bonded interactions. The anticipated *trans*-decalin ring geometry of **4** is that present in the quassin series, whereas epimerization of this ring junction is required to secure either the kaurane or quadrone systems.

We commenced the synthesis of **1** by alkylating the dianion derived from the β-keto ester **5**[5] with *trans*-1-iodo-3,5-hexadiene (**6**)[6] to obtain **7**, which without purification was decarboxylated into the cyclopentanone **8** by using LiCl in Me_2SO/H_2O.[7] Treatment of **8** with Brederick's reagent,[8] $[(CH_3)_2N]_2CHO$-*t*-Bu, gave the vinylogous amine ketone **9**, which was then reduced with diisobutylaluminum hydride into the α-methylene ketone **2**.[9] Intramolecular Diels–Alder cyclization of **2** in a mixture of toluene and acetonitrile at 120 °C gave the tricyclic ketone **4** as the sole reaction product (oil; 48% overall yield from **5** after chromatography).[10] While the ^{13}C NMR spectrum of **4** indicated it to be only one material, a completely clear assignment of the decalin ring fusion of **4** was not forthcoming from its ^1H NMR spectrum taken at 400 MHz. Furthermore, crystalline derivatives of **4** suitable for X-ray analysis were not easily obtained. Hence, we assumed *trans*-decalin geometry for the adduct and set about developing a means of converting this substance into the synthetic target.

A variety of means to convert **4** into a *cis*-decalin system were investigated, and after considerable experimentation, it was found that allylic oxidation of **4** with a mixture of CrO_3 and 3,5-dimethylpyrazole followed by basic workup gave the enone **10** in 75% yield after chromatography.[11] At this point, several tactics for securing **1** from **10** were examined—the following proved to be the most efficient. Kinetic deprotonation of **10** with LDA and alkylation with iodomethane resulted in production of the methylated enone **11**. Hydrogenation of **11** using 5% palladium on carbon in ethanol containing HCl gave the *cis*-decalin system **12** in 66% yield from **10** after chromatography.[12] Compound **12** was then reacted with trimethylsilyl iodide and hexamethyldisilazane to afford the enol silane **13**.[13] In crude form, this substance was oxidized with a mixture consisting of 4-methylmorpholine 4-oxide containing a catalytic amount of OsO_4 to give the hydroxy ketone **14** in 84% yield from **12**.[14]

Cleavage of the hydroxy ketone **14** was then initiated by deprotonation of the molecule with LDA followed by trapping of the resulting dianion with trimethylsilyl chloride to obtain **15**. Crude **15**, treated with ozone followed by oxidative degradation of the ozonide with $NaIO_4$ and CrO_3, gave the diketo acid **16** (mp 110–113 °C) in 68% yield from **14**.[15] Finally, aldol cyclization of **16** into the cyclopentanone **17** was accomplished in 45% yield by using sodium hydride in refluxing xylene solution.[16] Since **17** has been converted by Danishefsky in excellent yield into quadrone, we terminated our synthetic efforts at this point.[17] Compound **17**, prepared as described above, showed identical spectra, IR, NMR, and mass spectrum, as well as melting point to a sample of **17** kindly supplied to us by Professor Danishefsky.[18] By this route, compound **17** was obtained in 13 steps from **5** in 6% overall yield.

Acknowledgment. We thank the National Institutes of Health for support of this work. A.J.P. and R.A.N. gratefully acknowledge receipt of Sherman-Clarke Fellowships from the University of Rochester. We also thank H. G. Hemken for the preparation of several grams of the adduct **4**.

Registry No. (±)-**1**, 74807-65-1; (±)-**2**, 85083-89-2; (±)-**4**, 85083-90-5; (±)-**5**, 68691-06-5; **6**, 85083-91-6; **7**, 85083-92-7; (±)-**8**, 85083-93-8; (±)-**9**, 85083-94-9; (±)-**10**, 85083-95-0; (±)-**11**, 85083-96-1; (±)-**12**, 85083-97-2; (±)-**13**, 85083-98-3; **14**, 85083-99-4; **15**, 85084-00-0; (±)-**16**, 85084-01-1; (±)-**17**, 78739-64-7.

