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Asymmetric Total Synthesis of (−)-Linderol A

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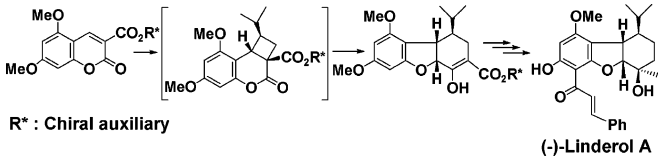
Received April 3, 2007



The first asymmetric total synthesis of (−)-Linderol A, a potent inhibitor of melanin biosynthesis of cultured B-16 melanoma cells, has been achieved via two key reactions: a diastereoselective [2+2] photocycloaddition of a coumarin-3-carboxylate bearing a chiral auxiliary with 3-methyl-1-butene and a subsequent stereoconvergent transformation of the photoadducts with use of dimethylsulfoxonium methylide to afford a tetrahydrodibenzofuran 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 bark of *Lindera umbellata* (Lauraceae) (Figure 1).[1,2] It has four asymmetric carbon atoms at the 5a, 6, 9, and 9a positions. In Sashida's report, the potent inhibitory activity of **1** on melanin biosynthesis in cultured B-16 melanoma cells was also reported without any cytotoxic effects to the cultured cells or skin irritation in guinea pigs.[1]

We were interested in the total synthesis of **1** due to its unique structural and biological features. The first-[3] and second-generation syntheses of (±)-**1** have been previously reported by our group.[4] In the first-generation synthesis, the key step involved reaction of a coumarin-3-carboxylate derivative (**2**) with dimethylsulfoxonium methylide to afford the 2-substituted cyclopenta[*b*]benzofuran-3-ol derivative (**3**).[5] The key step of the second-generation synthesis involved direct conversion of 1,2a-disubstituted benzo[*b*]cyclobuta[*d*]pyranone derivative (**5**), which was easily prepared by a [2+2] photocycloaddition of **2** to 3-methyl-1-butene, to tetrahydrodibenzofuran derivative (**4**) by treatment with dimethylsulfoxonium methylide (Scheme 1).[4]

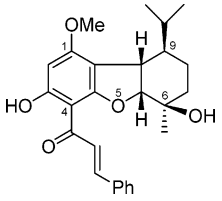


FIGURE 1. (−)-Linderol A [(−)-**1**].

The first synthesis of (−)-**1** and (+)-**1** was achieved via optical resolution of the 6-acetoxymethyl derivative [(±)-**7**], using HPLC on chiral stationary phases.[6] On the basis of X-ray analysis of the (−)-camphanate of (−)-**6** [R = (−)-camphanoyl], we were able to determine the absolute configuration of (−)-**1**, which was not previously reported by Sashida et al.[1] (Figure 1). Herein, we describe the first asymmetric total synthesis of (−)-**1**.

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

(2) At that time, the absolute structure of (−)-**1** was not determined.

(3) (a) Yamashita, M.; Ohta, N.; Shimizu, T.; Matsumoto, K.; Matuura, Y.; Kawasaki, I.; Tanaka, T.; Maezaki, N.; Ohta, S. *J. Org. Chem.* **2003**, *68*, 1216. (b) Yamashita, M.; Ohta, N.; Kawasaki, I.; Ohta, S. *Org. Lett.* **2001**, *3*, 1359.

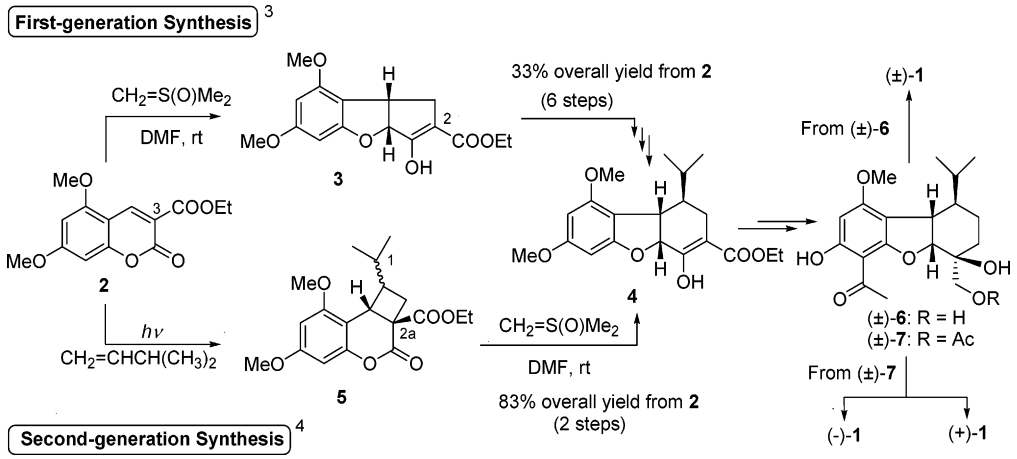
(4) (a) Yamashita, M.; Shimizu, T.; Inaba, T.; Takada, A.; Takao, I.; Kawasaki, I.; Ohta, S. *Hetreocycles* **2005**, *65*, 1099. (b) Yamashita, M.; Inaba, T.; Nagahama, M.; Shimizu, T.; Kosaka, S.; Kawasaki, I.; Ohta, S. *Org. Biomol. Chem.* **2005**, *3*, 2296. (c) Yamashita, M.; Inaba, T.; Shimizu, T.; Kawasaki, I.; Ohta, S. *Synlett* **2004**, 1897.

