup; only starting material was recovered. Other borane complexes such as BH_3−THF, 9-BBN, and catechol borane were tried in various solvents (THF, DCM, and hexanes) without success. Keeping in mind that the free hydroxyl group at C5 may be detrimental to the hydroboration reaction, **11** was converted to the corresponding silyl ether **12** and submitted to the above conditions. After **12** was stirred for 24 h, starting material was recovered along with degradation products. It became apparent that the synthetic strategy would require a modification. Thus, **10** was exposed to $BH_3 \cdot$DMS followed by an oxidative workup to give triol **14** in 81% yield. Next, the secondary alcohol moiety in **14** was subjected to an oxidation with TPAP to give the corresponding ketone. In addition, the primary alcohol was converted to an aldehyde moiety whereupon cyclization with the tertiary alcohol formed a lactol. This was further oxidized in situ to provide lactone **15** in 74% yield.

Having **15** in hand, we first investigated the formation of the β-hydroxy spirolactone subunit (Scheme 4). To this end, addition of vinylmagnesium bromide followed by a quench with Ac_2O gave ester **16** in 42% yield along with alcohol **16a** (26%). Ozonolysis of the terminal double bond afforded aldehyde **17** in 73% yield. At this point, we envisioned an intramolecular aldol condensation without elimination to form the desired β-hydroxy spirolactone **18**. Ester **17** was therefore first treated with LDA in THF at −78 °C. To our dismay, no desired spirolactone **18** was isolated; only degradation products were observed by ^{1}H NMR. Other bases such as KHMDS, DBU, and freshly sublimed potassium *tert*-butoxide gave either starting material or alcohol **19** in low yield. Pleasingly, exposure of **17** to NaH in

(6) (a) Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2*, 3937. (b) Ward, D. E.; Souweha, M. S. *Org. Lett.* **2005**, *7*, 3533.

(7) (a) Barriault, L.; Thomas, J. D. O.; Clement, R. *J. Org. Chem.* **2003**, *68*, 2317. (b) Barriault, L.; Ang, P. A. J.; Lavigne, R. M. A. *Org. Lett.* **2004**, *6*, 1317. (c) Barriault, L.; Grisé, C. M.; Clément, R. *Chem. Commun.* **2008**, 3004. (d) For a review on tethers in cycloaddition, see: (k) Shea, K. J.; Zandi, K. S.; Gauthier, D. R. *Tetrahedron* **1998**, *54*, 2289. (e) For other examples of the use of temporary tethers in Diels−Alder reactions, see: Souweha, M. S.; Arab, A.; ApSimon, M.; Fallis, A. G. *Org. Lett.* **2007**, *9*, 615. (f) Nicolaou, K. C.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3256. (g) Zografos, A. L.; Yiotakis, A.; Georgiadis, D. *Org. Lett.* **2005**, *7*, 4515. (h) Rath, J.-P.; Kinast, S.; Maier, M. E. *Org. Lett.* **2005**, *7*, 3089. (i) Olsson, R.; Bertozzi, F.; Fredj, T. *Org. Lett.* **2000**, *2*, 1283. (j) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450.

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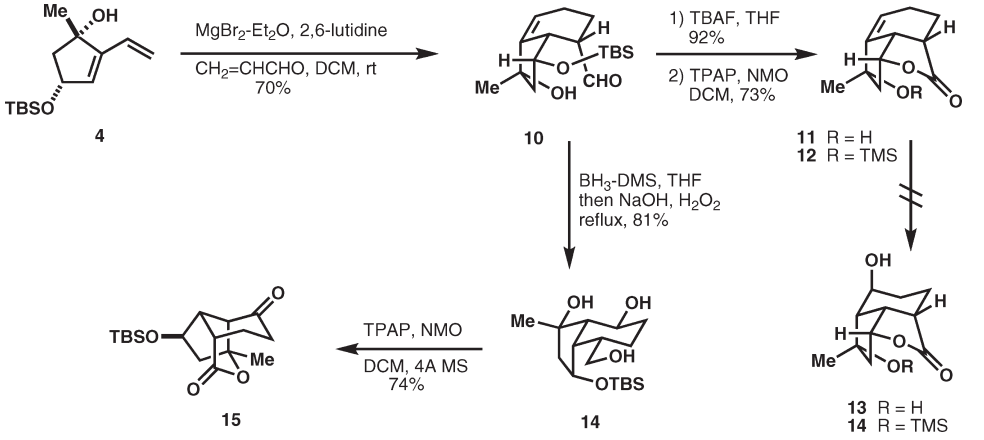
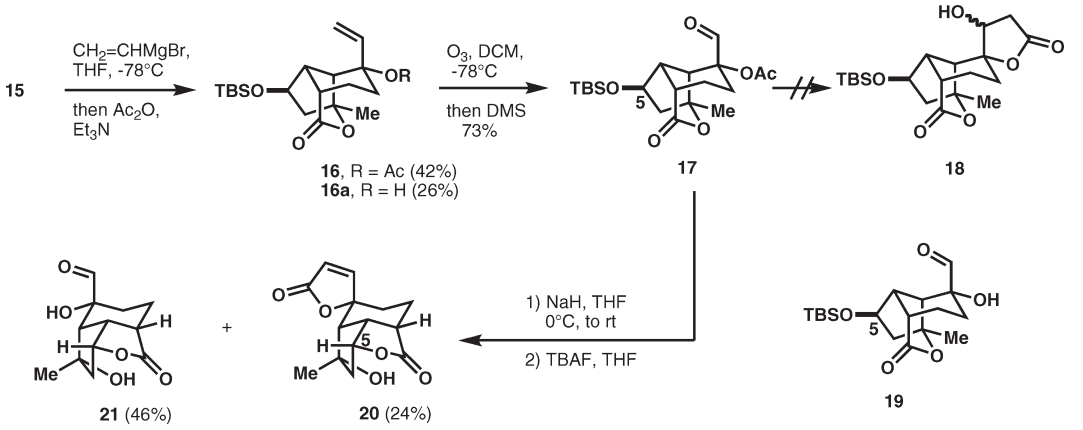
(9) Johnson, C. R.; Adams, J. P.; Matthew, P. B.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 917.

(10) Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W. *Tetrahedron Lett.* **1992**, *33*, 919.

SCHEME 3



SCHEME 4



THF at 0 °C followed by removal of the TBS group with TBAF gave lactones **20** and **21** in 24% and 46% yield, respectively, over two steps. The complete carbocyclic core of havellockate **20** was achieved in 12 steps from commercially available furfuryl alcohol **6**. Two vital pieces of information had been acquired during the synthesis of **20**. First, the facile elimination of the β-hydroxyl group upon closure of the spirocycle suggested that the spirolactone should be installed at the very end of the synthesis. Second, the lactone in havellockate (**1**) can be established upon a simple deprotection with TBAF. The free secondary alcohol at C5 that is generated spontaneously attacks the rigid 6-membered lactone moiety which after fragmentation of the tetrahedral intermediate liberates the core of havellockate. Having this information in mind, we began the exploration of the side-chain synthesis.

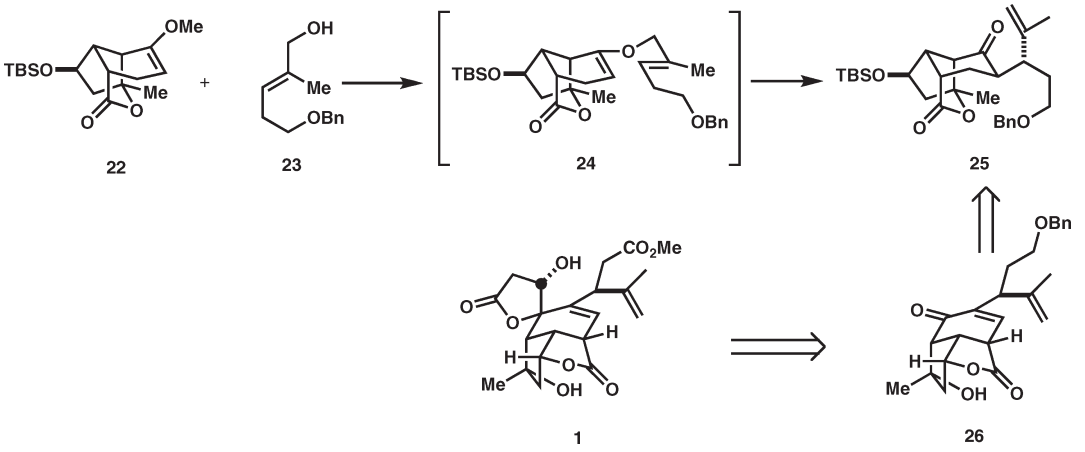
Synthesis of the Side Chain. The retrosynthetic analysis depicted in Scheme 5 reveals that havellockate (**1**) could be generated from enone **26**, which could be derived from ketone **25**. Upon closer inspection of **25**, one can recognize the presence of a γ,δ-unsaturated ketone. This type of molecular organization is characteristic of a Claisen rearrangement of allyl ether **24**. One can propose that intermediate **24** could be synthesized in situ via the enol ether of **22** and allylic alcohol **23** in the presence of a catalytic proton source.[11] We anticipated that the Claisen rearrangement would operate on the less hindered face of the molecule, thus installing the isopropenyl group with the correct stereochemistry.

