Lewis Acid-Mediated Stereoselective Spiroannelation: A Facile Access to Aphidicolane and Stemodane B/C/D Ring Systems

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A novel and stereoselective spiroannelation reaction was developed. Treatment of the suitably functionalized cyclohexene derivative (3) with trimethylsilyl trifluoromethanesulfonate (TMSOTf) afforded the spiro[5.5]undecanes 4A and 5S exclusively. Changing the solvent from CH_2Cl_2 to CH_3CN or THF increased the stereoselectivity; predominant formation of 4A in CH_3CN and 5S in THF was observed. The spirocyclic compounds 4A and 5S were transformed into the tricyclo[6.3.1.$0^{1,6}$]dodecane derivatives (19A and 27S) corresponding to the B/C/D rings of aphidicolanes (1) and stemodanes (2).

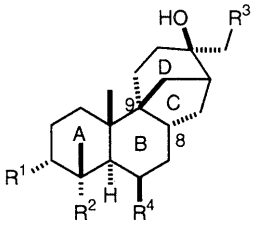
Key words stereoselective spiroannelation; trimethylsilyl trifluoromethanesulfonate; spiro[5.5]undecane; solvent effect; tricyclo[6.3.1.$0^{1,6}$]dodecane; aphidicolane

Numerous spiroannelation reactions have been reported, especially in the 1970's, though most of them focused on the construction of the quaternary carbon itself.[1] Recently, synthetic organic chemistry has become more concerned with stereoselectivity and even enantioselectivity. However, few methodologies are available to control the stereochemistry at a spirocenter carbon atom.[2] Thus, developing a new stereoselective spiroannelation is a challenging and formidable task. Spiro[5.5]undecanes are commonly found in various natural products, and the spirocenter carbons in these natural products are often asymmetric. Therefore, the construction of spiro[5.5]undecanes in a stereoselective manner is an important goal.

The aphidicolane (**1**)[3] and stemodane (**2**)[4] families are tetracyclic diterpenes containing the same carbon skeleton, as shown in Chart 1. These diterpenes contain spiro[5.5]-undecane, which corresponds to their B/D rings. While the absolute configuration at C-8 is *S* in both diterpenes, the configuration at the spirocenter (C-9) differs, *i.e.*, *S* in **1** and *R* in **2**. In other words, **1** has a *trans*-B/C ring junction, whereas **2** has a *cis*-junction. Therefore, an appropriately organized spiroannelation reaction would provide a useful means for syntheses of these diterpenes. In this paper, we wish to present full details of a novel spiroannelation, together with facile stereoselective syntheses of the tricyclo[6.3.1.$0^{1,6}$]dodecane derivatives corresponding to the B/C/D ring systems of **1** and **2**.[5]

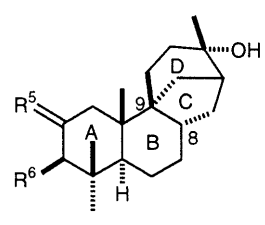
There are two strategically important points in developing a new stereoselective spiroannelation for our purpose. First, a substrate should be suitably functionalized for the spiroannelation reaction as well as for transformation into the B/C/D ring systems of aphidicolane (**1**) and stemodane (**2**). Second, high stereoselectivity should be expected based on the predicted reaction mechanism. An acid-catalyzed spiroannelation reaction of a 4-substituted 3-cyclohexen-1-one derivative, affording a spiro-enone, was reported, although the stereochemistry of the spiro compound was not mentioned.[6] In the light of that work and based on our strategy, a spiroannelation reaction of the bisacetal (**3**) promoted by Lewis acid was judged to be of interest (Chart 2). The anticipated products from the bisacetal (**3**) could be classified into two types of spirocyclic compounds (**4** and **5**). In compound **4**, the relationship of the carbon–carbon double bond and the tosyloxymethyl group is *cis*, while in **5** it is *trans*. The former is an aphidicolane-type product (A-type) and the latter is a stemodane-type product (S-type), because treatments of **4** or **5** with base would produce an A-type tricyclic enone (**6**) or an S-type compound (**7**), respectively. If the plausible intermediate (I) takes an anti-periplanar transition state (II) regarding the enol ether and the oxonium ion moiety to minimize the electrostatic repulsion of the positively charged oxygen, as suggested by Murata *et al.*,[7] considerable stereoselectivity would be expected.

The substrate (**3**) for the spiroannelation reaction was synthesized as follows (Chart 3). Commercially available 1,4-cyclohexanedione (**8**) was converted to **10** by Horner–Emmons reaction with diethyl ethoxycarbonylmethylphosphonate followed by dimethyl ketalization. Deconjugative alkylation of the α,β-unsaturated ester[8] (**10**) was conducted by using the complex of lithium diisopropylamide (LDA) and hexamethylphosphoric tri-



1

a: $R^1=R^3=OH$, $R^2=CH_2OH$, $R^4=H$
b: $R^1=R^4=H$, $R^2=CH_2OH$, $R^3=OH$
c: $R^1=OH$, $R^2=CH_2OH$, $R^3=OAc$, $R^4=H$
d: $R^1=R^3=H$, $R^2=COOH$, $R^4=OCOPh$



2

a: $R^5=$  , $R^6=H$
b: $R^5=O$, $R^6=H$
c: $R^5=H_2$, $R^6=OH$
d: $R^5=H_2$, $R^6=H$

