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Domino Ring-Opening Metathesis−Ring-Closing Metathesis of Bicyclo[2.2.2]octene Derivatives: Scope and Limitations

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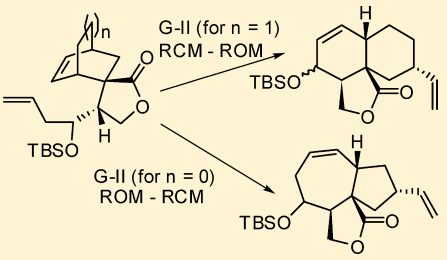
Supporting Information

ABSTRACT: Domino metathesis involving ring-opening metathesis−ring-closing metathesis (ROM−RCM) of a bicyclo[2.2.2]octene derivative having an appropriate alkene chain, expected to produce a 7/6 fused bicyclic system, provided a decalin system in contrast to ROM−RCM of the corresponding bicyclo[2.2.1]heptene analogues, which as expected produced the 7/5 fused bicycles. The expected 6/7 bicyclic system could, however, be made through RCM of the elusive ROM product prepared from the same bicyclo[2.2.2]octene analogue by a nonmetathetic route. A rationale to explain the difference in reactivity pattern between these two systems toward ROM−RCM has been forwarded.



Domino ring-opening metathesis (ROM)−ring-closing metathesis (RCM)[1] of strained cyclic olefins has emerged as a unique tool for rapid construction of multicyclic ring systems. This protocol has been used extensively for creating molecular complexity in a single step. Ring-opening metathesis of bicyclo[2.2.1]heptenes combined with ring-closing metathesis has been employed very successfully by us[2] and others[3] to construct a variety of structural patterns having a fused five-membered ring. In contrast, ring-opening metathesis of bicyclo[2.2.2]octene derivatives, which could be a unique source of six-membered ring, has hardly been investigated. An attempt to ring open a bicyclo[2.2.2]octene derivative through olefin metathesis by Hagiwara et al.[4] was unsuccessful. On the contrary, Phillips et al.[5] have demonstrated that ROM−RCM of bicyclo[2.2.2]octenes can be accomplished to construct hydrindanes as well as decalins. Subsequently, this group has extended[6] it for the synthesis of cyanthiwigin U, a natural product containing an angularly fused 5/6/7 ring system. To the best of our knowledge, this is the only successful report on ROM−RCM of bicyclo[2.2.2]octenes where a 6/7 fused ring system has been obtained.

We had an occasion to investigate the ROM−RCM of a bicyclo[2.2.2]octene derivative in connection to a program aimed at the synthesis of anthecularin **1** (Figure 1).[7]

Anthecularin is a sesquiterpene possessing a novel 6/7 fused bicyclic skeleton with an angularly fused γ-butyrolactone. It exhibits antiplasmodial and antitrypanosomal activities. The proposed biosynthetic route to **1** projected the diol **3** as an advanced intermediate. Encouraged by the observation of Phillips et al., we envisaged that the diol **3** could, in principle, be obtained from a domino ROM−RCM of the bicyclo[2.2.2]-octene derivative **4** (Scheme 1). The latter could be derived from the Diels−Alder adduct **5** of the α-methylene γ-butyrolactone **6** and 1-methoxy-1,3-cyclohexadiene. A sequence analogous to that in Scheme 1 can be extended to the synthesis of the decalin moiety present in fudecalone **2**.[9] Herein we describe the results of this investigation.

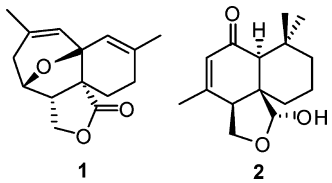
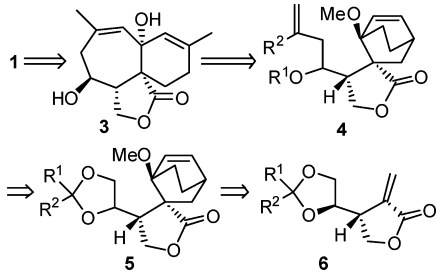


Figure 1. Structures of anthecularin and fudecalone.

Scheme 1. Retrosynthesis



The Diels−Alder reaction of the β-substituted α-methylene-γ-butyrolactone **6** with various cyclic dienes was initially investigated in order to determine the stereochemical outcome. Diels−Alder reaction of α-methylene-γ-butyrolactone with cyclic dienes has been investigated[10] in connection with the synthesis of natural products and has been reported to produce exoadducts. However, there is no report on the Diels−Alder reaction of β-substituted α-methylene-γ-butyrolactone. Thus it was of great interest to investigate the stereochemical outcome in this reaction. The lactone **6** was prepared from the aldehyde

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7[11] (Scheme 2). Reaction of **6** with cyclopentadiene in dichloromethane solution proceeded smoothly at rt to produce

Scheme 2. Diels–Alder Reaction of 6

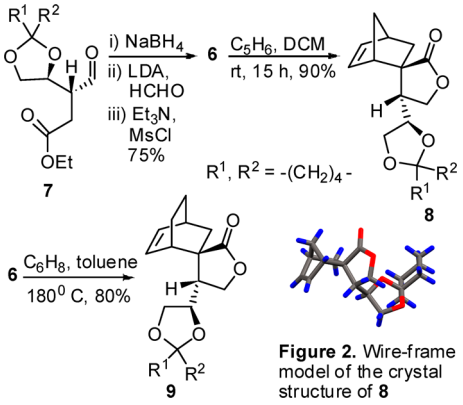


Figure 2. Wire-frame model of the crystal structure of **8**.

the exoadduct **8**, mp 121–123 °C, as the only isolable product in 85% yield. The structure of the product was established by single-crystal X-ray (Figure 2),[12] clearly showing that addition of the diene took place from the face opposite to the ketal substituent at the β-position of the α-methylene lactone **6**.

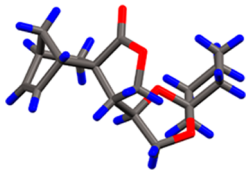


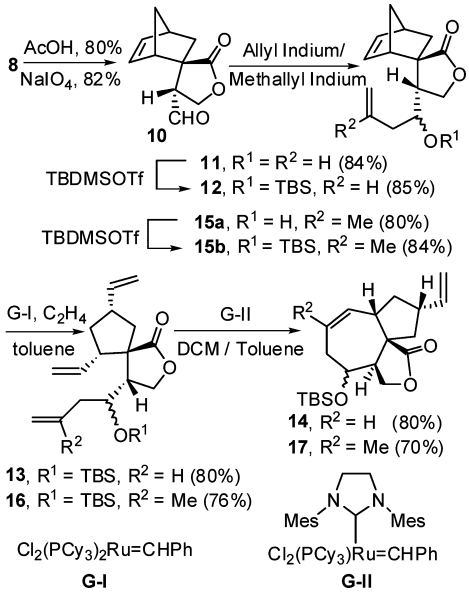
Figure 2. Wire-frame model of the crystal structure of **8**.

