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# Synthesis of Dimethyl Gloiosiphone A by Way of Palladium-Catalyzed Domino Cyclization

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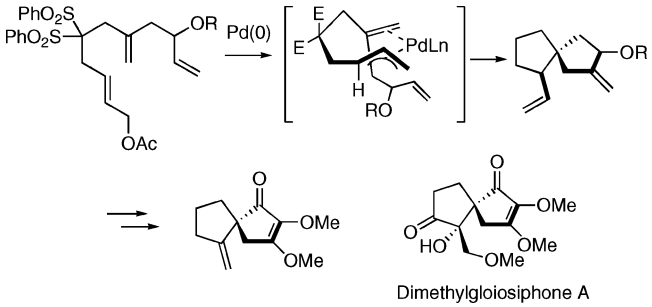


Dimethylgloiosiphone A

The synthesis of a spiro[4.4]nonane skeleton by the palladium-catalyzed domino cyclization of a linear 7-methylene-2,10-undecadienyl acetate is described. The $\pi$-allylpalladium intermediate underwent intramolecular alkene insertion with high intraannular diastereoselectivity, followed by intramolecular Heck-type cyclization, leading to a spiro[4.4]nonane system. Oxidation of the allylic ether moiety and transformation of the vinyl group to an *exo*-methylene unit provided **3**, which is the known synthetic intermediate of dimethyl gloiosiphone A (**2**).

## Introduction

Reactions of $\pi$-allylpalladium complexes with various nucleophiles are important for carbon−carbon bond formations.[1] Since Oppolzer reported that palladium-catalyzed cyclization of 2,7-octadienyl acetate in acetic acid provides 1-methylene-2-vinylcyclopentane,[2] intramolecular insertion of alkene, alkyne, and allene moieties to the $\pi$-allylpalladium complex[3] has been applied to the construction of not only five- and six-membered rings but also fused ring systems.[4] We have already demonstrated that palladium-catalyzed domino cyclization of 6-vinyl-2,8-nonadienyl acetate formed a trans fused bicyclo[3.3.0]octane system.[5] It was further applied to the construction of a four ring fused system from a linear alkenyl−allenyl−allylic acetate via six consecutive carbon−carbon bond formations under carbonylation conditions.[6] Few examples using the intramolecular alkene insertion to a $\pi$-allylpalladium complex in the formation of a spiro ring system have been reported, although the Heck-type polyene cyclizations were demonstrated.[7−10] We wish to report palladium-catalyzed domino cyclization of a 7-methylene-2,10-undecadienyl acetate derivative providing a spiro[4.4]-

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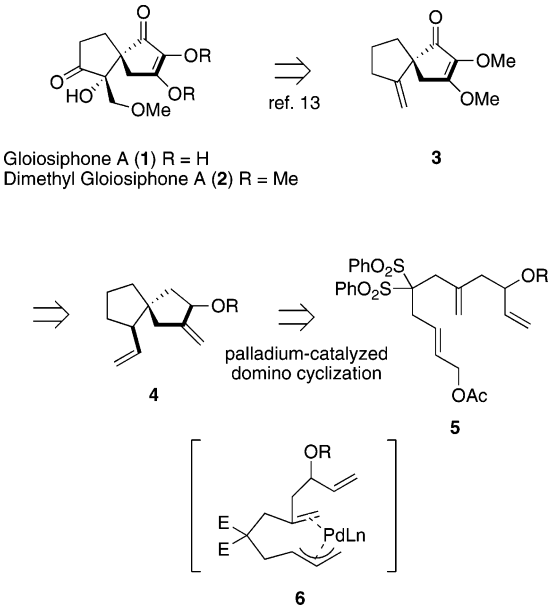



