An Efficient Approach toward Taxane Analogs: Atrop- and Diastereoselective Eight-Membered B Ring Cyclizations for Synthesis of Aromatic C-Ring Taxinine Derivatives

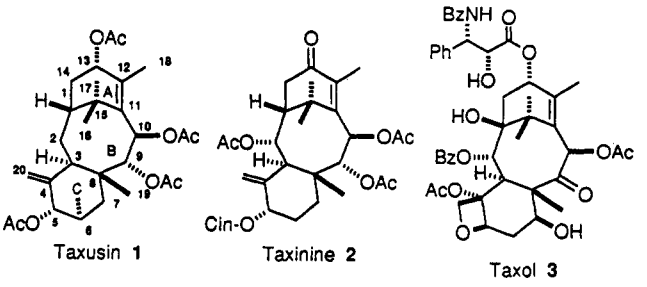
Masaki Seto, Koichiro Morihira, Yoshiaki Horiguchi, and Isao Kuwajima*

Department of Chemistry, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

Received December 13, 1993®

We have developed efficient methods for construction of the C-2 oxygenated aromatic C-ring taxane skeleton based on an eight-membered ring cyclization involving a Lewis acid-mediated intramolecular coupling reaction of the dienol silyl ether at C-10 and the acetal at C-9. The C-2 stereogenic center strongly influences the conformation of the forming eight-membered ring during the cyclization reaction. 1β,2α-Siloxy derivative **13b** gives exo isomer **15** as the major product, and 1β,2β-siloxy derivative **13a** exclusively yields endo isomer **14**. Both of these cyclization products, which had undesired stereochemistry, were converted to stereochemically refined aromatic C-ring taxinine analogs by multistep transformations. The chelation-controlled, eight-membered ring cyclization of 1β,2α-hydroxy derivative **31** was found to give exclusively the desired 1β,2α,9α,10β-endo isomer **16** in good yield. This remarkably stereoselective cyclization, when combined with stereocontrolled AC ring coupling reactions, should provide an efficient, convergent route toward various taxane derivatives. The aromatic C-ring taxinine analogs could be converted to natural taxinine by further transformation of the aromatic C-ring.

The unique tricarbocyclic skeleton of taxane diterpenes **1–3** has attracted much interest from synthetic organic chemists.[1] The remarkable potential of the congener taxol (**3**) as a promising chemotherapeutic lead[2] has further accelerated synthetic efforts as well as investigation in other scientific fields.[3] However, because of the structural complexity of taxanes except for Holton's synthesis of antipode taxusin,[4] there have been no total syntheses of taxanes until today, and the short supply of natural taxol has made the progress of the clinical tests slow. Though practical semisynthetic routes to taxol[5] and some of its analogs, e.g., Taxotere,[6] from a naturally occurring taxane derivative, 10-deacetylbaccatin III, were recently developed, a total synthesis is needed for the clarification of the still unclear structure–activity relationship, for the determination of its molecular mechanism of action, and ultimately for the development of new taxol-like drugs. Aiming at the total synthesis of taxanes, we have developed an efficient route to aromatic C-ring taxane derivatives[7] featuring an atrop- and diastereoselective eight-membered B-ring cyclization. The aromatic C-rings of these cyclized intermediates could be appropriately derivatized to the corresponding natural C-ring portion. This article describes the full details of the synthesis of aromatic C-ring taxinine derivatives.[8]



Our plan for the synthesis of the aromatic C-ring taxinine derivatives is illustrated in Scheme 1. The key reaction is the formation of the eight-membered B-ring *via* a Lewis acid-mediated intramolecular coupling of the dienol silyl ether at C-10 and the acetal at C-9 (**D** → **E**). The cyclization precursor **D** could be prepared by the addition of C-aryl metal species **B** to A-ring aldehyde **A** and subsequent transformation of the A-ring portion by the method developed in our laboratories.[7] Because structurally biased, medium-sized carbocycles may be frozen in a particular conformation, such molecules must be prepared in the desired conformation for the sake of the subsequent stereoselective transformations. The synthesis of taxane can be considered a typical example of this problem, and some previous work in this area indicates a route for the solution.[9] It is known that aromatic C-ring taxane

® Abstract published in *Advance ACS Abstracts,* May 1, 1994.

(1) Review: Swindell, C. S. *Org. Prep. Proced. Int.* **1991**, *23*, 465. For more recent references, see: Kess, M. H.; Ruel, R.; Miller, W. H.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 5999, 6003. Masters, J. J.; Jung, D. K.; Bornmann, W. G.; Danishefsky, S. J. *Tetrahedron Lett.* **1993**, *34*, 7253. Swindell, C. S.; Chander, M. C.; Heerding, J. M.; Klimko, P. G.; Rahman, L. T.; Raman, J. V.; Venkataraman, H. *Tetrahedron Lett.* **1993**, *34*, 7005 and references cited therein.

(2) McGuire, W. P.; Rowinsky, E. K.; Rosenchein, N. B.; Grumbine, F. C.; Ettinger, D. S.; Armstrong, D. K.; Donehower, R. C. *Ann. Intern. Med.* **1989**, *111*, 273. Rowinsky, E. K.; Cazenave, L. A.; Donehower, R. C. *J. Natl. Cancer Inst.* **1990**, *82*, 1247. Holms, F. A.; Walters, R. S.; Theriault, R. L.; Forman, A. D.; Newton, L. K.; Raber, M. N.; Buzdar, A. U.; Frye, D. K.; Hortobagyi, G. N. *J. Natl. Cancer Inst.* **1991**, *83*, 1797. Einzig, A. I.; Hochster, H.; Wiernik, P. H.; Trump, D. L.; Dutcher, J. P.; Garowski, E.; Sasloff, J.; Smith, T. J. *Invest. New Drugs* **1991**, *9*, 59.

(3) *Chem. Eng. News* **1991**, Sept 2, 11–18; *Chem. Eng. News* **1992**, Oct 12, 30–32. Stierle, A.; Strobel, G.; Stierle, D. *Science* **1993**, *260*, 214.

(4) Holton, R. A.; Kim, J. H.; Williams, A. D.; Harusawa, S.; Lowenthal, R. E.; Yogai, S. *J. Am. Chem. Soc.* **1988**, *110*, 6558.

(5) Denis, J.-N.; Greene, A. E.; Guénard, D.; Guéritte-Voegelein, F.; Mangatal, L.; Potier, P. *J. Am. Chem. Soc.* **1988**, *110*, 5917. Mangatal, L.; Adeline, M. T.; Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Tetrahedron* **1989**, *45*, 4177. Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985.

(6) Denis, J.-N.; Correa, A.; Greene, A. E. *J. Org. Chem.* **1990**, *55*, 1957.

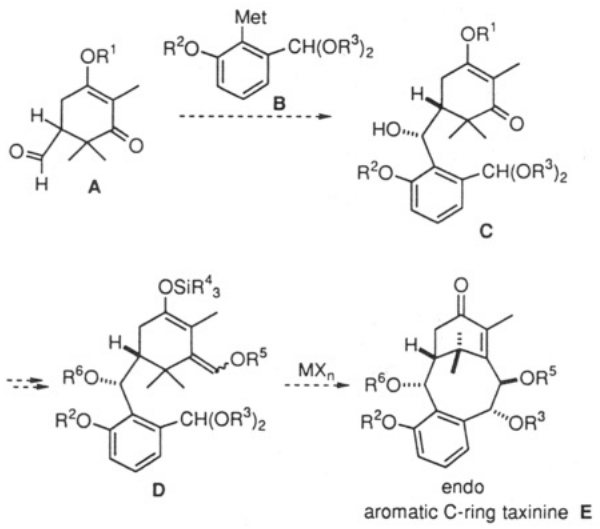
(7) Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 8277. Furukawa, T.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron* **1992**, *48*, 6975. Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Synth. Org. Chem. Jpn.* **1992**, *50*, 554.

(8) The preliminary results, see: Seto, M.; Morihira, K.; Katagiri, S.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Chem. Lett.* **1993**, 133.

(9) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1993**, *115*, 354. Jackson, R. W.; Higby, R. G.; Gilman, J. W.; Shea, K. J. *Tetrahedron* **1992**, *48*, 7013.

0022-3263/94/1959-3165$04.50/0

Scheme 1



derivatives possess two stable conformations, endo **F** and exo **G** (Figure 1), and that the increased substitution on the skeleton increases the energy barrier for the interconversion of the two conformers.[10] In fact, there are some that do not interconvert even at room temperature. Since our target molecule, **E**, is more substituted than those that are known not to interconvert, the conformation of the eight-membered ring is considered to be frozen. Of the two conformers, the endo conformer seems to offer advantages for the subsequent stereoselective manipulation of the aromatic C-ring toward taxinine, e.g., introduction of the C-19 methyl group and the C-5 oxygen functionality. Our previous synthesis of the less oxygenated aromatic C-ring taxusin derivative revealed that the cyclization of the eight-membered ring yielded the desired endo conformer.[7] However, the influence of the stereogenic oxygen functionality at C-2 was unpredictable. The C-2 oxygen functional group has been revealed to play a critical role in determining the stereochemical outcome of the cyclization reaction (*vide infra*). Notably, the previous study also revealed that, at least in the endo conformation, the stereochemistry of the newly formed stereocenters at C-9 and C-10 could be thermodynamically controlled in the desired manner; that is, the vinylogous retro-aldol-type ring opening between C-9 and C-10 gave 9α,10β stereochemistry.[7] In this study, we focused on the endo-selective construction of the eight-membered B-ring with the C-2 oxygen functionality.

Results and Discussions

Synthesis of the Cyclization Precursors. A-ring aldehyde **9** was prepared in a straightforward manner in 43% overall yield by the eight-step procedure shown in Scheme 2. Addition of the lithiated THP ether of propargyl alcohol (**4**) to propanal, followed by partial reduction of the triple bond with Lindlar catalyst,[11] Swern oxidation,[12] and Michael addition of the lithium enolate of ethyl isobutyrate to the resulting enone **6**, afforded keto ester **7**. Dieckmann cyclization of **7** with t-BuOK yielded

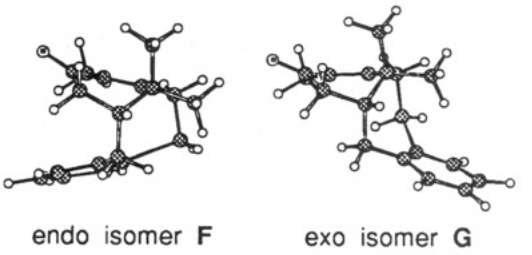


Figure 1. Atropisomers of aromatic C-ring taxanes.