(5) (a) 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. (b) Yamashita, M.; Okuyama, K.; Kawasaki, I.; Ohta, S. *Tetrahedron Lett.* **1995**, *36*, 5603.

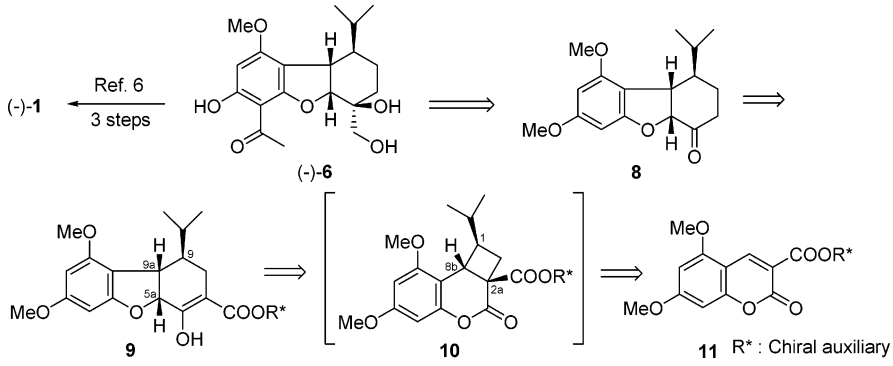
(6) Yamashita, M.; Shimizu, T.; Kawasaki, I.; Ohta, S. *Tetrahedron: Asymmetry* **2004**, *15*, 2315.

10.1021/jo070682+ CCC: $37.00
Published on Web 06/19/2007

SCHEME 1



SCHEME 2. Retrosynthesis of (−)-1



Results and Discussion

The retrosynthesis of (−)-**1** is shown in Scheme 2. The conversion of triol [(−)-**6**] to (−)-**1** was previously reported by our group,[6] and the transformation of **8** to (−)-**6** can be achieved by applying a similar route to that used in our total synthesis of (±)-**1**.[3] This route allows for the installation of the stereochemistry at the 5a-, 9-, and 9a-positions of **9**. This was expected because we previously reported that the transformation of a mixture of 1-*exo*- and 1-*endo*-cyclobutane derivatives (**13**, **14**, *ent*-**13**, and *ent*-**14**), obtained by [2+2] photocycloaddition of **12** with a monosubstituted alkene[7] using dimethylsulfoxonium methylide proceeded stereoconvergently, irrespective of the stereochemistry of the 2a- and 8b-positions of **13**, **14**, *ent*-**13**, and *ent*-**14** (Scheme 3).[4]

Thus, the stereoselective introduction of the isopropyl group at the 1-position in **10** was crucial. Therefore, we first planned to explore the diastereoselective [2+2] photocycloaddition of 3-methyl-1-butene using a coumarin derivative (**11**) bearing a chiral auxiliary.[8,9]

5,7-Dimethoxycoumarin-3-carboxylates with various chiral auxiliaries (**11a**−**c**) were prepared according to well-known literature procedures, and subjected to [2+2] photocycloadditions with 3-methyl-1-butene to obtain mixtures of the four possible diastereoisomers (**10a**−**c**) in various ratios. These mixtures were treated without separation with dimethylsulfoxonium methylide to afford a mixture of the stereoconvergently formed tetrahydrodibenzofurans (**16a**−**c** and **17a**−**c**, respectively). The results are shown in Table 1.

Upon irradiation of the ester (**11c**) bearing a (−)-8-(2-naphthyl)menthyl group as the chiral auxiliary, using a 400 W high-pressure mercury lamp in MeOH, the ratio **16c**:**17c** = 29:71 (estimated from the ^{1}H NMR peak area of the 2- and 4-Hs) was obtained in 77% overall yield (entry 7). The coumarin (**11c**) was subjected to X-ray crystal structure analysis (see the Supporting Information), and the naphthyl group in **11c** was determined to be located behind the 3,4-double bond of the coumarin ring in order to control the direction of the photoreaction by blocking the back side. If the conformation of **11c** in

(7) (a) Yamashita, M.; Yadav, N. D.; Nagahama, M.; Inaba, T.; Nishino, Y.; Miura, K.; Kosaka, S.; Fukao, J.; Kawasaki, I.; Ohta, S. *Heterocycles* **2005**, *65*, 2411. (b) Ratiner, B. D.; Elia, L. P.; Otsuki, T. *Chem. Express* **1990**, *5*, 225. (c) Ratiner, B. D.; Otsuki, T. *Chem. Lett.* **1989**, 1035. (d) Suginome, H.; Liu, C. F.; Seko, S.; Kobayashi, K.; Furusaki, A. *J. Org. Chem.* **1988**, *53*, 5952. (e) Otsuki, T. *Chem. Lett.* **1987**, 453. (f) Pfoertner, K.-H. *Helv. Chim. Acta* **1976**, *59*, 834.

(8) We have already discussed the detailed reaction mechanism of the stereoconvergent transformation of **13** and **14** to **15** in refs 4a and 4b. See the Supporting Information.

