simple neutral uranyl-containing receptors show high association constants for anion complexation.[19] Moreover, the unique combination of a Lewis acidic uranyl center and the presence of amide NH groups which can form a favorable H-bond with a coordinated anion guest, in a preorganized receptor, can lead to highly specific anion recognition.

Acknowledgment. This investigation was supported by the Netherlands Technology Foundation [STW, Future Technology Science Branch of the Netherlands Organization for the Advancement of Pure Research (NWO)].

Supplementary Material Available: Tables of positional and thermal parameters, bond lengths, and bond angles for **1** (5 pages). Ordering information is given on any current masthead page.

(18) Thatcher, G. R. J.; Cameron, D. R.; Nagelkerke, R.; Schmitke, J. *J. Chem. Soc., Chem. Commun.* **1992**, 386-388.

(19) Recently, Beer et al.[20] reported an anion receptor in which a positively charged cobalticinium unit and an NH group are the essential components, and Reetz et al.[3b] published an anion receptor consisting of a σ-bonded boron center for anion complexation and a conventional crown ether moiety for cation complexation.

(20) Beer, P. D.; Hesek, D.; Hodacova, J.; Stokes, S. E. *J. Chem. Soc., Chem. Commun.* **1992**, 270-272.

Total Synthesis of (±)-Byssochlamic Acid

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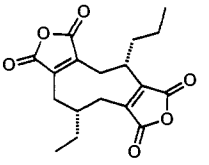
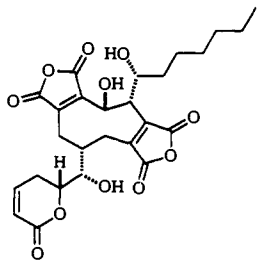
Byssochlamic acid (**1**), a metabolite first isolated from the ascomycete *Byssochlamys fulva*,[1] is a member of the small but structurally unique class of natural products known as nonadrides.[2] This family is characterized by the presence of a nine-membered carbocycle fused to two five-membered anhydride residues and includes the potent hepatotoxin rubratoxin B (**2**).[3] The constitution of **1** and its absolute configuration were established through an elegant series of degradative studies by Barton et al.,[4,5] and the relative configuration was confirmed by X-ray crystallographic analysis of its (*p*-bromophenyl)hydrazide.[6] We report here a synthesis of **1** which hinges on a photoaddition–cycloreversion metathesis to construct the core cyclononadiene system.[7] This route is significantly different from that described by Stork[8] in the only published synthesis of a nonadride.

Before embarking on our approach to **1**, we confirmed by experiment the prediction made from theory that the natural, cis configuration of alkyl chains is more stable than the trans orientation.[9] This removed the potential difficulty of controlling relative stereochemistry across a medium-sized ring en route to **1**.



1



2

Sensitized irradiation through Pyrex of bromomaleic anhydride in the presence of 1-pentene afforded a mixture of three photoadducts in the ratio 4:1:1 (Scheme I). These were conveniently isolated as the corresponding diacids **3** after basic hydrolysis and characterized as dimethyl esters **4**.[10] Dehydrobromination of **4** cleanly afforded the cyclobutene **5**, which was saponified to give dicarboxylic acid **6**. The second component required for the synthesis, diol **11**, was prepared by the sequence shown in Scheme II. Thus, 4-ethylcyclohexanone (**7**), obtained by Jones' oxidation of the corresponding alcohol, was carboxylated and the resulting β-keto ester **8** was brominated to give **9**. Favorskii rearrangement of the latter yielded diester **10**,[11] which was reduced with the ate complex of diisobutylaluminum hydride[12] to **11**.

