(20), 95 (25.8). $C_{20}H_{16}O_5$ requires M^+ at m/z 336.

Conversion of 4 to 5. Compound **4** (92 mg) in THF (10 mL) was added to a suspension of $LiAlH_4$ (130 mg) in THF. The mixture was stirred at 0 °C under Ar for 21 h. After the usual workup 88 mg of crude product was obtained, which was acetylated without purification, with Ac_2O (1 mL) in C_5H_5N (1 mL) for 14 h at room temperature. After the usual workup, 82 mg of crude product was obtained. It was purified by flash chromatography to yield 42 mg of **5** as an oily product: IR ($CHCl_3$) ν_{max} (cm^{-1}) 1735, 1377, 1241, 1025, 958; ^1H NMR, see Table I; MS m/z (relative intensity) 514 (0.4), 513 (1.6), 512 (3.8), 452 (20), 410 (20), 350 (40), 308 (20), 291 (20), 290 (20), 95 (10), 81 (20), 43 (100). $C_{28}H_{32}O_9$ requires M^+ at m/z 512.

X-ray Analysis of Isopuberulin. Colorless crystals of isopuberulin were grown by slow evaporation from methylene chloride/methanol. Intensities were collected on a single crystal (0.36 × 0.36 × 0.44 mm) on a Nicolet R3m automated diffractometer using graphite-monochromatized Mo Kα radiation (λ 0.7107 Å). Lattice constants were as follows: a = 7.557 (2) Å, b = 11.021 (4) Å, c = 18.573 (7) Å; space group $P2_12_12_1$, V = 1547 (1) Å^3, $F(000)$ = 696, T = 293 K, D_{calcd} = 1.43 g cm^{-3}, Z = 4, and μ(Mo Kα) = 0.97 cm^{-1}. Of the 1582 reflections within the 2θ range of 3-50° collected, 1191 had values of $|Fo|^2$ that were greater than three times their estimated standard deviations, and these were used in the final refinement. The crystal structure was solved by direct methods as incorporated by Sheldrick (1981) into the SHELXTL[15] system. The program SOLV was employed with 186 phases with $|E| > 1.6$ and 12 reflections in the starting set. The trial structure was refined by a blocked cascade least-squares procedures with anisotropic temperature factors for the non-H atoms and with a fixed isotropic temperature factor, U = 0.06 Å^2, for the H atoms. The final R factor was 0.047 and Rw = 0.045 and S = 1.22 (see supplementary material).

Acknowledgment. We are very grateful to Messrs. R. Villena, L. Velasco, R. Gaviño, and A. Cuellar for technical assistance. We thank Dr. T. P. Ramamoorthy, Botany Department, Instituto de Biología, UNAM, for botanical classification of the plant material and fruitful discussions. This work was supported in part by the Consejo Nacional de Ciencia y Tecnología, CONACYT, México, (Project PCCBBNA-021142).

Registry No. **2**, 115321-31-8; **3**, 115321-32-9; **4**, 115321-33-0; **5**, 115338-19-7; β-sitosterol, 83-46-5; oleanolic acid, 508-02-1.

Supplementary Material Available: Tables of thermal parameters, bond distances, and bond angles (4 pages); tables of observed and calculated structure factors (8 pages). Ordering information is given on any current masthead page.

(15) Sheldrick, G. M. SHELXTL-81, revision 3, an integrated system for crystal structure determination, University of Göttingen, Federal Republic of Germany, 1981.

A New Coumarin Synthesis and Its Utilization for the Synthesis of Polycyclic Coumarin Compounds with Anticarcinogenic Properties

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A novel synthesis of coumarins based on the ortho-directed metalation of methoxymethyl phenolic ethers with alkyllithium reagents is described. The method entails reaction of the ortho-lithiated intermediates with dimethylformamide to yield the corresponding ortho-aldehydes. Reaction of the latter with lithio-*N*,*N*-dimethylacetamide affords the addition products which on heating in refluxing acetic acid undergo smooth conversion directly to coumarins. This synthetic approach affords good overall yields and appears general in its applicability. A wide range of coumarins containing substituents in the 6- and 7-positions as well as the polycyclic coumarin analogues of phenanthrene, benz[*a*]anthracene, and benzo[*a*]pyrene and their methyl-substituted derivatives were synthesized by appropriate modification of this method. Preliminary assays of biological activity indicate that the benzo[*a*]pyrene coumarin analogue **11b** is a potent inhibitor of tumor induction when administered prior to the carcinogen 7,12-dimethylbenz[*a*]anthracene, and **11b** is itself devoid of tumorigenic activity. The polycyclic coumarins hold promise as agents for the chemoprevention of cancer.

Coumarins constitute an important class of naturally occurring compounds many of which exhibit useful pharmacological activity. Several polycyclic coumarin derivatives have also been shown to be potent inhibitors of tumor induction by carcinogenic polycyclic aromatic hydrocarbons.[1-3] However, investigations of anticarcinogenic activity have been primarily confined to coumarin derivatives available from plant sources, the majority of which are highly oxygenated. Systematic investigations of structural modifications of molecules of this type in relation to anticarcinogenic activity have not been reported.

As the initial phase in a program to examine the structure-activity relationships of anticarcinogenic coumarin compounds, we undertook the synthesis of a series of polycyclic coumarins. For this purpose, we required an efficient method that would be adaptable to the synthesis of both simple coumarins as well as polycyclic coumarin analogues of potent carcinogenic hydrocarbons, such as benzo[*a*]pyrene and 7,12-dimethylbenz[*a*]anthracene, having three to five rings. Interest in the latter compounds was dictated by evidence that suggested that polycyclic coumarins with these dimensions may be more effective than their smaller analogues in blocking tumor induction. Although various synthetic routes to coumarins are known,[4-6] these methods were generally unsatisfactory for

(1) Feuer, G.; Kellen, J. A.; Kovacs, K. *Oncology* **1976**, *33*, 35.
(2) Wattenberg, L. W.; Lam, L. K.; Fladmoe, A. V. *Cancer Res.* **1979**, *39*, 1651.
(3) Wood, A. W.; Huang, M.-T.; Chang, R. L.; Newmark, H. L.; Lehr, R. E.; Yagi, H.; Sayer, J. M.; Jerina, D. M.; Conney, A. H. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 5513.
(4) Sethna, S.; Phadke, R. *Org. React.* (*N.Y.*) **1953**, *7*, 1.
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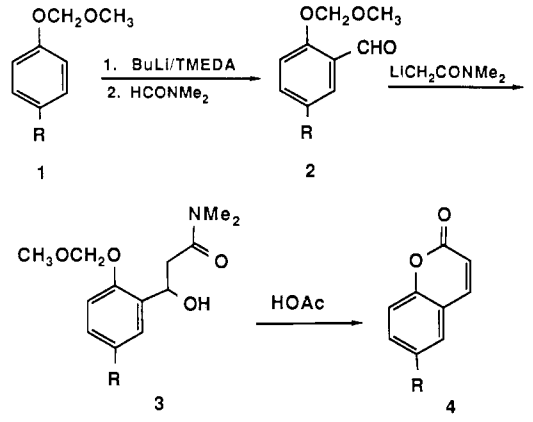
0022-3263/88/1953-3936$01.50/0

Scheme I



a: R = H; b: R = Cl; c: R = CH_3; d: R = C_6H_5.

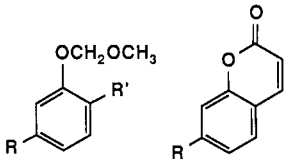
our purpose due to the likelihood of substitutions in multiple ring positions and formation of mixtures of products under the relatively harsh conditions employed. we now report a novel coumarin synthesis which utilizes readily available reagents and mild conditions, entails few steps, affords good overall yields, and appears general in its applicability.[7]

Results

General Method. The synthetic approach envisioned is based upon the ready availability of phenols as starting compounds. Ortho-directed metalation of the methoxymethyl phenolic ethers 1 potentially provides synthetic access to coumarins via reaction of the ortho-lithiated intermediates with dimethylformamide to afford the corresponding ortho-aldehydes, e.g., 2-(methoxymethoxy)benzaldehyde (**2a**).[8,9] Therefore, the initial objective of this investigation was to develop a convenient synthetic method for the conversion of **2a** to coumarin under mild conditions.

