(7.7×10^4), 204 (9.3×10^4); UV (C_6H_6) 398 nm (ϵ 3.7×10^3), 378 (5.7×10^3), 361 (5.4×10^3), 344 (4.1×10^3). Anal. Calcd for $C_{28}H_{18}$: C, 94.88; H, 5.12. Found: C, 95.04; H, 5.07.

5-Phenylbenzo[*a*]naphthacene (21, Ar = Phenyl): pale yellow crystals; mp 160.0–165.0 °C; yield 33%; NMR ($CDCl_3$) δ 6.6–8.4 (14 H, m), 8.45 (1 H, s), 8.58 (1 H, s), 8.69 (1 H, s), 8.85 (1 H, d, J = 8 Hz); MS m/e 354 (M^+). Anal. Calcd for $C_{28}H_{18}$: C, 94.88; H, 5.12. Found: C, 94.35; H, 5.01.

Dinaphtho[1,2-*c*:2,3-*e*]pyrene (27): yellow crystals; mp 298.0–300.5 °C; yield 58%; IR (KBr) neither CO nor OH; UV (C_6H_6) 462 nm (ϵ 2.4×10^4), 434 (2.0×10^4), 410 (1.0×10^4), 388 (4.5×10^3), 366 (sh, 3.8×10^3), 338 (sh, 6.5×10^4), 329 (1.1×10^5), 317 (8.6×10^4), 294 (3.9×10^4), 281 (4.7×10^4); MS m/e 402 (M^+). Anal. Calcd for $C_{32}H_{18}$: C, 95.49; H, 4.51. Found: C, 95.02; H, 4.39.

Reductive Acetylation of *p*-Quinones. *p*-Quinone (0.1 mmol) and an excess amount of zinc powder were added to acetic anhydride (10 mL). Then the reaction mixture was refluxed for 30 min. After the yellow color of the solution due to the *p*-quinone disappeared completely, the reaction mixture was hydrolyzed and neutralized with sodium acetate. The diacetate was extracted with ether from the reaction mixture and purified further by column chromatography on silica gel.

Physical Properties of Diacetates. 7,12-Diacetoxy-5-(2-naphthyl)benzo[*b*]chrysene (23, Ar = 2-Naphthyl): pale yellow crystals; mp 289.0–290.0 °C; yield 64%; NMR ($CDCl_3$) δ 2.54 (3 H, s), 2.58 (3 H, s), 6.6–8.3 (17 H, m), 9.11 (1 H, d, J = 10 Hz); IR (KBr) 1765 cm^{-1}; UV ($CHCl_3$) 415 nm (ϵ 7.8×10^3), 392 (1.1×10^4), 372 (8.4×10^3), 352 (5.9×10^3), 314 (7.7×10^4), 301 (8.7×10^4), 259 (5.0×10^4), 248 (5.2×10^4); MS m/e (relative intensity) 520 (M^+, 29), 478 (41), 436 (100). Anal. Calcd for $C_{36}H_{24}O_4$: C, 83.06; H, 4.56. Found: C, 83.04; H, 4.50.

9,14-Diacetoxy-7-phenyldibenzo[*b*,*d*]phenanthrene (24, Ar = Phenyl): pale yellow crystals; yield 78%; NMR ($CDCl_3$) δ 1.60 (3 H, s), 2.62 (3 H, s), 7.6 (5 H, br s), 7.2–8.4 (11 H, m); IR (KBr) 1765 cm^{-1}; MS m/e 470 (M^+).

Photochemical Cyclization Reaction of a *p*-Quinone to the Higher Homologue. On irradiation of a benzene solution (400 mL) of **25** (0.15 mmol) and iodine (0.6 mmol) with a high-pressure Hg arc lamp for 30 h, the starting *p*-quinone (**25**) was consumed completely. The reaction mixture was washed with an aqueous solution of sodium bisulfite to eliminate iodine, and the organic layer was dried over sodium sulfate. Concentration of the reaction mixture gave red crystals of **dinaphtho[1,2-*c*:2,3-*e*]pyrene-11,16-dione (26)**: mp 284.0–286.0 °C; yield 85%; IR (KBr) 1670 cm^{-1}; UV ($CHCl_3$) 494 nm (ϵ 1.1×10^4), 380 (sh, 1.2×10^4), 349 (2.8×10^4), 335 (2.8×10^4), 304 (6.1×10^4), 282 (3.9×10^4), 250 (sh, 4.3×10^4), 245 (4.5×10^4); MS m/e 432 (M^+). Anal. Calcd for $C_{32}H_{16}O_2$: C, 88.82; H, 3.73. Found: C, 88.03; H, 3.85.

Registry No. **1a**, 26037-61-6; **2a**, 530-48-3; **2f**, 4333-70-4; **2g**, 395-10-8; **2h**, 947-77-3; **2i**, 4356-69-8; **2j**, 10605-48-8; **2k**, 2919-19-9; **2l**, 72853-68-0; **3Af**, 72853-69-1; **3Bf**, 72853-70-4; **3Ag**, 72853-71-5; **3Bg**, 72853-72-6; **3Ah**, 72853-73-7; **3Bh**, 72853-74-8; **3Ai**, 72735-91-2; **3Aj**, 72853-75-9; **3Ak**, 72853-76-0; **3Al**, 72853-77-1; **3Bl**, 72853-78-2; **4**, 72853-79-3; **5a**, 28358-65-8; **5b**, 28358-66-9; **5c**, 39666-29-0; **5d**, 39799-27-4; **5e**, 67132-22-3; **5f**, 67132-23-4; **6a**, 72853-50-0; **6b**, 72853-51-1; **7a**, 67132-24-5; **7c**, 67132-25-6; **7e**, 67132-26-7; **7f**, 67132-27-8; **8b**, 72853-52-2; **8d**, 72853-53-3; **8e**, 72853-54-4; **8f**, 72853-55-5; **9**, 4425-82-5; **10**, 72853-56-6; **11**, 58024-08-1; **12**, 54988-91-9; **13**, 72853-57-7; **14a**, 72853-58-8; **14b**, 72853-59-9; **15**, 38969-08-3; **16**, 72853-60-2; **17**, 72853-61-3; **19**, 67132-28-9; **20**, 72853-62-4; **21**, 72853-63-5; **23**, 72853-64-6; **24**, 72853-65-7; **25**, 67132-26-7; **26**, 72853-66-8; **27**, 72853-67-9.

Microbial Stereodifferentiating Reduction of (±)-4-Methyl- and (±)-6-Methyl-1-oxo[2.2]metacyclophanes and Revision of the Absolute Configuration of 4-Substituted [2.2]Metacyclophanes

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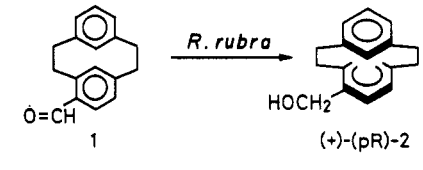
Partial oxidative hydrolysis of 4-bromo-1,1,10,10-bis(trimethylenedithio)[2.2]metacyclophane (**7**) yielded the bromo ketones **8** and **9** which were respectively converted into (±)-4-methyl- (**3**) and (±)-6-methyl-1-oxo[2.2]-metacyclophanes (**4**). The unambiguous synthesis of (±)-**3** from 2,5-dimethylbenzoic acid (**18**) assigned their structures. Incubation of (±)-**3** with *Rhodotorula rubra* gave a mixture of (−)-ketone **3**, (−) axial alcohol **38**, and (−) equatorial alcohol **39**. The observed (−) Cotton effect indicated the *pS* configuration of (−)-**3**, and transformation of (−)-**3** into (+)-4-methyl[2.2]metacyclophane (**5**) permitted the assignment of the *pR* configuration to (+)-**5**, opposite to Schlögl's proposal. This conclusion was further supported by the parallel sequence of steps starting from (±)-6-methyl ketone **4**.

In our preceding paper[1] which described our exploration of the application of the proposed "quadrant rule"[2] in [2.2]metacyclophane derivatives, we reported isolation of 4-hydroxymethyl[2.2]metacyclophane (**2**) (optical purity 11.7%) enriched in the (+)-(*pR*)-enantiomer from a culture solution of *Rhodotorula rubra* containing (±)-[2.2]metacyclophane-4-carboxaldehyde (**1**). (See Chart I.)

If a favorable conformation of the substrate **1** is assumed, the quadrant rule suggests the *pR* configuration for the (+)-hydroxymethyl derivative **2**, which is opposite to Schlögl's proposal[3] based on the "kinetic resolution" method. This discrepancy prompted us to reinvestigate the absolute configuration of 4-substituted [2.2]metacyclophanes.

Chart I

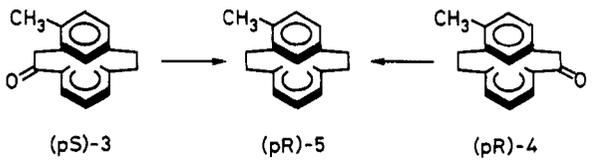


1 (+)-(pR)-2

(1) Nakazaki, M.; Chikamatsu, H.; Hirose, Y.; Shimizu, T. *J. Org. Chem.* **1979**, *44*, 1043.
(2) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Hirose, Y.; Shimizu, T.; Asao, M. *J. Chem. Soc., Chem. Commun.* **1978**, 668.
(3) Kainradl, B.; Langer, E.; Lehner, H.; Schlögl, K. *Justus Liebigs Ann. Chem.* **1972**, *766*, 16.

