Enantioselective Total Synthesis of (+)-Taxusin

Ryoma Hara, Takashi Furukawa, Hajime Kashima, Hiroyuki Kusama, Yoshiaki Horiguchi, and Isao Kuwajima*,†

Contribution from the Department of Chemistry, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152-8551, Japan

Received December 7, 1998

Abstract: For the total synthesis of (+)-taxusin, the AC-ring fragment **8** was prepared from an optically active 2-bromo-3-siloxycyclohexenecarbacetal **5** via 4 steps and was converted to the dienol silyl ether **13**. The thus-obtained **13** underwent B-ring cyclization in the presence of Me_2AlOTf to produce the ABC *endo*-tricarbocycle **14** having C9α, C10*β*-substituents, which was converted to the cyclopropyl ketone **21a**. Introduction of C19 methyl via reductive cleavage of the cyclopropane ring under Birch conditions and successive in situ treatment of the resulting enol with methanol gave the C3α-protonated ketone **24**. Next, **24** was converted to the allylsilane **29**, which was then oxidized with *m*-CPBA to produce the fully functionalized taxusin carbon skeleton. Finally, removal of the silyl protecting groups followed by acetylation completed the total synthesis of (+)-taxusin.

The taxane diterpenes (Figure 1) isolated from yew trees have a common tricarbocyclic structure containing sp^2 carbon on their bridgehead C11-site. Such a unique structural feature as well as many oxygenated asymmetric centers has made their syntheses extremely difficult, and these natural products still remain as very challenging synthetic targets.[1] In addition, a well-documented taxol, one of the taxane family, exhibits promising activity against a number of human cancers, which has prompted its synthetic studies to lead to six successful total syntheses.[2] Several other natural taxanes such as taxinine and taxuspines were recently revealed to exhibit multidrug resistance reversing activity.[3,4]

With a similar background, taxusin[5] has also attracted much attention from the synthetic viewpoint, and the first total synthesis of its antipode was achieved by Holton and his colleagues[6] by deducing the carbon skeletal rearrangement of a (−)-patchino derivative. After our achievement of the second synthesis as a racemic form,[7] Paquette et al. have recently described the third total synthesis as a natural (+)-form starting from D-camphor.[8]

We also attempted enantioselective total synthesis of (+)-taxusin starting from an appropriate substrate containing a chiral center corresponding to the C1 site.[9] This paper fully describes in detail of our synthetic studies of (+)-taxusin.

Synthetic Plan

For total syntheses of taxanes, the most critical problem is how to construct the unique ABC tricarbocyclic structure. Our basic plan for taxusin synthesis was to start from a C-ring fragment, then to connect with an A-ring fragment, and finally to construct an ABC tricarbocycle **I** (Scheme 1) via the previously described methodology[10] (step b of Scheme 1). This transformation could be effected not only with C-aromatic substrates but also with precursors containing latent cyclohexenone moieties as C-ring fragments **II**. Appropriate functional group elaboration of **I** would complete the total synthesis.

The tricarbocycle containing cyclohexenone as a C-ring appeared to furnish several synthetic advantages: (1) stereocontrol at the C1 site of **II** would allow us an asymmetric

* To whom correspondence should be addressed.

† Present address: The Kitasato Institute, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8642, Japan.

(1) (a) *Taxol: Science and Applications*; Suffness, M., Ed.; CRC, Boca Raton, FL, 1995. (b) Georg, G. I.; Chen, T. T.; Ojima, I.; Vyas, D. M., Eds. *Taxane Anticancer Agents: Basic Science and Current Status*; ACS Symposium Series 583; American Chemical Society: Washington, DC, 1995. (c) Kingston, D. G. I.; Molinero, A. A.; Rimoldo, J. M. *Prog. Chem. Org. Nat. Prod.* **1993**, *61*, 1. (d) Rowinsky, E. K.; Onetto, N.; Canetta, R. M.; Arbuck, S. G. *Semin. Oncol*. **1992**, *19*, 646.

(2) (a) Holton, R. A.; Somoza, C.; Kim, H.-B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. Holton, R. A.; Kim, H.-B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599. (b) Nicolaou, K. C.; Nantermet, P. G.; Ueno, H.; Guy, R. K.; Couladouros, E. A.; Sorensen, E. J. *J. Am. Chem. Soc.* **1995**, *117*, 624. Nicolaou, K. C.; Liu, J.-J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C.-K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634. Nicolaou, K. C.; Yang, Z.; Liu, J.-J.; Nantermet, P. G.; Claiborne, C. F.; Renaud, J.; Guy, R. K.; Shibayama, K. *J. Am. Chem. Soc.* **1995**, *117*, 645. Nicolaou, K. C.; Ueno, H.; Liu, J.-J.; Nantermet, P. G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *J. Am. Chem. Soc.* **1995**, *117*, 653. (c) Danishefsky, S. J.; Masters, J. J.; Young, W. B.; Link, J. T.; Snyder, L. B.; Magee, T. V.; Jung, D. K.; Isaacs, R. C. A.; Bornmann, W. G.; Alaimo, C. A.; Coburn, C. A.; Di Grandi, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 2843. (d) Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Gränicher, C.; Houze, J. B.; Jänichen, J.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Mühlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.; Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755. Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757. (e) Mukaiyama, T.; Shiina, I.; Iwadare, H.; Sakoh, H.; Tani, Y.; Hasegawa, M.; Saitoh, K. *Proc. Japan. Acad. Ser. B* **1997**, *73*, 95. Shiina, I.; Iwadare, H.; Sakoh, H.; Hasegawa, M.; Tani, Y.; Mukaiyama, T. *Chem. Lett.* **1998**, 1. Shiina, I.; Saitoh, K.; Fréchard-Ortuno, I.; Mukaiyama, T. *Chem. Lett.* **1998**, 3. Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem. Eur. J.* **1999**, *5*, 121. (f) Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980.

(3) Kobayashi, J.; Ogiwara, A.; Hosoyama, H.; Shigemori, H.; Yoshida, N.; Sasaki, T.; Li, Y.; Iwasaki, S.; Naito, M.; Tsuruo, T. *Tetrahedron* **1994**, *50*, 7401.

(4) Kobayashi, J.; Hosoyama, H.; Wang, X.-x.; Shigemori, H.; Koiso, Y.; Iwasaki, S.; Sasaki, T.; Naito, M.; Tsuruo, T. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 393. Kobayashi, J.; Hosoyama, H.; Wang, X.-x.; Shigemori, H.; Sudo, Y.; Tsuruo, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1555.

10.1021/ja984250f CCC: $18.00
Published on Web 03/20/1999

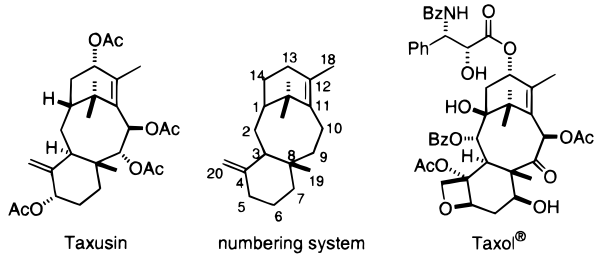
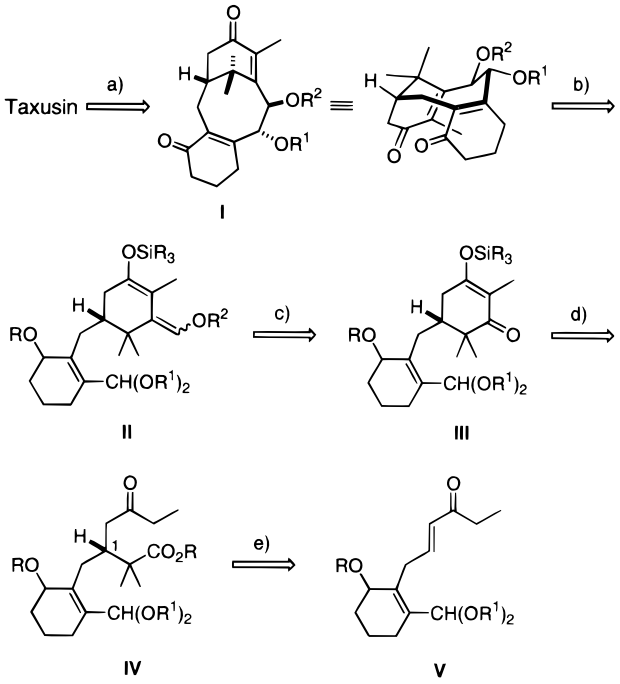


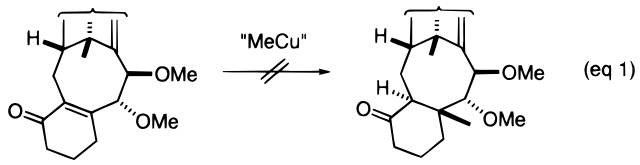
Figure 1.

Scheme 1. Retrosynthetic Analysis of Taxusin

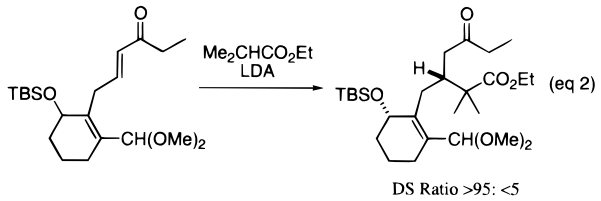


synthesis, and (2) introduction of the C19 methyl group would occur from the sterically less-demanding convex β-face of **I** to afford the desired diastereomer. For the preparation of the AC-ring fragment **II**, we planned to use **V** as the starting material, which may lead to the formation of **II** via conjugate addition of an isobutyric ester (step e), Dieckmann-like cyclization (step d), and alkoxymethylenation of the carbonyl group (step c).

Preliminary experiments according to the design mentioned above led us to important findings shown in eqs 1 and 2. First, introduction of the C19 methyl onto the C8 site was examined by using various methyl copper as well as manganese species, but all attempts failed: some gave back the starting material, while the others produced a 1,2-addition product on warming up the reaction temperature.



Second, it was also disclosed that conjugate addition of the lithium enolate derived from the isobutyric ester to the enone took place with exceedingly high diastereoselectivity to form the keto ester.

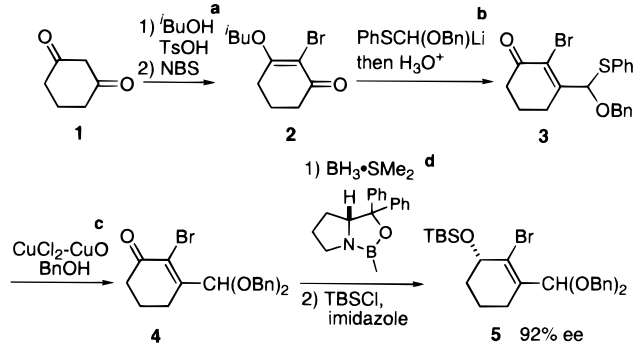


With a clue to construct an asymmetric center at the C1 site, we examined an enantioselective total synthesis of (+)-taxusin. Unfeasibility to introduce the C19 methyl via conjugate addition led us to explore another strategy, which involves an initial cyclopropanation onto the $\Delta^{3,8}$-double bond and a subsequent cleavage of the cyclopropane ring under reductive conditions.

Results and Discussion

Preparation of the Cyclization Precursor. Considering the requisite functional group manipulations at later stages, we chose a dibenzylacetal **5** as a C-ring fragment, which was prepared from 1,3-cyclohexanedione **1** as shown in Scheme 2. Conversion of **1** to an *i*-butyl enol ether and its bromination with NBS gave a bromide **2**. 1,2-Addition of (benzyloxy)phenylthiomethyllithium[11] to **2** followed by acidic workup afforded an enone **3**, which underwent acetal exchange[12] to give a dibenzyl acetal **4**. For introduction of an asymmetric center, **4** was subjected to asymmetric reduction by using Corey's procedure,[13] and a

Scheme 2. Preparation of the Optically Active C-Ring Fragment[a]



[a] (a) (1) benzene, reflux, 7 h, 97%; (2) $ClCH_2CH_2Cl$, 0 °C, 3 h, 93%. (b) THF-TMEDA, −78 °C, 1 h acidic workup, 93%. (c) CH_3CN, 40 °C, 4 h, 76%. (d) (1) THF-toluene, −23 to 0 °C, 2 h; (2) DMF, rt, overnight, 88% from **4**.