(5) Berkowitz, W. F.; Grenetz, S. C. *J. Org. Chem.* **1976**, *41*, 10. For a description of the generation of acyclic β-keto ester dianions, see: Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(6) Compound **6** was prepared starting from methyl sorbate in the following manner: (a) deprotonation of methyl sorbate followed by kinetic quenching of the resulting enolate as described by Stevens et al. (Stevens, R. V.; Cherpeck, R. E.; Harrison, B. L.; Lai, J.; Lapalme, R. *J. Am. Chem. Soc.* **1976**, *98*, 6317). (b) Reduction of the deconjugated ester with $LiAlH_4$. (c) Mesylation of the homoallylic alcohol with methanesulfonyl chloride in pyridine. (d) Displacement of the mesylate with sodium iodide in acetone.

(7) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138.

(8) Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41.

(9) Ziegler, F. E.; Fang, J.-M. *J. Org. Chem.* **1981**, *46*, 825.

(10) Satisfactory spectral and physical data were obtained for all new compounds.

(11) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057. This reagent was originally prepared by Corey and Fleet (Corey, E. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1973**, 4499).

(12) Caine, D.; Smith, T. L., Jr. *J. Org. Chem.* **1978**, *43*, 755.

(13) Miller, R. D.; McKean, D. R. *Synthesis* **1979**, 730.

(14) McCormick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607.

(15) Hase, T. A.; McCoy, K. *Synth. Commun.* **1979**, *9*, 63.

(16) Two other groups have used this same type of aldol condensation in their efforts on quadrone, see: Smith et al. and Kende et al. (ref 2).

(17) References 2a and 2b.

(18) We thank Professor Danishefsky for a generous sample of compound **17**. IR comparison made on a Perkin-Elmer 299B spectrometer, NMR on a Bruker WH-400 spectrometer, and mass spectra on a VG 7035 spectrometer. Melting point of **17** prepared as described, 145–146 °C; lit. 142–146 °C, ref 2a and 2b.

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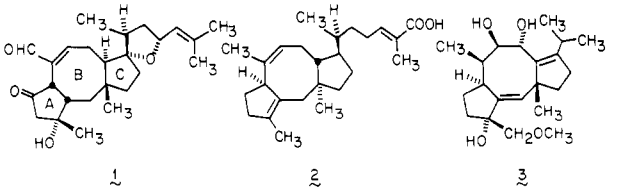
Rapid and Efficient Construction of the Ophiobolin Nucleus

Summary: The angularly fused 5-8-5 ring system that comprises the fundamental architectural element of the ophiobolins, ceroplastols, and fusicoccins can be simply produced in two laboratory manipulations. The scheme is general and allows for placement of one or more sites of unsaturation in ring A and positioning of an incipient carbonyl group in ring C. The latter feature should allow in particular for required epimerization of the α proton and proper side-chain installation.

Sir: The assignment of structure and absolute configuration to ophiobolin A (**1**) achieved by Nozoe et al. in 1965[2,3] represents the first definitive characterization of a naturally occurring sesterterpene. Compound **1** has



1 **2** **3**

(1) Author to whom inquiries regarding the X-ray analysis should be directed.

(2) Nozoe, S.; Morisaki, M.; Tsuda, K.; Iitaka, Y.; Takahashi, N.; Tamura, S.; Ishibashi, K.; Shirasaka, M. *J. Am. Chem. Soc.* **1975**, *87*, 4968.

