(Figure 1), while in 18C6A₄, a water bridges each pair of coaxial carboxylic acids (Figure 2).

The crystal structure of 18C6A₆ contains four water molecules.⁶ In addition to the encapsulated water dimer, two waters solvate carboxyls in the syn direction. The host has 3-fold symmetry with the required six-point recognition to satisfy all of the hydrogenbonding sites on the water dimer. Three carboxyl oxygens accept hydrogen bonds in the preferred anti direction.⁷ The other three host carboxylic acids donate hydrogen bonds with the hydroxyl hydrogen in the less preferred, more acidic, anti conformation.8 Distances of the macrocyclic oxygens to the hydrogen that connects the dimer range from 2.75 to 2.78 Å. These distances give a mean cavity radius of 1.37 Å, somewhat larger than the van der Waals radius of hydrogen. The length of these contacts excludes significant interactions with the macrocyclic oxygens.

The crystal structure of 18C6A₄ contains two waters that are similarly hydrogen bonded to the host with three-point recognition.⁶ One carboxyl oxygen accepts a hydrogen bond from water, one carboxylic acid donates the hydroxyl hydrogen in an anti conformation, and a macrocyclic oxygen accepts the remaining hydrogen from water. The two waters are close to each other, O2W...O1W, 3.77 Å, but outside the sum of the van der Waals radii, and the orientations of the hydrogen atoms are not indicative of dipolar interactions.

Table I summarizes the parameters of the water dimer in the crystal structure and from recent experiments and calculations. The dimer in the 18C6A₆ crystal structure is virtually identical with one of the three unique dimers that define the ice IX structure.9 A comparison of the solid-state structures of the tetraand hexaacids suggests that the antiprismatic six-point recognition provided by $18C6A_6$ (or ice IX) is required for binding the water dimer. Four-point recognition is insufficient. Cavity size is also important. Compare the water dimer complex of 18C6A₆ with the inclusion hydrate of α -cyclodextrin.¹⁰ The included water molecules in the latter have a significantly longer O---O separation and contact the host with only two hydrogen bonds, suggestive of an adventitious hydrate rather than a defined complex.¹¹

Employment of the less preferred anti conformation of the carboxylic acid for donation of hydrogen bonds begs the question of whether this conformation is as unfavored in solution or the solid state as it is in the gas phase. The host carboxylic acids can only bind guests in the cavity in the anti direction. If the carboxyls did not donate the hydrogen but adopted a syn conformation, a

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repulsion would be created by the close proximity of the lone pairs on water and on hydroxyl or carbonyl. The interatomic distances preclude additional intramolecular hydrogen bonding to stabilize the anti configuration, e.g., O29-H to O7 or O10 in the 18C6A₆ structure. We don't know how much of the stability of the crystal structure comes from the complex and how much from the crystal-packing forces. We do know that a 100-mg sample crystallized to a 100-mg single crystal. The crystal structure reveals a chain of syn-oriented carboxyls hydrogen bonded to other carboxyls and the other two waters. Even so, there are only two of these lattice hydrogen bonds per water molecule, compared to four per water molecule in the $18C6A_6$ -water dimer complex.

These macrocycles provide an expanded architecture for binding guests by hydrogen bonding together with the usual toroidal array of macrocyclic oxygens. In 18C6A₆, the macrocycle serves as collar to anchor six carboxyls in 3-fold symmetry to form a cylindrical cavity with potentially 12 points for recognition of guests. The structures of $18C6A_6$ complexes with the water dimer and monohydrated cations suggest a reason for the success of this ligand as complexing agent in water: cationic guests do not have to be completely dehydrated, as the host can recognize the water too. This solid-state structure of the water dimer joins structures in other phases to provide a clear picture of this most fundamental example of molecular recognition-the water-water hydrogen bond.

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Supplementary Material Available: Tables of atomic positional coordinates, bond distances, bond angles, torsional angles, and anisotropic thermal parameters (27 pages); listing of observed and calculated structure factors for 18C6A4.2H2O and 18C6A6.4H2O (68 pages). Ordering information is given on any current masthead page.