Scheme 2

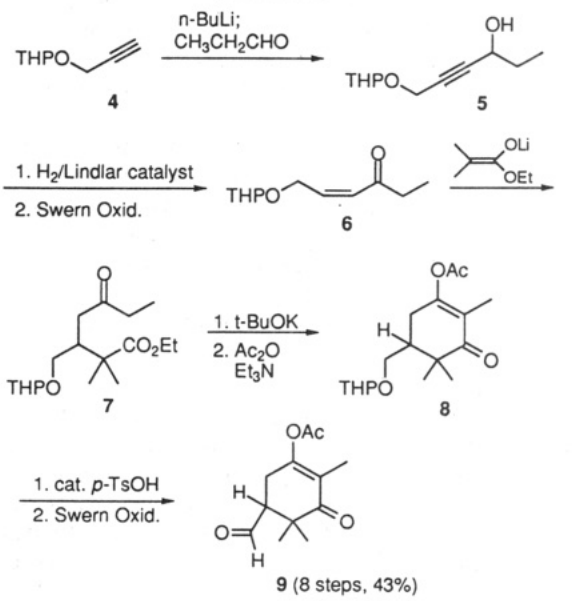


Table 1. AC Ring Coupling Reaction

9 $\xrightarrow{\text{Ar-Met}}$ **11**

Met	% yield	11a:11b
Li	28	3:1
ZnCl	NR	
$CeCl_2$	88	3:1

an unsymmetrical 1,3-diketone, which was regioselectively acetylated at the less hindered site to give **8** (52% overall yield from **4**, six steps). Then, acidic hydrolysis of the THP ether and Swern oxidation of the resulting primary alcohol afforded A-ring aldehyde **9** (83%, two steps).

Of the several reagents tested for the addition reaction of the C-aryl metal reagent to A-ring aldehyde **9**, cerium reagent **10**[13] gave the adduct in the best yield (88%, Table 1). The adduct was an approximately 3:1 mixture of diastereomers **11a** and **11b**, the stereochemistry of which could not be determined at this stage. It should be pointed out that the changes in reaction conditions did not markedly alter the diastereomeric ratio. In order to clarify the influence of the stereogenic oxygen functionality at C-2 on the cyclization reaction, both isomers were converted to the corresponding cyclization precursors (Scheme 3). The rigid structure of the taxane-like tricycles was expected to be advantageous for the identification of the relative stereochemistry at C-1 and C-2. Thus, subjecting the mixture of diastereomers to the following three-step transformation[7] led to **13a** (59%) and **13b** (37%): (1) exchange of the acetyl group with the TBS group and

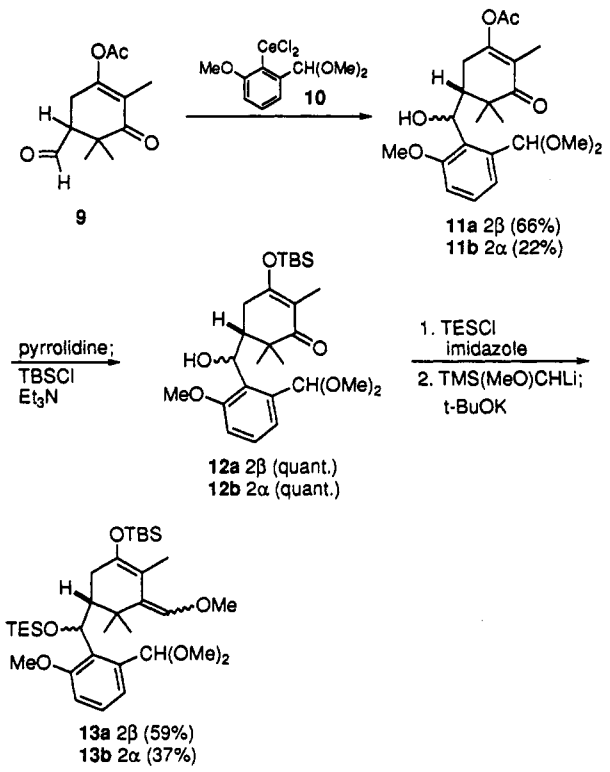
(10) Shea, K. J.; Gilman, J. W. *Tetrahedron Lett.* **1984**, *25*, 2451. Shea, K. J.; Gilman, J. W.; Haffner, C. D.; Dougherty, T. K. *J. Am. Chem. Soc.* **1986**, *108*, 4953. Shea, K. J.; Higby, R. G.; Gilman, J. W. *Tetrahedron Lett.* **1990**, *31*, 1221.

(11) Lindlar, H.; Dubuis, R. *Org. Synth.* **1966**, *46*, 89.

(12) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

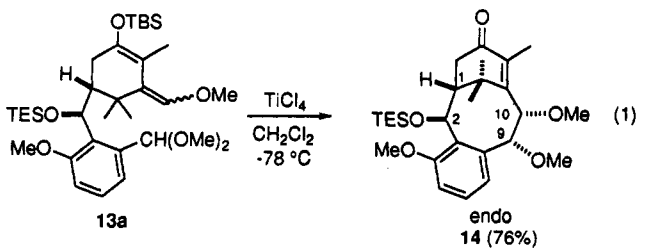
(13) Imamoto, T.; Sugiura, Y.; Takayama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.

Scheme 3



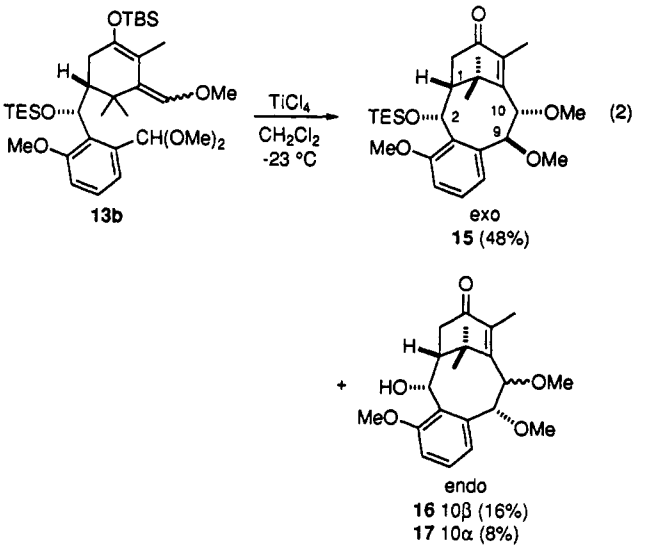
separation of the diastereomers, (2) triethylsilylation of the C-2 hydroxy group, and (3) Peterson olefination.[14] The C-2 hydroxy group was protected to prevent anticipated side reactions under the Lewis acid-mediated cyclization conditions, and the TES group was chosen as a suitable protective group. The synthesized precursors, **13a** derived from the major isomer of the AC ring addition and **13b** derived from the minor one, were subjected to the cyclization reaction.

The Cyclization Reactions. Under the influence of $TiCl_4$ in CH_2Cl_2 at low temperature, both **13a** and **13b** underwent the eight-membered ring cyclization to give the corresponding tricarbocyclic products. In contrast to the strong endo preference observed in the cyclization of the C-2 unsubstituted substrate,[7] the endo/exo atropselectivity of this cyclization depends strongly on the stereochemistry of the C-2 siloxy group. Namely, **13a** exclusively yielded a single cyclization product, endo-1β, 2β, 9α, 10α **14** (76%), in which the C-1/C-2 relative stereochemistry was proven to be unnatural. On the other



hand, **13b**, with the natural 1β,2α-relationship, afforded exo isomer **15** (1β,2α,9β,10α) as the major product (48%) with small amounts of endo isomers **16** (16%) and **17** (8%).[15] It should be noted that none of the cyclization products undergo endo/exo isomerization at room temperature or under the cyclization reaction conditions. At this point, it is clear that the AC ring addition reaction proceeded according to the Felkin–Ahn model.

The conformation of the skeleton and the relative stereochemistry at C-1, C-2, C-9, and C-10 of each product were determined by ^1H NMR (Figure 2). For their structurally related aromatic C-ring taxanes, Shea et al. reported that the C-18 methyl group of the endo isomer and the C-16 methyl group of the exo isomer appear at higher field in the ^1H NMR spectra owing to the aromatic C-ring.[10] In the present case, the methyl signals could be identified on the basis of the observed NOEs between the C-16 and C-17 methyls and between the C-16 methyl and the B-ring proton(s). The high-field shift of the C-18 allyl methyl signal of **14** (δ 1.00 ppm) revealed that it is in the endo conformation, whereas the shift of the C-16 methyl signal of **15** (δ 0.10 ppm) indicated that it is the exo isomer. Further, on the basis of NOEs shown with arrows in Figure 2, the relative stereochemistries on the B-rings of these compounds were assigned as depicted. The stereochemistries of **16** and **17** were determined similarly.[16] These structure identifications were further confirmed by X-ray crystallographic analyses of **14**,[17] **15**,[18] and **16**.[19]



MM2 calculations on the simplified C-2 methoxy derivatives were carried out to evaluate the stabilities of the cyclization products (Table 2). That the endo-1β,2β,9α,10α isomer was the sole cyclization product from 1β,2β-precursor **13a** and that the exo-1β,2α,9β,10α isomer was preferentially formed from 1β,2α-precursor **13b** suggest that the cyclization reactions were not under full thermodynamic control. The observation that the endo/exo isomerization does not take place under the cyclization conditions indicates kinetic control of the endo/exo selection of the products.

The remarkable directing effect of the C-2 siloxy group on the kinetic atropselectivity is probably due to steric and/or electrostatic repulsion between it and the C-4 methoxy group in the transition state (Figure 3). The

(14) Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1979**, 822.
(15) It is not clear whether removal of the C-2 triethylsilyl group occurs before or after the cyclization reaction.
(16) For structure determination of compounds **16**, **17**, and **21** by NOE studies, see the supplementary materials.
(17) Sakai, Y.; Kojima, Y.; Ohashi, Y.; Morihira, K.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Acta. Crystallogr.* **1991**, *C47*, 2700.
(18) Kamei, S.; Takenaka, Y.; Sakai, Y.; Ohashi, Y.; Seto, M.; Horiguchi, Y.; Kuwajima, I. *Anal. Sci.* **1993**, *9*, 741.
(19) The X-ray crystallographic analysis was performed by S. Kamei, H. Uekusa, and Y. Ohashi of this institute. The details will be reported elsewhere.

