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# Spiro[bicyclo[3.2.0]heptane-2,2'-[1,3]dioxolan]-6-one - a versatile intermediate for the synthesis of cyclopentane-derived natural products

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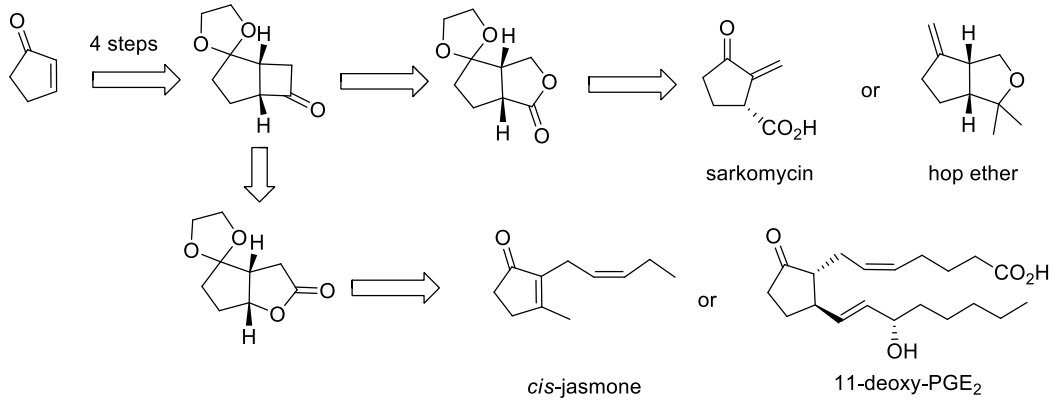
## Abstract

An efficient preparation of racemic spiro[bicyclo[3.2.0]heptane-2,2'-[1,3]dioxolan]-6-one is described in which the four-membered ring is assembled by way of a photochemically-induced 2+2 cycloaddition reaction between vinyl acetate and 2-cyclopenten-1-one. The synthetic versatility of spiro[bicyclo[3.2.0]heptane-2,2'-[1,3]dioxolan]-6-one is demonstrated by topologically complementary oxidative processes that selectively expand the fused cyclobutanone ring to isomeric lactones. A Baeyer-Villiger oxidative process that follows the conventional path in which the more substituted carbon atom migrates provided a lactone that functioned as a synthetic precursor to jasmonoids and prostanoids. The isomeric lactone was obtained by way of ozonolysis of the trimethylsilyl enol ether derived from spiro[bicyclo[3.2.0]heptane-2,2'-[1,3]dioxolan]-6-one and transformed into the Japanese hop constituent hop ether and the antitumor/antibiotic agent sarkomycin.




**Keywords**: Prostanoids, jasmonoids, sarkomycin, hop ether, synthetic approaches

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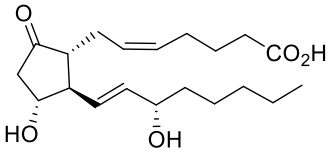
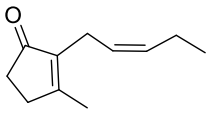
## Introduction

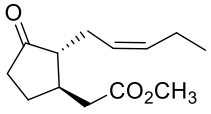
Functionalized cyclopentanes are ubiquitous scaffolds in natural products that express a range of biological activities.[1,2] This carbocyclic class includes, most prominently, prostanoids represented by $PGE_2$ (**1**) and jasmonoids represented by *cis*-jasmone (**2**) and methyl jasmonate (**3**).[1,2] The challenges presented by the synthesis of prostanoids and jasmonoids has proved to be an important backdrop for the development of innovative synthetic methodologies that have extended more broadly into the realm of organic chemistry and which remain of contemporary interest.[3,4] Other cyclopentane-based natural products include the iridoid (±)-hop ether (**4**) and the antitumor antibiotic agent (*R*)-(-)-sarkomycin (**5**).[5-7] We have disclosed a synthetic approach to the synthesis of **4** that assembled the racemic ketone **6** in seven steps from a known bicyclo[3.1.0]hexan-2-one precursor.[8] Subjecting **6** to a Wittig-like process of ketone methylation that relied upon an optical resolution using the less chromatographically-mobile diastereomer of the phosphinothioic amide **7** afforded the individual enantiomers of **4**.[8,9] As a continuation of our interest in the synthesis of cyclopentane-based natural products, we were attracted to the potential of the bicyclo[3.2.0]heptane-6-one derivative (±)-**8** to function as a versatile synthetic intermediate. We envisioned that selective manipulation of the cyclobutanone could allow for oxidative elaboration in two complementary reaction manifolds, one of which would afford access to prostanoids and jasmonoids while the other would provide a synthetic route to hop ether (**4**) and (±)-sarkomycin (**5**). The versatility of bicyclo[3.2.0]heptane derivatives as synthetic intermediates in the preparation of prostanoids and other cyclopentane-containing natural products is well-established but (±)-**8** offers a unique constellation of selectively-protected functionality that allows for productive controlled synthetic manipulations.[10] We describe herein a straightforward synthesis of (±)-**8** and demonstrate its value by elaboration into known synthetic precursors of (±)-$PGE_2$ (**1**), (±)-11-deoxy $PGE_2$, *cis*-jasmone (**2**) and (±)-methyl jasmonate (**3**), the individual enantiomers of hop ether (**4**) and (±)-sarkomycin (**5**).



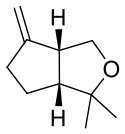

**1** $PGE_2$



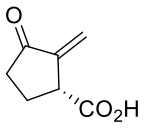

**2** *cis*-jasmone



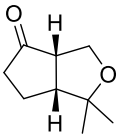

**3** (±)-methyl jasmonate



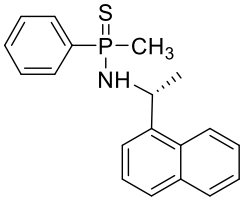

**4** (±)-hop ether



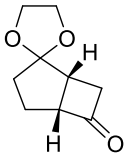

**5** (*R*)-(-)-sarkomycin




(±)-**6**




**7**



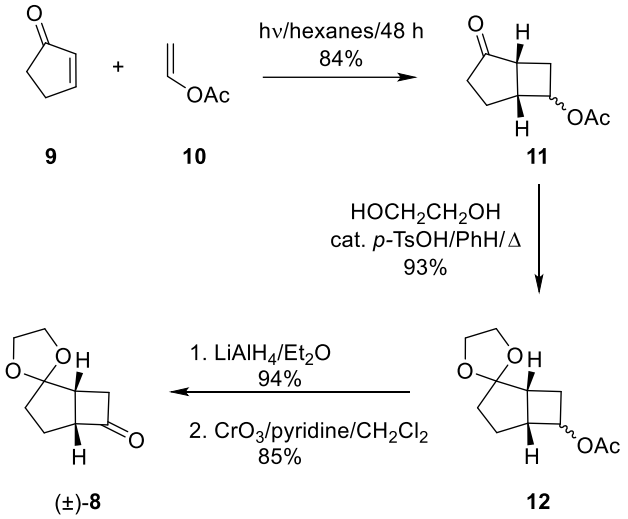

(±)-**8**

## Results and Discussion

The bicyclo[3.2.0]heptane (±)-**8** was assembled in a four-step process that proceeded by way of a photochemically-induced 2+2 cycloaddition between 2-cyclopenten-1-one (**9**) and vinyl acetate (**10**) to establish the core ring system, as depicted in Scheme 1.[11] Thus, irradiation of a solution of **9** in argon-

degassed, HPLC grade hexanes in the presence of a 10-fold excess of **10** in a Pyrex® vessel for 42 h provided the known adduct **11**, which was isolated in 84% yield after silica gel chromatography to separate it from quantities of polymerized **10**.[12,13] Although **11** was isolated as an approximately equal mixture of epimers at C-6, this was inconsequential to the overall synthetic strategy since this chiral center was destined to be sacrificed by oxidization to the racemic ketone after manipulation of the cyclopentane carbonyl moiety. Elaboration of **11** to racemic **8** was accomplished by first protecting the cyclopentanone moiety of **11** as the dioxolane **12** with subsequent reductive removal of the ester functionality under anhydrous conditions by treatment with $LiAlH_4$ in $Et_2O$. The resulting alcohol was oxidized to (±)-**8** using Collins' reagent prepared *in situ.*[14] On a large scale, these transformations were generally accomplished without purification of the intermediates and racemic **8** was isolated in 80% overall yield from **11** after distillation at reduced pressure, collecting the fraction boiling between 105-110 °C at 0.07 mm Hg.