**FIGURE 1.** Synthetic strategy of dimethyl gloiosiphone A (**2**).

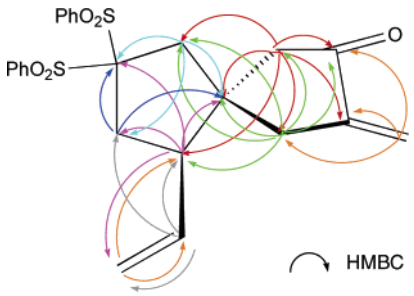
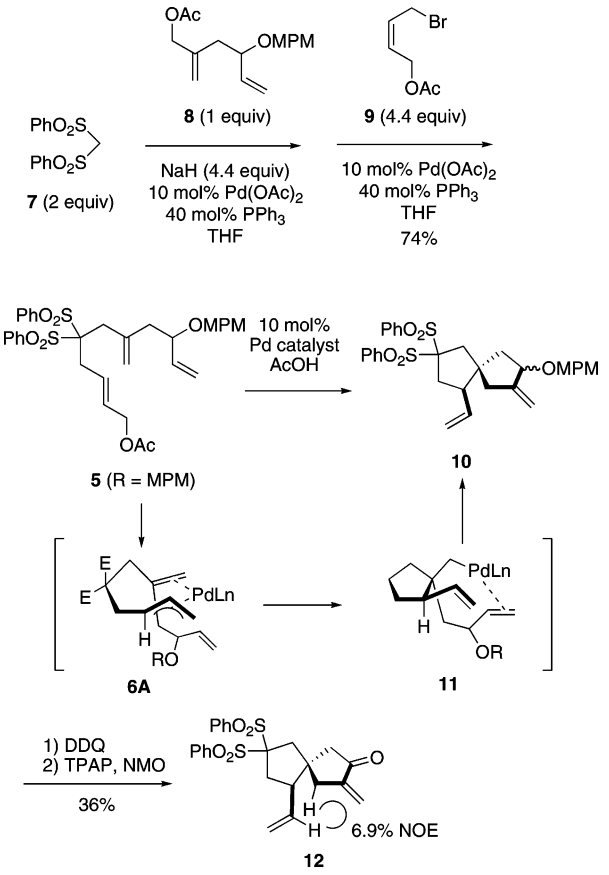



**FIGURE 2.** HMBC analysis of compound **12**.

nonane system and its application to a formal total synthesis of dimethyl gloiosiphone A (**2**).

Gloiosiphone A (**1**), isolated from *Gloiosiphonia verticillaris*, exhibits antimicrobial activity against several *Staphylococcus*, *Bacillus*, and *Salmonella* species.[11] Since **1** is not stable, the structure was proved as its di-*O*-methylated derivative **2**. These compounds have a highly oxygenated spiro[4.4]nonenedione system. Three total syntheses of dimethyl gloiosiphone A (**2**) utilizing unique construction of the spiro[4.4]nonane system have been reported.[12−14] Our synthetic strategy for **2** is illustrated in Figure 1. Spiro[4.4]nonane **4** can be constructed from a linear precursor **5** by way of palladium-catalyzed domino cyclization, such as intramolecular alkene insertion to a $\pi$-allylpalladium intermediate **6**, followed by Heck-type cyclization. Oxidative transformation of the allylic ether moiety in **4** would form 2,3-dimethoxy-2-cyclopentenone, and the vinyl moiety in **4** can be converted to a methylene unit to provide **3**, which is the known synthetic intermediate in the total synthesis of **2**.[13]

**SCHEME 1. Palladium-Catalyzed Domino Cyclization of 5**




## Results and Discussion

A linear precursor **5** (R = MPM) was prepared by palladium-catalyzed one-pot sequential allylation of bis(phenylsulfonyl)-methane (**7**) (Scheme 1).[15] A suspension of **7** (2 equiv) and an excess amount of NaH (4.4 equiv) were treated with 2-substituted allyl acetate **8** (1 equiv) in the presence of a palladium catalyst. In the first allylation, 2 equiv of **7** was used to avoid diallylation of **7**. After the reaction was complete, *cis*-4-bromo-2-butenyl acetate (**9**) (4.4 equiv) was added to the reaction mixture in one pot. It is theoretically essential to add 4 equiv of NaH and **9** to complete the second allylation and to consume remaining **7**. Although it was necessary to add an additional amount of the palladium catalyst to complete the second allylation, the bromo group in **9** was selectively displaced by forming a $\pi$-allylpalladium intermediate to provide (*E*)-**5** in 74% overall yield.[16] The product **5** was isolated by silica gel column chromatography, whereas the diallylation product of **7** with **9** was also obtained.

