heated in a sealed tube at 120 °C for 4.5 h. The reaction mixture was analyzed by GC-MS and contained 0.01% of propionaldehyde (0.00014 g, 0.0024 mmol). Relative to the original concentration of **1a**, the yield of propionaldehyde can be estimated as 0.53%.

Proof of 2-Hydroxy-4-methyl-1,3,2-dioxaphospholane 2-Oxide (18) Formation from 7. The reaction mixture prepared previously containing *O*-ethyl phosphoric acid monoester was dissolved in $CDCl_3$ (1.5 mL), left at room temperature for 48 h, and then analyzed (^{31}P NMR ($CDCl_3$) δ 19.07 (**18**), 16.67, and 16.43 (both **7**), with a broad complex signal at −2.0 to +2.0). The solvent was evaporated in vacuo and replaced by ether (5 mL). To the resultant solution was added a solution of diazomethane (0.0369 g, 0.880 mmol) in ether (40 mL). After 5 h at room temperature, the reaction mixture had ^{31}P ($CDCl_3$) δ 17.81, 17.54, 16.67, 16.44, and a broad complex signal at −2.0 to +2.0. The observed intensity of the signals with δ 17.81 and 17.54 increased considerably after a mixture of the authentic[24] isomeric methyl esters **19** (δ 17.66 and 17.43) was added to the sample.

Reaction of *N,N*-Diethyl Metaphosphoramidate with 2-Methyloxirane. A solution of **20** (0.0928 g, 0.247 mmol) and 2-methyloxirane (0.032 g, 0.551 mmol) in 3 mL of toluene was heated in a closed tube for 4.5 h at 120 °C. The solvent was then removed by evaporation and the residue was taken up in $CDCl_3$. The ^{31}P NMR spectrum contained only one signal for a reaction product (δ 16.9), along with a small signal for unreacted starting material. Analysis by GC showed the product to consist of a 1:2 mixture of isomers with retention times of 11.3 and 11.7 min, respectively. The mass spectra of the GC peaks were nearly identical. For both the base peak had m/z 178 ($M^+ - CH_3$). For the former, M^+ (calcd for $C_7H_{16}NO_3P$ 193, found 193) had 14.3% relative abundance and for the latter 12.9%. Other strong signals included m/z 150 ($M^+ - CH_3 - C_2H_4$), 138, and 110.

Generation of *trans*- and *cis*-2-Ethoxy-5-methyl-1,3,2-oxathiaphospholane 2-Oxides (26) and -2-Ethoxy-4-methyl-1,3,2-oxathiaphospholane 2-Oxides (25) by Heating 23 and 2-Methyloxirane. A solution of **23** (0.097 g, 0.269 mmol) and 2-methyloxirane (0.0390 g, 0.671 mmol) in toluene (3 mL) was heated in a sealed tube at 120 °C for 4 h. Evaporation of the solvent in vacuo gave a yellow oil (0.121 g) that was dissolved in $CDCl_3$ (1.5 mL) having ^{31}P NMR δ 44.85, 43.95, 42.15, and 41.29 for isomers of **26** and **25**, respectively, with others at 16.68, 16.44, and −2.03 (broad) in the ratio 1.0:1.0:4.0:4.0:9.0:9.0:23.0, respectively. GC-MS data are given in Table III.

Generation of *trans*- and *cis*-2-Ethoxy-5-methyl-1,3,2-oxathiaphospholane 2-Oxides (26) and -2-Ethoxy-4-methyl-1,3,2-oxathiaphospholane 2-Oxides (25) from *O,O*-Diethyl Phosphorothioate (29) and 2-Methyloxirane. To a solution of **29** (0.0839 g, 0.493 mmol) at 0 °C in toluene (2.5 mL) was added dropwise with stirring a solution of 2-methyloxirane (0.030 g, 0.518 mmol) in toluene (25 mL). The reaction mixture was allowed to warm to room temperature, the solvent evaporated in vacuo, and the residue dissolved in $CDCl_3$; ^{31}P NMR δ 45.47 and 44.50 for the isomers of **26** and 42.79 and 42.09 for isomers of **25**, with others at 30.98, 29.58, 0.69, and 0.059 in the ratio 1.0:1.2:2.0:2.5:9.8:1.0:2.0:5.5. Some unreacted **29** was also present (δ 67.48).

To prepare a sample for GC-MS measurements, a mixture of **29** (0.158 g, 0.927 mmol) and 2-methyloxirane (0.0554 g, 0.954 mmol) was maintained at room temperature for 4 h. GC-MS data are given in Table III.

Reaction of 2-Methyloxetane with Ethyl Metaphosphate. A mixture of 0.464 g (0.644 mmol) of 2-methyloxetane (refluxed over NaH and distilled) and **1a** (0.0860 g, 0.248 mmol) in 3 mL of toluene was heated for 6 h at 120 °C. Toluene was removed and the residue dissolved in $CDCl_3$. The ^{31}P NMR spectrum contained strong complex signals at δ −0.5 to −1.8 and very weak signals at δ −4.8 and −7.5, attributed to cyclic esters **30** (cis-trans). When the same reaction was conducted in acetonitrile, no signals for **30** were observed.

