formed by grinding gave high-quality X-ray powder photographs without further treatment. It has been pointed out that the optimal particle size for powder photography is 10^3–10^5 Å.[19]

The reaction may involve features of certain gas–solid reactions which have been studied[20]—reaction at the surface of a crystalline particle leading to disruption of the structure as product is formed and then diffusion through the partially disordered region by the penetrating reagent. A preliminary examination of the reaction of single crystals of the α form of hydroquinone showed rapid and rather uniform surface attack by the vapor of 1,4-benzoquinone. When the quinone was removed the color of the complex disappeared in a few minutes leaving somewhat pitted surfaces. There was no evidence of anisotropic attack, but with the large number of molecular orientations in this structure[16a] (with 54 molecules per unit cell) this is not surprising. Attempts to find other more suitable crystals with a hydroquinone structure have thus far been unsuccesful.

Conclusion

It has been demonstrated that in the formation of quinhydrones by mixing the solid quinone and hydroquinone reactants, the solids have sufficient mobility to react completely to form a new product but not so much mobility that there is rearrangement of that product to its more stable isomer by a hydrogen-transfer reaction. This example of the use of the solid state to provide restricted (and hence selective) molecular mobility illustrates one of the more promising areas of solid-state chemistry with (among others) potential value for applications in stability studies of herbicides, insecticides, and drug products.[21] Studies of the isomerization in the solid state of the unstable quinhydrones made available by this method to the more stable isomers by hydrogen transfer will be described in a subsequent paper.

Acknowledgment. We are indebted to the National Science Foundation for support of this work.

Registry No. 7a, 106-51-4; **7a·8a** (1:1 complex), 106-34-3; **7a·8b** (1:1 complex), 55836-33-4; **7a·10** (1:1 complex), 87970-33-0; **7a·12** (1:1 complex), 87970-32-9; **7b·8a** (1:2 complex), 87970-36-3; **7b·8b** (1:1 complex), 87970-31-8; **7c**, 363-03-1; **7c·8c** (1:1 complex), 41758-38-7; **7c·10** (1:1 complex), 87970-35-2; **8a·9** (1:1 complex), 60706-28-7; **8a·11** (2:1 complex), 87970-37-4; **8c·9** (1:1 complex), 87970-34-1; **9**, 130-15-4; **9·10** (1:1 complex), 21414-85-7; **10**, 571-60-8; **11**, 137-18-8; **12**, 615-90-7; benzenediazonium chloride, 100-34-5.

(19) Brown, C. J. "X-Ray Diffraction of Polycrystalline Materials"; Peiser, H. S., Rooksby, H. P., Wilson, A. J. C., Eds.; Reinhold Publishing Corp.: New York, 1960.
(20) Paul, I. C.; Curtin, D. Y. *Science* **1975**, *187*, 19–26.
(21) Byrn, S. R. "Chemistry of Drugs"; Academic Press: New York, 1983; pp 1–368. Byrn, S. R. *J. Pharm. Sci.* **1976**, *65*, 1–22.

NOC Approach to Spiroketals. A Total Synthesis of (±)-Talaromycin B

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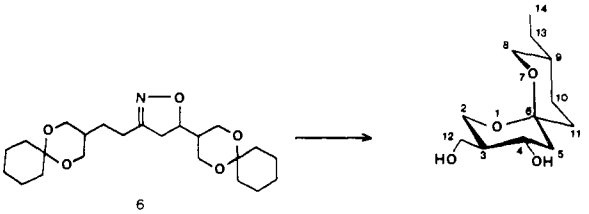
Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. *Received May 3, 1983*

Abstract: A total synthesis of the unqiue spiroketal natural product talaromycin B (**1**) is reported. This molecule, produced in nature by the toxicogenic fungus *Talaromyces stipitatus*, was constructed in the laboratory from the isoxazoline **6** generated



on reacting the oxime **4** with the olefin **5** in the presence of $NaOCl/Et_3N/H_2O/CH_2Cl_2$. The synthesis scheme is sufficiently flexible and efficient so as to be of practical use in the preparation of suitable quantities of this material for biological evaluation.