The palladium-catalyzed domino cyclization of **5** was investigated by tuning ligands and reaction temperature (Table 1). The reaction proceeded at 90 °C better than at the lower temperature (entry 3 vs entries 1 and 2).[6b] Addition of triphenylphosphine provided better results than other ligands, such as tri(2-furyl)phosphine (38% in entry 4) and *o*-tolylphosphine (40% in entry 5). The desired spiro[4.4]nonane **10** was obtained as a 60:40 diastereomer mixture in 66% yield (entry 3). Deprotection of the MPM group in **10**, followed by oxidation,

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**TABLE 1. Palladium-Catalyzed Domino Cyclization of 5 to 10**

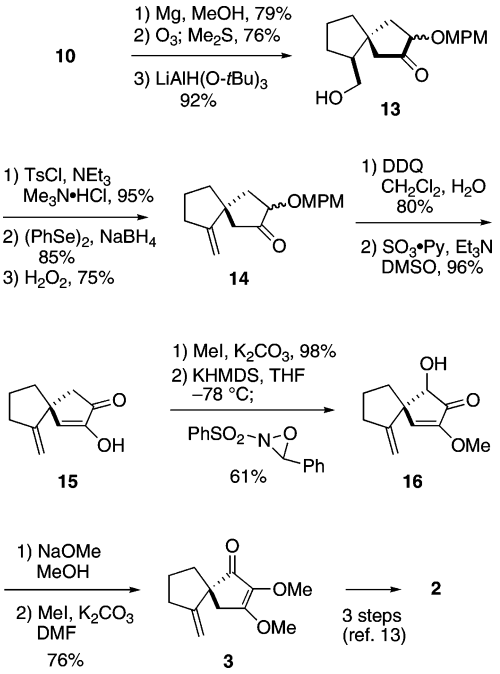
| entry | $Pd(OAc)_2$ (10 mol %) + ligand (40 mol %) | temp (°C) | yield (%) of **10** |
|---|---|---|---|
| 1 | $PPh_3$ | 70 | 58 |
| 2 | $PPh_3$ | 80 | 57 |
| 3 | $PPh_3$ | 90 | 66 |
| 4 | P(2-furyl)$_3$ | 90 | 38 |
| 5 | P(*o*-tol)$_3$ | 90 | 40 |

provided **12** as a single product, whose structure was determined by analysis of H−H COSY, HMBC (Figure 2), and HMQC spectra and NOE measurement. The results exhibited that this system exclusively controlled the intraannular diastereoselection in the Pd(0)-catalyzed cyclization via **6A**, and the resulting $\sigma$-palladium intermediate **11** underwent the intramolecular Heck reaction, followed by $\beta$-hydride elimination, leading to the formation of a spiro compound **10**.[17] On the other hand, diastereoselectivity induced from the stereogenic center of the methoxyphenylmethyloxy (OMPM) substituent was not high.

Removal of the phenylsulfonyl groups in **10** with Mg,[18] ozonolysis of the two alkene moieties, and selective reduction of the resulting aldehyde with LiAlH(O-*t*Bu)$_3$ provided **13**. The primary alcohol in **13** was converted into a phenylselenyl group[19] by displacement of its tosylate.[20] Oxidative $\beta$-hydride elimination of the phenylselenyl group afforded **14** in 61% overall yield. Removal of the MPM group, followed by oxidation of the resulting alcohol with $SO_3$•Py afforded **15**, which was in equilibrium with 1,2-diketone. After *O*-methylation, α-hydroxyketone **16** was prepared by treatment with KHMDS and the Davis reagent.[21] Base treatment of **16** provided the thermodynamically stable 2-hydroxy-3-methoxy-6-methylenespiro[4.4]non-2-en-1-one, which was immediately converted to **3** by *O*-methylation in 76% overall yield. The spectral data of **3** were identical to those reported by Sha and Ho, who have demonstrated the total synthesis of **2** from **3** in three steps.[13] Thus, this synthesis constitutes a formal total synthesis of dimethyl gloiosiphone A (**2**) (Scheme 2).

In conclusion, we have demonstrated palladium-catalyzed domino cyclization of **5**, synthesized by a one-pot two-step allylation, which stereoselectively provides a spiro[4.4]nonane skeleton. Oxidation of the allylic ether moiety and transformation of the vinyl group to an *exo*-methylene unit furnished the desired 6-methylene-2,3-dimethoxyspiro[4.4]non-2-en-1-one (**3**).

