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(16) (a) Hodgson, E. K.; Fridovich, I. *Biochemistry* **1975**, *14*, 5294-5303. (b) Klug-Roth, D.; Fridovich, I.; Rabani, J. *J. Am. Chem. Soc.* **1973**, *95*, 2786-2790. (c) Klug, D.; Rabani, J.; Fridovich, I. *J. Biol. Chem.* **1972**, *247*, 4839-4842.
(17) (a) McAdam, M. E.; Fielden, E. M.; Lavelle, F.; Calabrese, L.; Cocco, D.; Rotilio, G. *Biochem. J.* **1977**, *167*, 271-274. (b) Rigo, A.; Viglino, P.; Rotilio, G. *Biochem. Biophys. Res. Commun.* **1975**, *63*, 1013-1018. (c) Rotilio, G.; Bray, R. C.; Fielden, E. M. *Biochim. Biophys. Acta* **1972**, *268*, 605-609. (d) Fielden, E. M.; Roberts, P. B.; Bray, R. C.; Lowe, D. J.; Mautner, G. N.; Rotilio, G.; Calabrese, L. *Ibid.* **1974**, *139*, 43-48.
(18) Lawrence, G. D.; Sawyer, D. T. *Biochemistry* **1979**, *18*, 3045-3050.
(19) Strothkamp, K. G.; Lippard, S. J. *Acc. Chem. Res.* **1982**, *15*, 318-326.
(20) Fee, J. A.; Dicorleto, P. E. *Biochemistry* **1973**, *12*, 4893-4899.
(21) Osman, R.; Basch, H. *J. Am. Chem. Soc.* **1984**, *106*, 5710-5714.
(22) Rosi, M.; Sgamellotti, A.; Tarantelli, F.; Bertini, I.; Luchinat, C. *Inorg. Chim. Acta* **1985**, *107*, L21-L22.
(23) Fee, J. A.; Bull, C. *J. Biol. Chem.* **1986**, *261*, 13000-13005.
(24) Strothkamp, K. G.; Lippard, S. J. *Biochemistry* **1981**, *20*, 7488-7493.

Total Synthesis of (±)-Crassin by Titanium-Induced Pinacol Coupling

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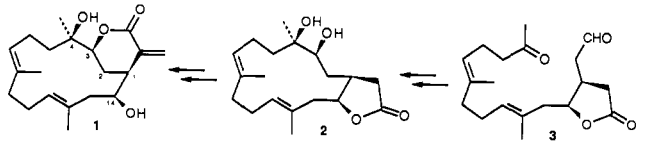
Crassin (**1**), a diterpenoid cembrane isolated in 1960 from the Caribbean gorgonian *Pseudoplexaura porosa*, has a remarkable range of biological activities. Its acetate has mild analgesic,[1] antibiotic,[2] and antineoplastic[3] properties and shows in vitro activity against human epidermoid carcinoma of the nasopharynx (KB cell line) at concentrations of 2 μg/mL, while crassin itself is about 2 times as potent.[3] Both compounds are also active against the PS cell line,[4] and cinnamoyl esters of crassin show significant in vitro antileukemic activity.[3] This bioactivity, together with the difficulties posed by large-ring synthesis, have prompted synthetic efforts by several groups in the last decade.[5-7] We now report the first total synthesis of crassin by a route that significantly extends the range of the titanium-induced carbonyl-coupling reaction.[8]

