Structure of Hydroazulenoid Diterpenes from a Marine Alga and Their Absolute Configuration Based on Circular Dichroism

Jesús T. Vázquez, Mayland Chang, and Koji Nakanishi*

Department of Chemistry, Columbia University, New York, New York 10027

Eduardo Manta, Cirilo Pérez, and Julio D. Martín*

Centro de Productos Naturales Orgánicos Antonio González, Universidad de La Laguna-CSIC, Carretera de La Esperanza 2, 38206 La Laguna, Tenerife, Spain

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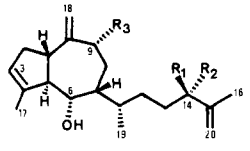
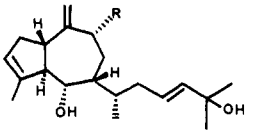
First, we describe the isolation of three new diterpenoids with a hydroazulene skeleton, dictyotriol C (**1**), D (**2**), and E (**3**), as well as the previously known pachydictyol A (**4**), dictyol B (**5**), dictyol C (**6**), and dictyotadiol (**7**), from a *Dictyota* sp. The structures of the new diterpenoids **1–3** were proposed on the basis of their spectral data and confirmed by chemical transformation of dictyol B (**5**). This is followed by absolute configuration studies, based on the circular dichroic (CD) allylic benzoate method. The absolute stereochemistries of the new compounds as well as that of the known dictyol B (**5**) and dictyotadiol (**7**) were determined. These absolute configurations were opposite to that reported for pachydictyol A (**4**).

The circular dichroic allylic benzoate method, an extension of the nonempirical exciton chirality method, has been successfully used in various compounds for absolute configuration studies.[1] We have applied this method to several diterpenoids isolated from brown seaweeds of the genus *Dictyota*.

Results and Discussion

From an undetermined species of seaweed of the genus *Dictyota*, collected in the Canary Islands,[2,3] were isolated three new bicarbocyclic diterpenes, dictyotriol C (**1**), D (**2**), and E (**3**), in addition to the previously isolated pachydictyol A (**4**),[4] dictyol B (**5**),[5] dictyol C (**6**),[6] and dictyotadiol (**7**).[7]





1 R_1 = OH, R_2 = H, R_3 = OH

2 R_1 = H, R_2 = OH, R_3 = OH

8 R_1 = OAc, R_2 = H, R_3 = OAc

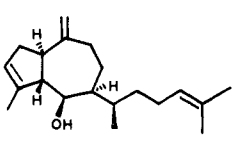
9 R_1 = H, R_2 = OAc, R_3 = OAc

16 R_1 = OBz, R_2 = H, R_3 = OAc

17 R_1 = H, R_2 = OBz, R_3 = OAc

3 R = OH

10 R = OAc



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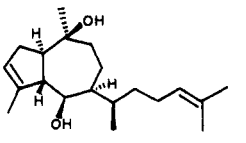

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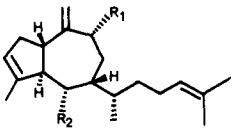


5 R_1 = OH, R_2 = OH

11 R_1 = OAc, R_2 = OH

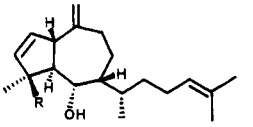
18 R_1 = OBz, R_2 = OH

19 R_1 = OBz, R_2 = OBz

20 R_1 = OBz, R_2 = O

21 R_1 = OBnPh, R_2 = OBnPh

22 R_1 = OBnPh, R_2 = OH



7 R = OH

23 R = OBz

The structures of compounds **1–3** have been determined on the basis of spectroscopic evidence. The ^{1}H NMR spectra indicated that **1** and **2** have a structure very similar to that of dictyol B, with the exception of the side-chain moiety. The absence of the isopropylidene group and the presence of an isopropenyl group in the side chain, δ 1.70 (s, 3 H), 5.17 (s, 1 H), and 4.94 (s, 1 H) and δ 1.73 (s, 3 H), 5.19 (s, 1 H), and 4.95 (br s, 1 H), for dictyotriol C (**1**) and D (**2**) respectively, were clear from the ^{1}H NMR spectra, and upon acetylation the corresponding diacetate derivatives **8** and **9** were obtained.

Difficulties arising with the isolation of compound **3** suggested acetylation. Dictyotriol E acetate (**10**) has a structure very similar to that of dictyol B acetate (**11**), from which it differs only in the side-chain moiety. The presence of a signal in the ^{1}H NMR spectrum at δ 1.27 (s, 6 H), together with another in the ^{13}C NMR spectrum at 70.8 ppm (s), was assigned to an isopropyl alcohol moiety, and the signals at δ 5.67 (d, J = 16.2 Hz, 1 H) and 5.56 (dd, J = 16.2 and 5.7 Hz, 1 H) in the ^{1}H NMR spectrum and at 125.4 (d) and 140.5 (d) ppm in the ^{13}C NMR spectrum also showed the presence of a disubstituted unconjugated double bond (Table I).