(5) (a) Miyazaki, M.; Shimizu, K.; Mishima, H.; Kurabayashi, M. *Chem. Pharm. Bull.* **1968**, *16*, 546. (b) Liu, C. L.; Lin, Y. C.; Lin, Y. M.; Chen, F. C. *T'ai-wan K'o Hsueh* **1984**, *38*, 119. (c) Erdtman, H.; Tsuno, K. *Phytochemistry* **1969**, *8*, 931. (d) Lee, C. L.; Hirose, Y. Nakatsuka, T. *Mokuzai Gakkaishi* **1975**, *21*, 249. (e) Chan, W. R.; Halsall, T. G.; Hornby, G. M.; Oxford, A. W.; Sabel, W.; Bjamer, K.; Ferguson, G.; Robertson, J. M. *J. Chem. Soc., Chem. Commun.* **1966**, 923.

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

(7) Hara, R.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **1996**, *118*, 9186.

(8) Paquette, L. A.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5203. Paquette, L. A.; Wang, H.-L.; Su, Z.; Zhao, M. *J. Am. Chem. Soc.* **1998**, *120*, 5213.

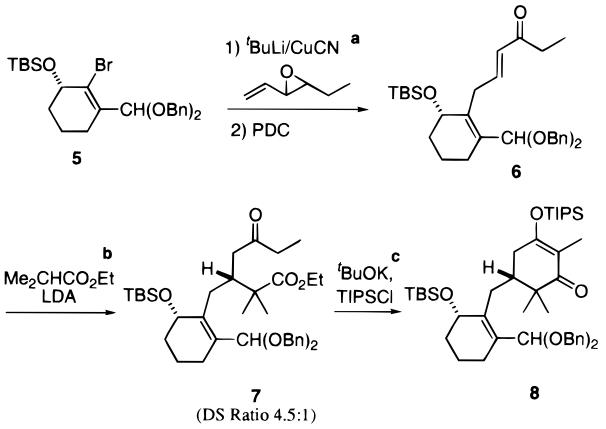
(9) The taxane numbering system, as illustrated in Figure 1, is used throughout.

(10) (a) Horiguchi, Y.; Furukawa, T.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 8277. (b) Furukawa, T.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron* **1992**, *48*, 6975. (c) Seto, M.; Morihira, K.; Katagiri, S.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Chem. Lett.* **1993**, 133. (d) Morihira, K.; Seto, M.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Tetrahedron Lett.* **1993**, *34*, 345. (f) Nakamura, T.; Waizumi, N.; Tsuruta, K.; Horiguchi, Y.; Kuwajima, I. *Synlett* **1994**, 584. (g) Seto, M.; Morihira, K.; Horiguchi, Y.; Kuwajima, I. *J. Org. Chem.* **1994**, *59*, 3165.

(11) Otera, J. *Synthesis* **1988**, 95.

(12) Mukaiyama, T.; Narasaka, K.; Furusato, M. *J. Am. Chem. Soc.* **1972**, *94*, 8641.

Scheme 3. Preparation of the AC-Ring fragment[a]



[a] (a) (1) Et_2O, −78 °C, 1.5 h; −45 °C, 1 h; −23 °C, 2 h; (2) CH_2Cl_2, MS4A, rt, 1.5 h, 66% from **5**. (b) THF, −78 to 5 °C, 7 h; quant. (c) THF, 0 °C, 1 h; then 0 °C, 4 h, 60%.

subsequent protection of the hydroxy group gave **5** (Scheme 2). Optical purity of the product was determined by ^{1}H NMR analyses of the corresponding MTPA ester[14,15] as 92% ee.

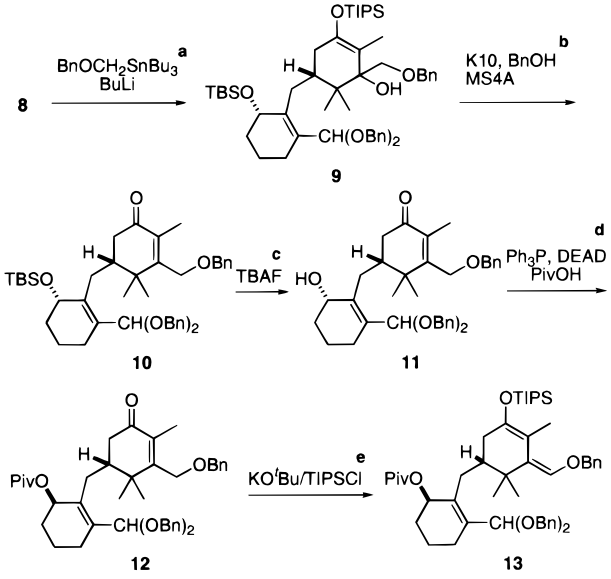
A successive treatment of the resulting bromide **5** with ^{t}BuLi and CuCN produced the corresponding cyanocuprate, which reacted with 3,4-epoxy-1-hexene[16] giving an S_N2' coupling product. PDC oxidation[17] of the crude product afforded an enone **6** (Scheme 3).

Conjugate addition of isobutyric ester enolate to **6** took place smoothly to give an adduct in high yield as an inseparable mixture of diastereomers. Although its diastereoselectivity was much lower (4.5:1) than that expected from the previous result (eq 2), the desired **7** was obtained as a major product.[18] The Dieckmann-type cyclization of **7** upon treatment with ^{t}BuOK followed by in situ silylation (TIPSCl) afforded a diastereomerically pure β-siloxyenone **8** in 60% yield after separation with column chromatography (Scheme 3).

After several attempts for benzyloxymethylenation of the enone **8**, the following operation was found to give the most satisfactory results (Scheme 4). Treatment of **8** with benzyloxymethyllithium generated from the corresponding stannyl compound[19] gave the 1,2-addition product **9**, and elimination of TIPSOH was carried out by exposure to Montmorillonite K10 and MS4A in BnOH/CH_2Cl_2 mixture to afford **10**. Removal of the TBS group with TBAF furnished **11** in 56% yield (three steps).

Separate experiments revealed that the C4α-substituent prevented B-ring cyclization as well as methylenation on the

Scheme 4. Preparation of B Ring Cyclization Precursor[a]



[a] (a) THF, −78 °C, 2.5 h, 86%. (b) CH_2Cl_2, −45 °C, 1 h, 79%; (c) THF, rt, overnight, 83%. (d) THF, rt, 1 week, 67%. (e) THF, 0 °C, 1 h; −78 °C, 1 h, quant.

$\Delta^{3,8}$-double bond at later stages, and hence the configuration at C4 site was inverted to C4β-OH. In the case of using benzoic acid as a nucleophile in the Mitsunobu reaction,[20] the resulting benzoate was partially removed when the C13 carbonyl group was reduced at a later stage. Hence, a more stable pivalate was prepared as **12**. Treatment with ^{t}BuOK generated the thermodynamically favored dienolate selectively, and a subsequent silylation with TIPSCl afforded the cyclization precursor **13** as a single isomer in 67% yield via two steps. The geometry of the double bond was determined as *Z* based on an NOE between the olefinic proton and the *gem*-dimethyl group.

Construction of the ABC Tricarbocyclic Skeleton. The crucial eight-membered B-ring cyclization was investigated using various Lewis acids (Table 1). In the reactions with $TiCl_4$ or $TiCl_2(O^iPr)_2$, the yield of the desired **14** (*endo*-9α, 10β) was quite low, and considerable amounts of aldehydes were detected in the crude NMR spectra (entries 1 and 2). When the reaction was carried out using TMSOTf, the yield of **14** was still low and, in this case, spirocyclization between the C3 and C12 atoms proceeded to give **15** as a major product. On the contrary, the reaction with Me_2AlOTf (3 equiv, CH_2Cl_2, −45 °C) was found to proceed quite nicely, giving **14** in good yield along with a small amount of its stereoisomer **16** (*exo*-9β, 10β).[21] The stereochemistries of **14** and **16**, namely, conformation of the B-ring and configuration of the C9 and C10 sites, were determined by ^{1}H NMR analyses. Characteristic NOEs of **14** are shown below.

Among the cyclized products (**14**, **15**, and **16**), the desired **14** was assumed to be the thermodynamically most favored isomer. Hence, the byproducts **15** and **16** were expected to isomerize to **14** via ring opening followed by recyclization under the influence of Lewis acid. In fact, the reactions with $TiCl_3(O^iPr)$ gave the expected **14** in good yield in both cases.[22]

(13) (a) Corey, E. J.; Bakshi, R. K.; Shibasaki, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751. (c) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763. (d) For review, see Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(14) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(15) Absolute stereochemistry of **5** was assumed to be *S* based on Corey's results using similar substrates[13] and confirmed by the completion of the total synthesis of (+)-taxusin.

(16) Sauleau, J.; Bouget, H.; Huet, J. *C. R. Acad. Sci., Ser. C* **1971**, *273*, 829.

(17) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

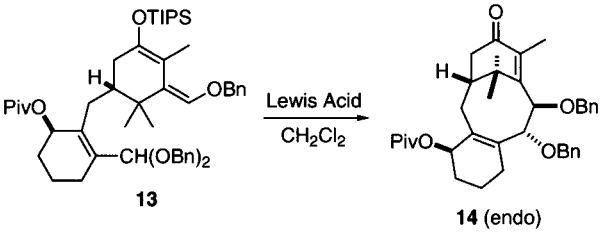
(18) The relative stereochemistry was inferred from the analogy of a closely related compound, the stereochemistry of which was confirmed by the X-ray analysis of its derivative, see: Takenaka, Y.; Sakai, Y.; Ohashi, Y.; Furukawa, T.; Horiguchi, Y.; Kuwajima, I. *Anal. Sci.* **1993**, *9*, 883.

(19) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.

(20) Mitsunobu, O. *Synthesis* **1981**, 1.

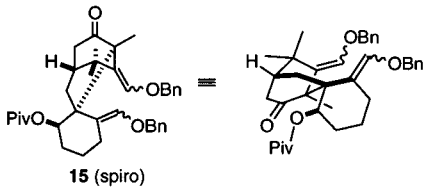
(21) Although the cyclization precursor **13** consisted of *Z* configuration at the benzyl enol ether moiety exclusively, *E*/*Z* isomerization took place under the cyclization reaction conditions and the thermodynamically most stable tricarbocycle **14** with the C10β substituent was obtained as a major product. For the proposed mechanism of the *E*/*Z* isomerization; see, ref 10d.

