Contignasterol, a Highly Oxygenated Steroid with the "Unnatural" 14β Configuration from the Marine Sponge *Petrosia Contignata* Thiele, 1899

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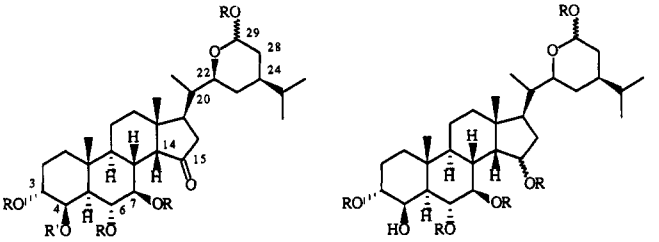
Contignasterol (1), a highly oxygenated steroid with the "unnatural" 14β proton configuration and a cyclic hemiacetal functionality in its side chain, has been isolated from the marine sponge *Petrosia contignata*. The structure of contignasterol was elucidated via spectroscopic studies of its tetraacetate 2 and its reduction product pentaacetate 5. Contignasterol (1) is the first example of a naturally occurring steroid with the "unnatural" 14β proton configuration.

Marine sponges continue to be a rich source of interesting new steroids.[1] As part of an ongoing investigation of metabolites isolated from marine invertebrates collected in Papua New Guinea,[2] it was found that extracts of the sponge *Petrosia contignata* Thiele[3] contain the highly oxygenated steroid contignasterol (1). Contignasterol is apparently the first steroid from a natural source known to have the "unnatural" 14β proton configuration,[4] and the cyclic hemiacetal functionality in the side chain is also without precedent in previously described steroids.

Specimens of *P. contignata* (2.5 kg wet weight) were collected by hand using SCUBA at Madang, Papua New Guinea, and transported to Vancouver frozen over dry ice. The frozen sponge specimens were immersed in methanol (3 L) and soaked at room temperature for 48 h. Concentration of the decanted methanol in vacuo gave an aqueous suspension (1800 mL) that was sequentially extracted with hexanes (4 × 500 mL) and chloroform (4 × 1 L). Evaporation of the combined chloroform extracts in vacuo gave a brown solid (2.1 g) that was subjected to Sephadex LH 20 chromatography (3:1 MeOH/H_2O) to give a fraction containing almost pure contignasterol. Final purification was achieved by sequential application of reversed-phase flash chromatography (4:1 MeOH/H_2O) and reversed-phase HPLC (3:1 MeOH/H_2O) to give contignasterol (1) as colorless crystals (153 mg: mp 239–41 °C).

Contignasterol (1) gave a parent ion in the EIHRMS at *m/z* 508.3394 Da corresponding to a molecular formula of $C_{29}H_{48}O_7$ (ΔM −0.6 mmu). The ^{13}C NMR spectrum of 1 contained 44 resolved resonances (see Experimental Section) and the ^1H NMR spectrum contained a number of resonances (i.e., δ 5.16) that integrated for less than one proton suggesting that the molecule existed as two slowly interconverting isomeric forms. Two of the resonances in the ^{13}C NMR spectrum of 1 had chemical shifts appropriate for acetal carbons (δ 95.6 (CH) and 90.4 (CH)). An HMQC experiment[5] showed correlations from each of these two carbon resonances to resonances in the ^1H NMR spectrum of 1 that each integrated for less than one proton. These data were consistent with the presence of a hemiacetal functionality in contignasterol that was undergoing slow spontaneous epimerization.



1 R=R'=H
2 R=Ac R'=H
3 R=R'=Ac

4 R=H
5 R=Ac

Acetylation of contignasterol with acetic anhydride in pyridine gave a mixture of polyacetates that were separated on HPLC to give the tetraacetate 2 as the major product and the pentaacetate 3 as one of the minor products. Evidence for the formation of the tetraacetate 2 came from its ^{13}C (δ 20.4, 20.6, 20.7, 20.8, 169.1, 169.3, 169.4, 172.7) and ^1H NMR spectra (δ 1.61(s), 1.71(s), 1.82(s), and 1.88(s)) which contained resonances that could be readily assigned to the four acetyl residues (Table I). A peak at *mz* 616.3605 Da ($C_{35}H_{52}O_9$ ΔM −0.6 mmu) that could be assigned to a [M^+ ($C_{37}H_{56}O_{11}$) − HOAc] fragment was the highest mass observed in the EIHRMS of the tetraacetate 2. The observation of only the expected 37 resolved resonances in the ^{13}C NMR spectrum of 2 (Table I) indicated that the acetylation reaction had successfully eliminated the effects of the hemiacetal epimerization that had complicated the NMR data collected on 1. Conse-