Reaction of **6** with cyclohexadiene at 180 °C afforded a single adduct in 80% yield as a liquid. This adduct was assigned the structure **9** in analogy to the formation of the adduct **8**.

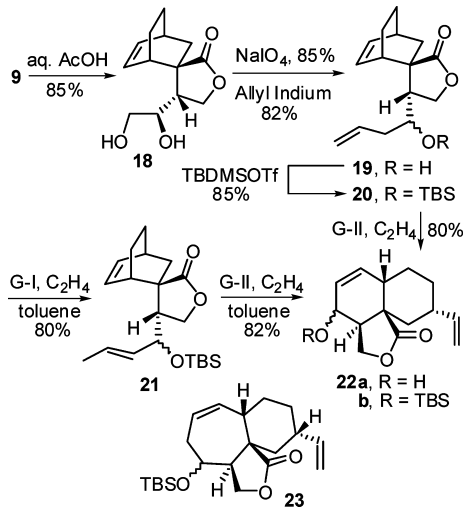
We initially chose to investigate ROM–RCM of the bicyclo[2.2.1]heptene derivative **12** to demonstrate the feasibility of constructing a bicyclic system with a fused seven-membered ring. The required substrate **12** for this investigation was prepared as shown in Scheme 3. Treatment of the ketal **8** with 80% aqueous acetic acid at 60 °C followed by treatment of the corresponding diol with $NaIO_4$ afforded the aldehyde **10**. Reaction of the aldehyde **10** with allyl indium in anhydrous THF led to a diastereoisomeric mixture[8] of the hydroxylactone **11**. The hydroxyl group in **11** was protected to provide the silyl ether **12**. Reaction of the silyl ether **12** with Grubbs' first generation catalyst G-I led only to the ring-opened product **13** as revealed by NMR spectral data. Treatment of **13** with Grubbs' second generation catalyst G-II led to smooth ring closure to afford the tricyclic lactone **14**. Similarly, the methyl-substituted analogue **17** was obtained through ROM of the norbornene derivative **15b** with G-I as the catalyst followed by RCM of the resulting triene **16** with G-II.

For the synthesis of the core structure of anthecularin, ROM–RCM of the bicyclo[2.2.2]octene derivative **20** was required. Toward this end, the adduct **9** was transformed to the corresponding aldehyde following the protocol similar to that used for transformation of the adduct **8** to the aldehyde **10** (Scheme 4). Addition of allyl indium to the aldehyde obtained from the diol **18** followed by silylation of the resulting hydroxy compounds **19** afforded **20** in overall good yield. When

Scheme 3. ROM–RCM of Bicyclo[2.2.1]heptenes



Scheme 4. ROM–RCM of Bicyclo[2.2.2]octene Derivative



compound **20** was subjected to metathesis with G-I, no compound arising from either ROM or ROM–RCM was formed. The only product obtained was the more stable alkene **21** arising from isomerization[13] of the double bond in the alkene chain. On changing the catalyst from G-I to G-II, **20** underwent ROM–RCM. However, the expected 6/7 fused bicyclic system **23** was not formed at all. The only product isolated was the decalin derivative **22b** in 80% yield arising from ROM–RCM of the isomerized alkene **21** (Scheme 4). The hydroxy analogue **19** with G-II under identical conditions also gave the decalin derivative **22a** in 79% yield. The decalin derivatives **22a,b** represent the core structure present in fudecalone **2**.

We thought if the bicyclo[2.2.2]octene derivative could be designed in a way so that double bond isomerization in the alkene chain could not take place, a 6/7 bicyclic system would be formed. Thus, we decided to carry out metathesis of the conjugated enone **25**, a system closely related to the one used by Philips et al.[6] The enone **25** was prepared in the following way (Scheme 5). Homologation of the aldehyde obtained from

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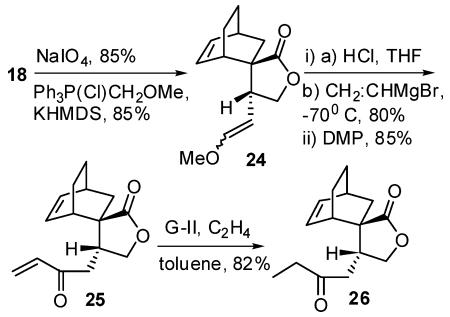
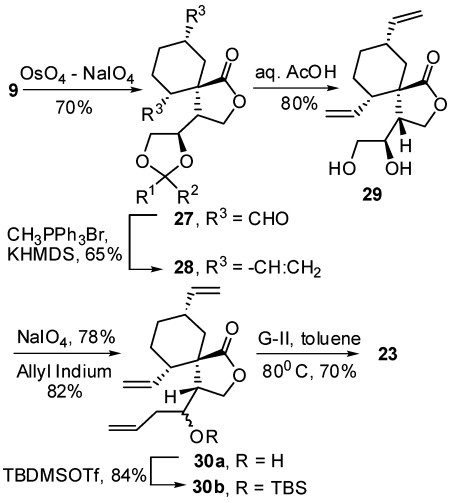
Scheme 5. Synthesis and Metathesis of 25



diol **18** through Wittig reaction with the ylide generated from methoxymethyl triphenylphosphonium chloride afforded the enol ether **24**, which on acid treatment afforded the corresponding aldehyde. Addition of vinyl magnesium bromide to this aldehyde followed by oxidation of the resulting carbinol with Dess–Martin periodinane (DMP) afforded the enone **25**. Unexpectedly, attempted metathesis of the enone **25** led to reduction of the conjugated alkene to the keto-lactone **26** in excellent yield. **26** possibly arises through conjugate reduction of **25** by an in situ generated ruthenium hydride complex.[14]

The inertness of bicyclo[2.2.2]octene derivative **20** to form the ROM product **30b** with Grubbs' catalyst G-II probably initiated a nonmetathetic process that led to isomerization of the double bond in the side chain to produce **21**. The latter then underwent domino metathesis to produce the decalin system **22b**. In case ROM would take place to produce **30b**, RCM should have occurred to lead to a 6/7 bicyclic system. To substantiate it, the ring-opened product **30b** was prepared through a nonmetathetic route, as delineated in Scheme 6.