**SCHEME 2. Formal Total Synthesis of Dimethyl Gloiosiphone A (2)**




## Experimental Section

**(*E*)-9-(4-Methoxybenzyloxy)-7-methylene-5,5-di(phenylsulfonyl)-2,10-undecadienyl acetate (5).** To a suspension of sodium hydride (1.26 g, 28.9 mmol, 55%, washed with dry hexane) in THF (10 mL) was added bis(phenylsulfonyl)methane (**7**) (3.89 g, 13.1 mmol) in THF (10 mL) at 0 °C. When gas evolution was complete, a solution of 4-(4-methoxybenzyloxy)-2-methylene-5-hexenyl acetate (**8**) (1.91 g, 6.57 mmol), palladium acetate (148 mg, 0.657 mmol), and triphenylphosphine (689 mg, 2.63 mmol) in THF (20 mL) was added at room temperature and stirred at reflux for 3 h. A solution of (*Z*)-4-bromo-2-butenyl acetate (**9**) (4.19 g, 28.9 mmol), palladium acetate (148 mg, 0.657 mmol), and triphenylphosphine (689 mg, 2.63 mmol) in THF (20 mL) was added at room temperature and stirred under reflux for another 1 h. The reaction mixture was poured into 1 M HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (25% ethyl acetate in hexane) to give (*E*)-9-(4-methoxybenzyloxy)-7-methylene-5,5-di(phenylsulfonyl)-2,10-undecadienyl acetate (**5**) (3.11 g, 4.86 mmol, 74%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.96−8.00 (m, 4H), 7.65−7.69 (m, 2H), 7.49−7.54 (m, 4H), 7.20−7.22 (m, 2H), 6.86−6.88 (m, 2H), 5.86−5.94 (m, 1H), 5.65−5.73 (m, 2H), 5.17−5.21 (dd, $J$ = 17.5, 10.2 Hz), 5.10 (s, 1H), 5.08 (s, 1H), 4.44−4.49 (m, 3H), 4.21 (d, 1H, $J$ = 11.1 Hz), 3.80−3.88 (m, 4H), 3.12 (d, 2H, $J$ = 6.3 Hz), 3.01 (s, 2H), 2.32−2.41 (m, 2H), 2.06 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 170.8, 159.2, 138.4, 137.4, 137.3, 134.6, 131.8, 130.7, 129.4, 129.3, 128.6, 127.6, 120.7, 117.4, 113.8, 91.7, 79.6, 69.9, 64.5, 55.4, 43.9, 36.0, 33.4, 21.0; IR (neat) 1739, 1514, 1448, 1311, 1247, 1144, 1077, 725, 689, 572 cm$^{-1}$; HRMS (ESI-TOF) calcd for $[C_{34}H_{38}O_8S_2 + Na]^+$ 661.1906, found 661.1900.

**7-(4-Methoxybenzyloxy)-8-methylene-3,3-di(phenylsulfonyl)-1-vinylspiro[4.4]nonane (10).** To a solution of (*E*)-9-(4-methoxybenzyloxy)-7-methylene-5,5-di(phenylsulfonyl)-2,10-undecadienyl acetate (**5**) (2.50 g, 3.92 mmol) in acetic acid (15 mL) were added palladium acetate (88 mg, 0.392 mmol) and triphenylphosphine (411 mg, 1.57 mmol) at room temperature. After being stirred at 90 °C for 2 h, the reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (7% ethyl acetate in toluene) to give 7-(4-methoxybenzyloxy)-8-methylene-3,3-di(phenylsulfonyl)-1-vinylspiro[4.4]nonane (**10**) (1.50 g, 2.60 mmol, 66%, dr = 60:40). The diastereomers were separated by HPLC (20% ethyl acetate in hexane, 3.00 mL/min, RT = 19.5 min (minor isomer), 20.7 min (major isomer)). Major isomer: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02−8.06 (m, 4H), 7.69−7.72 (m, 2H), 7.56−7.59 (m, 4H), 7.19−7.22 (m, 2H), 6.84−6.87 (m, 2H), 5.57−5.66 (m, 1H), 4.98−5.09 (m, 4H), 4.47 (d, 1H, $J$ = 11.1 Hz), 4.36 (d, 1H, $J$ = 11.6 Hz), 4.09−4.13 (m, 1H), 3.81 (s, 3H), 2.77 (d,

(17) After conversion of **10** to *exo*-methylene **14**, a diastereomer mixture was still observed though the stereogenic center at the vinyl group in **10** was lost in **14**. This result also proved the high intraannular diastereoselectivity.