(1) For recent examples, see: (a) Koehn, F. E.; Gunasekera, M.; Cross, S. S. *J. Org. Chem.* **1991**, *56*, 1322. (b) Madaio, A.; Notaro, G.; Piccialli, V.; Sica, D. *J. Nat. Prod.* **1990**, *53*, 565. (c) Doss, G. A.; Silva, C. J.; Djerassi, C. *Tetrahedron* **1989**, *45*, 1273. (d) Tischler, M.; Ayer, S. W.; Andersen, R. J.; Mitchell, J. F.; Clardy, J. *Can. J. Chem.* **1988**, *66*, 1173. (e) Capon, R. J.; Faulkner, D. J. *J. Org. Chem.* **1985**, *50*, 4771.

(2) For previous work, see: de Silva, E. D.; Racok, J. S.; Andersen, R. J.; Allen, T. M.; Brinen, L. S.; Clardy, J. *Tetrahedron Lett.* **1991**, *32*, 2707.

(3) Identified by Dr. R. van Soest. A voucher specimen is deposited at the Zoological Museum of Amsterdam. We initiated studies of *Petrosia contignata* because its extracts were active in a L1210 in vitro cytotoxicity assay ($ED_{50} \approx 5$ μg/mL). A family of previously described polybrominated diphenyl ethers was found to be responsible for the biological activity.

(4) 15-Dehydro-14β-ansomagenin, a steroidal aglycon isolated from the saponins of the plant *Solanum vespetilio* also has the 14β proton configuration; however, the authors expressed considerable doubt about whether the 14β configuration exists in the natural product or was formed by epimerization during the workup. See: Gonzalez, A. G.; Barreira, R. F.; Francisco, C. G.; Rocio, J. A.; Lopez, E. S. *Ann. Quimica* **1974**, *70*, 250. Aplykurodins A and B, two 20-carbon isoprenoids that are possibly degraded steroids, have relative stereochemistries that would correspond to the 14β proton configuration in a putative steroidal precursor. See: Miyamoto, T.; Higuchi, R.; Komori, T.; Fujioka, T.; Mihashi, K. *Tetrahedron Lett.* **1986**, *27*, 1153.

(5) (a) Summers, M. F.; Marzilli, L. G.; Bax, A. *J. Am. Chem. Soc.* **1986**, *108*, 4285. (b) Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565.

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Table I. ^1H and ^{13}C NMR Data for Contignasterol Tetraacetate (2) Recorded in Benzene-d_6