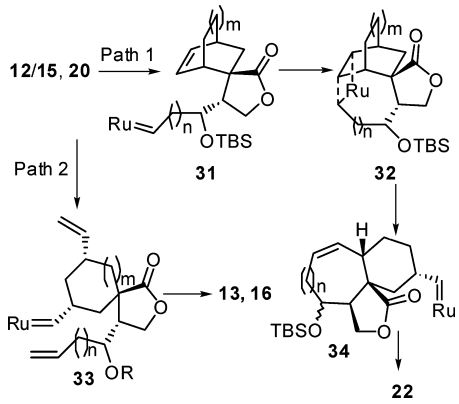
Scheme 6. Synthesis and Metathesis of 30



Oxidative cleavage (OsO_4–$NaIO_4$) of the double bond in bicyclo[2.2.2]octene derivative **9** provided the dialdehyde **27**. Wittig olefination of **27** afforded the diene **28** in good yield. The diene **28** was next transformed to **30b**, the expected ROM product of the diene **20**, as follows. Deketalization of **28** afforded the diol **29**, which on periodate cleavage gave the corresponding aldehyde. Addition of allyl indium to this aldehyde followed by silylation of the resulting carbinol **30a** gave the triene **30b**. As expected, the triene **30b**, when treated with G-II, underwent smooth ring closure to produce the 6/7 ring system **23**. The tricyclic lactone **23** is appropriately functionalized for elaboration to anthecularin. Thus it may be concluded that 7/6 bicyclic systems cannot be prepared directly by metathesis of bicyclo[2.2.2]octene derivatives.

The difference in reactivity pattern between the bicyclo[2.2.2]octene derivatives and [2.2.1]heptene derivatives may be attributed as follows (Scheme 7). As experimentally

Scheme 7. Plausible Reaction Course



demonstrated by Hagiwara et al.,[4] domino metathesis of bicyclo[2.2.1]heptene derivatives **12** and **15b** proceeds through the ruthenium carbene **33** (m = 0) (Path 2). The isolation of ROM products **13** and **16** substantiates the observation of Hagiwara et al. The results observed above for metathesis of the bicyclo[2.2.2]octene derivative **20** indicate that metathesis proceeds through Path 1. Initially, the Ru catalyst reacts with the alkene unit in the side chain to form the new Ru carbene **31** (m = 1). This adds intramolecularly to the bridged alkene to form the ruthena-cyclobutane **32** (m = 1), which underwent cycloreversion to the carbene **34**. Exchange of **34** with ethylene then leads to the product **22**. Thus it is the side chain alkene that facilitates ROM in the case of bicyclo[2.2.2]octene. This is supported by the fact that bicyclo[2.2.2]octene derivative **9**, lacking any alkene chain on treatment with G-II, failed to undergo ring opening to produce the product **28**. The formation of ruthena-cyclobutane **32** (m = n = 1) required for the formation of the 7/6 bicyclic system is probably entropically unfavorable compared to those required for the formation of decalins such as **32** (m = 1, n = 0). The observation of Philips et al.[6] to construct 5/6/7 from ROM–bidirectional RCM of bicyclo[2.2.2]octene can be accounted by initiation of metathesis to form an entropically favorable five-membered ring followed by a second RCM. Thus the present investigation experimentally determines that, out of the two proposed paths[4,6] commonly thought of for domino ROM–RCM, Path 1 is operative in the case of bicyclo[2.2.2]octene derivatives.

EXPERIMENTAL SECTION

3-Methylene-4-(1,4-dioxaspiro[4.5]decan-2-yl)dihydrofuran-2(3*H*)-one (6). A solution of the aldehyde **7**[11] (644 mg, 2.38 mmol) in MeOH (10 mL) was treated with $NaBH_4$ (181 mg, 4.77 mmol) at rt. After usual workup and column chromatography, the lactone (458 mg) thus obtained was treated with LDA (3.58 mmol) in THF (10 mL) at −78 °C for 30 min followed by bubbling HCHO gas to afford after workup a viscous mass (404 mg). This in DCM (8 mL) was treated with Et_3N (0.9 mL, 6.3 mmol) and MsCl (0.3 mL, 3.16 mmol) at 0 °C for 1 h. Usual workup followed by column chromatography

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afforded **6** (307 mg, 75%): $[\alpha]^{25}_{D}$ = −1.8 (*c* 0.02, $CHCl_3$); IR ν_{max} 1759 cm^{-1}; ^1H NMR (500 MHz) δ 1.40 (2H, d, *J* = 4.5 Hz), 1.53−1.74 (7H, m), 1.83−1.88 (0.5H, m), 2.33 (0.5H, t, *J* = 6.5 Hz), 3.32−3.37 (1H, m), 3.58−3.63 (1H, m), 4.03 (1H, dd, *J* = 8.8, 6.5 Hz), 4.13 (1H, dd, *J* = 9.5, 4.5 Hz), 4.24 (1H, q, *J* = 6 Hz), 5.86 (1H, d, *J* = 2 Hz), 6.36 (1H, d, *J* = 2.5 Hz); ^{13}C NMR δ 23.9, 24.1, 25.2, 34.7, 36.5, 41.5, 66.1, 66.9, 76.5, 110.6, 125.0, 134.9, 170.3; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}O_4Na$ 261.1103; found 261.1103.

(1*S*,2*R*,4*S*,4′*R*)-4′-((*R*)-1,4-Dioxaspiro[4.5]decan-2-yl)-4′,5′-dihydro-2′*H*-spiro[bicyclo[2.2.1]hept[5]ene-2,3′-furan]-2′-one (8). A solution of **6** (500 mg, 2.1 mmol) in DCM (10 mL) and cyclopentadiene (1.76 mL, 21.0 mmol) was stirred at rt for 12 h. The residual mass after removal of solvent was purified by column chromatography (5% ethy acetate (EA)/petroleum ether (PE)) to afford **8** (542 mg, 85%) as a crystalline solid: mp 121−123 °C; $[\alpha]^{26}_{D}$ = −16.1 (*c* 1.2, $CHCl_3$); IR ν_{max} 1749 cm^{-1}; ^1H NMR δ 1.21−1.56 (11H, m), 1.94 (1H, d, *J* = 8.7 Hz), 2.02 (1H, dd, *J* = 12, 3.6 Hz), 2.38−2.40 (2H, m), 3.01 (2H, s), 3.42−3.48 (1H, m), 3.82 (1H, dd, *J* = 8.3, 6 Hz), 3.95−3.98 (1H, m), 4.25−4.34 (2H, m), 6.15 (1H, dd, *J* = 5.4, 3 Hz), 6.41 (1H, dd, *J* = 5.4, 3 Hz); ^{13}C NMR δ 23.8, 23.9, 25.1, 29.8, 32.4, 35.1, 36.2, 43.1, 44.5, 45.6, 51.0, 65.6, 66.6, 75.4, 109.5, 134.0, 141.4, 181.4; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{24}O_4Na$ 327.1573; found, 327.1572.

