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IMPROVED SYNTHESIS OF (±)-LINDEROL A AND ITS FIRST CONVERSION TO (±)-6-*epi*-ADUNCTIN E

Masayuki Yamashita,^{a,b} Takashi Shimizu,^a Tomoki Inaba,^a Ai Takada,^a
Ikuko Takao,^{a,c} Ikuo Kawasaki,^a and Shunsaku Ohta*^{a,b}

^a Department of Functional Molecular Chemistry, ^b 21st COE Program, ^c Center for Instrumental Analysis, Kyoto Pharmaceutical University, Misasagi-Nakauchi 5, Yamashina, Kyoto 607-8414, Japan. E-mail: sohta@mb.kyoto-phu.ac.jp

Abstract – The synthetic route to a dibenzofuranone (**7**), a key intermediate of the total synthesis of (±)-linderol A (**2**), was considerably improved by using a novel stereoconvergent transformation of a cyclobutane (**5**), and the first synthesis of (±)-6-*epi*-adunclin E (**8**) was achieved by application of this route.

INTRODUCTION

In 1993, (+)-adunclin E (**1**) was isolated from the leaves of *Piper aduncum* (Piperaceae) in Papua New Guinea (PNG) together with monoterpene-substituted dihydrochalcones (Figure 1). There has been no report on the bioactivity of adunclin E itself (**1**), but the cytotoxicity and antibacterial effects of other components in the plant have been reported. *P. aduncum* has been used by traditional healers in PNG for the treatment of fresh wounds, and a decoction of the leaves has been used for the treatment of diarrhea in Peru. Furthermore, in Colombia, the leaves have been also used to treat dysentery and as haemostatic.¹

In 1995, Sashida *et al.* reported isolation of (-)-linderol A (**2**) from the fresh bark of *Lindera umbellata* (Lauraceae) and the potent inhibitory activity of **2** on melanin biosynthesis of cultured B-16 melanoma cells without causing any cytotoxicity in the cultured cells or skin irritation in guinea pigs (Figure 1).² Although those plants belong to different families, it is interesting that the structures of **1** and **2** are similar. They have four successive asymmetric carbons at the 6, 5a, 9a, 9-positions, but the stereochemistry at the 6-position and the bond order of the side chain at the 4-position are different.

We previously developed novel transformation reactions of 3-substituted coumarins (**3**) to cyclopenta[*b*]benzofurans (**4**) and benzo[*b*]cyclobuta[*d*]pyrans (**5**) to tetrahydrodibenzofurans (**6**) by using dimethylsulfoxonium methylide, and these methodologies were applied to the first- and

second-generation total syntheses of (\pm)-**2**.^{3,4,5} In the first-generation synthesis, it took six steps to prepare an intermediate (**6a**) having the same stereochemistry as that at the 5a-, 9-, and 9a-positions of **2** in 33% overall yield from 3-ethoxycarbonyl-5,7-dimethoxycoumarin (**3a**).⁵ In the second-generation synthesis, the route to **6a** was shortened to two steps from **3a** as shown in Scheme 1.⁴ As a result, the overall yield of **6a** from **3a** was substantially increased to 83% from 33%.

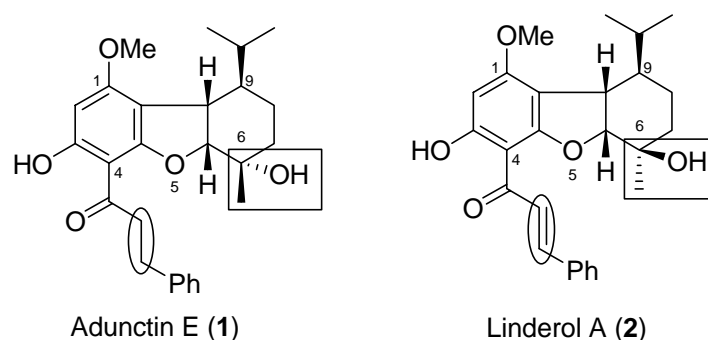
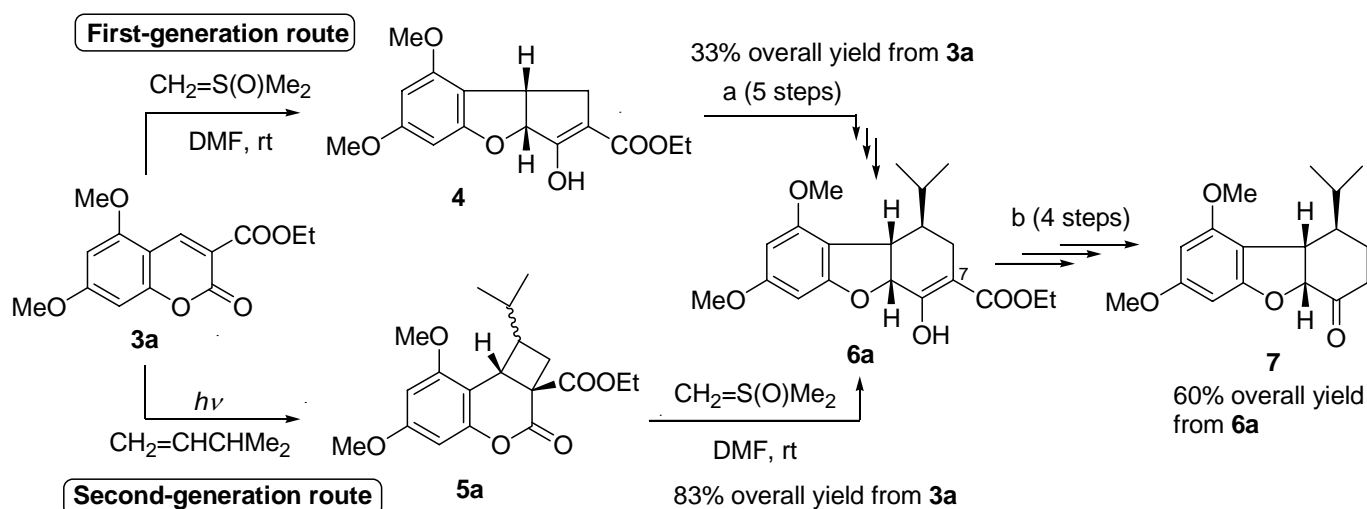


