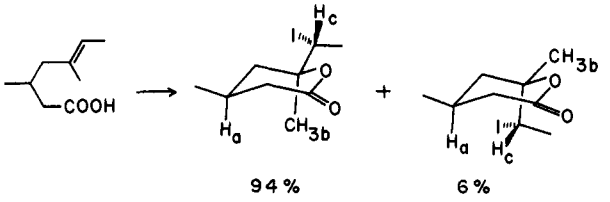

Figure 6.

J = 7 Hz), 1.07 (3 H, d, J = 7 Hz)), and ^{13}C NMR ($(CDCl_3)$ δ 20.26, 23.91, 24.63, 32.07, 36.72, 38.31, 42.29, 69.66, 121.58, 138.63, 173.44). With the C39 asymmetry effectively incorporated, saponification ($KOH–MeOH–H_2O$) and iodolactonization (KI_3, $NaHCO_3$, H_2O) proceeded with high 1,3-asymmetric induction to yield the equatorial iodoalkyl derivative as the only product (**7**, 82%)[11] (see Figure 4). Saponification ($KOH–H_2O$) and subsequent acidification ($HCl–H_2O$) inverted both asymmetric centers via an intermediate epoxy acid and led directly to **8** (mp 92–94 °C, 95% yield). Although the relative configuration of C34 and C36 in **9** were readily determined by ^1H NMR (H_a and H_b are axial), the remaining stereochemistry was best proven by an X-ray crystallographic analysis of **8**, which confirmed the stereochemistry shown above.[12]

Transformation to the palytoxin segment **1** (R, R′ = H) required three final operations: (1) side-chain addition at C41; (2) internal ketalization; (3) side-chain addition at C34 with retention of configuration. The first of these constructions caused some difficulty in that organometallic addition to C41 was quite sluggish and tended toward double addition. Although a completely satisfactory solution that avoids the problems of 1,3-diaxial interactions has yet to be discovered, it was found that treatment of **8** with excess EtMgBr in chloroform at −30 °C for 6 h gave a 69% yield (50% conversion) of the required ketal **10** (see Figure 5).

While our original plan for C34 side-chain addition involved a double inversion sequence in which an intermediate C34 bromide is displaced by an alkylcuprate, the required bromide (from tribromoimidazole, Ph_3P;[13] 96%) turned out to be unreactive under a variety of conditions with dibutylcuprate. In examining other potential leaving groups, it was found that the tosylate of **10** gave acceptable coupling with Bu_2CuLi in Et_2O (−20 °C). Our final problem then became to prepare the tosylate **11** by inversion at C34. While this could be accomplished along known lines ((1) PhCOOH, Ph_3P, DEAD;[14] (2) $KOH–H_2O$; (3) TsCl, C_5H_5N; 50% overall yield), a more concise route was found that used lithium tosylate with triphenylphosphine/diethylazodicarboxylate in THF and led directly to **11** in 52% yield. This reaction presumably proceeded by a process similar to that of the Mitsunobu alcohol inversion.[14] It is anticipated that improvements in the procedure will lead to increased product yields in this potentially useful reaction. Final conversion to **1** was effected as outlined above in 47% yield with the balance of the material being isolated as elimination products.[15]

Registry No. 1 (R = R′ = H), 80764-92-7; **2**, 80764-93-8; **3**, 80764-94-9; **4**, 80764-95-0; **5**, 80764-96-1; **6**, 80764-97-2; **7**, 80764-98-3; **8**, 80764-99-4; **9**, 80765-00-0; **10**, 80765-01-1; tosylate **10**, 80765-02-2; tosylate **11**, 80795-31-9; propylene oxide, 75-56-9; butenyl bromide, 5162-44-7; propyne, 74-99-7.

(11) Similar 1,3-asymmetric induction was observed previously by Kenneth R. Shaw with the related olefinic acid shown in Figure 6. The stereochemistry of the cyclization followed from NOE studies on the major product which showed a 12–15% enhancement of CH_{3b} on irradiation of H_a. Corresponding irradiation of the minor product showed a comparable enhancement of H_c.

(12) We thank Drs. J. P. Springer and E. H. Cordes at Merck, Sharp & Dohme Research Laboratories, Rahway, NJ, for their assistance in conducting the X-ray crystallographic analysis of **8**.

(13) B. Classon, P. J. Caregg, and B Samuelsson, *Can. J. Chem.*, **59**, 339 (1981).

