Total Synthesis of Natural Dysidiolide

Hiroaki Miyaoka, Yasuhiro Kajiwara, Yoshinori Hara, and Yasuji Yamada*

School of Pharmacy, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

yamaday@ps.toyaku.ac.jp

Received November 6, 2000

Dysidiolide (**1**), a novel sesterterpenoid previously isolated from the Caribbean sponge *Dysidea etheria* de Laubenfels, inhibits the action of the protein phosphatase, cdc25A. The authors establish a novel total synthesis of natural dysidiolide (**1**) using intramolecular Diels−Alder reaction as the key step from optically active cyclohexenone **3**. Decalin, the core structure of **1**, was constructed by intramolecular Diels−Alder reaction of the diene ester generated by elimination of the phenyl sulfoxide group from sulfoxide ester **6** prepared from cyclohexenone **3**. Diastereoselective methylation at C-7, alkylation at C-6, and deoxygenation of C-12 and C-24 positions gave the fully substituted bicyclic core of **1**. The two side chains of the bicyclic core were further extended so as to afford natural dysidiolide (**1**). The total yield of this synthesis exceeds that of previous syntheses of **1**.

Dysidiolide (**1**, Figure 1), isolated from the Caribbean sponge *Dysidea etheria* de Laubenfels by Gunasekera et al. in 1996, is a novel sesterterpenoid possessing a unique new carbon skeleton.[1,2] Dysidiolide is the first compound noted to be a natural inhibitor of protein phosphatase cdc25A (IC_{50} = 9.4 μM), which is essential for cell proliferation. Dysidiolide inhibits the growth of A-549 human lung carcinoma (IC_{50} = 4.7 μM) and P388 murine leukemia cells (IC_{50} = 1.5 μM). The relative configuration of **1** was determined by single-crystal X-ray diffraction, and its conformation includes two large side chains that occupy axial and pseudoaxial positions on the same side of the decalin ring. These chains may possibly be importantly involved in the expression of biological activity. Thus, many efforts have been made to establish a mode of synthesis for **1** in consideration of its unique structure features and potential biological significance. The first total synthesis of natural dysidiolide (**1**) was reported by Corey et al. in 1997, and its absolute configuration was determined by this total synthesis.[3] Total syntheses of enantiomeric,[4] racemic,[5−8] and natural[9] dysidiolide (**1**) and synthetic studies[10,11] have subsequently been reported. The authors previously reported the total synthesis of (±)-dysidiolide using intramolecular Diels−Alder reaction as the key reaction.[6]

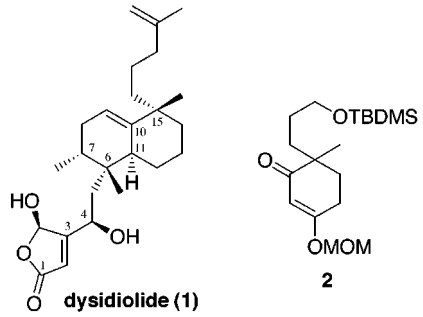


Figure 1.

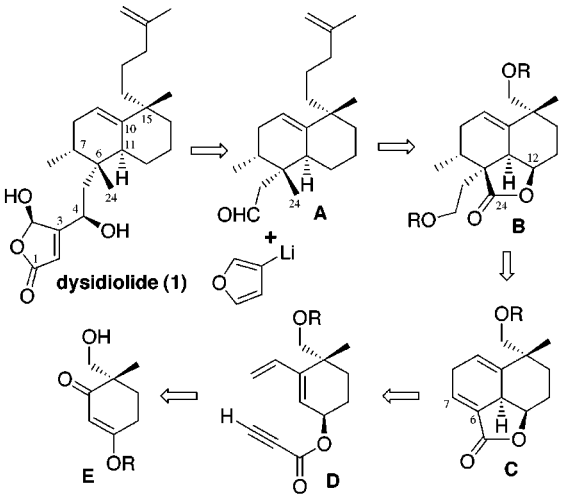
The inhibitory activity of the enantiomer and racemate of dysidiolide (**1**) toward protein phosphatase cdc25A has been investigated and found to be weak.[12] For detailed pharmacological reseach on dysidiolide, an efficient total synthesis of natural dysidiolide would be required. The authors thus undertook the total synthesis of natural dysidiolide. The stereoselective total synthesis of natural dysidiolide from an optically active cyclohexenone derivative is presented in this paper.

The route for the synthesis of natural dysidiolide (**1**) is presented in Scheme 1. The total synthesis of natural dysidiolide may be conducted essentially in accordance with the method for synthesizing (±)-dysidiolide, as previously reported.[6] Optically active enone **E** may be used instead of enone **2**, the starting material for the synthesis of (±)-dysidiolide, since the efficient synthesis of optically active enone **E** was reported by the authors[13] and the optically active form of enone **2** is not accessible. The decalin framework, the core structure of dysidiolide, was constructed in such a way that lactone **C** would be obtained by intramolecular Diels−Alder reaction of diene ester **D** produced from cyclohexenone **E** via vinylation and esterification. Stereoselective methylation at C-7[14]

