nitrogen with sodium hydride (50% in oil, 0.4 g) added in portions over 1 hr. The brown solution was stirred for a further 2 hr at 0° and then for 2 hr at 20°. Methanol (3 ml) was added dropwise; the mixture was stirred for 10 min and poured into a mixture of water (500 ml) and ether–chloroform (6:1). The lower layer was discarded and the ether solution washed with water and then extracted with hydrochloric acid (2%, three 100-ml portions). The acid solution was basified by addition of ammonium hydroxide and extracted with methylene chloride (two 100-ml portions). Evaporation of the solvent gave the crude product **12** (4.8 g), λ_{max}^{KBr} 5.87 μ.

Formation of Thalicarpine (13b). A solution of the crude product **12** (0.48 g) in acetic acid (30 ml) containing water (6 ml) was stirred with zinc powder (30 mesh, 15 g) at 45–50° for 24 hr. The mixture was diluted with water (200 ml), warmed to dissolve zinc acetate, and filtered, and the filtrate was cooled and basified with ammonium hydroxide. Extraction of the alkaline mixture with ether (three 50-ml portions) followed by evaporation of the ether gave **13a** as a pale brown glass, which was dissolved in formic acid (97%, 4 ml) containing formalin (40%, 1 ml) and heated for 45 min on the steam bath. The cooled solution was diluted with water (50 ml), made alkaline with ammonium hydroxide, and extracted with ether (three 20-ml portions). The residue remaining after removal of the ether was dissolved in ethanol (3 ml); the solution was diluted slowly with water (2 ml) (warming if necessary to inhibit precipitation) to a faint turbidity and stirred 48 hr. The precipitate crystallized from aqueous ethanol to yield thalicarpine (**13b**, 101 mg, 25%), mp 108–110°, identical melting point, mixture melting point, and spectra with an authentic sample crystallized from aqueous ethanol. A portion crystallized from ether gave the isomorphic form,[19] mp 155–157°.

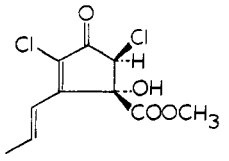
Total Synthesis of Racemic Cryptosporiopsin[1]

G. M. Strunz* and A. S. Court[2]

Contribution from the Canadian Forestry Service, Fredericton, New Brunswick, Canada. *Received November 2, 1972*

Abstract: A short synthesis of the fungitoxic chlorine-containing metabolite cryptosporiopsin (**1**) in racemic form is described. A key intermediate in the synthesis was 3,5,5-trichloro-1,4-dihydroxy-2-*n*-propyl-2-cyclopentene-1-carboxylic acid (**3d**), prepared from *m*-*n*-propylphenol through the agency of alkaline hypochlorite.

Several biogenetically related chlorine-containing metabolites of polyketide origin have been isolated from fermentations of the coprophilous fungus *Sporormia affinis* Sacc., Bomm and Rouss.[3,4] The most abundant of these was the fungitoxic dichlorocyclopentenone **1**. This compound, designated cryptosporiopsin, was discovered in an independent study[5] in culture filtrates of a *Cryptosporiopsis* species, an imperfect fungus isolated from yellow birch, *Betula alleghaniensis* Britt. Cryptosporiopsin was later detected chromatographically in extracts from *Periconia macrospinosa*,[6] from which, *inter alia*, the related metabolite **2** was also isolated. A plausible biosynthetic route to cryptosporiopsin has been postulated,[4] involving contraction of a six-membered cyclic precursor, similar to that demonstrated for terrein.[7]



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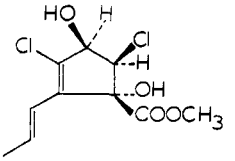


2

The distribution of functionality of cryptosporiopsin (**1**) suggested that this interesting, generously functionalized molecule should be accessible by a short synthetic route, involving skeletal rearrangement of a suitably substituted phenol through the agency of alkaline hypochlorite. Base-catalyzed chlorination of phenol, originally investigated by Hantzsch in 1887,[8] gives rise, *inter alia*, to 3,5,5-trichloro-1,4-dihydroxy-2-cyclopentene-1-carboxylic acid (**3a**).[9,10] Favorskii-type ring contraction of an intermediate such as **4** is one of several mechanisms which have been advanced for this transformation.[9,10] Although rigorous evidence for the stereochemistry at the asymmetric centers of **3a** was lacking, a trans relationship of the two hydroxyl groups was favored on the basis of ir data.[10] Reductive removal of one of the geminal chlorine atoms was effected by treatment of **3a** with sodium amalgam,[8] yielding a dichloro product **5a**.[9,10] In the nmr spectrum of **5a**, the coupling constant (6.5 Hz) of the protons on C-4 and C-5 is indicative of cis stereochemistry at these centers.[9,10] If, therefore, the tentative stereochemical assignment[10] for the Hantzsch acid is correct, similar reduction of a related compound, possessing a potential allyl chain precursor at C-2, could be expected to lead to the stereochemistry at C-1 and C-5 appropriate for a synthesis of cryptosporiopsin.

