A Novel Approach to the Taxane BC Ring System through Formation of α-Ketol by Oxidative Removal of the Phenylsulfonyl Group with Subsequent in Situ Oxidation

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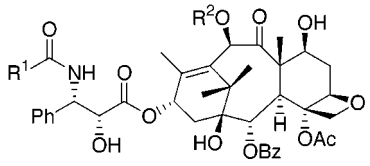
Cis-fused bicyclo[6.4.0]dodecene **11** was converted into taxane BC ring system **21** in three steps; transformation of the phenylsulfonyl group to an α-hydroxy carbonyl group by the treatment with potassium hexamethyldisilazide (KHMDS) and triethyl phosphite under oxygen atmosphere, followed by reductive elimination of the hydroxyl group of α-ketol moiety, and inversion of ring juncture. Epimerization of the sulfonyl group of **11** was indispensable for the first oxidation process (**17** → **18**) and the second oxidation of **12** leading to hydroxylation at the α-position of the carbonyl group proceeded with high regio- and stereoselectivity to give **13**. On the other hand, reaction of the cross-conjugated compound **5** with KHMDS at 0 °C brought about a complete reorganization of molecular framework to provide the compound **7** in which the five-membered ring and the conjugated seven-membered ring were connected through a single bond.

Introduction

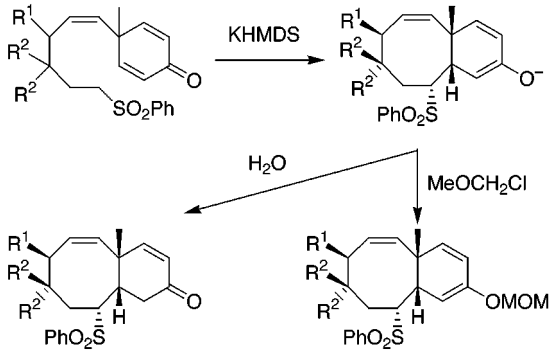
Taxol (**1**), isolated from the bark of the pacific yew tree (*Taxus brevifolia*) in the late of 1960s,[1] and its semisynthetic congener, Taxotere (**2**),[2] have become important chemotherapeutic agents for breast and ovarian cancers (Figure 1).[3] The stereochemical complexity arising from some stereocenters and unique structural features of the 6−8−6 fused framework prompted synthetic interest in these compounds. Over the past decade, six groups have succeeded in the total synthesis of Taxol (**1**).[4] We have also been investigating to establish a novel and concise synthetic route of Taxol (**1**). In our previous papers, we demonstrated effective methods for the synthesis of cis-fused bicyclo[6.4.0]dodecenone compounds (**3** and **4**) through intramolecular Michael addition of the phenylsulfonyl derivatives (Scheme 1).[5a,b] However, conversion of the phenylsulfonyl group into a carbonyl group and inversion of the ring juncture have remained synthetic problems to be overcome. We describe herein a novel method for the synthesis of taxane BC ring framework via molecular oxygen promoted double oxidation.



1: Taxol, R^1 = Ph, R^2 = Ac
2: Taxotere, R^1 = *t*-BuO, R^2 = H

Figure 1.

Scheme 1



3 : R^1 = TBDMSO, R^2 = Me
4 : R^1 = R^2 = H
5 : R^1 = TBDMSO, R^2 = Me

Results and Discussion

Studies Using Cross-Conjugated Compound 5. It is well documented that carbanions stabilized by the sulfonyl group can be easily generated under mild conditions by using various bases, and they react with some electrophiles to afford functionalized products.[6−8] To transform the sulfonyl group into a carbonyl group,

(1) Wani, M.; Taylor, H. L.; Wall, M. E. *J. Am. Chem. Soc.* **1971**, *93*, 2325−2327. Taxol is a registered trademark of Bristol-Myers Squibb.

(2) Ringel, I.; Horwitz, S. B. *J. Natl. Cancer. Inst.* **1991**, *83*, 288−291.

(3) (a) Rowinsky, E. K.; Carzenave, L. A.; Donehover, R. C. *Ibid.* **1980**, *82*, 1247−2599. (b) Bissey, M. G.; Guenard, D.; Gueritte-Voegelein, F.; Lavelle, F. *Cancer Res.* **1991**, *51*, 4848−4852.

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(5) (a) Fujishima, H.; Takeshita, H.; Suzuki, S.; Toyota, M.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2609−2616. (b) Ihara, M.; Suzuki, S.; Tokunaga, Y.; Fukumoto, K. *Chem. Commun.*, **1996**, 1801−1802.

(6) (a) Patai, S.; Stirling, J. M. *The Chemistry of Sulfones and Sulfoxides*; John Wiley: New York, 1988. (b) Jones, D. N. *Comprehensive Organic Synthesis*; Pergamon Press: Oxford, 1979; Vol. 3, pp 158−191. (c) Simpkins, N. S. *Sulfones in Organic Synthesis*; Pergamon Press: Oxford, 1993.