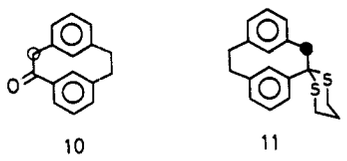
0022-3263/80/1945-1428$01.00/0

Chart II



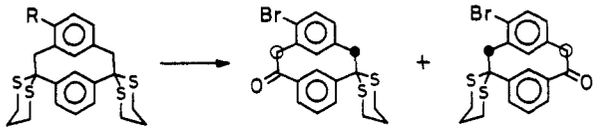
(pS)-3 (pR)-5 (pR)-4

Chart III



10 11

Scheme I



6 R=H
7 R=Br

8 9

Our strategy involved the following three steps (Chart II): (a) unambiguous syntheses of (±)-4-methyl- (3) and (±)-6-methyl-1-oxo[2.2]metacyclophanes (4), (b) optical resolution of these racemic ketones to yield optically active modifications whose absolute configurations should readily be secured by their CD analyses, and (c) conversion of these optically active ketones into 4-methyl[2.2]metacyclophane (5), providing the information on the absolute configuration.

Results and Discussion

Partial Oxidative Hydrolysis of 4-Bromo-1,1,10,10-bis(trimethylenedithio)[2.2]metacyclophane (7) (Scheme I). Gschwend's procedure[4] for the partial hydrolysis of 6, when applied to the bromo derivative 7,[3] led to formation of a 1.7:1 mixture of two bromo ketones: ketone A, mp 198 °C, and ketone B, mp 131 °C. Their NMR spectra with respect to the C-2 and C-9 bridge methylene protons (respectively indicated with the open and closed circles in Scheme I) are summarized in Table I, together with the corresponding proton signals of the reference compounds[5] 10 and 11 (Chart III). A conspicuous feature in the spectrum of ketone A was a remarkable low-field shift observed in the equatorial proton signal of the two C-2 protons, δ_{AB} 0.96. The same effect was also found in ketone B, which exhibited δ_{AB} 1.65, this time in the C-9 proton signals. These shifts must undoubtedly be associated with the anisotropic effect[6,7] of the neighboring bromine atom, and this automatically assigns 8 to ketone A and 9 to ketone B, with C-2 and C-9 bridge methylene protons, respectively, close to their bromine atoms. This conclusion was eventually confirmed by the independent synthesis of the 4-methyl ketone 3 (Scheme V).

Preparation of 4-Methyl- (3) and 6-Methyl-1-oxo-[2.2]metacyclophanes (4) from the Bromo Thioketal Ketones 8 and 9 (Scheme II). Scheme II illustrates the conversions of the bromo ketones 8 and 9 into 4-methyl- (3) and 6-methyl-1-oxo[2.2]metacyclophanes (4). These conversions were rather straightforward and involved replacement of the bromine substituents with methyl groups, followed by Raney nickel desulfurization of the dithioketal groups.

Table I. NMR Signals (δ) of Bridge Methylene Protons in Ketones A (8), B (9), 10, and 11

	C-2 protons (○)			C-9 protons (●)		
ketone	axial	equatorial	δ_{AB}	axial	equatorial	δ_{AB}
10	3.45	3.75	0.30			
11				2.41	3.34	0.93
A	3.37	4.33	0.96	2.43	3.34	0.91
B	3.38	3.57	0.19	2.25	3.90	1.65

After protection of the carbonyl group of 8 by conversion into the dimethyl ketal 12, the bromine substituent was replaced by a methyl group by treatment with butyllithium and methyl iodide in THF to give 14. Refluxing an ethanolic solution of 14 with Raney nickel removed the dithioketal group to afford the dimethyl ketal 16, whose acidic hydrolysis readily yielded the 4-methyl ketone 3, mp 85 °C. A parallel sequence of steps converted the bromo ketone 9 into the 6-methyl ketone 4, mp 56 °C.

Synthesis of (±)-4-Methyl-1-oxo[2.2]metacyclophane (3) from 2,5-Dimethylbenzoic Acid (18) (Schemes III–V). Our unambiguous synthesis of the methyl ketone 3 comprised the following three main steps: (a) preparation of the "toluene" component 27 (Scheme III), (b) preparation of the "benzene" component 31 (Scheme IV), and (c) coupling of these components followed by intramolecular cyclization to complete the [2.2]metacyclophane structure 37 (Scheme V).

Synthesis of the "Toluene" Component 27 (Scheme III). NBS bromination of 2,5-dimethylbenzoic acid (18)[8] yielded a 1:2.5:1.4 mixture of recovered 18 and the two bromides 19 and 20, from which a portion of the bromide 20, mp 140 °C, crystallized. Because of difficulty encountered in separating the desired bromide 19, the reaction products were refluxed with 10% K_2CO_3 solution to afford a mixture of 18 and the hydroxy acids 21 and 22. When a benzene solution of these hydroxy acids was refluxed with *p*-toluenesulfonic acid in a water separator, the hydroxy acid 22 was converted into 6-methylphthalide (23), which was separated as a neutral fraction.

Final isolation of the hydroxy acid 21 was carried out by extraction with 3% Na_2CO_3 solution, yielding a 27% overall yield of 21 from 18.

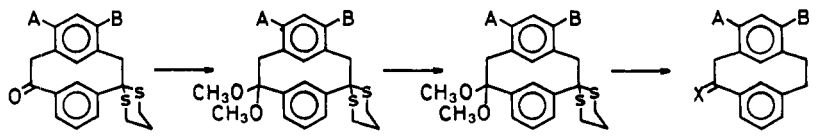
Continuation of the synthesis involved (a) diazomethane esterification to the ester 24, (b) conversion to the methyl ether 25 with NaH and methyl iodide in dimethoxyethane, (c) $LiAlH_4$ reduction to the alcohol 26, and (d) bromination with PBr_3 in benzene to the "toluene" component 27 in a 75% overall yield from the hydroxy acid 21.

Synthesis of the "Benzene" Component 31 (Scheme IV). Our modification of Boekelheide's synthesis[9] of 31 involving oxidation of the bromomethyl group with 2-nitropropane[10] is illustrated in Scheme IV.

Partial methoxylation of the dibromide 28 with $NaOCH_3$ in benzene, followed by a careful fractional distillation of the product, gave a 53% yield of the monomethyl ether 29. When the reaction of monomethyl ether 29, sodium methoxide, and 2-nitropropane was carried out in a

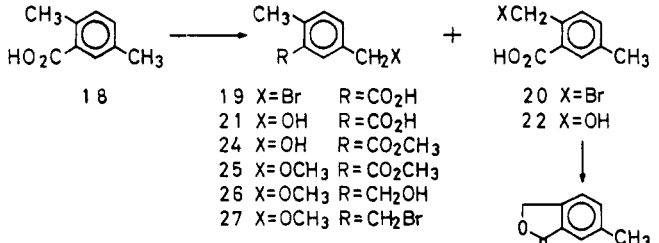
(4) Gschwend, H. W. *J. Am. Chem. Soc.* **1972**, *94*, 8430.
(5) Glotzmann, C.; Langer, E.; Lehner, H.; Schlögl, K. *Monatsh. Chem.* **1975**, *106*, 763.
(6) Poucherf, C. J.; Campbell, J. R. "The Aldrich Library of NMR Spectra"; Aldrich Chemical Co.: Milwaukee, WI, 1974; Vol. IV, pp 1, 43, and 53. Szymanski, A. A.; Yellin, R. E. "NMR Band Handbook"; IFI/Plenum: New York, 1968; pp 319–320.
(7) Akabori, S.; Sato, T.; Hata, K. *J. Org. Chem.* **1968**, *33*, 3277.
(8) Schmid, A.; Decker, H. *Chem. Ber.* **1906**, *39*, 933.
(9) Blaschke, H.; Ramey, C. E.; Calder, I.; Boekelheide, V. *J. Am. Chem. Soc.* **1970**, *92*, 3675.
(10) Hass, H. B.; Bender, M. L. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. 4, p 932.

