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SYNTHETIC STUDIES ON TAXANE CARBON FRAMEWORK. A HIGHLY EFFICIENT EIGHT-MEMBERED RING CYCLIZATION WITH COMPLETE STEREOCONTROL[1)]

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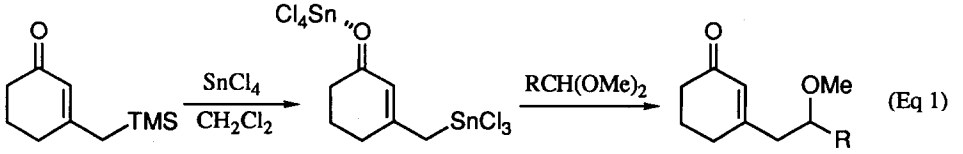
Abstract: Cyclization reaction of 5-[2-(dimethoxymethyl)-6-methoxy]benzyl-2,4,4-trimethyl-3-(trimethylsilylmethyl)cyclohexenone **2** and 5-[2-(dimethoxymethyl)-6-methoxy]benzyl-2,6,6-trimethyl-3-(siloxy)-1-methylenecyclohex-2-ene **9** gave the corresponding endo tricarbocycle bearing a sp^2 carbon on the bridge-head position. Phenylthio and methoxy derivatives of **9**, e.g. **11** and **12**, also underwent similar cyclization to afford the endo tricarbocyclic products **13** and **14** in high yields. Further, the stereochemistry of the substituents on 8-membered ring has been completely controlled in a desired manner in every case.

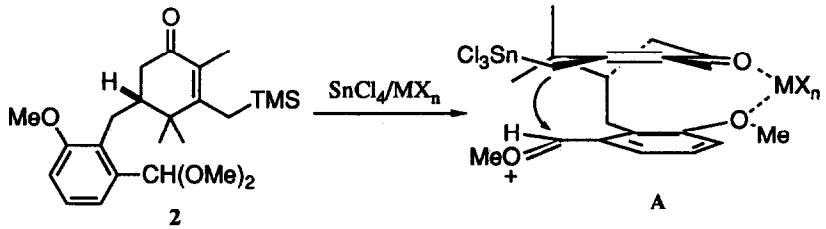
Due to their unique tricyclo[9.3.1.$0^{3,8}$]pentadecane skeleton,[2)] taxane diterpenoids have been one of the most challenging targets in synthetic organic chemistry.[3)] Further, important biological activities[4)] exhibited by taxol, one of its family, has recently prompted synthetic studies of many research groups, but only Holton's group succeeded in a total synthesis of taxusin as an antipode of the natural one.[5)] From synthetic viewpoints, the following structural features have made it very difficult to construct the taxane carbon skeletons themselves: (1) construction of an 8-membered ring system having a bridge-head sp^2 carbon, (2) stereocontrol of two functional groups at C-9 and C-10 positions, and (3) control of the tricarbocyclic ring system as endo conformation.

We previously reported the generation of stannylmethyl enones **1** through transmetallation of Me_3Si group with $SnCl_4$. They react with acetals selectively at their 4-positions as shown in Eq 1.[6)] The results



1 (Eq 1)

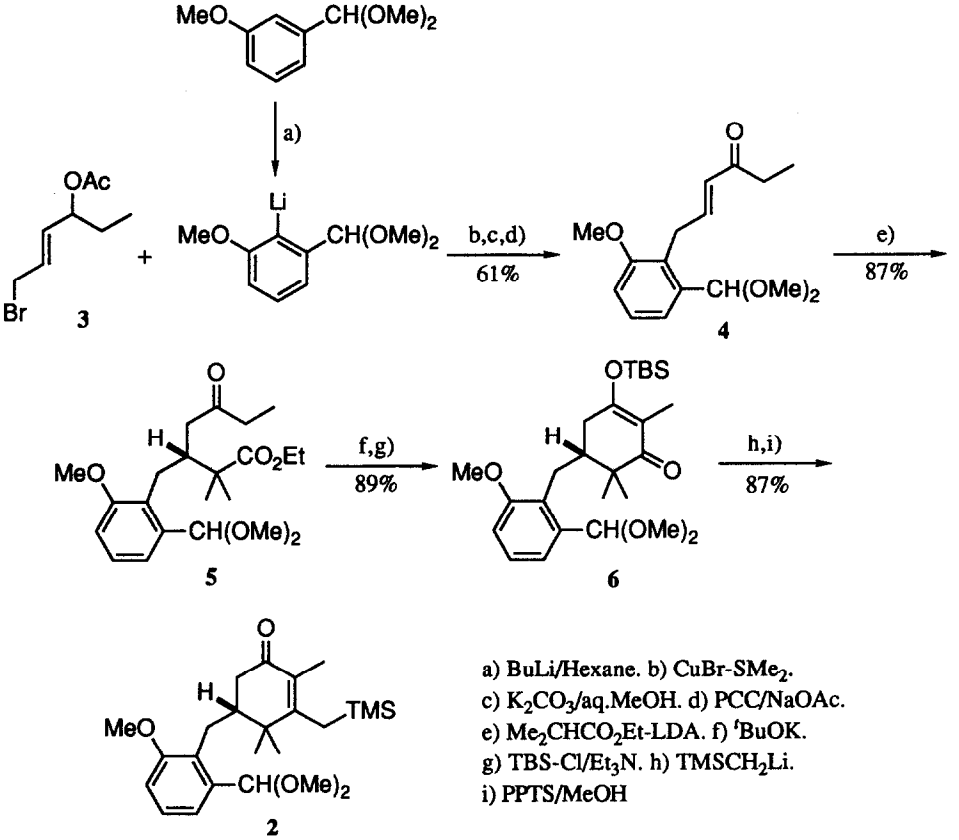
suggested use of substrate such as **2** may favor the desired 8-membered ring cyclization via transition state A due to the effect that coordination of a Lewis acid both on carbonyl and methoxy oxygens makes the two reaction sites situated closely as shown in Fig 1. To develop a useful method for construction of a taxane B ring aiming at a total synthesis of taxol, we examined the reaction of **2** containing an aromatic ring which corresponds to C-ring of taxane.[7)]