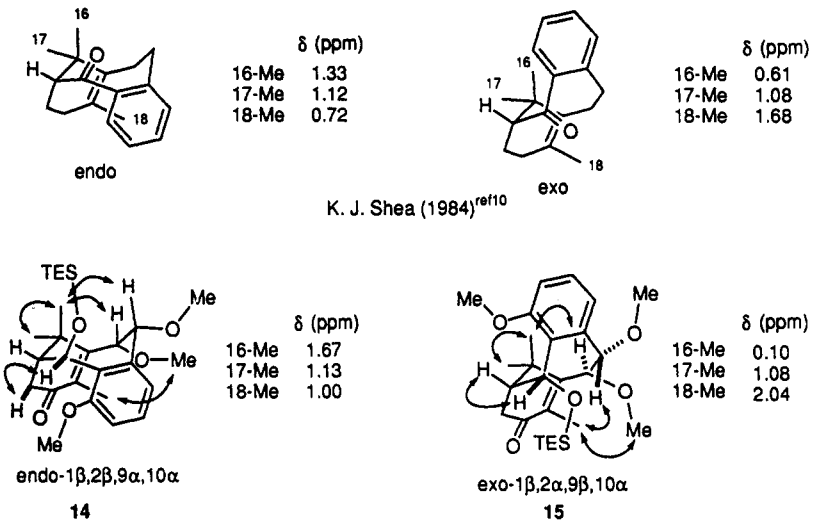
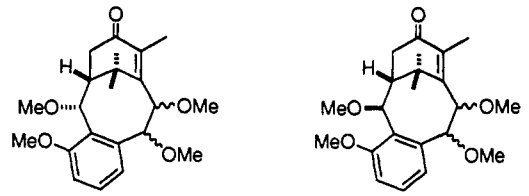


Figure 2. Structure determination by ^{1}H-NMR.

Table 2. MM2 Calculation on 2-MeO Compounds (kcal/mol)



	endo	exo		endo	exo
9α,10β	49.80	53.94	9α,10β	48.65	49.29
9β,10α	51.59	51.05	9β,10α	53.98	50.05
9α,10α	51.93	52.62	9α,10α	50.84	48.33
9β,10β	53.20	51.38	9β,10β	56.12	50.30

electrostatic attraction between the C-2 siloxy group and the intermediate oxonium ion might be cooperative.

Conversion of Cyclization Products 14 and 15 to Aromatic C-Ring Taxinine Derivatives with the Desired Stereochemistries. Thus, it was found that the C-2 oxygenated cyclization precursors yield the eight-membered cyclization products upon exposure to $TiCl_4$ and that the effect of the C-2 siloxy group on the atropselection is profound. However, both the endo-1β,2β,9α,10α cyclization product and the exo-1β,2α,9β,10α isomer have undesired stereochemistries. Therefore, some stereochemical modifications of these products were needed in order to obtain aromatic C-ring taxinine derivatives with the desired stereochemistry.

A. Inversion of the C-2 and C-10 Stereocenters of 14. Cyclization product **14**, derived from the major isomer of the AC ring addition reaction, has incorrect stereochemistry at C-2 and C-10. Inversion at C-10 was accomplished by means of a Lewis acid-mediated isomerization[7] (Scheme 4). As shown in Table 2, 9α,10β-isomer **18** should be the most stable diastereomer of the endo-1β,2β isomers. That **18** is probably the most stable suggests that the 10α-orientation is kinetically favored[20] and that the cyclization reaction conditions (−78 °C, 30 min) were not adequate for Lewis acid-mediated epimerization at C-10. As expected, reexposure of **14** to $TiCl_4$ in CH_2Cl_2 at higher temperature (0 °C, 2 h) cleanly induced epimerization at C-10 to give **18** (96%). Next, the stereochemistry at C-2 was inverted through an oxidation/reduction sequence. To distinguish the oxygen functionalities, the C-13 keto group was reduced with lithium tri-*tert*-butoxyaluminum hydride. The reduction exclusively gave the C-13α alcohol. This selectivity is noteworthy because the C-13α oxygen functionality is seen in taxusin and taxol. The resulting C-13α hydroxy group was protected as TBS ether **19**. Selective removal of the TES group with TBAF and PDC oxidation afforded ketone **20** (76%, four steps). Then, reduction of the C-2 keto group under thermodynamic control with Na in EtOH/ether at 0 °C[21] yielded 2α-isomer **21**[16] (70%) along with recovered starting ketone **20** (30%). Compound **21** has the desired endo conforma-

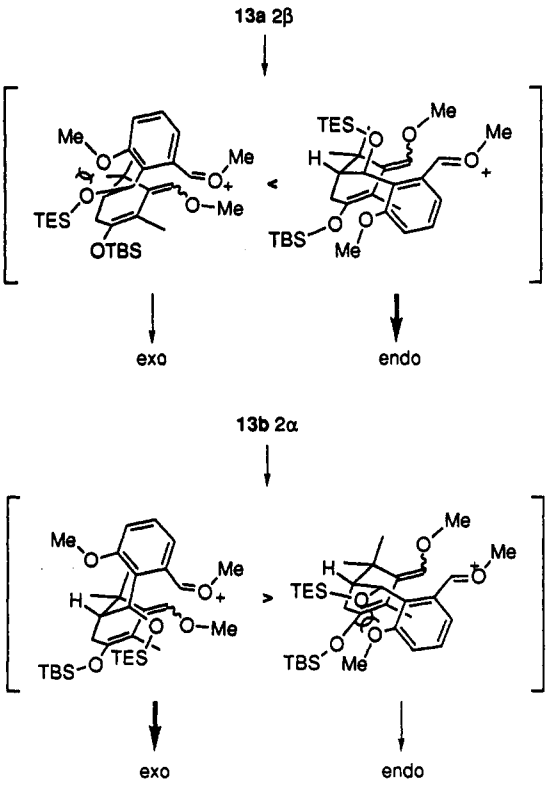
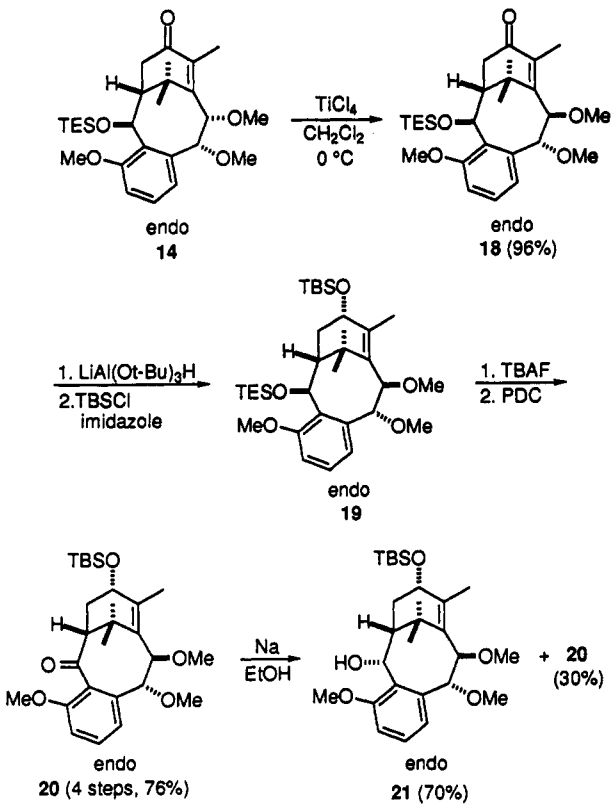


Figure 3. Proposed transition state for the cyclization of the C-2 TESO derivatives.

(20) The origin of the kinetic C-10α preference is not clear at present. It should be pointed out that preequilibration of the C-10/C-11 double bond before the eight-membered ring cyclization could take place through the seven-membered intermediates. For details on the seven-membered ring intermediates, see ref 23.

(21) Wender, P. A.; Mucciaro, T. P. *J. Am. Chem. Soc.* **1992**, *114*, 5878.

Scheme 4



tion and the correct stereochemistry at C-1, C-2, C-9, and C10.

B. Exo–Endo Isomerization and Inversion of the C-9 and C-10 Stereocenters of 15. Cyclization product **15**, derived from the minor isomer of the AC ring addition reaction, has the undesired exo conformation and the opposite stereochemistry at C-9 and C-10. It was expected that a Lewis acid-mediated isomerization[7] could be again applied for the stereochemical adjustment of C-9 and C-10 if the exo to endo atropisomerization could be achieved (see Table 2). Though **15** does not undergo the exo–endo isomerization at room temperature, as mentioned previously, the isomerization was found to take place gradually in refluxing toluene to lead to an equilibrium mixture of **15** and endo isomer **22** (ca. 2:1). MM2 calculations on the corresponding C-2 methoxy derivatives shown in Table 3 agree well with the equilibrium ratio. Further calculations on the corresponding C-2 hydroxy derivatives suggested that the endo isomer should be favored in the equilibrium. In fact, C-2 hydroxy derivative **23**, derived from **15** by desilylation with TBAF, almost quantitatively isomerized to the desired endo isomer **24** (97% endo). The drastic change of the equilibrium balance of these cases is attributable to the hydrogen bonding stabilization in **24** between the C-2 hydroxy group and the C-4 methoxy group **H**. Exo counterpart **23**, on the other hand, can not receive such stabilization. To avoid anticipated side reactions caused by the free hydroxy group in the Lewis acid-mediated inversion of C-9 and C-10, **24** was acetylated and then exposed to $TiCl_4$. When **25** was treated with 2.0 equiv of $TiCl_4$ in CH_2Cl_2 at −45 °C for 45 h, the desired 9α,10β-isomer **26**[22] could be obtained in 30% yield along with small amounts of 9α,10α-isomer **27**[22] (6%). It should be noted that the seven-membered products **28** (22%) and **29** (18%) inevitably formed concomitantly.[23]

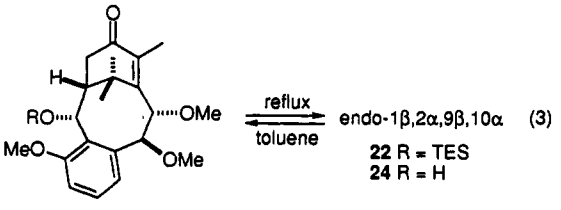
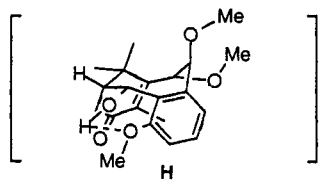
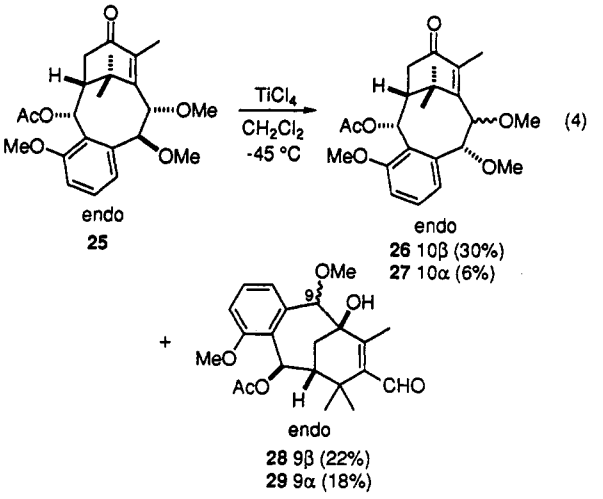


Table 3. MM2 Calculation on 1β,2α,9β,10α-Derivatives (kcal/mol)

R	exo	endo
Me	51.05	51.59
H	47.49	46.53





The Direct Endo Cyclization of the 1β,2α-Precursor under Chelation Control. The above-mentioned investigation has enabled us to prepare the aromatic C-ring taxinine skeleton from both of the diastereomers at C-1/C-2 by the Lewis acid-mediated eight-membered ring cyclization and to adjust the stereochemistry of both of the cyclization products to the desired endo-1β,2α,9α,10β. However, the route using the 1β,2α-natural-type derivative suffers from rather low efficiency. Though the route using the 1β,2β-unnatural-type derivative certainly makes the grade in this study, it is still unsatisfactory because it involves inversion of the C-2 oxygen functional-

(22) The structure assignments of **26** and **27** were made by chemical correlation with C-2 hydroxy derivatives **16** and **17**, the structures of which have been unambiguously determined. The ^1H NMR spectra of **26** and **27** were identical with those of the acetylated derivatives of **16** and **17**.

