JOC Article

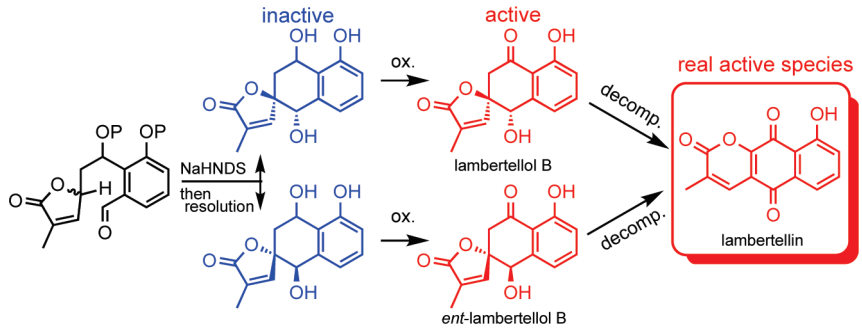
Syntheses of Lambertellols and Their Stable Analogues; Investigation of the Real Active Species in the Mycoparasitism by *Lambertella* Species

Masahiro Nomiya, Takanori Murakami, Noboru Takada, Toshikatsu Okuno, Yukio Harada, and Masaru Hashimoto*

Faculty of Agriculture and Life Science, Hirosaki University, 3-Bunkyo-cho, Hirosaki, 036-8561, Japan

hmasaru@cc.hirosaki-u.ac.jp

Received March 22, 2008



Lambertellols A (**1**) and B (**2**), isolated from mycoparasites *Lambertella* species, were synthesized. The synthesis features intramolecular aldol-type cyclizations of aldehydes **12** and **14** and site specific oxidations of 1-hydroxylambertellols as key steps. The synthesis also provided all diastereomers of 1-hydrolambertellols **17**−**19** and **25**. Chiral resolution made the optically active forms available, which enabled the investigation of the real active species in the mycoparasitism by *Lambertella* species against *Monilinia fructigena*. These experiments suggested that lambertellin (**3**) is responsible for this phenomenon. Chemically labile **1** and **2** should be converted to **3** during the bioassay. The parasite may excrete **1** and **2** as readily diffusible forms, which are then transformed into **3** to inhibit the host *M. fructigena*. The parasite may have acquired this "drug delivery system" mechanism as an evolutionary enhancement.

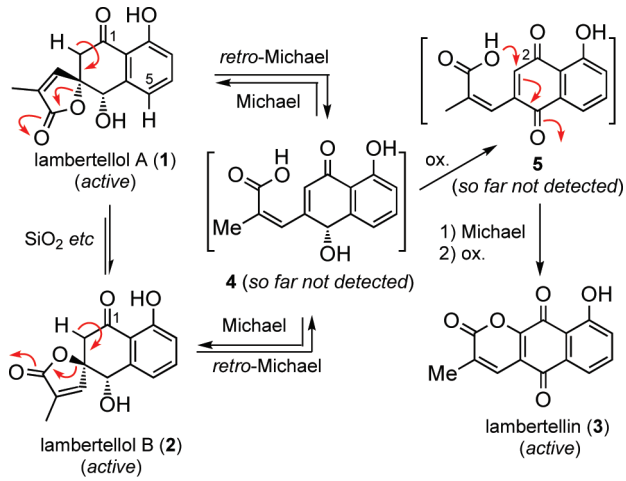
Introduction

Filamentous fungus *Lambertella corni-maris* invades the other pathogenic fungus *Monilinia fructigena* on PSA (potato-sucrose-agar) medium. Harada, one of the present authors, reported that neither *L. corni-maris* nor *M. fructigena* inhibited each other to be intermixed together after a month of simultaneous culture on PSA medium; however only *L. corni-maris* was isolated from anywhere on the medium.[1] The same behavior sometimes occurs on apple fruits in the field.[2] It was also found that only *L. corni-maris* could be detected from rotten apples which had been seeded with *M. fructigena* as a pretreatment and stored under ambient atmosphere for a couple of months.[1] This phenomenon is recognized as mycoparasitism.[1,3] In our study exploring chemical substances responsible for the phenomenon, we have isolated spirobutenolides, lambertellols A (**1**) and B (**2**),[4] along with known lambertellin (**3**)[5] from the culture broth of a congeneric fungus *Lambertella* sp. 1346 which also causes similar mycoparasitism on apple fruits.[1] These compounds were thought be responsible for the onset of the mycoparasitism, because these compounds potently inhibited the growth of the host hyphae.[6] The parasite *L. corni-maris* did not produce these metabolites when it was cultured alone. Recently we revealed that *L. corni-maris* exuded **1**−**3** in considerable amounts only when the host *M. fructigena* is also present. Our further investigations suggested that a particular stimulant does not exist, but "high acidity" stimulates the productions of **1**−**3**. The host remarkably acidified the environment. Since the spreading rate of the acidic area on PSA medium is almost identical to the

(1) Harada, Y.; Sasaki, M. *Rep. Tottori Mycol. Inst.* **1990**, *28*, 275.
(2) Hori, S. *ENGEINO TOMO (in Japanese)* **1912**, *8*, 949.
(3) Jeffries, P.; Young, T. W. K. *Interfungal Parasitic Relationships*; CABI International: Wallingford, 1994.
(4) Murakami, T.; Morikawa, Y.; Hashimoto, M.; Okuno, T.; Harada, Y. *Org. Lett.* **2004**, *6*, 157.
(5) Armstrong, J. J.; Turner, W. B. *J. Chem. Soc.* **1965**, 5927.
(6) Murakami, T.; Takahashi, Y.; Fukushi, E.; Kawabata, J.; Hashimoto, M.; Okuno, T.; Harada, Y. *J. Am. Chem. Soc.* **2004**, *126*, 9214.

10.1021/jo8005478 CCC: $40.75 © 2008 American Chemical Society
Published on Web 06/04/2008

SCHEME 1. Isomerization and Decomposition of Lambertellols



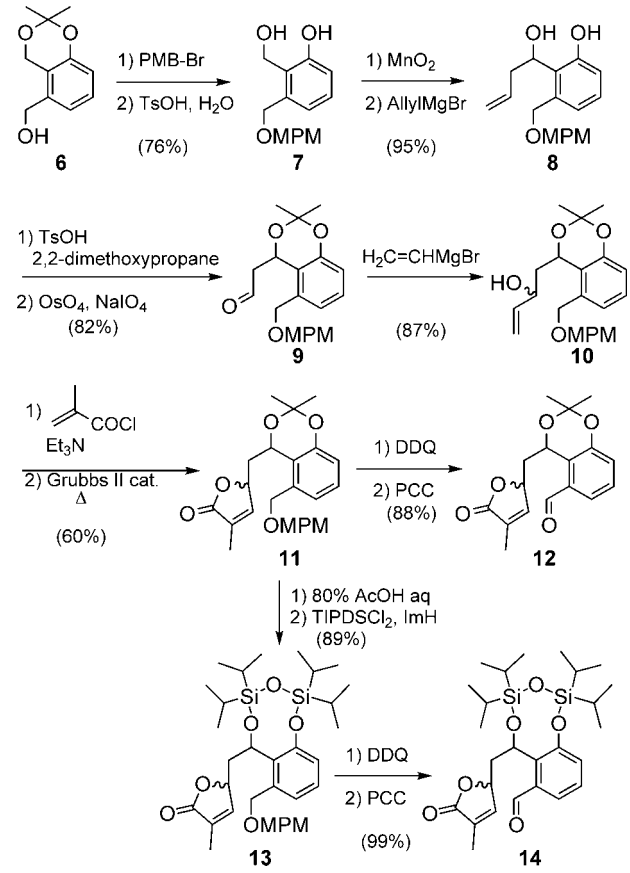
growth rate of the host hyphae, the parasite *L. corni-maris* detects the high acidity only in the case where the host inhabits very close to the parasite. Accordingly, the host can grow freely until its hyphae reach the parasite. On reaching the host, *L. corni-maris* begins to produce these antibiotics to deteriorate the host. We proposed these might be the reason why only *L. corni-maris* was isolated after simultaneous cultivation with *M. fructigena* without remarkable inhibition at a glance.[7]

During the course of structural studies, we observed isomerization between **1** and **2** under mild conditions such as on silica gel or in methanol. This interconversion can be explained by retro-Michael type opening of the butenolide ring to the carboxylic acid **4,** followed by Michael type ring closure to deliver the epimer as shown in Scheme 1.[8] Conversion of **1** and **2** into **3** also occurred under the isomerization conditions probably by the sequential (i) oxidation of semiquinone moiety of **4** into quinone **5**, (ii) intramolecular Michael type ring closure at the C2 position to furnish the pyrone, and finally (iii) oxidative aromatization. Accordingly, **4** and/or **5** might also be responsible for the observed mycoparasitism, although these have not been isolated from growing cultures thus far. We further investigated this subject by studying the activities employing **1**, **2**, and their congeners including their enantiomers. This paper reports the first syntheses of **1**, **2**, and stable analogues **17**−**19** and **25**. The syntheses involved chiral resolutions which enabled us to obtain the metabolites and their analogues in optically active forms. These studies suggest **3** is the active substance responsible for the mycoparasitism.