Chart 1

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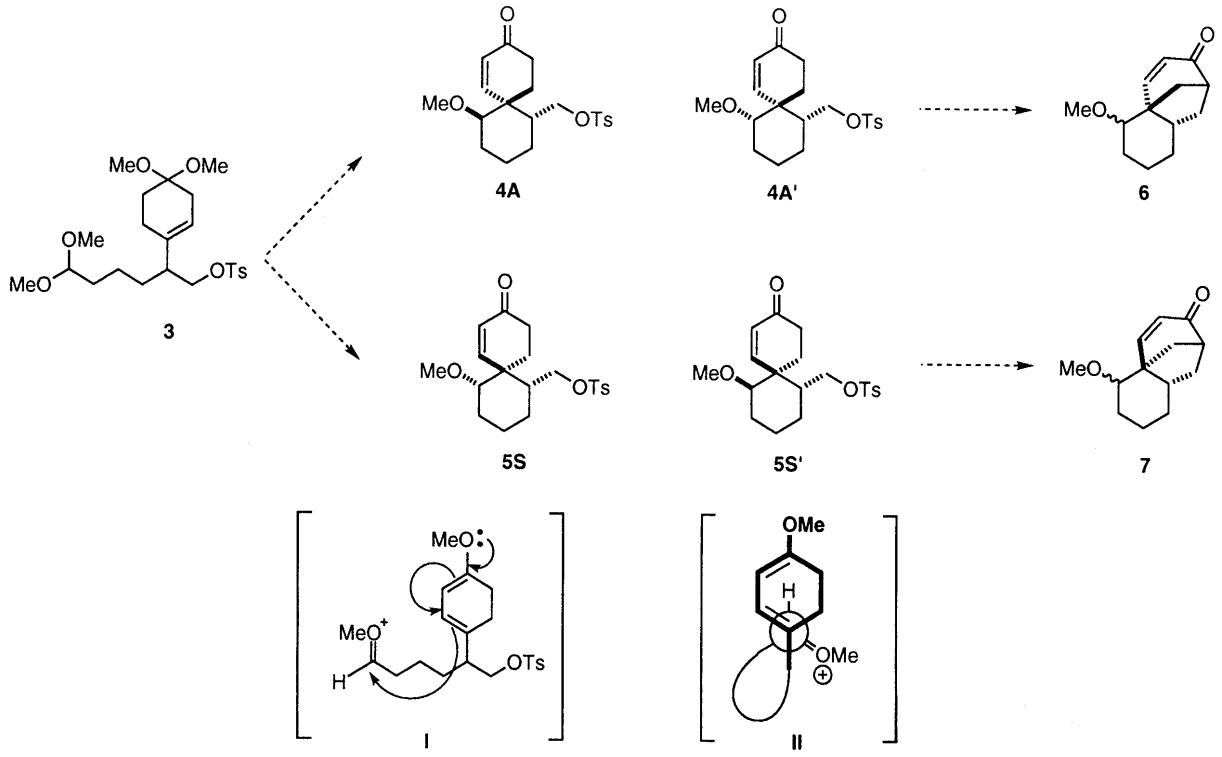
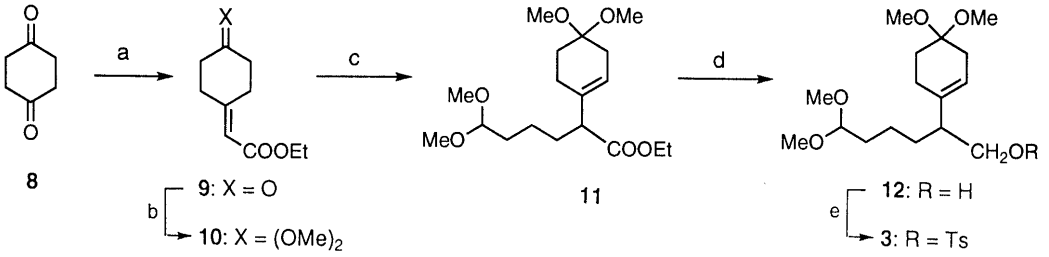


Chart 2



a) $(EtO)_2P(O)CH_2COOEt$, NaH, THF (90%) b) $CH(OMe)_3$, PPTS, MeOH (96%) c) LDA, HMPA, $(MeO)_2CH(CH_2)_3Br$, THF (77%) d) LAH, Et_2O (94%) e) TsCl, Et_3N, DMAP, CH_2Cl_2 (92%)

Chart 3

amide (HMPA) in tetrahydrofuran (THF) with 4-bromobutanal dimethyl acetal[9] to afford **11** in 77% yield. The ester (**11**) was reduced by lithium aluminum hydride (LAH) and the resulting alcohol was tosylated with *p*-toluenesulfonyl chloride (*p*-TsCl) to give the suitably functionalized bisacetal (**3**).

The spiroannelation reaction of the bisacetal (**3**) was investigated with various Lewis acids as depicted in Table 1. Among the Lewis acids examined, trimethylsilyl trifluoromethanesulfonate (TMSOTf) provided the highest yield. Treatment of **3** with 3 eq of TMSOTf in methylene chloride (CH_2Cl_2) at $-78\,^{\circ}C$ smoothly afforded a 57:43 mixture of the spiro-enone **4A** and **5S** in good yield. These two diastereoisomers were chromatographically inseparable due to their lability in contact with silica gel. As expected, only two diastereomers **4A** and **5S** were isolated; neither **4A'** nor **5S'** was obtained.