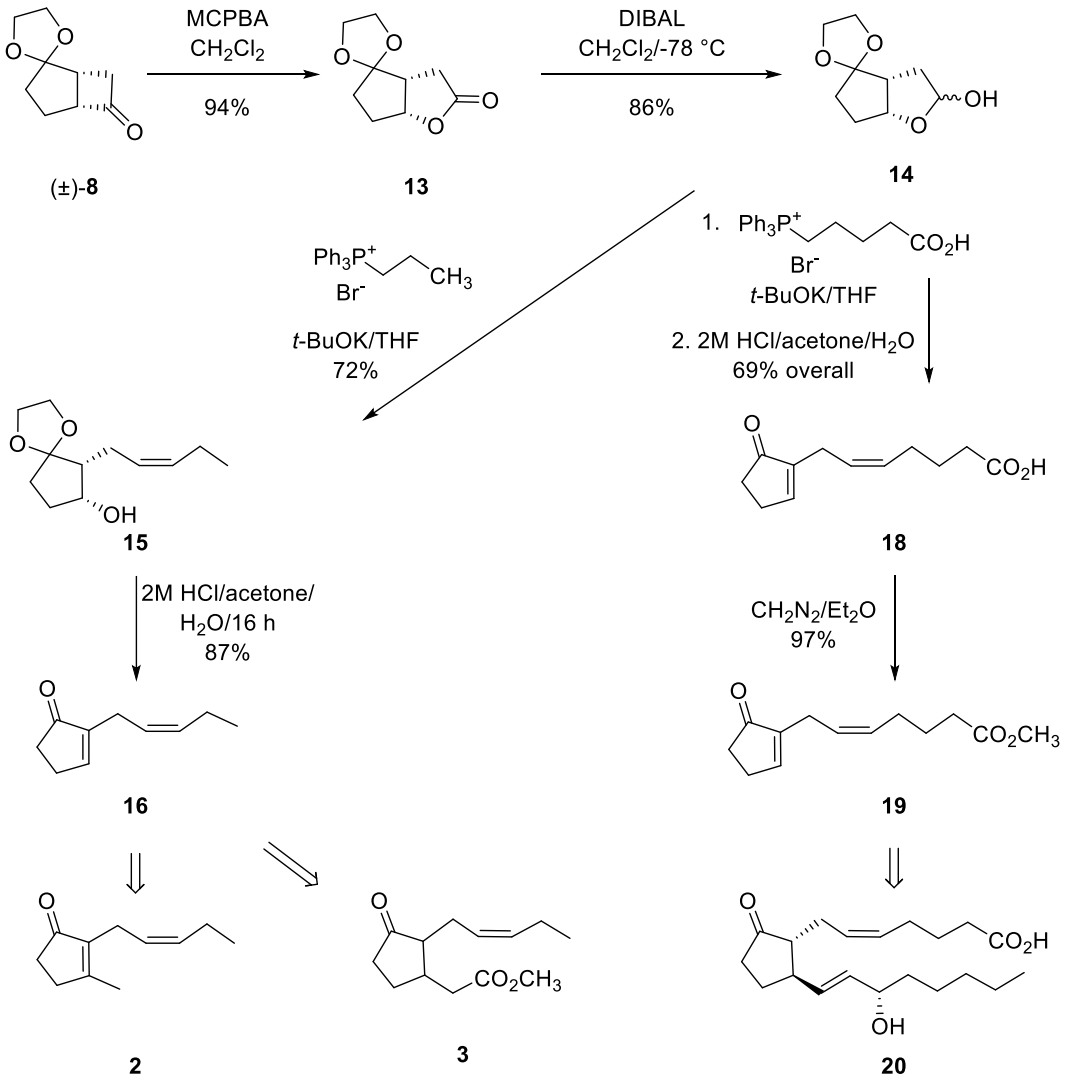



**Scheme 1.** Four-step synthetic approach to (±)-**8** from cyclopentenone **9**.

The elaboration of **8** into jasmonoids and 11-deoxy prostanoid derivatives required the lactone **13** which was anticipated to be the major product of a Baeyer-Villiger process.[15] In contrast, access to the isomeric lactone **29**, a more challenging target, required development of an alternative and complementary reaction manifold (*vide infra*).

Formal synthetic access to 11-deoxy-$PGE_2$ (**20**), *cis*-jasmone (**2**) and (±)-methyl jasmonate (**3**) from (±)-**8** proceeded through the intermediacy of the common precursor lactol **14** (Scheme 2). Treatment of **8** with *meta*-chloroperoxybenzoic acid (MCPBA) in $CH_2Cl_2$ effected oxidative ring expansion which proceeded in a classic Baeyer-Villiger fashion to afford lactone **13**, isolated in 94% yield.[14,15] Reduction of **13** to lactol **14** was accomplished in 86% yield by exposure to diisobutylaluminium hydride [($i$-$Bu_2AlH)_2$, DIBAL] in $CH_2Cl_2$ at -78 °C.[16] A Wittig reaction of **14** with the ylide prepared by treatment of propyltriphenylphosphonium bromide with *t*-BuOK in THF afforded olefin **15**, a synthetic precursor to *cis*-jasmone (**2**) and (±)-methyl jasmonate (**3**), in 72% yield.[16] Acid-induced unmasking of the carbonyl functionality in **15** was accompanied by elimination of water to provide the known cyclopentenone derivative **16** which has been transformed into **2** by way of the 1,2-addition of MeLi to the carbonyl moiety followed by an oxidative rearrangement mediated by $CrO_3$ in 5% $H_2SO_4$ in $Et_2O$ as solvent.[16] (±)-Methyl jasmonate (**3**) has been procured from **16** by a Michael addition reaction with a dialkyl malonate followed by de(methoxycarbonyl)ation.[4]



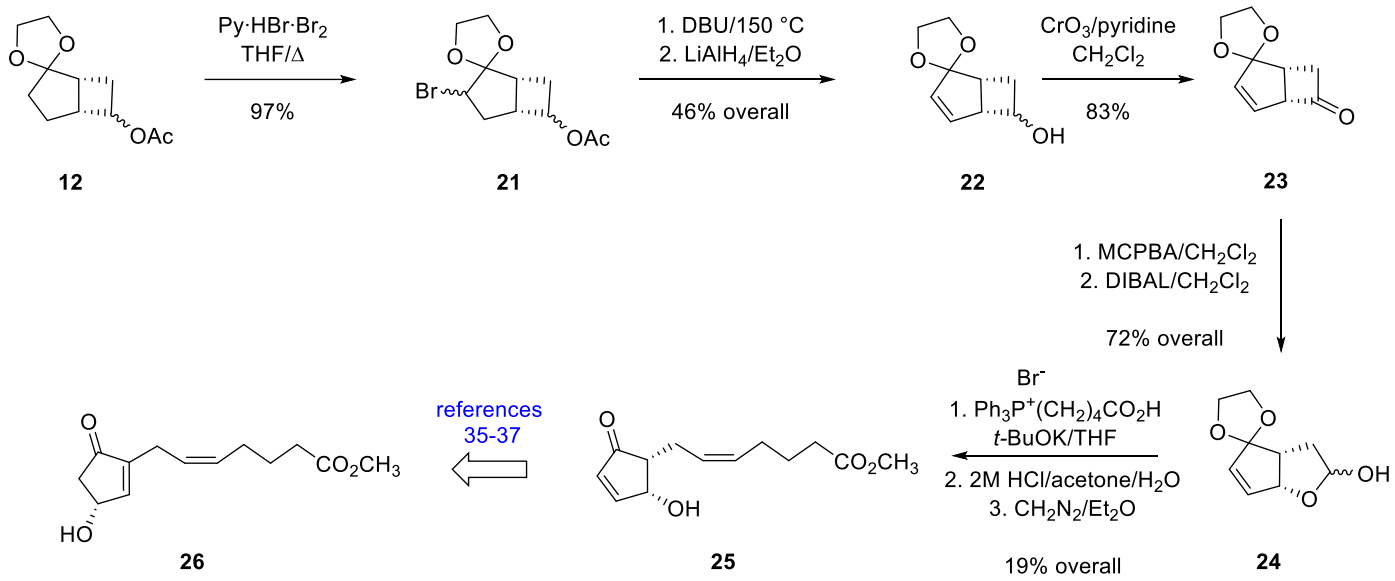

**Scheme 2.** Elaboration of (±)-**8** to **16**, a known synthetic precursor to *cis*-jasmone (**2**) and (±)-methyl jasmonate (**3**), and **19**, an established precursor to racemic 11-deoxy-$PGE_2$ (**20**).[4,16]

An analogous synthetic strategy provided access to the 11-deoxyprostaglandin precursor **18**. Thus, reaction of **14** with the ylide derived from (4-carboxybutyltriphenylphosphonium bromide followed by acid-catalyzed deprotection of the ketone accompanied by concomitant dehydration afforded the known carboxylic acid **18**.[17] Esterification of **18** by treatment with excess diazomethane gave the ester **19** which has been transformed into 11-deoxy-$PGE_2$ (**20**), its C-15 epimer and other prostaglandin derivatives by processes in which the fully functionalized prostaglandin β-side chain is introduced *via* a Michael-type reaction.[2,3,17]