Table 1. Construction of ABC Tricarbocyclic Structure

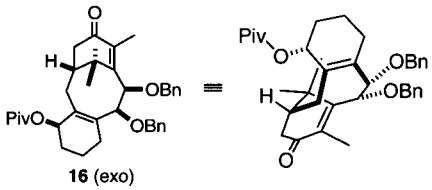


13 **14** (endo)

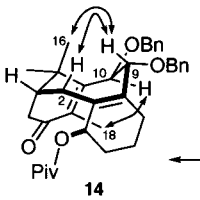
entry	conditions	14	15	16
1	$TiCl_4$, -78 °C, 1 h	17%		
2	$TiCl_2(O^iPr)_2$, -78 °C, 1 h	38%		
3	TMSOTf, -78 °C, 1 h	22%	47%	
4	Me_2AlOTf, -45 °C, 2 h	62%		20%



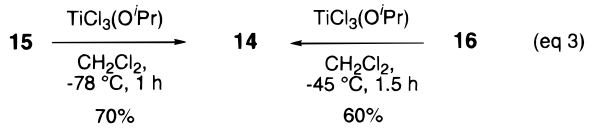
15 (spiro)



16 (exo)



14 ⟷ : NOEs



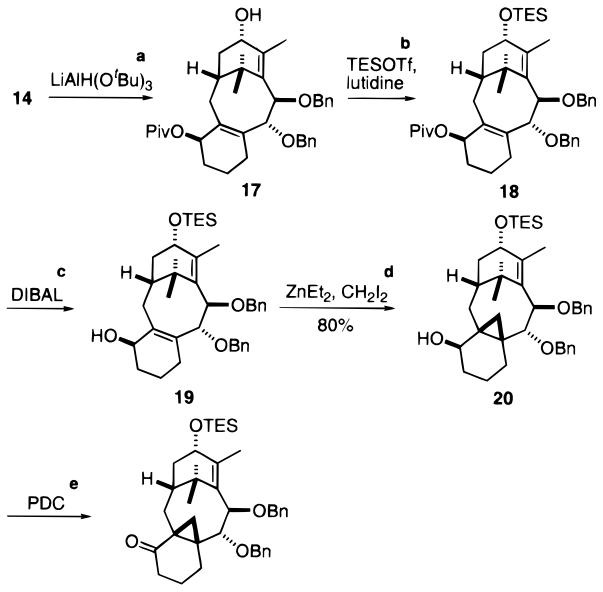
Introduction of C19 Methyl and Completion of the Total Synthesis. With the desired tricyclic compound **14** in hand, functional group manipulations toward completion of the total synthesis were carried out. Reduction of the C13 keto group of **14** [Li(*t*-BuO)$_3$AlH] followed by silylation of the resultant hydroxyl group (TESCl) and reductive removal of the pivalate group (DIBAL) gave an allyl alcohol **19** in 87% yield (three steps from **14**, Scheme 5). Exclusive formation of the C13α alcohol could be attributed to the concave nature of the α face.[2b,10a,c] Now the stage was set for investigation of the C19 methyl group installation according to Dauben's protocol[23] by utilizing the C-ring allyl alcohol moiety. Application of cyclopropanation (Et_2Zn and CH_2I_2)[24] to **19** and a subsequent oxidation afforded a cyclopropyl ketone **21a** in good yield.

(22) Judging from these experimental facts, $TiCl_3(O^iPr)$ was supposed to be a suitable Lewis acid for the cyclization of **13**. However, the reaction of **13** with $TiCl_3(O^iPr)$ gave considerable amounts of aldehydes (>50%) along with a small amount of **14** (ca. 30%).

(23) For angular methyl group introduction via reductive cleavage of cyclopropyl ketones, see: Dauben, W. G.; Deviny; E. J. *J. Org. Chem.* **1966**, *31*, 3794.

(24) Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* **1969**, *25*, 2647.

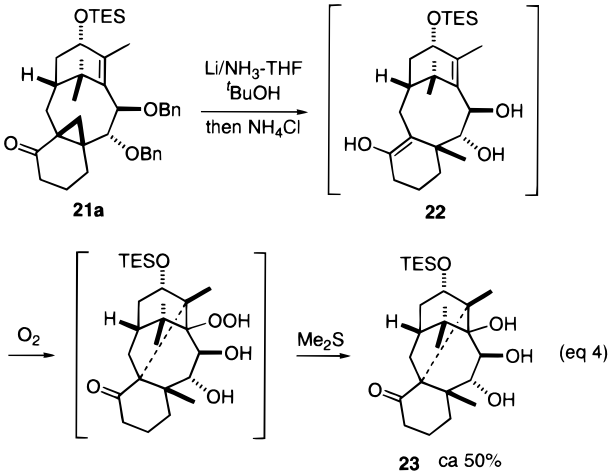
Scheme 5. Preparation of Cyclopropylketone[a]



[a] (a) THF, rt, overnight. (b) CH_2Cl_2, −23 °C, 1 h. (c) CH_2Cl_2, −78 °C, 1 h, 87% from 14. (d) Et_2O, rt, 6 h, quant. (e) CH_2Cl_2, MS4A, rt, 1.5 h, 85%.

Stereochemistry of the cyclopropanation was determined by NOEs between one of the C19 protons, C9β, and C2β protons.

Exposure of **21a** to the usual Birch conditions (excess Li, *t*-BuOH, liq. NH_3, THF, −78 °C) followed by quenching with saturated aqueous NH_4Cl induced cleavage of the cyclopropane ring smoothly (eq 4). However, the desired ketone was not detected, but a very unstable compound was obtained as a major product (not isolable). ^{13}C NMR analysis of this crude mixture revealed the existence of a carbonyl group and four oxygen-substituted sp^3-carbons and absence of the olefinic carbons. Although the structure of the major product could not be fully identified because of its lability, treatment of the crude mixture with dimethyl sulfide smoothly gave the stable compound, whose structure was identified as **23**. Presumably, transannular cyclization of the intermediate enol **22** occurred in the presence of air during workup to give the hydroperoxide, and its reduction with Me_2S afforded **23**.



23 ca 50%

The above result indicated that protonation of an enol **22**, which was generated by reductive cleavage of the cyclopropane ring, from the α-face of the C-ring was kinetically disfavored due to severe steric encumbrance. In addition, a kinetically

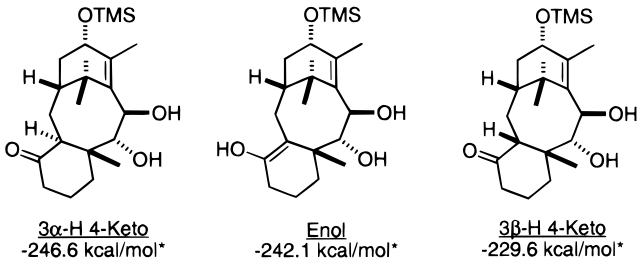


Figure 2. Comparison of relative thermodynamic stability.

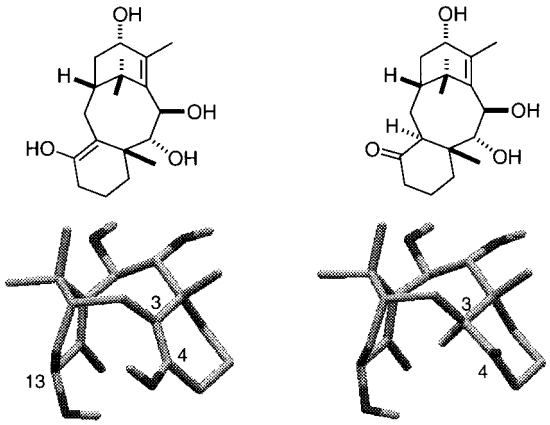
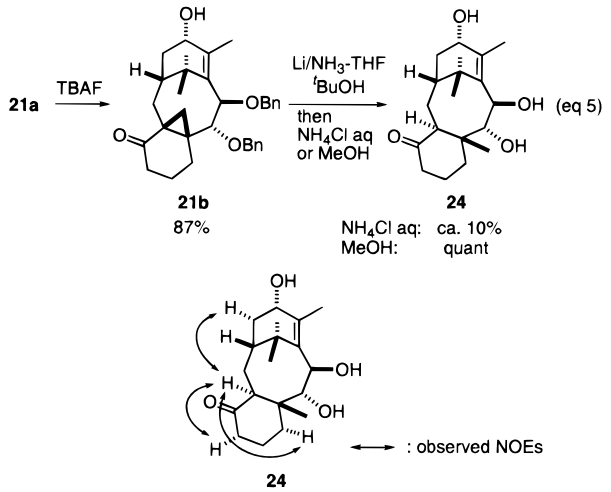


Figure 3. Structures of $\Delta^{3,4}$-enol and 3α-H keto derivatives.

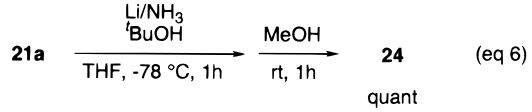
favored C3*β*-protonated ketone appeared to be thermodynamically less stable due to steric repulsion between the A- and C-rings (Figure 2).[25] As a result, the enol might have decomposed.

Molecular modeling studies[25] on the enol suggested that the C13−OH appeared to be positioned between the A- and C-rings (Figure 3). On the basis of this calculation, protonation on the $\Delta^{3,4}$-enol from the α-face can be directed by the C13−OH. Thus, we decided to use such characteristic feature for an α-face selective protonation.

The cyclopropyl ketone **21b** possessing a free C13−OH was prepared by desilylation of **21a** with TBAF. Birch reduction of **21b** followed by quenching with saturated aqueous NH_4Cl gave the desired ketone **24** as expected (ca. 10%). Furthermore, quenching with methanol greatly improved the yield of **24** (eq 5). The stereochemistry of the C3 site was determined by NOE experiments as well as the coupling constant of the C3 proton (doublet, $J = 6.3$ Hz).

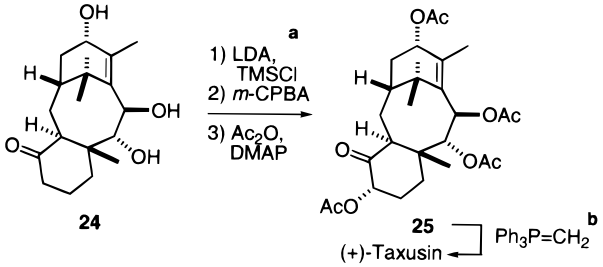


On the basis of the results mentioned above, we finally succeeded in gaining access to the desired C3α protonated ketone **24** quite efficiently by Birch reduction of **21a** followed by quenching with MeOH (excess Li, *t*-BuOH, liq. NH_3, THF, −78 °C, then MeOH, warming up to room temperature) (eq 6). Judging from the experimental facts, methanol or its alkoxide certainly generates the C13−OH, which facilitates the protonation from the α-face of the C-ring.



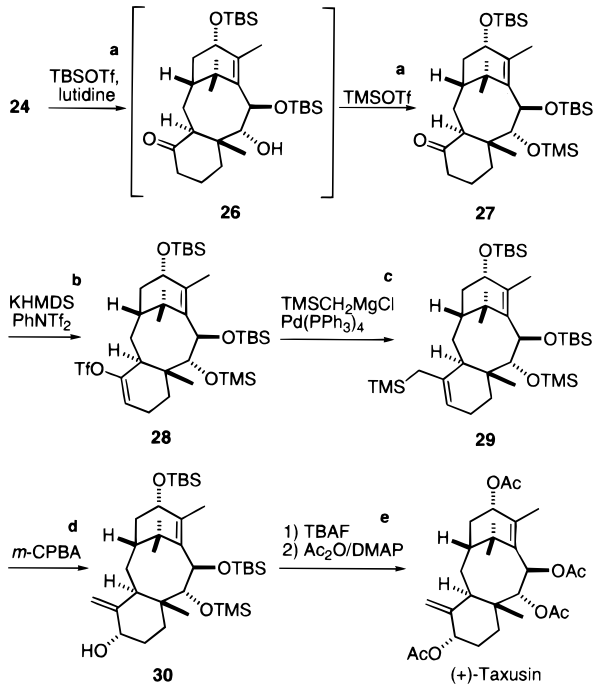
The accomplishment of installing the C19 methyl group has allowed us to move on to sequential operations for completion of the total synthesis of taxusin paralleling the protocol previously reported by Holton.[6] Treatment of **24** with excess amounts of LDA and TMSCl resulted in regioselective enol

Scheme 6. Conversion to (+)-Taxusin. 1[a]



[a] (a) (1) THF, −78 °C, 10 min, then 0 °C, 30 min; (2) CH_2Cl_2, $KHCO_3$, 0 °C, 10 min; (3) CH_2Cl_2, rt 1.5 h, 80% from **24**. (b) benzene-hexane, 0 °C, 1.5 h, 17% (53% based on 32% conversion).

Scheme 7. Conversion to (+)-Taxusin. 2[a]



[a] (a) CH_2Cl_2, 0 °C, 1 h; −78 °C, 1 h, 95%. (b) −45 °C, 1 h. (c) THF, rt, 1 h. 70% from **27**. (d) MeOH, rt, 30 min, 95%. (e) (1) THF-HMPA, rt, 2 h, 93%; (2) CH_2Cl_2-Et_3N, rt, 98%.

