(Figure 1), while in $18C6A_4$, a water bridges each pair of coaxial carboxylic acids (Figure 2).

The crystal structure of $18C6A_6$ 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 hydrogen-bonding 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 $18C6A_4$ 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 $18C6A_6$ 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 tetra- and 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 $18C6A_6$ 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 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 $18C6A_6$ 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 $18C6A_6$, 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.

Acknowledgment. We thank Niel Kestner for helpful discussions. The continuing support of the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

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 $18C6A_4 \cdot 2H_2O$ and $18C_6A_6 \cdot 4H_2O$ (68 pages). Ordering information is given on any current masthead page.

(6) The hexaacid $18C6A_6$ crystallizes from water as the tetrahydrate ($C_{18}H_{32}O_{22}$) 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) Å^3; 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 $18C6A_4$ 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; β = 102.225 (5)°; V = 1064.8 (1) Å^3; 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.

(7) Hillenbrand, E. A.; Scheiner, S. *J. Am. Chem. Soc.* **1986**, *108*, 7178-7186.

(8) Peterson, M. R.; Cszimadia, I. G. *J. Am. Chem. Soc.* **1979**, *101*, 1076-1079. Wiberg, K. B.; Laidig, K. W. *J. Am. Chem. Soc.* **1987**, *109*, 5935-5943.

(9) La Placa, S. J.; Hamilton, W. C.; Kamb, B.; Prakash, A. *J. Chem. Phys.* **1973**, *58*, 567-580.

(10) Manor, P. C.; Saenger, W. *J. Am. Chem. Soc.* **1974**, *96*, 3630-3639.

(11) Defined host-guest complexes of *monomeric* water are known: Goldberg, I. *Acta Crystallogr.* **1978**, *B34*, 3387-3390. Helgeson, R. C.; Tarnowski, T. L.; Cram, D. J. *J. Org. Chem.* **1979**, *44*, 2538-2546. Newkome, G. R.; Taylor, H. C. R.; Fronczek, F. R.; Delord, T. J.; Kohli, D. K.; Vögtle, F. *J. Am. Chem. Soc.* **1981**, *103*, 7376-7378.

(12) Dyke, T. R.; Mack, K. M.; Muenter, J. S. *J. Chem. Phys.* **1977**, *66*, 498-510. Octutola, J. A.; Dyke, T. R. *J. Chem. Phys.* **1980**, *72*, 5062-5066.

(13) Kestner, N. R.; Newton, M. D.; Mathers, T. L. *Int. J. Quantum Chem. Symp.* **1983**, *17*, 431-439. Amos, R. D. *Chem. Phys.* **1986**, *104*, 145-151. Dannenberg, J. J. *J. Phys. Chem.* **1988**, *92*, 6869-6871.

(14) Narten, A. H.; Venkatesh, C. G.; Rice, S. A. *J. Chem. Phys.* **1976**, *64*, 1106-1121.

(15) Narten, A. H. *J. Chem. Phys.* **1972**, *56*, 5681-5687.

Total Synthesis of (+)-Verrucosidin

Konghyun Whang, R. J. Cooke, Gürol Okay, and Jin K. Cha*,†

Department of Chemistry, Vanderbilt University Nashville, Tennessee 37235

Received August 14, 1990

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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(1) (a) Burka, L. T.; Ganguli, M.; Wilson, B. J. *J. Chem. Soc., Chem. Commun.* **1983**, 544. (b) Ganguli, M.; Burka, L. T.; Harris, T. M. *J. Org. Chem.* **1984**, *49*, 3762.

(2) (a) Hirata, Y.; Goto, T.; Sakabe, N. *Tetrahedron Lett.* **1964**, 1825. (b) Sakabe, N.; Goto, T.; Hirata, Y. *Tetrahedron* **1977**, *33*, 3077. (c) Frank, B.; Gehrken, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 461.