2 A (Fig 1)

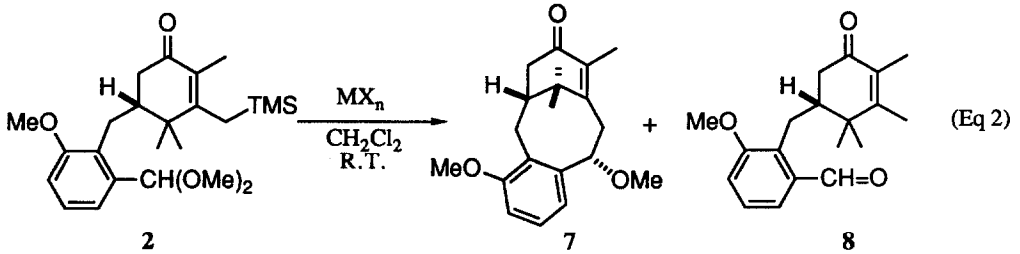
The substrate **2** was prepared as shown in Scheme 1. Thus, a cross-coupling of *o*-lithiated *m*-methoxybenzaldehyde dimethylacetal with 6-bromo-4-hexen-3-yl acetate **3** followed by hydrolysis and PCC oxidation gave the enone **4**. Conjugate addition of lithiated isobutyric ester to the enone **4** could be effected cleanly to give the keto ester **5** which underwent Dieckmann-like cyclization in the presence of ^{t}BuOK. As reported by Piers,[8] silylation of the resulting cyclohexane-1,3-dione took place selectively on the less hindered site to give siloxyenone **6**. Treatment of **6** with trimethylsilylmethyllithium followed by exposure to a catalytic amount of PPTS[9] in methanol afforded **2** in good yield.

Scheme 1. Preparation of **2**



At first, we examined the reaction under dilute concentration (0.01 M) at room temperature in order to exclude a possibility of intermolecular condensation. As expected, the cyclization of **2** occurred in the

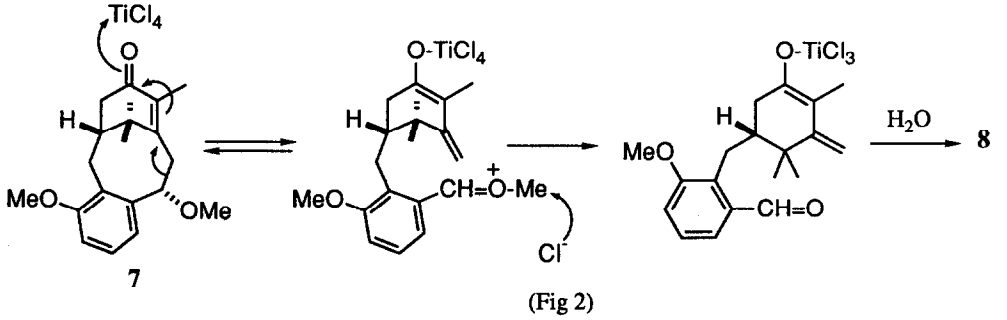
presence of $SnCl_4$ or $TiCl_4$ to give **7** in 15-17% yield (Eq 2), but the major product was the parent aldehyde **8** arising from removal of silyl and acetal groups. Further, prolonged reaction period or use of an excess amount of a Lewis acid resulted in the disappearance of **7**, accompanied with an exclusive formation of **8**.



