JOC Article

First Total Synthesis of (±)-Linderol A, a Tricyclic Hexahydrodibenzofuran Constituent of *Lindera umbellata* Bark, with Potent Inhibitory Activity on Melanin Biosynthesis of Cultured B-16 Melanoma Cells

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The first total synthesis of (±)-Linderol A, a hexahydrodibenzofuran constituent of *Lindera umbellata* bark, with potent inhibitory activity on the melanin biosynthesis of cultured B-16 melanoma cells, was achieved through 19 steps of reaction in 6.6% overall yield, in which the critical step was a tandem reaction of a 3-ethoxycarbonylcoumarin derivative with dimethylsulfoxonium methylide to yield the 2-ethoxycarbonylcyclopenta[*b*]benzofuran-3-ol derivative.

Introduction

In 1995, Sashida et al. reported the isolation of Linderol A (**1**), (5a*R**,6*R**,9*R**,9a*S**)-4-cinnamoyl-3,6-dihydroxy-1-methoxy-6-methyl-9-(1-methylethyl)-5a,6,-7,8,9,9a-hexahydrodibenzofuran, from the fresh bark of *Lindera umbellata* (Lauraceae; Figure 1).[1,2] It has four successive asymmetric carbons at the 6, 5a, 9a, and 9 positions. They also reported the potent inhibitory activity of **1** on the melanin biosynthesis of cultured B-16 melanoma cells without causing any cytotoxicity in the cultured cells or skin irritation in guinea pigs.[1]

On the other hand, we reported an interesting tandem reaction of the coumarin derivatives (**2**), which had an electron-withdrawing group at the 3 position, to yield the tricyclic 2-substituted cyclopenta[*b*]benzofuran-3-ol derivatives (**3**) by treatment with a small excess of more than 2 equiv of dimethylsulfoxonium methylide (Scheme 1).[3]

We have taken an interest in **1** in view of the structural and biological aspects. We projected the total synthesis of (±)-**1** by applying this tandem reaction to an appropriate substituted coumarin. Our designed synthetic route is outlined in Scheme 2. Each step is as follows: (i) the tandem reaction to the cyclopenta[*b*]benzofuran (**4** → **5**),

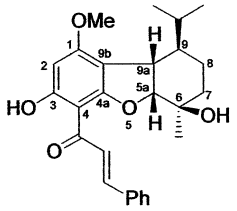
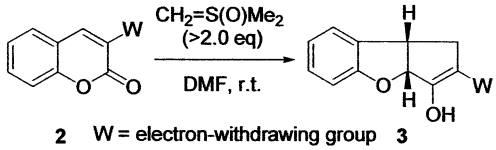


FIGURE 1. Structure of Linderol A (**1**).

SCHEME 1



2 W = electron-withdrawing group **3**

(ii) the regio- and stereoselective introduction of the isopropyl group at the 1 position (**5** → **6**), (iii) ring expansion to the cyclohexane derivative (**6** → **7**), (iv) the regio- and stereoselective conversion to the hydroxy group at the 6 position (**7** → **8**),[4] and (v) the regioselective introduction of the cinnamoyl group at the 4 position [**8** → (±)-**1**]. In this paper, we describe the first total synthesis of (±)-**1** according to this route (Scheme 2).[5]

Results and Discussion

The coumarin derivative (**4**)[6] was treated with 2.5 equiv of dimethylsulfoxonium methylide according to the previ-

† Kyoto Pharmaceutical University.

‡ Osaka University.

(1) Mimaki, Y.; Kameyama, A.; Sashida, Y.; Miyata, Y.; Fujii, A. *Chem. Pharm. Bull.* **1995**, *43*, 893.

(2) Professor Sashida (Tokyo University of Pharmacy and Life Science) proposed to us the name, Linderol A, for the compound **1**, which was treated as an unnamed natural product in the report (ref 1). In this paper, we will use the name "Linderol A".

(3) (a) Yamashita, M.; Okuyama, K.; Kawasaki, I.; Ohta, S. *Tetrahedron Lett.* **1995**, *36*, 5603. (b) Yamashita, M.; Okuyama, K.; Kawajiri, T.; Takada, A.; Inagaki, Y.; Nakano, H.; Tomiyama, M.; Ohnaka, A.; Terayama, I.; Kawasaki, I.; Ohta, S. *Tetrahedron* **2002**, *58*, 1497.

(4)) The numbering of the dibenzofuran derivatives in this text follows that of the natural product (**1**).

(5)) Yamashita, M.; Ohta, N.; Kawasaki, I.; Ohta, S. *Org. Lett.* **2001**, *3*, 1359.

(6)) (a) Kirkiacharian, B. S.; Danan, A. *Synthesis* **1986**, 383. (b) Bonsignore, L.; Cottiglia, F.; Maccioni, A. M.; Secci, D.; Lavagna, S. M. *J. Heterocycl. Chem.* **1995**, *32*, 573.

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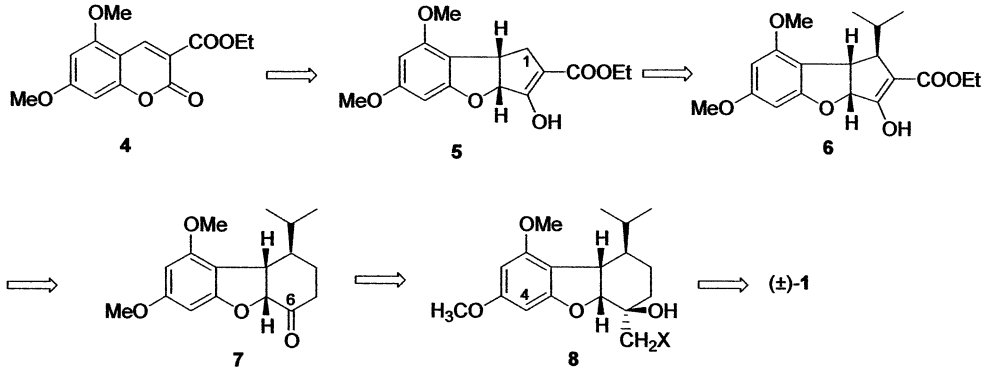
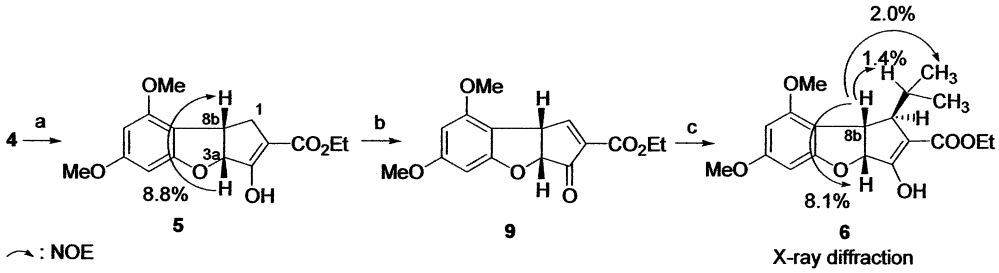
SCHEME 2. Projected Synthetic Route to (±)-Linderol A (1)



SCHEME 3[a]



[a] The steps are as follows. (a) $Me_3S(O)I$, NaH, DMF, rt, 76%. (b) i: PhSeCl, NaH, THF, 0 °C to rt. ii: $NaIO_4$, THF−H_2O, rt, 79%. (c) *i*-PrMgBr, CuBr/Me_2S complex, 0 °C, 19%.

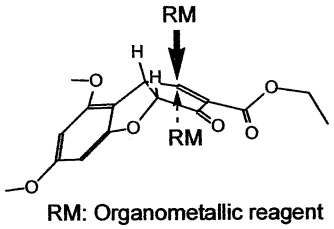


FIGURE 2. *β*-Face attack of an RM to **9**.

ously reported procedure[3] to afford the cyclopenta[*b*]-benzofuran derivative (**5**) in 76% yield. The stereochemistry of 3a-H and 8b-H of **5** was determined as shown in Scheme 3 on the basis of NOE experiment, by which 8.8% of the NOE was observed between 3a-H and 8b-H to be cis. To introduce regioselectively an isopropyl group to the 1 position of **5**, we applied a 1,4 addition of an appropriate isopropyl metal reagent to an α,*β*-unsaturated ketone such as **9**. To realize this plan, first the benzofuran (**5**) was converted to the α,*β*-unsaturated keto ester (**9**) according to the phenylselenenylation−oxidation methodology.[7]

We predicted that an appropriate organometallic reagent (RM) would attack exclusively from the less hindered side (convex face) of the 5,5 ring in **9**, so that the adduct would have the desired stereochemistry (Figure 2). In fact, the isopropyl group was introduced regio- and stereoselectively by the treatment of **9** with isopropylmagnesium bromide in the presence of a copper(I) bromide−dimethyl sulfide complex to afford the desired enol ester (**6**) as a single product. The stereochemistry of the introduced isopropyl group of **6** was confirmed on the basis of NOE and X-ray crystallography to be cis between 8b-H and the isopropyl group, as shown in Scheme 3.

TABLE 1. Introduction of an Isopropyl Group to the 1 Position of 9[a]

entry	Cu reagent (equiv)	*i*-PrMgBr (equiv)	Lewis acid (equiv)	temp (°C)	isolated yield of **6** (%)
1	CuBr/DMS (0.2)	2		0	19
2	CuCl (0.2)	2		0	22
3	CuI (0.2)	2		0	26
4	CuI (2.0)	2		0	38
5	CuI (2.0)	4		0	47
6	CuI (2.0)	4	$BF_3{\cdot}Et_2O$ (1.0)	−78	66

[a] The reaction was carried out in Et_2O/THF. The reaction time was 1 h.