Final confirmation of the assigned structures was achieved by chemical transformation of dictyol B (**5**) to dictyotriol C, D, and E, as shown in Scheme I. Acetylation

(1) (a) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590. (b) Gonnella, N. C.; Nakanishi, K.; Martín, V. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3775. (c) Harada, N.; Yokota, Y.; Iwabuchi, J.; Uda, H.; Ochi, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1220. (d) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

(2) González, A. G.; Martín, J. D.; González, B.; Ravelo, J. L.; Pérez, C.; Rafii, S.; Clardy, J. *J. Chem. Soc., Chem. Commun.* **1984**, 669.

(3) Clardy, J.; Duyne, G. V.; González, A. G.; Manta, E.; Martín, J. D.; Pérez, C.; Ravelo, J. L.; Schulte, G. K. *J. Chem. Soc., Chem. Commun.* **1987**, 767.

(4) Hirschfeld, D. R.; Fenical, W.; Lin, G. H. Y.; Wing, R. M.; Radlick, P.; Sims, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 4049.

(5) Fattorusso, E.; Magno, S.; Mayol, L.; Santacroce, C.; Sica, D.; Amico, V.; Oriente, G.; Piattelli, M.; Tringali, C. *J. Chem. Soc., Chem. Commun.* **1976**, 575.

(6) Danise, B.; Minale, L.; Riccio, R.; Amico, V.; Oriente, G.; Piattelli, M.; Tringali, C.; Fattorusso, E.; Magno, S.; Mayol, L. *Experientia* **1977**, *33*, 413.

(7) Faulkner, D. J.; Ravi, B. N.; Finer, J.; Clardy, J. *Phytochemistry* **1977**, *16*, 991.

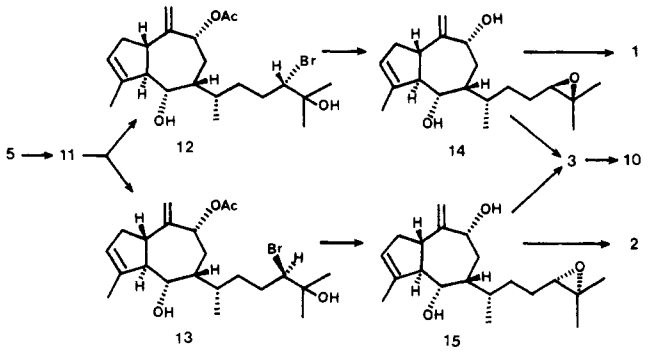
0022-3263/88/1953-4797$01.50/0

Table I. ^{13}C NMR Data[a]

carbon	4	1	2	5	10	11
1	46.1	43.0	43.1	43.0	43.3	43.1
2	34.8	33.9	33.7	33.8	33.9	33.7
3	124.0	124.0	124.1	123.8	124.3	123.9
4	141.4	141.3	141.2	140.9	140.8	141.0
5	60.5	61.0	61.3	61.2	61.5	61.1
6	75.1	74.4	74.6	74.9	74.9	74.5
7	47.8	44.6	44.4	43.8	43.4	43.9
8	23.5	29.6	30.9	33.4	33.9	30.2
9	40.6	76.5	76.5	76.4	77.3	77.4
10	152.6	154.7	154.7	154.5	149.6	149.6
11	35.1	34.1	35.5	35.0	35.5	34.7
12	33.9	33.9	33.7	35.1	38.2	35.0
13	25.7	32.0	32.6	25.7	125.4	25.6
14	124.7	74.9	76.8	124.6	140.5	124.6
15	131.5	147.9	147.8	131.5	70.8	131.6
16	25.6	18.1	17.6	25.7	30.1	25.6
17	15.8	15.8	15.8	15.6	15.7	15.6
18	107.1	104.1	104.2	104.0	105.1	104.7
19	17.7	17.9	17.9	17.5	17.9	17.4
20	17.5	110.8	111.5	17.7	30.1	17.7
					21.4 (q)	21.2 (q)
					159.0 (s)	169.9 (s)

[a] δ values are relative to TMS in $CDCl_3$.

Scheme I



of **5** with acetic anhydride in pyridine led to dictyol B acetate (**11**), which was treated with *N*-bromosuccinimide in THF/H_2O at 0 °C to give a mixture of **12** and **13**, which were isolated chromatographically over silica gel. These compounds were transformed separately with K_2CO_3/MeOH to give the epoxides **14** and **15**, respectively, which upon treatment with Al_2O_3/hexane[8] at room temperature were converted into the corresponding target compounds dictyotriol C and D. Alternatively, transformation of **14** or **15** with diphenyl diselenide/sodium borohydride/hydrogen peroxide[9] and acetylation led to dictyotriol E acetate (**10**).