2 **7** **8** (Eq 2)

MX_n (equiv.)	Conc. (M)	Period (h)	Yield (%) of **7**
$SnCl_4$(1.1)	0.01	19	17
$SnCl_4$(1.1)	0.01	42	trace
$TiCl_4$(1.1)	0.01	19	15
$TiCl_4$(3.0)	0.01	18	trace

These results indicate that the cyclization takes place to yield **7** initially, but it readily undergoes ring opening to give **8** under the reaction conditions (Fig 2). Indeed, on treating with $TiCl_4$ in CH_2Cl_2, **7** was quickly converted to **8** at room temperature. On the contrary, on performing the reaction at 0.1 M and at a low reaction temperature, the desired cyclization could be effected in good yield. Thus, the reaction of **2** with $TiCl_4$ at -23 °C for 2 h gave **7** in 40% NMR yield, whereas $SnCl_4$ failed to induce the cyclization at that temperature. Interestingly, use of a mixture of $TiCl_4$ and $SnCl_4$ greatly improved the yield of **7** (Eq 3).

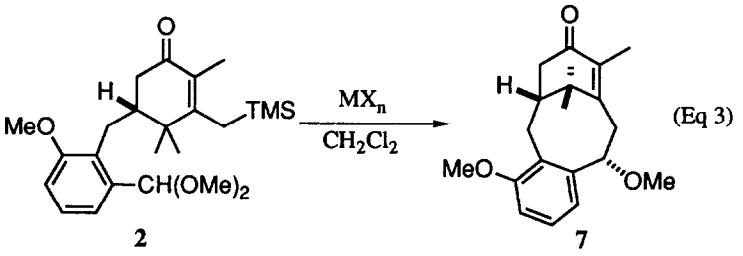


7

(Fig 2)

Further, ^1H NMR spectra have indicated the product obtained in both cases is a single stereoisomer, and its structure has been reasonably assigned as 9α-endo tricarbocycle **7**, based on its NOE measurement. As reported by Shea,[7a] ^1H NMR spectrum of **7** exhibited higher field shift of 18-methyl signal (0.88 ppm), compared with 16- (1.52 ppm) and 17-methyl (1.10 ppm), which also supports the endo conformation of this product.

Although this procedure appears to be useful for construction of taxane skeleton itself, it does not provide any clue to introduce another requisite oxygen functional group on the position corresponding to C-10. We chose the structural isomers of **2**, dienol silyl ethers **9**, as more appropriate precursors and their



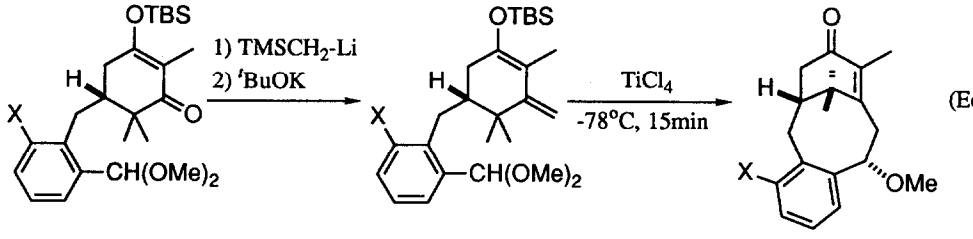
(Eq 3)

2 7

MX_n (equiv.)	Conc. (M)	Temp (°C)	Period (h)	Yield(%) of 7*
$SnCl_4$(1.1)	0.1	-23	very slow	trace
$TiCl_4$(1.1)	0.1	-23	2.5	40
$SnCl_4$(1.1)/$TiCl_4$(1.1)	0.1	-23	2.5	73(58[a])
$SnCl_4$(1.1)/$TiCl_4$(1.1)	0.1	R.T	1.0	36

* NMR Yield. [a]Isolated Yield.

cyclization reactions were also investigated. Dienol silyl ether **9a** was prepared from **6** by applying Peterson olefination. In the presence of $TiCl_4$, **9a** cleanly underwent cyclization at -78 °C within a short period to afford the endo tricyclic compound **7** in high yield. Further, substrate **9b** having no methoxy group on the aromatic ring also reacted in the same manner under the present reaction conditions (Eq 4).