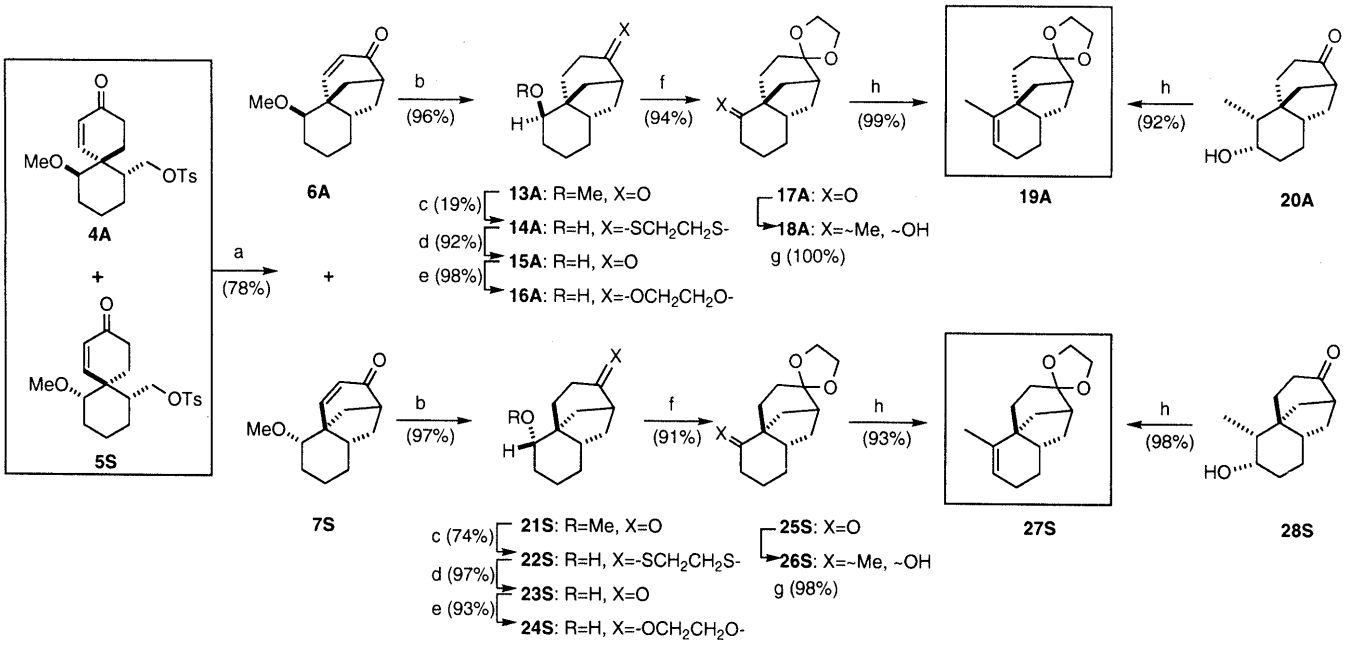
The stereochemistry of **4A** and **5S** was determined by their transformation into independently synthesized tricyclic compounds (**19A** and **27S**) as follows (Chart 4).

Table 1. Lewis Acid-Mediated Spiroannelation Reaction of Bisacetal (**3**)

Lewis acid	Temp. (°C)	Time (min)	**4A**:**5S**[a]	Yield (%)
TMSOTf	−78	40	57:43	82
TBDMSOTf	0	60	50:50	74
$TiCl_4$	−78	150	—	Trace
$Ti(Oiso\text{-}Pr)_2Cl_2$	−78	60	60:40	31
$Ti(Oiso\text{-}Pr)_4$	−78—r.t.	900	No reaction	
$AlCl_3$	−78—r.t.	120	—	Trace
$BF_3 \cdot Et_2O$	−78	40	—	Trace
$SnCl_4$	−78	40	—	0

a) Diastereomeric ratio was determined by 200 MHz ^{1}H-NMR. r.t., room temp.

The mixture of **4A** and **5S** was treated with potassium *tert*-butoxide (*tert*-BuOK) in THF to afford **6A** and **7S**. At this stage, the two diastereoisomers were easily separated by ordinary column chromatography. Therefore,



a) *t*-BuOK, THF b) H_2, Pd-C, AcOEt c) $BF_3 \cdot Et_2O$, ethanedithiol d) $Hg(ClO_4)_2 \cdot 3H_2O$, MeOH, $CHCl_3$ e) ethylene glycol, PPTS, benzene f) PCC, CH_2Cl_2 g) MeLi, Et_2O h) ethylene glycol, *p*-TsOH, benzene

Chart 4

further transformations were conducted individually. The tricyclic enone (**6A**) was hydrogenated to give **13A**. Some difficulty was encountered in cleaving the methyl ether of **13A** which is located at the congested neopentyl position. A relatively drastic condition had to be applied. The tricyclic enone (**6A**) was converted to **14A** by treatment with boron trifluoride etherate ($BF_3 \cdot Et_2O$) in ethanedithiol[10] at room temperature for 7 d although the isolated yield was as low as 19%. The stereochemistry of the hydroxyl group of **14A** was axial, based on the coupling constant (t-like, $J=2.0$ Hz) of the carbinol proton. Therefore, the configuration of the methoxyl group of the spirocyclic compound (**4A**) was determined to be axial. The hydroxy-thioketal (**14A**) was converted to the keto-alcohol (**15A**) and ketalized by ethylene glycol to give the hydroxy-ketal (**16A**), which was oxidized by pyridinium chlorochromate (PCC) to afford the ketal-ketone (**17A**). Compound **17A** was transformed into the ketal-olefin (**19A**) by addition of methyl lithium followed by dehydroxylation with *p*-toluenesulfonic acid (*p*-TsOH) in the presence of ethylene glycol in refluxing benzene. Compound **19A** was identical with the compound obtained by dehydroxylation of the aphidicolane-type tricyclic compound (**20A**), which has been independently synthesized.[11] Consequently, the relative stereochemistry of **4A** was determined; the relationship of the carbon–carbon double bond and the tosyloxymethyl group is *cis* and the methoxyl group is axially oriented. In a similar fashion, the tricyclic enone (**7S**) was converted to the hydroxy-thioketal (**22S**). Although the same reaction conditions were applied to cleave the methyl ether of **21S**, the reaction proceeded smoothly to afford **22S** in 74% isolated yield. The coupling constant (dd, $J=4.8$, 11.0 Hz) of the carbinol proton of **22S** demonstrated that the methoxyl group in the spirocyclic compound (**5S**) was equatorial. Further transformations of **22S** to the ketal-olefin (**27S**) were carried out similarly. Compound **27S** was identical with the sample obtained from **28S**.[11] Hence, the relative stereochemistry of **5S** was also determined.

Investigations to increase the selectivity of the spiroannelation reaction of the bisacetal (**3**) in various solvents were performed (Table 2). It was discovered that changing the solvent from CH_2Cl_2 to CH_3CN or THF increased the stereoselectivity. Interestingly, opposite selectivity was observed in those solvents. The spiroannelation reaction of **3** in CH_3CN at $-48\,^{\circ}C$ proceeded rapidly to afford a 71 : 29 mixture of **4A** and **5S**. In contrast, the reaction in THF at $-78\,^{\circ}C$ was somewhat slower and gave a 26 : 74 mixture of **4A** and **5S** in 52% isolated yield.

The solvent effects of CH_3CN and THF were studied by using mixed solvent systems with CH_2Cl_2 (Table 3). Fifty % of CH_3CN or THF is enough for maximum stereoselectivity, and more significantly, the isolated yields in both mixed solvent systems dramatically improved; 50% THF in CH_2Cl_2 furnished 90% isolated yield, while 50% CH_3CN provided 96% isolated yield.

