General Route to Anthraquinone Natural Products via Directed Metalation of *N,N*-Diethylbenzamides[1]

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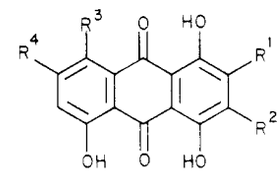
Regiospecific, short, and efficient synthesis of the naturally occurring anthraquinones islandicin (**1a**), digitopurpone (**1b**), erythroglaucin (**1c**), catenarin (**1d**), cynodontin (**1e**), and soranjidiol (**1f**) have been achieved in 20–30% overall yields by using directed metalation of easily accessible methoxylated *N,N*-diethylbenzamides (**3** and **10a–d**) as the key step. In a representative example (Scheme IV), sequential treatment of *N,N*-diethyl-3,5-dimethoxybenzamide (**3**) with *sec*-BuLi and 2,5-dimethoxy-4-methylbenzaldehyde (**4**) gives the hydroxyamide **5** which, without isolation, is subjected to *p*-toluenesulfonic acid in refluxing toluene to provide the phthalide **6**. Hydrogenolysis of **6** affords the benzylbenzoic acid **7** which upon Friedel–Crafts cyclization with trifluoroacetic anhydride yields the anthracenol **8**. Compound **8**, when exposed to chromium trioxide, undergoes facile oxidation to the anthraquinone **9**. Selective demethylation (BBr_3) of **9** gives erythroglaucin (**1c**), while vigorous conditions (pyridine hydrochloride) provide catenarin (**1d**). Formal syntheses of islandicin (**1a**) and digitopurpone (**1b**) and total syntheses of cynodontin (**1e**) and soranjidiol (**1f**) have been effected by analogous six-step sequences starting with the benzamides **10a–d** and, in three of the four cases (**10a–c**), the same *p*-tolualdehyde (**4**). Methoxy and methyl substituents on the aromatic ring offer no complications in metalation ortho to the $CONEt_2$ function. The condensation of the resulting species with aromatic aldehydes is compatible with acidic methyl hydrogens in the aldehyde component.

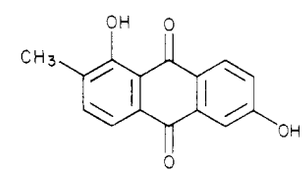
Anthraquinones (**1**) have long-standing interest for chemists both as plant[2] and insect[3] natural products and as important synthetic substances.[4] The independent and almost simultaneous synthesis of the principal madder pigment alizarin by Perkin and by Graebe and Liebermann in 1868 provided the cornerstone for the European dye industry[5] and stimulated intense synthetic activity in this field of investigation. In modern times, a multitude of new structural types have relegated the anthraquinone dyes to a minor position, and as a result, the synthetic work has been correspondingly minimal.[6]

The recent renaissance in anthraquinone synthesis[7] is due, in large part, to the discovery of useful antitumor activity in the related more complex anthracycline antibiotics (**2**).[8] A number of new syntheses of anthracyclines are dependent on the availability of unsymmetrically oxygenated anthraquinone intermediates.[9]

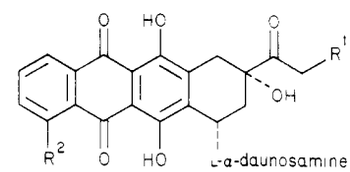
The classical synthesis of anthraquinones involves double Friedel–Crafts condensation of phthalic acid derivatives or phthalic anhydrides with substituted phenols



1a, R^1 = Me; R^2 = R^3 = R^4 = H (islandicin)
b, R^1 = R^3 = R^4 = H; R^2 = Me (digitopurpone)
c, R^1 = Me; R^2 = R^3 = H; R^4 = OMe (erythroglaucin)
d, R^1 = Me; R^2 = R^3 = H; R^4 = OH (catenarin)
e, R^1 = Me; R^2 = R^4 = H; R^3 = OH (cynodontin)



1f, soranjidiol



2a, R^1 = OH; R^2 = OMe (adriamycin)
b, R^1 = H; R^2 = OMe (daunomycin)
c, R^1 = H; R^2 = OH (carminomycin)

or phenol ethers.[10] For unsymmetrically oxygenated anthraquinones, this route (Scheme I) lacks regiochemical control in the intermolecular Friedel–Crafts reaction[11,12] and carries the potential of a Hayashi rearrangement[10,13]

(1) Dedicated to Professor Virgil Boekelheide in the year of his 60th birthday. A preliminary account of a portion of this work has appeared: S. O. de Silva and V. Snieckus, *Tetrahedron Lett.*, 5103 (1978).

(2) R. H. Thomson, "Naturally Occurring Anthraquinones", 2nd ed., Academic Press, New York, 1971.

(3) K. S. Brown, Jr., *Chem. Soc. Rev.*, **4**, 263 (1975); F. L. C. Baranyovits, *Endeavor*, **2**, 85 (1978).

(4) K. H. Schunderhutte, *Chem. Synth. Dyes*, **6**, 211 (1972).

(5) For a historical account, see L. F. Fieser, *J. Chem. Educ.*, **7**, 2609 (1930).

(6) E. Siegel, *Int. Rev. Sci.: Org. Chem., Ser. Two*, **3**, 259 (1976).

(7) See, inter alia: (a) G. Roberge and P. Brassard, *Synthesis*, 148 (1979); (b) P. G. Sammes and D. J. Dodsworth, *J. Chem. Soc., Chem. Commun.*, 33 (1979); (c) F. M. Hauser and R. P. Rhee, *J. Am. Chem. Soc.*, **101**, 1628 (1979); (d) M. Braun, *Angew. Chem., Int. Ed. Engl.*, **17**, 945 (1978); (e) D. W. Cameron, G. I. Feutrill, P. G. Griffiths, and D. J. Hodder, *J. Chem. Soc., Chem. Commun.*, 688 (1978); (f) R. K. Boeckman, Jr., T. M. Dolak, and K. O. Culos, *J. Am. Chem. Soc.*, **100**, 7098 (1978); (g) D. Rutolo, S. Lee, R. Sheldon, and H. W. Moore, *J. Org. Chem.*, **43**, 2304 (1978); (h) M. J. Broadhurst, C. H. Hassall, and G. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 2502 (1977).

(8) (a) F. Arcemone, *Lloydia*, **40**, 45 (1977); (b) T. R. Kelly, *Annu. Rep. Med. Chem.*, in press.

(9) See, for example: (a) F. Suzuki, S. Trenbeath, R. D. Gleim, and C. J. Sih, *J. Org. Chem.*, **43**, 4159 (1978); (b) L. M. Harwood, L. C. Hodgkinson, and J. K. Sutherland, *J. Chem. Soc., Chem. Commun.*, 712 (1978); (c) K. Krohn and M. Radeloff, *Chem. Ber.*, **111**, 3823 (1978).