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1H, $J$ = 16.4 Hz), 2.70 (d, 1H, $J$ = 16.4 Hz), 2.46−2.63 (m, 5H), 2.26 (d, 1H, $J$ = 16.9 Hz), 1.90−1.95 (m, 1H), 1.78−1.82 (m, 1H); $^{13}$C NMR (67.8 MHz, $CDCl_3$) $\delta$ 159.0, 150.7, 137.0, 136.2, 135.3, 134.5, 134.4, 131.4, 131.3, 130.7, 129.1, 128.7, 128.6, 118.2, 113.8, 110.7, 93.0, 79.7, 69.9, 55.3, 51.9, 51.8, 45.3, 44.2, 38.5, 37.1; IR (neat) 1613, 1514, 1448, 1328, 1310, 1144, 1078 cm$^{-1}$; HRMS (ESI-TOF) calcd for $[C_{32}H_{34}O_6S_2 + Na]^+$ 601.1694, found 601.1689.

**3-Methylene-8,8-di(phenylsulfonyl)-6-vinylspiro[4.4]nonan-2-one (12).** To a solution of 7-(4-methoxybenzyloxy)-8-methylene-3,3-di(phenylsulfonyl)-1-vinylspiro[4.4]nonane (**10**) (685 mg, 1.18 mmol) in dichloromethane (3.8 mL) and water (0.2 mL) was added DDQ (537 mg, 2.37 mmol) at 0 °C. After being stirred at room temperature, the reaction mixture was diluted with diethyl ether and quenched with saturated aqueous $NaHSO_3$ solution and saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude 3-methylene-8,8-di(phenylsulfonyl)-6-vinylspiro[4.4]nonan-2-ol (399 mg, 0.869 mmol) was used in the next reaction without further purification.

To a solution of 2-hydroxy-3-methylene-8,8-di(phenylsulfonyl)-6-vinylspiro[4.4]nonane (399 mg, 0.869 mmol) and NMO (204 mg, 1.74 mmol) in dichloromethane (5 mL) was added TPAP (15 mg, 0.0435 mmol). After being stirred at room temperature, the reaction mixture was directly subjected to silica gel chromatography (25% ethyl acetate in hexane) to give 3-methylene-8,8-di(phenylsulfonyl)-6-vinylspiro[4.4]nonan-2-one (**12**) (196 mg, 0.429 mmol, 36%, two steps): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.02−8.09 (m, 4H), 7.73−7.76 (m, 2H), 7.60−7.65 (m, 4H), 5.99 (s, 1H), 5.53−5.62 (m, 1H), 5.34 (s, 1H), 5.02−5.12 (m, 2H), 2.53−2.82 (m, 7H), 2.39 (s, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 203.9 (C), 144.3 (C,), 136.7 (C, Ph), 135.9 (C, Ph), 135.0 (CH, Ph), 134.9 (CH, Ph), 134.2 (CH), 131.6 (CH, Ph), 131.4 (CH, Ph), 129.0 (CH, Ph), 128.9 (CH, Ph), 119.8 ($CH_2$), 118.2 ($CH_2$), 92.4 (C), 52.0 (CH), 49.8 ($CH_2$), 48.1 (C), 43.0 ($CH_2$), 37.3 ($CH_2$), 37.0 ($CH_2$); IR (solid) 1727, 1638, 1447, 1309, 1143, 1075, 920, 731, 689, 552, 511, 483, 466 cm$^{-1}$.

**3-(4-Methoxybenzyloxy)-6-(hydroxymethyl)spiro[4.4]nonan-2-one (13).** Into dry methanol (100 mL) was added activated magnesium turnings (washed with 0.1 M HCl, water, methanol, and diethyl ether and heated at 100 °C) (1.25 g, 51.6 mmol). The mixture was stirred at 50 °C. When gas evolution started, a solution of 7-(4-methoxybenzyloxy)-8-methylene-3,3-di(phenylsulfonyl)-1-vinylspiro[4.4]nonane (**10**) (1.20 g, 2.06 mmol) in THF (5 mL) was added at the same temperature. After being stirred for 3 h, the reaction mixture was quenched with 3 M HCl at 0 °C. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (5% ethyl acetate in hexane) to give 2-(4-methoxybenzyloxy)-3-methylene-6-vinylspiro[4.4]nonane (489 mg, 1.63 mmol, 79%, diastereomer mixture).

