A New Synthesis of Depsidones. Diploicin and Gangaleoidin[1a]

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Abstract: A new depsidone synthesis is developed, depending on five-ring oxidative cyclization of a dihydroxybenzophenone to a grisan and solvolytic opening to a diphenyl ether which can be easily closed to a depsidone (**8** → **9** → **10**). The oxidation is greatly facilitated by the presence of halogens in one ring and it is this ring which suffers oxidative incursion exclusively when a choice is possible. The method is used in a short synthesis of diploicin (**2**). The biogenetically unlikely structure originally proposed for gangaleoidin (**3a**) was then assessed by two syntheses of isomers considered to be more reasonable. These substituted structures ("isogangaleoidins A and B"), however, proved to be incorrect. Biogenetic rationalization of the reported structure is offered as well as a discussion of the high specificity of internal oxidative coupling in the halogenated benzophenones. These couplings appear to be *bona fide* examples of phenoxy radical attack on phenoxide anion, yielding an intermediate radical anion.

The natural depsidones are a group of lichen products, the structures of over 20 having been reported during the classical period of structure determination.[2] The family is characterized by the tricyclic diphenyl ether lactone system seen in the structure of one of the simplest, diploicin (**2**), and it is apparently because of the great difficulty of creating polysubstituted diphenyl ethers by classical methods that no depsidone syntheses were reported during this period. The biosynthesis of these substances[3] is believed to proceed from acetate to orsellinic acid derivatives and then to esters (depsides) coupling two of these derivatives, the simplest depside from two molecules of orsellinic acid itself shown in **1**. Intramolecular oxidative coupling then creates the characteristic diphenyl ether ring of the depsidones. Decarboxylation, methylation, and chlorination serve to complete the diploicin (**2**) biosynthesis and the other depsidones are similarly characterized by generally accepted biogenetic variants of this kind.[3]

Our interest in depsides and depsidones arose from the almost perfect correlation of their structures with linear acetate biosynthesis,[3c] a correlation marred (among 56 structures) only by the published structure for gangaleoidin (**3a**).[4] As such correlations of structure with biogenetic theory form the basis for generalizing the biosynthesis paths established by tracer studies on particular organisms, it was important to reexamine the structure of gangaleoidin, which is either incorrect and the biogenetic correlation then perfect or else the structure implies an uncommon variant in depsidone biosynthesis. Since original samples from Nolan's work on gangaleoidin were not available,[5] we proposed a synthesis not of Nolan's published structure (**3a**) but rather of the structure (**3b**) which seemed most consistent not only with chemical evidence but also with biogenetic considerations, the only change being the placement of methyl on ring B to accord with the expectation of **1** and **2**.

Nolan's structure proof[4] rests on opening the lactone with methoxide, methylating the phenols and saponifying to a diacid which yielded a monoacid on pyrolysis. The carboxyl remaining re-formed the lactone with acetic anhydride and sulfuric acid (with concomitant demethylation of the lactonic phenol). Methoxide opening of this decarboxylated depsidone yielded a phenol (**4a**) with a free para position (indophenol test[6]), indicating the other carboxyl site in gangaleoidin. Chlorinative cleavage of the diphenyl ether link in **4a** yielded methyl 3,5-dichloroeverninate (4-*O*-methyl-3,5-dichloroorsellinate, **7i**), thus establishing the substituents on ring A. Pyrolysis of the diacid from gangaleoidin (above) also yielded a xanthone, implying a free position in ring B ortho to the diphenyl ether link.[7] While **3a** is a structure most consistent with the chemical evidence for gangaleoidin, **3b** is also consistent with biogenetic theory and all of the chemical evidence except the pyrolysis of the diacid to a xanthone. This pyrolysis might be rationalized mechanistically, however, if the diacid from **3b** first decarboxylated and was then closed to an intermediate (**5**) which could subsequently undergo two successive dienone–phenol rearrangements to xanthone (**6**). The acid catalysis for such a rearrangement would be supplied by the diacid in the pyrolysis melt itself, and it is noteworthy that the xanthone is also formed in hot formic acid.

Despite considerable effort on structure studies of the depsidones there were no syntheses of these compounds until 1960 when Ollis synthesized diploicin (**2**) by direct oxidative coupling emulating the biosynthesis (*cf.* **1**).[8] We also considered oxidative coupling as a viable route to diphenyl ethers despite the generally

(1) (a) For a preliminary account of part of this work, see J. B. Hendrickson and M. J. Ramsay, *Chem. Commun.*, 1101 (1968). (b) National Institutes of Health Postdoctoral Fellow, 1968–1969.

(2) (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.

(3) (a) D. H. R. Barton and T. Cohen, *Festschr. Prof. Dr. Arthur Stoll Siebzigsten Geburtstag 1957*, 117 (1957); (b) H. Erdtman and C. A. Wachtmeister, *ibid.*, 144 (1957); (c) J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes, and Acetogenins," Benjamin, New York, N. Y., 1964.

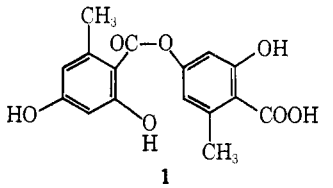
(4) T. J. Nolan and J. Keane, *Sci. Proc. Roy. Dublin Soc.*, 1943 (1938) (*Chem. Abstr.*, **32**, 5036 (1938); **34**, 3788 (1940); **38**, 1221 (1944)).

(5) Apparently none of Nolan's samples are still in existence to allow direct comparisons (W. D. Ollis, personal communication) but the reported melting points of gangaleoidin and its derivatives provide a basis for checking product identity.

(6) The test was positive with **4a** but negative with the methoxide product of gangaleoidin itself and consistent with other phenols tested in the series or as simple models. Another color test of less convincing validity was used to establish the meta orientation of phenolic hydroxyls in ring B.

(7) The placement of both chlorines in ring A is also forced by this observation, which leaves no position for chlorine in ring B. The xanthone contains two chlorines and was characterized essentially only by its elemental analysis.

(8) C. J. Brown, D. E. Clark, W. D. Ollis, and P. L. Veal, *Proc. Chem. Soc.*, 393 (1960).



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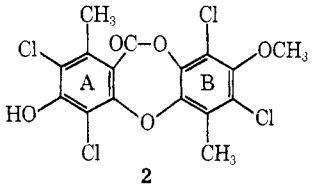

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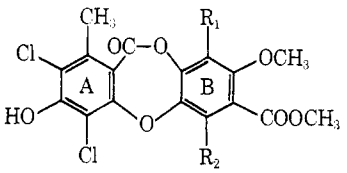
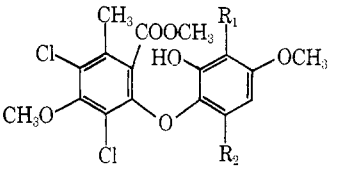
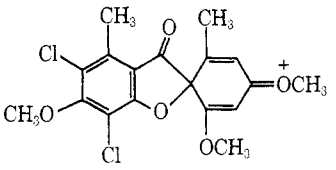


3a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$



4a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$



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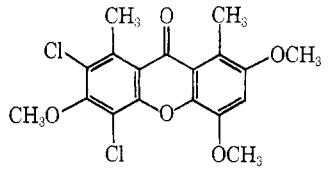

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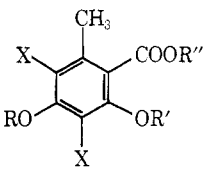


	X	R	R′	R″
7a	H	H	H	H
b	H	H	H	Et
c	H	Bz	Bz	Et
d	H	Bz	Bz	H
e	H	Me	H	Et
f	Cl	Me	H	Et
g	Cl	Me	Bz	Et
h	Cl	Me	Bz	H
i	Cl	Me	H	Me
j	Br	Me	H	Et
k	Br	Me	Bz	Et
l	Br	Me	Bz	H

poor history of oxidative coupling as a practical reaction.[9] While intramolecular coupling should be preferable over intermolecular, we were suspicious of the generality and efficacy of the seven-membered ring closure of the direct synthesis.[8] Accordingly, we sought a construction employing a kinetically more facile five-membered ring in the coupling. The formal structural possibilities for creating a diphenyl ether *via* a five-membered ring reduce to a dibenzofuran product or a grisan (**9**) and the latter presents the opportunity for further solvolytic opening (arrows on **9**) to a hydroxy acid (**10**) corresponding to the depsidone structure (*cf.* **2**). Indeed there is precedent for a facile oxidative coupling to form grisans in the griseofulvin syntheses.[10,11] Thus the sequence **8** → **9** →**10** promised a smooth and general route to depsidones, starting from Friedel–Crafts linking of two polysubstituted phenol synthons to the benzophenone precursors, **8**.

In order to test the central synthetic sequence for depsidone formation we required benzophenones of type **8**, which we found could easily be made by condensation of various substituted acids **7** with dibenzylorcinol in trifluoroacetic anhydride, but only if the phenolic oxygens were protected as ethers (not esters or free phenols); hydrogenolysis of benzyl ethers was used to recreate the phenols for oxidation. The simplicity of this benzophenone synthesis and other considerations leads to coupling with three instead of the minimum two (as used in griseofulvin synthesis[10]) phenolic groups, as in **8**. This is a potential source of difficulty both because of the greater potential for side reactions with more phenolic hydroxyls and because two grisan products may be formed by oxidative entry into either ring A or B. These two paths, possible when both rings A and B in **2** bear ortho OH, lead to the same or reversed substituent patterns in rings A and B of the ultimate hydrolysis products **10**.

The dibenzyl ether (**7d**) of orsellinic acid (**7a**)[12] was thus converted to the simplest benzophenone **8a**, mp 192–196°. On alkaline ferricyanide oxidation, however, **8a** yielded no dienone **9** or diphenyl ether acid **10**; other oxidants (lead oxide or tetraacetate, manganese dioxide, or silver oxide) were also unsuccessful. By contrast the chlorinated benzophenone **8b**, mp 212–215°, which could theoretically yield two different grisans, **9a** and **9b**, afforded only one dienone and this in moderate yield (~20%), the only other product being some unreacted starting material. The dienone was confirmed by the uv spectrum (λ_{max} 320 (ϵ 7000), 285 (30,000), 235 nm (25,000))[13] and the nmr showed only a partially resolved AB quartet of meta aromatic hydrogens at δ 6.4 (as in **8b**) and no vinyl protons. Thus the dienone formed in **9b**, from exclusive oxidative entry into the chlorinated ring.