Since only two diastereomeric spiro compounds (**4A**) and (**5S**) were isolated, it is surmised that the spiroannelation proceeded *via* the anticipated reaction mechanism. A plausible reaction pathway for the spiroannelation reaction of the bisacetal (**3**) is as follows (Chart 5). First, the ketal moiety of **3** is converted to a dienol and the acetal to an oxonium ion by the action of TMSOTf. In this intermediate (I), three transition states (II, III, and IV) are possible with regard to the relationship between the dienol and the oxonium ion. Among these, the transition state (II) should be most favorable concerning electrostatic repulsion of the dienol and the oxonium

Table 2. Solvent Effects of TMSOTf-Mediated Spiroannelation Reaction of Bisacetal (**3**)

Solvent	Temp. (°C)	Time (min)	**4A**:**5S**[a]	Yield (%)
CH_3CN	−48	30	71:29	77
n-PrCN	−78	40	67:33	73
$CHCl_3$	−63	30	60:40	40
CH_2Cl_2	−78	40	57:43	82
Toluene	−78	40	43:57	72
DME	−58	60	50:50	40
Dioxane	20	40	48:52	36
THF	−78	80	26:74	52
Et_2O	−78	60	—	0
CH_3NO_2	−29	30	—	0

a) Diastereomeric ratio was determined by 200 MHz ^{1}H-NMR.

Table 3. Evaluation of Solvent Effects on Stereoselectivity of TMSOTf-Mediated Spiroannelation Reaction

Solvent	**4A**:**5S**[a]	Yield (%)
$THF:CH_2Cl_2$		
1:7	33:67	85
1:1	22:78	90
3:1	25:75	84
1:0	26:74	52
$CH_3CN:CH_2Cl_2$		
1:7	62:38	93
1:1	73:27	96
3:1	75:25	92
1:0	71:29	77

a) Diastereomeric ratio was determined by 200 MHz ^{1}H-NMR.

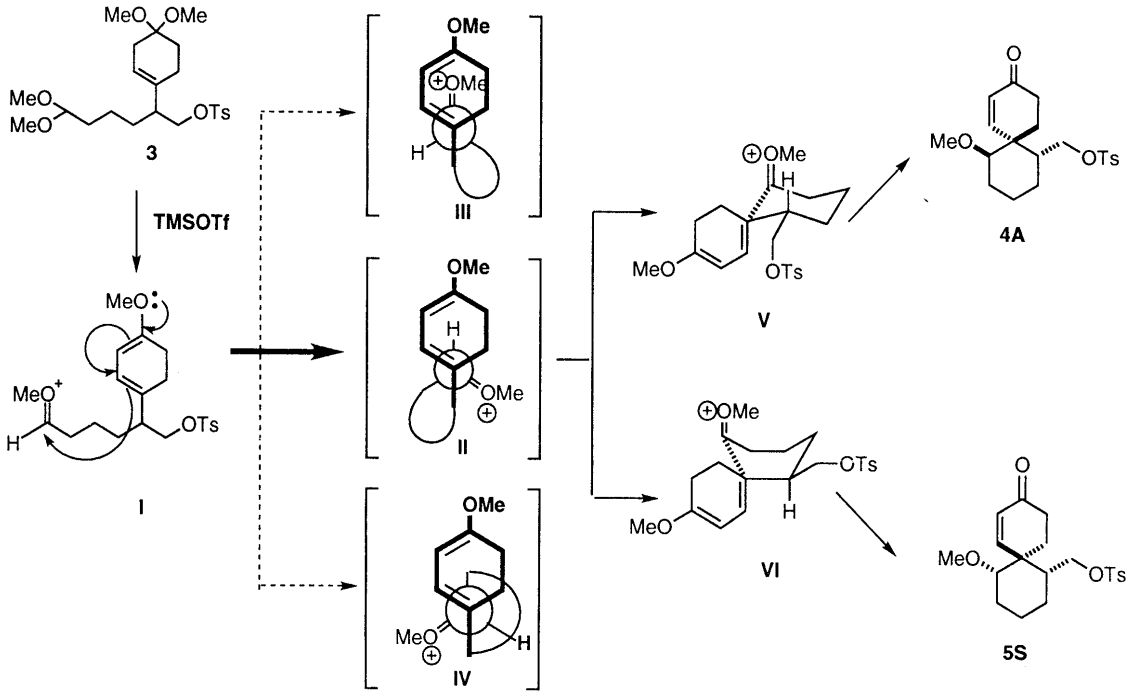


Chart 5

ion. In II, the dienol and the oxonium ion are located in an anti-periplanar manner to minimize the repulsion.[7] Then, two conformers (V and VI) can be anticipated for the transition state (II). The chair-like conformer (V) leads to **4A**, in which the resulting methoxyl group is axial, while the boat-like conformer (VI) provides **5S**, which has an equatorial methoxyl group. Presumably, in CH_2Cl_2, the energy difference between V and VI is insignificant so that almost equal amounts of **4A** and **5S** are formed. Although it is unclear that how the transition states are affected by the solvents, in CH_3CN, the conformer (V) is favored, while in THF, VI is preferred.

As described above, a novel and stereoselective spiroannelation reaction was developed. The selectivity could be controlled by changing the solvent. A plausible reaction pathway was proposed. Finally, tricyclic compounds corresponding to the B/C/D rings system of aphidicolanes (**1**) and stemodanes (**2**) were selectively synthesized.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 or a Horiba FT-210 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained in $CDCl_3$ solution on a Varian VXR 200 (200 MHz), a Hitachi R-250HT (250 MHz), a JEOL EX-270 (270 MHz), or a JEOL JNM-GX-500 (500 MHz). Mass spectra (MS) were obtained with a Shimadzu GCMS-QP-1000, and high-resolution mass spectra (HRMS) were measured with a JEOL JMS-D-3000 mass spectrometer. Column chromatography was performed on Merck Kieselgel 60 unless otherwise noted. All extracts were dried over anhydrous Na_2SO_4 before evaporation.