We disclose herein a total synthesis approach to the toxic metabolite, talaromycin B, product of the toxicogenic fungus *Talromyces stipitatus* isolated from a wood-shavings-based chicken litter.[1] The present literature indicates that the toxicity of this substance may be due to its ability to block outward potassium fluxes, thus leading to muscle dysfunction.[2] Talaromycin B represents but one of now many spiroketal structures to be produced by nature. It is the first, however, to be recognized as being elaborated by a fungus.[1] Others, which vary in structure from stereochemically complex to simple, have bacterial[3] or insect origins.[4]

(1) Lynn, D. G.; Phillips, N. J.; Hutton, W. C.; Shabanowitz, J.; Fennell, D. I.; Cole, R. J. *J. Am. Chem. Soc.* **1982**, *104*, 7319.
(2) See footnote 18 of ref 1.
(3) Westley, J. W. *Adv. Appl. Microbiol.* **1977**, *22*, 177. Westley, J. W. "The Polyether Antibiotics: Carboxylic Acid Ionophores"; Westley, J. W., Ed.; Marcel Dekker: New York, 1982; Chapter 1. Wierenga, W. "The Total Synthesis of Natural Products"; ApSimon, J., Ed.; Wiley: New York, 1981; Vol. 4, pp 263–351.
(4) Baker, R.; Herbert, R. H.; Parton, A. H. *J. Chem. Soc., Chem. Commun.* **1982**, 601 and references cited therein.

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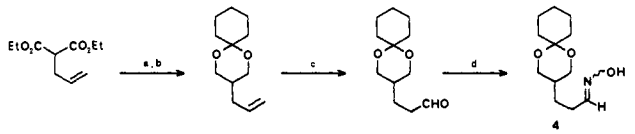
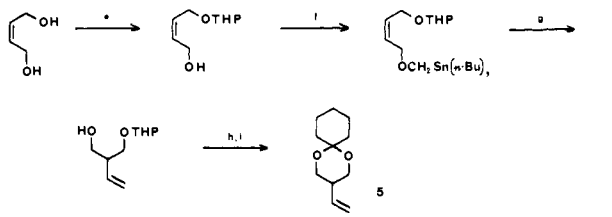
Scheme I. Preparation of the NOC Partners 4 and 5.

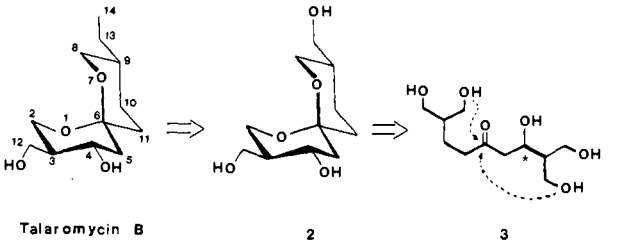


(a) $LiAlH_4$, THF (85%); (b) cyclohexanone, TsOH, PhH (94%); (c) $BH_3 \cdot SMe_2$, CH_2Cl_2; PCC, CH_2Cl_2 (67% overall); (d) $NH_2OH \cdot HCl$, NaOAc, EtOH (95%)



(e) DHP, Amberlyst 15, THF (93%); (f) NaH, HMPA, THF; ICH_2SnBu_3 (58%); (g) *n*-BuLi, THF, −78 °C (65%); (h) MeOH, Amberlyst 15 (96%); (i) cyclohexanone, TsOH, PhH (98%)

As revealed below, our synthetic scheme for the production of talaromycin B was made operationally simple through a symmetrization process. Retrosynthetically this was effected by

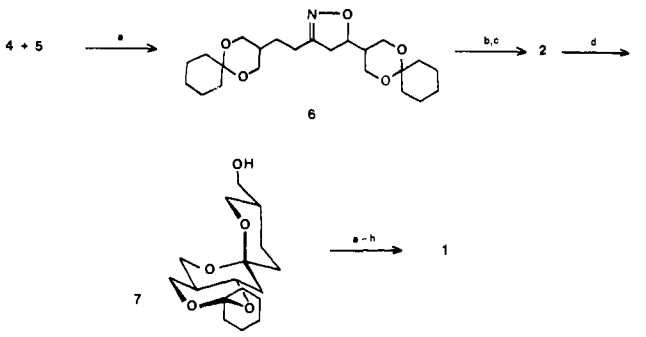


Talaromycin B (1)

converting the ethyl group of **1** to a hydroxymethyl group, a process which then leaves but one asymmetric center in the required starting β-hydroxy ketone **3**. The anomeric effect[5] in conjunction with the equatorial preference of (the non-anomeric) functional groups about the pyran rings would seem to guarantee that **2** should be the product of spirocyclization of **3**.