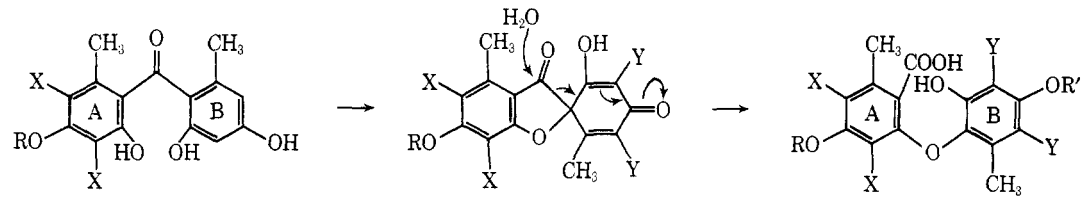
(9) General reviews of oxidative coupling are found in (a) A. I. Scott, *Quart. Rev., Chem. Soc.*, **19**, 1 (1965); (b) "Oxidative Coupling of Phenols," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1967.

(10) J. F. Grove, *Quart. Rev., Chem. Soc.*, **17**, 1 (1963).

(11) Precedent for the solvolytic grisan cleavage can be found in a case reported by E. Kyburz, J. Wursch, and A. Brossi, *Helv. Chim. Acta*, **45**, 813 (1962).

(12) See ref 8; an alternative synthesis is also offered in Vilsmeier carbonylation of orcinol followed by benzylation and permanganate oxidation (see Experimental Section).

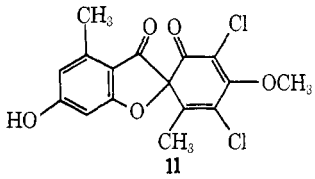
(13) Comparable grisadienone spectra may be found in the references in Grove's review[10] and the griseofulvin synthesis work from the Merck group: B. H. Arison, N. L. Wendler, D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, and N. R. Trenner, *J. Amer. Chem. Soc.*, **85**, 627 (1963); D. Taub, C. H. Kuo, and N. L. Wendler, *J. Org. Chem.*, **28**, 3344 (1963).



	R	X
8a	H	H
b	H	Cl
c	CH_3	Cl
d	CH_3	Br

	R	X	Y
9a	H	Cl	H
b	H	H	Cl
c	CH_3	Cl	H

	R	X	Y	R′
10a	CH_3	Cl	H	H
b	H	H	Cl	CH_3
c	H	H	Br	CH_3
d	CH_3	Br	H	H



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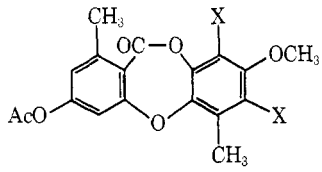
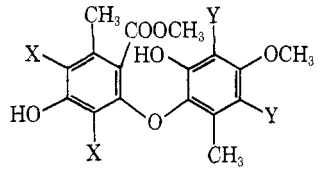
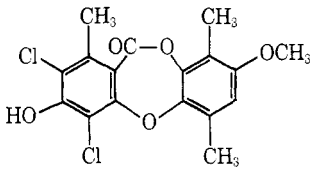


12a, X = Cl
b, X = Br



	X	Y
13a	H	Br
b	Cl	Br
c	Cl	H



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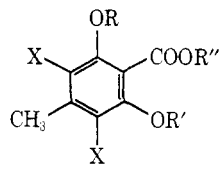
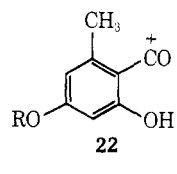


	R	R′	R″	X
15a	H	H	Me	H
b	Bz	Bz	Me	H
c	H	Bz	Me	Br
d	Me	Bz	H	Br



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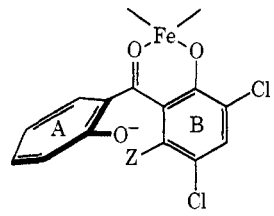

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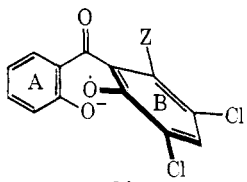

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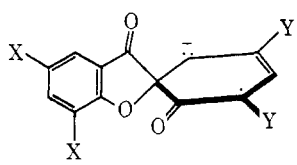
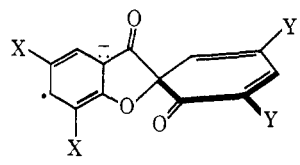


25a, X = H; Y = Hal
b, X = Hal; Y = H



26a, X = H; Y = Hal
b, X = Hal; Y = H

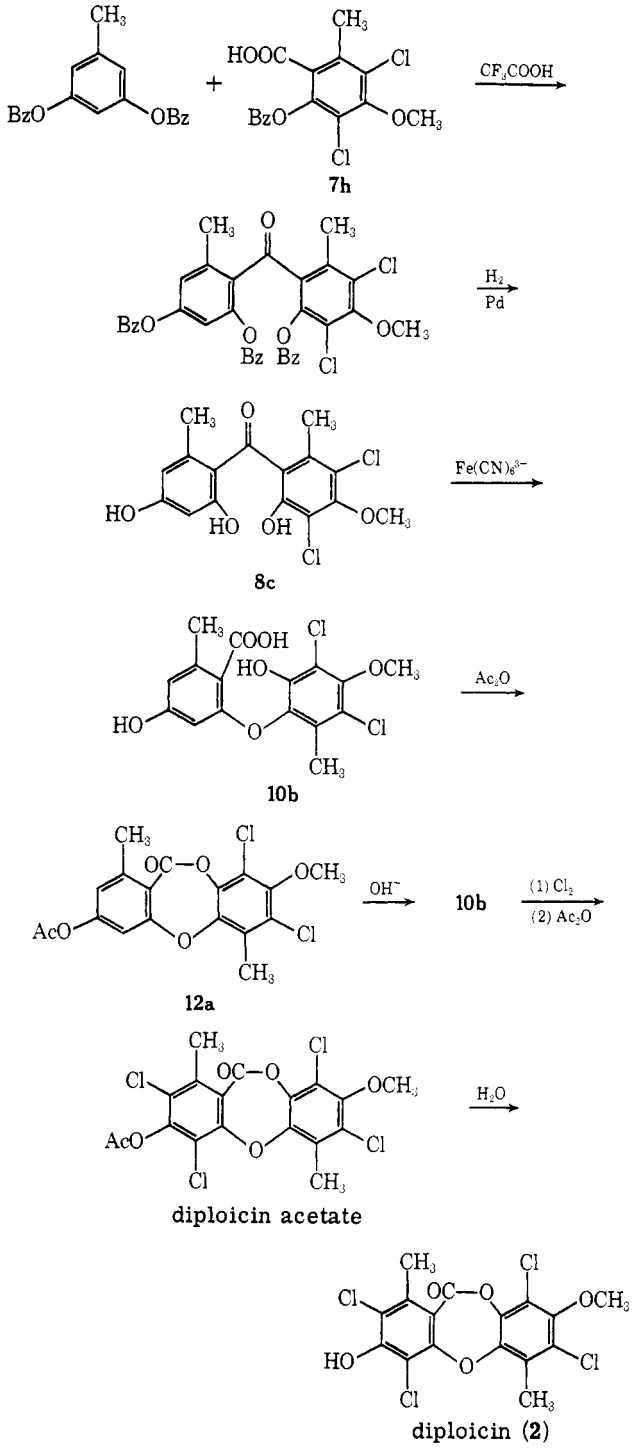
With a view to forcing oxidation into the unchlorinated ring we prepared the methyl ether precursor **8c**, expecting that the oxidative choice would favor the para dienone **9c** rather than the alternative ortho dienone, **11**. The dichloroeverninic acid benzyl ether (**7b**) was prepared by the series of standard transformations from ethyl orsellinate: **7b** → **7e** → **7f** → **7g** → **7h** (mp 166–168°) in 28% overall yield. This was condensed with dibenzylorcinol, hydrogenated to **8c**, and oxidized directly with alkaline ferricyanide. As spectral evidence showed that the oxidation product (**9c** or **11**) had spontaneously hydrolyzed to a diphenyl ether acid (**10a** or **10b**, respectively), the crude product was treated with acetic anhydride to yield a single crystalline depsidone acetate, mp 205–207°, in 30% overall yield without isolations or chromatography. The sequence implies not only an efficient oxidative coupling but one again which takes exclusively one course; the depsidone acetate is shown below to be **12a**.

That the oxidation has proceeded exclusively *via* the unexpected ortho dienone **11** was proved by saponification of the depsidone, chlorination of the other phenolic ring, and reclosure of the lactone with acetic anhydride to give diploicin acetate (27%, mp 233–234°). Mild hydrolysis with aqueous pyridine afforded diploicin, **2**, mp 232–233°. Both products were shown to be identical with natural materials[14] by mixture melting point and spectral comparisons; the synthesis is summarized in Chart I.

The synthesis of diploicin confirms the efficacy of the general synthetic conception as long as chlorines are present on the ultimate ring B to provide the discrimination necessary in the oxidative coupling of the benzophenones **8** (and apparently to enhance the yields). In order to create structures like gangaleoidin, with chlorines in ring A, we decided to test the coupling with bromine atoms in ring B for ultimate hydrogeno-

(14) We thank Professor W. D. Ollis for providing these samples.

Chart I. Total Synthesis of Diploicin



lytic removal. To this end we brominated ethyl everninate (**7b**) to **7j**, benzylated and saponified as before to **7l**, mp 168–170°. Condensation with dibenzylorcinol as before yielded the tribenzyl ether of **8d**, mp 131–133°. Hydrogenolysis of the benzyl ethers proceeded without concomitant loss of bromine and the crude **8d** was subjected to oxidation in alkaline ferricyanide, which yielded only a single acid, **10c**, mp 250–255°, in 54% yield. In both this case and the last, the intermediate **11** (Cl or Br) could not be isolated, as expected for the less stable ortho dienone in contrast to **9**.

