Total Synthesis of Natural (-)-Ptaquilosin, the Aglycon of a Potent Bracken Carcinogen Ptaquiloside, and the (+)-Enantiomer and Their DNA Cleaving Activities

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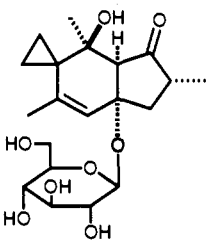
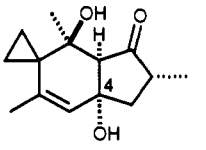
Abstract: The total synthesis of natural (-)-ptaquilosin (**2**) the aglycon of a potent carcinogen ptaquiloside (**1**) from bracken fern and its (+)-enantiomer (**2**) has been achieved starting with (+)-dimenthyl (1*R*,2*R*)-cyclopentane-1,2-dicarboxylate. The synthesis proceeds in 20 steps (2.9% overall yield). The key features of the synthesis are as follows: (i) diastereoselective alkylation of a common chiral compound **5** under different conditions has provided each of two diastereomers **6a** and **6b** predominantly, the former **6a** eventually leading to natural (-)-**2** and the latter **6b** giving unnatural (+)-**2** and (ii) the deformylative oxidation reaction of aldehyde **23** has been effected under the conditions mild enough to permit survival of the unstable product ptaquilosin (**2**). As to the DNA cleaving activities, dienone **4** prepared from natural (-)-ptaquilosin (**2**) was shown to be more efficient than dienone **4** derived from unnatural (+)-ptaquilosin (**2**).

Bracken fern (*Pteridium aquilinum*) is widely distributed in many parts of the world and used as a food for human consumption in Japan and some other countries. The carcinogenicity of bracken fern was discovered in 1960 in connection with cattle bracken poisoning, which was first reported in the late 19th century.[1] Since the discovery of the carcinogenicity of bracken fern, isolation of the carcinogen(s) has been a long-standing problem. Although the intense studies in search for the carcinogen had been made, it was extremely difficult to isolate the active principle because of (i) the instability of the carcinogen and (ii) the lack of the appropriate short-term bioassay systems such as the Ames test. Overcoming these difficulties, we isolated a new type of carcinogen ptaquiloside (**1**) from bracken in 1983,[2] determined the novel structure,[2] and proved its potent carcinogenicity.[3]

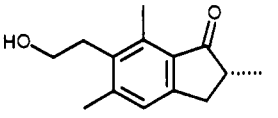
Ptaquiloside (**1**) and its aglycon ptaquilosin (**2**) are unstable under acidic or basic conditions. In aqueous solution they undergo aromatization to give pterosin B (**3**).[2a,d] Both ptaquiloside (**1**) and ptaquilosin (**2**) are converted under weakly basic conditions into dienone **4**, which is the activated form of ptaquiloside (**1**) and is regarded as the ultimate carcinogen[2a,d] (Scheme I). Dienone **4** is a powerful alkylating agent toward nucleophiles such as amino acids, nucleosides, and nucleotides;[2d] it also alkylates DNA and causes base-specific cleavage of DNA[4] (Scheme I).



1 ptaquiloside



2 (-)-ptaquilosin



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The synthetic challenge of ptaquilosin (**2**) structure, combined with the DNA cleaving activities of dienone **4** derived from **2**, prompted us to explore the synthesis and properties of both enantiomers of ptaquilosin (**2**). Previously we reported the synthesis of racemic ptaquilosin (**2**)[5] and of unnatural (+)-ptaquilosin (**2**).[6] In this full account, we describe the total synthesis of natural (-)- and unnatural (+)-ptaquilosin (**2**) using the novel method of stereoselective construction of the *R* or *S* quaternary stereocenter from a common chiral compound **5**. Further, we present the DNA cleaving activities of both enantiomers of dienone **4** derived from natural (-)- and unnatural (+)-ptaquilosin (**2**), respectively.

Synthetic Plan. The instability of ptaquilosin (**2**) poses a multitude of serious synthetic problems. The presence of the C-4 hydroxyl group in ptaquilosin (**2**), which undergoes dehydration easily, is one of the major reasons for the instability of **2**. We thus devised an approach wherein the angular hydroxyl group is introduced under extremely mild conditions at the very last stage

(1) (a) Evans, I. A. In *Chemical Carcinogens*, 2nd ed.; Searle, C. E., Ed.; American Chemical Society: Washington, DC, 1984; Vol. 2, pp 1171-1204. (b) Hirono, I.; Yamada, K. In *Naturally Occurring Carcinogens of Plant Origin*; Hirono, I., Ed.; Kodansha-Elsevier: Tokyo-Amsterdam, 1987; pp 87-120.

(2) (a) Niwa, H.; Ojika, M.; Wakamatsu, K.; Yamada, K.; Hirono, I.; Matsushita, K. *Tetrahedron Lett.* **1983**, *24*, 4117-4120. (b) Niwa, H.; Ojika, M.; Wakamatsu, K.; Yamada, K.; Ohba, S.; Saito, Y.; Hirono, I.; Matsushita, K. *Tetrahedron Lett.* **1983**, *24*, 5371-5372. (c) Ohba, S.; Saito, Y.; Hirono, I.; Niwa, H.; Ojika, M.; Wakamatsu, K.; Yamada, K. *Acta Crystallogr., Sect. C* **1984**, *40*, 1877-1879. (d) Ojika, M.; Wakamatsu, K.; Niwa, H.; Yamada, K. *Tetrahedron* **1987**, *43*, 5261-5274.

(3) (a) Hirono, I.; Yamada, K.; Niwa, H.; Shizuri, Y.; Ojika, M.; Hosaka, S.; Yamaji, T.; Wakamatsu, K.; Kigoshi, H.; Niiyama, K.; Uosaki, Y. *Cancer Lett.* **1984**, *21*, 239-246. (b) Hirono, I.; Aiso, S.; Yamaji, T.; Mori, H.; Yamada, K.; Niwa, H.; Ojika, M.; Wakamatsu, K.; Kigoshi, H.; Niiyama, K.; Uosaki, Y. *Gann* **1984**, *75*, 833-836. (c) Hirono, I.; Ogino, H.; Fujimoto, M.; Yamada, K.; Yoshida, Y.; Ikagawa, M.; Okumura, M. *J. Natl. Cancer Inst.* **1987**, *79*, 1143-1146.

(4) Ojika, M.; Sugimoto, K.; Okazaki, T.; Yamada, K. *J. Chem. Soc., Chem. Commun.* **1989**, 1775-1777.

(5) Kigoshi, H.; Sawada, A.; Nakayama, Y.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 1983-1986.

(6) Preliminary communication: Kigoshi, H.; Imamura, Y.; Niwa, H.; Yamada, K. *J. Am. Chem. Soc.* **1989**, *111*, 2302-2303.

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Scheme I

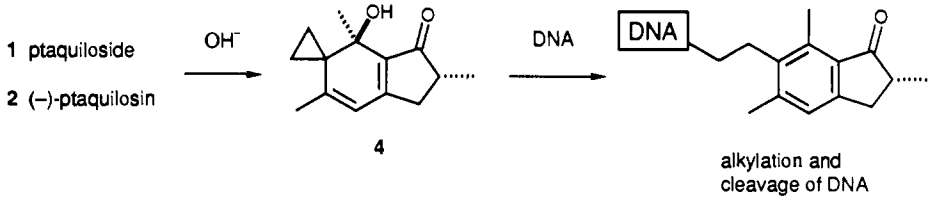
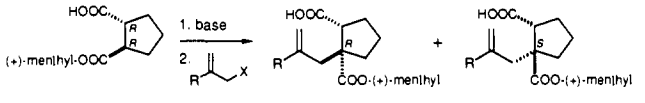


Table I. Alkylation of Alkali Metal Enolates Generated from (+)-Menthyl Hydrogen (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylate (**5**)



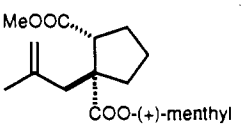
entry	base	RX	HMPA (equiv)	time (h)[a]	yield (%),[b] ratio of normal : contrasteric[c]
					6a : 6b
1	LDA	Cl	-	16.0[d]	86	1 : 4.0
2			2.3	6.5[d]	72	2.5 : 1
3		Br	-	4.7	91	3.4 : 1
4			2.3	3.0	92	11.5 : 1
5			2.3	e	93	45.0 : 1
					7a : 7b
6		Cl	-	3.7[d]	96	1 : 4.9
7			2.3	5.0[d]	95	1.4 : 1
8		Br	-	4.5	74	1.7 : 1
9			2.3	1.7	86	3.9 : 1
10		I	-	0.9	95	3.9 : 1
11			2.3	0.5	92	6.2 : 1
12		OTs	-	2.2	76[f]	1 : 4.0
13			2.3	2.2	80[f]	1 : 2.4
14			23	3.0	51[f]	1 : 1.2
15	$NaN(TMS)_2$	Cl	-	2.0[d]	90	1 : 1.3
16		Br	-	4.0[d]	66[c]	11.2 : 1
17	$KN(TMS)_2$	Cl	-	7.0[d]	57[c]	2.0 : 1
18		Br	-	3.0	81[c]	6.7 : 1

[a] Unless otherwise stated, the reaction was performed at −25 ~ −15 °C for a period of the indicated time. [b] Unless otherwise noticed, yields refer to isolated materials. [c] Determined by ^{1}H NMR spectra. [d] After addition of the alkylating agent at −25 °C, the reaction mixture was warmed to room temperature and was stirred for a period of the indicated time. [e] See Experimental Section. [f] Isolated as the corresponding methyl ester.

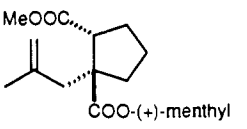
of the synthesis. For the purpose of synthesizing both enantiomers of ptaquilosin (**2**) efficiently, we adopted the strategy wherein each of two diastereomers **6a** and **6b** possessing respectively the *R* and *S* configuration at the newly formed quaternary carbon would be prepared stereoselectively from a common chiral compound **5** (Table I): the diastereomer **6a** would lead to natural (−)-ptaquilosin (**2**), while the diastereomer **6b** would ultimately afford unnatural (+)-ptaquilosin (**2**).

Results and Discussion

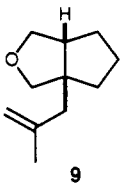
Control of Stereoselectivity in the Alkylation of (+)-Menthyl Hydrogen (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylate (5). (+)-Dimenthyl (1*R*,2*R*)-cyclopentane-1,2-dicarboxylate prepared according to the Yamamoto method[7] was partially hydrolyzed to afford monoester **5**. The dianion generated from **5** (LDA, THF) reacted with methallyl bromide in THF–HMPA (−78 °C → −20 °C) to afford in 94% yield a 45:1 mixture of diastereomeric esters **6a** and **6b** (Table I, entry 5), i.e., **6a** with 96% de. The ratio of **6a** and **6b** was determined by ^{1}H NMR spectral analysis. On the other hand, the dianion derived from **5** on reaction with methallyl chloride in THF (−25 °C → room temperature) in the absence of HMPA provided a 1:4 mixture of diastereomeric esters **6a** and **6b**, in 89% yield (Table I, entry 1), which was converted to the methyl esters and chromatographically separated to give **8a** (19%) and **8b** (77%): in this case the predominant product **6b** was the one that was alkylated from the sterically more hindered side of the enolate, namely the contrasteric[8] alkylation product. Stereochemistry of **6a** and **6b** was determined as follows: methyl ester **8a** could be converted into a tetrahydrofuran derivative **9** in two steps (1. $LiAlH_4$; 2. TsCl, pyr), whereas methyl ester **8b** could not. Thus, we could establish the method that allows us to prepare each of two diastereomers (**6a** and **6b**) preferentially through stereoselective alkylation of the common compound **5**.



8a



8b



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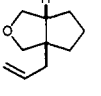
We examined the stereochemical outcome in the alkylation of the dianion derived from monoester **5** under a variety of conditions in order to investigate the factor(s) causing contrasteric alkylation.[9] The dianion generated from **5** with an appropriate base was alkylated with various alkylating agents in the absence or presence of HMPA, and the results are summarized in Table I. The alkylation of the Li enolate with alkyl chlorides or alkyl tosylate in the absence of HMPA proceeded in the contrasteric manner to give **6b** and **7b** predominantly (entries 1, 6, 12), while alkylation with alkyl bromides or alkyl iodide gave mainly normal alkylation products, **6a** and **7a** (entries 3, 8, 10).[10] The stereochemical results in these reactions may depend on the

(7) Misumi, A.; Iwanaga, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 3343–3345. Furuta, K.; Iwanaga, K.; Yamamoto, H. *Org. Synth.* **1988**, *67*, 76–85.

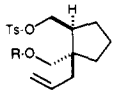
(8) Other examples for contrasteric alkylation, see: (a) Naef, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 1030–1031. (b) Ladner, W. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 449–450. (c) Ladner, W. *Chem. Ber.* **1983**, *116*, 3413. (d) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194–1216.

