to the National Science Foundation (CHE 8305785) and the National Institutes of Health (RR 01912) for instrumentation grants used for the acquisition of 360-MHz and 500-MHz NMR spectrometers. We are also grateful to Mr. Carlton L. Campbell for technical assistance and to Dr. Franz Scheidl of Hoffman-LaRoche, Inc. for performing the combustion analyses.

Registry No. (±)-**2**, 28405-98-3; (±)-**3**, 79068-83-0; **11**, 120-57-0; **12**, 92143-67-4; **13**, 92143-68-5; **14**, 107201-33-2; **16**, 92143-84-5; **17d**, 92143-69-6; (±)-**18a** (isomer 1), 107201-37-6; (±)-**18a** (isomer 2), 107201-39-8; (±)-**18d** (isomer 1), 92143-70-9; (±)-**18d** (isomer 2), 92143-71-0; **19** (X = Br, R = OMe), 107201-34-3; (±)-**22a**, 107201-35-4; (±)-**22b**, 107201-36-5; **26**, 107201-38-7; (±)-**27**, 92143-73-2; (±)-**28**, 92143-74-3; (±)-**32**, 92143-80-1; (±)-**33**, 107222-36-6; (±)-**34**, 92143-81-2; (±)-**35**, 92143-83-4; (±)-**36**, 92143-75-4; (±)-**37**, 92143-76-5; (±)-**45**, 92143-78-7; (±)-**46**, 92143-77-6; (±)-**48**, 92143-79-8; *N*-methylaminoacetaldehyde diethyl acetal, 20677-73-0; *N*-[(allyloxy)carbonyl]-*N*-methylaminoacetaldehyde diethyl acetal, 107201-32-1; diethyl [(benzylideneamino)methyl]phosphonate, 50917-73-2; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6; allyl chloroformate, 2937-50-0; benzyl chloroformate, 501-53-1.

Total Synthesis of Isoflavones: Jamaicin, Calopogonium Isoflavone-B, Pseudobaptigenin, and Maxima Substance-B. Friedel-Crafts Acylation Reactions with Acid-Sensitive Substrates†

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Received November 13, 1986

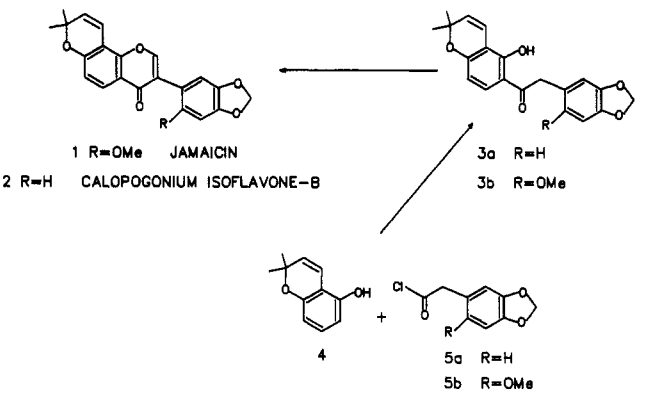
The Friedel-Crafts acylation reaction was studied on several acid-sensitive substrates. Under the proper conditions of varying Lewis acids, solvents, and reaction temperatures, the acylation indeed took place, thus obviating the necessity for functional group protection-deprotection sequences. By use of these procedures, the naturally occurring isoflavones jamaicin (**1**), calopogonium isoflavone-B (**2**), maxima substance-B (**30**), and pseudobaptigenin (**31**) were synthesized and characterized.

We have been examining the scope and limitations of the Lewis acid (titanium tetrachloride and aluminum chloride) mediated Friedel-Crafts acylation reaction using sensitive substrates and acylating agents and have found that, under certain conditions, not only do the reactants survive the process, but the reaction is highly regioselective. As a demonstration of the potential of this methodology for synthesizing heterocycles, we decided to try to synthesize several naturally occurring isoflavones that contain sensitive functionality in a highly efficient manner without resorting to any of the often employed functional group protection-deprotection sequences.

Isoflavones[1] are the most abundant subset of the flavonoid class of compounds which also includes pterocarpans,[2] rotenoids,[3] and coumestans.[4] Structurally, isoflavones are highly substituted and oxygenated derivatives of 3-phenylchromans. Much work on the biosynthesis of isoflavones from phenylpropyl precursors (e.g., shikimic, prephenic, and phenylpyruvic acids and phenylalanine) has been reported,[5] but the complete pathway has not yet been defined.

The highly oxygenated versions of isoflavones often have estrogenic activity.[6] Crude preparations of these compounds have also been used as fish narcotics,[6] insecticides, and antifungals[7] for many years in Central and South America. This wide range of biological properties has stimulated interest in the synthesis of natural and unnatural analogues of isoflavones.

Scheme I



Previous syntheses of isoflavones fall into two main categories: (1) routes deriving from chalcone-based systems[8,9] and (2) syntheses from benzoin precursors.[10-12]

† This manuscript and work is dedicated with the greatest respect and admiration to Professor George Büchi of the Massachusetts Institute of Technology on the occasion of his 65th birthday.

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(1) (a) Dewick, P. M. In *The Flavonoids: Advances in Research*; Harborne, J. B.; Mabry, T. J.; Eds.; Chapman and Hall: London, 1982; Isoflavonoids, pp 535-640. (b) Torck, M. *Fitoterapia* **1976**, *47*, 195. (c) Ollis, W. D. In *The Chemistry of Flavonoid Compounds*; Geissman, T. A.; Ed.; Pergamon: Oxford, 1962; p 353. (d) Dean, F. M. *Naturally Occurring Oxygen Ring Compounds*; Butterworths: London, 1963; p 366. (e) Wong, E. *Fortschr. Chem. Org. Naturst.* **1970**, *28*, 61.

(2) Jain, A. C.; Tuli, D. K. *J. Sci. Ind. Res.* **1978**, *37*, 287.

(3) Jain, A. C.; Kumar, A.; Kohli, A. K. *J. Sci. Ind. Res.* **1978**, *37*, 606.

(4) Darbarwar, M.; Sundaramurthy, J.; Subba Rao, N. V. *J. Sci. Ind. Res.* **1976**, *35*, 297.

(5) Wong, E. In *The Flavonoids*; Harborne, J. B.; Mabry, T. J.; Mabry, H.; Eds; Chapman and Hall: London, 1975; p 743. (b) McClure, J. W., ref 5a, p 970.

(6) Russel, A.; Kaczka, E. A. *J. Am. Chem. Soc.* **1944**, *66*, 548.

(7) Auxence, E. C. *J. Econ. Bot.* **1954**, *7*, 270.

(8) (a) Jain, A. C.; Sarpal, P. D.; Seshadri, T. R. *Indian J. Chem.* **1965**, *3*, 369. (b) Jain, A. C.; Gupta, S.; Gupta, A.; Bambah, P. *Indian J. Chem., Sect. B* **1985**, *24B*, 609.

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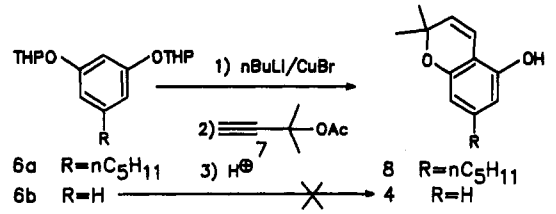
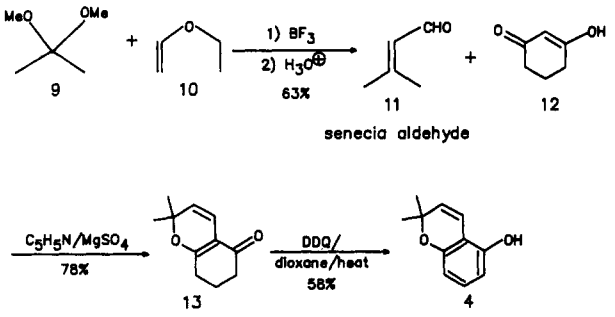
Scheme II



Scheme III

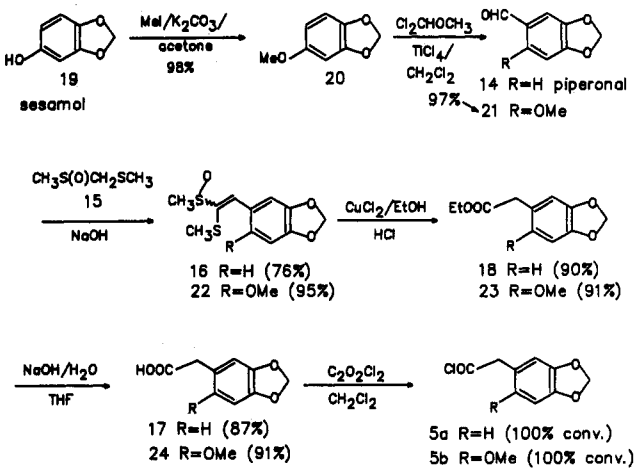


Friedel–Crafts acylation reactions to form the benzoin derivatives[13] have been used infrequently because of a combination of harsh reaction conditions coupled with often sensitive substrates, regiochemical uncertainties, and instability of the requisite phenacetyl halides.