C no.	^1H (400 MHz)	COSY	NOEs[e]	^{13}C (125 MHz)	HMBC[f]
1				20.5[a]	
1′	1.27	H2, H2′			
2′	2.02	H1′, H2′, H3		32.6[b]	
2	1.60	H1′, H2, H3			
3	5.24, bm	H2′, H2, H4	H2, H2′, OH4, H4	71.6	OH4
4	3.87, bm	H2′, H3, H5	H3, OH4, H5	66.6	H3
4OH	3.05, bd				
5	1.80	H4, H6		45.9	H3, H6, H19
6	5.40, dd (8.6, 12.1)	H5, H7	OH4, H5, H7, H19	73.8	H7
7	6.63, dd (8.6, 10.4)	H6, H8	H5, H6, H14	74.7	H6
8	1.95	H7, H9, H14		37.3	H7
9	1.26	H8		32.6	H19
10				36.4	H19
11				21.5[a]	
12_{ax}	1.06	H12′		36.3[b]	H18
$12'_{eq}$	1.33	H12, H14			
13				42.2	H16, H16′, H18
14	2.34, bs	H8, H12′	H7, H8, H18, H22	51.7	H18
15				216.0	H16, H16′
16	2.06, bd (19.7)	H16′, H17		40.5	
16′	2.30, dd (19.7, 9.9)	H16, H17			
17	2.0	H16, H16′, H20		43.0	H18, H21
18	1.20, s, 3 H		H14, H22	19.3[c]	
19	1.12, s, 3 H		H2, OH4, H6, H8	14.5[d]	
20	1.68	H17, H21, H22		41.7	
21	0.77	H20		15.2[d]	
22	3.33, bt (8.2, 9.0)	H20, H23, H23′	H14, H16, H18, $H23_{eq}$, H29	78.0	H21, $H23_{ax}$, $H23_{eq}$
23_{ax}	0.64, m (10.8, 12.2)	H22, H23′, H24		32.8[b]	
$23'_{eq}$	1.41, bd (12.2)	H22, H23, H24			
24	1.09	H23, H23′, H25, H28′		40.6	H26, H27
25	1.23	H24, H26, H27		46.6	
26	0.77[a]	H25		19.8[c]	
27	0.75[a]	H25		19.5[c]	
28_{ax}	1.17	H28′, H29		33.4[b]	
$28'_{eq}$	1.60	H24, H28, H29			
29	5.60, dd (2.2, 9.5)	H28, H28′	H22, H24, $H28_{eq}$	94.3	H28
OAc	1.61, s; 1.71, s; 1.82, s; 1.88, s			20.4, 20.6, 20.7, 20.8, 169.1, 169.3, 169.4, 172.7	

[a–d] May be interchanged. [e] Proton in carbon no. column irradiated. [f] Protons correlated to carbon resonances in ^{13}C NMR column.

quently, the structure of contignasterol was solved by analysis of the much simpler spectroscopic data collected on the tetraacetate 2.

The observation of two methyl singlet resonances (δ 1.12 and 1.20) and three methyl doublet resonances (δ 0.75, 0.77, and 0.77) in the ^1H NMR spectrum of 2, in combination with the EIHRMS-determined count of 29 carbon atoms in the skeleton of the underivatized metabolite 1, provided initial evidence that contignasterol was a steroid. A resonance at δ 216.0 ppm, assigned to a saturated ketone carbonyl carbon, was the only indication of an unsaturated functionality in addition to the four acetate carbonyls that could be identified in the ^{13}C NMR spectrum of 2. Therefore, the five remaining sites of unsaturation required by the molecular formula ($C_{37}H_{56}O_{11}$ requires 10 dbe) were attributed to rings. The four acetoxy residues and the saturated ketone accounted for nine of the 11 oxygen atoms in 2. An OH stretching vibration in the IR spectrum of 2 (3476 cm^{-1}) in conjunction with the formation of a small amount of the pentaaacetate 3 in the acetylation reaction of 1 demonstrated that one of the remaining oxygen atoms in 2 was present as a free hydroxyl. The final oxygen atom had to be present as the ether oxygen component of the acetal functionality.

A detailed analysis of the COSY, APT,[6] and HMQC spectra of tetraacetate 2 (Table I) identified a ^1H NMR spin system consisting of seven contiguous methine resonances and a pair of geminal methylene resonances that could be uniquely assigned to the H14 (δ 2.34), H8 (1.95), H7 (6.63), H6 (5.40), H5 (1.80), H4 (3.87), H3 (5.24), $H2_{ax}$ (1.60), and $H2_{eq}$ (2.02) protons of a steroid nucleus containing acetoxy substituents at C3 (^{13}C: δ (71.6), C6 (73.8), and C7 (74.7)) and a hydroxyl substituent at C4 (66.6). Difference NOE and HMBC[7] experiments supported the assignments and provided stereochemical information for some centers. Irradiation of the methyl singlet at δ 1.12 (Me19) induced NOEs in the resonances at δ 1.60 ($H2_{ax}$), 1.95 (H8), 3.05 (4OH), and 5.40 (H6), while irradiation of the H6 resonance at δ 5.40 induced NOEs in the resonances at δ 1.12 (Me19), 3.05 (4OH), and 6.63 (H7). This set of NOE results was consistent with the standard 5α steroidal configuration and with 4β-hydroxyl and 6α-acetoxy substituents. A strong HMBC correlation between the Me19 proton resonance (δ 1.12) and the C5 carbon resonance (δ 45.9) and an overlapping network of correlations from the H3, 4OH, H6 and H7 proton resonances to the C2–C8 carbon resonances (Table I) were in complete agreement with the proposed substitution pattern in the A and B rings. The H3 resonance (δ 5.24) appeared as a broad singlet with a $W_{1/2}$ = 8.3 Hz indicating that H3 was equatorial and that the C3 acetoxy substituent had the α configuration. The observed coupling constant of 10.4 Hz between H7 (δ 6.63) and H8 (δ 1.95) showed that the two protons were trans diaxial and, therefore, that the C7 acetoxy substituent had the β configuration.