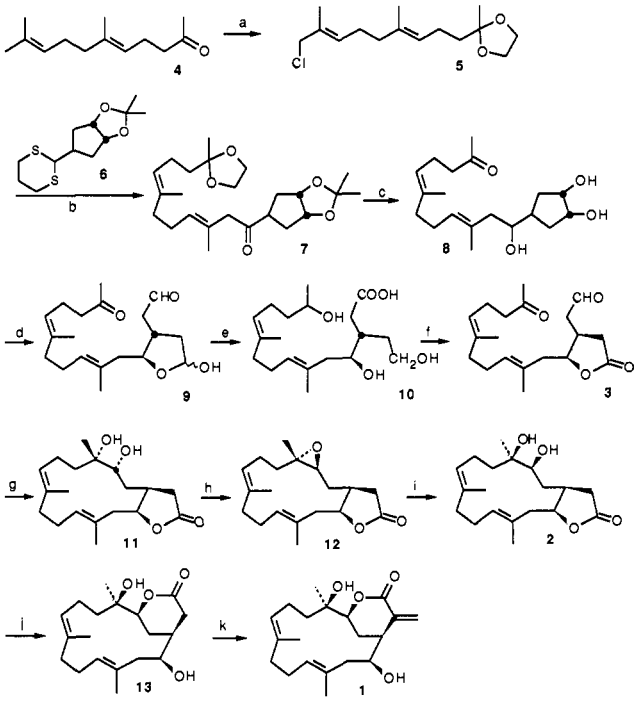
Our idea was to take advantage of the fact that crassin is regenerated after base-induced hydrolysis followed by acid-catalyzed relactonization.[9,10] It therefore follows that the isomeric butyrolactone **2** might also be convertible into norcrassin (**13**) by translactonization. Compound **2**, in turn, is a cyclic 1,2-diol that might be accessible by titanium-induced pinacol coupling of the corresponding keto aldehyde **3** according to our recently published procedure.[11]



There are two evident drawbacks to this plan. One is that we have no obvious method of stereocontrol over the coupling reaction; four stereoisomeric diols might result. A second, more crucial problem is that titanium-induced carbonyl-coupling reactions have thus far been limited almost exclusively to the synthesis of hydrocarbons.[8] Low-valent titanium is a powerful oxophile capable of reducing all kinds of carbonyl groups, and it is not clear that a lactone grouping in the molecule can survive the coupling conditions. Nevertheless, the simplicity of the overall scheme, the relative ease of hydroxyl inversion if the wrong stereoisomer predominates, and the desire to extend the titanium-induced carbonyl-coupling reaction for the synthesis of complex, oxygenated macrocycles led us to attempt the synthesis.

Keto aldehyde **3** was prepared by the route shown in Scheme I.[12] Starting with geranylacetone (**4**), selective allylic oxidation with selenium dioxide,[13] acetalization, and treatment with *N*-chlorosuccinimide and triphenylphosphine[14] gave the chloride **5**. Alkylation with the anion of dithiane **6**[15] followed by removal of the thioacetal group[16] gave **7**, and reduction with $NaBH_4$ followed by acid-catalyzed hydrolysis gave keto triol **8**. Cleavage of **8** by treatment with periodic acid then gave an intermediate dialdehyde, which underwent stereoselective cyclization to yield exclusively the trans-disubstituted hemiacetal **9**, thereby differentiating be-

Scheme I. Total Synthesis of Crassin (**1**)[a]



[a] (a) SeO_2, *t*-BuOOH, 76%; then $HOCH_2CH_2OH$, H^+; then NCS, PPh_3, 85%. (b) BuLi; then **6**; then $AgNO_3$, NCS, H_2O, 70%. (c) $NaBH_4$, then H_3O^+. (d) $NaIO_4$, THF, 73% from **7**. (e) $AgNO_3$, NaOH; then $NaBH_4$. (f) *p*-TSA, CH_2Cl_2; then $(COCl_2)_2$, DMSO, 56% from **9**. (g) $TiCl_3(DME)_{1.5}$, Zn-Cu, DME, 20%. (h) MsCl, $PhCH_2NMe_3OH$, 68%. (i) H_3O^+, 77%. (j) NaOH, H_2O, then H_3O^+, 100%. (k) LDA, then CH_2O; then MsCl, DBU, 53%.