(10) R. H. Thomson in "The Chemistry of the Quinonoid Compounds", Part 1, S. Patai, Ed., Wiley, New York, 1974, p 136 ff. See also footnote 10 in ref 9a.

(11) Recent examples: (a) R. J. Blade and P. Hodge, *J. Chem. Soc., Chem. Commun.*, 85 (1979); (b) S. Terashima, S.-s. Jew, and K. Koda, *Tetrahedron Lett.*, 4937 (1978); (c) D. G. Davies, R. Hodge, and P. Yates, *J. Chem. Soc., Perkin Trans. 1*, 2399 (1974); (d) C. M. Wong, R. Schwenk, D. Popien, and T.-L. Ho, *Can. J. Chem.*, **51**, 466 (1973); (e) Z. Horii, H. Hakusai, and T. Momose, *Chem. Pharm. Bull.*, **16**, 1262 (1968).

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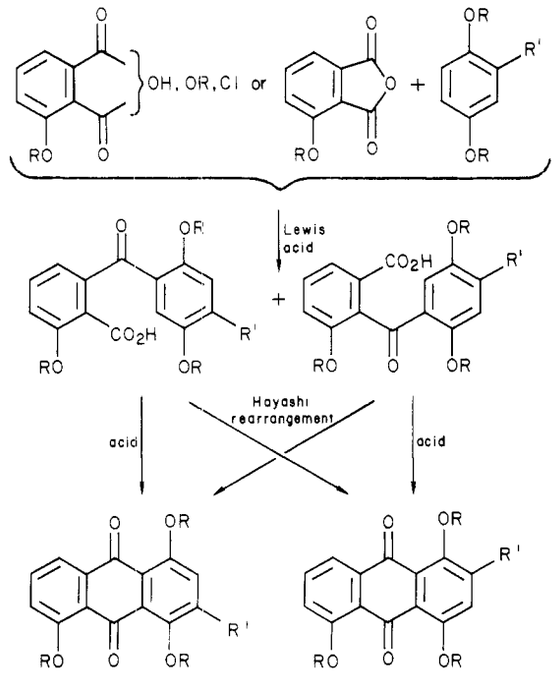
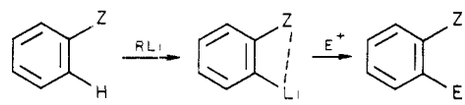
Scheme I



Scheme II

Directed Metalation

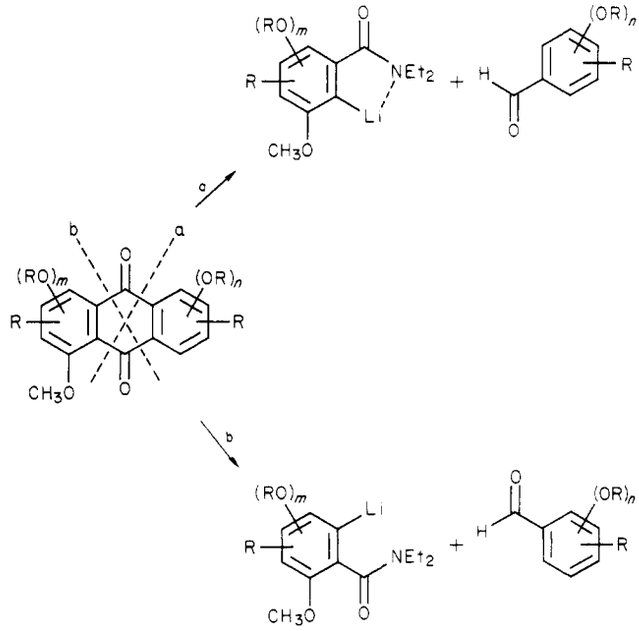


Z = NMe_2, $(CH_2)_nNMe_2$ (n = 1, 2), CONHR, CSNHMe, CH_2OH, OMe, OCH_2OMe, SO_2NMe_2, SO_2NHMe, CF_3, F, CH=NR, and 2-oxazolino

in the intramolecular acylation involving equilibrating *o*-benzoylbenzoic acid intermediates.[14] Consequently, syntheses of the related anthracyclines based on this approach are inefficient and ambiguous,[12] and efforts have been focused on developing new regiospecific routes to these substances.[15]

Discovered by Gilman and by Hauser, the directed metalation reaction[16] has recently matured into a major synthetic method which allows the introduction of diverse substituents into aromatic substrates ortho to certain functional groups (Scheme II). It provides useful methodology for the construction of 1,2-disubstituted benzene derivatives which are usually not accessible by classical electrophilic substitution chemistry. The observation of Beak and Brown[17] that the *N,N*-diethylcarboxamide

Scheme III



function promotes smooth ortho metalation triggered work in our laboratories on this directing group which resulted in (a) the efficient preparation of contiguously tri- and tetrasubstituted alkoxybenzene derivatives representing useful synthons for anthraquinones, anthracyclines, and several classes of benzylisoquinoline alkaloids,[18] (b) highly convergent syntheses of phthalideisoquinoline alkaloids,[19] and (c) regiospecific routes to the unsymmetrical anthraquinone natural products islandicin (**1a**) and digitopurpone (**1b**).[1,20] In the present paper, we report on the details of the latter work and demonstrate the generality of the directed metalation route by the preparation of the related naturally occurring anthraquinones erythroglaucin (**1c**), catenarin (**1d**), cynodontin (**1e**), and soranjidiol (**1f**).

Retrosynthetic analysis of the anthraquinone system based on the directed metalation strategy is shown in Scheme III. Four modes of initial coupling of two oxygenated, appropriately substituted amide and aldehyde aromatic units are possible. The two dissections a and b focus on the correct positioning of the anthraquinone's C-4 OCH_3 substituent and the regiospecific formation of the new C–C bond which forces the subsequent central ring closure via Friedel–Crafts reaction to proceed unidirectionally. The choice between a and b is dictated by the relative accessibility of the benzamide and benzaldehyde starting materials.

The synthesis of erythroglaucin (**1c**) and catenarin (**1d**), outlined in Scheme IV, illustrates our general approach to anthraquinone natural products via ortho-metalated *N,N*-diethylbenzamide intermediates. Lithiation of 3,5-dimethoxy-*N,N*-diethylbenzamide (**3**) with *sec*-BuLi in ether solution[21] followed by treatment with 2,5-dimethoxy-*p*-tolualdehyde (**4**) afforded the hydroxyamide **5** which

(12) For an exception, see the 3-bromophthalide route to anthraquinones [K. S. Kim, M. W. Spatz, and F. Johnson, *Tetrahedron Lett.*, 331 (1979)] and to anthracyclines [K. S. Kim, E. Vanotti, A. Suarato, and F. Johnson, *J. Am. Chem. Soc.*, **101**, 2483 (1979)].