(23) For details on the seven-membered products, see: Morihira, K.; Seto, M.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 345. Unexpectedly, seven-membered cyclization products **28** and **29** were the main products when the reaction was performed with 1.0 equiv of $TiCl_4$ at −78 to 0 °C. A similar result was obtained even with 2.0 equiv of $TiCl_4$ at −100 to −78 °C. These seven-membered products showed reasonable ^1H NMR and NOESY spectra. The structure of **28** was ascertained by X-ray crystallographic analysis (Kojima, Y.; Osano, Y. T.; Matsuzaki, T.; Horiguchi, Y.; Kuwajima, I. *Anal. Sci.* **1993**, *9*, 433).

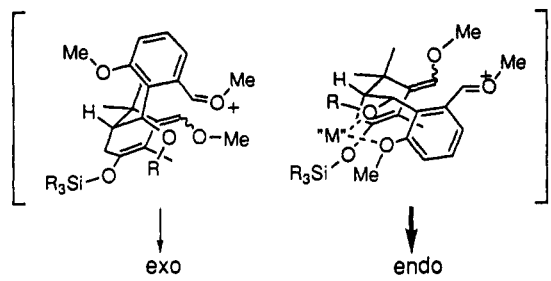
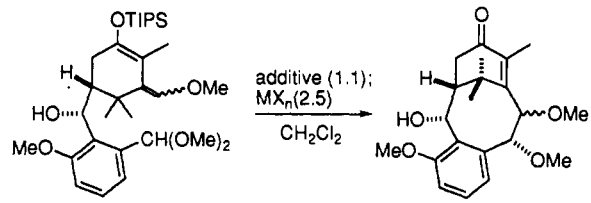


Figure 4. Chelation hypothesis for endo selective cyclization.

Table 4. Chelation-Controlled Endo Cyclization of 31



30 endo
16 10β
17 10α

entry	E/Z	additive	chelation condns (°C, h)	MX_n	cyclizn condns (°C, h)	yield[a] (%) 16	17
1	Z	Me_3Al	−23, 1	$TiCl_4$	−45, 1	39	8
2	Z	Me_3Al	−23, 1	$SnCl_4$	−78, 1.5	22	27
3	Z	R_2BH[b]	−78, 1	$TiCl_4$	−23, 3	20	
4	Z	R_2BH[b]	−78, 1	$SnCl_4$	−78, 0.5	21	39
5	Z	R_2BH[b]	−78, 1	$SnCl_4$	−45, 8.5	68	
6	Z	none		$SnCl_4$	−45, 5.5	77[c]	
7	E	none		$SnCl_4$	−45, 5.5	66[c]	

[a] NMR yield. [b] R_2BH = catecholborane. [c] Isolated yield.

ity. Such a process would make the synthesis lengthy and might lead to drawbacks in the synthesis of more complex molecules such as taxol. Therefore, it is desirable to find methods for the stereoselective preparation of the 1β,2α-natural-type precursor and for carrying out the direct endo cyclization, methods that will provide a straightforward-route to taxinine, and taxol. We examined the direct endo cyclization of the 1β,2α-natural-type precursor, even though the desired diastereoselection of the AC ring addition reaction has not been realized in this study.

The exo to endo thermal isomerization of the C-2 hydroxy derivative hinted at a method for the direct endo cyclization of the 1β,2α-derivative. Namely, linking the C-2 and C-4 oxygen atoms was expected to be favorable to the endo cyclization. To this end, *in situ* chelation of these oxygens with metallic reagents during the cyclization reaction was chosen rather than a covalent bond linkage (Figure 4). In order to make such chelation control efficient, the 1β,2α-hydroxy precursor was treated *in situ* with a chelating reagent with proton-scavenging ability before the Lewis acid-induced cyclization. Cyclization precursor **30** was prepared from **11b** in two steps (61%): (1) exchange of the acetyl group with the TIPS group and (2) methoxymethylenation.[14] Of the several combinations of a proton scavenger, chelating reagent, and Lewis acid examined, the combination of catecholborane (1.1 equiv)–$SnCl_4$ (2.5 equiv) appeared to be the best (Table 4). As expected, only the endo cyclization products were obtained. Though a mixture of C-10 epimers, **16** and **17**, forms at −78 °C, the C-10 epimerization proceeds gradually at −45 °C to lead to exclusive formation of the desired endo-1β,2α,9α,10β **16** (68% NMR yield).

Interestingly, it was found that the use of $SnCl_4$ without pretreatment with a chelating reagent gave essentially the same result in rather improved yields (66–77%). It is surprising that under such Lewis acidic conditions the free C-2 hydroxy group does not cause serious side reactions such as protonation of the dienol silyl ether moiety and/or hemiacetal formation with the acetal. In the absence of the proton scavenger, it is not clear whether $SnCl_4$ chelation or hydrogen bonding is responsible for the endo selection.

Conclusions

We have developed efficient methods for construction of the C-2 oxygenated aromatic C-ring taxane skeleton with complete stereocontrol of the eight-membered ring conformation as well as the configurations at C-9 and C-10. It is shown that the C-2 stereogenic center strongly influences the atropselectivity of the eight-membered ring cyclization and that the appropriate choice of the form of the C-2 hydroxy group and the cyclization conditions can tune the atropselectivity in the desired manner on both the diastereomers at C-1/C-2. In particular, the chelation-controlled direct endo cyclization of the eight-membered B-ring in combination with stereocontrolled AC ring coupling reactions should provide a remarkably efficient, convergent route not only toward natural taxanes such as taxinine and taxol but also toward various synthetic taxane analogues of great pharmacological potential. The obtained aromatic C-ring taxinine derivatives could be converted to natural taxinine by further transformation of the aromatic C-ring, and this manipulation is currently under investigation.

Experimental Section

General. All reactions were carried out under a dry nitrogen atmosphere. Routine flash column chromatography was performed with Merck silica gel 60. IR spectra were recorded on a JASCO IR-810 spectrometer. ^{1}H-NMR spectra were recorded at 200 MHz on a JEOL FX-200 instrument or at 270 MHz on a JEOL GSX-270 instrument. Microanalyses were performed on a Perkin-Elmer 240 instrument. Dichloromethane was dried by distillation from P_2O_5. THF and ether were distilled from sodium benzophenone ketyl in a recycling still. Toluene was distilled from sodium wire. Pyridine, DMSO, DMF, and HMPA were distilled from CaH_2. Methanol was distilled from magnesium methoxide. Ethanol was distilled from sodium ethoxide in the presence of diethyl succinate.

Preparation of Aldehyde 9. Butyllithium (198 mL of 1.65 M hexane solution, 327 mmol) was added to a THF (320 mL) solution of propargyl THP ether **4** (41.60 g, 297 mmol), and the mixture was stirred for 2 h at −78 °C. Then propionaldehyde (27.8 mL, 386 mmol) was added, and the mixture was stirred for 3 h at −70 to 0 °C. Usual aqueous workup gave propargyl alcohol **5** (64.97 g) as an oil.

Crude propargyl alcohol **5** (64.97 g), quinoline (4.2 mL), and Lindlar catalyst (4.2 g) in hexane (700 mL) were vigorously stirred for 7 h at rt under 1 atm of hydrogen. Removal of the catalyst as well as solvent gave the crude allylic alcohol (59.28 g) as an oil.

DMSO (42.0 mL, 592 mmol) was added to a dichloromethane (300 mL) solution of oxalyl chloride (33.6 mL, 385 mmol) at −40 °C. After the mixture stirred for 20 min, a dichloromethane (50 mL) solution of the crude alcohol (59.28 g) was added, and the resulting mixture was stirred for 20 min. After addition of triethylamine (124 mL, 888 mmol) and a 20-min stirring period, water and hexane were added to the reaction mixture. The organic layer was washed three times with 1 N HCl, saturated aqueous $NaHCO_3$, and then brine. Drying of the organic layer followed by removal of the solvent gave crude enone **6** (63.24 g), which was pure enough for the next operation.

Ethyl isobutyrate (43.6 mL, 326 mmol) was added to a THF (250 mL) solution of lithium diisopropylamide [prepared from

diisopropylamine (49.8 mL, 355 mmol) and BuLi (204 mL of 1.6 M hexane solution, 326 mmol)], and the resulting mixture was stirred for 2 h at −78 °C. Then, a THF (100 mL) solution of the crude enone (63.24 g) was added, and the mixture was stirred at −78 °C for 15 min and at 0 °C for 20 min. Usual extractive workup afforded crude keto ester **7** (93.0 g) as a colorless oil.

To an ether (290 mL) solution of crude keto ester **7** (93.0 g) was added t-BuOK (39.9 g, 355 mmol), and the mixture was stirred for 3 h at 0 °C. After water was added, the organic layer was separated. The aqueous layer was acidified with 1 N HCl with Congo red as an indicator and was extracted three times with ether (200 mL). After drying and removal of the solvent, the resulting crude diketone was treated with acetic anhydride (27.2 mL, 288 mmol) and triethylamine (54.8 mL, 393 mmol) in dichloromethane (500 mL) overnight at 0 °C. Extractive workup followed by chromatographic purification (20–25% EtOAc/hexane) gave acetoxycyclohexenone **8** (48.28g, 52% overall yield from the propargyl THP ether) as a colorless oil: IR (neat) 1756, 1660, 1450, 1430, 1362, 1190, 1150, 1130, 1120, 1090, 1070, 1028, 998, 900, 860, 822 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.06 (s), 1.07 (s), 1.22 (s), 1.23 (s) (these four singlets are assigned to those of *gem*-dimethyl groups separated by the chiral center of THP group), 1.47–1.90 (m, 6 H), 1.65 (t, J = 1.7 Hz, 3 H), 2.10–2.30 (m, 1 H), 2.23 (s, 3 H), 2.51–2.78 (m, 2 H), 3.45–3.57 (m, 4 H), 4.52–4.60 (m, 1 H). Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.73; H, 8.46.