Results and Discussions

1. Total Synthesis of Lambertellols. The total synthesis of **1** and **2** is described below. Since, the C1 carbonyl function of each compound facilitates the retro-Michael type ring opening of the butenolide ring, causing the interconversion and decomposition as discussed above, the C1 carbonyl group was to be introduced in the final step of the synthesis. We have also observed that the C4-OH group in both **1** and **2** is chemically inert, for example, toward acetylation,[9] due to the steric effect of the neighboring butenolide ring as well as the overhanging

SCHEME 2. Synthesis of Intermediates 12 and 14

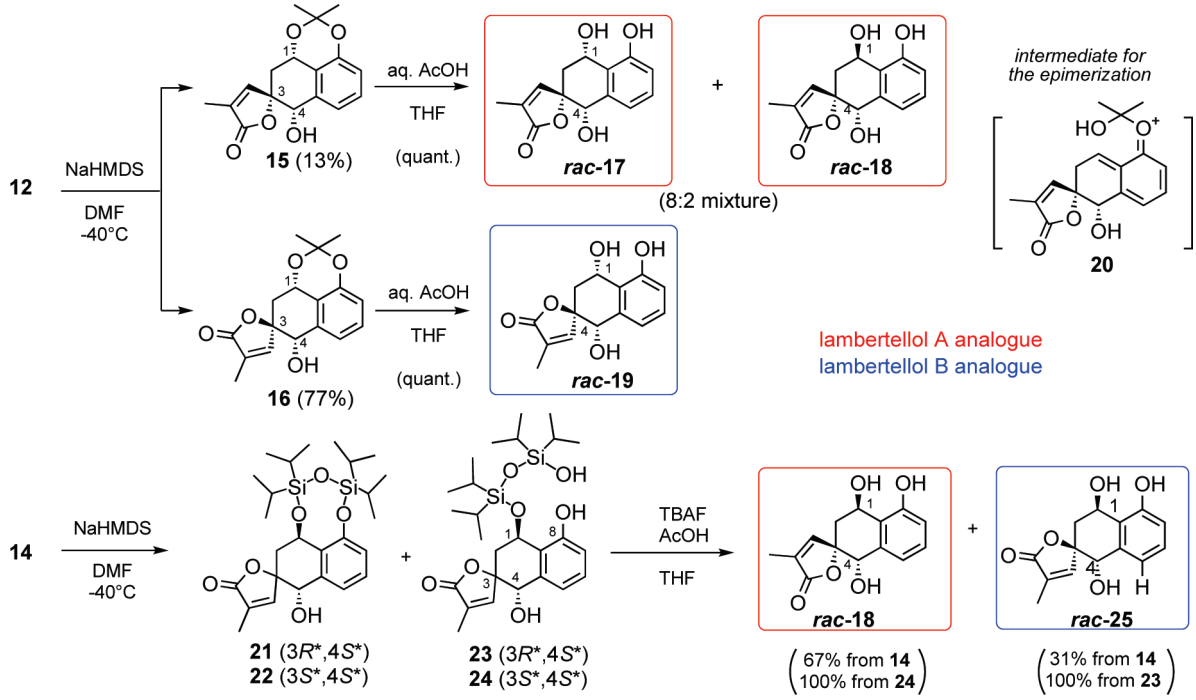


C5 aromatic proton located as pseudo-*peri* position.[10,11] Accordingly, we expected that this alcohol function would remain unaffected under oxidation conditions. Thus, we arrived at **17**−**19** and **25** as the synthetic precursors for the conversion to the final products. Since these triols were expected to be stable because of the absence of C1 carbonyl, these were to be employed as stable mimics of lambertellols in the biological studies.

The synthesis commenced with 2,3-bis(hydroxymethyl)phenol derivative **6** prepared from 2,3-dimethylphenol (5 steps, 40% overall yield) according to the published procedures (Scheme 2).[12,13] The alcohol moiety in **6** was protected as a MPM (*p*-methoxyphenylmethyl) ether, and the acetonide group was removed by *p*-TsOH in aqueous acetonitrile, yielding diol **7** in 76% yield over two steps. Oxidation of **7** with MnO_2 followed by treatment of the resultant aldehyde with allylmagnesium bromide furnished diol **8** in good overall yield. The diol moiety of **8** was then protected as an acetonide, and the terminal double bond was oxidatively cleaved to aldehyde **9** in 82% yield over two steps.

(7) Murakami, T.; Takada, N.; Harada, Y.; Okuno, T.; Hashimoto, M. *Biosci. Biotechnol. Biochem.* **2007**, *71*, 1230.
(8) Lee, S.; Zhao, Z. *Tetrahedron Lett.* **1999**, *40*, 7921.
(9) Lambertellol A (**1**) is slightly less stable than lambertellol B (**2**). So, **2** was mainly used for derivatizations. When **1** was subjected to acetylation conditions, polar materials were only observed by the TLC analysis.
(10) Murakami, T.; Sasaki, A.; Fukushi, E.; Kawabata, J.; Hashimoto, M.; Okuno, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2587.
(11) Murakami, T.; Hashimoto, M.; Okuno, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4185.
(12) Suzuki, M.; Sugiyama, T.; Watanabe, M.; Murayama, T.; Yamashita, K. *Agric. Biol. Chem.* **1987**, *51*, 2161.
(13) Nicolau, K. C.; Vassilikogiannakis, G.; Montagnon, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3276.

SCHEME 3. Synthesis of 1-Hydrolambertellols *rac*-17, *rac*-18, *rac*-19, and *rac*-25



Addition of vinyl Grignard reagent to **9** produced adduct **10** in 87% as a 1:1 mixture of diastereomers. The butenolide ring[14] was constructed in 60% yield via a two-step reaction, methacrylation and ring-closing metathesis using Grubbs II catalyst.[15] Compound **11** was then converted into the aldehyde **12** in 88% by cleavage of the MPM group ether[16] followed by PCC oxidation of the liberated alcohol. Disiloxanilydene derivative **14** was also prepared from **11** by (i) deprotection of the acetonide group, (ii) tetraisopropyldisiloxanylidene formation,[17] (iii) removal of the MPM group, and (iv) PCC oxidation.[18] We expected that a replacement of the acetonide group (six-membered ring) in **12** to a disiloxanylidene group (eight-membered ring) would alter the geometrical relationship between the aldehyde and the γ-carbon of the butenolide to give different stereoselectivity in the next cyclization.

Construction of the central cyclohexane ring was attempted next (Scheme 3). Treatment of the diastereomeric mixture **12** with NaHMDS in DMF at −40 °C led to the cyclization of the intermediate enolate to provide tetracyclic **15** and its diastereomer **16** in 13% and 77% yield, respectively. Other isomers were not observed. However, acidic removal of the acetonide group in **15** was accompanied by isomerization at the C1 position to give a 8:2 mixture of triols ***rac*-17** and ***rac*-18**. These structures were confirmed after HPLC separation. The stabilized cation **20** may contribute to the epimerization. Interestingly, similar treatment of **16** gave triol ***rac*-19** in quantitative yield without isomerization.

The reaction employing disiloxanylidene **14** exhibited different stereoselectivity. Triols ***rac*-18** and ***rac*-25** were obtained in 67% and 31% yield, respectively, after deprotection by TBAF-AcOH in THF.[19] The cyclization involved incomplete deprotection of the disiloxanilydene group, and silanols **23** and **24** were isolated as minor products along with **21** and **22**. These were stable enough to be isolated by silica gel. The FDMS of both **23** and **24** provided pseudomolecular ion signals at m/z = 522, which is 18 larger than the molecular weights of **21** and **22**. Fragment patterns in the EIMS were quite similar between **23** and **24**. Both of them showed exchangeable phenolic protons [δ 8.00 ppm (**23**), 7.92 ppm (**24**)] in their ^{1}H NMR spectra, which led to their proposed structures as depicted. Independent treatments of pure **23** and **24** with TBAF-AcOH system provided ***rac*-25** and ***rac*-18**, respectively, both in quantitative yields. Needless to say, disiloxanilidenes **21** and **22** could be isolated, and these also gave ***rac*-25** and ***rac*-18** in quantitative yields under the same conditions.

It is notable that remarkable line broadenings were observed for some signals of the precursors **13** and **14** in the ^{1}H NMR spectra (see Supporting Information). These might be caused by slow conformational movement around their 1,3,5,2,4-trioxadisilocine moieties. Interestingly, these broadenings were not observed in those of **21** and **22**. The NMR spectra of ***rac*-17**, ***rac*-18**, ***rac*-19**, and ***rac*-25** resembled each other but were not identical. Their relative stereochemistries were established based on observed NOEs as shown in Figure 1.

The C1-OH group was selectively oxidized to complete the synthesis as shown in Scheme 4. Treatment of ***rac*-17** with PCC in CH_2Cl_2 provided lambertelol A (***rac*-1**) in a racemic form. As anticipated, the sterically hindered C4-OH was not oxidized. However, the substrate was less soluble in CH_2Cl_2 and the reaction required a long reaction time (more than 12 h). Use of

(14) Albrecht, U.; Langer, P. *Tetrahedon* **2007**, *63*, 4648.
(15) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.
(16) Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
(17) Ohtsuka, E.; Ohkubo, M.; Yamane, A.; Ikehara, M. *Chem. Pharm. Bull.* **1983**, *31*, 1983.
(18) We succeeded in preparing **13** on a small scale by another route including a disiloxanylidene formation of diol **8** and the following similar reactions to those described in the text. We have not met difficulties in this scheme. However, this needs 14 steps of reactions for preparing **12** and **14** from **8**. The scheme in the manuscript requires totally 11 steps for preparing both of them from **8**. Taking the total efficiency into account, we adopted the route in the manuscript.
(19) Plfeiderer, W.; Pfister, M.; Farkas, S.; Schirmeister, H.; Charubala, R.; Stengele, K. P.; Mohr, M.; Bergmann, F.; Gokhale, S. *Nucleoside Nucleotide* **1991**, *10*, 377.