A number of pieces of evidence helped to locate the saturated ketone at C15 and establish the 14β configuration. First, the assignment of the ^1H NMR resonance at δ 2.34 in the spectrum of 2 to H14, and not to the alternate

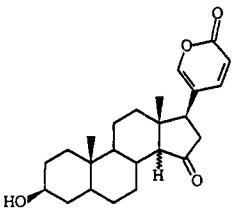
(6) Patt, S.; Shoolery, J. N. *J. Magn. Reson.* **1982**, *46*, 535.
(7) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.

methine hydrogen at C9, was secured by the observation of a three-bond HMBC correlation between the Me18 proton resonance at δ 1.20 and the C14 carbon resonance at δ 51.7 (correlated to δ 2.34 in the HMQC). The observation of a NOE in the Me18 resonance in the tetraacetate 2 (solvent: CCl_4 plus benzene-d_6 (2:1) δ 1.16) upon irradiation of H14 (δ 2.15) supported the assignment, and it also showed that H14 had the β configuration. The corresponding NOE was observed between the Me18 resonance (Me_2SO-d_6 δ 1.13) and the H14 resonances (δ 3.00 and 3.05) in the parent natural product 1. A COSY correlation observed between H14 and $H12_{eq}$ (δ 1.33) in 2 was attributed to long-range *W* coupling in agreement with the H14β assignment.

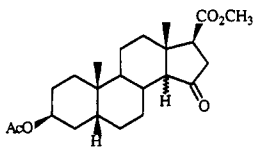
The relatively deshielded chemical shift of the H14 resonance (1: Me_2SO-d_6 δ 3.00 and 3.05; 2: benzene-d_6 δ 2.34) in contignasterol (1) and its tetraacetate 2 provided the initial indication that the saturated ketone was located at C15. Drieding models showed that the H7 methine proton would also experience a significant neighboring group effect from a C15 ketone, providing an explanation for its extremely deshielded chemical shift in both contignasterol (1) (H7: Me_2SO-d_6 δ 4.50) and the tetraacetate 2 (H7: benzene-d_6 δ 6.63). Reaction of contignasterol (1) with sodium borohydride gave the reduction product 4, which was acetylated with acetic anhydride and pyridine to give the reduction product pentaacetate 5. The resonances assigned to both H14 (5: benzene-d_6 δ 2.15) and H7 (5: δ 5.08) showed substantial upfield shifts in the pentaacetate 5 relative to their chemical shifts in contignasterol tetraacetate (2) (benzene-d_6: H14 δ 2.34; H7 δ 6.64), and analysis of the COSY spectrum of 5 revealed that the resonance assigned to H14 (δ 2.15) was coupled to the new H15 carbinol methine resonance (δ 5.25) in agreement with a C15 ketone in 1. The final evidence for placement of the ketone at C15 came from the COSY data for 2 which contained correlations that elaborated the spin system containing H16/H16′ (δ 2.06 and 2.30), H17 (2.0), H20 (1.68), and Me21 (δ 0.77) (Table I) and from the HMBC data for 2 which contained correlations between H16/H16′ (δ 2.06 and 2.30) and C15 (δ 216).

