Total Syntheses of Didemnenones C and D

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Total syntheses of the title compounds were achieved from the optically active (+)-Corey lactone alcohol (5).

Keywords didemnenone C; didemnenone D; chiral total synthesis; marine natural product; (+)-Corey lactone alcohol

Didemnenones C (**1**) and D (**2**) were isolated from the didemnid tunicate *Didemnum voeltzkowi* collected in Fiji and exhibited cytotoxicity to an L1210 murine leukemia cell line.[1] Similar C_{11} cyclopentenone metabolites, didemnenones A (**3**) and B (**4**), were isolated and their structures were determined along with those of didemnenones C (**1**) and D (**2**) as shown in Chart 1.

Didemnenones A (**3**) and B (**4**) have already been synthesized by us[2] and others.[3] We report here the total syntheses of didemnenones C (**1**) and D (**2**).

Results and Discussion

We have reported the efficient synthesis of both enantiomers, (+)-**5** and (−)-**6**, of Corey lactone alcohol derivatives from (±)-Corey lactone alcohol using lipases.[4] The (−)-Corey lactone alcohol (**6**) was converted to the (+)-diene lactone (**8**) *via* the allylic alcohol (**7**). The (+)-diene lactone (**8**) was transformed into didemnenones A (**3**) and B (**4**) by us.[2]

From the similarity of structures of didemnenones, it was envisioned that **1** and **2** could be synthesized by transformation of the (−)-diene lactone (**10**) which would be derived from the (+)-Corey lactone alcohol (**5**) (Chart 2). Accordingly, our synthesis of **1** and **2** started with the conversion of (+)-**5** to the allylic alcohol (**9**) by a three-step sequence[5] in 92% overall yield. The alcohol (**5**) was converted to the (−)-diene lactone (**10**) {$[\alpha]_D$ −204.0° (c=0.614, $CHCl_3$)} by the same procedure as previously described[2] for the preparation of the opposite enantiomer {$[\alpha]_D$ +205.3° (c=0.99, $CHCl_3$)} of **10** as outlined in Chart 3.

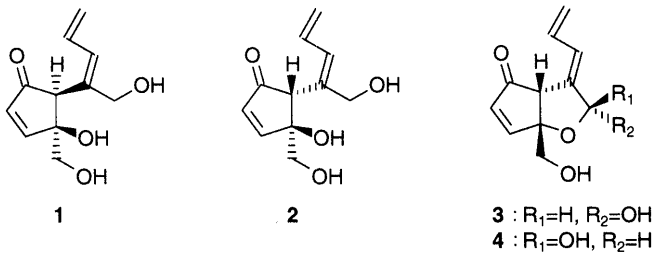

Chart 1

Compound **10** was reduced with diisobutylaluminum hydride (DIBAL) in toluene at 0 °C for 3 h to afford the diol (**15**) in 84% yield (Chart 4). Selective protection of the primary alcohol in **15** was achieved by treatment with triphenylmethyl chloride at room temperature to give **16** in 83% yield. Deprotection of the *tert*-butyldimethylsilyl-ether (TBDMS) of **16** with tetra-*n*-butylammonium fluoride followed by oxidation with pyridinium dichromate (PDC) in CH_2Cl_2 at room temperature afforded the α,β-unsaturated ketone (**18**) in 95% overall yield (2 steps).

Removal of the 4-methoxyphenyl protecting group in **18** with ammonium cerium(IV) nitrate (CAN)[6] in CH_3CN–H_2O at 0 °C gave didemnenone C (**1**) directly in 21% yield along with the diol (**20**) in 54% yield. Deprotection of the triphenylmethyl (Tr) protecting group of **20** with diethylaluminum chloride (Et_2AlCl)[7] in CH_2Cl_2 at −30 °C gave **1**, $[\alpha]_D^{24}$ −88.54° (c=0.238, MeOH), lit.,[1] $[\alpha]_D$ −25.3° (c=0.08, MeOH), in 71% yield.