Scheme II



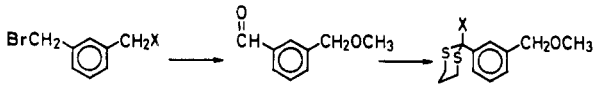
8 A = Br B = H 12 A = Br B = H 14 A = CH_3 B = H 16 A = CH_3 B = H X = $(OCH_3)_2$
9 A = H B = Br 13 A = H B = Br 15 A = H B = CH_3 17 A = H B = CH_3 X = $(OCH_3)_2$
3 A = CH_3 B = H X = O
4 A = H B = CH_3 X = O

Scheme III



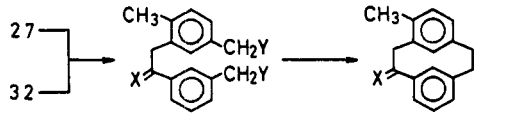
18 19 X = Br R = CO_2H; 21 X = OH R = CO_2H; 24 X = OH R = CO_2CH_3; 25 X = OCH_3 R = CO_2CH_3; 26 X = OCH_3 R = CH_2OH; 27 X = OCH_3 R = CH_2Br
20 X = Br; 22 X = OH
23

Scheme IV



28 X = Br; 29 X = OCH_3
30
31 X = H; 32 X = Li

Scheme V



33 X = $S(CH_2)_3S$ Y = OCH_3
34 X = O Y = OCH_3
35 X = O Y = Br
36 X = $S(CH_2)_3S$ Y = Br
37 X = $S(CH_2)_3S$
3 X = O

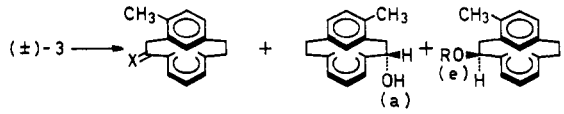
methanolic solution, there was formed the aldehyde **30**, which was converted into the dithioketal **31**.

Coupling of the "Toluene" Component 27 and the "Benzene" Component 31 (Scheme V). Coupling[3] of the bromide **27** and the lithio derivative **32**, prepared from the dithio ketal **31** and butyllithium, gave **33** whose direct transformation into the bromide **36** was unfeasible because of undesirable side reactions.

We then first removed the dithioketal group by oxidative hydrolysis with NBS; the resulting keto ether **34** was heated with 47% HBr solution to give the dibromide **35**, mp 103–104 °C, whose dithioketalization yielded **36**.

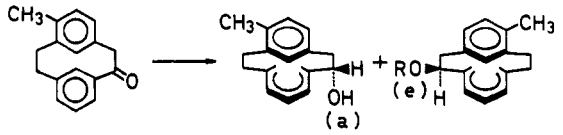
Intramolecular cyclization[9] of the dithioketal **36** with butyllithium[11] under a high dilution condition provided a 45% yield of the 4-methyl[2.2]metacyclophane dithioketal **37**, mp 135 °C, whose reaction with NBS led to the required (±)-4-methyl-1-oxo[2.2]metacyclophane (**3**), mp 82–85 °C. The identity demonstrated for the two ketones **3** derived via two synthetic routes eventually confirmed

Scheme VI



(±)-3
(+)-(pS)-37 X = $S(CH_2)_3S$ (−)-(pR,1S)-38 (−)-(pS,1S)-39 R = H
(−)-(pS)-3 X = O (−)-(pS,1S)-40 R = Ac

Scheme VII



(±)-4 (+)-(pR,1S)-41 (−)-(pS,1S)-42 R = H
(−)-(pS,1S)-43 R = Ac

our original structural assignments of ketones A and B.

Microbial Reduction of (±)-4-Methyl-1-oxo[2.2]-metacyclophane (3) with *R. rubra* (Scheme VI). Preparative TLC of the metabolite mixture from a 24-h incubation of (±)-**3** with *R. rubra* afforded three fractions: the recovered ketone **3**, an axial alcohol **38**, and an equatorial alcohol **39**. Tenacious contamination with waxy materials forced us to convert the crude ketone directly into (+)-dithioketal **37**, mp 128–133 °C, $[\alpha]_D$ +50.2° ($CHCl_3$), whose oxidative hydrolysis with NBS gave the (−)-ketone **3**: mp 119–120 °C; $[\alpha]_D$ −420° ($CHCl_3$); $[\theta]$ −2.73 × 10^4° (321 nm, isooctane).

While the axial alcohol **38**, mp 93 °C, $[\alpha]_D$ −2.5° ($CHCl_3$), could be directly purified by sublimation in vacuo, the equatorial alcohol **39** was difficult to free from waxy contaminants. Purification was finally accomplished via the (−)-acetate **40**, which was hydrolyzed to provide the pure equatorial alcohol **39**, mp 128–130 °C, $[\alpha]_D$ −9.8° ($CHCl_3$). Comparison of the (−) Cotton effect exhibited by the isolated (−)-4-methyl ketone **3** with that of (−)-1-oxo[2.2]-metacyclophane (**10**), $[\theta]$ −3.67 × 10^4°(318 nm, isooctane), with an established *pS* configuration[12] indicates the *pS* configuration[13] for (−)-**3** (optical purity 90%);[14] inspections of NMR spectra[1,4] readily assigned the axial and equatorial

(11) Intramolecular cyclization (30% yield) of the dithioketal **36** was also accomplished by utilizing a Na–tetraphenylethene reagent. See: Lindsay, W. S.; Stokes, P.; Humber, L. G.; Boekelheide, V. *J. Am. Chem. Soc.* **1961**, *83*, 943. Sato, T.; Akabori, S.; Kainosho, M.; Hata, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 856.

(12) Mislow, K.; Brzechffa, M.; Gshwend, H. W.; Puckett, R. T. *J. Am. Chem. Soc.* **1973**, *95*, 621.

(13) Cahn, R. S.; Ingold, C. K.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 385. In principle, there seem to be two alternative ways to specify the planar chirality of 4-methyl- and 6-methyl-1-oxygenated [2.2]metacyclophanes. To avoid ambiguity and to keep consistency with our preceding paper we use the *pR* and *pS* specifications for the 1-oxygenated [2.2]metacyclophanes in this paper to refer to the planar chirality of the 1-oxygenated [2.2]metacyclophane moiety; e.g., (−)-**3** = (−)-4-methyl-[(*pS*)-1-oxo[2.2]metacyclophane].

(14) From our studies of the enantiomeric differential shifts with addition of a chiral shift agent, Eu(facam)$_3$, 100% optical purity has been assigned to a specimen of (−)-(*pS*,10*S*)-10-hydroxy-1-oxo[2.2]metacyclophane[1] with $[\theta]$ −3.30 × 10^4°(321 nm, isooctane). This, together with the reported $[\theta]$ −3.67 × 10^4°(318 nm, isooctane)[12] of a pure sample of (−)-(*pS*)-1-oxo[2.2]metacyclophane suggests $[\theta]$ −3.5 × 10^4° for the absolute molecular ellipticity of (−)-**3**.

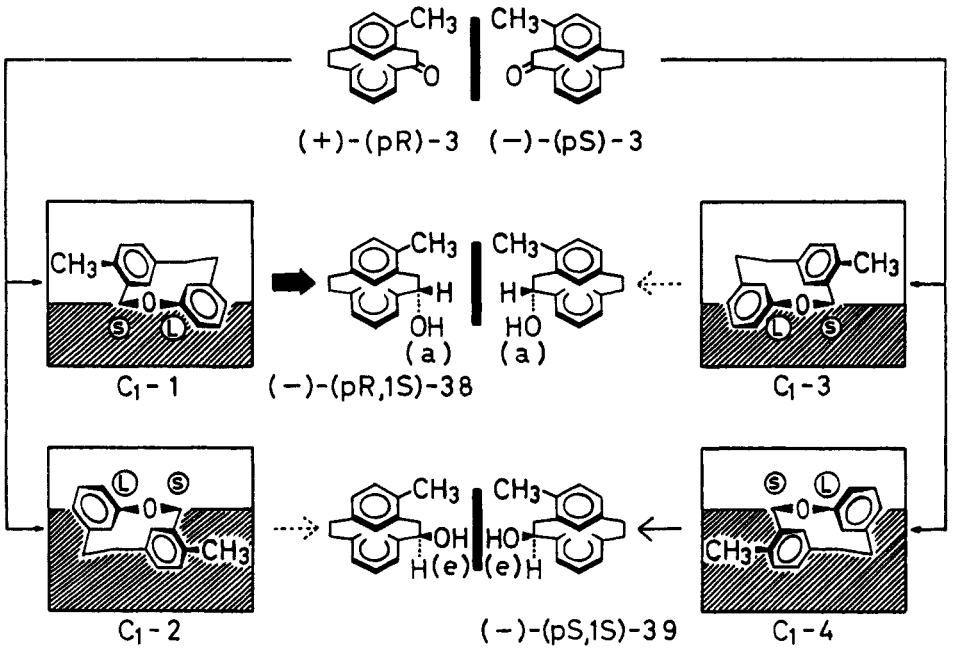


Figure 1. Schematic representation of the four quadrant orientations for (±)-4-methyl-1-oxo[2.2]metacyclophane (**3**). Substrate ketone molecules are orientated in a three-dimensional system with the carbonyl plane on the *xy* plane, the carbonyl axis coincident with the *x* axis, and the carbonyl oxygen pointing toward +*x* direction. Hydrogen delivery from the lower quadrants furnishes metabolite alcohols.

stereochemistry to the diastereomeric metabolite alcohols (−)-**38** and (−)-**39**, whose respective Jones oxidations yielded enantiomeric (+)-(*pR*)-**3** and (−)-(*pS*)-**3**, both with almost 100% optical purity.

