Lewis Acid Mediated Nucleophilic Substitution Reactions of 2-Alkoxy-3,4-dihydro-2*H*-1-benzopyrans: Regiochemistry and Utility in the Synthesis of 3,4-Dihydro-2*H*-1-benzopyran-2-carboxylic Acids

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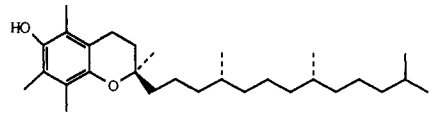
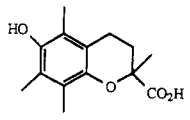
The Lewis acid mediated nucleophilic substitution reactions of a variety of 2-alkoxy-, 2-hydroxy-, and 2-(acyloxy)-3,4-dihydro-2*H*-1-benzopyrans (chromans) have been studied within the context of developing new synthetic routes to chroman-2-carboxylic acids, certain of which have utility as antioxidants and drug intermediates. The scope and limitations of these transformations have been determined. Treatment of 2-methoxychromans in the α-tocopherol structural class (**9**, **25**) with cyanotrimethylsilane in the presence of $TiCl_4$ or BF_3 etherate generally leads in good yield to the desired 2-cyanochromans **10** and **26**. On the other hand, ketals of the type **19** react less efficiently, giving poor to moderate yields of the cyanochromans **36** along with regioisomeric products (**37**, **38**). Spiro-fused ketals such as **28** exhibit dichotomous behavior dependent on the Lewis acid employed, while the pyranochroman **34b** affords **35** in good yield. Thus the regioselectivity of these processes appears to be highly dependent on substrate structure and the nature of the Lewis acid.

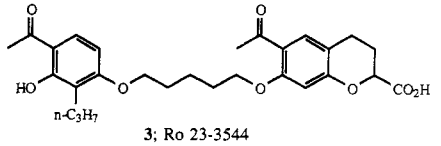
2-Substituted 3,4-dihydro-2*H*-1-benzopyrans (chromans), such as the prototypal antioxidant α-tocopherol (**1**) are an important class of biologically active oxygen heterocycles.[1] Studies in recent years have led to the discovery of acid **2**, which is not only an intermediate in certain total syntheses of **1**,[2] but also an interesting antioxidant in its own right.[3] Furthermore, acid **3**, a potent antagonist of the pharmacological actions of peptidoleukotrienes, is in clinical development.[4] Given the interest in acids of this type, and the relative paucity of methods for their synthesis, we embarked upon a study aimed at making such compounds more readily available. Herein, we report the results of some of these efforts.[5]



1; (2R,4'R,8'R)-α-Tocopherol (Natural Vitamin E)



2; Trolox™



3; Ro 23-3544

At the outset of our work, useful synthetic approaches to chroman-2-carboxylic acids were limited to the catalytic hydrogenation–hydrogenolysis of chromone-2-carboxylates[4c,6] and, in the α-tocopherol series, an elegant scheme developed in our laboratories in the early 1970s.[3,7,8] The latter route involves 2-alkoxy- and 2-hydroxychroman intermediates **4** (R^1, R^3, R^4, R^5 = CH_3; R^2 = OH; R^6 = H, CH_3; cf. **9** below), which are readily available via cyclocondensation of trimethylhydroquinone (TMHQ, **14a**) with methyl vinyl ketone (**15a**) in acidic methanol. In order to introduce the 2-carboxyl function, the pyran ring was cleaved by hydrolysis and acetylation, affording a 4-aryl-2-butanone to which was added HCN in a classical manner. Upon hydrolysis of the resulting cyanohydrin, the chroman ring was re-formed,[2a] producing acid **2** and analogues thereof.

In view of the ready availability of the ketals **4**, it occurred to us that an alternative protocol for introduction of the carboxyl moiety would involve the direct treatment of the ketal **4** with a nucleophile (eg. cyanide, alkyl or aryl isocyanides), in the presence of a Lewis acid to give the product **5**. Such processes have precedent in related studies with simple acetals[9] and would probably proceed

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(1) (a) *The Chemistry of Heterocyclic Compounds*; Ellis, G. P., Lockhart, I. M., Eds.; John Wiley-Interscience: New York, 1981; Vol. 36. (b) *Vitamin E. A Comprehensive Treatise*; Machlin, L. J., Ed.; Marcel Dekker: New York, 1980. (c) Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194–201.