Next, we examined the deprotonation and the isom-

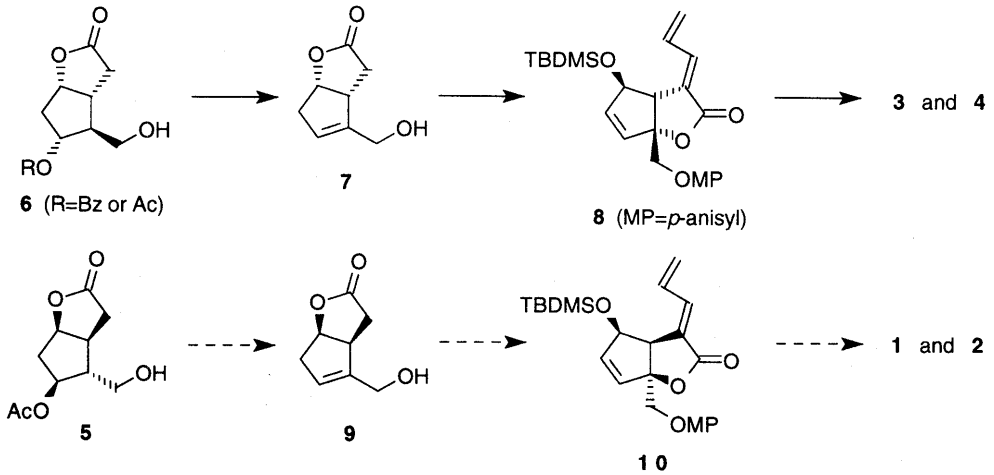

Chart 2

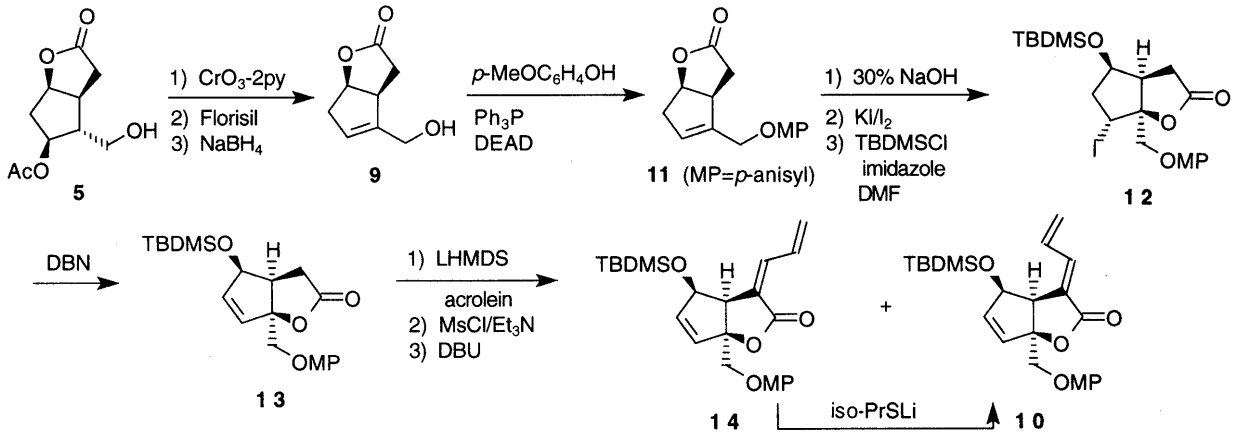

Chart 3

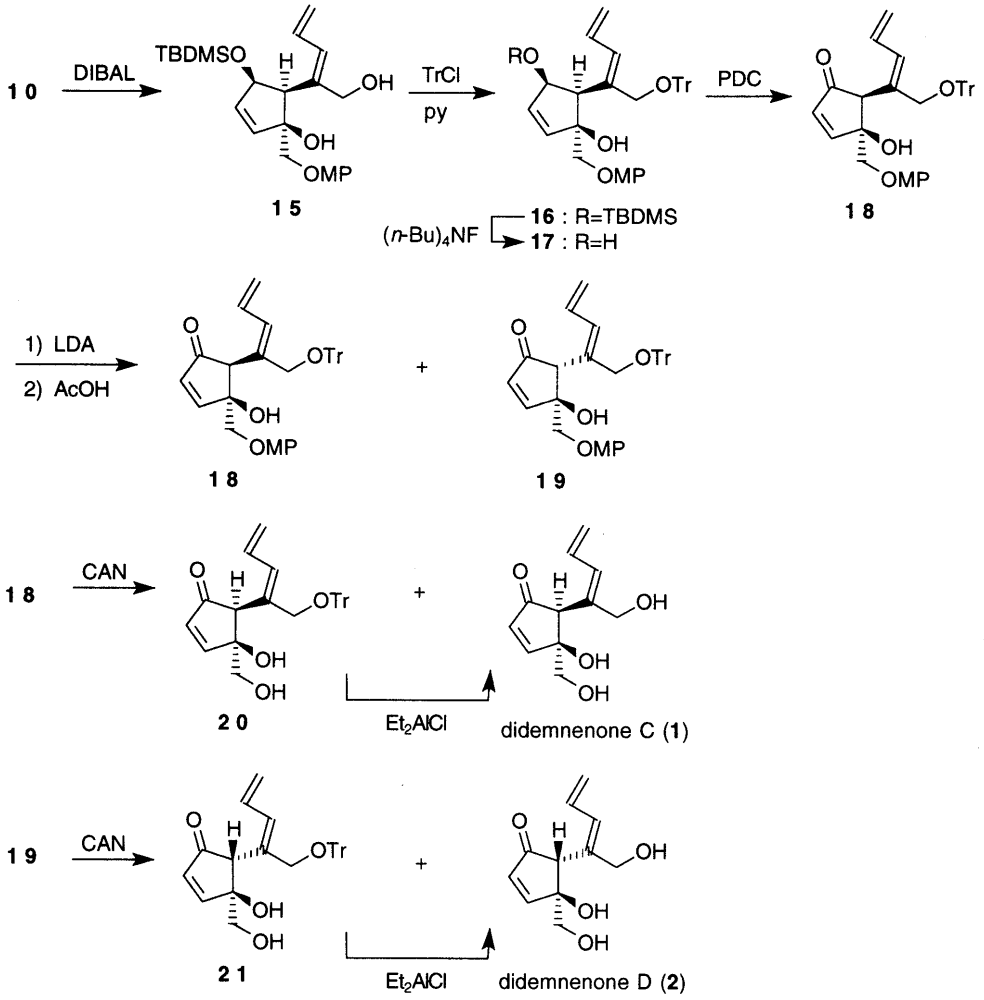

Chart 4

erization of the side chain containing the diene function in **18** under a variety of basic conditions for the synthesis of **2**. When **18** was treated with lithium diisopropylamide (LDA) in THF at $-78\,^{\circ}C$ for 40 min and quenched with acetic acid, an easily separable mixture of **18** and **19** was obtained in a ratio of 1:2 in 97% yield. Treatment of **19** according to the same procedure (CAN, CH_3CN–H_2O, at $0\,^{\circ}C$) afforded didemnenone D (**2**) directly in 11% yield along with the diol (**21**) in 31% yield. Finally, deprotection of the Tr group in **21** with Et_2AlCl gave didemnenone D (**2**), $[\alpha]_D^{26}$ -32.24° ($c=0.17$, MeOH), lit.,[1] $[\alpha]_D$ -12.6° ($c=0.15$, MeOH), in 65% yield. The ^{1}H-NMR spectra of synthetic didemnenones C and D were identical with those of the natural didemnenones C and D.

In conclusion, we have achieved the first total syntheses

of didemnenone C and D from the (+)-Corey lactone alcohol (**5**). Thus, we developed synthetic methods leading to didemnenones A—D from both enantiomers of the Corey lactone alcohol.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus without correction. The IR spectra were recorded with a JASCO IR-700 spectrometer. The ^{1}H-NMR spectra were recorded with JEOL-FX90A (90 MHz) and Hitachi R-3000 (300 MHz) instruments. The chemical shifts are given as δ (ppm) values from tetramethylsilane (TMS) as an internal standard. Optical rotations were recorded with a JASCO DIP-370 polarimeter. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained with a JEOL JMS-DX-303 mass spectrometer. The following abbreviations are used: br=broad, d=doublet, m=multiplet, q=quartet, s=singlet, t=triplet. Merck Silica gel 60 (70—230 mesh) was employed for column chromatography and 230—400 mesh for flash column chromatography. Anhydrous organic solvents were used in all anhydrous reactions under an Ar atmosphere. Extracts were dried over anhydrous $MgSO_4$.