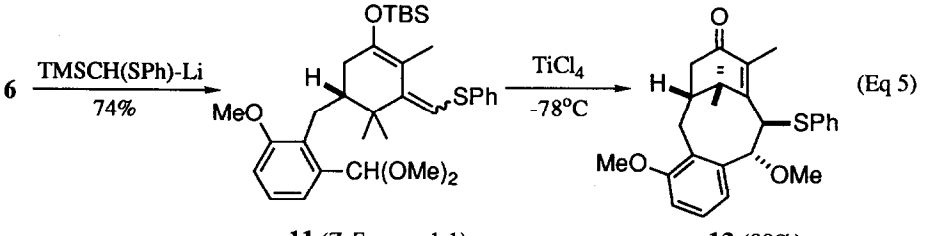


(Eq 4)

9a (X = OMe)
9b (X = H)

7 (X = OMe) ; 74%
10 (X = H) ; 60%

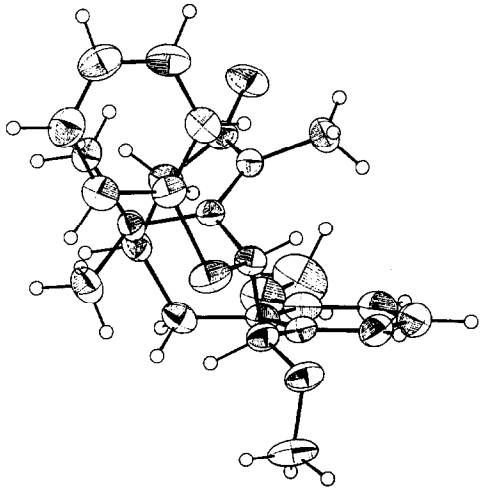
For the synthetic studies on C-aromatic taxane skeleton having C-9 and C-10 functional groups, enol silyl ethers **11** and **12** were prepared similarly and their cyclization reactions were also investigated. Geometry of an olefinic part was expected to have a great influence on the stereochemical outcome on C-10 position, but we performed experiments by using a mixture of geometrical isomers. On treating with $TiCl_4$

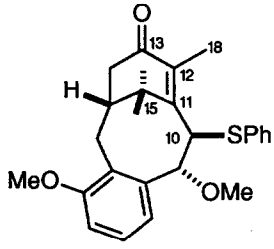


(Eq 5)

11 (*Z*:*E* = ca. 1:1) **13** (80%)

(1.1 equiv) at low temperature, **11** (*Z*:*E* = ca. 1:1) readily underwent cyclization, and remarkably, gave the product as a single stereoisomer (Eq 5). The structure of **13** has been assigned as endo-9α,10β by NOE and the following ^{1}H NMR spectrum: Two methyne protons on C-9 and C-10 appear at 4.48 and 4.87 ppm with a coupling constant (J = 10.2 Hz). Furthermore, X-ray crystallographic analysis has verified the structure of **13** (Fig 3). The dihedral angles around C(11)-C(12) bond observed by X-ray analysis of **13** show how greatly distorted this ring system is.





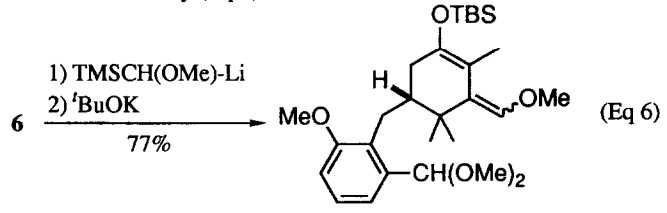
13

Dihedral Angle (degree)	
C(10)-C(11)-C(12)-C(13)	23.20
C(15)-C(11)-C(12)-C(13)	12.75
C(15)-C(11)-C(12)-C(18)	6.74
C(10)-C(11)-C(12)-C(18)	17.19

(Fig 3. ORTEP Drawing of **13** and Dihedral Angles)

In contrast, the reaction of **12** (*Z*:*E* = 82:18) at -78 °C for 15 min gave a mixture of two stereoisomers **14a** (64%) and **14b** (16%). The stereochemical relationships of these isomers have been confirmed as endo-9α,10β and endo-9α,10α by their ^{1}H NMR spectra. Two protons on C-9 and C-10 appear as follows: **14a**, 4.48 and 4.84 (J = 9.0 Hz), and **14b**, 4.60 and 4.80 (J = 5.8 Hz).

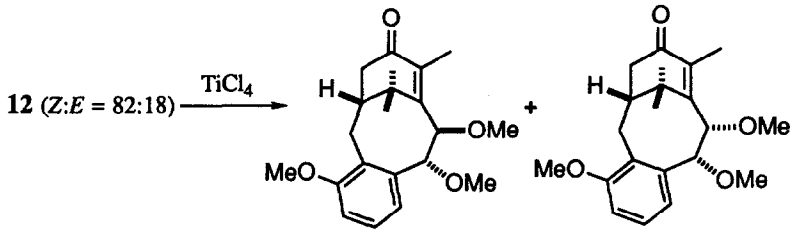
We were pleased to find that **14b** quickly isomerized to the desired **14a** at higher reaction temperature in the presence of $TiCl_4$. Thus, on performing the reaction initially at -78 °C (45 min) and then at -25 °C (45 min), **14a** was obtained exclusively (Eq 7).