(9) Preliminary communication: Kigoshi, H.; Imamura, Y.; Yoshikawa, K.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1991**, *32*, 4541–4544.

(10) Stereochemistry of **7a** and **7b** was established by the chemical method. Diastereomer **7a** was transformed into cyclic ether I by a three-step sequence (1. CH_2N_2; 2. $LiAlH_4$; 3. TsCl, pyr), while diastereomer **7b** led to monotosylate II and ditosylate III by the same sequence of reactions.



I



II R = H
III R = Ts

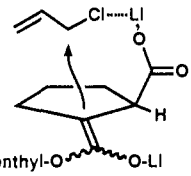
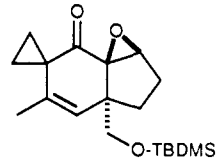


Figure 1. The plausible intermediary complex for the contrasteric alkylation.

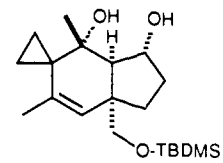
hardness[11] of the leaving groups in the alkylating reagents. Formation of contrasteric alkylation products (**6b** and **7b**) decreased with decreasing the hardness of the leaving groups (OTs, Cl > Br > I), and this tendency is consonant with the ability of the leaving groups for complexation to Li cation. Thus, the harder leaving groups may coordinate more tightly to the Li counterion of the carboxylate group adjacent to the enolate moiety. The tighter complexation may cause the contrasteric alkylation to a larger extent. A cation-complexing agent HMPA may inhibit complexation of the leaving group to the Li cation of the carboxylate group. Thus the alkylation of the Li enolate in the presence of HMPA was carried out (entries 2, 4, 5, 7, 9, 11, 13, 14), and, as was expected, formation of contrasteric alkylation products (**6b** and **7b**) decreased in all cases in comparison with the alkylation in the absence of HMPA. The alkylation of the Na and K enolates was performed in the absence of HMPA (entries 15–18) in order to examine the effect of metal counterions on stereoselectivity. In the cases of the Na and K enolates contrasteric alkylation occurred to a smaller extent (entries 15 and 17) in comparison with the case of the Li enolate (entry 6). These results are ascribed to the fact that the affinity of Na and K cations for halide ions is weaker than that of Li cation. The findings described above strongly suggest that the factor causing contrasteric alkylation of the Li enolate derived from **5** is complexation of the alkylating agent to the Li counterion located on the neighboring carboxylate group in the enolate: complexation of the harder leaving group (e.g., Cl) of the alkylating agent to the carboxylate Li counterion causes contrasteric alkylation to a larger extent. The plausible intermediary complex for the contrasteric alkylation is shown in Figure 1.

Preparation of Bicyclic Enone 12 and Its Cyclopropanation. The ester **6a** with 96% de was converted into the acyl chloride, which was subjected to cyclization with Lewis acid to give enone **10** (83% from **6a**) (Scheme II). Direct cyclization of **6a** with polyphosphoric acid or methanesulfonic acid–P_2O_5 afforded enone **10** in lower yield (40–60%). Conversion of **10** into enone **11** was accomplished in 81% yield by the following sequence: (1) reduction with $LiAlH_4$ to give two diastereomeric diols and (2) oxidation of the allylic hydroxyl group of the diols with imidazolium dichromate.[12] A single crystallization of this material provided pure **11**, which was silylated to furnish bicyclic enone **12** in quantitative yield. The enantiomeric purity of **12** was determined to be >99% ee on the basis of the ^1H NMR spectral analysis in the presence of chiral shift reagent Eu(hfc)$_3$. Spirocyclopropanation of **12** was effected by using (2-chloroethyl)-dimethylsulfonium iodide[13] and potassium *tert*-butoxide to form a separable 4.5:1 mixture of two ketones **13a** (45%) and **13b** (10%), the latter **13b** being isomerized by acid catalysis[14] to the former **13a** (81%). Spirocyclopropanation of **12** could also be carried out under the conditions employing 1,2-dibromoethane and sodium amide[14,15] in lower yield (20–30%): the silyl protecting group in **12** was partially removed during the reaction.

Functionalization of the Cyclopentane Moiety of Ketone 13a and Total Synthesis of (−)- and (+)-Ptaquilosin (2). The next phase of the synthesis was functionalization of the cyclopentane part of ketone **13a** (Scheme III). Conversion of **13a** into conjugated ketone **14** was executed in 73% yield by the two-step sequence via a selenide. Oxidation of the double bond conjugated with the keto group in **14** provided a mixture of two diastereomeric



15b



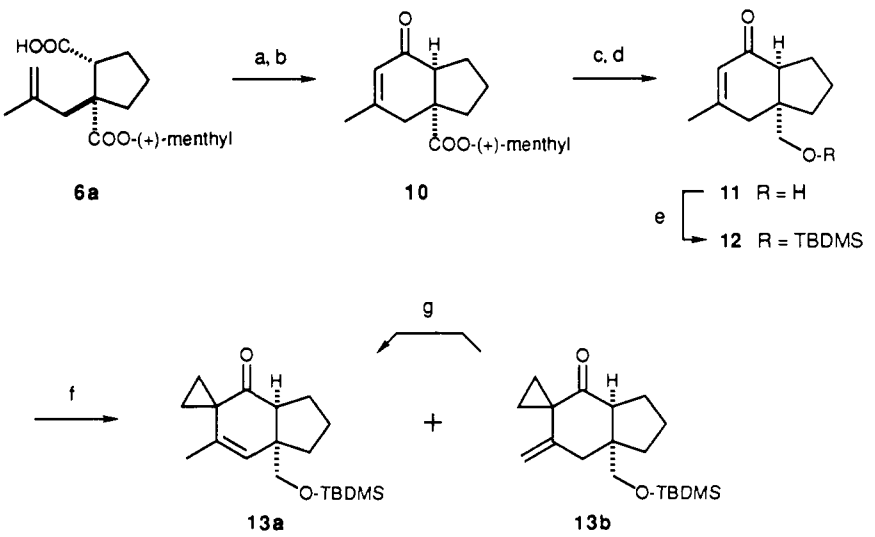
17b

epoxides **15a** (85%) and **15b** (12%). Reduction of epoxide **15a** with calcium in liquid ammonia–THF at −78 °C afforded β-hydroxy ketone **16** in 90% yield. The reaction of the Grignard reagent (MeMgI) with **16** proceeded highly stereoselectively from the less hindered, convex face of the substrate to provide a mixture of two diols **17a** (93%) and **17b** (1%). The addition of methyllithium to **16** was shown to proceed with lower stereoselectivity to give a mixture of **17a** (54%) and **17b** (23%). In order to confirm the stereostructure of **17a** unambiguously, the X-ray crystallographic analysis was performed on racemic triol **17c** (mp 146–148 °C) obtained by desilylation (Bu_4NF, THF) of racemic **17a**,[16] proving the correctness of the assigned stereochemistry. Swern oxidation of **17a** provided ketone **18** in 94% yield. Monomethylation α to the keto group in **18** was performed by the Noyori method:[17] silyl enol ether **19** prepared from **18** was allowed to react with methyl iodide in the presence of $(Me_2N)_3S(Me_3SiF_2)$ to give a separable mixture of two diastereomeric ketones **20a** (49%) and **20b** (42%), the former **20a** being converted into the latter **20b** by base treatment (77%). Stereochemistry of the secondary methyl groups in **20a** and **20b** was determined by the ^1H NMR spectral analysis: **20a** and **20b** were transformed into conformationally rigid acetonides **25a** and **25b**, respectively, and their coupling constants (**25a**, $J_{1,2} = J_{1,9} = 4.0$ Hz; **25b**, $J_{1,2} = J_{1,9} = 9.6$ Hz) were compared with those ($J_{1,2} = J_{1,9} = 9.7$ Hz) of the acetonide **26** derived from natural **1** (Scheme IV). These ^1H NMR spectral data clearly showed that the thermodynamically more stable isomer **20b** has the desired stereochemistry concerning the secondary methyl group. Transformation of **20b** into aldehyde **23** was effected in 88% overall yield through the sequence: (1) reduction of the keto group and removal of the TMS group to afford diol **21**; (2) deprotection of the TBDMS group to give triol **22**; and (3) Swern oxidation (Scheme III).

The final phase of the synthesis required deformylative oxidation of aldehyde **23** in order to introduce an angular hydroxyl group or its equivalent under conditions mild enough to permit survival of the unstable product ptaquilosin (**2**). We found that this transformation was achieved by warming a concentrated solution of **23** in ethyl acetate under an oxygen atmosphere[18] to afford hydroperoxide **24**, which was reduced with triphenylphosphine providing (−)-ptaquilosin (**2**) in 34% yield. The structural

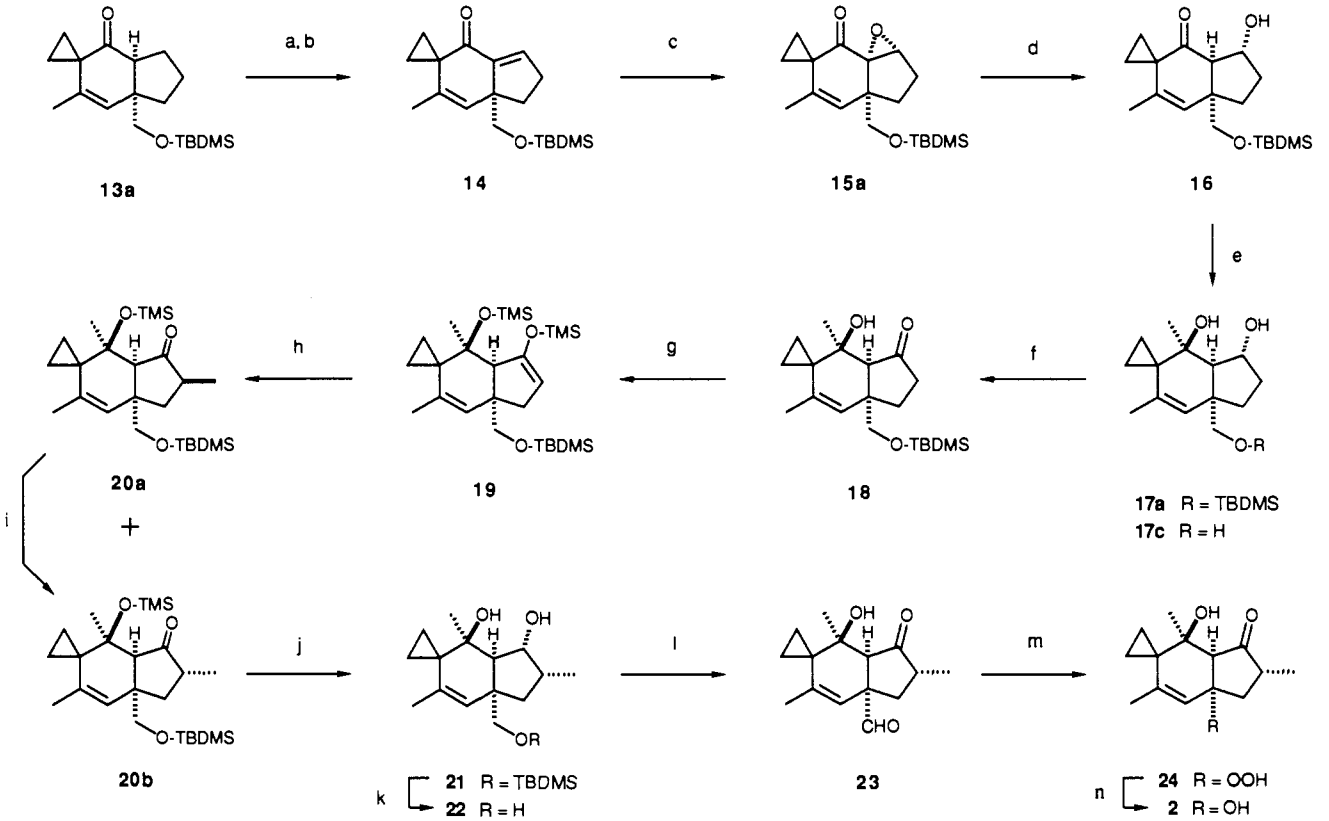
(11) Ho, T.-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977.
(12) Kim, S.; Lhim, D. C. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3297–3298.
(13) For spirocyclopropanation of saturated ketones with this reagent, see: Ruder, S. M.; Ronald, R. C. *Tetrahedron Lett.* **1984**, *25*, 5501–5504.
(14) Yates, P.; Helferty, P. H.; Mahler, P. *Can. J. Chem.* **1983**, *61*, 78–85.
(15) Newman, M. S.; DeVries, J.; Darlak, R. *J. Org. Chem.* **1966**, *31*, 2171–2174.
(16) Racemic **17a** was available by an alternative synthetic route starting from α-allyl-δ-valerolactone: Kigoshi, H.; Sawada, A.; Nakayama, Y.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1989**, *30*, 1983–1986. The compound **17a** was obtained by a more efficient route starting with cyclopentene-1,2-dicarboxylic acid anhydride: Kigoshi, H.; Tanaka, H.; Hirokawa, J.; Mizuta, K.; Yamada, K. *Tetrahedron Lett.* **1992**, *33*, 6647–6650.
(17) Noyori, R.; Nishida, I.; Sakata, J. *Tetrahedron Lett.* **1980**, *21*, 2085–2088.
(18) It was found that decarbonylation of acyl radicals which were generated from aldehydes proceeded smoothly when the alkyl radicals that were formed could be stabilized by allylic conjugation. Further conjugation of the double bond in the allyl radical with a carbonyl or a cyclopropyl group allowed position-selective peroxidation of the alkyl radical. For details, see: Kigoshi, H.; Imamura, Y.; Sawada, A.; Niwa, H.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3735–3737.