Methyl enol ether **22** was readily obtained by treating ketone **15** with KHMDS in THF at −78 °C followed by addition of dimethyl sulfate (Scheme 6). A variety of Bronsted acids such as PTSA, TFA, pivalic acid, CSA, phenol, and 2,6-dimethylphenol were employed to promote the enol ether exchange between **22** and **23**. Various solvents such as DCM, toluene, and benzene as well as temperature were also scanned. Unfortunately, under these conditions, neither the desired Claisen product **25** nor enol ether **24** was isolated from the crude reaction mixture. Only degradation products and ketone **15** were observed. While exploring other strategies for preparing intermediate **24**, we investigated Buchwald's domino copper(I)-catalyzed C−O bond/Claisen rearrangement.[12] The synthesis of the required vinyl iodide intermediate **29** for this reaction was achieved by first preparing vinyl triflate **27** in 91% yield using standard conditions. Then, a $Pd(PPh_3)_4$-catalyzed stannylation using Me_6Sn_2 in the presence of LiCl in 1,4-dioxane at 70 °C gave **28** in 75% yield, which upon exposure to molecular iodine gave the corresponding vinyl iodide **29** in 83% yield. At this point, we were able to examine the Cu(I)-catalyzed coupling between **29** and **23**. All of the reactions were carried out in the presence of CuI (10 mol %), 1,10-phenanthroline, or tetramethyl-1,10-phenanthroline (20 mol %) and 3.0 equiv of cesium carbonate as prescribed

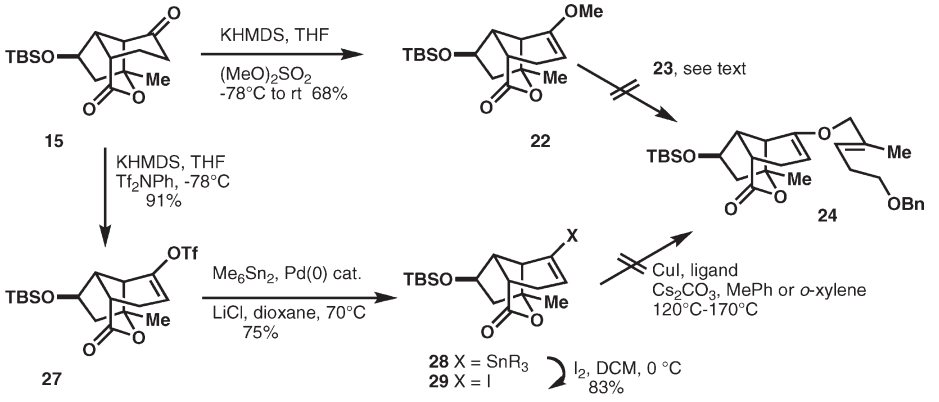
(11) (a) Nakai, T.; Sugiura, M. *Tetrahedron Lett.* **1996**, *37*, 7991. (b) Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28*, 5879.

(12) Nordmann, F.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978.

SCHEME 5



SCHEME 6

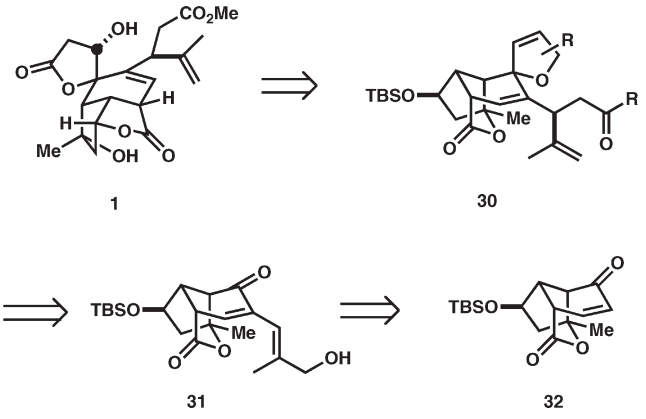


by Buchwald. In addition, highly concentrated mixtures (0.1−0.5 M of vinyl iodide) were prepared as this was deemed to be critical for the success of the reaction. Unfortunately, vinyl iodide **29** failed to react at temperatures ranging from 120 to 150 °C. As the temperature was increased beyond 150 °C, **29** began to decompose and there was no evidence of **24** or **25** by ^{1}H NMR of the crude reaction mixture.

In the light of the difficulties encountered to generate enol ether **24**, we hypothesized that it would be easier to generate havellockate (**1**) from diene **31** (Scheme 7). Our premise was founded on the basis that (1) intermediate **30** could be formed via a Claisen rearrangement or adapted variations using allylic alcohol **31** and (2) having the internal double bond already in place, prior to the Claisen rearrangement, would avoid potential problems of late-stage elimination regioselectivity. In order to validate this approach, the synthesis of alcohol **31** was investigated.

We began by first converting ketone **15** to enone **32** (Scheme 8). Ketone **15** was therefore treated with KHMDS in THF followed by addition of PhSeCl to give **33** in 48% yield. Selenium oxidation with H_2O_2 gave the desired enone **32**, but in a low yield of 20%. This was further optimized to 80% by changing the oxidant to $NaIO_4$. Despite this improvement, however, the overall yield of the process remained low (38% over two steps). Other methods such as Saegusa oxidation[13] and dehydrogenation

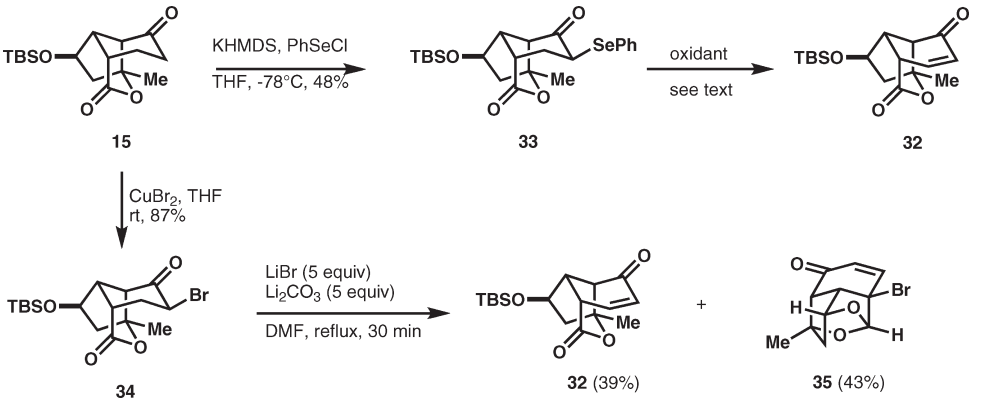
SCHEME 7



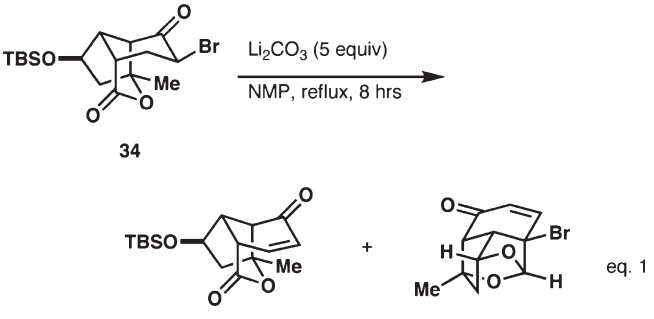
using IBX[14] and related hypervalent iodide reagents[15] were also investigated without giving any tangible success. However, we found that the treatment of **15** with $CuBr_2$ gave the corresponding α-bromoketone **34** in 87% yield.[16] Exposure of the latter to LiBr (5 equiv) and Li_2CO_3 (5 equiv) in dry DMF at 150 °C gave enone **32** in 39% yield along with side product **35** (43%).[17] The structure of **35** was established by X-ray analysis.

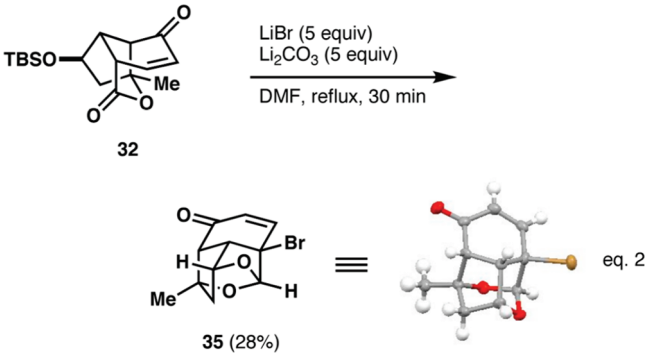
(13) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(14) Nicolaou, K. C.; Zhang, Y. L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596.
(15) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1386.
(16) Berkowitz, W. F.; Wilson, P. J. *J. Org. Chem.* **1991**, *56*, 3097.
(17) Jackman, L. M.; Webb, R. L.; Yick, H. C. *J. Org. Chem.* **1982**, *47*, 1824.

