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Reductive Opening of α-Methylspiroketals

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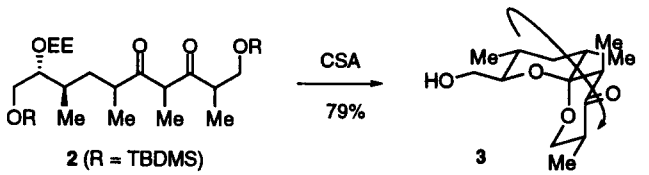
Abstract: Syntheses of 5-methyl-1,7-dioxaspiro[5.5]undecane **4** and its three congeners **5**, **6**, and **7** (α-methylspiroketals), and their reductive ring opening using aluminum hydride or silane - Lewis acid system have been investigated. Each spiroketal was synthesized through stereocontrolled acetalization with 42 - 96% diastereomeric excess (de). The diisobutylaluminum hydride reduction of α-methylspiroketals proceeded *via* the tight oxocarbenium ion pair complex wherein the C - O bond which located at the opposite site against the C(α) - methyl bond was cleaved, affording a configuration-retentive product with 50 - 100% de.

The regioselectivity in the silane - Lewis acid reduction of the simplest monomethylspiroketal **4** was controlled by the equilibration of the two possible oxocarbenium ionic intermediates. On the other hand, dimethylspiroketal **5** and siloxyspiroketal **6** showed moderate to high regio- and stereoselectivity (10 - 100% de), that originated from regioselective formation of the oxocarbenium ionic species and the subsequent stereoselective hydride attack. In these cases, the coordination site of the Lewis acid was controlled by the steric interaction of the methyl group on C(α) with the Lewis acid. To the resultant oxocarbenium ion, stereoelectronically-favored axial hydride attack occurred with high stereoselection. The reduction of benzyloxyspiroketal **7** also exhibited good selectivity (62 - 100% de) while the outcome was opposite to those of **5** and **6**. Such a dramatic change could be attributed to the bidentate chelation of the Lewis acid to both the benzyl ether and the neighboring acetal oxygens. The whole procedure, the thermodynamic spiroketalization and the subsequent reductive ring opening, could be regarded as a remote stereochemical control using the spiroketal templates.

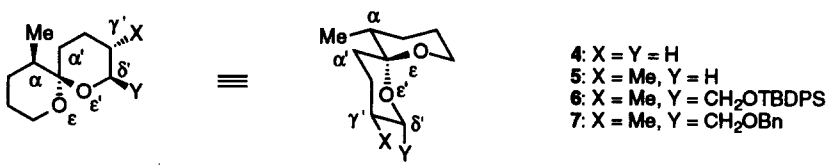
In our program directed toward the synthesis of the polyketide antibiotic, tautomycin, an efficient method was required for preparing a short (C_{10}) chain building block, which possesses skipped stereogenic centers.[1a] In such a short carbon chain synthesis, an intramolecular stereochemical control (induction or transfer) seemed to be more attractive than either a reagent-controlled asymmetric introduction or a coupling of two chiral segments in terms of economy. While there have been reported various types of remote stereochemical control on 1,4- or more far relationships with[2] or without[3] chiral auxiliaries, we turned our attention to spiroketal, that represents 1,7-dioxaspiro[5.5]undecane framework **1** in this article, as a useful template.

1,7-dioxaspiro[5.5]undecane framework **1**

Spiroketal template has been often utilized in organic synthesis to control stereogenic centers.[4] It has two important nature: (1) the stereoselective synthesis of the most stable isomer of spiroketal is easy by the thermodynamic equilibration, and (2) the stereochemistry of the most stable one can be readily predicted beforehand by consideration of steric interactions of substituents and an anomeric effect stabilization.[5] For example, Schreiber *et al.* achieved controlling four stereogenic centers from two non-isomerizable stereogenic carbon on a spiroketal by thermodynamic formation (eq 1).[4a] This reaction can be formally regarded as a remote (1,7- in maximum shown by arrow) stereochemical control because spiroketal **3** is synthetically equivalent to the corresponding keto diol, in which the stereogenicity of the acetal carbon disappears. So if one can attain a nucleophilic ring opening of such a spiroketal template selectively, it would provide us a new methodology for remote stereochemical control.

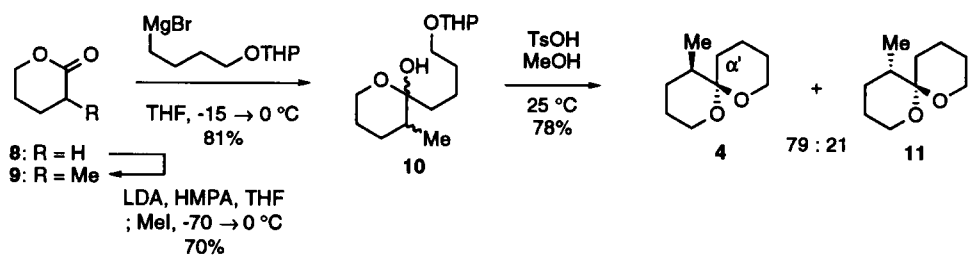


For examining the diastereoselection in the thermodynamic spiroketalization and the subsequent nuculeophilic ring opening, we designed four α-methylspiroketals; 5-methyl-1,7-dioxaspiro[5.5]undecane **4** and its congeners **5**, **6**, and **7**. Here we describe the stereocontrolled syntheses and the reductive cleavage of α-methylspiroketals.[6,7]



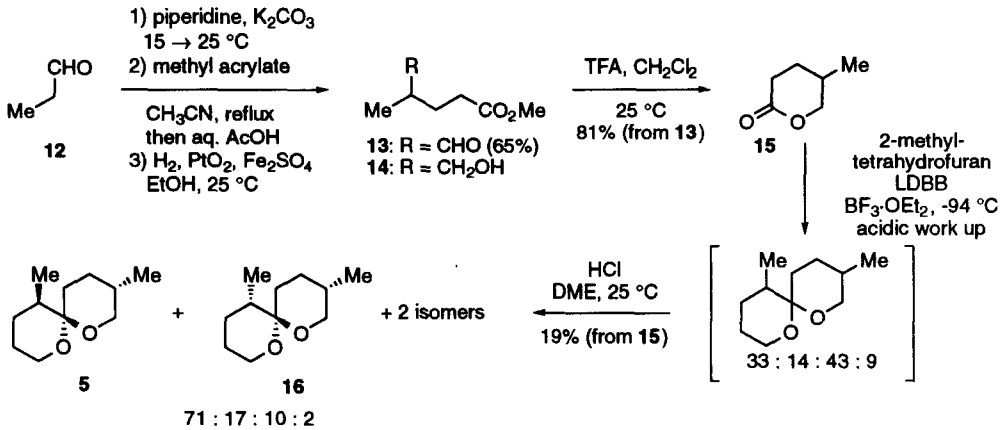
SYNTHESES OF THE SPIROKETALS 4, 5, 6, AND 7

The synthesis of monomethylspiroketal **4** was begun from δ-valerolactone **8** (Scheme 1). Lactone **8** was methylated (lithium diisopropylamide, MeI) and a four carbon unit was introduced to **9** by the addition of the Grignard reagent. The resultant hemiacetal **10** was next treated with *p*-toluenesulfonic acid (TsOH) in methanol to furnish transacetalization and a spiroketal equilibration affording **4** and **11** in a ratio of 79 : 21 in 78% yield.[8] The structure of **4** was established by the NOE-D measurement of methyl protons to axial proton at C(α'), and that of **11** was determined by detailed ^{1}H-NMR analysis.[9]



Scheme 1.

Dimethylspiroketal **5** was synthesized from propionaldehyde **12** as shown in Scheme 2. Aldehyde **12** was condensed with methyl acrylate *via* piperidine enamine to yield **13** in 65% yield.[10] After **13** was reduced by hydrogenation (H_2, PtO_2), the resultant hydroxyester **14** was lactonized by trifluroacetic acid. For the spiroketal formation, we employed Cohen's protocol.[11] That is, lactone **15** was coupled with the dianion derived from 2-methyltetrahydrofuran to provide a 33:14:43:9 mixture of isomeric spiroketals, which was then equilibrated under acidic condition (hydrochloric acid, dimethoxyethane).[12] Thus, the most stable isomer **5**, second-major isomer **16**, and other two minor isomers were obtained in 71%, 17%, 10%, and 2% ratio, respectively.[8] The chemical shifts of methyl protons of **5** and **16** on ^{1}H-NMR were well correlated with those of **4** or **11**, allowing the structure determination of these isomers.[9,13]



Scheme 2.

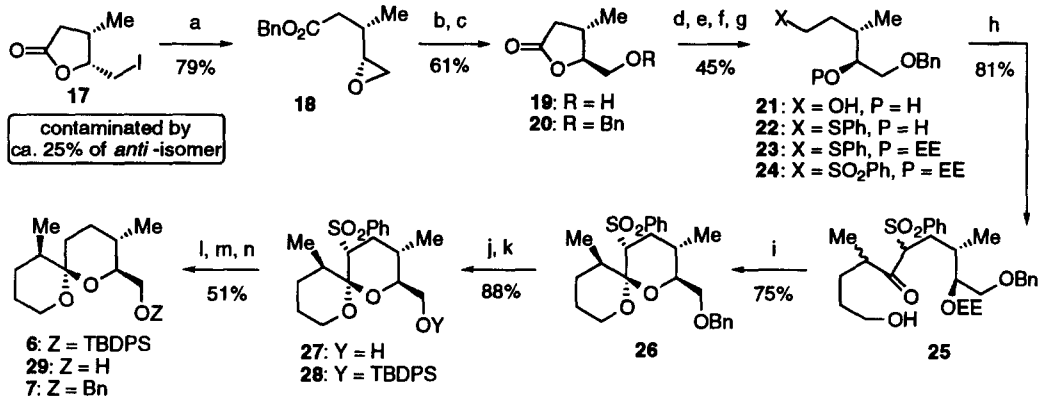
The structure of α-methylspiroketals, **4**, **5**, and their isomers were determined on the basis of ^{1}H-NMR analyses including NOE-D measurements. It was also confirmed by a molecular mechanics calculation (MM2). As shown in Table 1, the spiroketal ratios on monomethyl- (**4** : **11**) and dimethylspiroketals (**5** : **16** : two others) derived through thermodynamic equilibration[8] were found to be good agreement with the mole fractions from MM2 calculations.