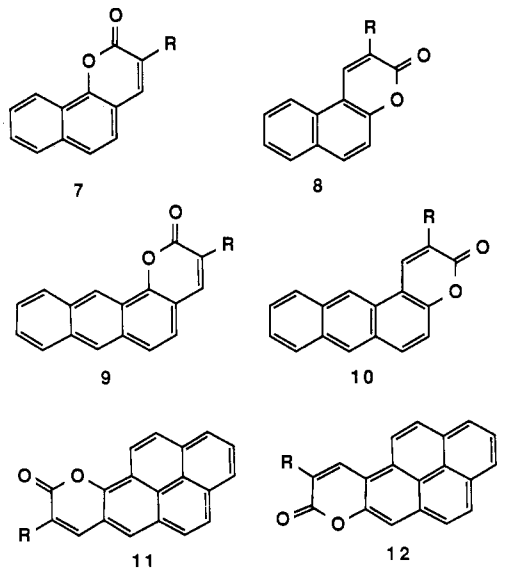
This was achieved by the two-step sequence depicted in Scheme I. α-Lithio-*N*,*N*-dimethylacetamide was generated in situ by the reaction of *n*-butyllithium with *N*,*N*-dimethylacetamide in the presence of diisopropylamide by the method of Woodbury and Rathke.[10] Addition of this reagent to **2a** furnished the product **3a**, which on heating in refluxing acetic acid underwent smooth conversion directly to coumarin (**4a**). Deprotection of the phenolic group, cyclodehydration, and dehydration all take place in this step. Conversion of the adduct **3a** to coumarin was markedly dependent upon the relative acidity of the acid. With acids stronger than acetic acid, such as polyphosphoric or *p*-toluenesulfonic acid, tarry products and considerably diminished yields resulted. The efficacy of acetic acid apparently lies in its relative inefficiency as a dehydrating agent in relation to its ability to catalyze removal of the methoxymethyl group and subsequent cyclization. This allows intramolecular cyclization of the saturated amide **3a** to compete effectively with its dehydration to the more rigidly constrained unsaturated amide. Cyclization of the latter requires the molecule to adopt the sterically less favorable cis-stereoisomeric configuration.

Substituted coumarins were readily prepared by appropriate modification of the synthetic sequence in Scheme I. The methoxymethyl ethers **1b–d** containing substituents (R = Cl, CH_3, or phenyl) in the para position were prepared from the corresponding phenols by reaction with dimethoxymethane in the presence of *p*-toluenesulfonic acid.[11] These ethers underwent conversion to the corresponding coumarins **4b–d** via the method in Scheme I in good overall yield, independent of the nature of the groups present on the aromatic ring. Similar reactions were conducted with the meta-substituted methoxymethyl aryl ethers derived from 3-methyl- and 3-phenylphenol (**5a,b**). In these cases the presence of a substituent in the meta position makes possible metalation in two nonequivalent ortho positions. However, lithiation of these two ethers with *tert*-butyllithium followed by reaction with dimethylformamide afforded regiospecifically the aldehyde products **5c** and **5d** arising from attack in the less sterically hindered site. Reaction of **5c** and **5d** with α-lithio-*N*,*N*-dimethylacetamide and cyclization of the products in acetic acid furnished the corresponding 7-methyl- and 7-phenylcoumarin derivatives **6a** and **6b**.



a: R = CH_3; R' = H
b: R = C_6H_5; R' = H
c: R = CH_3; R' = CHO
d: R = C_6H_5; R' = CHO

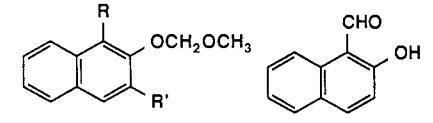
Synthesis of Unsubstituted Polycyclic Coumarins. This synthetic approach was then extended to the synthesis of a number of unsubstituted polycyclic coumarin analogues (**7a–12a**). The compounds 2*H*-naphtho[1,2-*b*]pyran-2-one (7,8-benzocoumarin) (**7a**) and 3*H*-naphtho[2,1-*b*]pyran-3-one (5,6-benzocoumarin) (**8a**), which may be considered analogues of phenanthrene, were prepared by appropriate modification of the method in



a: R = H; b: R = CH_3

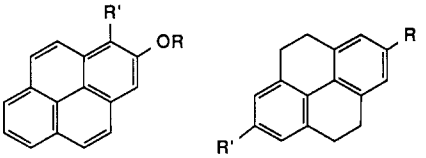
(6) Livingstone, R. In *Rodd's Chemistry of Carbon Compounds*; Coffey, S., Ed.; Elsevier: Amsterdam, 1977; Vol. IV, Part E, p 51.
(7) These results were reported in a preliminary communication: Harvey, R. G.; Cortez, C.; Ananthanarayan, T. P.; Schmolka, S. *Tetrahedron Lett.* **1987**, *28*, 6137.
(8) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923.
(9) Christensen, H. *Synth. Commun.* **1975**, *5*, 65.
(10) Woodbury, R. P.; Rathke, M. W. *J. Org. Chem.* **1977**, *42*, 1688.
(11) Yardley, J. P.; Fletcher, H., III *Synthesis* **1976**, 244.

Scheme I. In the case of **8a**, attempted synthesis of the starting compound, 2-(methoxymethoxy)-1-naphthaldehyde (**13b**), via the metalation of 2-(methoxymethoxy)naphthalene (**13a**) gave a mixture of **13b** and a second aldehyde derivative identified as 2-(methoxymethoxy)-3-naphthaldehyde (**13c**) in a 4:3 ratio (by NMR). However, the phenolic aldehyde **14** was readily obtained regiospecifically by the Reimer–Tieman reaction of 2-naphthol with chloroform and sodium hydroxide.[12] Reaction of the lithium salt of **14** with α-lithio-*N*,*N*-dimethylacetamide followed by cyclization of the adduct in refluxing acetic acid gave smoothly the isomeric three-ring coumarin **8a**.



13a: R = R' = H
b: R = CHO; R' = H
c: R = H; R' = CHO

14



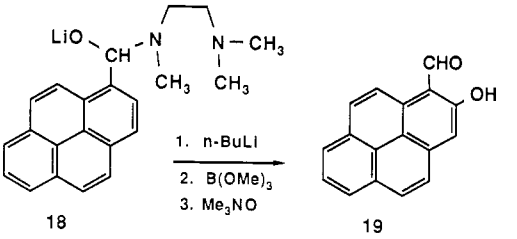
15a: R = R' = H
b: R = CH_2OCH_3; R' = H
c: R = CH_2OCH_3; R' = CHO

16a: R = R' = H
b: R = Br; R' = H
c: R = R' = Br

The two benz[*a*]anthracene coumarin analogues 2*H*-anthra[1,2-*b*]pyran-2-one (**9a**) and 3*H*-anthra[2,1-*b*]-pyran-3-one (**10a**) and the benzo[*a*]pyrene coumarin analogue 9*H*-pyreno[1,2-*b*]pyran-9-one (**11a**) were synthesized in good overall yield by the general method in Scheme I. The *o*-methoxymethoxy aldehydes required as starting materials in these syntheses were all readily prepared by formylation of the appropriate methoxymethyl aryl ethers via the metalation route. Surprisingly, metalation of 2-(methoxymethoxy)anthracene, the precursor of **10a**, took place almost exclusively in the 1-position. This finding contrasts with the previously observed nonregiospecific metalation of the close structural analogue 2-(methoxymethoxy)naphthalene. The reason for this difference is not known.

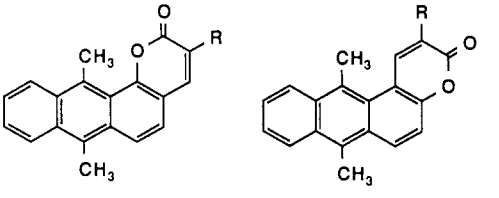
Synthesis of the isomeric benzo[*a*]pyrene coumarin analogue 8*H*-pyreno[2,1-*b*]pyran-8-one (**12a**) was frustrated by the unavailability of the required phenolic starting compound, 2-hydroxypyrene (**15a**). Initial attempts to synthesize **15a** from 4,5,9,10-tetrahydropyrene (**16a**) via the monobromo derivative **16b** were not successful due to the strong tendency of the latter to undergo further bromination to yield 2,7-dibromo-4,5,9,10-tetrahydropyrene (**16c**) and/or dehydrogenation to pyrene.[13] However, it was subsequently found that with the use of dimethylformamide as the solvent, bromination of **16a** takes place smoothly to afford the monobromo derivative **16b** in good yield.[14] Dehydrogenation of **16b** with *o*-chloranil gave 2-bromopyrene, which was converted to 2-hydroxypyrene by reaction was magnesium followed by treatment with diborane and alkaline peroxide. The phenol **15a** was transformed to its methoxymethyl ether **15b** by reaction with dimethoxymethane and *p*-toluenesulfonic acid. The latter was utilized to synthesize 1-formyl-2-(methoxymethoxy)pyrene (**15c**), which in turn was converted to the polycyclic coumarin compound **12a** by the usual procedure.