Consideration of the mechanism of formation of **3a** suggested that hypochlorite-induced rearrangement of a *m*-alkylphenol might lead to a C-2 alkylated Hantzsch acid, **3b**, in which the R group could subsequently be elaborated to the allyl side chain. A series of model

(1) All synthetic substances described herein are racemic whether or not this is specified.

(2) From the Ph.D. Thesis of A. S. C., University of New Brunswick, Fredericton, Canada, 1971.

(3) W. J. McGahren and L. A. Mitscher, *J. Org. Chem.*, **33**, 1577 (1968).

(4) W. J. McGahren, J. H. van den Hende, and L. A. Mitscher, *J. Amer. Chem. Soc.*, **91**, 157 (1969).

(5) (a) M. A. Stillwell, F. A. Wood, and G. M. Strunz, *Can. J. Microbiol.*, **15**, 501 (1969); (b) G. M. Strunz, A. S. Court, J. Komlossy, and M. A. Stillwell, *Can. J. Chem.*, **47**, 2087, 3700 (1969).

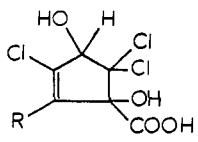
(6) D. Giles and W. B. Turner, *J. Chem. Soc. C*, 2187 (1969).

(7) A. J. Birch, A. Cassera, and A. R. Jones, *Chem. Commun.*, 167 (1965).

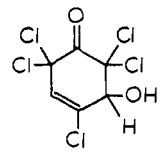
(8) A. Hantzsch, *Chem. Ber.*, **20**, 2780 (1887); **22**, 1238 (1889).

(9) C. J. Moye and S. Sternhell, *Tetrahedron Lett.*, 2411 (1964); *Aust. J. Chem.*, **19**, 2107 (1966).

(10) A. W. Burgstahler, T. B. Lewis, and M. O. Abdel-Rahmen, *J. Org. Chem.*, **31**, 3516 (1966).



3a R = H
b R = alkyl
c R = CH_3
d R = n-Pr



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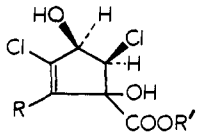
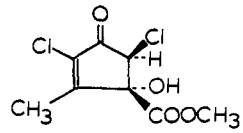


5a R = R′ = H
b R = n-Pr R′ = CH_3

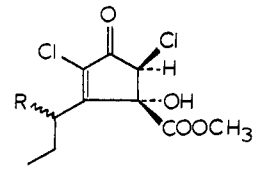


6

studies was conducted using *m*-cresol as starting material, with a view to investigating the feasibility of the proposed synthetic strategy.[11] This substance appeared to be a particularly suitable starting material, since it was abundantly available, and, furthermore, the target of the model synthesis, **6**, could in fact be considered as a potential intermediate in the eventual total synthesis of cryptosporiopsin. In the event, treatment of an alkaline solution of *m*-cresol with chlorine, under conditions based on the earlier studies,[8-10] gave rise to a 5.4% yield of the desired product, 3,5,5-trichloro-1,4-dihydroxy-2-methyl-2-cyclopentene-1-carboxylic acid (**3c**).[11] The latter was smoothly converted into **6** by a three-step sequence.[11] The results of preliminary attempts at the conversion of **6** to cryptosporiopsin (**1**) were discouraging, and in the sequence subsequently developed, the three-carbon side chain was carried through from the start of the synthesis.[12]

m-*n*-Propylphenol (prepared by reduction of isosafrole with sodium in ethanol[13]) was treated with chlorine in alkaline solution under conditions similar to those employed for the *m*-cresol rearrangement. The hydroxy acid **3d** could be isolated from the complex mixture of acidic products by partition chromatography on silica gel.[14] Alternatively, the corresponding methyl ester could more readily be obtained in a pure state, mp 144–145°, on chromatography of the mixture obtained after treatment of the acidic reaction products with diazomethane. For the purposes of the synthesis, it was found expedient to effect purification at a later stage. Accordingly, the crude acidic mixture was treated with sodium amalgam to effect the desired reduction of the *gem*-dichloro grouping in **3d**.[8-10] After esterification with diazomethane, chromatography afforded the dichlorodihydroxy ester, **5b**, mp 178–180° (1.5% overall yield from *m*-*n*-propylphenol). In accord with expectations based on the earlier observations,[9,10] the vicinal protons at C-4 and C-5 exhibited a coupling constant of 6.5 Hz, indicative of a cis relationship. In view of the tentative stereochemical assignments discussed earlier (and the subsequent transformation of **5b** into products with known configurations at C-1 and C-5), it is likely that the relative stereochemistry of **5b** is identical with that of the *Periconia* metabolite, **2**.