The natural, C-11-substituted prostaglandins are at a higher oxidation state than that represented by **19** and one synthetic entry into this series would therefore require the cyclopentenone **23**, an oxidized derivative of (±)-**8** that was prepared by the route depicted in Scheme 3. Heating a solution of bicyclo[3.2.0]heptan-6-ol acetate ester **12** in THF with pyridinium hydrobromide perbromide afforded the bromo derivative **21** as a mixture of diastereomers.[18,19] Heating a solution of crude **21** in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) under an argon atmosphere effected the elimination of HBr to provide the cyclopentene derivative which proved difficult to purify from an unidentified contaminant. Consequently, the ester group was cleaved from the impure material by reduction with $LiAlH_4$ in $Et_2O$ to afford the mixture of alcohols **22**, isolated in 46%

overall yield after chromatographic purification. Oxidation of **22** with Collins' reagent gave the bicyclo[3.2.0]heptenone **23** which was elaborated by a sequence of reactions identical to those described above for the preparation of the 11-deoxy $PGE_2$ precursor **19**.[14] A Baeyer-Villiger protocol effected oxidative expansion of the cyclobutanone ring to furnish the corresponding lactone which was reduced with DIBAL in $CH_2Cl_2$ at -78 °C to afford the lactol **24**. The prostaglandin α-side chain was introduced using the Wittig methodology utilized for the preparation of **18** and the crude material subjected to acid-catalyzed deprotection of the ketal which was accompanied by simultaneous dehydration to provide the known ester **25** after treatment of the product with diazomethane.[17,20] An elegant rearrangement of **25** to the thermodynamically more stable **26**, a racemic precursor to prostanoid derivatives including $PGE_2$, $PGF_{2\alpha}$ and analogues, by sequential treatment of an ethereal solution with anhydrous chloral hydrate and $Et_3N$ has been described.[20]



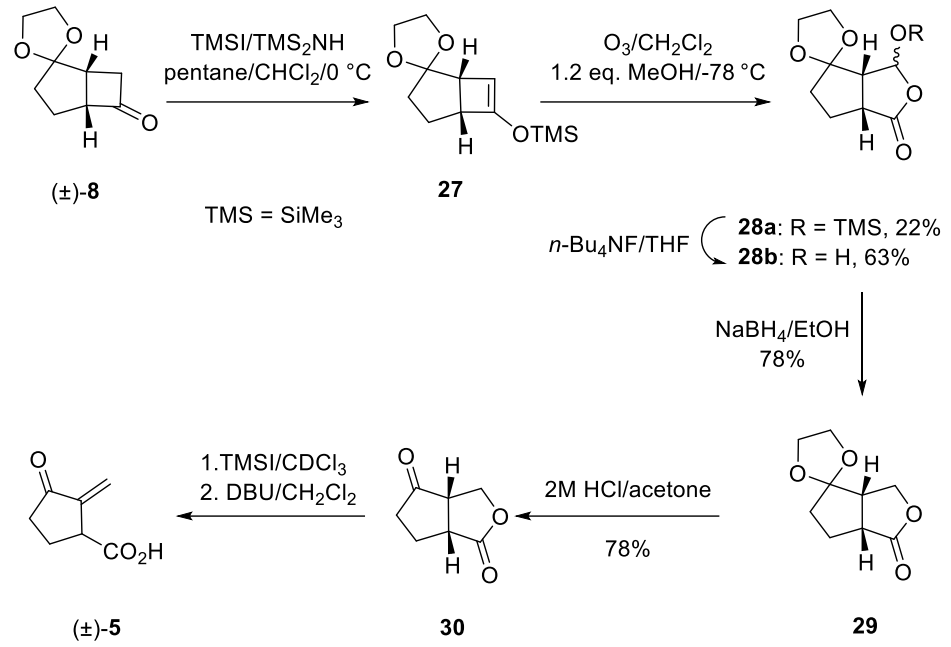

**Scheme 3.** An approach to the synthesis of the cyclopentenone-based $PGE_2$ precursor **25**, a known precursor to **26**, from the bicyclo[3.2.0]heptan-6-ol acetate ester **12**.

Synthetic access to (±)-sarkomycin (**5**) and ketone **6**, the racemic precursor to the enantiomers of hop ether (**4**), required access to the lactone **29** that is isomeric with **13** and Scheme 4 delineates the sequence developed to provide access to this useful synthetic intermediate. The approach adopted relied upon ozonolysis of the silyl enol ether derived from the cyclobutanone fragment of **8** planned to be conducted in the presence of MeOH to intercept the transient carbonyl oxide intermediate derived from rearrangement of the primary ozonide (molozonide).[21-23] Enolization of **8** and trapping with a silyl chloride was anticipated to favor the depicted regioisomer based on Bredt's rule, in contrast to the homologous bicyclo[4.2.0]octan-7-one systems where the formation of bridgehead enolates was observed.[24-26] However, attempts to prepare the silyl enol ether **27** by deprotonating **8** with lithium diisopropylamide (LDA) and quenching the enolate with either trimethylsilyl chloride (TMS-Cl) or *tert*-butyldimethylsilyl chloride (TBDMS-Cl) followed by an aqueous work up were less than successful, affording only poor yields of the respective products. This observation was attributed to the ring strain inherent to the fused bicyclic system that conferred lability to **27**.[25] However, treatment of **8** with trimethylsilyl iodide (TMS-I) and hexamethyldisilazane ($TMS_2NH$) at 0 °C in pentane containing a small amount of $CH_2Cl_2$ under an argon atmosphere provided the trimethylsilyl enol ether **27**

cleanly after a non-aqueous work-up in which the reaction mixture was diluted with pentane, filtered and concentrated.[27] Under these conditions, the potentially sensitive ketal moiety of **27** was preserved while significant amounts of ring expansive rearrangement were not observed.[28,29] As a consequence of its hydrolytic lability, silyl enol ether **27** was not purified; rather, the crude material was directly subjected to ozonolytic degradation at -78 °C in $CH_2Cl_2$. MeOH was included in this process to capture the transient carbonyl oxide intermediate derived from the primary ozonide (molozonide) and preclude its rearrangement to the secondary ozonide, which is more stable than the molozonide and can require a strong reducing agent for degradation.[21-23] However, the lability of the enol silane of **27** toward MeOH at room temperature required careful consideration of reaction choreography to arrive at the optimum conditions which relied upon use of only a 10% excess of MeOH which was added to the solution of **27** in $CH_2Cl_2$ at -78 °C immediately prior to the introduction of ozone.[30] Variation from this protocol led to inferior yields of **28** accompanied by the recovery of significant amounts of ketone **8**, presumably due to the facile transfer of the trimethylsilyl (TMS) group from **27** to the added MeOH. Quenching the hydroperoxy intermediates with $Me_2S$ led to a mixture of the TMS ether **28a** (22%) and alcohol **28b** (63%), which were readily separated by flash chromatography.[21-23,30] Ether **28a** decomposed slowly to **28b** over several days of exposure to the atmosphere but this transformation was more rapidly achieved by treatment of **28a** with *n*-$Bu_4NF$ in THF. Both **28a** and **28b** were isolated as mixtures of diastereomers and a sample of the major constituent **28b** was separated from **28a** after a single recrystallization. However, the presence of mixtures of isomers was of no consequence to the overall strategy since the chiral center was to be destroyed in the subsequent transformation. Reduction of **28b** with $NaBH_4$ in MeOH followed by quench with dilute acid provided the known lactone intermediate **29** in 65% yield accompanied by a small amount (13%) of the deprotected ketone cyclosarkomycin (**30**).[31] Complete conversion of **29** to **30** was effected by treatment with aqueous HCl in acetone.[31] While cyclosarkomycin (**30**) is converted slowly into (±)-sarkomycin (**5**) under acidic conditions, we examined an alternative approach employing TMS-I.[31-34] Treatment of a solution of **30** in $CDCl_3$ with a slight excess of TMS-I resulted in the complete disappearance of starting material overnight, a reaction conveniently monitored by $^1H$ NMR.[35,36] Treatment of the crude product with DBU afforded unstable (±)-sarkomycin (**5**) after filtration through a plug of silica gel.[6,31-34,37-39] Interestingly, TMS-I, generated *in situ* from TMS-Cl and NaI in $CH_3CN$, has been reported to be an ineffective reagent for an analogous transformation.[40]