Figure 1. Structure of Adunctin E (**1**) and Linderol A (**2**).



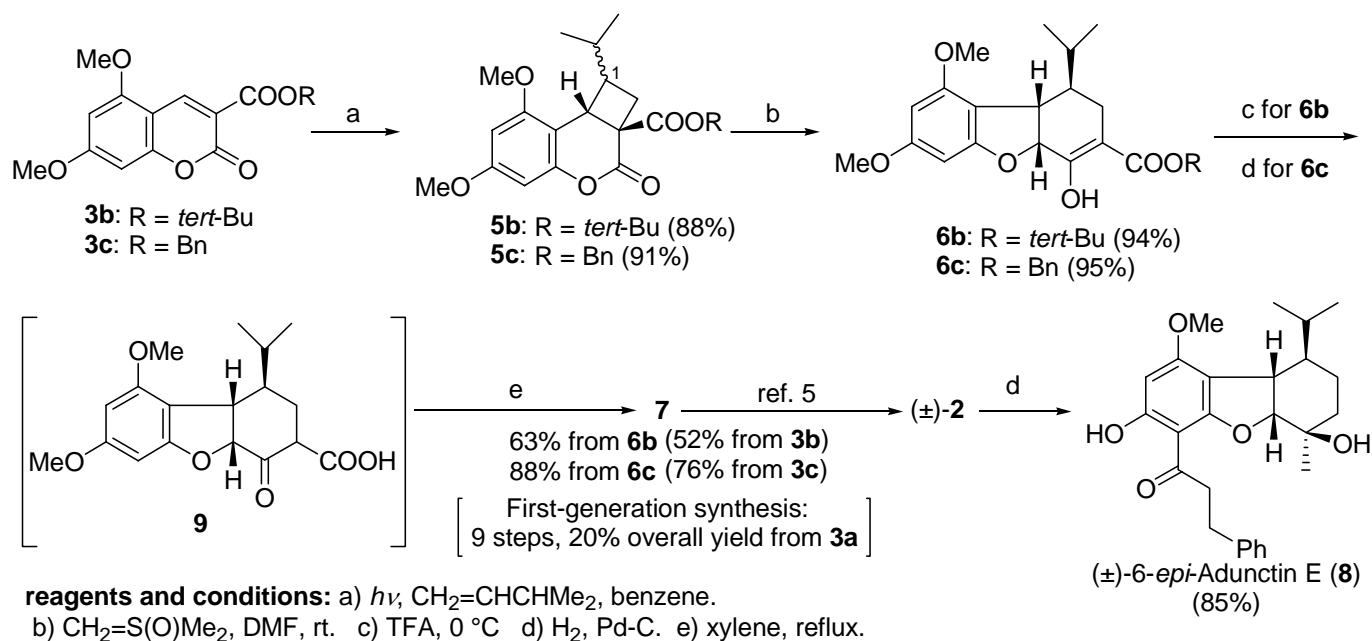
reagents and conditions: a; 1) PhSeCl, NaH. 2) NaIO₄. 3) *i*-PrMgBr, CuI. 4) AcOH, 100 °C. 5) N₂CHCO₂Et, BF₃·Et₂O.
b; 1) MOMCl, NaH. 2) NaOH-H₂O. 3) *c*-HCl. 4) xylene, reflux

Scheme 1. Synthetic Route to **7**, a Key Intermediate in Total Synthesis of (\pm)-Linderol A (**2**).

In the first-generation synthesis of **2**, decarboethoxylation at the 7-position⁶ of **6a** to benzofuranone (**7**) was not so easy because of the stable enol structure, and it took four steps.^{5,7} In this paper, we describe an efficient synthesis of (\pm)-linderol A (**2**) and the first synthesis of (\pm)-6-*epi*-adunctin E (**8**) by overcoming these problems.