Oxidation of **5b** with Jones' reagent[15] in acetone resulted in quantitative conversion to racemic dihydrocryptosporiopsin, **7**, a substance previously obtained



7 R = H

8 R = Br

(as a single enantiomer) by hydrogenation of cryptosporiopsin in ethyl acetate solution, using a palladium-on-charcoal catalyst.[5b] The identity of synthetic and naturally derived material was established by ir, uv, nmr, and mass spectrometry, and by tlc.

Synthetic dihydrocryptosporiopsin (**7**) was converted in 98% yield to the crude crystalline allylic bromide (**8**) through the agency of *N*-bromosuccinimide.[16] A sample, recrystallized from cyclohexane, had mp 116–121°; it displayed a molecular ion at *m/e* 344 in the mass spectrum, together with the appropriate characteristic isotope peaks.[17]

Reaction with dimethylformamide[18] proved to be the most effective method for converting **8** to racemic cryptosporiopsin. Attempts to effect the required dehydrobromination under a variety of other conditions were attended by extensive decomposition. Thus, a solution of **8** in dry dimethylformamide was heated at 135–140° for 20 min in a nitrogen atmosphere. Preparative layer chromatography of the product on silica gel plates afforded a 17% yield of racemic cryptosporiopsin,[19] whose identity was established by comparison of ir (CCl_4 solution), uv, nmr, and mass spectra, as well as tlc behavior, with those of the natural metabolite.

Synthetic racemic cryptosporiopsin was assayed for its activity against sporangial germination of *Phytophthora infestans*[20] in aqueous solution. Germination was almost completely prevented at a concentration of 12.5 μg/ml. Natural (dextrorotatory) cryptosporiopsin showed about the same degree of inhibition at 6.25 μg/ml (control, 70% germination). These results suggest that the dextrorotatory enantiomer alone is

(11) G. M. Strunz, A. S. Court, and J. Komlossy, *Tetrahedron Lett.*, 3613 (1969).

(12) For a preliminary announcement of this work, see G. M. Strunz and A. S. Court, *Experientia*, **26**, 714, 1054 (1970).

(13) S. G. Cousin and F. Lyons, *J. Proc. Roy. Soc. N. S. W.*, **70**, 413 (1937); *Chem. Abstr.*, **31**, 6637 (1937).

(14) C. S. Marvel and R. D. Rands, Jr., *J. Amer. Chem. Soc.*, 72, 2642 (1950).

(15) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(16) A. I. Vogel, "A Text-Book of Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1966.

(17) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967.

(18) (a) N. Kornblum and R. K. Blackwood, *J. Amer. Chem. Soc.*, **78**, 4037 (1956); (b) B. Pelc, S. Heřmánek, and J. Holubek, *Collect. Czech. Chem. Commun.*, **26**, 1852 (1961).

(19) The yield was 20% based on unrecovered starting material.

(20) M. A. Stillwell and W. A. Hodgson, *Can. J. Microbiol.*, **14**, 807 (1968). We thank Mr. M. A. Stillwell for this determination.

responsible for the observed inhibition of sporangial germination.

Experimental Section

Melting points were determined on a hot-stage apparatus and are uncorrected. Ir and uv spectra were recorded on Beckman IR-10 and DK-2A spectrophotometers, respectively. Nmr spectra were obtained using a Varian Associates T-60 spectrometer [solutions in $CDCl_3$ or $(CD_3)_2CO$; TMS internal standard]. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6D mass spectrometer. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

***m*-*n*-Propylphenol.** Slight modification of the procedure described by Cousin and Lyons[13] resulted in improved yields of *m*-*n*-propylphenol. Freshly cut sodium (46.0 g, 2.0 g-atoms) was melted in dry xylene (300 ml) and evenly dispersed by vigorous mechanical stirring. Isosafrole (50.0 g, 0.308 mol) was added dropwise to the hot dispersion. Absolute ethanol (450 ml) was then added cautiously to the hot mixture during 3 hr, at a rate such that reflux was maintained and coagulation of the precipitated salts did not interfere with the stirring. When all the sodium had dissolved, the mixture was steam distilled, after which phenolic products were isolated from the residual aqueous phase by standard procedures. Distillation of the products yielded 23.9 g (57%) of *m*-*n*-propylphenol, bp 110° (10 mm) (lit.[13] 117–118° (11 mm)).