(9) (a) Furutani, A.; Tsutsumi, K.; Nakano, H.; Morimoto, T.; Kakiuchi, K. *Tetrahedron Lett.* **2004**, *45*, 7621. (b) Sarkar, N.; Nayek, A.; Ghosh, S. *Org. Lett.* **2004**, *6*, 1903. (c) Shintani, T.; Kusabiraki, K.; Hattori, A.; Furutani, A.; Tsutsumi, K.; Morimoto, T.; Kakiuchi, K. *Tetrahedron Lett.* **2004**, *45*, 1849. (d) Tsutsumi, K.; Nakano, H.; Furutani, A.; Endou, K.; Merpuge, A.; Shintani, T.; Morimoto, T.; Kakiuchi, K. *J. Org. Chem.* **2004**, *69*, 785. (e) Tsutsumi, K.; Endou, K.; Furutani, A.; Ikki, T.; Nakano, H.; Shintani, T.; Morimoto, T.; Kakiuchi, K. *Chirality* **2003**, *15*, 504. (f) Lange, G. L.; Humber, C. C.; Manthorpe, J. M. *Tetrahedron*: *Asymmetry* **2002**, *13*, 1355. (g) Sato, M.; Abe, Y.; Takayama, K.; Sekiguchi, K.; Kaneko, C.; Inoue, N.; Fukuya, T.; Inukai, N. *J. Heterocycl. Chem.* **1991**, *28*, 241. (h) Seebach, D.; Zimmermann, J. *Helv. Chim. Acta* **1986**, *69*, 1147. (i) Lange, G. L.; Decicco, C.; Tan, S. L.; Chamberlian, G. *Tetrahedron Lett.* **1985**, *26*, 4707. (j) Lange, G.; Lee, M. *Tetrahedron Lett.* **1985**, *26*, 6163.

SCHEME 3

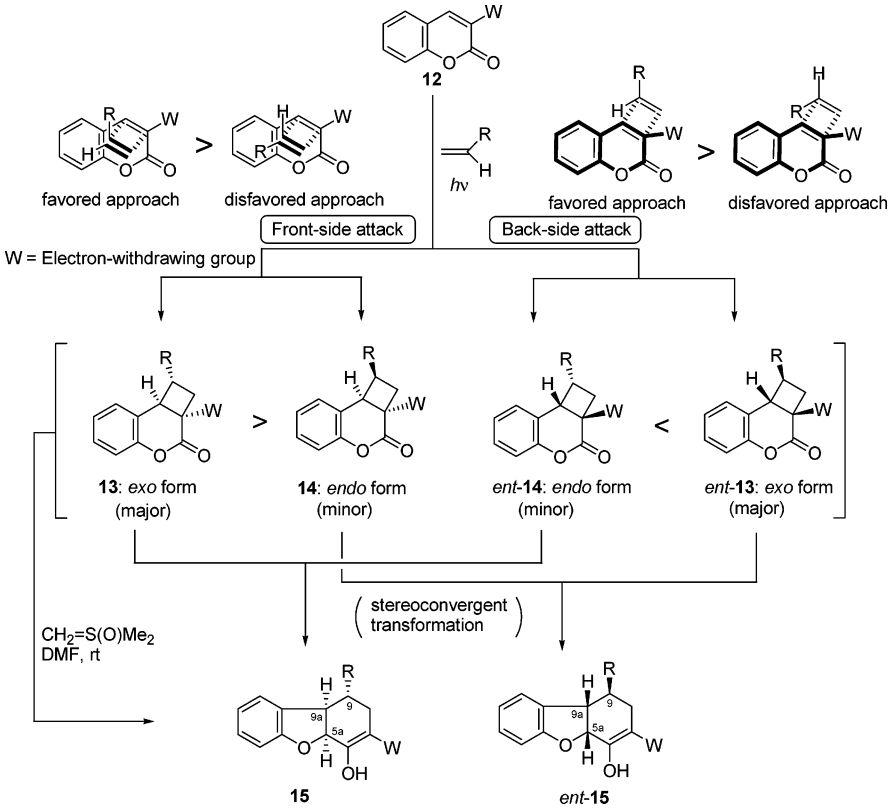
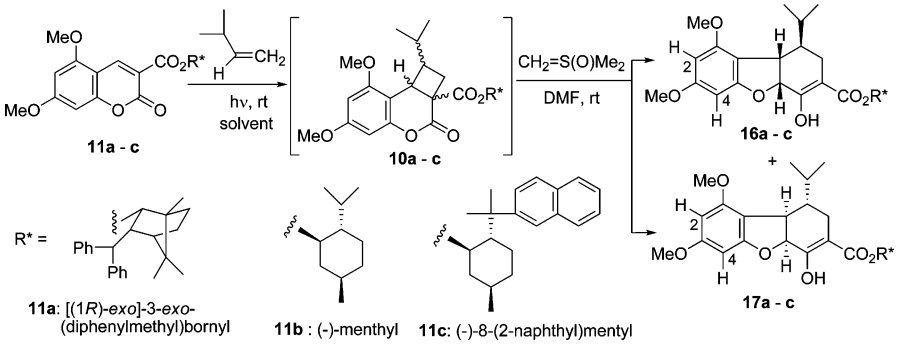


TABLE 1. [2+2] Photocycloaddition of 11a−c Followed by Treatment with Dimethylsulfoxonium Methylide



entry	**11**	photoreaction solvent	photoreaction time (h)	yield (%)[a] (**16** + **17**)	diastereomeric ratio[b,c]
1	**11a**	MeOH	2	61	43:57
2	**11a**	CH_2Cl_2	2	62	43:57
3	**11a**	$C_6H_5CH_3$	3	37	50:50
4	**11b**	MeOH	2	79	48:52
5	**11b**	CH_2Cl_2	2	75	50:50
6	**11b**	$C_6H_5CH_3$	3	83	45:55
7	**11c**	MeOH	2	77	29:71
8	**11c**	CH_2Cl_2	2	80	42:58
9	**11c**	$C_6H_5CH_3$	3	81	57:43

[a] Overall yield from **11**. [b] Estimated from ^{1}H NMR spectrum. [c] Configuration of the products (**16** + **17**) was not determined.

the solid state was also maintained in solution, it is expected that 3-methyl-1-butene would approach predominantly from the front side of **11c,** as shown in A of Figure 2.