Ozone was bubbled into a solution of 2-(4-methoxybenzyloxy)-3-methylene-6-vinylspiro[4.4]nonane (230 mg, 0.770 mmol) in dichloromethane (2 mL) and methanol (2 mL) at −78 °C. The solution was purged by bubbling nitrogen to remove excess ozone, and the ozonide was reduced by addition of dimethyl sulfide (225 $\mu$L, 3.08 mmol) at the same temperature. The reaction mixture was allowed to gradually warm to room temperature and diluted with diethyl ether. The organic layer was washed with 1 M HCl and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (20% ethyl acetate in hexane) to give 3-(4-methoxybenzyloxy)-6-formylspiro[4.4]-nonan-2-one (177 mg, 0.586 mmol, 76%, diastereomer mixture).

To a solution of 3-(4-methoxybenzyloxy)-6-formylspiro[4.4]-nonan-2-one (1.80 g, 5.95 mmol) in THF (25 mL) was added LiAl(O$t$-Bu)$_3$H (0.5 M in diglyme, 13.1 mL, 6.55 mmol) at −78 °C. The reaction mixture was quenched with a 10% aqueous solution of potassium sodium tartrate at −78 °C. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (30% ethyl acetate in hexane) to give 3-(4-methoxybenzyloxy)-6-(hydroxymethyl)spiro[4.4]nonan-2-one (**13**) (1.67 g, 5.50 mmol, 92%, diastereomer mixture). Major isomer: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.30−7.27 (m, 2H), 6.88 (d, $J$ = 8.7 Hz, 2H), 4.78 (d, $J$ = 11.1 Hz, 2H), 4.61 (d, $J$ = 11.6 Hz, 2H), 3.91 (dd, $J$ = 9.2, 8.7 Hz, 1H), 3.80 (s, 3H), 3.68 (dd, $J$ = 10.6, 6.8 Hz, 1H), 3.59 (dd, $J$ = 10.6, 6.3 Hz, 1H), 2.43 (d, $J$ = 17.8 Hz, 1H), 2.18−1.87 (m, 5H), 1.69−1.57 (m, 4H), 1.37−1.32 (m, 1H); $^{13}$C NMR (67.8 MHz, $CDCl_3$) $\delta$ 216.2, 159.4, 129.7, 129.6, 113.8, 78.9, 72.0, 63.7, 55.3, 49.5, 44.1, 43.5, 41.5, 40.5, 27.7, 22.0; IR (neat) 3463, 2951, 1744, 1612, 1586, 1513, 1466, 1399, 1302, 1248, 1174, 1034, 822, 754, 518 cm$^{-1}$; HRMS (ESI-TOF) calcd for $[C_{18}H_{24}O_4 + Na]^+$ 327.1567, found 327.1564.

**3-(4-Methoxybenzyloxy)-6-methylenespiro[4.4]nonan-2-one (14).** To a solution of 3-(4-methoxybenzyloxy)-6-(hydroxymethyl)spiro-[4.4]nonan-2-one (**13**) (175 mg, 0.569 mmol), trimethylamine hydrochloride (5 mg, 0.0569 mmol), and triethylamine (0.16 mL, 1.14 mmol) in dichloromethane (3 mL) was added $p$-toluenesulfonyl chloride (163 mg, 0.853 mmol) at 0 °C. After being stirred at the same temperature for 30 min, the reaction mixture was quenched with 1 M HCl. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (15% ethyl acetate in hexane) to give 3-(4-methoxybenzyloxy)-6-($p$-toluenesulfonyloxymethyl)spiro[4.4]-nonan-2-one (247 mg, 0.539 mmol, 95%, diastereomer mixture). Major isomer: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.76 (d, $J$ = 7.7 Hz, 2H), 7.36−7.26 (m, 4H), 6.87 (d, $J$ = 8.7 Hz, 2H), 4.75 (d, $J$ = 11.6 Hz, 1H), 4.58 (d, $J$ = 11.6 Hz, 1H), 4.01−3.80 (m, 6H), 2.44 (s, 3H), 2.23−1.24 (m, 11H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 215.0, 159.4, 145.0, 132.7, 130.0, 129.6, 127.9, 113.9, 78.6, 72.0, 70.7, 55.3, 46.1, 44.0, 43.3, 41.3, 39.7, 27.6, 21.8, 21.6; IR (neat) 2957, 1749, 1613, 1598, 1515, 1464, 1361, 1249, 1176, 1097, 955, 817, 667, 555 cm$^{-1}$; HRMS (ESI-TOF) calcd for $[C_{25}H_{30}O_6S + Na]^+$ 481.1655, found 481.1656.