3,5,5-Trichloro-1,4-dihydroxy-2-*n*-propyl-2-cyclopentene-1-carboxylic Acid (3d) and Methyl Ester. The procedure employed was based on earlier work on the reaction of 2,4,6-trichlorophenol[10] and *m*-cresol[11] with alkaline hypochlorite. A solution of *m*-*n*-propylphenol (23.9 g, 0.175 mol) in 2.5 *M* aqueous sodium hydroxide (435 ml) was cooled to −2° with an acetone–Dry Ice bath. Chlorine was slowly passed into the stirred mixture through a gas dispersion tube, while the temperature was maintained at 0–4° by judicious regulation of gas flow and application of the cooling bath. When an abrupt increase in temperature was observed after 10–15 min, the flow of chlorine was stopped and cold 5 *M* sodium hydroxide solution (85 ml) was added. The stirred mixture was again cooled to −2° and the flow of chlorine was resumed. This procedure was repeated three times, after which no further spontaneous change in temperature was observed. The mixture was then acidified with 12 *M* hydrochloric acid, and residual chlorine was removed with a stream of nitrogen. After filtering through Celite, the solution was extracted thoroughly with ether. Separation of acidic products was effected by extraction of the ether solution with aqueous sodium bicarbonate. The aqueous phase was acidified with 10% hydrochloric acid, and extraction with ether yielded, after drying ($MgSO_4$) and evaporation of solvent, 8.3 g of an oily mixture of acids containing **3d**. For the purposes of the synthesis, it was found expedient to postpone purification until a later stage, and the crude product was used directly in the subsequent reduction step (*vide infra*).

The acid **3d** was most readily characterized as its methyl ester, obtained by treatment of the crude reaction product with ethereal diazomethane, followed by chromatography on silica gel. The ester, eluted with benzene–ether (95:5), was crystallized from chloroform–cyclohexane: mp 144–145°; ir (KBr) 1725, 1630 cm^{-1}; nmr ($CDCl_3$) δ 0.97 (distorted t, 3 H, $J \sim 6$ Hz), 1.4–2.2 (m, 4 H), 3.58 (s, 1 H), 3.85 (s, 1 H), 3.95 (s, 3 H), and 6.00 (s, 1 H). Signals at δ 3.58 and 3.85 disappeared on deuterium exchange.

Anal. Calcd for $C_{10}H_{13}Cl_3O_4$: C, 39.57; H, 4.32; Cl, 35.04. Found: C, 39.56; H, 4.17; Cl, 35.29.

3,5-Dichloro-1,4-dihydroxy-2-*n*-propyl-2-cyclopentene-1-carboxylic Acid Methyl Ester (5b). The crude product containing **3d** from the hypochlorite reaction (8.3 g) was dissolved in water (400 ml) and 2% sodium amalgam[21] (342 g) was added portionwise with vigorous stirring during 1.5 hr. When the addition was complete, the mixture was set aside at 25° with stirring for a further 2 hr. The aqueous phase was decanted, and the residual mercury washed with several portions of water. The combined aqueous phase was made acidic by the addition of 20% sulfuric acid; it was then saturated with sodium chloride and extracted thoroughly with ether. The extracts, after drying ($MgSO_4$) and evaporation of solvent, yielded 4.2 g of oily material which was treated directly with excess ethereal diazomethane. Crystallization of the product from methylene chloride afforded 660 mg of pure **5b**: mp 178–180°; ir (KBr) 1740 and 1660 cm^{-1}; nmr [$(CD_3)_2CO$] δ 0.88 (distorted t, 3 H, $J \sim 6$ Hz), 1.1–*ca.* 2.2 (partially obscured by acetone signal), 2.85 (s, 1 H), 3.80 (s, 3 H), 4.01 (d, 1 H, $J = 6.5$ Hz), 4.67 (m, 1 H), and 5.3–5.45 (m, 1 H) (on deuterium exchange, the signals at δ 2.85 and 5.3–5.45 disappeared, and the multiplet at δ 4.67 collapsed to a doublet at δ 4.64 ($J = 6.5$ Hz)); mass spectrum *m/e* 268 (M^+).

Anal. Calcd for $C_{10}H_{14}Cl_2O_4$: C, 44.63; H, 5.25; Cl, 26.35. Found: C, 44.47; H, 5.16; Cl, 26.26.