The dipotassium alkoxide from **11** was reacted with **5** but gave the desired cyclobutene half-ester in only low yield. Although this hydroxy acid lactonized readily to **12**, an improved procedure for preparation of the latter was found by treatment of a mixture of **6** and **11** under Steglich–Keck conditions.[13] This resulted in diolide **12** directly as a mixture of cis and trans stereoisomers (Scheme III). Irradiation of this mixture in dilute solution afforded the intramolecular photoadducts **13**, **14**, and **15** in the ratio 2:1.6:1. Careful 2D NMR analysis[14] of these adducts indicated that they were exo-exo, exo-endo, and endo-endo stereoisomers with respect to the propyl and ethyl side chains. Conformational analysis using MM2 calculations suggests that the apparent, severe steric congestion of the side chains in **15** can be relieved by folding of the cyclopentane into a pronounced envelope conformation. No evidence for formation of the fourth, endo-exo isomer was found, implying that the trans isomer of **12** gives only **14**.

Exposure of the mixture of **13**, **14**, and **15** to refluxing toluene led to quantitative cycloreversion by opening of the central cyclobutane ring in the direction opposite to that by which it was formed. This produced a 2:1 mixture of cis and trans cyclononadienes, **16** and **17**, the former presumably originating from **13** and **15**, and the latter from **14**.[15] Direct oxidation of the bis(butenolide) moieties to **1** and its trans isomer was unsuccessful, but basic hydrolysis of the mixture of **16** and **17**, followed by oxidation of the carboxylates **18** with permanganate and acidification, afforded **1** exclusively. Evidently, in the process of oxidizing **17**, epimerization of the propyl side chain had occurred

(1) Raistrick, H.; Smith, G. *Biochem. J.* **1933**, *27*, 1814.

(2) Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1769.

(3) Büchi, G.; Snader, K. M.; White, J. D.; Gougoutas, J. Z.; Singh, S. *J. Am. Chem. Soc.* **1970**, *92*, 6638.

(4) (a) Baldwin, J. E.; Barton, D. H. R.; Bloomer, J. L.; Jackman, L. M.; Rodriguez-Hahn, L.; Sutherland, J. K. *Experientia* **1962**, *18*, 345. (b) Baldwin, J. E.; Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1787.

(5) For a summary of the work leading to the constitution and stereochemistry of **1**, see: Sutherland, J. K. *Fortschr. Chem. Org. Naturst.* **1967**, *25*, 131.

(6) Paul, I. G.; Sim, G. A.; Hamor, T. A.; Robertson, J. M. *J. Chem. Soc.* **1963**, 5505.

(7) Schaumann, E.; Ketcham, R. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 225. This concept has been exploited by Wender in an approach to naturally occurring medium-ring carbocycles (Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 267).

(8) Stork, G.; Tabak, J. M.; Blount, J. F. *J. Am. Chem. Soc.* **1972**, *94*, 4735.

(9) MM2 calculations predict that **1** is more stable than its trans isomer by ca. 3.8 kcal/mol. Treatment of **1** with base (NaH, THF) under conditions which led to formation of a sodium enolate resulted in *no* isomerization to the trans compound.

(10) Thus far, it has not been possible to assign regio- and stereochemistry to these photoadducts.

(11) Cf.: Schorno, K. S.; Adolphen, G. H.; Eisenbraun, E. J. *J. Org. Chem.* **1969**, *34*, 2801.

(12) Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717.

(13) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

(14) After identification of protons associated with each stereoisomer using ^1H–^1H COSY, analysis of one-dimensional sections of the phase-sensitive ^1H–^1H COSY gave the coupling constants of protons on the cyclobutane ring for **13**, **14**, and **15**. Confirmation of stereochemistry was obtained by ^1H–^1H NOESY, which showed a large NOE for the lactone methylene protons and a smaller NOE for the protons on the carbocyclic rings.

(15) Small amounts of the cycloreversion products **16** and **17** invariably accompanied the photoadducts in the irradiation of **12**.