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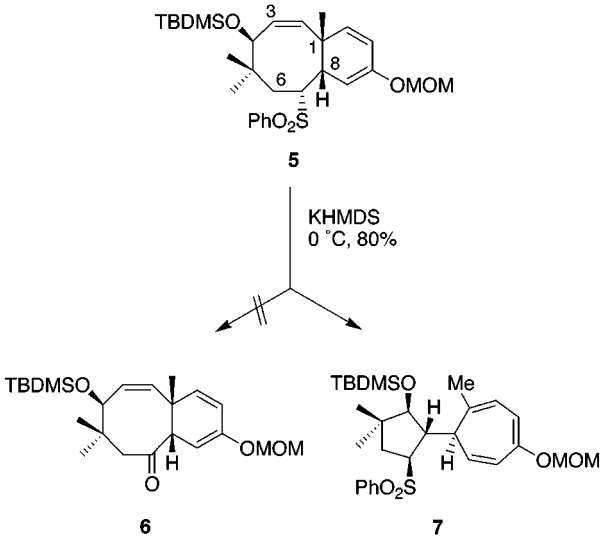
Scheme 2

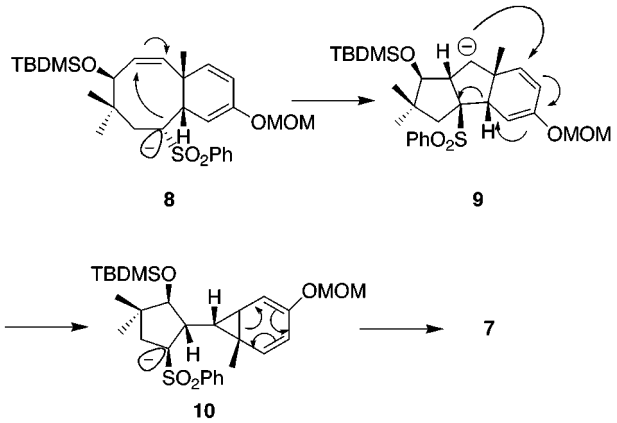


several useful oxidizing reagents have been developed; for example, molybdenum peroxide (MoO_5·Py·HMPA),[9a,b] chlorodimethoxyborane [$ClB(OMe)_2$],[10] bis(trimethylsilyl)peroxide $(TMSO)_2$,[11] and *tert*-butyltrimethylsilylperoxide.[12a,b] On the other hand, the use of molecular oxygen in this transformation, despite its availability, is limited due to its potential explosive reactivity.[13]

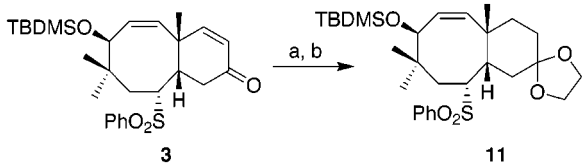
Initial attempts to convert the sulfonyl group of **5**[9b] under conditions similar to those described above gave recovery of **5** along with a complex mixture of products; the desired compound **6** was not detected. However, the reaction, carried out with KHMDS for 0.5 h at 0 °C, unexpectedly provided the compound **7** as a sole product in 80% yield (Scheme 2).

In the ^1H NMR spectrum of **7**, remarkable change of signals was observed; disappearance of the vinyl protons at the C(2) and the C(3) positions in the eight-membered ring and the low-field shift from 1.24 ppm[5a] to 2.02 ppm of the angular methyl group. These observations suggested a possibility of reorganization of the framework of **5**. The X-ray analysis of this molecule unequivocally established its structure as **7**. Compound **7** was also obtained in 27% yield by treatment with BuLi at 0 °C. It is noteworthy that this drastic transformation of **5** was not observed when **5** was treated with other bases such as lithium hexamethyldisilazide (LiHMDS), *t*-BuOK, and NaOMe at the same temperature.

Scheme 3. Proposed Pathway Leading to 7



Scheme 4[a]



[a] Conditions: (a) 10% Pd−C, EtOAc, rt, 100%; (b) $HOCH_2CH_2OH$, PPTS, PhH, 5 h, 95%.

To explain this interesting rearrangement, a plausible mechanism could be proposed as shown in Scheme 3. Intramolecular nucleophilic attack of carbanion in **8** would afford the 5−5−6-membered tricyclic intermediate **9**, which could be further transformed into the bicyclic compound **10**. Ring expansion of the bicyclo[4.1.0]heptane ring moiety of **10** could then take place to produce the compound **7**.

Based upon results observed here, we suspected that the cross-conjugated diene unit would play an important role in this unexpected rearrangement. To avoid this undesirable transformation, we next selected the nonconjugated compound **11**, which can be prepared from enone **3**[5a] by reduction (H_2, 10% Pd/C in EtOAc) followed by protection (ethylene glycol, PPTS in benzene) in 95% overall yield for two steps (Scheme 4).

Studies Using Nonconjugated Sulfonyl Derivative 11. With the desired material in hand, we next examined transformation reaction of **11** under the same conditions as above. Reactions of **11** with LDA or BuLi in the presence of oxidizing reagents such as MoO_5·Py·HMPA and $(TMSO)_2$ resulted in the recovery of starting material. The same outcome was observed when **11** was treated with *s*-BuLi (2 equiv) or KHMDS (2 equiv). Since it was considered that steric hindrance owing to the *gem*-dimethyl and the angular methyl groups would interrupt the oxidation process of sulfonyl carbanion, our attention then turned to the utilization of molecular oxygen. All reactions were carried out by the following operations; the mixture containing starting material **11** and an equimolar amount of $(EtO)_3P$ was treated with base (ca. 2 equiv) at −78 °C. After 15−30 min, oxygen gas was bubbled into the reaction mixture (Scheme 5). Experimental results are outlined in Table 1.