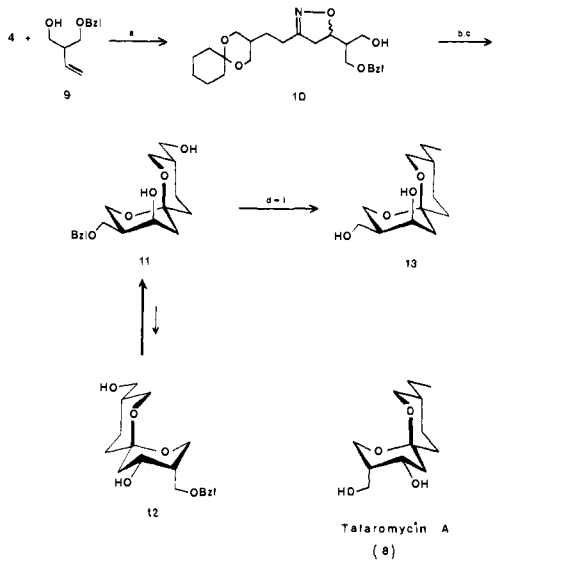
The required β-hydroxy ketone **3** was assembled through utilization of the NOC reaction.[6] The oxime **4** was prepared from diethyl allylmalonate in a very conventional (but high-yielding) fashion. The olefinic partner **5** was generated readily from *cis*-2-butene-1,4-diol via the Wittig rearrangement process.[7] On simply adding sodium hypochlorite to a mixture of **4** and **5** (1:10 ratio), the isoxazoline **6** (mp 108–108.5 °C) was produced in 67% yield.[8] Cleavage of the N–O bond of **6** with H_2/Raney nickel[6] gave the corresponding protected β-hydroxy ketone (mp 99–100 °C) which was then stirred with an acid resin in methanol to afford only **2**. To elongate the C_9 hydroxymethyl to ethyl, the C_3–C_4 1,3-diol unit of **2** was protected as its cyclohexylidene ketal, the primary alcohol converted to its iodide via mesylate, and this intermediate reacted in turn with lithium dimethylcuprate.[9] Deprotection with aqueous methanolic HCl then provided pure **1**, whose spectral properties corresponded fully with those available from the literature.[1,10]

Scheme II. Completion of the Talaromycin B Synthesis



(a) NaOCl, Et_3N, H_2O, CH_2Cl_2 (67%); (b) H_2, Raney Ni (72%); (c) MeOH, Amberlyst 15 (93%); (d) 1-methoxycyclohexene, Amberlyst 15, THF (80%); (e) MsCl, Et_3N, Et_2O (93%); (f) NaI, Me_2CO (65%); (g) Me_2CuLi, THF (61%); (h) HCl, MeOH, H_2O (95%)

Scheme III. An Attempted Synthesis of Talaromycin A



(a) NaOCl, Et_3N, H_2O, CH_2Cl_2 (63%); (b) H_2, Raney Ni, $AlCl_3$, MeOH, H_2O (92%); (c) separate diastereomers; (d) PCC, CH_2Cl_2 (65%); (e) $CH_2{=}PPh_3$, PhH (83%); (f) H_2, 10% Pd/C, EtOAc (100%)

An attempt was also undertaken to make this unidirectional synthesis of talaromycin B diverge so as to produce the related spiroketal talaromycin A (**8**, Scheme III). Accordingly, one of the hydroxyl groups of the dipolarophile **9** was protected as its benzyl ether.[11] The NOC reaction was then carried out, and the isoxazoline intermediate was subjected to ring cleavage and spiroketalization in a single flask through the agency of Raney nickel/$AlCl_3$/MeOH/H_2O.[12] After chromatographic separation

(5) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105.

(6) For other synthetic applications of nitrile oxides in synthesis, see: Kozikowski, A. P.; Goldstein, S. *J. Org. Chem.* **1983**, *48*, 1139 and references cited therein.

(7) Wittig, G. *Angew. Chem.* **1954**, *66*, 10. Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927.

(8) Lee, G. A. *Synthesis* **1982**, 508.

(9) Since the cuprate coupling reaction has on occasion proven erratic, we have found that conversion of the hydroxymethyl group to ethyl is best effected through the same oxidation/Wittig reaction/hydrogenation sequence as in Scheme III.

(10) Satisfactory ^1H NMR, IR, and mass spectral data were obtained for all new compounds. 1: ^1H NMR (300 MHz, $CDCl_3$) δ 4.05 (ddd, 1, J = 4.9, 10.7, 10.7 Hz), 3.68 (d, 2, J = 6.1 Hz), 3.55 (dd, 1, J = 4.9, 11.3 Hz), 3.45 (br d, 1, J = 10.5 Hz), 3.27 (dd, 1, J = 11.3, 11.3 Hz), 3.16 (dd, 1, J = 10.3, 10.3 Hz), 2.35 (br s, 1), 2.16 (br s, 1), 1.96 (dd 1, J = 5.3, 12.5 Hz), 1.83 (m, 1), 1.70–1.40 (m, 6), 1.10 (m, 2), 0.84 (t, 3, J = 7.4 Hz); MS, m/z 230 (M^+), 213, 200, 147, 144, 129, 126. Exact mass calculated for $C_{12}H_{22}O_4$ 230.1518, found 230.1513. Professor David Lynn of the University of Virginia has confirmed the authenticity of our product through ^1H NMR and TLC comparisons.