The absolute configurations of these diterpenoids with allylic alcohol functionalities were determined by the circular dichroic (CD) allylic benzoate method.[1] In the case of dictyotriol C and D, the absolute configurations of the two allylic alcohol moieties, one in the side chain and the other in the ring, were determined independently. Acetylation of compounds **14** and **15** followed by treatment with Al_2O_3/hexane and benzoylation with *p*-bromobenzoyl chloride/pyridine yielded the two diastereomeric acyclic allylic benzoates **16** and **17**, respectively. Subsequent CD analyses clarified their absolute configurations:[1b] **16**, λ_{ext} = 236 nm ($\Delta\epsilon$ = −3.4) and **17**, λ_{ext} = 248 nm ($\Delta\epsilon$ = +0.8); hence 14*R* and 14*S*, respectively.

Determination of the absolute configuration of the exocyclic allylic alcohol moiety was performed on dictyol B (**5**), which belongs to the same stereochemical series as compounds **1**–**3**.

Benzoylation of **5** with *p*-bromobenzoyl chloride/silver triflate in CH_2Cl_2/pyridine[10] gave the monobenzoate derivative **18**, which showed a negative Cotton effect at λ_{ext} = 239 nm ($\Delta\epsilon$ = −2.7). The CD data of the allylic benzoates containing exocyclic[1c,11,12] as well as endocyclic double bonds can be similarly annotated; the negative CD sign of **18** thus results in the absolute stereochemistry shown.[13] However, since this turns out to be opposite to the absolute configuration of pachydictyol A (**4**, isolated from the brown alga *Pachydictyon coriaceum*) as determined by X-ray crystallography,[4] other methods were explored. Dibenzoate **19**, obtained in a very small yield, showed no split CD due to the coplanarity of the two benzoate groups, and therefore the common dibenzoate chirality method[14] was not applicable. Epimerization of compound **18** at C-6 was then attempted in order to avoid coplanarity of these chromophores. However, oxidation of the severely hindered 6-OH with CrO_3·2Py/CH_2Cl_2 to the keto benzoate **20**, followed by $NaBH_4$/MeOH reduction, gave the same alcohol benzoate **18**.

It has recently been shown that the CD spectra of *p*-phenylbenzyl ethers can be interpreted in a manner similar to those of the benzoates in the exciton chirality treatment.[15] Application of this chromophore to dictyol B (**5**) was thereby investigated. The 6,9-bis(*p*-phenylbenzyl ether) **21**, prepared by treatment of **5** with *p*-phenylbenzyl bromide/NaH/THF:DMF (4:1), displayed no coupled Cotton effects, again due to coplanarity of the two chromophores. However, the 9-mono(*p*-phenylbenzyl ether) **22**, obtained as a minor product in the *p*-phenyl-

(8) Soshi, V. S.; Damodaran, N. P.; Dev, S. *Tetrahedron* **1968**, *24*, 5817.
(9) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.
(10) Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3875.
(11) Harada, N.; Ohashi, M.; Nakanishi, K. *J. Am. Chem. Soc.* **1968**, *90*, 7349.
(12) The CD spectrum of the 3-acetate 17-*p*-bromobenzoate of 16-methylene-5-androstene-3β,17α-diol (239 nm, $\Delta\epsilon$ = +4.3) is also in agreement with the general allylic benzoate method.[1a] The stereochemistry at C-17 was determined by the appearance of a NOE at 17-H upon irradiation of the C-18 methyl. We are grateful to Dr. J. Edwards, Syntex Research, for the gift of the starting steroid sample.
(13) Conformational analysis is not necessarily required, because the exciton chirality between the *p*-bromobenzoate and double-bond chromophores is always negative, regardless of the conformational change of the methylenecycloheptane ring.
(14) Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1969**, *91*, 3989.
(15) Takeda, R.; Zask, A.; Nakanishi, K.; Park, M. H. *J. Am. Chem. Soc.* **1987**, *109*, 914.

benzylation, exhibited a negative CD at λ_{ext} = 247 nm ($\Delta\epsilon$ = −1.1), thus supporting the same absolute configuration as that derived from benzoate 18.

Additional support was given by the CD data of the 4-*p*-bromobenzoate of dictyotadiol (**23**): λ_{ext} = 235 nm ($\Delta\epsilon$ = +5.0).

The absolute stereochemistry of the new compounds dictyotriol C (**1**), D (**2**), and E (**3**), as well as of the known dictyol B (**5**) and dictyotadiol (**7**), were thus found to be as shown.