SCHEME 8



Closer examination of this intriguing molecule revealed an acetal at C11 and a bromine at C7. We contemplated whether the reagents and solvent were contributing to the synthesis of **35**. In particular, it was possible that the excess amount of LiBr used in the reaction was providing the source of bromine at C7. Therefore, the E2 elimination was repeated using only Li_2CO_3 and NMP as a solvent (eq 1). Although the yield of **32** was greatly improved over two steps (55%), compound **35** was still present in a low yield.[18] In a subsequent experiment, enone **32** was subjected to LiBr and Li_2CO_3 in DMF to give lactol **35** in 28% yield (eq 2). On the basis of these results, it is likely that LiBr which was being produced in situ from the E2 elimination reaction of **34** was further reacting with enone **32** to generate the side product **35**.





Having **32** in hand, halogenation of the enone moiety in the presence of iodine proceeded smoothly to give iodo **36** in 84% yield (Scheme 9). The latter underwent a Stille-cross coupling reaction[10] with stannane **37** to afford diene **38** in 81% yield, which upon treatment with DDQ in a biphasic mixture of methylene chloride and water at 0 °C gave **31** in 77% yield. At this point, formation of enol ether **39** proved to be more challenging than expected. Various Hg(II) salts, temperatures, and solvents were tried, and only degradation products were observed. Suspecting that the enone moiety may be detrimental to the reaction, we envisaged the formation of the spiro ether prior to the Claisen rearrangement.

Thus, **38** was treated with vinylmagnesium bromide to provide the alkylated adduct **40** in 74% yield (Scheme 10). Following an allylation reaction of the tertiary alcohol, the allyl ether **41** was subjected to a catalytic amount of Grubb's catalyst to give **42** in 94% yield.[19] Removal of the PMB group followed by the conversion of **43** to the corresponding enol ether afforded **44** in 71% yield.[20] Finally, the Claisen rearrangement was effected by treating **44** in xylene at 155 °C in the presence of Et_3N to provide the desired product **45** in 75% as an equal mixture of diastereomers. Despite this mixture, the Claisen rearrangement was proven to be an effective strategy for constructing the side chain portion of the molecule. Most importantly, this approach allows for the endocyclic double bond within the six-membered ring to be installed.

Conclusion

During the course of this study, the whole carbocycle framework was assembled in 18 chemical operations where six of the eight stereogenic centers of havellockate (**1**) have been installed in the proper relative configuration. This approach clearly highlights the efficiency and utility of the hydroxy-directed Diels−Alder (HDDA) reaction to quickly access the cis-fused hydrindane core and securing the correct stereochemistry at C6 and C7. A description of our studies to install the isopropenyl group on the chain with the correct stereochemistry using a modified approach and completion of havellockate (**1**) will be reported in due course.

Experimental Section

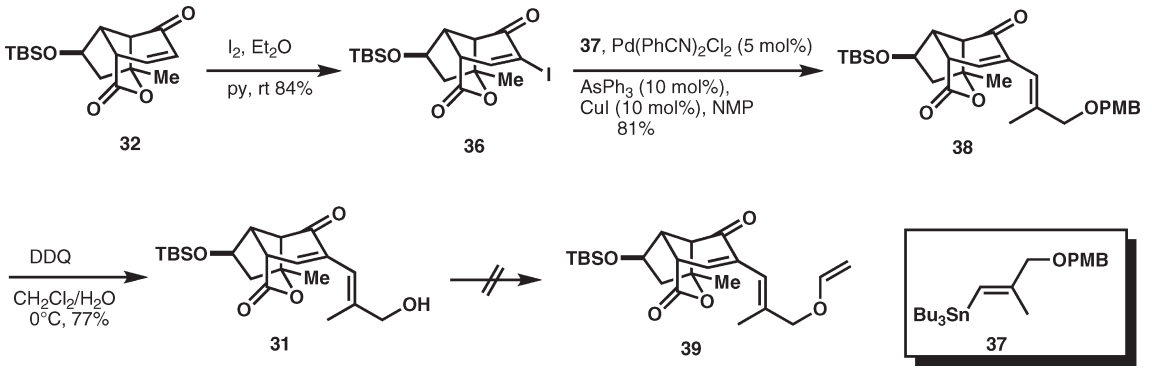
(±)-(*R*)-4-(*tert*-Butyldimethylsilanyloxy)-2-vinylcyclopent-2-enone (9). Triphenylarsine (1.21 g, 10 mol %, 3.96 mmol), Pd(PhCN)$_2$Cl$_2$ (760 mg, 5 mol %, 1.98 mmol), and CuI (755 mg, 10 mol %, 3.96 mmol) were weighed in the glovebox and placed into a

(18) We noticed that the yield of this elimination is highly dependent on the reaction scale. On a scale larger than 100 mg, the yield varies between 30 and 50%.

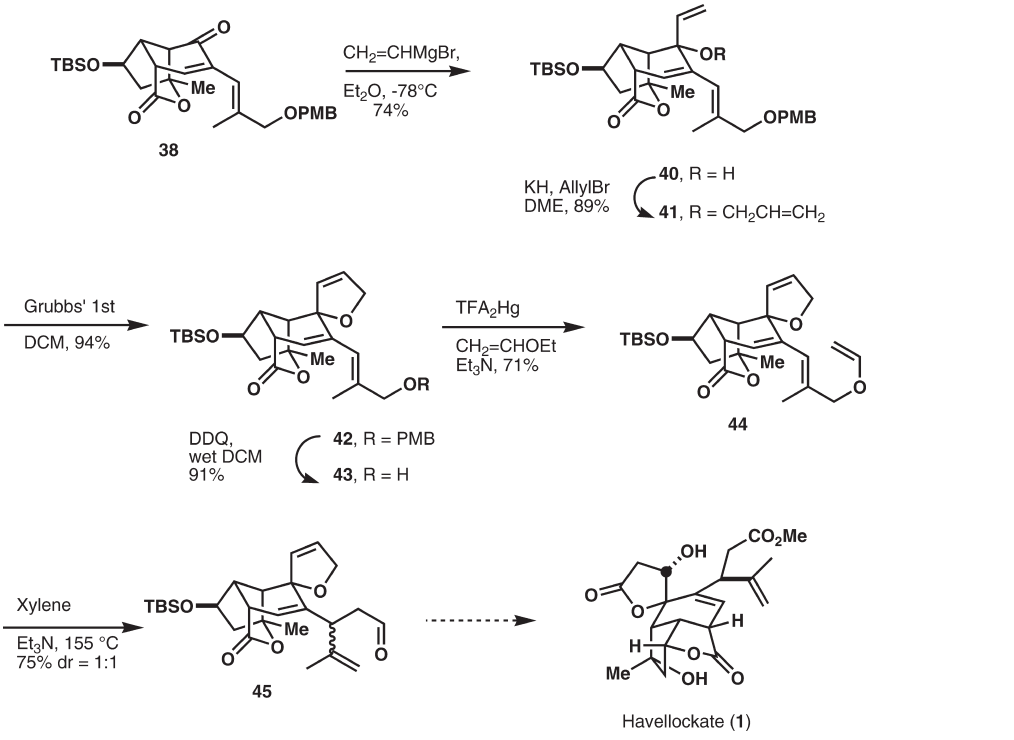
(19) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(20) Tulshian, D. B.; Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 2347.

SCHEME 9



SCHEME 10



flame-dried round-bottom flask. A solution of enone **8** (13.4 g, 39.6 mmol) in NMP (80 mL) was then added followed by tributylvinyltin (12.7 mL, 43.6 mmol). The reaction was stirred for 30 min before the contents of the flask were poured into H_2O (50 mL). The product was extracted with Et_2O (3 × 20 mL), and the combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (10:1 hexanes/EtOAc) provided **9** as a clear colorless oil (9.4 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (d, J = 2.6 Hz, 1H), 6.34 (dd, J = 17.8, 11.2 Hz, 1H), 6.11 (dd, J = 17.8, 1.5 Hz, 1H), 5.38 (dd, J = 11.2, 1.6 Hz, 1H), 4.91−4.87 (m, 1H), 2.78 (dd, J = 18.3, 6.1 Hz, 1H), 2.32 (dd, J = 18.3, 2.3 Hz, 1H), 0.88 (s, 9H), 0.09 (d, J = 3.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.4 (C), 157.1 (CH), 141.2 (C), 126.0 (CH), 121.1 (CH_2), 68.5 (CH), 46.4 (CH_2), 25.7 (3 × CH_3), 18.1 (C), −4.7 (2 × CH_3); IR (neat, cm^{-1}) 2957 (m), 2930 (m), 2893 (w), 2859 (m), 1723 (s); HRMS (EI) m/z (M^+) calcd for $C_{13}H_{22}O_2Si$ 238.1389, found 238.1379.