(13) M. S. Newman, *Acc. Chem. Res.*, **5**, 354 (1972).

(14) Recent examples: (a) R. D. Gleim, S. Trenbeath, F. Suzuki, and C. J. Sih, *J. Chem. Soc., Chem. Commun.*, 242 (1978); (b) A. S. Kende, J. L. Belletire, J. L. Hermmann, R. F. Romanet, E. L. Hume, R. H. Schlessinger, J. Fayos, and J. C. Clardy, *Synth. Commun.*, **3**, 387 (1973).

(15) Successful alternatives: photochemical Fries route [A. S. Kende, J. L. Belletire, T. J. Bentley, E. Hume, and J. Airey, *J. Am. Chem. Soc.*, **97**, 4425 (1975)], intramolecular base-catalyzed route (see ref 9), anionic quinone bisketal route [J. S. Swenton and P. W. Reynolds, *J. Am. Chem. Soc.*, **100**, 6188 (1978); see also ref 7d], Diels-Alder route [T. R. Kelly, J. W. Gillard, R. N. Goerner, Jr., and J. M. Lyding, *J. Am. Chem. Soc.*, **99**, 5513 (1977)].

(16) H. W. Gschwend and H. R. Rodriguez, *Org. React.*, in press; D. W. Slocum and D. I. Sugarman, *Adv. Chem. Ser.*, **No. 130**, 222 (1974); H.-P. Abicht and K. Issleib, *Z. Chem.*, **17**, 1 (1977); D. W. Slocum and C. A. Jennings, *J. Org. Chem.*, **41**, 3653 (1976).

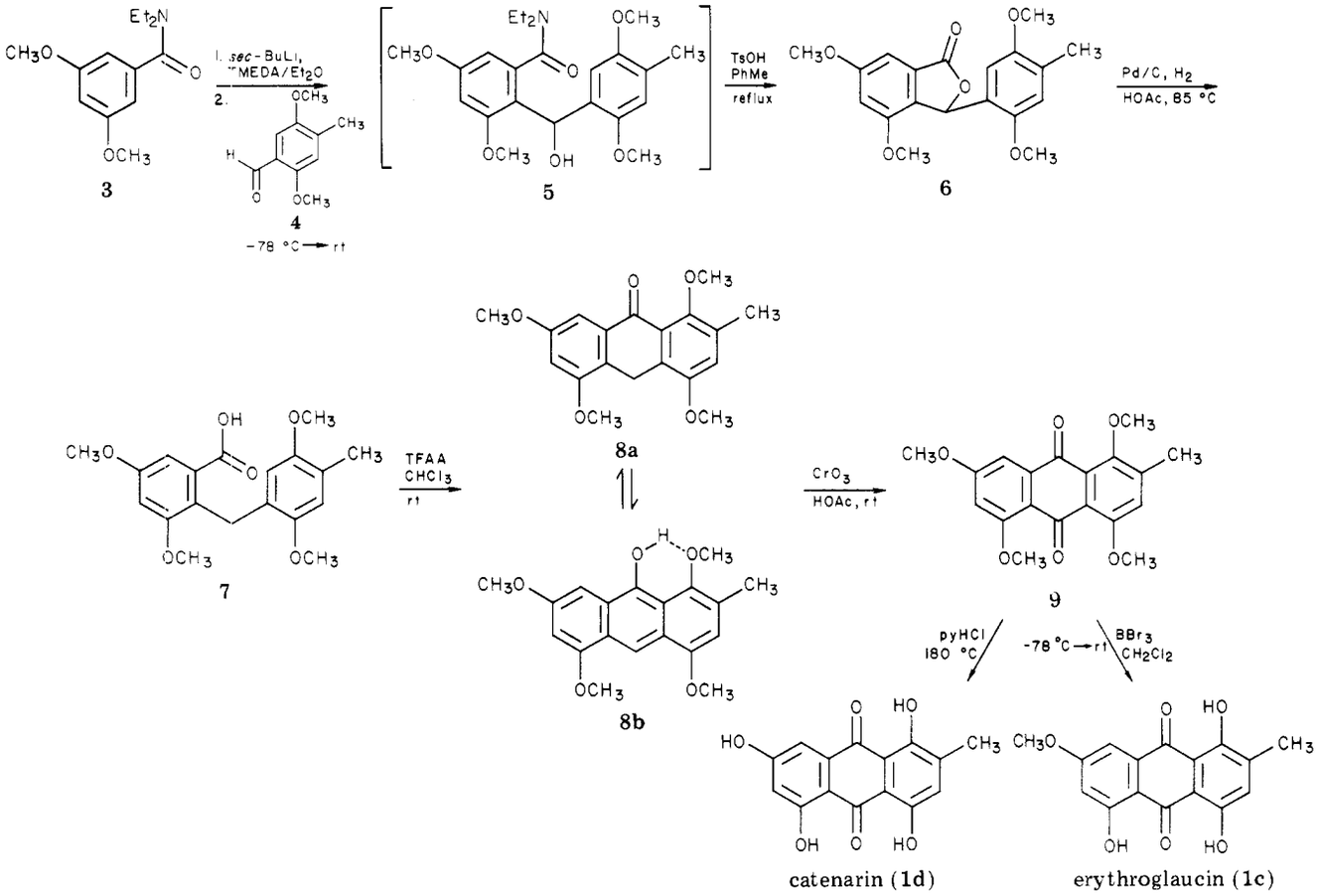
(17) P. Beak and R. A. Brown, *J. Org. Chem.*, **42**, 1823 (1977).

(18) S. O. de Silva, J. N. Reed, and V. Snieckus, *Tetrahedron Lett.*, 5099 (1978).

(19) S. O. de Silva, I. Ahmad, and V. Snieckus, *Tetrahedron Lett.*, 5107 (1978); S. O. de Silva, I. Ahmad, and V. Snieckus, *Can. J. Chem.*, **57**, 1598 (1979).

(20) After the completion of our work, independent investigations leading to anthraquinones by directed metalation of secondary benzamides were reported: J. E. Baldwin and K. W. Blair, *Tetrahedron Lett.*, 2559 (1978); I. Forbes, R. A. Pratt, and R. A. Raphel, *ibid.*, 3965 (1978).