RESULTS AND DISCUSSION

In the previous decarboxylation, reflux of **6a** in AcOH in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) gave **7** in only 27% yield and many spots appeared in TLC.⁵ This reaction condition for decarboxylation would be drastic, and next we considered decarboxylation of 7-*tert*-butyl ester (**6b**). 3-*tert*-Butoxycarbonyl-5,7-dimethoxycoumarin (**3b**), which was prepared in 91% yield from 4,6-dimethoxysalicylaldehyde⁸ and di-*tert*-butyl malonate by Knoevenagel condensation,⁹ was treated with 3-methyl-1-butene under irradiation by a high-pressure mercury lamp (400W) to give a cyclobutane derivative (**5b**) in 88% yield as a diastereomeric mixture (*exo/endo* = 5.6/1, estimated by ¹H-NMR spectrum).¹⁰ When the diastereomeric mixture of **5b** was treated with two equivalents of dimethylsulfoxonium methylide, this transformation reaction proceeded stereoconvergently to give a dibenzofuran derivative (**6b**) as a single isomer in 94% yield regardless of the stereochemistry at the 1-position on **5b**.⁴ Although the benzofuran (**6b**) in toluene was stirred at room temperature in the presence of a catalytic amount of *p*-TsOH to result in no change of **6b**, the solution was refluxed to give the desired dibenzofuranone (**7**) in fair yield (55%) from **6b**. When the benzofuran (**6b**) in TFA-CH₂Cl₂ was stirred for 1 h at 0 °C to give a carboxylic acid (**9**) and a solution of the crude **9** in xylene was refluxed, the dibenzofuranone (**7**) was obtained in 63% yield from **6b** (Scheme 2). Though the reaction steps decreased to two steps from four steps as shown in Scheme 1, the overall yield was almost the same as that of the previous synthesis of **7**.⁵



Scheme 2

We planned the decarboxylation *via* debenzoylation by hydrogenolysis. 3-Benzyloxycarbonyl-5,7-dimethoxycoumarin (**3c**), which was prepared in 93% yield from 4,6-dimethoxysalicylaldehyde and dibenzyl malonate by Knoevenagel condensation, was subjected to

photochemical [2+2] cycloaddition with 3-methyl-1-butene to give a cyclobutane derivative (**5c**) in 91% yield as a diastereomeric mixture (*exo/endo* = 6.0/1, estimated by ¹H-NMR spectrum). The cyclobutane (**5c**) was treated with dimethylsulfoxonium methylide to give a dibenzofuran derivative (**6c**) as a single isomer in 95% yield. The benzofuran (**6c**) was hydrogenolyzed over 10% Pd-C in AcOEt, and the xylene solution of the crude carboxylic acid (**9**) was refluxed to give **7** in 69% yield from **6c**. The debenzoylation of **6c** in xylene in the presence of Pd-C at room temperature followed by reflux without filtration gave **7** in 88% yield (Scheme 2). As a result, the synthesis of **7** from **3** was much improved to three steps in 76% overall yield from nine steps in 20% overall yield of the first-generation synthesis. Dibenzofuranone (**7**) was derived to (±)-linderol A (**2**) according to the first-generation synthesis. In consequence, the reaction steps to (±)-**2** decreased to twelve steps from nineteen steps, and the total yield of (±)-**2** was increased to 25% from 6.6% (Table 1).

Table 1. Comparison of the reaction steps and overall yields of total synthesis of (±)-**2**

Total synthesis of (±)- 2	Reaction steps	Overall yield (%)
First-generation ⁷	19 steps from 3a	6.6% from 3a
Second-generation ⁵	15 steps from 3a	17% from 3a
Present synthesis	13 steps from 3b	17% from 3b
	12 steps from 3c	25% from 3c

Sticher *et al.* determined the stereochemistry at the 6-position of **1** on the basis of the NOE experiment, namely, as NOE between 5a-H and 6-Me was observed, 5a-H and 6-Me were *cis*.¹ In our previous report, we prepared epimers (**10** and **11**).⁵ As shown in Figure 2, NOE between 5a-H and 6-Me in both **10** and **11** were observed.¹¹ Therefore, we would like to confirm the stereochemistry at the 6-position of **1**, and planned the preparation of (±)-6-*epi*-adunclin E (**8**) and comparison of the spectral data of (+)-**1** with those of (±)-**8**.

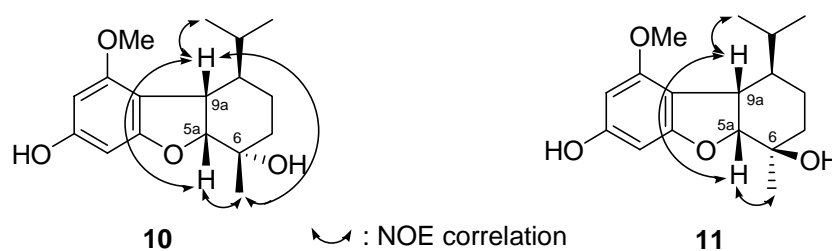


Figure 2. NOE correlations of epimers (**10** and **11**)

In order to prepare **8**, (\pm)-**2** was hydrogenated over 10% Pd-C in AcOEt to give (\pm)-**8** in 85% yield. ^1H - and ^{13}C -NMR spectra of the obtained **8** were compared with those of the reported **1** as shown in Figures 3 and 4. Due to distinction of the stereochemistry at the 6-position, the underlined chemical shifts around the 6-position differed somewhat in the ^1H - and ^{13}C -NMR spectra of **1** and **8**, whereas those far from the 6-position were very close.