Table 1. Comparison of Spiroketal Ratio: Experimental and MM2 Calculation

spiroketals	thermodynamic spiroketalization	mole fractions N*i* (MM2)[a]
4 : **11**	0.79 : 0.21	0.83 : 0.17
5 : **16** : two others[b]	0.71 : 0.17 : 0.10 : 0.02	0.74 : 0.14 : 0.010 : 0.018

[a] Calculated from steric energy E*i* (cal/mol) according to Boltzmann's distribution, $Ni = gi \cdot e^{-\Delta Ei/kT}/\Sigma(gi \cdot e^{-\Delta Ei/kT})$ wherein $gi = 1$, $k = 1.986$ (cal/mol·deg), and $T = 298$ (deg). Calculations were performed on Chem 3D Plus™ (ver. 3.0) program. [b] Two others would be the isomers concerning about two methyl groups, see EXPERIMENTAL SECTION.

For the preparation of siloxyspiroketal **6** and benzyloxyspiroketal **7**, *syn*-iodolactone **17**,[14] that was contaminated by ca. 25% of *anti*-isomer, was used as a starting compound (Scheme 3). Epoxyester **18** was synthesized by the literature procedure (potassium benzyloxide)[15] from **17**, although the contaminating material derived from *anti*-isomer corresponding to **17** could not be removed till the stage of **28**. Benzyl (Bn) group of **18** was deprotected by hydrogenolysis (H_2, Pd/C), and the hydroxy group of *anti*-lactone **19** was protected as a benzyl ether (BnBr, Ag_2O). Subsequent $LiAlH_4$ reduction gave diol **21** which was converted to sulfone **24** in a three-step sequence; selective substitution of the primary hydroxyl by a phenylthio group,[16] protection of the secondary hydroxyl by the 1-ethoxyethyl (EE) group, and oxidation to sulfone. Sulfone **24** was then lithiated by *n*-butyllithium and coupled with 2-methyl-δ-valerolactone **9** to afford **25** as a considerable diastereomeric mixture. For thermodynamic spiroketalization of **25**, the Lewis acid treatment (BF_3·OEt_2) gave the best results in both yield (75%) and diastereoselection (>95%) among other protic conditions such as TsOH or hydrochloric acid. Further protective group manipulations including debenzylation (H_2, $Pd(OH)_2$) and silylation (TBDPSCl, imidazole) provided crystalline **28** that was purified by recrystallization, and the structure of **28** was established by X-ray crystallographic analysis.[17] Finally, siloxyspiroketal **6** was obtained by desulfurization (Raney nickel W-2),[18] which was followed by desilylation (tetra-*n*-butylammonium fluoride) and benzylation (BnBr, NaH) to yield isomerically pure benzyloxyspiroketal **7**.



Reagents and conditions: (a) KOBn, THF, -20 °C. (b) H_2, Pd/C, Et_2O, 25 °C. (c) BnBr, Ag_2O, DMF, 25 °C. (d) $LiAlH_4$, Et_2O, 3 → 25 °C. (e) $(PhS)_2$, *n*-Bu_3P, pyridine, 3 → 25 °C. (f) ethyl vinyl ether, PPTS, CH_2Cl_2, 25 °C. (g) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 3 → 25 °C. (h) *n*-BuLi, **9**, Et_2O-hexane, -80 → 25 °C. (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 3 → 25 °C. (j) H_2, $Pd(OH)_2/C$, EtOH, 25 °C. (k) TBDPSCl, imidazole, DMF, 3 → 25 °C. (l) Raney-Ni (W-2), EtOH, reflux. (m) *n*-Bu_4NF, THF, 25 °C. (n) BnBr, NaH, THF-DMF, 25 °C.

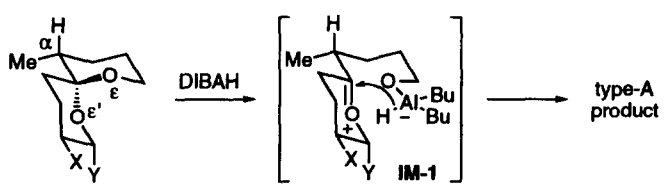
Scheme 3.

REDUCTIVE OPENING OF THE SPIROKETALS

The reducing agents that we adopted in this study were diisobutylaluminum hydride (DIBAH) and the silane - Lewis acid system. In both the reduction, the cleaved C - O site should be controlled by the coordinate position of the reagent. From a molecular model consideration, we anticipated that the methyl group on C(α) would play an effective role in selecting which ether oxygen functionality, O(ε) or O(ε'), was to be coordinated by the aluminum reagent or the Lewis acid.

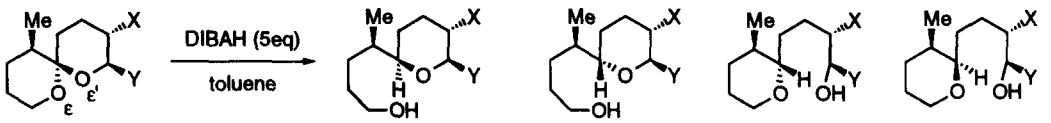
Reduction with DIBAH

The DIBAH reduction of acetals usually gives a product with a retention of configuration.[19] Such a tendency was also observed in the spiroketal reduction (Table 2).[20,21,22,23] Namely, the configuration-retentive type-A product was greatly predominated in the reduction of isomerically pure **4**, **5**, and **6** (runs 1, 5, and 6, respectively). In these cases, the cleaved C - O bond was that located at the opposite site against C(α) - methyl bond. Therefore intermediate (**IM-1**), a tight oxocarbenium ion pair generated by the coordination of the aluminum reagent to the sterically less-hindered acetal oxygen O(ε) that occupied the *anti* position against the methyl group on C(α), seemed to be the plausible intermediate for the DIBAH reduction (eq 2). The following internal hydride attack in **IM-1** yielded the type-A product.[24]



(2)

Table 2. Spiroketal Reduction with DIBAH

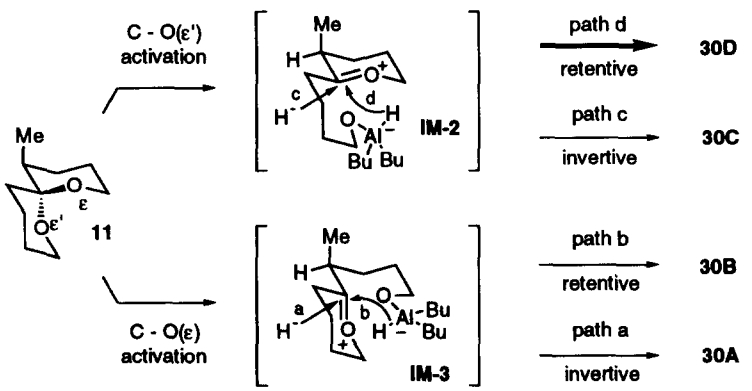


4 (and **11**)	**30A**: X = Y = H	**30B**	**30C**	**30D**
5	**31A**: X = Me, Y = H	**31B**	**31C**	**31D**
6	**32A**: X = Me, Y = $CH_2OTBDPS$	**32B**	**32C**	**32D**
7	**33A**: X = Me, Y = CH_2OBn	**33B**	**33C**	**33D**

run	spiroketal (% purity)	conditions	% yield	selectivity (%) A : B : C : D
1	**4** (99%)[a]	-12 → 25 °C, 11 h	92%[a]	94 : <2 : 2 : 3[a]
2	**4** / **11** (79% : 21%)[a]	-15 → 25 °C, 12 h	85%[a]	85 : <1 : 1 : 14[a]
3	**4** / **11** (65% : 35%)[a]	-5 → 25 °C, 11 h	69%[a]	75 : <2 : 2 : 21[a]
4	**11** (98%)[a]	-6 → 25 °C, 26 h	16%[a]	6 : 13 : 5 : 76[a,d]
5	**5** (98%)[a]	4 → 25 °C, 9 h	62%[c]	100 : 0 : 0 : 0[b]
6	**6** (>98%)[b]	4 → 25 °C, 23 h	<10%[c]	100 : 0 : 0 : 0[b]
7	**7** (>98%)[b]	5 → 25 °C, 1.5 h	74%[c]	76 : 0 : 7 : 17[b]

[a] Determined by GC. [b] Determined by 270 MHz ^{1}H-NMR. [c] Isolated yield. [d] The recovered material contained **4** and **11** in 1 : 1.2 ratio.

This proposed mechanism was supported by the result that **11**, the isomer of **4**, was reduced predominantly into **30D** (runs 2, 3, and 4 in Table 2). The configuration-retentive product **30D** would be derived through the formation of tight oxocarbenium ion pair **IM-2** in which the aluminum reagent coordinated to the sterically less-hindered O(ε') followed by an internal hydride delivery, as illustrated by path d in Scheme 4.

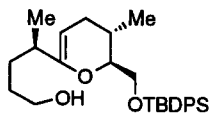


Scheme 4.

Thus, the reductions (runs 1 - 4 in Table 2) of both **4** and **11** occured mainly *via* tight oxocarbenium ion pairs **IM-1** and **IM-2**, affording **30A** and **30D**, respectively. Comparing these reduction runs, a slight difference was observed between the spiroketal ratio and the product ratio. The difference concerning **30A** and **30D** would be accounted by the reactivity divergence of **4** and **11**, as can be seen from the fact that the yield declined

in order of runs 1 → 2 → 3 → 4, and/or the spiroketal isomerization to each other *via* enol ether like **34** or **35** (*vide infra*) through the epimerization at C(α). In run 4, the low reactivity of **11** caused also the reduction at C - O(ε), which was sterically more hindered than C - O(ε'), giving configuration-retentive **30B** in the ratio of 13% (path b in Scheme 4) though we cannot clearly explain why **11** is so unreactive toward DIBAH. Especially in this case, an external hydride attack (S_N2 mechanism) to an oxocarbenium ion pair **IM-2** (path c) may occur leading to **30C**, while **30A** would be derived either from **4**, which was produced by isomerization, or an external hydride attack to an oxocarbenium ion pair **IM-3** (path a).