Experimental Section

General. Melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer, and UV spectra were performed on a Perkin-Elmer Model 320UV. CD spectra were recorded on a JASCO J-500A spectropolarimeter interfaced with a JASCO DP500N data processor and an IBM-PC apparatus. Optical rotations were determined with a Perkin-Elmer Model 241 polarimeter. ^1H and ^{13}C NMR were recorded on Bruker Model WP 200SY and Model WM 250 spectrometers (δ scale). Low-resolution MS data were obtained with a Ribermag R10-10 and a VG Micromass Model ZAB-2F. High-resolution MS were obtained from a VG Micromass ZAB-2F. Column and dry column chromatography were performed on silica gel G, all Merck products. The TLC plates were developed by spraying with $AcOH/H_2O/H_2SO_4$ (80:16:4) and heating. All solvents were purified by standard techniques. Anhydrous sodium sulfate was used for drying solutions. All reagents used were of the best grade commercially available. Prior to measurement of the CD spectra, all compounds were purified by HPLC (EtOAc/*n*-hexane solvent systems, silica gel column). The concentrations of the CD samples (CH_3CN)[16] were ascertained from the UV spectra, using the standard values of 21 300 for the mono-*p*-bromobenzoates[1b] and 20 300 for the mono-*p*-phenylbenzylates.[15]

General Procedure for Benzoylation. The solution of the starting material in dry pyridine with DMAP as catalyst is treated with a 1.5× excess of *p*-bromobenzoyl chloride. The resulting pale yellow solution is heated at 60 °C and stirred overnight (12 h). The reaction is quenched with a few drops of MeOH, and the excess solvent is removed under reduced pressure in the presence of heptane or toluene. The residue is then spotted on preparative TLC or fractionated on flash column chromatography to give the benzoate.

General Procedure for Acetylation. The starting material dissolved in dry pyridine is treated with an excess of acetic anhydride, leaving the solution with stirring at room temperature overnight (12 h). The mixture is quenched with MeOH, and the excess solvent is removed under reduced pressure in the presence of heptane or toluene. The residue is then spotted on preparative TLC or fractionated on flash column chromatography to give the acetate.

Collection, Extraction, and Chromatographic Separation. The *Dictyota* sp. was collected in Orzola, Lanzarote (Canary Islands), during the summer of 1983, air-dried, and ground in a Wiley mill to a 1-mm particle size. The dried alga (5.35 kg) was extracted in a Soxhlet apparatus with acetone. The extracts were concentrated, and the resulting suspension was extracted with $CHCl_3$. The $CHCl_3$ extracts were evaporated to leave a dark green viscous oil (195 g, 3.6% dry weight), which was chromatographed on silica gel, with *n*-hexane and mixtures of increasing polarity obtained with *n*-hexane and EtOAc as eluents; 1-L fractions were collected.

Pachydictyol A (4). Fractions eluted in the general chromatography in *n*-hexane/EtOAc (95:5) were combined and rechromatographed to obtain pachydictyol A (600 mg, 0.3%), which had physical and spectral properties identical with those quoted for authentic material.[4]

Dictyotadiol (7), Dictyol B (5), and Dictyol C (6). These diterpenoids were eluted by using mixtures of *n*-hexane/EtOAc (85:15). They were obtained in pure form by successive chromatographies on silica gel; properties of dictyotadiol (157 mg, 0.08%), dictyol B (490 mg, 0.25%), and dictyol C (82 mg, 0.04%) were identical in all respects with those reported for authentic material.[7,5,6]

Compound 1. The diterpenoid compound **1** was eluted by using mixtures of *n*-hexane/EtOAc (60:40). It was obtained in pure form by rechromatography (19.5 mg, 0.01%): mp 165–167 °C; $[\alpha]_D$ 77.4° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) ν_{max} = 3600, 3420, 3000, 2920, 1450, 1380, and 905 cm^{-1}; MS (EI), *m/e* (relative intensity) 302 (0.6, $M^+ - H_2O$), 284 (4.1, $M^+ - 2H_2O$), 266 (2.5, $M^+ - 3H_2O$), 251 (6.7), 202 (2.8), 199 (15.2), 185 (17.8), 157 (100.0); ^1H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.0 Hz, 3 H), 1.70 (s, 3 H), 1.77 (s, 3 H), 3.97 (m, 2 H), 4.10 (t, *J* = 6.0 Hz, 1 H), 4.83 (s, 1 H), 4.94 (br s, 2 H), 5.17 (s, 1 H), 5.32 (br s, 1 H); HRMS *m/e* calcd for $C_{20}H_{30}O_2$ ($M^+ - H_2O$) 302.2244, found 302.2257; calcd for $C_{20}H_{28}O$ ($M^+ - 2H_2O$) 284.2138, found 284.2104; calcd for $C_{20}H_{26}$ ($M^+ - 3H_2O$) 266.2033, found 266.2067.