(2) (a) Cohen, N.; Lopresti, R. J.; Neukom, C. *J. Org. Chem.* **1981**, *46*, 2445–2450 and references cited therein. (b) Saucy, G.; Cohen, N. In *New Synthetic Methodology and Biologically Active Substances*; Yoshida, Z., Ed.; Elsevier: New York, 1981; Chapter 9 and references cited therein. (c) Cohen, N.; Scott, C. G.; Neukom, C.; Lopresti, R. J.; Weber, G.; Saucy, G. *Helv. Chim. Acta* **1981**, *64*, 1158–1173.

(3) (a) Scott, J. W.; Cort, W. M.; Harley, H.; Parrish, D. R.; Saucy, G. *J. Am. Oil Chem. Soc.* **1974**, *51*, 200–203. (b) *Chem. Abstr.* **1977**, *86*, 190279*u*; U.S. Patent No. 4,003,919, Jan. 18, 1977, Hoffmann-La Roche, Inc. (c) *Chem. Abstr.* **1977**, *87*, 184732*r*; U.S. Patent No. 4,026,907, May 31, 1977, Hoffmann-La Roche, Inc.

(4) (a) Cohen, N.; Weber, G.; Banner, B. L.; Lopresti, R. J.; O'Donnell, M.; Welton, A. F.; Brown, D.; Crowley, H.; Zitelli, A. Paper presented at the 191st ACS National Meeting, April 13–18, 1986, New York, NY; Abstr. MEDI44. (b) O'Donnell, M.; Welton, A. F.; Crowley, H.; Brown, D.; Garippa, R.; Cohen, N.; Weber, G.; Banner, B.; Lopresti, R. J. *Adv. Prostaglandin, Thromboxane, Leukotriene Res.* **1987**, *17*, 512–518; (c) Eur. Pat. Appl. EP 129,906 (U.S. Appl. 507,383, June 24, 1983); F. Hoffmann-La Roche and Co. A. G. *Chem. Abstr.* **1985**, *103*, 6223*s*.

(5) A portion of this work has been previously reported: Cohen, N.; Schaer, B.; Saucy, G.; Borer, R.; Todaro, L.; Chiu, A.-M. Paper presented at the 17th ACS NERM, Rochester, NY, Nov. 8–11, 1987; Abstr. No. 294. All chiral compounds described herein are racemic even though one enantiomer is depicted.

(6) Witiak, D. T.; Stratford, E. S.; Nazareth, R.; Wagner, G.; Feller, D. R. *J. Med. Chem.* **1971**, *14*, 758–766.

(7) (a) Scott, J. W.; Bizzarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim. Acta* **1976**, *59*, 290–306. (b) Cohen, N.; Scott, J. W.; Bizzarro, F. T.; Lopresti, R. J.; Eichel, W. F.; Saucy, G. *Helv. Chim. Acta* **1978**, *61*, 837–843.

(8) In addition, there have appeared descriptions in the patent literature of alternative approaches to antioxidant chroman-2-carbonitriles, of unknown generality: (a) Diels–Alder addition of an *o*-quinone methide to methacrylonitrile, see ref 3c. (b) Lewis acid catalyzed cyclocondensations of unsaturated cyanohydrins with hydroquinones: *Chem. Abstr.* **1980**, *93*, 239234*m*; Ger. Offen. 2,909,601, Sept. 25, 1980 (U.S. Patent No. 4,268,446, May 19, 1981), BASF.

(9) See: Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043–1054 and references cited therein. In addition, there exists an enormous literature involving C-glycoside formation via related reactions of carbohydrate derivatives.