The acid **10c** was characterized as the corresponding depsidone acetate **12b**, mp 184–186°. Treatment with methoxide yielded the ester **13a** which proved very difficult to chlorinate (as did the acid **10c**).[15a] Chlorination was effected, however, in two steps with *tert*-butyl hypochlorite (to a monochloro ester) followed by chlorine and silver oxide in aqueous trifluoroacetic acid,[15b] to yield **13b**, followed by hydrogenolysis to **13c**, mp 182–184°. Since Nolan[4] had reported the ring A methyl ether of **13c**[16] (*i.e.*, his structure **4a**) to be unreactive to diazomethane, we treated **13c** with diazomethane to yield a monomethyl ether also (**4b**). Although the two compounds should have been identical, our derivative melted at 132–134°, his at 164°. This indication that their structures were different was unhappily confirmed by formation of the diethyl ether of **13c**, mp 82–83° (lit.[4] 103–104°). The synthesis is summarized in Chart II. Attempts to convert the synthesis to one of the natural depsidones, vicanicin (**14**),[17] by chloromethylation of **13c** were also unsuccessful.

There is only one other structure for gangaleoidin which incorporates a ring B orsellinic acid unit and bears carboxyl para to the lactonic oxygen, *i.e.*, **3b** with ring B methyl and methoxyl reversed. We turned our synthetic approach to derivatives of this structure, as summarized in Chart III. The approach demands γ-orsellinic acid derivatives **15** (rather than **7**) as starting materials for ring B, the carboxyl being transferred to ring A in the oxidative sequence. Accordingly, methyl γ-orsellinate (**15a**, from carboxylation of orcinol[18]) was converted to the dibenzyl ether, **15b**, partially hydrogenolyzed and brominated to **15c**, and this derivative methylated and saponified to **15d**, mp 199–202°. Condensation with dibenzylorcinol to **16** followed by hydrogenolysis to **17** and alkaline ferricyanide oxidation as before yielded an unstable neutral dienone **18** with normal aromatic protons in the nmr at δ 6.86 and uv absorption at 272 nm. This was opened directly with methoxide to the ester **19**, corresponding to **13a** with ring B methyl and methoxyl reversed. The same difficult chlorination[15] yielded **20** and hydrogenolysis **21**. The two series, **13** and **19–21**, were very similar in physical and spectral properties. The monomethyl ether of **21** was similarly formed by diazomethane and melted at 110–111°, compared to Nolan's reported 164° for this derivative.

Further proof that the oxidative coupling followed only one route among the two formally available in the benzophenones (**8**) is found in the mass spectra of the compounds following oxidation in each of the last two routes. In general these spectra show the expected features of clustered halogen isotope signals and successive losses of halogens, methoxyls, and methyls. Previous studies of depsidones[18] have revealed a characteristic cleavage of the A ring fragment **22**. By retaining the lactone carbonyl, this fragment should distinguish between the two reversed aromatic ring orientations possible from the two couplings, as typ-

(15) (a) Had oxidative coupling taken exclusively the other course, to **10a** (Br for Cl), the chlorination would have been very fast on the activated resorcinol ring B. (b) A. Himoe and L. M. Stock, *J. Amer. Chem. Soc.*, **91**, 1452 (1969).

(16) Nolan's formulation, of course, places the methyl on ring B at Y instead of as shown.

(17) S. Neelakanton, T. R. Seshadri, and S. S. Subramanian, *Tetrahedron Lett.*, **9**, 1 (1958).

(18) S. Huneck, C. Djerassi, D. Becher, M. Barber, M. vonArdenne, K. Steinfelder, and R. Tümmler, *Tetrahedron*, **24**, 2707 (1968).

Chart II. Synthesis of Derivatives of Isogangaleoidin (A)

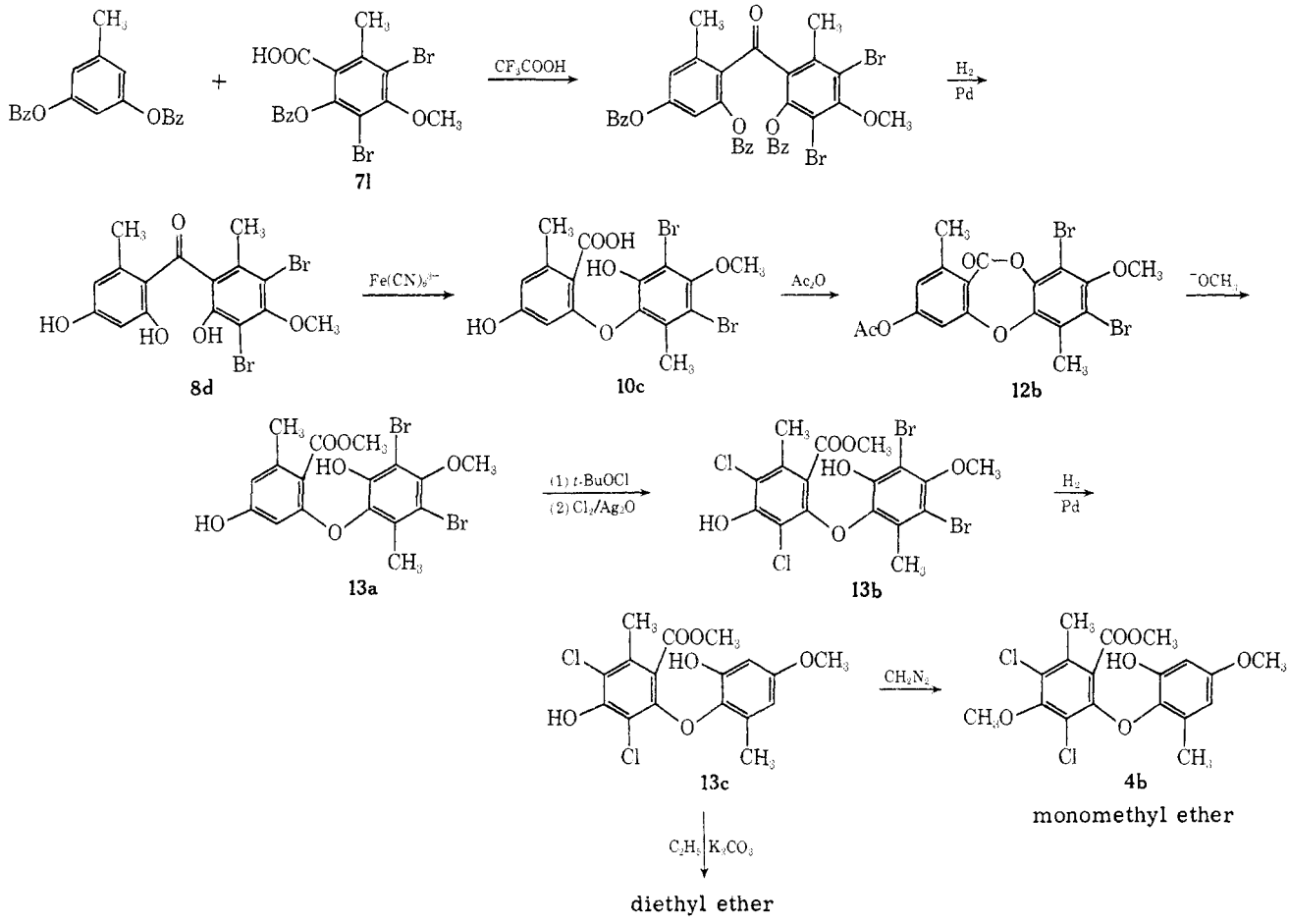
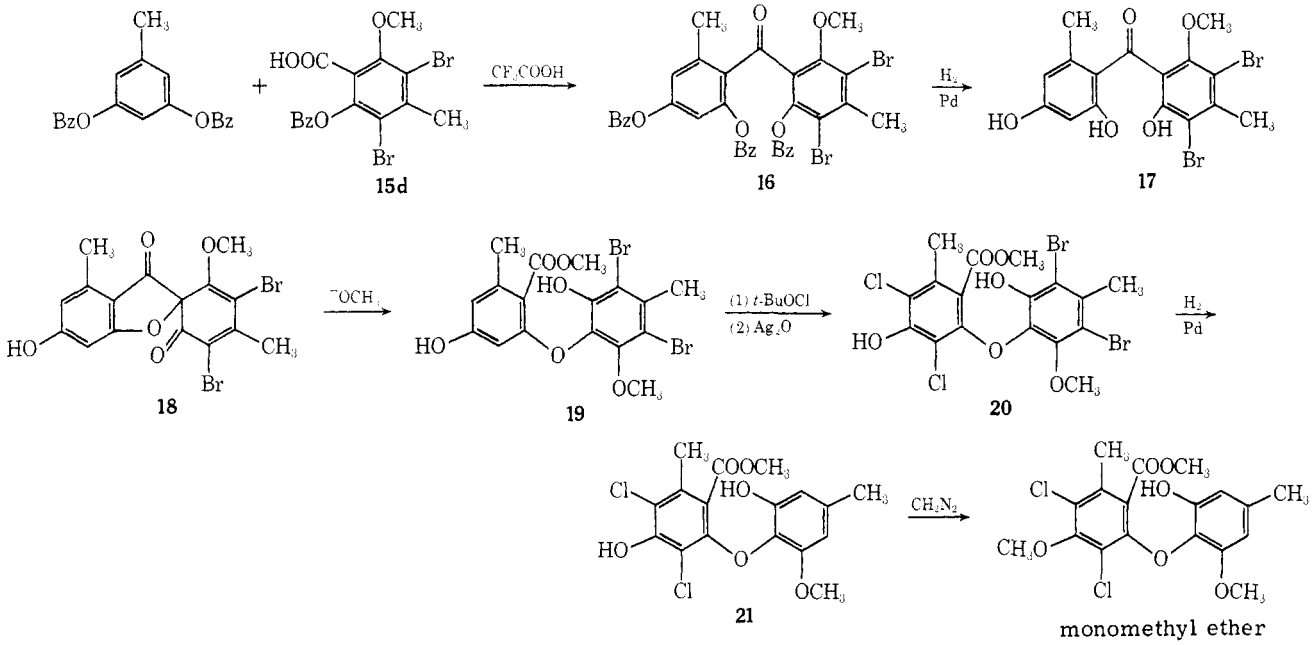


Chart III. Synthesis of Derivatives of Isogangaleoidin (B)



ified by the distinction between **10c** and **10d**. Mass spectra were obtained for nine compounds in the latter two syntheses (Table I). In general the reversed orientation of structure requires a dibromo derivative of **22** (R = CH_3), *m/e* 321, 323, and 325, and in no case was this characteristic triplet observed nor were there important signals at any one of the three masses. The debrominated derivatives similarly showed negligible or no signals at *m/e* 165 for **22** (R = CH_3). However, the spectra all showed the expected fragment for the assigned structures as usually the most prominent absorption in that mass region, *i.e.*, *m/e* 150 and 151 for the acetoxydepsidones (**22**, R = H from initial loss of acetyl), a doublet of *m/e* 185 and 187 for the

Table I. Mass Spectra

Compound	Parent peaks	Fragment 22
12b	484 (10), 486 (20), 488 (10)	151 (20) (193 negligible)
Monochloro-**13a**	508 (50), 510 (90), 512 (90), 514 (40)	185 (90)
13b	542 (20), 544 (50), 546 (50), 548 (20)	219 (50), 221 (25), 223 (10)
13c	386 (50), 388 (40), 390 (10)	219 (10), 221 (20), 223 (10)
4b	400 (100), 402 (75), 404 (40)	233 (40), 235 (30), 237 (5)
iso-**12b**[a]	484 (100), 486 (200), 488 (100)	150 (30), 151 (35) (193 negligible)
19	474 (30), 476 (70), 478 (40)	150 (60), 151 (70)
21	386 (100), 388 (90), 390 (25)	219 (80), 221 (60), 223 (15)
21-methyl ether	400 (60), 402 (80), 404 (20)	233 (25), 235 (15), 237 (5)

[a] Acetoxydepsidone, analogous to **12b**, made from **18** (see Experimental Section).

monochloro derivative of **13a**, triplets of *m/e* 219, 221, and 223 for the dichloro derivatives of **22** (R = H), and *m/e* 233, 235, and 237 for those of **22** (R = CH_3).