***trans*- and *cis*-2-Ethoxy-4-methyl-1,3,2-dioxaphosphorinane 2-Oxide (30).** A solution of 2-ethoxy-4-methyl-1,3,2-dioxaphosphorinane[23] (2.3 g, 0.014 mol) in benzene (25 mL) was added dropwise to a cooled (ice bath) and vigorously stirred suspension of yellow mercuric oxide (4.7 g, 0.021 mol) in benzene (100 mL). The mixture was stirred for 15 h and then filtered. The filtrate was concentrated in vacuo, and the residue was distilled under reduced pressure to give **30** as a colorless liquid (15.0 g, 59.5%): bp 100-110 °C (0.05 mm); ^{31}P NMR ($CDCl_3$) δ −5.02, −7.40 (ratio 0.07:1); ^1H NMR ($CDCl_3$) δ 1.38 (t, $^3J_{HH}$ 7.1 Hz, 3 H); 1.39 (dd, $^3J_{HH}$ 7.1 Hz, $^4J_{PH}$ 2.6 Hz, 3 H); 1.6-2.28 (m, 2 H); 4.15 (dq, $^3J_{HH}$ 7.1 Hz, $^3J_{PH}$ 5.6 Hz, 2 H); 4.2-4.8 (m, 3 H). Anal. Calcd for $C_6H_{13}O_4P$: C, 40.00; H, 7.27. Found: C, 39.57; H, 6.90.

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Absolute Configuration of Hydroazulenoid Diterpenes Based on Circular Dichroism

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The structure of a new hydroazulenoid diterpene, 9-*epi*-dictyol B (**1**), isolated from the brown alga *Glossophora kuntii*, was proposed on the basis of its spectral data and confirmed by chemical transformations. Absolute stereochemistry studies, based on the CD exciton chirality method, of the new diterpenoid 9-*epi*-dictyol B (**1**) as well as those of the previously reported dictyotadiol (**6**) led to the determination of the absolute configuration of the new compound 9-*epi*-dictyol B (**1**) and revisions of absolute configurations of previously reported diterpenoids dictyotriols C (**2**), D (**3**), and E (**4**), dictyol B (**5**), and dictyotadiol (**6**). The cause of previous erroneous results is discussed and indeed points to the extreme care which must be exercised by anyone using this method.

The exciton chirality method, a powerful tool for absolute configuration studies, has been successfully applied to a great number of synthetic and natural organic compounds,[1] and its utility has been expanded with new ap-

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plications in carbohydrates[2-4] by the recently demonstrated general validity of pairwise additivity in exciton-coupled systems.[4]

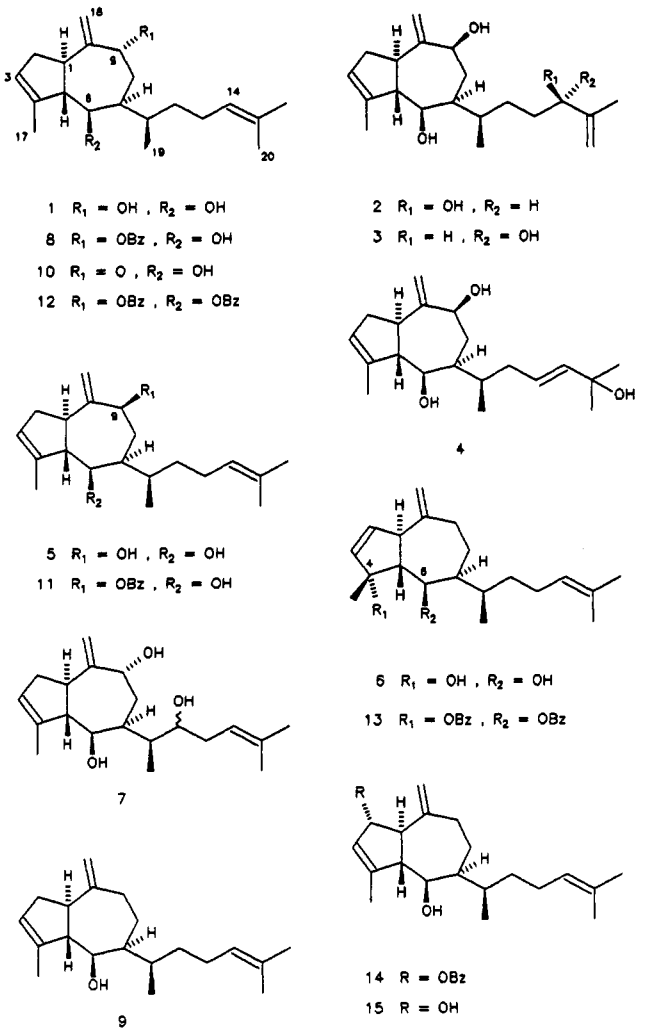
This method was applied to several diterpenoids isolated from a brown seaweed of the genus *Dictyota*.[5] We report here a revision of the absolute configurations of these hydroazulenoid diterpenes as well as the absolute configuration of a new compound, 9-*epi*-dictyol B, isolated from the brown alga *Glossophora kuntii*. It has been found that the previous opposite configurations resulted from the occurrence of an unsuspected allylic rearrangement and also by "conformational distortion". The uncorrected interpretation of the CD data of the previously reported diterpenoids is discussed.