Scheme II[a]



[a] (a) $(COCl)_2$, benzene, 23 °C; (b) $SnCl_4$, CH_2Cl_2, -78 °C; (c) $LiAlH_4$, THF, 23 °C; (d) imidazolium dichromate, DMF, 23 °C; (e) *t*-$BuMe_2SiCl$, imidazole, DMF, 23 °C; (f) $ClCH_2CH_2SMe_2I$, KI, *t*-BuOK, *t*-BuOH, 23 °C; (g) *p*-TsOH, dioxane, reflux.

Scheme III[a]



[a] (a) LDA, then PhSeCl, THF, -78 °C; (b) 30% H_2O_2, pyr, CH_2Cl_2, 23 °C; (c) 30% H_2O_2, NaOH, MeOH, 10 °C; (d) Ca, liquid NH_3/THF (2:1), -78 °C; (e) MeMgI, ether, 23 °C; (f) DMSO, $(COCl)_2$, CH_2Cl_2, -78 °C, then Et_3N, -78 °C → 23 °C; (g) TMS-OTf, 2,6-lutidine, CH_2Cl_2, -78 °C; (h) $(Me_2N)_3S(Me_3SiF_2)$, MeI, THF, 23 °C; (i) *t*-BuOK, *t*-BuOH, 23 °C; (j) $LiAlH_4$, ether, 23 °C; (k) Bu_4NF, THF, 45 °C; (l) DMSO, $(COCl)_2$, CH_2Cl_2, -65 °C, then Et_3N, -65 °C → 23 °C; (m) O_2, EtOAc, 50 °C; (n) PPh_3, ether, 23 °C.

feature embodied by the β,γ-unsaturated aldehyde unit was shown to be a requisite for the success of this intriguing deformylative oxidation reaction.[18,19] Synthetic (-)-ptaquilosin (**2**) proved to be identical with natural **2**[20] by spectral (^{1}H NMR, IR, MS, α_D) and chromatographic comparison.

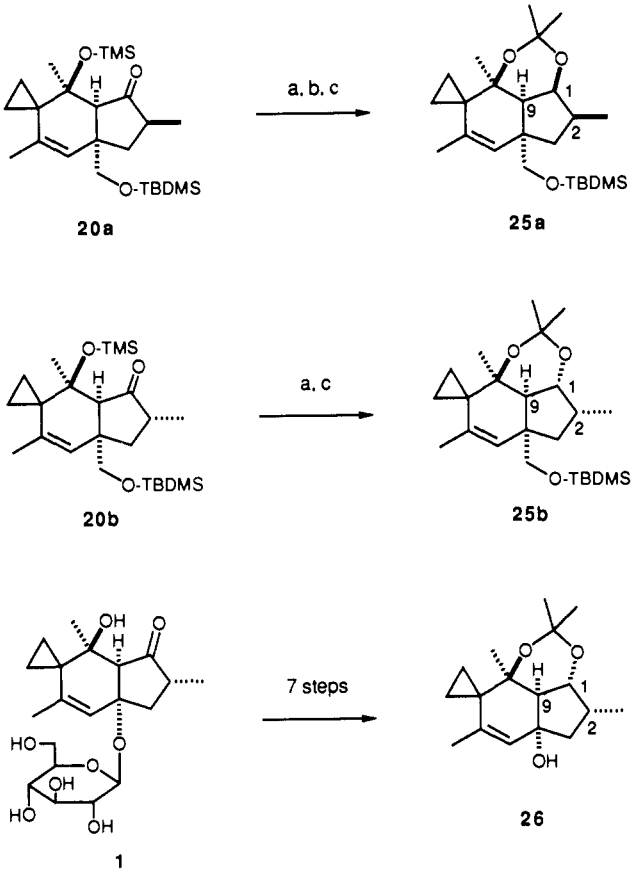
The (+)-enantiomer of natural (-)-ptaquilosin (**2**) was also synthesized from methyl ester **8b** (Scheme V). Alkaline hydrolysis of **8b** afforded a mixture of diastereomeric acids **6b** and **6c** (91%), which, through their acyl chlorides, was converted into enone **27** (89% from a mixture of **6b** and **6c**) (Scheme V). In the manner similar to the synthesis of (-)-ptaquilosin (**2**) described above, enone **27** furnished (+)-ptaquilosin (**2**). Synthetic (+)-ptaquilosin (**2**) proved to be identical with natural (-)-**2** in every respect (^{1}H NMR, IR, MS, α_D, TLC) except for the sign of the specific rotation.

DNA Cleaving Activities of Both Enantiomers of Dienone 4 Derived from (-)- and (+)-Ptaquilosin (2). Previously we reported

(19) This deformylative oxidation reaction proceeded also in benzene at 50 °C in the presence of AIBN in less yield.

(20) Natural **2** was derived from **1** by chemical means: Kigoshi, H.; Sawada, A.; Imamura, Y.; Niwa, H.; Yamada, K. *Tetrahedron* **1989**, *45*, 2551-2556.

Scheme IV[a]



[a] (a) $LiAlH_4$, ether, 23 °C; (b) K_2CO_3, MeOH, reflux; (c) CH_2=C(OMe)Me, *p*-TsOH, benzene, 23 °C.

the DNA cleaving activities of dienone **4** obtained from bracken carcinogen ptaquiloside (**1**) as well as from ptaquilosin (**2**).[4] Having secured both enantiomers of ptaquilosin (**2**) by synthesis, we were interested in the problem whether or not there is a difference in reactivities between two enantiomers of derived dienone **4** toward DNA from the viewpoint of chiral molecular recognition. Thus, the DNA cleaving properties of both enantiomers of dienone **4** were explored using pBR322 double-stranded supercoiled DNA (Figure 2). Both enantiomers of dienone **4** were prepared by treatment of (−)- and (+)-ptaquilosin (**2**) with sodium carbonate in methanol, respectively. Incubation of **4** with pBR322 form I DNA at 37 °C produced form II DNA and subsequently form III DNA as shown by agarose gel electrophoresis analysis (Figure 2). Since dienone **4** reacts with DNA and also with other nucleophiles such as water and inorganic anions in the reaction mixture, high [**4**]/[DNA nucleotide] ratios (25–50) were required for the complete relaxation of form I DNA into form II DNA and finally into form III DNA (Figure 2). Interestingly, dienone **4** derived form natural (−)-ptaquilosin (**2**) was found to be more efficient than dienone **4** obtained from unnatural (+)-ptaquilosin (**2**) with respect to the DNA cleaving activities.[21]

Conclusion

The synthesis of both enantiomers of ptaquilosin (**2**), the aglycon of a bracken carcinogen ptaquiloside (**1**), has been achieved stereoselectively by employing a common chiral compound **5**. Further, concerning the DNA cleaving activities, dienone **4** prepared from natural (−)-ptaquilosin (**2**) was observed to be more efficient than dienone **4** derived from unnatural (+)-ptaquilosin (**2**).

(21) In all of three experiments performed the small but clear difference of DNA cleaving activities between both enantiomers of dienone **4** was observed.

Experimental Section

General Methods. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF), diethyl ether, and 1,2-dimethoxyethane (DME) were distilled from sodium/benzophenone prior to use. Diisopropylamine, triethylamine, dichloromethane, pyridine, and *tert*-butyl alcohol were distilled from CaH_2. Hexamethylphosphoric triamide (HMPA), *N,N*-dimethylformamide (DMF), and dimethyl sulfoxide were distilled from CaH_2 under reduced pressure. All reactions involving organometallic reagents were conducted under a nitrogen atmosphere. Evaporation of solvents was carried out with a rotary evaporator under reduced pressure (ca. 20 Torr). Fuji-Davison silica gel BW-820MH was employed for column chromatography. Merck precoated silica gel 60 F_{254} plates were used for thin-layer chromatography (TLC). Melting points are uncorrected. IR spectra were obtained with a JASCO IR-810 instrument in chloroform solutions. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-C675 instrument (270 MHz). Chemical shifts are reported in ppm downfield from internal tetramethylsilane. *J* values are in hertz. Mass spectra (EIMS/CIMS) are recorded on a JEOL JMS-LG2000 spectrometer. Methane was used as a reagent gas for chemical ionization method.

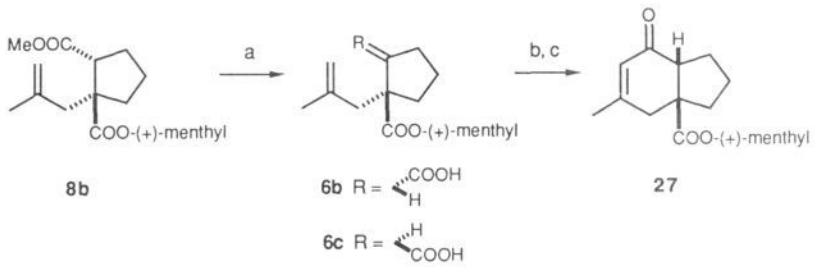
The purity of all compounds submitted for high-resolution mass spectrometric analysis was determined to be >90–95% by ^{1}H NMR analysis. Optical rotations were measured with a JASCO DIP-4 polarimeter.

(+)-Menthyl Hydrogen (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylate (5). To a solution of (+)-dimenthyl (1*R*,2*R*)-cyclopentane-1,2-dicarboxylate (3.00 g, 6.91 mmol) in methanol (100 mL) were added KOH (0.80 g, 14 mmol) and 30% aqueous H_2O_2 (2.0 mL, 18 mmol). The mixture was stirred at 50 °C for 14 h, and methanol was removed in vacuo. The residual aqueous solution was diluted with 5% aqueous $NaHCO_3$ solution (30 mL) and hexane (40 mL), and the aqueous layer was separated. The hexane layer was extracted with 5% aqueous $NaHCO_3$ solution (2 × 10 mL). The aqueous layer and the aqueous extracts were combined and washed with hexane (10 mL). The aqueous layer was acidified with a 6 M HCl solution (50 mL), saturated with NaCl, and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–ether 1:1) to give monoester **5** (1.47 g, 72%) as a colorless oil: $[\alpha]^{24}_D$ +7.7° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 3500–2400 (br), 1710, 1460, 1375, 1195 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.74 (d, *J* = 6.9 Hz, 3 H), 0.80–1.13 (m, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H), 1.34–1.55 (m, 2 H), 1.58–2.20 (m, 10 H), 3.08–3.16 (m, 2 H), 4.67 (ddd, *J* = 10.9, 10.9, 4.3 Hz, 1 H); CIMS (*m/z*, rel intensity) 297 [(M + H)$^+$, 3], 159 (50), 138 (100). Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.89; H, 9.52. Found: C, 68.85; H, 9.64.

Methallylation of (+)-Menthyl Hydrogen (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylate (5). (**A**) A solution of monoester **5** (0.92 g, 3.1 mmol) in THF (7.5 mL) was added at −20 °C to a solution of lithium diisopropylamide (LDA) prepared from diisopropylamine (1.1 mL, 7.9 mmol), a 1.68 M solution of *n*-BuLi in hexane (4.3 mL, 7.2 mmol), and THF (7.5 mL) at −20 °C. After the mixture was stirred at −24 ~ −17 °C for 1 h, HMPA (1.4 mL, 8.0 mmol) was added. The mixture was cooled to −78 °C, and methallyl bromide (0.97 mL, 9.3 mmol) was added. The reaction mixture was stirred at −78 °C for 1.5 h, allowed to warm to −20 °C over 5.5 h, diluted with 2 M HCl (43 mL), and extracted with ethyl acetate (3 × 40 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (100 g, hexane–ether 5:1 → 2:1) to afford a 45:1 mixture of acids **6a** and **6b**, i.e., acid **6a** with 96% de (1.02 g, 93%) as an oil: $[\alpha]^{21}_D$ +34.0° (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) 3500–2400 (br), 1705, 1640, 1450, 900 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (d, *J* = 6.9 Hz, 3 H), 0.78–1.13 (m, 3 H), 0.89 (d, *J* = 6.6 Hz, 6 H), 1.33–1.52 (m, 2 H), 1.59–2.10 (m, 10 H), 1.75 (br s, 3 H), 2.22 (m, 1 H), 2.46 (d, *J* = 13.9 Hz, 1 H), 2.66 (d, *J* = 13.9 Hz, 1 H), 2.83 (dd, *J* = 8.1, 8.1 Hz, 1 H), 4.64 (ddd, *J* = 10.9, 10.9, 4.3 Hz, 1 H), 4.75 (m, 1 H), 4.87 (m, 1 H); EIMS (*m/z*, rel intensity) 350 (M$^+$, 10), 294 (15), 213 (55), 194 (85), 166 (45), 157 (100), 149 (55), 138 (80). Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.05; H, 9.76.