Photocycloaddition of **11c** with 3-methylbutene followed by treatment of dimethylsulfoxonium methylide was examined in various solvents, and the results are shown in Table 2.

In polar solvents such as alcohols and acetonitrile (entries 1−8), the benzofuran **17c** was found to be the predominant product of the photoreaction and subsequent stereoconvergant transformation reaction. Higher diastereomeric ratios and yields were obtained when fluorinated alcohols such as 2,2,2-trifluoroethanol, 1,1,1,3,3,3-hexafluoro-2-propanol, and nonafluoro-

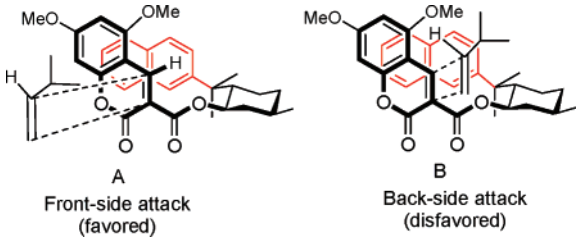


FIGURE 2. A diastereoselective [2+2] photocycloaddition of **11c** with 3-methyl-1-butene.

TABLE 2. Photocycloaddition of 11c with 3-Methyl-1-butene Followed by Treatment with Dimethylsulfoxonium Methylide.

entry	photoreaction solvent	yield (%)[a]	diastereomeric ratio[b] [**16c**:**17c**]	pK_a
1	CH_3CN	82	34:66	
2	MeOH	77	29:71	15.1[c]
3	EtOH	62	34:66	15.9[c]
4	*n*-BuOH	74	37:63	16.1[c]
5	5%AcOH/MeOH	65	27:73	
6	CF_3CH_2OH	86	18:82	12.3[d]
7	$(CF_3)_2CHOH$	79	14:86	9.5[d]
8	$(CF_3)_3COH$	90	12:88	9.3[d]
9	benzene	60	63:37	
10	methylcyclohexane	94	61:39	

[a] Isolated overall yield of **16c** and **17c**. [b] Determined on the basis of ^{1}H NMR spectrum. [c] Murto, J. *Acta Chem. Scand.* **1964**, *18*, 1043. [d] Forman, G. S.; McConnell, A. E.; Tooze, R. P.; Rensburg, W. J. V.; Meyer, W. H.; Kirk, M. M.; Dwyer, C. L.; Serfontein, D. W. *Organometallics* **2005**, *24*, 4528−4542.

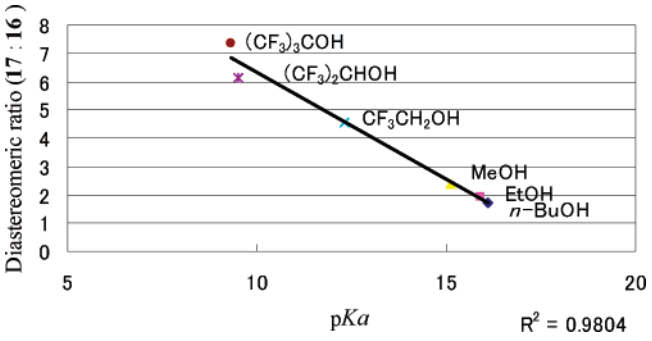


FIGURE 3. A relationship between the pK_a value and the diastereomeric ratio (**17c**:**16c**).

tert-butanol were used as reaction solvents (entries 6−8). This suggests that the conformation of **11c** in the solid state is also maintained in these solvents. The relationship between the pK_a value and diastereomeric ratio of **17c**:**16c** was translated to graphical form (Figure 3). With a decrease in the pK_a, the diastereomeric ratio increased, and a good correlation was observed between these values. It seems that the chelating hydrogen bonds between the two carbonyl groups in **11c** and the hydrogen in the solvent would exist, as shown in Figure 4. Furthermore, as the acidity of the solvents increases, the blocking effect of the naphthylmenthyl group becomes more effective.

Interestingly, when less polar solvents such as benzene, toluene, and methylcyclohexane were used, the diastereomeric ratios were reversed (entries 9 and 10 in Table 2, and entry 9 in Table 1). In these solvents, intramolecular dipole−dipole repulsion between the two carbonyl groups in **11c** is thought to be the primary cause for the inversion (Figure 5).

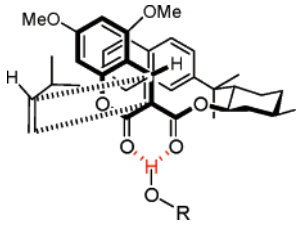


FIGURE 4. The hydrogen bond between the two carbonyl groups in **11c** and solvent OH.

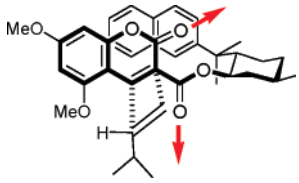


FIGURE 5. Intramolecular dipole−dipole repulsion between the two carbonyl groups in **11c**.