(1*S*,2*R*,4*S*,4′*R*)-4′-((*R*)-1,4-Dioxaspiro[4.5]decan-2-yl)-4′,5′-dihydro-2′*H*-spiro[bicyclo[2.2.2]oct[5]ene-2,3′-furan]-2′-one (9). Heating a mixture of **6** (200 mg, 0.63 mmol) and cyclohexadiene (0.3 mL, 3.8 mmol) in toluene (3 mL) in a sealed tube at 180 °C afforded after solvent removal and chromatography (5% EA/PE) the adduct **9** (liquid) (215 mg, 80%): $[\alpha]^{26}_{D}$ = 4.42 (*c* 1.5, $CHCl_3$); IR ν_{max} 1753 cm^{-1}; ^1H NMR (500 MHz) δ 1.17−1.26 (2H, m), 1.37 (2H, brs), 1.53−1.54 (5H, d, *J* = 6.5 Hz), 1.57 (5H, d, *J* = 3.5 Hz), 1.68−1.73 (1H, m), 1.78−1.86 (3H, m), 2.60 (1H, t, *J* = 6 Hz), 2.66 (1H, t, *J* = 3 Hz), 3.79 (1H, dd, *J* = 8, 6 Hz), 4.06 (1H, m), 4.25 (1H, d, *J* = 10.5 Hz), 4.36 (1H, dd, *J* = 10.2, 6.5 Hz), 6.30 (1H, t, *J* = 7 Hz), 6.42 (1H, t, *J* = 7.5 Hz); ^{13}C NMR (125 MHz) δ 21.0 (×2), 23.86, 23.9, 25.2, 30.0, 31.7, 35.1, 36.0, 36.2, 46.1, 49.4, 65.3, 66.2, 74.3, 109.3, 132.3, 136.7, 180.2; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{26}O_4Na$ 341.1729; found 341.1729.

General Procedure for Deketalization and Diol Cleavage. *(1S,2R,4S,4′R)-2′-Oxo-4′,5′-dihydro-2′H-spiro[bicyclo[2.2.1]hept[5]-ene-2,3′-furan]-4′-carbaldehyde (**10**).* The adduct **8** (542 mg, 1.8 mmol) and aqueous AcOH (15 mL, 80%) were stirred at 60 °C for 12 h. The residual mass after removal of solvents was purified by column chromatography (40% EA/PE) to afford the corresponding diol (viscous mass) (320 mg, 80%): $[\alpha]^{26}_{D}$ = 10.28 (*c* 2.1, $CHCl_3$); IR ν_{max} 1747 cm^{-1}; ^1H NMR δ 1.27 (1H, dd, *J* = 12.1, 2.1 Hz), 1.37 (1H, d, *J* = 8.4 Hz), 1.89 (1H, d, *J* = 8.7 Hz), 2.02 (1H, dd, *J* = 11.9, 3.3 Hz), 2.30 (1H, t, *J* = 4.8 Hz), 3.0 (2H, brs), 3.30−3.37 (4H, m), 3.64 (1H, d, *J* = 4.5 Hz), 4.26−4.31 (1H, m), 4.44 (1H, d, *J* = 9.9 Hz), 6.16 (1H, dd, *J* = 5.6, 2.8 Hz), 6.41 (1H, dd, *J* = 5.3, 3 Hz); ^{13}C NMR δ 32.4, 43.1, 45.6, 46.8, 50.7, 51.4, 63.0, 66.7, 71.7, 134.0, 141.3, 182.5; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{16}O_4Na$ 247.0943; found 247.0946.

This diol (320 mg, 1.42 mmol) in CH_3CN/H_2O (3:2, 8 mL) was stirred with $NaIO_4$ (1.82 g, 8.5 mmol) for 1 h. Usual workup afforded the aldehyde **10** (oil) (233 mg, 85%): $[\alpha]^{28}_{D}$ = 4.15 (*c* 3.0, $CHCl_3$); IR ν_{max} 1766, 1726 cm^{-1} ; ^1H NMR δ 1.36−1.44 (2H, m), 2.04−2.13 (2H, m), 3.0−3.06 (3H, m), 4.32 (1H, dd, *J* = 9.6, 6.6 Hz), 4.46 (1H, dd, *J* = 9.6, 4.2 Hz), 6.22 (1H, dd, *J* = 5.7, 3 Hz), 6.41 (1H, dd, *J* = 5.4, 3 Hz), 9.54 (1H, d, *J* = 2.4 Hz); ^{13}C NMR δ 33.7, 43.0, 46.2, 51.0, 51.2, 55.4, 64.3, 134.4, 141.7, 179.9, 199.3; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}O_3Na$ 215.0685; found 215.0684.

*(1S,2R,4S,4′R)-4′-((R)-1,2-Dihydroxyethyl)dihydro-2′H-spiro-[bicyclo[2.2.2]octane-2,3′-furan]-2′-one (**18**).* The compound **9** (50 mg, 0.16 mmol) gave the diol **18** (liquid) (32 mg, 85%): $[\alpha]^{26}_{D}$ = 6.95 (*c* 0.6, $CHCl_3$); IR ν_{max} 1749 cm^{-1}; ^1H NMR δ 1.09−1.14 (1H, m), 1.19−1.23 (1H, m), 1.44 (1H, d, *J* = 12.9 Hz), 1.63−1.82 (3H, m), 2.48 (1H, t, *J* = 4.7 Hz), 2.65 (2H, t, *J* = 2.7 Hz), 3.06 (2H, s), 3.33 (2H, d, *J* = 5.7 Hz), 3.79 (1H, m), 4.29−4.41 (2H, m), 6.29 (1H, t, *J* = 7.4 Hz), 6.41 (1H, t, *J* = 7 Hz); ^{13}C NMR δ 21.0, 23.8, 29.9, 31.8, 35.5, 48.2, 48.8, 62.8, 66.3, 70.4, 132.4, 136.6, 181.3; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}O_4Na$ 261.1102; found 261.1103.

*(1R,2S,4S,4′R)-4′-((R)-1,2-Dihydroxyethyl)-1,4-divinyl-4′,5′-dihydro-2′H-spiro[bicyclo[2.2.2]oct[5]ene-2,3′-furan]-2′-one (**29**).* The compound **28** (96 mg, 0.28 mmol) gave the diol **29** (liquid) (57 mg, 78%): $[\alpha]^{26}_{D}$ = 1.73 (*c* 0.3, $CHCl_3$); IR ν_{max} 1776 cm^{-1}; ^1H NMR (500 MHz) δ 1.25−1.33 (0.5H, m), 1.50 (0.5H, t, *J* = 13 Hz), 1.61 (2H, d, *J* = 11.5 Hz), 1.70 (0.5H, dd, *J* = 13.7, 4 Hz), 1.78−1.85 (0.5H, m), 2.11−2.17 (1H, m), 2.45 (1H, d, *J* = 9.5 Hz), 2.60−2.63 (1H, m), 2.86 (1H, dd, *J* = 19.2, 11 Hz), 2.97−2.98 (1H, m), 3.46 (1H, dd, *J* = 11, 8 Hz), 3.62 (1H, dd, *J* = 11.2, 2.5 Hz), 3.82−3.87 (1H, m), 4.07−4.12 (1H, m), 4.16 (1H, dd, *J* = 9.7, 3 Hz), 4.21−4.24 (1H, m), 4.91−5.03 (2H, m), 5.11−5.21 (3H, m), 5.68−5.75 (1H, m), 6.05−6.12 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.9, 27.7, 30.3, 31.4, 35.5, 43.4, 47.3, 63.8, 65.8, 70.4, 113.1, 118.2, 137.4, 143.6, 180.0; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{22}O_4Na$ 289.1414; found 289.1416.