Figure 3. Comparison of Chemical Shifts in ^1H -NMR Spectrum of (\pm)-**8** with Those of (+)-**1**.

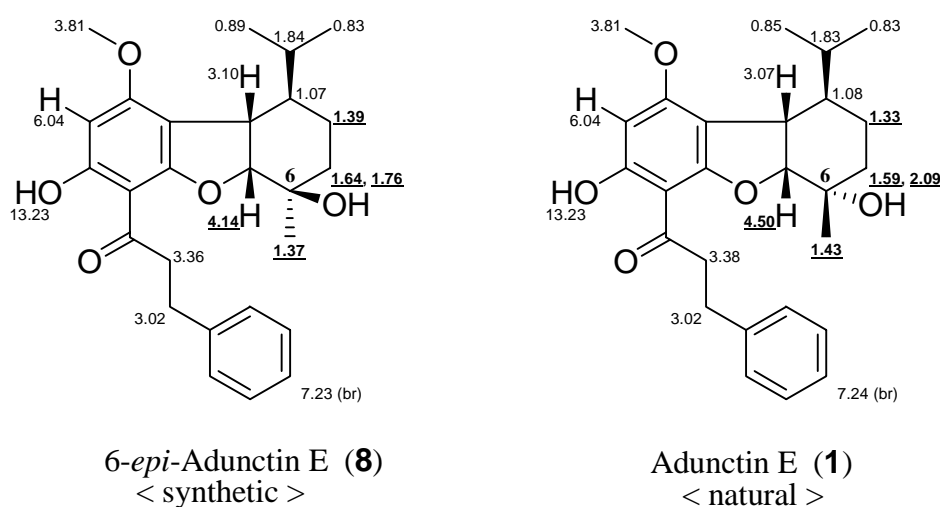
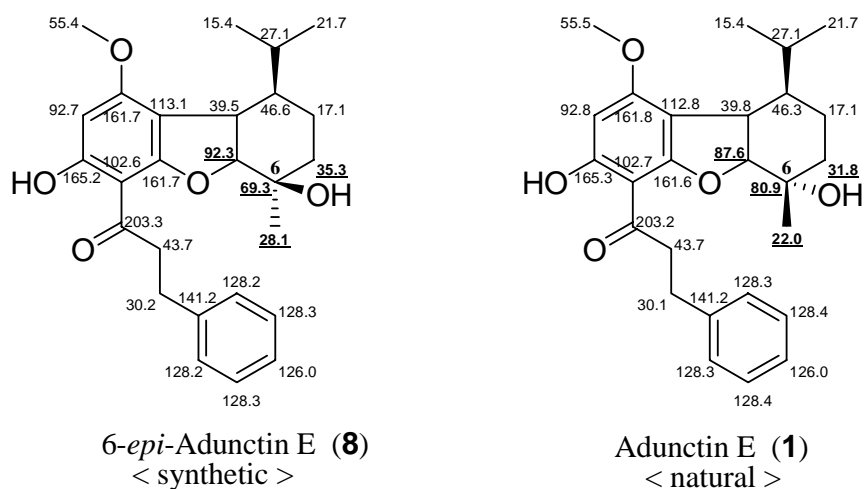


Figure 4. Comparison of Chemical Shifts in ^{13}C -NMR of (\pm)-**8** with Those of (+)-**1**.



CONCLUSION

An efficient synthesis of a dibenzofuranone (**7**), a key intermediate of the total synthesis of (\pm)-linderol A (**2**), was performed by using a novel stereoconvergent transformation from a cyclobutane (**5**) to a

dibenzofuran (**6**) followed by decarboxylation. Therefore, the reaction steps were decreased to three steps from nine steps of the first-generation total synthesis of (\pm)-**2**. Furthermore, prepared (\pm)-**2** was hydrogenated to achieve the first synthesis of (\pm)-6-*epi*-adunctin E (**8**).

EXPERIMENTAL

Melting points were measured with a Yanaco MP micro-melting point apparatus and are uncorrected. NMR spectra were measured on a JEOL AL-300 (^1H ; 300 MHz, ^{13}C ; 75.5 MHz) and a Varian INOVA 400NB (^1H ; 400 MHz, ^{13}C ; 100 MHz) with tetramethylsilane as an internal standard and chemical shifts are reported in ppm. IR spectra were taken with a Shimadzu IR-435 spectrophotometer. A JEOL JMS-GC mate spectrometer was used for low-resolution electron ionization MS (MS) and high-resolution electron ionization MS (HRMS). Elemental analysis was performed with a PERKIN ELMER Series II CHNS/O Analyzer 2400. UV spectrum was recorded on a Shimadzu UV-240 spectrophotometer. All extracts were washed with water and brine, dried over anhydrous MgSO_4 , and evaporated under reduced pressure in the usual work-up procedure. Silica gel 60 (grade 7734, 60 – 230 mesh, Merck) was used for column chromatography.