Total Synthesis of (+)-Verrucosidin

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A potent mycotoxin, verrucosidin (1) was isolated from the fungus Penicillium verrucosum var. cyclopium in 1983.¹ Verrucosidin has a close structural relationship to citreoviridin $(2)^2$ and related polyene α -pyrone mycotoxins,³ most of which are known to be potent inhibitors of mitochondrial ATPase and oxidative phosphorylation.⁴ Herein we report a total synthesis of (+)-verrucosidin (1) which highlights an efficient, stereocontrolled

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⁽⁶⁾ The hexaacid $18C6A_6$ crystallizes from water as the tetrahydrate $(C_{18}H_{12}O_{22})$ in orthorhombic space group $P2_12_12_1$: a = 11.214 (2), b = 11.7829 (11), c = 19.920 (2) Å; V = 2632.0 (10) Å³; R = 0.0284 for 5124 observed of 5312 unique data. All hydrogen atoms were refined except for two on uncomplexed water molecules. The absolute configuration was assigned from starting materials; the enantiomorphous structure has R = 0.0286. The tetraacid 18C6A₄ crystallizes from water as the dihydrate ($C_{16}H_{28}O_{16}$) in monoclinic space group $P2_a$: a = 11.2002 (9), b = 8.0803 (4), c = 12.0390 (5) Å; $\beta = 102.225$ (5)°; V = 1064.8 (1) Å³; R = 0.0277 for 4235 observed of 4374 unique data. The absolute configuration was assigned from starting materials; the enantiomorphous structure has R = 0.0281. Tables of atomic positional coordinates, bond lengths, bond angles, torsion angles, and structure factor amplitudes are available as supplementary material.

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Scheme I⁴



^a (a) CH₃COC(CH₃)=PPh₃, PhCH₃, reflux (85%). (b) DBU, CHCl₃, followed by CH₃I (76%). (c) 2 equiv of BH₃, (S)-2-amino-3-methyl-1,1-diphenylbutan-1-ol, THF, -78 °C (70%). (d) 0.02 equiv of OsO₄, 1.2 equiv of NMO, 2:1 THF-H₂O, 0 °C, followed by NaHCO₃ (68-77%). (e) DIBAL-H, THF, -78 °C. (f) Ph₃P=CH₂, toluene, reflux (68% overall from 4). (g) PdCl₂(PhCN)₂, PhH, reflux (90%). (h) MsCl, pyr, CH₂Cl₂, room temperature (75%). (i) O₃, CH₂Cl₂-MeOH, -78 °C/Me₂S. (j) Ph₃P=C(CH₃)CO₂Et, PhH, reflux (93% overall from 12). (k) NaOEt, EtOH (93%). (1) MnO₂, CH₂Cl₂ (90%).

construction of the densely functionalized tetrahydrofuran 3 and the monoepoxy trisubstituted triene moiety present in 1.5,6



Shown in Scheme I is our enantioselective synthesis of tetrahydrofuran 3,⁷ starting from the homochiral 5, $[\alpha]^{20}_{D} = -15.0^{\circ}$ (c 0.8, CHCl₃), which is readily prepared by the asymmetric Itsuno reduction⁸ of the prochiral ketone 9. The requisite one-carbon oxidative degradation of lactone 4 was achieved by the straightforward side-chain elaboration. Thus, DIBAL-H reduction and subsequent Wittig reaction (Ph₃P=CH₂, toluene, reflux) gave allyltetrahydrofuran 10 in 68% overall yield. The terminal olefin 10 was then isomerized to provide 11 ($\geq 8:1, 90\%$), which was converted into mesylate 12 in 75% yield. Ozonolysis followed by a Wittig reaction and epoxide formation (NaOEt) furnished the epoxy ester 3, $[\alpha]^{28}_{D} = -44^{\circ} (c \ 0.9, \text{CHCl}_3)]$, in 88% overall yield. The latter was identical in every aspect with an authentic sample prepared from (+)-verrucosidin (1) [(1) OsO_4 -NaIO₄; (2) $Ph_3P = C(CH_3)CO_2Et$, benzene, reflux].⁹

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^a(a) DMS, K₂CO₃, acetone, reflux (80%). (b) LDA, HMPA-THF, -78 °C, followed by CH₃CH₂CHO (82%). (c) MsCl DMAP, pyr, room temperature, followed by DBU, CH₂Cl₂, reflux (72%). (d) Os-mylation at 0 °C (78%). (e) CH₃COCl, pyr, 0 °C (98%). (f) PLAP, pH 7.0 buffer, room temperature, followed by recrystallization (85%). (g) Swern oxidation (85%). (h) TMSOTf, pyr-CH₂Cl₂, 0 °C to room temperature (84%).