Compound 2. The fractions eluted in the general chromatography in *n*-hexane/EtOAc (50:50) were submitted to successive chromatographies. The compound was purified by recrystallization in *n*-hexane/$CHCl_3$ (74.5 mg, 0.03%): mp 164–166 °C; $[\alpha]_D$ +72.4° (*c* 0.4, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3600, 3250, 3000, 2920, 1450, 1380, and 905 cm^{-1}; MS (EI), *m/e* (relative intensity) 302 (1.1, $M^+ - H_2O$), 284 (7.1, $M^+ - 2H_2O$), 266 (4.5, $M^+ - 3H_2O$), 251 (7.5), 202 (15.6), 199 (12.9), 185 (10.9), 157 (84.5); ^1H NMR ($CDCl_3$) δ 1.03 (d, *J* = 6.0 Hz, 3 H), 1.73 (s, 3 H), 1.79 (s, 3 H), 3.93 (br d, *J* = 6.0 Hz, 1 H), 4.05 (m, 2 H), 4.85 (s, 1 H), 4.95 (br s, 2 H), 5.19 (s, 1 H), 5.34 (br s, 1 H); HRMS *m/e* calcd for $C_{20}H_{30}O_2$ ($M^+ - H_2O$) 302.1244, found 302.1214; calcd for $C_{20}H_{28}O$ ($M^+ - 2H_2O$) 284.2138, found 284.2099; calcd for $C_{20}H_{26}$ ($M^+ - 3H_2O$) 266.2033, found 266.2025.

Compound 8: diacetate of compound **1**; ^1H NMR ($CDCl_3$) δ 0.96 (d, *J* = 6.1 Hz, 3 H), 1.67 (s, 3 H), 1.73 (s, 3 H), 2.01 (s, 3 H), 2.08 (s, 3 H), 3.85 (m, 1 H), 4.82 (s, 1 H), 4.86 (s, 1 H), 4.88 (s, 1 H), 4.92 (s, 1 H), 5.07 (m, 2 H), 5.28 (br s, 1 H).

Compound 9: diacetate of compound **2**; ^1H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.0 Hz, 3 H), 1.70 (s, 3 H), 1.76 (s, 3 H), 2.04 (s, 3 H), 2.12 (s, 3 H), 3.89 (m, 1 H), 4.90 (br s, 2 H), 4.95 (br s, 2 H), 5.13 (t, *J* = 6.3 Hz, 2 H), 5.32 (br s, 1 H).

Compound 3. The triol was obtained from the same fractions as compound **2**, *n*-hexane/EtOAc (50:50). Acetylations of the mother liquors of compound **2** with acetic anhydride (2 mL) and pyridine (2 mL) and further chromatography on silica gel, using a mixture of *n*-hexane/EtOAc (60:40) as eluent, led to the monoacetate of compound **3** (**10**, 23.5 mg, 0.01%): oil, $[\alpha]_D$ + 56.8° (*c* 2.29, $CHCl_3$); IR (film) ν_{max} 3585, 3450, 3000, 2960, 2920, 1720, 1640, 1370, 1245, and 900 cm^{-1}; MS (EI), *m/e* (relative intensity) 344 (0.7, $M^+ - H_2O$), 326 (1.10, $M^+ - 2H_2O$), 302 (1.15, $M^+ -$ AcOH), 284 (19.0, $M^+ -$ AcOH $- H_2O$), 266 (16.7), 157 (100.0); ^1H NMR ($CDCl_3$) δ 0.98 (d, *J* = 6.2 Hz, 3 H), 1.27 (s, 6 H), 1.76 (s, 3 H), 2.12 (s, 3 H), 3.87 (br d, *J* = 6.8 Hz, 1 H), 4.90 (br s, 1 H), 4.96 (br s, 1 H), 5.12 (m, 1 H), 5.31 (br s, 1 H), 5.67 (d, *J* = 16.2 Hz, 1 H), 5.56 (dd, *J* = 16.2 and 5.7 Hz, 1 H); HRMS *m/e* calcd and found for $C_{20}H_{28}O$ ($M^+ -$ AcOH $- H_2O$) 284.2139; calcd for $C_{20}H_{26}$ ($M^+ -$ AcOH $- 2H_2O$) 266.2033, found 266.1998.

Preparation of 11. Dictyol B acetate (410 mg, 1.13 mmol) was prepared from dictyol B (355 mg, 1.17 mmol) according to the standard procedure for acetylation and had spectral properties identical with those quoted for authentic material.[7]