Prior to the development of a satisfactory preparation for **15a**, an alternative synthetic approach to **12a** not involving **15a** was investigated. This method entailed utilization of pyrene-1-carboxaldehyde (**17**) as the starting compound for the preparation of 1-formyl-2-hydroxypyrene (**19**). Reaction of **17** with *N*-lithio-*N*,*N*,*N*-trimethylenediamine by the method of Comins[15] gave the α-amino alkoxide **18**. Metalation of **18** with *n*-butyllithium furnished the 2-lithio salt which was converted to **19** in moderate yield (25%) by consecutive treatment with trimethylborate and trimethylamine *N*-oxide.[16] Reaction of the lithium salt of **19** with α-lithio-*N*,*N*-dimethylacetamide followed by cyclization in acetic acid yielded **12a**. Attempted preparation of the same coumarin derivative through reaction of **19** with $POCl_3$ and *N*,*N*-dimethylacetamide by the method of Phadke et al.[17] failed to afford **12a**.



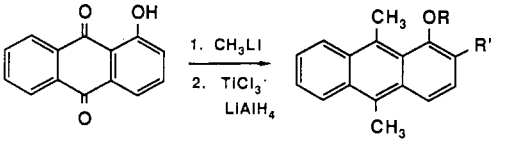
18 19

Synthesis of Methyl-Substituted Polycyclic Coumarins. Synthetic routes to polycyclic coumarins bearing methyl groups in the aromatic portion of the molecule and/or the coumarin ring were also investigated. Selected for initial study were the dimethyl derivatives of **9a** and **10a**, 7,12-dimethyl-2*H*-anthra[1,2-*b*]pyran-2-one (**20a**) and 7,12-dimethyl-3*H*-anthra[2,1-*b*]pyran-3-one (**21a**), analogues of the potent carcinogenic hydrocarbon 7,12-dimethylbenz[*a*]anthracene. 1-Hydroxy-9,10-dimethylanthracene (**22a**), required as the starting material for the synthesis of **20a**, was prepared from 1-hydroxyanthraquinone by addition of methyllithium followed by deoxygenation with the $TiCl_3$·$LiAlH_4$ complex.[18] Treatment of



20 21

a: R = H; b: R = CH_3

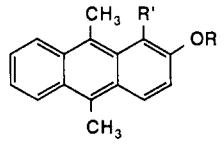


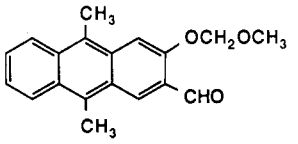
22a: R = H; R' = H
b: R = CH_2OCH_3; R' = H
c: R = CH_2OCH_3; R' = CHO

(12) Russell, A.; Lockhart, L. B. *Organic Syntheses*; Wiley: New York, 1955; Collect Vol. 3, p 463.
(13) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1986**, *51*, 2847.
(14) Harvey, R. G.; Schmolka, S.; Cortez, C.; Lee, H. *Synth. Commun.*, in press.
(15) Comins, D. L.; Brown, J. D. *J. Org. Chem.* **1984**, *49*, 1078.
(16) Kabalka, G. W.; Hedgecock, H. C., Jr. *J. Org. Chem.* **1975**, *40*, 1776.
(17) Phadke, C. P.; Kelkar, S. L.; Wadia, M. S. *Synth. Commun.* **1984**, *14*, 407.
(18) Walborsky, H. M.; Wust, H. H. *J. Am. Chem. Soc.* **1982**, *104*, 5807. Harvey, R. G.; Cortez, C. *J. Org. Chem.* **1986**, *51*, 5023.

22a with chloromethyl methyl ether and NaH furnished its 1-methoxymethyl ether **22b**. Formylation of **22b** with *n*-butyllithium/TMEDA and dimethylformamide gave the corresponding ortho-aldehyde **22c**, which in turn underwent conversion smoothly to **20a** by the usual two-step sequence.

2-Hydroxy-9,10-dimethylanthracene (**23a**), required as the starting compound for the synthesis of **21a**, was itself synthesized from 2-hydroxyanthraquinone via reaction with methyllithium and $TiCl_3$·$LiAlH_4$ and converted to 2-(methoxymethoxy)-9,10-dimethylanthracene (**23b**) by treatment with chloromethyl methyl ether and NaH. However, attempted transformation of **23b** to the corresponding 1-formyl derivative **23c** via lithiation and reaction with dimethylformamide gave a mixture of **23c** and the less sterically hindered isomeric ortho-aldehyde 2-(methoxymethoxy)-3-formyl-9,10-dimethylanthracene (**24**). The





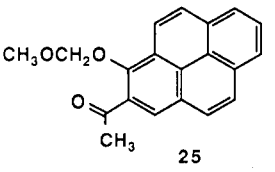
24

23a: R = R' = H
b: R = CH_2OCH_3; R' = H
c: R = CH_2OCH_3; R' = CHO
d: R = H; R' = CHO

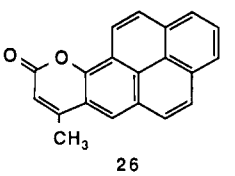
presence of both isomers in approximately equal ratio is clearly indicated by the presence of distinctive singlet peaks at low field in the proton NMR spectrum at δ 8.86 and 10.60. Introduction of the formyl group into the 1-position of 2-hydroxy-9,10-dimethylanthracene was successfully accomplished by direct formylation of **23a** with dimethylformamide and $POCl_3$. 1-Formyl-2-hydroxy-9,10-dimethylanthracene (**23d**) obtained as a product of this reaction was treated with 1-lithiodimethylacetamide and the resulting adduct was cyclized in acetic acid to yield the second coumarin analogues of 7,12-dimethylbenz[*a*]-anthracene **21a**.

In view of the likelihood that methyl substituents in the coumarin ring might enhance the anticarcinogenic activity of the polycyclic coumarins by blocking metabolism on the olefinic bond by the P-450 microsomal enzymes, leading to deactivation, the synthesis of analogous polycyclic coumarins containing methyl groups in the 3- and 4-positions of the coumarin ring were also investigated.[19] For introduction of methyl into the 4-position, a modification of the general method in Scheme I involving use of an *o*-acetyl rather than the *o*-formyl derivative of the appropriate mehoxymethyl aryl ether was examined. Thus, reaction of 2-lithio-1-(methoxymethoxy)pyrene with acetaldehyde afforded the corresponding alcohol which underwent oxidation with pyridine–sulfur trioxide and dimethyl sulfoxide[20] to yield 2-acetyl-1-methoxymethoxypyrene (**25**). Reaction of **25** with α-lithio-*N*,*N*-dimethylacetamide followed by cyclization of the adduct in acetic acid provided 7-methyl-9*H*-pyreno[1,2-*b*]pyran-9-one (**26**) in good overall yield.

Methods for the preparation of coumarins bearing methyl groups is the 3-position adjacent to the carbonyl function were also explored. Modification of the general method in Scheme I by substitution of the lithio salt of *N*,*N*-dimethylpropionamide for that of *N*,*N*-dimethyl-



25



26

acetamide afforded generally good yields of the desired adducts. The methyl-substituted polycyclic coumarins **7b**, **8b**, and **21b** were synthesized via this route. In a variation of this approach the dilithio salt of propionic acid was employed to synthesize 8-methyl-9*H*-pyreno[1,2-*b*]pyren-9-one (**11b**) from 1-(methoxymethoxy)-2-pyrenaldehyde. However, the yield of **11b** obtained via this route was only moderate (25%). Another practical alternative approach was provided by reaction of the ortho-aldehyde intermediates (or their methoxymethyl ethers) with *N*,*N*-dimethylpropionamide and $POCl_3$.[17] Thus, reaction of 2-hydroxy-1-naphthaldehyde (**14**) with these reagents afforded smoothly 2-methyl-3*H*-naphtho[2,1-*b*]pyran-3-one (**8b**). This latter approach was utilized to synthesize the analogous methyl-substituted polycyclic coumarin derivatives **9b**, **10b**, **11b**, **12b**, and **20b**.

Discussion

The method outlined in Scheme I provides convenient synthetic access to coumarin derivatives from the readily available methoxymethyl phenolic ethers under mild conditions. This synthetic approach affords good overall yields and is applicable to the synthesis of a wide range of substituted coumarins and polycyclic coumarins.