(Eq 6)

12 (*Z*:*E* = 82:18)

Two reaction pathways may be conceivable on this cyclization. One involves the transmetallation (Eq 1) to proceed through a transition state fixed by coordination as assumed initially (Fig 1). In this cyclization pathway, 4-methoxy group should play an important role for both cyclization and endo control. However, several observations have disfavored this assumption as the cyclization mechanism of dienol silyl ethers.



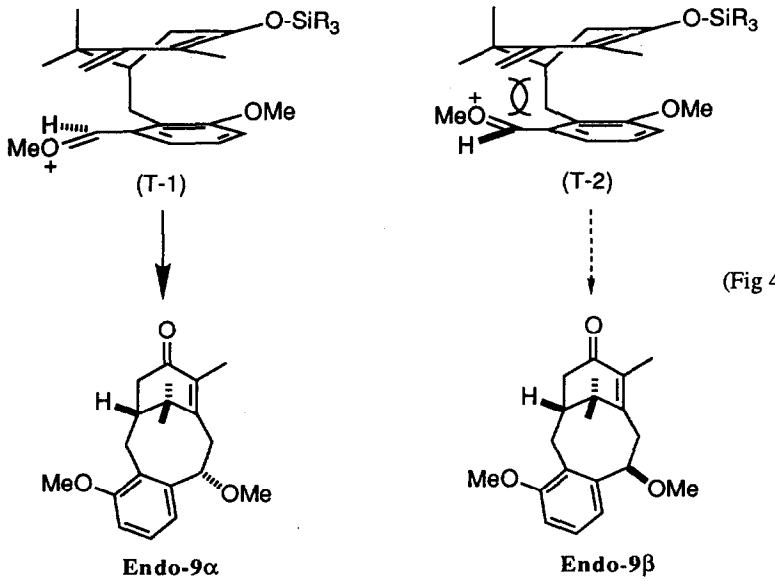
(Eq 7)

Reaction Conditions	14a	14b
-78 °C: 15 min	64%	16%
-78 °C: 45 min, -25 °C: 45 min	84%	--

First, our previous observations[10] do not support the transmetallation between $TiCl_4$ and ^{t}butyldimethylsilyl group at such low temperature (-78 °C) where the cyclization took place rapidly. Second, the substrate **9b** having no 4-methoxy group also underwent endo cyclization similarly.

Alternatively, we would like to suggest the mechanism shown in Fig 4, where a dipole attraction between an electron-rich A ring and an electron-deficient C ring may fix the transition state to facilitate the endo cyclization.

In addition to endo preference, such transition states also explain the stereocontrol at C-9; comparison of these two transition states indicates that (T-1) seems to be more favored than (T-2) because of severe steric repulsion of the methoxy group with both methyl (C-16) and methylene (C-2) group opposed to the latter.

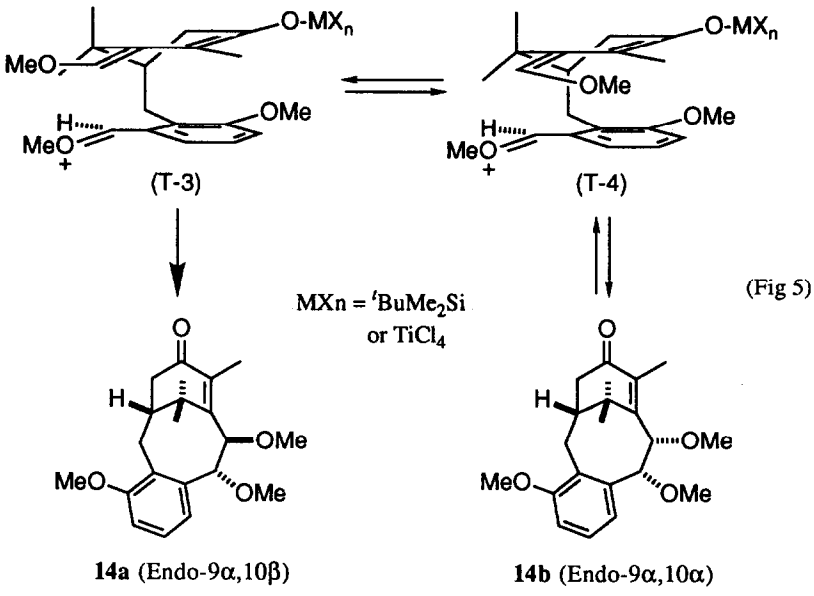


(Fig 4)

Accordingly, if the reaction is kinetically controlled, the product should possess the methoxy group below the face of 8-membered ring. On the other hand, MM2 calculation shows the endo-9α conformer is more stable than the 9β isomer by ca. 2.3 kcal/mol. Thus, the preferential formation of the desired endo-9α

cyclization product can be rationalized irrespective of the fact that the reaction is controlled either kinetically or thermodynamically.