3-*tert*-Butoxycarbonyl-5,7-dimethoxycoumarin (3b): A solution of 4,6-dimethoxysalicylaldehyde (5.46 g, 30.0 mmol), di-*tert*-butyl malonate (9.72 g, 10.1 mL, 45.0 mmol), piperidine (511 mg, 0.59 mL, 6.00 mmol), and AcOH (5 drops) in benzene (20 mL) was refluxed for 6 h under N_2 atmosphere and during that time, the generated water was removed with a Dean-Stark trap. The resultant precipitates were collected by filtration, and recrystallized from benzene-*n*-hexane to give **3b** (8.34 g, 91%). Pale yellow needles. mp 152.1-153.9 °C. ^1H -NMR (300 MHz, CDCl_3) δ : 1.59 (9H, s), 3.88 (3H, s), 3.92 (3H, s), 6.27 (1H, d, $J = 2.0$ Hz), 6.40 (1H, d, $J = 2.0$ Hz), 8.70 (1H, s). ^{13}C -NMR (75.5 MHz, CDCl_3) δ : 28.1, 55.9, 56.0, 81.9, 92.5, 94.8, 103.4, 113.0, 143.4, 157.4, 158.1, 158.2, 162.4, 166.0. IR (CHCl_3): 1746, 1690, 1599 cm^{-1} . MS m/z (relative intensity, %): 306 (M^+ , 10.3), 250 (54.4), 233 (22.8), 206 (61.7), 178 (39.4), 56 (100). HRMS Calcd for $\text{C}_{16}\text{H}_{18}\text{O}_6$: 306.1103. Found: 306.1112. *Anal.* Calcd for $\text{C}_{16}\text{H}_{18}\text{O}_6$: C, 62.74; H, 5.92. Found: C, 62.56; H, 5.78.

Diastereomeric mixture of *tert*-Butyl *rel*-(1*R*,2*aR*,8*S*)- and *rel*-(1*R*,2*aS*,8*R*)-1,8*b*-dihydro-6,8-dimethoxy-1-(1-methylethyl)-3-oxo-2*H*-benzo[*b*]cyclobuta[*d*]pyran-2*a*(3*H*)-carboxylate (5b): A solution of **3b** (3.06 g, 10.0 mmol) and 3-methyl-1-butene (25.0 g, 357 mmol) in benzene (120 mL) was added in a photochemical reactor vessel with a 400-W high-pressure mercury lamp in a water-cooled quartz immersion well. The stirred solution was irradiated for 24 h. After evaporation of the volatile materials, the residue was purified with silica gel column chromatography ($\text{AcOEt} / n\text{-hexane} = 1 / 5$) to

give diastereomeric mixture (*exo* / *endo* = 5.6 / 1, determined by $^1\text{H-NMR}$ spectrum) of **5b** (3.32g, 88%). Recrystallization from AcOEt - *n*-hexane afforded pure *exo*-**5b**. **exo-5b**; Colorless plates (from AcOEt-*n*-hexane). mp 100.0 - 103.8 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.85 (3H, d, $J = 6.0$ Hz), 0.86 (3H, d, $J = 5.9$ Hz), 1.36 (9H, s), 1.65-1.75 (1H, m), 1.95 - 2.08 (1H, m), 2.49 (1H, ddd, $J = 11.5, 8.2, 0.5$ Hz), 2.54 (1H, dd, $J = 11.5, 10.4$ Hz), 3.60 (1H, d, $J = 8.8$ Hz), 3.79 (3H, s), 3.80 (3H, s), 6.23 (1H, d, $J = 2.2$ Hz), 6.24 (1H, d, $J = 2.4$ Hz). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 18.7, 19.2, 27.6, 32.3, 32.5, 40.1, 48.0, 48.2, 55.3, 55.4, 82.4, 93.8, 94.7, 103.9, 152.9, 157.0, 160.3, 168.0, 168.4. IR (CHCl_3): 1749, 1723, 1623, 1590 cm^{-1} . MS m/z (relative intensity, %): 376 (M^+ , 0.8), 306 (33.1), 250 (100), 206 (50.2). HRMS Calcd for $\text{C}_{21}\text{H}_{28}\text{O}_6$: 376.1886. Found: 376.1882 (M^+). Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{O}_6$: C, 67.00; H, 7.50. Found: C, 66.72; H, 7.39.