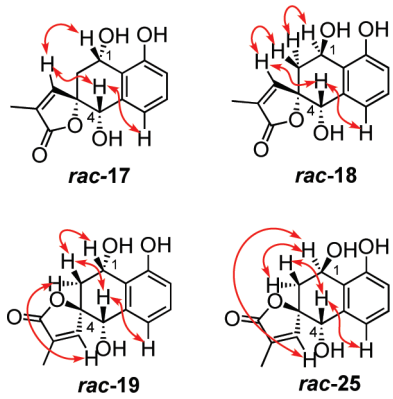
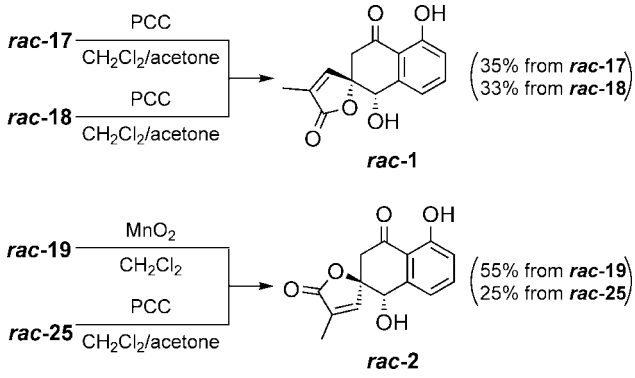


FIGURE 1. Characteristic NOEs and stereochemistries of ***rac*-17**, ***rac*-18**, ***rac*-19**, and ***rac*-25**

mixed solvent (1:1 CH_2Cl_2−acetone) led to complete dissolution of the substrates, which shortened the reaction time, yielding the best results without significant decomposition of the products. Decomposition to **3** during purification could be minimized by employing rapid silica gel column chromatography (loaded with 20:80 EtOAc−hexane and then eluted with 100% EtOAc) to provide ***rac*-1** (35% yield) in satisfactory purity. Other conditions such as MnO_2 or Dess−Martin periodinane[20] oxidations also gave ***rac*-1** but in lower yield. In the same manner, diastereomers ***rac*-18** and ***rac*-25** were converted into ***rac*-1** and lambertellol B (***rac*-2**) in 33% and 25% yield, respectively. Interestingly, ***rac*-19** was soluble in CH_2Cl_2 and oxidation with MnO_2 in CH_2Cl_2 gave the best results to afford ***rac*-2** in 55% yield after purification. The ODS HPLC retention time, the UV−vis profile, the ^{1}H NMR, and the IR spectra of synthetic ***rac*-1** and ***rac*-2** were identical to those of natural **1** and **2.**

SCHEME 4. Oxidation To Complete the Synthesis of 1 and 2

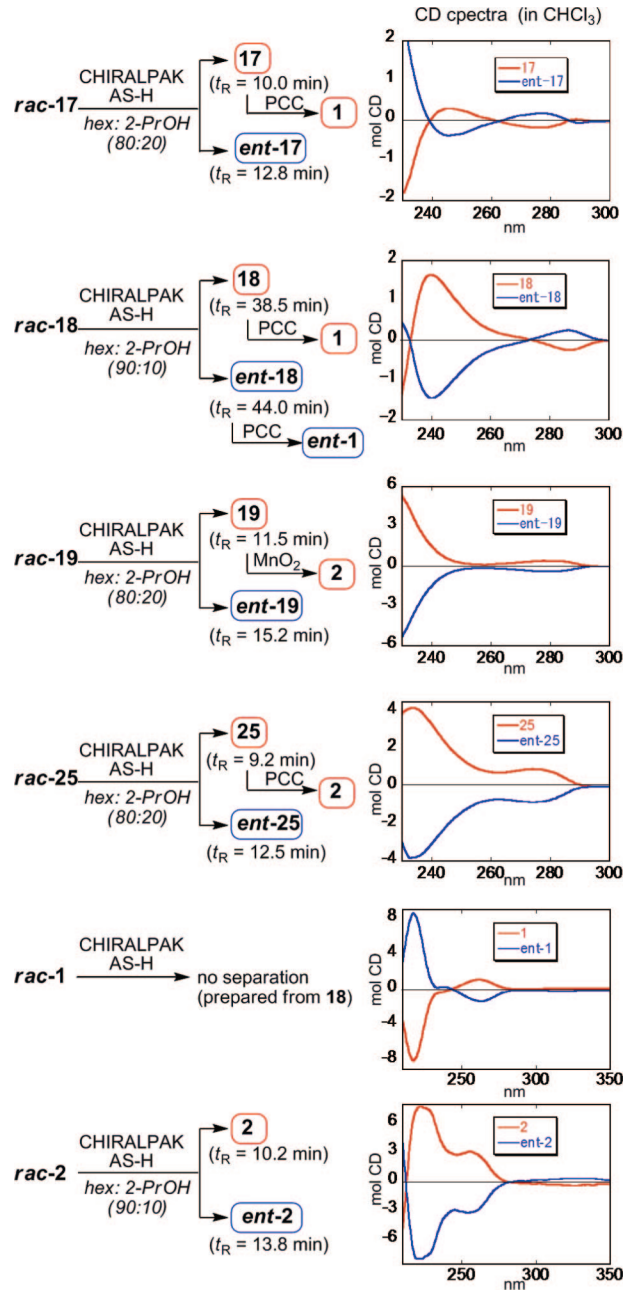


2. Optical Resolution for the Bioassay. We envisoned triols **17**−**19** and **25** as the stable mimics of **1** and **2** for biological experiments because the triols are not capable of retro-Michael type butenolide ring opening. Thus, enantiomeric pairs of lambertellols **1**, **2**, and analogous triols **17**−**19** and **25** were prepared by chiral resolution. Chiral HPLC using CHIRAL PAK AS-H (DAICEL Co. Ltd.)[21] was found to be effective for their resolutions (Scheme 5).

Only ***rac*-1** could not be separated by this system. However, an enantiomeric pair of **1** and ***ent*-1** was provided by independent

(20) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(21) Kennedy, J. H. *J. Chromatogr. A* **1996**, *725*, 219.

SCHEME 5. Optical Resolution with Chiral HPLC



oxidation of the resolved **18** and ***ent*-18**, respectively. The CD spectra of **1** and **2** were identical with those obtained for the natural products. Absolute configurations of the resolved triols were established by conversion into **1** or **2** followed by comparison of the CD spectra with those of the natural products.[4] Interestingly, all enantiomers with (4*S*)-configurations eluted faster than their corresponding antipodes in the HPLC resolutions.

3. Biological Study and Discovery of the Active Species. Having in hand the enantiomeric pairs of **1**, **2** and all possible stereoisomers of triols (**17**−**19**, **25**), their inhibitory activities against the host fungus *M. fructigena* were investigated. Since host *M. fructigena* makes the spores only under specific conditions and it was technically difficult to prepare the host spores in the laboratory, the assays were performed by the paper disk method.

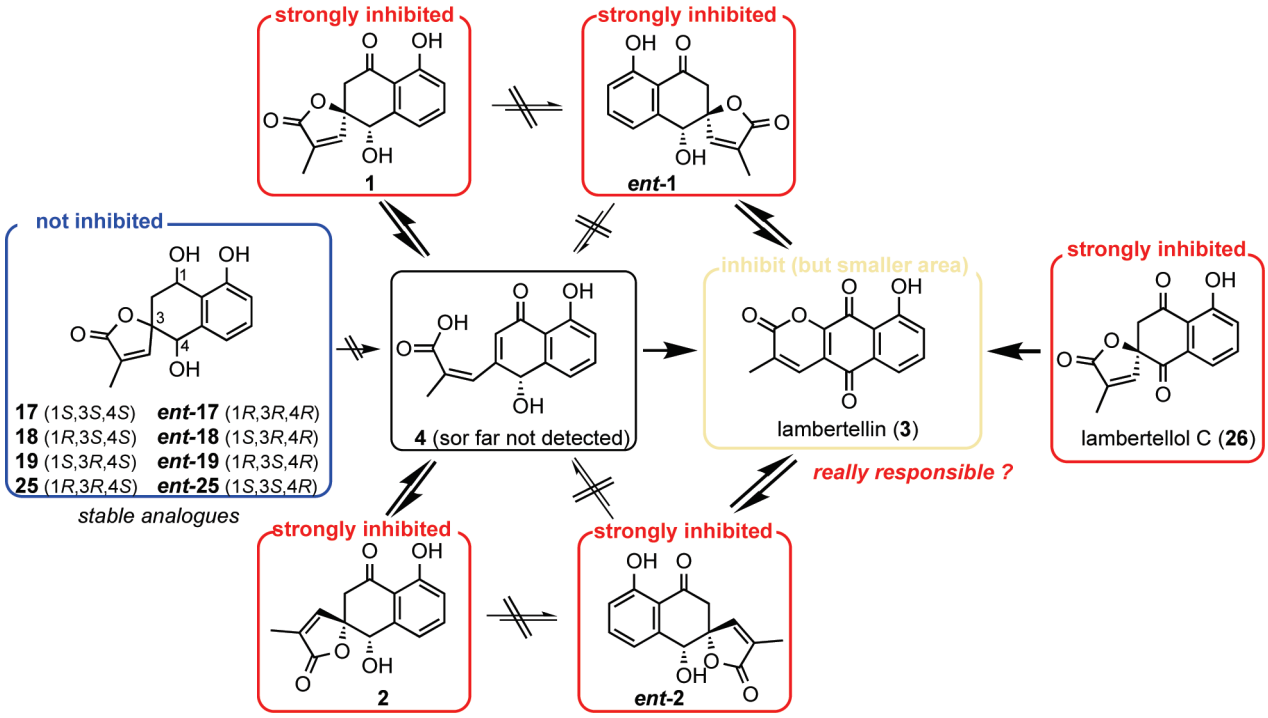


FIGURE 2. Structure−activity relationship of lambertellols and the related compounds.