In summary, then, while the new synthetic approach is a very viable one for depsidone formation, our gamble on synthesis of a "biogenetically correct" structure for gangaleoidin was unsuccessful and, until further natural samples become available, Nolan's structure must be regarded as correct. If so, the biosynthesis must involve methylation at the "methylene" site of the polyacetyl precursor, between the ultimate resorcinol oxygens of ring B (*cf.* **3a**). Furthermore, the orsellinic acid methyl (at R_2 in **3**) must then be oxidized, presumably to carboxyl, and removed altogether.

The important synthetic discrimination observed here in the oxidative coupling, **8** → **9** or **11**, has interesting implications on the coupling mechanism. It is generally assumed in intermolecular oxidative coupling that the oxidant rapidly forms a fairly high concentration of phenoxy radicals and that these then dimerize.[9] An alternative mechanism (see Barton's summary in the forward to ref 9b) involves attack of phenoxide radical on another phenol or phenoxide anion. This appears to have been disproved in one intermolecular crossing experiment in which no cross products appeared in the ferricyanide oxidation of a mixture of two phenols of different oxidation potential.[19] However, the present intramolecular case appears to provide a *bona fide* example of this alternative. If the radical is first formed on the halogenated phenol (**23**), it may attack the phenoxide anion in two ways (**24** and **25**, only one resonance form of each is shown) but one of these (**25**) will be seen to afford more resonance stabilization to the intermediate radical anion than the other and so should provide the favored route to product, which is indeed that which is observed (**8** → **9** or **11**).

The first step here must be complexation of ferric chloride to the more acidic halogenated phenolic ring B, yielding the generalized chelate **23**; steric crowding (*cf.* ortho group Z) presumably forces the other phenolic ring (A) out of coplanarity as shown. The chelate then affords a basis for more rapid oxidation of the halogenated phenolic ring B. From the conformation **23** the molecule must undergo a rotation prior to coupling; the least molecular motion occurs with a 90° rotation of ring A (toward coplanarity and π orbital overlap with the carbonyl). This rotation must push against substituent Z, causing a synchronous 90° rotation of ring B to the conformer **24**; in this conformation the greatest negative charge density (on the phenolic oxygen of ring A) is in the nearest possible position to the electron-deficient radical diffused in ring B, specifically to the carbon adjacent to the carbonyl. Bonding (coupling) here now creates the radical anion **25a** or **26a** and so the observed product. The corresponding alternative rotation of ring B by 180° to a conformation analogous to **24**, leading to the coupled radical anion **25b** or **26b** (and the unobserved product), requires more extensive molecular motion with less driving force (this path appears to follow a higher energy surface).[20]

The foregoing analysis is essentially a kinetic one and assumes that rotations are faster than a second and intermolecular electron abstraction to a diradical intermediate. The latter course is apparently ruled out since the diradical affords no rationale for discrimination between the two possible coupling products. A different, and thermodynamic, view of the observed specificity arises from an assessment of the relative energies of the four possible radical anions which coupling can create, *i.e.*, **25** and **26**. Structures **25** should be the more stable by retaining a fully aromatic (six-electron) ring and of these **25a** should be preferred by providing halogen atom stabilization of both radical and anion. Alternatively, if one considers addition of one electron to the unfilled orbitals of a benzene ring (actually, benzoyl) or a cyclohexadienone, the latter should be the lower energy, *i.e.*, **25**. Hence the thermodynamic view separately selects **25a** also as the preferred primary coupling product and both views rationalize the observation of clear discrimination between the two possible products.

If this analysis is correct, its application to the design of other oxidative couplings for synthesis could afford considerable improvement in these reactions. Studies are currently underway to test this idea. Financial support of this work from the National Institutes of Health (GM-13929) is gratefully acknowledged. We wish to thank Dr. G. Davies for initial exploratory work on related lines as well as the preparation of orcylaldehyde. Our appreciation is also extended to Professor W. D. Ollis for providing us with procedures for the preparation of orsellinic acid derivatives, for

(19) C. G. Haynes, A. H. Turner, and W. A. Waters, *J. Chem. Soc.*, 2823 (1956).

(20) Four twisted conformers of the intermediate phenoxide–phenoxy radical are possible. The one shown (**24**) has phenoxide anion (ring A) coplanar with carbonyl; the other coplanar phenoxide ring A, with phenoxide oxygen next to carbonyl oxygen, is unproductive for coupling although as easily reached as **24**. This form may lead to other products. The other two show the radical ring B comparably coplanar with carbonyl, with the radical oxygen in either ortho position. One of these corresponds to **23** and represents no molecular motion after initial oxidation, but is unproductive of coupling; the other requires 180° rotation of the radical ring B and couples to **25b** or **26b**, and the wrong product. The ortho group Z is omitted from formulas **25** and **26** but is of course always on the halogenated ring.

samples of diploicin and diploicin acetate, and for discussions and encouragement.

Experimental Section

Melting points are uncorrected and were determined on a Fisher-Johns apparatus. Elemental analyses were performed by Werby Laboratories, Boston. Unless otherwise stated petroleum ether refers to the fraction boiling at 60–110°. Column chromatography was done using Davison Grade 923 silica gel; tlc was done on Brinkmann silica gel HF254. The infrared absorption spectra were determined on either a Perkin-Elmer 137 or a Beckman IR-10 spectrophotometer. The nmr spectra were recorded on an A-60 Varian Associates spectrometer using TMS as internal standard. Ultraviolet spectra were recorded on a Perkin-Elmer 202 spectrophotometer and mass spectra were determined on an AEI MS-12 mass spectrometer (purchased under NSF research instrument grant No. GP-3644).

Ethyl Orsellinate Dibenzyl Ether (7c). Ethyl orsellinate (0.49 g)[21] was dissolved in 20 ml of acetone and 5 g of freshly roasted K_2CO_3 was added followed by 0.90 g of benzyl bromide, and the mixture was stirred 24 hr. After pouring into ether–water the ether layer was washed with aqueous KOH and then water, dried, and evaporated to 1.07 g of crystalline solid. The product crystallized from hexane as 0.75 g (80%) of fine white needles: mp 83–84°; ir ($CHCl_3$) no OH, 1730 cm^{-1}.

Orsellinic Acid Dibenzyl Ether (7d). When aqueous KOH (1.2 g in 4 ml of H_2O) was added to a solution of the ester **7c** (0.40 g) in 4 ml of ethanol an oily layer separated. On refluxing 5 hr the solution became clear; 2 ml of water was added and refluxing continued 15 hr more. The cooled solution was diluted to 50 ml with water and washed with ether. Acidification with concentrated HCl to pH 2, extraction of the precipitate with $CHCl_3$, and drying and evaporation of the $CHCl_3$ layer yielded a colorless gum which crystallized from hexane as 0.33 g of white needles (90%): mp 100–101°; ir ($CHCl_3$) 3500–3000 and 1736 cm^{-1}.

Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.91; H, 5.82.

***O,O*-Dibenzylorcinol.** To a solution of 12.4 g of anhydrous orcinol and 32 ml of benzyl bromide in 200 ml of acetone was added 42 g of freshly roasted K_2CO_3. The mixture was refluxed under N_2 24 hr and then allowed to cool. The inorganic salts were removed by filtration and rinsed with acetone. The filtrate and rinse were combined, concentrated, and distilled. The material boiling at 182–197° (0.01 mm) was collected to give 23.4 g (77%) of a pale yellow oil which slowly crystallized (mp ~44–47°) after addition of a seed crystal. This material was of satisfactory purity for further use but deteriorated on prolonged standing. Recrystallization from methanol afforded analytically pure material: mp 48–50°; nmr (CCl_4) δ 2.20 (s, 3), 4.90 (s, 4), and 7.33 ppm (m, 13).

Anal. Calcd for $C_{21}H_{20}O_4$: C, 82.85; H, 6.64. Found: C, 83.07; H, 6.62.

Orcylaldehyde. To a solution of phosphorus oxychloride (0.74 ml) in dimethylformamide (3 ml), after 0.5 hr, was added 1 g of orcinol portionwise with stirring. A further 2 ml of dimethylformamide was added to dissolve gums and the reaction left for 20 hr. On addition of water fine needles separated which were recrystallized from water to give 0.61 g of orcylaldehyde (52%): mp 180–181° (lit.[22] 180°).

Orcylaldehyde Dibenzyl Ether. To a stirred solution of 0.42 g of orcylaldehyde in 20 ml of acetone was added 5 g of freshly roasted K_2CO_3 and 1.1 g of benzyl bromide. Stirring was continued 24 hr, then the solution was poured into water and extracted with ether, and the ether layer washed with aqueous NaOH and water and dried. Removal of solvent gave 1 g of pale yellow oil which was chromatographed in 16 g of SiO_2. Benzyl bromide was removed with petroleum ether and elution with benzene then yielded 0.74 g of white crystalline solid (80%) which was recrystallized from petroleum ether: mp 68–69°; ir ($CHCl_3$) 1670 cm^{-1} (no OH, ~ 3 μ).