The DIBAH reduction of sterically-hindered siloxyspiroketal **6** afforded only <10% of **32A** with high regio- and diastereoselectivity, and the major products were the enol ethers **34** and **35** in 20% combined yield (run 6 in Table 2).[25] In contrast, the stereoselectivity in the reduction of benzyloxyspiroketal **7** (run 7) was lower than the other examples such as runs 1, 5, and 6. The benzyl ether oxygen probably caused a disorder of a coordination site of the aluminum reagent, but it accelerated the reaction rate as can be seen also in the reduction of silane - Lewis acid system (*vide infra*).



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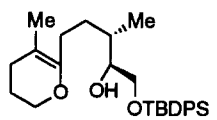

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Reduction with the Silane - Lewis Acid System

It is an important problem whether the reaction of acetals proceeds by an S_N1 or by an S_N2 mechanism in the reaction with the silicon-containing nucleophile and Lewis acid system.[26] In the cases of α-methylspiroketals that we examined, the configuration-retentive type-**A** and type-**C** products were obtained predominantly (Table 3). The observed stereoselectivities ruled out the S_N2 mechanism in the reduction of α-methylspiroketals.

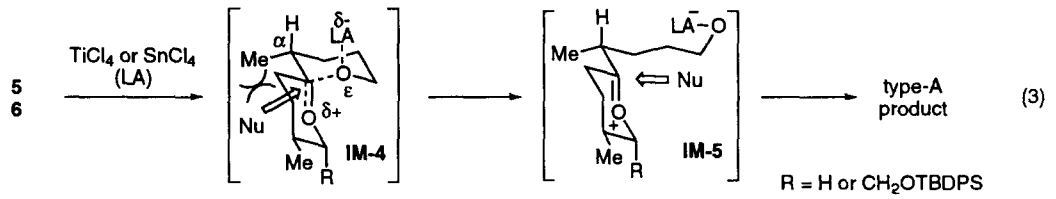
Table 3. Spiroketal Reduction with Silane - Lewis Acid

run	spiroketal (% purity)	conditions[a]	% yield	selectivity (%) **A** : **B** : **C** : **D**
1	**4** (99%)[d]	Ph_2SiH_2 - $TiCl_4$, -70 → -40 °C, 2 h	86%[c]	7 : 9 : 79 : 5[d]
2	**4** / **11** (79% : 21%)[d]	Ph_2SiH_2 - $TiCl_4$, -70 → -20 °C, 1 h	84%[d]	8 : 7 : 80 : 5[d]
3	**5** (94%)[d]	Ph_2SiH_2 - $TiCl_4$, -65 → -40 °C, 1 h	86%[c]	100 : 0 : 0 : 0[e]
4	**5** (91%)[d]	Ph_2SiH_2 - $TiCl_4$, 4 °C, 0.5 h	71%[c]	4 isomers[f]
5	**6** (>98%)[e]	Ph_2SiH_2 - $TiCl_4$, -75 → -15 °C, 2 h	81%[c]	55 : 15 : 0 : 0[e,g]
6	**6** (>98%)[e]	Et_3SiH - $SnCl_4$, -78 → -60 °C, 2 h[b]	98%[c]	100 : 0 : 0 : 0[e]
7	**6** (>98%)[e]	Et_3SiH - $BF_3{\cdot}OEt_2$, -75 → 25 °C, 24 h	no reaction	-
8	**7** (>98%)[e]	Ph_2SiH_2 - $TiCl_4$, -78 → 0 °C, 3 h	100%[c]	19 : 0 : 81 : 0[e]
9	**7** (>98%)[e]	Et_3SiH - $SnCl_4$, -78 → -30 °C, 2 h[b]	70%[c]	0 : 0 : 100 : 0[e]

[a] All reactions were carried out with 1.2 equiv. of silane and 1.2 equiv. of Lewis acid in CH_2Cl_2. [b] Followed by acid treatment to destroy the resultant triethylsilyl ether. [c] Isolated yield. [d] Determined by GC. [e] Determined by 270 MHz ^{1}H-NMR. [f] 21% ratio of type-**A** and other three isomers, two of which were C(α)-epimerized product, were obtained. But the ratio and the structure were not determined. [g] 30% of C(α)-epimerized product was also obtained.

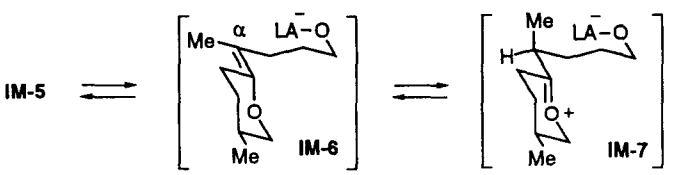
The reaction pathway of the silane - Lewis acid reduction for dimethylspiroketal **5** (run 3) and siloxyspiroketal **6** (run 6) would be explained as illustrated in eq 3. The coordinating site of the Lewis acid would be O(ε) which occupied the *anti* position against the methyl group on C(α), like the aluminum reagent in

the DIBAH reduction. The resultant intermediate **IM-4** could not suffer the hydride attack from the rear side of the C - O(ε) bond (S_N2 substitution shown by arrow) because severe steric interactions were present between the incoming nucleophile and the axial substituents such as the methyl group on C(α). Hence, **IM-4** would be subsequently led to the ring-opened, free oxocarbenium ion **IM-5** which is then reduced by hydride from the stereoelectronically-favored[27] axial side to afford the type-A product. The plausible state of the oxocarbenium ion was "free" rather than "tight" on the basis of the stereochemical outcome.



(3)

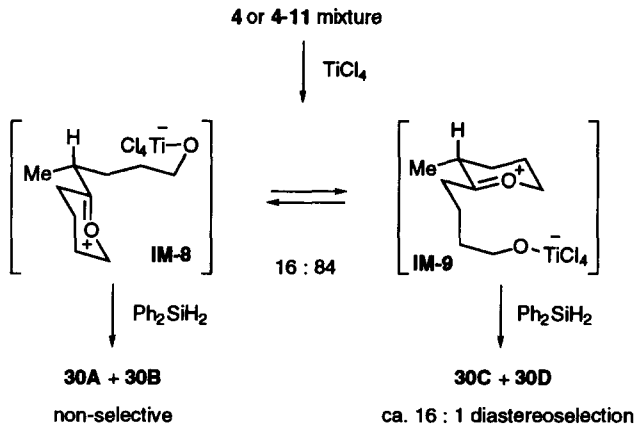
In contrast to run 3 in Table 3, raising the reaction temperature to 4 °C caused an isomerization at C(α) and a significant decrease of selectivity (run 4). This was probably due to the isomerization at the oxocarbenium ion stage (eq 4). Thus, an equilibration between **IM-5** and **IM-7** would occur *via* enol ether **IM-6**, which could originate from **IM-5** by an antiperiplanar proton subtraction, and after **IM-7** was attacked by nucleophile, the isomerization at C(α) was realized.



(4)

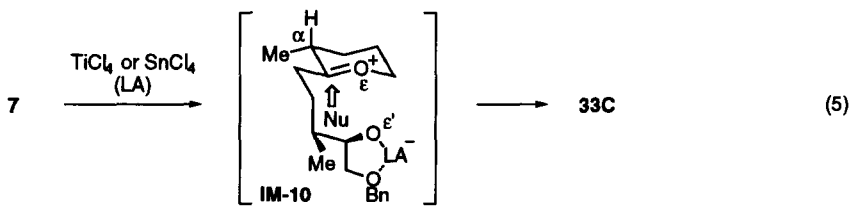
Run 5 in Table 3 reveals that, in the Ph_2SiH_2 - $TiCl_4$ reduction of **6**, there was a non-stereoselective hydride attack to an oxocarbenium ion or an S_N2 displacement to some extent, while the Et_3SiH - $SnCl_4$ reduction of **6** showed high selectivity (run 6). It was also found that the weak Lewis acid, $BF_3{\cdot}OEt_2$, could not induce the formation of an oxocarbenium ion on siloxyspiroketal **6** (run 7). From our limited experimental results, it is difficult, however, to explain how the nature of silane and Lewis acid reflects on the selectivity of the reaction.

The Ph_2SiH_2 - $TiCl_4$ reduction of the simplest spiroketal **4** yielded the type-C product mainly (run 1 in Table 3). Because the Lewis acidity of $TiCl_4$ is stronger than that of DIBAH, rather unreactive **11** (*vide supra*) can also react under the conditions in run 2. But it was quite unexpected that the mixture of **4** and **11** (run 2) exhibited the same selectivity as pure **4** (run 1). In the reduction of monomethylspiroketals, a thermodynamic equilibration between the two possible oxocarbenium ionic species, **IM-8** and **IM-9**, would be present even at low temperature (-70 → -20 °C) as shown in Scheme 5. If both intermediates were reduced at a similar reaction rate, the products ratio (**30A** + **30B** / **30C** + **30D**) should reflect the population of **IM-8** and **IM-9**. Considering the structures of the intermediates, it is reasonably explained that the reduction of **IM-8** occurred in non-stereoselective manner while the nucleophilic attack of hydride to **IM-9** proceeded predominantly from an axial side in about 16 : 1 diastereoselection.



Scheme 5.

The reduction of benzyloxyspiroketal **7** exhibited an opposite regioselectivity to that of dimethylspiroketal **5** and siloxyspiroketal **6** in the silane - Lewis acid system (runs 8 and 9 in Table 3). The significant reversal of the regioselectivity of the bond cleavage suggested that the sterically-hindered O(ε') was activated by the Lewis acid. In these cases, the reductions occurred *via* the bidentate chelation structure **IM-10** mainly, leading to the C - O(ε') cleaved product **33C** (eq 5).[28] While $SnCl_4$ showed a complete ability for a bidentate chelation exhibiting high regioselectivity (run 8), the use of $TiCl_4$ was not completely effective providing 19% ratio of **33A** (run 9). For **IM-10** hydride attack also took place from an axial side to afford **33C** stereoselectively.