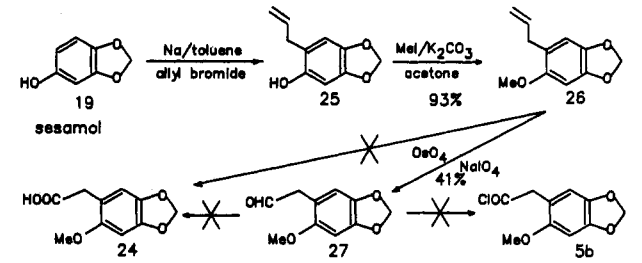
In order to test the limits of the Friedel–Crafts methodology for forming the crucial carbon–carbon bond of a sensitive deoxybenzoin via direct acylation, we first targeted the isoflavones jamaicin (1) and calopogonium isoflavone-B (2). Jamaicin (1) was isolated from *Piscidia erythrina* bark root and the structure determined.[14] Only one synthesis of jamaicin (1) has been reported[15] and was accomplished by oxidative rearrangement (thallium trinitrate (TTN)) of the requisite chalcone derivative. Calopogonium isoflavone-B (2) was isolated from ether extracts of *Calopogonium mucunoides* seeds[16] and a synthesis reported by Vilain.[17]

Our synthetic plan for the synthesis of these substances is shown in Scheme I. Jamaicin (1) and calopogonium isoflavone-B (2) could easily be formed from the deoxybenzoin systems **3b** and **3a**, respectively, by any of a number of excellent formylation procedures.[18] This crucial and sensitive[19] deoxybenzoin would be prepared directly by the Friedel–Crafts acylation of 2,2-dimethyl-5-hydroxychrom-3-ene (4) with a suitably homologated pi-

Scheme IV



Scheme V



peronal- (**5a**) or sesamol- (**5b**) derived acid halide.

Although there are a number of reported methods for synthesizing 2,2-dimethylchrom-3-enes,[20] many of these do not easily lend themselves to the preparation of the 5-hydroxy derivative **4** because of the necessity of substitution occurring at some point between two meta hydroxyl groups on the phenyl ring. Our initial attempts to synthesize **4** were based on the report by Spronck and co-workers[21] (Scheme II) that olivetol bis(tetrahydropyranyl) ether (**6a**) could be efficiently metalated and subsequently reacted with 3-acetoxy-3-methyl-1-butyne (**7**) to afford chromene **8**. However, repeated attempts of this sequence using the analogous resorcinol bis(tetrahydropyranyl) ether (**6b**) gave none of the desired product **4**.[22] Ultimately, we prepared quantities of the phenol **4** by the route outlined in Scheme III. 2,2-Dimethoxypropane (**9**) and ethyl vinyl ether (**10**) were reacted by using a modification of the procedure of Julia,[23] to afford senecia aldehyde **11** in approximately 63% yield. Reaction of aldehyde **11** with 1,3-cyclohexanedione (**12**) using the method of deGroot[24] afforded enone **13** (78%). This was readily aromatizied to the desired phenol **4** with DDQ (58%). We have found this overall procedure to be very adaptable to produce relatively large amounts of material.

The phenacetyl halides for the syntheses of **1** and **2** were prepared as shown in Scheme IV. Piperonal (**14**) was condensed with methyl methylsulfinylmethyl sulfide (**15**) according to the procedure of Tsuchihashi[25] to give a 76%

(9) (a) Ollis, W. D.; Ormand, K. L.; Sutherland, I. O. *J. Chem. Soc., Chem. Commun.* **1968**, 1237. (b) Farkas, L.; Gottsegen, A.; Nogradi, J.; Antus, D. *J. Chem. Soc., Perkin Trans. 1* **1974**, 305.

(10) Narasimhachari, N.; Seshadri, T. R. *Proc. Indian Acad. Sci., Sect. A* **1949**, *30A*, 151.

(11) Row, L. R.; Seshadri, T. R. *Proc. Indian Acad. Sci., Sect. A* **1951**, *34A*, 187.

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(13) (a) Whalley, W. B. *J. Chem. Soc.* **1957**, 1833. (b) Krishnamurki, M.; Seshadri, T. R. *Proc. Indian Acad. Sci., Sect. A* **1954**, *39A*, 144.

(14) (a) Stamm, O. A.; Schmid, H.; Buchi, J. *Helv. Chim. Acta* **1958**, *41*, 2006. (b) Buchi, J.; Schmid, H.; Kapoor, A. L. *Arch. Pharm. Chemi* **1961**, *68*, 183. (c) Moore, J. A.; Eng, S. *J. Am. Chem. Soc.* **1956**, *78*, 395.

(15) Antus, S.; Farkas, L.; Goettsegen, A.; Kardos-Balogh, Z.; Nogradi, J. *Chem. Ber.* **1976**, *109*, 3811.

(16) Vilain, C.; Jadot, J. *Bull. Soc. R. Sci. Liege* **1976**, *45*, 468.

(17) Vilain, C.; Jadot, J. *Bull Soc. Chem. Belg.* **1977**, *86*, 237.

(18) (a) Pelter, A.; Foot, S. *Synthesis* **1976**, 326. (b) Baker, W.; Harborne, J. B.; Ollis, W. D. *J. Chem. Soc.* **1953**, 1860. (c) Bass, R. J. *J. Chem. Soc., Chem. Commun.* **1976**, 78.

(19) Jain (cf. ref 8b) and Whiting (cf. Thomas, P.; Whiting, D. A. *Tetrahedron Lett.* **1984**, 1099 and references contained therein) have reported that the 2,2-dimethylchrom-3-ene moiety does not survive under the oxidative TTN conditions.

(20) For a recently published, excellent method for the synthesis of 2,2-dimethyl-5-hydroxychrom-3-ene (4) and a thorough compilation of references for previous work in the area see: ApSimon, J. W.; Herman, L. W.; Huber, C. *Can. J. Chem.* **1985**, *63*, 2589.

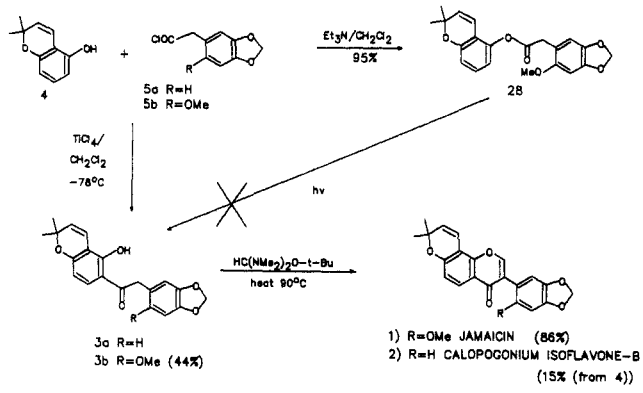
(21) Luteijn, J. M.; Spronck, H. J. W. *J. Chem. Soc., Perkin Trans. 1* **1979**, 201.

(22) Our attempts to carry out this sequence using olivetol and orcinol bis-THP ethers were in fact successful, thus duplicating the work of Spronck.

(23) (a) Julia, M.; Julia, S.; Langlois, M. *Bull. Soc. Chim. Fr.* **1965**, 1007. (b) Julia, M.; Julia, S.; Langlois, M. *Chem. Abstr.* **1965**, *63*, 3001C.

(24) deGroot, A.; Jansen, B. J. M. *Tetrahedron Lett.* **1975**, 3407.

Scheme VI

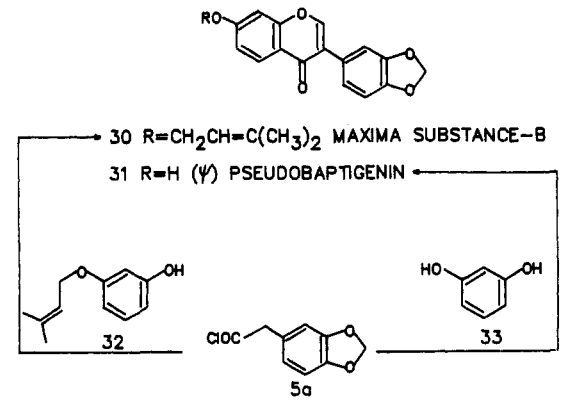


yield of the ketene thioacetal **16**. We were unable to reproducibly hydrolyze the acetal **16** to the phenylacetic acid **17** or ester **18** derivatives in high yield by the reported methods.[25] However, modification of Tsuchihashi's later procedure[26] by using cupric chloride in ethanol and adding saturated ethanolic HCl afforded a 90% yield of ethyl ester **18**, which was subsequently hydrolyzed to the desired acid **17** in 87% yield. Finally, conversion of **17** to acid chloride **5a** was by treatment with oxalyl chloride (100%). (It must be mentioned at this point that these acid halides[27] (**5a** and **5b**) are quite unstable when solutions are concentrated and thus were freshly prepared in methylene chloride just prior to the Friedel–Crafts acylation reaction.)