Orsellinic Acid Dibenzyl Ether (7d). A solution of 0.25 g of orcylaldehyde dibenzyl ether in 2.5 ml of acetone was treated with aqueous $KMnO_4$ (0.15 g in 1.5 ml of H_2O) and stirred for 1 hr. This mixture was diluted with water and acidified with dilute H_2SO_4, and the MnO_2 was removed with $NaHSO_3$. This was extracted with ether and the ether extracts in turn extracted with aqueous NaOH. Acidification of the basic aqueous solution with concentrated HCl to pH 2 precipitated a gum which was extracted with $CHCl_3$. Drying and evaporation yielded 0.10 g of pale yellow gum, which crystallized from petroleum ether yielding 30 mg, mp 100–101° (mixture melting point with authentic sample 100–101°). The ether layer afforded 0.14 g of unreacted aldehyde so that the yield of acid is 26% after subtraction of unreacted aldehyde.

Benzophenone (8a). Orcinol dibenzyl ether (2.00 g) and orsellinic acid dibenzyl ether (0.50 g) were dissolved in CH_2Cl_2 and 1 ml of trifluoroacetic anhydride was added. After 5 min the solution was evaporated and the gum dissolved in 1:1 benzene–petroleum ether for chromatography on 30 g of SiO_2. Elution with benzene–petroleum ether (400 ml) afforded 1.48 g of recovered dibenzyl orcinol and further elution with $CHCl_3$ (600 ml) yielded 0.98 g of gum which crystallized in hexane. This was recrystallized from hexane to a colorless microcrystalline solid, mp 116–120° (75%), as the tetrabenzyl ether.

The tetrabenzyl ether (0.64 g) was hydrogenated in ethyl acetate over 10% palladium–carbon (100 mg) until hydrogen uptake ceased. Filtration and evaporation yielded 0.24 g which was crystallized from water: mp 195–198° (90%); uv max (C_2H_5OH) 298 (ϵ 13,000) and 333 nm (sh, ϵ 7000); ir (KBr) 3500–3000 (broad, OH) and 1625 cm^{-1} (C=O); nmr (CD_3COCD_3) δ 2.00 (s, 6, CH_3), 6.30 (s, 4, Ar*H*), and 4.0–7.0 (broad, OH).

Anal. Calcd for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.51; H, 5.06.

3,5-Dichloroorsellinic Acid Dibenzyl Ether. Direct chlorination of orsellinic acid, its dibenzyl ether, or their esters proved difficult or intractable and so the longer procedure *via* the monobenzyl ether was used. A solution of 4-*O*-benzyl-3,5-dichloroorsellinic acid[21] (1.10 g) in 30 ml of ether was esterified with ethereal diazomethane, the ether evaporated, and the residue crystallized from hexane to 1.11 g of ester, mp 112–113°. The ester was dissolved in 30 ml of acetone and 8 g of freshly roasted K_2CO_3 and 0.65 g of benzyl bromide were added. The slurry was stirred overnight at 40° and poured into ether–water. The ether layer was washed twice with aqueous KOH and with water, dried, and evaporated to a gum which was crystallized from petroleum ether as fine white needles (1.10 g): mp 77–78°. This ester was then saponified by the procedure above for ethyl orsellinate dibenzyl ether, yielding 0.85 g of acid after crystallization from ether–hexane as fine needles; mp 185–187° (overall yield 62%).

Anal. Calcd for $C_{29}H_{18}O_4Cl_2$: C, 63.35; H, 6.75. Found: C, 63.18; H, 6.66.

Benzophenone (8b). A solution of 50 mg of 3,5-dichloroorsellinic acid dibenzyl ether, 230 mg of dibenzyl orcinol, and 0.5 ml of trifluoroacetic anhydride in 6 ml of $CHCl_3$ with a few drops of trifluoroacetic acid was refluxed gently for 3 hr and then evaporated. The gum was dissolved in 20 ml of ethanol and hydrogenated over 10% palladium–carbon (80 mg) for 3 hr. Filtration and evaporation yielded a gum which crystallized on trituration with water. The crystals were washed well with water to remove excess orcinol and recrystallized from aqueous acetone to 21 mg of yellowish needles: mp 213–216° (51%); uv_{max} (C_2H_5OH) 298 (ϵ 10,000) and 356 nm (15,000); nmr (CD_3COCD_3) δ 2.00 (s, 3, CH_3), 2.25 (s, 3, CH_3), 6.3 (rough d, 2, $J \sim 3$ Hz, ArH), and 1.5–5.0 (broad, OH).

Anal. Calcd for $C_{15}H_{12}O_5Cl_2$: C, 52.46; H, 3.53. Found: C, 52.38; H, 3.41.

Oxidation of Tetrahydroxybenzophenones (8a and 8b). When a solution of 40 mg of dichlorobenzophenone (**8b**) in aqueous K_2CO_3 solution (0.3 g in 10 ml of H_2O) was treated with potassium ferricyanide (80 mg in 5 ml of H_2O) an immediate transient brown-red color appeared, followed by a return to bright yellow solution. After 0.5 hr the solution was acidified dropwise with concentrated HCl and the precipitate (20 mg) filtered. The solid showed one major spot on tlc and little starting material. Charcoaling in acetone–ether, filtration, concentration, and addition of chloroform slowly precipitated a solid (8 mg) which was pure by tlc and apparently crystalline (with no satisfactory melting point): uv (C_2H_5OH) 320 (sh, ϵ ~7000), 285 (30,000), 235 nm (25,000); nmr (CD_3COCD_3) δ 1.9 (s, 3, CH_3), 2.4 (s, 3, CH_3), 6.4 (rough d, 2, ArH), and broad OH.

Similar oxidation of the nonchlorinated tetrahydroxybenzophenone (**8a**) under conditions of varying time, including rapid quenching, invariably gave mixtures containing some starting material (<15%) and (by tlc) a number of other products, none of which could be separated in a pure form. Treatment of the mix-

(21) P. Veal, Ph.D. Thesis, Bristol, 1960. We thank Professor W. D. Ollis for making available preparations from Dr. Veal's thesis; see ref 8.

(22) L. Gattermann and M. Köbner, *Ber.*, **32**, 279 (1899).

ture with zinc and acetic acid (15 min at room temperature) to regenerate the benzophenone[23] afforded no new starting material.

3,5-Dichloroeverninic Acid Ethyl Ester (7f). To a solution of 5 g of everninic acid ethyl ester (**7e**)[21] and 4 g of anhydrous sodium acetate in 75 ml of glacial acetic acid was added a solution of 4.3 g of chlorine in 100 ml of glacial acetic acid. After 10 min the solution was poured into 2.5 l. of water and the yellow precipitate coagulated by cooling in ice. The solid was filtered and crystallized from aqueous methanol yielding 3 g (45%): mp 57–59°; ir ($CHCl_3$) 3000–3600 (broad OH) and 1665 cm^{-1} (C=O); nmr (CCl_4) δ 1.46 (t, 3, CH_2CH_3, J = 7.5 Hz), 2.58 (s, 3, CH_3), 3.89 (s, 3, OCH_3), 4.47 (q, 2, OCH_2CH_3, J = 7.5 Hz), and 11.45 (s, 1, ArOH).

3,5-Dichloroeverninic Acid Benzyl Ether (7h). The dichloro ester **7f** (6 g) was benzylated with 5 g of benzyl bromide and freshly roasted K_2CO_3 in 130 ml of acetone for 36 hr and worked up as before to 9.9 g of gum; ir ($CHCl_3$) no OH, C=O at 1730 cm^{-1}. The gum was dissolved in 100 ml of ethanol and refluxed with aqueous KOH (32 g in 100 ml of H_2O) for 2.5 hr. Then 100 ml of H_2O was added and refluxing continued for 15 hr. After cooling, addition of 500 ml of H_2O, and washing with ether the aqueous layer was acidified with concentrated HCl to pH 2 and extracted with $CHCl_3$. Drying and evaporation of the $CHCl_3$ layer yield a crystalline mass which was recrystallized from aqueous ethanol yielding 6 g of white crystals (82%): mp 166–168°; nmr (CD_3COCD_3) δ 1.92 (s, 3, CH_3), 3.44 (s, 3, OCH_3), 4.64 (s, 2, OCH_2Ar), and 6.97 (m, 5, ArH).

Acetoxydepsidone (12a). The benzyl ether (**7h**) of 3,5-dichloroeverninic acid (0.50 g) and excess dibenzylorcinol (1.20 g) were dissolved in 30 ml of $CHCl_3$ containing 3 ml of trifluoroacetic anhydride and 0.5 ml of trifluoroacetic acid and refluxed 6 hr under a drying tube. Evaporation yielded a gum which was dissolved in ether and washed with aqueous K_2CO_3. The dried ether layer was evaporated and the residue taken up in 80 ml of ethanol and hydrogenolyzed over 250 mg 10% palladium–carbon, with a few drops of trifluoroacetic acid added, until uptake eased (3.4 hr). Filtration and evaporation yielded a gum (**8c**) which was washed well with water to remove excess orcinol. The 0.57 g of residue was dissolved in aqueous K_2CO_3 (6 g in 200 ml of H_2O) and treated with potassium ferricyanide solution (1.7 g in 100 ml of H_2O). A transient red color soon darkened to brown and after 5 min the solution was acidified with concentrated HCl to pH 2 and filtered. The dark brown solid was oven dried and heated with 10 ml of acetic anhydride on a steam bath for 1 hr. The solution was poured slowly into aqueous pyridine and left for 0.5 hr. The solution was extracted with $CHCl_3$ and the $CHCl_3$ layer was washed well with aqueous K_2CO_3 and dilute HCl. Drying and evaporation left 0.61 g of dark gum which was chromatographed on 30 g of SiO_2 in benzene. Benzene elution gave 0.30 g of crystalline solid which was crystallized from methanol yielding 0.18 g (30% overall) of fine colorless needles: mp 205–207°; ir ($CHCl_3$) 1745 and 1750 cm^{-1}; nmr ($CDCl_3$) δ 2.28 (s, 3, $COCH_3$), 2.49 (s, 3, CH_3), 2.51 (s, 3, CH_3), 3.85 (s, 3, OCH_3), and 6.92 ($\sim$ d, 2, $J \sim 3$ Hz, ArH).

Anal. Calcd for $C_{18}H_{14}O_6Cl_2$: C, 54.48; H, 3.56. Found: C, 54.36; H, 3.41.