Scheme IV



was not isolated[22] but was subjected to treatment with *p*-toluenesulfonic acid[23] in refluxing toluene to give the highly crystalline phthalide **6** in 63% overall yield. Hydrogenolysis[24] of **6** provided a high yield of the *o*-benzylbenzoic acid **7** which upon mild Friedel–Crafts cyclization[25] using trifluoroacetic anhydride[12,26] gave the anthracenol **8**. NMR and IR spectra provided evidence for a concentration-dependent anthracenol (**8a**)–anthracenone (**8b**) equilibrium. This was generally observed for analogous intermediates prepared in this work (see Experimental Section). Furthermore, some loss of material was experienced in the isolation of **8** (and the analogous systems), owing to partial air oxidation to the anthraquinone **9**. The experimentally controlled conversion of **8** into **9** was easily achieved by using CrO_3 in acetic acid–water solution. Treatment of the anthraquinone **9** with BBr_3 resulted in the expected[27] demethylation at the positions peri to the quinone carbonyls to produce erythroglaucin (**1c**)[28] in 22% overall yield.

On the other hand, forcing conditions using pyridinium hydrochloride[27] gave catenarin (**1d**)[28,29] (29% overall yield) which was shown to be identical with an authentic sample by melting point and spectral comparison. Although a quantitative comparison cannot be made due to insufficient yield data,[28] the present route appears to be the most efficient route to erythroglaucin and catenarin.

The pair of anthraquinones islandicin (**1a**) and digitopurpone (**1b**) have served as synthetic models and intermediates for the anthracyclines.[7d,9a,12,14] Maximum synthetic efficiency may be realized by retrosynthetic analysis (Scheme III) to *m*- and *o*-anisamides, **10a** and **10b**, and *the same tolualdehyde derivative* (*4*) used in the synthesis of **1c** and **1d**. The sequence to islandicin trimethyl ether (**14a**) proceeds via the intermediates phthalide **11a**, benzylbenzoic acid **12a**, and anthracenol **13a** in 41% overall yield while that leading to digitopurpone trimethyl ether (**14b**) involves the analogous compounds **11b**, **12b**, and **13b** (39% overall yield). In the latter synthesis, it was possible

(21) Use of the general solvent THF[18] resulted in substantial reduction of the *p*-tolualdehyde **4** to the corresponding benzyl alcohol (NMR δ 4.65) with a proportionate decrease in the yield of the coupling product **5**. Reduction of ketones by LDA has been recently observed: C. Kowalski, X. Creary, A. J. Rollin, and M. C. Burke, *J. Org. Chem.*, **43**, 2601 (1978); L. T. Scott, K. J. Carlin, and T. H. Schultz, *Tetrahedron Lett.*, 4637 (1978).

(22) With the exception of the hydroxyamide **15** leading to digitopurpone trimethyl ether (see Experimental Section), hydroxyamide products were not characterized since NMR spectra of the crude materials indicated that partial conversion into the corresponding phthalides had occurred in the workup. This facile cyclization undoubtedly originates in the highly crowded environment of the hydroxyamides as also is evident from their NMR spectra [doubling of the triplets and quartets associated with the $CONEt_2$ function due to amide hindered rotation phenomenon, see G. Binsch, *Top. Stereochem.*, **3**, 97 (1968)].

(23) For a mechanistic study of acid- and base-catalyzed formation of phthalides from hydroxyamides, see C. R. Hauser and T. C. Adams, Jr., *J. Org. Chem.*, **42**, 3029 (1977).

(24) B. J. Arnold, S. M. Mellows, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 1266 (1973).

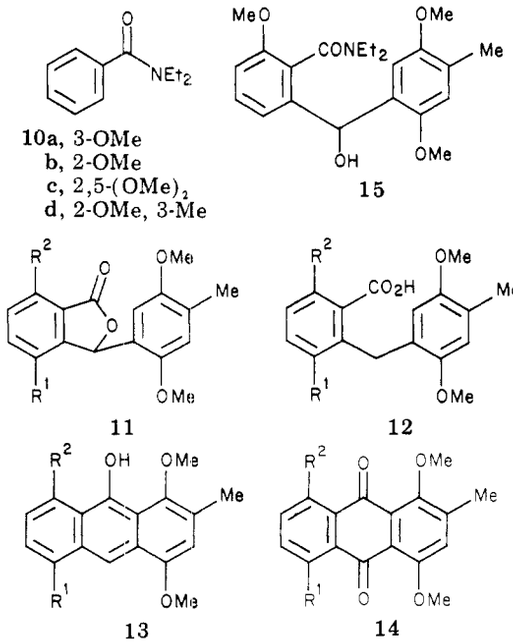
(25) As precedented,[10,14b,22] the Friedel–Crafts condensation of *o*-benzylbenzoic acids occurs with greater facility and without the potential complications of the Hayashi rearrangement compared to the analogous reaction of *o*-benzoylbenzoic acids.

(26) R. J. Ferrier and J. M. Tedder, *J. Chem. Soc.*, 1435 (1957).

(27) R. F. Curtis, C. H. Hassall, and D. R. Parry, *J. Chem. Soc., Perkin Trans. 1*, 240 (1972).

(28) K. Chandrasenan, S. Neelakantan, and T. R. Seshadri, *Proc. Indian Acad. Sci., Sect. A*, **51**, 296 (1960).

(29) S. Shibata and S. Natori, *Chem. Pharm. Bull.*, 1, 160 (1953).



10a, 3-OMe
b, 2-OMe
c, 2,5-(OMe)$_2$
d, 2-OMe, 3-Me

15

11 12

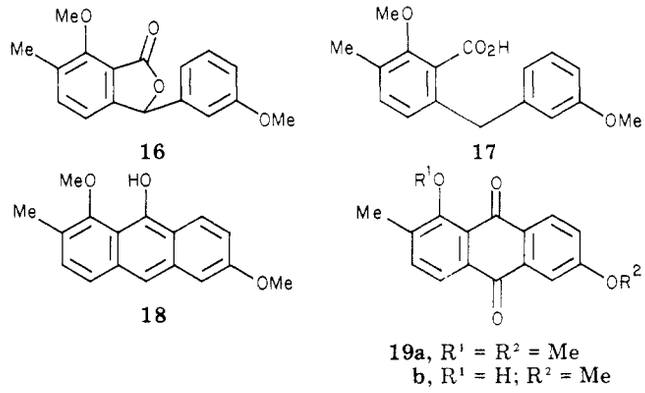
13 14

a, R^1 = OMe; R^2 = H; b, R^1 = H; R^2 = OMe; c, R^1 = R^2 = OMe

to isolate the hydroxyamide **15**, presumably owing to the less encumbered environment of the "outside" hydroxybenzyl moiety in **15** compared to other benzamide plus benzaldehyde condensation products obtained in this work in which the hydroxybenzyl group is "inside" (between amide and methoxy substituents). Both **14a** and **14b** were shown to be identical with authentic samples[14b] by comparison of melting point, mixture melting point, and spectral (IR and NMR) data. Since compounds **14a** and **14b** have been previously converted[14b,30] by BBr_3 demethylation into islandicin (**1a**) and digitopurpone (**1b**), we have completed a formal synthesis of these natural products.