(±)-(**1*S*,4*R*)-4-(*tert*-Butyldimethylsilanyloxy)-1-methyl-2-vinylcyclopent-2-enol (4).** Ketone **9** (8.2 g, 34 mmol) was placed into a flame-dried round-bottom flask and diluted with THF (50 mL). After the mixture was cooled to −78 °C, MeLi (86.0 mL, 1.6 M in Et_2O, 138 mmol) was added dropwise, and the mixture was stirred for 2 h at −78 °C. The reaction was then quenched with water (75 mL) at 0 °C, and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (4:1 hexanes/Et_2O) provided **4** as a clear colorless oil (4.8 g, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (dd, J = 17.9, 11.3 Hz, 1H), 5.73−5.67 (m, 2H), 5.21 (dd, J = 16.3, 1.8 Hz, 1H), 4.64−4.59 (m, 1H), 2.45 (dd, J = 13.2, 6.7 Hz, 1H), 1.99 (s, 1H), 1.84 (dd, J = 13.3, 5.0 Hz, 1H), 1.36 (s, 3H), 0.87 (s, 9H), 0.06 (d, J = 0.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3 (C), 131.8 (CH), 129.5 (CH), 117.8 (CH_2), 80.8 (C), 72.9 (CH), 53.3 (CH_2), 26.1 (CH_3), 25.9 (3 × CH_3), 18.2 (C), −4.7 (2 × CH_3); IR (neat, cm^{-1}) 3409 (w), 2962 (s), 2935 (s), 2897 (w), 2859 (m); HRMS (EI) m/z (M^+−H_2O) calcd for $C_{14}H_{24}OSi$ 236.1597, found 236.1564.

(±)-(**1*S*,3*R*,3a*S*,4*S*)-3-(*tert*-Butyldimethylsilanyloxy)-1-hydroxy-1-methyl-2,3,3a,4,5,6-hexahydro-1*H*-indene-4-carbaldehyde (10).** A mixture of $MgBr_2 \cdot OEt_2$ (18.0 g, 69.6 mmol) in CH_2Cl_2 (100 mL) at room temperature under an atmosphere of argon was treated with 2,6-lutidine (13.5 mL, 116 mmol). After the mixture was stirred

for 20 min, a solution of diene **4** (5.9 g, 23 mmol) in CH_2Cl_2 (20 mL) was added. Following an additional 20 min, acrolein (7.75 mL, 116 mmol) was added and stirring continued for 14 h. The reaction was then quenched with H_2O (50 mL), and the product was extracted with CH_2Cl_2 (5 × 50 mL). The combined organic layers were washed with a saturated aqueous solution of brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by silica gel flash chromatography on silica gel basified with Et_3N (10:1 hexane/Et_2O) provided **10** as a colorless crystals (5.1 g, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (d, J = 5.2 Hz, 1H), 5.99 (dd, J = 6.6, 3.3 Hz, 1H), 4.36 (t, J = 3.6 Hz, 1H), 2.95 (s, 1H), 2.71−2.63 (m, 2H), 2.22−2.14 (m, 2H), 2.02−1.96 (m, 1H), 1.97 (dd, J = 14.0, 1.3 Hz, 1H), 1.90−1.81 (m, 1H), 1.82 (dd, J = 14.0, 3.5 Hz, 1H), 1.38 (s, 3H), 0.83 (s, 9H), 0.04 (d, J = 14.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6 (CH), 147.4 (C), 121.0 (CH), 77.0 (C), 74.6 (CH), 49.4 (CH_2), 48.9 (CH), 45.8 (CH), 26.4 (CH_2), 25.9 (CH_3), 25.8 (3 × CH_3), 21.9 (CH_2), 17.9 (C_4), −4.9 (CH_3), −5.4 (CH_3); IR ($CHCl_3$, cm^{-1}) 3481 (w), 2952 (m), 2931 (s), 2851 (m), 1713 (s); HRMS (EI) m/z ($M^+ - C_4H_9$) calcd for $C_{13}H_{21}O_3Si$ 253.1260, found 253.1278; mp = 68.6−69.0 °C.

(±)-(1*S*,3*R*,3a*S*,4*S*,7*S*,7a*S*)-3-(*tert*-Butyldimethylsilanyloxy)-4-hydroxymethyl-1-methyloctahydroindene-1,7-diol (14). To a solution of alkene **10** (1.691 mmol, 524.6 mg) in THF (16.9 mL) was added $BH_3 \cdot DMS$ (4 mmol, 0.4 mL) dropwise during which bubbles were produced in solution. The jelly-like solution was stirred at room temperature (21 °C) for 4 h after which the borane was oxidized with 3 N NaOH (1 mL) and 30% H_2O_2 (1 mL). *Caution*: on a large scale, the reaction is very vigorous! The resulting solution was refluxed overnight and the aqueous layer was extracted with EtOAc (3×). The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated in vacuo, and the product was purified by flash column chromatography (60% EtOAc in hexanes) to afford triol **14** as colorless crystals (455.1 mg, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.29 (t, J = 4.1 Hz, 1H), 4.22 (dt, J = 11.1, 4.7 Hz, 1H), 3.67−3.64 (m, 2H), 2.38 (bs, 2H), 2.14−2.09 (m, 1H), 2.01−1.79 (m, 4H), 1.71−1.50 (m, 3H), 1.35 (s, 3H), 1.32−1.21 (m, 2H), 0.87 (s, 9H), 0.05 (d, J = 3.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.1 (C), 74.5 (CH), 70.2 (CH), 65.3 (CH_2), 57.4 (CH), 52.3 (CH), 45.1 (CH), 40.2 (CH), 33.1 (CH_2), 32.2 (CH_3), 25.9 (3 × CH_3), 25.0 (CH_2), 17.7 (C), −3.9 (CH_3), −4.8 (CH_3); IR ($CHCl_3$, cm^{-1}) 3342 (m), 2961 (m), 2925 (s), 2861 (m); HRMS (EI) m/z (M^+-[$C_4H_9 + 2(H_2O)$]) calcd for $C_{13}H_{21}O_2Si$: 237.1309, found 237.1333. Mp = 163.1−163.8 °C.

(±)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyl-dimethyl-silanyloxy)-4-methyl-3-oxatricyclo-[5.4.0.0^{2,6}]undecane-2,9-dione (15). Molecular sieves (4 Å) (550 mg, 500 mg/mmol of alcohol) were flame-dried under vacuum in a round-bottom flask. After cooling to room temperature, the flask was filled with argon and a solution of triol **14** (456 mg, 1.10 mmol) in CH_2Cl_2 (25 mL) was added, followed by NMO (451 mg, 3.85 mmol) and TPAP (19 mg, 0.055 mmol). The dark green solution was stirred for 4 h at room temperature and was then filtered through a pad of silica gel, eluting with 5% MeOH in EtOAc. The organic solvent was removed *in vacuo* and the crude product was purified by silica gel flash chromatography (5:1 hexanes/Et_2O) to provide **15** as a white solid (264 mg, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (ddd, J = 9.2, 6.6, 2.8 Hz, 1H), 3.17 (s, 1H), 2.77−2.72 (m, 1H), 2.56 (dd, J = 16.3, 5.6 Hz, 1H), 2.43 (d, J = 4.8 Hz, 1H), 2.40−2.22 (m, 2H), 2.12 (dd, J = 14.7, 9.1 Hz, 1H), 2.00 (dd, J = 14.7, 2.7 Hz, 1H), 1.95−1.88 (m, 1H), 1.34 (s, 3H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 206.0 (C), 170.7 (C), 87.5 (C), 80.0 (CH), 57.5 (CH), 48.7 (CH_2), 47.4 (CH), 37.9 (CH_2), 37.5 (CH_2), 27.9 (CH_2), 25.8 (3 × CH_3), 22.0 (CH_3), 18.1 (C_4), −4.8 (CH_3), −5.1 (CH_3); IR ($CHCl_3$, cm^{-1}) 2960 (m), 2935 (m), 2858 (w), 1747 (s), 1708 (m); HRMS (EI) m/z ($M^+ - C_4H_9$) calcd for $C_{13}H_{19}O_4Si$ 267.1053, found 267.1048; mp = 104.8−105.4 °C.