Compounds 12 and 13. To a solution of **11** (401 mg, 1.11 mmol) in THF (20 mL) and a few drops of water at −10 °C was slowly added NBS (213 mg, 1.2 mmol) in THF (10 mL), and the mixture was stirred for 10 min. Subsequently, the reaction mixture was poured onto ice and extracted with ether in the usual way. Removal of the solvent and chromatography on silica gel with a mixture of *n*-hexane/EtOAc (40:60) as eluent afforded the bromohydrins **12** (39.4 mg, 0.09 mmol) and **13** (64.8 mg, 0.15 mmol). Compound **12**: oil; $[\alpha]_D$ +25.9° (*c* 0.11, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.00 (d, *J* = 6.0 Hz, 3 H), 1.32 (s, 3 H), 1.35 (s, 3 H), 1.77 (s, 3 H), 2.13 (s, 3 H), 3.90 (d, *J* = 8.1 Hz, 1 H), 3.95 (d, *J* = 10.0 Hz, 1 H), 4.91 (s, 1 H), 4.96 (s, 1 H), 5.14 (br d, *J* = 10.1 Hz, 1 H), 5.35 (br s, 1 H); MS (EI), *m/e* (relative intensity) 384/382 (0.2/0.2, $M^+ -$ AcOH), 366 (3.4), 364 (6.4), 362 (3.3), 284 (4.9), 267 (9.4), 185 (19.0), 183 (24.7), 157 (71.3). Compound **13**: oil; $[\alpha]_D$ +70.2° (*c* 0.37, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.94 (d, *J* = 6.1

(16) CD spectra were measured in CH_3CN rather than in MeOH to avoid ester exchange during CD/UV measurements: Golik, J.; Liu, H. W.; Dinovi, M.; Furukawa, J.; Nakanishi, K. *Carbohydr. Res.* **1983**, *118*, 135.

Hz, 3 H), 1.29 (s, 3 H), 1.30 (s, 3 H), 2.09 (s, 3 H), 3.90 (br d, J = 8.0, 1 H), 3.97 (br d, J = 10.5 Hz, 1 H), 4.87 (s 1 H), 4.93 (s, 1 H), 5.09 (br d, J = 12.0 Hz, 1 H), 5.29 (br s, 1 H); MS (EI), m/e (relative intensity) 366/364 (1.3/1.3, $M^+ - AcOH - H_2O$), 284 (4.7), 267 (8.8), 185 (14.1), 183 (4.9), 157 (70.3).

Compound 14. An excess of K_2CO_3 was added to a solution of compound **12** (39.4 mg, 0.09 mmol) in MeOH (5 mL) at room temperature. After 30 min, the reaction was quenched with water and extracted with ether in the usual way. The residue obtained was submitted to chromatography to give the epoxide **14** (27.6 mg, 0.09 mmol) as a noncrystalline solid: $[\alpha]_D$ +71.1° (c 0.90, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.01 (d, J = 6.2 Hz, 3 H), 1.24 (s, 3 H), 1.28 (s, 3 H), 1.77 (s, 3 H), 2.73 (t, J = 5.8 Hz, 1 H), 3.90 (br d, J = 8.1 Hz, 1 H), 4.00 (t, J = 8.0 Hz, 1 H), 4.93 (s, 1 H), 5.18 (s, 1 H), 5.31 (br s, 1 H); MS (EI), m/e (relative intensity) 302 (1.2, $M^+ - H_2O$), 284 (7.7), 264 (5.0), 256 (10.9), 213 (11.0), 198 (20.1), 185 (25.4), 175 (21.3), 157 (100.0).

Compound 15. Similarly to **12**, compound **13** (64.8 mg, 0.15 mmol) was treated with an excess of K_2CO_3 to give the epoxide **15** as a noncrystalline solid (44.5 mg, 0.14 mmol): $[\alpha]_D$ +64.7° (c 2.72, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.00 (d, J = 6.0 Hz, 3 H), 1.23 (s, 3 H), 1.27 (s, 3 H), 1.75 (s, 3 H), 2.74 (t, J = 5.2 Hz, 1 H), 3.87 (br d, J = 7.6 Hz, 1 H), 3.99 (t, J = 6.5 Hz, 1 H), 4.91 (s, 1 H), 5.16 (s, 1 H), 5.30 (br s, 1 H); MS (EI), m/e (relative intensity) 302 (1.0, $M^+ - H_2O$), 284 (5.8), 264 (2.0), 256 (6.3), 213 (6.6), 198 (19.0), 185 (24.0), 175 (19.6), 157 (100.0).

Preparation of 1. The epoxide **14** (10.2 mg, 0.032 mmol) dissolved in CH_2Cl_2 (1 mL) was adsorbed in activated Al_2O_3 (200 mg). After evaporation of the CH_2Cl_2 by passage of Ar, n-hexane (10 mL) was added. The suspension was stirred for 18 h at room temperature under N_2. The reaction mixture was chromatographed on silica gel, with mixtures of n-hexane/EtOAc (30:70) as eluents, to give compound **1** (2.7 mg, 0.008 mmol).

Preparation of 2. Compound **15** (15.0 mg, 0.047 mmol) was treated similarly to **14** to afford compound **2** (3.8 mg, 0.012 mmol).