*(1S,2R,4S,4′R)-4′-(1-(tert-Butyldimethylsilyloxy)but-3-enyl)-4′,5′-dihydro-2′H-spiro[bicyclo[2.2.1]hept[5]ene-2,3′-furan]-2′-one (**12**).* The aldehyde **10** (300 mg, 1.6 mmol) in THF (6 mL) was added to allyl indium [prepared from allyl bromide (0.34 mL, 3.2 mmol) and indium (358 mg, 3 mmol) in THF (5 mL)] at rt and stirred for 1 h, then quenched with saturated aqueous NH_4Cl solution. The precipitated solid was filtered off and washed with diethyl ether. The combined filtrate and washings were dried and concentrated under vacuum. The residual mass was chromatographed (20% EA/PE) to afford[8] alcohols **11** (liquid) (300 mg, 82%): $[\alpha]^{28}_{D}$ = −40.67 (*c* 6.8, $CHCl_3$); IR ν_{max} 1747, 3444 cm^1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{18}O_3Na$ 257.1154; found 257.1156.

The alcohols **11** (300 mg, 1.27 mmol) in DCM (8 mL), 2,6-lutidine (0.22 mL, 1.9 mmol), and TBDMSOTf (0.22 mL, 1.3 mmol) were stirred at 0 °C for 30 min. Removal of solvent followed by column chromatography (2% EA/PE) afforded the silyl ether **12** (liquid) (373 mg, 84%): $[\alpha]^{26}_{D}$ = −38.38 (*c* 5.8, $CHCl_3$); IR ν_{max} 1766 cm^1; ^1H NMR δ 0.08 (6H, s), 0.90 (9H, s), 1.32 (1H, dd, *J* = 11.6, 2.8 Hz), 1.51 (1H, td, *J* = 8.7, 1.3 Hz), 1.70−1.74 (1H, m), 2.06 (1H, dd, *J* = 11.5, 3.8 Hz), 2.17 (1H, d, *J* = 8.2 Hz), 2.39−2.49 (1H, m), 2.64−2.73 (1H, m), 2.9 (1H, s), 3.06 (1H, s), 3.62 (1H, dd, *J* = 10.9, 3.5 Hz), 3.75 (1H, dd, *J* = 10.9, 1.9 Hz), 4.34−4.40 (1H, m), 5.08−5.16 (2H, m), 5.76−5.89 (1H, m), 6.16 (1H, dd, *J* = 5.9, 2.8 Hz), 6.26 (1H, dd, *J* = 5.9, 3 Hz); ^{13}C NMR δ −5.7, −5.6, 18.1, 25.8 (×3), 34.6, 40.7, 42.0, 46.1, 48.1, 50.5, 51.6, 60.0, 78.4, 117.8, 133.9, 134.8, 139.4, 181.1; HRMS (ESI) *m*/*z* (M + H)$^+$ calcd for $C_{20}H_{32}O_3Si$ 349.2197; found 349.2194.

*(1S,2R,4S,4′R)-4′-(1-(tert-Butyldimethylsilyloxy)-3-methylbut-3-enyl)-4′,5′-dihydro-2′H-spiro[bicyclo[2.2.1]hept[5]ene-2,3′-furan]-2′-one (**15b**).* Following the above procedure, aldehyde **10** was converted to **15b** (liquid) (84%): $[\alpha]^{25}_{D}$ = −13.2 (*c* 0.07, $CHCl_3$); IR ν_{max} 1768 cm^{-1}; ^1H NMR δ 0.09 (6H, s), 0.90 (9H, s), 1.34 (1H, dd, *J* = 11.3, 2.6 Hz), 1.78 (3H, s), 2.06−2.20 (4H, m), 2.51 (0.5H, s), 2.62 (0.5H, m), 2.87−2.91 (2H, m), 3.08 (1H, s), 3.61 (1H, dd, *J* = 10.8, 3.1 Hz), 3.75 (1H, d, *J* = 10.7 Hz), 4.49−4.58 (1H, m), 4.75 (1H, s), 4.83 (1H, s), 6.11−6.18 (1H, m), 6.25−6.32 (1H, m); ^{13}C NMR δ −5.7, −3.5, 18.1, 23.1, 25.8 (×3), 37.9, 40.8, 42.0, 46.1, 48.1, 50.8, 51.5, 59.9, 77.3, 112.6, 134.8, 139.3, 141.9, 181.1; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{34}O_3SiNa$ 385.2174; found 385.2175.

*(1S,2R,4S,4′R)-4′-(1-(tert-Butyldimethylsilyloxy)but-3-enyl)-4′,5′-dihydro-2′H-spiro[bicyclo[2.2.2]oct[5]ene-2,3′-furan]-2′-one (**20**).* The aldehyde derived from diol **18** gave the silyl ether **20** (liquid) (85%): $[\alpha]^{26}_{D}$ = −4.3 (*c* 0.03, $CHCl_3$); IR ν_{max} 1778 cm^{-1}; ^1H NMR δ 0.06 (6H, s), 0.88 (9H, s), 1.01−1.11 (1H, m), 1.16−1.37 (3H, m), 1.57−1.62 (1H, m), 1.72−1.83 (2H, m), 2.39−2.48 (1H, m), 2.59−2.66 (2H, m), 2.76−2.84 (1H, m), 3.66−3.77 (2H, m), 4.32−4.39 (1H, m), 5.07−5.15 (2H, m), 5.75−5.89 (1H, m), 6.23−6.31 (2H, m); ^{13}C NMR δ −5.8, −5.7, 18.0, 19.1, 25.1, 25.7 (×3), 30.5, 32.5, 34.6, 39.0, 47.4, 52.6, 59.6, 76.7, 117.7, 133.3, 134.1, 134.2, 180.5; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{35}O_3Si$ 363.2344; found 363.2349.