Stereocontrol at C-10 substituent seems to be determined by thermodynamic control: The reaction of **12** gave a mixture of two stereoisomers, **14a** (endo-9α,10β) and **14b** (endo-9α,10α), through T-3 (MX_n =



(Fig 5)

^{t}BuMe$_2$Si) and T-4 (MX_n = ^{t}BuMe$_2$Si) respectively, at low reaction temperature, and **14b** was converted to **14a** at higher reaction temperature. Lability of this 8-membered ring as shown in the previous experiment (see Fig 2) may account for such isomerization. Since **14a** has been estimated to be about 2.2 kcal/mol more stable than **14b** by MM2 calculation, thermodynamically less stable *cis* isomer undergoes 8-membered ring opening under the influence of $TiCl_4$ to form the intermediate (T-4: MX_n = $TiCl_4$) which yields the more stable **14a** through geometrical isomerization to the intermediate (T-3: MX_n = $TiCl_4$) followed by recyclization as shown in Fig 5. It is quite interesting that a labile nature of the taxane ring system has made it difficult to be constructed, but, on the contrary, allows us to control the stereochemistry in the desired manner.

Thus, the present reaction has provided a powerful method to resolve three of the most challenging problems for taxane synthesis. We are currently pursuing a total synthesis of taxusin and taxinine by applying this methodology.

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Experimental

General. All reactions were carried out under a dry nitrogen atmosphere. Routine flash column chromatography was achieved with Wako C-300 silica gel for purification of products. IR spectra were recorded on a JASCO IR-810 spectrometer. ^{1}H NMR spectra taken were recorded on Hitachi R24B (60 MHz), JEOL FX-200 (200 MHz), or JEOL GSX-270 (270 MHz) spectrometers. ^{13}C NMR (65 MHz)

were recorded on JEOL GSX-270 instrument. MS spectra were taken on a Shimadzu GCMS 9020-DF spectrometer at 70 eV ionization irradiation. Microanalyses were performed on a Perkin-Elmer 240 instrument.

Preparation of the Siloxyenone **6**. *m*-Methoxybenzaldehyde dimethylacetal (4.55 g, 25 mmol) was treated with butyllithium (27.5 mmol) in hexane (50 mL) at room temperature for 4 h. Then, the resulting solution was added to CuBr/Me_2S (5.654 g, 27.5 mmol) in ether (100 mL) at -45 °C. After stirring for 1 h at that temperature, 6-bromo-4-hexen-3-yl acetate **3** (6.080 g, 27.5 mmol) was added and was stirred for 1 h at -45 °C. Usual workup of the reaction mixture gave the allylic acetate. The acetate was treated with K_2CO_3 (10.37 g, 75 mmol) in MeOH (300 mL) and water (100 mL) at room temperature for 7 h, and the resulting allylic alcohol was oxidized by treating with PCC (6.60 g, 37.5 mmol) in the presence of NaOAc (12.31 g, 150 mmol) in dichloromethane (30 mL) overnight at room temperature. Workup of the reaction mixture followed by purification on silica gel column chromatography gave the enone **4** (4.24 g) in 61% yield. ^{1}H NMR (60 MHz, CCl_4) δ 1.00 (t, 3H, J = 7.0 Hz), 2.40 (q, 2H, J = 7.0 Hz), 3.20 (s, 6H), 3.55 (m, 2H), 3.73 (s, 3H), 5.33 (s, 1H), 5.77-6.03 (m, 2H), 6.53-7.13 (m, 3H). IR (neat) 2930, 1670, 1260 cm^{-1}.

Ethyl isobutyrate (1.77 g, 15.23 mmol) was treated with LDA (16.76 mmol) in THF (40 mL) at -78 °C for 1.5 h. Then, the enone **4** (4.24 g, 15.23 mmol) in THF (10 mL) was added and it was stirred at -78 °C for 1.5 h and at 0 °C for 1.5 h. Aqueous workup of the reaction mixture gave the keto ester **5** (5.26 g, 87%), which was exposed to ^{t}BuOK (1.70 g, 15 mmol) in ether (30 mL) for 4 h at room temperature. The cyclohexane-1,3-dione thus obtained was treated with ^{t}butyldimethylsilyl chloride (2.49 g, 16.5 mmol) and triethylamine (3.83 mL, 27.5 mmol) in CH_2Cl_2 (30 mL) at 0 °C for 30 min, giving the siloxy enone **6** (5.66 g) in 47% overall yield from the acetal. ^{1}H NMR (60 MHz, CCl_4) δ -0.66 (s, 6H), 0.80 (s, 9H), 0.95 (s, 3H), 1.20 (s, 3H), 1.53 (s, 3H), 1.73-2.46 (m, 4H), 2.80 (m, 1H), 3.13 (s, 3H), 3.23 (s, 3H), 3.70 (s, 3H), 5.40 (s, 1H), 6.90-7.23 (m, 3H). IR (neat) 1720, 1630, 780 cm^{-1}.