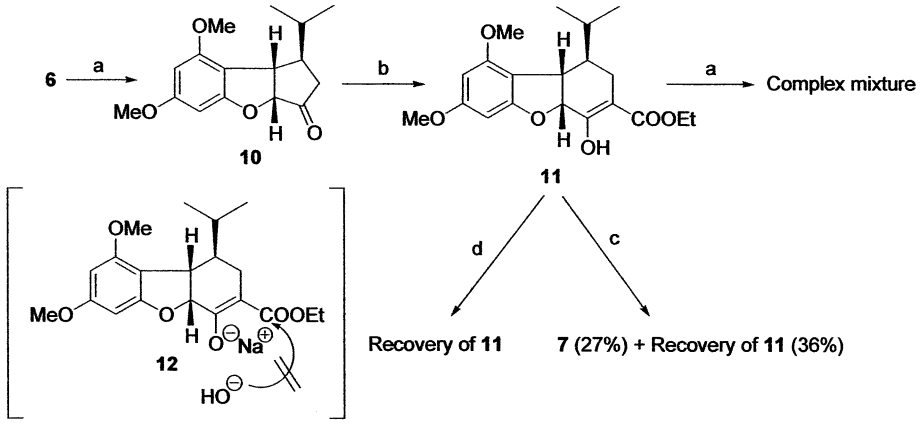
Because the yield of the desired **6** was low (19%), several reaction conditions were examined in order to improve the yield and the results are summarized in Table 1. As shown in entry 6 in Table 1, the yield was raised to 66% by using CuI and $BF_3{\cdot}Et_2O$ (etherate) as an additive.

The ester (**6**) was readily decarboxylated by heating in acetic acid to give **10** in 96% yield. The one-carbon ring enlargement of the cyclopentanone ring of **10** was carried out by treatment with ethyl diazoacetate in the presence of $BF_3{\cdot}Et_2O$ to afford successfully the six-membered enol ester (**11**) in 86% yield.[8] The decarboxylation of **11** by heating in AcOH unexpectedly afforded a complex mix-

(7) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

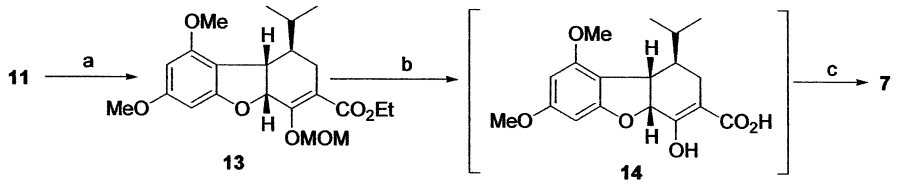
(8) Tai, W. T.; Warnhoff, E. W. *Can. J. Chem.* **1964**, *42*, 1333. Liu, H. J.; Majumdar, S. P. *Synth. Commun.* **1975**, *5*, 125. Marchad, A. P.; Rajapaksa, D.; Reddy, S. P. *J. Org. Chem.* **1989**, *54*, 5086. Ghosh, A. K.; Biswas, S.; Venkastewaran, R. V. *J. Chem. Soc., Chem. Commun.* **1988**, 1421.

SCHEME 4[a]



[a] The steps are as follows. (a) AcOH, 100 °C, 96%. (b) $N_2CHCOOEt$, $BF_3{\cdot}Et_2O$, 0 °C, 86%. (c) AcOH, TsOH (catalytic amount), reflux, 6 h. (d) NaOH/EtOH.

SCHEME 5[a]



[a] The steps are as follows. (a) MOMCl, NaH, THF, rt, 84%. (b) i: $NaOH/H_2O$, rt. ii: *c*-HCl, 0 °C. (c) Xylene, reflux, 72% from **13**.

ture; however, the desired cyclohexanone (**7**) was obtained in 27% yield by heating in AcOH in the presence of a catalytic amount of TsOH with a considerable recovery of **11**. Attempts for the alkaline hydrolysis of **11** resulted in the almost complete recovery of **11**. The enolate anion (**12**), generated first from the enol ester (**11**), would prevent the approach of the hydroxy anion to the ester carbonyl group of **12** (Scheme 4).

Therefore, it was considered that the alkaline hydrolysis of the ethoxycarbonyl group in **11** should be completed after protection of the enol group. Thus, the enol (**11**) was converted to the corresponding MOM ether (**13**), and alkaline hydrolysis followed by acidification and refluxing in xylene gave the ketone (**7**) in 72% yield from **13** (five steps, 52% from **10**; Scheme 5).[9]

The next step is the stereoselective introduction of a methyl group at the 6 position of **7**. A methylmetallic reagent would attack from the less hindered side of **7** to give the undesired α-tertiary alcohol, as shown in Figure 3. On the other hand, oxidation would occur from the less hindered side of the *exo*-olefin (**15**) to afford the *β*-tertiary alcohol with the desired stereochemistry, as shown in Figure 4.

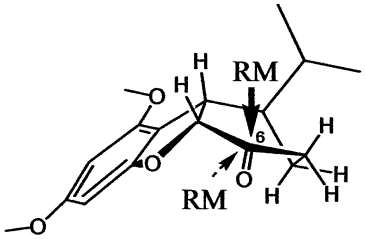


FIGURE 3. *β*-Face attack of an RM to **7**.

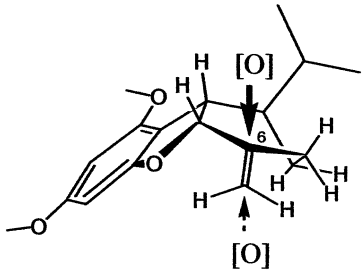
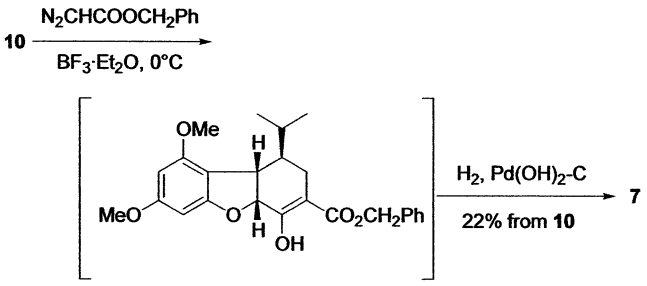


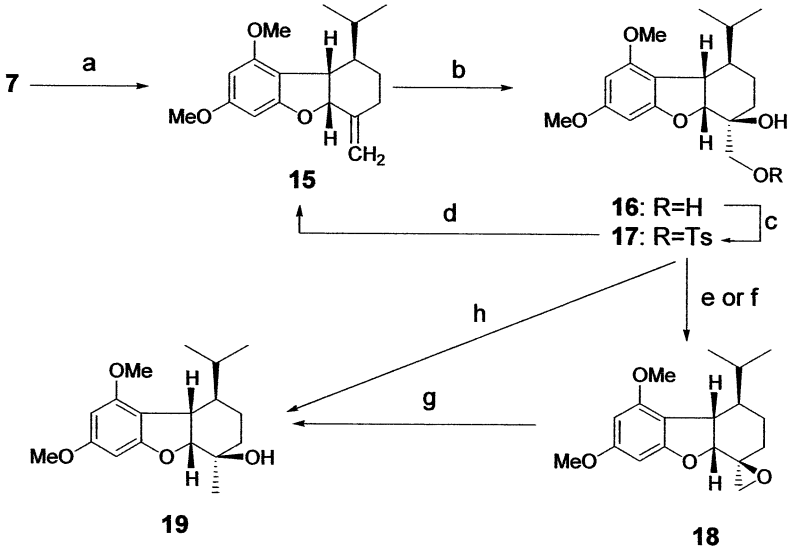
FIGURE 4. *β*-Face attack of an oxidizing reagent to **15**.

The cyclohexanone (**7**) was derived to **15** by Wittig olefination. Although the epoxidation of **15** with *m*-chloroperoxybenzoic acid gave a complex mixture, the *cis*-1,2-dihydroxylation with a catalytic amount of microencapsulated (MC) OsO_4 in the presence of *N*-methylmor-

(9) To shorten the process from **10** to **7**, the cyclopentanone (**10**) was treated with benzyl diazoacetate instead of ethyl diazoacetate in the presence of $BF_3{\cdot}Et_2O$ and the crude cyclohexane was subjected to hydrogenolysis over $Pd(OH)_2$/carbon (Baldwin, S. W.; Landmesser, N. G. *Synth. Commun.* **1978**, *8*, 413). This route was expected to be shortened to two steps, but the total yield was unfortunately reduced to 22% from **10**.

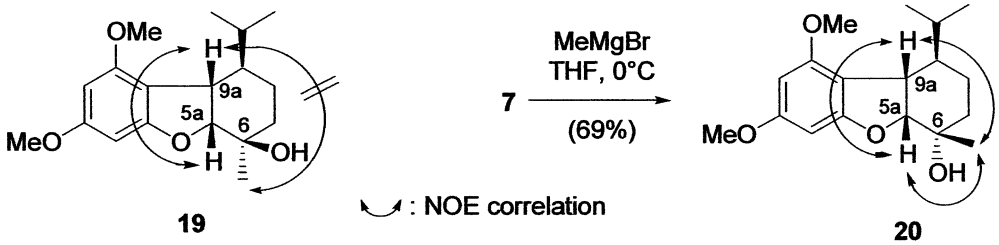


SCHEME 6[a]



[a] The steps are as follows. (a) CH_3PPh_3Br, *n*-BuLi, THF, 0 °C, 97%. (b) MC OsO_4, NMO, rt, acetone/H_2O, 100%. (c) TsCl, Et_3N, CH_2Cl_2, rt, 94%. (d) NaI, Zn, DME, rt, 83%. (e) $LiAlH_4$, THF, rt, 78%. (f) DBU, THF, rt, 70%. (g) $LiAlH_4$, toluene, reflux, 76%. (h) $NaBH_3CN$, HMPA, 120 °C, 85%.