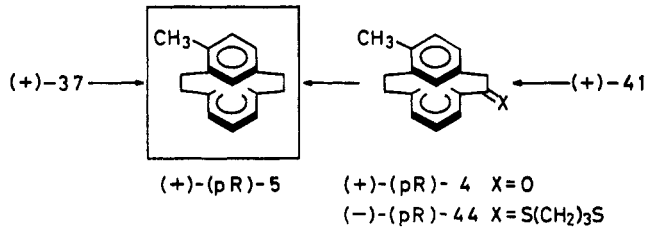
This stereochemical information clearly established a (*pR*,1*S*) configuration for the major metabolite (−) axial **38** and a (*pS*,1*S*) configuration for the minor (−) equatorial alcohol **39**, consistent with the prediction from the quadrant rule (Figure 1).

Microbial Reduction of (±)-6-Methyl-1-oxo[2.2]metacyclophane (4) with *R. rubra* (Scheme VII). A small-scale trial incubation showed that after 10 h of incubation (±)-6-methyl ketone **4** completely disappeared and gave rise to a 1:1 formation of two metabolite alcohols.[15] Separation of these metabolites from a 24-h incubation experiment was carried out by preparative TLC to yield 36% of (+) axial alcohol **41**, mp 188 °C, $[\alpha]_D$ +428° ($CHCl_3$), and impure (−) equatorial alcohol **42**. Purification through formation of the (−)-acetate **43** gave a 35% yield of the (−) equatorial alcohol **42**: mp 137 °C, $[\alpha]_D$ −135° ($CHCl_3$).

Parallel to the 4-methyl ketone series (Scheme VI), the axial–equatorial stereochemistry of the (+)-**41** and (−)-**42** metabolite alcohols could be deduced from their NMR spectra; their respective Jones oxidations to enantiomeric (+)- and (−)-6-methyl ketone **4** indicated (*pR*,1*S*) and (*pS*,1*S*) configurations, respectively, as well as almost 100% optical purity.

Absolute Configuration of 4-Methyl[2.2]metacyclophane (5) (Scheme VIII). Stirring an ethanol–ethyl acetate solution of (+)-(*pS*)-4-methyl dithioketal **37** with Raney nickel for 2 h produced a 71% yield of (+)-4-methyl[2.2]metacyclophane (**5**), mp 85–87 °C, $[\alpha]_D$ +23° ($CHCl_3$), which indicated a *pR* configuration for the (+)-4-substituted [2.2]metacyclophane **5**.

Scheme VIII



Further support for this conclusion was secured from the parallel series of experiments on 6-methyl-1-oxygenated compounds. Jones oxidation of (+)-(*pR*) axial alcohol **41** gave (+)-(*pR*)-6-methyl-1-oxo[2.2]metacyclophane (**4**) which was transformed into the (−) dithio ketal **44**. When an ethanolic solution of (−)-**44** was stirred with Raney nickel at room temperature for 3 h, a 63% yield of (+)-4-methyl[2.2]metacyclophane (**5**), mp 84–86 °C, $[\alpha]_D$ +22.7° ($CHCl_3$), was isolated.

Our assignment of the *pR* configuration to (+)-4-methyl[2.2]metacyclophane is opposite to the one proposed by Schlögl et al., and this should suggest a complete revision of their absolute configuration assignment of 4-monosubstituted[3,16] as well as 4,12-[17] and 4,14-disubstituted[18] [2.2]metacyclophanes.

Experimental Section

All melting and boiling points were uncorrected. Infrared spectral data were obtained from a Hitachi EPI-SII spectrophotometer, and NMR spectra were measured with JNM-NH-100 and JNM-C-60HL spectrometers with Me_4Si as an internal standard. Elemental analyses were performed by a Yanagimoto CHN-Corder Type II instrument. Unless otherwise indicated, optical rotations refer to $CHCl_3$ solutions and were measured with

(15) As can be seen from Figure 1, all quadrant orientations for (±)-4-methyl ketone **3** have the methyl substituent close to the carbonyl reaction center protruding toward the front quadrants. This would explain the observed sluggish reduction of (±)-4-methyl ketone **3** compared to that of (±)-6-methyl ketone **4**.

(16) Langer, E.; Lehner, H. *Monatsh. Chem.* **1973**, *104*, 644. Langer, E.; Lehner, H.; Schlögl, K. *Tetrahedron* **1973**, *29*, 2473.

(17) Keller, H.; Krieger, C.; Langer, E.; Lehner, H. *Justus Liebigs Ann. Chem.* **1977**, 1296. Keller, H.; Lehner, H.; Derflinger, G. *Tetrahedron* **1978**, *34*, 871.

(18) Krieger, C.; Lehner, H.; Schlögl, K. *Monatsh. Chem.* **1976**, *107*, 195.

a JASCO DIP-SL automatic polarimeter. Circular dichroism data were measured on a JASCO J-40 spectropolarimeter. The culture of *Rhodotorula rubra* was obtained from the Institute for Fermentation, Osaka, Japan, and was identified by the IFO Catalog serial number IFO 0889.

Partial Oxidative Hydrolysis of 4-Bromo-1,1,10,10-bis(trimethylenedithio)[2.2]metacyclophane (7). To a chilled (−5 °C) solution of the 4-bromo bis(dithioacetal) **7**[3] (5 g, 10 mmol) in THF (520 mL), acetone (250 mL), and water (100 mL) was added with stirring a solution of NBS (5.10 g, 28.1 mmol) in acetone (1 L) and water (250 mL). After being stirred for 20 min, the mixture was decolorized with 10% Na_2SO_3 solution and then THF and acetone were evaporated in vacuo to afford a concentrate which was diluted with a small amount of acetone. The separated **8** (0.38 g, 0.93 mmol) was filtered, and the filtrate was chromatographed on silica gel. Elution with benzene afforded **7** (2.17 g, 4.37 mmol), **8** (0.91 g, 2.23 mmol), and **9** (0.78 g, 1.91 mmol). The combined **8** was recrystallized from benzene–hexane to give a 30% yield of **8**: mp 198–199 °C; IR (KBr) 1700 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.8–3.3 (m, 6 H), 2.43 (d, J = 13.0 Hz, 1 H), 3.37 (d, J = 13.0 Hz, 1 H), 3.38 (d, J = 13.0 Hz, 1 H), 4.43 (d, J = 13.0 Hz, 1 H), 4.85 (d, J = 2 Hz, 1 H), 5.65 (t, J = 2 Hz, 1 H), 7.0–8.12 (m, 5 H); mass spectrum, m/e 405 (M^+).

Anal. Calcd for $C_{19}H_{17}BrOS_2$: C, 56.30; H, 4.23; Br, 19.71; S, 15.82. Found: C, 56.52; H, 4.14; Br, 19.80; S, 15.79.

Recrystallization of **9** from acetone–hexane afforded colorless crystals (0.74 g, 18%): mp 131–132 °C; IR (KBr) 1710 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.8–3.3 (m, 6 H), 2.37 (d, J = 12.8 Hz, 1 H), 3.50 (d, J = 13.4 Hz, 1 H), 3.68 (d, J = 13.4 Hz, 1 H), 4.02 (d, J = 12.8 Hz, 1 H), 4.64 (d, J = 2 Hz, 1 H), 5.94 (t, J = 2 Hz, 1 H), 6.98–8.14 (m, 5 H); mass spectrum, m/e 405 (M^+).

Anal. Calcd for $C_{19}H_{17}BrOS_2$: C, 56.30; H, 4.23; Br, 19.71; S, 15.82. Found: C, 56.51; H, 4.21; Br, 19.90; S, 15.84.

4-Bromo-1,1-dimethoxy-10,10-trimethylenedithio[2.2]metacyclophane (12). To a solution of **8** (2.98 g, 7.35 mmol) in methanol (150 mL) was added a 22% HCl–ether solution (3.5 g), and the mixture was refluxed for 4 h. The product was filtered and washed with methanol to give **12** (2.75 g, 82%): mp 177–179 °C; IR (KBr) 1120, 1100, 1080 cm^{-1}.

Anal. Calcd for $C_{21}H_{23}BrO_2S_2$: C, 55.87; H, 5.13; Br, 17.70; S, 14.20. Found: C, 55.70; H, 5.06; Br, 17.63; S, 14.20.

4-Methyl-1,1-dimethoxy-10,10-trimethylenedithio[2.2]metacyclophane (14). To a chilled solution (−10 °C) of **12** (3.31 g, 7.28 mmol) in absolute THF (70 mL) was added with stirring a 15% BuLi–hexane solution (13.5 mL, 21.9 mmol). After the mixture was stirred for 10 min at −10 °C, methyl iodide (1.36 g, 21.9 mmol) was added to the mixture and gave rise to a vigorous exothermic reaction. Stirring was continued for 30 min, and the reaction mixture was quenched by addition of water. Extraction with $CHCl_3$, drying over $MgSO_4$, and removal of the solvent gave a residue which was allowed to stand with a small amount of ethanol. The deposited **14** was washed with ethanol (2.45 g, 87%): mp 148.5–149.5 °C; IR (KBr) 1125, 1100, 1080 cm^{-1}. Anal. Calcd for $C_{22}H_{26}O_2S_2$: C, 68.36; H, 6.78; S, 16.59. Found: C, 68.11; H, 6.82; S, 16.31.