The other acid chloride **5b** was prepared in a similar fashion from sesamol (**19**). Sesamol (**19**) was O-methylated to afford ether **20** (98%) and the formyl group then introduced by using α,α-dichloromethyl methyl ether/$TiCl_4$[28] to give the regioisomerically pure aldehyde **21** (97%). Homologation using the Tsuchihashi procedure[25] gave ketene thioacetal **22** (95%), which underwent smooth ethanolysis (91%) to **23** and subsequent hydrolysis (91%) to phenylacetic acid **24**. Acid halide **5b** was then prepared by treatment of **24** with oxalyl chloride. Overall, we have found these transformations to be very easy to carry out and extremely efficient, affording the desired acid halides **5a** and **5b** in 60% overall yield each from piperonal (**14**) and sesamol (**19**), respectively.[29]

A potentially shorter route to acid **24** from sesamol (**19**) was briefly explored (Scheme V). Sesamol (**19**) was converted into the C-alkylated phenol **25**,[30] which was O-methylated to yield **26** (93%). Attempts to oxidatively cleave the olefin directly to the acid **24**[31] met with little success, and although cleavage to the aldehyde **27** was accomplished in 41% yield (osmium tetraoxide/$NaIO_4$),[32] further oxidation to acid **24**[33] or acid halide **5b** directly[34]

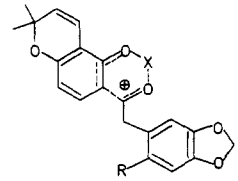
Scheme VII



was similarly unsuccessful. These studies were abandoned when the ketene thioacetal homologation route proved to be highly efficient overall (vide supra).

Our attentions now turned to the key coupling of phenacetyl halides **5a** and **5b** with the hydroxychromene **4**. A mild and potentially very attractive method for forming the required deoxybenzoins using the photo–Fries rearrangement was first considered (Scheme VI). It has been shown[35] that aryl esters can undergo irreversible photochemical rearrangement to the ortho and para C-acylated products, in most cases with the ortho-rearranged product predominating.[36] Treatment of phenol **4** with acid chloride **5b** gave a 95% yield of aryl ester **28**. However, irradiation of **28** disappointingly gave either no reaction or extensive destruction of the reactant functional groups under experimental conditions varying wavelength, solvent, concentration, and reaction times.

The direct acylation using Lewis acids was explored next. Standard Lewis and protic acids (e.g., $AlCl_3$, $SnCl_4$, etc.) in normal Friedel–Crafts solvents gave only extensive decomposition of the starting materials or no reaction. However, treatment of a mixture of acid chloride **5b** and phenol **4** in methylene chloride at −78 °C with a dilute solution of freshly distilled titanium tetrachloride[37] (Scheme VI) gave a 44% yield of regioisomerically pure[38] deoxybenzoin **3b**. No other products were isolated from this reaction. A possible explanation for this observed regiospecificity is shown in **29**, wherein a phenol or a titanium phenolate species (X = H or Ti, respectively)



29 X=H or Ti

(25) (a) Ogura, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1972**, 1383. (b) Ogura, K.; Ito, Y.; Tsuchihashi, G. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2013.

(26) Ogura, K.; Katoh, N.; Yoshimura, I.; Tsuchihashi, G. *Tetrahedron Lett.* **1978**, 375.

(27) The acid bromides could be prepared with equal efficiency by substituting oxalyl bromide in this reaction.

(28) (a) Reiche, A.; Gross, H.; Hoft, E. *Org. Synth.* **1967**, *47*, 1. (b) Cresp, T. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Chem. Commun.* **1972**, 214. (c) Cresp, T. M.; Sargent, M. V.; Elix, J. A.; Murphy, D. P. H. *J. Chem. Soc., Perkin Trans 1* **1973**, 340.

(29) The azalactone-based homologation on aldehyde **21** (cf.: Snyder, H. R.; Buck, J. S.; Ide, W. S. *Org. Synth.* **1943**, 333. Crawford, M.; Little, W. T. *J. Chem. Soc.* **1959**, 729) produced only low yields of the acid **24** in our hands.

(30) Alexander, B. H.; Gertler, S. I.; Brown, R. T.; Oda, T. A.; Beroza, M. *J. Org. Chem.* **1959**, *24*, 1504. (b) Beroza, M. *J. Agric. Food Chem.* **1956**, *4*, 49.

(31) (a) Carlsen, R. J. H.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Krapcho, A. P.; Larson, J. R.; Eldridge, J. M. Ibid. **1977**, *42*, 3749. (c) Sam, D. J.; Simmons, H F. *J. Am. Chem. Soc.* **1972**, *94*, 4024.

(32) Shamma, M.; Rodriguez, H. R. *Tetrahedron* **1968**, *24*, 6583.

(33) (a) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399. (b) Scholz, D. *Monatsh. Chem.* **1979**, *110*, 1471. (c) Ho, T.-L.; Olah, G. A. *Synthesis* **1976**, 807.

(34) (a) Cheung, Y.-F. *Tetrahedron Lett.* **1979**, 3809. (b) Winstein, S.; Seubold, F. H. *J. Am. Chem. Soc.* **1947**, *69*, 2916.

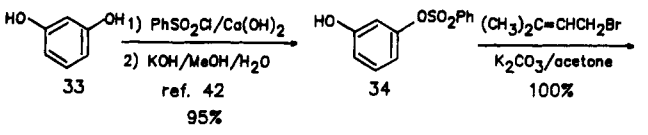
(35) (a) Jortner, F. *J. Polym. Sci.* **1959**, *37*, 199. (b) Meyer, L. W. A.; Georhart, W. M. *Ind. Eng. Chem.* **1951**, *43*, 1585.

(36) For reviews on the photochemical Fries rearrangement see: (a) Bellus, D.; Hrdlovic, P. *Chem. Rev.* **1967**, *67*, 599. (b) Pitts, J. N.; Hammond, G. S.; Noyes, W. A. *Adv. Photochem.* **1971**, *8*, 109.

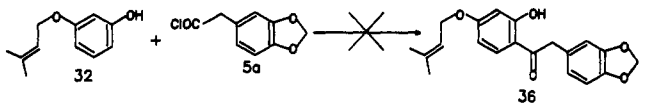
(37) (a) Olah, G. A. In *Friedel–Crafts Chemistry*; p 277; Wiley: New York, 1973; Chapter V, p 277. (b) DeHaan, F. P.; Covey, W. D.; Ezelle, R. L.; Margetan, J. E.; Pace, S. A.; Sollenberger, M. J., Wolf, D. S. *J. Org. Chem.* **1984**, *49*, 3954.

(38) Gross et al. (cf. Gross, H.; Rieche, A.; Matthey, G. *Chem. Ber.* **1963**, *96*, 308) have shown that the titanium tetrachloride formylation of phenols with α,α-dichloromethyl methyl ether gives, in many cases, the ortho-substituted aldehyde.

Scheme VIII



Scheme IX

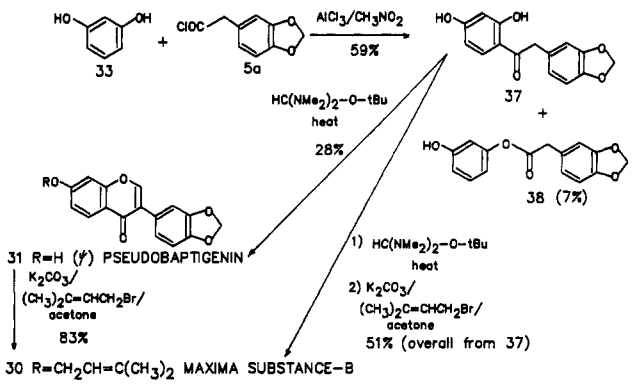


complexes with the phenacetyl acylium ion to proceed through a six-membered transition state and thereby promote the ortho-acylation that is observed. Formylation of deoxybenzoin **3b** occurred upon treatment with neat bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent[39]) to give jamaicin (**1**) in 86% yield. The advantage of this method over that using *N,N*-dimethylformamide dimethyl acetal[18a] is that the reaction is complete in <30 min at 90 °C as compared with 3–4 h. The spectroscopic data and physical properties of synthetic jamaicin (**1**) were in agreement with those reported.[14c]

In an analogous manner, calopogonium isoflavone-B (**2**) was synthesized (Scheme VI). Phenol **4** was acylated with phenacetyl chloride **5a** under the conditions previously developed for jamaicin (**1**). Surprisingly, this yielded a very complex mixture of products from which the desired deoxybenzoin **3a** could not be separated. However, the crude product mixture was formylated by using Bredereck's reagent,[39] and calopogonium isoflavone-B (**2**) was isolated in 15% overall yield (from **4**). The physical and spectroscopic properties of this material were identical with those previously reported.[16] It has not as yet been determined what is the role of the 2′-methoxy group (**5a** vs. **5b**) in the acylation reaction, but it is clear that it causes a significant change in the efficiency.