Results and Discussion

While we were studying the absolute configuration of 9-*epi*-dictyol B (1), a new bicarbocyclic diterpene isolated from the brown alga *G. kuntii* belonging to the family Dictyotaceae, we arrived at an interesting CD observation which prompted us to carry out further studies of its absolute configuration and those of the previously reported dictyotriols C (2), D (3), and E (4), dictyol B (5), and dictyotadiol (6).[5]

The structure of the new compound 9-*epi*-dictyol B (1) was determined on the basis of spectroscopic evidence and chemical transformations. This compound had a molecular formula of $C_{20}H_{32}O_2$ in accordance with its HRMS, the oxygen atoms being due to the presence of two secondary hydroxyl groups. From its spectroscopic data, we concluded that this compound was an isomer of dictyol B (5),[6] a metabolite isolated from *Dictyota dichotoma*. Comparison of their NMR spectral data showed that they were similar. However, in the ^1H NMR spectrum of 1, both the chemical shift and the multiplicity of the H-9 hydroxy methine proton (4.53, dd, J = 2.3 and 5.2 Hz) and the chemical shifts of the exocyclic double bond protons (4.96 and 5.03) were substantially different from those reported for dictyol B,[6b] but similar to those observed in dictyotriol A (7),[7] indicating the configuration of the hydroxyl group at C-9. This was confirmed by the NOE effect observed in H-9 when the H-18 proton (5.06) was irradiated. All this spectroscopic evidence supported the structure of *epi*-dictyol B as shown in 1.

The circular dichroic (CD) allylic benzoate method[8] was



applied in order to determine the absolute configuration of this new compound. Benzoylation of 1 with *p*-bromobenzoyl chloride/pyridine gave the monobenzoate derivative 8, which showed a negative Cotton effect at λ_{ext}246.2 nm ($\Delta\epsilon = -3.3$). This result leads to an absolute configuration such as that reported for pachydictyol A (9) based on X-ray crystallography[9] and opposite to that of dictyol B (5) based on CD.[5] Although natural products with identical skeletons can occur in nature with opposite absolute configurations, this feature is rarely present. To confirm the above result we decided to transform 9-*epi*-dictyol B into its epimer at carbon 9 and, by preparing its corresponding 9-*p*-bromobenzoate derivative, to check the expected positive Cotton effect in CD. This transformation was achieved by treatment of compound 1, with MnO_2 in $CHCl_3$ to yield the corresponding keto derivative 10,[10] which was treated with $LiAlH_4$ in dry THF to lead to the desired β epimer at carbon 9.[11] This compound showed spectroscopic data identical with those of dictiol B (5),[6] including its optical activity and the negative CD spectrum of its monobenzoate derivative 11, λ_{ext} 239 nm ($\Delta\epsilon = -2.7$).[5]

The above results indicate that both dictyol B and 9-*epi*-dictyol B belong to the same stereochemical series. Then why do the two diastereomeric allylic benzoates 8 and 11 both exhibit negative Cotton effects?

In order to gain further information and thus answer this question, several studies were carried out. First, we pre-

(1) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

(2) Spectroscopic method for assigning relative and absolute configuration in acyclic 1,2,3-triols: (a) Wiesler, W. T.; Nakanishi, K. *J. Am. Chem. Soc.* **1989**, *111*, 3446. (b) Wiesler, W. T.; Nakanishi, K. *Croat. Chem. Acta* **1989**, *62*, 211.

(3) Microscale structure determination of oligosaccharides by the exciton chirality method: (a) Vázquez, J. T.; Wiesler, W. T.; Nakanishi, K. *Carbohydr. Res.* **1988**, *176*, 175. (b) Meyers, H. V.; Ojika, M.; Wiesler, W. T.; Nakanishi, K. *Carbohydr. Res.* **1990**, *197*, 15. (c) Chang, M.; Meyers, H. V.; Nakanishi, K.; Ojika, M.; Park, J. H.; Takeda, R.; Vázquez, J. T.; Wiesler, W. T. *Pure Appl. Chem.* **1989**, *61*, 1193. (d) Wiesler, W. T.; Berova, N.; Ojika, M.; Meyers, H. V.; Chang, M.; Zhou, P.; Lo, L.-C.; Niwa, M.; Takeda, R.; Nakanishi, K. *Helv. Chim. Acta* **1990**, *73*, 509.

(4) Wiesler, W. T.; Vázquez, J. T.; Nakanishi, K. *J. Am. Chem. Soc.* **1987**, *109*, 5586.

(5) Vázquez, J. T.; Chang, M.; Nakanishi, K.; Manta, E.; Pérez, C.; Martín, J. D. *J. Org. Chem.* **1988**, *53*, 4797.

(6) (a) 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. (b) Minale, L.; Riccio, R. *Tetrahedron Lett.* **1976**, *31*, 2711.

(7) Rivera, A. P.; Astudillo, L. A.; González, A. G.; Manta, E.; Cataldo, F. *J. Nat. Prod.* **1987**, *50*, 965.

(8) (a) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590. (b) Gonnella, N. C.; Nakanishi, K.; Martin, 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.

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

(10) Kubota, T.; Takeda, K. *Tetrahedron* **1960**, *10*, 1.

(11) Nasipuri, D.; Eliel, E. L. *J. Org. Chem.* **1965**, *30*, 3804.