To a solution of diphenyl diselenide (27 mg, 0.0876 mmol) in THF (1 mL) and methanol (1 mL) was added sodium borohydride (6.6 mg, 0.175 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 30 min. A solution of 3-(4-methoxybenzyloxy)-6-($p$-toluenesulfonyloxymethyl)spiro[4.4]-nonan-2-one (57.4 mg, 0.125 mmol) in THF (1 mL) was added and stirred at reflux. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (20% ethyl acetate in hexane) to give 3-(4-methoxybenzyloxy)-6-(phenylselenylmethyl)spiro[4.4]nonan-2-one (47 mg, 0.106 mmol, 85%, diastereomer mixture).

To a solution of 3-(4-methoxybenzyloxy)-6-(phenylselenylmethyl)-spiro[4.4]nonan-2-one (390 mg, 0.879 mmol) in THF (5 mL) was added hydrogen peroxide (107 $\mu$L, 1.06 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was concentrated in vacuo. The residue was purified by chromatography on silica gel (20% ethyl acetate in hexane) to give 3-(4-methoxybenzyloxy)-6-methylenespiro[4.4]-nonan-2-one (**14**) (190 mg, 0.663 mmol, 75%, diastereomer mixture): $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 7.32−7.26 (m, 2H), 6.91−6.84 (m, 2H), 4.99−4.77 (m, 3H), 4.66−4.55 (m, 1H), 4.08−3.94 (m, 1H), 3.80 (s, 3H), 2.49−2.18 (m, 4H), 2.04−1.56 (m, 6H); IR (neat) 3070, 2956, 1748, 1651, 1613, 1586, 1515, 1465, 1398, 1302, 1248, 1174, 1112, 1036, 881, 821 cm$^{-1}$.

**3-Hydroxy-6-methylenespiro[4.4]non-3-en-2-one (15).** To a solution of 3-(4-methoxybenzyloxy)-6-methylenespiro[4.4]nonan-2-one (**14**) (215 mg, 0.751 mmol) in dichloromethane (3.3 mL) and water (0.18 mL) was added DDQ (256 mg, 1.13 mmol) at 0 °C. After being stirred at room temperature, the reaction mixture was diluted with diethyl ether and quenched with a saturated

aqueous solution of $NaHSO_3$ and a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with diethyl ether. The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (20% ethyl acetate in hexane) to give 3-hydroxy-6-methylenespiro-[4.4]nonan-2-one (100 mg, 0.602 mmol, 80%, diastereomer mixture).

To a solution of 3-hydroxy-6-vinylspiro[4.4]nonan-2-one (22.8 mg, 0.126 mmol) and triethylamine (87 $\mu$L, 0.630) in DMSO (1 mL) was added sulfur trioxide pyridine complex (60 mg, 0.379 mmol) in one portion at room temperature. After being stirred at the same temperature for 10 min, the reaction mixture was quenched with 1 M HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (15% ethyl acetate in hexane) to give 3-hydroxy-6-methylenespiro[4.4]non-3-en-2-one (**15**) (21.6 mg, 0.121 mmol, 96%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.30 (s, 1H), 5.60 (s, 1H), 4.89 (t, $J$ = 1.9 Hz, 1H), 4.76 (t, $J$ = 2.4 Hz, 1H), 2.58−2.35 (m, 4H), 1.89−1.69 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 204.1, 157.4, 151.1, 136.1, 106.1, 49.3, 48.8, 40.7, 32.2, 23.4; IR (neat) 3344, 2955, 2871, 1702, 1655, 1625, 1401, 1256, 1201, 1108, 887 cm$^{-1}$; HRMS (ESI-TOF) calcd for $[C_{10}H_{12}O_2 + Na]^+$ 187.0730, found 187.0725.