We sought to test the limits of this acylation reaction in terms of substrate sensitivity and therefore examined synthetic routes to maxima substance-B (**30**)[40] and pseudobaptigenin (**31**).[41] A direct route to maxima substance-B (**30**) would require *O*-prenylresorcinol (**32**) as the nucleophilic partner, while the pseudobaptigenin (**31**) precursor would be resorcinol (**33**) (Scheme VII).

Scheme X



O-Prenylresorcinol (**32**) was synthesized by using a very efficient route in four steps (>91% overall) from resorcinol (**33**) (Scheme VIII). Resorcinol monobenzenesulfonate (**34**) was prepared from resorcinol (**33**) (95%),[42] and subsequently converted to prenyl ether **35** (100%). The sulfonate ester was then hydrolyzed to afford phenol **32** in 95% yield.

Unfortunately, when **32** subjected to the acylation reaction conditions previously used (Scheme IX), extensive decomposition of the prenyl phenol **32** occurred and none of the expected deoxybenzoin **36** was isolated. Since the prenyl group in **32** appeared to be even more labile than the similar moiety found in **4**, it was decided to make its addition the penultimate stage of the synthesis. Thus, the immediate target became pseudobaptigenin (**31**), as this material had previously been converted into maxima substance-B (**30**)[40g] (vide infra).

Resorcinol (**33**) is often a difficult substrate for Friedel–Crafts acylation because of its limited solubility in standard solvents and high reactivity. The best conditions found to effect the acylation were to treat a mixture of freshly prepared acid chloride **5a** and resorcinol (**33**) in nitromethane at 0 °C with anhydrous $AlCl_3$ (Scheme X). This gave deoxybenzoin **37** (59%), and a small amount (7%) of aryl ester **38**.[43] Formylation of **37** with Bredereck's reagent[39] gave pseudobaptigenin (**31**) (28%)[44] that had physical and spectroscopic properties that were identical with those reported.[41i] Pseudobaptigenin (**31**) was converted into maxima substance-B (**30**) by *O*-alkylation with prenyl bromide (83% from pure pseudobaptigenin (**31**); 51% overall from deoxybenzoin **37**[44] using crude pseudobaptigenin (**31**) obtained directly from the formylation reaction of **37**). The physical and spectroscopic properties were in full accord with those reported for maxima substance-B (**30**).[40e] The syntheses of the isoflavones maxima substance-B (**30**) and pseudobaptigenin (**31**) are thus secured.

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(43) Our melting point for deoxybenzoin **37** (87–89 °C) differs from that reported by Sastry (ref 40c) (146–148 °C) even after repeated purifications. Using Sastry's recrystallization solvent (acetone–benzene) led to complete dissolution of **37**, even at −76 °C. Furthermore, the reported elemental analysis (ref 40c) was off on carbon by >0.5%. Therefore, it is likely that we were dealing with a different molecule. We have firmly established the identity of deoxybenzoin **37** through spectroscopic and physical properties as well as conversion to pseudobaptigenin (**31**) and maxima substance-B (**30**).

(44) We believe that the low yield for the formylation is attributable to the difficulty in chromatographic purification as pseudobaptigenin (**31**) is an extremely insoluble compound. This is supported by the observation that the crude pseudobaptigenin (**31**) from the formylation is converted with fairly high efficiency (51% from **37**) into maxima substance-B (**30**).

In conclusion, we have found that by judicious choice of the Lewis acid, solvent, and reaction temperature, the Friedel–Crafts acylation reaction can occur using very sensitive substrates and acylating agents with reasonable efficiency. By use of this concept, the naturally occurring isoflavones jamaicin (1), calopogonium isoflavone (2), maxima substance-B (30), and pseudobaptigenin (31) have been synthesized without the need for protection of sensitive functional groups during the acylation. This application may find considerable use in the synthesis of heterocyclic systems in the future.

Experimental Section

Proton NMR spectra were obtained as $CDCl_3$ solutions on either a Varian EM-360, a Varian XL-100, or an IBM WP-200 spectrometer using tetramethylsilane as an internal reference. Infrared spectra were recorded on a Perkin-Elmer 281 spectrometer using polystyrene (1601 cm^{-1}) as a reference. Mass spectra were obtained on either Bell & Howell 21-4592 (70 eV), Hitachi RMU-6E, or VG Analytical 7070E high-resolution mass spectrometers (HRMS).

Melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus. Elemental analyses were performed by Dr. Franz Kasler of the University of Maryland.

Flash chromatography refers to the method of Still,[45] and E. Merck silica gel 60 (230–400 mesh) was used. Thin-layer chromatography (TLC) was performed on E. Merck glass-supported silica gel plates (silica gel 60 F-254; 0.25 mm). Product visualization was achieved with either vanillin spray, I_2, or ultraviolet light as appropriate.

Ethyl acetate, hexanes, pentane, and Skellysolve-F were all distilled prior to use. Benzene, methylene chloride, and *p*-dioxane were distilled from calcium hydride. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone. Solvent concentrations were prepared prior to use by percent volume to volume.

3-Methylbut-2-enal (Senecia Aldehyde) (11). The synthesis of senecia aldehyde was adapted from the procedure of Julia.[23] 2,2-Dimethoxypropane (**9**) (201.05 g, 1.93 mol) and boron trifluoride etherate (1.3 mL) were cooled to 0 °C and stirred vigorously as ethyl vinyl ether (**10**) (102.00 g, 135.00 mL, 1.41 mol) was added dropwise over a period of 2 h; an internal temperature of 10–20 °C was maintained throughout the addition. The brown mixture was then stored at −5 °C for 12 h. Sodium ethoxide (1.7 g) was added to the mixture, and unreacted 2,2-dimethoxypropane (**9**) and methanol were removed by simple distillation at atmospheric pressure. The remaining material was distilled under reduced pressure (38 mmHg, 80 °C) to afford 96.86 g of a clear white liquid. The distillate was treated with 120 mL of 15% phosphoric acid and 1.25 g of hydroquinone and was vigorously stirred at 85 °C for 2.5 h. The darkened reaction mixture was neutralized with solid sodium bicarbonate and extracted with 2 × 75 mL of ether. The combined organic layers were dried over anhydrous magnesium sulfate, and most of the ether was removed by careful evaporation on a rotary evaporator. The residue was distilled twice by using a 48-in. Vigreux column to afford 75.00 g (63%) of senecia aldehyde **11** (bp 35 °C (60 mmHg)) as a clear white liquid that was ca. 95% pure by NMR analysis: NMR ($CDCl_3$, 60 MHz) δ 2.00 (s, 3 H), 2.20 (s, 3 H), 5.88 (d, 1 H, J = 8 Hz), 10.02 (d, 1 H, J = 8 Hz); IR (neat) 2980, 2940, 2760, 1720, 1680, 1380, 1200 cm^{-1}.

2,6,7,8-Tetrahydro-2,2-dimethyl-5*H*-1-benzopyran-5-one (13). This compound was prepared by the method of deGroot and Jansen[24] in 78% yield. It was purified by flash chromatography (15% ethyl acetate in Skellysolve-F as eluant) to afford orange-yellow crystals: mp 40–41 °C (lit.[24] mp 42 °C); NMR ($CDCl_3$, 60 MHz) δ 1.40 (s, 6 H), 2.00 (m, 2 H), 2.32 (m, 4 H), 2.32 (m, 4 H), 5.12 (d, 1 H, J = 10 Hz), 6.31 (d, 1 H, J = 10 Hz); IR (neat) 3380 (br), 2975, 1725, 1640, 1590 cm^{-1}.