(**B**) A solution of monoester **5** (1.03 g, 3.48 mmol) in THF (6 mL) was added at −25 °C to a solution of LDA prepared from diisopropylamine (1.25 mL, 9.0 mmol), a 1.56 M *n*-BuLi in hexane (5.5 mL, 8.5 mmol), and THF (8 mL) at −25 °C. After the mixture was stirred at −25 ~

Scheme V[a]



[a] (a) KOH, *i*-PrOH/H_2O (10:1), reflux; (b) $(COCl)_2$, benzene, 23 °C; (c) $SnCl_4$, CH_2Cl_2, –78 °C.

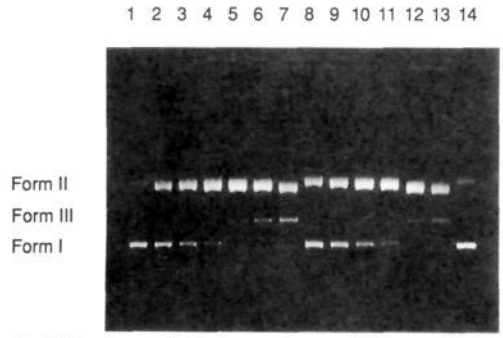


Figure 2. DNA cleavage by both enantiomers of dienone **4** derived from natural (–)- and unnatural (+)-ptaquilosin (**2**), respectively. Reaction mixtures containing (in a total volume of 20 μL) pBR322 DNA (42 μM nucleotide concentration), 8 mM Tris-borate buffer (pH 7.5), 0.4 mM ethylenediaminetetraacetic acid (EDTA), and 17% (v/v) acetonitrile were incubated with natural **4** or unnatural **4** at 37 °C for 13.5 h. Lanes 1 and 14, DNA alone (control). The values of [natural **4**]/[DNA nucleotide] for lanes 2–7: 2.5, 5, 10, 25, 50, 100 and those of [unnatural **4**]/[DNA nucleotide] for lanes 8–13: 2.5, 5, 10, 25, 50, 100. The samples were electrophoresed on a 1% agarose gel containing 50 mM Tris-borate buffer (pH 8.0) and 1 mM EDTA. Key: form I, supercoiled DNA; form II, nicked DNA; form III, linear DNA.

–20 °C for 1 h, methallyl chloride (1.1 mL, 11 mmol) was added. The reaction mixture was stirred at room temperature for 16 h, diluted with 2 M HCl (30 mL), and extracted with ethyl acetate (3 × 40 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (60 g, hexane–ethyl acetate 10:1) to give a 1:4 mixture of acids **6a** and **6b** (1.04 g, 86%) as an oil.

The mixture of acids (1.04 g, 2.97 mmol) was dissolved in ether (3 mL), and an ethereal diazomethane solution was added in small portions until the yellow color of diazomethane persisted. After decomposition of unreacted diazomethane with acetic acid, the mixture was concentrated and purified by column chromatography on silica gel (55 g, hexane–ether 30:1 → 10:1) to afford methyl ester **8a** (201 mg, 19%) and methyl ester **8b** (828 mg, 77%) as an oil, respectively.

Methyl ester 8a: $[\alpha]^{23}_D$ +41.7° (*c* 0.915, $CHCl_3$); IR ($CHCl_3$) 3080, 1720, 1640, 1455, 1365, 1195, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.65–1.12 (m, 3 H), 0.72 (d, *J* = 6.9 Hz, 3 H), 0.90 (d, *J* = 6.8 Hz, 6 H), 1.31–1.52 (m, 2 H), 1.60–2.06 (m, 9 H), 1.74 (br s, 3 H), 2.24 (m, 1 H), 2.39 (d, *J* = 14.1 Hz, 1 H), 2.69 (d, *J* = 14.1 Hz, 1 H), 2.79 (dd, *J* = 8.1, 8.1 Hz, 1 H), 3.66 (s, 3 H), 4.62 (ddd, *J* = 10.8, 10.8, 4.4 Hz, 1 H), 4.73 (br s, 1 H), 4.85 (br s, 1 H); EIMS (*m/z*, rel intensity) 364 (M^+, 25), 308 (8), 226 (95), 180 (100), 138 (70). Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95. Found: C, 72.50; H, 10.11.

Methyl ester 8b: $[\alpha]^{15}_D$ –12.7° (*c* 1.12, $CHCl_3$); IR ($CHCl_3$) 3080, 1715, 1650, 1455, 1365, 1200, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.72 (d, *J* = 6.9 Hz, 3 H), 0.75–1.15 (m, 3 H), 0.90 (d, *J* = 6.3 Hz, 6 H), 1.35–1.55 (m, 2 H), 1.55–1.75 (m, 2 H), 1.67 (br s, 3 H), 1.75–2.05 (m, 7 H), 2.25 (m, 1 H), 2.26 (d, *J* = 14.6 Hz, 1 H), 2.57 (d, *J* = 14.6 Hz, 1 H), 3.23 (dd, *J* = 6.9, 6.9 Hz, 1 H), 3.66 (s 3 H), 4.63 (br s, 1 H), 4.64 (ddd, *J* = 10.9, 10.9, 4.3 Hz, 1 H), 4.75 (br s, 1 H); EIMS (*m/z*, rel intensity) 364 (M^+, 10), 310 (3), 226 (70), 95 (100). Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.95. Found: C, 72.44; H, 10.10.

Tetrahydrofuran 9: To a solution of methyl ester **8a** (98.9 mg, 0.27 mmol) in THF (2 mL) was added a 1 M solution of lithium aluminum hydride in THF (0.8 mL, 0.8 mmol), and the mixture was stirred at room temperature for 1 h. Sodium fluoride (350 mg, 8.3 mmol) was added to the reaction mixture, and the mixture was stirred at room temperature for 10 min. To the ice-cooled reaction mixture was added a solution of H_2O–THF (1:9) (1.5 mL). The mixture was stirred at room temperature for 10 min and filtered through a pad of Celite. The residue was washed with ether, and the filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–ethyl acetate, 2:1) to give a diol (40.6 mg, 82%) as a colorless oil: $[\alpha]^{22}_D$ –16.8° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3620, 3350 (br), 3070, 1640, 1065, 1040, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (m, 1 H), 1.45–1.85 (m, 6 H), 1.82 (d, *J* = 1.0 Hz, 3 H), 1.94 (d, *J* = 13.5 Hz, 1 H), 2.53 (d, *J* = 13.5 Hz, 1 H), 3.30–3.60 (br s, 2 H), 3.44 (d, *J* = 11.5 Hz, 1 H), 3.56 (d, *J* = 11.5 Hz, 1 H), 3.72 (m, 2 H), 4.78 (m, 1 H), 4.88 (m, 1 H); EIMS (*m/z*, rel intensity) 184 (M^+, 10), 169 (5), 153 (30), 81 (100).

To a solution of the diol obtained above (21.8 mg, 0.12 mmol) in pyridine (0.3 mL) was added *p*-toluenesulfonyl chloride (28 mg, 0.15 mmol). The flask was stoppered, and the mixture was stirred at room temperature for 3 h. *p*-Toluenesulfonyl chloride (20 mg, 0.11 mmol) was added, and the mixture was stirred for further 2 h. The unreacted *p*-toluenesulfonyl chloride was hydrolyzed by adding a small amount of ice. The reaction mixture was diluted with water (3 mL) and extracted with ether (4 × 5 mL). The combined extracts were washed with 2 M HCl, saturated aqueous $NaHCO_3$ solution, and saturated aqueous NaCl solution, successively. The organic layer was dried (Na_2SO_4) and concentrated. The residual oil was purified by column chromatography on silica gel (4 g, hexane–ethyl acetate 20:1 → 10:1) to give tetrahydrofuran **9** (12.6 mg, 63%) as a colorless volatile oil: $[\alpha]^{21}_D$ –0.63° (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) 3080, 1645, 1350, 1070, 910, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (m, 1 H), 1.54–1.85 (m, 5 H), 1.74 (s, 3 H), 2.22 (d, *J* = 13.7 Hz, 1 H), 2.24 (m, 1 H), 2.29 (d, *J* = 13.7 Hz, 1 H), 3.43 (dd, *J* = 8.9, 4.6 Hz, 1 H), 3.52 (d, *J* = 8.9 Hz, 1 H), 3.71 (d, *J* = 8.9 Hz, 1 H), 3.90 (dd, *J* = 8.9, 7.6 Hz, 1 H), 4.68 (m, 1 H), 4.81 (m, 1 H); EIMS (*m/z*, rel intensity) 166 (M^+, 2), 151 (2), 148 (1), 110 (100), 82 (80); HREIMS calcd for $C_{11}H_{18}O$ (M^+) 166.1358, found 166.1361.

Ketone 10. A mixture of acid **6a** with 96% de (2.42 g, 6.91 mmol) and oxalyl chloride (6.6 mL, 76 mmol) in benzene (240 mL) was stirred at room temperature for 3 h and concentrated. The residue was dissolved in benzene (20 mL), concentrated, and dissolved in dichloromethane (290 mL). To the solution tin(IV) chloride (2.4 mL, 21 mmol) was added at –78 °C. After being stirred at –78 °C for 3.7 h, the reaction mixture was diluted with 2 M HCl (290 mL) and extracted with chloroform (3 × 250 mL). The combined organic extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was heated at 50 °C for 2.5 h under reduced pressure and purified by column chromatography on silica gel (100 g, benzene–ether 20:1) to give ketone **10** (1.90 g, 83%) as a colorless oil: $[\alpha]^{15}_D$ +64.6° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3010, 1715, 1660, 1380, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68–1.11 (m, 3 H), 0.72 (d, *J* = 6.9 Hz, 3 H), 0.88 (d, *J* = 6.4 Hz, 6 H), 1.31–1.93 (m, 10 H), 1.96 (s, 3 H), 2.02–2.18 (m, 2 H), 2.34 (br d, *J* = 18.4 Hz, 1 H), 2.72 (d, *J* = 18.4 Hz, 1 H), 3.04 (dd, *J* = 8.6, 8.6 Hz, 1 H), 4.66 (ddd, *J* = 10.9, 10.9, 4.3 Hz, 1 H), 5.85 (br s, 1 H); EIMS (*m/z*, rel intensity) 332 (M^+, 5), 195 (85), 149 (100). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.92; H, 9.81.

Ketone 27. Potassium hydroxide (414 mg, 7.4 mmol) was added to a solution of methyl ester **8b** (828 mg, 2.27 mmol) in isopropyl alcohol (20 mL) and water (2 mL). The mixture was refluxed for 6 h and concentrated in vacuo. The resulting aqueous layer was diluted with 2 M HCl (20 mL), saturated with NaCl, and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was

purified by column chromatography on silica gel (30 g, hexane–ether, 10:1) to give a mixture of acids **6b** and **6c** (725 mg, 91%, 7:3 diastereomeric mixture) as a colorless oil. A mixture of acids **6b** and **6c** (839 mg, 2.40 mmol) and oxalyl chloride (2.5 mL, 29 mmol) in benzene (84 mL) was stirred at room temperature for 3 h and concentrated. The residue was dissolved in benzene (10 mL), concentrated, and dissolved in dichloromethane (84 mL). To the solution tin(IV) chloride (0.85 mL, 7.3 mmol) was added at −78 °C. After being stirred at −78 °C for 2 h, the reaction mixture was diluted with 2 M HCl (50 mL) and extracted with chloroform (3 × 50 mL). The combined organic extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was heated at 50 °C for 30 min under reduced pressure and purified by column chromatography on alumina (8 g, benzene–ethyl acetate, 1:1) and subsequently on silica gel (40 g, hexane–ethyl acetate, 10:1) to give ketone **27** (707 mg, 89%) as a colorless oil: $[\alpha]^{15}_D$ +50.4° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3010, 1715, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.69 (d, *J* = 6.9 Hz, 3 H), 0.85–1.15 (m, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 1.20–2.00 (m, 10 H), 1.96 (s, 3 H), 2.00–2.20 (m, 2 H), 2.36 (br d, *J* = 18.1 Hz, 1 H), 2.69 (d, *J* = 18.1 Hz, 1 H), 3.03 (dd, *J* = 8.6, 8.6 Hz, 1 H), 4.65 (ddd, *J* = 10.9, 10.9, 4.3 Hz, 1 H), 5.84 (br s, 1 H); EIMS (*m/z*, rel intensity) 332 (M^+, 10), 195 (100), 149 (90). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.88; H, 9.87.