The desired oxidative transformation did not proceed (entries 1−3 and 5−7) except for entries 4, 8, and 9 in which *s*-BuLi (entry 4) or KHMDS were employed (entries 8 and 9). The required carbonyl compound **12**

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Scheme 5

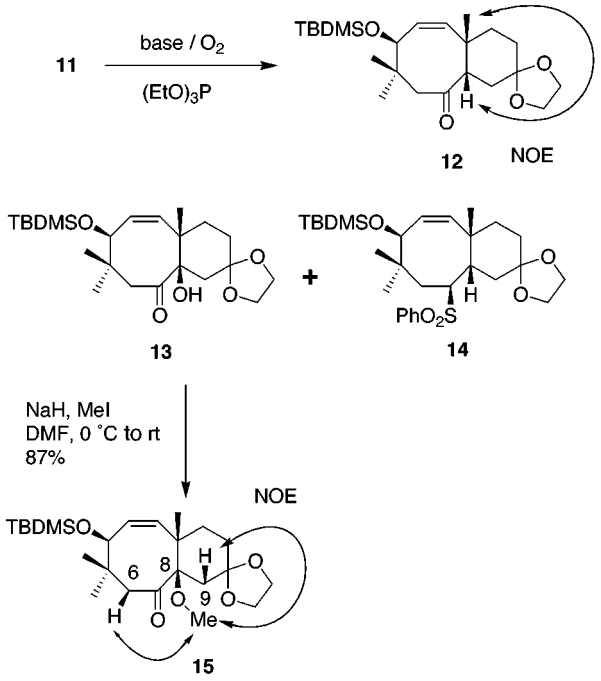


Table 1. Treatment of 11 with Various Bases[a]

				yield[c] (%)			
entry	base[b]	*T* (°C)	time (h)	**11**	**12**	**13**	**14**
1	LDA (1.5)	−78	1.5	99	0	0	0
2	BuLi (1.2)	−78	1.5	98	0	0	0
3[d]	BuLi (2.2)	−78	1.5	84[e]	0	0	0
4	*s*-BuLi (2.2)	−78	1.0	52	8	0	18
5	*t*-BuOK (2.2)	−78 to −40	1.5	98	0	0	0
6	LiHMDS (2.2)	−78 to −30	2.5	95	0	0	0
7	NaHMDS (2.2)	−78 to −30	2.5	99	0	0	0
8	KHMDS (2.2)	−78 to −50	3.5	48	7	28	<5
9[d]	KHMDS (2.2)	−78	2.0	23[e]	16	10	<5

[a] All reactions were carried out in 0.1 M THF solution in the presence of 1.2 equiv of $(EtO)_3P$. [b] Values in parentheses represent molecular equivalent of bases. [c] Isolated yield. [d] Reactions were carried out in the absence of $(EtO)_3P$. [e] Unidentified complex molecules were also formed.

was given in low yield as a single isomer, and its ring juncture was determined to be cis by NOE between the angular methyl group and C(8) hydrogen. It was unexpected that epimerization at the α-sulfonyl carbon took place simultaneously to give the epimer **14** in 18% yield (entry 4). More interestingly, reaction with KHMDS provided a mixture of the ketone **12**, the α-hydroxy carbonyl compound **13**, and the epimer **14** (entries 8 and 9).

Judging from the monitoring by TLC and the NMR measurements, epimerization at the α-sulfonyl carbon took place very quickly at low temperature (−78 to −50 °C) when KHMDS was utilized. It was supposed that epimerization would be required for the desired transformation due to minimization of steric repulsion between the 6-membered and 8-membered rings and to chelation between countercation (K^+) and one of acetal oxygens leading to a preferable 6-membered chelation (Figure 2).

Moreover, it was proved that the second oxidation process leading to an α-hydroxylation proceeded with high regio- and stereoselectiviy to afford the cis-fused derivative **13**. Under the reaction conditions, the thermodynamic enolate formation might be also favorable.

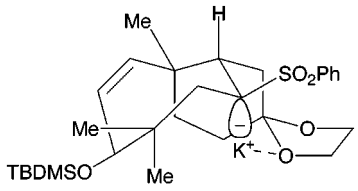


Figure 2.

Table 2. Treatment of 11 with KHMDS under Various Conditions[a]

					yield[b] (%)			
entry	equiv of base	*T* (°C)	additive	time (h)	**11**	**12**	**13**	**14**
1[c]	1.2	−78		5 min	68	0	0	32
2[c]	1.2	−50		5 min	7	0	0	90
3	1.2	−78 to −50	$(MeO)_3P$	3.5	30	<5	66	0
4	1.2	−78 to −50	$(EtO)_3P$	2.0	32	0	60	0
5	1.2	−78 to −50	$(Pr^iO)_3P$	3.5	31	<5	40	0
6	1.2	−78 to −30	Ph_3P	3.5	45	<5	21	0
7[d]	2.2	−78 to −50	$(EtO)_3P$	2.0	66	12	10	0
8[e]	2.2	−78 to −50	$(EtO)_3P$	2.0	55	8	28	0
9[f]	2.2	−78 to −50	$(EtO)_3P$	2.0	68	10	6	0
10[g]	3.3	−78 to −40	$(EtO)_3P$	5.0	13	8	76	0
11[g]	3.3	−78 to −10	$(EtO)_3P$	5.0	0	3	85	0

[a] All reactions were carried out in 0.1 M THF solution in the presence of 1.2 equiv of additive except for entries 1−2. [b] Isolated yields. [c] Reaction was carried out without oxygen. [d] Reaction was carried out in 0.01 M in THF. [e] Reaction was carried out in Et_2O. [f] Reaction was carried out in DME. [g] 1.1 equiv of KHMDS was added three times every 1 h in the presence of an excess of $(EtO)_3P$ at −78 °C (see the Experimental Section).