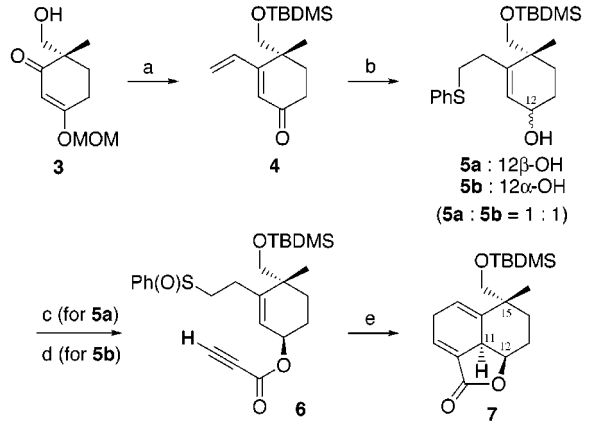
(1) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759−8780.
(2) Recently, cladocorans A and B, having the same carbon skeleton, were reported. Fontana, A.; Ciavatta, M. L.; Cimino, G. *J. Org. Chem.* **1998**, *63*, 2845−2849.
(3) Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425−12431.
(4) Boukouvalas, J.; Cheng, Y.-X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228−229.
(5) Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 1615−1616.
(6) Miyaoka, H.; Kajiwara, Y.; Yamada, Y. *Tetrahedron Lett.* **2000**, *41*, 911−914.
(7) Piers, E.; Caillé, S.; Chen, G. *Org. Lett.* **2000**, *2*, 2483−2486.
(8) Demeke, D.; Forsyth, C. J. *Org. Lett.* **2000**, *2*, 3177−3179.
(9) Takahashi, M.; Dodo, K.; Hashimoto, Y.; Shirai, R. *Tetrahedron Lett.* **2000**, *41*, 2111−2114.
(10) Brohm, D.; Waldmann, H. *Tetrahedron Lett.* **1998**. *39*, 3995−3998.
(11) Jung, M. E.; Nishimura, N. *J. Am. Chem. Soc.* **1999**, *121*, 3529−3530.
(12) Blanchard, J. L.; Epstein, D. M.; Boisclair, M. D.; Rudolph, J.; Pal, K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2537−2538.
(13) Miyaoka, H.; Kajiwara, Y.; Hara, M.; Suma, A.; Yamada, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 3189−3196.

10.1021/jo0015772 CCC: $20.00
Published on Web 01/27/2001

Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) (i) TBDMS-Cl, imidazole, DMF, rt, 94%; (ii) vinylmagnesium bromide, THF, 0 °C, then silica gel, 92%; (b) (i) PhSH, Et_3N, benzene, rt, 93%, (ii) DIBAL-H, toluene, −78 °C, 96%; (c) (i) *m*-CPBA, $CHCl_3$, −42 °C, 99%, (ii) propiolic acid, DCC, DMAP, toluene, rt, quant; (d) i) *m*-CPBA, $CHCl_3$, −42 °C, 97%, (ii) propiolic acid, DEAD, Ph_3P, THF, rt, 98%; (e) pyridine, ethyl propiolate, toluene, reflux, 89%.

and alkylation at C-6 of lactone **C** may occur to provide lactone **B** since the α-face of lactone **C** is the less hindered side. Lactone **B** was converted to aldehyde **A** by deoxygenation at C-12 and C-24 and elongation of the side chain. The highly functional γ-hydroxybutenolide was obtained by addition of 3-lithiofuran to aldehyde **A** and photochemical oxidation of the furan moiety gave natural dysidiolide (**1**).

Construction of decalin, the core structure of dysidiolide, was investigated via intramolecular Diels−Alder reaction (Scheme 2). The synthesis of dysidiolide (**1**) was initiated from optically active cyclohexenone **3** (99%ee) readily obtained by the lipase-catalyzed kinetic resolution of racemic **3** in the presence of vinyl acetate.[13] The hydroxy group of cyclohexenone **3** was protected by treatment with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole to give TBDMS ether in 94% yield. The cyclohexenone was vinylated with vinylmagnesium bromide and then treated with silica gel to afford conjugated dienone **4** in 92% yield.

(14) Numbering of compounds is in accordance with that for dysidiolide in this paper.

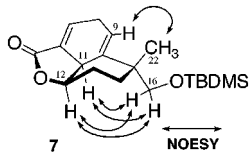


Figure 2. NOESY correlations of compound **7**.

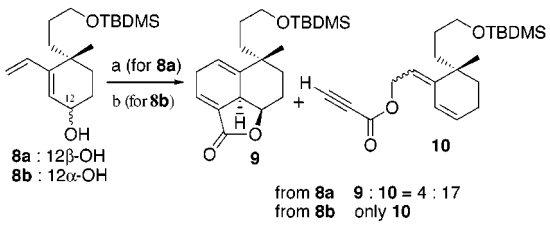
Protection of the conjugated dienone moiety in **4** with thiophenol in the presence of Et_3N gave α,β-unsaturated ketone in 93% yield, which was subsequently reduced with diisobutylaluminum hydride (DIBAL-H) at −78 °C to give a diastereomeric mixture of allylic alcohols **5a** and **5b** (**5a**/**5b** = 1:1) in 96% yield. After separation of alcohols **5a** and **5b**, absolute configurations of the secondary hydroxy groups in **5a** and **5b** were determined as *R* and *S*, respectively, by the modified Mosher method.[15] Oxidation of the sulfide in **5a** with *m*-chloroperbenzoic acid (*m*-CPBA) gave sulfoxide in 99% yield, and the secondary hydroxy group of sulfoxide was acylated with propiolic acid, 1,3-dicyclohexylcarbodiimide (DCC), and 4-(dimethylamino)pyridine (DMAP) in toluene to afford ester **6** in quantitative yield. Allylic alcohol **5b** was converted to ester **6** via oxidation of the sulfide with *m*-CPBA (97% yield) and Mitsunobu reaction[16] using propiolic acid, DEAD, and Ph_3P (98% yield).[17] A solution of ester **6** in toluene was refluxed in the presence of ethyl propiolate and pyridine to regenerate the diene by elimination of phenyl sulfoxide followed by intramolecular Diels−Alder reaction to give decalin **7**, which corresponds to lactone **C** in the synthetic strategy, as the sole product in 89% yield. In the absence of pyridine, no decalin **7** was obtained. In the absence of ethyl propiolate, a mixture of decalin **7**, the addition product of **7** with phenylsulfenic acid (structure not determined) and the addition product of reaction intermediate diene with phenylsulfenic acid (structure not determined) was obtained.