Preparation of TMS-methylenone **2**. The siloxyenone **6** (2.14 g, 4.63 mmol) was reacted with (trimethylsilyl)methyllithium (6.95 mmol) in ether (20 mL) at -78 °C for 2 h, and the resulting alcohol was treated with PPTS (8 mg, 0.032 mmol) in methanol (1.9 mL) at 0 °C for 1 h, giving TMS-methylenone **2** (1.717 g) in 87% yield. ^{1}H NMR (60 MHz, CCl_4) δ -0.15 (s, 9H), 1.00 (s, 3H), 1.10 (s, 3H), 1.3-2.8 (m, 7H), 1.47 (s, 3H), 2.90 (s, 3H), 3.06 (s, 3H), 3.57 (s, 3H), 5.10 (s, 1H), 6.40-7.00 (m, 3H). IR (neat) 2880, 1650, 1590 cm^{-1}. Anal. Calcd for $C_{24}H_{38}O_4Si$: C, 68.86; H, 9.15. Found: C, 69.03; H, 9.25.

Cyclization of **2**. The TMS-methylenone **2** (62.75 mg, 0.15 mmol) was treated with a mixture of $SnCl_4$ (0.165 mmol) and $TiCl_4$ (0.165 mmol) in CH_2Cl_2 (1.4 mL) at -23 °C for 2.5 h. Usual workup followed by purification on a silica gel column chromatography afforded **7** (27.4 mg, 58%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.88 (s, 3H), 1.10 (s, 3H), 1.52 (s, 3H), 2.25 (m, 1H), 2.46 (dd, 1H, J = 14.4 and 1.2 Hz), 2.62 (dd, 1H, J = 11.4 and 10.0 Hz), 2.67 (m, 2H), 3.00 (dd, 1H, J = 11.4 and 6.2 Hz), 3.33 (dd, 1H, J = 14.4 and 6.0 Hz), 3.41 (s, 3H), 3.76 (s, 3H), 4.73 (dd, 1H, J = 10.0 and 6.2 Hz), 6.70-7.18 (m, 3H). ^{13}C NMR (65 MHz, $CDCl_3$) δ 12.6, 24.8, 25.3, 34.5, 38.1, 38.9, 39.8, 42.4, 55.5, 57.9, 80.1, 109.7, 117.2, 126.7, 126.8, 134.2, 140.7, 155.3, 156.2, 200.5. IR (CH_2Cl_2) 1665 cm^{-1}. MS 314 (P^+), 282, 135 (base peak) Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.38; H, 8.40.

Preparation and cyclization of **11**. After treating (phenylthiomethyl)trimethylsilane (299 mg, 1.522 mmol) with BuLi (1.343 mmol) in THF (3 mL) at 0 °C for 1 h, a THF (3 mL) solution of the siloxyenone **6** (4143 mg, 0.8954 mmol) was added and it was stirred at 0 °C for 1 h and at room temperature for 0.5 h. Usual workup followed by purification on a silica gel column chromatography gave **11** (371 mg, 74%) as an almost 1:1 mixture of (*E*)- and (*Z*)-isomers. The ratio was determined by comparison of integrals of signals appeared at 5.37 and 5.43, and 6.00 and 6.07 which were attributable to the absorptions of C<u>H</u>$(OMe)_2$ and C<u>H</u>=C, respectively. ^{1}H NMR (200 MHz, $CDCl_3$) δ -0.03-0.08 (four singlets, 6H), 0.89 and 0.91 (two singlets, 9H), 1.23-2.94 (m, 5H), 1.23 (s, 3H), 3.25-3.37 (four singlets, 6H), 3.80 (s, 3H), 5.37 (s, 0.5H), 5.43 (s, 0.5H), 6.00 (s, 0.5H), 6.07 (s, 0.5H), 6.86-7.43 (m, 3H). The dienol silyl ether **11** (285 mg, 0.513 mmol) was treated with $TiCl_4$ (0.564 mmol) in CH_2Cl_2 (5 mL) at -78 °C for 15 min. Workup with aq $NaHCO_3$ followed by purification in usual manner gave **13** (167 mg, 80%). ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.00 (s, 3H), 1.82 (s, 3H), 2.18 (br t, 1H, *J* = 6.0 Hz), 2.57 (d, 1H, *J* = 20.0 Hz), 2.64 (d, 1H, *J* = 14.4 Hz), 2.71 (dd, 1H, *J* = 20.0 and 6.0 Hz), 3.36 (dd, 1H, *J* = 14.4 and 6.0 Hz), 3.45 (s, 3H), 3.76 (s, 3H), 4.48 (d, 1H, *J* = 10.2 Hz), 4.87 (d, 1H, *J* = 10.2 Hz), 6.70-7.545(m, 8H). ^{13}C NMR (65 MHz, $CDCl_3$) δ 13.0, 25.3, 26.8, 35.0, 38.0, 41.0, 43.8, 55.5, 58.4, 60.7, 82.2, 110.1, 117.6, 126.9, 127.0, 128.8, 131.7 (br s), 134.6, 137.2, 140.9, 154.3, 156.3, 200.6. IR (CH_2Cl_2) 1662 cm^{-1}. MS 422 (P^+), 407, 135 (base peak). Anal. Calcd for $C_{26}H_{30}O_3S$: C, 73.90; H, 7.16; S, 7.59. Found: C, 74.07; H, 7.27; S, 7.60.