Acetoxycyclohexenone **8** (6.64 g, 21.4 mmol) was stirred with *p*-TsOH (0.17 g, 0.99 mmol) in methanol (50 mL) for 3 h at rt. After triethylamine (0.44 mL, 3.16 mmol) was added, removal of solvent and volatile materials under reduced pressure afforded the free alcohol. Oxidation of the crude alcohol was performed in a similar manner to that described above with oxalyl chloride (2.8 mL, 32.1 mmol), DMSO (4.6 mL, 64.2 mmol), and triethylamine (17.9 mL, 128.3 mmol). Purification of the crude product by column chromatography on silica gel (25% EtOAc/hexane) gave aldehyde **9** (3.97 g, 83% yield from acetoxycyclohexenone **8**) as an oil: IR (neat) 1760, 1720, 1664, 1370, 1190, 1156, 1090 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.15 (s, 3 H), 1.42 (s, 3 H), 1.70 (t, J = 1.7 Hz, 3 H), 2.27 (s, 3 H), 2.49–2.72 (m, 1 H), 2.75–2.97 (m, 2 H), 9.85 (d, J = 1.2 Hz, 1 H). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.15; H, 7.15.

Preparation of 11a and 11b. To a hexane solution of *n*-BuLi (1.61 M, 12.4 mL, 20.0 mmol) at 0 °C was added *m*-anisaldehyde dimethyl acetal (3.45 mL, 20.0 mmol). After the mixture stirred at rt for 4 h, the brown suspension was dissolved in 10 mL of THF and then cooled to −78 °C. The solution was added to a THF suspension of $CeCl_3$ (5.42 g, 22.0 mmol) (stirred at rt for 2 h) at −78 °C. After 30 min, a THF (10 mL) solution of aldehyde **9** (2.24 g, 10 mmol) was added, and the reaction mixture was stirred for an additional 30 min at −78 °C. The mixture was poured into a vigorously stirred mixture of hexane and saturated aqueous $NaHCO_3$ and then filtered through Celite. The aqueous layer was separated and extracted three times with Et_2O. The combined organic extracts were washed with brine, dried with $MgSO_4$, and concentrated in vacuo. Chromatographic purification (30% EtOAc/hexane) afforded **11a** and **11b** as a diastereomeric mixture (3.47 g, 88%). The diastereomer ratio (**11a**:**11b** = 3:1) was determined by ^1H NMR on the basis of the acetal methyl signals at 3.28, 3.37 for **11a** and at 3.31, 3.38 for **11b**.

11a: IR (neat) 3450, 1760, 1675, 1030–1130, 795 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (s, 3 H), 1.32 (s, 3 H), 1.67 (s, 3 H), 2.20 (s, 3 H), 2.50 (ddd, J = 13 Hz, 3.7 Hz, 1.1 Hz, 1 H), 2.73 (ddd, J = 13 Hz, 5.2 Hz, 1.5 Hz, 1 H), 3.28 (s, 3 H), 3.37 (s, 3 H), 3.86 (s, 3 H), 5.49–5.60 (m, 1 H), 5.55 (s, 1 H), 6.93 (dd, J = 5.7 Hz, 4.6 Hz, 1 H), 7.27–7.31 (m, 2 H). Anal. Calcd for $C_{22}H_{29}O_7$: C, 65.17; H, 7.21. Found: C, 65.35; H, 7.43.

11b: IR (neat) 3450, 1760, 1675, 1030–1130, 795 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.18 (s, 3 H), 1.46 (s, 3 H), 1.61 (s, 3 H), 2.07 (s, 3 H), 2.06–2.83 (m, 3 H), 3.31 (s, 3 H), 3.38 (s, 3 H), 3.87 (s, 3 H), 5.23–5.37 (m, 1 H), 5.39, (br s, 1 H), 6.90 (d, J = 8.6 Hz, 1 H), 7.13 (d, J = 8.6 Hz, 1 H), 7.26 (dd, J = 8.6 Hz, 8.6 Hz, 1 H). Anal. Calcd for $C_{22}H_{29}O_7$: C, 65.17; H, 7.21. Found: C, 65.23; H, 7.25.

Preparation of 12a and 12b. Acetoxy enones **11a** and **11b** (4.54 g, 11.2 mmol, **11a**:**11b** = 2.5:1) were treated with pyrrolidine (1.40 mL, 16.8 mmol) in dichloromethane (50 mL) at rt for 3 h. Then imidazole (3.05 g, 44.8 mmol) and *tert*-butyldimethylsilyl chloride (2.03 g, 13.4 mmol) were added, and the solution was stirred for 30 min at 0 °C. Pouring the solution into a vigorously stirred mixture of hexane and saturated aqueous $NaHCO_3$ followed by usual workup and column chromatography (20% EtOAc/hexane including 0.5% triethylamine) gave siloxy enones **12a** (3.77 g, 70%) and **12b** (1.42 g, 27%) as oils.

12a: IR (neat) 3450–3500, 1630, 1248, 1052, 780 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.10 (s, 3 H), 0.15 (s, 3 H), 0.90 (s, 9 H), 1.22 (s, 3 H), 1.25 (s, 3 H), 1.65 (s, 3 H), 2.09–2.31 (m, 2 H), 2.69 (dd, J = 17 Hz, 9.7 Hz, 1 H), 3.22 (s, 3 H), 3.30 (s, 3 H), 3.82 (s, 3 H), 4.16 (d, J = 8.6 Hz, 1 H), 5.54 (s, 1 H), 5.55, (dd, J = 8.6 Hz, 2.9 Hz, 1 H), 6.90 (dd, J = 6.8 Hz, 3.4 Hz, 1 H), 7.23–7.29 (m, 2 H). Anal. Calcd for $C_{25}H_{42}O_6Si$: C, 64.34; H, 9.07. Found: C, 64.39; H, 8.89.

12b: IR (neat) 3450–3500, 1630, 1248, 1052, 780 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ −0.16 (s, 3 H), −0.15 (s, 3 H), 0.78 (s, 9 H), 1.11 (s, 3 H), 1.43 (s, 3 H), 1.50–1.68 (m, 1 H), 1.63 (s, 3 H), 1.95–2.15 (m, 1 H), 2.48–2.64 (m, 1 H), 3.33 (s, 3 H), 3.37 (s, 3 H), 3.84, (s, 3 H), 5.17–5.43 (m, 2 H), 6.91 (d, J = 6.8 Hz, 1 H), 7.17 (d, J = 6.8 Hz, 1 H), 7.27 (dd, J = 6.8 Hz, 6.8 Hz, 1 H). Anal. Calcd for $C_{25}H_{42}O_6Si$: C, 64.34; H, 9.07. Found: C, 64.64; H, 9.36.

Preparation of Cyclization Precursor 13a. A dichloromethane (15 mL) solution of siloxy enone **12a** (1.50 g, 3.13 mmol), imidazole (0.852 g, 12.5 mmol), and triethylsilyl chloride (1.05 mL, 6.27 mmol) was heated to reflux for 6 h. Standard aqueous workup followed by column chromatography (10% AcOEt/hexane including 0.5% triethylamine) gave the C-2 silylated product (1.85 g, 100%) as an oil: IR 1630, 1250, 1065, 835, 780, 740 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.286–0.971 (m, 21 H), 1.01 (s, 9 H), 1.69 (s, 3 H), 2.23–2.97 (m, 3 H), 3.21 (s, 3 H), 3.40 (s, 3 H), 3.86 (s, 3 H), 5.51 (d, J = 11 Hz, 1 H), 6.06 (s, 1 H), 6.80 (dd, J = 5.1 Hz, 5.1 Hz, 1 H), 7.20–7.29 (m, 2 H).

To a THF (8 mL) solution of [methoxy(trimethylsilyl)methyl]-lithium [prepared from s-BuLi (1.2 M cyclohexane solution, 5.8 mL, 6.9 mmol) and (methoxymethyl)trimethylsilane (1.3 mL, 6.9 mmol) in THF at −23 °C for 1 h] at −78 °C was added a THF (4 mL) solution of the C-2 triethylsilyl ether (2.40 g, 4.07 mmol). After the mixture stirred for 1 h, t-BuOK (0.593 g, 5.29 mmol) was added. The mixture was allowed to warm to rt and stirred for 2 h. Standard aqueous workup and column chromatography (5% AcOEt/hexane including 0.5% triethylamine) gave dienol silyl ether **13a** (1.49 g, 59%) as an oil. Dienol silyl ether **13a** was a mixture of geometrical isomers (E:Z = 4:5), and the ratio was determined by ^1H NMR on the basis of the C-2 methine protons (at 5.27 for the E isomer and 5.28 for the Z isomer): IR 1620, 1250, 1165, 1075, 840, 780, 740, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.186 (s, 1.4 H), 0.206 (s, 1.6 H), 0.446 (q, J = 7.4 Hz, 6 H), 0.69–1.12 (m, 27 H, including s at δ 1.00, 9 H), 1.93 (s, 3H), 2.20–2.39 (m, 1 H), 2.43–2.51 (m, 2 H), 3.21 (s, 3 H), 3.43 (s, 1.33 H), 3.44 (s, 1.67 H), 3.51 (s, 1.3 H), 3.52 (s, 1.7 H), 3.86 (s, 3 H), 5.27 (d, J = 8.0 Hz, 0.56 H), 5.28 (d, J = 8.0 Hz, 0.44 H), 5.49 (s, 1 H), 5.80 (s, 1 H), 6.78 (dd, J = 5.1 Hz, 5.1 Hz, 1 H), 7.24–7.26 (m, 2 H).

Cyclization of 13a. Dienol silyl ether **13a** (1.4 g, 2.25 mmol) was allowed to react with $TiCl_4$ (2.48 mmol) in dichloromethane (76 mL) at −78 °C for 30 min. The reaction mixture was poured into a stirred mixture of hexane and saturated aqueous $NaHCO_3$. Extractive workup and column chromatography (20% AcOEt/hexane) afforded cyclized product **14** (0.81 g, 76%) as white plates: IR 1660 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.50 (q, J = 7.4 Hz, 6 H), 0.80 (t, J = 7.4 Hz, 9 H), 1.00 (s, 3 H), 1.13 (s, 3 H), 1.67 (s, 3 H), 2.33 (dd, J = 7.2 Hz, 4.8 Hz, 1 H) 2.40 (d, J = 19.5 Hz, 1 H), 2.75 (dd, J = 19.5 Hz, 7.2 Hz, 1 H), 3.32 (s, 1 H), 3.48 (s, 3 H), 3.78 (s, 3 H), 4.66 (d, J = 5.5 Hz, 1 H), 5.79 (d, J = 4.8 Hz, 1 H), 5.90 (d, J = 5.5 Hz, 1 H), 6.72 (d, J = 8.2 Hz, 1 H), 7.12 (dd, J = 8.2 Hz, 8.2 Hz, 1 H), 7.30 (d, J = 8.2 Hz, 1 H). Anal. Calcd for $C_{27}H_{42}O_5Si$: C, 68.31; H, 8.92. Found: C, 68.04; H, 8.82.