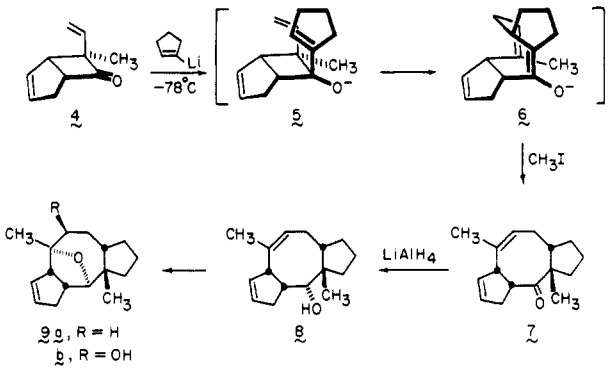
(3) For the original isolation, see: Ishibashi, K.; Nakamura, R. *J. Agric. Chem. Soc. Jpn.* **1958**, *32*, 739.

0022-3263/83/1948-1147$01.50/0

become the forerunner of what is now recognized to be the most prevalent class of sesterterpenes. In common with the various ophiobolins,[4,5] ceroplastols typified by albolic acid (2)[6] and fusicoccin diterpenes such as cotylenol (3)[7] feature an angularly fused 5-8-5 ring system as their molecular backbone. The stereochemical differences that distinguish these groups of compounds are reflected in their varied biological activities, some of which are impressive. These properties, in combination with the attractive and novel architecture of the individual molecular arrays have not escaped attention.[8] Notwithstanding, these higher terpenoids continue to defy de novo synthesis.

In this communication, we disclose the development of a highly expedient, efficient, and regiospecific procedure for the elaboration of ophiobolins that delivers the fundamental 5-8-5 carbocyclic framework already containing (a) an appropriately positioned cyclooctenyl double bond, (b) an associated sp^2-bound methyl group, (c) a properly positioned angular methyl substituent in an all-cis-fused stereochemical arrangement, (d) an incipient carbonyl group in ring C to allow for requisite epimerization of the α proton and side-chain installation, and (e) one or more sites of unsaturation in ring A adequate for introduction of the remaining substituents in that sector.

Nucleophilic addition to bicyclic ketone **4**, readily available by addition of methyl vinyl ketene to cyclopentadiene,[9,10] occurs on the exo face of the molecule for obvious steric reasons. When the nucleophile happens to



be cyclopentenyllithium and reaction is conducted at −78 °C, rapid condensation ensues to give **5**. Perhaps because

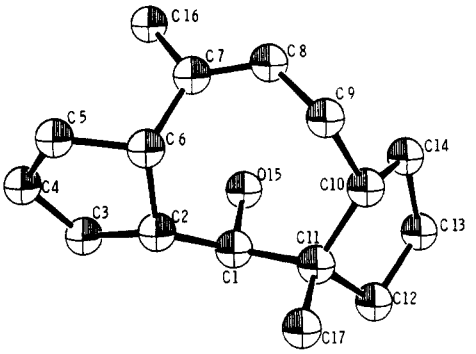


Figure 1. Perspective drawing of 8 with hydrogens omitted.

of the oxyanionic nature[11] of **5**, its conjugate acid cannot be isolated, even following the mildest of possible workup procedures. We conclude that oxy-Cope rearrangement to produce **6** occurs with low activation energy, as expected.[12] If methyl iodide is introduced at this point, a single ketone is isolated (65%) to which structure **7** is assigned. The gross features of noncrystalline **7** follow from its particularly informative 300-MHz ^1H NMR spectrum, its 16-line ^{13}C NMR spectrum, and a 1700-cm^{-1} infrared carbonyl absorption. The stereochemistry of its four chiral centers derive in part from the stereochemical features of **4**, in part from the anticipated[13] boat-like transition state of the **5** → **6** sigmatropic shift, and in part from steric considerations that dictate exo methylation of **6**.