Ethyl 4,4-Dimethoxycyclohexylideneacetate (10) Diethyl ethoxycarbonylmethylphosphonate (0.23 ml, 1.16 mmol) was added dropwise to a suspension of NaH (60% in oil, 43 mg, 1.1 mmol) and THF (5.0 ml) at room temperature and the mixture was stirred for 30 min, then added to a solution of **3** (100 mg, 0.89 mmol) in THF at 0 °C. Stirring was continued for 10 min. Water was added and the whole was extracted with ethyl acetate (AcOEt). The extract was washed with water and brine, dried, and evaporated. The residue was purified by column chromatography (*n*-hexane:AcOEt = 5:1) to give **9** (147 mg, 90%) as colorless crystals. Trimethyl orthoformate (4 ml) and pyridinium *p*-toluenesulfonate (PPTS) (25 mg, 0.1 mmol) were added to a solution of **9** (182 mg, 1.0 mmol) in MeOH (4 ml) and the mixture was stirred at

room temperature for 3 h. Saturated $NaHCO_3$ aqueous solution was added and methanol and trimethyl orthoformate were evaporated off. The residue was extracted with ether, and the extract was washed with water and brine, dried, then evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 8 : 1) to afford **10** (220 mg, 96%) as a colorless oil. IR (KBr) cm^{-1}: 1714, 1651. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.27 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.75—1.86 (4H, m, $(CH_2)_2(OMe)_2$), 2.28 (2H, t-like, $CH_2C{=}C_{trans}$), 2.91 (2H, t, J = 6.5 Hz, $CH_2C{=}C_{cis}$), 3.22 (6H, s, $(OMe)_2$), 4.15 (2H, q, J = 7.0 Hz, CH_2CH_3), 5.65 (1H, s, CH=C). MS *m/z* (%): 228 (M^+, 1.2) *Anal.* Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 62.87; H, 8.66.

Ethyl 6,6-Dimethoxy-2-(4,4-dimethoxy-1-cyclohexenyl)hexanoate (11) A solution of **10** (100 mg, 0.44 mmol) in THF (0.52 ml) was added dropwise to LDA solution [prepared from iso-Pr_2NH (0.074 ml, 0.53 mmol), *n*-BuLi (1.6 M in *n*-hexane, 0.33 ml, 0.52 mmol) and HMPA (0.09 ml, 0.52 mmol) in THF (0.52 ml) at 0 °C] at −78 °C, and the mixture was stirred for 30 min. Then, a solution of 4-bromobutanal dimethyl acetal (104 mg, 0.53 mmol) in THF (0.3 ml) was added dropwise. The whole was stirred for 12 h with a gradual increase of the temperature to 25 °C. Saturated NH_4Cl aqueous solution and water were added and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, then evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 4 : 1) to afford **11** (116 mg, 77%) as a colorless oil. IR (KBr) cm^{-1}: 1732, 1587. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.24 (3H, t, J = 7.1 Hz, CH_2CH_3), 1.30—2.10 (8H, m), 2.24—2.33 (2H, m, $CH_2CH{=}C$), 2.94 (1H, t, J = 7.6 Hz, $CHC{=}C$), 3.21 (6H, s, $C(OMe)_2$), 3.30 (6H, s, $CH(OMe)_2$), 4.13 (2H, q, J = 7.1 Hz, CH_2CH_3), 4.35 (1H, t, J = 5.7 Hz, $CH(OMe)_2$), 5.45 (1H, br s, CH=C). MS *m/z* (%): 344 (M^+, 0.9) *Anal.* Calcd for $C_{18}H_{32}O_6$: C, 62.76; H, 9.36. Found: C, 62.57; H, 9.28.

6,6-Dimethoxy-2-(4,4-dimethoxy-1-cyclohexenyl)hexan-1-ol (12) A solution of **11** (5.00 g, 14.5 mmol) in Et_2O (10 ml) was added dropwise to a suspension of LAH (1.10 g, 29.0 mmol) in Et_2O (50 ml) at 0 °C and the mixture was stirred for 15 min at room temperature. Water (1.1 ml), 10% NaOH aqueous solution (1.1 ml) and water (3.3 ml) were successively added at 0 °C and the whole was stirred for 30 min at room temperature. The resulting mixture was filtered and the filtrate evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 2) to afford **12** (4.12 g, 94%) as a colorless oil. IR (KBr) cm^{-1}: 3494. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.14—2.37 (13H, m), 3.21 (6H, s, $C(OMe)_2$), 3.30 (6H, s, $CH(OMe)_2$), 3.42—3.53 (2H, m, CH_2OH), 4.35 (1H, t, J = 5.7 Hz, $CH(OMe)_2$), 5.41 (1H, br s, CH=C). MS *m/z* (%): 302 (M^+, 0.1), 270 (M^+ − MeOH, 4.1), HRMS Calcd for $C_{16}H_{30}O_5$: 302.2093. Found: 302.2098.

6,6-Dimethoxy-2-(4,4-dimethoxy-1-cyclohexenyl)hexan-1-yl *p*-Toluenesulfonate (3) *p*-TsCl (1.51 g, 7.94 mmol) was slowly added to a solution of **12** (2.00 g, 6.62 mmol), triethylamine (Et_3N) (1.85 ml, 13.24 mmol), and 4,4-dimethylaminopyridine (DMAP) (81 mg, 0.66 mmol) in CH_2Cl_2 at 0 °C. The solution was stirred for 3 h at room temperature. Water was added at 0 °C and the whole was extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and then evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to afford **3** (2.78 g, 92%) as a colorless oil. IR (KBr) cm^{-1}: 1599. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.05—2.40 (13H, m), 2.45 (3H, s, Ar-CH_3), 3.19, 3.19 (total 6H, each s, $C(OMe)_2$), 3.28, 3.28 (total 6H, each s, $CH(OMe)_2$), 3.90, 3.92 (total 2H, each d, J = 3.2 Hz, CH_2OTs), 4.30 (1H, t, J = 5.7 Hz, $CH(OMe)_2$), 5.27 (1H, br s, CH=C), 7.31—7.79 (4H, AA'BB' type aromatic H). MS *m/z* (%): 392 (M^+ − 2MeOH, 1.1). HRMS Calcd for $C_{21}H_{28}O_5S$ (M^+ − 2MeOH): 392.1655. Found: 392.1654.