4-Methyl-1,1-dimethoxy[2.2]metacyclophane (16). A solution of **14** (2.45 g, 6.34 mmol) in ethanol (150 mL) was refluxed with "sedimented Raney nickel" (24 mL) for 2 h. The filtrate freed from Raney nickel was concentrated in vacuo to furnish **16** (1.64 g, 92%), which was sublimed in vacuo: mp 95–96 °C; IR (KBr) 1095, 1070 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.59; H, 7.92.

(±)-4-Methyl-1-oxo[2.2]metacyclophane (3). A solution of **16** (1.09 g, 3.86 mmol) and *p*-toluenesulfonic acid (1.0 g) in acetone (50 mL) was allowed to stand at room temperature for 3 h and the mixture was extracted with $CHCl_3$. After the mixture was washed with water and dried over $MgSO_4$, the solvent was removed to give a residue which was purified by preparative TLC (silica gel, benzene–$CHCl_3$). The product (0.85 g, 93%) was sublimed in vacuo: mp 83.5–85.0 °C; IR (KBr) 1700 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.8–2.3 (m, 2 H), 2.33 (s, 3 H), 2.9–3.2 (m, 2 H), 3.23 (d, J = 13.5 Hz, 1 H), 4.01 (d, J = 13.5 Hz, 1 H), 4.41 (br s, 1 H), 4.89 (br s, 1 H), 6.8–7.4 (m, 5 H); mass spectrum, m/e 236 (M^+).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.15; H, 6.87.

$LiAlH_4$ Reduction of (±)-4-Methyl-1-oxo[2.2]metacyclophane (3). Reduction of (±)-**3** (0.20 g, 0.85 mmol) with $LiAlH_4$ (0.04 g, 1.05 mmol) in THF was carried out by a routine procedure to give a mixture (192 mg) of **38** and **39**. Upon elution with $CHCl_3$/methanol (100:3), a preparative TLC (silica gel) of the mixture separated **38** (R_f 0.75) and **39** (R_f 0.58).

(±) Axial alcohol 38: mp 82–83 °C (63 mg, 31%); NMR (100 MHz, $CDCl_3$) δ 1.59 (s, 1 H), 1.84–2.25 (m, 3 H), 2.42 (s, 3 H), 2.8–3.2 (m, 2 H), 3.53 (d,d, J = 12 Hz, 4 Hz, 1 H), 4.10 (s, 1 H), 4.75 (s, 1 H), 5.26 (t, J = 4 Hz, 1 H, (CHOH)), 6.84–7.32 (m, 5 H).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.72; H, 7.67.

(±) Equatorial alcohol 39: mp 134–137 °C (44 mg, 21.2%); NMR (100 MHz, $CDCl_3$) δ 1.8–2.2 (m, 2 H), 2.14 (m, 1 H), 2.8–3.2 (m, 2 H), 2.72 (s, 1 H), 2.39 (s, 3 H), 3.49 (d,d, J = 12 Hz, 4 Hz, 1 H, CHOH), 4.16 (br s, 2 H), 4.1–4.3 (m, 1 H), 6.8–7.4 (m, 5 H).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.87; H, 7.69.

(±)-4-Methyl-1,1-trimethylenedithio[2.2]metacyclophane (37). A mixture of 1,3-propanedithiol (35 mg, 0.32 mmol) and BF_3 etherate (10 mg) was added to a mixture of **3** (79 mg, 0.33 mmol), acetic acid (3 mL), and benzene (1 mL), and the mixture was allowed to stand at room temperature for 3 days. After addition of water, the mixture was extracted with $CHCl_3$. Washing with 5% $NaHCO_3$ solution and drying over $MgSO_4$ followed by removal of the solvent gave an oil (125 mg, 97%) which crystallized on standing. Sublimation in vacuo furnished **37**, mp 130–132 °C.

Anal. Calcd for $C_{20}H_{22}S_2$: C, 73.57; H, 6.97; S, 19.64. Found: C, 73.61; H, 6.78; S, 19.43.

(±)-4-Methyl[2.2]metacyclophane (5). Desulfurization of (±)-**37** (50 mg, 0.15 mmol) was carried out with "sedimented Raney nickel" (0.7 mL) in ethanol/ethyl acetate (1:1, 20 mL), to afford (±)-**5** (26 mg, 76%): mp 85–87 °C; NMR (100 MHz, $CDCl_3$) δ 1.8–2.3 (m, 4 H), 2.36 (s, 3 H), 2.9–3.2 (m, 3 H), 4.24 (br s, 1 H), 4.28 (br s, 1 H), 6.8–7.4 (m, 5 H); mass spectrum, m/e 222 (M^+).

Anal. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.72; H, 8.20.

6-Bromo-1,1-dimethoxy-10,10-trimethylenedithio[2.2]metacyclophane (13). Dimethyl ketalization of **9**, following the same procedure as for **8**, afforded an 87% yield of **13**: mp 174–175 °C; IR (KBr) 1100, 1060, 1050 cm^{-1}.

Anal. Calcd for $C_{21}H_{23}BrO_2S_2$: C, 55.87; H, 5.31; Br, 17.70; S, 14.20. Found: C, 55.62; H, 5.02; Br, 17.82; S, 14.18.

6-Methyl-1,1-dimethoxy-10,10-trimethylenedithio[2.2]metacyclophane (15). **13** was treated with BuLi and then with methyl iodide, following the procedure for **12**, to give an 85% yield of the methyl derivative **15** which was recrystallized from ethanol: mp 160–162 °C; IR (KBr) 1100, 1080, 1070 cm^{-1}.

Anal. Calcd for $C_{22}H_{26}O_2S_2$: C, 68.35; H, 6.78; S, 16.59. Found: C, 86.45; H, 6.82; S, 16.63.

6-Methyl-1,1-dimethoxy[2.2]metacyclophane (17). Desulfurization of **15** with "sedimented Raney nickel" in ethanol gave a 70% yield of the dimethyl ketal **17**, which was recrystallized from ethanol: mp 77–78 °C; IR (KBr) 1100, 1080, 1070 cm^{-1}.

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.58; H, 7.90.

(±)-6-Methyl-1-oxo[2.2]metacyclophane (4). Hydrolysis of **17** to (±)-**4** followed the procedure described for the 4-methyl series; sublimation (in vacuo) of the product afforded an 82% yield of **4**; mp 55–57 °C; IR (KBr) 1700 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.6–2.2 (m, 2 H), 2.34 (s, 3 H), 2.97 (m, 1 H), 3.24–3.45 (m, 1 H), 3.31 (d, J = 13.5 Hz, 1 H), 3.62 (d, J = 13.5 Hz, 1 H), 4.11 (br s, 1 H), 4.84 (br s, 1 H), 6.8–7.3 (m, 5 H); mass spectrum, m/e 236 (M^+).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.40; H, 6.83.

$LiAlH_4$ Reduction of (±)-6-Methyl-1-oxo[2.2]metacyclophane (4). Reduction utilizing (±)-**4** (0.238 g, 1.01 mmol) and $LiAlH_4$ (38 mg, 1.0 mmol) in THF (15 mL) gave a 1:1.3 mixture of the diastereomeric alcohols **41** and **42**. Preparative TLC (silica gel) followed by sublimation in vacuo separated these alcohols.

(±) Axial alcohol 41: mp 173–173.5 °C (38 mg, 16%); IR (KBr) 3330 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.7–2.2 (m, 2 H), 1.74 (s, 1 H), 2.32 (d,d, J = 13.5 Hz, 4 Hz, 1 H), 2.39 (s, 3 H), 2.9–3.5

(m, 2 H), 3.09 (d,d, J = 13.5 Hz, 4 Hz, 1 H), 4.24 (br s, 1 H), 4.60 (br s, 1 H), 5.20 (t, J = Hz, 1 H, (CHOH)), 6.8–7.4 (m, 5 H).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.63; H, 7.57.

(±) Equatorial alcohol 42: mp 138–139 °C (120 mg, 50%); IR (KBr) 3250 cm^{-1}; NMR (100 MHz, $CDCl_3$) δ 1.6–2.4 (m, 3 H), 2.24 (s, 1 H), 2.36 (s, 3 H), 2.92–3.48 (m, 2 H), 3.23 (d,d, J = 12 Hz, 4 Hz, 1 H), 4.17 (br s, 1 H), 4.22 (br s, 1 H), 4.23 (d,d, J = 12 Hz, 4 Hz, 1 H, (CHOH)), 6.9–7.5 (m, 5 H).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.45; H, 7.64.

(±)-6-Methyl-1,1-trimethylenedithio[2.2]metacyclophane (44). Dithioketalization of (±)-**4** was carried out by following the procedure for (±)-**3**; preparative TLC and sublimation in vacuo gave a 95% yield of (±)-**44**: mp 123–125 °C; NMR (100 MHz, $CDCl_3$) δ 1.7–2.6 (m, 6 H), 2.37 (s, 3 H), 2.43 (d, J = 13.0 Hz, 1 H), 2.6–3.5 (m, 4 H), 3.32 (d, J = 13.0 Hz, 1 H), 4.11 (br s, 1 H), 5.46 (t, J = 2 Hz, 1 H), 7.04–7.91 (m, 5 H).