(1) Borders, D. B.; Osterberg, A. C.; Wallo, K. G. (American Cyanamid Co.) U.S. 3706835, 19 Dec 1972; *Chem. Abstr.* **1973**, *78*(14), 88622y.
(2) Ciereszko, L. S.; Sifford, D. S.; Weinheimer, A. J. *Ann. N.Y. Acad. Sci.* **1960**, *90*, 917-919.
(3) Weinheimer, A. J.; Matson, J. A. *Lloydia* **1975**, *38*, 378-382.
(4) Petit, G. R.; Day, J. F.; Hartwell, J. L.; Wood, H. B. *Nature* **1970**, *227*, 962-963.
(5) Dauben, W. G.; Saugier, R. K.; Fleischhauer, I. *J. Org. Chem.* **1985**, *50*, 3767-3774.
(6) Marshall, J. A.; Royce, R. D., Jr. *J. Org. Chem.* **1982**, *47*, 693-698.
(7) Marshall, J. A.; Coghlan, M. J.; Watanabe, M. *J. Org. Chem.* **1984**, *49*, 747-753.
(8) For reviews of the titanium-induced carbonyl-coupling reaction, see: (a) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405-411. (b) McMurry, J. E. *Chem. Rev.* In press.
(9) Weinheimer, A. J.; Chang, C. W. J.; Matson, J. A. *Fortschr. Chem. Org. Naturst.* **1979**, *36*, 342-344.
(10) Marshall, J. A.; Karas, L. J.; Coghlan, M. J. *J. Org. Chem.* **1982**, *47*, 699-701.
(11) McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169-1172.
(12) Experimental and spectroscopic details for the preparation and characterization of all synthetic intermediates are included in the supplementary material.
(13) Sharpless, K. B.; Umbreit, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 5526-5528.
(14) Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, 3937-3940.
(15) Prepared from methyl 3-cyclopentenecarboxylate: Depres, J.-P.; Greene, A. E. *J. Org. Chem.* **1984**, *49*, 928-931.
(16) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553-3560.

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tween the two aldehyde groups. Mild oxidation of the free aldehyde with Tollens' reagent and reduction with $NaBH_4$ gave acid **10**, which was lactonized by treatment with toluenesulfonic acid and oxidized under Swern conditions[17] to give the pinacol cyclization substrate **3**.

Slow addition of keto aldehyde **3** in dimethoxyethane (DME) at room temperature to a stirred slurry prepared by reduction of $TiCl_3(DME)_{1.5}$[18] with Zn-Cu gave a mixture of four cyclic diols (10:9:5:<1) in a combined yield of 48%. The major diol (20% yield) was readily identified as **11**, a substance previously prepared by Marshall[19,20] and epimeric with crassin at C3 and C4. The minor diol (<1% yield) was identified as **2**, the substance necessary for conversion into crassin, and the other two diols (18% and 10% yields) were identified as the C4 and C3 epimers[21] of **2**, respectively. Thus, the coupling does in fact proceed without destroying the lactone ring, but the wrong stereoisomers are produced.

Fortunately, we were able to solve the stereochemical problem easily by carrying out a double inversion, **11** → **2**. Treatment of the major diol product (**11**) with methanesulfonyl chloride and benzyltrimethylammonium hydroxide gave the known[9] epoxide **12**, epimeric with crassin at C4, and mild treatment with aqueous acid opened the epoxide with selective inversion at the tertiary center to provide **2**. Isomerization of butyrolactone **2** gave **15**, and methylenation then proceeded without incident to give (±)-crassin, mp 174-176 °C, spectroscopically identical with an authentic sample prepared from natural crassin acetate.

We believe that this synthesis is a first step in opening an important new direction for titanium-induced carbonyl-coupling reactions, making possible the synthesis of complex, highly oxygenated macrocycles.

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Supplementary Material Available: Experimental details on the preparation and characterization of all synthetic intermediates (10 pages). Ordering information is given on any current masthead page.

(17) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480-2482.

(18) For the synthesis and use of this material in carbonyl couplings, see: McMurry, J. E.; Rico, J. G.; Lectka, T. C. *J. Org. Chem.* **1989**, *54*, 3748-3749.

(19) Marshall, J. A.; Andrews, R. C.; Lebioda, L. *J. Org. Chem.* **1987**, *52*, 2378-2388.

(20) We thank Professor James Marshall, University of South Carolina, for invaluable help in providing copies of the ^1H NMR spectra of numerous synthetic cembranoid lactones.

(21) The C4 epimer was identified by X-ray crystallography of the related δ lactone.