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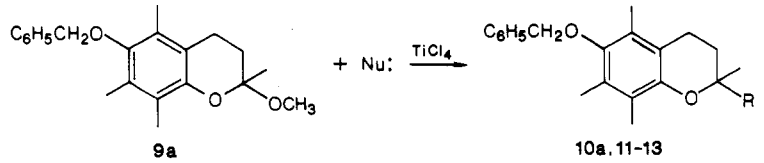
Table I. Reactions of 2-Methoxy-3,4-dihydro-2*H*-1-benzopyran 9a with Nucleophiles

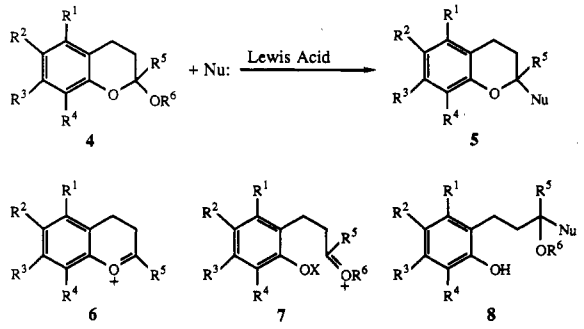


9a 10a,11-13

prod.	Nu	R	yield,[a] %	mp, °C	formula[b]
10a	$(CH_3)_3SiCN$	CN	79	110–112[c]	$C_{21}H_{23}NO_2$
11	$CH_2{=}CHCH_2Si(CH_3)_3$	$CH_2{=}CHCH_2$	70	oil	$C_{23}H_{28}O_2$
12	C_2H_5MgBr	C_2H_5	34	oil	$C_{22}H_{28}O_2$
13	$C_6H_5CH_2N{=}C$:	$CONHCH_2C_6H_5$	40	88–90[d]	$C_{28}H_{31}NO_3$

[a] Yield of pure (^{1}H NMR, IR, UV, MS, TLC) recrystallized or chromatographed product. [b] C, H analyses were within ±0.4% of the calculated values. [c] Recrystallized from ether. [d] Recrystallized from hexanes.

through the oxocarbonium species **6**.[10] The key question in this approach involves regioselectivity as compound **4** can also cleave in an endocyclic manner with rupture of the chroman system to generate **7** and ultimately the unwanted phenol 8. Thus the utility of this attractive scheme would be dependent on the balance of exocyclic vs endocyclic ketal cleavage,[11] which, in turn, could involve a variety of factors such as the substrate structure, the leaving group, the relative stability and rate of formation of the oxocarbonium ion intermediates, and the nature of the Lewis acid.



Our initial screening studies were performed using 2-methoxy-6-(benzyloxy)chroman **9a**, readily available from our earlier α-tocopherol work.[3,7b] The results with four nucleophiles, with use of titanium tetrachloride as the Lewis acid, are presented in Table I. We were encouraged to find that cyanide could be efficiently installed with cyanotrimethylsilane, affording nitrile **10a** in 79% yield. Allyltrimethylsilane, under similar conditions, furnished the 2-allylchroman **11** in comparable yield. Less efficient were the reactions with ethylmagnesium bromide and benzyl isocyanide, in which cases the desired adducts **12** and **13** were obtained in less than 50% yield. These screening studies suggested that the key cyanation reaction offered significant potential, and the scope and limitations of this process were determined with several structurally diverse 2-alkoxychromans.

The new 2-alkoxy-, 2-hydroxy-, and 2-(acyloxy)chromans are presented in Table II. Ketals **9f,g,j,m** were prepared via cyclocondensation[7] of TMHQ (**14a**) or the hydroquinones **14b–d** with methyl vinyl ketone (**15a**) and, in the case of **9j**, vinyl ketone **15b**.[12] Ethers **9d,e** were secured via standard benzylation of the corresponding 6-hydroxy compounds. The 7-oxygen-substituted analogues **19** were not as readily available as the tocopherol-like intermediates and required some study. In one approach, we started with the commercially available coumarins **16a,b**. Thus catalytic hydrogenation of **16a** followed by benzylation afforded **17a**[13] whereas hydrogenation of **16b** gave the dihydrocoumarin **17b**.[14] Dibal reduction smoothly furnished the lactols **18a**[4c] and **18b**, transformation of which into the acetals **19** was not straightforward. For example, only polymeric products were obtained when these hemiacetals were treated with acidic methanol–trimethyl orthoformate. In order to obtain the desired ketal **19a**, a different sequence, in which lactol **18a** was first treated with thionyl chloride and then methanol, was required. This procedure provided the 2-methoxychroman in 93% yield.[15] An alternative approach, which is concise although not extremely efficient, was employed to produce **19b**. This involves the condensation of 3-methoxyphenol (**20**) with acrolein dimethyl acetal, giving the desired 2,7-dimethoxychroman in around 30% yield along with several other components which were easily removed by chromatography.[16] Exposure of **18b** to methylmagnesium bromide gave an alcohol which was then oxidized. The resulting hemiketal, without purification, was treated with acidic methanol, providing **19e**. The latter substance could also be obtained in low yield by condensation of **20** with methyl vinyl ketone. Standard acetylation of **18a,b** gave the 2-