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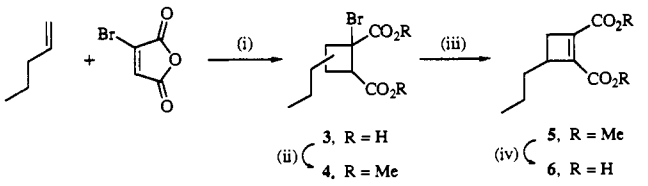
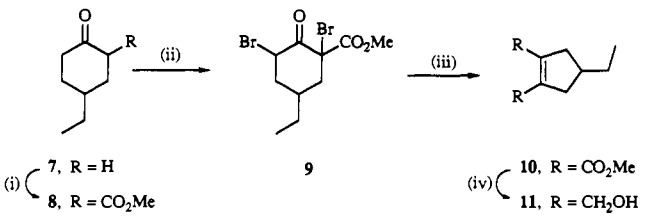
Scheme I[a]



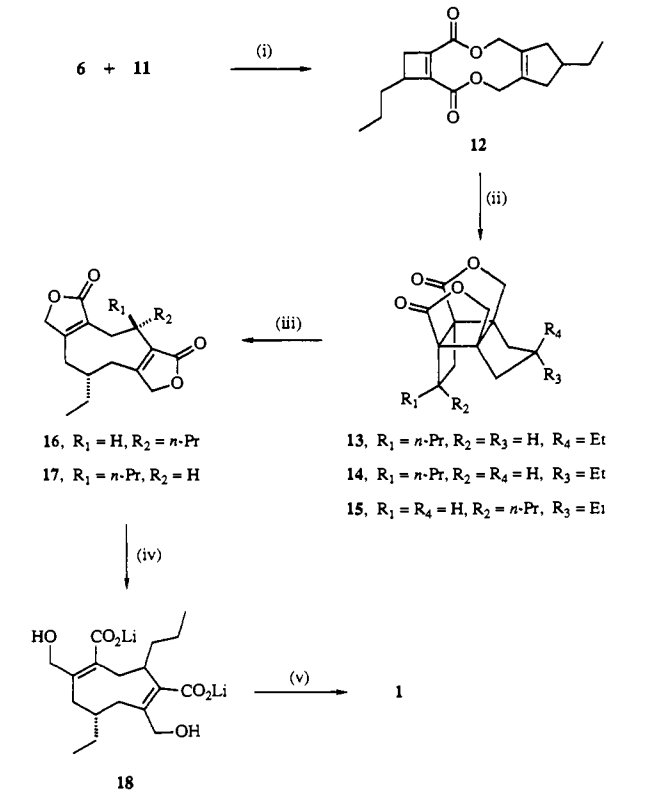
[a] (i) $h\nu$, Ph_2CO, MeCN, then Na_2CO_3 (aqueous), then HCl (aqueous) (68%); (ii) CH_2N_2, Et_2O (91%); (iii) DBU, $CHCl_3$ (100%); (iv) LiOH, THF-H_2O (72%).

Scheme II[a]



[a] (i) NaH, $(MeO)_2CO$, C_6H_6 (86%); (ii) Br_2, Et_2O; (iii) NaOMe, MeOH (37% from 8); (iv) DIBALH-*n*-BuLi, hexane-THF, -78 °C → room temperature (62%).

Scheme III[a]



[a] (i) DCC, DMAP, DMAP·HCl, $CHCl_3$, Δ, 20 h (51%); (ii) $h\nu$, CH_2Cl_2, 4 h (63%); (iii) toluene, Δ, 2 h (100%); (iv) LiOH, H_2O-dioxane; (v) $KMnO_4$, then HCl (aqueous) (37% from 17).

to give the more stable cis isomer **1**. The synthetic material was identical with a sample of natural byssochlamic acid by comparison of IR, ^1H and ^{13}C NMR, and mass spectra.

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Supplementary Material Available: Spectral and analytical data for compounds **3-6**, **8-17**, and **1** (4 pages). Ordering information is given on any current masthead page.