*(4R,5R,6S,9S)-4-(1-(tert-Butyldimethylsilyloxy)but-3-enyl)-6,9-divinyl-2-oxaspiro[4.5]decan-1-one (**30b**).* The aldehyde derived from the diol **29** gave the silyl ether **30b** (liquid) (84%): $[\alpha]^{25}_{D}$ = −3.6 (*c*

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0.05, $CHCl_3$); IR ν_{max} 1764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.042 (6H, d, J = 7 Hz), 0.887 (9H, s), 1.47−1.62 (3H, m), 1.92−2.01 (2H, m), 2.28−2.30 (1H, m), 2.43−2.48 (1H, m), 2.66−2.71 (1H, m), 2.86−2.93 (2H, m), 3.69 (1H, d, J = 11 Hz), 3.96 (1H, d, J = 10.5 Hz), 4.63 (1H, q, J = 6.5 Hz), 4.92−5.01 (2H, m), 5.06−5.19 (5H, m), 5.66−5.73 (1H, m), 5.84 (1H, dd, J = 20, 10.5 Hz), 6.02−6.09 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.8, −5.6, 18.0, 25.7 (×3), 26.5, 29.2, 34.5, 34.6, 36.8, 38.7, 47.1, 49.6, 58.1, 77.6, 113.1, 116.5, 117.9, 134.1, 139.8, 143.2, 178.1; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{23}H_{38}O_3SiNa$ 413.2488; found 413.2489.

General Procedure for Metathesis. The substrate in deoxygenated DCM at rt or toluene at 80 °C (100 mL for per mmol of substrate) was treated with G-I/G-II (5 mol %) under ethylene atmosphere for 4−8 h. Chromatography of the residual mass obtained after removal of the solvent afforded the product.

13: liquid (80%); $[\alpha]^{28}_D$ = −6.87 (c 0.5, $CHCl_3$); IR ν_{max} 1768 cm^{-1}; ^1H NMR δ 0.018−0.065 (6H, m), 0.90 (9H, s), 1.36 (1H, dd, J = 7.3, 2.5 Hz), 1.67 (1H, d, J = 4.8 Hz), 1.73−1.80 (1H, m), 2.14 (1H, t, J = 3.4 Hz), 2.30 (1H, dd, J = 13.2, 6.9 Hz), 2.42−2.52 (1H, m), 2.64−2.74 (1H, m), 2.80−2.92 (2H, m), 3.05 (1H, d, J = 7.5 Hz), 3.73 (1H, dd, J = 10.8, 1.4 Hz), 4.03 (1H, dd, J = 10.8, 3.5 Hz), 4.52−4.59 (1H, m), 4.89−5.06 (3H, m), 5.12−5.20 (2H, m), 5.73−5.93 (3H, m); ^{13}C NMR δ −5.7, −5.4, 18.0, 25.7 (×3), 34.6, 39.2, 39.5, 41.3, 45.8, 48.3, 55.9, 58.3, 79.8, 113.4, 114.9, 117.9, 133.9, 140.9, 142.7, 179.2; HRMS (ESI) m/z $(M + H)^+$ calcd for $C_{22}H_{36}O_3Si$ 377.2505; found 377.2500.

14: liquid (75%); $[\alpha]^{28}_D$ = 18.4 (c 0.5, $CHCl_3$); IR ν_{max} 1766 cm^{-1}; ^1H NMR δ 0.51 (6H, s), 0.87 (9H, s), 1.17−1.24 (1H, m), 1.54−1.66 (1H, m), 2.0−2.09 (1H, m), 2.42−2.52 (1H, td, J = 22.6, 2.8 Hz), 2.62−2.85 (5H, m), 3.83−3.93 (2H, m), 4.76−4.79 (1H, m), 4.95−5.05 (2H, m), 5.36−5.40 (1H, d, J = 13.8 Hz), 5.48−5.53 (1H, td, J = 12.5, 1.5 Hz), 5.74−5.85 (1H, m); ^{13}C NMR δ −5.4, −5.3, 18.28, 26.0 (×3), 32.4, 41.1, 41.2, 41.6, 52.0, 52.0, 53.2, 59.7, 77.6, 113.8, 123.7, 127.1, 141.4, 181.7; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{32}O_3Si$ 349.2194; found 349.2188.

16: liquid (76%); $[\alpha]^{26}_D$ = 32.7 (c 0.14, $CHCl_3$); IR ν_{max} 1763 cm^1; ^1H NMR δ (of the mixture) 0.01−0.04 (6H, m), 0.88 (9H, s), 1.17−1.41 (2H, m), 1.62 (1H, brs), 1.79 (3H, s), 2.13−2.14 (1H, m), 2.26−2.41 (2H, m), 2.46−2.67 (1H, m), 2.79−2.90 (2H, m), 3.04 (1H, t, J = 7.1 Hz), 3.69 (1H, dd, J = 10.8, 11.2 Hz), 3.86−4.03 (1H, m), 4.67−5.09 (6H, m), 5.71−5.90 (2H, m); ^{13}C NMR δ (for major isomer) −5.4, −5.3, 17.9, 23.2, 25.68, 25.72, 25.89, 37.9, 39.3, 39.5, 41.4, 45.8, 48.6, 55.8, 58.3, 78.9, 112.7, 113.4, 114.8, 141.0, 141.9, 142.7, 179.2; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{38}O_3Si$ 391.2662; found 391.2663.

17: liquid (70%); $[\alpha]^{24}_D$ = −18.64 (c 0.05, $CHCl_3$); IR ν_{max} 1766 cm^{-1}; ^1H NMR δ 0.08 (6H, s), 0.90 (9H, s), 1.20−1.24 (1H, m), 1.32−1.36 (1.5H, m), 1.39−1.44 (1.5 H, m), 1.71 (3H, t, J = 7.7 Hz), 1.78 (3H, s), 2.06 (1H, d, J = 6.4 Hz), 2.19 (1H, d, J = 15 Hz), 2.20 (0.5H, m), 2.60 (0.5H, d, J = 13.6 Hz), 2.91 (0.5H, s), 3.08 (0.5H, s), 3.48 (0.5H, m), 3.60−3.64 (0.5H, m), 3.76 (0.5H, d, J = 17.5 Hz), 4.08 (0.5H, d, J = 6.7 Hz), 4.30 (1H, t, J = 5.4 Hz), 4.50−4.53 (0.5H, m), 4.75 (0.5H, s), 4.83 (0.5H, s), 6.17−6.18 (0.5H, m), 6.25−6.28 (0.5H, m); ^{13}C NMR (125 MHz) δ −5.4 (×2), 13.9, 19.3, 23.2, 25.8, 30.7, 38.0, 42.0, 46.2, 48.2, 50.9, 51.6, 60.0, 65.7, 72.5, 112.4, 134.9, 139.4, 142.0, 181.1; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{34}O_3SiNa$ 385.2176; found, 385.2175.