General Procedure for Spiroannelation of 3. (6*RS*,7*RS*,11*SR*)- and (6*RS*,7*SR*,11*SR*)-11-Methoxy-7-tosyloxymethylspiro[5.5]undec-1-en-3-one (4A and 5S) Under an argon atmosphere, TMSOTf (0.116 ml, 0.60 mmol) was added to a solution of **3** (91.4 mg, 0.20 mmol) in CH_2Cl_2 (20 ml) at −78 °C. The solution was stirred for the time indicated in Table 2. Saturated $NaHCO_3$ aqueous solution was added and the mixture was extracted with CH_2Cl_2. The extract was washed with water and brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to give a 57 : 43 mixture of **4A** and **5S** (62.3 mg, 82%), as a colorless oil. IR (KBr) cm^{-1}: 1680, 1599. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.05—2.35 (11H, m), 2.44 (3H, s, Ar-CH_3), 2.94 (1 × 43/100H, dd, J = 3.8, 9.8 Hz, CHOMe), 3.21 (3H, s, OMe), 3.38 (1 × 57/100H, br s, CHOMe), 3.75—4.01 (2H, m, CH_2OTs), 5.92 (1 × 57/100H, d, J = 10.1 Hz, CH=CHC=O), 6.02 (1 × 43/100H, d, J = 10.5 Hz, CH=CHC=O), 6.45 (1 × 43/100H, d, J = 10.5 Hz, CH=CHC=O), 6.86 (1 × 57/100H, d, J = 10.1 Hz, CH=CHC=O), 7.31—7.74 (4H, AA'BB' type aromatic H). MS *m/z* (%): 378 (M^+, 4.1). HRMS Calcd for $C_{20}H_{26}O_5S$: 378.1501. Found: 378.1501.

(1*RS*,2*RS*,6*SR*,8*RS*)- and (1*RS*,2*RS*,6*RS*,8*SR*)-2-Methoxytricyclo-[6.3.1.0^{1,6}]dodec-10-en-9-one (6A and 7S) A solution of **4A** and **5S** (28.2 mg, 0.075 mmol) in THF (1.0 ml) was added to a suspension of potassium *tert*-butoxide (*t*-BuOK) (16.7 mg, 0.15 mmol) in THF (2.7 ml) at 0 °C. The whole was stirred for 30 min at room temperature. Water was added and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, then evaporated. The residue was purified by flash column chromatography (*n*-hexane : AcOEt = 4 : 1) to give **6A** (6.9 mg, 45%) and **7S** (5.0 mg, 33%), each as a colorless oil. For **6A**, IR ($CHCl_3$) cm^{-1}: 1680, 1601. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.14—2.11 (11H, m), 2.85 (1H, t, J = 6.3 Hz, CHC(=O)), 3.36 (1H, br s, CH(OMe)), 3.38 (3H, s, OMe), 5.82 (1H, dd, J = 1.8, 9.8 Hz, C-10 H), 7.52 (1H, dd, J = 1.8, 9.8 Hz, C-9 H). MS *m/z* (%): 206 (M^+, 14.9). *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.31; H, 8.74. For **7S**, IR ($CHCl_3$) cm^{-1}: 1678, 1603. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.13—2.09 (11H, m), 2.89 (1H, t, J = 6.4 Hz, CHC(=O)), 3.39 (3H, s, OMe), 3.43 (1H, dd, J = 4.9, 11.0 Hz, CH(OMe)), 5.84 (1H, dd, J = 1.8, 9.8 Hz, C-10 H), 6.98 (1H, dd, J = 1.8, 9.8 Hz, C-9 H). MS *m/z* (%): 206 (M^+, 18.3). *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.52; H, 8.81.

(1*RS*,2*SR*,6*RS*,8*SR*)-2-Methoxytricyclo[6.3.1.0^{1,6}]dodecan-9-one (13A) Pd–C (10%, 40 mg) was added to a solution of **6A** (213 mg, 1.03 mmol) in AcOEt (50 ml), and the mixture was stirred for 30 min under 1 atm of H_2 at room temperature. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 8 : 1) to give **13A** (206 mg, 96%), as a colorless oil. IR ($CHCl_3$) cm^{-1}: 1710. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.00—2.58 (15H, m), 2.65 (1H, t, J = 6.3 Hz, CHC(=O)), 3.19—3.27 (1H, m, CH(OMe)), 3.31 (3H, s, OMe). MS *m/z* (%): 208 (M^+, 42.2). *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.66; H, 9.62.

(1*RS*,2*SR*,6*RS*,8*SR*)-2-Hydroxytricyclo[6.3.1.0^{1,6}]dodecan-9-one Ethylene Dithioacetal (14A) $BF_3 \cdot Et_2O$ (2.0 ml) was added to a solution of **13A** (40.0 mg, 0.19 mmol) in ethanedithiol (2.0 ml). The whole was stirred at room temperature for 7 d, then 10% NaOH aqueous solution was added and the mixture was extracted with CH_2Cl_2. The extract was washed with 10% NaOH aqueous solution and water and brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 8 : 1) to give **14A** (9.8 mg, 19%), as colorless crystals, mp 83—85 °C (from *n*-hexane). IR (KBr) cm^{-1}: 3354. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 0.95—2.40 (15H, m), 2.46 (1H, t, J = 6.1 Hz, $CHC(SCH_2)_2$), 3.07—3.36 (4H, m, SCH_2CH_2S), 3.72 (1H, t-like, J = 2.0 Hz, CHOH). MS *m/z* (%): 270 (M^+, 49.4). *Anal.* Calcd for $C_{14}H_{22}OS_2$: C, 62.18; H, 8.20; S, 23.71. Found: C, 62.07; H, 8.00; S, 23.45.