5-Hydroxy-2,2-dimethyl-2*H*-1-benzopyran (4). A solution of enone **13** (5.92 g, 33.2 mmol) in 100 mL of dry *p*-dioxane was added to a solution of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (16.58 g, 73.0 mmol) in 400 mL of *p*-dioxane over a period of 3 h under a nitrogen atmosphere. The darkened reaction mixture was then heated at reflux for 42 h, cooled, filtered through a pad of Celite, and concentrated in vacuo. The tarry residue was purified by flash chromatography (5% ethyl acetate in Skellysolve-F as eluant) to afford 3.36 g (57%) of phenol **4** as light yellow needles: mp (recrystallized from ether) 114–116 °C (lit.[46a] mp 130–133 °C; lit.[46b] oil); NMR ($CDCl_3$, 200 MHz) δ 1.42 (s, 6 H), 5.31 (br s, 1 H, exchangeable with D_2O), 5.58 (d, 1 H, J = 10 Hz), 6.29 (dd, 1 H, J_1 = 8 Hz, J_2 = 1 Hz), 6.40 (d of t, 1 H, J = 8 Hz), 6.63 (dd, 1 H, J_1 = 10 Hz, J_2 = 0.6 Hz), 6.92 (dd, 1 H, J_1 = 8 Hz, J_2 = 8 Hz); IR ($CHCl_3$) 3700, 3500–3200 (br), 2985, 1640, 1610, 1585, 1460, 1115, 1040 cm^{-1}.

2-Allyl-4,5-methylenedioxyphenol (25). A solution of 5.21 g (37.7 mmol) of sesamol (**19**) in 70 mL of dry toluene was stirred at 40 °C, and 0.98 g (42.6 mmol) of sodium metal was added to the warm solution. The reaction mixture was then heated at reflux for 6.5 h. The mixture was cooled to 60 °C, and a solution of 4.3 mL (1.3 equiv) of allyl bromide in 5 mL of toluene was added dropwise over a 15-min period. The mixture was brought to reflux and monitored by TLC. Over the next 72 h, three more 4.3-mL aliquots of allyl bromide were added to the reaction. After a total of 85 h, the reaction was cooled to room temperature and filtered and the volatiles evaporated in vacuo. The residue was diluted with 75 mL of water and extracted with 100 mL of pentane. The organic layer was washed with 5 × 30 mL of Claisen's alkali (35 g of KOH/25 mL of H_2O/75 mL of MeOH). The combined aqueous layers were washed with 100 mL of pentane and then acidified with concentrated hydrochloric acid to ca. pH 7. The solution was extracted with 3 × 200 mL of ether; the combined ether layers were dried over magnesium sulfate and evaporated in vacuo. The crude brown oil was filtered through a small layer of 100 g of 60–200 mesh silica gel with 25% ethyl acetate in Skellysolve-F to remove polar constituents. The eluate was evaporated and the residue purified by flash chromatography (5% ethyl acetate in pentane as eluant) to give 3.09 g (46%) of phenol **25** as light tan crystals: mp (recrystallized from ether) 73–74 °C (lit.[47] mp 74.5–75.5 °C). Unreacted sesamol (**19**) (0.51 g) was also recovered: NMR ($CDCl_3$, 60 MHz) δ 3.20 (d, 2 H, J = 6 Hz), 4.90 (m, 1 H), 5.12 (br s, 1 H), 5.22 (br s, 1 H, exchangeable with D_2O), 5.50–6.05 (m, with sharp s at δ 5.78, 3 H), 6.30 (s, 1 H), 6.48 (s, 1 H); IR ($CHCl_3$) 3610, 3400 (br), 3020, 2900, 1640, 1505, 1485, 1170, 1045 cm^{-1}.

2-Allyl-4,5-methylenedioxyanisole (26). Anhydrous potassium carbonate (2.73 g, 19.7 mmol) was added to a solution of 3.05 g (17.1 mmol) of phenol **25** in 75 mL of acetone. The reaction mixture was stirred vigorously for 15 min, and 4.90 g (3.20 mL, 51.0 mmol) of iodomethane was added. The reaction mixture was heated at reflux for 29 h and filtered and the volatiles evaporated in vacuo. Water (100 mL) was added and the mixture extracted with 2 × 50 mL of ether. The combined ether was dried over anhydrous magnesium sulfate and filtered and the volatiles evaporated in vacuo to give a pale yellow oil. Purification by flash chromatography (5% ethyl acetate in Skellysolve-F as eluant) afforded 3.07 g (93%) of anisole **26** as a water white liquid: NMR ($CDCl_3$, 60 MHz) 3.24 (d, 2 H, J = 5 Hz), 3.70 (s, 3 H), 4.80 (m, 1 H), 5.00 (br s, 1 H), 5.53–6.08 (m with sharp s at δ 5.78, 3 H), 6.40 (s, 1 H); IR (neat) 3010, 2900, 1640, 1505, 1490, 1195, 1040 cm^{-1}. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.79; H, 6.43.

(2-Methoxy-4,5-methylenedioxyphenyl)acetaldehyde (27). A solution of 0.164 g (0.853 mmol) of anisole **26** in 8 mL of 3:1 dioxane:water was stirred vigorously and treated with 0.10 mL of 2.5% osmium tetraoxide/*tert*-butyl alcohol solution. After 15 min, 0.417 g (1.95 mmol) of sodium metaperiodate was added in small portions over a 25-min period. The reaction mixture was stirred for an additional 2 h and then diluted with 10 mL of water and extracted with 2 × 30 mL of ether. The combined ether was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to a brown oil. The oil was purified by flash chromatography (20% ethyl acetate in Skellysolve-F as eluant)

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to afford 0.067 g (41%) of pure aldehyde **27** as a clear white oil: NMR ($CDCl_3$, 60 MHz) δ 3.50 (d, 2 H, J = 3 Hz), 3.72 (s, 3 H), 5.85 (s, 2 H), 6.47 (s, 1 H), 6.54 (s, 1 H), 9.50 (t, 1 H, J = 2 Hz); IR (neat) 3015, 2940, 2890, 2780, 1505, 1485, 1195, 1045 cm^{-1}.

3,4-Methylenedioxyanisole (20). A solution of 2.92 g (21.2 mmol) of sesamol (**19**) in 80 mL of acetone was treated with 3.06 g (22.1 mmol) of anhydrous potassium carbonate. After stirring for 1 h, 11.86 g (7.40 mL, 116.6 mmol, 5.5 equiv) of iodomethane was added and the reaction mixture was heated at reflux with vigorous stirring for 42 h. The slurry was filtered through Celite and the filtrate evaporated in vacuo. The residue was diluted with 50 mL of water, and this was extracted with 2 × 35 mL of ether. The combined organic layers were washed with 50 mL of 10% (aqueous) sodium hydroxide, 2 × 50 mL of water, dried over anhydrous magnesium sulfate, and filtered, and the volatiles were evaporated in vacuo. The residue was distilled in vacuo (bulb to bulb) to afford 3.15 g (98%) of anisole **20** as a light yellow oil: bp 80 °C (2 mmHg) (lit.[48] bp 110–114 °C (18 mmHg)); NMR ($CDCl_3$, 60 MHz) δ 3.70 (s, 3 H), 5.84 (s, 2 H), 6.42 (m, 3 H); IR (neat) 3030, 2950, 2900, 1640, 1490, 1250, 1200, 1040, 940 cm^{-1}.

2-Methoxy-4,5-methylenedioxybenzaldehyde (21). A solution of 4.83 g (31.9 mmol) of anisole **20** and 9.79 g (7.70 mL, 85.1 mmol) of α,α-dichloromethyl methyl ether (Aldrich) was dissolved in 20 mL of dry methylene chloride, and the solution was cooled to 0 °C under a nitrogen atmosphere. The solution was stirred vigorously as a solution of 8.65 g (5 mL, 45.5 mmol) of titanium tetrachloride in 20 mL of dry methylene chloride was added via syringe pump over a period of 45 min. The dark green mixture was warmed to room temperature and stirred for an additional 2 h. The reaction was poured into 200 mL of ice water and the aqueous layer thoroughly extracted with 3 × 200 mL of ether. The combined ether layers were washed with saturated sodium bicarbonate (400 mL), water (500 mL), and saturated sodium chloride (450 mL) and dried over anhydrous magnesium sulfate and the volatiles evaporated in vacuo. The residual blue-green solid was purified by flash chromatography (8% ethyl acetate in Skellysolve-F as eluant) to yield 5.56 g (97%) of aldehyde **21** as light yellow needles: mp (recrystallized from ether) 113–114 °C (lit.[49] mp 112 °C); NMR ($CDCl_3$, 60 MHz) δ 3.80 (s, 3 H), 5.90 (s, 2 H), 6.43 (s, 1 H), 7.15 (s, 1 H), 10.13 (s, 1 H); IR ($CHCl_3$) 3020, 2900, 1675, 1620, 1480, 1430, 1270, 1200, 1045 cm^{-1}. Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 59.75; H, 4.31.