(25) SPARTAN ver. 4.1 (PM3) and MacroModel ver. 6.0 (MM2) were used for calculation.

silyl ether formation at C5 accompanied with silylation of the hydroxy groups. Oxidation of the resulting tetrasilyl ether with *m*-CPBA followed by acidic workup produced a tetrol, acetylation of which gave a tetraacetate **25**. Finally, the Wittig methylenation of the C4 carbonyl was attempted; however, it could not be performed so efficiently in our hands (Scheme 6).[26] Hence, we attempted to utilize other methodology via an allylsilane **29**[2f] for introduction of the $\Delta^{4,20}$-methylene group as well as the C5α-OH functionality.

For such purpose, protection of three hydroxy groups of **24** was examined at first. We initially chose an acetonide group for C9, C10−OH protection; however, its removal at the final stage of the synthesis caused partial decomposition of the product under acidic reaction conditions.[27] On the other hand, tri-TES ether of **24** could be prepared quite easily, but in the formation of $\Delta^{4,5}$-enolate at the next step, migration of the TES on the C13−OH to the C4-oxygen rapidly occurred to give a $\Delta^{4,5}$-enol TES ether. Therefore, a much more stable TBS group was chosen as the protecting group. Silylation of the hydroxy groups of **24** (TBSOTf/lutidine) resulted in exclusive formation of bis-TBS ether **26** and successive in situ protection of the remaining C9−OH with the TMS group gave a trisilyl ether **27** in high yield (Scheme 7). The carbonyl group of **27** was converted to an enol triflate **28** by treating with KHMDS and $PhNTf_2$. The cross-coupling reaction of the crude enol triflate with $TMSCH_2MgCl$ in the presence of $Pd(Ph_3P)_4$ efficiently proceeded to yield an allylsilane **29**, oxidation of which with *m*-CPBA in MeOH led to an exclusive formation of a C5α-allylic alcohol **30**. Finally, removal of the silyl groups followed by acetylation of the resulting tetrol with Ac_2O/DMAP-Et_3N[8] afforded (+)-taxusin, identical to natural taxusin in respect of ^{1}H NMR, ^{13}C NMR, IR, and TLC mobility.

In conclusion, we have achieved an enantioselective total synthesis of (+)-taxusin (28 steps from commercially available 1,3-cyclohexanedione). The synthetic route is highlighted by (1) remarkably effective eight-membered B-ring cyclization leading to the C ring allyl ester-type tricyclic taxane skeleton with the desired B-ring conformation and C9, C10 stereochemistry and (2) subsequent installation of the C19 methyl group via the Birch reduction of the cyclopropyl ketone followed by enol/keto isomerization owing to the stereoselective protonation directed by the C13−OH.

Experimental Section

General. All reactions were carried out under a dry nitrogen atmosphere with dry, distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and ethyl ether (Et_2O) were distilled from sodium-benzophenone before use. All other solvents were distilled according to the usual procedures and stored over molecular sieves 4A (MS4A) before use. All reagents were purchased at highest commercial quality and used without further purification unless otherwise noted. Yields of the crude products were determined by ^{1}H NMR analysis using $CHBr_3$ or $(CHCl_2)_2$ as an internal standard.

Preparation of 2. To a solution of 1,3-cyclohexanedione (100 g, 892 mmol) and isobutanol (250 mL, 2.70 mol) in benzene (1.10 L) was added *p*-toluenesulfonic acid (0.770 g, 4.47 mmol). The mixture was heated to reflux under azeotropic removal of water. After 7 h, the mixture was cooled to room temperature. To this was added triethylamine (3.00 mL, 22.4 mmol), and the mixture was concentrated under reduced pressure. Distillation (106 °C/2.0 mmHg) of the resulting residue gave 3-isobutoxy-2-cyclohexen-1-one (145 g, 97%).

To a solution of 3-isobutoxy-2-cyclohexen-1-one (32.9 g, 195 mmol) in 1,2-dichloroethane (100 mL) was added NBS (37.8 g, 212 mmol) at −45 °C over 20 min. The reaction mixture was warmed to 0 °C and stirred for 3 h. Then the mixture was diluted with hexane (100 mL) and was filtered. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine. The solvent was removed under reduced pressure, and the resulting white powder was washed with hexane to give 3-isobutoxy-2-bromo-2-cyclohexen-1-one **2** (44.7 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (d, 6H, J = 6.7 Hz), 2.00−2.18 (m, 3H), 2.56 (t, 2H, J = 6.7 Hz), 2.69 (t, 2H, J = 6.7 Hz), 3.90 (d, 2H, J = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.9, 20.6, 27.4, 28.7, 36.8, 75.4, 103.1, 172.8, 191.2. IR (CH_2Cl_2): 2970, 1670, 1590, 1375, 1200 cm^{-1}. Anal. calcd for $C_{10}H_{15}BrO_2$: C, 48.60; H, 6.12. Found: C, 48.75; H, 6.24.

Preparation of 3. To a solution of TMEDA (1.50 mL, 10.0 mmol) in THF (10 mL) were added *n*-BuLi (6.20 mL, 1.61 M in hexane, 10.0 mmol) and benzyloxy(phenylthio)methane (2.00 mL, 10.0 mmol) at −78 °C. The mixture was stirred for 2 h at that temperature. To this was added a THF solution (5 mL) of **2** (1.24 g, 5.00 mmol), and the mixture was stirred for 1 h. The reaction was quenched by saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with 2 M HCl and then with brine. After being dried over $MgSO_4$, the mixture was filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 3% AcOEt/hexane) to give 3-benzyloxy(phenylthio)methyl-2-bromo-2-cyclohexen-1-one **3** (1.88 g, 93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.70−1.80 (m, 1H), 1.80−1.89 (m, 1H), 2.16 (dt, 1H J = 18.6, 5.5 Hz), 2.46−2.60 (m, 3H), 4.58 (d, 1H, J = 11.8 Hz), 4.96 (d, 1H, J = 11.8 Hz), 5.92 (s, 1H), 7.25−7.38 (m, 8H), 7.52−7.56 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 28.1, 38.1, 71.0, 90.7, 121.2, 127.9, 128.1, 128.5, 128.9, 129.1, 131.4, 135.2, 136.6, 159.0, 191.2. IR ($CDCl_3$): 3070, 3040, 2960, 1690, 1595, 1172, 1133, 1070, 985 cm^{-1}. Anal. calcd for $C_{20}H_{19}BrO_2S$: C, 59.56; H, 4.75; S, 7.95. Found: C, 59.81; H, 4.68; S, 8.10.

Preparation of 4. To a solution of **3** (2.00 g, 5.00 mmol) and BnOH (1.00 mL, 10.0 mmol) in CH_3CN (10 mL) were added CuO (1.60 g, 20.0 mmol) and $CuCl_2$ (1.30 g, 10.0 mmol), and the mixture was stirred for 4 h at 40 °C. The mixture was diluted with ether and inorganic materials were filtered off through a short pad of Celite. Saturated aqueous Rochelle salt was added to the filtrate, and the mixture was vigorously stirred. The layers were separated, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered and concentrated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 5% AcOEt/hexane) to give 3-dibenzyloxymethyl-2-bromo-2-cyclohexen-1-one **4** (1.52 g, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.91−1.97 (m, 2H), 2.55−2.60 (m, 2H), 2.63 (t, 2H, J = 6.0 Hz), 4.57 (d, 2H, J = 11.9 Hz), 4.72 (d, 2H, J = 11.9 Hz), 5.72 (s, 1H), 7.28−7.38 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.7, 26.6, 38.4, 69.9, 102.5, 123.0, 127.97, 128.04, 128.5, 137.1, 157.2, 191.5. IR ($CDCl_3$): 2960, 1690, 1450, 1340, 1170, 1130, 1045, 1030 cm^{-1}. Anal. calcd for $C_{21}H_{21}BrO_3$: C, 62.85; H, 5.28. Found: C, 62.78; H, 5.42.

Preparation of 5. To a solution of **4** (21.0 g, 52.2 mmol) and oxazaborolidine[13] (5.30 mL, 1.0 M in toluene, 5.30 mmol) in THF (250 mL) was added borane−dimethyl sulfide complex (3.50 mL, 36.9 mmol) at −23 °C. After 0.5 h, the reaction mixture was warmed to 0 °C and stirred for 1.5 h. Methanol (100 mL) was cautiously added to this mixture. The mixture was warmed to room temperature and stirred overnight. The resulting solution was treated according to Jones' procedure[13c] to give a crude allyl alcohol, which was directly used in the next step.

$[\alpha]_D^{28}$: −34° (c = 0.89, CH_2Cl_2, 92% ee). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.55−1.75 (m, 2H), 1.80−1.93 (m, 2H), 2.18 (br s, 1H, O*H*), 2.23 (ddd, 1H, J = 6.5, 8.5, 17.9 Hz), 2.41 (dt, 1H, J = 5.1, 17.8 Hz), 4.20 (br s, 1H), 4.53 (d, 1H, J = 12.0 Hz), 4.53 (d, 1H, J = 12.0 Hz), 4.67 (d, 1H, J = 12.0 Hz), 4.69 (d, 1H, J = 12.0 Hz), 5.47 (s, 1H), 7.27−7.42 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 25.9,

(26) Though Holton reported 70% yield for the olefination, we obtained a rather lower yield (53% yield on 32% conversion) after several examinations in small scale. As Holton stated, **26** is susceptible to deacetylation during the olefination reaction, see Holton, R. B. In *Strategies and Tactics in Organic Synthesis*; Lindberg, T., Ed.; Academic Press: San Diego, 1991; Vol. 3, pp 165−197.

(27) A quite similar result has been already reported by Paquette et al.; see ref 8.

32.1, 69.2, 69.3, 71.2, 102.6, 125.9, 127.7, 127.89, 127.94, 128.33, 128.34, 137.7, 137.8, 137.9. IR (neat): 3410, 2940, 2860, 1500, 1455, 1340, 1210, 1120, 1040 cm^{-1}. Anal. calcd for $C_{21}H_{23}BrO_3$: C, 62.54; H, 5.75. Found: C, 62.33; H, 5.80.

Optical purity of the allyl alcohol was determined by ^1H NMR analysis of the corresponding MTPA ester. The MTPA ester was prepared as follows: to a CH_2Cl_2 solution (0.22 mL) of the allyl alcohol (17.5 mg, 0.04 mmol) were added triethylamine (12 μL), (*S*)-MTPA chloride (12 μL, 0.07 mmol), and DMAP (7.9 mg, 0.07 mmol) at room temperature. After 18 h, the reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by thin-layer chromatography (silica gel, 10% AcOEt/hexane) to give the corresponding (*R*)-MTPA ester (29 mg, quant). ^1H NMR analysis of the MTPA ester derived from racemic allyl alcohol showed a set of two singlet signals at 3.57 and 3.63 ppm. The optical purity of the present sample was determined as 92% ee based on the integral values of these two peaks.

(*R*)-MTPA ester. ^1H NMR (500 MHz, $CDCl_3$) (major diastereomer): δ 1.60−1.75 (m, 2H), 1.88−2.02 (m, 2H), 2.21 (ddd, 1H, J = 6.0, 9.9, 18.0 Hz), 2.49 (dt, 1H, J = 4.2, 18.0 Hz), 3.57 (s, 3H), 4.45 (d, 1H, J = 11.9 Hz), 4.51 (d, 1H, J = 12.0 Hz), 4.58 (d, 1H, J = 11.9 Hz), 4.69 (d, 1H, J = 12.0 Hz), 5.46 (s, 1H), 5.69 (t, 1H, J = 3.8 Hz), 7.23−7.63 (m, 15H).

To a solution of the allyl alcohol in DMF (100 mL) were added imidazole (5.39 g, 79.2 mmol) and TBSCl (9.52 g, 63.2 mmol) at room temperature, and the mixture was stirred overnight. The reaction was quenched by saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 10% AcOEt/hexane) to give the C-ring fragment **5** (23.6 g, 88% in two steps).