(3) (a) Mulheirn, L. J.; Beechey, R. B.; Leworthy, D. P.; Osselton, M. D. *J. Chem. Soc., Chem. Commun.* **1974**, 874. (b) Steyn, P. S.; Vleggaar, R.; Wessels, P. L. *Ibid.* **1979**, 1041. (c) Kruger, G. J.; Steyn, P. S.; Vleggaar, R.; Rabie, C. J. *J. Chem. Soc., Chem. Commun.* **1979**, 441. (d) Vleggaar, R. *Pure Appl. Chem.* **1986**, *58*, 239.

(4) (a) Boyer, P. D.; Chance, B.; Ernster, L.; Mitchell, P.; Racker, E.; Slater, E. C. *Annu. Rev. Biochem.* **1977**, *46*, 955. (b) Muller, J. L. M.; Rosing, J.; Slater, E. C. *Biochim. Biophys. Acta* **1977**, *462*, 422. (c) Gause, E. M.; Buck, M. A.; Douglas, M. G. *J. Biol. Chem.* **1981**, *256*, 557.

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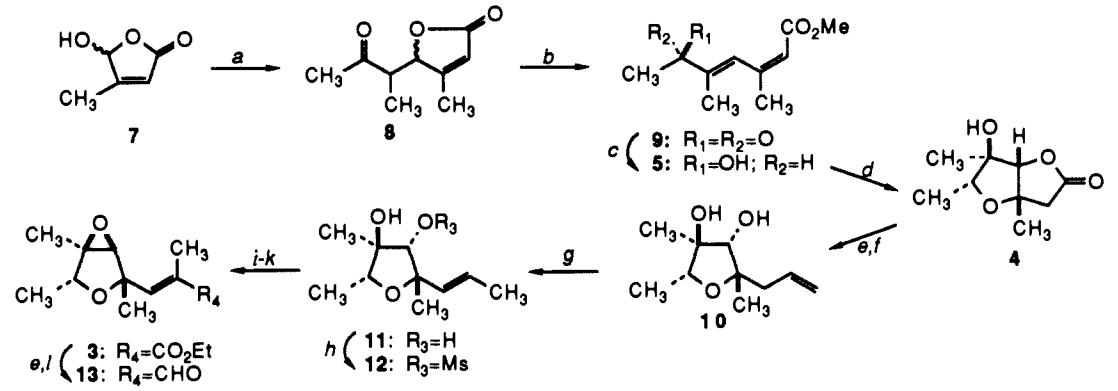
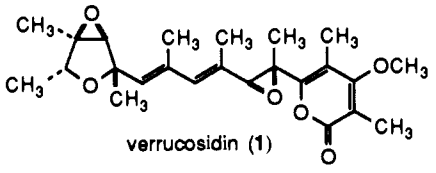
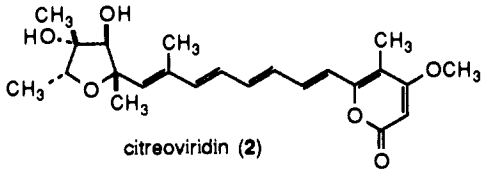
Scheme I[a]



[a] (a) $CH_3COC(CH_3)=PPh_3$, $PhCH_3$, reflux (85%). (b) DBU, $CHCl_3$, followed by CH_3I (76%). (c) 2 equiv of BH_3, (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol, THF, −78 °C (70%). (d) 0.02 equiv of OsO_4, 1.2 equiv of NMO, 2:1 THF–H_2O, 0 °C, followed by $NaHCO_3$ (68–77%). (e) DIBAL-H, THF, −78 °C. (f) $Ph_3P=CH_2$, toluene, reflux (68% overall from **4**). (g) $PdCl_2(PhCN)_2$, PhH, reflux (90%). (h) MsCl, pyr, CH_2Cl_2, room temperature (75%). (i) O_3, CH_2Cl_2–MeOH, −78 °C/Me_2S. (j) $Ph_3P=C(CH_3)CO_2Et$, PhH, reflux (93% overall from **12**). (k) NaOEt, EtOH (93%). (l) MnO_2, CH_2Cl_2 (90%).