2-(2-Methoxy-4,5-methylenedioxyphenyl)-1-(methylsulfinyl)-1-(methylthio)ethylene (22). A mixture of 3 mL of methyl methylsulfinylmethyl sulfide (**15**) and 0.070 g (1.7 mmol) of finely powdered sodium hydroxide was stirred at 80 °C for 30 min. At this time, 0.966 g (5.36 mmol) of aldehyde **21** was added and the resulting mixture stirred at 80 °C for 1 h. The reaction mixture was cooled and diluted with 40 mL of methylene chloride, and the organic solution was washed with 50 mL of 1 N sulfuric acid and 50 mL of water. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the volatiles were evaporated in vacuo. The residue was purified by flash chromatography (10% ethyl acetate in Skellysolve-F as eluant) to give 1.45 g (95%) of ketene thioacetal **22** as pale yellow crystals: mp (recrystallized from ether) 101–103 °C; NMR ($CDCl_3$, 200 mHz) δ 2.30 (s, 3 H), 2.72 (s, 3 H), 3.80 (s, 3 H), 5.97 (s, 2 H), 6.53 (s, 1 H), 7.94 (s, 1 H), 7.95 (s, 1 H); IR ($CHCl_3$) 3020, 2490, 1205, 1050 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_4S_2$: C, 50.33; H, 4.93. Found: C, 50.30; H, 4.98.

Ethyl (2-Methoxy-4,5-methylenedioxyphenyl)acetate (23). A solution of 1.83 g (6.40 mmol) of ketene thioacetal **22** in 40 mL of 100% ethanol was treated with 0.640 g (3.70 mmol) of copper(II) chloride dihydrate. The darkened solution was then treated with 1 mL of saturated ethanolic hydrogen chloride and the resulting solution heated at reflux for 36 h. The reaction mixture was cooled and the ethanol evaporated in vacuo. The crude product was purified by flash chromatography (4% ethyl acetate in Skellysolve-F as eluant) to afford 1.09 g (72%) of ester **23** as a pale yellow oil that slowly crystallized to a low-melting solid: mp 39–40 °C; NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, J = 7 Hz), 3.50 (s, 2 H), 3.71 (s, 3 H), 4.12 (q, 2 H, J = 7 Hz), 5.84 (s, 2 H), 6.50 (s, 1 H), 6.66 (s, 1 H); IR (neat) 3000, 1740, 1510, 1495, 1205, 1165, 1045 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.13; H, 5.97.

(2-Methoxy-4,5-methylenedioxyphenyl)acetic Acid (24). A solution of 7.24 g (30.4 mmol) of ethyl ester **23** in 75 mL of tetrahydrofuran was treated with 65 mL of 1 N sodium hydroxide (aqueous). The biphasic mixture was stirred vigorously (the mixture became homogeneous over a period of 1 h) for 17 h. The tetrahydrofuran was evaporated in vacuo and the aqueous layer acidified with 10% hydrochloric acid, which caused precipitation of a white solid. The solid was filtered, rinsed with 200 mL of ice water, and dried by vacuum desiccation to afford 5.83 g (91%) of acid **24** as flaky white crystals: mp 153–155 °C (lit.[49] mp 97–98 °C; lit.[50] mp 155–157 °C); NMR ($CDCl_3$, 60 MHz) δ 3.57 (s, 2 H), 3.77 (s, 3 H), 5.91 (s, 2 H), 6.53 (s, 1 H), 6.68 (s, 1 H), 9.24 (br s, 1 H exchangeable with D_2O); IR ($CHCl_3$) 3400–2700 (br), 1715, 1510, 1490, 1195, 1045 cm^{-1}. Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 56.85; H, 4.81.

(2-Methoxy-4,5-methylenedioxyphenyl)acetyl Chloride (5b). A solution of 0.373 g (1.77 mmol) of carboxylic acid **24** in 18 mL of dry methylene chloride was treated with 0.233 g (1.83 mmol, 0.16 mL) of oxalyl chloride and the resultant mixture stirred at room temperature under a nitrogen atmosphere for 17 h. Solutions prepared in this manner were used without purification in the Friedel–Crafts acylation reaction that follow. In order to ascertain completeness of the reaction, it was also run in an NMR tube in $CDCl_3$. After ca. 3–5 h the reaction was complete. The NMR that follows was obtained from this experiment: NMR ($CDCl_3$, 60 MHz) δ 3.70 (s, 3 H), 3.95 (s, 2 H), 5.82 (s, 2 H), 6.44 (s, 1 H), 6.55 (s, 1 H); IR (neat) (contaminated with some carboxylic acid due to rapid hydrolysis of the unstable acid chloride) 2900, 1800, 1740, 1505, 1480, 1430, 1200, 1040, 935 cm^{-1}.

2,2-Dimethyl-5-(2-methoxy-4,5-methylenedioxyphenylacetoxy)-2*H*-1-benzopyran (28). A cold (0 °C) solution of 0.517 g (2.94 mmol) of phenol **4** in 20 mL of dry methylene chloride was treated with 0.45 mL of triethylamine followed by a solution of acid chloride **5b** (prepared from 0.699 g of acid **24** as previously described (vide supra)) added dropwise over a period of 45 min. The resulting mixture was stirred at 0 °C for 3 h, and the volatiles were evaporated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in Skellysolve-F as eluant) to yield 1.02 g (95%) of ester **28** as an oil that slowly crystallized: mp (recrystallized from ether:petroleum ether) 89–90 °C; NMR ($CDCl_3$, 200 MHz) δ 1.41 (s, 6 H), 3.77 (s, 2 H), 3.80 (s, 3 H), 5.60 (d, 1 H, J = 10 Hz), 5.92 (s, 2 H), 6.28 (d, 1 H, J = 10 Hz), 6.60 (m, 3 H), 6.77 (s, 1 H), 7.06 (m, 2 H); IR (neat) 2990, 1770, 1615, 1510, 1490, 1465, 1200, 1115 cm^{-1}. Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.18; H, 5.39.

2,2-Dimethyl-5-hydroxy-6-(2-methoxy-4,5-methylenedioxyphenylacetyl)-2*H*-1-benzopyran (3b). A solution of 0.107 g (0.608 mmol) of phenol **4** in 6 mL of a solution (ca. 0.1 M) of acid chloride **5b** (vide supra) was stirred under a nitrogen atmosphere and cooled to −78 °C. A solution of 0.121 g (0.64 mmol, 0.07 mL) of freshly distilled titanium(IV) chloride in 2 mL of dry methylene chloride was added dropwise via syringe pump over a period of 20 min. After 1.5 h, the deep red-brown mixture was quenched with 20 mL of saturated sodium bicarbonate while still at −78 °C. The mixture was allowed to warm to room temperature and extracted with 6 × 20 mL of ether. The combined organic layers were washed with 50 mL of saturated sodium bicarbonate, 50 mL of water and 100 mL of saturated sodium chloride, dried over anhydrous magnesium sulfate, and filtered and the volatiles removed in vacuo to give a foamy brown solid. Purification by flash chromatography (15% ethyl acetate in Skellysolve-F as eluant) gave 0.099 g (44% based on phenol **4**) of deoxybenzoin **3b** as pale yellow crystals: mp 130–131 °C (lit.[14a] mp 129–131 °C); NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 6 H), 3.74 (s, 3 H), P 4.12 (s, 2 H), 5.57 (d, 1 H, J = 10 Hz), 5.91 (s, 2 H), 6.33 (d, 1 H, J = 9 Hz), 6.55 (s, 1 H), 6.70 (m, 2 H), 7.70 (d, 1 H, J = 9 Hz), 12.92 (s, 1 H, exchangeable with D_2O); IR ($CHCl_3$) 3400–3200 (br), 3015, 2990, 1640, 1610, 1480, 1425, 1300, 1190, 1110, 1035 cm^{-1}. Anal. Calcd for: $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.42; H, 5.46.