(14) O. Mitsunobu, M. Wada, and J. Sano, *J. Am. Chem. Soc.*, **94**, 680 (1972); A. K. Bose, B. Lal, W. A. Hoffman, and M. S. Manhas, *Tetrahedron Lett.*, 1619 (1973).

(15) This work was supported by Grants NIH R01-HL25634 and NSF CHE81-03030.

Biomimetic Synthesis of Dibromophakellin

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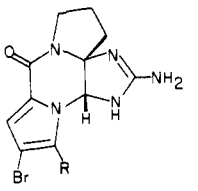
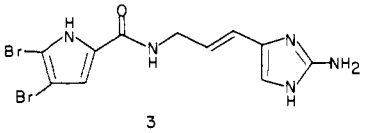
Marine rather than terrestrial organisms produce a structurally broad spectrum of intriguing metabolites containing guanidine units. Among these, tetrodotoxin, saxitoxin, cypridina luciferin, and the zoanthoxanthins received most attention in the past.[1] The two phakellins **1** and **2**,[2,3] isolated from *Phakellia flabellata*, a



1 R = Br
2 R = H



3

sponge, and oroidin (**3**),[4] from *Agelas oroides*, another sponge, belong to a more recently discovered group of marine products containing both bromopyrrole and guanidine substituents. The structure of dibromophakellin (**1**), confirmed by X-ray analysis[2] of its acetate, is noteworthy because despite the presence of both aminoacetal and diaminoketal functionalities the substance exhibits considerable stability toward hydrolytic agents. Oroidin (**3**) and dibromophakellin (**1**) are isomers and are undoubtedly biogenetically related.[5] Neither metabolite has been synthesized, but rather than synthesize oroidin (**3**) and attempt isomerization to dibromophakellin (**1**), we decided to investigate the oxidative cyclization of dihydrooroidin (**9**) (see Chart I) and the brominative cyclization of the halogen-free compound **11**, processes that we hoped to be related to the biosynthesis of the metabolites.

The initial phase of the synthesis was concerned with the preparation of dihydrooroidin (**9**). Commercially available L-(+)-citrulline (**4**) was converted to its ethyl ester **5** with ethanolic hydrogen chloride. Reduction of **5** with sodium amalgam under strict pH control was followed by condensation of the crude aldehyde with cyanamide at pH 4.5. Cyclization with 15% aqueous hydrochloric acid gave 2-amino-4(5)-(3-ureidopropyl)imidazole (**6**) purified as the picrate, mp 203–206 °C dec (73% overall yield).[6] The corresponding hydrochloride (97%), mp 130–142 °C dec, was hydrolyzed with 4 N NaOH (reflux, 8 h)[7] to the hydroscopic amine **7**, best stored in the form of its crystalline dihydrochloride, mp 215–217 °C dec (yield >70%). Acylation was accomplished by condensation with **8**[8] in dimethylformamide in the presence of 3 equiv of sodium carbonate (20 °C, 4–5 h). Dihydrooroidin **9** (free base) [mp 118–121 °C (from methanol), UV max (CH_3OH) 274 nm (ϵ 13 400); IR (Nujol) 1685, 1625, 1590, 1525 cm^{-1}; NMR (Me_2SO-d_6) δ 1.69 (quin, 2, J = 7.5 Hz), 2.34 (t, 2, J = 7.5 Hz), 3.25 (m, 2), 6.24 (s, 1), 6.83 (s, 1), 8.04 (t, 1, J = 4.5 Hz, exch), 5.5 (br, 1, exch), 7.0 (br, 4, exch)] was

(1) Reviewed by: Chevolot, L. In "Marine Natural Products", Scheuer P. J., Ed.; Academic Press: New York, 1981; Vol. IV, p 53–91.

(2) Sharma, G. M.; Burkholder, P. R. *J. Chem. Soc., Chem. Commun.* **1971**, 151.

(3) Sharma, G.; Magdoff-Fairchild, B. *J. Org. Chem.* **1977**, *42*, 4118.

(4) Garcia, E. E.; Benjamin, L. E.; Fryer, R. I. *J. Chem. Soc., Chem. Commun.* **1973**, 78. Forenza, S.; Minale, L.; Riccio, R.; Fattorusso, E. *Ibid.* **1971**, 1129.

(5) Faulkner, D. J.; Andersen, R. J. "The Sea"; Wiley: New York, 1974; Vol. 5, p 679.