SCHEME 7. NOE Correlations of the Diastereoisomers (19 and 20)



pholine *N*-oxide afforded the diol (**16**) as a single isomer in quantitative yield.[10] The primary alcohol portion in **16** was selectively tosylated in the usual manner, and the reductive detosyloxylation of **17** was carried out using zinc and sodium iodide to give, unfortunately, **15**. Treatment of **17** with $LiAlH_4$[11] in THF at room temperature or with DBU afforded only the epoxide (**18**). The obtained **18** was treated with $LiAlH_4$ in refluxing toluene to give the tertiary alcohol (**19**), which was also obtained in one step from **17** by reduction with $NaBH_3CN$ in HMPA[12] (Scheme 6).

The stereochemistry of **19** was confirmed as shown in Scheme 7 on the basis of NOE experiments. The diastereoisomer (**20**) was prepared by the treatment of the cyclohexanone (**7**) with MeMgBr. In the NOESY spectrum of **20**, NOE correlations were observed between the 6-methyl group and 9a-H and the 6-methyl group and 5a-H but not between the 6-methyl group and 9a-H in **19** (Scheme 7). Therefore, it was concluded that the C_6-methyl group and C_6-hydroxy group in **19** were α and *β*, respectively, which were the same as those of the natural product (**1**).

The tertiary alcohol (**19**) was derived to the corresponding acetate (**21**)[13] and silyl ether (**22**)[14] before the introduction of a cinnamoyl group on the aromatic ring; however, attempts by using the Friedel−Crafts reactions with acylating reagents or lithiation followed by acylation under various conditions all failed (Scheme 8).[15] These compounds (**21** and **22**) would be unstable under these reaction conditions. Therefore, we abandoned this route.

Next, we considered the introduction of an acyl group at the 4 position prior to the transformation of the hydroxymethyl group to a methyl group at the 6 position. The 1,2-diol portion in **16** was protected as a cyclic carbonate in the usual manner.[16] The Friedel−Crafts reaction of **24** was carried out by treatment with acetic anhydride in the presence of a catalytic amount of $Sc(OTf)_3$ to give the desired 4-acetyl compound (**25**) as a major product in 73% yield together with the 2-acetylated product (**26**) in 27% yield (Scheme 9).[17,18] The positions

(10) Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* **1998**, *63*, 6094.

(11) This reaction did not afford the expected **19**; furthermore, the yield of the epoxide (**18**) was poorly reproducible. The epoxide (**18**) was exclusively obtained even by the treatment of **17** with $LiAlH_4$ in refluxing THF.

(12) Hutchins, R. O.; Maryanoff, B. E.; Milewski, C. A. *J. Chem. Soc., Chem. Commun.* **1971**, 1097. Hutchins, R. O.; Kandasamy, D.; Maryanoff, C. A.; Maryanoff, B. E. *J. Org. Chem.* **1977**, *42*, 82. Hutchins, R. O.; Maryanoff, B. E.; Milewski, C. A. *Organic Syntheses*; Wiley: New York, 1988; Collect. Vol. VI, p 376.

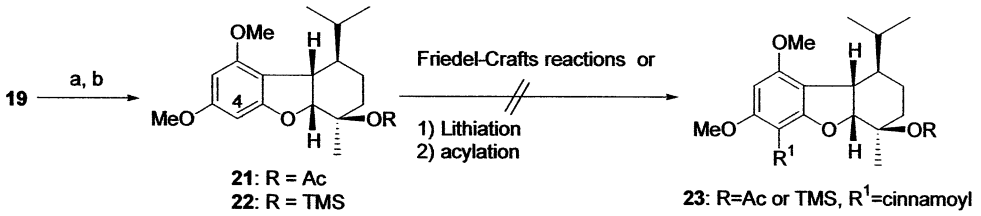
(13) Hofle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(14) Nishiguti, I.; Kita, Y.; Watanabe, M.; Ishino, Y.; Ohno, T.; Maekawa, H. *Synlett* **2000**, 1025.

(15) Also, an attempt via the halogen−metal exchange reaction of the 2,4-dibromo derivative of **19**, which was derived by the bromination of **19** with NBS, failed.

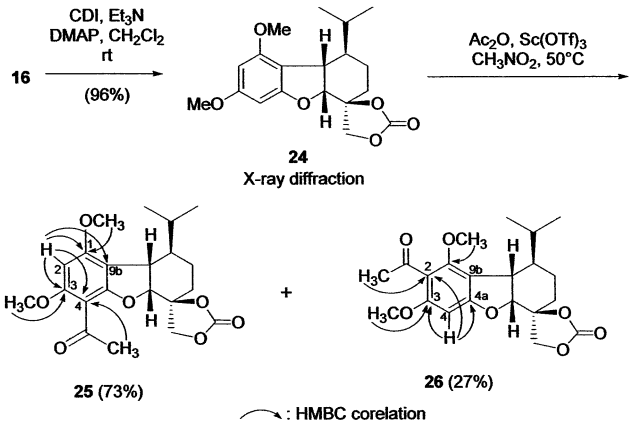
(16) The relative stereochemistry of the carbonate (**24**) was further confirmed on the basis of X-ray crystallography.

SCHEME 8[a]



[a] The steps are as follows. (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; **21**, 98%. (b) TMSCl, Mg, DMF, rt; **22**, 72%.

SCHEME 9



of the introduced acetyl group were confirmed on the basis of the heteronuclear multiple bond coherence spectra of **25** and **26**, by which the correlations between 2-H and the 1, 3, 4, and 9b carbons in **25** and between 4-H and the 2, 3, 4a, and 9b carbons in **26** were observed.

The selective demethylation of the 3-methoxy group of **25** by treatment with BBr_3 afforded the phenol (**27**) in 98% yield.[19] To convert the cyclic carbonate in **27** to the tertiary alcohol, the cyclic carbonate function was hydrolyzed by NaOH or K_2CO_3[20] to give the diol (**28**) in 74% or 94% yield, respectively. The bistosylate (**29**) was prepared in the usual manner, and its treatment with $NaBH_3CN$ reduced selectively only the C_6-CH_2-OTs portion to an α-methyl group in 78% yield (**29** → **30**). Finally, the treatment of **30** with benzaldehyde in the presence of sodium hydroxide in methanol gave (±)-**1** in 54% yield together with **31** in 38% yield.[21] The hydrolysis of the tosylate portion in **30** would compete with the aldol condensation. The aldol condensation of **30** with *t*-BuOK followed by alkaline hydrolysis gave only (±)-**1** in 71% yield without **31** (Scheme 10). The spectral data such as NMR, IR, MS, and UV of the synthetic (±)-**1** were identical with those of an authentic sample.[1]

Conclusion

In conclusion, we have succeeded in the first total synthesis of (±)-**1** through 19 steps of reaction in 6.6% overall yield, in which the critical step was a novel tandem reaction of 3-ethoxycarbonylcoumarin (**4**) with dimethylsulfoxonium methylide to yield the cyclopenta[*b*]benzofuran derivative (**5**). Now, work on the asymmetric total synthesis of **1** is in progress.

Experimental Section

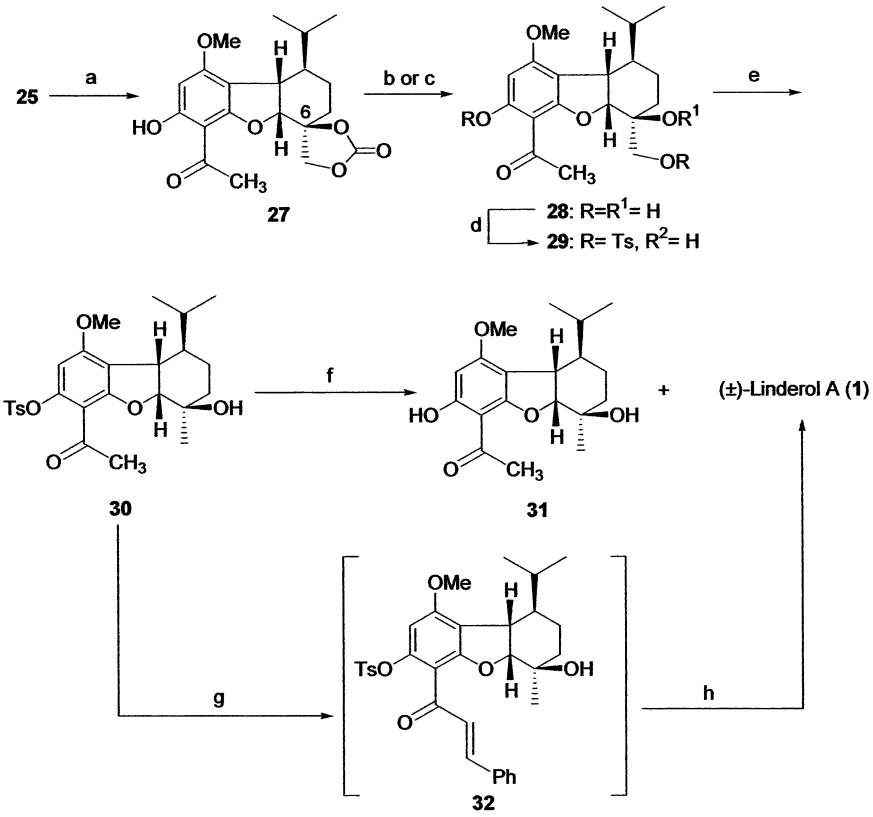
Melting points are uncorrected. Mass spectra were recorded by the electron impact method. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ with TMS as an internal standard. IR spectra were measured in $CHCl_3$, except for (±)-**1**. The extracts were washed with H_2O and brine, unless otherwise stated, dried over Na_2SO_4, and evaporated under reduced pressure with a rotary evaporator. Silica gel was used for column chromatography and preparative TLC.