$[\alpha]_D^{18}$: −26° (c = 1.83, CH_2Cl_2, 92% ee). ^1H NMR (500 MHz, $CDCl_3$): δ 0.12 (s, 3H), 0.18 (s, 3H), 0.93 (s, 9H), 1.54−1.62 (m, 1H), 1.75−1.85 (m, 3H), 2.16−2.25 (m, 1H), 2.40 (dt, 1H, J = 4.7, 17.5 Hz), 4.25 (br, 1H), 4.53 (d, 1H, J = 11.9 Hz), 4.54 (d, 1H, J = 11.9 Hz), 4.64 (d, 1H, J = 11.9 Hz), 4.69 (d, 1H, J = 11.9 Hz), 5.54 (s, 1H), 7.26−7.37 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.5, −4.4, 17.5, 18.2, 25.8, 25.9, 33.9, 69.1, 69.2, 72.1, 102.8, 126.3, 127.62, 127.63, 127.87, 127.94, 128.29, 128.32, 136.8, 137.89, 137.90. IR (neat): 2940, 1650, 1455, 1350, 1255, 1125, 1090 cm^{-1}. Anal. calcd for $C_{27}H_{37}BrO_3Si$: C, 62.65; H, 7.21. Found: C, 62.35; H, 7.10.

Preparation of 6. To a solution of the C-ring fragment **5** (41.2 g, 79.7 mmol) in ether (200 mL) was added *t*-BuLi (65.0 mL, 1.56 M in pentane, 101 mmol) at −78 °C, and the mixture was stirred for 1.5 h. Then CuCN (8.66 g, 96.7 mmol) was added to the mixture. The reaction mixture was warmed to −45 °C and stirred for 1 h. To this was added 3,4-epoxy-1-hexene (11.0 mL, 100 mmol), and the mixture was warmed to −23 °C. After 2 h, the reaction was quenched by saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with hexane. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the crude coupling product, which was directly used in the next step.

To a suspension of PDC (54.5 g, 115 mmol) and MS4A (36.0 g) in CH_2Cl_2 (200 mL) was added a CH_2Cl_2 solution (200 mL) of the crude coupling product at 0 °C. The mixture was stirred at room temperature for 1.5 h, and then inorganic materials were filtered off through a short pad of Celite. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography (silica gel, 7% AcOEt/hexane) to give the enone **6** (28.0 g, 66% in two steps).

$[\alpha]_D^{20}$: −56° (c = 0.79, CH_2Cl_2). ^1H NMR (270 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.02 (t, 3H, J = 7.2 Hz), 1.44−1.85 (m, 4H), 2.08−2.36 (m, 2H), 2.39 (q, 2H, J = 7.2 Hz), 2.84−3.03 (m, 2H), 4.04−4.11 (m, 1H), 4.46 (d, 1H, J = 12.0 Hz), 4.49 (d, 1H, J = 12.0 Hz), 4.54 (d, 1H, J = 12.0 Hz), 4.59 (d, 1H, J = 12.0 Hz), 5.14 (s, 1H), 5.83 (br d, 1H, J = 16.0 Hz), 6.69 (ddd, 1H, J = 5.6, 6.4, 16.0 Hz), 7.23−7.38 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ -4.7, −4.0, 8.1, 18.0, 18.3, 24.0, 25.8, 31.9, 32.5, 32.9, 68.2, 68.4, 68.9, 98.8, 127.69, 127.73, 127.9, 128.0, 128.4, 130.3, 134.8, 135.1, 137.8, 137.9, 145.3, 200.9. IR (neat): 2940, 1675, 1630, 1460, 1360, 1255 cm^{-1}. Anal. calcd for $C_{33}H_{46}O_4Si$: C, 74.11; H, 8.67. Found: C, 74.10; H, 8.80.

Preparation of 8. To a solution of LDA [prepared from diisopropylamine (0.440 mL, 3.15 mmol) and *n*-BuLi (1.61 M in hexane, 1.90 mL, 3.06 mmol), 0 °C, 10 min] in THF (6 mL) was added ethyl isobutyrate (0.410 mL, 3.07 mmol) at −78 °C, and the mixture was stirred for 1 h. A THF solution (2.5 mL) of the enone **6** (1.35 g, 2.52 mmol) was added, and the mixture was gradually warmed to 5 °C over 7 h. The reaction was quenched by saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with hexane. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give crude Michael adducts **7** as an inseparable mixture of diastereomers (4.5:1, quant), which was directly used in the next step.

A solution of the crude adduct **7** in THF (12.5 mL) was treated with *t*-BuOK (0.383 g, 3.41 mmol) at 0 °C for 1 h. Then, triethylamine (0.520 mL, 3.41 mmol) and triisopropylsilyl chloride (0.650 mL, 3.04 mmol) were added dropwise. After being stirred for 4 h at 0 °C, the reaction mixture was treated with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with hexane. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 10% AcOEt/hexane) to give **8** (1.16 g, 60% in two steps) and its epimer (0.318 g, 17% in two steps).

(**8**) $[\alpha]_D^{21}$: −2.1° (c = 1.28, CH_2Cl_2). ^1H NMR (270 MHz, $CDCl_3$): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.78 (s, 3H), 0.80 (s, 3H), 0.91 (s, 9H), 0.94−1.23 (m, 21H), 1.42−2.40 (m, 11H), 1.70 (s, 3H), 3.94 (br, 1H), 4.43 (d, 1H, J = 12.0 Hz), 4.44 (d, 1H, J = 12.0 Hz), 4.57 (d, 1H, J = 12.0 Hz), 4.69 (d, 1H, J = 12.0 Hz), 5.11 (s, 1H), 7.15−7.38 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ -4.6, −4.0, 8.8, 12.3, 13.2, 17.7, 17.8, 18.0, 18.7, 22.3, 22.9, 25.8, 27.9, 32.5, 33.2, 43.3, 43.6, 68.1, 69.1, 70.7, 98.2, 115.6, 127.76, 127.79, 127.84, 128.1, 128.3, 128.5, 134.2, 136.4, 137.5, 138.0, 166.3, 203.9. IR (neat): 2940, 1740, 1650, 1630, 1480, 1375, 1350, 1320, 1250 cm^{-1}. Anal. calcd for $C_{46}H_{72}O_5Si_2$: C, 72.58; H, 9.53. Found: C, 72.77; H, 9.74.

(epimer) ^1H NMR (270 MHz, $CDCl_3$): δ 0.06 (s, 3H), 0.07 (s, 3H), 0.73 (s, 3H), 0.89 (s, 9H), 0.93−1.20 (m, 21H), 1.08 (s, 3H), 1.45−2.45 (m, 11H), 1.70 (s, 3H), 4.05 (br, 1H), 4.42 (d, 1H, J = 12.0 Hz), 4.49 (d, 1H, J = 12.0 Hz), 4.51 (d, 1H, J = 12.0 Hz), 4.75 (d, 1H, J = 12.0 Hz), 5.26 (s, 1H), 7.10−7.40 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ -4.4, −3.8, 8.9, 13.2, 17.5, 17.9, 18.0, 18.5, 22.6, 24.1, 25.9, 26.3, 32.4, 33.0, 39.6, 43.8, 66.1, 67.2, 68.8, 98.4, 115.5, 127.6, 127.7, 128.1, 128.3, 128.4, 133.9, 136.3, 137.9, 138.0, 167.2, 204.6. IR (neat): 2935, 1725, 1630, 1460, 1375, 1355, 1325, 1255 cm^{-1}.

Preparation of 10. To a solution of benzyloxymethyltributylstannane (0.125 mL 0.340 mmol) in THF (0.670 mL) was added *n*-BuLi (0.205 mL, 1.61 M in hexane, 0.330 mmol) at −78 °C, and the mixture was stirred for 5 min. Then, a THF solution (0.400 mL) of the β-siloxyenone **8** (0.127 g, 0.167 mmol) was added. After the mixture was stirred for 2.5 h, it was treated with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with hexane. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude adduct **9** (86%), which was directly used in the next step.

To a CH_2Cl_2 suspension (0.900 mL) of the crude adduct **9**, MS4A (0.309 g), and benzyl alcohol (26.0 mL, 0.251 mmol) was added Montmorillonite K10 (0.262 g) at −45 °C. After the mixture was stirred for 1 h, it was treated with triethylamine (0.120 mL, 0.861 mmol). Inorganic materials were filtered off through a short pad of Celite, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 10% AcOEt/hexane) to give the γ-benzyloxyenone **10** (80.4 mg, 79%).

$[\alpha]_D^{21}$: −6.8° (c = 0.79, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ 0.04 (s, 3H), 0.07 (s, 3H), 0.79 (s, 3H), 0.88 (s, 12H), 1.65−1.85 (m,

6H), 1.80 (s, 3H), 2.04−2.13 (m, 1H), 2.12 (dd, 1H, J = 11.6, 16.9 Hz), 2.23−2.35 (m, 2H), 2.36 (dd, 1H, J = 4.2, 16.9 Hz), 3.91−3.95 (m, 1H), 4.03 (s, 2H), 4.47 (d, 1H, J = 12.2 Hz), 4.50 (d, 1H, J = 12.2 Hz), 4.50 (s, 2H), 4.58 (d, 1H, J = 12.2 Hz), 4.67 (d, 1H, J = 12.2 Hz), 5.12 (s, 1H), 7.14−7.38 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.5, −3.9, 11.6, 17.3, 18.0, 20.2, 23.0, 24.8, 25.8, 28.8, 32.2, 38.4, 39.0, 44.7, 67.1, 67.9, 68.7, 70.6, 73.2, 98.3, 127.6, 127.7, 127.81, 127.83, 127.9, 128.3, 128.40, 128.41, 133.89, 133.93, 137.0, 137.86, 137.90, 138.3, 158.0, 199.0. IR (neat): 2925, 1670, 1625, 1450, 1360, 1325, 1250, 1070 cm^{-1}. Anal. calcd for $C_{45}H_{60}O_5Si$: C, 76.22; H, 8.53. Found: C, 76.27; H, 8.77.

Preparation of 11. The γ-benzyloxyenone **10** (80.4 mg, 0.113 mmol) was treated with TBAF (0.170 mL, 1.0 M in THF, 0.170 mmol) at room temperature. After being stirred overnight, the mixture was poured into saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 30% AcOEt/hexane) to give the allyl alcohol **11** (55.9 mg, 83%).

$[\alpha]_D^{21}$: −6.2° (c = 0.52, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (s, 3H), 0.93 (s, 3H), 1.40−1.51 (m, 1H), 1.54−1.67 (m, 2H), 1.67−1.77 (m, 2H), 1.81−1.89 (m, 1H), 1.82 (s, 3H), 1.91−1.99 (m, 1H), 2.07−2.17 (m, 2H), 2.28−2.42 (m, 3H), 3.87 (br s, 1H), 4.06 (s, 2H), 4.49−4.56 (m, 2H), 4.53 (s, 2H), 4.61 (d, 1H, J = 12.0 Hz), 4.62 (d, 1H, J = 12.0 Hz), 5.15 (s, 1H), 7.15−7.42 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.5, 16.9, 20.0, 23.0, 24.7, 29.5, 31.5, 38.4, 39.0, 44.3, 67.0, 68.5, 68.6, 69.7, 73.2, 98.4, 127.6, 127.7, 127.78, 127.80, 127.84, 128.32, 128.33, 128.35, 133.9, 135.2, 135.9, 137.6, 137.7, 138.1, 157.9, 199.0. IR (neat): 3445, 2925, 1660, 1450, 1370, 1325, 1240, 1065 cm^{-1}. Anal. calcd for $C_{39}H_{46}O_5$: C, 78.75; H, 7.80. Found: C, 78.56; H, 8.10.

Preparation of 12. To a solution of triphenylphosphine (3.61 g, 13.8 mmol) in THF (27.0 mL) was added DEAD (2.10 mL, 13.3 mmol) at −23 °C. After the mixture was stirred for 10 min, it was treated with a THF solution (26 mL) of the allyl alcohol **11** (3.16 g, 5.31 mmol) and stirred for additional 10 min. Then, pivalic acid (1.37 g, 13.4 mmol) was added, and the solution was warmed to room temperature. After the mixture was stirred for a week, it was treated with iodomethane (3.30 mL, 53.0 mmol) and again stirred overnight. The reaction was quenched by saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with hexane. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 5−15% AcOEt/hexane) to give the pivalate **12** (2.42 g, 67%).