Preparation of Cyclization Precursor 13b. A dichloromethane (5 mL) solution of siloxy enone **12b** (0.575 g, 1.20 mmol), imidazole (0.164 g, 2.40 mmol), and triethylsilyl chloride (0.242 mL, 1.44 mmol) was stirred overnight at rt. After addition of triethylamine (0.5 mL), basic aqueous workup followed by column chromatography (10% AcOEt/hexane including 0.5%

triethylamine) gave the C-2 silylated product (0.45 g, 63%) as an oil: IR 1640, 1250, 1180, 840 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$), the signals could not be fully identified because of the complexity of the spectrum, which was presumably due to the lack of free rotation of a certain bond(s) in the molecule, δ −0.140 (s), 0.27–0.63 (m), 0.71–1.00 (m), 1.10 (s), 1.43 (s), 1.44 (s), 1.61 (s), 1.85–2.03 (m), 2.40–2.52 (m), 3.22 (s), 3.23 (s), 3.29 (s), 3.43 (s), 3.46 (s), 3.77 (s), 3.80 (s), 5.26 (d, J = 8.0 Hz), 5.41 (s), 5.71 (d, J = 10 Hz), 5.72 (d, J = 10 Hz), 6.21 (s), 6.22 (s), 6.78–6.86 (m), 7.21–7.30 (m).

To a THF (5 mL) solution of methoxy(trimethylsilyl)-methyllithium [prepared from s-BuLi (1.3 M cyclohexane solution, 0.91 mL, 1.2 mmol) and (methoxymethyl)trimethylsilane (0.22 mL, 1.4 mmol) THF at −23 °C for 45 min] at −78 °C was added a THF (4 mL) solution of the C-2 triethylsilyl ether (0.450 g, 0.759 mmol). After the mixture stirred for 1 h, t-BuOK (0.130 g, 1.16 mmol) was added. The mixture was allowed to warm to rt and then stirred for 2 h. Standard aqueous workup and column chromatography (6% AcOEt/hexane including 0.5% triethylamine) gave dienol silyl ether **13b** (0.270 g, 58%) as an oil. Dienol silyl ether **13b** was a mixture of geometrical isomers. The ratio could not be determined by ^1H NMR because of the complexity of the spectrum, which was presumably due to the lack of free rotation of a certain bond(s) in the molecule: IR 1250, 1060–1150, 840, 780 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ −0.24 (s), −0.18 (s), −0.15 (s), 0.06 (s), 0.07 (s), 0.24–0.60 (m), 0.72–1.00 (m), 1.12 (s), 1.13 (s), 1.20 (s), 1.25 (s), 1.54 (s), 1.85 (s), 2.03–2.16 (m), 2.37–2.49 (m), 3.24 (s), 3.25 (s), 3.28 (s), 3.41 (s), 3.48 (s), 3.49 (s), 3.56 (s), 3.58 (s), 3.59 (s), 3.75 (s), 3.77 (s), 4.96 (d, J = 8.1 Hz), 5.37 (s), 5.57 (d, J = 9.0 Hz), 5.61 (d, J = 8.1 Hz), 5.82 (s), 5.85 (s), 6.23 (s), 6.28 (s), 6.72–6.80 (m), 7.10–7.25 (m).

Cyclization of 13b. Dienol silyl ether **13b** (0.0233 g, 0.0377 mmol) was allowed to react with $TiCl_4$ (0.0415 mmol) in dichloromethane (76 mL) at −78 °C for 45 min and then at −23 °C for 2 h. The reaction mixture was poured into a stirred mixture of hexane and saturated aqueous $NaHCO_3$. Extractive workup and column chromatography (16% AcOEt/hexane) afforded **15** (0.0085 g, 48%) as white plates along with **16** (16%, NMR yield) and **17** (8%, NMR yield).

15: IR (CH_2Cl_2 solution) 1672, 1263, 1065–1115 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.099 (s, 3 H), 0.456 (q, J = 6.3 Hz, 6 H), 0.773 (t, J = 6.3 Hz, 9 H), 1.08 (s, 3 H), 2.04 (s, 3 H), 2.28 (dd, J = 5.4 Hz, 5.4 Hz, 1 H), 2.43 (d, J = 18.0 Hz, 1 H), 2.89 (dd, J = 18.0 Hz, 5.4 Hz, 1 H), 3.24 (s, 3 H), 3.46 (s, 3 H), 3.81 (s, 3 H), 3.99 (d, J = 9.3 Hz, 1 H), 5.23 (d, J = 9.3 Hz, 1 H), 5.74 (d, J = 5.4 Hz, 1 H), 6.80 (d, J = 8.3 Hz, 1 H), 7.30 (dd, J = 8.3 Hz, 8.3 Hz, 1 H), 7.48 (d, J = 8.3 Hz, 1 H). Anal. Calcd for $C_{27}H_{42}O_5Si$: C, 68.31; H, 8.92. Found: C, 68.39; H, 8.90.

$TiCl_4$-mediated C-10 Epimerization of 14. To a dichloromethane (98 mL) solution of **14** (1.40 g, 2.95 mmol) at −78 °C was added a dichloromethane solution of $TiCl_4$ (0.99 M, 3.27 mL, 3.24 mmol). The solution was allowed to warm to 0 °C and stirred for 2.5 h. Standard aqueous workup and column chromatography (20% AcOEt/hexane) afforded **18** (1.34 g, 96%) as white crystals: IR (CCl_4 solution) 2950, 2930, 2874, 2820, 1666, 1580, 1464, 1245, 1124, 1102, 1064, 1003, 980, 842, 730 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.51 (q, J = 6.2 Hz, 6 H), 0.80 (t, J = 6.2 Hz, 9 H), 0.97 (s, 3 H), 1.16 (s, 3 H), 1.80 (s, 3 H), 2.31–2.43 (m, 2 H), 2.73 (dd, J = 20 Hz, 7.0 Hz, 1 H), 3.37 (s, 3 H), 3.38 (s, 3 H), 3.74 (s, 3 H), 4.44 (d, J = 9.2 Hz, 1 H), 5.75 (d, J = 5.2 Hz, 1 H), 5.82 (d, J = 9.2 Hz, 1 H), 6.68 (d, J = 8.8 Hz, 1 H), 7.08 (dd, J = 8.8 Hz, 8.8 Hz, 1 H), 7.31 (d, J = 8.8 Hz, 1 H). Anal. Calcd for $C_{27}H_{42}O_5Si$: C, 68.31; H, 8.92. Found: C, 68.43; H, 8.86.

$Li(^tBuO)_3AlH$ Reduction of Enone 18. To crystalline enone **18** (75.6 mg, 0.16 mmol) was added a THF solution of $Li(^tBuO)_3AlH$ (1.0 M, 0.48 mL, 0.48 mmol). The mixture was stirred at rt for 15 min to dissolve **18** and then heated to 50 °C for 24 h. After the mixture cooled to rt, saturated aqueous $NaHCO_3$ and ether were added, and the mixture was vigorously stirred for 15 min until the organic layer became clear. Standard aqueous workup gave the corresponding 13α-alcohol (85 mg) as an amorphous solid: IR ($CDCl_3$ solution) 3570, 2955, 2910, 2880, 1580, 1464, 1452, 1244, 1112, 1085, 1066, 1050, 1002, 840, 785 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.42–0.56 (m, 6 H), 0.80 (t, J = 8.1 Hz, 9 H), 0.93 (s, 6 H), 1.60 (dd, J = 16.0 Hz, 3.4 Hz, 1 H), 1.73 (s, 3 H), 1.93 (dd, J = 8.4 Hz, 5.2 Hz, 1 H), 2.67 (ddd, J = 16.0 Hz, 10.0 Hz, 8.4 Hz, 1 H), 3.37 (s, 3 H), 3.39 (s, 3 H), 3.83 (s, 3 H), 4.06 (br dd, J = 10 Hz, 10 Hz, 1 H), 4.39 (d, J = 9.8 Hz, 1 H), 5.67 (d, J = 5.2 Hz, 1 H), 5.80 (d, J = 9.8 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 7.17 (dd, J = 8.0 Hz, 8.0 Hz, 1 H), 7.39 (d, J = 8.0 Hz, 1 H).

***tert*-Butyldimethylsilyl Ether 19.** To a THF (1 mL) suspension of potassium hydride (26.8 mg, 0.67 mmol) at 0 °C were added a THF (4 mL) solution of the crude alcohol (<0.16 mmol) and then *tert*-butyldimethylsilyl chloride (51.5 mg, 0.34 mmol). After the mixture stirred at rt for 3 h, saturated aqueous sodium bicarbonate and ether were added. Standard aqueous workup gave *tert*-butyldimethylsilyl ether **19** (114 mg) as an oil: IR (neat) 2950, 2930, 2875, 1579, 1462, 1245, 1122, 1095, 1070, 1045, 1000, 880, 835, 780, 741, 670 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ −0.06 (s, 3 H), 0.01 (s, 3 H), 0.49 (q, J = 8.1 Hz, 6 H), 0.79 (t, J = 8.1 Hz, 9 H), 0.81 (s, 9 H), 0.86 (s, 3 H), 0.99 (s, 3 H), 1.53 (dd, J = 14.4 Hz, 4.4 Hz, 1 H), 1.74 (s, 3 H), 1.93 (dd, J = 9.0 Hz, 5.4 Hz, 1 H), 2.38 (ddd, J = 14.4 Hz, 9.8 Hz, 9.8 Hz, 1 H), 3.35 (s, 3 H), 3.38 (s, 3 H), 3.78 (s, 3 H), 4.26–4.33 (m, 1 H), 4.43 (d, J = 9.8 Hz, 1 H), 5.62 (d, J = 5.4 Hz, 1 H), 5.78 (d, J = 9.8 Hz, 1 H), 6.69 (d, J = 8.1 Hz, 1 H), 7.10 (dd, J = 8.1 Hz, 8.1 Hz, 1 H), 7.28 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (50 MHz) 155.4, 141.1, 140.2, 131.1, 129.4, 126.8, 118.5, 109.6, 87.1, 81.3, 71.3, 67.8, 57.5, 56.8, 55.7, 49.2, 39.5, 33.2, 31.4, 28.7, 25.8, 18.1, 15.4, 6.8, 4.5, −4.1, −5.2. Anal. Calcd for $C_{33}H_{58}O_5Si_2$: C, 67.07; H, 9.89. Found: C, 67.01; H, 9.83.