Ethyl *rac*-(3a*R*,8b*S*)-3-Hydroxy-6,8-dimethoxy-3a,8b-dihydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (5). Trimethylsulfoxonium iodide (990 mg, 4.50 mmol) was added to a suspension of NaH (60% dispersion in mineral oil, 180 mg, 4.50 mmol) in DMF (5 mL) at rt under a N_2 atmosphere, and the whole was stirred for 30 min. To the reaction mixture was added **4** (500 mg, 2.03 mmol) in one portion at rt, and the whole was stirred for an additional 1 h. After acidification with 10% HCl under ice cooling, the precipitates were filtered and recrystallized from ethanol to give **5** (417 mg, 76%) as colorless needles. Mp: 148.2−150.2 °C. ^1H NMR (400 MHz) δ: 1.29 (t, 3H, J = 7.1 Hz), 2.76 (dt, 1H, J = 15.2, 1.8 Hz), 2.90 (dd, 1H, J = 7.9, 15.2 Hz), 3.75 and 3.81 (each s, each 3H), 4.02 (dt, 1H, J = 1.7, 8.2 Hz), 4.21 (q, 2H, J = 7.1 Hz), 5.65 (dd, 1H, J = 1.5, 8.8 Hz), 6.03 and 6.10 (each d, each 1H, J = 2.0 Hz), 10.02 (*s*, 1H). ^{13}C NMR (100 MHz) δ: 14.3, 32.4, 38.4, 55.3, 55.6, 60.5, 88.5, 88.7, 91.7, 103.1, 109.0, 156.8, 160.2, 162.1, 167.7, 169.5. IR: 3500−3000, 1668, 1623, 1599 cm^{-1}. MS *m*/*z* (relative intensity): 306 (M^+, 31.7), 260 (100). HRMS *m*/*z*: M^+ calcd for $C_{16}H_{18}O_6$, 306.1103; found, 306.1092. Anal. Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.64; H, 5.85.

Ethyl *rac*-(3a*R*,8b*S*)-6,8-Dimethoxy-3-oxo-3a,8b-dihydro-3*H*-cyclopenta[*b*]benzofuran-2-carboxylate (9). To a suspension of **5** (6.12 g, 20.0 mmol) in THF (40 mL) was added one portion of NaH (60% dispersion in mineral oil, 960 mg, 24.0 mmol) under ice cooling and a N_2 atmosphere, and the whole was stirred for 30 min at rt. After ice cooling, a solution of PhSeCl (4.60 g, 24.0 mmol) in THF (30 mL) was added dropwise to the reaction mixture, and the whole was stirred for an additional 1 h at rt. After evaporation of the THF, the residue was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was passed through a short column (1:1 AcOEt/*n*-hexane) to remove the remaining PhSeCl. To the solution of the obtained phenylselenenylated product in THF (40 mL) was added an aqueous solution (80 mL) of sodium metaperiodate (9.56 g, 40.0 mmol) dropwise at rt, and the whole was vigorously stirred for 3 h. After evaporation of the THF, the mixture was extracted with AcOEt. The combined extracts were washed with H_2O, saturated sodium thiosulfate, and brine; dried; and evaporated. The residue was chromatographed (1:1 AcOEt/*n*-hexane) to give **9** (4.80 g, 79%) as pale yellow-green powders. Mp: 106.5−109.6 °C (AcOEt/petroleum ether). ^1H NMR (400 MHz) δ: 1.32

(17) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545.
(18) The transition states in the reaction of **24** and the acetylium ion were calculated by the MOPAC PM3 method. The heat of formation in the reaction of **24** with the acetylium ion at the 4 position was lower by 0.48 kcal/mol than that at the 2 position.
(19) Scäfer, W.; Franck, B. *Chem. Ber.* **1966**, *99*, 160.
(20) Gendre, P. L.; Braun, T.; Bruneau, C.; Dixneuf, P. H. *J. Org. Chem.* **1996**, *61*, 8453.
(21) The yields were obtained on the basis of the integration ratio of the ^1H NMR spectrum because of the difficult isolation. The pure **31** was prepared by the hydrolysis of **30** with KOH in 87% yield.

SCHEME 10[a]



[a] The steps are as follows. (a) BBr_3, CH_2Cl_2, 0 °C, 98%. (b) NaOH/dioxane (1:1), rt, 74%. (c) K_2CO_3, MeOH, 60 °C, 94%. (d) TsCl, Et_3N, DMAP, THF, rt, 96%. (e) $NaBH_3CN$, HMPA, 120 °C, 78%. (f) PhCHO, NaOH (solid)/MeOH, rt; **31**, 38%; (±)-**1**, 54%. (g) PhCHO, *t*-BuOK, *t*-BuOH, rt. (h) KOH/MeOH, 71% from **30**.

(t, 3H, J = 7.1 Hz), 3.74 and 3.84 (each s, each 3H), 4.26 and 4.30 (each dq, each 1H, J = 10.8, 7.1 Hz), 4.60 (dd, 1H, J = 2.9, 7.0 Hz), 5.09 (d, 1H, J = 7.0 Hz), 6.02 and 6.06 (each d, each 1H, J = 2.0 Hz), 8.56 (d, 1H, J = 2.9 Hz). ^{13}C NMR (100 MHz) δ: 14.1, 44.6, 55.4, 55.6, 61.2, 83.8, 89.0, 91.9, 103.7, 135.6, 156.7, 161.4 × 2, 163.1, 170.3, 197.2. IR: 1753, 1699, 1614, 1605 cm^{-1}. MS *m*/*z* (relative intensity): 304 (M^+, 74.2), 178 (100). HRMS *m*/*z*: M^+ calcd for $C_{16}H_{16}O_6$, 304.0947; found, 304.0945. Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 62.85; H, 5.28.

Ethyl *rac*-(1*R*,3a*R*,8b*S*)-3-Hydroxy-6,8-dimethoxy-1-(1-methylethyl)-3a,8b-dihydro-1*H*-cyclopenta[*b*]benzofuran-2-carboxylate (6). CuI (95 mg, 0.50 mmol) and BF_3·Et_2O (35 mg, 0.25 mmol) were added to a suspension of **9** (76 mg, 0.25 mmol) in Et_2O (1 mL) at −78 °C under a N_2 atmosphere. After 5 min, *i*-PrMgBr (1.0 M in THF, 1.0 mL, 1.0 mmol) was added dropwise to the mixture at −78 °C, and the whole was stirred for an additional 1 h at the same temperature. After the addition of saturated NH_4Cl, the mixture was passed through a Celite 500 pad, and the filtrate was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was purified with PTLC (1:2 AcOEt/*n*-hexane) to give **6** (57 mg, 66%) as colorless needles. Mp: 124.0−124.7 °C (AcOEt/*n*-hexane). ^{1}H NMR (400 MHz) δ: 0.73 and 1.13 (each d, each 3H, J = 6.8 Hz), 1.28 (t, 3H, J = 7.1 Hz), 2.13 [d of sept (d × 7), 1H, J = 3.3, 7.0 Hz], 3.22 (ddd, 1H, J = 1.1, 1.8, 3.3 Hz), 3.70 (dd, 1H, J = 1.1, 8.1 Hz), 3.74 and 3.79 (each s, each 3H), 4.19 and 4.25 (each dq, each 1H, J = 10.8, 7.1 Hz), 5.59 (dd, 1H, J = 1.8, 8.2 Hz), 6.01 and 6.09 (each d, each 1H, J = 2.0 Hz), 10.24 (s, 1H). ^{13}C NMR (67.8 MHz) δ: 14.2, 16.6, 20.9, 30.1, 41.1, 51.2, 55.1, 55.5, 60.4, 88.0, 88.4, 91.7, 106.0, 108.6, 156.9, 160.1, 161.9, 168.9, 169.8. IR: 3500−3000, 1706, 1659, 1620, 1600 cm^{-1}. MS *m*/*z* (relative intensity): 348 (M^+, 39.2), 178 (100). HRMS *m*/*z*: M^+ calcd for $C_{19}H_{24}O_6$, 348.1573; found, 348.1580. Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.39; H, 6.92.

***rac*-(1*R*,3a*R*,8b*S*)-6,8-Dimethoxy-1-(1-methylethyl)-2,3,-3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-3-one (10).** A solution of **6** (310 mg, 0.891 mmol) in AcOH (10 mL) was heated at 100 °C for 5 h under a N_2 atmosphere. After evaporation of the AcOH, the residue was chromatographed (1:5 AcOEt/*n*-hexane) to give **10** (235 mg, 96%) as colorless needles. Mp: 106.5−108.3 °C (AcOEt/*n*-hexane). ^{1}H NMR (400 MHz) δ: 0.94 and 0.96 (each d, each 3H, J = 6.8 Hz), 1.87 (d × 7, 1H, J = 5.1, 6.8 Hz), 2.20 (ddq, 1H, J = 18.7, 3.8, 1.5 Hz), 2.32 (dd, 1H, J = 18.7, 9.2 Hz), 2.57 (m, 1H), 3.75 and 3.80 (each s, each 3H), 3.96 (dd, 1H, J = 1.6, 9.2 Hz), 4.77 (dt, 1H, J = 9.2, 0.7 Hz), 6.03 and 6.06 (each d, each 1H, J = 2.0 Hz). ^{13}C NMR (100 MHz) δ: 18.9, 19.9, 32.2, 38.7, 44.3, 44.8, 55.3, 55.6, 84.9, 88.2, 92.1, 107.8, 156.9, 160.7, 162.1, 214.7. IR: 1745, 1620, 1598 cm^{-1}. MS *m*/*z* (relative intensity): 276 (M^+, 26.2), 178 (100). HRMS *m*/*z*: M^+ calcd for $C_{16}H_{20}O_4$, 276.1361; found, 276.1360. Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.52; H, 7.42.