Structures of Ciguatoxin and Its Congener

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Ciguatoxin (CTX) is a toxic principle of ciguatera, one of the largest scale food poisonings of nonmicrobial origins, which results from eating coral reef fish. Despite the great deal of effort made by Scheuer's group of the University of Hawaii,[1,2] extreme difficulties in collecting toxic fish coupled with the complexity of the CTX molecule have hampered chemical studies. Its structure has thus become one of the most challenging targets among natural-product chemists. In the previous reports, we have presented a molecular formula, $C_{60}H_{86}O_{19}$, and a partial structure (C1-C22) of the toxin, including the stereochemistry.[3,4] We report here the elucidation of the rest of the molecule (C23-C60), resulting in the determination of the planar structure of the whole molecule.

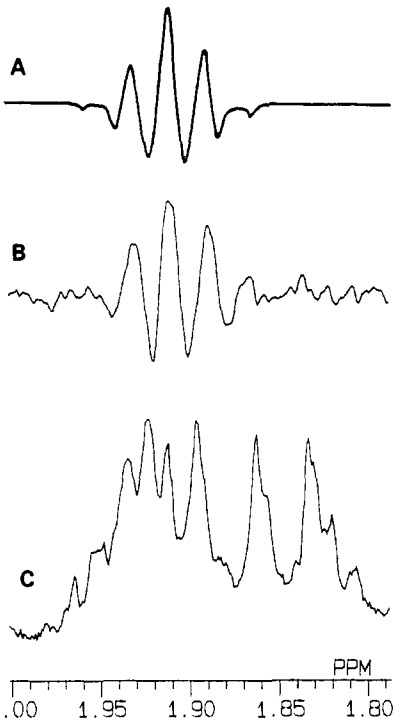

Figure 1. Simulation of decoupling difference ^1H NMR spectrum (A) of H-39 of **2**. The difference spectrum (B) was determined by subtracting a nondecoupling spectrum (C) (pyridine-d_5, 25 °C) from a decoupling one with irradiation at δ 0.917 (Me-57). Simulation was done as to an eight-spin system due to H_2-38/H-39(Me-57)/H_2-40 using chemical shifts obtained from cross peaks on COSY and coupling constants of H-39 (qt, 7.7, 8.4 Hz).

CTX (0.35 mg) was extracted from the moray eel, *Gymnothorax javanicus*, as reported previously.[3] A less polar congener **2** (0.74 mg) was obtained from the causative epiphytic dinoflagellate, *Gambierdiscus toxicus*, collected in the Gambier Islands. Its HR-FABMS suggested a probable molecular formula of $C_{60}H_{84}O_{16}$ (MH^+, m/z 1061.584; found, 1061.587). ^1H NMR chemical shifts and coupling constants of **2** clearly showed **2** to be identical with **1** except for both terminal parts of the molecule.[5-7] Thus the structure elucidation of the common part will be discussed according to the data obtained on **2**. The same set of ^1H NMR measurements were also made as on **1**.

In ^1H NMR spectra of **1** or **2** measured at 25 °C, signals due to H-22 through H_2-31 were extremely broadened or missing, probably because of slow conformational perturbation of ring F, as observed with brevetoxin A.[8] The problem was solved by measurements at low temperatures (-20 or -25 °C) in which missing signals appeared and broad signals sharpened. Since we could match each proton with a single signal, which had a chemical shift close to that of the broad signal observed at 25 °C, rings F and G were presumed to take a single conformation at the low temperatures.

The proton connectivities including hydroxy protons were mainly established by ^1H-^1H COSY data obtained under various con-

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(1) Tachibana, K. Ph.D. Thesis, University of Hawaii, 1980.
(2) Nukina, M.; Koyanagi, L. M.; Scheuer, P. J. *Toxicon* **1984**, *22*, 169.
(3) Legrand, A. M.; Litaudon, M.; Genthon, J. N.; Bagnis, R.; Yasumoto, T. *J. Appl. Phycol.*, in press.
(4) Murata, M.; Legrand, A. M.; Yasumoto, T. *Tetrahedron Lett.* **1989**, *30*, 3793.

0002-7863/89/1511-8929$01.50/0