(1*RS*,2*SR*,6*RS*,8*SR*)-2-Hydroxytricyclo[6.3.1.0^{1,6}]dodecan-9-one (15A) A solution of mercury(II) perchlorate trihydrate ($Hg(ClO_4)_2 \cdot 3H_2O$) (47.0 mg, 0.10 mmol) in MeOH (0.3 ml) was added to a solution of **14A** (12.7 mg, 0.047 mmol) in MeOH (0.1 ml) and $CHCl_3$ (0.3 ml) at room temperature. The whole was stirred for 10 min. The precipitate was filtered off, saturated $NaHCO_3$ aqueous solution was added to the filtrate, and the mixture was extracted with $CHCl_3$. The extract was washed with diluted HCl, water and brine, dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 1) to give **15A** (8.4 mg, 92%), as a colorless oil. IR (KBr) cm^{-1}: 3450, 1713. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.06—2.60 (15H, m), 2.67 (1H, t, J = 6.6 Hz, CHC=O), 3.80—3.87 (1H, m, CHOH). MS *m/z* (%): 194 (M^+, 43.9). HRMS Calcd for $C_{12}H_{18}O_2$: 194.1301. Found: 194.1318.

(1*RS*,2*SR*,6*RS*,8*SR*)-2-Hydroxytricyclo[6.3.1.0^{1,6}]dodecan-9-one Ethylene Acetal (16A) A mixture of **15A** (50.0 mg, 0.26 mmol), ethylene glycol (0.14 ml, 2.6 mmol), PPTS (7.5 mg, 0.03 mmol), and benzene (5.0 ml) was refluxed under a Dean–Stark water separator for 3 h. After cooling, saturated $NaHCO_3$ aqueous solution was added and the mixture was extracted with Et_2O. The extract was washed with brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to give **16A** (60 mg, 98%), as colorless crystals, mp 49—50 °C (from *n*-hexane). IR (KBr) cm^{-1}: 3508. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.95—2.20 (15H, m), 3.75 (1H, br s, CHOH), 3.79—4.02 (4H, m, OCH_2CH_2O). MS *m/z* (%): 238 (M^+, 5.5). *Anal* Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.07. Found: C, 70.38; H, 9.07.

(1*RS*,6*RS*,8*SR*)-Tricyclo[6.3.1.0^{1,6}]dodecan-2,9-dione 9,9-Ethylene Acetal (17A) A solution of **16A** (55.0 mg, 0.23 mmol) in CH_2Cl_2 (1 ml) was added to a suspension of PCC (75 mg, 0.35 mmol) and AcONa

(29 mg, 0.35 mmol) and aluminum oxide (Al_2O_3) (440 mg) in CH_2Cl_2 (2.3 ml) at 0 °C. The whole was stirred for 1 h at room temperature. Et_2O (3.3 ml) was added and the mixture was passed through a pad of Florisil. The eluate was evaporated, and the residue was purified by column chromatography (*n*-hexane : AcOEt = 3 : 1) to give **17A** (51.4 mg, 94%), as a colorless oil. IR (KBr) cm^{-1}: 1707. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 1.20—2.30 (15H, m), 2.50—2.58 (1H, m, $CH_2(=O)_{eq}$), 3.70—4.02 (4H, m, OCH_2CH_2O). MS *m/z* (%): 236 (M^+, 0.8). *Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.08; H, 8.43.

(1*RS*,6*RS*,8*SR*)-2-Methyltricyclo[6.3.1.0^{1,6}]dodec-2-en-9-one Ethylene Acetal (19A) from 17A MeLi (1.04 M in Et_2O, 4.7 ml, 4.9 mmol) was added to a solution of **17A** (460 mg, 1.95 mmol) in Et_2O (15 ml) at −78 °C under N_2. The mixture was stirred for 30 min. Water was added and the mixture was extracted with AcOEt. The extract was washed with brine, dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to give **18A** (490 mg, 100%), as a colorless oil. A mixture of **18A** (180 mg, 0.71 mmol), ethylene glycol (0.4 ml, 7.1 mmol), *p*-TsOH·H_2O (6.7 mg, 0.035 mmol), and benzene (7 ml) was refluxed under a Dean–Stark water separator for 6 h. It was allowed to cool, then saturated $NaHCO_3$ aqueous solution was added and the whole was extracted with Et_2O. The extract was washed with brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 12 : 1) to give **19A** (166 mg, 99%), as a colorless oil. IR (KBr) cm^{-1}: 1651. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.25—2.21 (17H, m), 3.80—4.00 (4H, m, OCH_2CH_2O), 5.04—5.09 (1H, m, C=CH). MS *m/z* (%): 234 (M^+, 2.1). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.02; H, 9.34.

From 20A A mixture of **20A** (82 mg, 0.39 mmol), ethylene glycol (0.04 ml, 0.69 mmol), *p*-TsOH·H_2O (8 mg, 0.04 mmol), and benzene (25 ml) was refluxed under a Dean–Stark water separator for 3 h. It was allowed to cool, saturated $NaHCO_3$ aqueous solution was added, and the mixture was extracted with Et_2O. The extract was washed with brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 15 : 1) to give **19A** (85 mg, 92%), as a colorless oil, which was identical with the compound derived from **18A**.

(1*RS*,2*SR*,6*SR*,8*RS*)-2-Methoxytricyclo[6.3.1.0^{1,6}]dodecan-9-one (21S) Pd–C (10%, 10 mg) was added to a solution of **7S** (50.0 mg, 0.24 mmol) in AcOEt (12 ml), and stirred for 1 h under 1 atm of H_2 at room temperature. The catalyst was filtered off, and the filtrate was concentrated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 8 : 1) to give **21S** (49.1 mg, 97%), as a colorless oil. IR (KBr) cm^{-1}: 1716. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.95—2.62 (15H, m), 2.68 (1H, t-like, CHC(=O)), 3.08 (1H, dd, J = 5.2, 10.2 Hz, C<u>H</u>(OMe)), 3.36 (3H, s, OMe). MS *m/z* (%): 208 (M^+, 23.7). *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.75; H, 9.59.