Lithium aluminum hydride reduction of **7** leads to a single alcohol **8** (64%), mp 40.5–42 °C, whose 4-cyclooctenol character was made apparent by its tendency to cyclize to **9a** upon standing in $CDCl_3$ (100%) and to **9b** upon treatment with 1 equiv of *m*-chloroperbenzoic acid (87%). The complete structural elucidation of **8**, which served to establish the relative configuration of its five chiral centers, was conveniently realized by X-ray crystal structure analysis as shown in Figure 1.[14]

Crystals of **8** formed with symmetry $P2_1$ with a = 9.199 (1) Å, b = 21.073 (3) Å, c = 7.515 (2) Å, and β = 111.17 (1)° for Z = 4. Of the 1896 reflections measured with an automatic four-circle diffractometer, 1721 were observed ($I \geq 3\sigma I$). Application of direct methods[15] gave an incomplete initial model that was refined by using Fourier[16] and full-matrix least-squares techniques. The function $\sum\omega(|F_o| - |F_c|)^2$ with $\omega = 1/\sigma(F_o)^2$ was minimized to give an unweighted residual of 0.036. The conformation of the two crystallographically independent molecules is virtually identical with bond distances and angles within generally

(4) Cordell, G. A. *Phytochemistry* **1974**, *13*, 2343.

(5) (a) Ophiobolins B and C: Nozoe, S.; Hirai, K.; Tsuda, K. *Tetrahedron Lett.* **1966**, 2211. Canonica, L.; Fiecchi, A.; Kienle, M. G.; Scala, A. *Ibid.* **1966**, 1329. Ishibashi, K. *J. Antibiot.* **1962**, *A15*, 88. (b) Ophiobolin D: Itai, A.; Nozoe, S.; Tsuda, K.; Okuda, S.; Iitaka, Y.; Nakayama, Y. *Tetrahedron Lett.* **1967**, 4111. Nozoe, S.; et al. *Ibid.* **1967**, 4113. (c) Ophiobolin F: Nozoe, S.; Morisaki, M.; Fukushima, K.; Okuda, S. *Ibid.* **1968**, 4457. Nozoe, S.; Morisaki, M. *J. Chem. Soc. D* **1969**, 1319.

(6) (a) Ceroplastol I and ceroplasteric acid: Iitaka, Y.; Watanabe, I.; Harrison, I. T.; Harrison, S. *J. Am. Chem. Soc.* **1968**, *90*, 1092. (b) Ceroplastol II: Rios, T.; Quijano, L. *Tetrahedron Lett.* **1969**, 1317. (c) Albolic acid: Rios, T.; Gomez, F. *Ibid.* **1969**, 2929.

(7) (a) Fusicoccin A: Hough, E.; Hursthouse, M. B.; Neidle, S.; Rodgers, D. *Chem. Commun.* **1968**, 1197. Ballio, A.; Brufani, M.; Casinori, C. G.; Cerrini, S.; Fedeli, W.; Pellicciari, R.; Santurbano, B.; Vaiaga, A. *Experientia* **1968**, *24*, 631. Barrow, K. D.; Barton, D. H. R.; Chain, E.; Ohnsorge, U. F. W.; Thomas, R. *J. Chem. Soc. C* **1971**, 1265. (b) Fusicoccin H: Barrow, K. D.; Barton, D. H. R.; Chain, E.; Ohnsorge, U. F. W.; Sharma, R. P. *J. Chem. Soc., Perkin Trans. 1* **1973**, 159. (c) Fusicoccin J: Barrow, K. D.; Barton, D. H. R.; Chain, E.; Bageend-Kasujja, D.; Mellows, G. *Ibid.* **1975**, 877. (d) Cotylenol: Sassa, T. *Agric. Biol. Chem.* **1972**, *36*, 2037; **1975**, *39*, 1729.

(8) Das, T. K.; Gupta, A. D.; Ghosal, P. K.; Dutta, P. C. *Indian J. Chem., Sect. B* **1976**, *14B*, 238. (b) Das, T. K.; Dutta, P. C. *Synth. Commun.* **1976**, *6*, 253. (c) Boeckman, R. K., Jr.; Bershas, J. P.; Clardy, J.; Solheim, B. *J. Org. Chem.* **1976**, *41*, 6062. (d) Dauben, W. G.; Hart, D. J. *Ibid.* **1977**, *42*, 922. (d) Baker, W. R.; Senter, P. D.; Coates, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1011. Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3597.