The synthesis of cynodontin (**1e**) was easily achieved in 23% overall yield in analogous fashion from the 2,5-dimethoxybenzamide **10c** and, *again*, 2,5-dimethoxy-*p*-tolualdehyde (**4**) via the intermediates **11c**, **12c**, **13c**, and **14c**. Synthetic cynodontin was shown to be identical with authentic material[31] by melting point, mixture melting point, and spectral comparison. As far as can be estimated from the previous synthetic reports,[32] cynodontin has been obtained at best[32a] in about 6% overall yield.

We chose the preparation of soranjidiol (**1f**) as a test case of the directed metalation reaction proceeding on a methyl-substituted benzamide (**10d**). In the event, condensation of **10d** with *m*-anisaldehyde followed by acid-catalyzed cyclization occurred efficiently to give the phthalide **16** (76% yield). The subsequent three steps to soranjidiol dimethyl ether (**19a**) via the intermediate benzylbenzoic acid **17** and anthracenol **18** proved unexceptional. Although **19a** is not a natural product, its identity with an authentic sample[33] was established by melting point, mixture melting point, and spectral comparison. Selective demethylation of **19a** with BBr_3 afforded the monomethyl ether **19b** (also not a natural product) while the more vigorous conditions using pyridine hydrochloride provided soranjidiol (**1f**) (21% overall yield) whose melting point and spectral data proved to be identical with those reported. The only accessible[2] synthesis of soranjidiol is due to Simonsen and Rau,[34] but the overall yield cannot be determined for lack of data.



16 17

18

19a, R^1 = R^2 = Me
b, R^1 = H; R^2 = Me

We conclude that ortho-lithiated *N,N*-diethylbenzamide derivatives are useful starting points for efficient and regiospecific syntheses of unsymmetrical anthraquinone natural products. The amides used in this work (**3** and **10**) are all derived from commercially available benzoic acids. Furthermore, in five of the six syntheses, the same readily available *p*-tolualdehyde (**4**) served as the other aromatic component. The highly selective ortho-directing effect of the $CONEt_2$ function in the presence of OMe and 1,3-$(OMe)_2$ substitution and the tolerance of methyl groups both in amide (**10d**) and aldehyde (**4**) components in the metalation and condensation reactions, respectively, bode well for the preparation of a variety of anthraquinones according to the methodology developed here.

Experimental Section

General Methods. Microanalyses were performed by Guelph Chemical Laboratories Ltd., Guelph, Ontario, and Baron Consulting Co., Orange, CT. Melting points were measured on a Fisher-Johns or a Büchi SMP-20 apparatus and are uncorrected. Infrared spectra were determined on a Beckmann IR-10 spectrometer. Ultraviolet spectra were recorded on a SP-800E ultraviolet spectrophotometer in methanol solution. Nuclear magnetic resonance spectra were obtained with a Varian T-60 spectrometer using tetramethylsilane as internal standard in deuteriochloroform unless otherwise indicated. Mass spectra were determined on an AEI MS-30 double-beam, double-focussing mass spectrometer. For column chromatography, silica gel 60 (70–230 mesh) and aluminum oxide (neutral, activity 1) obtained from Brinkmann (Canada) were used. Silica gel GF-254 and aluminum oxide G (type E) adsorbents were used for thick-layer chromatography. *sec*-Butyllithium as a solution in hexane and tetramethylethylenediamine (TMEDA) were purchased from Aldrich Chemical Co. All metalation reactions were carried out in an air-conditioned laboratory by using septum cap techniques.

Benzamide Derivatives 3 and 10a–d. These compounds were prepared under standard conditions, distilled, and stored in sealed containers.

***N,N*-Diethyl-3,5-dimethoxybenzamide (3)**: bp 154 °C (0.6 mm) [lit.[37,38] bp 166.5–167 °C (3.5 mm).

(30) A. S. Kende, J. L. Belletire, and E. L. Hume, *Tetrahedron Lett.*, 2935 (1973).
(31) K. Schofield and D. E. Wright, *J. Chem. Soc.*, 6642 (1965).
(32) (a) W. K. Anslow and H. Raistrick, *Biochem. J.*, **34**, 1546 (1940); (b) S. Neelakantan, T. R. Rajagopalan, and T. R. Seshadri, *Proc. Indian Acad. Sci., Sect. A*, **49**, 234 (1959); (c) V. M. Chari, S. Neelakantan, and T. R. Seshadri, *Indian J. Chem.*, **7**, 40 (1969).
(33) L. H. Briggs and B. R. Thomas, *J. Chem. Soc.*, 1246 (1949).
(34) J. L. Simonsen and M. G. Rau, *J. Chem. Soc.*, **119**, 1339 (1921).
(35) W. K. Anslow and H. Raistrick, *Biochem. J.*, **34**, 1124 (1940).
(36) L. H. Briggs, G. A. Nichols, and R. M. L. Paterson, *J. Chem. Soc.*, 1718 (1952).
(37) C. M. Suter and A. W. Weston, *J. Am. Chem. Soc.*, **61**, 232 (1939).
(38) A. Baruffini, G. Pagani, and G. Caccialanza, *Farmaco, Ed. Sci.*, **29**, 317 (1974); *Chem. Abstr.*, **81**, 73303 (1974).

Table I. Physical and Spectral Data of Phthalide Derivatives

compd[a]	yield, %	mp, °C (solvent)	IR ($CHCl_3$) ν_{CO}, cm^{-1}	NMR ($CDCl_3$), δ (multiplicity, no. of H, assignment)	MS, *m/e* (M^+)
6	64	186 (PhH)	1760	2.23 (s, 3 H, Me), 3.63, 3.70, 3.81, 3.91 (4 s, 12 H, 4 OMe), 6.33 (s, C-3 H), 6.70 (d, 1 H, J = 2 Hz, C-5 H), 6.76 (s, 1 H, C-2′ or C-5′ H), 6.80 (s, 1 H, C-2′ or C-5′ H), 7.07 (d, 1 H, J = 2 Hz, C-7 H)	344
11a	68	176 (MeOH)	1770	2.23 (s, 3 H, Me), 3.60, 3.76, 3.80 (3 s, 9 H, 3 OMe), 6.32 (s, 1 H, C-3 H), 6.78 (s, 2 H, Ar H), 6.97-7.58 (m, 3 H, Ar H)	314
11b	62	168 (MeOH)	1760	2.23 (s, 3 H, Me), 3.70, 3.90, 4.03 (3 s, 9 H, 3 OMe), 6.59 (s, 1 H, C-3 H), 6.77-7.75 (m, 5 H, Ar H)	314
11c	63	201 (MeOH)	1760	2.23 (s, 3 H, Me), 3.63, 3.68, 3.85, 4.00 (4 s, 12 H, 4 OMe), 6.39 (s, 1 H, C-3 H), 6.80-7.10 (m, 4 H, Ar H)	344
16	76	62 (petroleum ether, 30-60 °C)	1760	2.32 (s, 3 H, Me), 3.75 (s, 3 H, OMe), 4.13 (s, 3 H, OMe), 6.23 (s, 1 H, C-3 H), 7.49-7.76 (m, 6 H, Ar H)	284