(1*RS*,2*SR*,6*SR*,8*RS*)-2-Hydroxytricyclo[6.3.1.0^{1,6}]dodecan-9-one Ethylene Dithioacetal (22S) $BF_3 \cdot Et_2O$ (1.0 ml) was added to a solution of **21S** (20.0 mg, 0.096 mmol) in ethanedithiol (1.0 ml). The whole was stirred at room temperature for 7 d. A 10% NaOH aqueous solution was added and the mixture was extracted with CH_2Cl_2. The extract was washed with 10% NaOH aqueous solution and water and brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 8 : 1) to give **22S** (19.3 mg, 74%), as colorless crystals, mp 73—75 °C (from iso-Pr_2O). IR ($CHCl_3$) cm^{-1}: 3452. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.92—2.28 (15H, m), 2.52 (1H, t-like, C<u>H</u>C($SCH_2)_2$), 3.11—3.36 (4H, m, SCH_2CH_2S), 3.47 (1H, dd, J = 4.8, 11.0 Hz, C<u>H</u>OH). MS *m/z* (%): 270 (M^+, 86.6). *Anal.* Calcd for $C_{14}H_{22}OS_2$: C, 62.17; H, 8.20; S, 23.71. Found: C, 61.88; H, 8.10; S, 23.68.

(1*RS*,2*SR*,6*SR*,8*RS*)-2-Hydroxytricyclo[6.3.1.0^{1,6}]dodecan-9-one (23S) A solution of $Hg(ClO_4)_2 \cdot 3H_2O$ (70 mg, 0.15 mmol) in MeOH (0.6 ml) was added to a solution of **22S** (19.2 mg, 0.07 mmol) in MeOH (0.2 ml) and $CHCl_3$ (0.6 ml) at room temperature. The whole was stirred for 10 min. The precipitate was filtered off, saturated $NaHCO_3$ aqueous solution was added to the filtrate, and the mixture was extracted with $CHCl_3$. The extract was washed with diluted HCl, water and brine, dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 1) to give **23S** (13.2 mg, 97%), as colorless crystals, mp 70—72 °C (from iso-Pr_2O). IR (KBr) cm^{-1}: 3442, 1713. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.95—2.65 (15H, m), 2.71 (1H, t-like, CHC=O), 3.63 (1H, dd, J = 4.8, 10.8 Hz, C<u>H</u>OH). MS *m/z* (%): 194 (M^+, 19.1). HRMS Calcd for $C_{12}H_{18}O_2$: 194.1306. Found: 194.1306.

(1*RS*,2*SR*,6*SR*,8*SR*)-2-Hydroxytricyclo[6.3.1.0^{1,6}]dodecan-9-one Ethylene Acetal (24S) A mixture of **23S** (815 mg, 4.20 mmol), ethylene glycol (2.3 ml, 42 mmol), PPTS (53 mg, 0.21 mmol), and benzene (14 ml) was refluxed under a Dean–Stark water separator for 3 h. After cooling, saturated $NaHCO_3$ aqueous solution was added and the mixture was extracted with Et_2O. The extract was washed with brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to give **24S** (925 mg, 93%), as a colorless oil. IR (KBr) cm^{-1}: 3479. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 0.85—2.20 (14H, m), 3.51 (1H, dd, J = 4.5, 10.8 Hz, C<u>H</u>OH), 3.78—4.02 (4H, m, OCH_2CH_2O). MS *m/z* (%): 238 (M^+, 6.8). HRMS Calcd for $C_{14}H_{20}O_3$: 238.1567. Found: 238.1555.

(1*RS*,6*SR*,8*RS*)-Tricyclo[6.3.1.0^{1,6}]dodecane-2,9-dione 9,9-Ethylene Acetal (25S) A solution of **24S** (1.00 g, 4.2 mmol) in CH_2Cl_2 (12 ml) was added to a suspension of PCC (1.8 g, 8.4 mmol) and Al_2O_3 (9.0 g) in CH_2Cl_2 (30 ml) at 0 °C. The mixture was stirred for 1 h at room temperature, then Et_2O (42 ml) was added and the mixture was passed through a pad of Florisil. The eluate was evaporated, and the residue was purified by column chromatography (*n*-hexane : AcOEt = 3 : 1) to give **25S** (0.90 g, 91%), as a colorless oil. IR (KBr) cm^{-1}: 1695. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.15—2.28 (14H, m), 2.30—2.43 (total 2H, m, C<u>H</u>C($OCH_2)_2$ and C<u>H</u>$_2(=O)_{eq}$), 3.78—4.02 (4H, m, OCH_2CH_2O). MS *m/z* (%): 236 (M^+, 11.4). *Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.08; H, 8.48.

(1*RS*,6*RS*,8*SR*)-2-Methyltricyclo[6.3.1.0^{1,6}]dodec-2-en-9-one Ethylene Acetal (27S) from 25S MeLi (1.4 M in Et_2O, 0.30 ml, 0.42 mmol) was added to a solution of **25S** (40.0 mg, 0.17 mmol) in Et_2O (1.6 ml) at −78 °C under N_2. The whole was stirred for 30 min. Water was added and the mixture was extracted with AcOEt. The extract was washed with brine, dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to give **26S** (42.0 mg, 98%), as a colorless oil. A mixture of **26S** (790 mg, 3.13 mmol), ethylene glycol (1.7 ml, 31.3 mmol), *p*-TsOH·H_2O (120 mg, 0.63 mmol), and benzene (31 ml) was refluxed under a Dean–Stark water separator for 12 h. It was allowed to cool, saturated $NaHCO_3$ aqueous solution was added, and the mixture was extracted with Et_2O. The extract was washed with brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 12 : 1) to give **27S** (680 mg, 93%), as a colorless oil. IR ($CHCl_3$) cm^{-1}: 1659. ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.00—2.21 (17H, m), 3.80—4.05 (4H, m, OCH_2CH_2O), 5.42 (1H, br s, C=CH). MS *m/z* (%): 234 (M^+, 3.3). *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.79; H, 9.47.

From 28S A mixture of **28S** (82 mg, 0.39 mmol), ethylene glycol (0.24 ml, 4.3 mmol), *p*-TsOH·H_2O (6 mg, 0.03 mmol), and benzene (6 ml) was refluxed under a Dean–Stark water separator for 7 h. It was allowed to cool, then saturated $NaHCO_3$ aqueous solution was added and the mixture was extracted with Et_2O. The extract was washed with brine, then dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to give **27S** (90 mg, 98%), as a colorless oil, which was identical with the compound obtained from **26S**.

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