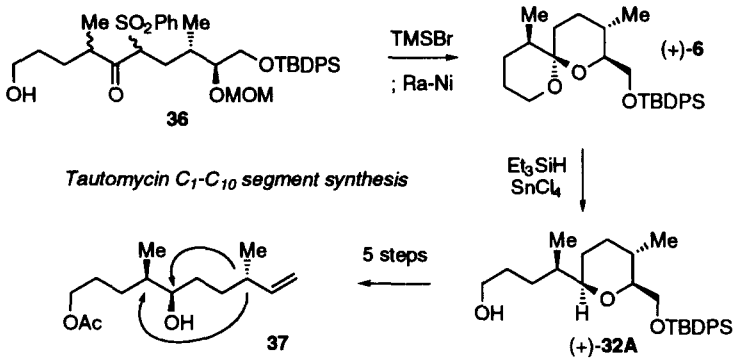
(5)

CONCLUSION

As a result of the present study, we found three key points in the reductive opening of α-methylspiroketals: (1) The DIBAH reduction proceeds through the sterically-controlled formation of the tight oxocarbenium ion pair complex followed by the internal hydride delivery affording a configuration-retentive product, (2) The silane - Lewis acid reduction proceeds *via* the free oxocarbenium ion, whose formation is controlled by either a steric interaction between methyl group and the Lewis acid, or a chelation of the Lewis acid to benzyl ether oxygen in a bidentate manner, (3) However, the isomerization between spiroketal isomers or oxocarbenium ion intermediates causes unexpected selectivity in some cases.

As we have been demonstrated, the regio- and stereoselective ring opening reaction induced by various reducing agents now offers a new stage for a stereochemical control on a spiroketal template. In combination with a thermodynamic spiroketalization, stereocontrolled syntheses of not only the substituted pyranyl alcohol but also the short carbon chain will be possible. Indeed, the effectiveness of the process **6** → **32A** has been shown in our total synthesis of tautomycin (Scheme 6).[1] Within eight steps including a thermodynamic

spiroketalization and a selective reduction, a 1,4- and 1,5-stereochemical control from **36**, a diastereomeric mixture, was attained as indicated by two arrows in **37**.



Scheme 6.[1]

EXPERIMENTAL SECTION

General Methods

Infrared spectra were recorded on a Hitachi model 285 infrared spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Hitachi R-22HR, a JEOL EX-270 or a Bruker AM-500 spectrometers. Chemical shifts were reported in ppm down field from the peak of tetramethylsilane as an internal standard. ^{1}H-NMR splitting patterns are designated as "s, d, t, q, m, or br", which indicate "singlet, doublet, triplet, quartet, multiplet, or broad", respectively. Low and high resolution mass spectra were obtained on a JEOL JMS-DX300, a JMS-DX303, or a JMS-01SG-2 spectrometers. Analytical and preparative thin layer chromatographies were performed on Merck Kieselgel 60 F_{254} Art.5574 (0.25-mm) and Art.5744 (0.5-mm), respectively. Silica gel flash chromatography was performed on Merck Kieselgel 60 Art.9385 or Wako Wakogel C-200 using the indicated solvent system. Capillary gas chromatography was carried out on a Shimadzu GC-9A using GL SCIENCE OV-1 Bonded (0.53-mm I.D. × 25-m). Unless otherwise noted, nonaqueous reactions were carried out under argon atmosphere. Diethyl ether (Et_2O), tetrahydrofuran (THF), and 2-methyltetrahydrofuran were distilled from sodium metal/benzophenone-ketyl. Benzene (PhH), CH_2Cl_2, *N,N*-dimethylformamide (DMF), hexamethylphosphoramide, and triethylamine were distilled from calcium hydride and were stored under argon atmosphere. Hexane was distilled from *n*-butyllithium, and methanol was from magnesium methoxide. All other commercially obtained solvents and reagents were used as received.

2-Methyl-δ-valerolactone (9). To a solution of 0.295 mL (2.11 mmol) of diisopropylamine in 1.5 mL of THF at 5 °C was added 1.32 mL (2.11 mmol) of 1.60 M *n*-butyllithium in hexane. After being stirred for 30 min, 201 mg (2.01 mmol) of δ-valerolactone in 1.5 mL of THF, and 0.367 mL (2.11 mmol) of hexamethylphosphoramide were added successively at -16 °C. This was stirred for 5 min, cooled to -70 °C, and introduced 0.137 mL (2.20 mmol) of iodomethane. The temperature was allowed to warm to 0 °C over 6 h, then the reaction was quenched by the addition of 0.121 mL (2.11 mmol) of acetic acid and 20 mL of water. This was extracted with Et_2O (2 × 20 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 2:3) gave 161 mg (70%) of 2-methyl-δ-valerolactone **9** as a colorless oil which was further purified by Kugelrohr distillation (ca. 80 °C, 14 Torr). Data for **9**: IR (thin film) 2930, 1725, 1150 cm^{-1}; ^{1}H-NMR (270MHz, $CDCl_3$) δ 4.32 (m, 2H), 2.58 (m, 1H), 2.10 (m, 1H), 1.91 (m, 2H), 1.55 (m, 1H), 1.27 (d, J = 6.6 Hz, 3H); EI-MS *m/z* 114 (M^+), 42 ($C_3H_6^+$); EI-HR-MS calcd for $C_6H_{10}O_2$ (M^+) *m/z* 114.0681, found 114.0667.

2-[4-(Tetrahydropyran-2-yl)oxybutyl]-2-hydroxy-3-methyltetrahydropyran (10). To a well-stirred suspension of 475 mg (19.5 mg-atom) of magnesium turnings in 5 mL of THF at ambient temperature was added 4.64 g (19.6 mmol) of 4-bromo-1-(tetrahydropyran-2-yl)oxybutane in 17 mL of THF. This was stirred for 30 min, cooled to -15 °C, and then introduced 1.49 g (13.0 mmol) of **9** in 10 mL of THF. After being stirred at 0 °C for 5 h, 50 mL of water was added and extracted with 30 mL of Et_2O. Insoluble material in aqueous layer was dissolved by the addition of minimum amount of 1 N hydrochloric acid, and aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 1:4 → 3:2) gave 2.86 g (81%) of labile hemiacetal **10** as a colorless oil: IR (thin film) 3400 (br), 2940, 1740 cm^{-1}; ^{1}H-NMR (90MHz, $CDCl_3$) δ 4.49 (m, 1H), 4.10-3.13 (m, 6H), 2.60-2.20 (m, 2H), 1.90-1.20 (m, 15H), 1.18-0.80 (m, 3H); EI-MS *m/z* 254 (M^+-H_2O), 187 (M^+-THP), 85 (THP^+), 41 ($C_3H_5^+$); EI-HR-MS calcd for $C_{15}H_{26}O_3$ (M^+-H_2O) *m/z* 254.1882, found 254.1895.

[5*R,6*S**]-5-Methyl-1,7-dioxaspiro[5.5]undecane (4) and [5*S**,6*S**]-5-Methyl-1,7-dioxaspiro[5.5]undecane (11).** To a solution of 462 mg (1.70 mmol) of **10** in 10 mL of methanol at ambient temperature was added 16 mg (84 μmol) of *p*-toluenesulfonic acid monohydrate. After being stirred for 2 h, 0.03 mL of triethylamine was added and the whole was concentrated at about 20 °C *in vacuo*. Purification of the residue by silica gel flash chromatography (Et_2O/hexane, 1:19) gave 226 mg (78%) of 79 : 21 of spiroketal mixture (**4** / **11**) as a colorless oil. This was further purified by silica gel flash chromatography (Et_2O/hexane, 1:24) to give 130 mg (45%) of **4**, 7.0 mg (2.4%) of **11**, and 43 mg (15%) of **4** / **11** mixture as colorless oils. Retention time of **4** and **11** on GC is reported in *representative procedure for DIBAH reduction of spiroketals* later. Data for **4**: IR (thin film) 2940, 1090 cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ 3.67 (dt, *J* = 3.1, 11.7 Hz, 1H), 3.65-3.57 (m, 3H), 1.85 (dt, *J* = 13.1, 4.2 Hz, 1H), 1.75 (dt, *J* = 4.2, 13.2 Hz, 1H, C_{11}-*Hax*), 1.64 (dt, *J* = 5.2, 12.3 Hz, 1H), 1.59-1.42 (m, 7H), 1.38 (dt, *J* = 13.0, 1.8 Hz, 1H), 0.91 (d, *J* = 6.3 Hz, 3H, C_5-CH_3); ^{13}C-NMR (125.8MHz, $CDCl_3$) δ 97.5 (C_6), 60.3 (C_8), 59.9 (C_2), 38.8 (C_5), 31.8 (C_{11}), 27.3 (C_4), 26.2 (C_3), 25.3 (C_9), 18.5 (C_{10}), 16.8 (C_5-Me); EI-MS *m/z* 170 (M^+), 101 ($C_5H_9O_2^+$); EI-HR-MS calcd for $C_{10}H_{18}O_2$ (M^+) *m/z* 170.1307, found 170.1293.

Data for **11**: IR (thin film) 2940, 1090 cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ 3.73-3.57 (m, 4H), 2.12 (tt, *J* = 12.9, 4.7 Hz, 1H, C_4-*Hax*; the *J* value between C_4-*Hax* and C_5-*Heq* is 4.7 Hz), 1.90-1.24 (m, 10H), 0.99 (d, *J* = 6.3 Hz, 3H, C_5-CH_3); ^{13}C-NMR (125.8MHz, CDCl3) δ 97.4 (C_6), 60.6 (C_2 or C_8), 60.5 (C_8 or C_2), 35.9 (C_5), 32.3 (C_{11}), 25.7 (C_4), 25.2 (C_9), 20.0 (C_3), 18.6 (C_{10}), 14.4 (C_5-Me); EI-MS *m/z* 170 (M^+), 101 ($C_5H_9O_2^+$).