Diploicin (2). The acetoxydepsidone (50 mg) in 25 ml of ethanol was saponified with aqueous NaOH (100 mg in 2 ml of H_2O) for 0.5 hr at room temperature and then acidified by dropwise addition of concentrated HCl. The solvent was evaporated and the residue was taken up in $CHCl_3$–H_2O; the $CHCl_3$ layer was separated, dried, and evaporated. The crude crystalline acid (ir (KBr) 1700 cm^{-1}) was dissolved in $CHCl_3$ and treated with excess chlorine in CCl_4 until pale yellow-green color persisted for 10 min. The solvent was evaporated and the semicrystalline residue heated with 4 ml of acetic anhydride on the steam bath for 20 min. The brown solution was pipetted into aqueous pyridine and then extracted with $CHCl_3$ after 20 min. The $CHCl_3$ layer was washed well with dilute HCl and water, dried, and evaporated to 55 mg, which was chromatographed on SiO_2 (tlc). The major uv active band was removed with $CHCl_3$ and evaporated to a crystalline material which was recrystallized from methanol to give 16 mg of white needles (27%), mp 233–234°, mixture melting point with authentic diploicin acetate,[14] 233–234°. The ir and nmr spectra were identical with those of the authentic sample: ir (CH_2Cl_2) 1767 and 1789 cm^{-1}; nmr ($CDCl_3$) δ 2.42 (s, 3, $COCH_3$), 2.55 (s, 3, CH_3), 2.63 (s, 3, CH_3), and 3.88 (s, 3, OCH_3).

When the diploicin acetate was warmed in pyridine containing some water and then this solvent evaporated, the residue was recrystallized from benzene yielding diploicin: mp 230° (mixture melting point with authentic diploicin,[14] 229–230°).

Ethyl 3,5-Dibromoeverninate (7j). To a stirred solution of 12.15 g of ethyl everninate (**7e**)[21] in 450 ml of absolute ethanol was added dropwise over 1 hr approximately 200 ml of a solution of 20 g of Br_2 and 30 g of KBr in 200 ml of H_2O. Addition of the bromine solution was continued until a yellow color persisted for several minutes. The clear yellow reaction solution was then poured into 2.5 l. of H_2O and the resulting precipitate collected by filtration. After drying *in vacuo* the solid was taken up in 150 ml of petroleum ether and filtered. The filtrate was reduced in volume to 100 ml and then allowed to stand overnight at −15° whereupon crystals separated. Filtration afforded 17.9 g (84%) of white needles: mp 49–51°. Recrystallization from hexane afforded an analytical sample: mp 49.5–51.5°; ir (CCl_4) 3500–2800 and 1600 cm^{-1}; nmr (CCl_4) δ 1.42 (t, 3, J = 7 Hz, OCH_2CH_3), 4.52 (q, 2, J = 7 Hz, OCH_2CH_3), 2.65 (s, 3, CH_3), 3.90 (s, 3, OCH_3), and 11.02 ppm (s, 1, OH).

Anal. Calcd for $C_{11}H_{12}O_4Br_2$: C, 35.89; H, 3.28. Found: C, 35.56; H, 3.09.

Ethyl *O*-Benzyl-3,5-dibromoeverninate (7k). To a solution of 16.50 g of ethyl dibromoeverninate (**7j**) in 200 ml of acetone was added 11 g of freshly roasted K_2CO_3 and 5.5 ml of benzyl bromide. The reaction was refluxed with stirring for 21 hr and then allowed to cool. Dilution with 1 l. of H_2O caused the separation of an oil which crystallized upon the addition of a few seed crystals. The solid was collected by filtration and dried *in vacuo* to give 20.3 g of off-white solid which was then dissolved in 90 ml of hexane and stored at −15° overnight. Filtration gave 17.91 g (87%) of the desired benzyl ether (**7k**): mp 61–64°. Several recrystallizations from methanol afforded analytically pure material: mp 65–66°; ir (CCl_4) 1730 cm^{-1}; nmr (CCl_4) δ 1.20 (t, 3, J = 7 Hz, OCH_2CH_3), 4.22 (q, 2, J = 7 Hz, OCH_2CH_3), 2.32 (s, 3, CH_3), 3.85 (s, 3, OCH_3), 5.02 (s, 2, OCH_2Ar), and 7.34 ppm (m, 5).

Anal. Calcd for $C_{18}H_{18}O_4Br_2$: C, 47.19; H, 3.94. Found: C, 46.94; H, 4.07.

***O*-Benzyl-3,5-dibromoeverninic Acid (7l).** To 23 g of **7k** was added 250 ml of Claisen alkali.[24] The heterogeneous reaction mixture was refluxed under N_2 with stirring for 15 hr and then allowed to cool. The resulting clear reaction solution was diluted with 1 l. of H_2O and acidified with 6 *N* HCl. The resulting suspension was stirred a few minutes and the solid was then collected by filtration to give, after air drying, 20.6 g (95.5%). An analytically pure sample (mp 168–70°) was secured upon recrystallization from benzene–petroleum ether: ir (KBr) 3300–2400 and 1705 cm^{-1}; nmr ($CDCl_3$) δ 2.46 (s, 3), 3.98 (s, 3), 5.17 (s, 2, OCH_2Ar), and 7.5 ppm (m, 5).

Anal. Calcd for $C_{16}H_{14}O_4Br_2$: C, 44.69; H, 3.94. Found: C, 46.94; H, 4.07.

Preparation of the Tribenzyl Ether of Benzophenone 8d. In 1 l. of ethanol free chloroform were dissolved 20.8 g of *O*-benzyl-3,5-dibromoeverninic acid (**7l**), 33.6 g of *O*,*O*-dibenzylorcinol, 90 ml of trifluoroacetic anhydride, and 15 ml of trifluoroacetic acid. The resulting solution was refluxed under N_2 for 5 hr, then evaporated to give 67 g of an oil which was dissolved in $CHCl_3$, and shaken with dilute sodium hydroxide (emulsion broken with ether). The $CHCl_3$ layer was dried and concentrated to give 48.1 g of a viscous oil which was dissolved in 500 ml of hot petroleum ether. After filtration the solution was allowed to cool to room temperature very slowly with stirring. Seed crystals were added occasionally until crystallization commenced. Filtration gave 13.6 g of solid which proved to be a mixture of desired benzophenone (**8d**) and the demethylated[25] analog. This mixture was methylated with methyl iodide and potassium carbonate in refluxing acetone to give 13.2 g of material which was pure by tlc.

The mother liquors from the recrystallization were chromatographed on 1 kg of SiO_2. Unreacted dibenzylorcinol was eluted with benzene. Elution with benzene–ether (10:1) gave a mixture containing some demethylated benzophenone which was also methylated as above. Several recrystallizations from petroleum ether gave an additional 2.9 g of pure benzophenone **8d** for a total yield of 47%. Recrystallization from petroleum ether gave material melting at 131–133°: ir ($CHCl_3$) 1650 and 1590 cm^{-1}; nmr ($CDCl_3$) δ 2.13 (s, 3, CH_3), 2.33 (s, 3, CH_3), 3.83 (s, 3, OCH_3), 4.56 (s, 2, OCH_2Ar), 4.72 (s, 2, OCH_2Ar), 5.05 (s, 2, OCH_2Ar), 6.4 (q, 2, J = 2 Hz, chemically nonequivalent protons on benzophenone nucleus), and 7.3 ppm (m, 15).

(23) D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, **19**, 1 (1963).

(24) L. Claisen, *Ann.*, **418**, 96 (1919).

(25) When the reaction was run on a smaller scale no demethylation was observed.

Anal. Calcd for $C_{37}H_{32}O_5Br_2$: C, 62.02; H, 4.50. Found: C, 62.21; H, 4.45.

Conversion of Benzophenone 8d into Acid 10c. A solution of 11.9 g of benzophenone tribenzyl ether in 325 ml of ethyl acetate and 525 ml of ethanol was hydrogenated at room temperature and atmospheric pressure over 2.2 g of 10% palladium–charcoal until the theoretical uptake of hydrogen had been reached. The catalyst was removed by filtration and the filtrate evaporated to give 8.7 g of crude **8d** which was oxidized directly. To the crude **8d** was added 50 ml of CH_2Cl_2 and a solution of 39 g of K_2CO_3 in 1.3 l. of water. When all had dissolved the two-phase mixture was combined with a solution of 19.5 g of potassium ferricyanide in 1.2 l. of water. The resulting mixture was stirred 6 min; 500 ml of $CHCl_3$ was then added and the mixture was acidified with 10% HCl while being stirred vigorously. The layers separated (some of the desired product remains suspended in the $CHCl_3$ layer) and the aqueous layer extracted (3 × 500 ml) with $CHCl_3$. All the $CHCl_3$ layers were combined, dried by filtration through filter paper, and evaporated to give 6.9 g of solid which was recrystallized from 600 ml of benzene to give 3.33 g of acid **10c**: mp 250–255°. Concentration of the mother liquors afforded an additional 0.49 g: mp 245–251° (54% total yield). This compound was best characterized by conversion to the depsidone acetate **12b**.

Depsidone Acetate (12b). To 3.82 g of acid **10c** was added 125 ml of acetic anhydride and the resulting mixture was heated on a steam bath for 1 hr with occasional swirling. Acetic anhydride was removed *in vacuo* to give 4.14 g (**12b**) which was usually converted to dibromo ester **13a** without further purification.

In one run analytically pure material, mp 184–186°, was obtained by preparative tlc (benzene) and sublimation (160° (0.02 mm)): ir ($CHCl_3$) 1750 cm^{-1}; nmr ($CDCl_3$) δ 2.33 (s, 3, CH_3), 2.57 (s, 6, CH_3), 3.90 (s, 3, OCH_3), and 7.05 ppm (s, 2, ArH); mass spectrum, see Table I.

Anal. Calcd for $C_{18}H_{14}O_6Br_2$: C, 44.47; H, 2.90. Found: C, 44.37; H, 2.78.

Dibromo Ester 13a. The 4.14 g of depsidone acetate (*vide supra*) was dissolved in 120 ml of anhydrous methanol containing 12 g of sodium methoxide. After refluxing under N_2 for 0.75 hr the solution was poured into 1 l. of H_2O (giving a clear solution) and quickly acidified with 6 *N* HCl. The precipitate was stirred until granular, collected by filtration, and allowed to dry, affording 3.97 g essentially pure by tlc (0.75% ethanol in $CHCl_3$) except for a small spot at the origin.