An Empirical Correlation between $^1J_{C\alpha H\alpha}$ and Protein Backbone Conformation

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Determination of the solution structure of a protein by NMR relies primarily on the analysis of a large number of ^1H-^1H NOE interactions, supplemented by dihedral angle information derived from vicinal ^1H-^1H J couplings. Three-bond couplings are commonly interpreted in terms of dihedral angles using the well-known Karplus relationship and can provide information on the backbone angle ϕ and the side-chain torsion angles χ_n. In principle, $^3J_{H\alpha N}$ couplings can be used to extract information about the backbone angle ψ, but in practice the variation in $^3J_{H\alpha N}$ as a function of ψ is too small for this purpose.[1] The correlation between the magnitude of $^1J_{C\alpha H\alpha}$ and the backbone angles ϕ and ψ has been investigated previously both by MO calculations and by experimental measurements on conformationally constrained cyclic peptides.[2] From this work, it was concluded that the magnitude of $^1J_{C\alpha H\alpha}$ is influenced primarily by the interaction between the H-C_α bonding orbital and the p_z orbital of the lone pair N electrons; i.e., $^1J_{C\alpha H\alpha}$ was expected to depend primarily on ϕ.[3] Here we present experimental results that indicate that $^1J_{C\alpha H\alpha}$ is determined primarily by ψ and to a lesser extent by ϕ.

$^1J_{C\alpha H\alpha}$ couplings have been measured for the proteins basic pancreatic trypsin inhibitor (BPTI), staphylococcal nuclease (SNase), and calmodulin (CaM). Previous NMR studies have indicated that the solution structures of these proteins for residues 3-56 (BPTI), 8-42 and 55-140 (SNase), and 6-76 and 83-146 (CaM) are in good agreement with the crystal structures.[4-6] In the present work, we correlate the magnitude of $^1J_{C\alpha H\alpha}$ with dihedral angles obtained from the X-ray crystal structures.[7-9] $^1J_{C\alpha H\alpha}$ values were measured from the F_2 splittings in the purged[10] HMQC spectrum of natural abundance BPTI (11 mM, p^2H 5.8) and from the antiphase F_3 splittings in the 3D CT-HCACO[11] and HCCH-COSY[12] spectra of uniformly (>95%) ^{13}C-enriched SNase

(1) Kopple, K. D.; Ahsan, A.; Barfield, M. *Tetrahedron Lett.* **1978**, *38*, 3519-3522.
(2) Egli, H.; von Philipsborn, W. *Helv. Chim. Acta* **1981**, *64*, 976-988.
(3) Gil, V. M. S.; von Philipsborn, W. *Magn. Reson. Chem.* **1989**, *27*, 409-430.
(4) Wagner, G.; Braun, W.; Havel, T. F.; Schaumann, T.; Go, N., Wüthrich, K. *J. Mol. Biol.* **1987**, *196*, 611-639.
(5) Ikura, M.; Spera, S.; Barbato, G.; Kay, L. E.; Krinks, M.; Bax, A. *Biochemistry* **1991**, *30*, 9216-9228.
(6) Torchia, D. A.; Sparks, S. W.; Bax, A. *Biochemistry* **1989**, *28*, 5509-5524.
(7) Wlodawer, A.; Deisenhofer, J.; Huber, R. *J. Mol. Biol.* **1987**, *193*, 145-156.
(8) Loll, P. J.; Lattman, E. E. *Proteins: Struct., Funct., Genet.* **1989**, *5*, 183-201.
(9) Babu, Y. S.; Bugg, C. E.; Cook, W. I. *J. Mol. Biol.* **1988**, *204*, 191-204.
(10) Sørensen, O. W.; Ernst, R. R. *J. Magn. Reson.* **1983**, *51*, 477-489.
(11) Powers, R.; Gronenborn, A. M.; Clore, G. M.; Bax, A. *J. Magn. Reson.* **1991**, *94*, 290-213.
(12) Bax, A.; Gronenborn, A. M.; Clore, G. M. *J. Magn. Reson.* **1990**, *88*, 425-431.

0002-7863/92/1514-9674$03.00/0