Removal of the Triethylsilyl Group from 19. To a THF (0.32 mL) solution of crude *tert*-butyldimethylsilyl ether **19** at 0 °C was added a THF solution of tetrabutylammonium fluoride (1.0 M, 0.64 mL, 0.64 mmol). After the solution stirred at rt for 2 days, saturated aqueous sodium bicarbonate and ether were added. Standard aqueous workup and column chromatography (30% AcOEt/hexane) gave the corresponding 2β-alcohol (63.1 mg, 83%, three steps from **18**) as white crystals: IR ($CDCl_3$ solution) 3680, 3600, 2930, 2885, 2850, 1598, 1580, 1464, 1246, 1120, 1080, 1042, 875, 776 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ −0.08 (s, 3 H), 0.00 (s, 3 H), 0.80 (s, 9 H), 0.86 (s, 3 H), 1.00 (s, 3 H), 1.56 (dd, J = 14.4 Hz, 4.2 Hz), 1.77 (s, 3 H), 2.07 (dd, J = 9.0 Hz, 5.4 Hz, 1 H), 2.42 (ddd, J = 14.4 Hz, 9.6 Hz, 9.6 Hz, 1 H), 3.33 (s, 3 H), 3.38 (s, 3 H), 3.75 (s, 3 H), 4.27–4.37 (m, 1 H), 4.42 (d, J = 9.8 Hz), 5.71–5.82 (m, 2 H), 6.72 (d, J = 8.1 Hz, 1 H), 7.13 (dd, J = 8.1 Hz, 8.1 Hz, 1 H), 7.33 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (67.5 MHz) 155.9, 141.3, 140.5, 130.9, 128.6, 127.4, 118.8, 109.9, 87.0, 81.5, 71.7, 67.7, 57.7, 56.8, 55.7, 48.4, 39.4, 33.3, 31.2, 28.5, 25.8, 18.0, 15.3, −4.2, −5.3. Anal. Calcd for $C_{27}H_{44}O_5Si$: C, 68.03; H, 9.30. Found: C, 68.01; H, 9.34.

Ketone 20. A dichloromethane (0.5 mL) suspension of pyridinium dichromate (50 mg, 0.13 mmol) and 4-Å molecular sieves (70 mg) was stirred overnight at rt. To the suspension was added a dichloromethane (0.4 mL) solution of the 2β-alcohol (45 mg, 0.094 mmol). After the mixture stirred at rt for 5 h, Celite (ca. 50 mg) was added, and then the mixture was filtered through Celite. Concentration of the filtrate and column chromatography (30% AcOEt/hexane) gave 2-keto derivative **20** (41.3 mg, 92%) as white crystals: IR (CH_2Cl_2 solution) 3050, 2930, 2852, 1678, 1596, 1575, 1462, 1273, 1254, 1122, 1091, 1074, 886, 766 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ −0.01 (s, 3 H), 0.02 (s, 3 H), 0.81 (s, 9 H), 1.07 (s, 3 H), 1.11 (s, 3 H), 1.49 (s, 3 H), 2.23 (dd, J = 14.2 Hz, 5.6 Hz, 1 H), 2.38–2.59 (m, 2 H), 3.34 (s, 3 H), 3.38 (s, 3 H), 3.75 (s, 3 H), 4.39–4.48 (m, 1 H), 4.43 (d, J = 9.8 Hz, 1 H), 4.51 (d, J = 9.8 Hz, 1 H), 6.76 (dd, J = 7.6 Hz, 2.0 Hz, 1 H), 7.15–7.24 (m, 2 H); ^{13}C NMR (50 MHz) 211.6, 154.2, 142.5, 136.0, 132.1, 130.6, 128.4, 117.9, 110.1, 86.5, 83.0, 67.1, 60.9, 58.4, 57.1, 55.5, 37.9, 31.1, 29.6, 26.7, 25.8, 18.0, 15.7, −4.0, −5.2. Anal. Calcd for $C_{27}H_{42}O_5Si$: C, 68.31; H, 8.92. Found: C, 68.47; H, 8.67.

2α-Alcohol 21. To ketone **20** (15.4 mg, 0.032 mmol) in ether (0.5 mL)/ethanol (0.5 mL) at 0 °C was added sodium metal (ca. 30 mg, ca. 1.3 mmol). Stirring was continued at 0 °C for 7 h during which time ether (0.5 mL), ethanol (0.5 mL), and sodium metal (ca. 30 mg, ca. 1.3 mmol) were added three times. The reaction was quenched with water, and then ethanol was removed by evaporation. Extractive workup followed by column chromatography (20% AcOEt/hexane) afforded 2α-alcohol **21** (10.7 mg, 70%) as a white amorphous solid along with starting ketone **20** (4.6 mg, 30%): IR (CH_2Cl_2 solution) 3680, 3500, 3050, 2975, 2925, 2850, 1600, 1579, 1464, 1436, 1275, 1254, 1235, 1124, 1090,

1077, 1023, 1002, 907, 866, 837 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.04 (s, 3 H), 0.03 (s, 3 H), 0.83 (s, 9 H), 0.84 (s, 3 H), 1.01 (s, 3 H), 1.62 (s, 3 H), 1.98–2.10 (m, 2 H), 2.41 (ddd, J = 14.4 Hz, 10.0 Hz, 8.0 Hz, 1 H), 3.32 (s, 3 H), 3.39 (s, 3 H), 3.89 (s, 3 H), 4.28–4.37 (m, 1 H), 4.38 (d, J = 9.4 Hz, 1 H), 4.65 (d, J = 9.4 Hz, 1 H), 4.98 (d, J = 10.2 Hz, 1 H), 5.71 (d, J = 10.2 Hz, 1 H), 6.82 (d, J = 8.0 Hz, 1 H), 7.15 (dd, J = 8.0 Hz, 8.0 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H); ^{13}C NMR (67.5 MHz) 156.9, 141.6, 139.1, 129.8, 129.6, 126.9, 119.2, 111.2, 87.3, 83.4, 73.3, 67.5, 58.2, 57.0, 55.8, 53.5, 38.0, 31.6, 29.2, 27.2, 25.9, 18.1, 15.5, −4.1, −5.3. Anal. Calcd for $C_{27}H_{44}O_5Si$: C, 68.03; H, 9.30. Found: C, 68.26; H, 9.27.

Thermal Isomerization of 15. A toluene (0.3 mL) solution of **15** (0.0163 g) was heated to reflux for 24 h. Concentration in *vacuo* afforded a mixture of **15** and its endo isomer **22** (0.0163 g) in a 2:1 ratio.

22: ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.33–0.49 (m, 6 H), 0.82 (t, J = 8.0 Hz, 9 H), 0.90 (s, 3 H), 1.14 (s, 3 H), 1.47 (s, 3 H), 2.25 (d, J = 5.7 Hz, 1 H), 2.65 (dd, J = 20 Hz, 5.7 Hz, 1 H), 3.22 (s, 3 H), 3.36 (d, J = 20 Hz, 1 H), 3.40 (s, 3 H), 3.73 (s, 3 H), 4.59 (s, 1 H), 4.64 (s, 1 H), 5.68 (s, 1 H), 6.79–6.88 (m, 2 H), 7.03 (dd, J = 8.6 Hz, 6.9 Hz, 1 H).

Desilylation of 15. To a THF (2.0 mL) solution of **15** (0.306 g, 0.644 mmol) at 0 °C was added a THF solution of tetrabutylammonium fluoride (1.0 M, 2.37 mL, 2.37 mmol). The solution was stirred at rt for 11.5 h. Concentration in *vacuo*, addition of ether and brine, and extractive workup afforded **23** (0.232 g) as white crystals. The crude product was pure enough for use in the next step: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.160 (s, 3 H), 1.10 (s, 3 H), 2.02 (s, 3 H), 2.35 (dd, J = 6.0 Hz, 6.0 Hz, 1 H), 2.59 (d, J = 18 Hz, 1 H), 2.93 (dd, J = 18 Hz, 6.0 Hz, 1 H), 3.25 (s, 3 H), 3.43 (s, 3 H), 3.80 (s, 3 H), 4.03 (d, J = 9.6 Hz, 1 H), 5.39 (d, J = 9.6 Hz, 1 H), 5.74 (dd, J = 6.0 Hz, 6.0 Hz, 1 H), 6.82 (d, J = 7.2 Hz, 1 H), 7.33 (dd, J = 7.2 Hz, 7.2 Hz, 1 H), 7.52 (d, J = 7.2 Hz, 1 H).

Thermal Isomerization of 23. A toluene (1 mL) solution of **23** (0.259 g) was heated to reflux for 1 h. Concentration in *vacuo* afforded a 3:97 mixture of **23** and its endo isomer **24** (0.259 g) as white crystals.

24: IR 3610, 3520, 1684, 1588, 1465, 1370, 1258, 1104, 1067 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.97 (s, 3 H), 1.19 (s, 3 H), 1.53 (s, 3 H), 2.40 (d, J = 6.0 Hz, 1 H), 2.72 (dd, J = 18.0 Hz, 6.0 Hz, 1 H), 2.90 (d, J = 18.0 Hz, 1 H), 3.24 (s, 3 H), 3.27 (s, 3 H), 3.89 (s, 3 H), 4.61 (s, 1 H), 4.74 (s, 1 H), 5.29 (d, J = 11.6 Hz), 5.62 (d, J = 11.6 Hz, 1 H), 6.90 (d, J = 7.2 Hz, 2 H), 7.09 (dd, J = 7.2 Hz, 7.2 Hz, 1 H). Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.90; H, 7.62.

Acetylation of 24. To a dichloromethane (3.2 mL) solution of **24** (0.135 g, 0.284 mmol) at 0 °C were added DMAP (0.0408 mg, 0.330 mmol), triethylamine (0.22 mL, 1.6 mmol), and Ac_2O (0.12 mL, 1.28 mmol). The reaction mixture was stirred at rt for 14 h. Standard aqueous workup and chromatographic purification (25% EtOAc/hexane) afforded acetylated product **25** (0.095 mg, 74%) as white crystals: IR 1732, 1670, 1468, 1250, 1112 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.99 (s, 3 H), 1.18 (s, 3 H), 1.56 (s, 3 H), 2.02 (s, 3 H), 2.32 (d, J = 8.1 Hz, 1 H), 2.73 (dd, J = 18 Hz, 8.1 Hz, 1 H), 3.18 (d, J = 18 Hz, 1 H), 3.24 (s, 3 H), 3.33 (s, 3 H), 3.73 (s, 3 H), 4.63 (s, 1 H), 4.74 (s, 1 H), 6.77 (s, 1 H), 6.88 (d, J = 8.1 Hz, 2 H), 7.11 (dd, J = 8.1 Hz, 8.1 Hz, 1 H). Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.86; H, 7.79.