Reduction of Ketone 10. A solution of ketone **10** (1.90 g, 5.72 mmol) in ether (10 mL) was added to a mixture of lithium aluminum hydride (500 mg, 13 mmol) in ether (12 mL). After the mixture was stirred at room temperature for 2 h, sodium fluoride (5.5 g) and a solution of H_2O–THF (1:9) (10 mL) were added to the cooled reaction mixture. After being stirred at room temperature for 10 min, the mixture was filtered through a pad of Celite. The residue was washed with ether thoroughly and the filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (90 g, benzene–ethyl acetate, 2:1 → 1:1) to give diol (+)-**A** (434 mg, 42%) and diol (+)-**B** (605 mg, 58%) as colorless crystals, respectively.

Diol (+)-A: mp 66.0–68.0 °C (hexane); $[\alpha]^{19}_D$ +71.7° (*c* 0.582, MeOH); IR ($CHCl_3$) 3600, 3370 (br), 1680, 1450, 1040, 1005 cm^{-1}; ^1H NMR (C_6D_6) δ 1.10–1.51 (m, 5 H), 1.55–1.74 (m, 2 H), 1.60 (s, 3 H), 1.74–1.88 (m, 2 H), 2.8–3.8 (br s, 2 H), 3.41 (d, *J* = 10.7 Hz, 1 H), 3.47 (d, *J* = 10.7 Hz, 1 H), 3.95 (br s, 1 H), 5.43 (br s, 1 H); EIMS (*m/z*, rel intensity) 182 (M^+, 4), 167 (8), 164 (35), 151 (100), 133 (60). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.50; H, 9.92.

Diol (+)-B: mp 98.5–100.0 °C (benzene); $[\alpha]^{21}_D$ +1.5° (*c* 0.582, MeOH); IR ($CHCl_3$) 3600, 3430 (br), 1680, 1440, 1380, 1025 cm^{-1}; ^1H NMR (C_6D_6) δ 0.70–1.10 (br s, 2 H), 1.25–1.64 (m, 7 H), 1.53 (d, *J* = 0.7 Hz, 3 H), 1.76 (m, 1 H), 1.95 (m, 1 H), 3.10 (d, *J* = 10.4 Hz, 1 H), 3.18 (d, *J* = 10.4 Hz, 1 H), 4.25 (br s, 1 H), 5.33 (br s, 1 H); EIMS (*m/z*, rel intensity) 182 (M^+, 2), 167 (10), 164 (40), 151 (100), 133 (60). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.51; H, 10.04.

In the same manner as in the case of ketone **10**, reduction of ketone **27** was carried out to give diol (−)-**A** (46%) and diol (−)-**B** (51%). **Diol (−)-A**: mp 59.0–60.5 °C (hexane–ether); $[\alpha]^{12}_D$ −63.3° (*c* 0.510, MeOH). **Diol (−)-B**: mp 97.0–99.0 °C (hexane–ether); $[\alpha]^{14}_D$ −2.7° (*c* 0.515, MeOH).

Ketone 11. (A) From Diol (+)-A. A mixture of diol (+)-**A** (403 mg, 2.22 mmol) and imidazolium dichromate (1.57 g, 4.44 mmol) in DMF (6 mL) was stirred at room temperature for 1.5 h. The mixture was diluted with water (36 mL) and extracted with ether (2 × 20 mL) and with ethyl acetate (6 × 20 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (35 g, hexane–ethyl acetate, 1:1) to give ketone (+)-**11** (328 mg, 82%) as colorless crystals. The enantiomeric excess of ketone (+)-**11** obtained by recrystallization from pentane–ether was found to be >99% by ^1H NMR spectral analysis of derived bicyclic enone (+)-**12** in C_6D_6 in the presence of 45 mol % of Eu(hfc)$_3$: mp 45.0–47.5 °C (pentane–ether); $[\alpha]^{24}_D$ +32.1° (*c* 0.555, MeOH); IR ($CHCl_3$) 3630, 3430 (br), 3010, 1655, 1440, 1380, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57–1.65 (m, 2 H), 1.68–1.81 (m, 3 H), 1.90–2.14 (m, 2 H), 1.96 (d, *J* = 0.7 Hz, 3 H), 2.22 (br d, *J* = 19.1 Hz, 1 H), 2.40 (dd, *J* = 8.4, 8.4 Hz, 1 H), 2.44 (d, *J* = 19.1 Hz, 1 H), 3.43 (d, *J* = 10.6 Hz, 1 H), 3.56 (d, *J* = 10.6 Hz, 1 H), 5.86 (br s, 1 H); EIMS (*m/z*, rel intensity) 180 (M^+, 30), 162 (6), 149 (100), 82 (85). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.18; H, 9.10. Found: C, 73.30; H, 8.95. (−)-**11**: mp 45.0–47.5 °C (pentane–ether); $[\alpha]^{11}_D$ −33.8° (*c* 0.590, MeOH).

(B) From Diol (+)-B. A mixture of diol (+)-**B** (599 mg, 3.29 mmol) and imidazolium dichromate (2.33 g, 6.58 mmol) in DMF (9 mL) was stirred at room temperature for 50 min. The mixture was diluted with water (55 mL) and extracted with ether (2 × 25 mL) and with ethyl acetate (7 × 25 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (30 g, hexane–ethyl acetate, 1:1) to give ketone (+)-**11** (529 mg, 89%) as colorless crystals.

Bicyclic Enone 12. A solution of ketone (+)-**11** (910 mg, 5.06 mmol), *tert*-butyldimethylsilyl chloride (1.24 g, 8.23 mmol), and imidazole (1.05 g, 15.4 mmol) in DMF (15 mL) was stirred at room temperature for 1 h. The reaction mixture was diluted with water (80 mL) and extracted with ether (3 × 80 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–ethyl acetate, 20:1) to give bicyclic enone (+)-**12** (1.49 g, 100%) as a colorless oil: $[\alpha]^{23}_D$ +11.3° (*c* 1.13, $CHCl_3$); IR ($CHCl_3$) 3010, 1650, 1255, 1100, 840 cm^{-1}; ^1H NMR (C_6D_6) δ −0.03 (s, 3 H), −0.02 (s, 3 H), 0.92 (s, 9 H), 1.27–1.54 (m, 4 H), 1.43 (s, 3 H), 1.74 (br d, *J* = 18.8 Hz, 1 H), 1.87–2.17 (m, 2 H), 2.12 (br d, *J* = 18.8 Hz, 1 H), 2.43 (br dd, *J* = 8.2, 8.2 Hz, 1 H), 3.14 (d, *J* = 9.6 Hz, 1 H), 3.33 (d, *J* = 9.6 Hz, 1 H), 5.90 (br s, 1 H); CIMS (*m/z*, rel intensity) 295 [(M + H)$^+$; 100], 279 (20), 237 (50), 163 (60). Anal. Calcd for $C_{17}H_{30}O_2Si$: C, 69.33; H, 10.27. Found: C, 68.95; H, 10.54. (−)-**12**: $[\alpha]^{11}_D$ −11.1° (*c* 0.710, $CHCl_3$).

Cyclopropanation of Bicyclic Enone 12. A solution of bicyclic enone (+)-**12** (802 mg, 2.73 mmol) in *tert*-butyl alcohol (6.5 mL) was added to a stirred mixture of potassium *tert*-butoxide (1.23 g, 11.0 mmol) in *tert*-butyl alcohol (6.5 mL). After the mixture was stirred at room temperature for 15 min, potassium iodide (0.91 g, 5.5 mmol) and (2-chloroethyl)dimethylsulfonium iodide (1.28 g, 5.1 mmol) were added in portions under a stream of nitrogen. The mixture was stirred at room temperature for 1 h, diluted with saturated aqueous NH_4Cl solution (40 mL), and extracted with ether (3 × 40 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (50 g, hexane–ether 40:1 → 20:1 → 10:1) to give ketone (−)-**13a** (395 mg, 45%) and ketone (+)-**13b** (89.7 mg, 10%) as a colorless oil, respectively.

Ketone (−)-13a: $[\alpha]^{23}_D$ −13.1° (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) 1690, 1660 (sh), 1255, 1095, 910, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 (s, 6 H), 0.85 (s, 9 H), 0.98–1.23 (m, 3 H), 1.47–1.88 (m, 7 H), 1.49 (d, *J* = 1.3 Hz, 3 H), 2.59 (ddd, *J* = 9.2, 9.2, 1.3 Hz, 1 H), 3.38 (d, *J* = 9.6 Hz, 1 H), 3.48 (d, *J* = 9.6 Hz, 1 H), 5.27 (br s, 1 H); CIMS (*m/z*, rel intensity) 321 [(M + H)$^+$; 13], 305 (30), 263 (45), 189 (100), 161 (40). Anal. Calcd for $C_{19}H_{32}O_2Si$: C, 71.19; H, 10.06. Found: C, 71.19; H, 10.38. (+)-**13a**: $[\alpha]^{12}_D$ +12.7° (*c* 1.18, $CHCl_3$).

Ketone (+)-13b: $[\alpha]^{24}_D$ +84.9° (*c* 0.851, $CHCl_3$); IR ($CHCl_3$) 3080, 1685, 1650, 1260, 1100, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H), 0.89 (s, 9 H), 0.98 (m, 1 H), 1.18 (m, 1 H), 1.38–1.84 (m, 7 H), 1.93 (m, 1 H), 2.19 (d, *J* = 13.4 Hz, 1 H), 2.42 (dd, *J* = 8.6, 8.6 Hz, 1 H), 2.57 (d, *J* = 13.4 Hz, 1 H), 3.37 (d, *J* = 9.2 Hz, 1 H), 3.43 (d, *J* = 9.2 Hz, 1 H), 4.57 (br s, 1 H), 4.69 (br s, 1 H); CIMS (*m/z*, rel intensity) 321 [(M + H)$^+$; 11], 305 (25), 263 (40), 189 (100), 161 (45); HRCIMS calcd for $C_{19}H_{33}O_2Si$ (M + H)$^+$ 321.2250, found 321.2229. (−)-**13b**: $[\alpha]^{12}_D$ −86.8° (*c* 0.660, $CHCl_3$).

Isomerization of Ketone 13b to Ketone 13a. A mixture of ketone **13b** (89.7 mg, 0.280 mmol) and *p*-toluenesulfonic acid (25.1 mg, 0.132 mmol) in dioxane (6 mL) was refluxed for 50 min. The reaction mixture was allowed to cool to room temperature, and Et_3N (1.6 mL) was added. The mixture was diluted with saturated $NaHCO_3$ solution (15 mL) and extracted with benzene (3 × 15 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (10 g, hexane–ether, 50:1) to give ketone **13a** (72.3 mg, 81%) as a colorless oil.

Conjugated Ketone 14. A solution of ketone (−)-**13a** (250 mg, 0.781 mmol) in THF (3 mL) was added to a solution of LDA prepared from diisopropylamine (0.35 mL, 2.5 mmol), a 1.64 M solution of *n*-BuLi in hexane (1.45 mL, 2.4 mmol), and THF (3 mL) at −78 °C. After the mixture was stirred at −78 °C for 1 h, a solution of phenylselenenyl chloride (460 mg, 2.4 mmol) in THF (2 mL) was added. The mixture was stirred at −78 °C for 2 h, diluted with saturated aqueous NH_4Cl solution (20 mL), and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual yellow oil was purified

by column chromatography on silica gel (30 g, benzene) to give a crude selenide (328 mg) as a yellow oil. The selenide (328 mg) was dissolved in dichloromethane (31 mL) and pyridine (5.6 mL), and 30% H_2O_2 (5.5 mL, 49 mmol) was added. The mixture was stirred at room temperature for 40 min, diluted with saturated aqueous $NaHCO_3$ solution (22 mL), and extracted with dichloromethane (3 × 25 mL). The combined extracts were washed with 2 M $Na_2S_2O_3$ solution and saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (9 g, hexane–ether, 20:1) to give conjugated ketone (-)-**14** (182 mg, 73% from ketone (-)-**13a**) as a colorless oil: $[\alpha]^{26}_D$ -205° (*c* 1.06, $CHCl_3$); IR ($CHCl_3$) 3000, 1670, 1620, 1305, 1255, 1100, 850, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.03 (s, 6 H), 0.85 (s, 9 H), 1.08 (m, 1 H), 1.26 (m, 1 H), 1.38–1.46 (m, 2 H), 1.50 (d, *J* = 1.3 Hz, 3 H), 1.89 (ddd, *J* = 12.5, 9.6, 9.6 Hz, 1 H), 2.17 (ddd, *J* = 12.5, 6.9, 1.5 Hz, 1 H), 2.34–2.60 (m, 2 H), 3.41 (d, *J* = 9.4 Hz, 1 H), 3.50 (d, *J* = 9.4 Hz, 1 H), 5.61 (br s, 1 H), 6.57 (dd, *J* = 3.0, 2.6 Hz, 1 H); EIMS (*m/z*, rel intensity) 318 (M^+; 9), 303 (2), 261 (85), 173 (100); HREIMS calcd for $C_{19}H_{30}O_2Si$ (M^+) 318.2015, found 318.2019. (+)-**14**: $[\alpha]^{11}_D$ +203° (*c* 0.868, $CHCl_3$).