The relative configuration of **7** was confirmed on the basis of the NOESY spectrum (Figure 2). NOESY correlations were noted between the methine proton at C-11 and both methylene protons at C-16, between the methine proton at C-12 and both methylene protons at C-16, and between the olefinic proton at C-9 and methyl

(15) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092−4096.

(16) Mitsunobu, O. *Synthesis* **1981**, 1−28.

(17) In the synthesis of racemic **1**, diene alcohol **8a**, which was derived from enone **2** by a similar method, was treated with propiolic acid and *N*,*N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl)[18] in benzene to give decalin **9** and S_N2'-type adduct **10** (**9**/**10** = 4:17).[6] Diene alcohol **8b** was treated with propiolic acid, diethyl azodicarboxylate (DEAD), and Ph_3P[16] in tetrahydrofuran (THF) to give S_N2' type adduct **10** as the sole product (eq 1). Acylation of diene alcohol **8a** and Mitsunobu reaction of diene alcohol **8b** were not successful and these reactions gave S_N2' type adduct **10** as the major product. Thus, to prevent generation of the S_N2' type adduct, the conjugated diene moiety of **4** was initially protected as phenyl sulfide, which was then converted to the ester (reagents and conditions: (a) propiolic acid, BOP-Cl, benzene, rt, 79%; (b) propiolic acid, DEAD, Ph_3P, THF, rt, 92%).



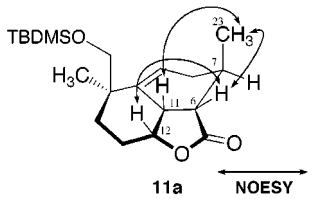
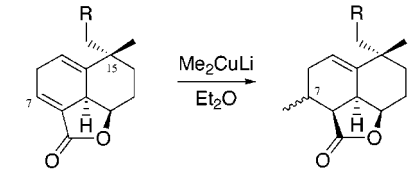


Figure 3. NOESY correlations of compound **11a**.

Scheme 3



7 : R = OTBDMS
9 : R = $CH_2CH_2OTBDMS$
13 : R = H

11a : R = OTBDMS, 7α-Me
11b : R = OTBDMS, 7β-Me
91% (**11a** : **11b** = 30 : 1)
12a : R = $CH_2CH_2OTBDMS$, 7α-Me
12b : R = $CH_2CH_2OTBDMS$, 7β-Me
91% (**12a** : **12b** = 9 : 1)
14 : R = H,7α-Me
89%

protons at C-22. The relative configuration of **7** thus determined is shown in Figure 2.

The stereoselective methylation of **7** was carried out. α,β-Unsaturated lactone **7** was treated with Me_2CuLi at 0 °C in Et_2O to afford diastereoselectively 7α-methyl lactone **11a** with a small amount of 7β-methyl lactone **11b** (**11a**/**11b** = 30:1) in 91% yield (Scheme 3). After separation of the mixture, the relative configurations of C-6 and C-7 in **11a** were determined on the basis of NOESY correlations between H-6 and H-12, between H-11 and Me-23, and between H-6 and Me-23 (Figure 3). The stereoselectivity of methylation of **7** with Me_2-CuLi may be explained as due to approach of the reagent from the less hindered side (convex face) of **7**. The stereoselectivity of methylation of **7** was greater than the stereoselectivity of methylation of **9**.[6] Greater selectivity in methylation was observed by shortening the length of the α-side chain at C-15 and as was also confirmed by the finding that enone **13** possessing geminal methyl groups at the C-15 position, reacted with Me_2CuLi to give 7α-methyl lactone **14** as the sole product in 89% yield.

Attention was then directed to stereoselective alkylation at C-6 (Scheme 4). TBDMS ether **11a** was converted to benzyl ether **15** in two steps: (1) removal of the TBDMS group with excess tetrabutylammonium fluoride (TBAF) (quantitative yield) and (2) protection of the hydroxy group as its benzyl ether with benzyl bromide (Bn-Br), NaH and *n*-Bu_4NI (93% yield). Lactone **15** was treated with lithium diisopropylamide (LDA) and then 1-iodo-2-(tetrahydro-2-pyranyloxy)ethane to give lactone **16**, which corresponds to lactone **B** in the synthetic strategy, in 92% yield as the sole product. The relative configuration at C-6 in **16** was determined from the NOESY spectrum of alcohol **16a**, which was prepared from **16** by methanolysis of the tetrahydropyranyl (THP) group (Figure 4). NOESY correlations were observed between both methylene protons at C-5 and methyl protons at C-23 methyl, between one of the methylene protons at C-5 and the methine proton at C-11 and between one of the methylene protons at C-5 and the methine proton at C-12.