After culturing the host *M. fructigena* on the PSA medium for 5 days, paper disks (8 mm diameter) containing the samples (20 μg/disk = 40 μg/cm^2) were placed on the media, ca. 2 cm apart from the end of the growing hyphae. Within 3 days post-treatment, remarkable inhibition was observed around the disks containing **1** and **2** at the same concentration as the natural products. The results for other compounds are summarized in Figure 2.

Interestingly, the enantiomers ***ent*-1** and ***ent*-2** as well as natural lambertellol C (**26**, racemate)[10] inhibited the growth by the same level. These results might suggest that the enzyme or other substrate responsible for the observed activity has some tolerance with regards to the structure of the inhibitor. This suggested that the structurally similar triols **17**−**19** or **25** might exhibit activity, but none of them did so. Their enantiomers ***ent*-17**, ***ent*-19**, or ***ent*-25** were also not active. [22]

In an early stage of these studies, we thought that **3** was not a candidate for the observed activity, because the zone of inhibition exhibited by **3** was smaller than those observed for **1** and **2**. However we now propose that **3** but not **1** nor **2** is the true active species in the mycoparasitism between *Lambertella* spp. and *M. fructigena* for the following reasons:

(i) If **4** was the responsible compound, the activity of ***ent*-1** and ***ent*-2** cannot be explained. Compound **4** is chiral and can be generated from **1** and **2**, but not from their enantiomers.

(ii) Lambertellin (**3**) is a planar compound, and all the lambertellols **1**, **2** and enantiomers can provide **3**; the activity of **3** is consistent with both enantiomers exhibiting activity.

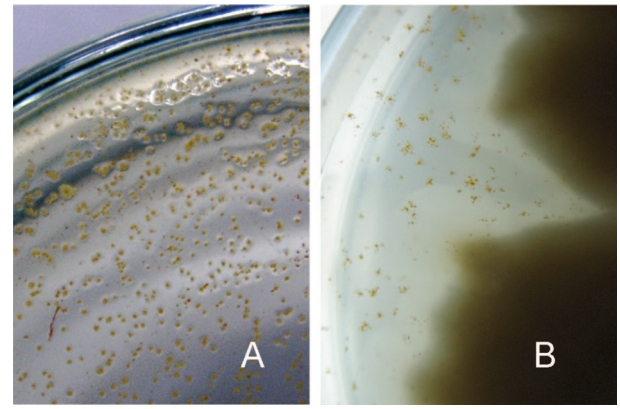


FIGURE 3. Precipitations of lambertellin (**3**, the reddish particles) found in PSA medium. (A) The PSA medium at 36 h at 20 °C after aqueous lambertellol B solution (**2**, 40 μg/cm^2) was added. The HPLC analysis detected only **3** from this medium. (B) The culture medium at 40 days at 20 °C after *Lambertella* sp. 1346 was seeded. The dark right part in B is the hyphae.

(iii) We found that PSA medium completely decomposed lambertellols within 36 h to precipitate **3** (Figure 3A), as confirmed by HPLC after extraction. The assays took 3 days. Lambertellols could not survive through these experiments. Since neither **4** nor **5** have been detected, theie lifetimes should be shorter than that of **3**. Accordingly, none of **4**, its enantiomer, and **5** must be present when the hyphae reached to the samples as a result of running out of their source lambertellols. These ruled out the possibility of undetected **4** and **5** being the active factors.[23]

(iv) Lambertellin (**3**) is sparingly soluble and readily precipitates in PSA under the conditions employed for the assay. This suggests that the concentration of **3** around the paper

(22) Antibiotic assays against another pathogenic fungus, *Cochlibolus miyabeanus*, were also examined and showed similar results. Compounds **1**, **2**, **3**, ***ent*-1**, and ***ent*-2** inhibited the growth of *C. miyabeanus* similarly (EC_{50} = ca. 1.0 μg/mL). On the other hand, the EC_{50} values for the triols (**17**, **18**, **19**, and **25**) and their enantiomers (***ent*-17**, ***ent*-18**, ***ent*-19**, and ***ent*-25**) were estimated to be more than 100 μg/mL in each case.

(23) It is hard to discuss the biological activities of the intact **1**, **2**, and **4** and their enantiomers because of their instabilities in these experiments.

disks can not become high, and **3** does not diffuse readily, which can explain why the zone of inhibition observed for **3** is smaller than that observed for **1** and **2**.

(v) Lambertellol C (**26**)[10] exhibited inhibition at a level similar to that of **1** and **2**. However, it can readily provide **3**, but not **4**. This is also evidence that **3** is the active agent.

Conclusion

As described, we have achieved the first synthesis of **1**, **2**, and their enantiomers. These studies also enabled us to utilize triols (**17**−**19**, **25**) and their enantiomers as congeners. Our synthesis provided all of them in one protocol. Biological investigations using these synthetic samples have clarified the role of lambertellols with regards to the onset of mycoparasitism between *Lambertella* spp. and *M. fructigena*. More specifically lambertellin (**3**), the degradation product of **1** and **2**, is responsible for the observed activity. The parasite may excrete **1** and **2** as the diffusible forms, which are later converted into **3** to exhibit hyphal inhibition against the host *M. fructigena*. In fact, precipitation of **3** was observed considerably detached from the hyphae in the PSA medium culturing *Lambertella* sp. 1346 (Figure 3, B). These *Lambertella* species might have acquired this "drug delivery system" mechanism in the course of their evolution.

Experimental Section

5-((5-((4-Methoxybenzyloxy)methyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-yl)methyl)-3-methylfuran-2(5*H*)-one (11). Preparation of **10** is described in Supporting Information. A solution of the starting **10** (29 mg, 75.4 μmol) in CH_2Cl_2 (1.0 mL) was stirred with methacryloylchloride (23.5 mg, 223 μmol) and Et_3N (30.5 mg, 301 μmol) at room temperature for 2 h. The mixture was poured into H_2O (25 mL) and extracted with AcOEt (25 mL × 3). The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The polar material was removed by passing through a short silica gel column to give the crude 1-(5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-yl)but-3-en-2-yl methacrylate (21.0 mg, 62%) as oil. This sample was immediately used for the next step.

The crude ester in toluene (500 μL) was refluxed with Grubbs second catalyst[15] (2.0 mg, 2.4 μmol) for 1 h. After cooling, the mixture was directly subjected to silica gel column. Elution with AcOEt−hexane (18:82) gave **11** (19 mg, 97%, 60% in 2 steps) as an oil. The ^{1}H NMR spectrum indicated that the sample thus obtained was a 7:3 diatereomeric mixture. IR (film) 2990, 2935, 2860, 1760, 1510, 1460, 1275, 1250, 1060, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (3H × 0.7, s), 1.41 (3H × 0.3, s) 1.58 (3H × 0.7, s), 1.59 (3H × 0.3, s), 1.86 (3H × 0.3, dd, J = 1.5, 2.9 Hz), 1.8**7** (3H × 0.7, dd, J = 1.5, 2.9 Hz), 1.98 (1H × 0.3, ddd, J = 4.4, 9.3, 14.6 Hz), 2.12 (1H × 0.7, ddd, J = 2.9, 9.3, 14.6 Hz), 2.23 (1H × 0.3, ddd, J = 2.0, 8.8, 14.6 Hz), 2.51 (1H × 0.7, ddd, J = 4.4, 6.3, 14.6 Hz), 3.807 (3H × 0.3, s), 3.815 (3H × 0.7, s), 4.33 (1H × 0.3, d, J = 11.2 Hz), 4.37 (1H × 0.7, d, J = 12.0 Hz), 4.429 (1H × 0.3, d, J = 11.2 Hz), 4.430 (1H × 0.3, d, J = 11.2 Hz), 4.455 (1H × 0.7, d, J = 11.7 Hz), 4.470 (1H × 0.3, d, J = 11.2 Hz), 4.486 (1H × 0.7, d, J = 11.7 Hz), 4.57 (1H × 0.7, d, J = 12.0 Hz), 4.81 (1H × 0.7, m), 5.22 (1H × 0.3, m), 5.24 (1H × 0.7, dd, J = 2.4, 6.3 Hz), 5.36 (1H × 0.3, dd, J = 2.9, 9.3 Hz), 6.78 (1H × 0.3, dd, J = 1.0, 8.3 Hz), 6.79 (1H × 0.7, dd, J = 1.0, 8.3 Hz), 6.87 (2H × 0.3, brd, J = 8.8 Hz), 6.88 (1H × 0.3, quint, J = 1.2 Hz), 6.89 (2H × 0.7, brd, J = 8.8 Hz), 6.95 (1H × 0.7, dd, J = 1.0, 7.3 Hz), 6.97 (1H × 0.3, dd, J = 1.0, 7.3 Hz), 7.13 (1H × 0.7, quint, J = 1.5 Hz), 7.161 (1H × 0.3, dd, J = 7.3, 8.3 Hz), 7.167 (1H × 0.7, dd, J = 7.3, 8.3 Hz), 7.23 (2H × 0.3, brd, J = 8.8 Hz), 7.26 (2H × 0.7, brd, J = 8.8 Hz); EIMS (rel int %) m/z = 424 (0.2, M^+), 366 (0.9, [M − acetone]$^+$), 286 (3.9, [M − $CH_3OC_6H_4CH_2OH$]$^+$), 121 (100, $CH_3OC_6H_4CH_2^+$); EIHRMS found m/z 424.1878 calcd for $C_{25}H_{28}O_6$, M^+ 424.1886.