Epoxidation of Conjugated Ketone 14. A mixture of conjugated ketone (-)-**14** (392 mg, 1.23 mmol), 30% H_2O_2 (4.2 mL, 37 mmol), and 2 M aqueous NaOH solution (0.62 mL, 1.24 mmol) in methanol (19 mL) was stirred at 5–10 °C for 8 h. The mixture was diluted with saturated aqueous NH_4Cl solution (20 mL) and extracted with benzene (4 × 20 mL). The combined extracts were washed with 2 M $Na_2S_2O_3$ solution and saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, hexane–ether, 10:1 → 2:1) to give epoxide (-)-**15a** (348 mg, 85%) as a colorless oil and epoxide (-)-**15b** (49.7 mg, 12%) as colorless crystals.

Epoxide (-)-**15a**: $[\alpha]^{24}_D$ -140° (*c* 1.10, $CHCl_3$); IR ($CHCl_3$) 3010, 1710, 1650, 1255, 1115, 1085, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.01 (s, 3 H), 0.00 (s, 3 H), 0.85 (s, 9 H), 1.12–1.43 (m, 4 H), 1.51–1.67 (m, 2 H), 1.54 (d, *J* = 1.3 Hz, 3 H), 1.89 (m, 1 H), 2.09 (br dd, *J* = 14.2, 8.2 Hz, 1 H), 3.52 (d, *J* = 9.4 Hz, 1 H), 3.57 (br s, 1 H), 3.64 (d, *J* = 9.4 Hz, 1 H), 5.40 (br s, 1 H); ClMS (*m/z*, rel intensity) 335 [(M + H)$^+$; 100], 317 (55), 203 (60); HRClMS calcd for $C_{19}H_{31}O_3Si$ (M + H)$^+$ 335.2043, found 335.2030. (+)-**15a**: $[\alpha]^{12}_D$ +139° (*c* 0.783, $CHCl_3$).

Epoxide (-)-**15b**: mp 43.5–44.5 °C (pentane); $[\alpha]^{24}_D$ -113° (*c* 0.635, $CHCl_3$); IR ($CHCl_3$) 3000, 1715, 1635, 1255, 1115, 1095, 845 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.02 (s, 3 H), -0.01 (s, 3 H), 0.85 (s, 9 H), 1.15 (ddd, *J* = 9.4, 7.6, 3.3 Hz, 1 H), 1.29 (ddd, *J* = 9.7, 7.6, 3.6 Hz, 1 H), 1.44 (ddd, *J* = 9.4, 7.6, 3.6 Hz, 1 H), 1.48–1.60 (m, 2 H), 1.56 (d, *J* = 1.3 Hz, 3 H), 1.65 (ddd, *J* = 9.7, 7.6, 3.3 Hz, 1 H), 1.86 (m, 1 H), 2.05 (br ddd, *J* = 13.9, 6.9, 2.0 Hz, 1 H), 3.47 (d, *J* = 10.1 Hz, 1 H), 3.52 (d, *J* = 10.1 Hz, 1 H), 4.11 (br s, 1 H), 5.65 (q, *J* = 1.3 Hz, 1 H); ClMS (*m/z*, rel intensity) 335 [(M + H)$^+$; 15], 319 (15), 277 (10), 203 (70), 173 (100); HRClMS calcd for $C_{19}H_{31}O_3Si$ (M + H)$^+$ 335.2043, found 335.2071. (+)-**15b**: mp 42.5–44.0 °C (pentane); $[\alpha]^{15}_D$ +117° (*c* 1.06, $CHCl_3$).

β-Hydroxy Ketone 16. Calcium (76.9 mg, 1.92 mmol) was added to a solution of epoxide (-)-**15a** (339 mg, 1.02 mmol) in THF (10 mL) and liquid ammonia (20 mL) at -78 °C. After the mixture was stirred at -78 °C for 30 min, calcium (32.9 mg, 0.821 mmol) was added, and the mixture was stirred for 30 min. Further, calcium (39.9 mg, 0.996 mmol) was added, and the mixture was stirred at -78 °C for 35 min. Ammonium chloride (1.5 g) and $Fe(NO_3)_3 \cdot 9H_2O$ (0.52 g) were added, and the mixture was stirred at -78 °C for 2 h. The mixture was allowed to warm to room temperature. The residue was dissolved in saturated aqueous NH_4Cl solution (30 mL), and the aqueous mixture was extracted with ethyl acetate (4 × 30 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, hexane–ether 2:1 → 1:1) to give β-hydroxy ketone (-)-**16** (308 mg, 90%) as colorless crystals: mp 60.0–62.0 °C (pentane); $[\alpha]^{24}_D$ -46.8° (*c* 0.549, $CHCl_3$); IR ($CHCl_3$) 3590, 3410 (br), 1680, 1260, 1100, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.01 (s, 3 H), 0.00 (s, 3 H), 0.85 (s, 9 H), 1.10 (m, 1 H), 1.20–1.34 (m, 2 H), 1.47–1.72 (m, 3 H), 1.49 (br s, 3 H), 1.70–1.94 (m, 2 H), 2.08 (m, 1 H), 2.51 (br d, *J* = 7.9 Hz, 1 H), 3.40 (d, *J* = 9.6 Hz, 1 H), 3.44 (d, *J* = 9.6 Hz, 1 H), 4.28 (br ddd, *J* = 7.9, 7.9, 7.9 Hz, 1 H), 5.30 (br s, 1 H); ClMS (*m/z*, rel intensity) 337 [(M + H)$^+$; 19], 319 (23), 279 (100), 205 (75), 188 (65), 173 (35). Anal. Calcd for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58. Found: C, 67.94; H, 9.67. (+)-**16**: mp 60.0–64.0 °C (pentane); $[\alpha]^{16}_D$ +48.3° (*c* 0.515, $CHCl_3$).

Diols 17a and 17b. A solution of β-hydroxy ketone (-)-**16** (431 mg, 1.28 mmol) in ether (6 mL) was added at room temperature to an ethereal solution of methylmagnesium iodide prepared from magnesium (357 mg, 14.7 mmol) and methyl iodide (0.80 mL, 13 mmol) in ether (15 mL). After being stirred for 1 h, the mixture was cooled to 0 °C, and the reaction was quenched by careful addition of saturated aqueous NH_4Cl solution (40 mL). The aqueous mixture was extracted with ether (3 × 40 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, hexane–ether, 4:1 → 2:1 → 1:1 → 1:2) to give diol (-)-**17a** (418 mg, 93%) as a colorless oil and diol (-)-**17b** (4.7 mg, 1%) as colorless crystals.

Diol (-)-**17a**: $[\alpha]^{24}_D$ -102° (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 3610, 3460 (br), 1650, 1255, 1090, 870, 855, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3 H), 0.06 (s, 3 H), 0.44–0.58 (m, 2 H), 0.73 (m, 1 H), 0.92 (s, 9 H), 1.20–1.56 (m, 3 H), 1.23 (s, 3 H), 1.40 (d, *J* = 1.3 Hz, 3 H), 1.86–2.00 (m, 3 H), 2.00–3.00 (br m, 2 H), 3.38 (d, *J* = 9.4 Hz, 1 H), 3.48 (d, *J* = 9.4 Hz, 1 H), 4.42 (ddd, *J* = 9.6, 9.6, 5.9 Hz, 1 H), 5.14 (br s, 1 H); EIMS (*m/z*, rel intensity) 352 (M^+; 9), 295 (50), 277 (60), 207 (90), 185 (100), 171 (65); HREIMS calcd for $C_{20}H_{36}O_3Si$ (M^+) 352.2434, found 352.2412. (+)-**17a**: $[\alpha]^{11}_D$ +101° (*c* 1.04, $CHCl_3$).

Diol (-)-**17b**: mp 96.0–97.0 °C (pentane); $[\alpha]^{27}_D$ -67° (*c* 0.25, $CHCl_3$); IR ($CHCl_3$) 3600, 3380 (br), 1655, 1255, 1105, 1075, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.08 (s, 6 H), 0.56 (m, 1 H), 0.75–0.95 (m, 3 H), 0.90 (s, 9 H), 1.09 (s, 3 H), 1.32–1.65 (m, 2 H), 1.44 (d, *J* = 1.0 Hz, 3 H), 1.62 (br s, 1 H), 1.71–1.90 (m, 2 H), 1.92 (br d, *J* = 3.6 Hz, 1 H), 3.53 (d, *J* = 9.7 Hz, 1 H), 3.63 (d, *J* = 9.7 Hz, 1 H), 4.24 (m, 1 H), 4.54 (1 H, br m), 5.12 (br s, 1 H); EIMS (*m/z*, rel intensity) 352 (M^+; 2), 295 (10), 277 (60), 207 (60), 189 (100); HREIMS calcd for $C_{20}H_{36}O_3Si$ (M^+) 352.2434, found 352.2427. (+)-**17b**: mp 90.5–92.0 °C (benzene); $[\alpha]^{16}_D$ +60° (*c* 0.27, $CHCl_3$).

Ketone 18. A solution of dimethyl sulfoxide (0.16 mL, 2.3 mmol) in dichloromethane (0.5 mL) was added at -78 °C to a solution of oxalyl chloride (0.10 mL, 1.2 mmol) in dichloromethane (2 mL). After 3 min, a solution of diol (-)-**17a** (87.2 mg, 0.248 mmol) in dichloromethane (1.2 mL) was added. The reaction mixture was stirred for an additional 15 min at -78 °C, and triethylamine (0.80 mL, 5.7 mmol) was added. After being stirred at -78 °C for 5 min, the mixture was warmed to room temperature over 30 min. The mixture was diluted with 1 M phosphate buffer (pH 7, 10 mL) and extracted with dichloromethane (4 × 10 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (3.5 g, hexane–ether, 8:1) to give ketone (-)-**18** (81.1 mg, 94%) as colorless crystals: mp 63.0–65.0 °C (pentane); $[\alpha]^{24}_D$ -212° (*c* 0.555, $CHCl_3$); IR ($CHCl_3$) 3440 (br), 1715, 1650, 1255, 1095, 860, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.41 (ddd, *J* = 9.6, 6.6, 4.0 Hz, 1 H), 0.64–0.80 (m, 2 H), 0.88 (m, 1 H), 0.90 (s, 9 H), 1.20 (s, 3 H), 1.44 (d, *J* = 1.3 Hz, 3 H), 1.61 (ddd, *J* = 11.9, 6.9, 2.6 Hz, 1 H), 2.12 (ddd, *J* = 13.2, 11.9, 7.9 Hz, 1 H), 2.19–2.41 (m, 2 H), 2.51 (br s, 1 H), 3.52 (d, *J* = 9.9 Hz, 1 H), 3.65 (d, *J* = 9.9 Hz, 1 H), 4.93 (br s, 1 H), 5.14 (br s, 1 H); EIMS (*m/z*, rel intensity) 350 (M^+, 7), 293 (80), 275 (35), 205 (100), 187 (50), 159 (65). Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.52; H, 9.78. Found: C, 68.54; H, 9.91. (+)-**18**: mp 64.0–66.0 °C (pentane); $[\alpha]^{17}_D$ +202° (*c* 0.952, $CHCl_3$).

Methylation of Ketone 18: Ketones 20a and 20b. To a solution of ketone (-)-**18** (57.1 mg, 0.163 mmol) in dichloromethane (2 mL) were added 2,6-lutidine (0.30 mL, 2.6 mmol) and trimethylsilyl trifluoromethanesulfonate (0.25 mL, 1.3 mmol) at -78 °C. The mixture was stirred at -78 °C for 1 h, diluted with saturated $NaHCO_3$ solution (2 mL), and extracted with hexane (2 × 10 mL) and benzene (2 × 5 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated to give silyl enol ether **19** (84 mg) as a colorless oil: IR ($CHCl_3$) 1645, 1250, 1095, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.20 (s, 9 H), 0.22 (s, 9 H), 0.44 (m, 1 H), 0.60 (m, 1 H), 0.82 (m, 1 H), 0.93 (m, 1 H), 0.98 (s, 9 H), 1.20 (s, 3 H), 1.44 (d, *J* = 1.3 Hz, 3 H), 2.14 (m, 1 H), 2.36–2.47 (m, 2 H), 3.52 (br s, 2 H), 4.70 (m, 1 H), 5.56 (br s, 1 H); EIMS (*m/z*, rel intensity) 494 (M^+, 1), 479 (4), 404 (40), 259 (100).