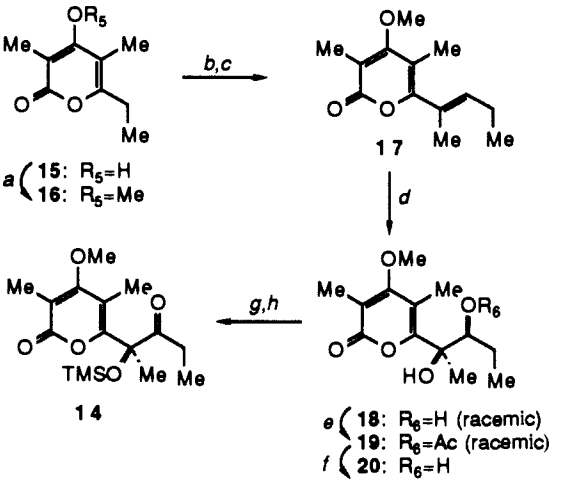
construction of the densely functionalized tetrahydrofuran **3** and the monoepoxy trisubstituted triene moiety present in **1**.[5,6]





Shown in Scheme I is our enantioselective synthesis of tetrahydrofuran **3**,[7] starting from the homochiral **5**, $[\alpha]^{20}_D = -15.0°$ (*c* 0.8, $CHCl_3$), which is readily prepared by the asymmetric Itsuno reduction[8] 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 ($Ph_3P=CH_2$, toluene, reflux) gave allyltetrahydrofuran **10** in 68% overall yield. The terminal olefin **10** was then isomerized to provide **11** (≥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**, $[\alpha]^{28}_D = -44°$ (*c* 0.9, $CHCl_3$)], in 88% overall yield. The latter was identical in every aspect with an authentic sample prepared from (+)-verrucosidin (**1**) [(1) OsO_4–$NaIO_4$; (2) $Ph_3P=C(CH_3)CO_2Et$, benzene, reflux].[9]

Scheme II[a]



[a] (a) DMS, K_2CO_3, acetone, reflux (80%). (b) LDA, HMPA–THF, −78 °C, followed by CH_3CH_2CHO (82%). (c) MsCl DMAP, pyr, room temperature, followed by DBU, CH_2Cl_2, reflux (72%). (d) Osmylation at 0 °C (78%). (e) CH_3COCl, pyr, 0 °C (98%). (f) PLAP, pH 7.0 buffer, room temperature, followed by recrystallization (85%). (g) Swern oxidation (85%). (h) TMSOTf, pyr-CH_2Cl_2, 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, $CHCl_3$), 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** {$[\alpha]^{25}_D = +68.3°$ (*c* 0.77, $CHCl_3$), 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

(5) For the previous and only synthesis of (+)-verrucosidin, see: Hatakeyama, S.; Sakurai, K.; Numata, H.; Ochi, N.; Takano, S. *J. Am. Chem. Soc.* **1988**, *110*, 5201.

(6) For total syntheses of (−)-citreoviridin, see: (a) Nishiyama, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 231. (b) Williams, D. R.; White, F. H. *J. Org. Chem.* **1987**, *52*, 5067. (c) Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 470. (−)-Aurovertin B has also been prepared: (d) Nishiyama, S.; Toshima, H.; Kanai, H.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 3643. (+)-Asteltoxin has been prepared: (e) Schreiber, S. L.; Sakate, K. *J. Am. Chem. Soc.* **1984**, *106*, 4186; *Tetrahedron Lett.* **1986**, *27*, 2575. For other synthetic studies of verrucosidin, see also: (f) Nishiyama, S.; Shizuri, Y.; Shigemori, H.; Yamamura, S. *Tetrahedron Lett.* **1986**, *27*, 723. (g) Klein, L. L. *Ibid.* **1986**, *27*, 4545.

(7) (a) Cha, J. K.; Cooke, R. J. *Tetrahedron Lett.* **1987**, *28*, 5473. (b) Kim, Y. G.; Whang, K.; Cooke, R. J.; Cha, J. K. *Ibid.* **1990**, *31*, 3275.