2,2-Dimethyl-4-((4-methyl-5-oxo-2,5-dihydrofuran-2-yl)methyl)-4*H*-benzo[*d*][1,3]dioxine-5-carbaldehyde (12). A solution of **11** (180 mg, 424 μmol) in a mixture of CH_2Cl_2 (1.0 mL) and H_2O (0.1 mL) was stirred with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (154 mg, 639 μmol) at room temperature for 1.5 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (25 mL) and extracted with AcOEt (15 mL × 3). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$ and then concentrated in vacuo. Silica gel column chromatography of the residue (AcOEt−hexane = 26:74) gave 5-((5-(hydroxymethyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-yl)methyl)-3-methylfuran-2(5*H*)-one (115 mg, 89%) as an oil. The ^{1}H NMR spectrum indicated that the sample thus obtained was a 42:38 diatereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$, a = 0.42, b = 0.38) δ 1.39 (3H × b, s), 1.42 (3H × a, s), 1.595 (3H × b, s), 1.603 (3H × a), 1.890 (3H × b, dd, J = 1.5, 2.9 Hz), 1.895 (3H × a, dd, J = 1.9, 2.9 Hz), 2.06 (1H × a, ddd, J = 3.9, 8.8, 14.2 Hz), 2.21 (1H × a, ddd, J = 2.4, 8.8, 14.2 Hz), 2.23 (1H × b, ddd, J = 2.9, 8.3, 14.6 Hz), 2.56 (1H × b, ddd, J = 4.8, 6.3, 14.6 Hz), 4.52 (1H × a, d, J = 12.2 Hz), 4.58 (1H × b, d, J = 12.7 Hz), 4.65 (1H × a, d, J = 12.2 Hz), 4.72 (1H × b, d, J = 12.7 Hz), 4.85 (1H × b, m), 5.26 (1H × a, m), 5.28 (1H × b, dd, J = 2.9, 6.3 Hz), 5.38 (1H × a, dd, J = 2.4, 8.8 Hz), 6.79 (1H × a, dd, J = 1.0, 8.3 Hz), 6.80 (1H × b, dd, J = 1.0, 7.8 Hz), 6.95 (1H × a, quint, J = 2.9 Hz), 7.00 (1H × b, dd, J = 1.0, 7.3 Hz), 7.02 (1H × a, dd, J = 1.0, 7.3 Hz), 7.20 (1H + 1H × b).

A solution of the alcohol (69.0 mg, 227 μmol) in CH_2Cl_2 (1.5 mL) was stirred with pyridinium chlorochromate (PCC, 140 mg, 651 μmol) at room temperature for 1 h. After Celite (ca. 200 mg) and diethyl ether (10 mL) were added, the resulting suspension was stirred for additional 10 min, and then it was filtered through Celite pad. After concentration in vacuo, the residue was quickly purified with short silica gel column chromatography (AcOEt−hexane = 25:75) gave **12** (99%) as an oil. The ^{1}H NMR spectrum indicated that the sample thus obtained was a 55:45 diatereomeric mixture. IR (film) 2990, 1755, 1695, 1460, 1275, 1210, 1145, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, a = 0.55, b = 0.45) δ 1.44, 1.62 (each 3H, s), 1.87 (3H × a, t, J = 1.9 Hz), 1.91 (3H × b, t, J = 1.7 Hz), 1.97 (1H × a, ddd, J = 5.4, 8.3, 14.2 Hz), 2.01 (1H × b, ddd, J = 2.9, 8.3, 14.2 Hz), 2.24 (1H × a, ddd, J = 2.4, 7.3, 14.2 Hz), 2.33 (1H × b, ddd, J = 5.4, 6.3, 14.2 Hz), 4.94 (1H × b, m), 5.21 (1H × a, m), 5.72 (1H × b, dd, J = 2.9, 6.3 Hz), 5.75 (1H × a, dd, J = 2.4, 8.3 Hz), 6.98 (1H × a, quint, J = 1.5 Hz), 7.08 (1H × a, dd, J = 1.5, 7.8 Hz), 7.10 (1H × b, dd, J = 1.5, 7.8 Hz), 7.25 (1H × b, quint, J = 1.5 Hz), 7.39 (1H × a, t, J = 7.8 Hz), 7.42 (1H × b, t, J = 7.8 Hz), 7.45 (1H × b, dd, J = 1.5, 7.8 Hz), 7.47 (1H × a, dd, J = 1.5, 7.8 Hz), 9.94 (1H × b, s), 9.98 (1H × a, s); EIMS (rel int %) m/z = 302 (9.7, M^+), 284 (25.4, [M − H_2O]$^+$), 244 (2.1, [M − acetone]$^+$), 147 (100, not assigned); EIHRMS found m/z 302.1158 calcd for $C_{17}H_{18}O_5$, M^+ 302.1154.

5-((7-((4-Methoxybenzyloxy)methyl)-2,2,4,4-tetraisopropyl-6*H*-benzo[*f*][1,3,5,2,4]trioxadisilocin-6-yl)methyl)-3-methylfuran-2(5*H*)-one (13). A solution of **11** (119 mg, 280 mmol) in 80% aqueous acetic acid (10 mL) was stirred at 55 °C for 5 h. After concentration in vacuo below 30 °C, the residue was purified with silica gel column chromatography (AcOEt−hexane = 30:70) to give 5-(2-(2-((4-methoxybenzyloxy)methyl)-6-hydroxyphenyl)-2-hydroxyethyl)-3-methylfuran-2(5*H*)-one (101 mg, 94%) as needles. The ^{1}H NMR spectrum indicated that the sample thus obtained was a 60:40 diatereomeric mixture. ^{1}H NMR (400 MHz, $CDCl_3$ a = 0.60, b = 0.40) δ 1.857 (3H × a, t, J = 2.0 Hz), δ 1.862 (3H × b, t, J = 2.2 Hz), 2.10 (2H × a + 1H × b, m), 2.36 (1H × b, ddd, J = 3.4, 11.0, 14.5 Hz), 3.78 (3H × b, s), 3.79 (3H × a, s), 4.33, 4.38 (each 1H × b, d, J = 11.1 Hz), 4.431 (2H × a, s), 4.431 (1H × b, d, J = 11.5 Hz), 4.432 (1H × a, d, J = 11.4 Hz), 4.47 (1H × b, d, J = 11.5 Hz), 4.58 (1H × a, d, J = 11.4 Hz), 4.77 (1H ×

a, m), 5.19 (1H × b, m), 5.37 (1H × a, m), 5.46 (1H × b, m), 6.72 (1H × a, quint, J = 1.6 Hz), 6.77 (1H × b, brd, J = 7.6 Hz), 6.79 (1H × a, brd, J = 7.6 Hz), 6.82−6.88 (4H × a + 4H × b, m), 6.99 (1H × b, quint J = 1.6 Hz), 7.10 (1H × b, brt, J = 7.8 Hz), 7.10 (1H × a, brt, J = 7.8 Hz), 6.82−6.88 (2H, m), 8.51 (1H × a, br), 8.68 (1H × b, br).

A solution of the diol (576 mg, 1.50 mmol) in DMF (15.0 mL) was stirred with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (493 mg, 1.56 mmol) and imidazol (273 mg, 4.54 mmol) at room temperature for 2 h. The mixture was poured into aqueous NH_4Cl solution (50 mL) and extracted with ether (30 mL × 3). The ethereal extracts were combined, dried over $MgSO_4$, and concentrated in vacuo. Silica gel column chromatography (AcOEt−hexane = 5:95) of the residue gave **13** (882 mg, 94%) as a solid. Mp 106−109 °C (from MeOH−H_2O = 7:3); IR (KBr) 2945, 2865, 1760, 1465, 1250, 1040, 885, 835, 700 cm^{-1}. The ^1H NMR spectrum showed broaden signals. Thus, only characteristic signals are described. ^1H NMR (400 MHz, $CDCl_3$) δ 0.28−0.73 (7H, m), 0.96−1.25 (21H, m), 1.78 (3H, t, J = 1.7 Hz), 2.03, 2.21, 2.47, 2.72 (each 1H × 0.5, br), 3.81 (3H, s), 4.96 (1H, brt, J = ca. 8 Hz), 6.62 (1H × 0.5, br); ESIMS (rel int %) m/z = 649 (100, $[M + Na]^+$), 645 (6.2, $[M + H_3O]^+$), 644 (12.8, $[M + H_2O]^+$), 627 (4.9, $[M + H]^+$); ESI-HRMS found m/z 649.2997 calcd for $C_{34}H_{50}O_7Si_2Na$, $[M + Na]^+$ 649.2993.

2,2,4,4-Tetraisopropyl-6-((4-methyl-5-oxo-2,5-dihydrofuran-2-yl)methyl)-6*H*-benzo[*f*][1,3,5,2,4]trioxadisilocine-7-carbaldehyde (14). A solution of **13** (97.0 mg, 155 μmol) in a mixture of CH_2Cl_2 (4.0 mL) and water (0.4 mL) was stirred with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (44.2 mg, 194 μmol) at room temperature for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$ solution (30 mL) and extracted with AcOEt (20 mL × 3). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified with silica gel column chromatography (AcOEt−hexane = 20:80) gave 5-((7-(hydroxymethyl)-2,2,4,4-tetraisopropyl-6*H*-benzo-[*f*][1,3,5,2,4]trioxadisilocin-6-yl)methyl)-3-methylfuran-2(5*H*)-one (74.6 mg, 95%) as an oil. The ^1H NMR spectrum showed broaden signals. Thus, only characteristic signals are described. ^1H NMR (400 MHz, $CDCl_3$) δ 0.30−0.75 (7H, m), 1.01−1.26 (21H, m), 1.82 (3H, brs), 2.15−2.70 (2H), 3.30 (1H × 0.5, brd, J = 7.0 Hz, exchangeable with D_2O), 3.40 (1H × 0.5, brd, J = 8.2 Hz, exchangeable with D_2O), 4.67−5.07 (3H, Br), 5.67 (1H, brt, J = 7.7 Hz), 5.75 (1H, brdd, J = 5.0, 8.5 Hz), 6.89−7.23 (4H, m); ESIMS (rel int %) m/z = 529 (100, $[M + Na]^+$), 524 (8.6, $[M + H_2O]^+$), 507 (30.9, $[M + H]^+$), 489 (27.9, $[M + H - H_2O]^+$).