tert-Butyl *rel*-(1R,4aR,9bS)-1,2,4a,9b-tetrahydro-4-hydroxy-7,9-dimethoxy-1-(1-methylethyl)-3-dibenzofurancarboxylate (6b): To a suspension of trimethylsulfoxonium iodide (2.60 g, 11.8 mmol) in DMF (10 mL), NaH (60% in oil, 472 mg, 11.8 mmol) was added by portions under ice-cooling and the whole was stirred for 30 min at rt under N_2 atmosphere. A solution of **5b** (2.22 g, 5.90 mmol) in DMF (10 mL) was added dropwise to the reaction mixture, and the whole was stirred for additional 24 h. After acidification with 10% HCl under ice-cooling, the mixture was extracted with AcOEt. The combined extracts were washed, dried, and concentrated. The residue was purified with silica gel column chromatography (AcOEt / *n*-hexane = 1 / 10) to give **6b** (2.16g, 94%). Colorless plates (from AcOEt-*n*-hexane). mp 152.5 - 156.6 °C. $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ : 0.94 (6H, d, $J = 6.6$ Hz), 1.52 (9H, s), 1.68 (1H, tt, $J = 9.5, 4.1$ Hz), 1.80 (1H, septet,d, $J = 6.8, 4.8$ Hz), 2.02 (1H, dd, $J = 16.1, 9.3$ Hz), 2.25 (1H, dd, $J = 16.3, 4.0$ Hz), 3.40 (1H, dd, $J = 9.3, 7.7$ Hz), 3.76 (3H, s), 3.77 (3H, s), 4.95 (1H, d, $J = 7.6$ Hz), 6.04 (1H, d, $J = 2.0$ Hz), 6.14 (1H, d, $J = 1.8$ Hz), 12.11 (1H, s). $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ : 17.2, 21.2, 21.8, 27.2, 28.1, 42.1, 42.7, 55.1, 55.5, 81.3, 81.8, 89.1, 91.5, 102.6, 109.3, 157.3, 161.0, 161.6, 163.4, 171.7. IR (CHCl_3): 1655, 1618, 1595 cm^{-1} . MS m/z (relative intensity, %): 390 (M^+ , 9.0), 290 (20.8), 220 (31.8), 178 (100), 154 (84.2). HRMS Calcd for $\text{C}_{22}\text{H}_{30}\text{O}_6$: 390.2042. Found: 390.2052 (M^+). Anal. Calcd for $\text{C}_{22}\text{H}_{30}\text{O}_6$: C, 67.67; H, 7.74. Found: C, 67.39; H, 7.56.

3-Benzoyloxycarbonyl-5,7-dimethoxycoumarin (3c): A solution of 4,6-dimethoxysalicylaldehyde (1.82 g, 10.0 mmol), dibenzyl malonate (3.13 g, 2.75 mL, 11.0 mmol), piperidine (170 mg, 0.2 mL, 2.00 mmol), and AcOH (3 drops) in benzene (10 mL) was refluxed for 7 h under N_2 atmosphere, and during that time, the generated water was removed with a Dean-Stark trap. The resultant precipitates were collected by filtration, and recrystallized from benzene to give **3c** (3.16 g, 93%). Pale yellow needles. mp 132.9 - 133.5 °C. $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ : 3.87 (3H, s), 3.90 (3H, s), 5.37 (2H, s), 6.25 (1H,

d, $J = 2.0$ Hz), 6.39 (1H, d, $J = 2.0$ Hz), 7.29 - 7.41 (3H, m), 7.46 - 7.50 (2H, m), 8.82 (1H, s). ^{13}C -NMR (75.5 MHz, CDCl_3) δ : 56.0, 56.1, 66.9, 92.6, 95.0, 103.6, 111.3, 113.4, 128.16, 128.19, 128.5, 135.9, 144.8, 157.3, 158.4, 163.4, 166.4. IR (CHCl_3): 1749, 1698, 1614, 1561 cm^{-1} . MS m/z (relative intensity, %): 340 (M^+ , 12.7), 233 (29.3), 206 (82.4), 178 (31.5), 149 (17.4), 91 (100). HRMS calcd for $\text{C}_{19}\text{H}_{16}\text{O}_6$: 340.0947. Found: 340.0941. Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{O}_6$: C, 67.05; H, 4.74. Found: C, 66.91; H, 4.78.

Diastereomeric mixture of Benzyl *rel*-(1*R*,2*aS*,8*S*)- and *rel*-(1*R*,2*aR*,8*R*)-1,8*b*-dihydro-6,8-dimethoxy-1-(1-methylethyl)-3-oxo-2*H*-benzo[*b*]cyclobuta[*d*]pyran-2*a*(3*H*)-carboxylate (5c): A solution of **3c** (1.02 g, 3.00 mmol) and 3-methyl-1-butene (4.50 g, 64.3 mmol) in benzene (20 mL) was added in a photochemical reactor vessel with a 400-W high-pressure mercury lamp in a water-cooled quartz immersion well. The stirred solution was irradiated for 24 h. After evaporation of the volatile materials, the residue was purified with silica gel column chromatography (AcOEt / *n*-hexane = 1 / 3) to give a diastereomeric mixture (*exo* / *endo* = 6.0 / 1, determined by ^1H -NMR spectrum) of **5c** (1.12 g, 91%). Recrystallization from AcOEt - *n*-hexane afforded pure *exo*-**5c**. *exo*-**5c**; Colorless powders. mp 79.4 - 80.5 °C. ^1H -NMR (300 MHz, CDCl_3) δ : 0.83 (3H, d, $J = 6.6$ Hz), 0.85 (3H, d, $J = 6.4$ Hz), 1.55 - 1.80 (1H, m), 2.00 - 2.15 (1H, m), 2.56 (1H dd, $J = 11.4, 8.3$ Hz), 2.61 (1H, dd, $J = 11.4, 10.6$ Hz), 3.66 (1H, d, $J = 9.0$ Hz), 3.77 (3H, s), 3.78 (3H, s), 5.10 (1H, d, $J = 12.8$ Hz), 5.14 (1H, d, $J = 12.7$ Hz), 6.22 (1H, d, $J = 2.4$ Hz), 6.25 (1H, d, $J = 2.2$ Hz), 7.10 - 7.20 (2H, m), 7.22 - 7.30 (3H, m). ^{13}C -NMR (75.5 MHz, CDCl_3) δ : 18.8, 19.1, 32.4, 33.0, 40.4, 47.5, 48.3, 55.4, 55.5, 67.0, 94.0, 95.0, 103.9, 127.1, 128.0, 128.4, 135.3, 153.1, 157.0, 160.5, 168.0, 168.8. IR (CHCl_3): 1750, 1624, 1590 cm^{-1} . MS m/z (relative intensity, %): 410 (M^+ , 0.6), 340 (21.8), 234 (54.8), 206 (100), 91 (70.1). HRMS calcd for $\text{C}_{24}\text{H}_{26}\text{O}_6$: 410.1729. Found: 410.1731. Anal. Calcd for $\text{C}_{24}\text{H}_{26}\text{O}_6$: C, 70.23; H, 6.38. Found: C, 70.12; H, 6.47.