Preparation of 10. To a solution of diphenyl diselenide (6.8 mg, 0.024 mmol) in anhydrous EtOH (3 mL) was added $NaBH_4$ (1.8 mg, 0.048 mmol) under N_2. To this was added a solution of **15** (13.5 mg, 0.042 mmol) in anhydrous EtOH (1 mL), and the mixture was refluxed for 3 h. The solution was cooled to 0 °C and treated with 30% H_2O_2 (45 μL). After completion of the addition, the mixture was stirred at room temperature for 2 h. The solution was diluted with water, washed with $NaHCO_3$, dried (Na_2SO_4), and evaporated to yield compound **3** (9.7 mg, 0.030 mmol) after chromatographic purification. Acetylation of **3** gave compound **10** (10.4 mg, 0.029 mmol).

As described for compound **15** (vide supra), compound **14** (8.3 mg, 0.026 mmol) led to **10** (6.2 mg, 0.017 mmol).

Preparation of 16 and 17. The acetate epoxide derivative (12.7 mg, 0.035 mmol) obtained by treatment of **15** (11.5 mg, 0.036 mmol) with $(AcO)_2O$ and pyridine was transformed with Al_2O_3, as described for compound **1** (vide supra), into the corresponding allylic alcohol (3.4 mg, 0.009 mmol), which was benzoylated with p-bromobenzoyl chloride (0.014 mmol) in dry pyridine (1 mL) according to the standard procedure for benzoylation. The reaction mixture was chromatographed on a preparative TLC plate, n-hexane/EtOAc (70:30), to afford the pure product **17** (4.5 mg, 0.008 mmol): ^1H NMR ($CDCl_3$) δ 0.98 (d, J = 6.0 Hz, 3 H), 1.65 (s, 3 H), 1.74 (s, 3 H), 2.08 (s, 3 H), 3.84 (m, 1 H), 4.87 (s, 1 H), 4.94 (s, 2 H), 4.99 (s, 1 H), 5.11 (m, 1 H), 5.29 (br s, 1 H), 5.35 (m, 1 H), 7.60 (d, J = 8.5 Hz, 2 H), 7.90 (d, J = 8.5 Hz, 2 H); UV (CH_3CN) λ_{max} 243 nm; CD (CH_3CN) λ_{ext} 248 nm ($\Delta\epsilon$ = +0.8).

Similarly to **15**, compound **14** (6.5 mg, 0.020 mmol) was transformed into the allylic benzoate **16** (2.6 mg, 0.005 mmol), which was chromatographed on a preparative TLC plate, n-hexane/EtOAc (70:30): ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6.0 Hz, 3 H), 1.65 (s, 3 H), 1.74 (s, 3 H), 2.08 (s, 3 H), 3.81 (br dd, J = 3.5 and 7.5 Hz, 1 H), 4.87 (br s, 2 H), 4.92 (s, 1 H), 4.98 (s, 1 H), 5.09 (m, 1 H), 5.28 (br s, 1 H), 5.38 (m, 1 H), 7.53 (d, J = 8.5 Hz, 2 H), 7.85 (d, J = 8.5 Hz, 2 H); UV (CH_3CN) λ_{max} 243 nm; CD (CH_3CN) λ_{ext} 236 nm ($\Delta\epsilon$ = −3.4).

Benzoylation of Dictyol B (5). This reaction was performed by an alternative in situ method[17] to afford also some of the bis(p-bromobenzoate) derivative, because the hydroxyl at C-6 is severely hindered. To a solution of dictyol B (8.6 mg, 0.028 mmol) in dry CH_2Cl_2/pyridine (8:2) (2 mL) were added 4-bromobenzoyl chloride (18.6 mg, 0.085 mmol) and silver triflate (21.8 mg, 0.085 mmol). The suspension was stirred for 1 h at room temperature under N_2, and the excess reagent was destroyed with H_2O (6 drops). The precipitated silver salt was filtered and washed with CH_2Cl_2 (three times), and the filtrate was dried in vacuo. Purification by preparative TLC, n-hexane/EtOAc (80:20), afforded the monobenzoate (11.1 mg, 0.023 mmol) and the dibenzoate (0.8 mg, 0.001 mmol) derivatives of dictyol B, compounds **18** and **19**, respectively. **18**: ^1H NMR ($CDCl_3$) δ 1.03 (d, J = 6.4 Hz, 3 H), 1.59 (s, 3 H), 1.66 (s, 3 H), 1.79 (s, 3 H), 3.94 (br dd, J = 3.4 and 7.6 Hz, 1 H), 4.95 (s, 1 H), 5.03 (s, 1 H), 5.10 (t, J = 7.3 Hz, 1 H), 5.34 (br s, 1 H), 5.36 (m, 1 H), 7.59 (d, J = 8.4 Hz, 2 H), 7.96 (d, J = 8.4 Hz, 2 H); MS-DCI (NH_3), m/e (relative intensity) 506/504 (100/100, $M^+ + NH_3$), 426 (35, $M^+ + H + NH_3 - Br$), 304 (43, $M^+ + NH_3 - BrBzOH$), 287 (15, $M^+ + H - BrBzOH$), 269 (23, $M^+ + H - BrBzOH - H_2O$); UV (CH_3CN) λ_{max} 243 nm; CD (CH_3CN) λ_{ext} 239 nm ($\Delta\epsilon$ = −2.7).