Anal. Calcd for $C_{20}H_{22}S_2$: C, 73.57; H, 6.79; S, 19.64. Found: C, 73.36; H, 6.85; S, 19.64.

NBS Monobromination of 2,5-Dimethylbenzoic Acid (18). To a refluxing solution of **18**[8] (40.5 g, 0.27 mol) in CCl_4 (1 L) was added powdered NBS (50.5 g, 0.28 mol) by portions during a period of 3 h with stirring and irradiation (100-W tungsten lamp). After being stirred and refluxed for another 3 h, the mixture was cooled to separate succinimide. A portion of the filtrate, freed from succinimide, was esterified with diazomethane to give a mixture of methyl esters whose GLC analysis exhibited a 1:1.4:2.5 ratio of the methyl esters of **18**, **19**, and **20**, respectively. When concentrated to 500 mL, the filtrate deposited **20** (see below) which was recrystallized from CCl_4 to yield crystals, mp 139.5–140 °C (16.2 g, 26%). The filtrate freed from **20** was concentrated to a solid (40.9 g) which was refluxed with 10% K_2CO_3 solution (500 mL) for 6 h. The alkaline hydrolysate was made acidic with HCl, and the separated acid was extracted with ether. Removal of the solvent gave a residue (25.9 g) whose benzene solution (300 mL) was refluxed with p-toluenesulfonic acid (0.3 g) in a water separator for 3 h. After evaporation of the solvent, the residue was taken into ether (200 mL) and extracted with three 80-mL portions of 3% Na_2CO_3 solution, followed by three 50-mL portions of 10% Na_2CO_3 solution. Concentration of the ether layer gave crystals (6.5 g, 16%) which were recrystallized from benzene–hexane to furnish **23**, mp 84–85.5 °C (see below). The combined 3% Na_2CO_3 solutions were acidified with HCl and saturated with NaCl. Ether extraction afforded needles which were recrystallized from acetone–hexane to give **21** (11.9 g, 27%): mp 120.5–121.5 °C; IR (KBr) 3300, 1680 cm^{-1}.

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.08; H, 6.02.

Acidification followed by ether extraction of the combined 10% Na_2CO_3 solutions gave recovered **18** (5 g, 15%).

Hydrolysis of 20 to 6-Methylphthalide (23). Hydrolysis of **20** with 10% K_2CO_3 solution gave an 89% yield of **22**, mp 126–127 °C. Azeotropic dehydration of **22** (1.5 g, 9.0 mmol) by refluxing with p-toluenesulfonic acid (50 mg) in benzene (120 mL) yielded 1.28 g (88%) of **23**, which was recrystallized from benzene–hexane: mp 85 °C; IR (KBr) 1760 cm^{-1}.

Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 73.06; H, 5.38.

Methyl 5-(Hydroxymethyl)-2-methylbenzoate (24). Diazomethane esterification of **21** gave a 92% yield of **24**, bp 139–146 °C (4 mm).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.52; H, 6.79.

Methyl 5-(Methoxymethyl)-2-methylbenzoate (25). To a stirred suspension of NaH (2.1 g, 87.5 mmol) in dimethoxyethane (DME) was added a solution of **24** (12.0 g, 66.6 mmol) in DME (50 mL) at room temperature during a period of 5 min. After the mixture was stirred for 10 min, a solution of methyl iodide (10.4 g, 72.3 mmol) in DME (50 mL) was added dropwise during a period of 10 min, and stirring was continued for 2 h. Removal of half of the solvent was followed by dilution with water, and the mixture was washed with 3% $Na_2S_2O_3$ solution followed by water. Removal of the solvent and distillation in vacuo yielded **25** (11.5 g, 89%) as an oil: bp 110–111 °C (5 mm); IR (neat film) 1725 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.88; H, 7.28.

5-(Methoxymethyl)-2-methylbenzyl Alcohol (26). $LiAlH_4$ reduction in THF converted **25** into **26** (97%), an oil: bp 124 °C (4 mm); IR (neat film) 3400 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.83; H, 8.59.

5-(Methoxymethyl)-2-methylbenzyl Bromide (27). A solution of **26** (11.1 g, 66.5 mmol) and PBr_3 (6.0 g, 22.2 mmol) in benzene (60 mL) was stirred at room temperature for 1.5 h. The usual procedure gave **27** (14.3 g, 95%), an oil, bp 111–113 °C (4 mm).

Anal. Calcd for $C_{10}H_{13}BrO$: C, 52.42; H, 5.72; Br, 34.88. Found: C, 52.37; H, 5.71; Br, 34.83.

3-(Methoxymethyl)benzyl Bromide (29). To a chilled (0 °C) solution of **28** (212 g, 0.80 mol) in benzene (300 mL) was added with stirring a methanolic solution of sodium methoxide prepared from sodium (14.8 g, 0.64 mol) and methanol (350 mL). Stirring was continued for 3 h at 0 °C, and the mixture was quenched with water and extracted with ether. The product was fractionally distilled through a Podbielniak-type column (60 cm) to give an oil (73.2 g, 53%), bp 104–105 °C (4 mm). A GLC analysis indicated about 1% contamination from 1,3-bis(methoxymethyl)benzene.

***m*-(Methoxymethyl)benzaldehyde (30).** To a stirred methanolic solution of sodium methoxide prepared from sodium (4.5 g, 0.2 mol) and methanol (200 mL) was added 2-nitropropane (18.2 g, 0.21 mol). After the mixture was stirred for 30 min at room temperature, a solution of **29** (40 g, 0.19 mol) was added dropwise over a period of 10 min, and stirring was continued for 2 h. Extraction and distillation of the product gave **30** as an oil (23.6 g, 85%), bp 100–105 °C (6 mm), which was directly converted into the dithioacetal **31**; IR (neat film) 1690, 1100 cm^{-1}.

***m*-(Methoxymethyl)benzaldehyde Trimethylene Dithioacetal (31).** Dithioacetalization of **30** (19.9 g, 0.13 mol) with 1,3-propanedithiol (12.9 g, 0.12 mol) gave **31** (24.2 g, 89%), bp 125–130 °C (10^{-3} mm).

Anal. Calcd for $C_{11}H_{15}OS_2$: C, 59.96; H, 6.71; S, 26.19. Found: C, 59.68; H, 6.73; S, 26.68.

3,5′-Bis(methoxymethyl)-2′-methyldeoxybenzoin Trimethylene Dithioketal (33). To a chilled solution (−30 °C) of **31** (6.35 g, 26.4 mmol) in THF (150 mL) was added 15% BuLi–hexane solution (18 mL, 29.1 mmol) with stirring, and the stirring was continued for 20 min in an atmosphere of argon. This solution of the lithio derivative **32** was added dropwise into a chilled (−5 °C) and stirred solution of **27** (6.0 g, 26.4 mmol) in THF (150 mL) over a period of 5 min in an atmosphere of argon. After the solution was stirred for 1 h at room temperature, water was added to decompose the reaction complex. Ether extraction followed by evaporation of the solvent gave an oil (11.3 g), a portion of which was distilled in vacuo for an anayltical specimen: bp 179 °C (10^{-3} mm); IR (neat film) 1095 cm^{-1}.

Anal. Calcd for $C_{22}H_{28}O_2S_2$: C, 68.88; H, 7.26; S, 16.50. Found: C, 68.16; H, 7.27; S, 16.56.

3,5′-Bis(methoxymethyl)-2′-methyldeoxybenzoin (34). To a stirred and chilled mixture (−12 °C) of **33** (4.9 g, 12.7 mmol), acetone (135 mL), and water (15 mL) was added a chilled mixture (−12 °C) of NBS (13.5 g, 76.4 mmol), acetone, and water (15 mL). After the resulting yellow colored mixture was stirred for 20 min at 0 °C, a saturated Na_2SO_3 solution (about 15 mL) was added to decolorize the mixture. Extraction with ether followed by removal of the solvent afforded an oil (3.1 g) which was directly converted into **35**; IR (neat film) 1695, 1100 cm^{-1}.

3,5′-Bis(bromomethyl)-2′-methyldeoxybenzoin (35). A mixture of crude **34** (1.0 g) and 47% HBr solution (30 mL) was refluxed for 3.5 h, diluted with water (150 mL), and extracted with $CHCl_3$. Washing with water, drying, and removal of the solvent left a dark-colored oil (1.2 g) which was chromatographed on silica gel to give colorless crystals (0.81 g). Recrystallization from benzene–hexane afforded crystals (0.48 g, 32% overall yield from **27**): mp 103–104 °C; IR (KBr) 1690 cm^{-1}.

Anal. Calcd for $C_{17}H_{16}Br_2O$: C, 51.54; H, 4.07; Br, 40.34. Found: C, 51.79; H, 4.02; Br, 39.78.

3,5′-Bis(bromomethyl)-2′-methyldeoxybenzoin Trimethylene Dithioketal (36). Dithioketalization utilizing **35** (1.0 g, 2.52 mmol) and 1,3-propanedithiol (0.30 g, 2.8 mmol) gave a light-colored oil (1.4 g) which was directly cyclized to **37** because

of its instability at room temperature.