(−)-(3a*S*,6a*R*)-3,3a,6,6a-Tetrahydro-4-(hydroxymethyl)-2*H*-cyclopenta[*b*]furan-2-one (9) Chromium trioxide dipyridine complex[8] (7.53 g, 29 mmol) and Celite 545 (7.5 g) were added to CH_2Cl_2 (98 ml). This mixture was stirred at 0 °C, and the alcohol (**5**) (622 mg, 2.9 mmol) in CH_2Cl_2 (5 ml) was added. The whole was stirred for 30 min at room temperature, then chromatographed on Florisil (100—200 mesh, 60 g) with AcOEt. The eluate was concentrated to afford the crude α,β-unsaturated aldehyde, which was used immediately in the next step. A solution of the above aldehyde in MeOH (40 ml) was treated portionwise with $NaBH_4$ (92 mg, 2.4 mmol) at 0 °C. After 5 min, the MeOH was evaporated off, water (2 ml) was added, and the whole was extracted with AcOEt. The extract was dried and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 1) to give **9** (412 mg, 92%) as a colorless solid, $[\alpha]_D^{28}$ −14.17° (c=1.098, $CHCl_3$). IR (Nujol) ν: 3444, 1743 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.55—2.8 (m, 5H), 3.55 (br s, 1H), 5.16 (m, 1H), 5.80 (s, 1H). MS *m/z* (%): 154 (M^+, 54), 136 (27), 125 (82), 95 (75), 79 (100). HRMS Calcd for $C_8H_{10}O_3$: 154.0630. Found: 154.0632.

(−)-(3a*S*,6a*R*)-3,3a,6,6a-Tetrahydro-4-[(4-methoxy)phenyloxymethyl]-2*H*-cyclopenta[*b*]furan-2-one (11) A solution of diethyl azodicarboxylate (945 mg, 5.4 mmol) in CH_2Cl_2 (1.8 ml) was added at room temperature to a solution of **9** (557 mg, 3.6 mmol), triphenylphosphine (1.42 g, 5.4 mmol) and *p*-methoxyphenol (471 mg, 3.8 mmol) in CH_2Cl_2 (18 ml). After 2.5 h, water was added, and the aqueous layer was extracted with CH_2Cl_2. The whole extract was washed with brine, dried, and evaporated. The residue was purified by flash column chromatography (*n*-hexane : AcOEt = 7 : 1) to give **11** (820 mg, 87%) as a colorless solid, mp 64—65 °C (AcOEt–*n*-hexane). IR (Nujol) ν: 1750 cm^{-1}. $[\alpha]_D^{26}$ −51.7° (c=1.002, $CHCl_3$). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.70 (m, 4H), 3.57 (m, 1H), 3.76 (s, 3H, OMe), 4.54 (s, 2H), 5.19 (m, 1H), 5.79 (s, 1H, –CH=), 6.82 (s, 4H). MS *m/z* (%): 260 (M^+). HRMS Calcd for $C_{15}H_{16}O_4$: 260.1049. Found: 260.1047. *Anal.* Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.07; H, 6.14.