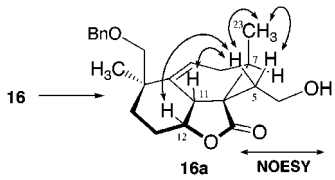
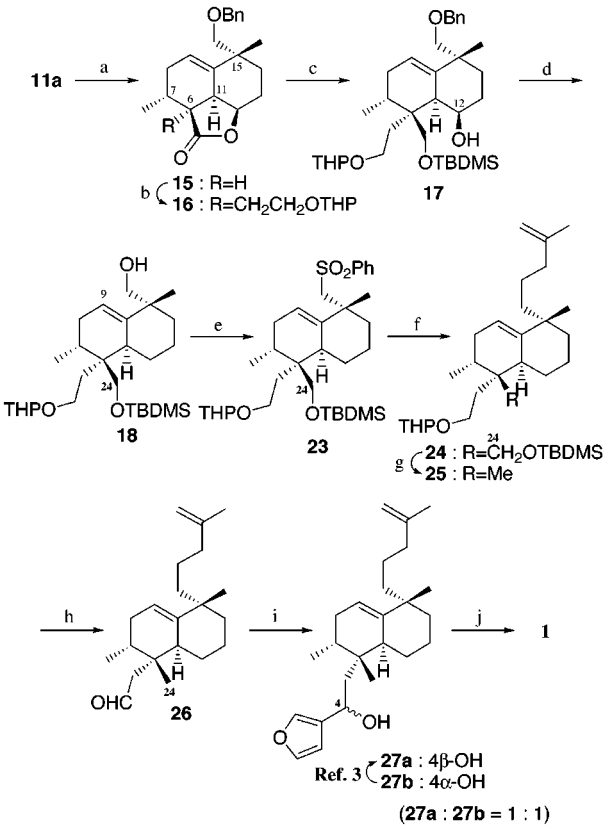


Figure 4. NOESY correlations of compound **16a**.

Scheme 4[a]

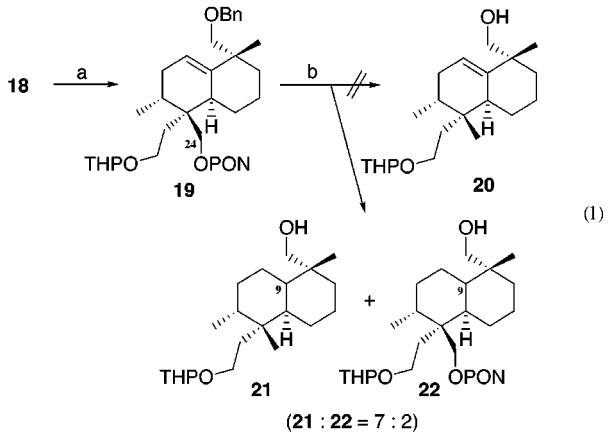


[a] Reagents and conditions: (a) (i) TBAF, THF, rt, quant, (ii) Bn-Br, NaH, *n*-Bu_4NI, THF−DMF, rt, 93%; (b) LDA, $THPOCH_2CH_2I$, THF, 0 °C, 92%; (c) (i) DIBAL-H, toluene, −78 °C, (ii) $LiBH_4$, MeOH−THF, 0 °C, quant (two steps), (iii) TBDMS-Cl, imidazole, DMF, rt, 96%; (d) (i) PON-Cl, MeLi, TMEDA, THF, 0 °C to rt, 93%, (ii) Li, $MeNH_2$, *t*-BuOH, 2-methyl-2-butene, reflux, 92%; (e) (i) *N*-phenylthiosuccinimide, *n*-Bu_3P, pyridine, 60 °C, then H_2O_2, (ii) TPAP, NMO, CH_2Cl_2, rt, 88% (two steps); (f) (i) *n*-BuLi, 4-iodo-2-methyl-1-butene, THF, 50 °C, 92%, (ii) Na−Hg, Na_2HPO_4, MeOH, rt, 96%; (g) (i) TBAF, THF, 50 °C, 93%, (ii) TPAP, NMO, CH_2Cl_2, rt, 95%, (iii) H_2NNH_2, KOH, diethylene glycol, 200 °C, 95%; (h) (i) PPTS, MeOH, rt, 97%, (ii) TPAP, NMO, CH_2Cl_2, rt, 90%; (i) 3-bromofuran, *n*-BuLi, THF, −78 °C, 93%; (j) O_2, *hν*, Rose Bengal, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 88%.

Deoxygenation of the C-12 and C-24 positions was carried out. Lactone **16** was reduced with DIBAL-H to give hemiacetal followed by reduction with $LiBH_4$ to afford the diol in quantitative yield (two steps). Selective protection of the primary hydroxy group in the diol was done by treatment with TBDMS-Cl and imidazole to give TBDMS ether **17** as the sole product in 96% yield. Deoxygenation of the secondary hydroxy group at C-12 in **17** was conducted in two steps: (1) conversion to phosphoramidate with $(Me_2N)_2P(O)Cl$ (PON-Cl), MeLi, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (93% yield) and (2) Benkeser reduction[19] using Li in CH_3-NH_2 in the presence of *t*-BuOH and 2-methyl-2-butene (92% yield) to afford alcohol **18**, which possesses the

requisite chiral centers at C-6, C-7, C-11, and C-15 of dysidiolide. In the absence of 2-methyl-2-butene, a mixture of alcohol **18** and its reduction product of the double bond at C-9 was obtained.

The hydroxy group of **18** was protected by treatment with Bn-Br, NaH, and *n*-Bu_4NI to give benzyl ether and deprotection of the TBDMS group afforded the alcohol in 92% yield (two steps) (eq 1; reagents and conditions: (a) (i) Bn-Br, NaH, *n*-Bu_4NI, THF−DMF, rt; (ii) TBAF, THF, reflux, 92% (two steps); (iii) PON-Cl, MeLi, TMEDA, THF, 0 °C to rt, 99%; (b) Li, $MeNH_2$, *t*-BuOH, 2-methyl-2-butene, reflux, 90%). The alcohol was then



(1)

converted to phosphoramidate **19** with PON-Cl, MeLi, and TMEDA in 99% yield. Benkeser reduction of phosphoramidate **19** in the presence of *t*-BuOH and 2-methyl-2-butene gave a mixture of two olefin-reduced products **21** and **22** in 90% yield (**21**/**22** = 7:2). The desired reduction product **20** could not be produced, regardless of what reduction conditions implemented. Deoxygenation of C-24 was thus conducted by a different method after elongation of the side chain.