(11) Dipolarophile **9** was most conveniently prepared from diethyl bis(hydroxymethyl)malonate through a sequence of steps involving benzylidene acetal formation, hydrolysis, decarboxylation, reduction ($LiAlH_4$), oxidation (Me_2SO_4, $(COCl)_2$), Wittig reaction ($CH_2{=}PPh_3$), and reduction $LiAlH_4$, $AlCl_3$). For the preparation of diethyl bis(hydroxylmethyl)malonate, see: Block, P. In "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 381.

(12) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123.

of the 1:1 mixture of diastereomeric spiroketals, the primary hydroxyl of **11** was oxidized to aldehyde, a Wittig reaction with methylenetriphenylphosphorane was carried out, and the product was subjected to hydrogenation over 10% Pd/C. Since the ^{1}H NMR of this new spiroketal **13** failed to match that reported for talaromycin A,[1] we can only assume that **11** and not **12** is the thermodynamically favored product of the spiroketalization event, a product favored perhaps by intramolecular hydrogen bonding as well as by the preference for the benzyloxymethyl group to assume the equatorial position because of its size.

In summation, the present synthesis further underscores the utility of NOC chemistry in the construction of the molecules of nature. The scheme is sufficiently flexible and efficient so as to be of practical use in the preparation of suitable quantities of talaromycin B for biological evaluation. A total synthesis approach to talaromycin B is especially timely, for *T. Stipitatus* has been reported to lose its ability to produce this spiroketal upon subculturing.[1]

Experimental Section

General Methods. Melting points were taken on a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 247 infrared spectrophotometer with the polystyrene absorption at 1601 cm^{-1} as a reference. The ^{1}H NMR spectra were recorded on a Brüker WH-300 spectrometer. Low-resolution mass spectra were obtained on a LKB 9000A gas chromatograph–mass spectrometer. High-resolution mass spectra were obtained on a Varian MAT CH-5DF mass spectrometer.

Dipolar Cycloaddition Reaction of 4 and 5. A two-phase system comprised of the aldoxime **4** (133 mg, 0.59 mmol), alkene **5** (1.03 g, 5.67 mmol) and 0.02 mL of triethylamine in 10 mL of methylene chloride and a 5.25% solution of sodium hypochlorite in water (1.30 g, 0.91 mmol) was stirred vigorously for 10 h. The layers were separated, and the aqueous layer was extracted with 10 mL of methylene chloride. The organic layers were combined, dried, filtered, and concentrated. The residue was chromatographed on silica gel with 60% ethyl acetate–hexanes to yield 160 mg (67%) of isoxazoline **6**: mp 108–108.5 °C; IR (CH_2Cl_2) 2920, 2850, 1440, 1360, 1250, 1150, 1130, 1100, 900 cm^{-1}; NMR ($CDCl_3$) δ 4.64 (m, 1), 4.03–3.57 (m, 8), 3.06–2.70 (d of ABq, 2, J = 9.7, 7.5 Hz), 2.34 (br t, 2, J = 7.8 Hz), 1.90–1.40 (m, 24).

Exact mass calcd for $C_{23}H_{37}NO_5$ 407.2673, found 407.2672. Anal. C, H, N.

Hydrogenolysis of the Isoxazoline 6. To a solution of the isoxazoline **6** (206 mg, 0.51 mmol) dissolved in 10 mL of methanol and 2 mL of water was added 2.35 mL of a 1 M solution of boron trichloride in methylene chloride and 50 mg of W-2 Raney nickel catalyst. The flask was flushed with hydrogen, and the reaction mixture was stirred under a balloon-filled atmosphere of hydrogen for 1 h. The reaction mixture was filtered through a cotton plug, the filtrate was concentrated, and the residue was taken up in ethyl acetate. The solution was again filtered and concentrated to yield 148 mg (71%) of the β-hydroxy ketone: mp 99–100 °C; IR (CH_2Cl_2) 3500, 2920, 2850, 1705, 1440, 1350, 1240, 1150, 1130, 1100, 900 cm^{-1}; NMR ($CDCl_3$) δ 4.16 (m, 1), 4.02–3.54 (m, 8), 3.23 (br s, 1), 2.67 (d of ABq, 2, J = 8.9, 3 Hz), 2.49 (t, 2, J = 7.3 Hz), 1.85–1.40 (m, 24).