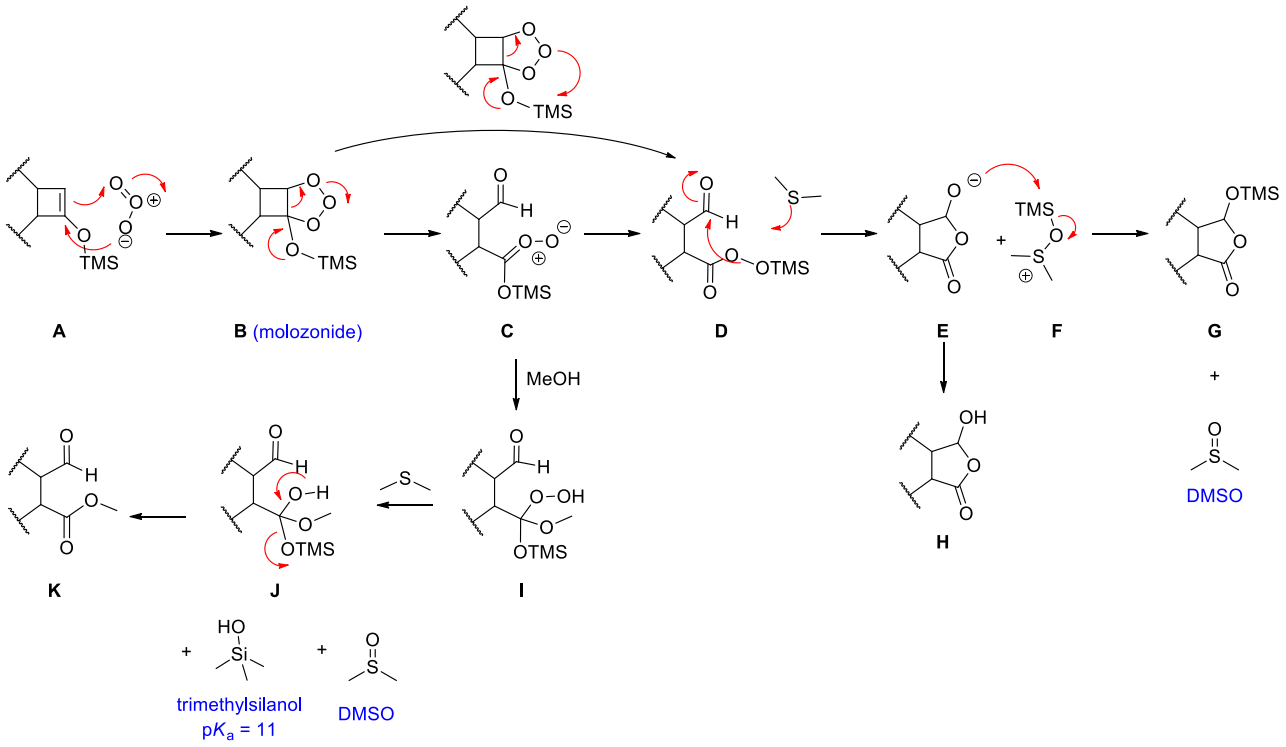
 




**Scheme 4.** The synthesis of (±)-sarkomycin (**5**) from the fused cyclobutanone (±)-**8**.

The ozonolytic degradation of silyl enol ether **27** to afford **28a** and **28b** and the results of this process described in the literature are deserving of additional comment. The original experimental protocol developed for the ozonolysis of silyl enol ethers used a 50:50 mixture of MeOH and $CH_2Cl_2$ as the solvent, presumably to maximize the potential for capture of the carbonyl oxide intermediate by MeOH.[22] The typical products from the ozonolysis of silyl enol ethers are molecules with a carboxylic acid at one terminal carbon atom of the olefin and a carbonyl moiety, either an aldehyde or ketone dependent on the substitution patten, at the other terminal carbon atom of the olefinic element of the substrate.[22] As depicted in Scheme 5, the mechanism of ozonolysis is believed to proceed *via* a 3+2 cycloaddition of $O_3$ to the silyl enol ether **A** to afford the primary ozonide (molozonide) **B**.[21-23] In the case of enol ethers, cycloreversion would be expected to produce the carbonyl oxide **C** which is typically intercepted by the MeOH used as a cosolvent to afford the hydroperoxide intermediate **I**. At this juncture, the addition of $Me_2S$ would reduce hydroperoxide **I** to the acid **J** which would be expected to expel trimethylsilanol, p$K_a$ = 11, rather than the more basic MeOH, p$K_a$ = 14, to generate a methyl ester **K** rather than a carboxylic acid.[41] However, carboxylic acids are typically isolated from the reaction of silyl enol ethers with $O_3$, which is suggestive of an alternative degradation pathway.[22,42] One possibility involves an intramolecular transfer of the trimethylsilyl moiety of **C** to the proximal nucleophilic hydroperoxyl anion to generate the silylated peroxy acid **D** which could also be produced directly from **B** if silyl transfer occurred concomitantly with the rearrangement, as depicted mechanistically above the arrow. This decomposition pathway would be expected to be facilitated by the enhanced nucleophilicity of the hydroperoxyl anion as a consequence of the adjacent lone pair or α-effect.[43] Reduction of **D** with $Me_2S$ would then release the carboxylic acid product that is typically observed. In the case of cyclic silyl enol ethers, reactive association of the carboxylic acid and pendent aldehyde would afford the heterocycle **E** and, after protonation, the 5-hydroxydihydrofuran-2(3*H*)-one **H**, which is the major product **28b** observed after exposing **27** to ozone. The dimethyl[(trimethylsilyl)oxy]sulfonium side product **F** could function as a source of TMS, reacting with **E** to afford the silylated derivative **G**, which was also isolated as compound **28a** from the reaction of **27** with $O_3$.[42,44]

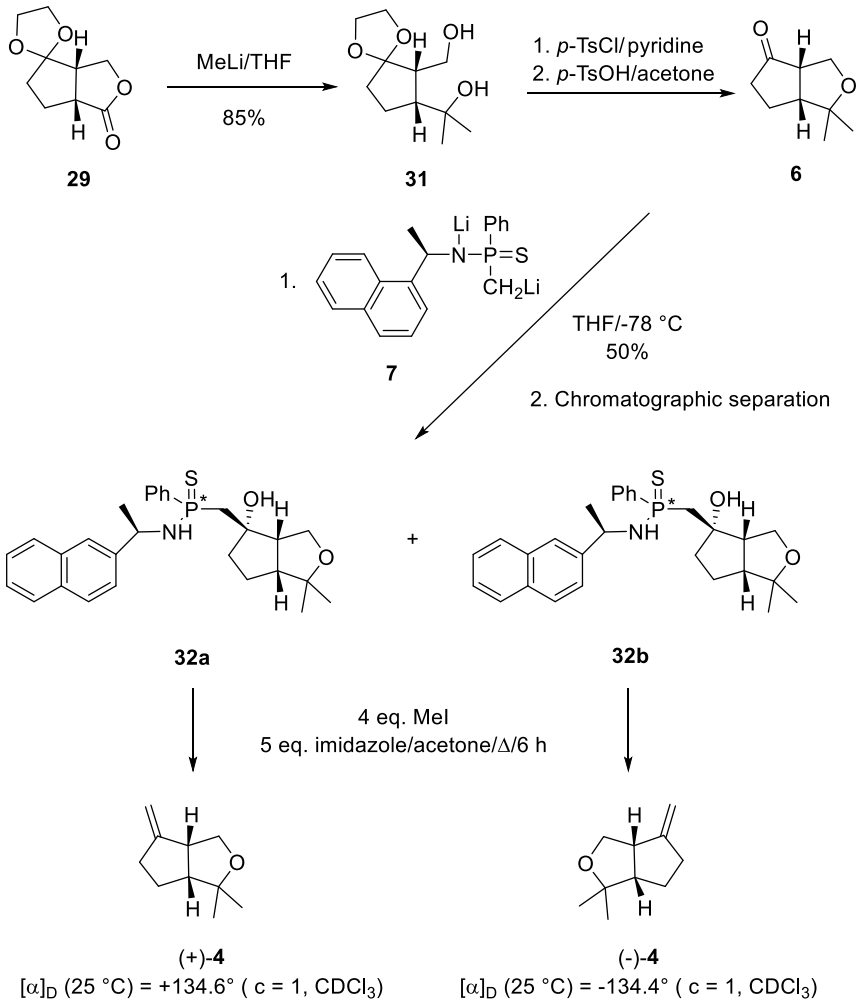
 




**Scheme 5.** Mechanistic considerations in the reaction of silyl enol ethers with ozone.

The lactone **29** also served as a useful synthetic precursor to the Japanese hop constituent hop ether (**4**) by the synthetic sequence summarized in Scheme 6.[8,45,46] Treatment of **29** with an excess of MeLi in THF afforded the diol **31**, a key intermediate in the process described earlier, which was converted to the bicyclic ketone **32** by exposure to *para*-toluenesulfonyl chloride (*p*-TsCl) in pyridine to effect ring closure.[8,47] Removal of the carbonyl protecting moiety was accomplished by exposure to a catalytic quantity of *para*-toluenesulfonic acid (*p*-TsOH) in acetone which afforded the bicyclic ketone **32**.[8,47] Methylenation with concomitant resolution was explored using variants of the protocols developed in these laboratories.[8,9,48] Addition of the dianion of the more polar diastereomer of phosphinothioic amide **7** to **6** provided a mixture of diastereomers **32a** and **32b** which were separable by careful medium pressure liquid chromatography (MPLC), unlike the adducts of **6** derived by the addition of the lithium anion of (±)-*N*,*S*-dimethyl-*S*-phenylsulfoximine.[8,9,49] The more mobile alcohol, **32a**, was isolated as a crystalline solid, mp 172-173 °C while the more polar material **32b** was obtained as an oil.[8] Alkylative fragmentation of **32a** using MeI and imidazole in refluxing acetone provided (+)-hop ether (**4**), $[\alpha]_D$ (25 °C) = +134.6° (c = 1, $CDCl_3$), which appears to be of higher optical purity than the material isolated from natural sources, $[\alpha]_D$ (25 °C) = +36.7° (c = 0.97, $CHCl_3$).[8,50,51] When **32b** was subjected to the same conditions to promote elimination, (-)-hop ether (**4**), $[\alpha]_D$ (25 °C) = -133.4° (c = 1, $CDCl_3$), was isolated in 61% yield.




**Scheme 6.** The synthesis of hop ether (**4**) from lactone **29** exploiting an optical resolution of intermediates from a modified Wittig-type reaction. Note that the absolute configuration of natural hop ether (**4**) is unknown and the designation depicted is arbitrary in nature.