A solution of the alcohol (74.6 mg, 147 μmol) in CH_2Cl_2 (3.0 mL) was stirred with PCC (74.7 mg, 347 μmol) at room temperature for 1 h. Ether (10 mL) and Celite (ca. 500 mg) was added and the resulting suspension was further stirred at the same temperature for 30 min. After filtration through Celite pad, the filtrate was concentrated in vacuo to give **14** (73.2 mg, 99%) as almost pure state. IR (film) 2945, 2870, 1765, 1695, 1460, 1260, 1060, 885, 830, 700 cm^{-1}. The ^1H NMR spectrum showed broaden signals. Thus, only characteristic signals are described. ^1H NMR (400 MHz, $CDCl_3$) δ 0.62−1.25 (28H, m), 1.85, 1.88 (each 3H × 0.5, brs), 2.01−2.51 (2H, m), 4.68 (1H × 0.5, br), 5.17 (1H × 0.5, brd, J = 5.5 Hz), 5.69 (1H, br), 6.87−7.61 (4H, m), 10.79 (1H, br); ESIMS (rel int %) m/z = 1031 (25.6, $[2M + Na]^+$), 543 (16.6, $[M + K]^+$), 527 (100, $[M + Na]^+$), 522 (11.6, $[M + H_2O]^+$), 505 (27.8, $[M + H]^+$); ESI-HRMS found m/z 527.2265 calcd for $C_{26}H_{40}O_6Si_2Na$, $[M + Na]^+$ 527.2261.

(1*S,3*S**,4*S**)-1-Hydrolambertellol 1,8-*O*-Isopropylidene Acetal (15) and Its (3*R**)-Isomer (16).** To a solution of **12** (75.0 mg, 248 μmol) in DMF (2.0 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in THF solution, 250 μL) was added at −40 °C under Ar atmosphere. Upon addition of sodium bis(trimethylsilyl)-amide, the clear solution turned to green and changed to orange solution after 2 min. After stirring for 5 min, saturated aqueous NH_4Cl solution (ca. 3 mL) was added. The mixture was poured into H_2O (30 mL) and extracted with AcOEt (20 mL × 3). The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue eluted successively with AcOEt−hexane = 22:78 and 28:72 gave **15** (58.1 mg, 77%) and **16** (10.0 mg, 13%), respectively, both as needles.

Physical Properties of (1*S,3*S**,4*S**)-1-Hydrolambertellol 1,8-*O*-Isopropylidene Acetal (15).** Mp 210−212 °C (from AcOEt−hexane = 4:6). IR (KBr) 3410, 3000, 2870, 1740, 1590, 1470, 1270, 1140, 1015, 870, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *lambertellol numbering*) δ 1.57, 1.60 (each 3H, s, $C(CH_3)_2$), 1.97 (3H, d, J = 1.1 Hz, C3′CH_3), 2.30 (1H, dd, J = 6.8, 12.8 Hz, C2*H*H), 2.51 (1H, dd, J = 10.6, 12.8 Hz, C2*H*H), 4.57 (1H, brs, C4*H*), 4.85 (1H, dd, J = 6.8, 10.6 Hz, C1*H*), 6.83 (1H, d, J = 8.4 Hz, C7*H*), 6.99 (1H, d, J = 7.4 Hz, C5*H*), 7.04 (1H, q, J = 1.1 Hz, C4′*H*), 7.27 (1H, dd, J = 7.4, 8.4 Hz, C6*H*), NOE C1*H* ↔ C2*Hβ*, C2*Hβ* ↔ C4′*H*, C4′*H* ↔ C1*H*, C4′*H* ↔ C4*H*, C4*H* ↔ C5*H*; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7, 23.9, 28.2, 34.2, 63.3, 70.6, 86.5, 101.7, 116.3, 118.9, 119.1, 129.3, 131.3, 133.6, 148.9, 150.6, 172.5; EIMS (rel int %), m/z = 302 (15.0, M^+), 244 (89.2, $[M -$ acetone$]^+$), 192 (100); EIHRMS found m/z 302.1156 calcd for $C_{17}H_{18}O_5$, M^+ 302.1154.

Physical Properties of (1*S,3*R**,4*S**)-Isomer (16).** Mp 165−167 °C (from AcOEt−hexane = 3:7). IR (KBr) 3390, 2990, 2850, 1760, 1595, 1470, 1285, 1140, 870, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, *lambertellol numbering*) δ 1.58, 1.59 (each 3H, s, $C(CH_3)_2$), 1.95 (3H, d, J = 1.6 Hz, C3′CH_3), 2.16 (1H, dd, J = 5.8, 13.0 Hz, C2*H*H), 2.22 (1H, brd, J = 4.8 Hz, OH, exchangeable with D_2O), 2.24 (1H, dd, J = 10.8, 13.0 Hz, C2*H*H), 4.52 (1H, d, J = 4.8 Hz, C4*H*), 5.11 (1H, dd, J = 5.8, 10.3 Hz, C1*H*), 6.78 (1H, d, J = 8.2 Hz, C7*H*), 6.94 (1H, d, J = 7.6 Hz, C5*H*), 7.15 (1H, q, J = 1.6 Hz, C4′*H*), 7.23 (1H, dd, J = 7.6, 8.2 Hz, C6*H*), NOE C2*Hα* ↔ C1*H*, C4*H* ↔ C1*H*, C4*H* ↔ C5*H*, C4′*H* ↔ C2*Hβ*; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.7, 23.8, 28.4, 33.2, 63.3, 71.8, 86.7, 101.6, 116.1, 118.6, 118.9, 129.4, 123.0, 134.8, 150.5, 151.6, 173.3; EIMS (rel int %), m/z = 302 (7.6, M^+), 244 (100, $[M -$ acetone$]^+$), 134 (95.3); EIHRMS found m/z 302.1146 calcd for $C_{17}H_{18}O_5$, M^+ 302.1154.

(1*S,3*S**,4*S**)-1-Hydrolambertellol A (*rac*-17) and (1*R**,3*S**,4*S**)-Isomer (*rac*-18).** A solution of **15** (15.0 mg, 49.6 μmol) in 80:20 mixture of acetonitrile and H_2O (1.0 mL) was stirred with *p*-TsOH (ca. 0.5 mg) at room temperature for 6 h. The mixture was poured into H_2O (15 mL) and extracted with AcOEt (15 mL × 3). The combined organic solution was washed with brine, dried over $MgSO_4$, and then concentrated in vacuo. Silica gel column chromatography of the residue (AcOEt−hexane = 50:50) gave a 80:20 mixture of ***rac*-17** and ***rac*-18** (13.0 mg, 100%) as white solid. Analytical samples were obtained by HPLC (column, Merck LiChroCART RP 18e (ϕ 4 mm × 125 mm); eluent, CH_3CN−H_2O 1.0 mL/min flow, detected at 210 nm) to give pure ***rac*-17** and ***rac*-18**.

Physical Properties of (1*S,3*S**,4*S**)-1-Hydrolambertellol A (*rac*-17).** Amorphous powder, HPLC retention time t_R = 16.4 min (above conditions); IR (KBr) 3450, 3235, 2925, 1750, 1595, 1475, 1290, 1260, 1065 cm^{-1}; ^1H NMR (400 MHz, CD_3OD, *lambertellol numbering*) δ 1.88 (3H, d, J = 1.5 Hz, C3′CH_3), 2.26, 2.51 (each 1H, dd, J = 6.5, 14.0 Hz, C2H_2), 4.51 (1H, s, C4*H*), 5.10 (1H, t, J = 6.5 Hz, C1*H*), 6.80 (1H, d, J = 7.7 Hz, C7*H*), 6.94 (1H, d, J = 7.7 Hz, C5*H*), 7.08 (1H, q, J = 1.5 Hz, C4′*H*), 7.19 (1H, t, J = 7.7 Hz, C6*H*). NOE C1*H* ↔ C2*Hβ*, C1*H* ↔ C4′*H*, C4*H* ↔ C4′*H*, C4H ↔ C5H; ^{13}C NMR (100 MHz, CD_3OD) δ 10.6, 37.1, 65.2, 72.1, 88.2, 116.3, 120.7, 124.6, 130.4, 132.0, 138.1, 152.1, 157.6, 175.4; EIMS (rel int %), m/z = 262 (7.4, M^+), 244 (49.3, $[M - H_2O]^+$), 226 (56.9, $[M - H_2O \times 2]^+$) 134 (100); EIHRMS found m/z 262.0865 calcd for $C_{14}H_{14}O_5$, M^+ 262.0841.