Acetic Acid 6-(*tert*-Butyldimethylsilanyloxy)-4-methyl-2-oxo-9-vinyl-3-oxatricyclo[5.4.0.0^{4,8}]undec-9-yl Ester (16). To a solution of ketone **15** (32.8 mg, 0.0992 mmol) in THF (4.0 mL) at −78 °C was added vinylmagnesium bromide (0.25 mmol, 0.31 mL). The reaction mixture was stirred at −78 °C for 30 min. Acetic anhydride (0.30 mmol, 30 μL) and triethylamine (0.298 mmol, 41.5 μL) were added, and the yellow solution was warmed to room temperature. The reaction was quenched with saturated NH_4Cl (aq), the aqueous phase was extracted with CH_2Cl_2 (3×), and the combined organic phases were dried over anhydrous $MgSO_4$. The organic solvent was removed in vacuo, and the product was purified by flash column chromatography (20% EtOAc in hexanes) to afford acetate **16** as colorless crystals (16.6 mg, 42%) and alcohol **16a** as colorless crystals (9.0 mg, 26%). **16**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.18 (dd, J = 17.6, 10.9 Hz, 1H), 5.33 (d, J = 17.3 Hz, 1H), 5.29 (d, J = 10.7 Hz, 1H), 4.33 (ddd, J = 9.2, 6.6, 2.4 Hz, 1H), 4.01−4.06 (m, 1H), 2.85 (d, J = 2.8 Hz, 1H), 2.54 (d, J = 4.0 Hz, 1H), 2.38−2.33 (m, 1H), 2.30−2.25 (m, 1H), 2.19−2.07 (m, 1H), 2.03 (d, J = 6.4 Hz, 1H), 1.99−1.96 (m, 3H), 1.85 (dd, J = 14.9, 2.2 Hz, 1H), 1.68−1.58 (m, 1H), 1.47 (s, 3H), 0.84 (s, 9H), −2.6 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6 (C), 169.9 (C), 140.3 (CH), 116.3 (CH_2), 88.3 (C), 82.0 (C), 69.3 (CH), 51.0 (CH_2), 46.9 (CH), 45.5 (CH), 37.8 (CH), 31.1 (CH_2), 26.8 (CH), 25.7 (3 × CH_3), 22.4 (CH_3), 22.2 (CH_3), 17.9 (C), −4.8 (CH_3), −5.1 (CH_3); IR ($CHCl_3$, cm^{-1}) 2952 (m), 2929 (s), 2891 (m), 2853 (m), 1739 (s); HRMS (EI) m/z (M^+) calcd for $C_{21}H_{34}O_5Si$ 394.2176, found 394.2208; mp = 141.5−142.5 °C. **16a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.13 (dd, J = 17.3, 10.8 Hz, 1H), 5.33 (d, J = 17.4 Hz, 1H), 5.15 (d, J = 10.8 Hz, 1H), 4.33 (ddd, J = 9.2, 6.5, 2.3 Hz, 1H), 2.89 (d, J = 3.0 Hz, 1H), 2.35 (ddd, J = 7.1, 4.0, 4.0 Hz, 1H), 2.15−2.01 (m, 2H), 1.94 (dd, J = 13.8, 4.8 Hz, 1H), 1.88 (d, J = 2.2 Hz, 1H), 1.83−1.62 (m, 4H), 1.58 (s, 3H), 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (C), 143.9 (CH), 113.4 (CH_2), 89.0 (C), 73.9 (C), 69.7 (CH), 51.1 (CH_2), 50.3 (CH), 45.6 (CH), 37.9 (CH), 32.9 (CH_2), 27.5 (CH_2), 25.7 (3 × CH_3), 23.9 (CH_3), 18.0 (C), −4.8 (CH_3), −5.1 (CH_3); IR ($CHCl_3$, cm^{-1}) 3431 (w), 2952 (s), 2932 (s), 2888 (m), 2862 (m), 1737 (s), 1720 (s); HRMS (EI) m/z ($M^+ - C_4H_9$) calcd for $C_{15}H_{23}O_4Si$ 295.1366, found 295.1396; mp = 133.2−135.5 °C.

Acetic Acid 6-(*tert*-Butyldimethylsilanyloxy)-9-formyl-4-methyl-2-oxo-3-oxatricyclo[5.4.0.0^{4,8}]undec-9-yl Ester (17). A solution of alkene **16** (0.0421 mmol, 16.6 mg) in CH_2Cl_2 (5.0 mL) was degassed with O_2 for 10 min at room temperature. The solution was cooled to −78 °C, and ozone was bubbled into the solution. After 5 min, dimethyl sulfide (0.21 mmol, 15 μL) was added to the blue solution, and the reaction mixture was warmed to room temperature. The solution was concentrated, and the product was purified by flash column chromatography (30% EtOAc in hexanes) to yield aldehyde **17** as colorless crystals (12.2 mg, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.27 (s, 1H), 4.39 (ddd, J = 9.3, 6.6, 2.5 Hz, 1H), 2.92−2.83 (m, 2H), 2.45 (d, J = 4.3 Hz, 1H), 2.15−1.95 (m, 6H), 1.86 (dd, J = 15.1, 2.4 Hz, 1H), 1.67−1.58 (m, 2H), 1.45 (s, 3H), 0.85 (s, 9H), 0.00 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7 (CH), 173.0 (C), 170.8 (C), 88.6 (C), 83.9 (C), 69.5 (CH), 50.2 (CH_2), 44.9 (CH), 41.8 (CH), 37.2 (CH), 25.7 (3 × CH_3), 25.6 (CH_2), 25.2 (CH_2), 22.7 (CH_3), 20.8 (CH_3), 17.9 (C), −4.9 (CH_3), −5.1 (CH_3); IR ($CHCl_3$, cm^{-1}) 2955 (m), 2932 (m), 2888 (w), 2857 (m), 2721 (w), 1740 (s); HRMS (EI) m/z ($M^+ - [C_6H_{15}Si + H_2O + OAc]$) calcd for $C_{12}H_{12}O_3$ 193.0865, found 193.0880; mp = 113.7−116.1 °C.

Tetracyclic Core (20). To a solution of NaH (0.031 mmol, 1.2 mg) in THF (1.0 mL) at 0 °C was canulated the aldehyde **17** (0.021 mmol, 8.2 mg) in THF (2.0 mL). The solution was gradually warmed to room temperature and was quenched with H_2O. The aqueous layer was extracted with EtOAc (3×), the combined organic layers were dried over anhydrous $MgSO_4$,

and the solvent was evaporated in vacuo. The crude product was diluted in THF (2.0 mL), and TBAF (0.030 mmol, 30 μL) was added to the solution. After 1 h, the reaction mixture was concentrated in vacuo, and the product was purified by flash column chromatography (60% EtOAc in hexanes) using a Pasteur pipet to afford the tetracyclic core **20** as a colorless oil (1.3 mg, 24%) and tricyclic core **21** as a colorless oil (2.3 mg, 46%). **20**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 5.7 Hz, 1H), 6.90 (d, J = 5.7 Hz, 1H), 5.00 (dd, J = 6.6, 4.9 Hz, 1H), 3.25 (dt, J = 10.5, 6.6 Hz, 1H), 2.90−2.84 (m, 1H), 2.68 (dt, J = 14.2, 4.6 Hz, 1H), 2.49−2.43 (m, 1H), 2.32 (d, J = 10.1 Hz, 1H), 1.94−1.76 (m, 3H), 1.68 (s, 1H), 1.50 (s, 3H), 1.44−1.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9 (C), 171.1 (C), 159.1 (CH), 119.9 (CH), 89.4 (C), 81.9 (C), 81.6 (C), 49.9 (CH_2), 47.7 (CH), 41.6 (CH), 37.2 (CH), 29.6 (CH_3), 28.8 (CH_2), 21.4 (CH_2); IR (neat, cm^{-1}) 3443 (w), 2964 (w), 2930 (w), 2854 (w), 1750 (s); HRMS (EI) m/z ($M^+ - H_2O$) calcd for $C_{14}H_{14}O_4$ 246.0892, found 246.0892. **21**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.51 (s, 1H), 4.95 (t, J = 5.9 Hz, 1H), 3.49 (bs, 1H), 3.22 (dt, J = 10.7, 6.7 Hz, 1H), 2.87−2.80 (m, 1H), 2.30 (d, J = 3.4 Hz, 1H), 2.26 (s, 1H), 2.23−2.15 (m, 1H), 1.96 (dd, J = 15.3, 5.2 Hz, 1H), 1.91−1.84 (m, 1H), 1.81−1.59 (m, 2H), 1.48 (s, 3H), 1.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8 (CH), 178.5 (C), 82.7 (C), 82.5 (CH), 78.2 (C), 47.8 (CH_2), 47.5 (CH_2), 41.3 (CH), 37.8 (CH), 30.0 (CH_3), 28.7 (CH_2), 18.7 (CH_2); IR (neat, cm^{-1}) 3443 (m), 2969 (w), 2932 (m), 2869 (w), 1733 (s); HRMS (EI) m/z ($M^+ - [H_2O + CHO]$) calcd for $C_{11}H_{12}O_3$ 193.0865, found 193.0857.

(±)-(1*S*,4*S*,6*R*,7*R*,8*S*,10*S*)-10-Bromo-6-(*tert*-butyldimethylsilanyloxy)-4-methyl-3-oxatricyclo[5.4.0.0^{2,6}]undecane-2,9-dione (34). Copper bromide (28 mg, 0.12 mmol) was added to a solution of ketone **15** (20 mg, 0.062 mmol) in THF (1.0 mL) and stirred overnight at room temperature. H_2O (5 mL) was added, and the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (10:1 hexanes/Et_2O) provided **34** as a white solid (19 mg, 87%): ^{1}H NMR (500 MHz, C_6D_6) δ 4.34 (dd, J = 13.0, 7.1 Hz, 1H), 3.63 (ddd, J = 9.5, 6.5, 2.2 Hz, 1H), 2.88−2.87 (m, 1H), 2.63 (ddd, J = 13.2, 7.2, 4.0 Hz, 1H), 2.04−2.03 (m, 1H), 1.81−1.72 (m, 2H), 1.57 (dd, J = 14.9, 2.4 Hz, 1H), 1.20 (dd, J = 14.8, 9.6 Hz, 1H), 0.93 (s, 3H), 0.90 (s, 9H), −0.11 (s, 3H), −0.12 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 198.0 (C), 169.7 (C), 87.9 (C), 71.0 (CH), 58.5 (CH), 51.1 (CH), 48.9 (CH_2), 47.8 (CH), 40.7 (CH), 40.1 (CH_2), 26.1 (3 × CH_3), 22.1 (CH_3), 18.5 (C), −4.5 (CH_3), −4.8 (CH_3); IR (neat, cm^{-1}) 2930 (s), 2857 (s), 1749 (s), 1721 (s); HRMS (EI) m/z ($M^+ - C_4H_9$) calcd for $C_{13}H_{18}O_4BrSi$ 345.0158, found 345.0203; mp = 151.8−152.9 °C.