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3-(2-Methoxy-4,5-methylenedioxyphenyl)-8,8-dimethyl-4*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-4-one: Jamaicin (1). A solution of 0.055 g (0.15 mmol) of deoxybenzoin **3b** in 1.5 mL of bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent)[39] was stirred at 95 °C under a nitrogen atmosphere for 1 h. The mixture was evaporated to dryness in vacuo and the residue purified by flash chromatography (7% ethyl acetate in Skellysolve-F as eluant) to give 0.049 g (87%) of jamaicin (1) as a light yellow powder: mp 169–170 °C. A single recrystallization from 1:1 ether:hexanes gave white needles: mp 199–200 °C (lit.[15] mp 167–168 °C; lit.[14c] mp 163 °C and 193 °C); NMR ($CDCl_3$, 200 MHz) δ 1.49 (s, 6 H), 3.72 (s, 3 H), 5.70 (d, 1 H, J = 10 Hz), 5.94 (s, 2 H), 6.61 (s, 1 H), 6.82 (s, 1 H), 6.83 (d, 1 H, J = 9 Hz), 7.90 (s, 1 H), 8.04 (d, 1 H, J = 9 Hz); IR ($CHCl_3$) 3010, 1635 (shoulder at 1650), 1490, 1195, 1115, 1040 cm^{-1}; M^+ (378) (parent).

2-(3,4-Methylenedioxyphenyl)-1-(methylsulfinyl)-1-(methylthio)ethylene (16). A mixture of 22 mL of methyl methylsulfinylmethyl sulfide (**15**) and 1.37 g (0.034 mmol) of finely powdered sodium hydroxide was stirred at 80 °C for 30 min. At this time 15.00 g (0.100 mol) of piperonal (**14**) was added and the mixture stirred at 80 °C under nitrogen atmosphere for 3 h. The thick reaction was diluted with 500 mL of methylene chloride and washed with 2 × 500 mL of water. The organic layer was dried over anhydrous magnesium sulfate and filtered, and the volatiles were evaporated in vacuo. The residue was purified by flash chromatography (40% ethyl acetate in Skellysolve-F as eluant), affording 19.48 g (76%) of ketene thioacetal **16** as a thick golden oil: NMR ($CDCl_3$, 200 MHz) δ 2.33 (s, 3 H), 2.74 (s, 3 H), 6.02 (s, 2 H), 6.85 (d, 1 H, J = 8 Hz), 7.28 (dd, 1 H, J_1 = 8 Hz, J_2 = 2 Hz), 7.51 (s, 1 H), 7.73 (d, 1 H, J = 2 Hz); IR (neat) 3015, 1505, 1490, 1450, 1260, 1065, 1040 cm^{-1}.

Ethyl (3,4-Methylenedioxyphenyl)acetate (18). A solution of 1.00 g (3.90 mmol) of ketene dithioacetal **16** in 35 mL of 100% ethanol was treated with 0.390 g (2.30 mmol) of copper(II) chloride dihydrate. The resulting solution was treated with 1 mL of saturated ethanolic hydrogen chloride and the mixture heated at reflux for 7 h. During equal intervals in this period, two additional 0.400-g portions of copper(II) chloride dihydrate and 3-mL portions of saturated ethanolic hydrogen chloride were added. The reaction mixture was refluxed for another 16 h and then cooled to room temperature and concentrated in vacuo. Purification of the residue by flash chromatography (3% ethyl acetate in Skellysolve-F as eluant) afforded 0.730 g of ester **18** (90%) as a clear colorless liquid: NMR ($CDCl_3$, 60 MHz) δ 1.22 (t, 3 H, J = 7 Hz), 3.47 (s, 2 H), 4.15 (q, 2 H, J = 7 Hz), 5.88 (s, 2 H), 6.72 (m, 3 H); IR (neat) 2990, 1735, 1490, 1450, 1250, 1040 cm^{-1}.

(3,4-Methylenedioxyphenyl)acetic Acid (17). A solution of 8.67 g (0.042 mol) of ester **18** in 80 mL of tetrahydrofuran was treated with 80 mL of 1 N sodium hydroxide (aqueous). The mixture was stirred vigorously at room temperature for 1.5 h. At this time the tetrahydrofuran was evaporated in vacuo and the remaining aqueous layer acidified with 10% hydrochloric acid (aqueous) to effect precipitation of the acid. The crystals were filtered and washed with several 50-mL portions of ice water. The product was dried by vacuum desiccation to afford 6.49 g (87%) of carboxylic acid **17** as white needles: mp 131–132 °C (lit.[25b] mp 132–133 °C; lit.[51] mp 128–129 °C); NMR ($CDCl_3$, 60 MHz), δ 3.51 (s, 2 H), 5.88 (s, 2 H), 6.70 (br s, 3 H), 8.91 (br s, 1 H, exchangeable with D_2O); IR ($CHCl_3$) 3300–2700 (br), 1715, 1505, 1490, 1450, 1250, 1045 cm^{-1}.

(3,4-Methylenedioxyphenyl)acetyl Chloride (5a). A solution of 0.323 g (1.79 mmol) of carboxylic acid **17** in 25 mL of dry methylene chloride was treated with 0.247 g (1.95 mmol, 0.17 mL) of oxalyl chloride and the reaction mixture stirred at room temperature under a nitrogen atmosphere for 15 h. This solution was used without concentration or purification in the reaction that follows. In order to determine the amount of time required for completion of the reaction, this reaction was also run in an NMR tube in $CDCl_3$ as solvent. The NMR data for **5a** were taken from this sample: NMR ($CDCl_3$, 60 MHz) δ 3.96 (s, 2 H), 5.87 (s, 2 H), 6.67 (br s, 3 H).

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3-(3,4-Methylenedioxyphenyl)-8,8-dimethyl-4*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-4-one: Calopogonium Isoflavone-B (2). A solution of 0.250 g (1.42 mmol) of phenol **4** and acid chloride **5a** (synthesized from 0.323 g (1.79 mmol) of carboxylic acid **17** and 0.17 mL of oxalyl chloride as previously described (vide supra)) in 20 mL of dry methylene chloride was cooled to −78 °C under a nitrogen atmosphere. A solution of 0.294 g (1.55 mmol, 0.17 mL) of freshly distilled titanium(IV) chloride in 3 mL of dry methylene chloride was added dropwise over a 10-min period. The resulting dark solution was stirred at −78 °C for 1.5 h. At this time the reaction was quenched with 10 mL of water and 10 mL of saturated sodium chloride solution. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo. The crude deoxybenzoin **3a** was not isolated, but used directly.

The crude deoxybenzoin **3a** mixture from the preceding acylation reaction (0.573 g of crude material) was dissolved in 2 mL of bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent[39]) and the resulting mixture heated at 100 °C for 0.5 h. The reaction mixture was cooled, and the volatiles were removed completely in vacuo. The residue was purified by flash chromatography (15% ethyl acetate in Skellysolve-F as eluant) to afford 0.075 g (15% overall from **4**) of calopogonium isoflavone-B (**2**) as pale yellow crystals: mp (recrystallized from ether) 169–171 °C (lit.[16] mp 167 °C); NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 6 H), 5.72 (d, 1 H, J = 10 Hz), 5.99 (s, 2 H), 6.84 (m, 1 H), 6.85 (d, 1 H, J = 10 Hz), 6.95 (m, 1 H), 7.09 (s, 1 H), 7.93 (s, 1 H), 8.06 (d, 1 H, J = 9 Hz); IR ($CHCl_3$) 1630 (br), 1490, 1440, 1275, 1250, 1115, 1040 cm^{-1}; HRMS calcd for $C_{21}H_{16}O_5$ 348.0997, found 348.0983.

Resorcinol Monoprenyl Ether Monobenzenesulfonate (35). A mixture of 2.00 g (7.99 mmol) of resorcinol monobenzenesulfonate (**34**) and 1.22 g (8.82 mmol) of anhydrous potassium carbonate in 75 mL of acetone was treated with 1.81 g (12.1 mmol) of 1-bromo-3-methyl-2-butene (prenyl bromide), and the reaction mixture was heated at reflux with vigorous stirring for 4 h. The reaction mixture was cooled to room temperature, filtered, and concentrated in vacuo. The residual material was diluted with 100 mL of ether and washed with 2 × 100 mL of 10% (aqueous) sodium hydroxide, 150 mL of water, and 100 mL of saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo. This afforded 2.54 g (100%) of the sulfonate ester **35** as a pale gold oil that was very pure: NMR ($CDCl_3$, 200 MHz) δ 1.71 (s, 3 H), 1.78 (s, 3 H), 4.39 (br d, 2 H, J = 7 Hz), 5.41 (br t, 1 H, J = 7 Hz), 6.56 (m, 2 H), 6.79 (ddd, 1 H, J_1 = 9 Hz, J_2 = 2 Hz), 7.15 (m, 1 H), 7.52 (m, 2 H), 7.66 (m, 1 H), 7.83 (m, 2 H); IR (neat) 2930, 1610, 1590, 1485, 1460, 1375, 1195, 1095, 800 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_4S$: C, 64.13; H, 5.70. Found: C, 63.85; H, 5.71.