The scope of the method in potentially limited by the regiospecificity of the initial metalation reaction in cases where two nonequivalent ortho sites are available. However, metalation of the meta-substituted methoxymethyl aryl ethers **5a** and **5b** was directed efficiently to the less sterically hindered site by the use of the bulky *tert*-butyllithium reagent. In the case of 2-(methoxymethoxy)-naphthalene (**13a**) where metalation followed by reaction with dimethylformamide furnished the two possible orotho-aldehydes in a 4:3 ratio, the desired 2-hydroxy-1-naphthaldehyde was obtained regiospecifically by the Reimer–Tieman reaction of 2-naphthol. In the case of 2-(methoxymethoxy)-9,10-dimethylanthracene (**23b**), where a similar problem was encountered, the formyl group was introduced directly into the 1-position of the parent phenol (**23a**) by reaction with $POCl_3$ and dimethylformamide, despite the steric crowding in this site. These options provide practical solutions to the isomer problem in some cases.

It is also interesting in this connection that metalation of 2-methoxynaphthalene followed by reaction with *N*-methylformanilide is reported to afford the 3-formyl derivative (67%) accompanied by only 7% of the 1-formyl isomer.[21] This difference in product ratio from the present findings may be due to the greater steric bulk of *N*-methylformanilide, which is likely to interfere more with reaction in the 1-position. In any case, this observation suggests an alternative method to direct formylation to a sterically less crowded ring position.

The present coumarin synthesis complements older established methods and offers significant advantages for the synthesis of polycyclic coumarins and coumarins having acid-sensitive functional groups. In contrast, the well-known von Pechmann synthesis[4] entails strongly acidic conditions and frequently affords low and erratic yields. Thus, the yields of **4a–c** were poor to moderate by the von

(19) Methyl substituents in this region are anticipated to block metabolism by the P-450 microsomal enzymes on the olefinic bond leading to inactive oxidized metabolites.

(20) Parikh, J. R.; von E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

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Pechmann method[4] and in excess of 70% by the method in Scheme I.

An inherent limitation of most coumarin syntheses is the availability of the requisite phenol isomers as starting compounds. This problem is more acute for polycyclic coumarin analogues where a large number of phenol isomers are often possible and only one or two of these are obtainable by electrophilic substitution (indirectly via bromination, nitration, or sulfonation). One solution to this problem is to utilize hydrogenation to alter the site of preferred substitution of the parent hydrocarbon molecule. Hydrogenation of polycyclic hydrocarbons preferentially in specific molecular regions can be readily accomplished under mild conditions using appropriate catalysts.[22] This approach was effectively utilized to synthesize 2-hydroxypyrene (**15a**) via bromination of 4,5,9,10-tetrahydropyrene. A second approach to the isomer problem is illustrated by the use of ortho-lithiation to introduce a phenolic group adjacent to an appropriately protected aldehyde function[15] in the synthesis of 2-hydroxy-1-pyrenaldehyde (**19**). Further investigation of both of these method will be required to establish their utility and scope.

Biological Activity. Several of the polycyclic coumarin analogues have been screened for anticarcinogenic properties. The benzo[*a*]pyrene coumarin analogue **11b** was found to be a potent inhibitor of tumor induction by 7,12-dimethylbenz[*a*]anthracene (DMBA) on the skins of female SENCAR mice when administered prior to the latter; a 200-nmol dose of **11b** given 24 h prior to a 10-nmol dose of DMBA decreased tumor incidence by 75%.[23] In related studies, **11a**, **11b**, and the DMBA coumarin analogue **20b** were found to markedly inhibit the covalent binding of ^{3}H-DMBA to mouse epidermal DNA. The compound **11b** was also found to be a good inducer of the aryl hydrocarbon hydroxylase (AHH) enzyme and a strong competitive binder to the Ah-receptor in rat hepatic cytosol, only slightly less active than tetrachlorodibenzo-*p*-dioxin. Preliminary assays of anticarcinogenic activity as measured by induction of the NAD(P)H: quinone reductase enzyme in the Hepa 1c1c7 system[24] indicate that while coumarin and **7** are essentially inactive in this system, **11a** is more active than the phenolic antioxidant *tert*-butylhydroquinone but less active than the azo dye Sudan III.[25] Preliminary assays of the tumorigenicity of **11a** and **11b** on the skins of female SENCAR mice reveal no significant activity. The findings taken together indicate that the polycyclic coumarins are a potent class of anticarcinogens which hold promise as chemopreventative anticancer agents.

Experimental Section

Materials and Methods. 2-Hydroxy-1-naphthaldehyde (**14**) was synthesized from 2-naphthol by reaction with chloroform and NaOH.[12] 2-Bromopyrene and 2-hydroxypyrene were synthesized by the procedure reported.[14] *N,N,N,N'*-tetramethylenediamine (TMEDA) was dried over $LiAlH_4$ and redistilled. Tetrahydrofuran (THF) was freshly distilled from benzophenone ketyl. Ether was dried over sodium. Dimethylformamide was distilled and stored over BaO.

The NMR spectra were obtained on a Varian EM 360 and/or the University of Chicago 500-MHz NMR spectrometer in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise. Integration was consistent with all molecular structural assignments. Melting points are uncorrected. All new compounds gave satisfactory microanalyses for C, H within ±0.3% and/or mass spectra consistent with the assigned structures.

Synthesis of Methoxymethyl Aryl Ethers. Method A. This procedure is based on that reported by Yardley and Fletcher[11] and is here illustrated by the preparation of 4-(methoxymethoxy)toluene (**1c**). A solution of *p*-cresol (54 g, 0.5 mol), dimethoxymethane (200 mL, 2.25 mol), and *p*-toluenesulfonic acid (1.0 g) in methylene chloride (600 mL) was heated at reflux under N_2 by using a Soxhlet apparatus containing type 4-Å molecular sieves (75 g) for 48 h. The molecular sieves were changed three times at 8–12-h intervals. The reaction mixture was allowed to cool, treated with triethylamine to neutralize the acid catalyst, washed with 1 N NaOH and water, and dried over Na_2SO_4. Evaporation of the solvent gave **1c** (56 g, 72%): NMR δ 2.27 (s, 3, CH_3), 3.45 (s, 3, CH_3O), 5.11 (s, 2, CH_2), 6.7–7.3 (m, 4, Ar). This compound was used directly in the next step. In later preparations the use of triethylamine was dispensed with, and the reaction product was poured through a short column of silica gel prior to workup. The yields of the methoxymethyl aryl ethers were as follows: **1a**, 68%; **1b**, 90%; **1d**, 76%; **5a**, 64%; **5b**, 75%; 1-(methoxymethoxy)naphthalene, 71%; 1-(methoxymethoxy)pyrene, 96% (mp 64–66 °C); 2-(methoxymethoxy)pyrene (**15b**), 90% (mp 70–72 °C).

Method B. The preparation of 1-methoxymethoxyanthracene is a typical example of this procedure. To a stirred suspension of NaH (50% in oil, 0.80 g, 16.1 mmol) in 150 mL of THF at 0 °C was added dropwise a solution of 1-hydroxyanthracene (2.88 g, 14.8 mmol) in 50 mL THF. The reaction mixture was stirred for 1 h at 0 °C, the $ClCH_2OCH_3$ (2 mL, 29.4 mmol) was added, and stirring was continued for 1 h at room temperature. Chromatography of the product on a column of silica gel yielded 1-(methoxymethoxy)anthracene (1.89 g, 51%): mp 52–53 °C; NMR (500 MHz) δ 3.59 (s, 3, OCH_3), 5.46 (s, 2, CH_2), 6.99 (d, 1, H_4, J = 7.4 Hz), 7.33 (br t, 1, H_3), 7.43 (m, 2, $H_{6,7}$), 7.62 (d, 1, H_2, J = 8.5 Hz), 7.98 (m, 2, $H_{5,8}$), 8.35 (s, 1, H_{10}), 8.82 (s, 1, H_9).

2-(Methoxymethoxy)anthracene: 60%; mp 126–127 °C; NMR (500 MHz) δ 3.54 (s, 3, OCH_3), 5.32 (s, 2, CH_2), 7.19 (dd, 1, H_4), 7.39 (m, 2, $H_{6,7}$), 7.45 (d, 1, H_1, J = 2.14 Hz), 7.89 (d, 1, H_3), 7.92 (m, 2, $H_{5,8}$), 8.25 (s, 1, H_{10}), 8.13 (s, 1, H_9).