Elongation of the side chains and deoxygenation of the C-24 position were carried out so as to obtain natural dysidiolide (**1**). Alcohol **18** was treated with *N*-phenylthiosuccinimide, *n*-Bu_3P, and pyridine and then with H_2O_2 to give a sulfoxide that was then oxidized with tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO) to afford sulfone **23** in 88% yield (two steps). Coupling of lithio derivative of sulfone **23** with 4-iodo-2-methyl-1-butene at 50 °C in 92% yield followed by removal of the phenylsulfonyl group with Na−Hg provided silyl ether **24** (96% yield). Deoxygenation of **24** at C-24 was conducted in three steps: (1) removal of the TBDMS group in **24** with excess TBAF (93% yield), (2) TPAP-oxidation of hydroxy group to provide aldehyde (95% yield), and (3) Wolff−Kishner reduction[20] of the formyl group with H_2NNH_2 and KOH in diethylene glycol at 200 °C to give compound **25** (95% yield). Methanolysis of the THP group with pyridinuim *p*-toluenesulfonate (PPTS) in **25** followed by oxidation with TPAP and NMO gave aldehyde **26**[3] which corresponds to aldehyde **A** in the synthetic strategy. Treatment of aldehyde **26** with 3-lithiofuran, prepared from 3-bromofuran and *n*-BuLi, gave a mixture of epimeric alcohols **27a** and **27b** (**27a**/**27b** = 1:1). Chemical conversion of the α-alcohol **27b** to the *β*-alcohol **27a** has been previously reported by Corey.[3] Photochemical oxidation[21] of **27a** afforded dysidiolide (**1**) ($[\alpha]^{28}_D = -10.8$ (*c* 0.51, CH_2Cl_2/MeOH = 1:1). Spectral data and the sign of optical rotation of synthetic **1** were identical to those of reported natural dysidiolide, $[\alpha]^{24}_D = -11.1$ (*c* 0.6, CH_2Cl_2/MeOH = 1:1).[1]

The asymmetric synthesis of natural dysidiolide was achieved in 27 steps and 9.7% overall yield (from **3**). The overall yield of the present synthesis exceeds that of any other method reported to date.

Experimental Section

(*R*)-4-*tert*-Butyldimethylsilyloxymethyl-4-methyl-3-vinyl-2-cyclohexenone (4). Imidazole (33.3 g, 489 mmol) and TBDMS-Cl (36.9 g, 245 mmol) were added sequentially to a solution of alcohol **3** (44.5 g, 222 mmol) in DMF (222 mL) at room temperature under an argon atmosphere. After the mixture was stirred at room temperature for 10 h, the reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give silyl ether (65.6 g, 209 mmol, 94% yield) as a colorless oil.

To a solution of the above silyl ether (18.9 g, 60.1 mmol) in THF (300 mL) was added vinylmagnesium bromide in THF (1.26 M, 95.4 mL, 118 mmol), followed by stirring for 6 h at 0 °C. The reaction mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give dienone **4** (21.6 g, 55.3 mmol, 92% yield) as a colorless oil.

(1*R*,4*R*)-4-*tert*-Butyldimethylsilyloxymethyl-4-methyl-3-(2-phenylthioethyl)-2-cyclohexenol (5a) and (1*S*,4*R*)-4-*tert*-Butyldimethylsilyloxymethyl-4-methyl-3-(2-phenylthioethyl)-2-cyclohexenone (5b). To a solution of dienone **4** (56.5 g, 202 mmol) in benzene (400 mL) were added PhSH (22.9 mL, 243 mmol) and Et_3N (8.4 mL, 60.3 mmol) sequentially, followed by stirring for 1 h at room temperature. The reaction mixture was diluted with Et_2O, washed with 3 N NaOH, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give enone (73.5 g, 188 mmol, 93% yield) as a colorless oil.

A solution of DIBAL-H in hexane (0.95 M, 64.2 mL, 61.0 mmol) was added to a cold (−78 °C) solution of the above enone (18.3 g, 46.9 mmol) in toluene (235 mL) under an argon atmosphere. After the mixture was stirred for 30 min at −78 °C, MeOH was added, the mixture was diluted with Et_2O, and saturated aqueous NaCl was added. The mixture was stirred for 10 h, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to give alcohol **5a** (8.76 g, 22.3 mmol, 48% yield) and alcohol **5b** (8.75 g, 22.3 mmol, 48% yield), each as a colorless oil.

(1*R*,4*R*)-4-*tert*-Butyldimethylsilyloxymethyl-4-methyl-3-(2-phenylsulfinylethyl)-2-cyclohexenyl Propiolate (6) from *β*-Alcohol 5a. A solution of *m*-CPBA (730 mg, 2.96 mmol (70%)) in $CHCl_3$ (7.4 mL) was added to a suspension of *β*-alcohol **5a** (1.16 g, 2.96 mmol) and Na_2HPO_4 (420 mg, 2.96 mmol) in $CHCl_3$ (7.4 mL) at −42 °C. After 30 min, the suspension was poured into saturated aqueous $NaHCO_3$. The organic layer was washed sequentially with saturated aqueous

(18) Diago-Meseguer, J.; Palomo-Coll, A. L.; Fernández-Lizarbe, J. R.; Zugaza-Bilbao, A. *Synthesis* **1980**, 547−551.

(19) Ireland, R. E.; Muchmore, D. C.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 5098−5100. See also: Trost, B. M.; Renaut, P. *J. Am. Chem. Soc.* **1982**, *104*, 6668−6672. Wender, P. A.; von Geldern, T. W.; Levine, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 4858−4860.

(20) Cram, D. J.; Sahyum, M. R. V.; Knox, G. R. *J. Am. Chem. Soc.* **1962**, *84*, 1734−1735.