## Conclusions

We have described a straightforward preparation of the uniquely-configured bicyclo[3.2.0]heptane derivative (±)-**8** which demonstrates versatility as a synthetic intermediate for the preparation of several cyclopentane-derived natural products. The fundamental elaborations of racemic **8** along complementary reaction manifolds are dependent upon synthetic methodology that facilitates access to the two isomeric lactones **13** and **29**. While **13** can be obtained by a standard Baeyer-Villiger process and elaborated into jasmonoids **2** and **3** and 11-deoxy prostanoids **20** or further functionalized to provide access to prostaglandins like $PGF_{2\alpha}$ (**1**) that have a higher oxidation state, synthetic access to hop ether (**4**) and (±)-sarkomycin (**5**) required methodology that would provide the alternate lactone **29**. This was accomplished by ozonolysis of the silyl enol ether **27** in which the topology of oxidation was essentially determined by Bredt's rule that dictated regioselective olefin formation away from the bridgehead carbon. Both oxidation processes provide excellent complementary regioselectivity, which is in contrast to the results observed with microbial-based ring expansion processes that, dependent upon the enzyme employed, are regiodivergent although asymmetric in nature.[52]

## Experimental Section

**General.** Melting points were recorded on a Thomas-Hoover capillary apparatus. Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on a Varian T60 or T60-A instrument operating at 60 MHz or a Nicolet FT spectrometer operating at 300 MHz. Carbon ($^{13}$C) spectra were recorded on a JEOL JNM-FX60 FT spectrometer. All spectra were recorded using tetramethylsilane as an internal standard and signal multiplicity was designated according to the following abbreviations: s = singlet, d = doublet, t = triplet, q=quartet, m = multiplet, bs = broad singlet. Infrared (IR) spectra were obtained using a Perkin-Elmer 267 spectrophotometer and are calibrated to the 1601 cm$^{-1}$ absorption of a polystyrene film. Mass spectral data were obtained on an AEI-MS-902 spectrometer operating at 24 or 70 eV. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter using a 1 decimeter cell maintained at a constant temperature with a Haake constant temperature bath. Elemental analyses were provided by Midwest Microlabs, Indianapolis, Indiana.

**6-(Acetyloxy)-bicyclo[3.2.0]heptan-2-one (11).** Argon was bubbled for 15 min through a solution of **9** (16.00 g, 0.19 mol) and **10** (168 g, 180 mL, 1.95 mol) in HPLC grade hexanes (180 mL) in a Pyrex glass vessel. The vessel was sealed and the mixture irradiated with a 450 W Hanovia medium pressure lamp for 42 h. The mixture was concentrated *in vacuo* and the residue chromatographed on a column of silica gel using a mixture of hexanes and $Et_2O$ (2:1) as eluant to afford **11** (27.63 g, 84%) that exhibited $^1$H NMR data consistent with that reported in the literature.[12]

**Spiro[bicyclo[3.2.0]heptane-2,2'-[1,3]dioxolan]-6-ol acetate (12).** A solution of **11** (2.00 g, 12 mmol), ethylene glycol (0.81 g, 0.74 mL, 13 mmol), pTsOH (catalytic amount) and benzene (40 mL) was stirred at reflux under a Dean and Stark trap for 90 min. The solvent was removed and the residue chromatographed on a column of silica gel eluting with a mixture of hexanes and $Et_2O$ (2:1) to afford **12** (2.35 g, 93%) as an oil. IR (film) 1740 (C=O) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.45-3.25 (8H, m), 2.06 (3H, bs, C$\underline{H}_3$CO), 3.77-4.03 (4H, m, OC$\underline{H}_2$C$\underline{H}_2$O), 4.50-5.27 (1H, m, C$\underline{H}$OCOCH$_3$). Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.26; H, 7.55. Found: C, 62.38; H, 7.70.

**Spiro[bicyclo[3.2.0]heptane-2,2'-[1,3]dioxolan]-6-ol.** A solution of **12** (1.00 g, 4.7 mmol) in anhydrous $Et_2O$ (5 mL) was added dropwise to a stirred slurry of $LiAlH_4$ (179 mg, 4.7 mmol) in anhydrous $Et_2O$ (15 mL) maintained at 0 °C. After 10 min, $H_2O$ was added dropwise until the inorganic salts aggregated, the ethereal layer was decanted and the residue washed several times with $Et_2O$. The combined organic phase was dried over $Na_2SO_4$, the solvent evaporated and the residual oil chromatographed on a column of silica gel using $Et_2O$ and hexanes (3:1) as eluant to afford the title compound (758 mg, 94%). IR (film) 3400 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.40-1.90 (8H, m), 3.33 (1H, bs, O$\underline{H}$), 3.70-4.00 (4H, m, OC$\underline{H}_2$C$\underline{H}_2$O), 4.00 to 4.58 (1H, m, C$\underline{H}$OH). Anal. Calcd. for $C_9H_{14}O_3$: C, 63.53; H, 8.24. Found: C, 63.64; H, 8.34.

**Spiro[bicyclo[3.2.0]heptane-2,2'-[1,3]dioxolan]-6-one ((±)-8).** Anhydrous pyridine (1.49 g, 1.53 mL, 19.2 mmol) was added to a stirred suspension of $CrO_3$ (960 mg, 9.6 mmol) in anhydrous $CH_2Cl_2$ (25 mL).[14] After 30 min, a solution of spiro[bicyclo[3.2.0]heptane-2,2'-[1,3]dioxolan]-6-ol (272 mg, 1.6 mmol) in anhydrous $CH_2Cl_2$ (5 mL) was added in one portion and the mixture stirred vigorously for 30 min. The organic phase was decanted, the residual salts were washed several times with $CH_2Cl_2$ and the combined organic extracts were washed with $H_2O$. After drying over $Na_2SO_4$, the solvent was evaporated to leave an oil which was chromatographed on a column of silica gel using a mixture of hexanes and $Et_2O$ (13:7) as eluant to furnish (±)-**8** (229 mg, 85%). IR (film) 1780 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.73-2.17 (4H, m), 2.47-3.73 (4H, m), 3.83-4.13 (4H, m, OC$\underline{H}_2$C$\underline{H}_2$O). Anal. Calcd. for $C_9H_{12}O_3$: C, 64.29; H, 7.14. Found: C, 64.05; H, 7.41.

When conducted on a large scale, 27.63 g of **11** was processed without purification of the intermediates to afford 22.30 g (80%) of (±)-**8** which was isolated by distillation at reduced pressure collecting the fraction boiling at 105-115 °C at 0.07 mm Hg.

**Hexahydrospiro[4*H*-cyclopenta[b]furan-4,2'-[1,3]dioxolan]-2-one (13).** MCPBA (85% pure, 1.33 g, 6.5 mmol) in $CH_2Cl_2$ (20 mL) was added to a stirred solution of **8** (1.00 g, 5.95 mmol) in $CH_2Cl_2$ (30 mL). After 30 min, the reaction mixture was diluted with $CH_2Cl_2$ and washed twice with 5N NaOH solution. The aqueous extracts were washed with $CH_2Cl_2$, the organic phases combined, washed with satd. $NH_4Cl$ solution and dried over $Na_2SO_4$ before being concentrated. The residual oil was chromatographed on a column of silica gel using a mixture of $Et_2O$ and hexanes (1:1) as eluant to give **13** (1.03 g, 94%). IR (film) 1780 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.60-2.17 (4H, m), 2.53-3.03 (3H, m), 3.83-4.07 (4H, m, OC<u>H</u>$_2$C<u>H</u>$_2$O), 4.85-5.17 (1H, m, C<u>H</u>O). High res. MS calcd. for $C_9H_{12}O_4$: 184.073. Found: 184.073.

**Hexahydrospiro[4*H*-cyclopenta[*b*]furan-4,2'-[1,3]dioxolan]-2-ol (14).** DIBAL (1.275 g, 9 mmol) in hexane (3.41 mL) was added dropwise to a stirred solution of **13** (1.27 g, 6.9 mmol) in anhydrous $CH_2Cl_2$ (20 mL) maintained at -78 °C under an atmosphere of Ar. After 2 h, anhydrous MeOH (5 mL) was added dropwise, the ice bath was removed and the mixture allowed to warm to room temperature. After stirring for 15 min, the mixture was diluted with $CH_2Cl_2$, filtered through Celite and the solvent evaporated. The residue was chromatographed on a column of silica gel using $Et_2O$ as eluant to furnish **14** (1.10 g, 86%). IR (film) 3420 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.48-2.98 (7H, m), 3.90 (4H, bs, OC<u>H</u>$_2$C<u>H</u>$_2$O), 4.47-4.90 (1H, m, C<u>H</u>.O), 5.23-6.00 (1H, m, C<u>H</u>OH). Anal. Calcd. for $C_9H_{14}O_4$: C, 58.06; H, 7.53. Found: C, 58.32; H, 7.49.