The side chain fragment of tetraacetate 2 had to account for an elemental composition of $C_{12}H_{21}O_3$, and it had to contain one ring as well as acetate, ether and acetal functionalities. Three methyl doublets were present in the ^1H NMR spectrum of 2 and analysis of the COSY spectrum (Table I) showed that they could be assigned to the Me21 (δ 0.77), Me26, and Me27 (0.75 and 0.77) groups of a normal steroid side chain carbon skeleton. Further analysis of the COSY spectrum revealed that there was a two carbon branch at C24 (i.e., C28: δ 1.17, 1.60 and C29: δ 5.60, HMQC correlation to δ 94.3) that terminated in the acetal carbon and that there was an oxygen substituent at C22 (δ 3.33–HMQC correlation to δ 78.0). A HMBC correlation between the acetal methine proton resonance at δ 5.60 and an acetate carbonyl resonance at δ 169 demonstrated that one of the oxygen attachments to the acetal carbon was part of an acetoxy residue. Connection of the C22 oxygen atom to C29 completed the acetal functionality and generated the ring in the side chain required by the unsaturation number. A pair of NOE experiments (irradiated H29 (δ 5.60)–NOE in H22 (3.33); irradiated H22 (δ 3.33)–NOE in H29 (5.60), Table 1), in conjunction with the observation of a 9.5 Hz scalar coupling constant attributed to trans diaxial coupling in the H29 resonance (dd, J = 2.2, 9.5 Hz), showed that the tetrahydropyran ring in the side chain of 2 occupied a chair conformation with the C22 and C29 substituents in equatorial orientations. Double resonance experiments revealed that there was a 12.3-Hz coupling constant between $H23_{ax}$ (δ 0.64) and H24 (1.09) indicating an equatorial orientation of the isopropyl substituent at C24. An attempt to determine the absolute configurations at C22 and C24 using empirical rules[8] established for steroids with side-chain functionalities similar to the reduction product 4 gave ambiguous results. Therefore, even though the relative stereochemistries at the C22, C24, and C29 centers in the side chain of 2 have been established, their relationship to the configuration of the nucleus is undetermined. The relative stereochemistry at C17 in 2 was assumed to be the "natural" β configuration. This assumption was supported by the observation of NOEs between the H14 and H22 ^1H NMR resonance (see Table I).

The relative stabilities of the 14α and 14β epimers of a number of semisynthetic 15-keto steroids have been determined by equilibration with base. In all cases studied, the 14β epimers (i.e., CD ring junction cis) was found to be the most stable. For example, at equilibrium 14α-artebufogenin (6) and its 14β epimer 7 are present in a ratio



6: 14-alpha
7: 14-beta



8: 14-alpha
9: 14-beta

of 35:65[9] and the 14α-steroid 8 and its 14β-epimer 9 have an equilibrium ratio of 13:87.[10] Attempts to epimerize contignasterol (1) with base ($NaOH/H_2O$ and NaH/DMF) led only to the formation of complex mixtures of degradation products so it was not possible to determine the relative stabilities of its 14α and 14β epimers. However, the extraction and chromatography conditions (extraction with neutral MeOH at rt followed by Sephadex LH20 chromatography eluting with $MeOH/H_2O$) are unlikely to have caused epimerization, and there was no TLC or ^1H NMR evidence for the presence the 14α epimer in the crude extracts or chromatography fractions indicating that contignasterol (1) exists exclusively as the 14β epimer in the sponge.

One of the significant features of steroids as a class of natural products is the almost universal occurrence of one particular set of configurations at the ring junction carbon atoms of the nucleus. In rare instances, some centers, most commonly C5,[11] are found with epimeric proton configurations and there are examples of biological hydroxylation at a ring junction carbon leading to inversion of the "normal" configuration.[12] Contignasterol (1) represents the first naturally occurring steroid with the 14β proton configuration, although steroids with a 14β-hydroxyl functionality (i.e., digitoxin) are well-known from nature. Since inverted ring junction configurations at any center in the nucleus of naturally occurring steroids are rare, the

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biogenetic origin of the "unnatural" H14 configuration in contignasterol (1) is of considerable interest.