(8) (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469. (b) Idem. *J. Org. Chem.* **1984**, *49*, 555. (c) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395. See also: (d) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (e) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861.

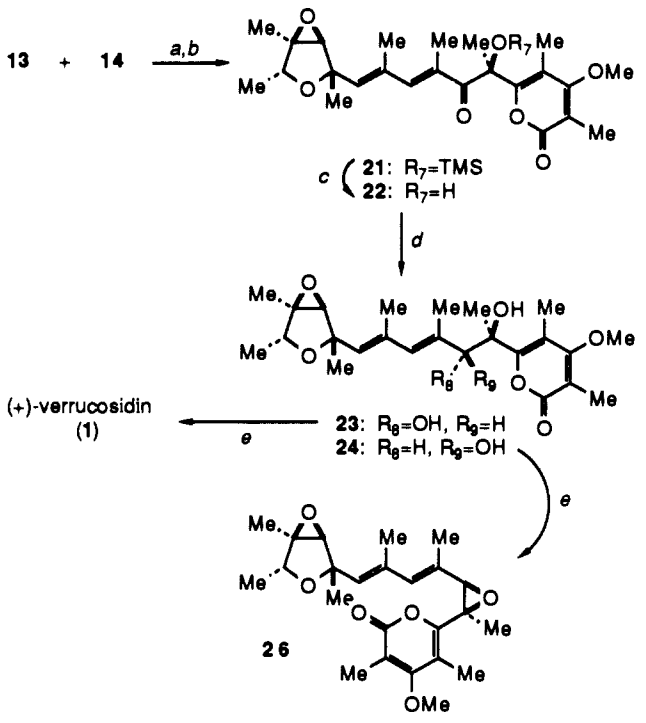
(9) Satisfactory spectroscopic data were obtained for all new compounds.

(10) For recent reviews in this area, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Bartlett, P. A. *Ibid.* **1980**, *36*, 2.

(11) (a) Osman, M. A.; Seibl, J.; Pretsch, E. *Helv. Chim. Acta* **1977**, *60*, 3007. (b) Koster, G.; Hoffmann, R. W. *Liebigs Ann. Chem.* **1987**, 987.

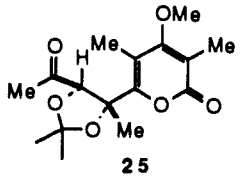
(12) cf.: Whitesell, J. K.; Lawrence, R. M. *Chimia* **1986**, *40*, 318.

Scheme III[a]



[a] (a) $LiN(TMS)_2$, THF, −78 °C (77% based on consumed SM). (b) TFAA, DMAP, DBU, CH_2Cl_2, −40 to 0 °C (83%). (c) CsF, EtOH, room temperature (90%). (d) 1 equiv of $NaBH_4$–0.5 equiv of *d*-tartaric acid–1 equiv of $PrCl_3 \cdot 6H_2O$, 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 $NaBH_4$–$CeCl_3$ (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 (~5:1) reduction of **22** leading to diol **23** was accomplished by the use of a sodium acyloxyborohydride[14] derived from $NaBH_4$ and tartaric acid in the presence of a lanthanide. On the other hand, diol **24** can be prepared stereoselectively (≥10:1) by LAH or $NaBH_4$ 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) OsO_4–$NaIO_4$] 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 sulfurane[17] stereoselectively afforded **1** and its epimer **26** in the same ratio. The synthetic substance was found to be identical in every aspect with an authentic sample of verrucosidin.[18]

Acknowledgment. We are grateful to the National Institutes of Health (GM 35956) for financial support. We also thank Professors Thomas and Constance Harris of this department for providing an authentic sample of the natural (+)-verrucosidin.