(10) A conceptually related approach to 2-substituted chromans is based upon the addition of nucleophiles to 1-benzopyrylium salts: (a) Goldsmith, D. J.; Helmes, C. T., Jr.; *Synth. Commun.* **1973**, *3*, 231–235. (b) Iwasaki, H.; Takashi, K.; Yamamoto, Y.; Akiba, K. *Tetrahedron Lett.* **1987**, *28*, 6355–6358.

(11) For pertinent studies involving the problem of exo- vs endocyclic cleavage of 2-alkoxytetrahydropyrans and related compounds, see: (a) Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967–973. (b) Guindon, Y.; Bernstein, M. A.; Anderson, P. C. *Tetrahedron Lett.* **1987**, *28*, 2225–2228. (c) Guindon, Y.; Anderson, P. C. *Ibid.* **1987**, *28*, 2485–2488. (d) Diner, U. E.; Brown, R. K. *Can. J. Chem.* **1967**, *45*, 2547–58. (e) Eliel, E. L.; Nowak, B. E.; Daignault, R. A.; Badding, V. G. *J. Org. Chem.* **1965**, *30*, 2441–2447. (f) Gupta, R. B.; Franck, R. W. *J. Am. Chem. Soc.* **1987**, *109*, 6554–6556. (g) Tomooka, K.; Matsuzawa, K.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 6339–6342. (h) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; Chapter 2.

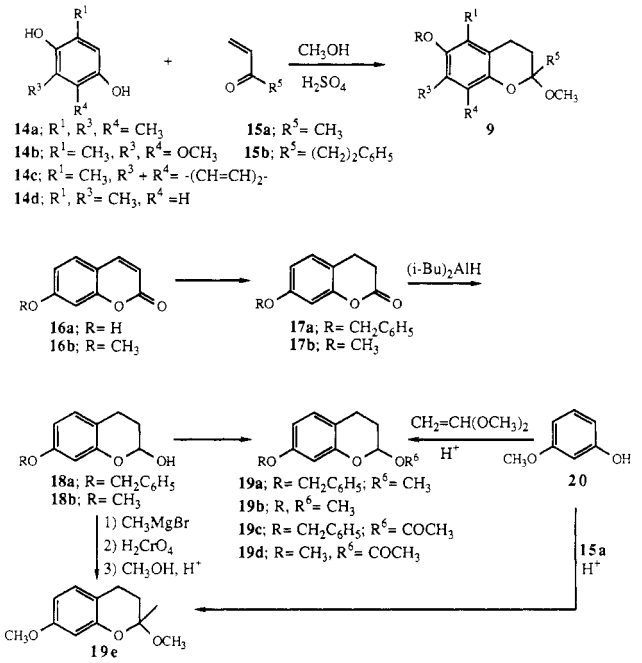
(12) Hertenstein, U.; Hünig, S.; Öller, M. *Chem. Ber.* **1980**, *113*, 3783–3802. We prepared this intermediate by addition of vinylmagnesium bromide to benzenepropanal followed by MnO_2 oxidation.

(13) Bridge, W.; Crocker, A. J.; Cubin, T.; Robertson, A. *J. Chem. Soc.* **1937**, 1530–1535.

(14) Leenders, L. H.; Schouteden, E.; De Schryver, F. C. *J. Org. Chem.* **1973**, *38*, 957–966.

(15) This process undoubtedly involves the 2-chlorochroman, which was not isolated. We have found that certain 2-chlorochromans (few examples of which can be found in the literature) are useful synthetic intermediates: Japanese Patent Appl. No. 62,178,581; *Chem. Abstr.* **1988**, *108*, 204495y. (U.S. Patent No. 4,752,646, June, 21, 1988, Hoffmann-La Roche, Inc.).