21: liquid (80%); $[\alpha]^{26}_D$ = −36.27 (c 0.12, $CHCl_3$); IR ν_{max} 1774 cm^1; ^1H NMR δ (for the mixture) −0.001−0.014 (6H, m), 0.85 (9H, s), 1.03−1.11 (1H, m), 1.12−1.24 (2H, m), 1.37−1.46 (1H, m), 1.54 (2H, d, J = 7.1 Hz), 1.64 (3H, d, J = 6.9 Hz), 1.82−1.90 (1H, m), 2.29 (0.5H, brs), 2.46 (0.5H, brs), 2.64 (2H, brs), 2.80 (0.5H, q, J = 2.6 Hz), 2.94 (0.5H, brs), 3.60−3.79 (2H, m), 4.65 (0.5H, q, J = 6.8 Hz), 5.21 (0.5H, q, J = 7.1 Hz), 6.21−6.35 (2H, m); ^{13}C NMR δ −5.6 (×2), 10.8, 18.3, 20.0, 24.9, 25.8 (×3), 30.3, 31.3, 39.1, 47.6, 52.1, 54.5, 63.9, 99.5, 133.3, 134.3, 149.7, 178.8; HRMS (ESI) m/z $[M + Na]^+$calcd for $C_{21}H_{34}O_3SiNa$ 385.2173; found 385.2175.

22b: liquid (80%); $[\alpha]^{26}_D$ = 6.26 (c 0.05, $CHCl_3$); IR ν_{max} 1764 cm^1; ^1H NMR (500 MHz) δ (for the mixture) 0.06−0.10 (6H, m), 0.89 (9H, s), 1.50−1.68 (5H, m), 1.95−2.07 (2H, m), 2.23−2.45 (3H, m), 2.62 (1H, brs), 4.12 (0.5H, dd, J = 11.5, 8.5 Hz), 4.21 (0.5H, dd, J = 11.7, 8.5 Hz), 4.36−4.45 (2H, m), 5.15−5.16 (0.5H, m), 5.36 (0.5H, d, J = 7 Hz), 5.55 (1H, d, J = 10 Hz), 5.66 (1H, dd, J = 10, 2 Hz); ^{13}C NMR (125 MHz) δ (for major isomer) −4.6, −4.2, 13.1, 18.2, 23.6, 25.9 (×3), 27.5, 28.7, 32.6, 38.4, 46.5, 50.3, 68.4, 119.4, 131.5, 132.9, 133.5, 177.5; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{32}O_3Si$ 349.2192; found 349.2194.

26: liquid (82%); $[\alpha]^{26}_D$ = 79.45 (c 0.07, $CHCl_3$); IR ν_{max} 1763, 1697 cm^{-1}; ^1H NMR (500 MHz) δ 1.03 (3H, t, J = 7.5 Hz), 1.09−1.13 (1H, m), 1.28 (2H, t, J = 3 Hz), 1.60 (1H, s), 1.69−1.71 (1H, m), 1.82−1.88 (2H, m), 2.27−2.32 (3H, m), 2.35−2.41 (1H, m), 2.46−2.72 (2H, m), 3.84 (1H, d, J = 9.5 Hz), 4.47 −4.50 (1H, m), 6.28 (1H, t, J = 7 Hz), 6.36 (1H, t, J = 7 Hz); ^{13}C NMR (125 MHz) δ 7.7, 21.4, 23.7, 30.1, 32.2, 35.0, 36.6, 40.9, 41.7, 50.0, 70.6, 132.6, 136.3, 180.3, 209.6; HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{15}H_{20}O_3Na$ 271.1311; found, 271.1310.

23: liquid (70%); $[\alpha]^{26}_D$ = −20.21 (c 0.04, $CHCl_3$); IR ν_{max} 1768 cm^{-1}; ^1H NMR (500 MHz) δ 0.059 (6H, s), 0.89 (9H, s), 1.01−1.08 (1H, m), 1.19−1.25 (2H, m), 1.46 (1H, d, J = 12.5 Hz), 1.75 (2H, d, J = 6 Hz), 1.93 (2H, d, J = 17.5 Hz), 2.64 (2H, brs). 2.82 (1H, brs), 3.61−3.74 (2H, m), 4.80 (1H, t, J = 7 Hz), 5.29−5.42 (1H, m), 5.68 (1H, dd, J = 15.7, 6.5 Hz), 5.76−5.83 (1H, m), 6.22−6.28 (2H, m); ^{13}C NMR (125 MHz) δ −5.6 (×2), 18.1, 18.2, 19.9, 24.7, 25.8, 29.9, 30.3, 32.8, 39.3, 47.2, 54.6, 58.6, 60.2, 78.8, 126.9, 130.8, 133.3, 134.3, 180.7; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{21}H_{34}O_3SiNa$ 385.2175; found, 385.2175. Anal. Calcd for $C_{21}H_{34}O_3Si$: C, 69.56; H, 9.45. Found: C, 69.85; H, 9.15.