(−)-(3a*R*,4*R*,6*R*,6a*R*)-3,3a,4,5,6,6a-Hexahydro-4-(*tert*-butyldimethylsilyloxy)-6-iodo-6a-[(4-methoxy)phenyloxymethyl]-2*H*-cyclopenta[*b*]furan-2-one (12) A 30% NaOH solution (1.22 ml, 15.5 mmol) was added at room temperature to a solution of **11** (815 mg, 3.1 mmol) in MeOH (12 ml) and the mixture was stirred for 13 h. After evaporation of MeOH, water was added and the water layer was washed with Et_2O. The cooled water layer was acidified to pH 3 with 5% HCl and the whole was extracted with CH_2Cl_2. The water layer was further extracted with CH_2Cl_2 and the combined CH_2Cl_2 layer was washed with brine, dried, then evaporated to give the hydroxy carboxylic acid, which was used in the next step. The hydroxy carboxylic acid was dissolved in water (6.27 ml) containing NaOH (250 mg, 6.2 mmol) at room temperature. The solution was neutralized to pH *ca.* 7 with CO_2 and treated with KI (5.62 g, 33.9 mmol) and I_2 (3 g, 11.9 mmol) in water (11 ml) at 0 °C. The mixture was stirred for 48 h at 0—5 °C and then CH_2Cl_2 was added followed by the addition of solid sodium sulfite to decolorize the solution. The aqueous layer was extracted with CH_2Cl_2 and the combined CH_2Cl_2 layer was washed with brine, dried, then evaporated to give the iodo-lactone, which was used in the next step. *tert*-Butyldimethylsilyl chloride (610 mg, 4 mM) and imidazole (633 mg, 9.3 mmol) were added to a solution of the iodo-lactone in DMF (2.2 ml) and the mixture was stirred at 35 °C for 13 h. Water was added, and the whole was extracted with Et_2O. The extract was washed with brine, dried, and then evaporated. The residue was purified by column chromatography (*n*-hexane : Et_2O = 19 : 1) to give **12** (1.44 g, 89%) as a white solid. IR (Nujol) ν: 1750 cm^{-1}. $[\alpha]_D^{28}$ −41.87° (c=0.51, $CHCl_3$). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.10 (s, 6H, Me×2), 0.93 (s, 9H, Me×3), 2.37 (m, 2H), 2.87 (m, 3H), 3.78 (s, 3H, OMe), 4.15 (s, 3H, –CH_2OAr), 4.43 (m, 2H), 6.87 (m, 4H). MS *m/z* (%): 518 (M^+, 43), 461 (29), 333 (33), 213 (25), 167 (20), 124 (100). HRMS Calcd for $C_{21}H_{31}IO_5Si$: 518.0986. Found: 518.0967.

(−)-(3a*R*,4*R*,6a*S*)-3,3a,4,6a-Tetrahydro-4-(*tert*-butyldimethylsilyloxy)-6a-[(4-methoxy)phenyloxymethyl]-2*H*-cyclopenta[*b*]furan-2-one (13) 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN, 0.37 ml, 2.94 mmol) was added to a solution of **12** (1.27 g, 2.45 mmol) in tetrahydrofuran (THF, 10 ml) and the resulting mixture was refluxed for 5 h. Water was added, and the whole was extracted with Et_2O. The extract was washed with brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 9 : 1) to give **13** (949 mg, 99%) as a white solid, mp 96—96.5 °C (Et_2O–pet. Et_2O). IR (Nujol) ν: 1774 cm^{-1}. $[\alpha]_D^{27}$ −44.86° (c=0.956, $CHCl_3$). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.01 (s, 6H, Me×2), 0.8 (s, 9H, Me×3), 2.3—3.25 (m, 3H), 3.67 (s, 3H, OMe), 3.84 (d, 1H, J=8.6 Hz), 4.05 (d, 1H, J=8.6 Hz), 4.8 (dd, 1H, J=2.7 Hz), 5.9 (m, 2H, olefinic protons), 6.73 (s, 4H). MS *m/z* (%): 390 (M^+, 53), 333 (43), 209 (54), 181 (80), 165 (68), 124 (100). HRMS Calcd for $C_{21}H_{30}O_5Si$: 390.1862. Found: 390.1847. *Anal.* Calcd for $C_{21}H_{30}O_5Si$: C, 64.58; H, 7.74. Found: C, 64.48; H, 7.96.