Ethyl *rac*-(1*R*,4a*R*,9b*S*)-4-Hydroxy-7,9-dimethoxy-1-(1-methylethyl)-1,2,4a,9b-tetrahydrodibenzofuran-3-carboxylate (11). To a solution of **10** (235 mg, 0.851 mmol) and BF_3·Et_2O (176 mg, 1.24 mmol) in Et_2O (9 mL) was added a solution of ethyl diazoacetate[22] (400 mg, 3.51 mmol) in Et_2O (0.5 mL) under 0 °C and a N_2 atmosphere, and the whole was stirred for an additional 1 h at 0 °C. After neutralization with saturated $NaHCO_3$, the mixture was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:1 Et_2O/*n*-hexane) to give **11** (264 mg, 86%) as colorless needles. Mp: 102.0−102.9 °C

(22) Searle, N. E. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 424.

(AcOEt/petroleum ether). ^{1}H NMR (400 MHz) δ: 0.947 (d, 3H, J = 7.7 Hz), 0.949 (d, 3H, J = 6.6 Hz), 1.33 (t, 3H, J = 7.1 Hz), 1.68 (ddd, 1H, J = 3.9, 4.5, 9.7 Hz), 1.81 (d × 7, 1H, J = 4.6, 6.8 Hz), 2.05 (dd, 1H, J = 9.5, 16.1 Hz), 2.32 (dd, 1H, J = 3.9, 16.1 Hz), 3.40 (dd, 1H, J = 7.5, 9.7 Hz), 3.76 and 3.78 (each s, each 3H), 4.24 and 4.28 (each dq, each 1H, J = 10.8, 7.1 Hz), 4.96 (d, 1H, J = 7.5 Hz), 6.04 and 6.15 (each d, each 1H, J = 2.0 Hz), 12.00 (s, 1H). ^{13}C NMR (100 MHz) δ: 14.2, 17.1, 20.9, 21.8, 27.2, 42.2, 42.7, 55.1, 55.5, 60.9, 81.2, 89.1, 91.6, 101.5, 109.2, 157.3, 160.9, 161.7, 164.1, 172.1. IR: 3500−3000, 1738, 1657, 1617 cm^{-1}. MS *m*/*z* (relative intensity): 362 (M^+, 18.9), 154 (100). HRMS *m*/*z*: M^+ calcd for $C_{20}H_{26}O_6$, 362.1729; found, 362.1716. Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.07; H, 7.16.

Ethyl *rac*-(1*R*,4a*R*,9b*S*)-7,9-Dimethoxy-4-methoxymethoxy-1-(1-methylethyl)-1,2,4a,9b-tetrahydrodibenzofuran-3-carboxylate (13). To a solution of **11** (602 mg, 1.66 mmol) in THF (8 mL) was added NaH (60% dispersion in mineral oil, 100 mg, 2.50 mmol) under 0 °C and a N_2 atmosphere, and the whole was stirred for 30 min at 0 °C. Chloromethyl methyl ether (201 mg, 2.50 mmol) was added to the reaction mixture at 0 °C, and the whole was stirred for 19 h at rt. After neutralization with saturated NH_4Cl, the mixture was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:4 AcOEt/*n*-hexane) to give **13** (567 mg, 84%) as a colorless oil. ^{1}H NMR (400 MHz) δ: 0.93 (d, 3H, J = 7.3 Hz), 0.94 (d, 3H, J = 7.0 Hz), 1.32 (t, 3H, J = 7.1 Hz), 1.64 (tt, 1H, J = 4.0, 10.4 Hz), 1.83 (d × 7, 1H, J = 4.0, 6.8 Hz), 2.13 (ddd, 1H, J = 1.3, 10.3, 17.0 Hz), 2.44 (dd, 1H, J = 3.8, 17.0 Hz), 3.31 (dd, 1H, J = 7.1, 10.4 Hz), 3.53 (s, 3H), 3.76 and 3.77 (each s, each 3H), 4.24 (q, 2H, J = 7.1 Hz), 5.02 and 5.34 (each d, each 1H, J = 6.6 Hz), 5.16 (d, 1H, J = 7.0 Hz), 6.04 and 6.09 (each d, each 1H, J = 2.0 Hz). ^{13}C NMR (100 MHz) δ: 14.3, 16.5, 21.8, 24.5, 27.0, 41.7, 42.9, 55.1, 55.5, 56.8, 60.5, 80.4, 89.1, 91.5, 95.4, 109.5, 115.5, 152.6, 157.2, 160.7, 161.6, 167.3. IR: 1702, 1616 cm^{-1}. MS *m*/*z* (relative intensity): 406 (M^+, 30.3), 178 (100). HRMS *m*/*z*: M^+ calcd for $C_{22}H_{30}O_7$, 406.1991; found, 406.1974.

***rac*-(1*R*,4a*R*,9b*S*)-7,9-Dimethoxy-1-(1-methylethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-one (7).** A solution of **13** (930 mg, 2.29 mmol) in EtOH (2.3 mL) and 4 N NaOH (1.15 mL, 4.60 mmol) was stirred for 8 h at rt. After acidification with concd HCl, the mixture was stirred for 30 min at rt and concentrated to one-third. The concentrate was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The solution of the residue in degassed xylene (2 mL) was refluxed for 15 min under a N_2 atmosphere. After evaporation of the xylene, the residue was chromatographed (1:7 AcOEt/*n*-hexane) to give **7** (480 mg, 72%) as colorless needles. Mp: 78.2−80.4 °C (AcOEt/petroleum ether). ^{1}H NMR (400 MHz) δ: 0.95 and 1.02 (each d, each 3H, J = 6.6 Hz), 1.62−1.68 (m, 1H), 1.71−1.84 (m, 2H), 1.85−1.93 (m, 1H), 2.43−2.58 (m, 2H), 3.77 and 3.78 (each s, each 3H), 3.84 (dd, 1H, J = 6.2, 8.6 Hz), 4.70 (dd, 1H, J = 0.6, 8.4 Hz), 6.05 and 6.14 (each d, each 1H, J = 2.0 Hz). ^{13}C NMR (100 MHz) δ: 18.5, 21.0, 21.6, 28.0, 35.5, 43.1, 45.8, 55.2, 55.5, 85.8, 88.8, 92.1, 109.1, 156.7, 161.2, 161.9, 208.2. IR: 1715, 1619 cm^{-1}. MS *m*/*z* (relative intensity): 290 (M^+, 27.0), 178 (100). HRMS *m*/*z*: M^+ calcd for $C_{17}H_{22}O_4$, 290.1518; found, 290.1528. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.12; H, 7.61.

***rac*-(5a*R*,9*R*,9a*S*)-1,3-Dimethoxy-9-(1-methylethyl)-6-methylidene-5a,6,7,8,9,9a-hexahydrodibenzofuran (15).** To a suspension of methyltriphenylphosphonium bromide (2.02 g, 5.65 mmol) in THF (10 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 3.53 mL, 5.65 mmol) dropwise at 0 °C under a N_2 atmosphere, and the whole was stirred for 30 min at 0 °C. A solution of **7** (410 mg, 1.41 mmol) in THF (10 mL) was added dropwise to the reaction mixture at 0 °C, and the whole was stirred for 1.5 h. After evaporation of the solvent, the mixture was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:5 AcOEt/*n*-hexane) to give **15** (395 mg, 97%) as colorless needles. Mp: 73.4−74.7 °C (AcOEt/*n*-hexane). ^{1}H NMR (400 MHz) δ: 0.872 (d, 3H, J = 6.6 Hz), 0.874 (d, 3H, J = 7.1 Hz), 1.12 (ddt, 1H, J = 4.2, 13.0, 11.4 Hz), 1.32 (ddt, 1H, J = 9.5, 11.4, 3.3 Hz), 1.69 (ddt, 1H, J = 3.1, 13.0, 4.6 Hz), 1.92 (d × 7, 1H, J = 4.0, 6.8 Hz), 2.32 (dddt, 1H, J = 4.6, 11.4, 13.9, 1.8 Hz), 2.42 (dt, 1H, J = 14.1, 4.4 Hz), 3.09 (dd, 1H, J = 6.2, 9.5 Hz), 3.76 and 3.77 (each s, each 3H), 4.78 (d, 1H, J = 6.0 Hz), 5.12 and 5.15 (each t, each 1H, J = 1.8 Hz), 6.04 and 6.11 (each d, each 1H, J = 2.0 Hz). ^{13}C NMR (67.8 MHz) δ: 16.3, 21.8, 22.8, 27.3, 30.2, 43.9, 46.0, 55.2, 55.5, 88.8, 89.2, 91.4, 113.2, 116.2, 144.2, 156.6, 161.2, 161.3. IR: 1613, 1590 cm^{-1}. MS *m*/*z* (relative intensity): 288 (M^+, 48.8), 218 (100). HRMS *m*/*z*: M^+ calcd for $C_{18}H_{24}O_3$, 288.1725; found, 288.1730. Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.71; H, 8.35.