(21) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773−2776.

$NaHCO_3$, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:2) to give sulfoxide alcohol (1.20 g, 2.93 mmol, 99% yield) as a colorless oil.

DCC (15.1 g, 73.4 mmol) and DMAP (448 mg, 3.67 mmol) were added sequentially to a stirred solution of the above β-alcohol (15.0 g, 36.7 mmol) and propiolic acid (3.83 mL, 62.3 mmol) in toluene (367 mL) at 0 °C. After being stirred for 1 h at 0 °C, the brownish suspension was filtered through a short column on silica gel. The mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give sulfoxide ester **6** (16.9 g, 36.7 mmol, quantitative yield) as a colorless oil.

(1*R*,4*R*)-4-*tert*-Butyldimethylsilyloxymethyl-4-methyl-3-(2-phenylsulfinylethyl)-2-cyclohexenyl Propiolate (6) from α-Alcohol 5b. A solution of *m*-CPBA (58.4 mg, 237 μmol (70%)) in $CHCl_3$ (2.4 mL) was added to a suspension of α-alcohol **5b** (105 mg, 237 μmol) and Na_2HPO_4 (33.6 mg, 237 μmol) in $CHCl_3$ (2.4 mL) at −42 °C. After being stirred for 30 min, the suspension was poured into saturated aqueous $NaHCO_3$. The organic layer was washed sequentially with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:2) to give sulfoxide alcohol (106 mg, 230 μmol, 97% yield) as a colorless oil.

DEAD (159 μL, 1.03 mmol), propiolic acid (63.3 μL, 1.03 mmol), and a solution of the above α-alcohol (183 mg, 448 μmol) in THF (4.5 mL) were added sequentially to a stirred solution of Ph_3P (270 mg, 1.03 μmol) in THF (4.5 mL). The mixture was followed by stirring for 1 h at room temperature under an argon atmosphere. After dilution with hexane and Et_2O (1:1), the reaction mixture was filtered through a short column on silica gel and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give sulfoxide ester **6** (201 mg, 437 μmol, 98% yield) as a colorless oil.

(6*R*,8a*R*,8b*R*)-4,6,7,8,8a,8b-Hexahydro-6-*tert*-butyldimethylsilyloxymethyl[1,8-*bc*]-6-methylnaphtho-2-furanone (7). Ethyl propiolate (290 mg, 2.96 mmol) was added to a solution of sulfoxide ester **6** (680 mg, 1.48 mmol) in toluene/pyridine = 60:1 (150 mL) at room temperature under an argon atmosphere. The mixture was refluxed for 8 h. The mixture was diluted with hexane/Et_2O = 2:1, filtered through a short column on silica gel, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give decalin **7** (442 mg, 1.32 mmol, 89% yield) as a colorless oil.

(2a*S*,3*R*,6*R*,8a*R*,8b*S*)-2a,3,4,6,7,8,8a,8b-Octahydro-6-*tert*-butyldimethylsilyloxymethyl[1,8-*bc*]-3,6-dimethylnaphtho-2-furanone (11a). A solution of MeLi in Et_2O (1.12 M, 1.26 mL, 1.41 mmol) was added to a cold (0 °C) suspension of CuI (135 mg, 709 μmol) in Et_2O (4.00 mL) under an argon atmosphere. The mixture was stirred for 30 min at 0 °C. α,β-Unsaturated lactone **7** (139 mg, 416 μmol) was added, and the mixture was stirred for 15 min at 0 °C. The reaction mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6:1) to give 7α-methyl lactone **11a** (128 mg, 366 μmol, 88% yield) as a white solid and 7β-methyl lactone **11b** (4.4 mg, 12.5 μmol, 3% yield) as a colorless oil. An analytical sample was obtained by recrystallization of the solid from Et_2O−hexane as colorless needles.

(2a*S*,3*R*,6*R*,8a*R*,8b*S*)-2a,3,4,6,7,8,8a,8b-Octahydronaphtho-6-benzyloxymethyl-3,6-dimethyl[1,8-bc]naphtho-2-furanone (15). A solution of TBAF in THF (1.0 M, 28.0 mL, 28.0 mmol) was added to 7α-methyl lactone **11a** (6.53 g, 18.6 mmol) at room temperature. After being stirred for 1 h, the reaction mixture was diluted with Et_2O, washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give alcohol (4.40 mg, 18.6 mmol, quantitative yield) as a white solid. An analytical sample was obtained by recrystallization of the solid from Et_2O−hexane as colorless needles.

NaH (2.15 g, 53.8 mmol (60%)), *n*-Bu_4NI (4.97 g, 13.5 mmol), and BnBr (8.22 mL, 67.3 mmol) were added sequentially to a solution of the above alcohol (6.36 g, 26.9 mmol) in THF/DMF = 4:1 (270 mL) at room temperature. The mixture was stirred for 24 h at this temperature. The reaction mixture was diluted with Et_2O, washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give benzyl ether **15** (8.17 g, 25.0 mmol, 93% yield) as a colorless oil.

(2a*S*,3*R*,6*R*,8a*R*,8b*S*)-2a,3,4,6,7,8,8a,8b-Octahydro-6-benzyloxymethyl-3,6-dimethyl-2a-[2-(tetrahydro-2-pyranyloxy)ethyl][1,8-*bc*]naphtho-2-furanone (16). A solution of *n*-BuLi in hexane (1.54 M, 4.18 mL, 6.47 mmol) was added to a cold (0 °C) solution of diisopropylamine (1.09 mL, 7.76 mmol) in THF (22 mL) under an argon atmosphere. The mixture was stirred for 30 min at 0 °C. A solution of lactone **15** (1.05 g, 3.22 mmol) in THF (10 mL) was added to the mixture and stirred for 30 min at 0 °C. 2-Tetrahydropyranyloxy-1-iodoethane (2.89 g, 11.3 mmol) was added to this mixture at 0 °C. After stirring at 0 °C for 2 h, the reaction mixture was diluted with Et_2O, washed with saturated aqueous NH_4Cl, water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6:1) to give lactone **16** (1.35 g, 2.96 mmol, 92% yield) as a colorless oil.