(±)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyldimethylsilanyloxy)-4-methyl-3-oxatricyclo[5.4.0.0^{2,6}]undec-10-ene-2,9-dione (32). A mixture of lithium carbonate (18 mg, 0.25 mmol) and ketone **34** (20 mg, 0.050 mmol) was refluxed in NMP (2 mL) for 8 h. After the mixture was cooled to room temperature, a saturated aqueous solution of NH_4Cl (5 mL) was added, and the organic product was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (10:1 hexanes/Et_2O) provided **32** as a clear colorless oil (10 mg, 63%) and **35** as a white solid (3 mg, 22%). **32**: ^{1}H NMR (500 MHz, C_6D_6) δ 6.51 (dd, J = 9.5, 7.7 Hz, 1H), 5.87 (d, J = 9.5 Hz, 1H), 3.71 (ddd, J = 9.1, 6.4, 2.3 Hz, 1H), 3.37 (ddd, J = 7.6, 3.6, 1.4 Hz, 1H), 2.33−2.30 (m, 1H), 1.84 (d, J = 5.0 Hz, 1H), 1.71 (dd, J = 15.1, 2.4 Hz, 1H), 1.36 (dd, J = 15.0, 9.6 Hz, 1H), 1.24 (s, 3H), 0.95 (s, 9H), −0.07 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 194.4 (C), 167.3 (C), 147.8 (CH), 132.4 (CH), 88.0 (C), 70.5 (CH), 54.2 (CH), 49.6 (CH_2), 48.1 (CH), 41.0 (CH), 26.2 (3 × CH_3), 22.4 (CH_3), 18.5 (C), −4.5 (CH_3), −4.8 (CH_3); IR (neat, cm^{-1}) 2930 (s), 2857 (s), 1746 (s), 1677 (s); HRMS (EI) m/z ($M^+ - C_4H_9$) calcd for $C_{13}H_{17}O_4Si$: 265.0897, found: 265.0895. **35**: ^{1}H NMR (500 MHz, C_6D_6) δ 6.45 (d, J = 10.1 Hz, 1H), 5.77 (dd, J = 10.1, 0.8 Hz, 1H), 5.04 (s, 1H), 4.34 (dd, J = 4.1, 4.1 Hz, 1H), 3.07 (ddd, J = 6.4, 4.8, 1.3 Hz, 1H), 1.84−1.80 (m, 2H), 1.00 (s, 3H), 0.75−0.72 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 193.9 (C), 147.8 (CH), 130.1 (CH), 102.1 (CH), 83.1 (C), 79.3 (CH), 65.7 (C), 60.9 (CH), 55.6 (CH), 45.6 (CH_2), 20.4 (CH_3); IR (neat, cm^{-1}) 2981 (m), 2935 (m), 1676 (s); HRMS (EI) m/z ($M^+ - CHO$) calcd for $C_{10}H_{10}O_2Br$ 240.9680, found 240.9875; mp = 129.8−131.8 °C).

(±)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyldimethylsilanyloxy)-10-iodo-4-methyl-3-oxatricyclo[5.4.0.0^{2,6}]undec-10-ene-2,9-dione (36). Enone **32** (119 mg, 0.369 mmol) was dissolved in a 1:1 solution of Et_2O/pyridine (5 mL) at room temperature. Iodine (73.0 mg, 0.369 mmol) was then added, and the dark red solution was stirred for 1 h. The contents of the flask were then poured into a 1 N solution of HCl (5 mL), and the product was extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with a saturated aqueous solution of Na_2SO_3, dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (20:1 hexanes/Et_2O) provided **36** as a white solid (105 mg, 84%): ^{1}H NMR (500 MHz, C_6D_6) δ 7.25 (d, J = 8.0 Hz, 1H), 3.62 (ddd, J = 9.1, 6.4, 2.3 Hz, 1H), 3.18 (ddd, J = 8.0, 3.4, 1.7 Hz, 1H), 2.17−2.14 (m, 1H), 1.92−1.91 (m, 1H), 1.61 (dd, J = 15.1, 1.8 Hz, 1H), 1.27 (dd, J = 14.8, 9.6 Hz, 1H), 1.84 (s, 3H), 0.93 (s, 9H), −0.14 (s, 3H), −0.11 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 188.2 (C), 165.8 (C), 155.7 (CH), 106.8 (C), 88.1 (C), 70.0 (CH), 53.1 (CH), 49.3 (CH_2), 48.0 (CH), 44.7 (CH), 26.1 (3 × CH_3), 22.2 (CH_3), 18.5 (C), −4.5 (CH_3), −4.8 (CH_3); IR (neat, cm^{-1}) 2950 (s), 2929 (s), 2866 (s), 2856 (s), 1732 (s); HRMS (EI) m/z ($M^+ - C_4H_9I$) calcd for $C_{13}H_{16}O_4Si$ 264.0818, found 264.0779; mp = 179.1−179.5 °C.

((*E*)-3-(4-Methoxybenzyloxy)-2-methylprop-1-enyl)tributylstannane (37). Sodium iodide (1 mg, 0.007 mmol) was flame-dried under vacuum in a round-bottom flask. After the mixture was cooled to room temperature, the flask was fitted with a balloon of argon, and DMF (1 mL) was added followed by NaH (28 mg, 0.69 mmol). The mixture was cooled to 0 °C, and then (*E*)-3-(tributylstannyl)-2-methylpropen-1-ol[21] (50 mg, 0.14 mmol) was cannulated into the flask as a solution in DMF (0.5 mL). After the mixture was stirred for 5 min, PMBCl (87 mg, 0.55 mmol) was added. The contents of the flask were warmed to room temperature and stirred overnight. The reaction was quenched with a saturated aqueous solution of NH_4Cl and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (10:1 hexanes/Et_2O) provided **37** as a clear colorless oil (63 mg, 94%): ^{1}H NMR (300 MHz, C_6D_6) δ 7.30−7.27 (m, 2H), 6.82−6.79 (m, 2H), 6.12 (m, 1H), 4.41 (s, 2H), 3.96 (s, 2H), 3.29 (s, 3H), 1.89−1.85 (m, 3H), 1.68−1.55 (m, 6H), 1.44−1.33 (m, 6H), 1.06−1.01 (m, 5H), 0.96−0.91 (m, 10H); ^{13}C NMR (75 MHz, C_6D_6) δ 160.5 (C), 152.0 (C), 131.6 (C), 129.8 (CH), 124.3 (CH), 114.4 (CH), 77.0 (CH_2), 72.1 (CH_2), 55.1 (CH_3), 30.1 (CH_2), 28.1 (CH_2), 22.3 (CH_3), 14.3 (CH_3), 10.8 (CH_2); IR (neat, cm^{-1}) 2955 (s), 2925 (s), 2851 (s); HRMS (EI) m/z ($M^+ - C_4H_9$) calcd for $C_{20}H_{33}O_2Sn$ 425.1503, found 425.1512.

(±)-(1*S*,4*S*,6*R*,7*R*,8*S*)-6-(*tert*-Butyldimethylsilanyloxy)-10-[(1*E*)-3-(4-methoxybenzyloxy)-2-methylprop-1-en-1-yl]-4-methyl-3-oxatricyclo[5.4.0.0^{2,6}]undec-10-ene-2,9-dione (38). Triphenylarsine (9 mg, 10 mol %, 0.03 mmol), $Pd(PhCN)_2Cl_2$ (5 mg, 5 mol %, 0.01 mmol), and CuI (5 mg, 10 mol %, 0.03 mmol) were weighed in the glovebox and placed into a flame-dried round-bottom flask. After the flask was equipped with a balloon of argon, a solution of enone **36** (96 mg, 0.28 mmol) in NMP

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(1.5 mL) was added. Vinylstannane **37** (136 mg, 0.140 mmol) was then cannulated into the mixture using 1 mL of NMP, and the reaction was stirred for 30 min. The contents of the flask were then poured into H_2O (5 mL), and the product was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (10:1 hexanes/EtOAc) provided **38** as a white solid (117 mg, 81%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.28 (m, 2H), 7.12 (dd, J = 8.0 Hz, 1H), 6.92−6.87 (m, 2H), 6.26 (m, 1H), 4.51 (ddd, J = 8.9, 6.6, 2.5 Hz, 1H), 4.43 (s, 2H), 3.98 (s, 2H), 3.82 (s, 3H), 3.65 (ddd, J = 7.8, 3.3, 1.7 Hz, 1H), 3.18 (ddd, J = 6.0, 5.1, 3.5 Hz, 1H), 2.56 (d, J = 5.1 Hz, 1H), 2.24 (dd, J = 15.0, 9.4 Hz, 1H), 2.12 (dd, J = 15.5, 2.1 Hz, 1H), 1.77 (d, J = 1.3 Hz, 3H), 1.47 (s, 3H), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3 (C), 168.8 (C), 159.4 (C), 143.9 (CH), 139.7 (C), 139.0 (C), 130.5 (C), 129.7 (CH), 118.9 (CH), 114.0 (CH), 88.5 (C), 75.6 (CH_2), 71.8 (CH_2), 70.0 (CH), 55.5 (CH_3), 54.2 (CH), 49.8 (CH_2), 47.6 (CH), 40.6 (CH), 25.9 (3 × CH_3), 22.1 (CH_3), 18.2 (C), 16.2 (CH_3), −4.6 (CH_3), −4.9 (CH_3); IR (neat, cm^{-1}) 2925 (s), 2854 (s), 1746 (s), 1698 (s); HRMS (EI) m/z (M^+) calcd for $C_{29}H_{40}O_6Si$ 512.2594, found 512.2568; mp = 60.8−61.9 °C.