Table I. Molecular Mechanics Data

conformer	strain energy, kcal/mol	dihedral angle O_9–C_9–C_{10}–C_{18}
1A (8A)	0.00 (0.00)	-109.2 (-112.9)
1B (8B)	1.09 (1.85)	12.8 (14.7)
5A (11A)	0.00 (0.00)	-6.4 (-7.2)
5B (11B)	1.09 (0.50)	108.7 (109.2)

pared the bis(*p*-bromobenzoate) of 9-*epi*-dictyol B (**12**), an ideal derivative since the two benzoate groups, unlike the case in dictyol B (where they were planar), now have a suitable angle to apply the dibenzoate chirality method.[1,12] Compound **12** was obtained by benzoylation of compound **8** with *p*-bromobenzoyl chloride/silver triflate in CH_2Cl_2/pyridine;[13] its CD spectrum exhibited typical split Cotton effects due to the chiral exciton coupling between the two intramolecular charge transfer transitions of the *p*-bromobenzoates (CH_3CN, λ_{max} 244.0 nm, ϵ = 38 200), first Cotton effect at 249.9 nm ($\Delta\epsilon$ = +15.0) and second Cotton effect at 231.5 nm ($\Delta\epsilon$ = -1.8). From this positive exciton chirality, it is evident that both *epi*-dictyol B (**1**) and dictyol B (**5**) belong to the stereochemical series reported for pachydictyol A.

Final confirmation of this conclusion was achieved by chemical transformation of pachydictyol A (**9**) to 9-*epi*-dictyol B (**1**). Hydroxylation of the former compound at the allylic position C-9, by treatment with selenium dioxide in dioxane/H_2O,[14] led to 9-*epi*-dictyol B in 53% yield.

The interesting fact that the monobenzoates of 9-*epi*-dictyol B (**8**) and dictyol B (**11**) both exhibited a negative exciton chirality in CD is unusual, since epimers of this type should lead to opposite CD Cotton effects. This observation prompted us to carry out a conformational study of these compounds. Molecular mechanics calculations[15] of 9-*epi*-dictyol B (**1**) and dictyol B (**5**), and their corresponding monobenzoates **8** and **11**, respectively, revealed two low-energy conformers for each one, conformers **A** and **B**. Their strain energy differences and the dihedral angles O_9–C_9–C_{10}–C_{18} are shown in Table I, the latter being of great interest for CD analysis.[1]

The more stable conformation is the twist-chair, presented in type **A** conformers. Unexpectedly, the sign of the dihedral angle O_9–C_9–C_{10}–C_{18} in conformers **5A** and **11A** was negative and not positive as observed in Dreiding models. The steric interaction between the exocyclic double bond and the allylic substituent at carbon 9 makes the dihedral angle adopt a different spatial disposition having a negative sign. The negative Cotton effect of the 9-benzoate dictyol B (**11**), which adopts conformation **11A**, Figure 1, the most stable found by molecular mechanics calculations, is therefore now in agreement with a left-handed screwness of the electric transition dipole moments of the two chromophores (negative exciton chirality).[1] The usefulness of molecular mechanics in these cases is evident and shows that great care is needed when dealing with nonrigid rings.

In order to clarify the wrong absolute configuration obtained[5] for dictyotadiol **6**,[16] the following procedure was carried out: benzoylation with *p*-bromobenzoyl chloride/silver triflate in CH_2Cl_2/pyridine yielded two compounds.

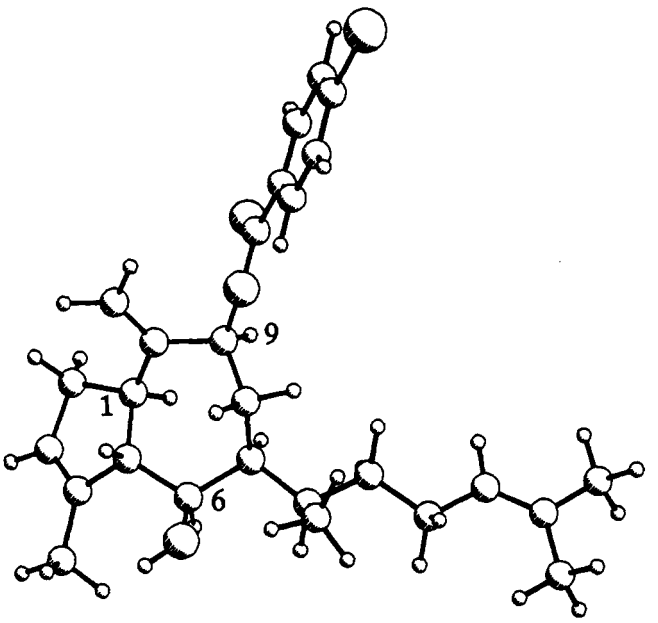


Figure 1. Lowest conformation of dictyol B mono-*p*-bromobenzoate (conformer **11A**).

The first compound, the bis(*p*-bromobenzoate) derivative **13**, showed spectroscopic data in agreement with its structure and, upon cleavage with $LiAlH_4$, led to the starting material. The second was a mono-*p*-bromobenzoate derivative of dictyotadiol, which exhibited spectroscopic data identical with those of the previously reported mono derivative,[5] including a positive CD Cotton effect at 235 nm. Comparison of the ^1H NMR spectrum of this monobenzoate with those of compounds **6** and **13**, however, revealed some important differences. The C-17 methyl group (δ 1.87) was downfield compared with the corresponding ones in compounds **6** and **13** (δ 1.53 and 1.56, respectively), and protons 2 and 3 appeared as a multiplet and as a broad singlet, respectively, instead of two double doublets as in compounds **6** and **13**. Treatment of this mono-*p*-bromobenzoate derivative with $LiAlH_4$ yielded a compound, different from dictyotadiol, whose ^1H NMR spectrum kept the C-17 methyl group downfield, while the signal at 6.12, assigned to the proton at C-2 by a COSY experiment, was shifted to 4.94, indicating the presence of a second hydroxyl group with an α configuration and a C-17 vinyl methyl group. From these data we believe that an allylic rearrangement of the benzoate group from C-4 to C-2 has taken place, the structure of this compound being tentatively assigned as shown in **14**.