**6-(2-Butenyl)-1,4-dioxaspiro[4.4]nonan-7-ol (15).** *t*-BuOK (451 mg, 4 mmol) was added to a stirred suspension of *n*-propyltriphenylphosphonium bromide (1.03 g, 2.7 mmol) in anhydrous THF (20 mL) maintained under an atmosphere of Ar. After 15 min, a solution of **14** (250 mg, 1.36 mmol) in THF (5 mL) was added in one portion and the mixture stirred at room temperature. After 2 h, the mixture was poured onto satd. $NH_4Cl$ solution, extracted with $CH_2Cl_2$ and the combined extracts were dried over $Na_2SO_4$. Evaporation of the solvent afforded an oil which was chromatographed on a column of silica gel using a mixture of $Et_2O$ and hexanes (1:1) as eluant to give **15** (205 mg, 72%). IR (film) 3500 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.93 (3H, t, $J$ = 8 Hz, C<u>H</u>$_3$), 1.55-2.57 (9H, m), 3.70-4.27 (5H, m, OC<u>H</u>$_2$C<u>H</u>$_2$O and C<u>H</u>OH), 5.22-5.67 (2H, m, olefinic <u>H</u>). Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.93; H, 9.43. Found: C, 67.48; H, 9.31.

**2-(2-Pentenyl)-2-cyclpenten-1-one (16).** A solution of **15** (282 mg, 1.33 mmol) in acetone (3 mL) and 2M HCl solution (3 mL) was stirred at room temperature for 16 h. The acetone was evaporated, the residue was extracted with $CH_2Cl_2$ and the extracts were combined and dried over $Na_2SO_4$. Removal of the solvent left an oil which was chromatographed on a column of silica gel using a mixture of hexanes and $Et_2O$ (3:1) as eluant to give **16** (173 mg, 87%) which exhibited spectral properties in accord with the published data.[16]

**7-(5-Oxocyclopent-1-en-1-yl)-5-heptenoic acid (18).**[17] *t*-BuOK (750 mg, 6.7 mmol) was added to a stirred suspension of (4-carboxybutyl)triphenylphosphonium bromide (1.87 g, 4.2 mmol) in anhydrous THF (20 mL). After 15 min, a solution of **14** (250 mg, 1.3 mmol) in anhydrous THF (5 mL) was added in one portion and the mixture stirred at room temperature for 2 h. The mixture was diluted with 2M HCl, extracted with $CH_2Cl_2$ and the combined extracts were dried over $Na_2SO_4$. Evaporation of the solvent left an oil which was dissolved in acetone (5 mL) and 2M HCl solution (1.5 mL) added. The mixture was stirred at ambient temperature for 2 h, concentrated and the residue extracted with $CH_2Cl_2$. The extracts were dried over $Na_2SO_4$, concentrated and the residual oil was subjected to chromatography on a column of silica gel. Elution with $Et_2O$ afforded **18** (276 mg, 69%). IR (film) 3400, 1710 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.42-3.05 (12H, m), 5.47 (2H, m, olefinic <u>H</u>), 7.23 (1H, m, olefinic <u>H</u> of ring).[17]

**Methyl 7-(5-oxocyclopent-1-en-1-yl)-5-heptenoate (19).** An excess of $CH_2N_2$ in $Et_2O$ was added to a solution of **18** (276 mg, 1.32 mmol) in $Et_2O$. After 20 min, AcOH (3 mL) was added, the mixture stirred for 10 min and then concentrated *in vacuo*. Chromatography of the residue on a column of silica gel using $Et_2O$ as eluant afforded **19** (285 mg, 97%) which exhibited IR and $^1$H NMR spectral data in accord with the published data.[17]

**3-Bromospiro[bicyclo[3.2.0]heptane-2,2'-[1,3]dioxolan]-6-ol acetate (21).** A solution of **12** (3.00 g, 14 mmol) in anhydrous THF (10 mL) was added to a stirred solution of pyridinium hydrobromide perbromide (4.99 g, 15.6 mmol) in anhydrous THF (50 mL). The mixture was heated at reflux under an atmosphere of Ar for 30 min, diluted with $H_2O$ and extracted with $Et_2O$. The extracts were dried over $Na_2SO_4$, concentrated and the residual oil subjected to chromatography on a column of silica gel. Elution with a mixture of hexanes and $Et_2O$ (7:3) afforded **21** (4.00 g, 97%). IR (film) 1740 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.68-2.87 (6H, m), 2.03 and 2.07 (3H, s, CO.C<u>H</u>$_3$), 3.67-5.47 (6H, m). High res. MS calcd. for $C_{11}H_{15}BrO_4$: 290.016. Found: 290.015.

**Spiro[bicyclo[3.2.0]hept-3-en-2,2'-[1,3]dioxolan]-6-ol acetate.** A mixture of **21** (4.20 g, 14.4 mmol) and DBU (8 mL) was stirred at 150 °C under an atmosphere of Ar for 45 min. The mixture was cooled and chromatographed on a column of silica gel using a mixture of hexanes and $Et_2O$ (1:1) as eluant to afford the title compound contaminated with an unidentified impurity (2.075 g). An analytical sample was prepared by acetylating ($Ac_2O$/$C_5H_5N$/cat. DMAP/$CH_2Cl_2$) a sample of the alcohol **22**. IR (film) 1740 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.75-3.40 (4H, m), 2.07 (3H, s, CO.C<u>H</u>$_3$), 3.57-4.08 (4H, m, OC<u>H</u>$_2$C<u>H</u>$_2$O), 4.33-5.18 (1H, m, C<u>H</u>.OCOCH$_3$), 5.53-6.30 (2H, m, olefinic <u>H</u>). High res. MS calcd. for $C_{11}H_{14}O_4$: 210.089. Found: 210.089.

**Spiro[bicyclo[3.2.0]hept-3-en-2,2'-[1,3]dioxolan]-6-ol (22).** A solution of impure spiro[bicyclo[3.2.0]hept-3-en-2,2'-[1,3]dioxolan]-6-ol acetate (2.075 g) in anhydrous $Et_2O$ (10 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (380 mg, 10 mmol) in anhydrous $Et_2O$ (80 mL). After completing the addition, the mixture was stirred at ambient temperature for 5 min, $H_2O$ added dropwise until the salts aggregated and the organic phase decanted. The residue was washed several times with $Et_2O$, the combined organic extracts were dried over $Na_2SO_4$ and concentrated. The residual oil was chromatographed on a column of silica gel using a mixture of $Et_2O$ and hexanes (3:2) as eluant to give **22** (1.13 g). IR (film) 3400 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.76-3.77 (4H, m), 3.77-4.77 (5H, m, OC<u>H</u>$_2$C<u>H</u>$_2$O + C<u>H</u>OH), 5.85 (1H, d, *J* = 6 Hz, olefinic <u>H</u>), 6.20 (1H, dd, *J* = 6 Hz, J' = 2 Hz, olefinic <u>H</u>).

**Spiro[bicyclo[3.2.0]hept-3-en-2,2'-[1,3]dioxolan]-6-one (23).** Pyridine (3.67 g, 3.75 mL, 46.4 mmol) was added dropwise to a suspension of $CrO_3$ (2.32 g, 23.2 mmol) in anhydrous $CH_2Cl_2$.[14] After 30 min, a solution of **22** (650 mg, 3.8 mmol) in anhydrous $CH_2Cl_2$ (5 mL) was added in one portion and the mixture stirred at ambient temperature for 30 min. The organic phase was decanted, the residue was washed several times with $CH_2Cl_2$ and the combined organic phase was washed with $H_2O$, dried over $Na_2SO_4$ and concentrated. The residual oil was chromatographed on a column of silica gel using a mixture of hexanes and $Et_2O$ (2:1) as eluant to afford **23** (533 mg, 83%). IR (film) 1790 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 2.53-3.39 (3H, m, C<u>H</u>.C<u>H</u>$_2$CO), 3.80-4.37 (5H, m, OC<u>H</u>$_2$C<u>H</u>$_2$O + CH=CH.C<u>H</u>), 5.88 (1H, d, *J* = 6 Hz, olefinic <u>H</u>), 6.07 (1H, dd, *J* = 6 Hz, *J*′ = 2 Hz, olefinic <u>H</u>). High res. MS calcd. for $C_9H_{10}O_3$: 166.063. Found: 166.063.

**Hexahydrospiro[4*H*-cyclopenta[*b*]furan-5-en-4,2'-[1,3]dioxolan]-2-one.** MCPBA (80% pure, 390 mg, 1.8 mmol) was added to a stirred solution of **23** (100 mg, 1.8 mmol) in $CH_2Cl_2$ (10 mL) maintained at 0 °C. The mixture was warmed to ambient temperature and stirred for 30 min before being diluted with $CH_2Cl_2$ and washed 3 times with satd. $NaHCO_3$ solution. The organic phase was dried over $Na_2SO_4$, concentrated and the residual oil chromatographed on a column of silica gel. Elution with a mixture of $Et_2O$ and hexanes (2:1) afforded the title compound (247 mg, 75%). $^1$H NMR ($CDCl_3$) $\delta$ 2.51-3.33 (3H, m, C<u>H</u>.C<u>H</u>$_2$CO), 3.78-4.13 (4H, m, OC<u>H</u>$_2$C<u>H</u>$_2$O), 5.41 (1H, dd, *J* = 6 Hz, *J*′ = 2 Hz, C<u>H</u>O), 5.98 (1H, d, *J* = 6 Hz, olefinic <u>H</u>), 6.20 (1H, dd, *J* = 6 Hz, *J*′ = 2 Hz, olefinic <u>H</u>). High res. MS calcd. for $C_9H_{10}O_4$: 182.057. Found: 182.057.