Dichlorodibromo Ester 13b. To a solution of 3.87 g (8.13 mmol) of dibromo ester **13a** in 500 ml of acetic acid was added 8.3 mmol (1.00 ml) of *tert*-butyl hypochlorite (Frinton). After stirring in the dark for 0.5 hr the clear solution was poured into 1.5 l. of water. The solid which precipitated was collected by filtration and dried to give 3.88 g of a monochloro derivative of **13a**, which recrystallized from benzene–petroleum ether: mp 187–188°; ir ($CHCl_3$) 1700 and 1735 cm^{-1}; nmr ($CDCl_3$) δ 2.33 (s, 3, CH_3), 2.42 (s, 3, CH_3), 3.89 (s, 3, OCH_3), 4.01 (s, 3, OCH_3), and 6.20 (s, 1, ArH); mass spectrum, see Table I.

To a mixture of 120 ml of trifluoroacetic acid and 60 ml of water was added 1.30 g of Ag_2O.[15b] The mixture was stirred until all the Ag_2O had dissolved and then a solution of 5.6 mmol (0.40 g) of Cl_2 in 65 ml of water was added. After stirring for a short period the suspension was centrifuged and the supernatant liquid decanted into a solution of 2.08 g of the monochloro ester (above) in 80 ml of trifluoroacetic acid. The reaction mixture was stirred at room temperature for 30 hr and then stored at 5° for an additional day. The reaction mixture was poured into water and extracted with chloroform (5 × 200 ml). The $CHCl_3$ extracts were combined, washed with brine, dried, and evaporated. The residue was recrystallized from 125 ml of CCl_4 to give a first crop of 0.55 g (mp 199–202°). Concentration of the mother liquor gave a second crop of 0.45 g (mp 189–198°). The mother liquor was shown by tlc to be primarily a mixture of the mono- and dichloro compounds. This mixture was resubmitted to chlorination conditions to afford an additional 0.37 g (homogeneous by tlc and nmr). The overall yield for the four-step conversion (without purification of intermediates) of **10c** and **13b** is 63%. Recrystallization from benzene and sublimation (180° (0.05 mm)) gave pure **13b**: mp 209–210°; ir (KBr) 3340 and 1680 cm^{-1}; nmr 2.35 (s, 3, CH_3), 3.76 (s, 3, OCH_3), and 3.86 ppm (s, 3, OCH_3); mass spectrum, see Table I.

Dichloro Ester 13c. A stirred solution of 1.00 g of dibromodichloro ester **13b** and 0.4 g of sodium acetate in 200 ml of methanol was hydrogenated over 300 mg of 10% palladium–carbon. The reaction took up 110 ml of H_2 over the course of 1.5 hr (2 equiv of H_2, ~90 ml). The catalyst was removed by filtration and the filtrate was poured into water. The clear solution was thrice extracted with $CHCl_3$; the $CHCl_3$ extracts were combined, washed with brine, dried, and evaporated. The residue was recrystallized from benzene to give 0.36 g: mp 175–178°. Concentration of the mother liquors gave an additional 76 mg. The dichloro ester (**13c**) sublimes readily at 160° (0.05 mm) to give analytically pure material: mp 182–184°; ir (CH_2Cl_2) 3500, 1730, and 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.96 (s, 3, CH_3), 2.20 (s, 3, CH_3), 3.60 (s, 3, OCH_3), 3.65 (s, 3, OCH_3), 6.17 (d, 1, J = 3 Hz, ArH), and 6.32 ppm (d, 1, J = 3 Hz, ArH); mass spectrum, see Table I.

Anal. Calcd for $C_{17}H_{16}O_6Cl_2$: C, 52.72; H, 4.17. Found: C, 52.65; H, 4.47.

Diethyl Ether of 13c. To a solution of 16 mg of **13c** in 20 ml of acetone was added 1 ml of ethyl iodide and 0.8 g of K_2CO_3. The mixture was refluxed with protection from moisture for 2.5 hr and the insoluble material removed by filtration. The insoluble solid was rinsed with acetone. The rinse and filtrate were combined and evaporated; lixiviation with ether gave 16 mg of ether-soluble material which was eventually induced to crystallize from aqueous methanol. Recrystallization from a small amount of methanol at −15° gave 6 mg of feathery needles: mp 82–83°; ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ 0.97 (t, 3, J = 7 Hz, OCH_2CH_3), 1.48 (t, 3, J = 7 Hz, OCH_2CH_3), 2.19 (s, 3, CH_3), 2.24 (s, 3, CH_3), 3.34 (s, 3, OCH_3), 3.71 (s, 3, OCH_3), 4.10 (q, J = 7 Hz, OCH_2CH_3), and 6.18 ppm (q, 2, J = 2 Hz, ArH); mass spectrum m/e 442 (M^+). The gangaleodin-derived diethyl ether of the same molecular formula is reported[4] to have mp 103–104° (from methanol).

Monomethyl Ether of 13c (4b). To an ice-cold ethereal solution of 35 mg of **13c** was added excess ethereal diazomethane. The reaction was allowed to warm to room temperature. After 1 hr the ether was evaporated on a steam bath. The residue was recrystallized twice from petroleum ether to give 16 mg of monoethyl ether **4b**, mp 126–129°, which was sublimed (115° (0.03 mm)) to give material with mp 132–134°; ir (CH_2Cl_2) 3500, 1730, and 1700 cm^{-1}; nmr (CCl_4) δ 2.02 (s, 3, CH_3), 2.28 (s, 3, CH_3), 3.64 (s, 3, OCH_3), 3.70 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 6.14 (d, 1, J = 3 Hz, ArH), and 6.28 ppm (d, 1, J = 3 Hz, ArH); mass spectrum, see Table I. The gangaleoidin-derived monoethyl ether of the same molecular formula[4] is reported to have mp 164° (from ligroin).

Methyl *O*,*O*-Dibenzyl-γ-orsellinate (15b). To a solution of 9.1 g (0.05 mmol) of methyl γ-orsellinate[26] in 300 ml of dimethylformamide was added 6.0 g of sodium methoxide. The mixture was stirred for a few minutes and then 14.5 ml of benzyl bromide was added. After 2 hr tlc showed that the reaction had not gone to completion. An additional 5.9 g of sodium methoxide and 14.5 ml of benzyl bromide were added. After stirring 1 hr more the solvent was evaporated. Water was added to the residue and the mixture was twice extracted with $CHCl_3$. The $CHCl_3$ extracts were combined, dried, and evaporated to give 23.5 g of red solid which was recrystallized from 800 ml of hot methanol to give 12.3 g of **15b** as fine white needles: mp 141–143°. A second crop of 1.0 g (mp 135–140°) was obtained upon concentrating the mother liquors (combined yield of 73%). Recrystallization from methanol gave analytically pure material: mp 146–148°; ir (CCl_4) 1730 cm^{-1}; nmr ($CDCl_3$) δ 2.25 (s, 3, CH_3), 3.87 (s, 3, OCH_3), 5.08 (s, 4, CH_2O), 6.43 (s, 2 equivalent protons on γ-orsellinic ring), and 7.35 ppm (broad s, 10, aromatic protons of benzyl groups).

Anal. Calcd for $C_{23}H_{22}O_4$: C, 76.22; H, 6.12. Found: C, 76.51; H, 6.12.

Methyl *O*-Benzyl-3,5-dibromo-γ-orsellinate (15c). To a stirred mixture of 800 ml of methanol and 200 ml of dioxane was added 13.2 g of methyl *O*,*O*-dibenzyl-γ-orsellinate (**15b**). When the ester had almost completely dissolved, 2.7 g of sodium methoxide and 0.5 g of 10% palladium–charcoal were added. The resulting mixture was hydrogenated until 1 equiv of hydrogen had been consumed and the catalyst was then quickly filtered off. The rate of hydrogen uptake was very high and gave no indication of abating after the uptake of 1 equiv. The filtrate was acidified with dilute HCl and evaporated. The residue was lixiviated with hot petroleum ether and the resulting solution was concentrated to give 10.6 g of crude solid: nmr ($CDCl_3$) δ 2.29 (s, 3, CH_3), 3.95 (s, 3, CH_3), 5.12 (s, 2, OCH_2), 6.38 (s, 1, ArH), 6.53 (s, 1, ArH), and 7.5 ppm (m, 5, aromatic protons of benzyl group). The ester so ob-

(26) Prepared from crude γ-orsellinic acid[27] by esterification with diazomethane. In our hands this procedure proved superior to the silver salt–methyl iodide esterification used by Robertson and Robinson.

(27) A. Robertson and R. Robinson, *J. Chem. Soc.*, 2196 (1927). Their procedure for the carboxylation of orcinol is based on the general procedure of K. Brunner, *Ann.*, **351**, 313 (1907).

tained was dissolved in 200 ml each of dioxane and ethanol containing 6.15 g of anhydrous sodium acetate. To the resulting solution was added over a few minutes a solution of 14 g of bromine and 21 g of KBr in 130 ml of water. After the addition was complete the reaction mixture was diluted with 500 ml of water. The material which precipitated was collected and dried to give 13.4 g of yellow solid. Recrystallization from 200 ml of petroleum ether gave 10.4 g of needles (66% overall yield from **15b**): mp 135–137°; ir (CH_2Cl_2) 3300 and 1660 cm^{-1}; nmr ($CDCl_3$) δ 2.75 (s, 3, CH_3), 3.94 (s, 3, OCH_3), 5.05 (s, 2, OCH_2), 7.58 (m, 5, aromatic protons in benzyl group), and 12.1 ppm (s, 1, OH). Recrystallization from petroleum ether gave analytically pure material: mp 135–137°.

Anal. Calcd for $C_{16}H_{14}O_4Br_2$: C, 44.68; H, 3.28. Found: C, 44.55; H, 3.17.

***O*-Benzyl-*O*-methyl-3,5-dibromo-γ-orsellinic Acid (15d).** To a solution of 9.6 g of **15c** in 240 ml of acetone was added 7.5 g of freshly roasted potassium carbonate and 15 ml of methyl iodide. The resulting mixture was refluxed 3 hr and cooled, and the solvent was evaporated. The residue was extracted with ether to afford 9.9 g of solid after removal of the ether. To this solid was added 100 ml of Claisen alkali[24] and the mixture was refluxed with stirring for 2 hr under N_2. The reaction mixture was cooled, decanted from a small amount of residual gum, and diluted with 1 l. of water. A small amount of insoluble material (0.15 g) separated and this was removed by extraction with ether. The aqueous layer was acidified with 6 *N* HCl. The solid which separated was stirred 0.5 hr, collected by filtration, and air dried to give 9.13 g of acid **15d** (95%). An analytically pure sample (mp 199–202°) was obtained upon recrystallization from benzene: ir (KBr) 3300–2300 and 1700 cm^{-1}; nmr (CD_3COCD_3) δ 2.75 (s, 3, CH_3), 4.04 (s, 3, OCH_3), 5.27 (s, 2, OCH_2), and 7.65 ppm (m, 5, aromatic).