Methyl 4-Formylpentanoate (13). A flask containing 79.1 mL (0.800 mol) of piperidine and 20.0 g (0.145 mol) of potassium carbonate was immersed in water bath, and added 28.9 mL (0.400 mol) of propionaldehyde over 20 min with vigorous stirring. After being stirred for 18 h, insoluble material was removed by filtering through a pad of Celite (Et_2O washing). The filtrate was dried over anhydrous Na_2SO_4 and filtered.

The crude enamine thus obtained was dissolved in 200 mL of acetonitrile, and to this was added 68.9 g (0.800 mol) of methyl acrylate in dropwise. The reaction mixture was stirred at reflux for 24 h, followed by the addition of 45.8 mL (0.800 mol) of acetic acid and 200 mL of water. After being stirred at reflux for 2 days, it was saturated with sodium chloride and extracted with Et_2O (3 × 200 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 1:4 → 3:7) gave 37.3 g (65%) of adduct **13** as a colorless oil: IR (thin film) 2940, 1735, 1720 cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ 9.63 (d, *J* = 1.7 Hz, 1H), 3.68 (s, 3H), 2.44-2.37 (m, 3H), 2.07 (m, 1H), 1.71 (m, 1H), 1.14 (d, *J* = 7.1 Hz, 3H); FI-MS *m/z* 145 (M^++H), 116 (M^++H-CHO).

Methyl 5-Hydroxy-4-methylpentanoate (14) and 4-Methyl-δ-valerolactone (15). To a solution of 14.9 g (0.103 mol) of **13** in 149 mL of ethanol at ambient temperature was added 372 mg of platinum(IV) oxide and 4.14 g (14.9 mmol) of iron(II) sulfate heptahydrate. The mixture was stirred vigorously under hydrogen atmosphere for 2 days. Then the insoluble material was removed by filtering

through a pad of Celite and the filtrate was concentrated *in vacuo* to give crude alcohol **14** which was used without further purification. Data for **14**: IR (thin film) 3450 (br), 2940, 1730 cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ 3.68 (s, 3H), 3.47 (d, J = 5.9 Hz, 2H), 2.38 (m, 2H), 1.79 (m, 1H), 1.66 (m, 1H), 1.50 (m, 1H), 0.93 (d, J = 6.8 Hz, 3H); EI-MS *m/z* 146 (M^+), 128 (M^+-H_2O).

To the above crude alcohol in 515 mL of CH_2Cl_2 was added 0.79 mL (10 mmol) of trifluoroacetic acid at ambient temperature. After being stirred for 15 h, 200 mL of saturated aqueous $NaHCO_3$ was added and aqueous layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was treated with trifluoroacetic acid again, quenched by aqueous $NaHCO_3$, and extracted. Purification by distillation *in vacuo* gave 9.49 g (81%) of lactone **15**[29] as a colorless oil: bp 59°C (5 Torr); IR (thin film) 2940, 1730 cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ 4.31 (m, 1H), 3.91 (t, J = 10.5 Hz, 1H), 2.64 (m, 1H), 2.51 (m, 1H), 2.07 (m, 1H), 1.98 (m, 1H), 1.55 (m, 1H), 1.01 (d, J = 6.8 Hz, 3H); EI-MS *m/z* 114 (M^+), 56 ($C_4H_8^+$); EI-HR-MS calcd for $C_6H_{10}O_2$ (M^+) *m/z* 114.0681, found 114.0694.

[3*S,6*R**,11*R**]-3,11-Dimethyl-1,7-dioxaspiro[5.5]undecane (5) and [3*S**,6*R**,11*S**]-3,11-Dimethyl-1,7-dioxaspiro[5.5]undecane (16).** To a solution of 9.87 g (37.0 mmol) of 4,4'-di-*tert*-butylbiphenyl in 93 mL of 2-methyltetrahydrofuran at 3 °C was added 282 mg (41 mg-atom) of lithium wire. It was stirred vigorously for 4 h, and the resultant dark blue solution was cooled to -94 °C. To the reaction mixture was added successively 1.82 mL (14.8 mmol) of boron trifluoride etherate, and 1.13 g (9.90 mmol) of **15** in 13 mL of 2-methyltetrahydrofuran. This was allowed to warm to ambient temperature over 10 h, then quenched by the addition of 100 mL of water. Resultant mixture was adjusted to pH 1 with concentrated hydrochloric acid and was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. This material contained four spiroketals in a ratio of 33(**5**, retention time = 24.8 min) : 14(**16**, 27.4 min) : 43(25.4 min) : 9(27.8 min) from GC analysis (column temperature was initiated at 60 °C and raised at a rate of 2 °C / min).

To the above crude spiroketal in 30 mL of 1,2-dimethoxyethane was added 15 mL of concentrated hydrochloric acid and 30 mL of water at ambient temperature. After being stirred for 5 days, the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with 50 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The product distribution was found to be 71(**5**) : 17(**16**) : 10 : 2 from GC analysis. 10% ratio of minor spiroketal was [3*R**,6*R**,11*R**]-3,11-dimethyl-1,7-dioxaspiro[5.5]undecane (500 MHz ^{1}H-NMR δ 1.09, d; 0.95, d), and 2% of minor spiroketal was [3*R**,6*R**,11*S**]-3,11-dimethyl-1,7-dioxaspiro[5.5]undecane (500 MHz ^{1}H-NMR δ 1.09, d; 1.01, d) on the basis of ^{1}H-NMR spectra. Purification by silica gel flash chromatography (Et_2O/hexane, 1:19) gave 80 mg (4.4%) of spiroketal **5** and 268 mg (15%) of four components mixture as colorless oils. Data for **5**: IR (thin film) 2930, 1440, 1075 cm^{-1}; ^{1}H-NMR (270MHz, $CDCl_3$) δ 3.66-3.46 (m, 3H), 3.24 (t, J = 11.2 Hz, 1H), 1.85-1.36 (m, 10H), 0.90 (d, J = 5.9 Hz, 3H, C_{11}-C*H*$_3$), 0.80 (d, J = 6.6 Hz, 3H, C_3-C*H*$_3$); ^{13}C-NMR (67.8MHz, $CDCl_3$) δ 97.0, 66.4, 59.9, 38.5, 32.0, 30.3, 27.5, 27.2, 26.2, 17.2, 16.8; EI-MS *m/z* 184 (M^+), 115 ($C_6H_{11}O_2^+$); EI-HR-MS calcd for $C_{11}H_{20}O_2$ (M^+) *m/z* 184.1463, found 184.1468.

Data for **16**: ^{1}H-NMR (500MHz, $CDCl_3$, selected) δ 1.01 (d, J = 6.8 Hz, C_{11}-C*H*$_3$), 0.80 (d, J = 6.6 Hz, C_3-C*H*$_3$); ^{13}C-NMR (67.8MHz, $CDCl_3$) δ 96.9, 66.7, 60.4, 35.8, 32.4, 30.2, 27.4, 25.8, 20.0, 16.1, 14.6; EI-MS *m/z* 184 (M^+), 115 ($C_6H_{11}O_2^+$).

Benzyl [3*S,4*R**]-4,5-Epoxy-3-methylpentanoate (18).** To a solution of 6.42 mL (0.0620 mol) of benzyl alcohol in 285 mL of THF at 0 °C was added 6.52 g (0.0569 mol) of 35% potassium hydride in mineral oil. After being stirred at ambient temperature for 10 h, it was cooled to -20 °C followed by the addition of 10.2 g (0.0424 mol) of ca. 3 : 1 of **17** / *anti*-isomer in 52 mL of THF. This was stirred for 1 h, then quenched by 100 mL of saturated aqueous NH_4Cl. Aqueous layer was separated and extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed successively with 100 mL of 10% aqueous $Na_2S_2O_3$ and 100 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel

flash chromatography (EtOAc/hexane, 3:47 → 3:22) gave 7.34 g (79%) of ca. 3 : 1 of **18** / isomer as a colorless oil: IR (thin film) 2940, 1730, 1085 cm^{-1}; ^1H-NMR (270MHz, $CDCl_3$, for **18**) δ 7.42-7.29 (m, 5H), 5.12 (s, 2H), 2.80 (m, 1H), 2.66 (t, *J* = 4.6 Hz, 1H), 2.50 (dd, *J* = 4.6, 2.6 Hz, 1H), 2.44 (dd, *J* = 15.2, 7.3 Hz, 1H), 2.30 (dd, *J* = 15.2, 7.3 Hz, 1H), 1.96 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 3H); FI-MS *m/z* 220 (M^+).

[3*S,4*S**]-4-Hydroxymethyl-3-methyl-γ-butyrolactone (19).** A suspension of 9.79 g (0.0333 mol) of ca. 3 : 1 of **18** / isomer and 0.98 g of 10% palladium on carbon in 148 mL of Et_2O was stirred vigorously under hydrogen atmosphere for 2 days. The catalyst was removed by filtering through a pad of Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (Et_2O/hexane, 1:4 → 3:2) to give 4.08 g (94%) of ca. 3 : 1 of **19** / isomer as a colorless oil: IR (thin film) 3400 (br), 2945, 1760 cm^{-1}; ^1H-NMR (270MHz, $CDCl_3$, for **19**) δ 4.15 (m, 1H), 3.93 (dd, *J* = 13, 3 Hz, 1H), 3.68 (dd, *J* = 13, 4 Hz, 1H), 2.76 (dd, *J* = 17, 8 Hz, 1H), 2.53 (m, 1H), 2.23 (dd, *J* = 17, 9 Hz, 1H), 1.18 (d, *J* = 7 Hz, 3H); EI-MS *m/z* 130 (M^+), 112 (M^+-H_2O).