Therefore, the predominant tetrahydrodibenzofuran is expected to be **17c**, which has the *S* configuration at the 1-position. The diastereomers of **16c** and **17c** could be isolated by preparative HPLC, respectively. The mixtures obtained from entries 6−8 were recrystallized only once from *n*-hexane to afford pure **17c**. The stereochemistry at the 9-position of **17c** was determined to be *S* by X-ray crystal structure analysis, as suggested below (Scheme 4), which corresponds to the undesired unnatural form of Linderol A.[10]

The asymmetric synthesis of (−)-**1** was therefore performed with (+)-**19** as described below. The carboxylic acid (**18**)[11] was esterified by using (+)-**19**,[12] prepared from (*S*)-(−)-pulegone, to give *ent*-**11c**. Diastereoselective [2+2] photocycloaddition reactions of *ent*-**11c** with 3-methyl-1-butene in 2,2,2-trifluoroethanol or 1,1,1,3,3,3-hexafluoro-2-propanol followed by a stereoconvergent transformation with dimethylsulfoxonium methylide in DMF afforded a mixture of *ent*-**16c** and *ent*-**17c** in diastereomeric ratios of 13:87 and 11:89, and yields of 87% and 75%, respectively. Separation of the mixture by HPLC gave *ent*-**17c**. Several attempts to hydrolyze *ent*-**17c** and its derivatives all failed, probably due to steric hindrance around the carbonyl carbon of the ester group. Successive hydrolysis−decarboxylation of *ent*-**17c** occurred upon microwave irradiation of the aqueous ethanolic solution in the presence of a catalytic amount of Amberlyst 15 in a sealed tube to give (−)-**8** in 96% yield.[13,14]

(10) Nonnatural (+)-**1**, the antipode of natural (−)-**1**, was derived from **17c**. See the Supporting Information.

(11) (a) Fringuelli, F.; Piermatti, O.; Pizzo, F. *Synthesis* **2003**, 2331. (b) Song, A.; Wang, X.; Lam, K. S. *Tetrahedron Lett.* **2003**, *44*, 1755. (c) Hassan, M. A.; Shiba, S. A.; Harb, N. S.; Abou-El-Regal, M. K.; El-Metwally, S. A. *Synth. Commun.* **2002**, *32*, 679. (d) Bonsignore, L.; Cottiglia, F.; Lavagna, S. M.; Loy, G.; Secci, D. *Heterocycles* **1999**, *50*, 469. (e) Watson, B. T.; Christiansen, G. E. *Tetrahedron Lett.* **1998**, *39*, 6087. (f) Bonsignore, L.; Cottiglia, F.; Maccioni, A. M.; Secci, D.; Lavagna, S. M. J. *Heterocycl. Chem.* **1995**, *32*, 573. (g) Heyes, R. G.; Robertson, A. *J. Chem. Soc.* **1936**, 1831.

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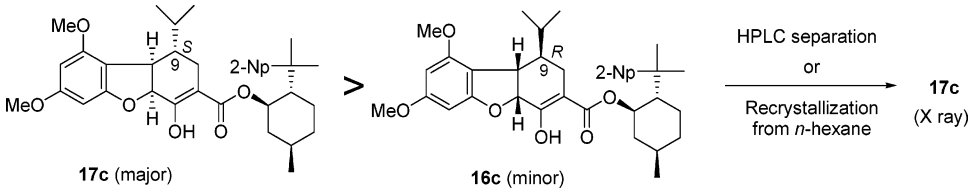
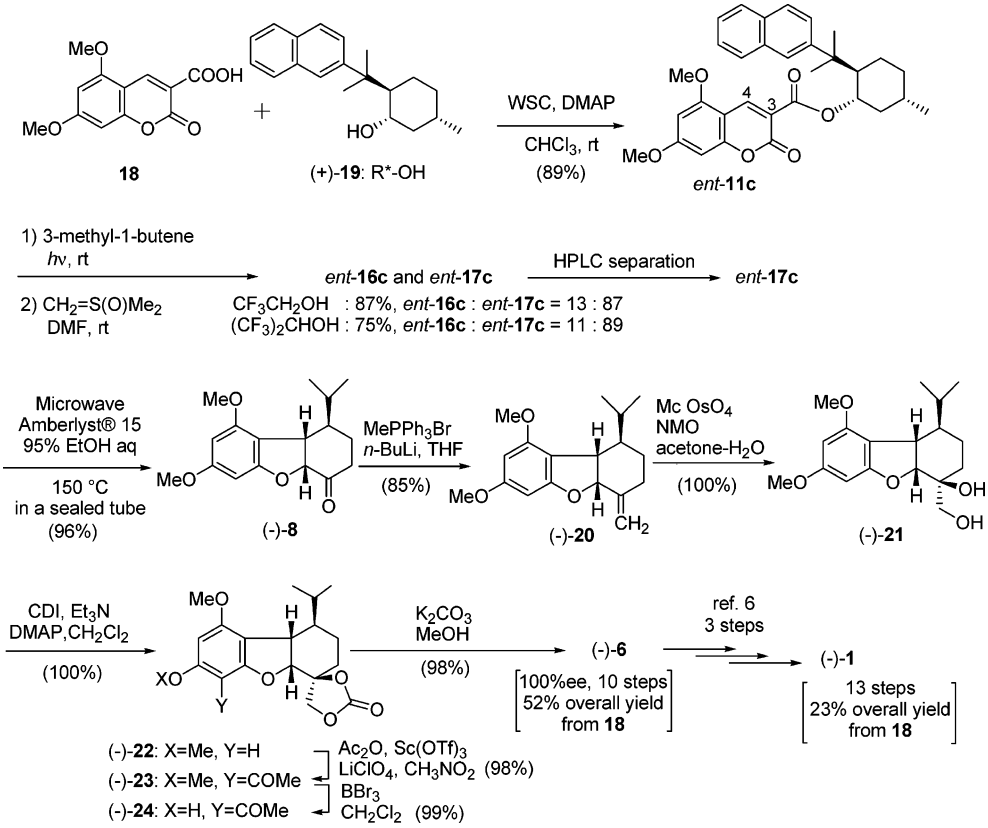
(13) The ee of (−)-**8** was 100% on the basis of HPLC analysis [column: Chiralcel OJ (4.6 mm I.D. × 250 mm); eluent: *i*-PrOH/*n*-hexane 10/90; flow: 1.0 mL/min; detect.: UV 254 nm; temp: rt; retention time: (−)-**8** 10.9 min, (+)-**8** 14.9 min].