Synthesis of *o*-(Methoxymethoxy)aryl Aldehydes. The general procedure employed is represented by the preparation of 2-(methoxymethoxy)-5-methylbenzaldehyde (**2c**). To a stirred solution of **1c** (15.2 g, 100 mmol) and TMEDA (20 mL, 120 mmol) in dry ether (400 mL) in an ice salt bath at −20 °C was added *n*-butyllithium (50 mL of a 1.2 M solution in hexane, 120 mmol). Stirring was continued at this temperature for 1 h, then dimethylformamide (14.6 g, 200 mmol) was added, and stirring was continued for an additional hour. The usual workup gave crude **2c** (18.8 g). This product was dissolved in minimum volume of ether, then stirred with 0.5 N $NaHSO_3$ for 20 min. The aqueous layer was cooled and the pH was adjusted to pH 11 by the addition of NaOH. The product was extracted into ether, dried, and evaporated to yield pure **2c** (14.26 g, 79%): by 78–84 °C (0.025 mmHg); NMR δ 2.33 (s, 3, CH_3), 3.53 (s, 3, CH_3O), 5.27 (s, 2, CH_2) 7.0–7.8 (m, 3, Ar), 10.53 (s, 1, CHO). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.76; H, 6.74.

2-(Methoxymethoxy)benzaldehyde (2a): 69%; bp 123 °C (2.5 mmHg); NMR δ 3.57 (s, 3, CH_3O), 5.30 (s, 2, CH_2) 6.9–8.1 (m, 4, Ar), 10.60 (s, 1, CHO). Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 64.83; H, 6.15.

2-(Methoxymethoxy)-5-chlorobenzaldehyde (2b): 91% bp 85–90 °C (0.025 mmHg); NMR δ 3.55 (s, 3, CH_3O), 5.35 (s, 2, CH_2), 7.2–8.25 (m, 4, Ar), 10.62 (s, 1, CHO). Anal. Calcd for $C_9H_9O_3Cl$: C, 53.88; H, 4.52. Found: C, 53.62; H, 4.57.

2-(Methoxymethoxy)-5-phenylbenzaldehyde (2d): 76%; mp 48–49 °C (benzene–hexane); NMR δ 3.52 (s, 3, CH_3O), 5.28 (s, 2, CH_2), 7.2–8.0 (m, 4, Ar), 10.48 (s, 1, CHO). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.29; H, 5.83.

2-(Methoxymethoxy)-4-methylbenzaldehyde (5c). *tert*-Butyllithium was employed in place of *n*-butyllithium, and TMEDA was omitted: 72%; bp 99.5 °C (0.05 mmHg); NMR δ 2.10 (s, 3, CH_3), 3.57 (s, 3, CH_3O), 5.17 (s, 2, CH_2), 6.8–7.8 (m, 3 Ar), 10.50 (s, 1, CHO). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.58; H, 6.73. A similar reaction with *n*-butyllithium and TMEDA in place of *tert*-butyllithium gave a mixture of the two isomeric ortho-aldehydes in the ratio of 4:1.

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2-(Methoxymethoxy)-4-phenylbenzaldehyde (5d): 68%; mp 54–55 °C; NMR δ 3.57 (s, 3, CH_3O), 5.37 (s, 2, CH_2), 7.2–8.0 (m, 3, Ar), 10.59 (s, 1, CHO). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.22; H, 5.83.

1-(Methoxymethoxy)-2-naphthaldehyde: 65%; mp 52–53 °C; NMR δ 3.65 (s, 3, CH_3O), 5.28 (s, 2, CH_2), 7.3–8.5 (m, 6, Ar), 10.60 (s, 1, CHO). Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.12; H, 5.59.

2-(Methoxymethoxy)-1-naphthaldehyde and 2-Naphthaldehyde (13b and 13c). Similar reaction of **13a** afforded a mixture of **13b** and **13c** in a 4:3 ratio (based on the ratio of the CHO peaks at δ 10.76 and 10.96, respectively, in the NMR spectrum).

1-(Methoxymethoxy)-2-anthracenecarbaldehyde: 72%; mp 108 °C; NMR δ 3.71 (s, 3, OCH_3), 5.39 (s, 2, CH_2), 8.23–7.22 (m, 6, Ar), 8.40 (s, 1, H_{10}), 8.80 (s, 1, H_9), 9.12 (s, 1, CHO). Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.76; H, 5.31.

2-(Methoxymethoxy)-1-anthracenecarbaldehyde: 66%; NMR (500 MHz) δ 3.57 (s, 3, OCH_3), 5.43 (s, 2, CH_2), 7.47 (d, 1, H_4, J = 9.4 Hz), 7.48 (m, 2, $H_{6,7}$), 7.94 (d, 1, $H_{5\text{ or }8}$, J = 8.2 Hz), 8.06 (d, 1, $H_{5\text{ or }8}$, J = 8.4 Hz), 8.21 (d, 1, H_3, J = 9.4 Hz), 8.34 (s, 1, H_{10}), 9.92 (s, 1, H_9), 10.99 (s, 1, CHO). Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.60; H, 5.24.

1-(Methoxymethoxy)-2-pyrenecarbaldehyde: 75%; mp 138.5–139.5 °C (benzene–hexane); NMR δ 3.57 (s, 3, CH_3CO), 5.43 (s, 2, CH_2), 7.8–8.8 (m, 8, Ar), 10.75 (s, 1, CHO). Anal. Calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.47; H, 4.92.

2-(Methoxymethoxy)-1-pyrenecarbaldehyde (15c): 85%; mp 159–160 °C dec (benzene–hexane); NMR δ 3.65 (s, 3, CH_3), 5.57 (s, 2, CH_2), 7.8–8.5 (m, 8, Ar), 11.23 (s, 1 CHO); MS m/e 290.

Addition of Lithio-*N*,*N*-dimethylacetamide to *o*-(Methoxymethoxy)aryl Aldehydes. The general procedure may be illustrated by the reaction of **2c**. To a solution of *n*-butyllithium (50 mmol in 20 mL hexane) in dry hexane (50 mL) under N_2 at 0 °C was added diisopropylamine (50 mmol). The cooling bath was removed, the reaction was stirred at room temperature for 5 min, and then sufficient dry THF (25 mL) was added to dissolve the precipitate. The solution was again cooled with an ice bath and dimethylacetamide (4.75 mL, 50 mmol) was added dropwise. When addition was complete, the reaction was stirred for 15 min more and then cooled to −78 °C. A solution of **2c** (7.2 g, 40 mmol) in THF (75 mL) was added, and stirring was continued for 3 h at this temperature. The reaction was quenched by the addition of 50 mL of 1 M acetic acid to the stirred solution at −78 °C. The precipitate was filtered cold, and the filtrate was evaporated to dryness to yield **3c** (10.5 g, 100%). This product was sufficiently pure to use directly in the next step. The analytical sample of **3c** had bp 165–168 °C (0.025 mmHg): NMR δ 2.32 (s, 3, CH_3), 2.40–2.75 (m, 3, CH_2), 2.93, 2.98 (2 s, 6, $N(CH_3)_2$), 3.47 (s, 3, CH_3O), 5.17 (s, 2, CH_2), 5.45 (m, 1, CHOH), 7.0–7.6 (m, 3, Ar). Anal. Calcd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.24. Found: C, 63.01; H, 7.95; N, 5.21.

Similar reactions of other *o*-(methoxymethoxy)arylaldehydes furnished the analogous adducts (yield and mp or bp): **3a** (100%, bp 160–164 °C (0.005 mmHg)); **3b** (100%, mp 73–74 °C); **3d** (80%, mp 111–112 °C); adduct of **5c** (100%, bp 155 °C (0.025 mmHg)); adduct of **5d** (91%, oil, decomposed on distillation); adduct of 1-(methoxymethoxy)-2-naphthaldehyde (88%, oil, decomposed on distillation); adduct of 1-(methoxymethoxy)-2-anthracenecarbaldehyde (100%); adduct of 2-(methoxymethoxy)-1-anthracenecarbaldehyde (92%); adduct of 1-(methoxymethoxy)-2-pyrenecarbaldehyde (100%, mp 128–129 °C); adduct of 2-(methoxymethoxy)-1-pyrenecarbaldehyde (100%).

Similar reaction of the lithium salt of 2-hydroxy-1-naphthaldehyde (**14**) (prepared in situ from reaction of **14** with *n*-butyllithium) afforded the corresponding adduct as an oil which was utilized directly in the next step.

Synthesis of Coumarins[26] by Cyclization in Acetic Acid. The general procedure is represented by the cyclization of **3c** to furnish 6-methylcoumarin (**4c**). A solution of **3c** (3 g, 11.4 mmol) in glacial acetic acid (25 mL) was heated at reflux for 6 h. The product was poured onto crushed ice, and the precipitate was filtered, washed with dilute $NaHCO_3$, and dried to yield **4c** (1.53 g, 90%). The crude **4c** was dissolved in benzene and passed through a short silica gel column eluted with benzene. Recrystallization from benzene–dioxane furnished pure **4c** (0.90 g): mp 73–74 °C (lit.[27] mp 75–76 °C); NMR (500 MHz) δ 2.44 (s, 3, CH_3), 6.33 (d, 1, H_3, $J_{3,4}$ = 9.5 Hz), 7.06 (d, 1, H_7, $J_{7,8}$ = 7.79 Hz), 7.12 (s, 1, H_5), 7.33 (d, 1, H_8), 7.63 (d, 1, H_4). Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 75.05; H, 5.06.