$TiCl_4$-Mediated Isomerization of 25. To a dichloromethane (0.75 mL) solution of **25** (10 mg, 0.0248 mmol) at −78 °C was added a dichloromethane solution of $TiCl_4$ (0.492 M, 0.111 mL, 0.0546 mmol), and the solution was stirred at −45 °C for 45 h. Standard aqueous workup afforded a mixture of seven-membered compounds **28** (22%) and **29** (18%) and eight-membered compounds **26** (30%) and **27** (6%). (These yields are NMR yields; tetrachloroethane was used as an internal standard). The structure assignments of **26** and **27** were made by chemical correlation with C-2 hydroxy derivatives **16** and **17**, the structures of which have been unambiguously determined (*vide infra*); the ^{1}H NMR spectra of **26** and **27** were identical with those of the acetylated derivatives of **16** and **17**. These seven-membered products showed reasonable ^{1}H NMR and NOESY spectra. The structure of **28** was ascertained by X-ray crystallographic analysis (Kojima, Y.; Osano, Y. T.; Matsuzaki, T.; Horiguchi, Y.; Kuwajima, I. *Anal. Sci.* **1993**, *9*, 433).

26: IR 1738, 1673, 1244 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.96 (s, 3 H), 1.17 (s, 3 H), 1.74 (s, 3 H), 2.06 (s, 3 H), 2.34 (d, J = 6.4 Hz, 1 H), 2.72 (dd, J = 20 Hz, 6.4 Hz, 1 H), 3.16 (d, J = 20 Hz, 1 H), 3.41 (s, 3 H), 3.47 (s, 3 H), 3.76 (s, 3 H), 4.42 (d, J = 9.0 Hz, 1 H), 4.92 (d, J = 9.0 Hz, 1 H), 6.17 (s, 1 H), 6.79 (d, J = 8.0 Hz, 1 H), 7.14 (dd, J = 8.0 Hz, 8.0 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H).

27: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.97 (s, 3 H), 1.16 (s, 3 H), 1.55 (br s, 3 H), 2.05 (s, 3 H), 2.30 (d, J = 6.0 Hz, 1 H), 2.70 (dd, J = 19 Hz, 6.0 Hz, 1 H), 3.24 (d, J = 19 Hz, 1 H), 3.29 (s, 3 H), 3.52 (s, 3 H), 3.75 (s, 3 H), 4.61 (d, J = 5.6 Hz, 1 H), 4.89 (d, J = 5.6 Hz, 1 H), 6.08 (br s, 1 H), 6.82 (dd, J = 8.0 Hz, 1.2 Hz, 1 H), 7.15 (dd, J = 8.0 Hz, 8.0 Hz, 1 H), 7.27 (dd, J = 8.0 Hz, 1.2 Hz, 1 H).

28: IR 1730, 1681, 1255, 1242 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.13 (s, 3 H), 1.35 (s, 3 H), 1.93 (dd, J = 13 Hz, 4.4 Hz, 1 H), 2.00 (s, 3 H), 2.01 (s, 3 H), 2.19–2.27 (m, 1 H), 2.68 (br s, 1 H), 3.11 (dd, J = 13 Hz, 3.2 Hz, 1 H), 3.24 (s, 3 H), 3.80 (s, 3 H), 4.28 (s, 1 H), 6.75 (d, J = 8.0 Hz, 1 H), 6.83 (d, J = 5.8 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 1 H), 7.21 (dd, J = 8.0 Hz, 8.0 Hz, 1 H), 9.77 (s, 1 H).

29: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.43 (s, 3 H), 1.86 (s, 3 H), 1.95–2.30 (m, 2 H), 2.03 (s, 3 H), 2.40 (dd, J = 9.0 Hz, 4.5 Hz, 1 H), 3.36 (s, 3 H), 3.81 (s, 3 H), 4.37 (s, 1 H), 4.76 (s, 1 H), 6.79 (d, J = 9.0 Hz, 1 H), 6.83–7.20 (m, 3 H), 9.67 (s, 1 H).

Preparation of the Cyclization Precursor 31. A diastereomeric mixture of **11a** and **11b** (**11a**:**11b** = ca. 3:1) (6.30 g, 15.5 mmol) was treated with pyrrolidine (1.55 mL, 18.6 mmol) in dichloromethane (78 mL) for 3 h at rt. Then, imidazole (14.2 g, 62 mmol) and triisopropylsilyl chloride (8.29 mL, 38.8 mmol) were added, and the resulting solution was stirred for 1 h at 0 °C. Usual aqueous workup and chromatographic purification (20–40% EtOAc/hexane; a few drops of *N*,*N*-dimethylaniline were passed through the column before use) gave the corresponding triisopropylsiloxy enone (2α-isomer, 1.67 g, 21%, and 2β-isomer, 3.94 g, 48%).

2α-Isomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.81–0.94 (m, 22 H), 1.15 (s, 3 H), 1.46 (s, 3 H), 1.69 (s, 3 H), 2.09–2.28 (m, 1 H), 2.60 (br s, 1 H), 3.37 (br s, 3 H) 3.39 (br s, 3 H), 3.87 (s, 3 H), 5.13–5.41 (m, 2 H), 6.79 (d, J = 8.1 Hz, 1 H), 7.09–7.19 (m, 1 H), 7.22–7.30 (m, 1 H).

2β-Isomer: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.93–1.17 (m, 21 H), 1.25 (s, 3 H), 1.31 (s, 3 H), 1.71 (s, 3 H), 2.15–2.30 (m, 2 H), 2.73–2.90 (m, 1 H), 3.23 (s, 3 H) 3.36 (s, 3 H), 3.85 (s, 3 H), 4.25 (d, J = 7.5 Hz, 1 H), 5.56–5.67 (m, 2 H), 6.92 (d, J = 8.1 Hz, 1 H), 7.19–7.33 (m, 2 H).

A hexane solution of s-BuLi (0.958 M, 6.26 mL, 6.00 mmol) was added to a THF (12 mL) solution of (methoxymethyl)-trimethylsilane (0.98 mL, 6.30 mmol) at −78 °C, and the resulting mixture was stirred for 2.5 h at −23 °C. Then, the reaction mixture was cooled to −78 °C and a THF (6.0 mL) solution of the 2α-isomer (1.04 g, 2.0 mmol) was added. After the mixture stirred for 50 min, t-BuOK (0.67 g, 6.0 mmol) was added, and the solution was warmed to rt and stirred for 30 min. Usual aqueous workup and chromatographic purification (15% EtOAc/hexane) gave (*Z*)-**30** (0.688 g, 63%) and (*E*)-**31** (0.115 g, 10%) as colorless oils.

(*E*)-**30**: ^{1}H NMR (270 MHz, $CDCl_3$), unresolved signals were observed due to lack of free rotation in the compound, δ 0.78–0.93 (m, 21 H), 1.00–2.30 (m, including s-like signals at δ 1.06, 1.26, 1.38, 1.40, 1.53, 1.67), 3.20–3.42 (m, including s-like signals at δ 3.30, 3.33, 3.37, 6 H), 3.60 (s, 3 H), 3.84 (s, 3 H), 4.97–5.16 (m, 1 H), 5.34 (br s, 1 H), 5.84 (s, 1 H), 6.82–6.90 (m, 1 H), 7.13–7.23 (m, 2 H).

(*Z*)-**30**: ^{1}H NMR (270 MHz, $CDCl_3$), unresolved signals were observed due to lack of free rotation in the compound, δ 0.73–0.96 (m, 21 H), 0.98–2.21 (m, including s-like signals at δ 1.00, 1.06, 1.15, 1.27, 1.39, 1.40, 1.43, 1.61, 1.90), 3.23–3.41 (m, including s-like signals at δ 3.32, 3.34, 3.36, 3.39, 6 H), 3.58 (s, 3 H), 3.83 (br s, 3 H), 4.88–5.01 (m, 1 H), 5.22–5.42 (m, 2 H), 5.89 (s, 1 H), 6.80–6.90 (m, 1 H), 7.11-7.23 (m, 2 H).

A mixture of two geometrical isomers: IR (neat) 3564, 3440, 1620, 1462, 1250, 1218, 1105–1167, 774 cm^{-1}. Anal. Calcd for $C_{31}H_{52}O_6Si$: C, 68.64; H, 7.51. Found: C, 68.53; H, 7.23.

Cyclization of 30. A solution of dienol silyl ether (*Z*)-**31** (19.9 mg, 0.0363 mmol) was treated with $SnCl_4$ (0.094 mL, 0.0906 mmol)

in dichloromethane (1.21 mL) under stirring at −78 °C for 1.5 h and then at −45 °C for 5.5 h. Usual aqueous workup and chromatographic purification (50% EtOAc/hexane) afforded cyclized product **16** (10 mg, 77%) as white crystals.

Similar procedures with (*E*)-**30** also afforded **16** in 68% yield.

16: IR (CCl_4 solution) 3540, 3020–2800, 1669, 1470, 1443, 1236, 1130, 1105, 1060 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.94 (s, 3 H), 1.20 (s, 3 H), 1.72 (s, 3 H), 2.46 (d, J = 5.6 Hz, 1 H), 2.70 (dd, J = 19 Hz, 5.6 Hz, 1 H), 2.86 (d, J = 19 Hz, 1 H), 3.38 (s, 3 H), 3.43 (s, 3 H), 3.85 (s, 3 H), 4.38 (d, J = 8.6 Hz, 1 H), 4.76 (d, J = 8.6 Hz, 1 H), 5.14 (d, J = 10 Hz, 1 H), 5.57 (d, J = 10 Hz, 1 H), 6.84 (d, J = 9.0 Hz, 1 H), 7.17 (dd, J = 9.0 Hz, 9.0 Hz, 1 H), 7.34 (d, J = 9.0 Hz, 1 H). Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 70.18; H, 7.57.

17: ^1H NMR (270 MHz, $CDCl_3$) δ 0.96 (s, 3 H), 1.16 (s, 3 H), 1.53 (s, 3 H), 2.40 (d, J = 5.4 Hz, 1 H), 2.71 (dd, J = 19 Hz, 5.4 Hz, 1 H), 2.90 (d, J = 19 Hz, 1 H), 3.27 (s, 3 H), 3.47 (s, 3 H), 3.83 (s, 3 H), 4.57 (d, J = 6.0 Hz, 1 H), 4.74 (d, J = 6.0 Hz, 1 H), 5.02 (d, J = 10 Hz, 1 H), 5.69 (d, J = 10 Hz, 1 H), 6.86 (d, J = 9.0 Hz, 1 H), 7.17 (dd, J = 9.0 Hz, 9.0 Hz, 1 H), 7.33 (d, J = 9.0 Hz, 1 H).

Acknowledgment. This work was partially supported by Grants from the Ministry of Education, Science, and Culture of the Japanese Government.

Supplementary Material Available: Structure determination of compounds **16**, **17**, and **21** by NOE studies (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.