[3*S,4*S**]-4-Benzyloxymethyl-3-methyl-γ-butyrolactone (20).** To a solution of 1.15 g (6.64 mmol) of ca. 3 : 1 of **19** / isomer in 11 mL of DMF at ambient temperature was added 2.11 mL (17.7 mmol) of benzyl bromide and 3.08 g (13.3 mmol) of silver(I) oxide. The mixture was stirred for 18 h, then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and purified by silica gel flash chromatography (EtOAc/hexane, 2:23 → 3:17) to give 0.951 g (65%) of ca. 3 : 1 of **20** / isomer as a colorless oil: IR (thin film) 2940, 1760, 1095 cm^{-1}; ^1H-NMR (270MHz, $CDCl_3$, for **20**) δ 7.38-7.26 (m, 5H), 4.59 (d, *J* = 5 Hz, 1H), 4.57 (d, *J* = 5 Hz, 1H), 4.19 (m, 1H), 3.71 (dd, *J* = 10, 4 Hz, 1H), 3.61 (dd, *J* = 10, 4 Hz, 1H), 2.78 (dd, *J* = 16, 8 Hz, 1H), 2.16 (dd, *J* = 16, 8 Hz, 1H), 1.16 (d, *J* = 7 Hz, 3H); EI-MS *m/z* 220 (M^+), 129 (M^+-Bn), 91 (Bn^+).

[3*S,4*S**]-5-Benzyloxy-3-methyl-1,4-pentanediol (21).** To a suspension of 819 mg (21.6 mmol) of lithium aluminum hydride in 38 mL of Et_2O at 3 °C was added 4.75 g (16.2 mmol) of ca. 3 : 1 of **20** / isomer in 19 mL of Et_2O. After being stirred at ambient temperature for 4 h, 1.01 mL of water, 1.27 mL of 3 N aqueous NaOH, and 0.3 mL of water were added successively with stirring. The mixture was stirred for 10 h, and then filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and purified by silica gel flash chromatography (EtOAc/PhH, 3:2) to give 3.45 g (95%) of ca. 3 : 1 of **21** / isomer as a colorless oil: IR (thin film) 3350 (br), 2940, 1095 cm^{-1}; ^1H-NMR (270MHz, $CDCl_3$, for **21**) δ 7.40-7.28 (m, 5H), 4.58 (s, 2H), 3.87-3.41 (m, 5H), 2.77 (br s, 2H), 1.90-1.49 (m, 3H), 0.92 (d, *J* = 7 Hz, 3H); EI-MS *m/z* 224 (M^+), 206 (M^+-H_2O).

[2*S,3*S**]-1-Benzyloxy-3-methyl-5-phenylthio-2-pentanol (22).** A mixture of diol **21** / isomer (ca. 3 : 1, 3.35 g, 11.2 mmol), 4.89 g (22.4 mmol) of diphenyl disulfide, 6.04 mL (74.7 mmol) of pyridine, and 5.58 mL (22.4 mmol) of tri-*n*-butylphosphine at 3 °C were blended and stirred at ambient temperature for 2 days. The mixture was added 200 mL of 10% aqueous copper(II) sulfate and extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed successively with 200 mL of water and 100 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 1:19) gave 3.03 g (86%) of ca. 3 : 1 of **22** / isomer as a colorless oil: IR (thin film) 3350 (br), 2940, 1100 cm^{-1}; ^1H-NMR (270MHz, $CDCl_3$, for **22**) δ 7.40-7.13 (m, 10H), 4.55 (s, 2H), 3.69-3.36 (m, 3H), 2.01-1.72 (m, 2H), 1.58 (m, 1H), 0.93 (d, *J* = 7 Hz, 3H); EI-MS *m/z* 316 (M^+), 298 (M^+-H_2O).

[2*S,3*S**]-[1-Benzyloxy-2-(1-ethoxyethoxy)-3-methyl-5-phenylthio]pentane (23).** To a solution of 507 mg (1.20 mmol) of ca. 3 : 1 of **22** / isomer in 8 mL of CH_2Cl_2 at ambient temperature was added 0.500 mL (5.23 mmol) of ethyl vinyl ether and 20 mg (0.080 mmol) of pyridinium *p*-toluenesulfonate. After being stirred for 18 h, 10 mL of saturated aqueous $NaHCO_3$ was introduced and aqueous layer was separated. Aqueous layer was extracted with $CHCl_3$ (2 × 20 mL) and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 1:9) gave 411 mg (88%) of ca. 3 : 1 of **23** / isomer as a colorless oil: IR (thin film) 2950, 1435, 1360, 1080 cm^{-1}; ^1H-NMR (270MHz, $CDCl_3$) δ 7.40-7.13 (m, 10H), 4.88-4.69 (m, 1H), 4.49 (s, 2H), 3.74-

3.40 (m, 5H), 3.02 (m, 1H), 2.90 (m, 1H), 1.97 (m, 1H), 1.83 (m, 1H), 1.52 (m, 1H), 1.30-0.93 (m, 9H); EI-MS *m/z* 388 (M^+), 342 (M^+-EtOH), 91 (Bn^+); EI-HR-MS calcd for $C_{23}H_{32}O_3S$ (M^+) *m/z* 388.2028, found 388.2072.

[2*S,3*S**]-[1-Benzyloxy-2-(1-ethoxyethoxy)-3-methyl-5-phenylsulfonyl]pentane (24).** To a solution of 547 mg (1.06 mmol) of ca. 3 : 1 of **23** / isomer in 10 mL of CH_2Cl_2 at 3 °C was added 520 mg (6.19 mmol) of $NaHCO_3$ and 668 mg (3.10 mmol) of 80% *m*-chloroperoxybenzoic acid. After the mixture was stirred at ambient temperature for 12 h, 30 mL of 10% aqueous $Na_2S_2O_3$ was added. Aqueous layer was separated and extracted with $CHCl_3$ (2 × 50 mL). The combined organic extracts were washed with 80 mL of saturated aqueous $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 1:9) gave 278 mg (62%) of ca. 3 : 1 of **24** / isomer as a colorless oil: IR (thin film) 2950, 1300, 1140, 1080 cm^{-1}; ^1H-NMR (270MHz, $CDCl_3$, for **24**) δ 7.92-7.88 (m, 2H), 7.68-7.51 (m, 3H), 7.38-7.26 (m, 5H), 4.80-4.62 (m, 1H), 4.47 (s, 2H), 3.65-3.38 (m, 5H), 3.31-3.12 (m, 2H), 1.98-1.78 (m, 2H), 1.63 (m, 1H), 1.25-1.08 (m, 6H), 0.91, 0.88 (doublets, ca. 1:1 ratio, *J* = 7 Hz, 3H); EI-MS *m/z* 347 (M^+-EE), 91 (Bn^+); EI-HR-MS calcd for $C_{19}H_{23}O_4S$ (M^+-EE) *m/z* 347.1318, found 347.1374.

[8*S,9*S**]-10-Benzyloxy-9-(1-ethoxyethoxy)-1-hydroxy-4,8-dimethyl-6-phenylsulfonyl-5-decanone (25).** To a solution of 3.04 g (5.42 mmol) of ca. 3 : 1 of **24** / isomer in 18 mL of Et_2O and 9 mL of hexane at -30 °C was added 5.42 mL (8.67 mmol) of 1.6 M *n*-butyllithium in hexane. After being stirred at 5 °C for 5 min, it was cooled to -80 °C and 1.07 g (9.37 mmol) of **9** in 12 mL of 1:1 Et_2O/hexane was added. The mixture was further stirred at that temperature for 2 h, then at ambient temperature for 10 h before the addition of 0.496 mL (8.66 mmol) of acetic acid and 70 mL of brine. Aqueous layer was separated and extracted with EtOAc (2 × 80 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (EtOAc/PhH, 1:4 → 2:3) gave 2.36 g (81%) of adduct **25** and 8,9-*syn* isomer as a colorless oil: IR (thin film) 3440 (br), 2930, 1710, 1300, 1140, 1100 cm^{-1}; ^1H-NMR (270MHz, $CDCl_3$) δ 7.81-7.61 (m, 3H), 7.55-7.50 (m, 2H), 7.35-7.23 (m, 5H), 4.87-4.57 (m, 1H), 7.49-7.40 (m, 2H), 4.12-4.01 (m, 1H), 4.70-4.33 (m, 7H), 3.12-2.97 (m, 1H), 2.52-2.40 (m, 1H), 2.13-1.35 (m, 7H), 1.27-1.08 (m, 9H), 0.93-0.81 (m, 3H); FI-MS *m/z* 534 (M^+).

[2*S,3*S**,5*R**,6*S**,11*R**]-2-Benzyloxymethyl-3,11-dimethyl-5-phenylsulfonyl-1,7-dioxaspiro[5.5]undecane (26).** To a solution of 262 mg (0.367 mmol) of **25** and 8,9-*syn* isomer in 2.5 mL of CH_2Cl_2 at 3 °C was added 0.120 mL (0.980 mmol) of boron trifluoride etherate. After being stirred at ambient temperature for 2 days, it was poured into 20 mL of saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$ (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 1:3) gave 122 mg (75%) of ca. 3 : 1 of **26** / 2,3-*syn* isomer as a colorless oil: IR (thin film) 2940, 1300, 1140, 1095 cm^{-1}; ^1H-NMR (270MHz, $CDCl_3$, for **26**) δ 7.92-7.87 (m, 2H), 7.65-7.50 (m, 3H), 7.39-7.24 (m, 5H), 4.62 (d, *J* = 13 Hz, 1H), 4.54 (d, *J* = 13 Hz, 1H), 3.61-3.28 (m, 5H), 2.97 (m, 1H), 1.96 (m, 1H), 1.81-1.48 (m, 7H), 1.07 (d, *J* = 7 Hz, 3H), 0.85 (d, *J* = 7 Hz, 3H); EI-MS *m/z* 444 (M^+), 91 (Bn^+); EI-HR-MS calcd for $C_{25}H_{32}O_5S$ (M^+) *m/z* 444.1970, found 444.1945.