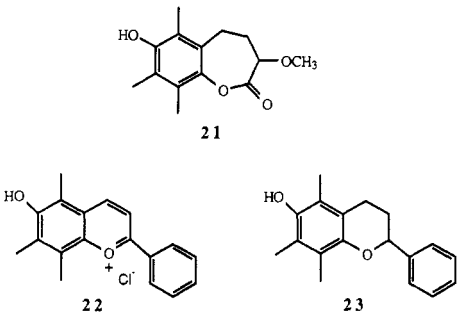
(16) Cf.: Panetta, J. A.; Rapoport, H. *J. Org. Chem.* **1982**, *47*, 946–950.



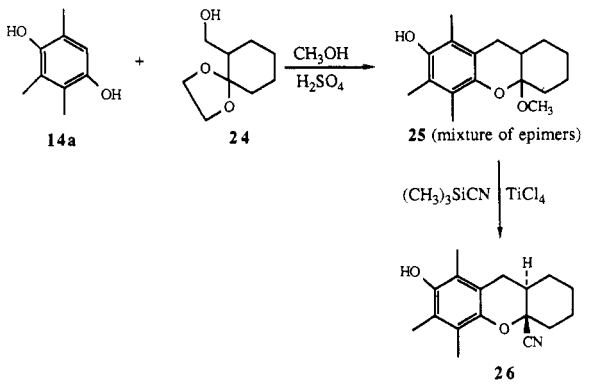
(acetyloxy)chromans **19c,d** with no ring-opened products being detectable.

Table III presents the results from cyanation of a variety of substrates in the α-tocopherol structural series. In general, the yields are good with $TiCl_4$ as long as a substituent other than hydrogen is present at the 2-position, in which case the desired, exocyclic cleavage mode is preponderant. The reaction works efficiently in the presence of a free phenol, as in the examples **9c,f–h,j,k**, as long as sufficient $TiCl_4$ is present to complex the phenolic moiety. The results with **9d,h,k** are of interest since they indicate that the regiochemistry of these transformations is not a result of steric hindrance (caused by the C-8-CH_3) to complexation of the chroman ring oxygen with the Lewis acid, thus retarding the endocyclic cleavage mode. Regarding substitution on the aromatic ring, examples **9f–h,k** reveal an apparent tolerance to variations in this region, although the effect of electron-withdrawing substituents was not examined. Even a 2-hydroxychroman (hemiketal **9l**) can be employed in this reaction, leading to the formation of **10b** in acceptable yield.

When C-2 is unsubstituted (**9e**), only trace quantities of the desired product (**10e**) were isolated; however, when BF_3 etherate was employed, **10e** was obtained in 29% yield along with nearly 40% of the corresponding 2-cyano-6-hydroxychroman **10n** arising from cleavage of the benzyl ether. The latter product was obtained in good yield when chromanol **9n** was employed as the substrate. Apparently, when the intermediate oxocarbonium is less stabilized, as in the C-2 unsubstituted case, the stronger Lewis acid is required to promote acetal cleavage. It should be noted, however, that the acetate **9o**, under the same reaction conditions as **9e,n** afforded only a 19% yield of **10n**, the major product (53%) being the benzoxepinone **21** arising from endocyclic cleavage followed by acid-catalyzed attack of the liberated phenol on the nitrile moiety. The presence of a phenyl substituent at C-2 (**9i**) led to an intriguing result. In this case, the desired nitrile **10i** was a minor product, the major components being the benzopyrylium salt **22** and the 2-phenylchroman **23**.[17] Upon exposure of **9i** to the reaction conditions in the absence of cyanotrimethylsilane, **22** and **23** were rapidly generated. On the other hand, when nitrile **10i** was similarly treated, it was recovered unchanged. Thus the cyanation process is irreversible, and disproportionation of the stabilized 2-phenyl oxocarbonium ion to **22** and **23** represents a significant and distinct pathway for consumption of this intermediate.



This chemistry could be extended to a fused ring system. Condensation in acidic methanol, of TMHQ with the known β-hydroxy ketal **24**[18] (the functional equivalent of α-methylenecyclohexanone) afforded the ketal **25** as a mixture of epimers. When this material was treated with cyanotrimethylsilane–$TiCl_4$, a single hexahydro-1*H*-xanthene-4a-carbonitrile was produced. The stereochemistry of this product (**26**) was proven to be trans by an X-ray crystallographic analysis. A perspective drawing is shown in Figure 1 (supplementary material) which reveals the axial introduction of the cyano group.