(9) (a) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943. (b) Huston, R.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1982**, *65*, 451.

(10) Although **4** and its epimer have not previously been separated, this can be readily achieved on multigram scale by preparative HPLC (Waters Prep 500).

(11) (a) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. (b) Evans, D. A.; Nelson, J. V. *Ibid.* **1980**, *102*, 774. (c) Paquette, L. A.; Crouse, G. D.; Sharma, A. K. *Ibid.* **1982**, *104*, 4411 and pertinent references cited therein.

(12) Other examples of 1,2-dialkenylcyclobutanols have been reported: (a) Kahn, M. *Tetrahedron Lett.* **1980**, 4547. (b) Levine, S. G.; McDaniel, R. L., Jr. *J. Org. Chem.* **1981**, *46*, 2199. (c) Gadwood, R. C.; Lett. R. M. *Ibid.* **1982**, *47*, 2268.

(13) Maier, G. "Valenzisomerisierungen", Verlag Chem: Weinheim, FRG, 1972; pp 54–57.

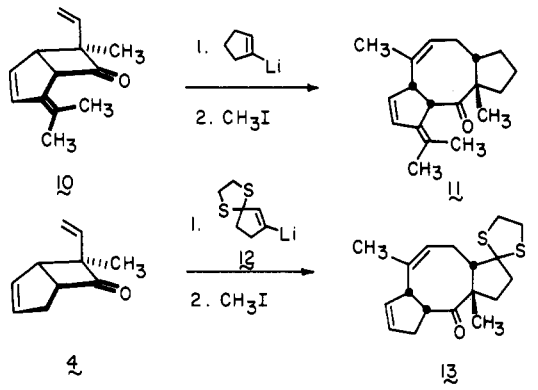
(14) Johnson, C. K. "ORTEP-II, A FORTRAN Thermal-Ellipsoid Plot Program", 1970, Oak Ridge National Laboratory, Oak Ridge, TN.

(15) Main, P. "MULTAN, Program for the Automatic Solution of Crystal Structures from X-ray Diffraction Data", 1980, University of York, England.

(16) Frenz, B. A. "SDP, Structure Determination Package V.17.O"; Molecular Structure Corporation: College Station, TN.

accepted values. Tables containing the final X-ray parameters may be found in the supplementary material.

The synthetic scheme outlined above is subject to ready modification. For example, analogous processing of **10**, an



10 **11** **4** **12** **13**

adduct of methyl vinyl ketene and dimethylfulvene,[9b] results in straightforward preparation of **11** (65%). This compound provides the opportunity for ring-A functionalization. Similarly, **4** condenses rapidly with 3-lithiocyclopentenone dithioketal **12**[17] to furnish **13** (56%). The "unwanted" carbonyl group in **13** is nicely differentiated from that which is protected. Following reductive removal of the oxygen atom, hydrolysis of the dithioketal function is expected to be accompanied by α epimerization in ring C as required for ophiobolin construction (see **1**).[18] Realization of these goals and overall application of this two-step procedure to the total synthesis of ophiobolane sesterterpenes are subjects of current investigation.

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Supplementary Material Available: Experimental details for synthesis and properties of compounds **7**, **8**, **9a**, **9b**, **11**, and **13** as well as fractional coordinates and temperature parameters, bond distances, and angles for **8** (8 pages). Ordering information is given on any current masthead page.

(17) Shih, C.; Swenton, J. S. *J. Org. Chem.* **1982**, *47*, 2825.

(18) Relatively facile epimerization at this center may already have been foreshadowed by the ease with which **7** experiences this equilibration in ring A.