Preparation of 21 and 22. To a solution of dictyol B (2.8 mg, 9.2 μmol) in anhydrous THF/DMF (4:1) (250 μL) was added NaH (excess) under N_2 at room temperature. After 1 h, a solution of p-phenylbenzyl bromide (11.4 mg, 46.2 μmol) in THF (200 μL) was added, leaving the solution with stirring for 2 days. The mixture was quenched with MeOH and filtered. The filtrate was then concentrated in vacuo and purified on a microflash silica gel column, n-hexane/EtOAc (90:10), to afford the mono(p-phenylbenzyl ether) (1.2 mg, 2.6 μmol) and the bis(p-phenylbenzyl ether) (2.5 mg, 3.9 μmol) derivatives of dictyol B, compounds **22** and **21**, respectively. Compound **22**: ^1H NMR ($CDCl_3$) δ 0.96 (d, J = 6.3 Hz, 3 H), 1.59 (s, 3 H), 1.66 (s, 3 H), 1.77 (s, 3 H), 3.78 (m, 1 H), 3.88 (m, 1 H), 4.55 (d, J = 12.2 Hz, 1 H), 4.70 (d, J = 12.2 Hz, 1 H), 5.02 (br s, 1 H), 5.08 (br t, J = 7.0 Hz, 1 H), 5.28 (s, 1 H), 5.34 (s, 1 H), 7.58–7.33 (m, 9 H); MS (EI), m/e 470 (M^+); UV (CH_3CN) λ_{max} 253 nm; CD (CH_3CN) λ_{ext} 247 nm ($\Delta\epsilon$ = −1.1).

Benzoylation of Dictyotadiol (7). Compound **7** was benzoylated similarly to dictyol B.[17] 4-Bromobenzoyl chloride (4.0 mg, 18.1 μmol) and silver triflate (4.6 mg, 18.1 μmol) were added to a solution of dictyotadiol (1.1 mg, 3.61 μmol) in dry CH_2Cl_2 (800 μL) and dry pyridine (100 μL). The suspension was stirred for 3 h at room temperature under N_2, and the excess reagent was destroyed with H_2O (4 drops). The precipitated silver salt was filtered and washed with CH_2Cl_2 (three times), and the filtrate was dried in vacuo and then extracted with n-hexane. Purification by HPLC (Phenomenex IB-SIL 5 μm, 4.6 × 250 mm, n-hexane/EtOAc (93:7), 2 mL/min, 254 nm) afforded the desired monobenzoate derivative **23** (400 μg, 0.82 μmol): ^1H NMR ($CDCl_3$; proton NMR assignments were based upon decoupling experiments) δ 1.00 (d, J = 5.5 Hz, 3 H, CH_3-19), 1.61 (s, 3 H, CH_3-16), 1.68 (s, 3 H, CH_3-20), 1.87 (s, 3 H, CH_3-17), 4.00 (m, 1 H, H-6), 4.80 and 4.89 (2 br s, 2 H, H-18's), 5.11 (m, 1 H, H-14), 5.51 (m, 1 H, H-3), 6.12 (m, 1 H, H-2), 7.53 (d, J = 8.5 Hz, 2 H, benzoate-3,5 H's), 7.87 (d, J = 8.5 Hz, 2 H, benzoate-2,6 H's); UV (CH_3CN) λ_{max} 243 nm; CD (CH_3CN) λ_{ext} 235 nm ($\Delta\epsilon$ = +5.0); MS-DCI (NH_3), m/e (relative intensity) 506/504 (1/1, $M^+ + H + NH_3$), 287 (40, $M^+ + H - BrBzOH$), 269 (100, $M^+ + H - BrBzOH - H_2O$).

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Registry No. 1, 115890-56-7; **1** (R_3 = OAc), 115890-71-6; **2**, 115940-72-2; **2** (R_3 = OAc), 115940-78-8; **3**, 115890-57-8; **4**, 50299-47-3; **5**, 61263-83-0; **6**, 62820-33-1; **7**, 63908-63-4; **8**, 115890-58-9; **9**, 115940-73-3; **10**, 115890-59-0; **11**, 115890-60-3; **12**, 115890-61-4; **13**, 115940-74-4; **14**, 115890-62-5; **14** (9-acetate), 115890-70-5; **15**, 115940-75-5; **15** (9-acetate), 115940-77-7; **16**, 115890-63-6; **17**, 115940-76-6; **18**, 115890-64-7; **19**, 115890-65-8; **20**, 115890-66-9; **21**, 115890-67-0; **22**, 115890-68-1; **23**, 115890-69-2.

(17) Vázquez, J. T.; Wiesler, W. T.; Nakanishi, K. *Carbohydr. Res.* **1988**, *176*, 175.