Physical Properties of (1*R,3*R**,4*S**)-Isomer (*rac*-18).** R_f = 0.21 (AcOEt−hexane = 60:40), mp 186 °C (prism, from hexane−AcOEt = 50:50); HPLC retention time t_R = 11.4 min (above conditions); IR (KBr) 3400, 2905, 1745, 1590, 1470, 1285, 1265, 1060, 770 cm^{-1}; ^1H NMR (400 MHz, CD_3OD, *lambertellol numbering*) δ 1.89 (3H, d, J = 1.5 Hz, C3′CH_3), 2.05 (1H, dd, J = 6.6, 13.6 Hz, C2*H*H), 2.56 (1H, dd, J = 6.0, 13.6 Hz, C2*H*H), 4.68 (1H, s, C4H), 5.25 (1H, dd, J = 6.0, 6.6 Hz, C1*H*), 6.79 (1H,

d, J = 7.7 Hz, C7*H*), 6.96 (1H, d, J = 7.7 Hz, C5*H*), 7.18 (1H, t, J = 7.7 Hz, C6*H*), 7.29 (1H, q, J = 1.3 Hz, C4′*H*), NOE C1*H* ↔ C2*Hβ*, C4*H* ↔ C4′*H*, C4*H* ↔ C2*H*α, C4*H* ↔ C5*H*, C4′*H* ↔ C2*H*α; ^{13}C NMR (100 MHz, CD_3OD) δ 10.6, 38.1, 65.6, 71.2, 89.5, 116.0, 120.2, 124.6, 130.3, 130.7, 138.7, 153.0, 157.1, 175.8; ESIMS (rel int %) m/z = 263 (29.7, $[M + H]^+$), 262 (16.3, M^+), 245 (51.8, $[M + H - H_2O]^+$), 227 (100, $[M + H - 2H_2O]^+$); ESI-HRMS found m/z 263.0926 calcd for $C_{14}H_{15}O_5$, $[M + H]^+$ 263.0919.

(1*S,3*R**,4*S**)-1-Hydrolambertellol B (*rac*-19).** In a similar manner to that described above, solution of **16** (9.8 mg, 32.5 μmol) was treated with *p*-TsOH (ca. 0.5 mg) for 3 h and the successive similar work up gave ***rac*-19**. (8.5 mg, 100%) as white solid after silica gel column chromatography (AcOEt−hexane = 40:60). Mp 192 °C (decompose, prism); IR (KBr) 3400, 2925, 1740, 1630, 1385, 1275, 1040 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, *lambertellol numbering*) δ 1.88 (3H, d, J = 1.6 Hz, C3′C*H*$_3$), 2.18 (1H, dd, J = 4.4, 13.7 Hz, C2*H*H), 2.42 (1H, dd, J = 5.4, 13.7 Hz, C2*H*H), 4.68 (1H, s, C4*H*), 5.23 (1H, dd, J = 4.4, 5.4 Hz, C1*H*), 6.78 (1H, d, J = 8.2 Hz. C7*H*), 6.99 (1H, d, J = 7.6 Hz, C5*H*), 7.18 (1H, dd, J = 7.6, 8.2 Hz, C6*H*), 7.38 (1H, q, J = 1.6 Hz, C4′*H*), NOE C1*H* ↔ C2*Hβ*, C4*H* ↔ C2*Hβ*, C4′*H* ↔ C2*H*α, C4*H* ↔ C5*H*; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 39.2, 64.6, 73.3, 89.1, 115.6, 119.4, 124.3, 130.4, 130.8, 139.0, 152.7, 157.2, 175.7; EIMS (rel int) m/z = 262 (3.6, M^+), 244 (42.5, $[M - H_2O]^+$), 226 (37.9, $[M - 2H_2O]^+$), 134 (100); EIHRMS found m/z 262.0819 calcd for $C_{14}H_{14}O_5$, M^+ 262.0841.

(1*R,3*S**,4*S**)-1-Hydrolambertellol A (*rac*-18) and (1*R**,3*R**,4*S**)-1-Hydrolambertellol B (*rac*-25) from 14.** To a solution of **14** (46.0 mg, 91.1 μmol) in DMF (1.0 mL) was added sodium bis(trimethylsilyl)amide (1.0 M in THF solution, 95 μL) at −40 °C under Ar atmosphere. Upon addition of sodium bis(trimethylsilyl)amide, the clear solution turned to green and changed to orange solution after several seconds. After stirring for 5 min, saturated aqueous NH_4Cl solution (ca. 3 mL) was added. The mixture was poured into H_2O (30 mL) and extracted with AcOEt (20 mL × 3). The combined extracts were washed with brine, dried over $MgSO_4$, and then concentrated in vacuo to give a crude mixture of **19**, **20**, **21**, and **22** (ca. 48 mg). After the crude mixture was dissolved in THF (1.0 mL), acetic acid (200 μL) and TBAF (1.0 M in THF, 200 μL) were successively added at room temperature. The mixture was stirred for 30 min. The mixture was poured into H_2O (20 mL) and extracted with AcOEt (20 mL × 3). Silica gel column chromatography of the residue eluted successively with AcOEt−hexane = 35:65 gave ***rac*-18** (16.1 mg, 67%) and ***rac*-25** (7.5 mg, 31%) both as solids. The ^{1}H NMR, ^{13}C NMR, IR, spectra as well as TLC behavior of ***rac*-18** were identical those of the sample provided from **15**.

Physical Properties of (1*R,3*R**,4*S**)-1-Hydrolambertellol B (*rac*-25).** R_f = 0.33 (AcOEt−hexane = 60:40); IR (KBr) 3455, 3235, 2940, 1735, 1595, 1475, 1280, 1040, 985, 815 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD, *lambertellol numbering*) δ 1.88 (3H, d, J = 1.6 Hz, C3′C*H*$_3$), 2.27 (1H, dd, J = 8.5, 13.1 Hz, C2*H*H), 2.39 (1H, dd, J = 6.7, 13.1 Hz, C2*H*H), 4.86 (1H, s, C4*H*), 5.20 (1H, dd, J = 6.7, 8.5 Hz, C1*H*), 6.78 (1H, brd, J = 8.0 Hz. C7*H*), 7.01 (1H, brd, J = 8.0 Hz, C5*H*), 7.02 (1H, q, J = 1.5 Hz, C4′*H*), 7.20 (1H, t, J = 8.0 Hz, C6*H*), NOE C1*H* ↔ C2*H*α ↔ C1*H* ↔ C4′*H* ↔ C4*H* ↔ C2*Hβ*, C4*H* ↔ C5*H*; ^{13}C NMR (100 MHz, $CDCl_3$) ↔ 10.7, 40.0, 66.4, 72.8, 89.4, 116.0, 119.2, 124.0, 130.4, 132.9, 139.0, 152.3, 157.3, 175.2; ESIMS (rel int %) m/z = 285 (23.9, $[M + Na]^+$), 280 (47.4, $[M + H_2O]^+$), 263 (17.6, $[M + H]^+$), 262 (30.3, M^+), 245 (100, $[M + H - H_2O]^+$), 227 (98.0, $[M + H - 2H_2O]^+$); ESI-HRMS found m/z 285.0737 calcd for $C_{14}H_{14}O_5Na$, $[M + Na]^+$ 285.0739. Analytical samples of the intermediates **21**, **22**, **23**, and **22** were isolated preparative silica gel TLC before treatment with TBAF .

Physical Properties of (1*R,3*R**,4*S**)-1-Hydrolambertellol B 1,8-*O*-Disiloxanylidene Acetal (21).** R_f = 0.62 (AcOEt−hexane = 40:60); IR (KBr) 3445, 2495, 2870, 1745, 1470, 1275, 1060, 1040, 995, 885, 670 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, *lambertellol numbering*) δ 0.68−1.18 (28H, SiC*H*(CH_3)$_2$ × 2), 1.88 (3H, d, J = 1.5 Hz, C3′C*H*$_3$), 2.40 (1H, dd, J = 6.4, 15.0 Hz, C2*H*H), 2.53 (1H, dd, J = 3.4, 15.0 Hz, C2*H*H), 2.54 (1H, br, O*H*), 5.36 (1H, dd, J = 3.4, 6.4 Hz, C1*H*), 5.40 (1H, s, C4*H*), 6.57 (1H, q, J = 1.5 Hz, C4′*H*), 6.89 (1H, brd, J = 7.6 Hz, C7*H*), 7.24 (1H, brd, J = 7.6 Hz, C5*H*), 7.28 (1H, t, J = 7.6 Hz, C6*H*), NOE C2*Hβ* ↔ C4′*H*, C4′*H* ↔ C1*H*, C4*H* ↔ C2*H*α, C4*H* ↔ C5*H*; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.6, 12.6, 12.79, 12.81, 13.3, 16.6, 16.8, 17.05, 17.07, 17.16, 17.25, 17.31, 39.4, 62.5, 70.5, 89.0, 118.6, 120.8, 127.7, 129.7, 130.5, 138.7, 149.4, 151.7, 173.7; EIMS (rel int) m/z = 461 (100, $[M - isopropyl]^+$), 443 (22.1, $[M - isopropyl - H_2O]^+$), 425 (23.3, $[M - isopropyl - 2H_2O]^+$); EIHRMS found m/z 461.1808 calcd for $C_{23}H_{33}O_6Si_2$, $[M - isopropyl]^+$ 461.1816.