SCHEME 4



SCHEME 5



According to our racemic synthetic route to (±)-**1** from (±)-**8**,[3] the obtained (−)-**8** was converted to (−)-**6** as described below. The cyclohexanone [(−)-**8**] was converted to the *exo*-olefin [(−)-**20**] by Wittig olefination. *cis*-1,2-Dihydroxylation with a catalytic amount of microencapsulated OsO_4 in the presence of *N*-methylmorpholine *N*-oxide afforded the diol [(−)-**21**] as a single isomer in quantitative yield.[15] The 1,2-diol portion of (−)-**21** was protected as a cyclic carbonate according to well-known transformations. Friedel−Crafts acylation of (−)-**22** 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 [(−)-**23**].[16] Selective demethylation of the 3-methoxy group of (−)-**23** by treatment with BBr_3 afforded the phenol [(−)-**24**] in 99% yield. Finally, the cyclic carbonate functionality was hydrolyzed with K_2CO_3 in MeOH to give the triol [(−)-**6**] in 98% yield. Conversion of (−)-**6** to (−)-**1** was previously reported, and the (−)-**6** achieved here was consistent with an authentic sample according to spectral data and specific rotation.[5] Therefore, the triol [(−)-**6**] could be prepared via 10 steps in 52% overall yield from **18** (Scheme 5).

Conclusion

Herein, we report the first asymmetric total synthesis of (−)-**1** in 13 steps with a 23% overall yield from 5,7-dimethoxycoumarin-3-carboxylic acid (**18**) via two key reactions: a diastereoselective [2+2] photocycloaddition of coumarin-3-carboxylate bearing a chiral auxiliary [*ent*-**11c**] with 3-methyl-1-butene and a subsequent stereoconvergent transformation with dimethylsulfoxonium methylide to the tetrahydrodibenzofuran derivative [*ent*-**17c**].

Experimental Section

(1*S*,2*R*,5*S*)-5-Methyl-2-[1-methyl-1-(2-naphthyl)ethyl]cyclohexyl 5,7-Dimethoxycoumarin-3-carboxylate (*ent*-11c). 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSC; 2.48 g, 13.0 mmol) was added portionwise to a solution of 5,7-dimethoxycoumarin-3-carboxylic acid (**18**; 1.08 g, 4.32 mmol), (+)-8-(2-naphthyl)menthol [(+)-**19**; 1.22 g, 4.32 mmol), and DMAP (527 mg, 4.32 mmol) in $CHCl_3$ (20 mL) under ice-cooling and N_2

(14) (+)-8-(2-Naphthyl)menthol (**19**) was recovered in 100% yield without any epimerization.

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atmosphere, and the whole was stirred for 48 h at rt. After addition of H_2O (15 mL) under ice-cooling, the mixture was extracted with Et_2O (3 × 30 mL). The combined organic layer was dried over Na_2SO_4 and evaporated. The obtained residue was chromatographed on silica gel (AcOEt/*n*-hexane = 1/10) to give *ent*-**11c** (2.30 g, 89%). Yellow columns (recrystallized from isopropanol), mp 162.0−163.5 °C. $[\alpha]^{25}_D$ +147.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (3H, d, J = 6.6 Hz), 1.03 (1H, dq, J = 3.4, 12.9 Hz), 1.15 (1H, q, J = 12.2 Hz), 1.26 (3H, s), 1.32 (1H, dq, J = 3.1, 12.8 Hz), 1.46 (3H, s), 1.51−1.64 (1H, m), 1.76−1.88 (2H, m), 2.05 (1H, ddd, J = 3.3, 6.8, 13.4 Hz), 2.32 (1H, dt, J = 3.7, 12.3 Hz), 3.86, 3.92 (3H each, s each), 5.15 (1H, dt, J = 4.6, 10.8 Hz), 6.12 (2H, s), 6.82 (1H, ddd, J = 1.1, 6.9, 8.1 Hz), 7.08 (1H, ddd, J = 1.2, 6.9, 8.1 Hz), 7.16 (1H, d, J = 8.1 Hz), 7.50−7.58 (4H, m), 7.53 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 21.8, 26.0, 30.4, 31.3, 34.5, 39.4, 41.7, 50.2, 55.8, 55.9, 73.4, 92.1, 94.3, 102.9, 110.0, 122.1, 124.0, 125.1, 125.3, 126.0, 127.0 × 2, 130.8, 133.2, 142.5, 149.4, 156.8, 157.8, 157.9, 161.3, 165.8. IR ($CHCl_3$) 1748, 1613 cm^{-1}. MS *m*/*z* (rel intensity, %) 514 (M^+, 12.6), 169 (100.0). HRMS *m*/*z* calcd for $C_{32}H_{34}O_6$ 514.2355, found 514.2354 (M^+).