***rac*-(1*R*,4*S*,4a*R*,9b*S*)-4-Hydroxymethyl-7,9-dimethoxy-1-(1-methylethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-ol (16).** A mixture of **15** (360 mg, 1.25 mmol), MC OsO_4 (160 mg, containing about 10% by weight as OsO_4, 0.063 mmol), *N*-methylmorpholine *N*-oxide (440 mg, 3.76 mmol) in acetone/H_2O (6:1, 10.5 mL) was stirred for 48 h at rt. The MC OsO_4 was filtered off, and the filtrate was concentrated to a quarter and extracted with AcOEt. The combined extracts were washed with H_2O, saturated sodium thiosulfate, and brine; dried; and evaporated. The residue was chromatographed (40:1 $CHCl_3$/MeOH) to give **16** (403 mg, 100%) as a colorless oil. ^{1}H NMR (400 MHz) δ: 0.83 (d, 3H, J = 7.1 Hz), 0.91 (d, 3H, J = 6.8 Hz), 1.09−1.16 (m, 1H), 1.40−1.58 (m, 2H), 1.43 (s, 1H), 1.72 (ddd, 1H, J = 3.2, 4.8, 13.2 Hz), 1.95 (d × 7, 1H, J = 2.8, 6.8 Hz), 2.00−2.06 (m, 1H), 2.34 (s, 1H), 3.13 (dd, 1H, J = 5.6, 11.2 Hz), 3.56 (dd, 1H, J = 6.0, 10.8 Hz), 3.76 and 3.77 (each s, each 3H), 3.93 (dd, 1H, J = 4.8, 11.2 Hz), 4.25 (dd, 1H, J = 1.6, 5.6 Hz), 6.05 and 6.11 (each d, each 1H, J = 2.0 Hz). ^{13}C NMR (100 MHz) δ: 15.5, 16.6, 21.8, 27.1, 30.2, 40.2, 46.9, 55.2, 55.5, 68.7, 71.2, 87.7, 89.5, 91.8, 113.7, 156.7, 160.7, 161.1. IR: 3600−3100, 1615, 1598 cm^{-1}. MS *m*/*z* (relative intensity): 322 (M^+, 16.6), 291 (100). HRMS *m*/*z*: M^+ calcd for $C_{18}H_{26}O_5$, 322.1780; found, 322.1785.

***rac*-(1*R*,4*S*,4a*R*,9b*S*)-7,9-Dimethoxy-1-(1-methylethyl)-4-tosyloxymethyl-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-ol (17).** A solution of **16** (70 mg, 0.22 mmol), *p*-toluenesulfonyl chloride (63 mg, 0.33 mmol), Et_3N (33 mg, 0.33 mmol), DMAP (catalytic amount) in dichloromethane (1.5 mL) was stirred for 24 h at rt under a N_2 atmosphere. After evaporation of the volatile matter, the residue was extracted with AcOEt. The combined extracts were washed with diluted HCl, H_2O, and brine; dried; and evaporated. The residue was purified with PTLC (1:1 AcOEt/*n*-hexane) to give **17** (97 mg, 94%) as colorless needles. Mp: 137.3−139.5 °C (AcOEt/petroleum ether). ^{1}H NMR (400 MHz) δ: 0.80 (d, 3H, J = 7.0 Hz), 0.88 (d, 3H, J = 6.8 Hz), 1.02−1.10 (m, 1H), 1.37−1.50 (m, 3H), 1.74−1.81 (m, 1H), 1.92 (d × 7, 1H, J = 2.8, 7.2 Hz), 2.26 (s, 1H), 2.47 (s, 3H), 3.09 (dd, 1H, J = 5.5, 11.2 Hz), 3.757 and 3.762 (each s, each 3H), 4.12 and 4.22 (each d, each 1H, J = 9.7 Hz), 4.13 (dd, 1H, J = 1.6, 5.6 Hz), 5.95 and 6.03 (each d, each 1H, J = 2.0 Hz), 7.37 (d, 2H, J = 8.4 Hz), 7.83 (d, 2H, J = 8.2 Hz). ^{13}C NMR (100 MHz) δ: 15.4, 16.2, 21.66, 21.72, 27.0, 29.9, 40.0, 46.7, 55.2, 55.5, 70.1, 75.5, 86.5, 89.5, 91.7, 113.5, 128.1, 129.9, 132.5, 144.9, 156.6, 160.5, 161.0. IR: 3535, 1611, 1600 cm^{-1}. MS *m*/*z* (relative intensity): 476 (M^+, 9.7), 291 (100). HRMS *m*/*z*: M^+ calcd for $C_{25}H_{32}O_7S$, 476.1868; found, 476.1871. Anal. Calcd for $C_{25}H_{32}O_7S$: C, 63.00; H, 6.77. Found: C, 62.92; H, 6.81.

***rac*-(1*R*,4*S*,4a*R*,9b*S*)-7,9-Dimethoxy-1-(1-methylethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-spiro-2′-oxirane (18). (a) With DBU.** A solution of **17** (123 mg, 0.258 mmol) and DBU (78.0 mg, 0.513 mmol) in THF (2 mL) was stirred for 24 h at rt under a N_2 atmosphere. After evaporation of the volatile matter, the residue was chromatographed (1:3 AcOEt/*n*-hexane) to give **18** (55.0 mg, 70%) as a colorless oil. ^{1}H NMR (400 MHz) δ: 0.88 (d, 3H, J = 7.0 Hz), 0.92 (d, 3H,

J = 6.8 Hz), 1.24−1.31 (m, 1H), 1.34−1.44 (m, 2H), 1.60−1.66 (m, 1H), 2.02 (d × 7, 1H, J = 3.3, 6.8 Hz), 2.12 (ddt, 1H, J = 1.8, 3.1, 13.6 Hz), 2.82 and 2.93 (each d, each 1H, J = 4.6 Hz), 3.22 (dd, 1H, J = 6.1, 10.3 Hz), 3.77 and 3.78 (each s, each 3H), 3.84 (dd, 1H, J = 1.2, 6.1 Hz), 6.05 and 6.11 (each d, each 1H, J = 2.0 Hz). ^{13}C NMR (100 MHz) δ: 15.9, 19.6, 21.8, 27.2, 29.4, 42.1, 46.2, 52.1, 55.2, 55.5, 55.8, 89.1, 89.6, 91.7, 112.9, 156.8, 160.8, 161.3. IR: 1616, 1597 cm^{-1}. MS *m*/*z* (relative intensity): 304 (M^+, 100). HRMS *m*/*z*: M^+ calcd for $C_{18}H_{24}O_4$, 304.1674; found, 304.1673.

(b) With $LiAlH_4$. A suspension of **17** (8 mg, 0.017 mmol) and $LiAlH_4$ (7 mg, 0.18 mmol) in THF (0.5 mL) was stirred for 3 h at rt under a N_2 atmosphere. After the addition of saturated NH_4Cl, the mixture was filtrated and the filtrate was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was purified with PTLC (1:3 AcOEt/*n*-hexane) to give **18** (4 mg, 78%).

***rac*-(1*R*,4*R*,4a*R*,9b*S*)-7,9-Dimethoxy-4-methyl-1-(1-methylethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-ol (19). (a) From 17.** A solution of **17** (41 mg, 0.086 mmol) and $NaBH_3CN$ (27 mg, 0.43 mmol) in HMPA (0.5 mL) was heated for 2 h at 120 °C under a N_2 atmosphere. The mixture was extracted with Et_2O. The combined extracts were washed, dried, and evaporated. The residue was purified with PTLC (1:1 AcOEt/*n*-hexane) to give **19** (22 mg, 85%) as a colorless oil. ^{1}H NMR (400 MHz) δ: 0.82 (d, 3H, J = 7.1 Hz), 0.90 (d, 3H, J = 6.8 Hz), 1.06−1.13 (m, 1H), 1.32−1.42 (m, 2H), 1.44 (s, 3H), 1.63−1.70 (m, 1H), 1.74 (ddt, 1H, J = 1.6, 14.0, 4.8 Hz), 1.93 (d × 7, 1H, J = 2.7, 6.8 Hz), 3.10 (dd, 1H, J = 5.3, 11.0 Hz), 3.76 and 3.77 (each s, each 3H), 4.06 (dd, 1H, J = 1.5, 5.3 Hz), 6.04 and 6.13 (each d, each 1H, J = 2.0 Hz). ^{13}C NMR (100 MHz) δ: 15.5, 17.3, 21.8, 27.0, 28.1, 35.1, 40.3, 46.4, 55.2, 55.5, 69.6, 89.4, 91.4, 91.7, 114.1, 156.7, 161.00, 161.04. IR: 3500−3400, 1611, 1600 cm^{-1}. MS *m*/*z* (relative intensity): 306 (M^+, 20.8), 221 (100). HRMS *m*/*z*: M^+ calcd for $C_{18}H_{26}O_4$, 306.1831; found, 306.1838.

(b) From 18. A suspension of **18** (52 mg, 0.17 mmol) and $LiAlH_4$ (36 mg, 0.95 mmol) in toluene (2 mL) was refluxed for 2 h under a N_2 atmosphere. After the addition of saturated NH_4Cl, the mixture was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:3 AcOEt/*n*-hexane) to give **19** (40 mg, 76%).

***rac*-(1*R*,4*S*,4a*R*,9b*S*)-7,9-Dimethoxy-4-methyl-1-(1-methylethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-ol (20).** To a solution of **7** (22 mg, 0.076 mmol) in THF (0.1 mL) was added methylmagnesium bromide (0.93 M in THF, 0.33 mL, 0.30 mmol) dropwise at 0 °C under a N_2 atmosphere, and the whole was stirred for an additional 1 h at rt. After neutralization with saturated NH_4Cl, the mixture was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was purified with PTLC (1:3 AcOEt/*n*-hexane) to give **20** (16 mg, 69%) as a colorless oil. ^{1}H NMR (400 MHz) δ: 0.82 (d, 3H, J = 7.1 Hz), 0.88 (d, 3H, J = 6.8 Hz), 1.03−1.18 (m, 2H), 1.29 (s, 3H), 1.55−1.60 (m, 1H), 1.70−1.81 (m, 2H), 1.96 (d × 7, 1H, J = 2.6, 7.0 Hz), 2.33 (s, 1H), 2.99 (dd, 1H, J = 5.1, 10.6 Hz), 3.768 and 3.770 (each s, each 3H), 4.19 (dd, 1H, J = 0.9, 5.1 Hz), 6.05 and 6.14 (each d, each 1H, J = 2.0 Hz). ^{13}C NMR (100 MHz) δ: 15.4, 20.5, 21.9, 24.9, 26.8, 36.0, 41.7, 46.5, 55.2, 55.5, 70.6, 89.6, 91.6, 91.7, 114.4, 156.2, 160.5, 161.1. IR: 3500−3000, 1616, 1600 cm^{-1}. MS *m*/*z* (relative intensity): 306 (M^+, 22.9), 221 (100). HRMS *m*/*z*: M^+ calcd for $C_{18}H_{26}O_4$, 306.1831; found, 306.1842.