$[\alpha]_D^{20}$: +7.9° (c = 0.33, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (s, 3H), 1.10 (s, 3H), 1.20 (s, 9H), 1.56−1.70 (m, 3H), 1.72−1.80 (m, 1H), 1.78 (s, 3H), 1.82−1.95 (m, 2H), 1.96−2.05 (m, 2H), 2.11−2.20 (m, 1H), 2.31 (dd, 1H, J = 3.2, 16.3 Hz), 2.41 (br d, 1H, J = 18.5 Hz), 4.07 (d, 1H, J = 12.0 Hz), 4.09 (d, 1H, J = 12.0 Hz), 4.50 (d, 1H, J = 12.0 Hz), 4.52 (s, 2H), 4.54 (d, 1H, J = 12.0 Hz), 4.55 (d, 1H, J = 11.6 Hz), 4.66 (d, 1H, J = 11.6 Hz), 5.16 (s, 1H), 5.28 (br, 1H), 7.24−7.39 (m, 15H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.6, 17.7, 20.2, 23.8, 25.2, 27.2, 27.8, 28.8, 38.0, 38.8, 38.9, 41.0, 67.0, 67.1, 67.7, 69.0, 73.3, 98.2, 127.7, 127.8, 127.86, 127.91, 128.0, 128.2, 128.39, 128.41, 128.43, 131.8, 134.1, 137.7, 137.8, 138.0, 157.8, 177.8, 198.8. IR (neat): 2940, 1725, 1670, 1455, 1370, 1325, 1280, 1245, 1150, 1060 cm^{-1}. Anal. calcd for $C_{44}H_{54}O_6$: C, 77.84; H, 8.01. Found: C, 77.55; H, 7.92.

Preparation of 13. A solution of the pivalate **12** (0.809 g, 1.19 mmol) in THF (6.00 mL) was treated with *t*-BuOK (0.207 g, 1.84 mmol) at 0 °C for 1 h. Then, the mixture was cooled to −78 °C and triisopropylsilyl chloride (0.306 mL, 1.43 mmol) was added. After being stirred for 1 h, the mixture was poured into saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography (FL100DX, 3% AcOEt/hexane) to give the cyclization precursor **13** (0.992 g, quant).

$[\alpha]_D^{24}$: +21° (c = 0.44, CH_2Cl_2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.87 (s, 3H), 0.95−1.05 (m, 24H), 1.20 (s, 9H), 1.50−2.25 (m, 10H), 2.04 (s, 3H), 2.41 (br d, 1H, J = 18.0 Hz), 4.44 (d, 1H, J = 12.0 Hz), 4.50 (d, 1H, J = 12.0 Hz), 4.51 (d, 1H, J = 12.0 Hz), 4.64 (d, 1H, J = 12.0 Hz), 4.67 (d, 1H, J = 12.0 Hz), 4.72 (d, 1H, J = 12.0 Hz), 5.26 (br, 1H), 5.34 (s, 1H), 5.88 (s, 1H), 7.10−7.40 (m, 15H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 13.1, 14.9, 18.0, 18.1, 18.1, 24.0, 27.2, 27.4, 27.5, 28.8, 32.0, 36.1, 38.8, 40.3, 67.4, 68.0, 69.7, 74.1, 100.1, 110.9, 122.8, 127.1, 127.3, 127.3, 127.4, 127.8, 128.1, 128.2, 128.3, 133.0, 137.6, 137.9, 138.3, 138.4, 139.8, 144.3, 178.0. IR (neat): 2950, 1725, 1615, 1460, 1385, 1365, 1285, 1210, 1150, 1120, 1050 cm^{-1}. Anal. calcd for $C_{53}H_{74}O_6Si$: C, 76.21; H, 8.93. Found: C, 76.51; H, 9.20.

Cyclization Reaction of 13 Using Me_2AlOTf. A solution of the dienol silyl ether **13** (4.10 g, 4.91 mmol) in CH_2Cl_2 (160 mL) was treated with Me_2AlOTf [15.9 mL, 0.936 M in hexane, 14.9 mmol, prepared from Me_3Al (29.4 mL, 1.02 M in hexane, 30.0 mmol) and TfOH (2.65 mL, 30.0 mmol)] at −78 °C for 10 min. The mixture was warmed to −45 °C and stirred for 1.5 h. Pyridine (1.98 mL, 24.5 mmol) was added, and the solution was cooled to −78 °C. The mixture was poured into vigorously stirring mixture of saturated aqueous $NaHCO_3$ (200 mL) and hexane (200 mL) at 0 °C. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 15% AcOEt/hexane) to give the tricarbocycles **14** (1.76 g, 62%) and **16** (20%).

(**14**) $[\alpha]_D^{27}$: +177° (c = 0.47, CH_2Cl_2,). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.18 (s, 3H), 1.19 (s, 9H), 1.40−1.48 (m, 1H), 1.48−1.62 (m, 3H), 1.51 (s, 3H), 1.63 (s, 3H), 1.79−1.88 (m, 1H), 1.90 (dd, 1H, J = 5.5, 15.0 Hz), 1.95−2.00 (m, 1H), 2.39 (d, 1H, J = 15.0 Hz), 2.39−2.46 (m, 1H), 2.44 (d, 1H, J = 19.9 Hz), 2.87 (dd, 1H, J = 6.6, 19.9 Hz), 4.62 (d, 1H, J = 12.0 Hz), 4.68 (d, 1H, J = 12.0 Hz), 4.71 (s, 2H), 4.75 (d, 1H, J = 10.0 Hz), 4.77 (d, 1H, J = 10.0 Hz), 5.14 (br t, 1H, J = 3.8 Hz), 7.26−7.42 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 17.6, 25.0, 25.9, 27.1, 28.6, 30.5, 36.0, 38.8, 38.9, 40.5, 43.8, 71.5, 72.9, 73.4, 80.9, 85.2, 127.46, 127.56, 127.61, 127.7, 128.3, 128.4, 131.6, 135.7, 138.37, 138.38, 140.3, 156.0, 178.2, 199.2. IR (neat): 2940, 1720, 1665, 1450, 1280, 1150, 1070 cm^{-1}. Anal. calcd for $C_{37}H_{46}O_5$: C, 77.86; H, 8.12. Found: C, 77.56; H, 8.40.

(**16**) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.24 (s, 9H), 1.51 (s, 3H), 1.52 (s, 3H), 1.63−1.80 (m, 4H), 1.82 (d, 1H, J = 18.9 Hz), 1.84−1.90 (m, 1H), 1.98 (dd, 1H, J = 5.8, 14.2 Hz), 2.10−2.20 (m, 1H), 2.25−2.37 (m, 1H), 2.59 (brd, 1H, J = 18.8 Hz), 2.76 (dd, 1H, J = 4.9, 18.9 Hz), 3.86 (s, 1H), 4.25 (d, 1H, J = 12.3 Hz), 4.48 (d, 1H, J = 12.5 Hz), 4.55 (d, 1H, J = 12.3 Hz), 4.65 (d, 1H, J = 12.5 Hz), 5.12 (s, 1H), 5.31 (br s, 1H), 7.22−7.40 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.3, 18.4, 27.38, 27.43, 28.1, 29.4, 36.6, 38.8, 39.3, 40.6, 42.1, 44.0, 71.3, 72.6, 73.9, 81.1, 86.4, 127.2, 127.46, 127.54, 127.8, 128.3, 128.4, 130.3, 131.6, 137.9, 138.0, 140.4, 158.9, 178.5, 200.6. IR (neat): 2935, 2865, 1720, 1670, 1480, 1455, 1280, 1150, 1060, 1030 cm^{-1}. HRFAB (NBA/NaI) Calcd for $C_{37}H_{46}O_5Na$ (MNa^+): 593.3243; Found: 593.3271.

Preparation of 19. The tricarbocycle **14** in THF was treated with lithium tri(*t*-butoxy)aluminum hydride (6.10 mL, 1.0 M in THF, 6.10 mmol) at room temperature. After being stirred overnight, the mixture was poured into saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude alcohol **17**, which was directly used in the next step.

To a solution of the crude alcohol **17** in CH_2Cl_2 (16 mL) were added 2,6-lutidine (0.850 mL, 7.30 mmol) and TESOTf (0.830 mL, 3.67 mmol) at −23 °C. After being stirred for 1 h, the mixture was poured into saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with hexane. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude silyl ether **18**, which was directly used in the next step.

A solution of the crude silyl ether **18** in CH_2Cl_2 (30 mL) was treated with DIBAL (11.4 mL, 0.93 M in hexane, 10.6 mmol) at −78 °C, and the mixture was stirred for 1 h. To this were added $Na_2SO_4 \cdot 10H_2O$ (4.91 g, 15.3 mmol) and ether (30 mL), and the mixture was warmed to room temperature. After being stirred for 1 h, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure, and the resultant residue was purified by column chromatography (silica gel, 10% AcOEt/hexane) to give the allyl alcohol **19** (0.991 g, 87%).

$[\alpha]_D^{21}$: + 111 ° (c = 0.67, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.64 (q, 6H, J = 7.9 Hz), 0.96 (s, 3H), 1.00 (t, 9H, J = 7.9 Hz), 1.44 (s, 3H), 1.50−1.70 (m, 5H), 1.61 (s, 3H), 1.72−1.81 (m, 1H), 1.84−1.93 (m, 1H), 2.27−2.40 (m, 3H), 2.63 (dt, 1H, J = 9.4, 15.0 Hz), 4.22 (br s, 1H), 4.43 (br d, 1H, J = 8.5 Hz), 4.54 (d, 1H, J = 12.0 Hz), 4.63 (d, 1H, J = 9.4 Hz), 4.66 (s, 2H), 4.66 (d, 1H, J = 12.0 Hz), 4.73 (d, 1H, J = 9.4 Hz), 7.25−7.45 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 5.0, 6.9, 16.8, 17.3, 25.1, 26.6, 31.0, 31.2, 31.8, 36.2, 39.3, 42.4, 67.5, 69.8, 71.6, 73.0, 82.1, 84.5, 127.0, 127.26, 127.27, 127.7, 128.13, 128.15, 133.7, 136.3, 137.4, 138.9, 139.33, 139.34. IR (neat): 3380, 2925, 1450, 1350, 1235, 1160, 1065, 1020 cm^{-1}. Anal. calcd for $C_{38}H_{54}O_4Si$: C, 75.70; H, 9.03. Found: C, 75.42; H, 9.23.

Preparation of 21a. To a solution of the allyl alcohol **19** (0.952 g, 1.58 mmol) in ether (16 mL) were added diethylzinc (3.16 mL, 1.0 M in hexane, 3.16 mmol) and diiodomethane (0.255 mL, 3.17 mmol) at room temperature. After 6 h, the reaction was quenched by saturated aqueous NH_4Cl. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give the crude cyclopropyl alcohol **20** (quant), which was used in the next step without purification.

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.04 (d, 1H, J = 4.6 Hz), 0.66 (q, 6H, J = 7.9 Hz), 0.82 (d, 1H, J = 4.6 Hz), 0.97−1.05 (m, 1H), 1.00 (t, 9H, J = 7.9 Hz), 1.01 (s, 3H), 1.22−1.34 (m, 3H), 1.32 (s, 3H), 1.46−1.52 (m, 1H), 1.55−1.72 (m, 3H), 1.84 (s, 3H), 1.92 (dd, 1H, J = 3.3, 15.4 Hz), 2.59 (dd, 1H, J = 5.2, 16.1 Hz), 2.71 (dt, 1H, J = 10.0, 15.4 Hz), 3.64 (d, 1H, J = 9.3 Hz), 4.36−4.41 (m, 1H), 4.45 (br d, 1H, J = 10.0 Hz), 4.53 (d, 1H, J = 12.1 Hz), 4.65 (d, 1H, J = 12.1 Hz), 4.78 (d, 1H, J = 12.1 Hz), 4.83 (d, 1H, J = 12.1 Hz), 4.84 (d, 1H, J = 9.3 Hz), 7.23−7.35 (m, 6H), 7.39−7.44 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 5.1, 6.9, 17.0, 18.1, 23.6, 24.4, 26.6, 30.4, 30.6, 31.28, 31.29, 36.0, 36.2, 38.6, 43.3, 67.86, 67.87, 70.9, 72.5, 81.4, 87.3, 127.0, 127.2, 127.3, 127.8, 128.1, 128.2, 136.9, 137.8, 139.50, 139.53.

