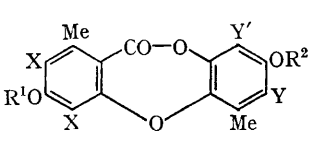
A New Synthesis of Depsidones; Diploicin

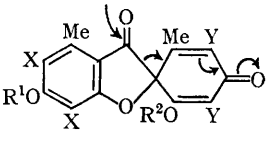
By JAMES B. HENDRICKSON* and MICHAEL V. J. RAMSAY

(*Edison Chemical Laboratories, Brandeis University, Waltham, Massachusetts* 02154)

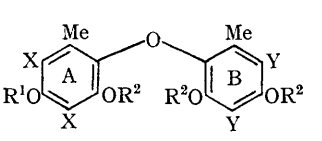
THE natural depsidones (I), a group of over twenty known lichen products,[1] are apparently synthesized in nature by oxidative coupling of depsides;[2] one example, diploicin, has been synthesized in the laboratory by a similar route.[3] In order to examine the published[4] but biogenetically unlikely structure of gangaleoidin,† we considered the solvolytic cleavage of grisans (II), formed by oxidative coupling, which is reported to yield diphenyl ethers.[5]



(I)



(II)



(III)

	R^1	X	Y	R^2
(a)	H	Cl	Cl	Me
(b)	H	Cl	H = Y′ / CO_2Me = Y	Me
(c)	Me	Cl	H	Ac
(d)	Ac	H	Cl	Me
(e)	Ac	Cl	Cl	Me

	R^1	X	R^2	Y
(a)	H	H	H	H
(b)	H	Cl	H	H
(c)	H	H	H	Cl
(d)	Me	Cl	H	H

	R^1	X	R^2	Y
(a)	H	H	H	H
(b)	H	Cl	H	H
(c)	Me	Cl	H	H
(d)	Me	Cl	Bz	H

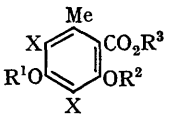
To test the method we prepared the benzophenones (III) from the acids (IV) with dibenzylorcinol in trifluoroacetic anhydride; it was found necessary to protect the phenolic groups as ethers, not esters. The simplicity of this benzophenone synthesis leads to a potential difficulty in that two *ortho*-hydroxyls are present and can lead to oxidative entry into either ring A or B, and hence to two products (V) with reversed ring A and B substitution patterns.

The starting acids (IV) were all made from ethyl orsellinate (IVa).[3] The simplest benzophenone, the symmetrical tetrahydroxy-variant, (IIIa) (m.p. 192—196°), was synthesized from (IVb) and yielded no dienone (IIa), or diphenyl ether acid (Va), on alkaline ferricyanide oxidation. Introduction of chlorine in ring A [for gangaleoidin (Ib)] from the chlorinated analogue of (IVb) led to (IIIa) (m.p. 212—215°), which is not symmetrical and could afford two grisans, (IIb) and (IIc). Oxidation, however, led exclusively to (IIc) in moderate yield, as shown by the absence of vinyl hydrogens (n.m.r.). To force oxidation into the unchlorinated ring B we prepared (IIIc) such that oxidation of the chlorinated ring A must yield the presumably less favoured *ortho*-dienone, (VI). Compound (IVf) (28%, m.p. 166—168°) was formed by the series of standard transformations, (IVa) → (IVc) → (IVd) → (IVe) → (IVf), and was then condensed with dibenzylorcinol to (IIId), hydrogenated to (IIIc), and oxidized with alkaline ferricyanide. Spectral evidence that the oxidation product (IId) or (VI) was spontaneously hydrolysed to a diphenyl ether [(Vb) or (Vc) respectively] led us to treat the crude product mixture with acetic anhydride, to give, after chromatography, a single crystalline depsidone (m.p. 205—207°), either (Ic) or (Id). The oxidation step must proceed in one direction with high efficiency since the five-reaction sequence (IVf) → (Ic) or (Id) gave 30% yield without any isolation or chromatography of intermediates. The identity of the depsidone (as Id) was confirmed by saponification, chlorination, and acetic anhydride treatment to give diploicin acetate, (Ic) (27%, m.p. 233—234°), and by mild hydrolysis of this to diplocin, (Ia), m.p. 231—233°. Both products were compared with authentic natural material by standard methods.‡ Hence the course of oxidation must have proceeded exclusively *via* (VI), not (IId), and hydrolysis to (Vb), not (Va). Thus the synthesis§ of diploicin is: (IVa) → (IVf) → [(IIId) → (IIIc) → (VI) → (Vb)] → (Id) → (Ie) → (Ia).

† We believe the correct structure to be (Ib) but samples of the natural product are not available.

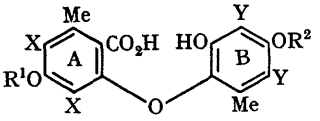
‡ We thank Dr. Peter Thieme for making these comparisons.

§ All analyses and spectral data on the synthetic intermediates were consistent with the formulations shown.



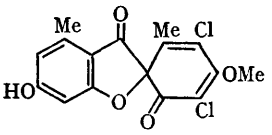
(IV)

	R^1	X	R^2	R^3
(a)	H	H	H	Et
(b)	Bz	H	Bz	H
(c)	Me	H	H	Et
(d)	Me	Cl	H	Et
(e)	Me	Cl	Bz	Et
(f)	Me	Cl	Bz	H



(V)

	R^1	X	Y	R^2
(a)	H	Cl	H	H
(b)	Me	Cl	H	H
(c)	H	H	Cl	Me



(VI)

Not only is this an easy synthetic route but it suggests that oxidative couplings may be far more effective with halogenated phenols.

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[1] (a) A. Asahina and S. Shibata, "The Chemistry of Lichen Substances," Japan Society for Promotion of Science, Tokyo, 1954; (b) F. M. Dean, "Naturally Occurring Oxygen Ring Compounds", Butterworths, London, 1963, p. 564.
[2] J. H. Richards and J. B. Hendrickson "The Biosynthesis of Steroids, Terpenes, and Acetogenins", Benjamin, New York, 1964.
[3] C. J. Brown, D. E. Clark, W. D. Ollis, and P. L. Veal, *Proc. Chem. Soc.*, 1960, 393.
[4] T. J. Nolan and J. Keane, *Sci. Proc. Roy. Dublin Soc.*, 1943, **23**, 143; (*Chem. Abs.*, 1938, **32**, 5036; 1940, **34**, 3788; 1944, **38**, 1221).
[5] E. Kyburz, J. Wursch, and A. Brossi, *Helv. Chim. Acta*, 1962, **45**, 813; J. F. Grove, *Quart. Rev.*, 1963, **17**, 1.
[6] A. I. Scott, *Quart. Rev.*, 1965, **19**, 1.