(−)-(3a*R*,4*R*,6a*S*)-3,3a,4,6-Tetrahydro-4-(*tert*-butyldimethylsilyloxy)-6a-[(4-methoxy)phenyloxymethyl]-3-(*Z*)-(2-propenylidene)-2*H*-cyclopenta[*b*]furan-2-one (14) and (−)-(3a*R*,4*R*,6a*S*)-3,3a,4,6-Tetrahydro-4-(*tert*-butyldimethylsilyloxy)-6a-[(4-methoxy)phenyloxymethyl]-3-(*E*)-(2-propenylidene)-2*H*-cyclopenta[*b*]furan-2-one (10) *n*-BuLi (1.56 M in hexane, 0.22 ml, 3.45 mmol) was added to a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.8 ml, 3.8 mmol) in THF (5.2 ml) at −78 °C and the mixture was stirred for 1 h. To this LHMDS solution, a solution of **13** (898 mg, 2.3 mmol) in THF (5 ml) was added at −78 °C, and the mixture was stirred for 1 h at this temperature. Acrolein (155 mg, 2.76 mmol) was added, and the resulting mixture was stirred at −78 °C. After 1 h, saturated NH_4Cl solution was added, and the whole was warmed to room temperature, then extracted with Et_2O. The extract was washed with brine, then dried, and evaporated. The crude adduct was used in the next step without further purification. Methanesulfonyl chloride (0.22 ml, 2.8 mmol) and triethylamine (0.7 ml, 5 mmol) were added to a solution of this adduct in CH_2Cl_2 (15 ml) at 0 °C, and the resulting mixture was stirred at room temperature for 13 h. After the addition of water, the whole was extracted with CH_2Cl_2. The extract was washed with brine, then dried, and evaporated. The residue was purified by flash column chromatography (*n*-hexane : Et_2O = 95 : 5) to give **14** (542 mg, 55%) and **10** (315 mg, 32%). Compound **14**: colorless solid. mp 121—122 °C (Et_2O–*n*-hexane). $[\alpha]_D^{25}$ −167.0° (c=0.992, $CHCl_3$). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.12 (s, 6H, Me×2), 0.9 (s, 9H, Me×3), 3.6 (m, 1H), 3.75 (s, 3H, OMe), 4.0 (d, 1H, J=10 Hz), 4.1 (d, 1H, J=10 Hz), 5.02 (dd, 1H, J=2, 7.5 Hz), 5.42 (m, 2H, CH_2=), 6.02 (dd, 2H, J=2.5 Hz), 6.71 (m, 1H), 6.82 (s, 4H), 7.7—7.95 (m, 1H). MS *m/z* (%): 428 (M^+, 24), 371 (20), 291 (18), 251 (8), 247 (10), 219 (25), 123 (48), 73 (100). HRMS Calcd for $C_{24}H_{32}O_5Si$: 428.2019. Found: 428.1983. *Anal.* Calcd for $C_{24}H_{32}O_5Si$: C, 67.26; H, 7.53. Found: C, 67.40; H, 7.56. Compound **10**: mp 102—103 °C (Et_2O–*n*-hexane). IR (Nujol) ν: 1740 cm^{-1}. $[\alpha]_D^{25}$ −204.0° (c=0.614, $CHCl_3$). ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.06 (s, 6H, Me×2), 0.8 (s, 9H, Me×3), 3.7 (s, 3H, OMe), 3.98, 4.02 (ABq, 2H, J=8 Hz), 5.0 (dd, 1H, J=2, 7.5 Hz), 5.6 (m, 2H, CH_2=), 6.04 (m, 2H), 6.4 (m, 1H), 6.75 (s, 4H), 7.2 (dd, 1H, J=2, 11 Hz). MS *m/z* (%): 428 (M^+, 30), 371 (18), 291 (28), 251 (22), 247 (18), 219 (29), 123 (52), 73 (100). HRMS Calcd for $C_{24}H_{32}O_5Si$: 428.2019. Found: 428.2027. *Anal.* Calcd for $C_{24}H_{32}O_5Si$: C, 67.36; H, 7.52. Found: C, 67.26; H, 7.53.

Isomerization of the (−)-(*Z*)-Diene Lactone (14) *n*-BuLi (1.56 M in hexane, 0.8 ml, 1.25 mmol) was added to a solution of iso-PrSH (0.116 ml, 1.25 mmol) in THF (3 ml) at room temperature. The resulting iso-PrSLi solution (0.39 ml, 0.12 mmol) was added to a solution of **14** (529 mg, 1.24 mmol) in THF (6.2 ml) at room temperature, and the whole was stirred for 48 h at this temperature. Water was added and the whole was extracted with Et_2O. The extract was washed with brine, then dried, and evaporated. The residue was purified by flash column chromatography

(*n*-hexane : Et_2O = 95 : 5) to give **14** (125 mg, 24%) and **10** (377 mg, 71%) with identical properties (IR, ^{1}H-NMR) to those of the compounds obtained from the lactone **13**.