**Hexahydrospiro[4*H*-cyclopenta[*b*]furan-5-en-4,2'-[1,3]dioxolan]-2-ol (24).** DIBAL (375 mg, 2.6 mmol) in hexane (1 mL) was added dropwise to a stirred solution of hexahydrospiro[4*H*-cyclopenta[*b*]furan-5-en-4,2'-[1,3]dioxolan]-2-one (370 mg, 2.0 mmol) in anhydrous $CH_2Cl_2$ (10 mL) maintained at -78 °C under an atmosphere of Ar. After 1 h, MeOH (2 mL) was added dropwise, the mixture warmed to room temperature and filtered through Celite. The solvent was evaporated and the residual oil chromatographed on a column of silica gel using $Et_2O$ as eluant to give **24** (360 mg, 96%). IR (film) 3420 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.65-2.32 (3H, m), 3.77-4.43 (5H, m, $OCH_2CH_2O$ + CHOH), 4.94-6.42 (3H, m, olefinic H + allylic H).

**Methyl 7-(7-hydroxy-1,4-dioxaspiro[4.4]non-8-en-6-yl)-5-heptenoate (25).** *t*-BuOK (1.095 g, 9.8 mmol) was added to a stirred suspension of (4-carboxybutyl)triphenylphosphonium bromide (1.733 g, 3.9 mmol) in anhydrous THF (15 mL). After 15 min, a solution of **24** (360 mg, 1.9 mmol) in anhydrous THF (5 mL) was added and the mixture stirred at ambient temperature overnight before being poured onto 2M HCl solution. The mixture was extracted with $Et_2O$ (once) and $CH_2Cl_2$ (twice) and the organic phases were combined and dried over $Na_2SO_4$. Concentration gave an oil which was dissolved in acetone (20 mL) and to which 2M HCl solution (1 mL) was added. The mixture was stirred for 2 h, concentrated, the residue extracted with $CH_2Cl_2$ and the combined extracts were dried over $Na_2SO_4$. Evaporation of the solvent left an oil which was dissolved in $Et_2O$ and excess $CH_2N_2$ in $Et_2O$ added. After 10 min, the excess $CH_2N_2$ was destroyed by adding AcOH, the mixture concentrated and the residue chromatographed on a column of silica gel. Elution with $Et_2O$ afforded **25** (90 mg, 19%). IR (film) 3450, 1750-1700, 1595 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.13-2.53 (9H, m), 3.65 (3H, s, $CO_2CH_3$), 5.00 (1H, m, CHOH), 5.43 (2H, m, olefinic H of side chain), 6.16 (1H, dd, $J$ = 6 Hz, $J'$ = 2 Hz, olefinic H of ring), 7.52 (1H, dd, $J$ = 6 Hz, $J'$ = 3 Hz, olefinic H of ring).[35]

**Trimethyl[spiro[3.2.0]hept-6-ene-2,2'-[1,3]dioxolan-6-yl]oxy]silane (27).** TMSI (654 mg, 0.47 mL, 3.3 mmol) was added by syringe to a stirred solution of **8** (500 mg, 3 mmol) and $TMS_2NH$ (718 mg, 0.92 mL, 4.5 mmol) in anhydrous pentane (10 mL) and anhydrous $CH_2Cl_2$ (2 mL) maintained at 0 °C under an atmosphere of Ar. After 1 h, the mixture was diluted with anhydrous pentane, filtered and the solvent evaporated to afford crude **27** which was used without further purification. IR (film) 1620 $cm^{-1}$; Key $^1H$ NMR signals were: ($CDCl_3$) $\delta$ 0.02 (9H, s), 3.80-3.92 (4H, bs, $OCH_2CH_2O$), 4.60 (1H, bs).

**Hexahydro-3-[(trimethylsilyloxy]spiro[4*H*-cyclopenta[*c*]furan-4,2'-1,3-dioxolan]-1-one (28a) and hexahydro-3-hydroxyspiro[4*H*-cyclopenta[*c*]furan-4,2'-1,3-dioxolan]-1-one (28b).**

A solution of crude **27** (presumed to be 714 mg, 2.98 mmol) in anhydrous $CH_2Cl_2$ (10 mL) was cooled to -78 °C and MeOH (104 mg, 0.132 mL, 3.25 mmol) added. $O_3$ was bubbled through the stirred solution until a blue color persisted. The $O_3$ supply was removed, the flask flushed with argon and $Me_2S$ (1 mL) added. The mixture was stirred at -78 °C for 30 min and at room temperature for 1 h. The solvent was removed *in vacuo* and the residue chromatographed on a column of silica gel using $Et_2O$ as eluant to afford **28a** (180 mg, 22%. IR (film) 1782 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.17 (9H, s), 1.50-2.30 (4H, m), 2.60 (1H, d, $J$ = 8 Hz), 3.00-3.57 (1H, m, CH.CO), 3.90 (4H, s, $OCH_2CH_2O$), 5.50 and 6.08 (1H, d, $J$ = 2 Hz, CHOTMS, ratio 1:7).

Further elution gave **28b** (375 mg, 63%) as a solid. IR ($CHCl_3$) 3580, 3480, 1775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.50-2.33 (4H, m), 2.66 (1H, d, $J$ = 8 Hz, CH.CHOH), 3.03-3.83 (1H, m, CH.CO), 3.96 (4H, s, $OCH_2CH_2O$), 4.93 (1H, bs, OH), 5.60 and 5.83 (1H, d, $J$ = 2 Hz, CHOH, ratio 1:4). Recrystallization from a mixture of $Et_2O$ and $CH_2Cl_2$ provided a pure sample of the major diastereomer, mp 102-104 °C. IR ($CHCl_3$) 3580, 3480, 1775 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.50-2.33 (4H, m), 2.70 (1H, dd, $J$ = 9 Hz, $J'$ = 2 Hz), 3.03-3.53 (1H, m, CH.CO), 4.00 (4H, s, $OCH_2CH_2O$), 4.60 (1H, bs, OH); 5.83 (1H, d, $J$ = 2 Hz, CHOH). Anal. calcd. for $C_9H_{12}O_5$: C, 54.00; H, 6.00. Found: C, 53.84; H, 6.16.

**Hexahydro-3-hydroxyspiro[4*H*-cyclopenta[*c*]furan-4,2'-1,3-dioxolan]-1-one (28b).** *n*-$Bu_4NF$ (1M in THF, 108 mg, 0.72 mmol) was added to a stirred solution of **28a** (180 mg, 0.66 mmol) in $CH_2Cl_2$ (5 mL). After 30 min, the mixture was diluted with satd. $NH_4Cl$ solution and extracted with $CH_2Cl_2$. The combined organic phase was dried over $Na_2SO_4$, concentrated and the residue was chromatographed on a column of silica gel. Elution with $Et_2O$ gave **28b** (79 mg, 60%).

**Hexahydrospiro[4*H*-cyclopenta[*c*]furan-4,2'-1,3-dioxolan]-1-one (29) and tetrahydro-1*H*-cyclopenta[*c*]furan-1,4(5*H*)-dione (30).** $NaBH_4$ (410 mg, 10.8 mmol) was added portion-wise over 5 min to a solution of **28b** (1.08 g, 5.4 mmol) in anhydrous MeOH (15 mL) maintained at -35 °C. After completion of the addition, the mixture was warmed to room temperature, stirred for 30 min and the solvent evaporated. The residue was diluted with satd. NaCl solution, acidified with 2M HCl solution and extracted 6 times with $CH_2Cl_2$. The combined extracts were dried over $Na_2SO_4$, concentrated and the residue was chromatographed on a column of silica gel using $Et_2O$ as eluant to give **29** (645 mg, 65%), mp 67-67.5 °C (needles from $Et_2O/CH_2Cl_2$), lit. mp 67-67.5 °C.[31] Further elution gave **30** (105 mg, 13%), mp 45.5-47 °C (needles from $Et_2O/CH_2Cl_2$), lit. mp 45-46 °C.[31]

**Tetrahydro-1*H*-cyclopenta[*c*]furan-1,4(5*H*)-dione (30).** A mixture of **29** (865 mg, 4.7 mmol), acetone (1 mL) and 2M HCl solution (10 mL) was stirred vigorously for 1 h. The mixture was diluted with satd. NaCl solution, extracted with $CH_2Cl_2$ and the combined extracts were dried over $Na_2SO_4$. Evaporation of the solvent and chromatography of the residue on a column of silica gel afforded **30** (517 mg, 78%).