***rac*-(1*R*,4*S*,4a*R*,9b*S*)-7,9-Dimethoxy-1-(1-methylethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-spiro-4′-dioxoran-2′-one (24).** A solution of **16** (511 mg, 1.59 mmol), 1,1′-carbonyldiimidazole (512 mg, 3.16 mmol), Et_3N (638 mg, 6.32 mmol), and DMAP (catalytic amount) in CH_2Cl_2 (5 mL) was stirred for 21 h at rt under a N_2 atmosphere. The mixture was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:3 AcOEt/*n*-hexane) to give **24** (533 mg, 96%) as colorless needles. Mp: 149.0−150.9 °C (AcOEt/petroleum ether). ^{1}H NMR (400 MHz) δ: 0.84 (d, 3H, J = 7.0 Hz), 0.90 (d, 3H, J = 6.8 Hz), 1.16 (ddt, 1H, J = 11.0, 12.5, 3.1 Hz), 1.46 (dq, 1H, J = 2.8, 13.2 Hz), 1.57 (ddd, 1H, J = 3.7, 7.1, 13.7 Hz), 1.81 (dt, 1H, J = 3.7, 14.1 Hz), 2.00 (d × 7, 1H, J = 2.9, 6.8 Hz), 2.12 (ddd, 1H, J = 3.1, 4.9, 14.1 Hz), 3.18 (dd, 1H, J = 5.5, 11.0 Hz), 3.77 and 3.78 (each s, each 3H), 4.34 (dd, 1H, J = 1.7, 5.5 Hz), 4.19 and 4.73 (each d, each 1H, J = 8.8 Hz), 6.08 and 6.09 (each d, each 1H, J = 2.0 Hz). ^{13}C NMR (100 MHz) δ: 15.4, 17.5, 21.7, 27.0, 32.0, 40.7, 46.1, 55.3, 55.5, 72.2, 81.2, 85.5, 89.4, 92.3, 113.0, 154.2, 156.7, 159.8, 161.4. IR: 1798, 1619 cm^{-1}. MS *m*/*z* (relative intensity): 348 (M^+, 100). HRMS *m*/*z*: M^+ calcd for $C_{19}H_{24}O_6$, 348.1573; found, 348.1579. Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.26; H, 6.94.

***rac*-(1*R*,4*S*,4a*R*,9b*S*)-6-Acetyl-7,9-dimethoxy-1-(1-methylethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-spiro-4′-dioxoran-2′-one (25) and *rac*-(1*R*,4*S*,4a*R*,9b*S*)-8-Acetyl-7,9-dimethoxy-1-(1-methylethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-spiro-4′-dioxoran-2′-one (26).** A solution of **24** (254 mg, 0.730 mmol), Ac_2O (149 mg, 1.46 mmol), and $Sc(OTf)_3$ (36 mg, 10 mol %) in nitromethane (5 mL) was heated at 50 °C for 3 h under a N_2 atmosphere. After the addition of H_2O, the whole was stirred for 30 min at rt. The mixture was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:3 AcOEt/*n*-hexane) to give **25**, the more polar compound (208 mg, 73%), and **26**, the less polar compound (76 mg, 27%). **25**: colorless needles; mp 174.5−177.0 °C (AcOEt/petroleum ether). ^{1}H NMR (400 MHz) δ: 0.84 (d, 3H, J = 7.0 Hz), 0.90 (d, 3H, J = 6.8 Hz), 1.20 (ddt, 1H, J = 11.5, 12.1, 2.9 Hz), 1.46 (dq, 1H, J = 13.4, 2.9 Hz), 1.55−1.62 (m, 1H), 1.87 (dt, 1H, J = 3.5, 14.1 Hz), 1.92 (d × 7, 1H, J = 2.9, 6.8 Hz), 2.12 (ddd, 1H, J = 2.9, 5.0, 14.3 Hz), 2.49 (s, 3H), 3.19 (dd, 1H, J = 5.7, 11.2 Hz), 3.86 and 3.88 (each s, each 3H), 4.38 (dd, 1H, J = 1.7, 5.7 Hz), 4.21 and 4.76 (each d, each 1H, J = 9.0 Hz), 6.07 (s, 1H). ^{13}C NMR (100 MHz) δ: 15.3, 17.5, 21.6, 27.1, 31.9, 32.5, 40.0, 45.8, 55.4, 56.1, 72.2, 80.9, 86.0, 89.0, 109.1, 113.8, 154.1, 158.3, 159.0, 160.2, 197.3. IR: 1796, 1667, 1604 cm^{-1}. MS *m*/*z* (relative intensity): 390 (M^+, 100). HRMS *m*/*z*: M^+ calcd for $C_{21}H_{26}O_7$, 390.1678; found, 390.1681. Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.40; H, 6.72. **26**: colorless needles; mp 180.1−181.6 °C. ^{1}H NMR (400 MHz) δ: 0.86 (d, 3H, J = 7.0 Hz), 0.92 (d, 3H, J = 6.8 Hz), 1.14 (tt, 1H, J = 2.9, 11.7 Hz), 1.49 (dq, 1H, J = 2.7, 13.4 Hz), 1.61 (dq, 1H, J = 3.5, 13.6 Hz), 1.82 (dt, 1H, J = 3.5, 14.1 Hz), 2.08 (d × 7, 1H, J = 2.6, 6.9 Hz), 2.14 (dq, 1H, J = 2.0, 14.2 Hz), 2.49 (s, 3H), 3.25 (dd, 1H, J = 5.5, 11.0 Hz), 3.78 and 3.84 (each s, each 3H), 4.40 (dd, 1H, J = 1.6, 5.5 Hz), 4.22 and 4.73 (each d, each 1H, J = 8.9 Hz), 6.26 (s, 1H). ^{13}C NMR (100 MHz) δ: 15.7, 17.6, 21.7, 26.8, 31.7, 32.6, 41.8, 46.0, 56.0, 62.1, 72.1, 80.8, 85.2, 91.0, 116.4, 118.9, 153.9, 154.6, 158.1, 160.8, 201.9. IR: 1798, 1688, 1610 cm^{-1}. MS *m*/*z* (relative intensity): 390 (M^+, 45.9), 375 (100.0). HRMS *m*/*z*: M^+ calcd for $C_{21}H_{26}O_7$, 390.1678; found, 390.1674. Anal. Calcd for $C_{21}H_{26}O_7$: C, 64.60; H, 6.71. Found: C, 64.36; H, 6.52.

***rac*-(1*R*,4*S*,4a*R*,9b*S*)-6-Acetyl-7-hydroxy-9-methoxy-1-(1-methylethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-spiro-4′-dioxoran-2′-one (27).** To a solution of **25** (132 mg, 0.338 mmol) in CH_2Cl_2 (3 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 1.36 mL, 1.36 mmol) under ice cooling and a N_2 atmosphere, and the whole was stirred for 1 h at 0 °C. After the addition of H_2O, the whole was stirred for 30 min at rt. The mixture was extracted with $CHCl_3$. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:3 AcOEt/*n*-hexane) to give **27** (124 mg, 98%) as colorless needles. Mp: 198.5−201.7 °C (AcOEt/petroleum ether). ^{1}H NMR (400 MHz) δ: 0.86 (d, 3H, J = 7.1 Hz), 0.90 (d, 3H, J = 6.8 Hz), 1.18 (ddt, 1H, J = 11.0, 12.3, 3.1 Hz), 1.49 (dq, 1H, J = 2.9, 13.0 Hz), 1.62 (dq, 1H, J = 13.7, 3.6 Hz), 1.83 (ddd, 1H, J = 3.7, 13.0, 14.1 Hz), 1.92 (d × 7, 1H, J = 2.9, 7.0 Hz), 2.18 (ddd, J = 1.7, 3.3, 14.3 Hz), 2.56 (s, 3H), 3.22 (dd, 1H, J = 5.9, 11.0 Hz), 3.83 (s, 3H), 4.48 (dd, 1H, J =

1.7, 5.7 Hz), 4.25 and 4.71 (each d, each 1H, $J = 8.8$ Hz), 6.09 (s, 1H), 13.15 (s, 1H). ^{13}C NMR (100 MHz) δ: 15.3, 17.4, 21.6, 27.1, 31.1, 32.0, 39.9, 46.2, 55.6, 72.0, 80.8, 86.6, 93.6, 102.8, 112.1, 153.8, 160.4, 161.8, 165.6, 201.0. IR: 3200−2500, 1797, 1627, 1599 cm^{-1}. MS *m*/*z* (relative intensity): 376 (M^+, 100). HRMS *m*/*z*: M^+ calcd for $C_{20}H_{24}O_7$, 376.1522; found, 376.1525. Anal. Calcd for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.73; H, 6.51.