4-Methyl-1,1-trimethylenedithio[2.2]metacyclophane (37). To a stirred solution of crude **36** (1.4 g) in THF (700 mL) was added 15% BuLi–hexane solution (20 mL) at room temperature in a period of 15 min. After the mixture was stirred for 1 h, water was added to decompose the reaction complex. Extraction with $CHCl_3$ and removal of the sovlent gave an oily residue which was purified by preparative TLC (silica gel). Elution with benzene–hexane (1:1) afforded a fraction with R_f 0.42, whose recrystallization from acetone yielded crystals (0.37 g, 45% overall yield from **35**), mp 135–135.5 °C.

Anal. Calcd for $C_{20}H_{22}S_2$: C, 73.57; H, 6.79; S, 19.64. Found: C, 73.66; H, 6.80; S, 19.34.

(±)-4-Methyl-1-oxo[2.2]metacyclophane (3). The routine procedure of oxidative hydrolysis of dithioketals utilizing **37** (250 mg, 0.77 mmol) and NBS (820 mg, 4.61 mmol) gave an oily residue which was purified by preparative TLC (silica gel). Elution with benzene/$CHCl_3$ (1:1) gave a fraction with R_f 0.56 which was sublimed to produce colorless crystals (140 mg, 77%), mp 82.5–85 °C. Its identity with a specimen prepared from **8** was established by a mixture melting point determination as well as IR and NMR spectral comparisons.

Microbial Reduction of (±)-4-Methyl-1-oxo[2.2]metacyclophane (3) with *R. rubra*. Five 500-mL Erlenmeyer flasks, each containing 200 mL of the culture medium,[19] were inoculated with *R. rubra* and incubated at 30 °C for 48 h on a thermostated shaker. After aliquots of a solution of (±)-**3** (630 mg, 2.63 mmol) in 95% ethanol (25 mL) were added to these flasks, incubation was continued for 24 h at 30 °C. Workup in the usual way,[1] via ether extraction, afforded 2.26 g of a mixture of metabolites as a pale yellow oil whose preparative TLC (silica gel) when eluted with $CHCl_3$/methanol (100:5) provided the following three fractions: ketone **3** (R_f 0.52), axial alcohol **38** (R_f 0.40), and equatorial alcohol **39** (R_f 0.26). Ketone **3** (920 mg) was directly converted into the dithioketal **37** with 1,3-propanedithiol (270 mg). Purification via preparative TLC (silica gel) yielded a 29% yield of **37** (246 mg), whose identity was established by spectral comparisons with (±)-**37**. An analytical specimen prepared by further preparative TLC melted at 128–133 °C; $[\alpha]^{25}_D$ +50.2° (*c* 1.295).

The axial alcohol **38** (284 mg) was purified by sublimation in vacuo [130–135 °C (20 mm)] to give a 39% yield of (±)-**38**. An analytical specimen obtained via preparative TLC melted at 93–94 °C; $[\alpha]^{25}_D$ −2.5° (*c* 1.08).

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.86; H, 7.66.

The crude equatorial alcohol **39** (130 mg) was converted into **40** with acetic anhydride (2.5 mL) and pyridine (5 mL). Preparative TLC (silica gel) gave (−)-**40** (73 mg, 9.8% yield from (±)-**3**): mp 129 °C; $[\alpha]^{25}_D$ −120.9° (*c* 1.315).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.47; H, 7.26.

Alkaline hydrolysis of (−)-**40** (65 mg) with 5% KOH–methanol afforded the (−) equatorial alcohol **39** (47 mg): mp 128–130 °C, $[\alpha]^{25}_D$ −98.3° (*c* 0.745). Spectral comparisons with (±)-**39** established its identity.

Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.69; H, 7.63.

(−)-4-Methyl-1-oxo[2.2]metacyclophane (3) from (+)-37. To a stirred and chilled (0 °C) solution of (+)-**37**, $[\alpha]^{20}_D$ +45.1° (100 mg, 0.31 mmol), in THF (1 mL), acetone (5 mL), and water (2 mL) was added a solution of NBS (230 mg, 1.29 mmol), acetone (15 mL), and water (3 mL). After the solution was stirred for 20 min, ketone **3** (78 mg) was isolated by the usual procedure and purified through preparative TLC (silica gel). Elution with benzene–$CHCl_3$ yielded a 58% yield of (−)-**3** (42 mg): mp 119–120.5 °C; $[\alpha]^{25}_D$ −420.0° (*c* 0.155); CD (*c* 1.69 × 10^{-4}, isooctane), $[\theta]$ [±] (nm) −2.73 × 10^4°(321). The NMR spectrum of (−)-**3** was indistinguishable from that of (±)-**3**.

(+)-4-Methyl-1-oxo[2.2]metacyclophane (3) from the (−) Axial Alcohol 38. Jones oxidation of the (−) axial alcohol **38** (160 mg, 0.67 mmol) was carried out in acetone (40 mL) with Jones reagent (2 mL) at 0 °C. Preparative TLC of the product furnished a 90% yield of (+)-**3** (142 mg): mp 121.5–122 °C; $[\alpha]^{27}_D$ +461.8° (*c* 0.275); CD (*c* 1.69 × 10^{-4}, isooctane), $[\theta]$ (nm) +3.33 × 10^4°(321).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.21; H, 6.77.

(−)-4-Methyl-1-oxo[2.2]metacyclophane (3) from the (−) Equatorial Alcohol 39. Jones oxidation of (−)-**39** (44 mg, 0.18 mmol) gave an oil whose preparative TLC (silica gel) furnished an 85% yield of (−)-**3** (37 mg): mp 120.5–121.5 °C; $[\alpha]^{25}_D$ −455.4° (*c* 0.390).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.20; H, 6.81.

(+)-4-Methyl[2.2]metacyclophane (5) from the (+)-Dithioketal 37. Raney nickel desulfurization of (+)-**37** (65 mg, 0.20 mmol) was carried out with "sedimented Raney nickel" (0.7 mL) in ethanol/ethyl acetate (1:1) to afford crude **5**, which was sublimed in vacuo to afford a 71% yield of (+)-**5** (31 mg): mp 85–87 °C, $[\alpha]^{24}_D$ +23.0° (*c* 1.27). The NMR spectrum was indistinguishable from that of (±)-**5**.

Anal. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.64; H, 8.26.

Microbial Reduction of (±)-6-Methyl-1-oxo[2.2]metacyclophane (4) with *R. rubra*. Eight 500-mL Erlenmeyer flasks, each containing 200 mL of the culture solution,[19] were inoculated with *R. rubra* and incubated at 30 °C for 48 h. Aliquots of a solution of (±)-**4** (1.00 g, 4.23 mmol) in 95% ethanol (40 mL) were added to these flasks, and incubation was continued for 24 h at 30 °C. Workup in the usual way, via ether extraction, afforded a residual oil from which crystals (607 mg) deposited. Preparative TLC (silica gel) of the crystalline material afforded the (+) axial alcohol **41** (373 mg) and the (−) equatorial alcohol **42** (189 mg). The mother liquor, freed from the crystals, was concentrated, and the residue was acetylated with acetic anhydride (5 mL) and pyridine (10 mL). Preparative TLC (silica gel) afforded the (−)-acetate **43** (203 mg), $[\alpha]^{24}_D$ −157.4° (*c* 1.02), which was hydrolyzed by refluxing with 5% KOH–methanol (30 mL) for 3 h to give the (−)-alcohol **42** (160 mg).

The (+) axial alcohol **41** was sublimed in vacuo to yield 36% of **41** (358 mg): mp 187.5–188 °C; $[\alpha]^{25}_D$ +42.8° (*c* 0.830). Spectral comparisons with (±)-**41** established its identity.

Anal. Calcd for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.77; H, 7.64.

The combined (−) equatorial alcohols were sublimed in vacuo to give a 34% yield of (−)-**42** (340 mg): mp 136–138 °C; $[\alpha]^{25}_D$ −134.7° (*c* 0.83). The identity was established by spectral comparison with (±)-**42**.

Anal. Calcd for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.42; H, 7.59.

(+)-6-Methyl-1-oxo[2.2]metacyclophane (4) from the (+) Axial Alcohol 41. Oxidation of (+)-**41** (200 mg, 0.84 mmol) with Jones reagent (1.0 mL) gave crude ketone **4** whose preparative TLC (silica gel) gave a 91% yield of (+)-**4** (181 mg): mp 95.5–97 °C; $[\alpha]^{25}_D$ +442.0° (*c* 0.314); CD (*c* 3.44 × 10^{-4}, isooctane), $[\theta]$ (nm) +3.33 × 10^4°(321). The NMR spectrum was found indistinguishable with that of (±)-**4**.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 85.65; H, 6.83.

(−)-6-Methyl-1-oxo[2.2]metacyclophane (4) from the (−) Equatorial Alcohol 42. Oxidation of (−)-**42** (90 mg, 0.38 mmol) with Jones reagent (0.5 mL) in acetone (20 mL) gave crude ketone **4** whose preparative TLC afforded a 90% yield of (−)-**4** (80 mg): mp 96–97 °C; $[\alpha]^{25}_D$ −444° (*c* 0.373). The identity was established by spectral comparison with (±)-**4**.