To a suspension of PDC (0.895 g, 2.38 mmol) and MS4A (0.914 g) in CH_2Cl_2 (6 mL) was added a CH_2Cl_2 solution (10 mL) of the crude cyclopropyl alcohol **20** at room temperature. After the reaction mixture was stirred for 1.5 h, it was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 15% AcOEt/hexane) to give the cyclopropyl ketone **21a** (0.826 g, 85%).

$[\alpha]_D^{21}$: +72 ° (c = 0.31, CH_2Cl_2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.35 (d, 1H, J = 5.0 Hz), 0.61 (q, 6H, J = 8.0 Hz), 0.97 (t, 9H, J = 8.0 Hz), 0.99 (s, 3H), 1.09 (brd, 1H, J = 16.0 Hz), 1.19 (d, 1H, J = 5.0 Hz), 1.30 (s, 3H), 1.26−1.47 (m, 1H), 1.47−1.54 (m, 1H), 1.56−1.74 (m, 3H), 1.82 (dt, 1H, J = 5.0, 13.0 Hz), 1.92 (s, 3H), 2.11−2.35 (m, 2H), 2.43 (dt, 1H, J = 10.0, 15.6 Hz), 3.25 (dd, 1H, J = 6.0, 16.0 Hz), 3.70 (d, 1H, J = 9.6 Hz), 4.34−4.43 (m, 1H), 4.51 (d, 1H, J = 12.0 Hz), 4.66 (d, 1H, J = 12.0 Hz), 4.81 (s, 2H), 4.96 (d, 1H, J = 9.6 Hz), 7.22−7.46 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 4.9, 6.9, 17.2, 18.5, 21.0, 24.4, 26.7, 31.1, 31.6, 32.9, 33.9, 35.7, 38.0, 38.6, 42.9, 67.9, 70.7, 72.8, 81.2, 85.1, 127.1, 127.3, 127.4, 127.9, 128.2, 136.7, 138.0, 139.0, 139.2, 208.6. IR (neat): 2950, 1680, 1460, 1380, 1335, 1250, 1215, 1090, 990 cm^{-1}. Anal. calcd for $C_{39}H_{54}O_4Si$: C, 76.17; H, 8.85. Found: C, 76.13; H, 9.15.

Birch Reduction of 21a: Preparation of 24. Under an argon atmosphere, a solution of the cyclopropyl ketone **21a** (0.341 g, 0.555 mmol) and *t*-BuOH (0.525 mL, 5.57 mmol) in THF (2.8 mL) was cooled to −78 °C. To the solution were added liquid NH_3 (6.0 mL, distilled from lithium) and several pieces of lithium wire (39.2 mg, 5.65 mmol). After 1 h, methanol (2.8 mL) was added until the dark blue color of the reaction mixture disappeared. Then, the colorless homogeneous solution was allowed to warm to ambient temperature with evaporation of ammonia. After 1 h, water and hexane were added. The layers were separated, and the aqueous layer was extracted with AcOEt. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 50% AcOEt/hexane) to give the desired ketone **24** (quant).

$[\alpha]_D^{30}$: + 78° (c = 0.95, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (s, 3H), 1.00 (s, 3H, C17), 1.07 (dd, 1H, J = 4.4, 15.2 Hz, C14α), 1.45 (s, 3H), 1.45 (ddd, 1H, J = 2.1, 6.3, 15.9 Hz, C2β), 1.57 (d, 1H, J = 4.2 Hz, C13−O*H*), 1.63 (dt, 1H, J = 4.7, 13.2 Hz, C7α), 1.69−1.73 (m, 1H, C1), 1.80 (tq, 1H, J = 5.1, 13.2 Hz, C6), 1.94−2.02 (m, 1H, C6), 2.03 (d, 3H, J = 1.3 Hz, C18), 2.06−2.12 (m, 1H, C7β), 2.18−2.26 (m, 1H, C5α), 2.21 (d, 1H, J = 2.8 Hz, C10−O*H*), 2.29−2.35 (m, 1H, C5β), 2.36 (ddd, 1H, J = 1.5, 5.1, 15.9 Hz, C2α), 2.52 (d, 1H, J = 3.8 Hz, C9−O*H*), 2.75 (dt, 1H, J = 9.6, 15.2 Hz, C14β), 3.06 (d, 1H, J = 6.3 Hz, C3), 3.99 (dd, 1H, J = 3.8, 9.6 Hz, C9), 4.47−4.52 (m, 1H, C13), 4.86 (dd, 1H, J = 2.8, 9.6 Hz, C10). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5, 19.5, 21.7, 23.4, 26.2, 29.9, 32.6, 35.7, 39.1, 39.2, 41.1, 45.4, 52.0, 67.7, 72.6, 78.2, 137.6, 138.8, 212.4. IR ($CDCl_3$): 3620, 2950, 1710, 1460, 1390, 1270, 1250, 1125, 1045, 1020, 990 cm^{-1}. Anal. calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.34. Found: C, 70.57; H, 9.44.

Preparation of 25. To a mixture of the triol **24** in THF (5.6 mL), triethylamine (77.5 mL, 0.556 mmol), and trimethylsilyl chloride (0.845 mL, 6.66 mmol) was added lithium diisopropylamide [9.30 mL, 0.718 M in THF, 6.68 mmol; prepared from BuLi (6.20 mL, 1.61 M in hexane, 10.0 mmol) and a solution of diisopropylamine (1.50 mL, 10.7 mmol) in THF (6.2 mL), 0 °C, 10 min] at −78 °C. The mixture was stirred at −78 °C for 10 min and then at 0 °C for 30 min. The reaction was quenched by saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with hexane. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude tetrasilyl ether, which was directly used in the next step.

To a mixture of the crude tetrasilyl ether and $KHCO_3$ (0.279 g, 2.78 mmol) in CH_2Cl_2 (5.6 mL) was added a CH_2Cl_2 solution (10 mL) of *m*-CPBA (0.289 g, 1.67 mmol) at 0 °C. After being stirred for 10 min, the reaction mixture was poured into saturated aqueous $Na_2S_2O_3$. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were concentrated under reduced pressure. The residue was dissolved in THF (17 mL) and acidified by 0.25 N HCl to ca. pH 3. After 1 h, saturated aqueous $NaHCO_3$ was added to this mixture. The layers were separated, and the aqueous layer was extracted with AcOEt. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude tetrol, which was directly used in the next step.

To a solution of the crude tetrol in CH_2Cl_2 (5.60 mL) were added DMAP (70.2 mg, 0.574 mmol), triethylamine (1.10 mL, 7.86 mmol), and Ac_2O (0.483 mL, 5.11 mmol) at 0 °C. After 1.5 h, saturated aqueous $NaHCO_3$ was added. The layers were separated, and the aqueous layer was extracted with AcOEt. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by column chromatography (silica gel, 30−60% AcOEt/hexane) to give the tetraacetate **25** (0.205 g, 80%).

$[\alpha]_D^{21}$: +65° (c = 0.12, CH_2Cl_2). ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.76 (s, 3H), 0.95 (dd, 1H, J = 4.0, 15.2 Hz), 1.09 (s, 3H), 1.55−1.70 (m, 1H), 1.59 (s, 3H), 1.81−2.16 (m, 5H), 2.02 (s, 3H), 2.06 (s, 6H), 2.12 (s, 3H), 2.20 (s, 3H), 2.27 (dd, 1H, J = 5.0, 16.0 Hz), 2.75 (dt, 1H, J = 9.6, 15.2 Hz), 3.42 (d, 1H, J = 6.0 Hz), 5.00 (br s, 1H), 5.76−5.86 (m, 1H), 5.80 (d, 1H, J = 11.0 Hz), 6.13 (d, 1H, J = 11.0 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$): δ 15.01, 19.84, 20.94, 21.28, 24.23, 26.60, 26.88, 31.09, 32.15, 39.16, 45.00, 48.12, 70.26, 72.36, 75.49, 76.37, 135.81, 137.13, 169.15, 169.83, 170.10, 170.19, 206.07. IR ($CDCl_3$): 1735, 1370, 1240, 1020 cm^{-1}. Anal. calcd for $C_{27}H_{38}O_9$: C, 64.01; H, 7.56. Found: C, 64.23; H, 7.52.

Conversion of 25 to (+)-Taxusin. To a suspension of methyltriphenylphosphonium bromide (5.9 mg, 0.017 mmol) in toluene (0.166

mL) was added *n*-BuLi (9.2 mL, 1.69 M in hexane, 0.016 mmol) at 0 °C. After 1.5 h, a toluene solution (0.150 mL) of the tetraacetate **25** (3.3 mg, 0.0065 mmol) was added to the mixture. The solution was warmed to room temperature and stirred overnight. Water was added, and the aqueous layer was extracted with ether. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The resultant residue was purified by preparative TLC (20% AcOEt/hexane) to give (+)-taxusin **1** (0.6 mg, 17%) and the recovered starting material **25** (2.2 mg, 68%). The spectral data of the synthesized (+)-taxusin were given in the last part of this section.

Preparation of 27. To a solution of the ketone **24** (7.1 mg, 0.022 mmol) in CH_2Cl_2 (0.3 mL) were added 2,6-lutidine (21 μL, 0.18 mmol) and TBSOTf (20 μL, 0.088 mmol) at 0 °C. After 0.5 h, the mixture was cooled to −23 °C and was treated with 2,6-lutidine (10 μL, 0.086 mmol) and TMSOTf (12 μL, 0.066 mmol). After being stirred for 1 h at that temperature, the mixture was poured into saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with hexane. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by preparative TLC (7% AcOEt/hexane) to give the trisilyl ether **27** (13.0 mg, 95%).

$[\alpha]_D^{26}$: +60° (c = 0.73, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (s, 3H), 0.03 (s, 3H), 0.07 (s, 3H), 0.14 (s, 3H), 0.17 (s, 9H), 0.77 (s, 3H), 0.85 (s, 9H), 0.95 (s, 9H), 0.99 (s, 3H), 1.09 (dd, 1H, J = 4.0, 15.0 Hz), 1.40 (br dd, 1H, J = 6.5, 15.5 Hz), 1.46 (s, 3H), 1.56−1.65 (m, 2H), 1.72 (tq, 1H, J = 5.0, 12.5 Hz), 1.94 (d, 3H, J = 1.0 Hz), 1.88−1.95 (m, 1H), 2.11 (brd, 1H, J = 13.0 Hz), 2.17 (dt, 1H, J = 7.0, 13.5 Hz), 2.24−2.34 (m, 2H), 2.62 (dt, 1H, J = 9.5, 15.0 Hz), 3.14 (d, 1H, J = 6.5 Hz), 3.99 (d, 1H, J = 9.0 Hz), 4.33 (dd, 1H, J = 4.0, 9.5 Hz), 4.77 (d, 1H, J = 9.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.1, −4.21, −4.20, −3.1, 1.8, 17.9, 18.0, 18.4, 21.56, 21.60, 23.7, 25.8, 26.3, 26.8, 30.4, 32.3, 36.9, 38.9, 39.7, 41.0, 46.5, 52.7, 68.4, 74.2, 80.9, 135.8, 139.5, 212.6. IR (neat): 2925, 2855, 1710, 1470, 1255, 1085, 1065 cm^{-1}. Anal. calcd for $C_{34}H_{66}O_4Si_3$: C, 65.53; H, 10.68. Found: C, 65.26; H, 10.47.