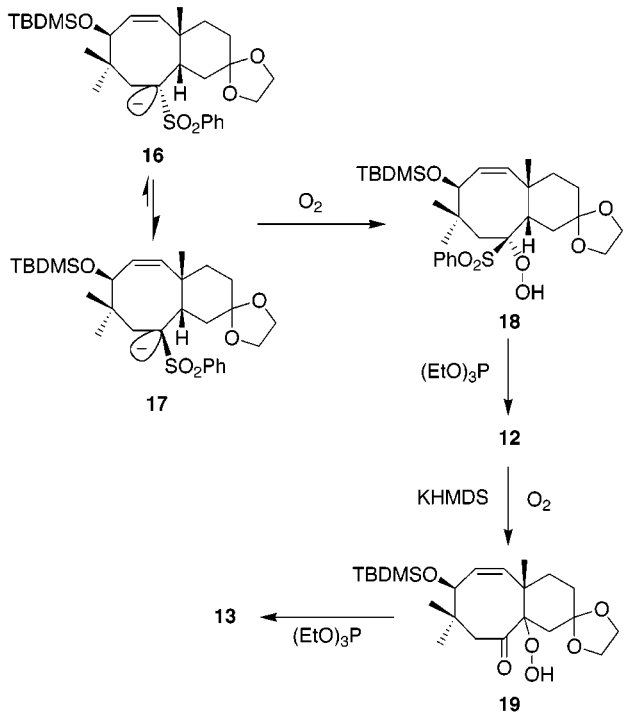
To determine the relative configuration, **13** was converted into the methyl ether **15** owing to broadening in ^1H NMR spectra of **13** (500 MHz, $CDCl_3$ or C_6D_6). The assignment was supported by the NOESY spectrum, which showed the correlation between methoxy group and protons at the C(6) and the C(9) positions. The stereochemistry was fully confirmed by X-ray diffraction analysis.

In the course of our experiments, it was also revealed that reactions in the absence of $(EtO)_3P$ furnished a complex mixture of products[14] together with recovered starting material **11** (entries 3 and 9) and the formation of complex molecules increased by longer reaction time. On the other hand, coexistence of $(EtO)_3P$ in the reaction mixture strongly interrupted the formation of side products in all cases. Moreover, it was interesting that the second oxidation leading to the hydroxy ketone **13** proceeded very quickly whenever KHMDS was utilized (entries 8 and 9). The second oxidation process was too fast to provide the desired ketone **12** in good yield. The unique outcome in these studies turned our attention to searching for proper reaction conditions for the production of the α-ketol **13**.

Accordingly, we investigated the optimization of reaction conditions by varying reaction temperature, running time and additives, with the results depicted in Table 2. Reaction of **11** with KHMDS at −78 °C provided an inseparable 68:32 mixture of **11** and **14** (entry 1), but higher temperature gave **14** in 90% yield accompanied with 7% recovery of **11** (entry 2). The ratio of **11** and **14** significantly depended on both reaction temperature and concentration. From the results of experiments using

(14) We obtained a compound in which the ortho position in the phenyl group in phenylsulfonyl moiety was selectively oxidized as a major byproduct. The lithiation at this position had already been reported by Gais et al.: Vollhardt, J.; Gais, H.-J.; Lukas, K. L. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 610−611 and see references therein.

Scheme 6. Proposed Pathway Leading to α-Ketol 13

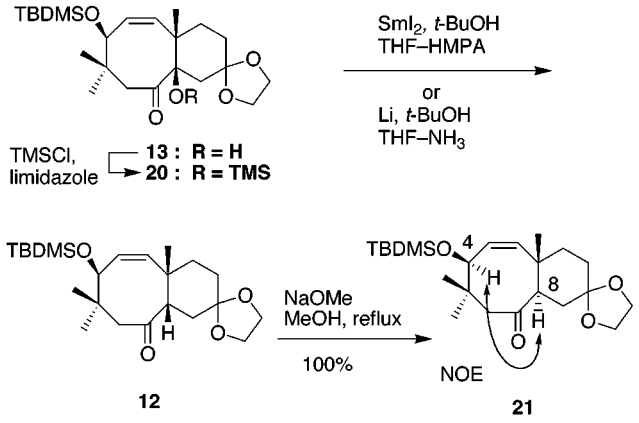


various additives, $(EtO)_3P$ was found to be the most effective one (entries 3−6).[15] Interestingly, the desired transformation took place rapidly when the reaction was performed in 0.1 M concentration. Influence of reaction concentration was obvious from the event performed in diluted conditions (entry 7). Changing of solvent (diethyl ether (Et_2O) and 1,2-dimethoxyethane (DME)) could not improve the result (entries 8 and 9). As a result of our effort to optimize reaction conditions, treatment of **11** with 3 equiv of KHMDS[16] in the presence of 3 equiv of $(EtO)_3P$ provided a better result (entry 10). The highest yield (85%) was given when the reaction temperature was warmed to −10 °C after final addition of KHMDS (entry 11). It is worth mentioning that treatment of **11** with KHMDS in the presence of $(EtO)_3P$ under an oxygen atmosphere did not generate an explosion in any case.[13]

Scheme 6 summarizes a plausible pathway leading to α-ketol **13**. Exposure of the sulfone **11** to KHMDS at low-temperature resulted in stereochemical inversion at the α-sulfonyl carbon to afford an equilibrium mixture of the carbanions **16** and **17**. Capture of molecular oxygen by the latter might furnish the peroxide intermediate **18**, and then successive reduction and desulfonylation gave the ketone **12**. Subsequent regio- and stereoselective oxidation at the α-position of the carbonyl group could proceed to provide **19**, which would be reduced by $(EtO)_3P$ to afford the α-ketol **13**.[17−19]

Preparation of Taxane BC Ring System. To prepare the taxane BC ring system, the hydroxyl group at the C(8) position of **13** must be removed. With respect to this objective, employment of samarium diiodide in THF−HMPA[20a,b] or lithium in liquid NH_3[21] was undertaken. The initial experiment of **13** with SmI_2 in the presence of *t*-BuOH in THF−HMPA at low temperature (−78 to 0 °C) afforded **12** in low yield (33%) together with many byproducts (Scheme 7). Treatment of **20** in which the hydroxyl group was protected by a TMS group[20b] with SmI_2 under the same conditions also gave a poor yield.