The CD spectrum of the bis(*p*-bromobenzoate) derivative **13** (λ_{max} 243.0 nm, ϵ = 38 200) exhibits only one Cotton effect at the long wavelength of λ_{ext} 249.2 nm ($\Delta\epsilon$ = -26.7). On the basis of the bathochromic position of this first Cotton effect and its intensity, we interpret that the second Cotton effect is buried in a strong negative background ellipticity and that the CD spectrum belongs to the exciton split type;[1] therefore, the dibenzoate chirality rule can be applied.

Application of the dibenzoate chirality rule[12] to the observed negative Cotton effect of compound **13**, as well as application of the allylic benzoate method[8] to the positive Cotton effect of the mono-*p*-bromobenzoate derivative **14**, leads to the absolute configuration shown for dictyotadiol (**6**), which is in agreement with other compounds in this series.

The unexpected dihedral angle O_9–C_9–C_{10}–C_{18} in dictyol B and the occurrence of an allylic rearrangement in dictyotadiol during its benzyolation thus had led to the wrong

(12) Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1969**, *91*, 3989.
(13) (a) Brown, L.; Koreeda, M. *J. Org. Chem.* **1984**, *49*, 3875. (b) Vázquez, J. T.; Wiesler, W. T.; Nakanishi, K. *Carbohydr. Res.* **1988**, *176*, 175.
(14) Francis, M. J.; Grant, P. K.; Low, K. S.; Weavers, R. T. *Tetrahedron* **1976**, *32*, 95.
(15) MMX force field. PCMODEL-PI (v 3.2), Serena Software: P.O. Box 3076, Bloomington, IN 47402-3076.
(16) Faulkner, D. J.; Ravi, B. N.; Finer, J.; Clardy, J. *Phytochemistry* **1977**, *16*, 991.

and opposite absolute configuration. The absolute configurations reported[5] for dictyol B (5), dictyotriol E (4), dictyotadiol (6), and the ring moieties of dictyotriols C (2) and D (3) must therefore be amended as depicted. The 14*R* and 14*S* configurations for dictyotriols C and D, respectively, remain unchanged, since they were determined independently of the ring moiety.

Experimental Section

General. Prior to measurement of CD spectra, all compounds were purified by HPLC with a μ-Porasil column, 30 cm × 7.8 mm ID, 254 mm, *n*-hexane/EtOAc (90:10). The concentrations of the CD samples (CH_3CN) were ascertained from the UV spectra (CH_3CN), the standard values of 21 300 for the mono-*p*-bromobenzoates[8] and 38 200 for the bis(*p*-bromobenzoates)[17] being used.

General Procedures for Benzoylation. Procedure A. 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.

Procedure B.[13] To the starting material in dry dichloromethane and pyridine (5:1) are added *p*-bromobenzoyl chloride and silver triflate (3 equiv of each/hydroxyl group) at room temperature under Ar. This reaction is usually complete within 1 h (TLC). After quenching of the reaction with an excess of methanol and filtration through Florisil with dichloromethane, the filtrate is evaporated under diminished pressure, and preparative TLC or fractionated flash column chromatography is carried out to give the purified product in high yield.

Collection, Extraction, and Chromatographic Separation. The brown alga *G. kuntii* was collected in December 1985 at Horcones Bay (V Region, Chile) and extracted with acetone. The crude extract was fractionated by silica gel and Sephadex LH-20 chromatographies. Together with 9-epi-dictyol B, other diterpenoids such as pachydictyol A, dictyotriol A, and dictyotriol A C-12 monoacetate were isolated.

9-*epi*-Dictyol B (1). This compound was eluted by using mixtures of *n*-hexane/EtOAc (80:20). It was obtained in pure form by rechromatography (540 mg, 0.022%): oil; $[\alpha]^{25}_D$ = 45.9° (c 0.26, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3500, 2900, 1630, 1490, and 900 cm^{-1}; MS (EI), *m/e* (relative intensity) 304 (M^+, 6), 286 (15), 271 (2), 253 (3), 243 (2), 225 (5), 219 (6), 109 (35), 69 (100); HRMS (EI) *m/z* calcd for $C_{20}H_{32}O_2$ 304.2402, found 304.2352; calcd for $C_{20}H_{30}O$ 286.2297, found 286.2275; ^1H NMR δ 1.05 (d, *J* = 6.5 Hz, 3 H), 1.65 (br s, 3 H), 1.73 (br s, 3 H), 1.84 (br s, 3 H), 2.06 (m, 1 H), 2.30 (m, 2 H), 2.35 (m, 1 H), 2.96 (q, *J* = 9.7 Hz, 1 H), 3.94 (dd, *J* = 3.2 and 7.7 Hz, 1 H), 4.53 (dd, *J* = 2.3 and 5.2 Hz, 1 H), 4.96 (br s, 1 H), 5.03 (br s, 1 H), 5.17 (br t, *J* = 7.0 Hz, 1 H), 5.38 (br s, 1 H); ^{13}C NMR δ 38.3 (d, C-1), 30.1 (t, C-2), 123.9 (d, C-3), 141.3 (s, C-4), 60.8 (d, C-5), 74.9 (d, C-6), 41.6 (d, C-7), 33.7 (t, C-8), 74.6 (d, C-9), 154.6 (s, C-10), 34.5 (d, C-11), 35.0 (t, C-12), 25.7 (t, C-13), 124.8 (d, C-14), 131.4 (s, C-15), 25.7 (q, C-16), 15.6 (q, C-17), 110.1 (t, C-18), 17.5 (q, C-19), 17.6 (q, C-20).