(±)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyldimethylsilanyloxy)-9-hydroxy-10-[(1*E*)-3-(4-methoxybenzyloxy)-2-methylprop-1-en-1-yl]-4-methyl-9-vinyl-3-oxatricyclo[5.4.0.0^{2,6}]undec-10-en-2-one (40). Vinylmagnesium bromide (130 μL, 0.86 M, 0.111 mmol) was added to a solution of **38** (19 mg, 0.037 mmol) in Et_2O (0.5 mL) at −78 °C and stirred for 1 h. The reaction was quenched with an aqueous solution of NH_4Cl, and the product was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (5:2 hexanes/Et_2O) provided **40** as a clear colorless oil (15 mg, 74%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.25 (m, 2H), 6.90−6.88 (m, 2H), 6.04 (d, J = 7.2 Hz, 1H), 5.95 (dd, J_{BX} = 17.1, J_{AX} = 10.5 Hz, 1H), 5.88−5.87 (m, 1H), 5.26 (dd, J_{BX} = 17.2, J_{AB} = 0.76 Hz, 1H), 5.15 (dd, J_{AX} = 10.5, J_{AB} = 0.92 Hz, 1H), 4.40 (s, 2H), 4.37 (ddd, J = 9.5, 6.1, 2.9 Hz, 1H), 3.92 (s, 2H), 3.82 (s, 3H), 3.42−3.40 (m, 1H), 2.70 (ddd, J = 6.5, 3.9, 3.9 Hz, 1H), 2.19 (dd, J = 15.1, 9.8, 1H), 1.95−1.92 (m, 2H), 1.77−1.76 (m, 3H), 1.63 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6 (C), 159.4 (C), 143.9 (CH), 141.4 (C), 140.7 (C), 130.5 (C), 129.6 (CH), 127.2 (CH), 121.7 (CH), 114.0 (CH), 113.2 (CH_2), 89.1 (C), 76.3 (C), 75.4 (CH_2), 71.9 (CH_2), 69.6 (CH), 55.5 (CH_3), 51.0 (CH_2), 50.2 (CH), 45.2 (CH), 39.7 (CH), 25.9 (3 × CH_3), 24.6 (CH_3), 18.2 (C), 16.1 (CH_3), −4.6 (CH_3), −4.8 (CH_3); IR (neat, cm^{-1}) 3441 (brs), 2926 (s), 2853 (s), 1738 (s); LRMS (EI) m/z (M^+) 540.3.

(±)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-9-(Allyloxy)-6-(*tert*-butyldimethylsilanyloxy)-10-[(1*E*)-3-(4-methoxybenzyloxy)-2-methylprop-1-en-1-yl]-4-methyl-9-vinyl-3-oxatricyclo[5.4.0.0^{2,6}]undec-10-en-2-one (41). A flame-dried round-bottom flask was charged with KH (211 mg, 35% in mineral oil, 1.85 mmol) and washed with hexanes (3 × 2 mL). Freshly distilled DME (2 mL) was then added, and the flask was cooled to 0 °C. Alcohol **40** (40 mg, 0.074 mmol) was cannulated into the flask, and the contents were stirred for 20 min before freshly distilled allyl bromide (224 μL, 1.85 mmol) was added. The mixture was stirred at 0 °C for 30 min before being quenched with an aqueous solution of NH_4Cl (5 mL). The product was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (10:1 hexanes/Et_2O) provided **41** as a clear colorless oil (38 mg, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.23 (m, 2H), 6.89−6.86 (m, 2H), 6.10 (d, J = 7.4 Hz, 1H), 6.11−6.10 (m, 1H), 5.95 (dd, J = 17.4, 10.8 Hz, 1H), 5.84 (dddd, J = 17.2, 9.7, 4.8, 4.8, 1H), 5.27−5.20 (m, 3H), 5.09 (dq, J = 10.6, 1.6 Hz, 1H), 4.38 (s, 2H), 4.33 (ddd, J = 9.1, 6.2, 2.5 Hz, 1H), 4.11 (dddd, J = 13.2, 4.9, 1.6, 1.6 Hz, 1H), 4.03 (dddd, J = 13.3, 4.6, 1.8, 1.8 Hz, 1H), 3.91 (m, 2H), 3.81 (s, 3H), 3.41−3.38 (m, 1H), 2.62 (ddd, J = 6.4, 3.8, 3.8 Hz, 1H), 2.19 (dd, J = 14.8, 9.6 Hz, 1H), 1.98−1.94 (m, 2H), 1.80−1.79 (m, 3H), 1.60 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2 (C), 159.4 (C), 142.1 (CH), 140.1 (C), 137.2 (C), 135.7 (CH), 130.6 (C), 129.5 (CH), 129.1 (CH), 124.9 (CH), 115.6 (CH_2), 115.5 (CH_2), 114.0 (CH), 88.6 (C_4), 81.6 (C), 75.8 (CH_2) 71.6 (CH_2), 69.3 (CH), 66.4 (CH_2), 55.5 (CH_3), 51.7 (CH_2), 49.8 (CH_3), 45.6 (CH), 39.7 (CH), 25.9 (3 × CH_3), 24.1 (CH), 18.2 (C), 16.2 (CH_3), −4.6 (CH_3), −4.8 (CH_3); IR (neat, cm^{-1}) 2954 (m), 2931 (s), 2855 (s), 1739 (s); HRMS (EI) m/z ($M^+ - C_4H_9$) calcd for $C_{30}H_{39}O_6Si$ 523.2516, found 523.2540.

(±)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyldimethylsilanyloxy)-10-[(1*E*)-3-(4-methoxybenzyloxy)-2-methylprop-1-en-1-yl]-4-methyl-9-spiro[3,4-dihydrofuran]-3-oxatricyclo[5.4.0.0^{2,6}]undec-10-en-2-one (42). Alkene **41** (55 mg, 0.095 mmol) was dissolved in CH_2Cl_2 (1.9 mL, 0.05 M) and degassed under a steady stream of argon for 20 min. Meanwhile, Grubbs' first-generation catalyst (8 mg, 0.009 mmol) was placed in a Schlenk tube, evacuated, and filled with argon. Once the degassing was complete, the alkene was cannulated in the Schlenk tube, and the contents were placed into a 40 °C oil bath for 30 min. After the mixture was cooled to room temperature, the solution was concentrated, and the crude product was purified by flash chromatography on silica gel (10:1 hexanes/Et_2O) to provide **42** as a clear colorless oil (47 mg, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25−7.24 (m, 2H), 6.89−6.87 (m, 2H), 5.97−5.94 (m, 2H), 5.85 (m, 1H), 5.72 (ddd, J = 5.3, 2.3, 2.3 Hz, 1H), 4.70 (m, 2H), 4.39−4.35 (m, 3H), 3.91−3.90 (m, 2H), 3.81 (s, 3H), 3.39−3.37 (m, 1H), 2.73 (ddd, J = 6.1, 4.1, 4.1 Hz, 1H), 2.13 (dd, J = 14.9, 9.5 Hz, 1H), 1.94 (dd, J = 15.1, 2.5 Hz, 1H), 1.87 (d, J = 4.3 Hz, 1H), 1.76−1.75 (m, 3H), 1.61 (s, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4 (C), 159.3 (C), 141.5 (C), 137.6 (C), 134.0 (CH), 130.8 (C), 129.5 (CH), 126.34 (CH), 126.28 (CH), 123.0 (CH), 114.0 (CH), 91.4 (C), 88.8 (C), 76.2 (CH_2), 75.9 (CH_2), 71.3 (CH_2), 70.0 (CH), 55.5 (CH_3), 51.0 (CH), 50.7 (CH_2), 46.6 (CH), 39.4 (CH), 25.9 (3 × CH_3), 23.8 (CH_3), 18.2 (C), 16.1 (CH_3), −4.6 (CH_3), −4.8 (CH_3); IR (neat, cm^{-1}) 2937 (s), 2857 (s), 1738 (s); HRMS (EI) m/z ($M^+ - C_4H_9$) calcd for $C_{28}H_{35}O_6Si$ 495.2203, found 495.2202.