**1-Hydroxy-3-methoxy-6-methylenespiro[4.4]non-3-en-2-one (16).** To a solution of 3-hydroxy-6-methylenespiro[4.4]non-3-en-2-one (**15**) (23 mg, 0.139 mmol) in DMF (0.7 mL) were added potassium carbonate (23 mg, 0.167 mmol) and methyl iodide (13 $\mu$L, 0.209 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was quenched with 1 M HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (20% ethyl acetate in hexane) to give 3-methoxy-6-methylenespiro[4.4]non-3-en-2-one (24.3 mg, 0.136 mmol, 98%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.13 (s, 1H), 4.89 (s, 1H), 4.76 (s, 1H), 3.75 (s, 3H), 2.58−2.34 (m, 4H), 1.85−1.69 (m, 4H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.2, 157.9, 155.7, 133.3, 105.8, 57.0, 49.7, 49.0, 41.1, 32.1, 23.3; IR (neat) 3071, 2955, 1720, 1650, 1625, 1453, 1405, 1347, 1290, 1221, 1121, 986, 885 cm$^{-1}$; HRMS (ESI-TOF) calcd for $[C_{11}H_{14}O_2 + Na]^+$ 201.0886, found 201.0884.

To a solution of KHMDS (0.5 M in toluene, 1.56 mL, 0.779 mmol) in THF (0.5 mL) was added a solution of 3-methoxy-6-methylenespiro[4.4]non-3-en-2-one (92.5 mg, 0.519 mmol) in THF (1 mL) at −78 °C and stirred 1 h. To the reaction mixture was added a solution of (±)-*trans*-2-(phenylsulfonyl)-3-phenyloxaziridine (272 mg, 1.04 mmol) in THF (1 mL) at −78 °C. The mixture was gradually allowed to warm to room temperature. The reaction mixture was quenched with 1 M HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (20% ethyl acetate in hexane) to give 1-hydroxy-3-methoxy-6-methylenespiro-[4.4]non-3-en-2-one (**16**) (61.2 mg, 0.315 mmol, 61%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.10 (s, 1H), 5.07 (s, 1H), 4.83 (t, $J$ = 2.4 Hz), 4.09 (s, 1H), 3.74 (s, 3H), 2.89 (br s, 1H), 2.59−2.40 (m, 2H), 2.13−2.07 (m, 1H), 1.91−1.59 (m, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.7, 158.2, 153.4, 132.8, 107.1, 81.0, 56.7, 53.8, 35.8, 33.1, 23.8; IR (neat) 3430, 2957, 1722, 1620, 1453, 1354, 1081, 1066 cm$^{-1}$; HRMS (ESI-TOF) calcd for $[C_{11}H_{14}O_3 + Na]^+$ 217.0835, found 217.0835.

**2,3-Dimethoxy-6-methylenespiro[4.4]non-2-en-1-one (3).** To a solution of 1-hydroxy-3-methoxy-6-methylenespiro[4.4]non-3-en-2-one (**16**) (14.3 mg, 0.0736 mmol) in THF (0.5 mL) and methanol (0.5 mL) was added sodium methoxide (6 mg, 0.110 mmol). After being stirred for 1 h at room temperature, the reaction mixture was quenched with 1 M HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude 2-hydroxy-3-methoxy-6-methylenespiro[4.4]non-2-en-1-one was used in the next reaction without further purification.

To a solution of the crude 2-hydroxy-3-methoxy-6-methylenespiro-[4.4]non-2-en-1-one were added potassium carbonate (15 mg, 0.110 mmol) and methyl iodide (9 $\mu$L, 0.147 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was quenched with 1 M HCl at 0 °C. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by chromatography on silica gel (15% ethyl acetate in hexane) to give 2,3-dimethoxy-6-methylenespiro[4.4]non-2-en-1-one (**3**)[13b] (11.7 mg, 0.0562 mmol, two steps, 76%): $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.93 (t, $J$ = 2.4, 1.9 Hz, 1H), 4.75 (t, $J$ = 2.4 Hz, 1H), 4.06 (s, 3H), 3.83 (s, 3H), 2.57 (d, $J$ = 16.9 Hz, 1H), 2.49 (d, $J$ = 16.9 Hz, 1H), 2.60−2.45 (m, 2H), 2.19−2.16 (m, 1H), 1.99−1.84 (m, 1H), 1.69−1.66 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 202.3, 170.0, 156.8, 134.3, 105.2, 59.3, 58.1, 54.5, 40.9, 38.2, 33.8, 24.1; IR (neat) 2954, 1705, 1633, 1463, 1342, 1132 cm$^{-1}$; HRMS (ESI-TOF) calcd for $[C_{12}H_{16}O_3 + Na]^+$ 231.0992, found 231.0991.

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**Supporting Information Available:** Experimental details, $^1$H and $^{13}$C NMR spectra of **5**, **10**, **12**, **13**, **15**, **16**, and **3**, and HMBC and HMQC spectra of **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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