(1*S*,2*R*,5*S*)-5-Methyl-2-[1-methyl-1-(2-naphthyl)ethyl]cyclohexyl (1*R*,4a*R*,9b*S*)-1,2,4a,9b-Tetrahydro-4-hydroxy-7,9-dimethoxy-1-(1-methylethyl)-3-dibenzofurancarboxylate (*ent*-17c) and (1*S*,2*R*,5*S*)-5-Methyl-2-[1-methyl-1-(2-naphthyl)ethyl]cyclohexyl (1*S*,4a*S*,9b*R*)-1,2,4a,9b-Tetrahydro-4-hydroxy-7,9-dimethoxy-1-(1-methylethyl)-3-dibenzofurancarboxylate (*ent*-16c). A solution of *ent*-**11c** (514 mg, 1.00 mmol) and a large excess of 3-methyl-1-butene (2.10 g, 30.0 mmol) in 1,1,1,3,3,3-hexafluoro-2-propanol (5 mL) was kept in a Pyrex photochemical reactor vessel, and the whole was irradiated with a 400-W high-pressure mercury lamp in a water-cooled quartz immersion well for 8 h. The volatile solvents were evaporated to afford crude products of the cyclobutane compounds. The solution of the cyclobutane compounds in DMF (1 mL) was added dropwise to a solution of dimethylsulfoxonium methylide, which was prepared from trimethylsulfoxonium iodide (440 mg, 2.00 mmol) and sodium hydride (60% dispersion in mineral oil, 80 mg, 2.00 mmol) in DMF (2 mL), under ice-cooling and N_2 atmosphere. The whole was stirred for 24 h at rt under N_2 atmosphere. After acidification with 10% HCl under ice-cooling, the mixture was extracted with AcOEt (3 × 25 mL). The combined organic layer was washed with saturated $Na_2S_2O_3$ aqueous solution, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel (AcOEt/*n*-hexane = 1/10) to give a mixture of *ent*-**16** and *ent*-**17** (488 mg, 75%, *ent*-**16c**:*ent*-**17c** = 11:89). The mixture was separated with HPLC {column: Cosmosil 5SL-II [(20 mm i.d. × 250 mm) × 2]; eluent: AcOEt/*n*-hexane = 5/95; flow: 5 mL/min; detect.: UV 254 nm; temp: rt; retention time: *ent*-**16c** 76.8 min, *ent*-**17c** 82.5 min} to give *ent*-**16c** and *ent*-**17c**.

***ent*-17c:** Retention time 82.5 min. Colorless powder (recrystallized from *n*-hexane). Mp 165.0−168.0 °C. $[\alpha]^{25}_D$ +3.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.18 (1H, dd, J = 11.5, 16.1 Hz), 0.66 (3H, d, J = 6.6 Hz), 0.68 (3H, d, J = 7.0 Hz), 0.91 (3H, d, J = 6.4 Hz), 0.94−1.14 (3H, m), 1.21−1.34 (1H, m), 1.26 (3H, s), 1.45−1.63 (3H, m), 1.50 (3H, s), 2.01−2.06 (2H, m), 2.22 (1H, dt, J = 3.6, 12.2 Hz), 3.72, 3.74 (3H each, s each), 4.29 (1H, d, J = 9.7 Hz), 5.17 (1H, dt, J = 4.5, 10.7 Hz), 5.99, 6.06 (1H each, d each, J = 2.0 Hz), 7.34−7.41 (2H, m), 7.50−7.54 (2H, m), 7.70−7.78 (3H, m), 11.84 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.5, 19.9, 21.6, 21.80, 21.83, 26.1, 26.5, 30.4, 31.4, 34.4, 39.5, 41.6, 41.9, 42.1, 49.9, 55.1, 55.4, 73.3, 81.3, 89.1, 91.4, 102.8, 110.0, 122.0, 125.1, 125.5, 125.7, 127.1, 127.3, 127.7, 131.3, 133.6, 149.0, 157.2, 160.6, 161.4, 162.3, 170.8. IR ($CHCl_3$) 1654, 1615 cm^{-1}. MS *m*/*z* (rel intensity, %) 598 (M^+, 18.9), 169 (100.0). HRMS *m*/*z* calcd for $C_{38}H_{46}O_6$ 598.3294, found 598.3295 (M^+).

***ent*-16c:** Retention time 76.8 min. Colorless powder (recrystallized from MeOH). Mp 97.0−99.5 °C. $[\alpha]^{25}_D$ +41.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (3H, d, J = 7.0 Hz), 0.86 (3H, d, J = 6.4 Hz), 0.88 (3H, d, J = 6.2 Hz), 1.06−1.17 (3H, m), 1.34, 1.44 (3H each, s each), 1.42−1.54 (2H, m), 1.57−1.72 (5H, m), 1.83−1.91 (2H, m), 2.16 (1H, dt, J = 3.1, 13.5 Hz), 3.11 (1H, t, J = 8.7 Hz), 3.75, 3.77 (3H each, s each), 4.71 (1H, d, J = 5.9 Hz), 5.10 (1H, dt, J = 4.4, 10.6 Hz), 6.02, 6.14 (1H each, d each, J = 2.0 Hz), 7.32 (1H, ddd, J = 1.1, 6.8, 8.1 Hz), 7.40 (1H, ddd, J = 1.3, 7.0, 8.1 Hz), 7.46 (1H, dd, J = 1.9, 8.7 Hz), 7.59 (1H, d, J = 1.5 Hz), 7.68−7.76 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.6, 20.4, 21.6, 21.8, 26.1. 27.0, 27.1 × 2, 31.4, 34.4, 40.2, 42.0 × 2, 42.3, 50.2, 55.1, 55.5, 75.0, 81.2, 89.1, 91.4, 101.9, 109.5, 123.1, 124.7, 125.2, 125.9, 127.1, 127.6, 127.9, 131.4, 133.3, 147.9, 157.2, 160.8, 161.6, 163.4, 170.7. IR ($CHCl_3$) 1653, 1595 cm^{-1}. MS *m*/*z* (rel intensity, %) 598 (M^+, 2.7), 169 (100.0). HRMS *m*/*z* calcd for $C_{38}H_{46}O_6$ 598.3294, found 598.3290 (M^+).