Benzyl *rel*-(1*R*,4*aR*,9*bS*)-1,2,4*a*,9*b*-tetrahydro-4-hydroxy-7,9-dimethoxy-1-(1-methylethyl)-3-dibenzofurancarboxylate (6c): To a suspension of trimethylsulfoxonium iodide (1.32 g, 6.00 mmol) in DMF (10 mL), NaH (60% in oil, 240 mg, 6.00 mmol) was added by portions under ice-cooling and the whole was stirred for 30 min at rt under N_2 atmosphere. A solution of **5c** (1.23 g, 3.00 mmol) in DMF (5 mL) was added dropwise to the reaction mixture, and the whole was stirred for additional 24 h. After acidification with 10% HCl under ice-cooling, the mixture was extracted with AcOEt. The combined organic extracts were washed, dried, and concentrated. The residue was purified with silica gel column chromatography (AcOEt / *n*-hexane = 1 / 5) to give **6c** (1.21 g, 95%). Colorless needles (AcOEt-*n*-hexane). mp 128.3 - 129.5 °C. ^1H -NMR (400 MHz, CDCl_3) δ : 0.93 (6H, d, $J = 6.6$ Hz),

1.70 (1H, tt, $J = 9.5, 4.1$ Hz), 1.80 (1H, septet,d, $J = 6.8, 4.8$ Hz), 2.10 (1H, dd, $J = 16.1, 9.3$ Hz), 2.35 (1H, dd, $J = 16.2, 3.9$ Hz), 3.41 (1H, dd, $J = 9.4, 7.6$ Hz), 3.75 (3H, s), 3.76 (3H, s), 4.96 (1H, d, $J = 7.7$ Hz), 5.21 (1H, d, $J = 12.5$ Hz), 5.27 (1H, d, $J = 12.5$ Hz), 6.04 (1H, d, $J = 2.0$ Hz), 6.14 (1H, d, $J = 2.0$ Hz), 7.31 - 7.41 (5H m), 11.92 (1H, s). ^{13}C -NMR (100 MHz, CDCl_3) δ : 17.2, 20.9, 21.8, 27.2, 42.1, 42.7, 55.1, 55.5, 66.4, 81.0, 89.1, 91.6, 101.3, 109.1, 128.0, 128.3, 128.6, 135.6, 157.3, 160.9, 161.7, 164.6, 171.8. IR (CHCl_3): 1660, 1620, 1595 cm^{-1} . MS m/z (relative intensity, %): 424 (M^+ , 8.8), 178 (26.2), 154 (63.0), 91 (100). HRMS calcd for $\text{C}_{25}\text{H}_{28}\text{O}_6$: 424.1886. Found: 424.1889. Anal. Calcd for $\text{C}_{25}\text{H}_{28}\text{O}_6$: C, 70.74; H, 6.65. Found; C, 70.85; H, 6.78.

***rel*-(1*R*,4*aR*,9*bS*)-2,3,4*a*,9*b*-Tetrahydro-7,9-dimethoxy-1-(1-methylethyl)-4(1*H*)-dibenzofuranone**

(7): (a) **From 6b with *p*-TsOH.** A solution of **6b** (141 mg, 0.362 mmol) and a catalytic amount of *p*-TsOH in toluene (1 mL) was refluxed for 1 h under N_2 atmosphere. After addition of saturated NaHCO_3 solution, the mixture was extracted with AcOEt. The combined extracts were washed, dried, and concentrated. The residue was purified with silica gel column chromatography (AcOEt / *n*-hexane = 1 / 5) to give **7** (58 mg, 55%).⁵

(b) **From 6b with TFA.** A solution of **6b** (390 mg, 1.00 mmol) in TFA (1 mL) and CH_2Cl_2 (1 mL) was stirred for 1 h at 0 °C under N_2 atmosphere. Evaporation of the volatile materials gave a crude carboxylic acid (**9**). A solution of the crude **9** in xylene (1mL) was refluxed for 30 min. Work-up the same as the above-mentioned method afforded **7** (183mg, 63%).