(−)-(1*S*,4*R*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-[(1*E*)-1-(hydroxymethyl)-1,3-butadienyl]-1-[(4-methoxy)phenyloxymethyl]-2-cyclopenten-1-ol (15) DIBAL (1.5 M in toluene, 4.2 ml, 6.3 mmol) was added dropwise to a solution of **10** (540 mg, 1.26 mmol) in toluene (6.5 ml) at 0 °C and the mixture was stirred for 1.5 h, then further DIBAL (1.5 M in toluene, 2.52 ml, 3.78 mmol) was added dropwise at the same temperature and stirring was continued for 1.5 h. The reaction was quenched with MeOH (*ca.* 1 ml) and then water (6 ml). The suspension was vigorously stirred for 30 min and filtered through a Celite pad. The inorganic material was washed with CH_2Cl_2. The extract was washed with brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : Et_2O = 4 : 1) to give **15** (458 mg, 84%) as a colorless oil, $[\alpha]_D^{29}$ −178.4° (*c* = 1.328, $CHCl_3$). IR (neat) *v*: 3200—3400 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 0.06 (s, 3H, Me), 0.1 (s, 3H, Me), 0.88 (s, 9H, Me × 3), 3.77 (s, 3H, OMe), 3.85 (d, 1H, *J* = 8.8 Hz), 3.90 (d, 1H, *J* = 8.8 Hz), 4.06 (d, 1H, *J* = 7.0 Hz), 4.25 (d, 1H, *J* = 13.2 Hz), 4.38 (d, 1H, *J* = 13.2 Hz), 4.90 (d, 1H, *J* = 7.0 Hz), 5.14 (d, 1H, *J* = 10 Hz), 5.27 (d, 1H, *J* = 16.5 Hz), 5.95 (d, 1H, *J* = 5.8 Hz), 5.98 (d, 1H, *J* = 5.8 Hz), 6.23 (d, 1H, *J* = 11 Hz), 6.58—6.65 (m, 1H), 6.83 (br s, 4H). MS *m/z* (%): 432 (M^+, 12), 383 (26), 295 (15), 277 (23), 159 (86), 124 (100). HRMS Calcd for $C_{24}H_{36}O_5Si$: 432.2332. Found: 432.2326.

(−)-(1*S*,4*R*,5*S*)-4-(*tert*-Butyldimethylsilyloxy)-5-[(1*E*)-1-(triphenylmethyloxymethyl)-1,3-butadienyl]-1-[(4-methoxy)phenyloxymethyl]-2-cyclopenten-1-ol (16) Triphenylmethyl chloride (504 mg, 1.8 mmol) was added to a mixture of **15** (390 mg, 0.9 mmol), triethylamine (0.38 ml, 2.7 mmol), 4-dimethylaminopyridine (10 mg) and CH_2Cl_2 (5 ml), and the resulting mixture was stirred at room temperature for 13 h. Water was added, and the whole was extracted with CH_2Cl_2. The extract was washed with saturated $NaHCO_3$ solution and brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 95 : 5) to give **16** (508 mg, 83%) as a colorless oil, $[\alpha]_D^{30}$ −49.17° (*c* = 0.884, $CHCl_3$). IR (neat) *v*: 3300—3400 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: −0.11 (s, 3H), −0.18 (s, 3H), 0.66 (s, 9H), 3.67 (s, 2H), 3.73 (d, 1H, *J* = 8.8 Hz), 3.90 (d, 1H, *J* = 8.8 Hz), 4.00 (d, 1H, *J* = 7.0 Hz), 4.74 (d, 1H, *J* = 7.0 Hz), 5.02 (br s, 1H, OH), 5.24 (d, 1H, *J* = 9.2 Hz), 5.33 (d, 1H, *J* = 5.5 Hz), 5.36 (d, 1H, *J* = 15.4 Hz), 5.52 (dd, 1H, *J* = 1.8, 5.5 Hz), 6.42 (d, 1H, *J* = 11 Hz), 6.7—6.8 (m, 1H), 6.81 (s, 4H), 7.2—7.5 (m, 15H). MS *m/z* (%): 674 (M^+, 0.08), 243 (100), 165 (22). HRMS Calcd for $C_{43}H_{50}O_5Si$: 674.3428. Found: 674.3463.

(−)-(1*S*,4*R*,5*S*)-1-[(4-Methoxy)phenyloxymethyl]-5-[(1*E*)-1-(triphenylmethyloxymethyl)-1,3-butadienyl]-2-cyclopenten-1,4-diol (17) Tetrabutylammonium fluoride (1 M in THF, 1.03 ml, 1.03 mmol) was added to a solution of **16** (463 mg, 0.69 mmol) in THF (10 ml) at room temperature and the mixture was stirred for 1.5 h. Water was added and the whole was extracted with Et_2O. The extract was washed with brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 4 : 1) to give **17** (384 mg, 100%) as a colorless oil, $[\alpha]_D^{29}$ −113.2° (*c* = 0.806, $CHCl_3$). IR (neat) *v*: 3300—3400 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 3.64 (d, 1H, *J* = 8.8 Hz), 3.76 (s, 3H), 3.78 (d, 1H, *J* = 8.8 Hz), 3.79 (d, 1H, *J* = 10.6 Hz), 3.84 (d, 1H, *J* = 10.6 Hz), 3.98 (d, 1H, *J* = 6.8 Hz), 4.74 (dd, 1H, *J* = 6.8, 8.8 Hz), 5.25 (dd, 1H, *J* = 1.5, 10 Hz), 5.36 (dd, 1H, *J* = 1.5, 16.5 Hz), 5.55 (dd, 1H, *J* = 1.8, 5.9 Hz), 5.57 (dd, 1H, *J* = 1.8, 5.9 Hz), 6.37 (d, 1H, *J* = 11 Hz), 6.7—6.85 (m, 1H), 6.8 (s, 4H), 7.2—7.5 (m, 15H). MS *m/z* (%): 560 (M^+, 0.4), 243 (100), 165 (62), 124 (65). HRMS Calcd for $C_{37}H_{36}O_5$: 560.2549. Found: 560.2535.