(1*R*,4*R*,7*R*,8*S*,8a*R*)-1,2,3,4,6,7,8,8a-Octahydro-4-benzyloxymethyl-4,7-dimethyl-8-*tert*-butyldimethylsilyloxymethyl-8-[2-(tetrahydro-2-pyranyloxy)ethyl]-1-naphthalenol (17). A solution of DIBAL-H in hexane (0.95 M, 47.1 mL, 49.6 mmol) was added to a cold (−78 °C) solution of lactone **16** (13.6 g, 29.8 mmol) in toluene (150 mL) under an argon atmosphere. The mixture was stirred for 30 min at −78 °C, MeOH was added, the mixture was diluted with Et_2O, and saturated aqueous NaCl was added. The mixture was stirred for 10 h,dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was used for next reaction without purification.

$LiBH_4$ (1.30 g, 59.7 mmol) was added to the crude product in MeOH (150 mL) at 0 °C. The mixture was stirred for 2 h at 0 °C. The reaction mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give diol (13.7 g, 29.8 mmol, quantitative yield, two steps) as a colorless oil.

Imidazole (4.87 g, 71.5 mmol) and TBDMS-Cl (5.39 g, 35.8 mmol) were added sequentially to a solution of the above diol (13.7 g, 29.8 mmol) in DMF (150 mL) at room temperature under an argon atmosphere. After the mixture was stirred at room temperature for 10 h, the reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 10:1) to give silyl ether **17** (16.6 g, 28.6 mmol, 96% yield) as a colorless oil.

(1*R*,4a*R*,5*S*,6*R*)-1,2,3,4,4a,5,6,7-Octahydro-5-*tert*-butyldimethylsilyloxymethyl-1,6-dimethyl-1-hydroxymethyl-5-[2-(tetrahydro-2-pyranyloxy)ethyl]-1-naphthalenol (18). To a solution of alcohol **17** (65.6 mg, 115 μmol) in THF (1.20 mL) were added TMEDA (60.5 μL, 401 mmol) and MeLi in Et_2O (1.13 M, 253 μL, 286 μmol), followed by stirring for 30 min at 0 °C. Tetramethylphosphorodiamidic chloride (34.0 μL, 230 μmol) was added to the mixture. After the mixture was stirred for 30 min at 0 °C, saturated aqueous $NaHCO_3$ was added. The mixture was diluted with EtOAc and washed with water and saturated aqueous NaCl. Organic layer was dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give phosphoramidate (69.3 mg, 107 mmol, 93% yield) as a colorless oil.

Lithium (70.3 mg, 10.1 mmol) was added to a methylamine (17.0 mL) at −78 °C under an argon atmosphere. After the mixture was refluxed for 30 min, a solution of the above phosphoramidate (358 mg, 507 μmol) in THF (500 μL) and 2-methyl-2-butene (851 μL, 10.1 mmol) were added. After the resulting mixture was refluxed for 30 min, 2-methyl-2-propanol (364 μL, 3.81 mmol) was added. After the resulting mixture was refluxed for 30 min, the solid NH_4Cl was carefully added until the color disappeared. The reaction mixture was diluted with Et_2O and washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The mixture was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to give alcohol **18** (218 mg, 466 μmol, 92% yield) as a colorless oil.

(1*S*,2*R*,5*R*,8a*R*)-1,2,3,5,6,7,8,8a-Octahydro-5-benzenesulfonylmethyl-1-*tert*-butyldimethylsilyloxymethyl-2,5-dimethyl-1-[2-(tetrahydro-2-pyranyloxy)ethyl]naphthalene (23). A solution of *N*-thiophenylsuccinimide (3.39 g, 16.4 mmol) in pyridine (10.2 mL) and *n*-Bu_3P (2.27 mL, 16.4 mmol) were added sequentially to a solution of alcohol **18** (1.91 g, 4.09 mmol) in pyridine (10.2 mL) under an argon atmosphere at room temperature. After being stirred for 6 h, the mixture was diluted with Et_2O and washed with water, 5% solution of H_2O_2, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and concentrated under reduce pressure. The brownish residue was filtered through a short column on silica gel. The crude product was used for next reaction without purification.

TPAP (410 mg, 1.17 mmol) was added to a stirred mixture of the crude product, NMO (2.73 g, 23.3 mmol), and powdered molecular sieves (1.95 g) in CH_2Cl_2 (19.5 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h, passed through a short pad of silica gel, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to give phenyl sulfone **23** (2.14 g, 3.63 mmol, 88% yield, two steps) as a colorless oil.

(1*S*,2*R*,5*S*,8a*R*)-1,2,3,5,6,7,8,8a-Octahyro-1-*tert*-butyldimethylsilyloxymethyl-2,5-dimethyl-5-(4-methyl-4-pentenyl)-1-[(2-tetrahydro-2-pyranyloxy)ethyl]naphthalene (24). To a solution of sulfone **23** (291 mg, 0.493 mmol) in THF (4.9 mL) was added a solution of *n*-BuLi in hexane (1.37 M, 720 μL, 986 μmol), and followed by stirring for 45 min at 50 °C. 4-Iodo-2-methylbutene (483 μL, 2.46 mmol) was added, and the mixture was stirred for 2 h at 50 °C. The reaction mixture was diluted with Et_2O and washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The mixture was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give the diastereomeric mixture (292 mg, 453 μmol, 92% yield) as a colorless oil.