Coumarin (4a): 80%; mp 68–69 °C (lit.[28] mp 69–70 °C); the ^1H NMR spectrum agreed closely with the published spectrum.[29]

6-Chlorocoumarin (4b): 62%; mp 164–165 °C (lit.[28] mp 161–162 °C); NMR (500 MHz) δ 6.44 (d, 1, H_3, $J_{3,4}$ = 9.6 Hz); 7.26 (d, 1, H_7, $J_{7,8}$ = 8.1 Hz), 7.45 (s, 1, H_5), 7.46 (d, 1, H_8), 7.60 (d, 1, H_4).

6-Phenylcoumarin (4d): 82%; mp 115–116 °C (lit.[30] mp 118 °C); NMR (500 MHz) δ 6.40 (d, 1, H_3, $J_{3,4}$ = 9.5 Hz), 7.2–7.7 (m, 8, Ar), 7.74 (d, 1, H_4).

7-Methylcoumarin (6a): 91%; mp 127–128 °C (lit.[31] mp 126–127 °C); NMR (500 MHz) δ 2.44 (s, 3, CH_3), 6.33 (d, 1, H_3, $J_{3,4}$ = 9.5 Hz), 7.07 (d, 1, $H_{5\text{ or }6}$, $J_{5,6}$ = 8.9 Hz), 7.12 (s, 1, H_8), 7.33 (d, 1, $H_{5\text{ or }6}$), 7.63 (d, 1, H_4).

7-Phenylcoumarin (6b): 91%; mp 189–190 °C NMR (500 MHz) δ 6.40 (d, 1, H_3, $J_{3,4}$ = 9.5 Hz), 7.30–7.55 (m, 7, Ar), 7.61 (d, 1, $H_{5\text{ or }6}$, J = 7.6 Hz), 7.70 (d, 1, H_4).

2*H*-Naphtho[1,2-*b*]pyran-2-one (7,8-benzocoumarin) (7a): 71%; mp 139–140 °C (benzene–hexane) (lit.[32] mp 141–142 °C); NMR (500 MHz) δ 6.48 (d, 1, H_3) 7.4–7.9 (m, 6, Ar + H_4), 8.53 (m, 1, H_{10}).

3*H*-Naphtho[2,1-*b*]pyran-3-one (5,6-benzocoumarin) (8a): 56%; mp 114–115 °C (benzene–hexane) (lit.[33] mp 118 °C); NMR (500 MHz) δ 6.56 (d, 2, H_3, $J_{3,4}$ = 9.7 Hz), 7.44 (d, 1, H_9, $J_{9,10}$ = 9.1 Hz), 7.55, 7.67 (pair t, 2, $H_{6,7}$), 7.88 (d, 1, H_8), 7.96 (d, 1, H_{10}), 8.20 (d, 1, H_5), 8.46 (d, 1 H_4).

2*H*-Anthra[1,2-*b*]pyran-2-one (9a): 87%; mp 223–225 °C; NMR (500 MHz) δ 6.53 (d, 1, H_3, J = 9.3 Hz), 7.38 (d, 1, H_5, J = 8.8 Hz), 7.55 (m, 2, $H_{9,10}$), 7.79 (d, 1, H_6, J = 8.8 Hz), 7.81 (d, 1, H_4, J = 9.53 Hz), 8.01 and 8.09 (m, 2, $H_{8,11}$), 8.39 (s, 1, H_7), 9.13 (s, 1, H_{12}). Anal. Calcd for $C_{17}H_{10}O_2$: C, 82.91; H, 4.09. Found: C, 82.79; H, 4.12.

3*H*-Anthra[2,1-*b*]pyran-3-one (10a): 75%; mp 198–199 °C; NMR (500 MHz) δ 6.63 (d, 1, H_2, J = 9.7 Hz), 7.45 (d, 1, H_5, J = 9.3 Hz), 7.57 (m, 2, $H_{9,10}$), 8.07 (br t, 2, $H_{8,11}$), 8.14 (d, 1, H_6, J = 9.2 Hz), 8.49 (s, 1, H_7), 8.67 (d, 1, H_1, J = 9.7 Hz), 8.75 (s, 1, H_{12}). Anal. Calcd for $C_{17}H_{10}O_2$: C, 82.91; H, 4.09. Found: C, 82.65; H, 4.13.

9*H*-Pyreno[1,2-*b*]pyran-9-one (11a): 85%; mp 208–209 °C (benzene–hexane); NMR (500 MHz) δ 6.59 (d, 1, H_8, $J_{7,8}$ = 9.5 Hz), 7.9–8.2 (m, 8, Ar), 8.61 (d, 1, H_{11}, J = 9.2 Hz). Anal. Calcd for $C_{19}H_{10}O_2$: C, 84.43; H, 3.73. Found: C, 84.33; H, 3.74.

8*H*-Pyreno[2,1-*b*]pyran-8-one (12a): 85%; mp 245–246 °C; NMR (500 MHz) δ 6.60 (d, 1, H_9, $J_{9,10}$ = 9.6 Hz), 7.2–8.4 (m, 8, Ar), 8.63 (d, 1, H_{10}). Anal. Calcd for $C_{19}H_{10}O_2$: C, 84.43; H, 3.73. Found: C, 84.50; H, 3.76.

Synthesis of 8*H*-Pyreno[2,1-*b*]pyran-8-one (12a) from Pyrene-1-carbaldehyde (17). 2-Hydroxy-1-pyrenecarbaldehyde (19). In a 500-mL, three-neck, round-bottom flask equipped with a nitrogen inlet, a pressure-equalizing addition funnel, and a rubber septum were placed *N*,*N*,*N*′-trimethylethylenediamine (5 g, 49 mmol) and 25 mL of anhydrous THF. To this solution under N_2 at −20 °C was added *n*-butyllithium (19.2 mL of a 2.5 M solution, 49 mmol) slowly via syringe. Stirring was continued at −20 °C for 30 min, then a solution of 1-pyrenecarbaldehyde (10.24 g, 44 mmol) in THF (100 mL) was slowly added, and stirring was continued for an additional h at −20 °C. To this solution was added *n*-butyllithium (52.8 mL of a 2.5 M solution, 132 mmol), and the reaction mixture was stirred at −20 °C for 1 h. Then trimethyl borate (5.96 mL, 5 mmol) was added

(26) The names employed for the polycyclic coumarins are in accord with IUPAC rules of organic nomenclature; they are also the Chemical Abstracts names for the 1967–71 index period. Common older names are given in parentheses in a few instances.

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at −42 °C, and the reaction was stirred in a freezer at −30 to −40 °C for 24 h. The product was partitioned between 440 mL of 10% HCl and 500 mL of ethyl acetate. The organic layer was washed twice with water, dried over $MgSO_4$, and evaporated under vacuum to yield the crude boronic acid (12.06 g). The latter was heated under N_2 in 80 mL of diglyme with trimethylamine oxide dihydrate (14.7 g, 132 mmol) at 110 °C for 4 h. The product was partitioned between benzene and water and further purified by chromatography on Florisil. Elution with benzene–ether (1:1) gave **19** (2.71 g, 25%): mp 180–181 °C dec; NMR δ 7.4–8.8 (m, 8, Ar), 11.13 (s, 1, CHO).

8*H*-Pyreno[2,1-*b*]pyran-8-one (12a). Addition of lithio-*N*,*N*-dimethylacetamide to the lithium salt of **19** (prepared in situ from reaction of **19** with *n*-butyllithium) gave the corresponding adduct which was cyclized in refluxng acetic acid by the usual procedure to furnish **12a** (27%): mp 245–246 °C; the NMR spectrum **12a** was identical with that of an authentic sample.