Physical Properties of (1*R,3*S**,4*S**)-1-Hydrolambertellol A 1,8-*O*-Disiloxanylidene Acetal (22).** R_f = 0.57 (AcOEt−hexane = 40:60); IR (KBr) 3435, 2495, 2870, 1765, 1460, 1275, 1050, 1015, 885, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$ *lambertellol numbering*) δ 0.84−1.16 (28H, SiC*H*(CH_3)$_2$ × 2), 1.90 (3H, d, J = 1.5 Hz, C3′C*H*$_3$), 1.95 (1H, brd, J = 13.4 Hz, C2*H*H), 2.60 (1H, d, J = 3.0 Hz, O*H* exchangeable with D_2O), 2.95 (1H, dd, J = 4.3, 13.4 Hz, C2*H*H), 4.53 (1H, br, C4*H*), 5.42 (1H, dd, J = 2.1, 4.3 Hz, C1*H*), 6.92 (1H, d, J = 7.9 Hz, C7*H*), 7.03 (1H, d, J = 7.9 Hz, C5*H*), 7.28 (1H, t, J = 7.9 Hz, C6*H*), 7.43 (1H, br, C4′ *H*), NOE C1*H* ↔ C2*Hβ*, C4*H* ↔ C4′*H*, C4*H* ↔ C5*H*; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 12.2, 12.75, 12.78, 13.1, 16.8, 16.9, 17.1, 17.20, 17.21, 17.27, 17.6, 17.7), 37.0, 63.3, 71.7, 86.8, 121.9, 123.6, 127.5, 128.3, 129.9, 135.7, 152.5, 153.4, 173.2; EIMS (rel int) m/z = 461 (100, $[M - isopropyl]^+$), 443 (22.8, $[M - isopropyl - H_2O]^+$), 425 (20.9, $[M - isopropyl\text{-}2\times H_2O]^+$); EIHRMS found m/z 461.1813 calcd for $C_{23}H_{33}O_6Si_2$, $[M - isopropyl]^+$ 461.1816.

Physical Properties of (1*R,3*R**,4*S**)-1-*O*-(Hydroxydiisopropylsilyloxy)diisopropylsilyloxy-1-hydrolambertellol B (23).** R_f = 0.36 (AcOEt−hexane = 40:60); IR (KBr) 3370, 2945, 2865, 1745, 1465, 1285, 1050, 880, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, *lambertellol numbering*) 0.90−1.10 (28H, m, SiC*H*(CH_3)$_2$ × 2), 1.91 (3H, d, J = 1.5 Hz, C3′C*H*$_3$), 2.48 (1H, dd, J = 6.4, 12.5 Hz, C2*H*H), 2.60 (1H, dd, J = 9.8, 15.0 Hz, C2*H*H), 3.26 (1H, br, O*H* exchangeable with D_2O), 5.19 (1H, s, C4*H*), 5.57 (1H, dd, J = 6.4, 9.8 Hz, C1*H*), 6.81 (1H, q, J = 1.5 Hz, C4′*H*), 6.88 (1H, brd, J = 7.9 Hz, C7*H*), 7.17 (1H, brd, J = 7.9 Hz, C5*H*), 7.27 (1H, t, J = 7.9 Hz, C6*H*), 8.00 (1H, br, phenolic proton), NOE C1*H* ↔ C4′*H*, C4*H* ↔ C2*H*α, C4*H* ↔ C5*H*; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.8, 13.28, 13.31, 13.6, 14.1, 16.8, 17.09, 17.13, 17.15, 17.16, 17.18, 17.22, 17.3, 40.9, 68.8, 71.7, 88.2, 116.5, 118.0, 121.4, 130.1, 132.7, 136.6, 147.2, 155.6, 173.4; FDMS (rel int) m/z = 523 (37.0, $[M + H]^+$), 522 (38.1, $[M]^+$), 374 (100, $[M - (i\text{-}Pr)_2Si(OH)_2]^+$); FD-HRMS found m/z 522.2474 calcd for $C_{26}H_{42}O_7Si_2$, M^+ 522.2469.

Physical Properties of (1*R,3*S**,4*S**)-1-*O*-(Hydroxydiisopropylsilyloxy)diisopropylsilyloxy-1-hydrolambertellol A (24).** R_f = 0.29 (AcOEt−hexane = 40:60); IR (KBr) 3370, 2945, 2865, 1745, 1460, 1290, 1250, 1050, 885, 690 cm^{-1}, ^{1}H NMR (400 MHz, $CDCl_3$, *lambertellol numbering*) δ 0.90−1.07 (28H, SiC*H*(CH_3)$_2$ × 2), 1.92 (3H, d, J = 1.5 Hz, C3′C*H*$_3$), 2.13 (1H, dd, J = 5.8, 13.4 Hz, C2*H*H), 2.75 (1H, dd, J = 5.2, 13.4 Hz, C2*H*H), 2.76 (1H, br, O*H* exchangeable with D_2O), 4.66 (1H, br, C4H), 5.63 (1H, dd, J = 5.2, 5.8 Hz, C1*H*), 6.86 (1H, br, J = 8.2 Hz, C7*H*), 7.01 (1H, brd, J = 7.9 Hz, C5*H*), 7.19 (1H, q, J = 1.5 Hz, C4′*H*), 7.28 (1H, brt, J = 8.0 Hz, C6*H*), 7.92 (1H, br, phenolic proton), NOE C4*H* ↔ C4′*H*, C4*H* ↔ C5*H*; ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 13.26, 13.29, 13.6, 13.8, 17.02, 17.04, 17.10, 17.11, 17.16, 17.23, 17.25, 17.4, 37.9, 66.2, 70.9, 87.1, 117.1, 120.4, 122.9, 128.2, 129.6, 136.1, 151.3, 155.1, 173.7; FDMS (rel int) m/z = 523 (72.7, $[M + H]^+$), 522 (100, $[M]^+$), 479 (82.7, $[M - isopropyl]^+$), 374 (100, $[M - (i\text{-}Pr)_2Si(OH)_2]^+$); FD-HRMS found m/z 522.2474 calcd for $C_{26}H_{42}O_7Si_2$, M^+ 522.2469.

***rac*-Lambertellol B (2) from *rac*-19.** A suspension of a mixture of the starting **18** (5.5 mg, 21.0 μmol) and manganese(IV) oxide (15.0 mg) in CH_2Cl_2 (2.0 mL) was stirred at room temperature for 4 h. The mixture was filtered through Celite and the filtrate was

concentrated in vacuo. After dissolving with a mixture of CH_3CN and H_2O (10:90) the sample was loaded on Sep-pak ODS (5 g). Elution with CH_3CN:H_2O (10:90) gave ***rac*-2** (3.0 mg, 55%) as needles. IR (KBr) 3500, 2925, 1760, 1635, 1340, 1245, 1040, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.96 (3H, d, J = 1.5 Hz), 2.51 (1H, br, exchangeable with D_2O), 2.95 (1H, d, J = 17.5 Hz), 3.20 (1H, d, J = 17.5 Hz), 4.88 (1H. s), 7.01 (1H, d, J = 8.5 Hz), 7.06 (1H, d, J = 7.5 Hz), 7.09 (1H, d, J = 1.5 Hz), 7.56 (1H, dd, J = 7.5, 8.5 Hz), 12.10 (1H, s, exchangeable with D_2O); EIHRMS found m/z 260.0678 calcd for $C_{14}H_{12}O_5$; M^+ 260.0685. The IR and ^1H NMR spectra of this sample were identical with that of the natural lambertellol B (**2**) except for the chemical shift for exchangeable OH signals in the ^1H NMR spectrum.[4]

***rac*-Lambertellol A (1) from *rac*-17.** A suspension ***rac*-17** (8.1 mg, 30.9 μmol) was treated with PCC (50.3 mg, 233.3 μmol) in CH_2Cl_2 (0.5 mL) acetone (0.5 mL). Ether (15 mL) was added and the resulting mixture was stirred for an additional 5 min. After filtration through Celite, concentration of the filtrate gave ***rac*-1** containing small amount of lambertellin (**3**) being generated during work up. After filtration through Celite, the eluent was passed through short silica gel filter (AcOEt−hexane = 20:80, then AcOEt 100%) gave ***rac*-1** (2.8 mg, 35%) as needles. IR (KBr) 3420, 2925, 1735, 1640, 1460, 1260, 1125, 1055, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.97 (3H, d, J = 1.5 Hz), 2.93 (1H, d, J = 17.5 Hz), 3.23 (1H, d, J = 17.5 Hz), 4.88 (1H. br), 6.97 (1H, br), 7.01 (1H, d, J = 8.5 Hz), 7.10 (1H, d, J = 7.5 Hz), 7.56 (1H, dd, J = 7.5, 8.5 Hz), 12.08 (1H, s, exchangeable with D_2O); ESIMS (rel int %) m/z = 283 (6.6, $[M + Na]^+$), 279 (13.6, $[M + H_3O]^+$), 278 (22.4, $[M + H_2O]^+$), 261 (100, $[M + H]^+$); ESI-HRMS found m/z 261.0770 calcd for $C_{14}H_{13}O_5$; $[M + H]^+$ 261.0763. The IR, and ^1H NMR spectra of this sample was identical with that of the natural lambertellol A (**1**) except for the chemical shift for exchangeable OH signals in the ^1H NMR spectrum.[4]

Acknowledgment. Part of this work was supported by Grant-in-Aid for Scientific Research (no. 17580090) from the Ministry of Education, Science, Sports, and Culture of Japan. The authors would like to thank Professor Jun Kawabata and Dr. Eri Fukushi of Hokkaido University for measurements of mass spectra. The authors are grateful to Professor Hiromasa Kiyota of Tohoku University for fruitful discussions about deprotection of the acetonide **15**. The authors thank to Professor Babak Borhan of Michigan State University for his kind reviewing of the manuscript before submission.

Supporting Information Available: Experimental procedures, compounds **7**−**10**, *rac*-lambertellol A (**1**) from ***rac*-18**, *rac*-lambertellol B (**2**) from ***rac*-25**, optical resolutions of ***rac*-17**, ***rac*-18**, ***rac*-19**, ***rac*-25**, ***rac*-2**, preparation of **1** and ***ent*-1**, antifungal assay against *Monilinia fructigena,* germination inhibition assay against *Cochlibolus miyabeanus,* physical data and spectra of **1**, **2**, **7**−**19**, and **21**−**25**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8005478