Scheme 7



In contrast, treatment of **13** with lithium in the presence of *t*-BuOH in liquid NH_3 furnished **12** in 63% yield along with the recovery of **13** in 23% yield. Gratifyingly, this method proceeded without side reaction. Exposure of **12** to 10 equiv of NaOMe in MeOH[22] under reflux conditions resulted in the complete inversion of the ring juncture to furnish the desired trans-fused compound **21** in quantitative yield. Thus, we could achieve the assembly of taxane BC ring system, which is very similar to the synthetic intermediate for the construction of the ABC framework by Swindell.[23]

Experimental Section

General methods. All moisture- or air-sensitive reactions were performed under an atmosphere of argon or nitrogen. All reagents and solvents were used as obtained from commercial suppliers except for the followings; THF and Et_2O were distilled from benzophenone ketyl under argon. CH_2Cl_2, DME, benzene, toluene, and diisopropylamine were freshly distilled from calcium hydride prior to use. Diisopropylethylamine and DMF were distilled from calcium hydride and stored over 4 Å molecular sieves. Column chromatography was carried out on silica gel (230−400 mesh). ^1H NMR data are described in the following order: chemical shift, multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broadened)], coupling constant(s) (*J*/Hz) and integration.

(±)-(1*R,1′*S**,2′*S**,5′*R**)-1-[2′-Phenylsulfonyl-4′,4′-dimethyl-5′-*tert*-butyldimethylsiloxycyclopentenyl]-2-methyl-5-methoxymethyloxy-2,4,6-cycloheptatriene (7).** To a solution of **5** (185.0 mg, 348 μmol) in THF solution (4 mL) was added KHMDS (0.5 M in toluene solution, 1.04 mL, 522 μmol) at 0 °C. The reaction mixture was stirred for 0.5 h at 0 °C and then treated with saturated NH_4Cl (2 mL). After usual workup, the residue was purified by column chromatography

(15) Reaction in the presence of $(MeO)_3P$ gave good result as well as the reaction with $(EtO)_3P$. However, the latter reaction proceeded smoother than the former one.

(16) Addition of KHMDS should be carried out at constant intervals to avoid the formation of complex molecules.

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(SiO_2, 8:1 hexanes/EtOAc) to afford 147 mg (80%) of **7** as a solid. For X-ray analysis, the products was recrystallized from hexanes to afford colorless prisms: mp 109−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.00 (s, 3H), 0.04 (s, 3H), 0.86 (s, 9H), 0.91 (s, 3H), 0.96 (s, 3H), 1.46 (dd, J = 12.6, 8.2 Hz, 1H), 2.03 (s, 3H), 2.12 (dd, J = 12.6, 9.6 Hz, 1H), 2.46 (t, J = 8.2 Hz, 1H), 2.87 (dd, J = 11.0, 5.5 Hz, 1H), 3.45 (s, 3H), 3.49 (dd, J = 8.0, 5.5 Hz, 1H), 3.57 (s, 1H), 5.02 (d, J = 6.6 Hz, 1H), 5.10 (d, J = 6.6 Hz, 1H), 5.66 (t, J = 10.1 Hz, 1H), 5.99 (d, J = 7.1 Hz, 1H), 6.04 (d, J = 7.1 Hz, 1H), 6.18 (d, J = 10.1 Hz, 1H), 7.50−7.62 (m, 3H), 7.86−7.98 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −3.8, −3.7, 18.3, 24.3, 24.9, 26.1, 26.6, 40.9, 44.0, 47.3, 47.9, 55.9, 67.7, 84.6, 94.5, 109.8, 121.3, 123.9, 124.1, 128.8, 129.0, 129.1, 133.2, 139.7, 156.0; IR (KBr) 1620, 1145, 1080 cm^{-1}; MS (EI) m/z 532 (M^+). Anal. Calcd for $C_{29}H_{44}O_5SSi$ (532.2667): C, 65.37; H, 8.32; S, 6.03. Found: C, 65.23; H, 8.37; S, 6.13.

X-ray Crystallography. Crystallographic data were collected at 13 °C on a RIGAKU AFC5R diffractometer with graphite-monochromated Mo Kα (λ = 0.710 69 Å) radiation and a rotating anode generator. The structure was solved using the programs in teXsan.

Crystal Structure of 7. The compound **7** belongs to the triclinic space group $P1$, a = 10.184(1) Å, b = 15.429(3) Å, c = 10.058(2) Å, α = 98.98 (2)°, β = 99.15(1)°, γ = 90.03(1)°, V = 1540.6(5) Å^3, Z = 2, μ = 1.77 cm^{-1}, D_c = 1.148 g/cm^3, $F000$ = 576, T = 286 K, R, R_w = 0.064, 0.060 for 3457 absorption-corrected reflections with $I > 3.00\sigma(I)$.