Preparation of 29. To a solution of the trisilyl ether **27** (10.5 mg, 0.017 mmol) in THF (0.6 mL) was added KHMDS (1.0 M in THF, 84 μL, 0.084 mmol) at −78 °C, and the mixture was immediately warmed to −45 °C. After being stirred for 1 h, the mixture was again cooled to −78 °C and was treated with a THF solution (0.12 mL) of $PhNTf_2$ (42.1 mg, 0.12 mmol). After 10 min, the reaction was quenched with phosphate buffer (pH 6.88). The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure to give a crude enol triflate **28**, which was directly used in the next step.

$[\alpha]_D^{29}$: +43° (c = 0.65, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01 (s, 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.20 (s, 9H), 0.88 (s, 9H), 0.95 (s, 9H), 1.02 (s, 3H), 1.04 (s, 3H), 1.15−1.28 (m, 1H), 1.46 (dd, 1H, J = 11.1, 15.1 Hz), 1.49 (s, 3H), 1.58−1.65 (m, 1H), 1.69 (ddd, 1H, J = 2.1, 4.8, 15.9 Hz), 1.76 (ddd, 1H, J = 1.8, 5.9, 15.9 Hz), 1.81 (d, 3H, J = 1.0 Hz), 2.05−2.21 (m, 3H), 2.67 (dt, 1H, J = 9.4, 15.1 Hz), 3.51 (br s, 1H), 4.18 (d, 1H, J = 9.0 Hz), 4.33−4.38 (m, 1H), 4.59 (d, 1H, J = 9.0 Hz), 5.55−5.61 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.1, −4.2, −4.2, −3.1, −1.8, 17.3, 17.9, 18.4, 19.8, 21.4, 25.5, 25.7, 26.3, 26.8, 27.5, 32.6, 36.1, 38.8, 38.9, 39.8, 43.6, 68.2, 74.2, 81.1, 115.0, 136.6, 139.0, 152.7. IR (neat): 2930, 2860, 1460, 1415, 1250, 1210, 1145, 1080, 1020 cm^{-1}. Anal. calcd for $C_{35}H_{65}F_3O_6SSi_3$: C, 55.66; H, 8.68; S, 4.25. Found: C, 55.80; H, 8.96; S, 4.32.

To a solution of the crude **28** in ether (0.3 mL) were added tetrakis(triphenylphosphine)palladium (4.0 mg, 0.005 mmol) and $TMSCH_2MgCl$ (0.98 M in THF, 0.15 mL, 0.15 mmol) at room temperature, and the mixture was stirred for 0.5 h. The reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with ether. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by preparative TLC (3% AcOEt/hexane) to give the allylsilane **29** (8.2 mg, 70% from **27**).

$[\alpha]_D^{28}$ +68° (c = 1.43, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ −0.02 (s, 9H), 0.00 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H), 0.11 (s, 3H), 0.18 (s, 9H), 0.88 (s, 9H), 0.95 (s, 9H), 0.95 (s, 3H), 1.01 (s, 3H), 1.18−1.28 (m, 1H), 1.45−1.65 (m, 6H), 1.50 (s, 3H), 1.79 (d, 3H, J = 1.1 Hz), 1.90−2.05 (m, 3H), 2.63 (dt, 1H, J = 9.0, 14.7 Hz), 2.90 (br s, 1H), 4.14 (d, 1H, J = 9.1 Hz), 4.36 (br d, 1H, J = 10.0 Hz), 4.58 (d, 1H, J = 9.1 Hz), 5.03−5.09 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.1, −4.2, −4.1, −3.1, −0.6, 2.0, 17.2, 18.0, 18.5, 20.1, 23.6, 25.1, 25.8, 26.6, 26.9, 27.4, 28.3, 32.3, 36.4, 38.9, 40.4, 40.9, 42.6, 68.5, 74.2, 81.6, 118.9, 135.7, 138.3, 138.9. IR (neat): 2960, 2860, 1460, 1360, 1248, 1120, 1080 cm^{-1}. Anal. calcd for $C_{38}H_{76}O_3Si_4$: C, 65.83; H, 11.05. Found: C, 65.66; H, 11.24.

Preparation of 30. To a solution of the allylsilane **29** (31.8 mg, 0.046 mmol) in CH_2Cl_2 (0.46 mL) and MeOH (1.40 mL) was added *m*-CPBA (15.8 mg, 0.092 mmol) at room temperature, and the mixture was stirred for 1.5 h. *m*-CPBA (12.3 mg, 0.072 mmol) was added to the reaction mixture. After the mixture was stirred for 30 min, it was poured into a mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with AcOEt. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by preparative TLC (2% AcOEt/hexane) to give the ally alcohol **30** (27.7 mg, 95%).

$[\alpha]_D^{28}$ +70° (c 1.37, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (s, 3H), 0.08 (s, 3H), 0.11 (s, 3H), 0.13 (s, 3H), 0.17 (s, 9H), 0.78 (s, 3H), 0.90 (s, 9H), 0.95 (s, 9H), 1.00 (s, 3H), 1.21 (dd, 1H, J = 4.5, 15.0 Hz), 1.49 (s, 3H), 1.44−1.55 (m, 1H), 1.56−1.60 (m, 1H), 1.58−1.65 (m, 2H), 1.69−1.81 (m, 3H), 1.92 (br s, 1H, O*H*), 2.02 (d, 3H, J = 1.5 Hz), 2.64 (dt, 1H, J = 9.0, 15.0 Hz), 3.38 (br s, 1H), 4.04 (d, 1H, J = 9.0 Hz), 4.19−4.23 (m, 1H), 4.43 (br d, 1H, J = 10.0 Hz), 4.67 (s, 1H), 4.78 (d, 1H, J = 9.0 Hz), 5.05 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.9, −4.4, −4.2, −3.1, 1.9, 17.5, 18.3, 18.5, 19.5, 25.8, 26.0, 26.5, 26.9, 27.5, 29.6, 32.2, 36.5, 37.0, 38.8, 40.3, 44.5, 69.6, 74.3, 74.7, 81.6, 110.0, 135.9, 139.1, 155.1. IR (neat): 3450, 2950, 2860, 1475, 1258, 1075, 1010 cm^{-1}. Anal. calcd for $C_{35}H_{68}O_4Si_3$: C, 65.98; H, 10.76. Found: C, 66.05; H, 10.79.

Conversion of 30 to (+)-Taxusin. To a solution of the allyl alcohol **30** (4.5 mg, 0.0071 mmol) in THF (0.2 mL) were added HMPA (50 μL) and TBAF (1.0 M in THF, 71 μL, 0.071 mmol) at room temperature. The mixture was warmed to ca. 40 °C and stirred for 1.5 h. After being cooled to room temperature, the mixture was poured into phosphate buffer (pH 7.2). The layers were separated, and the aqueous layer was extracted with AcOEt. The combined extracts were washed with water and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by preparative TLC (90% AcOEt/hexane) to give a tetrol (2.2 mg, 93%), whose spectral data were in good agreement with those of the literature.[8]

$[\alpha]_D^{31}$: +99.° (c = 0.41, MeOH). ^{1}H NMR (500 MHz, CD_3OD):[8] δ 0.85 (s, 3H), 0.99 (s, 3H), 1.22 (dd, 1H, J = 4.5, 15.0 Hz), 1.46 (s, 3H), 1.53−1.80 (m, 7H), 2.04 (d, 3H, J = 1.0 Hz), 2.76 (dt, 1H, J = 9.0, 15.0 Hz), 3.95 (d, 1H, J = 9.5 Hz), 4.20 (br, 1H), 4.34 (br d, 1H, J = 10.5 Hz), 4.67 (s, 1H), 4.79 (d, 1H, J = 9.5 Hz), 5.02 (s, 1H), the C-3 proton was overlapped with the solvent signal (ca. 3.3 ppm). ^{1}H NMR (500 MHz, C_5D_5N): δ 1.14 (s, 3H), 1.22 (s, 3H), 1.64 (dd, 1H, J = 3.9, 15.2 Hz), 1.66−1.71 (m, 1H), 1.74 (s, 3H), 1.71−1.90 (m, 3H), 1.95−2.04 (m, 1H), 2.18−2.32 (m, 2H), 2.37 (d, 1H, J = 0.9 Hz), 2.94 (dt, 1H, J = 9.3, 15.5 Hz), 3.86 (d, 1H, J = 4.0 Hz), 4.37 (d, 1H, J = 9.3 Hz), 4.53 (br s, 1H), 4.63 (m, 1H), 4.78 (s, 1H), 5.10 (d, 1H, J = 10.3 Hz, O*H*), 5.14 (s, 1H), 5.34 (d, 1H, J = 9.3 Hz), 5.78 (br s, 1H, O*H*), 6.15 (br s, 1H, O*H*), 6.54 (br s, 1H, O*H*). ^{13}C NMR (125 MHz, CD_3OD):[8] δ 16.8, 18.0, 26.7, 26.7, 28.5, 31.5, 33.2, 36.8, 37.7, 40.0, 41.5, 44.8, 69.5, 73.5, 75.6, 80.0, 110.1, 138.8, 140.4, 155.8. ^{13}C NMR (125 MHz, C_5D_5N): δ 17.3, 18.2, 26.5, 26.5, 28.0, 31.7, 33.5, 37.2, 37.3, 39.4, 40.7, 44.3, 68.6, 73.0, 74.6, 79.1, 108.6, 137.7, 140.6, 156.2. IR (neat): 3420, 2930, 1640, 1125, 1070, 1010 cm^{-1}. HRFAB (NBA/NaI) calcd for $C_{20}H_{32}O_4Na$ (MNa^+): 359.2198. Found: 359.2203.

To a solution of the tetrol (3.8 mg, 0.011 mmol) in CH_2Cl_2 (1.2 mL) were added DMAP (4.2 mg, 0.034 mmol), triethylamine (50 μL, 0.36 mmol), and acetic anhydride (23 μL, 0.24 mmol) at 0 °C. The

mixture was warmed to room temperature and stirred overnight. After 25 h, the mixture was treated with additional triethylamine (50 μL, 0.36 mmol) and acetic anhydride (23 μL, 0.24 mmol) and was stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with AcOEt. The combined extracts were washed with brine and dried over $MgSO_4$. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The resultant residue was purified by preparative TLC (50% AcOEt/hexane) to give (+)-taxusin (5.6 mg, 98%).

$[\alpha]_D^{29}$: +93° (c = 0.22, CH_2Cl_2, 92% ee), [natural (+)-taxusin, $[\alpha]_D^{21}$, +105° (c = 0.34, CH_2Cl_2)]. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75 (s, 3H), 1.07 (dd, 1H, J = 7.8, 14.4 Hz), 1.11 (s, 3H), 1.62 (s, 3H), 1.65−1.88 (m, 7H), 2.01 (s, 3H), 2.05 (s, 3H), 2.07 (s, 3H), 2.11 (d, 3H, J = 1.3 Hz), 2.16 (s, 3H), 2.69 (dt, 1H, J = 9.9, 14.4 Hz), 3.00 (d, 1H, J = 5.7 Hz), 4.85 (s, 1H), 5.21 (s, 1H), 5.36 (t, 1H, J = 2.8 Hz), 5.87 (d, 1H, J = 10.7 Hz), 5.83−5.90 (m, 1H), 6.08 (d, 1H, J = 10.7 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.8, 17.7, 20.8, 21.0, 21.4, 21.8, 27.3, 27.3, 27.4, 28.3, 31.1, 31.9, 38.0, 39.3, 40.4, 42.9, 70.8, 72.6, 76.3, 77.5, 114.1, 134.9, 137.0, 148.8, 169.9, 169.9, 170.4, 170.4. IR (neat): 2920, 1740, 1370, 1240, 1020 cm^{-1}.

Acknowledgment. This work was financially supported by Grant-in-Aids from the Ministry of Education, Science, Sports, and Culture of the Japanese Government. We also thank Professor Fa-Ching Chen, National Taiwan University, for providing a sample and spectral data of natural taxusin.

Supporting Information Available: Spectroscopic data and experimental procedures for the compounds **15**, **21b**, and **23** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA984250F