Experimental Section

Contignasterol (1): obtained as colorless needles from MeOH/H_2O (≈10:1), mp 239–41 °C; FTIR (film) 1719 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 6.21 (bs), 5.94 (bs), 5.72 (bs), 5.16 (bs), 4.53 (bm), 4.50 (bm), 4.34 (bs), 4.16 (bm), 4.04 (bs), 3.88 (bs), 3.78 (bt, J = 10.5 Hz), 3.62 (bs), 3.22 (bt, J = 9.4 Hz), 3.05 (bs), 3.00 (bs), 2.38 (bm), 2.09 (bd, J = 20.0 Hz), 1.13 (s), 0.93 (s) ppm; ^{13}C NMR (125 MHz, DMSO-d_6) δ 219.4, 219.3, 95.6, 90.4, 75.2, 73.9, 73.8, 70.3, 70.2, 68.6, 68.0, 67.7, 50.7, 50.5, 46.3, 45.8, 45.0, 44.9, 41.3, 41.2, 40.0, 38.8, 38.6, 38.3, 38.2, 36.9, 35.7, 35.5, 34.6, 34.0, 32.5, 32.1, 31.9, 31.8, 23.6, 20.1, 19.6, 19.3, 19.2, 18.9, 18.8, 16.7, 16.7, 14.8 ppm; EIHRMS M^+ m/z 508.3394 ($C_{29}H_{48}O_7$ ΔM −0.6 mmu); EILRMS m/z 508, 490, 472, 457, 447, 408, 319, 264, 246, 221, 203, 155, 119, 109.

Contignasterol Tetraacetate (2). Contignasterol (1) (18.0 mg) was stirred in pyridine (2 mL) and acetic anhydride (2 mL) at room temperature for 18 h. The reagents were removed in vacuo, and the resulting gum was purified using normal-phase HPLC (3:2 ethyl acetate/hexane) to yield the tetraacetate 2 (5.8 mg) and the pentaacetate 3 (≈1 mg). 2: colorless oil; $[\alpha]_D$ +63° (CH_2Cl_2, c 0.34); FTIR (film) 3477, 1748, 1736 cm^{-1}; ^1H NMR see Table I; ^{13}C NMR see Table I; EIHRMS (M^+ − HOAc) m/z 616.3605 ($C_{35}H_{52}O_9$ ΔM −0.6 mmu); EILRMS m/z 616, 556, 513, 496, 436, 123, 60, 43.

Contignasterol pentaacetate (3): colorless oil; ^1H NMR (400 MHz, benzene-d_6) δ 0.75 (d, J = 6.5 Hz, 3 H), 0.76 (d, J = 6.6 Hz, 3 H), 0.77 (d, J = 6.8 Hz, 3 H), 0.94 (s, 3 H), 1.24 (s, 3 H), 1.54 (s, 3 H), 1.80 (s, 3 H), 1.86 (s, 3 H), 1.89 (s, 3 H), 1.95 (s, 3 H), 2.10 (dd, J = 3.4, 12.4 Hz), 2.31 (dd, J = 10.3, 20.0 Hz), 2.39 (bs), 3.32 (m), 5.10 (m), 5.45 (dd, J = 9.0, 12.0 Hz), 5.47 (bs), 5.60 (dd, J = 2.2, 9.0 Hz), 6.54 (dd, J = 9.1, 10.6 Hz).

Contignasterol Reduction Product 4. $NaBH_4$ (21 mg) was added to a solution of contignasterol (1) (12.5 mg) in isopropyl alcohol (10 mL). The reaction mixture was stirred at room temperature for 1 h and quenched with H_2O (10 mL). The resulting suspension was extracted with EtOAc (2 × 10 mL), and the ethyl acetate layer was washed with 1 N HCl (10 mL) and H_2O (10 mL). Purification of the ethyl acetate soluble material using reversed-phase HPLC (25:75 H_2O/MeOH) gave the reduction product 4 (7.6 mg, 61%): white solid.