[2*S,3*S**,5*R**,6*S**,11*R**]-2-Hydroxymethyl-3,11-dimethyl-5-phenylsulfonyl-1,7-dioxaspiro[5.5]undecane (27).** A suspension of 972 mg (1.64 mmol) of ca. 3 : 1 of **26** / isomer and 200 mg of 20% palladium hydroxide on carbon in 11 mL of ethanol was stirred vigorously under hydrogen atmosphere for 54 h. The catalyst was removed by filtering through a pad of Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel flash chromatography (EtOAc/PhH, 1:19) to give 520 mg (89%) of ca. 3 : 1 of **27** / isomer as a colorless oil: IR (thin film) 3400 (br), 2940, 1300, 1140, 1080 cm^{-1}; ^1H-NMR (270MHz, $CDCl_3$, for **27**) δ 7.89-7.86 (m, 2H), 7.63-7.50 (m, 3H), 3.72 (m, 1H), 3.58-3.42 (m, 3H), 3.26 (m, 1H), 2.91 (m, 1H), 1.98 (m, 1H), 1.88-1.47 (m, 7H), 1.03 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* = 5.9 Hz, 3H); EI-MS *m/z* 354 (M^+), 336 (M^+-H_2O).

[2*S,3*S**,5*R**,6*S**,11*R**]-2-(*tert*-Butyldiphenylsiloxy)methyl-3,11-dimethyl-5-phenylsulfonyl-1,7-dioxaspiro[5.5]undecane (28).** To a solution of 693 mg (1.46 mmol) of ca. 3 : 1

of **27** / isomer in 5.2 mL of DMF at ambient temperature was added 0.540 mL (2.08 mmol) of *tert*-butylchlorodiphenylsilane and 294 mg (4.32 mmol) of imidazole. After the mixture was stirred for 5 h, it was poured into 50 mL of water and extracted with Et_2O (3 × 40 mL). The combined organic extracts were washed with 10 mL of brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/PhH, 1:19 → 1:9) gave 862 mg (99%) of ca. 3 : 1 of **28** / isomer which was recrystallized from hexane to afford pure **28** as colorless crystals. Data for **28** has been shown in reference 1c.

[2*S,3*S**,6*R**,11*R**]-2-(*tert*-Butyldiphenylsiloxy)methyl-3,11-dimethyl-1,7-dioxaspiro[5.5]undecane (6).** Experimental procedure for **28** → **6** has been reported in reference 1c.

[2*S,3*S**,6*R**,11*R**]-2-Hydroxymethyl-3,11-dimethyl-1,7-dioxaspiro[5.5]undecane (29).** To a solution of 75 mg (0.170 mmol) of **6** in 1.2 mL of THF at ambient temperature was added 0.50 mL (0.50 mmol) of 1.0 M tetra-*n*-butylammonium fluoride in THF. After the mixture was stirred for 20 h, it was concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/PhH, 1:9) gave 32 mg (90%) of alcohol **29** as a colorless oil: IR (thin film) 3350 (br), 2940, 1095 cm^{-1}; ^{1}H-NMR (270MHz, $CDCl_3$) δ 3.76 (dd, *J* = 11.2, 2.6 Hz, 1H), 3.60-3.53 (m, 3H), 3.37 (ddd, *J* = 9.9, 7.3, 3.3 Hz, 1H), 2.01 (br s, 1H), 1.85-1.38 (m, 10H), 0.91 (d, *J* = 5.3 Hz, 3H), 0.85 (d, *J* = 6.6 Hz, 3H); EI-MS *m/z* 214 (M^+), 196 (M^+-H_2O).

[2*S,3*S**,6*R**,11*R**]-2-Benzyloxymethyl-3,11-dimethyl-1,7-dioxaspiro[5.5]undecane (7).** To a solution of 32 mg (0.15 mmol) of **29** in 0.7 mL of THF and 0.3 mL of DMF at 3 °C was added 7.0 mg (0.18 mmol) of 60% sodium hydride in mineral oil. After it was stirred at ambient temperature for 30 min, 21 μL (0.18 mmol) of benzyl bromide was added and the mixture was stirred for 4 days. Then it was added 3 mL of water and 3 mL of brine, and extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by silica gel flash chromatography (Et_2O/hexane, 1:19) gave 29 mg (64%) of benzyloxyspiroketal **7** as a colorless oil: IR (thin film) 2930, 1100 cm^{-1}; ^{1}H-NMR (270MHz, $CDCl_3$) δ 7.40-7.23 (m, 5H), 4.69 (d, *J* = 12.5 Hz, 1H), 4.61 (d, *J* = 12.5 Hz, 1H), 3.69-3.52 (m, 4H), 3.43 (m, 1H), 1.87-1.38 (m, 10H), 0.94 (d, *J* = 5.9 Hz, 3H), 0.87 (d, *J* = 5.9 Hz, 3H); ^{13}C-NMR (67.8MHz, $CDCl_3$) δ 128.4, 128.3, 127.8, 127.6, 127.4, 127.3, 97.8, 75.2, 73.3, 71.5, 60.0, 38.6, 31.8, 31.1, 27.7, 27.6, 26.3, 17.7, 16.9; EI-MS *m/z* 304 (M^+), 213 (M^+-Bn), 91 (Bn^+); EI-HR-MS calcd for $C_{19}H_{28}O_3$ (M^+) *m/z* 304.2039, found 304.2064.

Representative procedure for DIBAH reduction of spiroketals. To a solution of 0.10 mmol of spiroketal in 0.67 mL of toluene was added 0.33 mL (0.50 mmol) of 1.5 M diisobutylaluminum hydride in toluene. The reaction was quenched by the successive addition of 20 μL of methanol and 5 mL of 1 N hydrochloric acid, and extracted with Et_2O (3 × 5 mL). In the case of monomethylspiroketal **4** or **11**, ca. 10 mg of 1-octanol was added to the combined extracts as an internal standard and products distribution was analyzed by GC (column temperature was initiated at 60 °C and raised at a rate of 2 °C / min). The retention time of each substances were; 7.0 min (1-octanol), 11.6 min (**4**), 13.4 min (**11**), 22.2 min (**30C**), 22.7 min (**30B**), 22.8 min (**30A**), and 24.0 min (**30D**). In the cases of spiroketals **5**, **6**, and **7**, the combined extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude material was filtered through a plug of silica gel (5 g) and concentrated to give products mixture which was analyzed by ^{1}H-NMR spectra. The pure reduction products were obtained by preparative thin layer chromatography using an indicated solvent system though **30B**, **30D**, and **33D** could not be obtained in pure form because the Rf values were close to the other producing isomers and the amount was too small. Data for **33D** is given as its acetyl derivative, which was prepared from the mixture of reduction products by the standard condition (Ac_2O, pyridine, DMAP, CH_2Cl_2), though it was contaminated by the inseparable acetyl derivative of **33C**.

Representative procedure for silane - Lewis acid reduction of spiroketals. To a solution of 0.10 mmol of spiroketal in 1.0 mL of CH_2Cl_2 was added 0.12 mmol of silane and 0.12 mmol of Lewis acid successively. The reaction was quenched by the addition of 5 mL of 1 N hydrochloric acid, and the resultant solution was extracted with $CHCl_3$ (3 × 5 mL). In the use of triethylsilane, the combined extracts were concentrated *in vacuo* followed by acid treatment (8.5 mL of 8:8:1 THF/acetic acid/water at ambient temperature for 1 h) which was quenched by 40 mL of 3 N aqueous NaOH and extracted with Et_2O (3 × 20 mL). Products

distributions were analyzed by the same manner as that of DIBAH reduction. Among these products pure **32B** was obtained as an acetyl ester (Ac_2O, pyridine, DMAP, CH_2Cl_2) which was purified by preparative thin layer chromatography using an indicated solvent system.

Data for **[δ*R**,2*R**]-δ-Methyltetrahydro-2-pyranylbutanol (30A)**: Rf 0.18 (EtOAc/PhH, 1:4); IR (thin film) 3350 (br), 2930, 1080 cm^{-1}; ^{1}H-NMR (270MHz, $CDCl_3$) δ 4.01-3.93 (m, 1H), 3.64 (t, *J* = 5.9 Hz, 2H), 3.40 (dt, *J* = 3.3, 11.2 Hz, 1H), 3.13 (ddd, *J* = 10.6, 4.0, 1.3 Hz, 1H), 1.87-1.14 (m, 11H), 0.91 (d, *J* = 6.6 Hz, 3H); EI-MS *m/z* 172 (M^+), 154 (M^+-H_2O), 85 ($C_5H_9O^+$ (pyran moiety)); EI-HR-MS calcd for $C_{10}H_{20}O_2$ (M^+) *m/z* 172.1463, found 172.1458.

Data for **[2*R**,3*R**]-3-Methyltetrahydro-2-pyranylbutanol (30C)**: Rf 0.19 (EtOAc/PhH, 1:4); IR (thin film) 3350 (br), 2920, 1095 cm^{-1}; ^{1}H-NMR (270MHz, $CDCl_3$) δ 3.96 (m, 1H), 3.64 (t, *J* = 6.6 Hz, 2H), 3.34 (dt, *J* = 2.6, 11.2 Hz, 1H), 2.87 (m, 1H), 1.78-1.11 (m, 11H), 0.82 (d, *J* = 6.6 Hz, 3H); EI-MS *m/z* 172 (M^+), 154 (M^+-H_2O), 99 ($C_6H_{11}O^+$ (pyran moiety)); EI-HR-MS calcd for $C_{10}H_{20}O_2$ (M^+) *m/z* 172.1463, found 172.1447.

Data for **[δ*R**,2*R**,5*S**]-δ,5-Dimethyltetrahydro-2-pyranylbutanol (31A)**: Rf 0.15 (EtOAc/hexane, 1:4); IR (thin film) 3370 (br), 2900, 1085 cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ 3.87 (ddd, *J* = 11.1, 4.3, 2.2 Hz, 1H), 3.64 (dt, *J* = 2.1, 6.4 Hz, 2H), 3.06 (ddd, *J* = 11.2, 4.4, 1.9 Hz, 1H), 2.96 (t, *J* = 11.1 Hz, 1H), 1.84 (m, 1H), 1.70-1.51 (m, 6H), 1.37 (m, 1H), 1.18 (m, 1H), 1.09 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.77 (d, *J* = 6.6 Hz, 3H); FI-MS *m/z* 186 (M^+), 99 ($C_6H_{11}O^+$ (pyran moiety)); FI-HR-MS calcd for $C_{11}H_{22}O_2$ (M^+) *m/z* 186.1620, found 186.1627.