(−)-(4*S*,5*R*)-4-(Hydroxy)-4-[(4-methoxy)phenyloxymethyl]-5-[(1*E*)-1-(triphenylmethyloxymethyl)-1,3-butadienyl]-2-cyclopentenone (18) A solution of **17** (347 mg, 0.62 mmol) and CH_2Cl_2 (4 ml) was added to a mixture of PDC (350 mg, 0.93 mmol) and CH_2Cl_2 (10 ml) at room temperature and the resulting mixture was stirred for 3 h. Insoluble materials were removed by filtration through a Celite pad which was washed with CH_2Cl_2. The filtrate and washing were combined and evaporated, and the residue was purified by column chromatography (*n*-hexane : AcOEt = 17 : 3) to give **18** (329 mg, 95%) as a colorless oil, $[\alpha]_D^{30}$ −49.43° (*c* = 1.174, $CHCl_3$). IR (neat) *v*: 3400, 1713 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 3.73 (d, 1H, *J* = 11 Hz), 3.80 (br s, 4H), 3.82 (d, 1H, *J* = 11 Hz), 4.06 (s, 2H), 5.18 (dd, 1H, *J* = 1.8, 9.3 Hz), 5.32 (dd, 1H, *J* = 1.4, 14.6 Hz), 6.2 (d, 1H, *J* = 5.5 Hz), 6.31 (d, 1H, *J* = 9.5 Hz), 6.3—6.5 (m, 1H), 6.81 (br s, 4H), 7.1—7.2 (m, 15H), 7.48 (d, 1H, *J* = 5.5 Hz). MS *m/z* (%): 558 (M^+, 0.4), 243 (100), 165 (47), 124 (23), 77 (12). HRMS Calcd for $C_{37}H_{34}O_5$: 558.240. Found: 558.2392.

Isomerization of 18 to (−)-(4*S*,5*S*)-4-(Hydroxy)-4-[(4-methoxy)phenyloxymethyl]-5-[(1*E*)-1-(triphenylmethyloxymethyl)-1,3-butadienyl]-2-cyclopentenone (19) *n*-BuLi (1.5 M in hexane, 0.72 ml, 1.12 mmol) was added to a solution of diisopropylamine (125 mg, 1.23 mmol) in THF (1.7 ml) at −78 °C and the mixture was stirred for 30 min. To the LDA solution, a solution of **18** (223 mg, 0.4 mmol) in THF (1.5 ml) was added at −78 °C, and the whole was stirred for 40 min at this temperature. AcOH (0.2 ml) was added, and the resulting mixture was warmed to room temperature. The mixture was neutralized with saturated $NaHCO_3$ solution and the whole was extracted with Et_2O. The extract was washed with brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 17 : 3) to give **18** (72 mg, 32%). *Rf* = 0.38 (*n*-hexane : AcOEt = 2 : 1) and **19** (145 mg, 65%). *Rf* = 0.29 (*n*-hexane : AcOEt = 2 : 1) as colorless oils. **19**: $[\alpha]_D^{30}$ −88.55° (*c* = 0.74, $CHCl_3$). IR (neat) *v*: 3400, 1712 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 3.55 (br s, 1H), 3.69 (br s, 2H), 3.76 (s, 3H), 4.02 (br s, 2H), 5.21 (d, 1H, *J* = 7.7 Hz), 5.30 (d, 1H, *J* = 15.8 Hz), 6.23 (d, 1H, *J* = 5.5 Hz), 6.46 (br s, 1H), 6.7—6.82 (m, 1H), 7.2—7.42 (m, 15H), 7.67 (d, 1H, *J* = 5.5 Hz). MS *m/z* (%): 558 (M^+, 0.4), 243 (100), 165 (33), 124 (8). HRMS Calcd for $C_{37}H_{34}O_5$: 558.240. Found: 558.2377.