[a] Anal. Calcd (found): 6($C_{19}H_{20}O_6$) C, 66.27 (66.49); H, 5.85 (6.04); 11a ($C_{18}H_{18}O_5$) C, 68.78 (68.47); H, 5.77 (5.87); 11b ($C_{18}H_{18}O_5$) C, 68.78 (68.78); H, 5.77 (5.88); 11c ($C_{19}H_{20}O_6$) C, 66.27 (66.22); H, 5.85 (6.18); 16 ($C_{17}H_{16}O_4$) C, 71.82 (71.50); H, 5.67 (5.37).

Table II. Physical and Spectral Data of *o*-Benzylbenzoic Acids

compd[a]	yield, %	mp, °C (solvent)	IR (Nujol) ν, cm^{-1}	NMR ($CDCl_3$), δ	MS, *m/e* (M^+)
7	95	176 (MeOH)	3200 (br), 1695	2.17 (s, 3 H, Me), 3.62, 3.72, 3.76, 3.83 (4 s, 12 H, 4 OMe), 4.28 (s, 2 H, CH_2), 6.50 (s, 1 H, Ar H), 6.64 (m, 2 H, Ar H), 7.06 (d, 1 H, J = 2 Hz, C-4 or C-6 H), 8.40 (br s, 1 H, OH)	346
12a	95	201[b] (EtOH)	3200 (br), 1690	2.10 (s, 3 H, Me), 3.50, 3.73, 3.76 (3 s, 9 H, 3 OMe), 4.20 (s, 2 H, CH_2), 6.31, 6.53 (2 s, 2 H, Ar H), 7.13-7.43 (m, 3 H, Ar H)[c]	316
12b	95	177 (EtOH)	3180 (br), 1690	2.13 (s, 3 H, Me), 3.63, 3.70, 3.77 (3 s, 9 H, 3 OMe), 3.83 (s, 2 H, CH_2), 6.53-7.27 (m, 5 H, Ar H)[c]	316
12c	93	184 (MeOH)	1695	2.17 (s, 3 H, Me), 3.63, 3.70, 3.72, 3.83 (4 s, 12 H, 4 OMe), 4.05 (s, 2 H, CH_2), 6.57, 6.03, 6.85 (3 s, 3 H, Ar H), 6.85 (s, 2 H, Ar H), 9.83 (br s, 1 H, OH)	346
17	93	67 (petroleum ether, 30-60 °C)	2940, 1700[d]	2.27 (s, 3 H, Me), 3.70, 3.82 (2 s, 6 H, 2 OMe), 4.03 (s, 2 H, CH_2), 6.73-7.33 (m, 6 H, Ar H), 11.37 (s, 1 H, OH)	286

[a] Anal. Calcd (found); 7 ($C_{19}H_{22}O_6$) C, 65.88 (65.51); H, 6.40 (6.61); 12b ($C_{18}H_{20}O_5$) C, 68.34 (68.13); H, 6.37 (6.49); 12c ($C_{19}H_{22}O_6$), C, 65.88 (65.89); H, 6.40 (6.35); 17 ($C_{17}H_{18}O_4$) C, 71.31 (71.01); H, 6.34 (6.00). [b] Lit.[14b] mp 191-192 °C. [c] Recorded in Me_2SO-d_6. [d] Measured as a neat sample.

***N,N*-Diethyl-3-methoxybenzamide (10a)**: bp 130 °C (0.2 mm) (lit.[17] bp not given).

***N,N*-Diethyl-2-methoxybenzamide (10b)**: bp 118 °C (0.2 mm) (lit.[39] bp not given).

***N,N*-Diethyl-2,5-dimethoxybenzamide (10c)**: bp 125 °C (0.35 mm). Anal. Calcd for $C_{13}H_{19}O_3N$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.61; H, 7.95; N, 5.63.

***N,N*-Diethyl-2-methoxy-3-methylbenzamide (10d)**: bp 110 °C (0.5 mm). Anal. Calcd for $C_{13}H_{19}O_2N$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.20; H, 8.79; N, 6.11.

General Procedures. (a) Phthalides 6, 11a, 11b, 11c, and 16. The following procedure for the preparation of the phthalide 6 is representative for the synthesis of compounds **11a**, **11b**, **11c**, and **16**. The solid products usually crystallized directly from the evaporated organic extract. Where this was not the case, rapid chromatography over silica gel ($CHCl_3$ elution) provided crystalline materials.

4,7-Dimethoxy-3-(2′,5′-dimethoxy-4′-methylphenyl)-1,-(3*H*)-isobenzofuranone (6). A solution of *sec*-BuLi (1.4 M in cyclohexane, 7.8 mL, 11 mmol) was injected into a stirred solution of *N,N*-diethyl-2,5-dimethoxybenzamide (3; 2.37 g, 10 mmol) and tetramethylethylenediamine (TMEDA; 15 mL, 10 mmol) in anhydrous ether (270 mL) at −78 °C under nitrogen. After the mixture was stirred (1 h), a solution of 2,5-dimethoxy-4-methylbenzaldehyde[40] (4; 1.8 g, 10 mmol) was injected, and the dry ice–acetone bath was removed. After being stirred further for 12 h, the solution was treated with water (5 mL) and acidified with dilute HCl. The organic layer was separated, washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to

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(40) R. T. Standridge, H. G. Howell, J. A. Gylys, R. A. Partyka, and A. T. Shulgin, *J. Med. Chem.*, **19**, 1400 (1976).