(±)-(1*R*,4S*,7R*,8S*)-4-*tert*-Butyldimethylsiloxy-5,5-dimethyl-1-methyl-7-phenylsulfonylbicyclo[6.4.0]dodec-2-en-10-one Ethylene Acetal (11). A mixture of **3** (1.00 g, 2.05 mmol) and 10% Pd/C (ca. 100 mg) in EtOAc (50 mL) was stirred for 5 h at room temperature under H_2 atmosphere. After the reaction was complete (monitored by TLC), the resulting solution was passed through column packed with dry silica gel and eluted with EtOAc. The solvent was removed under reduced pressure, and the resulting residue was used without further purification. A mixture of the ketone prepared above, ethylene glycol (1.27 g, 21 mmol), and pyridinium *p*-toluenesulfonate (ca. 50 mg) in benzene (100 mL) was refluxed for 6 h. After cooling to room temperature, the solvent was removed under reduced pressure. The residue was purified by column chromatography (SiO_2, 6:1 hexanes/EtOAc) to furnish 1.01 g (95%) of **11** as a viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.02 (s, 3H), 0.04 (s, 3H), 0.80 (s, 3H), 0.86 (s,12H), 0.93 (s, 3H), 1.47−1.57 (m, 5H), 1.67 (dd, J = 12.9, 8.8 Hz, 1H), 1.73 (dd, J = 8.8, 3.6 Hz, 1H), 1.95 (d, J = 14.0 Hz, 1H), 2.42 (dd, J = 12.9, 3.6 Hz, 1H), 3.56 (d, J = 8.8 Hz, 1H), 3.87−3.97 (m, 4H), 4.03 (d, J = 5.0 Hz, 1H), 5.14 (d, J = 14.3 Hz, 1H), 5.39 (dd, J = 14.3, 5.0 Hz, 1H), 7.51−7.64 (m, 3H), 7.86−7.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −4.5, −4.1, 18.2, 21.4, 25.8, 26.1, 29.8, 30.1, 31.5, 32.0, 34.4, 35.0, 38.5, 39.4, 60.3, 64.2, 64.3, 76.8, 108.9, 129.1, 129.5, 129.6, 133.6, 136.1, 138.0; IR (KBr) 1302, 1145 cm^{-1}; MS (EI) m/z 534, 477 (M^+ − ^{t}Bu; HRMS calcd for $C_{29}H_{46}O_5SSi$ 534.2823, found 534.2797.

(±)-(1*R*,4S*,8S*)-4-*tert*-Butyldimethylsiloxy-5,5-dimethyl-1-methyl-7-oxobicyclo[6.4.0]dodec-2-en-10-one Ethylene Acetal (12) and (±)-(1*R*,4S*,8R*)-4-*tert*-Butyldimethylsiloxy-5,5-dimethyl-1-methyl-8-hydroxy-7-oxobicyclo-[6.4.0]dodec-2-en-10-one Ethylene Acetal (13), Method A (Table 2, Entry 11). To a mixture of **11** (3.0 g, 5.61 mmol) and $(EtO)_3P$ (3.2 mL, 18.5 mmol) in THF (56 mL) was added KHMDS (0.5 M in toluene, 12.3 mL, 6.17 mmol) at −50 °C. After 10 min, the reaction temperature was cooled to −78 °C, and then O_2 gas (passed through concentrated H_2SO_4) was bubbled to the reaction mixture. After 1 h at −78 °C, KHMDS (12.3 mL, 6.17 mmol) was added to the reaction mixture (during injection of KHMDS, bubbling of oxygen gas was suspended). This process was repeated once again. The reaction temperature was allowed to warm to −10 °C over a period of 2 h. The reaction was quenched by saturated $NaHCO_3$ (10 mL), and the resulting mixture was extracted with ethyl acetate. The extracts was washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (SiO_2, 7:1 hexanes/EtOAc) gave 68 mg (3%) of ketone **12** as an oil and 2.1 g (85%) of **13** as an oil.

Ketone (12): ^{1}H NMR (400 MHz, C_6D_6) δ 0.08 (s, 3H), 0.13-(s, 3H), 0.42 (s, 3H), 0.93 (s, 3H), 0.96 (s, 9H), 1.20 (s, 3H), 1.35 (br s, 1H), 1.57 (d, J, = 8.5 Hz, 1H), 1.67 (dd, J = 10.5, 8.5 Hz, 2H), 1.95−2.03 (m, 1H), 2.53 (br d, J = 13.4 Hz, 1H), 2.64 (d, J = 13.4 Hz, 1H), 2.94 (br, 1H), 3.42−3.51 (m, 5H), 4.28 (br, 1H), 4.93 (d, J = 13.2 Hz, 1H), 5.52 (dd, J = 13.2, 6.3 Hz, 1H); ^{13}C NMR (110 MHz, C_6D_6) δ −5.2, −4.4, 18.1, 19.3, 22.2, 25.3, 25.9, 31.1, 33.4, 38.4, 38.9, 39.8, 54.9, 55.4, 64.2, 64.3, 75.0, 108.9, 129.7, 139.1, 209.7; IR (neat) 1683, 1087 cm^{-1}; MS (EI) m/z 408 (M^+); HRMS calcd for $C_{23}H_{40}O_4Si$ 408.2685, found 408.2664. Anal. Calcd for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87. Found: C, 67.43; H, 9.80.