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

(13) (a) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (b) Jacobi, P. A.; Kaczmarek, C. S. R.; Udodong, U. E. *Tetrahedron Lett.* **1984**, *25*, 4859. (c) Kishi, Y.; Christ, W. J.; Taniguchi, M. In *Natural Products and Biological Activities*; Imura, H., Goto, T., Murachi, T., Nakajima, T., Eds.; University of Tokyo Press: Tokyo, 1986; pp 87–98.

(14) (a) Gribble, G. W.; Nutaitis, C. F. *Org. Prep. Proced. Int.* **1985**, *17*, 317. (b) Adams, C. *Synth. Commun.* **1984**, *14*, 955.

(15) The observed 1,2-asymmetric induction can be rationalized by the open-chain Felkin–Anh model. See, for example: (a) Overman, L. E.; McCready, R. J. *Tetrahedron Lett.* **1982**, *23*, 2355. (b) Nakata, T.; Tanaka, T.; Oishi, T. *Ibid.* **1983**, *24*, 2653.

(16) A similar degradation of diol **23** gave a diastereomeric ketone of **25**.

(17) Martin, J. C.; Franz, J. A.; Arhart, R. J. *J. Am. Chem. Soc.* **1974**, *96*, 4604.

(18) Similarly, diol **24** was converted smoothly into *epi*-verrucosidin (**26**).

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

Lars R. Furenlid, Mark W. Renner, and Jack Fajer*

Department of Applied Science
Brookhaven National Laboratory
Upton, New York 11973

Received July 31, 1990

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 vitro[4] 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 M[10] and for its paramagnetic Ni(I) reduction in-

(1) Fässler, A.; Kobelt, A.; Pfaltz, A.; Eschenmoser, A.; Bladon, C.; Battersby, A. R.; Thauer, R. K. *Helv. Chim. Acta* **1985**, *68*, 2287.

(2) Ellefson, W. L.; Whitman, W. B.; Wolfe, R. S. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 3707. Hausinger, R. P.; Orme-Johnson, W. H.; Walsh, C. *Biochemistry* **1984**, *23*, 801. Daniels, L.; Sparling, R.; Sprott, G. D. *Biochim. Biophys. Acta* **1984**, *768*, 113.

(3) For recent reviews, see the following in *The Bioinorganic Chemistry of Nickel*; Lancaster, J. R., Ed.; VCH Publishers: New York, 1988: (a) Eidsness, M. K.; Sullivan, R. J.; Scott, R. A., p 73. (b) Ankel-Fuchs, D.; Thauer, R. K., p 93. (c) Wackett, L. P.; Honek, J. F.; Begley, T. P.; Shames, S. L.; Niederhoffer, E. C.; Hausinger, R. P.; Orme-Johnson, W. H.; Walsh, C. T., p 249. (d) Pfaltz, A., p 275.

(4) Jaun, B.; Pfaltz, A. *J. Chem. Soc., Chem. Commun.* **1986**, 1327.

(5) Albracht, S. P. J.; Ankel-Fuchs, D.; Van der Zwaan, J. W.; Fontjin, R. D.; Thauer, R. K. *Biochim. Biophys. Acta* **1986**, *870*, 50. Albracht, S. P. J.; Ankel-Fuchs, D.; Böcher, R.; Ellerman, J.; Moll, J.; Van der Zwaan, J. W.; Thauer, R. K. *Biochim. Biophys. Acta* **1988**, *955*, 86.

(6) Jaun, B.; Pfaltz, A. *J. Chem. Soc., Chem. Commun.* **1988**, 293.

(7) Based on corphin models,[3d] F430 is expected to be planar or significantly puckered, with long or short Ni–N distances, respectively, in the high- and low-spin Ni(II) forms.

(8) Cheesman, M. R.; Ankel-Fuchs, D.; Thauer, R. K.; Thompson, A. J. *Biochem. J.* **1989**, *260*, 613.

(9) Shiemke, A. K.; Kaplan, W. A.; Hamilton, C. L.; Shelnutt, J. A.; Scott, R. A. *J. Biol. Chem.* **1989**, *264*, 7276.

0002-7863/90/1512-8987$02.50/0