To a mixture of silyl enol ether **19** (84 mg), methyl iodide (0.51 mL, 8.2 mmol), and powdered molecular sieves 4A (0.15 g) in THF (1 mL) was added a mixture of tris(dimethylamino)sulfur (trimethylsilyl)-difluoride (Aldrich) (101 mg, 0.367 mmol) in THF (1 mL). The mixture was stirred at room temperature for 6 h, diluted with hexane (15 mL), and filtered through a pad of Celite. The residue was washed with hexane thoroughly, and the filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–benzene, 5:1 → 3:1 → 1:1) to give ketone (-)-**20a** (34.8 mg, 49%) as a colorless oil and ketone (-)-**20b** (29.9 mg, 42%) as colorless crystals.

Ketone (−)-20a: $[\alpha]^{30}_D$ −16.7° (*c* 1.03, $CHCl_3$); IR ($CHCl_3$) 1730, 1670, 1250, 1100, 1075, 1005, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.01 (s, 3 H), 0.00 (s, 3 H), 0.04 (s, 9 H), 0.41 (ddd, *J* = 9.4, 6.6, 4.6 Hz, 1 H), 0.62 (ddd, *J* = 9.9, 5.9, 4.6 Hz, 1 H), 0.71–1.08 (m, 2 H), 0.85 (s, 9 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 1.21 (s, 3 H), 1.47 (d, *J* = 1.3 Hz, 3 H), 1.74 (dd, *J* = 11.8, 11.8 Hz, 1 H), 2.08 (dd, *J* = 11.8, 9.2 Hz, 1 H), 2.09 (br s, 1 H), 2.29 (ddq, *J* = 11.8, 9.2, 6.9 Hz, 1 H), 3.33 (d, *J* = 9.7 Hz, 1 H), 3.37 (d, *J* = 9.7 Hz, 1 H), 5.42 (br s, 1 H); EIMS (*m/z*, rel intensity) 436 (M^+; 17), 421 (13), 379 (65), 291 (100), 201 (30); HREIMS calcd for $C_{24}H_{44}O_3Si_2$ (M^+) 436.2829, found 436.2852. (+)-**20a**: $[\alpha]^{14}_D$ +13.8° (*c* 0.603, $CHCl_3$).

Ketone (−)-20b: mp 70.0–71.5 °C (pentane); $[\alpha]^{29}_D$ −99.1° (*c* 0.565, $CHCl_3$); IR ($CHCl_3$) 1735, 1655, 1255, 1135, 1095, 1010, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H), 0.14 (s, 9 H), 0.23 (ddd, *J* = 9.6, 6.3, 3.3 Hz, 1 H), 0.55–0.70 (m, 2 H), 0.88 (s, 9 H), 0.95 (ddd, *J* = 9.6, 5.9, 3.3 Hz, 1 H), 1.01 (d, *J* = 6.8 Hz, 3 H), 1.29 (s, 3 H), 1.45 (d, *J* = 1.3 Hz, 3 H), 1.60 (dd, *J* = 13.2, 12.0 Hz, 1 H), 1.75 (dd, *J* = 12.0, 8.2 Hz, 1 H), 2.36 (ddq, *J* = 13.2, 8.2, 6.8 Hz, 1 H), 2.42 (br s, 1 H), 3.44 (d, *J* = 9.6 Hz, 1 H), 3.53 (d, *J* = 9.6 Hz, 1 H), 5.23 (br s, 1 H); EIMS (*m/z*, rel intensity) 436 (M^+, 3), 421 (12), 379 (100), 291 (65), 201 (25). Anal. Calcd for $C_{24}H_{44}O_3Si_2$: C, 66.00; H, 10.15. Found: C, 66.01; H, 10.26. (+)-**20b**: mp 68.5–70.0 °C (pentane); $[\alpha]^{15}_D$ +96.8° (*c* 0.751, $CHCl_3$).

Isomerization of Ketone 20a to Ketone 20b. A mixture of ketone **20a** (34.8 mg, 0.080 mmol) and potassium *tert*-butoxide (8.9 mg, 0.080 mmol) in *tert*-butyl alcohol (1.1 mL) was stirred at room temperature for 2.5 h. The mixture was diluted with saturated aqueous NaCl solution (3 mL) and extracted with ether (5 × 5 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (5 g, hexane–benzene, 5:1 → 3:1 → 1:1) to give ketone **20b** (26.7 mg, 77%) as colorless crystals.

Diol 21. A 1 M solution of lithium aluminum hydride in ether (0.15 mL, 0.15 mmol) was added to a solution of ketone (−)-**20b** (50.1 mg, 0.115 mmol) in ether (1 mL). The mixture was stirred at room temperature for 30 min. To the cooled reaction mixture were added sodium fluoride (137 mg) and a solution of H_2O–THF (1:9) (1.5 mL). The mixture was stirred at room temperature for 45 min and filtered through a pad of Celite. The residue was washed with ether thoroughly, and the filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (1.5 g, hexane–ethyl acetate, 1:1) to give diol (−)-**21** (40.4 mg, 96%) as colorless crystals: mp 164.0–166.0 °C (hexane); $[\alpha]^{30}_D$ −64.3° (*c* 0.662, $CHCl_3$); IR ($CHCl_3$) 3610, 3430 (br), 1655, 1255, 1100, 1085, 860, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.53 (ddd, *J* = 9.6, 6.6, 4.0 Hz, 1 H), 0.73 (ddd, *J* = 9.9, 6.6, 4.3 Hz, 1 H), 0.84 (ddd, *J* = 9.6, 5.6, 4.3 Hz, 1 H), 0.90 (s, 9 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 1.07 (ddd, *J* = 9.9, 5.6, 4.0 Hz, 1 H), 1.21 (s, 3 H), 1.32 (dd, *J* = 12.0, 6.1 Hz, 1 H), 1.43 (dd, *J* = 12.0, 12.0 Hz, 1 H), 1.46 (d, *J* = 1.3 Hz, 3 H), 1.82 (dddq, *J* = 12.0, 9.9, 6.1, 6.6 Hz, 1 H), 2.10–2.70 (br s, 2 H), 2.46 (d, *J* = 9.9 Hz, 1 H), 3.38 (d, *J* = 9.6 Hz, 1 H), 3.44 (d, *J* = 9.6 Hz, 1 H), 3.77 (dd, *J* = 9.9, 9.9 Hz, 1 H), 5.18 (br s, 1 H); EIMS (*m/z*, rel intensity) 366 (M^+, 11), 348 (6), 307 (19), 291 (16), 235 (25), 221 (35), 217 (35), 203 (100). Anal. Calcd for $C_{21}H_{38}O_3Si$: C, 68.80; H, 10.45. Found: C, 68.84; H, 10.53. (+)-**21**: mp 166.0–167.5 °C (hexane); $[\alpha]^{20}_D$ +65.0° (*c* 0.625, $CHCl_3$).

Triol 22. A 1 M solution of tetra-*n*-butylammonium fluoride in THF (0.22 mL, 0.22 mmol) was added to a solution of diol (−)-**21** (39.9 mg, 0.109 mmol) in THF (2.2 mL). The mixture was stirred at 45 °C for 18 h, diluted with saturated aqueous NaCl solution (10 mL), and extracted with ether (4 × 10 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (1.5 g, hexane–ethyl acetate, 1:1 → ethyl acetate) to give triol (−)-**22** (27.0 mg, 98%) as colorless crystals: mp 149.5–150.5 °C (EtOAc); $[\alpha]^{29}_D$ −73.3° (*c* 0.518, $CHCl_3$); IR ($CHCl_3$) 3620, 3350 (br), 1660, 1105, 1045 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.57 (ddd, *J* = 9.7, 6.3, 4.3 Hz, 1 H), 0.75 (ddd, *J* = 9.9, 6.3, 4.6 Hz, 1 H), 0.86 (ddd, *J* = 9.7, 5.6, 4.6 Hz, 1 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 1.08 (ddd, *J* = 9.9, 5.6, 4.3 Hz, 1 H), 1.24 (s, 3 H), 1.32 (dd, *J* = 12.2, 12.2 Hz, 1 H), 1.43 (dd, *J* = 12.2, 5.9 Hz, 1 H), 1.47 (d, *J* = 1.3 Hz, 3 H), 1.87 (dddq, *J* = 12.2, 9.9, 5.9, 6.6 Hz, 1 H), 2.36 (d, *J* = 9.9 Hz, 1 H), 2.60–3.30 (br s, 3 H), 3.50 (s, 2 H), 3.82 (dd, *J* = 9.9, 9.9 Hz, 1 H), 5.23 (br s, 1 H); EIMS (*m/z*, rel intensity) 252 (M^+; 14), 234 (14), 203 (80), 175 (35), 146 (100), 131 (55). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.42; H, 9.62. (+)-**22**: mp 155.0–156.0 °C (benzene); $[\alpha]^{18}_D$ +73.3° (*c* 0.534, $CHCl_3$).

Aldehyde 23. A solution of dimethyl sulfoxide (0.072 mL, 1.0 mmol) in dichloromethane (0.2 mL) was added to a stirred solution of oxalyl chloride (0.044 mL, 0.50 mmol) in dichloromethane (0.3 mL) at −65 °C. After 4 min, a solution of triol (−)-**22** (12.7 mg, 0.050 mmol) in dichloromethane–dimethyl sulfoxide (20:1, 0.7 mL) was added. The mixture was stirred for an additional 15 min at −65 °C, and triethylamine (0.35 mL, 2.5 mmol) was added. The mixture was stirred at −65 °C for 5 min and warmed to room temperature over 35 min. The mixture was diluted with 1 M phosphate buffer (pH 7, 5 mL) and extracted with dichloromethane (4 × 5 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel (1.0 g, hexane–ether, 2:1) to give aldehyde (−)-**23** (11.7 mg, 94%) as a colorless oil: $[\alpha]^{29}_D$ −217° (*c* 0.598, $CHCl_3$); IR ($CHCl_3$) 3460, 2810, 2720, 1720, 1650, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.44 (m, 1 H), 0.70–0.91 (m, 3 H), 1.07 (s, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 1.52 (d, *J* = 1.3 Hz, 3 H), 1.62 (dd, *J* = 12.4, 12.4 Hz, 1 H), 2.15 (dd, *J* = 12.4, 8.3 Hz, 1 H), 2.46 (ddq, *J* = 12.4, 8.3, 6.9 Hz, 1 H), 2.83 (br s, 1 H), 4.60 (br s, 1 H), 5.57 (br s, 1 H), 9.68 (s, 1 H); EIMS (*m/z*, rel intensity) 248 (M^+; 8), 233 (9), 219 (100), 201 (95); HREIMS calcd for $C_{15}H_{20}O_3$ (M^+) 248.1412, found 248.1403. (+)-**23**: $[\alpha]^{20}_D$ +222° (*c* 0.33, $CHCl_3$).

Ptaquilosin (2). A solution of aldehyde (−)-**23** (11.1 mg, 0.045 mmol) in ethyl acetate (0.1 mL) was stirred under an oxygen atmosphere at 50 °C for 10 h and concentrated. The resulting crude hydroperoxide **24** was dissolved in ether (2 mL), and triphenylphosphine (24 mg, 0.092 mmol) was added. The mixture was stirred at room temperature for 3.5 h and concentrated. The residue was purified by column chromatography on silica gel (0.7 g, hexane–ether 2:1 → 1:1) to give (−)-ptaquilosin (**2**) (3.6 mg, 34%) as a colorless oil. A sample for HRMS was obtained by purification using preparative HPLC (Develosil ODS-5, 10 mm × 25 cm, CH_3CN–H_2O 40:60, 4 mL/min, t_R = 7.9 min), which was of >95% purity as judged by ^1H NMR and HPLC (Develosil ODS-5, 4.6 mm × 25 cm, CH_3CN–H_2O 40:60, 1 mL/min, t_R = 9.0 min): $[\alpha]^{30}_D$ −236° (*c* 0.24, $CHCl_3$); IR ($CHCl_3$) 3600, 3450 (br), 1720, 1645, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.42 (m, 1 H), 0.71–0.95 (m, 3 H), 1.12 (d, *J* = 6.6 Hz, 3 H), 1.33 (d, *J* = 1.0 Hz, 3 H), 1.48 (d, *J* = 1.3 Hz, 3 H), 1.69–1.96 (m, 2 H), 2.18–2.38 (m, 2 H), 2.49 (d, *J* = 1.3 Hz, 1 H), 4.63 (br s, 1 H), 5.48 (br s, 1 H); EIMS (*m/z*, rel intensity) 236 (M^+, 65), 221 (11), 218 (10), 205 (65), 166 (35), 149 (100), 135 (95); HREIMS calcd for $C_{14}H_{20}O_3$ (M^+) 236.1413, found 236.1437. (+)-**2**: $[\alpha]^{20}_D$ +232° (*c* 0.17, $CHCl_3$).