(1*R*,4a*R*,9b*S*)-7,9-Dimethoxy-1-(1-methylethyl)-1,2,3,4,4a,9b-hexahydrodibenzofuran-4-one [(−)-8]. A suspension of *ent*-**17c** (50 mg, 0.083 mmol) and AMBERLYST 15 (5.6 mg, 4.7 mg equiv/g, 0.026 mmol) in 95% aqueous ethanol (5 mL) was irradiated with a microwave apparatus (2450 MHz) in a sealed tube at 150 °C for 2.5 h. The AMBERLYST 15 was filtrated and washed with ethanol. The obtained filtrate was evaporated and purified with PTLC ($CHCl_3$) to give (−)-**8** (23 mg, 96%) and (+)-**19** (23 mg, 100%). (−)-**8**: Colorless oil. $[\alpha]^{25}_D$ −66.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95, 1.02 (3H each, d each, J = 6.6 Hz), 1.62−1.68 (1H, m), 1.71−1.84 (2H, m), 1.85−1.93 (1H, m), 2.43−2.58 (2H, m), 3.77, 3.78 (3H each, s each), 3.84 (1H, dd, J = 6.2, 8.6 Hz), 4.70 (1H, dd, J = 0.6, 8.4 Hz), 6.05, 6.14 (1H each, d each, J = 2.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) 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 1714, 1617 cm^{-1}. MS *m*/*z* (rel intensity, %) 290 (M^+, 29.6), 178 (100). HRMS *m*/*z* calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1514 (M^+).

The compounds (−)-**20** to (−)-**24** and (−)-**6** were prepared by a similar method to the synthesis of (±)-**20** to (±)-**2**, and (±)-**6**.[3] Spectral data (^{1}H NMR, ^{13}C NMR, IR, and MS) of (−)-**20** to (−)-**24** and (−)-**6** were consistent with those of (±)-**20** to (±)-**24** and (±)-**6**.[3a]

(5a*R*,9*R*,9a*S*)-1,3-Dimethoxy-9-(1-methylethyl)-6-methylidene-5a,6,7,8,9,9a-hexahydrodibenzofuran (−)-20: Colorless oil. $[\alpha]^{25}_D$ −95.8 (*c* 1.0, $CHCl_3$).

(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 (−)-21: Colorless needles. Mp 58.0−61.0 °C ($CHCl_3$). $[\alpha]^{25}_D$ −46.0 (*c* 1.0, $CHCl_3$).

(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 (−)-22: Colorless needles. Mp 39.0−42.0 °C. $[\alpha]^{25}_D$ −58.3 (*c* 1.0, $CHCl_3$).

(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 (−)-23: Colorless needles. Mp 128.0−130.0 °C (AcOEt−*n*-hexane). $[\alpha]^{25}_D$ −102.6 (*c* 1.3, $CHCl_3$).

(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 (−)-24: Colorless powder. Mp 236.0−238.0 °C (AcOEt−*n*-hexane). $[\alpha]^{25}_D$ −113.2 (*c* 1.0, $CHCl_3$).

(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 (−)-6: Colorless powder. Mp: 216.0−222.0 °C (AcOEt−*n*-hexane). $[\alpha]^{33}_D$ −97.2 (*c* 1.0, $CHCl_3$) {lit.[6] $[\alpha]^{33}_D$ −97.2 (*c* 1.0, $CHCl_3$)}.

Acknowledgment. This research was supported in part by the Frontier Research Program and the 21st Century COE Program "Development of Drug Discovery Frontier Integrated from Tradition to Proteome" of the Ministry of Education, Culture, Sports, Science and Technology of Japan, by a Grant-in-Aid for the Promotion of the Advancement of Education and Research in Graduate Schools from The Promotion and Mutual

Aid Corporation for Private Schools of Japan, and by the Research for Promoting Technological Seeds of the Japan Science and Technology Agency (JST).

Supporting Information Available: Experimental details for the synthesis of (−)-**20**−**24**, (−)-**6**, **18**,and **11a**,**b**; specific rotation, HRMS, and/or elemental analysis of **11c**, **16c**, **17c**, (+)-**20**−**24**, and (+)-**6**; copies of ^{1}H and ^{13}C NMR spectra for *ent*-**11c**, *ent*-**16c**, *ent*-**17c**, (−)-**8**, (−)-**20**−**24**, (−)-**6**, **11c**, **16c**, **17c**, (+)-**8**, (+)-**20**−**24**, (+)-**6**, (±)-**1**, (−)-**1**, and (+)-**1**; comparison of the spectral data of the synthetic (−)-**1** with those of the natural-**1**; ORTEP drawing and CIF files of **11c** and **17c**; and the reaction mechanism of the stereoconvergent transformation (**13**/**14** to **15**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO070682+