Having developed an efficient route to the highly substituted tetrahydrofuran 3,¹⁰ our attention was turned next to its coupling with the 2-pyrone subunit of verrucosidin. After several approaches to this final union failed, we decided to reinvestigate an elegant coupling protocol previously reported by Takano and co-workers in their total synthesis of 1.5 Thus, ketone 14, $[\alpha]^{25}$ _D = +70.7° (c 1.79, CHCl₃), was prepared in an enantiomerically pure form from the readily available 6-ethyl-4-hydroxy-3,5-dimethyl-2-pyrone (15)¹¹ in a straightforward fashion as shown in Scheme II. It is particularly noteworthy that an enzyme-catalyzed kinetic resolution of the acetate ester 19 with use of porcine liver acetone powder (PLAP) gave the homochiral diol $20 \{ [\alpha]^{25} \}$ +68.3° (c 0.77, CHCl₃), mp 138-139 °C} after a single recrystallization.12

Following a slight modification of Takano's procedure (Scheme III), the enone 21 was obtained in 64% overall yield from the aldol condensation of 14 with aldehyde 13. Subsequent desilylation

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Scheme III⁴



 a (a) LiN(TMS)₂, THF, -78 °C (77% based on consumed SM). (b) TFAA, DMAP, DBU, CH₂Cl₂, -40 to 0 °C (83%). (c) CsF, EtOH, room temperature (90%). (d) 1 equiv of NaBH₄-0.5 equiv of d-tartaric acid-1 equiv of PrCl₃·6H₂O, 2-propanol, 0 °C (85%). (e) Martin's sulfurane (80%).

and reduction of the resulting α -hydroxy enone 22 with LAH (at -78 °C) or NaBH₄-CeCl₃ (at -23 °C)¹³ gave inseparable 1:2 or 3:2 mixtures of diols 23 and 24, respectively. In our hands, both reduction reactions gave poorer stereoselectivity than reported by Takano. More significantly, however, our unequivocal stereochemical assignment (vide infra) of 23 and 24 reveals that the stereostructures of these diols should be reassigned as shown in Scheme III. After considerable experimentation with several hydride reagents, the stereoselective (\sim 5:1) reduction of 22 leading to diol 23 was accomplished by the use of a sodium acyloxyborohydride¹⁴ derived from $NaBH_4$ and tartaric acid in the presence of a lanthanide. On the other hand, diol 24 can be prepared stereoselectively ($\geq 10:1$) by LAH or NaBH₄ reduction of **21** followed by desilylation.¹⁵ The stereochemical assignment of the diols was secured at this juncture by the conversion [(1) 2,2-dimethoxypropane, p-TsOH; (2) OsO₄-NaIO₄] of 24 to ketone 25 and an independent synthesis of the latter ketone starting from



pyrone 16.¹⁶ Finally, treatment of a 5:1 mixture of diols 23 and 24 with Martin's sulfurane¹⁷ stereoselectively afforded 1 and its

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epimer 26 in the same ratio. The synthetic substance was found to be identical in every aspect with an authentic sample of verrucosidin.18

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Supplementary Material Available: Description of the preparation of ketone 25 and ¹H/¹³C NMR spectra for key intermediates (27 pages). Ordering information is given on any current masthead page.

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EXAFS Studies of Nickel(II) and Nickel(I) Factor 430 M. Conformational Flexibility of the F430 Skeleton

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Factor 430 (F430) is a Ni(II) tetrapyrrole (corphin) found in methyl coenzyme M reductase, the enzyme that catalyzes the terminal stages of the conversion of carbon dioxide in methane biogenesis.¹⁻³ F430 can be reduced to Ni(I) in vitro⁴ and in vivo,⁵ and Ni(I) has been implicated as a catalytic transient in the enzymic methanogenesis.⁵ Ni(I) F430 M (the pentamethyl ester of F430) has also been shown to react with methyl halides and sulfonium salts to yield methane.⁶ The conformations of F430 that control the reactions are unknown,⁷ as are the consequences of metal reduction. F430 is deduced to exist as hexacoordinated, high-spin (HS) Ni(II) with oxygen axial ligands in vivo,⁸ and Ni-N distances of 2.10 Å have been determined by EXAFS for extracted HS F430 in aqueous solutions.9

We present here EXAFS results for the low-spin (LS) Ni(II) form of F430 M¹⁰ and for its paramagnetic Ni(I) reduction in-

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