Reduction Product Pentaacetate 5. Reduction product 4 (7.6 mg) was stirred in pyridine (1 mL) and acetic anhydride (1 mL) at room temperature for 17 h. The reagents were removed in vacuo, and the resulting gum was purified on normal-phase HPLC (1:1 EtOAc/Hex) to give the pentaacetate 5: colorless oil; ^1H NMR (400 MHz, benzene-d_6) δ 0.74 (d, J = 6.8 Hz, H27), 0.76 (d, J = 6.8 Hz, H26), 0.87 (m H23), 1.03 (d, J = 6.8 Hz, H21), 1.04 (s, H19), 1.07 (s, H18), 1.21 (m, H28), 1.25 (m, H1), 1.25 (m, H25), 1.26 (m, H16), 1.48 (m, H23′), 1.59 (s, OAc), 1.60 (m, H2′), 1.62 (m, H28′), 1.63 (m, H5), 1.72 (s, OAC), 1.76 (s, OAc), 1.80 (m, H17), 1.82 (s, OAc), 1.91 (m, H20), 1.99 (m, H8), 2.00 (m, H2), 2.08 (s, OAc), 2.15 (dd, J = 3.6, 7.8 Hz, H14), 3.54 (dd, J = 5.9, 9.4 Hz, H22), 3.82 (bm, H4), 5.07 (dd, J = 8.9, 11.2 Hz, H7), 5.18 (bm, H3), 5.25 (m, H15), 5.32 (dd, J = 8.9, 12.2 Hz, H6), 5.75 (dd, J = 2.2, 9.7 Hz, H29) ppm; EIHRMS (M^+ − HOAc) m/z 660.3871 ($C_{37}H_{56}O_{10}$ ΔM −0.2 mmu); EILRMS m/z 660, 642, 615, 600, 540.

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Registry No. 1, 137571-30-3; 2, 137571-31-4; 3, 137571-32-5; 4, 137571-33-6; 5, 137571-34-7.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for contignasterol (1) and the tetraacetate 2 (4 pages). Ordering information is given on any current masthead page.

C- and Z-Shaped Ditopic Cavitands, Their Binding Characteristics, and Monotopic Relatives[1]

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Readily available octol 1, when treated with 3 mol of CH_2ClBr, gave hexol 2 (3%), tetrol 3 (7%), diol 4 (17%), and tetra-bridged 5 (10%). The tetrol and diol served as starting materials for preparing mixed-bridged systems. Diol 4 reacted with 2,3-dichloroquinoxaline (7) to give 7% of cavitand 8, whereas tetrol 3 reacted with only one of the 2 mol of quinoxaline 7 to give the chiral diol 9 (18%). When 2 mol of diol 4 were treated with 1 mol of fluoranil (6), the mixture of 42% of Z-shaped 10 (**Z-10**) and 12% of C-shaped 10 (**C-10**) produced was easily separated. The crystal structures of **4**·$CHCl_3$·H_2O, **C-10**·3CH_3CN·CH_2Cl_2, **Z-10**·4$CH_3CO_2CH_2CH_3$, **Z-10**·4$CH_3COCH_2CH_3$, and **Z-10**·6$C_6H_5NO_2$ were determined and found to resemble what was predicted from molecular model examination. When 1 mol of diol 4 was mixed with tetrachlorotetraazaanthracene 12, a 16% yield of what is probably **Z-11** was obtained. One-to-one association constants of **C-10** in CD_2Cl_2 at 21 °C were determined by ^1H NMR titrations with guests as follows: $C_6D_5NO_2$ (K_a = 0.6 M^{-1}), $C_6D_5CD_3$ (K_a = 1.8 M^{-1}), p-$CD_3C_6D_4CD_3$ (K_a = 1.6), and $CH_3COCH_2CH_3$ (K_a = 1.2 M^{-1}). Attempts to detect binding failed with 2-butyne, 2-pentyne, and methylcyclohexane, although molecular model examination suggested that all seven of the above guests are complementary to the highly preorganized ditopic cavity of **C-10**.

Previous papers in this series established that octols such as 1 (Chart 1) were readily synthesized from a variety of aldehydes and resorcinol in high yields.[2,3] The conformational mobilities of their configurationally homogeneous all-syn isomer (see 1) were reduced by bridging the four sets of proximate oxygens with four units such as CH_2,

(1) (a) Host–Guest Complexation. 61. (b) We warmly thank the National Science Foundation for Grant Number CHE 88 02800 and L. A. Tunstad thanks the National Institutes of Health for Predoctoral Fellowship NIH NIGMS-MARC Grant F-31, GM 10277.

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