X-ray Crystallographic Data of **13**.

Crystal data: $C_{26}H_{30}O_3S$; FW = 422.58; a = 12.5986 (14), b = 8.9650 (7), c = 10.2678 (7) A; β = 97.622 (7), V = 1149.46 (18) A^3; space groups $P2_1$; Z = 2; ρ calcd = 1.220 $g{\cdot}cm^{-3}$; No. of reflections collected 3564; No. of reflections used in solution $F>3\sigma$ 2206; R = 0.052; Rw = 0.038.

Preparation and Cyclization of **12**. After treating (methoxymethyl)trimethylsilane (0.79 mL, 5.0 mmol) with *s*-BuLi (3.8 mmol) in THF (5 mL) at -23 °C for 45 min, a THF solution (5 mL) of **6** (1.165 g, 2.519 mmol) was added and was stirred for 1.5 h at the same temperature. Then, ^{t}BuOK (0.48 g, 4.28 mmol) was added and it kept stirring at room temperature for 1.5 h. Usual workup followed by purification gave **12** (0.952 g, 77%) as a 82:18 mixture of (*Z*)- and (*E*)-isomers. The ratio was determined based on the signals appeared at 5.40 and 5.47, and 5.81 and 5.91 which were attributable to the absorptions of acetal and vinyl protons of (*E*)- and (*Z*)-isomer, respectively. ^{1}H NMR (200 MHz, $CDCl_3$) δ -0.29 (s, 3H), 0.00 (s, 3H), 0.86 (s, 9H), 1.11 (s, 3H), 1.12 (s, 3H), 1.94 (s, 3H), 1.28-2.71 (m, 5H), 3.31 (s, 3H), 3.38 (s, 3H), 3.57 (s, 3H), 3.81 (s, 3H), 5.40 (s, 0.18H), 5.47 (s, 0.82H), 5.81 (s, 0.18H), 5.91 (s, 0.82H), 6.83-7.20 (m, 3H). The dienol silyl ether **12** (460 mg, 0.94 mmol) thus obtained was treated with $TiCl_4$ (1.0 mmol) in CH_2Cl_2 (10 mL) at -78 °C for 15 min. Workup with aq $NaHCO_3$ followed by purification on a silica gel column chromatography afforded **14a** (207 mg, 64%) and **14b** (51.4 mg, 16%). **14a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.15 (s, 3H), 1.68 (s, 3H), 2.22 (br t, 1H, *J* = 6.0 Hz), 2.57 (d, 1H, *J* = 19.8 Hz), 2.65 (d, 1H, *J* = 14.4 Hz), 2.73 (dd, 1H, *J* = 19.8 and 6.0 Hz), 3.37 (dd, 1H, *J* = 14.4 and 6.0 Hz), 3.40 (s, 3H), 3.41 (s, 3H), 3.78 (s, 3H), 4.48 (d, 1H, *J* = 9.0 Hz), 4.84 (d, 1H, *J* = 9.0 Hz), 6.70-7.25 (m, 3H). ^{13}C NMR (65 MHz, $CDCl_3$) δ 13.0, 25.3, 26.0, 35.1, 38.0, 40.0, 43.6, 55.6, 57.9, 58.1, 82.5, 88.0, 110.0, 118.2, 126.6, 127.0, 136.3, 139.8, 153.4, 156.5, 200.3. IR (CH_2Cl_2) 1665 cm^{-1}. MS 344 (P^+), 329, 312, 297, 281, 280, 269, 265, 237, 135 (base peak). **14b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.11 (s, 3H), 1.50 (s, 3H), 2.00-3.45 (m,

5H), 3.31 (s, 3H), 3.48 (s, 3H), 3.76 (s, 3H), 4.61 (d, 1H, J = 5.8 Hz), 4.78 (d, 1H, J = 5.8 Hz), 6.69-7.21 (m, 3H).

Stereocontrolled Cyclization of **12**. The dienol silyl ether **12** (650 mg, 1.32 mmol) was treated with $TiCl_4$ (1.46 mmol) in CH_2Cl_2 (12 mL) at -78 °C for 45 min and then at -23 °C for 45 min. Workup with aq $NaHCO_3$ followed by purification on a silica gel column chromatography afforded **14a** (377 mg, 84%).

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