Resorcinol Monoprenyl Ether (32). A solution of 3.99 g (12.5 mmol) of benzenesulfonate ester **35** in 12 mL of methanol was treated with 12 mL of a methanolic aqueous potassium hydroxide solution (prepared from 15.8 g of KOH/78 mL of methanol/9 mL of water) added dropwise over a 10-min period. The reaction mixture was heated at reflux for 1 h, cooled, and then poured into 500 mL of cold water. The aqueous phase was acidified with concentrated hydrochloric acid to pH 0–1 and then extracted with 4 × 200 mL of methylene chloride. The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and the volatiles were evaporated in vacuo. The residue was purified by flash chromatography (2% ethyl acetate in Skellysolve-F as eluant) to give 2.11 g (95%) of phenol **32** as a pale yellow liquid: NMR ($CDCl_3$, 200 MHz) δ 1.72 (s, 3 H), 1.78 (s, 3 H), 4.47 (br d, 2 H, J = 7 Hz), 6.44 (m, 3 H), 7.10 (m, 1 H); IR (neat) 3600–3200 (br), 1595 (with shoulder at 1625), 1495, 1150 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.92; H, 8.20.

2,4-Dihydroxy-2-(3,4-methylenedioxyphenyl)acetophenone (37). A solution of acid chloride **5a** (prepared from 0.485 g (2.69 mmol) of acid **17** and 0.378 g (2.98 mmol, 0.26 mL) of oxalyl chloride in 25 mL of dry methylene chloride (vide supra)) was diluted with 20 mL of dry nitromethane and the methylene chloride carefully removed in vacuo. The solution was cooled to 0 °C, and 0.247 g (2.25 mmol) of resorcinol (**33**) was added. The reaction was stirred at 0 °C under nitrogen for 15 min, at which time 0.333 g (2.50 mmol) of anhydrous aluminum chloride was added in several portions over a period of 10 min. The reaction mixture turned reddish purple and was stirred at 0 °C for a period

of 3 h and then at room temperature for an additional 20 h. The reaction was quenched with 50 mL of saturated sodium bicarbonate and extracted with 2 × 50 mL of methylene chloride. The combined organic solutions were washed with 100 mL of water, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo to a gold oil. This was purified by flash chromatography (10% ethyl acetate in Skellysolve-F as eluant) to afford 0.362 g (59%) of the desired deoxybenzoin **37** as white prisms: mp (recrystallized from petroleum ether) 87–89 °C (lit.[40c] mp 146–148 °C).[43] A small quantity (0.040 g; 7%) of aryl ester **38** was also isolated: mp (recrystallized from petroleum ether) 73–74 °C.

Deoxybenzoin 37: R_f = 0.55 (3:2 hexanes:ethyl acetate); NMR ($CDCl_3$, 60 MHz) δ 3.69 (s, 2 H), 5.88 (s, 2 H), 6.74 (m, 6 H), 12.68 (s, 1 H, exchangeable with D_2O); IR ($CHCl_3$) 3600, 3300 (br), 1750, 1605, 1505, 1490, 1445, 1250, 1140 cm^{-1}. Anal. Calcd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44. Found: C, 65.93; H, 4.28.

Aryl Ester 38: R_f = 0.60 (3:2 hexanes:ethyl acetate); NMR ($CDCl_3$, 60 MHz) δ 3.69 (s, 2 H), 5.91 (s, 2 H), 6.65–7.45 (m, 8 H); IR ($CHCl_3$) 3550–3400 (br), 3010, 2900, 1720, 1605, 1490, 1250, 1130 cm^{-1}.

7-Hydroxy-3-(3,4-methylenedioxyphenyl)benzopyran-4-one: Pseudobaptigenin (31). A solution of 0.171 g (0.626 mmol) of pure deoxybenzoin **37** dissolved in 2 mL of bis(dimethylamino)-*tert*-butoxymethane (Bredereck's reagent[39]) was heated at 90 °C under a nitrogen atmosphere for 1.5 h. The volatiles were completely removed in vacuo, and the residue was purified by flash chromatography (50% ethyl acetate in Skellysolve-F as eluant) to afford 0.050 g (28%) of pseudobaptigenin (**31**) as beige-colored microcrystals: mp (recrystallized from methanol) 299–301 °C (lit.[41i], mp 295–297 °C). This product is highly insoluble, and it was felt that a considerable amount was lost by crystallization while it was being purified by chromatography. In order to demonstrate this, the crude formylation product was used to synthesize maxima substance-B (**30**) (vide infra): NMR (CD_3COCD_3, 200 MHz) δ 6.07 (s, 2 H), 6.93 (m, 3 H), 7.03 (d, 1 H, J = 9 Hz), 7.11 (d, 1 H, J = 9 Hz), 7.20 (s, 1 H), 8.09 (d, 1 H, J = 9 Hz), 8.23 (s, 1 H); IR (KBr) 3400–2950 (br), 1620 (with shoulder at 1645), 1440, 1385, 1355, 1300 cm^{-1}; HRMS calcd for $C_{16}H_{10}O_5$ 282.0528, found 282.0562.

7-(3-Methyl-2-butenyloxy)-3-(3,4-methylenedioxyphenyl)-benzopyran-4-one: Maxima Substance-B (30). A mixture of crude pseudobaptigenin (**3**) (prepared by formylation from 0.170 g (0.625 mmol) of deoxybenzoin **37** and subsequent evaporation of the volatiles (vide supra)) and 0.200 g (1.45 mmol) of anhydrous potassium carbonate was suspended in 30 mL of acetone and treated with 0.951 g (6.38 mmol, 0.75 mL) of 1-bromo-3-methyl-2-butene (prenyl bromide). The mixture was heated at reflux for 5 h, then cooled and filtered, and the volatiles were evaporated in vacuo. The residue was purified by flash chromatography (5% ethyl acetate in Skellysolve-F as eluant) to give 0.112 g (51% overall from deoxybenzoin **32**) of maxima substance-B (**30**) as pale yellow needles: mp (recrystallized from petroleum ether:ether) 133–135 °C (lit.[40g] mp 134–135 °C); NMR ($CDCl_3$, 200 MHz) δ 1.79 (s, 3 H), 1.82 (s, 3 H), 4.61 (br d, 2 H, J = 5 Hz), 5.50 (br t, 1 H, J = 5 Hz), 5.99 (s, 2 H), 6.96 (m, 5 H), 7.90 (s, 1 H), 8.19 (d, 1 H, J = 9 Hz); IR ($CHCl_3$) 3010, 2940, 1650, 1625, 1605, 1440, 1250 cm^{-1}; HRMS calcd for $C_{21}H_{18}O_5$ 350.1154, found 350.1155.

Acknowledgment. We thank the U.S. Army (USAMRIID) (DAMD17-82-C-2240) for the partial support of this research. We also express our appreciation to Barbara Barsnica for typing portions of this manuscript.

Synthesis of Ring-Expanded Cytidine: Homocytidine

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Received September 3, 1986

The syntheses of ring-expanded cytidine (**7**, homocytidine) and its corresponding dihydro analogue (**9**) were accomplished in five and four steps, respectively, starting from the very simple and easily accessible tetramethyleneurea nucleoside **10** [1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)hexahydro-2*H*-1,3-diazepin-2-one]. The key reaction was the selective oxidation at C-4 accomplished with benzeneseleninic anhydride to give both the 4-oxo-1,3-diazepinone **14** and the 4-oxo-5-(phenylseleno)-1,3-diazepinone **17**. Transformation of **14** into the ring-expanded dihydrocytidine analogue **9** was easily accomplished by using a sequence involving thiation followed by reaction with methyl iodide and treatment of the resulting compound with methanolic ammonia. A similar approach starting with **17**, but preceded by the oxidative elimination of benzeneseleninic acid, afforded the corresponding target homocytidine (**7**). The ^1H NMR properties of **7** indicate that the C-7 protons are exchangeable by deuterium in D_2O solution through the intermediacy of a tautomeric form **27**. The corresponding ring-expanded uridine analogues could not be obtained as free nucleosides, since they underwent cleavage of the diazepine ring at C-4 under the conditions used to deblock the benzoyl protective groups. Both ring-expaned cytidine and its dihydro analogue behaved as moderate substrates for cytidine deaminase.

For several years we have developed methods of syntheses for the construction of ring-expanded pyrimidine nucleosides containing the 1,3-diazepin-2-one aglycon.[1-6] These compounds had been screened for their enzymatic inhibitory properties against enzymes involved in the metabolism of uridine and cytidine. In particular, cytidine deaminase (CDA), the catabolic enzyme that converts cytidine to uridine, is an example of an enzyme that has shown significant sensitivity toward inhibition by these 1,3-diazepin-2-one nucleosides, which incorporate a variety of functional groups (e.g., compounds **1–5**).[1,3,7] Inhibition of CDA by these compounds and their relative potency as

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