Synthesis of 7,12-Dimethyl-2*H*-anthra[1,2-*b*]pyran-2-one (20a). 1-Hydroxy-9,10-dimethylanthracene (22a). To a cooled solution (0 °C) of 1-hydroxyanthraquinone (25.3 g, 113 mmol) in 1.2 L of THF was added dropwise methyllithium (325 mL of 1.2 M solution, 390 mmol) over 15 min. The reaction was stirred at room temperature for 1 h, then quenched with saturated ammonium chloride solution, extracted with ether, and dried over $MgSO_4$ to yield the dimethyl adduct (28.1 g). This was employed directly in the next step. To a suspension of $2TiCl_3$·$LiAlH_4$ (35.4 g) in THF (600 mL) at 0 °C prepared by addition of the reagent to THF in portions (*Caution*: reverse addition may cause fire) was added a solution of the dimethyl adduct (10 g, 39 mmol) in 300 mL of THF dropwise over 10 min. The reaction mixture was stirred at room temperature for 2 h, then refluxed for 20 min, cooled, and quenched with saturated NH_4Cl. The usual workup gave crude **22a** (11.3 g). Chromatography on Florisil gave on elution with 5–25% EtOAc/hexane **22a** (4.8 g, 55%): mp 125–135 °C dec; NMR (500 MHz) δ 3.03 (s, 3, 10-CH_3), 3.37 (s, 3, 9-CH_3), 5.36 (s, 1, OH), 6.68 (d, 1, H_2, J = 7.3 Hz), 7.24 (dd, 1, H_3), 7.46 (m, 2, $H_{6,7}$), 7.85 (d, 1, H_4), 8.25 (m, 1, $H_{5\text{ or }8}$), 8.34 (m, 1, $H_{5\text{ or }8}$); IR 3580 cm^{-1} (sh), 3330 (h), 2950 (br), 1675 (sh). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.32; H, 6.43.

1-(Methoxymethoxy)-9,10-dimethylanthracene (22b) was synthesized from **22a** by method B with NaH and $ClCH_2OCH_3$: 56% NMR δ 2.77 (s, 3, 10-CH_3), 3.13 (s, 3, 9-CH_3), 3.40 (s, 3, OCH_3), 5.08 (s, 2, CH_2), 6.8–8.6 (m, 7, Ar).

1-(Methoxymethoxy)-9,10-dimethyl-2-anthracenecarbaldehyde (22c) was prepared from **22b** by the usual method: 72%; mp 99–101 °C; NMR δ 3.00 (s, 3, 10-CH_3), 3.30 (s, 3, 9-CH_3), 3.48 (s, 3, OCH_3), 5.04 (s, 2, CH_2), 8.5–7.4 (m, 6, Ar), 10.59 (s, 1, CHO). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.62; H, 6.32.

7,12-Dimethyl-2*H*-anthra[1,2-*b*]pyran-2-one (20a). Reaction of **22c** with lithio-*N*,*N*-dimethylacetamide by the usual procedure furnished the adduct, which was cyclized in acetic acid under the usual conditions to yield **20a** (59% overall): mp 220–224 °C; NMR δ 2.13 (s, 3, 7-CH_3), 2.48 (s, 3, 12-CH_3), 6.28 (d, 1, H_3, J = 10 Hz), 7.06–7.53 (m, 6, Ar), 7.57 (d, 1, H_4). Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.18; H, 5.14. Found: C, 83.30; H, 5.08.

Synthesis of 7,12-Dimethyl-3*H*-anthra[2,1-*b*]pyran-3-one (21a). 2-Hydroxy-9,10-dimethylanthracene (23a). This phenol was prepared from 2-hydroxyanthraquinone by the procedure employed for the preparation of **22a**. There was obtained **23a** (53%) as yellow needles: mp 215–220 °C dec; NMR (500 MHz) δ 2.06 (s, 3, CH_3), 2.17 (s, 3, CH_3), 6.78 (dd, 1, H_3, $J_{1,3}$ = 1.5, $J_{3,4}$ = 8 Hz), 7.00 (d, 1, H_1, $J_{1,3}$ = 1.5 Hz), 7.01 (m, 2, $H_{6,7}$), 7.65 (dd, 2, $H_{5,8}$), 7.66 (d, 1, H_4, J = 8 Hz), 8.98 (s, 1, OH). Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.43; H, 6.46.

2-(Methoxymethoxy)-9,10-dimethylanthracene (23b) was prepared from **23a** by method B: 66%; NMR δ 2.97 (br s, 6, CH_3), 3.52 (s, 3, OCH_3), 5.30 (s, 2, CH_2), 7.1–8.35 (m, 7, Ar).

1-Formyl-2-hydroxy-9,10-dimethylanthracene (23d). $POCl_3$ (2.4 mL) was added dropwise to dimethylformamide (2 mL) at 0 °C. The product was warmed to dissolve the crystalline solid and 1 mL of this was added to a solution of **23a** (100 mg, 0.45 mmol) in toluene (5 mL). The reaction mixture was refluxed for 3 h, cooled to 0 °C, and quenched with saturated Na_2CO_3 solution. Conventional workup followed by chromatography on silica gel furnished **23d** (33 mg, 30%): mp 127–128 °C; NMR (500 MHz) δ 2.80 (s, 3, 10-CH_3), 3.07 (s, 3, 9-CH_3), 7.33 (d, 1, H_3, J = 9.4 Hz), 7.57 (m, 2, $H_{6,7}$), 8.24 (dd, 1, $H_{5\text{ or }8}$, J = 7.15, 2.10 Hz), 8.28 (dd, 1, $H_{5\text{ or }8}$), 8.34 (d, 1, H_4, J = 9.5 Hz), 10.87 (s, 1, CHO). Anal. Calcd for $C_{17}H_{14}O_2$: C, 81.58, H, 5.64. Found: C, 81.66; H, 5.48.

7,12-Dimethyl-3*H*-anthra[2,1-*b*]pyran-3-one (21a). Reaction of **23d** (50 mg, 0.2 mmol) with lithio-*N*,*N*-dimethylacetamide by the usual procedure furnished the corresponding adduct which underwent cyclization in refluxing acetic acid under the usual conditions to yield **21a** (54%): NMR (500 MHz) δ 3.10 (s, 3, 7-CH_3), 3.20 (s, 3,12-CH_3), 6.42 (d, 2, H_2, J = 9.9 Hz), 7.3–8.5 (m, 6, Ar), 8.56 (d, 1, H_{11}, J = 9.9 Hz). Anal. Calcd for $C_{19}H_{14}O_2$: C, 83.18; H, 5.14. Found: C, 83.41; H, 5.08.

3-Methyl-2*H*-naphtho[1,2-*b*]pyran-2-one (7b). The general procedure for the addition of lithio-*N*,*N*-dimethylacetamide to *o*-(methoxymethoxy)aryl aldehydes was followed. Reaction of 1-(methoxymethoxy)-2-naphthaldehyde (330 mg, 1.53 mmol) with lithio-*N*,*N*-dimethylpropionamide by this procedure gave the adduct (540 mg) which was cyclized directly in refluxing acetic acid to furnish **7b** (320 mg, 100%): mp 134–135 °C (benzene–hexane); NMR (500 MHz) δ 2.27 (s, 3, CH_3), 7.82 (s, 1, H_4), 7.20–7.85 (m, 5, Ar), 8.51 (dd, 1, H_{10}). Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 79.93; H, 4.80.

2-Methyl-3*H*-naphtho[2,1-*b*]pyran-3-one (8b) was prepared from 2-hydroxy-1-naphthaldehyde (1.72 g, 10 mmol) and lithio-*N*,*N*-dimethylpropionamide by appropriate modification of the procedure employed to prepare **7b**. Excess *n*-butyllithium was employed to convert the phenol to its lithium salt. There was obtained **8b** (1.51 g, 77%): mp 159–160 °C (benzene–hexane); NMR (500 MHz) δ 2.33 (s, 3, CH_3), 7.42 (d, 1, H_5, J = 9.0 Hz), 7.60 (m, 2, $H_{8,9}$), 7.87 (pair d, 2, $H_{6,7}$), 8.47 (d, 1, H_{10}, J = 8.5 Hz), 8.26 (s, 1, H_1). Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 80.01; H, 4.83.

2,7,12-Trimethyl-3*H*-anthra[2,1-*b*]pyran-3-one (21b) was prepared from **23d** (50 mg, 0.20 mmol) and lithio-*N*,*N*-dimethylpropionamide by the procedure used for the preparation of **7b**. There was obtained **21b** (12 mg, 21%): mp 192–194 °C; NMR (500 MHz) δ 2.32 (s, 3, CH_3), 3.08 (s, 3, CH_3), 3.20 (s, 3, CH_3), 7.38 (d, 1, H_5, J = 9.6 Hz), 7.60 (m, 2 , $H_{9,10}$), 8.27 (d, 1, $H_{8\text{ or }11}$, J = 8.5 Hz), 8.31 (d, 1, $H_{8\text{ or }11}$, J = 8.2 Hz), 8.32 (d, 1, H_5), 8.37 (s, 1, H_1). Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.42; H, 5.66.

7-Methyl-9*H*-pyreno[1,2-*b*]pyran-9-one (26). Metalation of 1-(methoxymethoxy)pyrene (2.98 g, 11.4 mmol) with *n*-butyllithium by the usual procedure followed by reaction with acetaldehyde (5.02 g, 114 mmol) furnished 1-(methoxymethoxy)-2-(1-hydroxyethyl)pyrene (3.5 g, 52%) which was used directly in the next step.