9-*epi*-Dictyol B Monobenzoate (8). This compound was prepared according to general procedure A for benzoylation. Benzoylation of 9-*epi*-dictyol B (1) (12.0 mg, 0.039 mmol) led to compound 8 (10.8 mg, 0.022 mmol) (R_f = 0.66, *n*-hexane/EtOAc, 80:20). Compound 8 was further purified by HPLC (t_R = 18 min): ^1H NMR δ 0.88 (d, *J* = 6.5 Hz, 3 H), 1.56 (s, 3 H), 1.65 (s, 3 H), 1.82 (s, 3 H), 2.97 (q, *J* = 9.5 Hz, 1 H), 3.98 (m, 1 H), 4.98 (t, *J* = 8.1, 1 H), 5.10 (s, 1 H), 5.20 (s, 1 H), 5.37 (br s, 1 H), 5.83 (t, *J* = 3.5 Hz, 1 H), 7.56 (d, *J* = 8.6 Hz, 2 H), 7.87 (d, *J* = 8.6 Hz, 2 H); MS (EI), *m/z* (relative intensity) 486, 488 (M^+, 4:4), 468, 470 ($M^+ - H_2O$, 1:1), 303 ($M^+ - C_7OH_4Br$, 3), 286 ($M^+ - BrBzOH$, 81), 268 (23), 183, 185 (100:96); UV λ_{max} 243.0 nm; CD λ_{ext} 246.2 nm (Δε = −3.3).

Preparation of Enone 10. To a solution of 9-*epi*-dictyol B (1) (32 mg, 0.10 mmol) in CHCl (2 mL) was added freshly active MnO_2 (185 mg, 2.10 mmol), and the mixture was stirred at room temperature for 2 days. The solution was filtered and the filtrate dried in vacuo. The reaction mixture was chromatographed on silica gel 60G with *n*-hexane/EtOAc (90:10) as eluent, to give compound 10 (12.8 mg, 0.04 mmol), R_f = 0.54: ^1H NMR δ 0.98 (d, *J* = 6.5 Hz, 3 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.85 (s, 3 H), 3.95 (m, 1 H), 5.09 (t, *J* = 8.3 Hz, 1 H), 5.28 (br s, 1 H), 5.37 (br s, 1 H), 5.99 (br s, 1 H); MS (EI), *m/z* (relative intensity) 302 (M^+, 64), 284 ($M^+ - H_2O$, 53), 259 (17), 241 (11), 173 (77), 69 (100).

Dictyol B (5). Enone 10 (10 mg, 0.033 mmol) dissolved in anhydrous THF (3 mL) was treated with $LiAlH_4$ (12.5 mg, 0.33 mmol) under N_2 at −5 °C. After 1 h, the reaction mixture was quenched first with several drops of EtOAc and then with H_2O (80 μL), NaOH (20 μL), and H_2O (240 μL), filtered, and extracted with ether in the usual way. The residue obtained was chromatographed on silica gel 60G with *n*-hexane/EtOAc (85:15) as eluent, to give 7 mg (0.023 mmol) of dictyol B (5), R_f = 0.28. This compound had spectral properties identical with those quoted for authentic material.[6]

Dictyol B Monobenzoate (11). This reaction was performed according to general procedure A for benzoylation. Dictyol B (5) (4.5 mg, 0.014 mmol), obtained from reduction of enone 10, led to the mono-*p*-bromobenzoate derivative 11 (4.0 mg, 0.008 mmol) (R_f = 0.78, *n*-hexane/EtOAc, 80:20). Compound 11 was purified by HPLC (t_R = 27 min). Spectral properties of this compound were identical in all respects with those reported for authentic material.[5] UV: λ_{max} 243 nm. CD: λ_{ext} 239 nm (Δε = −2.7).

9-*epi*-Dictyol B Dibenzoate (12). This compound was prepared for compound 8 (6.0 mg, 0.012 mmol) according to general procedure B for benzoylation. Purification by HPLC (t_R = 55 min) afforded the desired bis(*p*-bromobenzoate) derivative 12 (3.6 mg, 0.0054 mmol): ^1H NMR δ 0.68 (d, *J* = 6.7 Hz, 3 H), 1.49 (s, 3 H), 1.55 (s, 6 H), 3.09 (q, *J* = 9.7 Hz, 1 H), 4.73 (t, *J* = 8.1 Hz, 1 H), 5.16 (s, 1 H), 5.27 (s, 1 H), 5.38 (br s, 1 H), 5.63 (dd, *J* = 3.4 and 8.4 Hz, 1 H), 5.90 (br t, *J* = 3.2 Hz, 1 H), 7.57 (d, *J* = 8.6 Hz, 2 H), 7.59 (d, *J* = 8.6 Hz, 2 H), 7.89 (d, *J* = 8.6 Hz, 2 H), 7.93 (d, *J* = 8.6 Hz, 2 H); MS (EI), *m/z* (relative intensity) 468, 470 (M^+ - BrBzOH, 3:3), 268 (M^+ - 2BrBzOH, 100), 200, 202 (6:5), 183, 185 (72:74), 157 (77); UV λ_{max} 244.0 nm; CD λ_{ext} 249.9 (Δε = 15.0), 231.5 (Δε = −1.8), 237.0 nm (Δε = 0.0).