To a solution of the above diastereomeric mixture (1.03 g, 1.57 mmol) in MeOH were added Na_2HPO_4 and Na−Hg (9.32 g, 5%), followed by stirring for 2 h at room temperature. The reaction mixture was passed through a short pad of silica gel and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 14:1) to give desulfone compound **24** (777 mg, 1.50 mmol, 96% yield) as a colorless oil.

(1*R*,2*R*,5*S*,8a*S*)-1,2,3,5,6,7,8,8a-Octahydro-5-(4-methyl-4-pentenyl)-1-[2-(tetrahydro-2-pyranyloxy)ethyl]-1,2,5-trimethylnaphthalene (25). A solution of TBAF in THF (1.0 M, 2.56 mL, 2.56 mmol) was added to **24** (133 mg, 256 μmol) at room temperature. After being stirred for 10 h at 50 °C, the reaction mixture was diluted with Et_2O, washed with water and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give alcohol (96.7 mg, 239 μmol, 93% yield) as a colorless oil.

TPAP (14.2 mg, 40.3 μmol) was added to a stirred mixture of the alcohol (163 mg, 403 μmol), NMO (236 mg, 2.01 mmol), and powdered molecular sieves (202 mg) in CH_2Cl_2 (4.0 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h, passed through a short pad of silica gel, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 4:1) to give aldehyde (154 mg, 382 μmol, 95% yield) as a colorless oil.

KOH (322 mg, 5.74 mmol) and hydrazine monohydrate (391 μL, 7.66 μmol) were added sequentially to a solution of the aldehyde (257 mg, 638 μmol) in diethylene glycol (12.8 mL) under an argon atmosphere at room temperature. After the mixture was stirred for 2 h at 200 °C, the reaction mixture was cooled, diluted with Et_2O, and washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 6:1) to give **25** (235 mg, 605 μmol, 95% yield) as a colorless oil.

(1*R*,2*R*,5*S*,8a*S*)-1,2,3,5,6,7,8,8a-Octahydro-1-(2-formylmethyl)-5-(4-methyl-4-pentenyl)-1,2,5-trimethylnaphthalene (26). A solution of PPTS in MeOH (1%, 3.40 mL, 0.17 M) was added to **25** (220 mg, 568 μmol) at room temperature. After being stirred for 5 h, the reaction mixture was diluted with Et_2O, washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 3:1) to give alcohol (168 mg, 551 mmol, 97% yield) as a colorless oil.

TPAP (1.7 mg, 4.86 μmol) was added to a stirred mixture of the above alcohol (14.8 mg, 48.6 μmol), NMO (28.5 mg, 243 μmol), and powder molecular sieves (24.3 mg) in CH_2Cl_2 (972 μL) at room temperature under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h, passed through a short pad of silica gel, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 8:1) to give aldehyde **26** (13.2 mg, 43.7 μmol, 90% yield) as a colorless oil.

(1*R*,2*R*,5*S*,8a*S*)-1,2,3,5,6,7,8,8a-Octahydro-1-[2*R*,*S*-2-hydroxy-2-(3-furyl)ethyl]-5-(4-methyl-4-pentenyl)-1,2,5-trimethylnaphthalene (27a and 27b). *n*-BuLi (1.53 M in hexane, 1.16 mL, 1.77 mmol) was added to a solution of 3-bromofuran (178 μL, 1.98 mmol) in THF (4.00 mL) at −78 °C, and after 30 min, the yellow solution was treated with a solution of aldehyde **26** (120 mg, 396 μmol) in THF (4.00 mL). After the mixture was stirred for 30 min, saturated aqueous NH_4Cl was added, the mixture was warmed to room temperature, and water and Et_2O were added. The organic layer was washed with saturated aqueous NH_4Cl, water, and saturated aqueous NaCl. The mixture was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to give alcohol **27a** (67.4 mg, 182 μmol, 46% yield) and alcohol **27b** (69.0 mg, 186 μmol, 47% yield) each as a colorless oil.

(−)-Dysidiolide (1). Rose Bengal (0.4 mg) was added to a solution of **27a** (9.1 mg, 24.6 μmol) and diisopropylethylamine (18 μL, 100 μmol) in CH_2Cl_2 (6.0 mL) at room temperature. The suspension was cooled to −78 °C, saturated with anhydrous O_2, and irradiated with a 270-W tungsten filament lamp under an atmosphere of O_2. After 6 h, irradiation was stopped, the pink solution was warmed to room temperature, and saturated aqueous oxalic acid (2 mL) was added. After 30 min of vigorous stirring, water and $CHCl_3$−EtOAc (1:2) were added to the colorless mixture, and the aqueous portion was extracted with $CHCl_3$−EtOAc (1:2). The combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexane/EtOAc = 1:1) to give (−)-dysidiolide (**1**) (8.7 mg, 21.6 μmol, 88% yield) as a white solid. An analytical sample was obtained by recrystallization of the solid from acetone−Et_2O as colorless needles.

Acknowledgment. This work was supported in part by a Grant-in-Aid for Scientific Research (Grant No. 09672165) from Ministry of Education, Science, Sports

and Culture, and a Grant for private universities from The Promotion and Mutual Aid Corporation for Private Schools of Japan and Ministry of Education, Science, Sports and Culture.

Supporting Information Available: Details for the preparation and spectroscopic data for MTPA ester of **5a**, MTPA ester of **5b**, **13**, **14**, and **16a**. Spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra for compounds **4**, **5a**,**b**, **6**, **7**, **11a**, **15**−**18**, **23**−**26**, **27a**,**b**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0015772