Ketol (13): ^{1}H NMR (400 MHz, C_6D_6) δ 0.03 (s, 3H), 0.07 (s, 3H), 0.95 (s, 9H), 1.12 (s, 3H), 1.14 (s, 3H), 1.38 (s, 3H), 1.65−1.72 (m, 2H), 1.80 (d, J = 12.6 Hz, 1H), 1.87 (d, J = 14.1 Hz, 1H), 2.24 (d, J = 14.1 Hz, 1H), 2.48 (d, J = 12.6 Hz, 1H), 2.56 (br s, 1H), 3.32−3.39 (m, 5H), 4.56 (br s, 1H), 4.66 (br s, 1H), 5.32 (d, J = 15.3 Hz, 1H), 5.42 (dd, J = 15.3, 6.5 Hz, 1H); ^{13}C NMR (110 MHz, C_6D_6) δ −4.8, −4.1, 18.3, 20.0, 25.4, 26.0, 28.5, 31.5, 32.1, 42.3, 43.2, 43.6, 49.5, 64.1, 64.4, 75.9, 108.8, 128.7, 136.1, 137.6, 212.1; IR (KBr) 3416, 1684 cm^{-1}; MS (EI) m/z 424 (M^+); HRMS calcd for $C_{23}H_{40}O_5Si$ 424.2674, found 424.2666.

Method B (Reduction of 13 with Li in NH_3). To a mixture of **13** (220 mg, 520 μmol), *t*-BuOH (0.24 mL, 2.50 mmol) in THF (3 mL), and liquid NH_3 (80 mL) was added lithium (35.9 mg, 5.20 mmol) over a period of 15 min. After 1.0 h, NH_4Cl (1 g) was added to the reaction mixture and the solvent was removed. The residue was dissolved in water and extracted with EtOAc. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated. Purification by column chromatography (SiO_2, 1:8 hexanes/EtOAc) furnished 134 mg (63%) of **12**, 44 mg (23%) of **13**.

(±)-(1*R*,4S*,7S*,8S*)-4-*tert*-Butyldimethylsiloxy-5,5-dimethyl-1-methyl-7-phenylsulfonylbicyclo[6.4.0]dodec-2-en-10-one Ethylene Acetal (14) (Table 2, Entry 2). To a solution of **11** (51.7 mg, 96.7 μmol) in THF (2 mL) was added KHMDS (0.5 M in toluene solution, 251.4 μL, 125.7 μmol) at −50 °C. After 5 min, water (100 μL) was added to the reaction mixture. The resulting mixture was dried over $MgSO_4$, filtered, and evaporated. Purification by column chromatography (SiO_2, 6:1 hexanes/EtOAc) gave 4.1 mg (7.1%) of recovered **11** and 42.8 mg (90%) of **14** as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.68 (s, 3H), 0.79 (s, 3H), 0.86 (s, 9H), 1.17 (s, 3H), 1.28 (d, J = 13.0 Hz, 1H), 1.42−1.53 (m, 2H), 1.60−1.67 (m, 2H), 1.77 (t, J = 13.0 Hz, 1H), 1.83 (d, J = 14.9 Hz, 1H), 2.04 (dd, J = 14.9, 9.9 Hz, 1H), 2.56 (d, J = 13.0 Hz, 1H), 2.76 (d, J = 9.9 Hz, 1H), 3.50−3.52 (m, 1H), 3.76−3.80 (m, 3H), 3.94 (d, J = 6.1 Hz, 1H), 5.00 (d, J = 13.5 Hz, 1H), 5.25 (dd, J = 13.5, 6.1 Hz, 1H), 7.55−7.64 (m, 3H), 7.85−7.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ − 4.7, −4.1, 18.0, 21.7, 23.4, 25.8, 31.1, 31.8, 33.7, 38.1, 38.8, 40.7, 41.5, 43.0, 64.0, 64.3, 66.3, 75.0, 108.0, 129.1, 129.5, 132.2, 133.3, 135.5, 137,9; IR (neat) 1302, 1146, 1081 cm^{-1}; MS (EI) m/z 534, 477 (M^+ − ^{t}-Bu); HRMS calcd for $C_{29}H_{46}O_5SSi$ 534.2823, found 534.2797.

(±)-(1*R*,4S*,8R*)-4-*tert*-Butyldimethylsiloxy-5,5-dimethyl-1-methyl-8-methoxy-7-oxobicyclo[6.4.0]-dodec-2-en-10-one Ethylene Acetal (15). To a suspension of NaH (60% in mineral oil, 38.5 mg, 0.96 mmol) and **13** (81.6 mg, 192.4 μmol) in dry DMF (2 mL) was added MeI (0.06 mL, 0.96 mmol) at 0 °C. After 1 h, the mixture was allowed to warm to room temperature, and stirring was continued for 8 h. The reaction mixture was slowly added to a mixture of ice-cold water and Et_2O. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. Purification by column chromatography (SiO_2, 2:1 hexanes/EtOAc) afforded 81.1 mg (96%) of **15**. For X-ray analysis, the product was recrystallized from hexanes to afford colorless prisms: mp 110.5−111.5 °C; ^{1}H NMR (500 MHz, C_6D_6) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.28 (s, 3H), 0.93 (s, 3H), 0.96 (s, 9H), 1.30 (s, 3H), 1.42 (br d, J = 15.6 Hz, 1H), 1.52 (d, J = 11.8 Hz, 1H), 1.65 (d, J = 14.1 Hz, 1H), 1.73 (br d, J = 15.6 Hz, 1H), 1.94 (ddd, J = 13.0, 9.2, 3.8 Hz, 1H),