***rac*-(5a*R*,6*S*,9*R*,9a*S*)-4-Acetyl-3,6-dihydroxy-6-hydroxymethyl-1-methoxy-9-(1-methylethyl)-5a,6,7,8,9,9a-hexahydrodibenzofuran (28). (a) With NaOH.** A solution of **27** (184 mg, 0.489 mmol) in 1,4-dioxane/0.5 N NaOH (1:1, 9 mL) was stirred for 2 h at rt. After neutralization with diluted HCl under ice cooling, the mixture was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:2 AcOEt/*n*-hexane) to give **28** (126 mg, 74%) as a colorless powder. Mp: 175.9−177.4 °C (AcOEt/petroleum ether). ^{1}H NMR (400 MHz) δ: 0.85 (d, 3H, $J = 7.0$ Hz), 0.91 (d, 3H, $J = 6.8$ Hz), 1.12 (tt, 1H, $J = 11.2$, 3.1 Hz), 1.37−1.57 (m, 3H), 1.76−1.92 (m, 3H), 2.34 (br, 1H), 2.59 (s, 3H), 3.14 (dd, 1H, $J = 5.7$, 11.2 Hz), 3.82 (s, 3H), 3.62 and 3.95 (each d, each 1H, $J = 10.8$ Hz), 4.35 (dd, 1H, $J = 1.5$, 5.7 Hz), 6.04 (s, 1H), 13.16 (s, 1H). ^{13}C NMR (100 MHz) δ: 15.4, 16.5, 21.7, 27.2, 30.3, 31.1, 39.4, 47.0, 55.5, 68.5, 70.9, 88.4, 92.7, 102.9, 112.8, 161.7, 161.8, 165.1, 201.5. IR: 3700−3200, 1627, 1597 cm^{-1}. MS *m*/*z* (relative intensity): 350 (M^+, 22.6), 319 (100). HRMS *m*/*z*: M^+ calcd for $C_{19}H_{26}O_6$, 350.1729; found, 350.1734. Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.13; H, 7.48. Found: C, 64.71; H, 7.67.

(b) With K_2CO_3. A suspension of **27** (73 mg, 0.19 mmol) and K_2CO_3 (40 mg, 0.29 mmol) in MeOH (5 mL) was stirred for 1 h at 60 °C. After neutralization with NH_4Cl under ice cooling, the mixture was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:2 AcOEt/*n*-hexane) to give **28** (64 mg, 94%).

***rac*-(5a*R*,6*R*,9*R*,9a*S*)-4-Acetyl-6-hydroxy-1-methoxy-9-(1-methylethyl)-6-*p*-tosyloxymethyl-5a,6,7,8,9,9a-hexahydrodibenzofuran-3-yl *p*-Toluenesulfonate (29).** A solution of **28** (50 mg, 0.143 mmol), *p*-toluenesulfonyl chloride (136 mg, 0.715 mmol), Et_3N (58 mg, 0.572 mmol), and DMAP (catalytic amount) in CH_2Cl_2 (5 mL) was stirred for 24 h at rt under a N_2 atmosphere. The mixture was extracted with AcOEt. The combined extracts were washed with diluted HCl, H_2O, and brine; dried; and evaporated. The residue was chromatographed (1:3 AcOEt/*n*-hexane) to give **29** (90 mg, 96%) as colorless needles. Mp: 172.9−174.7 °C (AcOEt/petroleum ether). ^{1}H NMR (400 MHz) δ: 0.83 (d, 3H, $J = 7.0$ Hz), 0.89 (d, 3H, $J = 6.8$ Hz), 1.06−1.14 (*m*, 1H), 1.42−1.50 (*m*, 3H), 1.73−1.80 (*m*, 2H), 1.81 (d × 7, 1H, $J = 2.8$, 7.0 Hz), 2.22 (s, 3H), 2.30 (s, 1H), 2.47 (s, 6H), 3.18 (dd, 1H, $J = 5.5$, 11.2 Hz), 3.73 (s, 3H), 4.06 and 4.20 (each d, each 1H, $J = 9.9$ Hz), 4.28 (dd, 1H, $J = 1.4$, 5.3 Hz), 6.32 (s, 1H), 7.36 (d, 4H, $J = 8.1$ Hz), 7.78 (d, 2H, $J = 8.2$ Hz), 7.82 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (100 MHz) δ: 15.3, 16.1, 21.6, 21.67, 21.73, 27.2, 29.7, 31.6, 39.5, 46.3, 55.7, 69.7, 75.0, 87.2, 101.0, 113.2, 120.6, 127.9, 128.7, 129.7, 130.1, 132.2, 132.4, 145.4, 145.5, 146.5, 157.3, 158.8, 195.5. IR: 3550−3000, 1724, 1682, 1610 cm^{-1}. MS *m*/*z* (relative intensity): 658 (M^+, 9.3), 91 (100). HRMS *m*/*z*: M^+ calcd for $C_{33}H_{38}O_{10}S_2$, 658.1906; found, 658.1895. Anal. Calcd for $C_{33}H_{38}O_{10}S_2$: C, 60.16; H, 5.81. Found: C, 60.06; H, 5.94.

***rac*-(5a*R*,6*R*,9*R*,9a*S*)-4-Acetyl-6-hydroxy-1-methoxy-6-methyl-9-(1-methylethyl)-5a,6,7,8,9,9a-hexahydrodibenzofuran-3-yl *p*-Toluenesulfonate (30).** A solution of **29** (80 mg, 0.121 mmol) and $NaBH_3CN$ (30 mg, 0.484 mmol) in HMPA (2 mL) was heated for 2 h at 120 °C under a N_2 atmosphere. The mixture was extracted with Et_2O. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:2 AcOEt/*n*-hexane) to give **30** (46 mg, 78%) as a colorless oil. ^{1}H NMR (400 MHz) δ: 0.85 (d, 3H, $J = 7.0$ Hz), 0.90 (d, 3H, $J = 6.8$ Hz), 1.08−1.16 (m, 1H), 1.32−1.48 (m, 2H), 1.43 (s, 3H), 1.65 (dt, 1H, $J = 4.6$, 13.7 Hz), 1.73−1.79 (m, 1H), 1.82 (d × 7, 1H, $J = 2.8$, 7.0 Hz), 2.40 (s, 3H), 2.46 (s, 3H), 3.18 (dd, 1H, $J = 5.4$, 11.2 Hz), 3.75 (s, 3H), 4.14 (dd, 1H, $J = 1.5$, 5.3 Hz), 6.36 (s, 1H), 7.36 (d, 2H, $J = 8.6$ Hz), 7.84 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (100 MHz) δ: 15.4, 17.2, 21.7, 27.2, 28.1, 31.7, 35.0, 39.9, 46.0, 55.7, 69.2, 77.2, 92.0, 100.8, 113.1, 121.1, 128.8, 129.7, 132.5, 145.4, 146.4, 157.5, 159.6, 195.9. IR: 3500−3000, 1723, 1681, 1608 cm^{-1}. MS *m*/*z* (relative intensity): 488 (M^+, 31.9), 207 (100). HRMS *m*/*z*: M^+ calcd for $C_{26}H_{32}O_7S$, 488.1868; found, 488.1874.

(±)-Linderol A (1) [*rac*-(5a*R*,6*R*,9*R*,9a*S*)-4-Cinnamoyl-3,6-dihydroxy-1-methoxy-6-methyl-9-(1-methylethyl)-5a,6,7,8,9,9a-hexahydrodibenzofuran]. To a solution of **30** (40 mg, 0.082 mmol) and benzaldehyde (13 mg, 0.123 mmol) in *t*-BuOH (2 mL) was added *t*-BuOK (9.0 mg, 0.082 mmol) at rt under a N_2 atmosphere, and the whole was stirred for 15 min. A solution of 1 N KOH/MeOH (1:1, 1 mL) was added, and the whole was stirred for an additional 1 h. After neutralization with saturated NH_4Cl, the mixture was extracted with AcOEt. The combined extracts were washed, dried, and evaporated. The residue was chromatographed (1:2 AcOEt/*n*-hexane) to give (±)-**1** (25 mg, 71%) as a yellow powder. ^{1}H NMR (400 MHz) δ: 0.85 (d, 3H, $J = 7.0$ Hz), 0.91 (d, 3H, $J = 6.8$ Hz), 1.14 (tt, 1H, $J = 3.5$, 11.4 Hz), 1.35−1.49 (m, 2H), 1.56 (s, 1H), 1.61 (s, 3H), 1.75 (dt, 1H, $J = 4.1$, 12.3 Hz), 1.83 (m, 1H), 1.86 (d × 7, 1H, $J = 2.9$, 7.0 Hz), 3.14 (dd, 1H, $J = 5.5$, 11.2 Hz), 3.84 (s, 3H), 4.24 (dd, 1H, $J = 1.5$, 5.5 Hz), 6.09 (s, 1H), 7.38−7.42 (m, 3H), 7.60−7.63 (m, 2H), 7.87 and 8.09 (each d, each 1H, $J = 15.7$ Hz), 13.97 (s, 1H). ^{13}C NMR (100 MHz) δ: 15.4, 17.2, 21.8, 27.2, 28.3, 35.4, 39.5, 46.5, 55.5, 69.4, 92.3, 93.1, 103.3, 113.3, 125.8, 128.4, 128.9, 130.3, 135.4, 143.4, 161.5, 162.2, 166.7, 191.1. IR (KBr): 3600−3200, 3395, 1630 cm^{-1}. MS *m*/*z* (relative intensity): 422 (M^+, 48.1), 337 (100). HRMS *m*/*z*: M^+ calcd for $C_{26}H_{30}O_5$, 422.2093; found, 422.2105.

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Supporting Information Available: Tables of the spectral comparison of the synthetic (±)-**1** with the natural **1**; extra experimental detail and data of **7**, **15**, **21**, **22**, 2,4-dibromo-**19**, and **31**; ORTEP drawings and X-ray crystallographic data of **6** and **24**; ^{1}H and ^{13}C NMR spectra of (±)-**1**, **5**−**7**, **9**−**11**, **13**, **15**−**22**, 2,4-dibromo-**19**, and **24**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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