The latter alcohol (1.8 g, 5.85 mmol) was dissolved in DMSO (16 mL) and Et_3N (4 mL), and to this solution was added pyridine. SO_3 complex (1.8 g). The reaction mixture was stirred at room temperature for 1.5 h and worked up in the usual manner. The crude product (1.7 g) was dissolved in benzene and purified by passage through a column of silica gel to yield 1-(methoxymethoxy)-2-acetylpyrene (**25**) (1.65 g, 93%): mp 80–81 °C (hexane). Anal. Calcd for $C_{20}H_{10}O_3$: C, 78.93; H, 5.30. Found: C, 78.76; H, 5.33.

Reaction of **25** (670 mg, 2.2mmol) with lithio-*N*,*N*-dimethylacetamide by the standard procedure furnished the corresponding adduct (860 mg, 100%): mp 120–121 °C (benzene–hexane). Anal. Calcd for $C_{24}H_{25}O_4N$: C, 73.63; H, 6.44; N, 3.58. Found: C, 73.47; H, 6.45; N, 3.50.

Cyclization of the adduct (840 mg, 2.2 mmol) in refluxing acetic acid by the usual procedure gave **26** (500 mg, 81%): mp 250 °C dec; NMR (500 MHz) δ 2.64 (s, 3, CH_3), 6.45 (s, 1, H_8), 7.23 (s, 1, H_6), 7.9–8.2 (m, 6, Ar), 8.63 (d, 1, H_{11}, J = 9.1 Hz). Anal. Calcd for $C_{20}H_{12}O_2$: C, 84.49; H, 4.25. Found: C, 84.32; H, 4.28.

Synthesis of Coumarins by the $POCl_3$ Method. The general procedure may be illustrated by the preparation of 8-methyl-9*H*-10-oxabenzo[*a*]pyren-9-one (**11b**). $POCl_3$ (10 mL) and *N*,*N*-dimethylpropionamide (4 mL) were cautiously mixed together in a flask at 0 °C. This mixture was added to a flask containing 1-(methoxymethoxy)pyrene-2-carbaldehyde (1.71 g, 5.9 mmol) under N_2, and the mixture was stirred for 3 h at 60–70 °C. The reaction mixture was cooled, and reaction was quenched by the addition of excess 10% sodium carbonate solution. The precipitate was filtered, dried, and purified by chromatography on silica gel

eluted with benzene to yield **11b** (1.51 g, 93%): mp 233–234 °C; NMR (500 MHz) δ 2.33 (s, 3, CH_3), 7.23 (s, 1, H_6), 7.78 (d, 1, H_7, J = 1.1 Hz), 7.9–8.2 (m, 6, Ar), 8.63 (d, 1, H_{11}, J = 7.5 Hz). Anal. Calcd for $C_{20}H_{12}O_2$: C, 84.50; H, 4.25. Found: C, 84.38; H, 4.34.

2-Methyl-3*H*-naphtho[2,1-*b*]pyran-3-one (8b): 39%; mp 159–160 °C; the 500-MHz ^1H NMR spectrum of **8b** was essentially identical with that of an authentic sample of **8b** prepared via the reaction with lithio-*N*,*N*-dimethylpropionamide.

3-Methyl-2*H*-anthra[1,2-*b*]pyran-2-one (9b): 58%; mp 189 °C (sharp); NMR (500 MHz) δ 2.33 (d, 3, CH_3, J = 1.3 Hz), 7.37 (d, 1, H_5, $J_{5,6}$ = 8.7 Hz), 7.56 (m, 2, $H_{5,8}$), 7.66 (d, 1, H_4, J = 1.3 Hz), 7.80 (d, 1, H_6, J = 8.7 Hz), 8.02 (m, 1, $H_{9 \text{ or } 10}$), 8.12 (m, 1, $H_{9 \text{ or } 10}$), 8.41 (s, 1, H_7), 9.14 (s, 1, H_{12}); the assignment of the multiplets at δ 7.56, 8.02, and 8.12 may be reversed. Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.64. Found: C, 82.95; H, 4.70.

2-Methyl-3*H*-anthra[2,1-*b*]pyran-3-one (10b): 62%; mp 173–175 °C (EtOAc); NMR (500 MHz) δ 2.38 (d, 3, CH_3, J = 1.1 Hz), 7.42 (d, 1, H_3, J = 9.2 Hz), 7.54 (m, 2, $H_{9,10}$), 8.04 (m, 3, $H_{6,8,10}$), 8.45 (s, 1, H_7), 8.46 (br s, 1, H_1), 8.73 (s, 1, H_{12}). Anal. Calcd for $C_{18}C_{12}O_2$: C, 83.06; H, 4.64. Found: C, 82.82; H, 4.60.

9-Methyl-8*H*-pyreno[2,1-*b*]pyran-8-one (12b): 89%; mp 154–156 °C; NMR (500 MHz) δ 2.38 (s, 3, CH_3), 7.34 (s, 1, H_6), 7.9–8.3 (m, 6, Ar), 8.38 (d, 1, H_{11}, J = 9.2 Hz), 8.42 (br s, 1, H_{10}); MS, m/e 284. Anal. Calcd for $C_{20}H_{12}O_2$: C, 84.49; H, 4.26. Found: C, 84.54; H, 4.22.

3,7,12-Trimethyl-2*H*-anthra[1,2-*b*]pyran-2-one (20b): 51%; mp 201–203 °C; NMR (500 MHz) δ 2.16 (s, 3, 7-CH_3), 2.19 (d, 3, 3-CH_3, J = 1.0 Hz), 2.50 (s, 3, 12-CH_3), 7.25–7.50 (m, 7, Ar + vinylic). Anal. Calcd for $C_{20}H_{16}O$: C, 83.31; H, 5.59. Found: C, 83.40; H, 5.68.

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Synthesis of Sugar Amino Acids by Triflate Substitution. 2.[1] Free 3- and 4-Amino Acid Deoxyaldopyranoses

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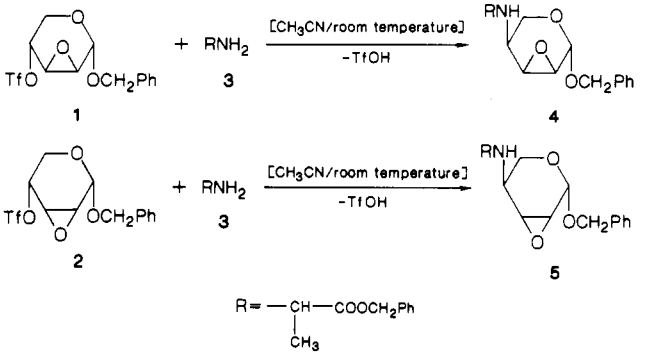
The S_N2 reactions of benzyl 2,3-anhydro-4-*O*-triflyl-α-D-lyxopyranoside (**1**) and benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (**2**) with an excess amount of L-alanine benzyl ester in acetonitrile afford benzyl 2,3-anhydro-4-[(L-alanine benzyl ester)-*N*-yl]-4-deoxypyranosides (**4** and **5**, respectively). Acidic hydrolysis of **4** yields **6** and **7** by way of direct epoxide cleavage, while **5** leads via an irreversible isomerization to its corresponding epimine **8**, which further undergoes diaxial ring cleavage, yielding **9** and **10**. Hydrogenation of **10** under neutral or slightly acidic conditions affords the title compound **15**, whereas that of **6** and **9** leads to the 1-L-alanino-1,4-anhydro-1-deoxypentitols **13** and **14**. The 4-L-alanino-4-deoxypentoses **11** and **12** are obtained by hydrogenation of **6** and **9** in a strong acidic medium. High-resolution ^1H and ^{13}C NMR spectroscopy shows that compounds **11** and **12** favor the pyranose at lower and the pyrrolidinose form at higher pH.

Introduction

Although the amine-like coupling of sugars and amino acids vicinal to the anomeric center can be achieved through Amadori or Heyns rearrangement of the corresponding glycosylamines,[2-5] this procedure is not appropriate for the introduction of amino acids at any other site of the carbohydrate moiety. Earlier we reported that the C–N coupling can be done under mild conditions through an S_N2 reaction of amino esters with oxirane-activated sugar triflates (Scheme I).[1,6-8] Stepwise deprotection of the coupling products provides a new class of free 3- and 4-amino-3-deoxy and -4-deoxy aldoses. By contrast, other strategies to synthesize even simple 4-imino-4-deoxy sugars encounter major difficulties.[9,10]

Scheme I



Results and Discussion

Benzyl 2,3-anhydro-4-*O*-triflyl-α-D-lyxopyranoside (**1**) and benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (**2**)

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