(6) First prepared by Dr. W. T. Zimmerman, Ph.D. Thesis, Massachusetts Institute of Technology, 1979, using the method of Lancini et al. (Lancini, G. C.; Lazzari, E.; Arioli, V.; Bellani, P. *J. Med. Chem.* **1969**, *12*, 775). See also: Braun, M.; Büchi, G.; Bushey, D. F. *J. Am. Chem. Soc.* **1978**, *100*, 4208.

(7) This hydrolysis was first performed by T. Holler.

(8) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *16*, 1300.

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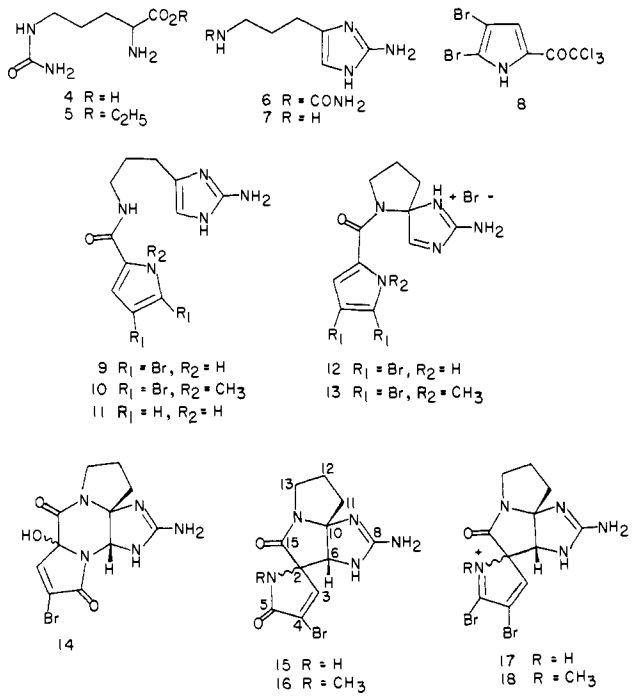
Chart I



obtained in ~50% yield after the free base had been chromatographed on silica gel with $CHCl_3$–CH_3OH–NH_4OH (80:20:3) as eluent.

Exposure of dihydrooroidin hydrochloride (**9**·HCl) to 1 equiv of bromine in acetic acid caused rapid precipitation of an insoluble, highly unstable salt which remains to be fully characterized. Its infrared spectrum (Nujol) lacks the amide II band at 1525 cm^{-1} present in the spectrum of dihydrooroidin (**9**). This salt combined rapidly with methanol to afford an equally unstable product, which according to field desorption mass spectrometry resulted from addition of methanol. Ultraviolet absorption at 279 nm pointed to the survival of the dibromopyrrolecarboxamido group, but quantitative evaluation is meaningless because tribromide ion [UV max (CH_3CN) 269 nm] may be present. An entirely analogous product was prepared by bromination of the *N*-methyl derivative **10**. These observations and others to be discussed in the sequel are in agreement with structures **12** and **13** but do not exclude others.

When treated with potassium *tert*-butoxide (1.5 equiv) in 2-butanol (20 °C, 20 min) **12** was quantitatively converted to racemic dibromophakellin (**1**). Comparison of IR, UV, and NMR spectral data of the hydrochloride of racemic **1**, mp 221–223 °C dec, racemic *N*-acetyldibromophakellin, mp 234–236 °C dec, and racemic hydroxylactam **14**, mp >300 °C dec, with literature[3] values of the corresponding derivatives prepared from natural dibromophakellin established identities. Bromination of the amide **11**[9] in acetic acid followed by treatment with base gave mostly dihydrooroidin (**9**) and very little dibromophakellin (**1**). This experiment demonstrated the following: (a) as shown previously,[10] pyrrole-2-carboxylates brominate at C-4 and C-5; (b) bromination of the pyrrole ring, under these conditions, is faster than oxidative cyclization; (c) the latter process is retarded and/or intermediate **12** is destroyed by excess hydrogen bromide.