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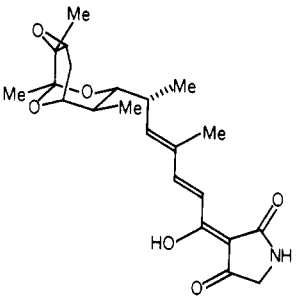
Methodology for the Synthesis of 3-Acyltetramic Acids

Summary: A general method for the preparation of 3-acyltetramic acids is described. The methodology can be extended to produce 3-enoyl or 3-dienoyl substituents via a Wadsworth–Emmons olefination sequence.

Sir: During the course of studies directed toward the total synthesis of tirandamycin (**1**)[1] and related natural products, it became obvious that a general method for the preparation of 3-enoyl or 3-dienoyl tetramic acids was required. Earlier studies by Rinehart[2] demonstrated that the methodology available for the preparation of simple 3-acyltetramic acids (**2**) could not be successfully extended to unsaturated derivatives **3**. A complicating factor was that the new methodology must also allow us to introduce a substituent at C-5 of the tetramic acid since this position is substituted in many tetramic acid containing natural products. This report describes a general method for the preparation of 3-acyltetramic acids. The method can be modified to introduce 3-enoyl or 3-dienoyl substituents via a Wadsworth–Emmons olefination sequence.



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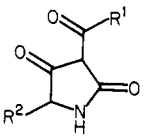

2, $R^1 = R^2$ = alkyl

3, R^1 =  ; R^2 = alkyl

In 1966, Woodward and Olofson[3] reported that isoxazolium salts (**5**) could be fragmented in dilute base solution to produce β-keto amides in excellent yield. Since β-keto amides such as **6** had been cyclized to 3-acyltetramic acids (**2**) with ethoxide in ethanol,[4] we anticipated that the process outlined in Scheme I would allow the preparation of a variety of 3-acyltetramic acids.

Treatment of 5-methylisoxazole (**4a**) or 5-phenylisoxazole (**4b**) with ethyl bromoacetate in nitromethane containing 1 equiv of $AgBF_4$ at 75 °C for 4-12 h resulted in formation of **5a** and **5b**, respectively, in high yield (>95%).[5] Although the salts could be purified by chromatography on ion-exchange resins or LH-20, pure material was routinely obtained by filtration of the precipitated AgBr and passage of the filtrate through LH-20 with CH_2Cl_2. In analogous fashion, **5c**[5] was prepared from **4a** and ethyl bromopropionate. Isoxazolium salt **5d**[5] was produced in quantitative yield by alkylation of **4a** with carbethoxy methyl trifluoromethanesulfonate (X = OSO_2CF_3)[6] in nitromethane. The triflate procedure was the preferred method for the preparation of this salt since the alkylation proceeds rapidly at reflux and it was not necessary to subject the crude product to further purification.

The alkylations could be conveniently monitored by ^1H NMR. The two proton signals of the isoxazole ring that

(1) Duchamp, D. J.; Branfman, A. R.; Bratton, A. C.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 4077 and references therein.

(2) Lee, V. J.; Branfman, A. R.; Herrin, T. R.; Rinehart, K. L., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4225. Cartwright, D.; Lee, V. J.; Rinehart, K. L., Jr. *Ibid.* **1978**, *100*, 4237.

(3) Woodward, R. B.; Olofson, R. A. *Tetrahedron* Suppl. **1966**, *No. 7*, 415.

(4) Lacey, R. N. *J. Chem. Soc.* **1954**, 850. Sticklings, C. E.; Townsend, R. J. *Biochem. J.* **1961**, *78*, 412. Mulholland, T. P. C.; Foster, R.; Haydock, D. B. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2121.

(5) Spectral data for all intermediates are given in the supplemental material.

(6) Vedejs, E.; Enger, D. A.; Mullins, M. J. *J. Org. Chem.* **1977**, *42*, 3109.

0022-3263/83/1948-1149$01.50/0