Table III. Physical and Spectral Data of Anthracenols

compd[a]	yield, %	mp, °C (solvent)	IR ($CHCl_3$) ν, cm^{-1}	NMR ($CDCl_3$), δ	MS, m/e (M^+)
8	97	156 (MeOH)	3300, 1635	2.47 (s, 3 H, Me), 3.96 (s, 3 H, OMe), 4.05 (s, 9 H, 3 OMe), 6.47 (s, 1 H, C-3 H), 6.55 (d, 1 H, J = 2 Hz, C-7 H), 7.27 (d, 1 H, J = 2 Hz, C-9 H), 8.60 (s, 1 H, C-5 H), 10.43 (s, 1 H, OH)	328
13a	75	173 (MeOH)	3300 (br), 1635 (w)	2.42 (s, 3 H, Me), 3.93, 4.0, 4.05 (3 s, 9 H, 3 OMe), 6.37-8.64 (m, 5 H, Ar H), 10.47 (s, 1 H, OH)	298
13b	74	182 (MeOH)	3320, 1630 (w)	2.45 (s, 3 H, Me), 3.90, 4.03, 4.10 (3 s, 9 H, 3 OMe), 6.50-8.23 (m, 5 H, Ar H), 11.90 (s, 1 H, OH)	298
13c	95	218-219 (MeOH)	3380, 1680, 1630	2.40 (s, 3 H, Me), 3.86 (s, 3 H, OMe), 3.97 (s, 6 H 2 OMe), 4.0 (s, 3 H, OMe), 6.42-6.53 (m, 3 H, Ar H), 8.49 (s, 1 H, C-5 H), 10.79 (s, 1 H, OH)	328
18	71	118 (Et_2O)	*b*	2.43 (s, 3 H, Me), 3.96, 4.03 (2 s, 6 H, 2 OMe), 6.86-7.46 (m, 5 H, Ar H), 8.46 (d, 1 H, J = 10 Hz, Ar H), 11.16 (s, 1 H, OH)	*b*

[a] Anal. Calcd (found): **13a** ($C_{18}H_{18}O_4$) C, 72.47 (72.44); H, 6.08 (6.27); **13b** ($C_{18}H_{18}O_4$) C, 72.47 (72.02); H, 6.08 (6.27); **8** ($C_{19}H_{20}O_5$), **13c** ($C_{19}H_{20}O_5$), and **18** ($C_{17}H_{16}O_3$), analysis precluded by rapid oxidation to **9**, **14c**, and **19a**, respectively. [b] Not obtained due to oxidation to **19a**.

Table IV. Physical and Spectral Data of Anthraquinones

compd[a]	yield, %	mp, °C (solvent)	IR ($CHCl_3$) ν, cm^{-1}	NMR ($CDCl_3$), δ	MS, m/e (M^+)
9[b]	62	193[c] (CH_2Cl_2-Et_2O)	1665	2.33 (s, 3 H, Me), 3.86 (s, 3 H, OMe), 3.93 (s, 9 H, 3 OMe), 6.66 (d, 1 H, J = 2 Hz, C-7 H), 7.09 (s, 1 H, C-4 H), 7.20 (d, 1 H, J = 2 Hz, C-9 H)	342
14a[b]	63[d]	162[e] (EtOH)	1670, 1590	2.40 (s, 3 H, Me), 3.84, 3.97, 4.00 (3 s, 9 H, 3 OMe), 7.0-7.72 (m, 4 H, Ar H)	312
14b[b]	67[f]	166-167[g] (EtOH)	1670, 1590	2.48 (s, 3 H, Me), 3.96 (s, 3 H, OMe), 4.0 (s, 6 H 2 OMe), 7.08-7.88 (m, 4 H, Ar H)	312
14c	51	239 (EtOH)	1675	2.38 (s, 3 H, Me), 3.96 (s, 12 H, 4 OMe), 7.10 (s, 1 H, Ar H), 7.23 (s, 2 H, Ar H)	342
19a[b]	71	192[h] (EtOH)	1665	2.45 (s, 3 H, Me), 3.98, 4.01 (2 s, 6 H, 2 OMe), 7.24-8.33 (m, 5 H, Ar H)	282
19b	97	186 (EtOH)	3470, 1670, 1630	2.42 (s, 3 H, Me), 4.17 (s, 3 H, OMe), 7.57-8.66 (m, 5 H, Ar H), 13.42 (s, 1 H, OH)	268
1c	60	204[i] (EtOH)		2.40 (s, 3 H, Me), 4.03 (s, 3 H, OMe), 6.73, 7.08, 7.33 (3 s, 3 H, Ar H)[j]	300
1d[b]	80	246[k] (EtOH)		*l*	286
1e[b]	80	261[m] (CH_2Cl_2-MeOH)		*l*	286
1f[b]	59	283-284[n] (EtOH)		*l*	254

[a] Anal. Calcd (found): **14c** ($C_{19}H_{18}O_6$) C, 66.66 (66.20); H, 5.30 (5.42); **19b** ($C_{16}H_{12}O_4$) C, 71.64 (71.39); H, 4.51 (4.66). [b] A sample of this compound showed no melting point depression when mixed with an authentic material. [c] Lit.[35] mp 190-191 °C. [d] Overall yield from **12a**. [e] Lit.[30] mp 161-161.5 °C. [f] Overall yield from **12b**. [g] Lit.[14b] mp 163-164 °C. [h] Lit.[33] mp 193 °C. [i] Lit.[28] mp 205-206 °C. [j] Determined in $CDCl_3$-Me_2SO-d_6. [k] Lit.[28] mp 245-246 °C, lit.[29] mp 244-246 °C. [l] Not determined owing to solubility problems. [m] Lit.[31] 260-263 °C, lit.[32b] 258-260 °C. [n] Lit.[36] mp 287-288 °C.

dryness to give the amide alcohol **5** as a viscous oil (3.1 g, 75%). A solution of this crude material and *p*-toluenesulfonic acid (500 mg, 2.6 mmol) in toluene (60 mL) was refluxed for 8 h. The cooled mixture was washed with three portions of a 5% aqueous Na_2CO_3 solution, dried (Na_2SO_4), and evaporated to dryness to afford crystalline material which upon recrystallization from MeOH gave 2.17 g (63% overall) of pure **6** as a colorless powder, mp 201 °C (see Table I).

(b) *o*-Benzylbenzoic Acids 7, 12a, 12b, 12c, and 17. The procedure given below for the preparation of **7** illustrates the method used for obtaining compounds **12a**, **12b**, **12c**, and **17**. Where the product was noncrystalline after workup, chromatography over a short column of silica gel (10:1 CH_2Cl_2:MeOH) provided a pure product (see Table II).

3,5-Dimethoxy-2-(2′,5′-dimethoxy-4′-methylbenzyl)benzoic Acid (7). A mixture of the phthalide **6** (344 mg, 1 mmol) and 5% palladium on charcoal (150 mg) in glacial acetic acid (150 mL) was heated at 85 °C for 8 h under a hydrogen atmosphere by using a balloon attachment to the condenser. The catalyst was removed by filtration, and the filtrate was evaporated to dryness to give crystalline material which upon recrystallization from MeOH afforded 320 mg (95%) of compound **7** as colorless needles, mp 176 °C.