(+)-4-Methyl[2.2]metacyclophane (5) from (+)-4. Dithioketalization of (+)-**4** (181 mg, 0.77 mol) with 1,3-propanedithiol (100 mg, 0.92 mmol) gave crude dithioketal **44** which was purified through preparative TLC (silica gel) to afford an 88% yield of (−)-**44** (221 mg), $[\alpha]^{23}_D$ −14.7° (*c* 1.257). The NMR spectrum was found indistinguishable from that of (±)-**44**. Stirring a mixture of (−)-**44** (72 mg), "sedimented Raney nickel" (2 mL), and ethanol (20 mL) at room temperature for 3 h gave crude **5** which was sublimed in vacuo to afford a 63% yield of (+)-**5** (31 mg): mp 84.5–86 °C; $[\alpha]^{24}_D$ +22.7° (*c* 0.665, ethanol); mass spectrum, *m/e* 222 (M^+) (calcd for $C_{17}H_{18}$ 222). Comparison of the NMR spectrum with that of (±)-**5** established its identity.

Anal. Calcd for $C_{17}H_{18}$: C, 91.84; H, 8.16. Found: C, 91.78; H, 8.24.

(19) Kieslish, K. *Synthesis* **1969**, *1*, 120.

Registry No. (±)-**3**, 72985-39-8; (-)-**3**, 73037-12-4; (+)-**3**, 73037-13-5; (±)-**4**, 72985-40-1; (+)-**4**, 73037-14-6; (-)-**4**, 73037-15-7; (±)-**5**, 73037-16-8; (+)-**5**, 36325-37-8; **7**, 41047-91-0; **8**, 72985-10-5; **9**, 72985-11-6; **10**, 54379-36-1; **11**, 72985-12-7; **12**, 72985-13-8; **13**, 72985-14-9; **14**, 72985-15-0; **15**, 72985-16-1; **16**, 72985-17-2; **17**, 72985-18-3; **18**, 610-72-0; **19**, 72985-19-4; **20**, 72985-20-7; **21**, 72985-21-8; **22**, 72985-22-9; **23**, 72985-23-0; **24**, 72985-24-1; **25**, 72985-25-2; **26**, 72985-26-3; **27**, 72985-27-4; **28**, 626-15-3; **29**, 22072-45-3; **30**, 28746-20-5; **31**, 5425-44-5; **32**, 53178-41-9; **33**, 72985-28-5; **34**, 72984-98-6; **35**, 72984-99-7; **36**, 72985-00-3; (±)-**37**, 72985-01-4; (+)-**37**, 73037-04-4; (±)-**38**, 72985-02-5; (-)-**38**, 73037-05-5; (±)-**39**, 73037-06-6; (-)-**39**, 73037-07-7; (-)-**40**, 72985-03-6; (±)-**41**, 72985-04-7; (+)-**41**, 73037-08-8; (±)-**42**, 73037-09-9; (-)-**42**, 73037-10-2; (-)-**43**, 73002-60-5; (±)-**44**, 72985-05-8; (-)-**44**, 73037-11-3.

Some Metabolites of the Marine Sponges *Smenospongia aurea* and *Smenospongia* (≡*Polyfibrospongia*) *echina*

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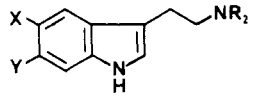
The antimicrobial metabolite of the marine sponge *Smenospongia aurea* was found to be 5-bromo-*N*,*N*-dimethyltryptamine (**4**). The same sponge also contained aureol (**6**), an unusual sesquiterpene–hydroquinone derivative. A second sample of *S. aurea* contained 8-epichromazonarol (**20**) and the indole **27**. Two samples of *Smenospongia echina* were examined and were shown to contain the antimicrobial constituent 5,6-dibromo-*N*,*N*-dimethyltryptamine (**3**), with small amounts of the phenol **25** in one sample. The structure of aureol (**6**) was determined by X-ray analysis while those of the remaining compounds were determined from spectroscopic data, particularly ^{13}C NMR spectra, and chemical interconversions.

A chemotaxonomic ideal is the assignment of a discrete class of secondary metabolites to a particular group of organisms, primarily at the genus level. Some marine sponges have been reported to contain so many different types of metabolites that they appear to defy chemotaxonomic classification. For example, *Disidea herbacea* has been reported to contain brominated phenols,[1] sesquiterpenes,[2] and some unusual chlorinated metabolites.[3] In this paper we will describe an unusual array of metabolites that have been isolated from *Smenospongia aurea* and *Smenospongia echina* (≡*Polyfibrospongia echina*), two closely related Caribbean sponges.

The sponge previously known as *Spongia fenestra* D + M or *Aplysina aurea* Hyatt has recently been reclassified as *Smenospongia aurea* (Hyatt).[4] Rützler[5] has suggested that *Polyfibrospongia echina* Laubenfels be reclassified as *Smenospongia echina* (Laubenfels). Chemical studies support Rützler's suggestion and furthermore provide evidence that *Polyfibrospongia maynardii* might also be reclassified as a *Smenospongia* species. Van Lear et al.[6] have reported the isolation of the antibacterial metabolites 5,6-dibromotryptamine (**1**) and 5,6-dibromo-*N*-methyltryptamine (**2**) from *P. maynardii*. We have isolated 5,6-dibromo-*N*,*N*-dimethyltryptamine (**3**) and 5-bromo-*N*,*N*-dimethyltryptamine (**4**) from *Smenospongia echina* and *S. aurea*, respectively.



1	R = H	X = Y = Br
2	R = H,Me	X = Y = Br
3	R = Me	X = Y = Br
4	R = Me	X = Br Y = H
5	R = Me	X = Y = H

Shipboard antimicrobial screening of the Caribbean sponges *Smenospongia echina* and *Smenospongia aurea*, collected at Glover and Lighthouse Reefs, Belize, showed that the crude extracts inhibited the growth of *Staphylococcus aureus* and *Candida albicans*. Silica gel chromatography of the ethanol extract of *Smenospongia echina* gave 5,6-dibromo-*N*,*N*-dimethyltryptamine (**3**; 0.95% dry weight). The dibromoindole **3**, mp 113–115 °C, had the molecular formula $C_{12}H_{14}N_2Br_2$. The structure was deduced from the ^1H NMR spectrum which showed a six-proton singlet at δ 2.27 due to the *N*-methyl groups and signals at δ 2.59 (t, 2 H, J = 7 Hz) and 2.86 (t, 2 H, J = 7 Hz) for the side-chain methylene groups, at δ 7.18 (br s, 1 H) due to the proton at C-2, and at δ 7.70 (s, 1 H) and 7.86 (s, 1 H) due to protons at C-7 and C-4, respectively, of a 5,6-disubstituted indole. Exchange of the NH proton by deuterium caused the signal at δ 7.18 to sharpen as expected. Hydrogenation of the dibromoindole **3** gave *N*,*N*-dimethyltryptamine (**5**).[7]

Silica gel chromatography of the ethanol extract of *Smenospongia aurea* gave 5-bromo-*N*,*N*-dimethyltryptamine (**4**; 0.88% dry weight). The bromoindole **4**, mp 98–99 °C, had the molecular formula $C_{12}H_{15}N_2Br$ and was obviously related to the dibromoindole **3**. It also gave *N*,*N*-dimethyltryptamine (**5**) on hydrogenation. The

(1) Sharma, G. M.; Vig, B. *Tetrahedron Lett.* **1969**, 1715.
(2) Kazlauskas, R.; Murphy, P. T.; Wells, R. J. *Tetrahedron Lett.* **1978**, 4949. Charles, C.; Braekman, J. C.; Daloze, D.; Tursch, B.; Declercq, J. P.; Germain, G.; Van Meerssche, M. *Bull. Soc. Chim. Belg.* **1978**, *87*, 481.
(3) Hofheinz, W.; Oberhänsli, W. E. *Helv. Chim. Acta* **1977**, *60*, 660. Kazlauskas, R.; Lidgard, R. O.; Wells, R. J.; Vetter, W. *Tetrahedron Lett.* **1977**, 3183. Charles, C.; Braekman, J. C.; Daloze, D.; Tursch, B.; Karlsson, R. *Ibid.* **1978**, 1519. Kazlauskas, R.; Murphy, P. T.; Wells, R. J. *Ibid.* **1978**, 4945.
(4) Wiedenmayer, F. *Experientia, Suppl.* **1977**, *No. 28*, 69.
(5) Rützler, K., personal communication. This is a new combination based on Wiedenmayer's definition of the genus *Smenospongia*. Until this combination is published in a taxonomic monograph, it must be regarded as temporary, and both genera should be used to refer to this sponge, i.e., *Smenospongia* (≡*Polyfibrospongia*) *echina*.
(6) Van Lear, G. E.; Morton, G. O.; Fulmor, W. *Tetrahedron Lett.* **1973**, 299.
(7) "Merck Index", 8th ed; Merck: Rahway, NJ, 1968; p 379.

0022-3263/80/1945-1435$01.00/0