(−)-(4*R*,5*R*)-4-(Hydroxy)-4-(hydroxymethyl)-5-[(1*E*)-1-(triphenylmethyloxymethyl)-1,3-butadienyl]-2-cyclopentenone (20) and didemnenone C (1) Ammonium cerium(IV) nitrate (315 mg, 0.58 mmol) was added portionwise at 0 °C to a solution of **18** (140 mg, 0.25 mmol) in CH_3CN (2 ml) and water (0.5 ml). The mixture was stirred for 6 min at 0 °C, and then saturated $NaHCO_3$ solution was added. The whole was extracted with AcOEt, and the extract was washed with brine, then dried, and evaporated. The residue was purified by column chromatography. The first eluate (*n*-hexane : AcOEt = 4 : 1) gave **21** (61 mg, 54%) as a colorless oil, $[\alpha]_D^{31}$ +78.49° (*c* = 0.498, $CHCl_3$). IR (Nujol) *v*: 3300—3400, 1712 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 3.6—3.8 (m, 7H), 5.31 (d, 1H, *J* = 11 Hz), 5.35 (d, 1H, *J* = 18 Hz), 6.10 (d, 1H, *J* = 5.5 Hz), 6.30 (d, 1H, *J* = 10.2 Hz), 6.5—6.7 (m, 1H), 7.2—7.35 (m, 15H), 7.48 (d, 1H, *J* = 5.5 Hz). MS *m/z* (%): 452 (M^+, 0.07), 243 (100), 165 (37), 105 (7.4). HRMS Calcd for $C_{30}H_{28}O_4$: 452.1985. Found: 452.2030. The second eluate (*n*-hexane : AcOEt = 2 : 3) gave **1** (11 mg, 21%) as an unstable white solid, $[\alpha]_D^{24}$ −88.54° (*c* = 0.238, MeOH) {lit.,[1] $[\alpha]_D$ −25.3° (*c* = 0.08, MeOH)}. IR (Nujol) *v*: 3200—3400, 1709 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 3.59 (d, 1H, *J* = 11 Hz), 3.69 (d, 1H, *J* = 11 Hz), 3.88 (s, 1H), 3.96 (d, 1H, *J* = 12.6 Hz), 4.24 (d, 1H, *J* = 12.6 Hz), 5.21 (d, 1H, *J* = 10.5 Hz), 5.31 (d, 1H, *J* = 16.5 Hz), 6.25 (d, 1H, *J* = 5.5 Hz), 6.39 (d, 1H, *J* = 11 Hz), 6.65 (ddd, 1H, *J* = 10.5, 11.0, 16.5 Hz), 7.51 (d, 1H, *J* = 5.5 Hz). MS *m/z* (%): 210 (M^+).

(−)-Didemnenone C (1) from 20 Et_2AlCl (1 M in hexane, 1.4 ml, 1.35 mmol) was added slowly at −30 °C to a stirred solution of **20** (61 mg, 0.135 mmol) in CH_2Cl_2 (5 ml) and the mixture was stirred for 10 min. Saturated $NaHCO_3$ solution and AcOEt were added, and the whole was filtered through a Celite pad. The aqueous layer was extracted with AcOEt. The combined extract was washed with brine, then dried, and evaporated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 2 : 3) to give **1** (20.4 mg, 71%) as an unstable white solid, which was identical with the sample obtained above.

(−)-(4*R*,5*S*)-4-(Hydroxy)-4-(hydroxymethyl)-5-[(1*E*)-1-(triphenylmethyloxymethyl)-1,3-butadienyl]-2-cyclopentenone (21) and Didemnenone D (2) In the same manner as described for the preparation of **21** and **1**, treatment of **19** (122 mg, 0.22 mmol) with CAN (301 mg, 0.55 mmol) at 0 °C for 6 min, followed by the same work-up and column chromatography, gave **21** (31 mg, 31%) and **2** (11 mg, 11%).

21: Colorless oil, $[\alpha]_D^{24}$ −24.1° (*c* = 1.06, $CHCl_3$). IR (Nujol) *v*: 3200—3600, 1716 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 3.2—3.6 (m, 4H), 3.6—3.8 (m, 3H), 5.24 (d, 1H, *J* = 10.3 Hz), 5.34 (d, 1H, *J* = 16 Hz), 6.20—6.32 (m, 1H), 6.23 (d, 1H, *J* = 5.5 Hz), 6.46 (d, 1H, *J* = 11.3 Hz), 7.2—7.6 (m, 16H). MS *m/z* (%): 452 (M^+, 0.08), 243 (100), 165 (35). HRMS Calcd for $C_{30}H_{28}O_4$: 452.1988. Found: 452.1960.

2: Unstable white solid, $[\alpha]_D^{26}$ −32.24° (*c* = 0.17, MeOH) {lit.,[1] $[\alpha]_D$ −12.6° (*c* = 0.15, MeOH)}. IR (Nujol) *v*: 3200—3400, 1710 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$) *δ*: 3.56 (br s, 3H), 4.05 (d, 1H, *J* = 13 Hz), 4.21 (d, 1H, *J* = 13 Hz), 5.16 (d, 1H, *J* = 10 Hz), 5.27 (d, 1H, *J* = 16.5 Hz), 6.26 (d, 1H, *J* = 5.5 Hz), 6.40 (d, 1H, *J* = 12 Hz), 6.60 (m, 1H), 7.58 (d, 1H, *J* = 5.5 Hz). MS *m/z* (%): 210 (M^+).

(−)-Didemnenone D (2) from 21 In the same manner as described for the preparation of **1**, treatment of **21** (39 mg, 0.09 mmol) with Et_2AlCl

(1 M in hexane, 0.9 ml, 0.9 mmol) at −30 °C for 10 min, followed by the same work-up and column chromatography, gave **2** (12 mg, 65%) as an unstable white solid having an ^{1}H-NMR spectrum identical with that of the sample obtained above.

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