Exact mass calcd for $C_{23}H_{38}O_6$ 410.2669, found 410.2671. Anal. C, H.

[3α,4β,6α(R*)]-4-Hydroxy-1,7-dioxaspiro[5.5]undecane-3,9-dimethanol (2). A mixture of the above β-hydroxy ketone (54 mg, 0.13 mmol) and 10 mg of Amberlyst 15 in 5 mL of methanol was stirred overnight at room temperature. After filtration the solvent was removed by rotary evaporation, and the residue was chromatographed on silica gel with 10% methanol–ethyl acetate to yield 28 mg (93%) of **2**: IR (neat) 3400, 2920, 2860, 1450, 1360, 1160, 1090, 1040 cm^{-1}; NMR ($CDCl_3$) δ 4.08 (ddd, 1, J = 10, 10, 4 Hz), 3.72 (d, 2, J = 6.1 Hz), 3.70–3.55 (m, 2), 3.33 (dd, 1, J = 11.5, 11.5 Hz), 3.31 (dd, 1, J = 11.1, 11.1 Hz), 2.02 (dd, 1, J = 12.7, 5.1 Hz), 1.85 (m, 1), 1.80–1.40 (m, 6).

Exact mass calcd for $C_{11}H_{20}O_5$–OH 215.1284, found 215.1284.

Acknowledgment. We are indebted to the National Institutes of Health (Grant No. HL20579-07) and the Camille and Henry Dreyfus Foundation for support of these investigations. We thank P. Stein for helpful discussions and Professor David Lynn of the University of Virginia for the sample comparisons.

Synthesis and Characterization of a New Polyquinone Exhibiting a Two-Electron, Single-Wave Reduction

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Contribution from the Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706. *Received June 8, 1983*

Abstract: Two dicyanomethylidene-substtuted quinocyclopropenes, **1a** and **2a**, have been synthesized and studied. Oxidation of **1a** produced only decomposition products but oxidation of **2a** yielded the new polyquinone **2**. Compound **2** was studied by cyclic voltammetry in aprotic media; it is unique among polyquinones in undergoing two-electron reduction within a single voltammetric wave, with E_1 = 0.00 V and E_2 = −0.04 V vs. SCE.

Earlier papers from these laboratories have reported the synthesis of a number of polyquinocycloalkanes and related compounds, including the cyclopropane derivatives **3–8** and the four-membered rings **9** and **10**[1] (Chart I). All of these compounds show intense long-wavelength electronic absorption bands and are powerful organic oxidants;[2] many also show photoconductive properties.[3]

In this paper we report attempts to replace the quinonoid oxygen of **11** and **4** with the dicyanomethylidene group to prepare compounds **1** and **2**. Compound **1a**, the dihydro precusor to **1**, was isolated but oxidation of **1a** produced only an intractable tar containing no **1**. This finding is not particularly surprising, since earlier work has shown that triquinocyclopropanes analogous to **11** are unstable unless bulky groups are present in the positions ortho to the oxygen atoms.[4] The anthraquino compound **4** is however stable and similarly it is possible to isolate the di-

(1) (a) West, R.; Zecher, D. C. *J. Am. Chem. Soc.* **1970**, *92*, 150, 161. (b) Benham, J. L.; West, R.; Norman, J. A. T. *Ibid.* **1980**, *102*, 5047. (c) Wendling, L. A.; West, R. *J. Org. Chem.* **1978**, *43*, 1577. (d) Koster, S. K.; West, R. *Ibid.* **1975**, *40*, 2300. (e) Wendling, L. A.; Koster, S. K.; Murray, J. E. West, R. *Ibid.* **1977**, *42*, 1126. (f) Komatsu, K.; West, R.; Beyer, D. *J. Am. Chem. Soc.* **1977**, *99*, 6290 and references therein.

(2) Komatsu, K.; West, R. *J. Chem. Soc., Chem. Commun.* **1976**, 570.

(3) Huffman, W. A.; Birkeland, S. P.; O'Leary, K. P. U. S. Patent 4052 209, Oct. 4, 1977.

(4) Zecher, D. C. Ph.D. Thesis, University of Wisconsin—Madison, Madison, WI, 1967.

0002-7863/84/1506-0355$01.50/0