Anal. Calcd for $C_{16}H_{14}O_4Br_2$: C, 44.69; H, 3.28. Found: C, 44.43; H, 3.34.

Preparation of Benzophenone (16). A solution of 2.15 g of acid **15d**, 4.00 g of *O,O*-dibenzylorcinol, 10 ml of trifluoroacetic anhydride, and 2 ml of trifluoroacetic acid in 100 ml of ethanol-free chloroform was refluxed under N_2 with stirring for 6.25 hr. After evaporation of solvents the residual oil was taken up in 200 ml of ether, washed with dilute aqueous KOH and brine, and dried. Evaporation of the ether gave 5.7 g of oil which was chromatographed on 250 g of SiO_2. Elution with 3:1 benzene–petroleum ether gave unreacted dibenzylorcinol. Elution with benzene and then 9:1 benzene–ether gave a total of 2.42 g (67%) of desired benzophenone **16** as a gum which appeared essentially pure by tlc. All attempts to induce this material to crystallize were unsuccessful and it was used in the subsequent reaction without further purification: ir ($CHCl_3$) 1640 and 1595 cm^{-1}; nmr (CCl_4) δ 2.43 (s, 3, CH_3), 2.48 (s, 3, CH_3), 3.57 (s, 3, OCH_3), 4.67 (s, 2, OCH_2), 4.82 (s, 2, OCH_2), 5.00 (s, 2, OCH_2), 6.39 (q, J = 2 Hz, two nonequivalent aromatic protons in benzophenone nucleus), and 7.3 ppm (m, 15, aromatic protons in benzyl groups).

Preparation of Spiro Compound 18. To a solution of 3.31 g of benzophenone **16** in 600 ml of absolute ethanol was added 5 ml of trifluoroacetic acid and 400 mg of 10% palladium–charcoal. The resulting mixture was hydrogenated at atmospheric pressure until 3 equiv of hydrogen had been consumed, at which point the rate of hydrogen uptake had greatly diminished. Filtration and evaporation afforded 2.05 g of solid foam (**17**).

The foam was dissolved in 400 ml of water containing 12 g of K_2CO_3 and added in one portion to a solution of 6.0 g of potassium ferricyanide in 400 ml of water. The reaction mixture was stirred 5 min, 200 ml of $CHCl_3$ was added and the vigorously stirred solution was acidified with 3 *N* HCl (foaming). The layers were separated and the aqueous layer was thrice extracted with ether. The chloroform and ether layers were combined and washed successively with brine, aqueous $NaHCO_3$, and brine. Drying and evaporation gave 1.66 g of yellow solid. The solid was dissolved in 125 ml of hot benzene, filtered while hot, and, while being heated on a steam bath, concentrated to a volume of 40 ml under a stream of N_2. Upon cooling to 5° the solution deposited 0.83 g of material (mp 220–237°) which was shown by tlc to be essentially pure except for a small amount of material at the origin. The mother liquors were concentrated to afford 0.13 g (mp 230–239°). Preparative tlc (4:1 benzene–ethyl acetate) of the mother liquors from the second crop afforded an additional 0.12 g for a total yield of 53%. Analytically pure material, mp 247–249° (previous sintering), was obtained by preparative tlc and recrystallization from benzene: ir ($CHCl_3$) 3700–2800, 1740, and 1620 cm^{-1}; nmr (acetone-d_6) δ 2.46 (very slightly broadened s, 3, CH_3), 2.61 (s, 3, CH_3), 4.13 (s, 3, OCH_3), 6.86 (s, 2), and 8.09 ppm (s, 1); uv (absolute C_2H_5OH) 272 nm (ϵ 9200).

Anal. Calcd for $C_{16}H_{12}O_5Br_2$: C, 43.27; H, 2.72. Found: C, 43.35; H, 2.86.

The spiro compound (**18**) was converted to an acetoxydepsidone (**12b** with CH_3 and OCH_3 interchanged in ring B) by mild hydrolysis of 70 mg in 10 ml of water and 5 ml of 1 *N* NaOH for 35 min on the steam bath under N_2. Acidification and extraction with $CHCl_3$ yielded a foam, of which 55 mg was heated for 0.5 hr on the steam bath in 5 ml of acetic anhydride, then evaporated to a gum, which was crystallized from petroleum ether and sublimed at 130° (20 μ) to crystals: mp 168–173°; ir ($CHCl_3$) 1755 cm^{-1}; nmr ($CDCl_3$) δ 2.29 (s, 3, CH_3), 2.53 (s, 3, CH_3), 2.59 (s, 3, CH_3), 4.03 (s, 3, OCH_3), 6.93 (d, 1, J = 2 Hz, ArH), and 6.99 ppm (d, 1, J = 2 Hz, ArH); mass spectrum, see Table I.

Dibromo Ester 19. A solution of 0.96 g of **18** in 20 ml of dry methanol containing 0.5 g of $NaOCH_3$ was refluxed under N_2 for 1 hr, cooled, diluted with 100 ml of water, and acidified with dilute HCl. The resulting mixture was thrice extracted with $CHCl_3$ and the combined extracts were dried and concentrated to give 1.06 g of a solid foam which was chromatographed on 20 g of SiO_2. Elution with 9:1 benzene–ethyl acetate gave 0.75 g of solid which was recrystallized yielding 0.61 g of **19**: mp 169–175°, recrystallized from benzene–petroleum ether to mp 176–179°; ir ($CHCl_3$) 3600–2800 and 1685 cm^{-1}; nmr ($CDCl_3$) δ 2.36 (s, 3, CH_3), 2.46 (s, 3, CH_3), 3.90 (s, 3, OCH_3), 4.04 (s, 3, OCH_3), 6.36 (broad s, 1, ArH), and 6.50 ppm (broad s, 1, ArH); mass spectrum, see Table I. An additional 0.10 g of **19** was obtained by preparative tlc of the mother liquors.

Monochlorination of Ester 19. To a solution of 0.60 g of **19** in 60 ml of acetic acid was added 0.16 ml of *tert*-butyl hypochlorite (Frinton). The solution was stirred in the dark for 1 hr and then poured into 250 ml of H_2O. The material which precipitated was collected and air dried to give 0.60 g as an amorphous solid which melted at 152–154° after sintering between 95 and 120°: ir ($CHCl_3$) 3500 and 1710 cm^{-1}; nmr ($CDCl_3$) δ 2.39 (s, 3, CH_3), 2.58 (s, 3, CH_3), 3.82 (s, 3, OCH_3), 3.97 (s, 3, OCH_3), and 6.41 (s, 1, ArH). An analytical sample was obtained upon recrystallization from petroleum ether: mp 159–160°.

Anal. Calcd for $C_{17}H_{13}O_6Br_2Cl$: C, 39.99; H, 2.96. Found: C, 39.80; H, 3.04.

Dichlorodibromo Ester 20. To a solution of 0.37 g of Ag_2O in 34 ml of CF_3COOH and 17 ml of H_2O was added a solution of 0.12 g of chlorine in 19 ml of H_2O.[15b] The precipitate was allowed to settle and the supernatant liquid added to a solution of 0.58 g of monochloro ester (above) in 23 ml of CF_3COOH. The resulting mixture was stirred in the dark at 35° for 17 hr at which point tlc showed that considerable starting material was still present even though the solution tested negative with starch–iodide paper. Additional chlorinating reagent (from 0.19 g of Cl_2) was added and the reaction was allowed to run a further 68 hr at 35°. The reaction mixture was poured into water, extracted with $CHCl_3$, dried, and concentrated to give 0.51 g of material which was submitted to preparative tlc (4:1 benzene–ethyl acetate) to give 0.31 g of yellow oil which crystallized on standing. An analytical sample, mp 181–183°, was obtained upon recrystallization from benzene: ir (CH_2Cl_2) 3520 and 1735 cm^{-1}; nmr δ ($CDCl_3$) 2.33 (s, 3, CH_3), 2.60 (s, 3, CH_3), 3.63 (s, 3, OCH_3), and 3.72 (s, 3, OCH_3).

Anal. Calcd for $C_{17}H_{14}O_6Br_2Cl_2$: C, 37.46; H, 2.59. Found: C, 37.46; H, 2.58.

Dichloro Ester 21. A stirred solution of 185 mg of dibromodichloro ester **20** and 80 mg of anhydrous sodium acetate in 25 ml of methanol was hydrogenated over 50 mg of 10% palladium–carbon. The catalyst was removed by filtration and the filtrate poured into water and extracted with $CHCl_3$ (4 × 40 ml). The $CHCl_3$ extracts were combined, washed with brine, dried, and evaporated to give 122 mg of a hard glass which was dissolved in CH_2Cl_2–petroleum ether. The CH_2Cl_2 was boiled off and the solution on cooling slowly deposited crystals which were recrystallized from benzene–petroleum ether: mp 164–166°; ir (CH_2Cl_2) 3560, 1735, and 1705 cm^{-1}; mmr ($CDCl_3$) δ 2.25 (s, 3, CH_3), 2.29 (s, 3, CH_3), 3.60 (s, 6, OCH_3), and 6.25 and 6.43 ppm (broad singlets, 2 ArH); mass spectrum, see Table I.

Monomethyl Ether of 21. An ice-cold solution of 33 mg of **21** in 10 ml of ether was treated with excess ethereal diazomethane and allowed to warm to room temperature in the dark over the course of 1 hr; the ether was then evaporated and the residue submitted to preparative tlc (4:1 benzene–ethyl acetate) to give 17 mg of a yellow oil which crystallized from petroleum ether at −15°. Recrystallization from petroleum ether gave the pure ether: mp 110–111°; nmr ($CDCl_3$) δ 2.27 (s, 3, CH_3), 2.29 (s, 3, CH_3), 3.59 (s, 3, OCH_3), 3.62 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 6.25 (broad s, 1, ArH), and 6.46 (broad, s, 1, ArH); mass spectrum, see Table I.