(±)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyldimethylsilanyloxy)-10-[(1*E*)-3-hydroxy-2-methylprop-1-en-1-yl]-4-methyl-9-spiro[3,4-dihydrofuran]-3-oxatricyclo[5.4.0.0^{2,6}]undec-10-en-2-one (43). 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (10 mg, 0.045 mmol) was added to a biphasic solution of **42** (25 mg, 0.045 mmol) in CH_2Cl_2 (2 mL) and H_2O (200 μL) at 0 °C. The reaction was stirred for 1 h at 0 °C before being quenched with a saturated aqueous solution of Na_2SO_3 (3 mL). The product was extracted with CH_2Cl_2 (3 × 10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (5:1 hexanes/Et_2O) provided **43** as a clear colorless oil (17.5 mg, 91%): ^{1}H NMR (500 MHz, C_6D_6) δ 5.95−5.93 (m, 2H), 5.43−5.42 (m, 1H), 5.38−5.36 (m, 1H), 4.52−4.49 (m, 1H), 4.39−4.36 (m, 1H), 3.89 (ddd, J = 12.1, 6.2, 2.7 Hz, 1H), 3.72−3.71 (m, 2H), 3.53−3.51 (m, 1H), 2.39−2.37 (m, 1H), 1.83 (dd, J = 14.8, 2.6 Hz, 1H), 1.61−1.55 (m, 4H), 1.55 (s, 3H), 1.41−1.40 (m, 1H), 1.02 (s, 9H), 0.79−0.77 (m, 1H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.2 (C), 142.2 (C), 140.7 (C), 134.3 (CH), 126.6 (CH), 126.5 (CH), 120.7 (CH), 92.0 (C), 88.2 (C), 76.4 (CH_2), 70.7 (CH), 68.5 (CH_2), 51.1 (CH), 51.0 (CH_2), 46.9 (CH), 40.4 (CH), 26.3 (3 × CH_3), 24.3 (CH_3), 18.6 (C), 15.9 (CH_3), −4.3 (CH_3), −4.6 (CH_3); IR (neat, cm^{-1}) 3422 (brs), 2929 (s), 2985 (s), 1737 (s), 1716 (m); HRMS (EI) m/z ($M^+ - C_4H_9$) calcd for $C_{20}H_{27}O_5Si$ 375.1628, found 375.1607.

(±)-(1*S*,4*S*,6*R*,7*R*,8*S*,9*S*)-6-(*tert*-Butyldimethylsilanyloxy)-10-[(1*E*)-2-methyl-3-(vinyloxy)prop-1-en-1-yl]-4-methyl-9-spiro[3,4-dihydrofuran]-3-oxatricyclo[5.4.0.0^{2,6}]undec-10-en-2-one (44). Mercury trifluoroacetate (2 mg, 0.07 mmol) was added to a solution

of **43** (30 mg, 0.069 mmol), Et_3N (5 drops), and freshly distilled ethyl vinyl ether (3 mL) in a Schlenk tube. The contents were placed in a 40 °C oil bath and stirred for 24 h. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL), and the product was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification by flash chromatography on silica gel (20:1 hexanes/Et_2O) provided **44** as a clear colorless oil (23 mg, 71%): ^{1}H NMR (500 MHz, C_6D_6) δ 6.37 (dd, J_{BX} = 14.2, J_{AX} = 6.7, 1H), 5.96 (m, 1H), 5.91 (d, J = 7.0 Hz, 1H), 5.42−5.41 (m, 1H), 5.33 (dt, J = 4.9, 2.3 Hz, 1H), 4.49 (dt, J = 13.2, 1.8 Hz, 1H), 4.36 (dt, J = 13.2, 1.9 Hz, 1H), 4.22 (dd, J_{BX} = 14.3, J_{AB} = 1.8 Hz, 1H), 3.96 (dd, J_{AX} = 6.7, J_{AB} = 1.8 Hz, 1H), 3.89 (s, 3H), 3.50−3.48 (m, 1H), 2.35 (ddd, J = 6.2, 3,9, 3,9 Hz, 1H), 1.82 (dd, J = 14.8, 2.6 Hz, 1H), 1.62−1.61 (m, 3H), 1.57 (dd, J = 14.7, 9.7 Hz, 1H), 1.54 (s, 3H), 1.39 (d, J = 4.0 Hz, 1H), 1.01 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 170.0 (C), 152.3 (CH), 141.8 (C), 136.6 (C), 134.2 (CH), 127.0 (CH), 126.5 (CH), 123.5 (CH), 91.9 (C), 88.1 (C), 87.5 (CH_2), 76.3 (CH_2), 74.0 (CH_2), 70.6 (CH), 51.1 (CH), 51.0 (CH_2), 46.9 (CH), 40.4 (CH), 26.3 (3 × CH_3), 24.3 (CH_3), 18.6 (C), 15.9 (CH_3), −4.3 (CH_3), −4.6 (CH_3); FTIR (neat, cm^{-1}) 2960 (s), 2929 (s), 2854 (s), 1739 (s), 1633 (m); HRMS (EI) m/z ($M^+ - C_2H_3O$) calcd for $C_{24}H_{35}O_4Si$ 415.2305, found 415.2305.

(±)-(**1*S*,4*S*,6*R*,7*R*,8*S*,9*S***)-6-(***tert***-Butyldimethylsilanyloxy)-10-[(**2-methyl-1-(2-oxoethyl)prop-2-en-1-yl**]-4-methyl-9-spiro[3,4-dihydrofuran]-3-oxatricyclo[5.4.0.0^{2,6}]undec-10-en-2-one (45).** Triethylamine (1 drop) was added to a solution of **44** (5 mg, 0.01 mmol) in xylene (0.5 mL). The contents of the Schlenk tube were degassed under a steady flow of argon for 20 min and then placed in a 155 °C wax bath for 24 h. The crude product was purified directly by flash chromatography on silica gel (100% hexanes then 10:1 hexanes/Et_2O) provided **45** as a clear colorless oil (75%, 3.7 mg, dr = 1:1, inseparable mixture). *Characterized as a mixture of diastereomers:* ^{1}H NMR (500 MHz, C_6D_6) δ 9.41−9.40 and 9.29−9.28 (m, 1H), 5.87 and 6.57 (d, J = 6.9 and J = 6.9, 1H), 5.41−5.40 and 5.37−5.36 (m, 1H), 5.32−5.31 and 5.22−5.20 (m, 1H), 4.80 and 4.71 (m, 1H), 4.66 and 4.50 (m, 1H), 4.43−4.42 and 4.41−4.40 (m, 1H), 4.31−4.25 (m, 2H), 3.85−3.80 (m, 2H), 3.41−3.36 (m, 2H), 3.13−3.07 (m, 2H), 2.53 (dd, J = 17.4, 3.9 Hz, 1H), 2.34 (ddd, J = 17.3, 10.2, 2.1 Hz, 1H), 2.27−2.24 (m, 2H), 2.18−2.16 (m, 2H), 1.80−1.75 (m, 2H), 1.65 and 1.52 (s, 3H), 1.55−1.49 (m, 2H), 1.48 and 1.46 (s, 3H), 1.29−1.28 (m, 2H), 1.00 (s, 18H), 0.01 and 0.00 (s, 3H), −0.01 and −0.02 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.5 and 200.2 (CH), 169.9 and 169.5 (C), 148.2 and 145.8 (C), 145.52 and 145.46 (C), 134.3 and 134.0 (CH), 127.0 and 126.9 (CH), 125.2 and 125.0 (CH), 111.9 and 110.8 (CH_2), 92.9 and 92.4 (C), 88.0 (2 × C), 76.4 and 76.2 (CH_2), 70.5 and 70.5 (CH), 51.2 and 51.0 (CH_3), 50.86 and 50.87 (CH_2), 49.1 and 48.1 (CH_2), 46.7 and 46.5 (CH), 41.1 and 40.7 (CH), 40.4 and 40.2 (CH), 26.26 and 26.28 (3 × CH_3), 24.2 and 24.1 (CH), 23.4 and 21.7 (CH_3), 18.6 (2 × C), −4.3 (2 × CH_3), −4.6 (2 × CH_3); IR (neat, cm^{-1}) 2956 (s), 2929 (s), 2855 (s), 1739 (s); HRMS (EI) m/z ($M^+ - C_4H_9$) calcd for $C_{22}H_{29}O_5Si$ 401.1784, found 401.1783.

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Supporting Information Available: Experimental procedures for **11**, **12**, **22**, **27**−**29**, and **31**. High-field ^{1}H and ^{13}C NMR spectra for compounds **4**, **9**−**12**, **14**−**17**, **20**−**22**, **27**−**29**, and **31**−**45**. Crystallographic data for **35**. ORTEP view of **35**. This material is available free of charge via the Internet at http://pubs.acs.org.