Preparation of *epi*-Dictyol B.[14] To a room temperature solution of pachydictyol A (9) (35 mg, 0.12 mmol) in dioxane (1.5 mL) and H_2O (0.5 mL) was added selenium dioxide (15.5 mg, 0.12 mmol). After 1 h, the reaction mixture was quenched by addition of Al_2O_3, filtered, and extracted with ether the usual way. The residue obtained was chromatographed on silica gel 60G with *n*-hexane/EtOAc (80:20) as eluent, to give 18.5 mg (0.06 mmol) of *epi*-dictyol B (1), R_f = 0.40.

Benzoylation of Dictyotadiol. Compounds 13 (dibenzoate) and 14 (monobenzoate) were prepared from dictyotadiol (6) (14.4 mg, 0.047 mmol) according to general procedure B for benzoylation. The residue obtained was submitted to chromatography, silica gel 60G (*n*-hexane/EtOAc, 80:20), to give compound 13 (3.5 mg, 0.005 mmol), R_f = 0.85, and compound 14 (8.5 mg, 0.17 mmol), R_f = 0.50. HPLC purification: t_R(13) = 14 min, t_R(14) = 25 min. Compound 13: ^1H NMR δ 0.86 (d, *J* = 6.4 Hz, 3 H), 1.56 (s, 3 H), 1.62 (s, 3 H), 1.66 (s, 3 H), 2.19 (t, *J* = 8.7 Hz, 1 H), 2.61 (m, 1 H), 3.45 (br d, *J* = 8.7 Hz, 1 H), 4.72 (br s, 1 H), 4.77 (br s, 1 H), 5.07 (t, *J* = 7.3 Hz, 1 H), 6.00 (dd, *J* = 1.6 and 5.9 Hz, 1 H), 6.33 (dd, *J* = 3.0 and 8.7 Hz, 1 H), 6.39 (dd, *J* = 2.4 and 5.9 Hz, 1 H), 7.57 (m, 4 H), 7.90 (m, 4 H); MS (EI), (*m/z* (relative intensity) 468, 470 (M^+ - BrBzOH, 7:7), 268 (M^+ - 2BrBzOH, 73), 200, 202 (48:46), 183, 185 (91:100); UV λ_{max} 243.0 nm; CD λ_{ext} 249.2 nm (Δε = −26.7).

Compound 14: ^1H NMR δ 1.00 (d, *J* = 5.5 Hz, 3 H), 1.61 (s, 3 H), 1.68 (s, 3 H), 1.87 (br s, 3 H), 2.33 (br t, *J* = 8.7 Hz, 1 H), 2.63 (m, 1 H), 2.75 (br t, *J* = 7.8 Hz, 1 H), 4.00 (m, 1 H), 4.80 (br s, 1 H), 4.89 (br s, 1 H), 5.11 (t, *J* = 7.1 Hz, 1 H), 5.51 (m, 1 H), 6.12 (m, 1 H), 7.53 (d, *J* = 8.5 Hz, 2 H), 7.87 (d, *J* = 8.5 Hz, 2 H); MS (EI), *m/z* (relative intensity) 303 ($M^+ - C_7OH_4Br$, 1), 286 (M^+ - BrBzOH, 70), 268 (M^+ - BrBzOH - H_2O, 23), 253 (13), 200, 202 (85:92), 183, 185 (99:100); UV λ_{max} 243.0 nm; CD λ_{ext} 235 nm (Δε = 5.0).

Compound 15. The monobenzoate 14 (3.0 mg, 0.006 mmol) in anhydrous THF (0.8 mL) was treated with $LiAlH_4$ (0.94 mg, 0.025 mmol) under N_2 and at −5 °C. After 1 h, the reaction was

(17) Liu, H. W.; Nakanishi, K. *J. Am. Chem. Soc.* **1982**, *104*, 1178.

worked up in the usual way and chromatographed, to give compound 15 (1.2 mg, 0.004 mmol): ^{1}H NMR δ 0.99 (d, J = 5.2 Hz, 3 H), 1.61 (s, 3 H), 1.69 (s, 3 H), 1.85 (s, 3 H), 3.95 (m, 1 H), 4.83 (s, 1 H), 4.87 (s, 1 H), 4.94 (m, 1 H), 5.11 (t, J = 7.1 Hz, 1 H), 5.43 (br s, 1 H).