A further 59 mg of pure **5b** was obtained by chromatography of the mother liquors on silica gel. Thus, the overall yield of **5b** from *m*-*n*-propylphenol was 1.5%.

3,5-Dichloro-1-hydroxy-4-oxo-2-*n*-propyl-2-cyclopentene-1-carboxylic Acid Methyl Ester (Dihydrocryptosporiopsin) (7). The dihydroxy ester **5b** (303 mg, 1.13 mmol) was dissolved in acetone (50 ml) and the solution was cooled to 15–20°. Jones' reagent[15] (1.09 ml, 2.91 mmol of CrO_3) was added dropwise while the temperature was maintained at 15–20°. The mixture was stirred at this temperature for a further 20 min, after which saturated sodium chloride solution (20 ml) was added, and the mixture was thoroughly extracted with ether. The extracts were dried ($MgSO_4$), and removal of solvent under reduced pressure afforded 290 mg of crystalline product, homogeneous on tlc. Recrystallization from cyclohexane gave pure racemic dihydrocryptosporiopsin (**7**):[5b] mp 101–103°; ir (CCl_4) 3500, 1758, 1750, and 1620 cm^{-1}; uv max (EtOH) 244 nm (ϵ 11,200); nmr ($CDCl_3$) δ 0.97 (distorted t, 3 H, $J \sim 6$ Hz), 1.15–1.83 (m, 2 H), 2.15–2.73 (m, 2 H), 3.83 (s, 3 H), 4.45 (s, 1 H), and 4.57 (s, 1 H) (the signal at δ 4.45 disappeared on deuterium exchange); mass spectrum *m/e* 266 (M^+), ($M^+ + 2$) 65%, ($M^+ + 4$) 11%.[17] The spectra were indistinguishable from those of dihydrocryptosporiopsin, mp 90–95° (from cyclohexane), derived from the natural metabolite.

Allylic Bromination of Racemic Dihydrocryptosporiopsin (7). *N*-Bromosuccinimide (300 mg, 1.68 mmol) was added to dihydrocryptosporiopsin (436 mg, 1.63 mmol) dissolved in carbon tetrachloride (75 ml). The mixture was refluxed for 2.5 hr while being irradiated with a tungsten lamp. It was then set aside for 30 min to cool and filtered, and the filtrates were washed (H_2O). After drying ($MgSO_4$), removal of the solvent *in vacuo* yielded 554 mg (97%) of crystalline product. Recrystallization from cyclohexane afforded pure **8** as colorless needles: mp 116–121°; ir 3480, 1760, 1750, and 1615 cm^{-1}; uv max (EtOH) 252 nm (ϵ 7500); nmr ($CDCl_3$) δ 1.05 (t, 3 H, $J = 7$ Hz), 1.98–2.45 (m, 2 H), 3.85 (s, 3 H), and 4.51–5.05 (m, 3 H, shown by deuteration to include hydroxyl signal); mass spectrum *m/e* 344 (M^+), ($M^+ + 2$) 157%, ($M^+ + 4$) 75%, ($M^+ + 6$) 11%.

Racemic 2-*trans*-Allyl-3,5-dichloro-1-hydroxy-4-oxo-2-cyclopentene-1-carboxylic Acid Methyl Ester (Cryptosporiopsin) (1). A solution of **8** (356 mg, 1.03 mmol) in dry dimethylformamide (5.0 ml) was heated at 135–140° in a nitrogen atmosphere for 20 min. The mixture was poured into cold saturated sodium chloride solution and extracted thoroughly with ether. The combined extracts were dried ($MgSO_4$), and evaporation of solvent under reduced pressure afforded 295 mg of brown oily material. Chromatography of the product on silica gel preparative layer plates furnished 58 mg of unchanged **8** and 47 mg of a colorless gum, identified as cryptosporiopsin (**1**) by comparison of its tlc behavior and spectral characteristics with those of the natural metabolite.[4,5] Based on unrecovered starting material, this represents a 20% conversion of **8** to racemic cryptosporiopsin: ir (CCl_4) 3500, 1745, and 1640 cm^{-1}; uv max (EtOH) 289 nm (ϵ 23,600); nmr ($CDCl_3$) δ 1.97 (d, 3 H, $J = 6$ Hz), 3.83 (s, 3 H), 4.42 (s, 1 H), 4.63 (s, 1 H), 6.30–7.23 (m, 2 H); mass spectrum *m/e* 264 (M^+), ($M^+ + 2$) 66%, ($M^+ + 4$) 10%.

Acknowledgments. We thank Mrs. G. Aarts, University of New Brunswick, for recording the mass spectra.

(21) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 1030.