**(±)-Sarkomycin (5).** TMSI (186 mg, 0.137 mL, 0.93 mmol) was added by syringe to a solution of **30** (100 mg, 0.7 mmol) in $CDCl_3$ (3 mL) maintained under an atmosphere of Ar. After standing overnight at room temperature, the mixture was diluted with $H_2O$ and extracted with $CH_2Cl_2$. The combined organic phase was washed with $Na_2S_2O_3$ solution and $H_2O$ and dried over $Na_2SO_4$. Evaporation of the solvent gave an oil which was dissolved in $CH_2Cl_2$ (5 mL) and DBU (350 mg, 0.35 mL, 2.3 mmol) added. After stirring at room temperature for 1 h, the mixture was diluted with 2M HCl solution and extracted with $CH_2Cl_2$. The combined extracts were washed with 2M HCl solution, dried over $Na_2SO_4$ and concentrated and the residue was dissolved in a mixture of $Et_2O$ and MeOH (9:1) and filtered through a plug of silica gel to give **5** (78 mg, 78%) which displayed $^1$H NMR spectral data in accord with that published.[37-39]

**2-[6-(Hydroxymethyl)-1,4-dioxaspiro[4.4]nonan-7-yl]propan-2-ol (31).** MeLi (90 mg, 4 mmol) in $Et_2O$ (2.72 mL) was added dropwise to a solution of **29** (250 mg, 1.36 mmol) in anhydrous THF (5 mL) maintained at -78 °C under an atmosphere of Ar. After 30 min, the mixture was warmed to 0 °C, poured onto satd. $NH_4Cl$ solution and extracted with $CH_2Cl_2$. The combined extracts were dried over $Na_2SO_4$ and concentrated to leave a solid which was chromatographed on a column of silica gel using $Et_2O$ as eluant to furnish **31** (250 mg, 85%). Recrystallization from $CH_2Cl_2$/hexanes gave analytically pure material, mp 111-112 °C. IR ($CHCl_3$) 3400 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.19 (3H, s, C$\underline{H}_3$), 1.35 (3H, s, C$\underline{H}_3$), 1.60-1.40 (6H, m), 3.60-4.13 (8H, m, OC$\underline{H}_2$C$\underline{H}_2$O + C$\underline{H}_2$OH + 2 x O$\underline{H}$). Anal. calcd. for $C_{11}H_{20}O_4$: C, 61.11; H, 9.26. Found: C, 61.31; H, 9.43.

**1,1-Dimethylhexahydrospiro[cyclopenta[*c*]furan-4,2'-[1,3]dioxolane.** A solution of **31** (216 mg, 1 mmol) and *p*TsCl (228 mg, 1.2 mmol) in anhydrous pyridine (5 mL) was allowed to stand at room temperature overnight. The mixture was diluted with $CH_2Cl_2$ and washed twice with 2M HCl solution before being dried over $Na_2SO_4$. The solvent was evaporated and the residue was chromatographed on a column of silica gel using a mixture of hexanes and $Et_2O$ (3:1) as eluant to give 1,1-dimethylhexahydrospiro[cyclopenta[*c*]furan-4,2'-[1,3]dioxolane (196 mg, 98%). IR ($CHCl_3$) 2800, 2400 cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 1.17 (3H, s, C$\underline{H}_3$), 1.25 (3H, s, C$\underline{H}_3$), 1.57-2.00 (4H, m), 2.17-2.97 (2H, m), 3.70-4.00 (6H, m, C$\underline{H}_2$O). Anal. calcd. for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09. Found: C, 66.99; H, 9.19.[8,47]

**1,1-Dimethyltetrahydro-1*H*-cyclopenta[*c*]furan-4(5*H*)-one (32).** A solution of 1,1-dimethylhexahydrospiro[cyclopenta[*c*]furan-4,2'-[1,3]dioxolane] (1.09 g, 5.1 mmol) and *p*-TsOH (catalytic quantity) in acetone (20 mL) was stirred at room temperature for 2 h. The mixture was filtered through a pad of neutral alumina and the solvent evaporated to leave **6** (847 mg, 100%) which exhibited spectral properties in accord with the published data.[47]

***P*-Methyl-*N*-[1-(1-naphthalenyl)ethyl]-*P*-phenylphosphinothioic amide (7).** A solution of methylphenylphosphinothioic chloride (19.06 g, 0.1 mol) in anydrous THF (80 mL) was added dropwise to a stirred solution of (+)-(*R*)-1-(1-naphthyl)ethylamine (17.12 g, 0.1 mol) and $Et_3N$ (20.24 g, 0.2 mol) in anydrous THF (800 mL) maintained at 0 °C. The mixture was stirred for 2 h and then warmed to room temperature. After stirring for 14 h, the mixture was filtered and concentrated to leave an oil which was purified by flash chromatography using hexane and EtOAc (10:1) as eluant. The diastereomers were subsequently separated by preparative MPLC using a mixture of hexane and EtOAc (10:1) as eluant. The more mobile material (12.99 g, 40%) was isolated as a viscous oil. IR ($CHCl_3$) 3370, 2980, 1298, 1176, 1118, 955, 895 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): See supplemental data; $[\alpha]_D$ (25 °C) +11.71° (c = 1.3, $CHCl_3$). Anal. calcd. for $C_{19}H_{20}NPS$: C, 70.13; H, 6.20. Found: C, 70.07; H, 6.05.

Further elution provided the more polar diastereomer as a solid (12.70 g, 39%), mp 113 °C. IR ($CHCl_3$) 3370, 2980, 1298, 1176, 1118, 955, 895 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): See supplemental data; $[\alpha]_D$ (25 °C) +47.07° (c = 0.98, $CHCl_3$). Anal. calcd. for $C_{19}H_{20}NPS$: C, 70.13; H, 6.20. Found: C, 70.08; H, 6.21.

**Adducts 32a and 32b.** A solution of nBuLi in hexane (11.2 mmol) was added dropwise to a solution of the more polar diastereomer of **7** (1.82 g, 5.6 mmol) in anhydrous THF maintained at -78 °C under an atmosphere of Ar. After 5 min, the mixture was warmed to room temperature, stirred 15 min and then re-cooled to -78 °C. A solution of **6** (0.86 g, 5.6 mmol) in THF (5 mL) was added dropwise, the mixture stirred at -78 °C for 3 h and warmed to 0 °C before being poured onto satd. $NH_4Cl$ solution. The mixture was extracted with $Et_2O$, the combined extracts were dried over $Na_2SO_4$ and the solvent removed. The residual colorless solid was subjected to medium pressure liquid chromatography (MPLC) over silica gel using a mixture of hexane, EtOAc and $CH_2Cl_2$ (12:3:1) as eluant to give **32a** (0.75 g, 28%), mp 172-173 °C. IR ($CHCl_3$) 3310, 2960, 1440, 1370, 1295, 1175, 1105, 955 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): See supplemental data; $[\alpha]_D$ (25 °C) +14.83° (c = 1, $CHCl_3$). Anal. calcd. for $C_{28}H_{34}NO_2PS$: C, 70.12; H, 7.15. Found: C, 70.18; H, 6.98.

Further elution gave **32b** (0.59 g, 22%). IR ($CHCl_3$) 3310, 2960, 1440, 1370, 1295, 1175, 1105, 955 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): See supplemental data; $[\alpha]_D$ (25 °C) -32.83° (c = 1, $CHCl_3$). Anal. calcd. for $C_{28}H_{34}NO_2PS$: C, 70.12; H, 7.15. Found: C, 69.98; H, 6.99.

**(+)-Hop ether ((+)-4).** A mixture of **32a** (0.55 g, 1.15 mmol), imidazole (0.39 g, 5.73 mmol), MeI (0.43 mL, 4.6 mmol) and acetone (9 mL) was stirred at 65 °C for 6 h. The mixture was diluted with $H_2O$, extracted with $Et_2O$ and the combined extracts were concentrated *in vacuo* to give an oil which was chromatographed on a column of silica gel. Elution with a mixture of pentane and $Et_2O$ (9:1) afforded (+)-hop ether (**4**) that displayed $^1H$ NMR data in accord with the literature.[5] IR (film) 3070, 2950, 1725, 1653 $cm^{-1}$; $^{13}C$ NMR ($CDCl_3$) $\delta$ 23.4 (q), 27.4 (2C, m), 34.9 (t), 49.5 (d), 54.1 (d), 72.3 (t), 82.6 (s), 105.8 (t), 156.3 (s);[50] $[\alpha]_D$ (25 °C) +134.6° (c = 1, $CDCl_3$).

**(-)-Hop ether ((-)-4).** A mixture of **32b** (0.34 g, 0.72 mmol), imidazole (0.24 g, 3.59 mmol), MeI (0.27 mL, 2.9 mmol) and acetone (6 mL) was stirred at 65 °C for 6 h. Isolation performed as described above afforded (-)-hop ether ((-)-**4**). IR, $^1H$ NMR and $^{13}C$ NMR ($CDCl_3$) identical to those recorded for the (+) enantiomer; $[\alpha]_D$ (25 °C) -133.4° (c = 1, $CDCl_3$).

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## Supplementary Material

NMR spectra for *P*-methyl-*N*-[1-(1-naphthalenyl)ethyl]-*P*-phenylphosphinothioic amide (**7**) and adducts **32a** and **32b**.

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50. Note that the $^{13}$C NMR data reported in reference 5 differs from the data that we obtained. Both (+)- and (-)-hop ether prepared either by the Wittig-type process or by the $CH_2Br_2$/Zn/$TiCl_4$ process reported in reference 8 gave $^{13}$C data that are slightly different from that disclosed in the article. A similar observation was made by Lin *et al.* who indicated the absence of one signal.[51]
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