2.23 (ddd, J = 13.0, 9.2, 3.8 Hz, 1H), 2.56 (d, J = 14.1 Hz, 1H), 2.77 (S, 3H), 3.27 (d, J = 11.8 Hz, 1H), 3.50 (d, J = 7.2 Hz, 1H), 3.58−3.70 (m, 2H), 4.01 (d, J = 7.2 Hz, 1H), 4.28 (d, J = 8.4 Hz, 1H), 5.42 (d, J = 13.0 Hz, 1H), 5.49 (dd, J = 13.0, 8.4 Hz, 1H); ^{13}C (125 MHz, $CDCl_3$) δ −4.8, −3.9, 1.4, 18.3, 22.2, 25.1, 26.0, 26.6, 32.1, 35.6, 40.9, 41.9, 47.7, 50.7, 64.0, 64.3, 74.6, 89.8, 108.6, 135.0, 137.9, 210.4; IR (KBr) 1704, 1089 cm^{-1}; MS (EI) m/z 438 (M^+), 407 (3), 184 (81). Anal. Calcd for $C_{24}H_{42}O_5Si$: C, 65.56; H, 9.64. Found: C, 65.27; H, 9.89.

Crystal Structure of 15. Crystallographic data were collected at 20 °C. The compound **15** belongs to the monoclinic space group $P2_1/c$ with a = 1.940(1) Å, b = 14.418(1) Å, c = 14.409(1) Å, β = 105.977(3)°, V = 2584.3(4) Å^3, Z = 4, μ = 1.20 cm^{-1}, D_c = 1.127 g/cm^3, $F000$ = 960, T = 293 K, R = 0.065 and R_w = 0.064 for 2818 absorption-corrected reflections with $I > 3.00\sigma(I)$.

(±)-(1*R,4*S**,8*R**)-4-*tert*-Butyldimethylsiloxy-5,5-dimethyl-1-methyl-8-trimethylsiloxybicyclo[6.4.0]dodec-2-en-7-oxo-10-one Ethylene Acetal (20).** A mixture of **13** (102 mg, 240 μmol), imidazole (114 mg, 1.7 mmol), and TMSCl (0.1 mL, 720 μmol) in DMF (1 mL) was stirred at 60 °C for 10 h. After being cooled to room temperature, the reaction mixture was passed through short column chromatography (SiO_2 1:6 hexanes/EtOAc) to afford 86 mg (73%) of **20** as an oil: IR (neat) 1694, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.02 (s, 3H), 0.00 (s, 3H), 0.07 (s, 9H), 0.87 (s, 3H), 0.88 (s, 9H), 1.17 (s, 3H), 1.27 (s, 3H), 1.49 (dt, J = 13.4, 5.1 Hz, 1H), 1.65 (dt, J = 13.4, 5.1 Hz, 1H), 1.75−1.82 (m, 2H), 1.84 (d, J = 13.9 Hz, 1H), 1.91−2.04 (m, 1H), 2.23 (d, J = 13.9 Hz, 1H), 3.08−3.12 (m, 1H), 3.83−4.17 (m, 5H), 5.36−5.43 (m, 2H); ^{13}C (125 MHz, $CDCl_3$) δ −4.7, −3.9, 2.2, 18.2, 22.0, 25.3, 25.9, 26.0, 30.4, 31.1, 31.3, 41.2, 42.4, 48.1, 63.9, 64.3, 74.3, 87.3, 108.4, 134.8, 136.8, 211.3; MS (EI) m/z 496 (M^+). Anal. Calcd for $C_{26}H_{48}O_5Si$ (496.3027): C, 62.86; H, 9.75. Found: C, 63.01 H, 9.81.

(±)-(1*R,4*S**,8*R**)-4-*tert*-Butyldimethylsiloxy-5,5-dimethyl-1-methyl-7-oxobicyclo[6.4.0]dodec-2-en-10-one Ethylene Acetal (21).** A mixture of **12** (1.1 g, 2.6 mmol) and NaOMe (1.4 g, 26.0 mmol) in MeOH (30 mL) was stirred under reflux for 10 h. After removal of the solvent, the residue was purified by short column chromatography (SiO_2, 1:9 hexanes/EtOAc) to give 1.1 g (100%) of **21** as a solid: mp 99−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.062, (s, 3H), 0.069 (s, 3H), 0.85 (s, 3H), 0.91 (s, 9H), 0.97 (s, 3H), 0.98 (s, 3H), 1.50−1.64 (m, 3H), 1.68−1.71 (m, 2H), 2.07 (dt, J = 12.0, 3.1 Hz, 1H), 2.16 (d, J = 12.8 Hz, 1H), 2.85 (d, J = 12.8 Hz, 1H), 2.98 (dd, J = 12.0, 3.7 Hz, 1H), 3.88−3.99 (m, 4H), 4.77 (t, J = 2.9 Hz, 1H), 5.31 (d, J = 2.9 Hz, 2H); ^{13}C NMR (110 MHz, $CDCl_3$) δ −5.1, −4.3, 18.1, 19.7, 22.3, 25.2, 25.9, 30.7, 32.6, 38.2, 38.9, 39.8, 54.6, 55.5, 64.3, 64.4, 74.5, 108.6, 129.7, 138.3, 211.5; IR (neat) 1682 cm^{-1}; MS (EI) m/z 409 ($M^+ + 1$). Anal. Calcd for $C_{23}H_{40}O_4Si$: C, 67.60; H, 9.87. Found: C, 67.43; H, 9.80.

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Supporting Information Available: X-ray crystallographic data for compounds **7** and **15** and copies of ^{1}H NMR spectra (300, 400, or 500 MHz) for compounds **11**, **13**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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