(c) **Two-steps synthesis from 6c.** A solution of **6c** (106 mg, 0.25 mmol) in AcOEt (1 mL) was hydrogenolized over 10% Pd-C (20 mg) under H_2 atmosphere for 30 min. After filtration of the Pd-C, the filtrate was evaporated to give crude **9**. ***rel*-(1*R*,4*aR*,9*bS*)-2,3,4*a*,9*b*-Tetrahydro-7,9-dimethoxy-1-(1-methylethyl)-4(1*H*)-oxo-3-dibenzofurancarboxylic Acid (9)** ^1H -NMR (400 MHz, CDCl_3) δ : 0.96 (6H, d, $J = 7.7$ Hz), 1.62 - 1.93 (3H, m), 2.12 (1H, dd, $J = 16.0, 9.4$ Hz), 2.37 (1H, dd, $J = 16.1, 3.8$ Hz), 3.44 (1H, dd, $J = 9.5, 7.7$ Hz), 3.77 (3H, s), 3.78 (3H, s), 4.98 (1H, d, $J = 7.7$ Hz), 6.05 (1H, d, $J = 2.0$ Hz), 6.15 (1H, d, $J = 1.8$ Hz), 11.6 (1H, br s). A solution of crude **9** in xylene (3 mL) was refluxed for 30 min. After evaporation of the volatile materials, the residue was purified with silica gel column chromatography (AcOEt / *n*-hexane = 1 / 5) to give **7** (50 mg, 69%) from **6c**.

(d) **One-pot synthesis from 6c.** A solution of **6c** (424 mg, 1.00 mmol) in xylene (3 mL) was hydrogenolized over 10% Pd-C (40 mg) under H_2 atmosphere for 30 min, and then refluxed for 30 min. After filtration of the Pd-C, the filtrate was evaporated. Work-up the same as the above-mentioned method afforded **7** (254 mg, 88%).

rel-1-[(5aR,6R,9R,9aS)-5a,6,7,8,9,9a-Hexahydro-3,6-dihydroxy-1-methoxy-6-methyl-9-(1-methyl-ethyl)-4-dibenzofuranyl]-3-phenyl-1-propanone [(±)-6-*epi*-Adunctin E] [(±)-8]: A solution of (±)-2 (27 mg, 0.064 mmol) in AcOEt (1 mL) was hydrogenated over 10% Pd-C (14 mg) under H₂ atmosphere for 1 h at rt. After filtration of the Pd-C, the filtrate was concentrated, and the residue was purified with silica gel column chromatography (AcOEt / *n*-hexane = 1 / 3) to give (±)-8 (23 mg, 85 %). Colorless powder (from AcOEt-*n*-hexane). mp 142.2 - 144.1 °C. ¹H-NMR (400 MHz, CDCl₃) δ: 0.83 (3H, d, *J* = 7.0 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 1.07 (1H, tt, *J* = 3.5, 11.3 Hz), 1.31 - 1.48 (3H, m), 1.37 (3H, s), 1.64 (1H, dt, *J* = 4.4, 13.2 Hz), 1.72 - 1.79 (1H, m), 1.84 (1H, septet, *J* = 2.7, 7.0 Hz), 3.02 (2H, t, *J* = 7.7 Hz), 3.10 (1H, dd, *J* = 11.2, 5.5 Hz), 3.27 - 3.44 (2H, m), 3.81 (3H, s), 4.14 (1H, dd, *J* = 5.4, 1.6 Hz), 6.04 (1H, s), 7.15 - 7.30 (5H, m), 13.23 (1H, s). ¹³C-NMR (100 MHz, CDCl₃) δ: 15.4, 17.1, 21.7, 27.1, 28.1, 30.2, 35.3, 39.5, 43.7, 46.6, 55.4, 69.3, 92.3, 92.7, 102.6, 113.1, 126.0, 128.2, 128.3, 141.2, 161.7, 165.2, 203.3. IR (KBr): 3440, 1630, 1599 cm⁻¹. UV (MeOH): 340, 283, 230 nm. MS *m/z* (relative intensity, %): 424 (M⁺, 46.6), 339 (100), 297 (14.4), 207 (32.6), 191 (19.7), 105 (26.6), 91 (43.9). HRMS Calcd for C₂₆H₃₂O₅: 424.2250. Found: 424.2241. *Anal.* Calcd for C₂₆H₃₂O₅: C, 73.56; H, 7.60. Found: C, 73.16; H, 7.61.

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6. Numbering according to that of linderol A (**2**) is used in a text.
7. Decarboxylation of **6a** under acidic condition afforded a complex mixture or low yield of **7**. Attempts for alkaline hydrolysis of **6a** resulted in almost complete recovery of **6a**. The enolate anion generated first from the enol-ester (**6a**) would prevent approach of the hydroxy anion to the ester carbonyl group. Therefore, alkaline hydrolysis of the ethoxycarbonyl group in **6a** was carried out after protection of the enol group.
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11. X-Ray crystallography of **11** analogue (**A**) was performed. The dihedral angle of (5a-H)-5a-6-(6-O) was -48 degrees, and that of (5a-H)-5a-6-(6-C) was 71 degrees. Crystallographic data (excluding structure factors) of **A** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 260501. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