Data for **[δ*R**,2*R**,5*S**,6*S**]-6-(*tert*-Butyldiphenylsiloxy)methyl-δ,5-dimethyltetrahydro-2-pyranylbutanol (32A)** has been reported in reference 1c.

Data for **[δ*R**,2*S**,5*S**,6*S**]-6-(*tert*-Butyldiphenylsiloxy)methyl-δ,5-dimethyltetrahydro-2-pyranylbutyl Acetate (acetyl ester of 32B)**: Rf 0.36 (EtOAc/hexane, 1:4); IR (thin film) 2950, 1740, 1110 cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.40-7.35 (m, 6H), 4.04 (t, *J* = 6.6 Hz, 2H), 4.02 (dd, *J* = 12.5, 2.0 Hz, 1H), 3.72 (dd, *J* = 12.5, 6.6 Hz, 1H), 3.23 (ddd, *J* = 11.2, 2.0, 1.3 Hz, 1H), 3.14 (ddd, *J* = 9.9, 6.6, 2.0 Hz, 1H), 2.17 (s, 3H), 1.78-1.10 (m, 10H), 0.95 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H); FI-MS *m/z* 497 (M^++H), 439 (M^+-^{t}Bu); FI-HR-MS calcd for $C_{30}H_{45}O_4Si$ (M^++H) *m/z* 497.3087, found 497.3101.

Data for **[δ*R**,2*R**,5*S**,6*S**]-6-Benzyloxymethyl-δ,5-dimethyltetrahydro-2-pyranylbutanol (33A)**: Rf 0.28 (EtOAc/PhH, 1:4); IR (thin film) 3450 (br), 2930, 1100 cm^{-1}; ^{1}H-NMR (270MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 4.64 (d, *J* = 12.5 Hz, 1H), 4.56 (d, *J* = 12.5 Hz, 1H), 3.65-3.50 (m, 4H), 3.13 (m, 1H), 1.86-1.08 (m, 10H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); FI-MS *m/z* 307 (M^++H).

Data for **[α*S**,β*S**,2*S**,3*R**]-α-Benzyloxymethyl-β,3-dimethyltetrahydro-2-pyranylbutanol (33C)**: Rf 0.28 (EtOAc/PhH, 1:4); IR (thin film) 3450 (br), 2925, 1100 cm^{-1}; ^{1}H-NMR (270MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 4.56 (s, 2H), 3.96 (m, 1H), 3.69-3.55 (m, 2H), 3.42 (t, *J* = 9.2 Hz, 1H), 3.33 (dt, *J* = 2.6, 11.6 Hz, 1H), 2.85 (dt, *J* = 1.0, 8.5 Hz, 1H), 2.00 (br s, 1H), 1.80-1.07 (m, 10H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H); EI-MS *m/z* 307 (M^++H), 288 (M^+-H_2O), 99 ($C_6H_{11}O^+$ (pyran moiety)), 91 (Bn^+); EI-HR-MS calcd for $C_{19}H_{31}O_3$ (M^++H) *m/z* 307.2273, found 307.2257.

Data for **[α*S**,β*S**,2*R**,3*R**]-α-Benzyloxymethyl-β,3-dimethyltetrahydro-2-pyranylbutyl Acetate (acetyl ester of 33D)**: Rf 0.38 (EtOAc/hexane, 2:8); ^{1}H-NMR (270MHz, $CDCl_3$) δ 7.37-7.26 (m, 5H), 4.93 (m, 1H), 4.56 (d, *J* = 11.9 Hz, 1H), 4.47 (d, *J* = 11.9 Hz, 1H), 3.93 (m, 1H), 3.56 (d, *J* = 5.3 Hz, 2H), 3.40 (dt, *J* = 2.6, 11.2 Hz, 1H), 3.28 (dt, *J* = 1.3, 6.6 Hz), 2.07 (s, 3H), 1.92-1.00 (m, 10H), 0.92 (d, *J* = 7.3 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H).

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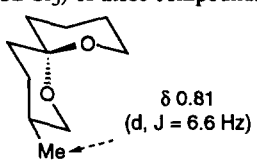
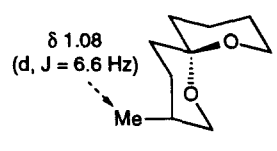
7. Several example of nucleophilic spiroketal opening have been reported. Alane reduction of sapogenin spiroketal: (a) Pettit, G. R.; Bowyer, W. J. *J. Org. Chem.* **1960**, *25*, 84-86. (b) Pettit, G. R.; Albert, A. H.; Brown, P. *J. Am. Chem. Soc.* **1972**, *94*, 8095-8099. Intramolecular oxido reduction and $NaBH_3CN$ reduction of spiroketal: (c) Deslongchamps, P.; Rowan, D. D.; Pothier, N. *Can. J. Chem.* **1981**, *59*, 2787-2791. Silane - Lewis acid opening of spiroketal: (d) Zhao, Y.-b.; Albizati, K. F. *Tetrahedron Lett.* **1993**, *34*, 575-578.
8. The spiroketal equilibration was realized from the experiments that the acid treatment (conc. HCl/water/DME 3:5:5 at ambient temperature for a few days) of pure **4** or **5** afforded spiroketal mixture in 79 : 21 and 71 : 17 : 10 : 2 ratio, respectively.
9. Partial structure assignments of **4**, **5**, **11**, and **16** are reported in EXPERIMENTAL SECTION.
10. Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207-222.
11. Mudryk, B.; Cohen, T. *J. Am. Chem. Soc.* **1991**, *113*, 1866-1867.
12. Trace amount (<10%) of two 2,9-dimethyl-1,7-dioxaspiro[5.5]undecane isomers derived from dianion isomer was obtained through Cohen's reaction.
13. Also we synthesized [3*S**,6*S**]-3-methyl-1,7-dioxaspiro[5.5]undecane and [3*R**,6*S**]-3-methyl-1,7-dioxaspiro[5.5]undecane, and used for the stereochemical assignments of **5** and **16**. Selected ^{1}H-NMR data (500 MHz in $CDCl_3$) of these compounds are:

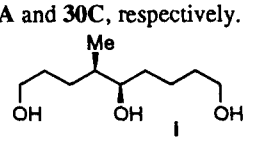


[3*S**,6*S**]-3-methyl-1,7-dioxaspiro[5.5]undecane

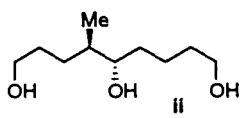


[3*R**,6*S**]-3-methyl-1,7-dioxaspiro[5.5]undecane

14. Gonzalez, F. B.; Bartlett, P. A. *Org. Synth.* **1985**, *64*, 175-181.
15. Collum, D. B.; McDonald, J. H. III; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118-2120.
16. Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, 1409-1412.
17. The X-ray crystallographic data has been deposited to the Cambridge Crystallographic Data Centre.
18. Another approach to siloxyspiroketal **6** has been reported in reference 1a.
19. (a) Ishihara, K.; Mori, A.; Yamamoto, H. *Tetrahedron* **1990**, *46*, 4595-4612. (b) Ishihara, K.; Hanaki, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10695-10704.
20. The structures of **30A**, **30B**, **30C**, and **30D** were determined as follows. Characteristic intense ion of the pyranyl moiety, *m/z* 85, of both **30A** and **30B** in GC-MS measurement revealed that the methyl group was out of the pyran ring, whereas *m/z* 99 of **30C** and **30D** revealed that it was on the pyran ring. The stereochemistry of **30C** was easily established by detailed ^{1}H-NMR analysis, and **30A** was elucidated after converting to linear triol **i** through the sequence of acetylation, RuO_4 oxidation, and $LiAlH_4$ reduction. The obtained triol was found to be not identical with triol **ii** derived from **30C** through the same operations, thus we concluded that the relative stereochemistry between oxymethine and neighboring stereogenic carbon was not identical in **30A** and **30C**. Though we could not obtain **30B** and **30D** as pure materials, the structures were established from the consideration that they were the diastereomers of **30A** and **30C**, respectively.



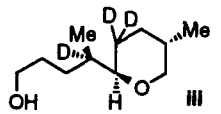
i



ii

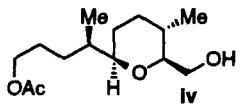
21. The structure of **31A** was at first examined on deuterated compound **iii**, which was derived from deuterated spiroketal by DIBAH reduction. Intense ion corresponding to the pyranyl moiety, *m/z* 101, of

iii revealed that there were two deuterium atoms on the pyran ring. This suggested that C - O(ε) bond was cleaved under these reaction conditions. The stereochemistry of **31A** was determined by detailed ^{1}H-NMR analysis.



iii

22. By acetylation, **32A** and **32B** were found to be occurred through C - O(ε) bond cleavage. The stereochemistry of **32A** was settled by NOE observation at two oxymethines, and **32B** was established by correlation with **32A**.
23. The structure of **33A** was found to be identical with that of **32A** by converting to **iv**, whose data has been reported in reference 1c, in two steps (acetylation followed by hydrogenolysis). The stereochemistry of **33C** and **33D** was established on the basis of the ^{1}H-NMR coupling constants after converting to the acetates.



iv

24. Dihalo alane reduction ($LiAlH_4$, $AlCl_3$ or $AlBr_3$) on 79 : 21 mixture of **4 / 11** resulted in >90% regioselection with no diastereoselectivity.
25. These enol ethers regenerated **6** selectively within one month at 3 °C.
26. (a) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107-6115. (b) Denmark, S. E.; Almstead, N. G. *J. Am. Chem. Soc.* **1991**, *113*, 8089-8110.
27. (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983. (b) reference 5a.
28. Regioselective but non-stereoselective chelation controlled acetal cleavage has been reported, see: Corcoran, R. C. *Tetrahedron Lett.* **1990**, *31*, 2101-2104.
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