A second mode of cyclization was observed when the hydrobromides of **12** and **13** were dissolved in dimethyl sulfoxide or dimethylformamide. Evaporation of the solvents under vacuum followed by crystallization of the residues from CH_3OH–$CHCl_3$ afforded the hydrobromides of the dilactams **15** and **16**. Compound **15** appears to be a single isomer: mp 239–241 °C dec (66% yield); IR (Nujol) 3500, 1720 (sh), 1710 (sh), 1690, 1600 cm^{-1}; UV (CH_3OH) 235 nm (ε 5300); NMR (Me_2SO-d_6) δ 9.50, 9.40, 8.58, 8.02 (2), all exchangeable with D_2O, 7.52 (s, 1), 4.63 (s, 1), 3.47 (m, 1), 3.2 (m, 1), 2.0–2.4 (m, 4); ^{13}C NMR δ 23.99 (C-12), 34.82 (C-11), 42.53 (C-13), 59.00 (C-6), 73.39 (C-2), 86.39 (C-10), 119.33 (C-4), 145.62 (C-3), 157.21 (C-8), 167.79, 168.57 (C-5 and C-15).

The *N*-methyl derivative **16** on the other hand is a mixture of diastereomers according to the ^1H NMR spectra. In the absence of added base, the pyrrole ring in **12** and **13** thus undergoes electrophilic substitution on carbon to afford the bromoimines **17** and **18**, which then hydrolyze to the pyrrolinones **15** and **16**. Under *basic* conditions the pyrrole is deprotonated, and the resulting highly nucleophilic anion cyclizes with formation of a new N–C rather than C–C bond.

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Registry No. (±)-**1**, 80875-81-6; (±)-**1** HCl, 80923-89-3; (±)-**1** N^2-Ac, 80875-82-7; L(+)-**4**, 372-75-8; L(+)-**5**, 80822-58-8; **6** PICRATE, 80822-60-2; **6** HCl, 80822-61-3; **7** 2HCl, 80822-62-4; **8**, 50371-52-3; **9**, 80822-63-5; **10**, 80822-64-6; **11**, 80822-65-7; (±)-**12** HBr, 80822-66-8; (±)-**13** HBr, 80822-67-9; **14**, 80923-90-6; **15**, 80822-68-0; **15** HBr, 80822-69-1; (±)-**16**, isomer I, 80822-70-4; (±)-**16**, isomer II, 80875-83-8; (±)-**16** HBr, isomer I, 80875-84-9; (±)-**16** HBr, isomer II, 80923-91-7; **17**·HBr, 80822-71-5; (±)-**18**·Br^-, isomer I, 80845-42-7; (±)-**18**·Br^-, isomer II, 80876-85-3.

(9) First prepared by P. Arrhenius.

(10) Hodge, P.; Rickards, R. W. *J. Chem. Soc.* **1965**, 459. Anderson, H. J.; Lee, S.-F. *Can. J. Chem.* **1965**, *43*, 409.

Additions of α-Keto Dianions to Sterically Congested Carbonyls[1]

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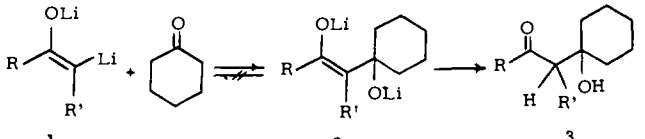
Herein we report the reaction of α-keto dianions[2] (**1**) with



aldehydes and ketones to afford aldol-type products (**3**) or the corresponding dehydrated enones. This process differs from the simple aldol condensation in three important respects. The dianions **1** appear to be considerably more nucleophilic than simple enolates and thus react even with very hindered carbonyl compounds. The initial reaction of such dianions (**1** → **2**) appears to be irreversible, unlike the often readily reversible aldol condensation.[3] The regiospecific alkoxy enolate intermediate (**2**)

(1) Presented in part at the 181st National Meeting of the American Chemical Society, Atlanta, GA, March 1981; American Chemical Society: Washington, D.C., 1981; ORGN 84.

(2) Kowalski, C. J.; O'Dowd, M. L.; Burke, M. C. Fields, K. W. *J. Am. Chem. Soc.* **1980**, *102*, 5411.

(3) For a recent discussion of some readily reversible aldol condensations see: (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. For several leading references to recent aldol chemistry see: (b) Heathcock, C. H.; Hagen, J. P.; Jarvi, E. T.; Pirrung, M. C.; Young, S. D. *J. Am. Chem. Soc.* **1981**, *103*, 4972. (c) Evans, D. A.; Nelson, J. V., Vogel, E.; Taber, T. R. *Ibid.* **1981**, *103*, 3099. (d) Evans, D. A.; McGee, L. R. *Ibid.* **1981**, *103*, 2876. (e) Meyers, A. I.; Yamamoto, Y. *Ibid.* **1981**, *103*, 4278. (f) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *Ibid.* **1981**, *103*, 1566.

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