(1S,2R,4S,4′R)-4′-(2-Oxobut-3-enyl)-4′,5′-dihydro-2′H-spiro-[bicyclo[2.2.2]oct[5]ene-2,3′-furan]-2′-one (***25***). KHMDS (3.5 mL, 1.74 mmol) was added to a solution of (methoxymethyl)-triphenylphosphonium chloride (2.61 mmol, 897 mg) in THF (4 mL) at 0 °C. After 15 min, a solution of **18** (180 mg, 0.87 mmol) in THF (3 mL) was added. Quenched by saturated aqueous NH_4Cl after 1 h, the reaction mixture was worked up and chromatographed (10% EA/PE) to afford enol ether **24** (liquid) (163 mg, 80%): $[\alpha]^{27}_D$ = 6.39 (c 0.20, $CHCl_3$); IR ν_{max} 1776 cm^{-1}; ^1H NMR (500 MHz) δ 1.08 (1H, dt, J = 4.5, 8.5 Hz), 1.17−1.22 (1.5H, m), 1.41 (0.5H, d, J = 13 Hz), 1.51−1.55 (1H, m), 1.64−1.75 (2.5H, m), 1.83−1.88 (1H, m), 2.58−2.66 (2H, m), 3.17 (0.5H, dd, J = 10, 5.5 Hz), 3.45, 3.52 (2s, 3H), 3.94 (1H, dd, J = 24, 9 Hz), 4.14 (0.5H, dd, J = 10, 6 Hz), 4.41−4.47 (1H, dd, J = 9, 5.5 Hz), 4.50−4.53 (1H, m), 5.93 (0.5H, d, J = 6 Hz), 6.19−6.28 (1.5H, m), 6.33 (0.5H, t, J = 7 Hz); ^{13}C NMR (125 MHz) δ (E/Z isomers) 21.19, 21.2, 23.8, 23.9, 29.9, 30.0, 32.4, 32.7, 34.6, 34.7, 42.3, 46.6, 50.3, 50.7, 56.1, 59.8, 71.4, 71.9, 101.0, 104.1, 132.1, 132.2, 136.1, 136.5, 148.3, 149.9, 180.5, 180.7; HRMS (ESI) m/z $[M + Na]^+$calcd for $C_{14}H_{18}O_3Na$ 257.1154; found 257.1154. This liquid in THF (1 mL) on treating with HCl (4 mL, 4N) at rt for 3 h afforded, after workup, the corresponding aldehyde (liquid) (140 mg, 90%): IR ν_{max} 1763, 1722 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{13}H_{16}O_3Na$ 243.0996; found 243.0997. To this aldehyde (140 mg, 0.6 mmol) in THF (6 mL) cooled to −70 °C was added dropwise vinylmagnesium bromide (0.2 mL, 1.3 mmol). The reaction mixture after being stirred at −70 °C for 3 h was quenched by saturated aqueous ammonium chloride. Usual workup of the reaction mixture afforded the corresponding alcohol (liquid) as a diastereoisomeric mixture (126 mg, 80%): IR ν_{max} 3385, 1764 cm^{-1}; ^1H NMR (500 MHz) δ 1.06−1.12 (1H, m), 1.20−1.29 (4H, m), 1.32−1.38 (1H, m), 1.46−1.49 (1H, m), 1.50−1.57 (1H, m), 1.68−1.69 (1H, m), 1.79 (0.5H, t, J = 2.5 Hz), 1.81 (0.5H, t, J = 2.5 Hz), 1.88−1.98 (1H, m), 2.19−2.20 (1H, m), 2.66−2.67 (1H, m), 2.72 (1H, t, J = 3 Hz), 4.07−4.20 (2H, m), 4.41−4.45 (1H, m), 5.76−5.86 (1H, m), 6.27 (1H, q, J = 7.5 Hz), 6.38 (1H, t, J = 7 Hz); ^{13}C NMR (125 MHz) δ 21.4, 23.8, 30.0, 32.0, 35.9, 39.8, 43.4, 50.3, 69.3, 70.3, 115.0, 132.6, 136.3, 140.9, 180.9; HRMS (ESI) m/z $(M + Na)^+$ calcd for $C_{15}H_{20}O_3Na$ 271.1311; found 271.1310.

This material (126 mg, 0.51 mmol) in DCM (5 mL) and DMP (26 mg, 0.61 mmol) was stirred at rt for 1 h. Usual workup after quenching with a 1:1 mixture of saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ followed by column chromatography (10% EA/PE) afforded the enone **25** (liquid) (106 mg, 85%): $[\alpha]^{26}_D$ = 8.9 (c 0.05, $CHCl_3$); IR

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ν_{max} 1776 cm^{-1}; ^1H NMR (500 MHz) 1.12−1.14 (1H, m), 1.20−1.32 (2H, m), 1.67−1.73 (2H, m), 1.84−1.89 (2H, m), 2.48 (1H, dd, J = 18.5, 11 Hz), 2.63−2.74 (4H, m), 3.87 (1H, d, J = 9 Hz), 4.49−4.52 (1H, m), 5.85 (1H, d, J = 11 Hz), 6.19 (1H, d, J = 17.5 Hz), 6.28−6.32 (1H, m), 6.34−6.38 (1H, m); ^{13}C NMR (125 MHz) δ 21.4, 23.7, 30.0, 32.3, 35.1, 39.0, 41.0, 50.1, 70.5, 94.8, 132.6, 133.5, 136.5, 180.4, 198.7; HRMS (ESI) m/z (M + Na)$^+$ calcd for $C_{15}H_{18}O_3Na$ 269.1154; found 269.1155.

*(4R,6R,9R)-4-(1,4-Dioxaspiro[4.5]decan-2-yl)-6,9-vinyl-2-oxaspiro[4.5]decan-1-one (**28**).* A solution of the adduct **9** (215 mg, 0.68 mmol) in THF−H_2O (2:1, 6 mL), $NaIO_4$ (278 mg, 1.3 mmol), and OsO_4(cat.) was stirred for 1 h. Usual workup afforded the dialdehyde **27** (liquid) (150 mg, 64%): IR ν_{max} 1763, 1720 cm^{-1}; ^1H NMR δ 1.39−1.60 (11H, m), 1.93−2.12 (5H, m), 2.33 (2H, m), 2.67 (2H, m), 3.54−3.73 (1H, m), 4.02−4.07 (1H. m), 4.24−4.34 (2H, m), 9.65 (1H, s), 9.79−9.84 (1H, m); ^{13}C NMR δ 21.5, 23.93, 23.98, 25.2, 25.5, 27.2, 34.7, 36.1, 44.3, 44.6, 46.4, 50.4, 66.0, 66.6, 73.2, 110.4, 178.2, 201.2, 203.1; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{19}H_{26}O_6Na$ 373.1628; found 373.1627.

The dialdehyde **27** on reaction with the ylide generated from methyltriphenylphosphonium bromide (307 mg, 0.857 mmol) in THF (3 mL) and KHMDS (1.28 mmol, 2.6 mL) afforded, after usual workup and column chromatography, **28** (liquid) (96 mg, 65%): $[\alpha]^{27}_D$ = −10.44 (c 0.8, $CHCl_3$); IR ν_{max} 1761 cm^{-1}; ^1H NMR (500 MHz) δ (for the mixture) 1.39−1.65 (15H, m), 2.09−2.12 (1H, m), 2.48 (1H, d, J = 10.5 Hz), 2.74 (1H, t, J = 5 Hz), 3.07−3.09 (1H, m), 3.55 (1H, t, J = 8 Hz), 3.97−3.99 (1H, m), 4.0−4.08 (1H, m), 4.18−4.35 (2H, m), 4.95 (1H, d, J = 10 Hz), 5.0−5.05 (1H, m), 5.10−5.22 (2H, m), 5.70−5.77 (1H, m), 6.04−6.12 (1H, m); ^{13}C NMR (125 MHz) δ 23.7, 23.9, 25.1, 25.6, 27.7, 31.0, 34.6, 35.2, 36.1, 43.2, 46.2, 46.4, 65.2, 65.8, 73.5, 109.1, 112.8, 118.1, 136.8, 143.5, 179.2; HRMS (ESI) m/z [M + Na]$^+$ calcd for $C_{21}H_{30}O_4Na$ 369.2043; found 369.2042.

■ ASSOCIATED CONTENT

Supporting Information

General experimental methods along with copies of NMR spectra for compounds **6**, **8**−**30b** and X-ray crystal data for compound **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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