Acetonide 25a. (i) A 1 M solution of lithium aluminum hydride in ether (0.1 mL, 0.1 mmol) was added to a solution of ketone **20a** (21.4 mg, 0.049 mmol) in ether (0.6 mL). After the mixture was stirred at room temperature for 1 h, sodium fluoride (42 mg) and a solution of H_2O–THF (1:9) (0.2 mL) were added to the cooled mixture. The mixture was stirred at room temperature for 15 min and filtered through a pad of Celite. The residue was washed with ether thoroughly, and the filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (2.5 g, hexane–benzene, 1:1 → 1:2) to give an alcohol (15.6 mg, 73%) as a colorless oil: $[\alpha]^{16}_D$ −32.0° (*c* 0.785, $CHCl_3$); IR ($CHCl_3$) 3580, 1255, 1105, 1090, 1005, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.13 (s, 9 H), 0.55–0.68 (m, 2 H), 0.90 (s, 9 H), 0.92–1.15 (m, 2 H), 1.00 (d, *J* = 6.3 Hz, 3 H), 1.35 (s, 3 H), 1.41 (d, *J* = 1.3 Hz, 3 H), 1.58 (dd, *J* = 11.6, 11.6 Hz, 1 H), 1.90 (dd, *J* = 11.6, 7.3 Hz, 1 H), 1.99 (m, 1 H), 2.31 (d, *J* = 3.6 Hz, 1 H), 2.61 (br s, 1 H), 3.38 (s, 2 H), 4.13 (br dd, *J* = 3.6, 3.6 Hz, 1 H), 5.33 (br s, 1 H); EIMS (*m/z*, rel intensity) 438 (M^+, 11), 348 (18), 293 (35), 203 (100); HREIMS calcd for $C_{24}H_{46}O_3Si_2$ (M^+) 438.2986, found 438.2991.

(ii) A mixture of the alcohol (15.5 mg, 0.035 mmol) and K_2CO_3 (2.8 mg, 0.02 mmol) in methanol (0.8 mL) was refluxed for 8 h and concentrated. The residue was dissolved in ether and filtered through a cotton plug. The residue was washed with ether thoroughly, and the filtrate and the washings were combined and concentrated. The residual oil was purified by column chromatography on silica gel (2.5 g, hexane–ether, 2:1 → 1:1) to give a diol (13.1 mg, 100%) as colorless crystals: mp 97.0–98.0 °C (hexane); $[\alpha]^{17}_D$ −48.2° (*c* 0.705, $CHCl_3$); IR ($CHCl_3$) 3580, 3450, 1255, 1095, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (s, 6 H), 0.65 (m, 1 H), 0.75 (m, 1 H), 0.89 (s, 9 H), 0.90–1.13 (m, 2 H), 0.98 (d, *J* = 6.4 Hz, 3 H), 1.26 (s, 3 H), 1.39 (m, 1 H), 1.43 (d, *J* = 1.3 Hz, 3 H), 1.92–2.11 (m, 4 H), 2.28 (d, *J* = 3.8 Hz, 1 H), 3.38 (s, 2 H), 4.16 (br dd, *J* = 3.8, 3.8 Hz, 1 H), 5.41 (br s, 1 H); EIMS (*m/z*, rel intensity) 366 (M^+, 25), 348 (9), 291 (13), 222 (50), 203 (100); HREIMS calcd for $C_{21}H_{38}O_3Si$ (M^+) 366.2590, found 366.2587.

(iii) To a solution of the diol (11.4 mg, 0.031 mmol) in benzene (1 mL) were added a solution of 2-methoxypropene (0.03 mL, 0.31 mmol) in benzene (0.2 mL) and a solution of camphorsulfonic acid (1.3 mg, 0.005 mmol) in benzene (0.1 mL). After the mixture was stirred at room temperature for 15 min, triethylamine (0.2 mL) was added. The mixture was concentrated and purified by column chromatography on silica gel (3 g, hexane–benzene, 4:1 → 2:1 → 1:1) to give acetonide **25a** (11.8 mg, 93%) as a colorless oil: $[\alpha]^{16}_D$ -2.7° (*c* 0.635, $CHCl_3$); IR ($CHCl_3$) 1380, 1250, 1195, 1095, 1085, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (s, 6 H), 0.19 (m, 1 H), 0.69 (m, 1 H), 0.78–0.93 (m, 2 H), 0.88 (s, 9 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 1.08 (s, 3 H), 1.25 (s, 3 H), 1.39 (s, 3 H), 1.48 (d, *J* = 1.3 Hz, 3 H), 1.56 (dd, *J* = 11.7, 11.7 Hz, 1 H), 1.80 (d, *J* = 4.0 Hz, 1 H), 1.92 (dd, *J* = 11.7, 7.1 Hz, 1 H), 2.07 (dddq, *J* = 11.7, 7.1, 4.0, 6.9 Hz, 1 H), 3.28 (d, *J* = 9.6 Hz, 1 H), 3.32 (d, *J* = 9.6 Hz, 1 H), 4.10 (dd, *J* = 4.0, 4.0 Hz, 1 H), 5.39 (br s, 1 H); EIMS (*m/z*, rel intensity) 406 (M^+, 4), 391 (2), 349 (9), 261 (59), 203 (100); HREIMS calcd for $C_{24}H_{42}O_3Si$ (M^+) 406.2903, found 406.2890.

Acetonide 25b. To a solution of diol **21** (22.2 mg, 0.061 mmol) in benzene (1 mL) were added a solution of 2-methoxypropene (0.03 mL, 0.31 mmol) in benzene (0.3 mL) and a solution of camphorsulfonic acid (1.2 mg, 0.005 mmol) in benzene (0.2 mL). The mixture was stirred at room temperature for 15 min, and triethylamine (0.2 mL) was added. The mixture was concentrated and purified by column chromatography on silica gel (2.5 g, hexane–benzene, 2:1) to give acetonide **25b** (22.1 mg, 90%) as a colorless oil: $[\alpha]^{17}_D$ -97.2° (*c* 1.19, $CHCl_3$); IR ($CHCl_3$) 1380, 1370, 1255, 1140, 1105, 1085, 860, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 3 H), 0.05 (s, 3 H), 0.37 (m, 1 H), 0.64 (m, 1 H), 0.77 (m, 1 H), 0.91 (s, 9 H), 1.01 (d, *J* = 6.4 Hz, 3 H), 1.21 (s, 3 H), 1.28–1.52 (m, 3 H), 1.34 (s, 3 H), 1.42 (d, *J* = 1.2 Hz, 3 H), 1.48 (s, 3 H), 2.05 (m, 1 H), 2.46 (d, *J* = 9.7 Hz, 1 H), 3.37 (s, 2 H), 3.63 (dd, *J* = 9.7, 9.7 Hz, 1 H), 5.17 (br s, 1 H); EIMS (*m/z*, rel intensity) 406 (M^+, 9), 391 (2), 349 (8), 261 (55), 203 (100); HREIMS calcd for $C_{24}H_{42}O_3Si$ (M^+) 406.2903, found 406.2901.

Acetonide 26. Ptaquiloside (**1**) was converted into **26** by the sequence of the following reactions: (1) acetylation (Ac_2O, pyr, 23 °C); (2) reduction ($NaBH_4$, THF–EtOH 1:1, 0 °C); (3) acetonide formation (2-methoxypropene, camphorsulfonic acid, benzene, 23 °C); (4) deacetylation (K_2CO_3, MeOH, 23 °C); (5) tosylation of the primary hydroxyl group (Bu_2SnO, MeOH, reflux, then TsCl, dioxane, 30 °C); (6) iodination (KI, DMF, 80 °C); (7) reduction (Zn, NH_4Cl, EtOH, reflux). Crude acetonide **26** thus obtained was purified by column chromatography on silica gel with chloroform–acetone (10:1) to afford pure **26** as a colorless oil.

(-)-**26**: $[\alpha]^{14}_D$ -84.7° (*c* 1.18, $CHCl_3$); IR ($CHCl_3$) 3600, 3450 (br), 1665, 1055, 1025, 1000 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.39 (ddd, *J* = 9.6, 6.9, 4.3 Hz, 1 H), 0.71 (ddd, *J* = 9.6, 6.9, 4.3 Hz, 1 H), 0.83 (m, 1 H), 1.05 (d, *J* = 5.9 Hz, 3 H), 1.32 (s, 3 H), 1.34 (s, 3 H), 1.39 (m, 1 H), 1.47 (d, *J* = 1.3 Hz, 3 H), 1.49 (s, 3 H), 1.70–1.94 (m, 3 H), 2.04–2.15 (m, 2 H), 2.58 (d, *J* = 9.7 Hz, 1 H), 3.92 (dd, *J* = 9.7, 9.7 Hz, 1 H), 5.43 (br s, 1 H); EIMS (*m/z*, rel intensity) 278 (M^+, 15), 260 (45), 245 (25), 220 (55), 203 (30), 202 (30), 187 (100); HREIMS calcd for $C_{17}H_{26}O_3$ (M^+) 278.1886, found 278.1899.

Procedure for Alkylation of the Enolate Generated From (+)-Menthyl Hydrogen (1*R*,2*R*)-Cyclopentane-1,2-dicarboxylate (5). A representative procedure for alkylation of the enolate of **5** with allyl bromide in the presence of HMPA (entry 9 in Table I) is as follows. A solution of monoester **5** (146 mg, 0.49 mmol) in THF (7.5 mL) was added at -20 °C to a solution of LDA prepared from diisopropylamine (0.17 mL, 1.2 mmol), a 1.55 M solution of *n*-BuLi in hexane (0.78 mL, 1.2 mmol), and THF (2 mL) at -25 °C. After the mixture was stirred at -25 ~ -17 °C for 1 h, HMPA (0.21 mL, 1.2 mmol) was added, and subsequently allyl bromide (0.13 mL, 1.5 mmol) was added. The reaction mixture was stirred at -25 ~ -17 °C for 1.7 h, diluted with 2 M HCl (15 mL), and extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and concentrated. The residual oil was purified by column chromatography on silica gel (20 g, hexane–ethyl acetate, 10:1 → 5:1) to afford a 3.9:1 mixture of acids **7a** and **7b** (142 mg, 86%) as an oil. The ratio of **7a** and **7b** was determined by ^1H NMR spectral analysis. After conversion to the methyl esters by treatment with ethereal diazomethane, the mixture was separated by column chromatography on silica gel (hexane–ether, 40:1 → 10:1) to afford methyl esters of **7a** and **7b** as an oil, respectively.

Methyl ester of 7a: $[\alpha]^{16}_D$ +33.1° (*c* 0.645, $CHCl_3$); IR ($CHCl_3$) 3080, 1725, 1640, 1170, 915 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.73 (d, *J* = 6.9 Hz, 3 H), 0.76–1.13 (m, 3 H), 0.89 (d, *J* = 7.2 Hz, 6 H), 1.33–1.54 (m, 2 H), 1.56–2.23 (m, 11 H), 2.43 (dd, *J* = 13.9, 7.6 Hz, 1 H), 2.61 (d, *J* = 13.9, 7.1 Hz, 1 H), 2.76 (dd, *J* = 8.2, 8.2 Hz, 1 H), 3.65 (s, 3 H), 4.64 (ddd, *J* = 10.9, 10.9, 4.3 Hz, 1 H), 5.06–5.15 (m, 2 H), 5.79 (m, 1 H); EIMS (*m/z*, rel intensity) 350 (M^+, 1), 335 (1), 308 (3), 249 (3), 212 (100), 138 (35); HREIMS calcd for $C_{21}H_{34}O_4$ (M^+) 350.2458, found 350.2469.

Methyl ester of 7b: $[\alpha]^{16}_D$ -26.8° (*c* 1.36, $CHCl_3$); IR ($CHCl_3$) 3080, 1720, 1640, 1230, 1165, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.74 (d, *J* = 6.9 Hz, 3 H), 0.79–1.15 (m, 3 H), 0.90 (d, *J* = 7.1 Hz, 3 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 1.35–1.56 (m, 2 H), 1.55–2.03 (m, 10 H), 2.12 (m, 1 H), 2.20 (dd, *J* = 14.2, 8.1 Hz, 1 H), 2.46 (dd, *J* = 14.2, 6.2 Hz, 1 H), 3.32 (dd, *J* = 7.8, 7.8 Hz, 1 H), 3.65 (s, 3 H), 4.69 (ddd, *J* = 10.9, 10.9, 4.3 Hz, 1 H), 4.88–5.06 (m, 2 H), 5.74 (m, 1 H); EIMS (*m/z*, rel intensity) 350 (M^+; 1), 335 (1), 308 (3), 249 (2), 212 (100), 138 (30); HREIMS calcd for $C_{21}H_{34}O_4$ (M^+) 350.2458, found 350.2435.

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Supplementary Material Available: Tables of X-ray crystallographic data for racemic triol **17c** (6 pages). Ordering information is given on any current masthead page.