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Preparation and Structural Properties of Large-Cavity Peraza Macrocycles Containing Pyridine, Phenanthroline, or Piperazine Subcyclic Units

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Ten large peraza macrocycles containing either two pyridine, two phenanthroline, or three, four, or six piperazine subcyclic groups have been prepared. Those containing pyridine or phenanthroline were prepared by reacting either 2,6-pyridinedicarbaldehyde or its dimethyl ketone analogue or 1,10-phenanthroline-2,9-dicarbaldehyde with the appropriate bisprimary amine to form the cyclic tetraSchiff base. Those macrocycles containing the piperazine units were prepared by the reaction of a crablike piperazine-containing bis(α-chloro amide) (formed from piperazine and 2 mol of chloroacetyl chloride) and piperazine to give tetrapiperazinoperaza-24-crown-8-tetramide, the 2:2 cyclization product, and hexapiperazinoperaza-36-crown-12-hexamide, the 3:3 cyclization product. The macrocyclic hexamide was fully reduced to form the hexapiperazino-36-crown-12 ligand. The reaction of equimolar amounts of the crablike piperazine-containing bis(α-chloro amide) and benzylamine gave N,N',N''-tribenzyltripiperazinoperaza-27-crown-9-hexamide. The structures of one of the diphenanthrolinoperaza-crowns and of the tetrapiperazinoperaza-24-crown-8-tetramide were determined by an X-ray crystallographic procedure. The diphenanthrolino-crowns contained water molecules as shown by their combustion analyses. These water molecules were replaced by solvent molecules as shown by two molecules of dimethylformamide in the solid-state structure of one phenanthrolino-crown. The dipyridinoperaza-crown formed a highly protonated ligand at neutral pH.

Introduction

Polyaza macrocycles with large cavities have received recent interest as inorganic and organic anion and cation receptors. The cyclic arrangement of a large number of donor atoms and the flexibility of these ligands make them good hosts for binuclear or even polynuclear metal ion complexes.[1-5] These complexes are potential candidates for supramolecular catalysts.[6] Macrocyclic and macropolycyclic polyaza ligands selectively form strong complexes with a variety of inorganic and organic anions.[7-9] This type of complexation with biologically important anions may allow these ligands to be used as model compounds for biological processes.[10-12]

A number of methods for the preparation of these large polyaza-crowns have been reported. The most common synthetic procedure requires the use of N-tosyl groups to both protect and activate the nitrogen atoms in the cyclization step.[2,3,13-16] Ring closure occurs by a condensation reaction of N-tosylated polyamines with the appropriate ditosylate ester or dihalide in DMF and in the presence of base. These reactions allow the production of polyaza macrocycles in moderate yields,[14-16] but removing the N-tosyl groups requires drastic conditions and is not always straightforward.

Another cyclization process uses the template ring closure formation of a cyclic di- or tetraSchiff base. This is a simple process, but it is often difficult to choose the correct template metal ion or to predict certain ring-contraction reactions where the template cation does not coordinate with all of the ring nitrogen atoms.[5,17] In some cases, reduction of the cyclic polySchiff base and removal of the template ion have been difficult.[1,5,18-22]

A nontemplate method for the formation of a macrocyclic polySchiff base has also been studied. This proce-

(1) Drew, M. G. B.; Waters, C. P.; McFall, S. G.; Nelson, S. M. *J. Chem. Res.* **1979**, 0360.
(2) Bencini, A.; Bianchi, A.; Garcia-Espana, E.; Micheloni, M.; Paoletti, P. *Inorg. Chem.* **1988**, *27*, 176.
(3) Bencini, A.; Bianchi, A.; Garcia-Espana, E.; Mangani, S.; Micheloni, M.; Orioli, P.; Paoletti, P. *Inorg. Chem.* **1988**, *27*, 1104.
(4) Menif, R.; Martell, A. E. *J. Chem. Soc., Chem. Commun.* **1989**, 1521.
(5) Cabral, F.; Murphy, B.; Nelson, J. *Inorg. Chim. Acta* **1984**, *90*, 169.
(6) Lehn, J. M. *Angew. Chem.* **1988**, *100*, 91. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 90.
(7) Hosseini, M. W.; Lehn, J. M. *Helv. Chim. Acta* **1986**, *69*, 587.
(8) Lehn, J. M. *Science* **1985**, *227*, 849.
(9) Pierre, J. L.; Baret, P. *Bull. Soc. Chim. Fr.* **1983**, *2*, 367.
(10) Jahansouz, H.; Jiang, Z.; Himes, R. H.; Mertes, M. P.; Mertes, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1409.
(11) Bergmann, N.; Schmidtchen, F. P. *Tetrahedron Lett.* **1988**, *29*, 6235.
(12) Kimura, E.; Kuramoto, Y.; Koike, T.; Fijioka, H.; Kodama, M. *J. Org. Chem.* **1990**, *55*, 42.
(13) Richman, J. E.; Atkins, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 2268.
(14) Atkins, T. J.; Richman, J. E.; Oettle, W. F. *Org. Synth.* **1978**, *58*, 86.
(15) Iwata, M.; Kuzuhara, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 198.
(16) Iwata, M.; Kuzuhara, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1102.
(17) Bailey, N. A.; Eddy, M. M.; Fenton, D. E.; Moss, S.; Mukhopadhyay, A.; Jones, G. *J. Chem. Soc., Dalton Trans.* **1984**, 2281.
(18) Nelson, S. M. *Pure Appl. Chem.* **1980**, *52*, 2461.
(19) Fenton, D. E. *Pure Appl. Chem.* **1986**, *58*, 1437.
(20) Drew, M. G. B.; Murphy, B. P.; Nelson, J.; Nelson, S. M. *J. Chem. Soc., Dalton Trans.* **1987**, 873.
(21) Murphy, B. P.; Nelson, J.; Nelson, S. M.; Drew, M. G. B.; Yates, P. C. *J. Chem. Soc., Dalton Trans.* **1987**, 123.
(22) Drew, M. G. B.; Cairns, C.; McFall, S. G.; Nelson, S. M. *J. Chem. Soc., Dalton Trans.* **1980**, 2020.

0022-3263/91/1956-2675$02.50/0