(c) Anthracenols 8, 13a, 13b, 13c, and 18. The following

procedure for compound 8 illustrates the preparation of the title anthracenols (see Table III).

1,4,6,8-Tetramethoxy-2-methylanthracen-10-one (8). To a solution of the benzylbenzoic acid **7** (100 mg, 0.29 mmol) in dry chloroform (200 mL) was added trifluoroacetic anhydride (0.04 mL, 0.3 mmol). The mixture was stirred at room temperature for 6 h and evaporated to dryness. The resulting viscous residue was triturated with methanol (10 mL) to give crystalline material which upon recrystallization from MeOH provided 92 mg (97%) of the anthracenol **8**, mp 156 °C. This was used directly in the next step.

(d) Anthraquinones 9, 14a, 14b, 14c, and 19a. The representative procedure for compound **9** illustrates the general method (see Table IV).

1,4,6,8-Tetramethoxy-2-methylanthra-5,10-quinone (9). A stirred mixture of the anthracenone **8** (50 mg, 0.15 mmol) and chromium trioxide (50 mg) in acetic acid (50 mL) was treated with 1 drop of water in order to initiate the reaction. After being stirred 12 h at room temperature, the mixture was evaporated to give a residue which was basified with 5% Na_2CO_3 solution and extracted with CH_2Cl_2 (2 × 50 mL). The organic extract was dried (Na_2SO_4) and evaporated to dryness to give a solid which upon chromatography (neutral Al_2O_3, activity 2, CH_2Cl_2 eluent) furnished 26 mg (51%) of catenarin tetramethyl ether (**9**) as yellow-orange needles, mp 239 °C.

(e) Naturally Occurring Anthraquinones. Erythroglaucin (1c). Boron tribromide (0.16 mL, 1.6 mmol) in dry methylene chloride (5 mL) was added dropwise to a stirred solution of catenarin tetramethyl ether (**9**; 65 mg, 0.19 mmol) in CH_2Cl_2 (50 mL) at −78 °C. The dry ice–acetone bath was removed, and the mixture was stirred for 12 h. Water (50 mL) and 5% Na_2CO_3 solution (1 mL) were added, and the resulting precipitate was collected. Chromatography (silica gel, CH_2Cl_2 as eluent) and recrystallization (EtOH) gave 34 mg (60%) of erythroglaucin (**1c**) as red-orange plates, mp 204 °C (lit.[35] mp 205–206 °C), identical by IR and UV with those reported in the literature.[2]

Catenarin (1d). Catenarin tetramethyl ether (**9**; 70 mg, 0.20 mmol) was heated with pyridine hydrochloride (3 g, 26 mmol) at 180 °C (oil bath temperature) for 8 h. The cooled mixture was treated with water, and the resulting precipitate was collected, washed with water, and air-dried. Chromatography (silica gel) gave in order of elution erythroglaucin (**1c**; CH_2Cl_2 as eluent) and catenarin (**1d**; 2% MeOH in CH_2Cl_2 as eluent). Recrystallization of both fractions from EtOH afforded respectively 6 mg (10%) of erythroglaucin, shown to be identical by melting point and mixture melting point with the sample obtained above, and 40 mg (80%) of catenarin as red plates, mp 246 °C (lit.[29] mp 244–246 °C). The identity of catenarin with an authentic sample supplied by Professor Shibata was established by melting point, mixture melting point, and spectral (IR) comparison.

Cynodontin (1e). Cynodontin tetramethyl ether (**14c**; 70 mg) was subjected to the exact reaction conditions used for the preparation of catenarin (**1d**) to give (without chromatography) 40 mg (80%) of cynodontin (**1e**) as fine brown plates, mp 261 °C (lit.[32b] mp 258–261 °C; lit.[32c] mp 259–260 °C), which was shown to be identical with an authentic sample provided by Professor Schofield by melting point, mixture melting point, and spectral (IR and UV) comparison.

Soranjidiol 7-Methyl Ether (19b). Soranjidiol dimethyl ether (**19a**; 28 mg) was treated according to the conditions used for the preparation of erythroglaucin (**1c**) except that the reaction mixture was stirred for only 3 h to furnish 26 mg (97%) of compound **19b** as yellow needles, mp 186 °C.

Soranjidiol (1f). Soranjidiol dimethyl ether (**19a**; 56 mg) was demethylated by using the conditions for the preparation of catenarin (**1d**) except that the period of heating was reduced to 6 h. Chromatography (silica gel) gave in order of elution soranjidiol 7-methyl ether (**19b**; 10 mg, 18% after recrystallization from EtOH), identical with the sample obtained above, and soranjidiol (**1f**; 30 mg, 59%, from EtOH). The sample of soranjidiol, orange-brown needles, showed a mp 283 °C (lit.[36] mp 287–288 °C) and UV spectrum identical with those reported in the literature.[2]

Hydroxyamide 15. Amide **10b** (2.07 g, 10 mmol) was sequentially treated with *sec*-BuLi (6.7 mL, 1.5 M solution) and the *p*-tolualdehyde **4** (1.8 g, 10 mmol) under the conditions described for the preparation of **6**. The same workup provided a gum which upon recrystallization from MeOH afforded 2.45 g (63%) of **15**: mp 154 °C; IR ($CHCl_3$) ν 3400, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.20 (2 overlapping t, 6 H), 2.25 (s, 3 H), 3.20–3.93 (2 overlapping q, 4 H), 3.55, 3.81, 3.85 (3 s, 9 H), 5.97 (s, 1 H), 6.43–7.37, m, 5 H); mass spectrum, *m/e* 387 (M^+). Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 67.87; H, 7.75; N, 3.51.

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Registry No. **1c**, 476-57-3; **1d**, 476-46-0; **1e**, 476-43-7; **1f**, 518-73-0; **3**, 38228-27-2; **4**, 4925-88-6; **5**, 72003-88-4; **6**, 72003-89-5; **7**, 72003-90-8; **8**, 72003-91-9; **9**, 72003-92-0; **10a**, 62924-93-0; **10b**, 51674-10-3; **10c**, 72003-93-1; **10d**, 72003-94-2; **11a**, 71011-52-4; **11b**, 70946-24-6; **11c**, 72003-95-3; **12a**, 51837-74-2; **12b**, 70946-25-7; **12c**, 72003-96-4; **13a**, 70946-22-4; **13b**, 70946-26-8; **13c**, 72003-97-5; **14a**, 50457-06-2; **14b**, 51837-73-1; **14c**, 72030-20-7; **15**, 70946-23-5; **16**, 72003-98-6; **17**, 72003-99-7; **18**, 72004-00-3; **19a**, 72004-01-4; **19b**, 72004-02-5.