Cyanation of the spiro-fused ketals **28a** and **28b** produced some interesting and unexpected results, as summarized in Table IV. These substrates were prepared by condensation of TMHQ with the hydroxy vinyl ketones **27a**[19] and **27b**,[20] respectively.[21] The relative stereochemistry of **28b** (a single epimer) could not be definitively established since crystals of this material and its derivatives were unsuitable for X-ray analysis; however, consideration of steric and stereoelectronic (anomeric effect) factors leads to the assignment shown, in which both ring oxygen atoms occupy the axial conformation with the

(17) *Chem. Abstr.* **1980**, *93*, 8018c; British Patent No. 1,552,628, Sept. 19, 1979, Fujisawa.

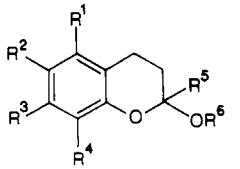
(18) Plieninger, H.; Zeltner, M. *Chem. Ber.* **1975**, *108*, 3286–3291.

(19) This intermediate was obtained by MnO_2 oxidation of the corresponding diol: Cohen, N.; Banner, B. L.; Lopresti, R. J.; Baruth, H. W. *J. Med. Chem.* **1978**, *21*, 895–900.

(20) Cohen, N.; Banner, B. L.; Blount, J. F.; Weber, G.; Tsai, M.; Saucy, G. *J. Org. Chem.* **1974**, *39*, 1824–1833.

(21) For an approach to some related spiroacetals, see: Cremins, P. J.; Wallace, T. W. *J. Chem. Soc., Chem. Commun.* **1986**, 1602–1603.

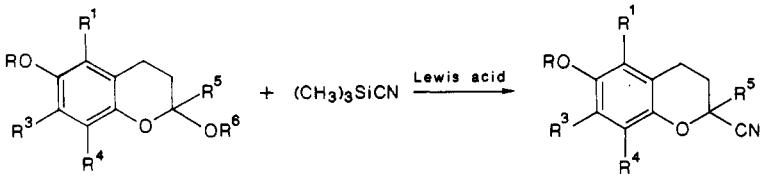
Table II. New 2-Methoxy-, 2-Hydroxy-, and 2-(Acetyloxy)-3,4-dihydro-2*H*-1-benzopyrans



compd	R^1	R^2	R^3	R^4	R^5	R^6	sm	method of synthesis	yield,[a] %	mp, °C	formula[b]
9d	CH_3	$C_6H_5CH_2O$	CH_3	H	CH_3	CH_3	**9m**	A[c]	92	oil	$C_{20}H_{24}O_3$
9e	CH_3	$C_6H_5CH_2O$	CH_3	CH_3	H	CH_3	**9n**	A[c,d]	93	oil	$C_{20}H_{24}O_3$
9f	CH_3	HO	OCH_3	OCH_3	CH_3	CH_3	**14b, 15a**	B[e]	67	71–73[f]	$C_{14}H_{20}O_5$
9g	CH_3	HO	-CH=CHCH=CH-		CH_3	CH_3	**14c, 15a**	B[e]	60	127.5–128.5[g]	$C_{16}H_{18}O_3$
9j	CH_3	HO	CH_3	CH_3	$(CH_2)_2C_6H_5$	CH_3	**14a, 15b**	B[e]	68	139–141[h]	$C_{21}H_{26}O_3$
9m	CH_3	HO	CH_3	H	CH_3	CH_3	**14d, 15a**	B[e]	74	129–131[g]	$C_{13}H_{18}O_3$
18b	H	H	CH_3O	H	H	H	**17b**	C[i]	87	oil	$C_{10}H_{12}O_3$[o]
19a	H	H	$C_6H_5CH_2O$	H	H	CH_3	**18a**	D[j]	93	oil	$C_{17}H_{18}O_3$
19b	H	H	CH_3O	H	H	CH_3	**20**	E[k]	29	oil	$C_{11}H_{14}O_3$[o]
19c	H	H	$C_6H_5CH_2O$	H	H	$COCH_3$	**18a**	F[l]	95	72–76	$C_{18}H_{18}O_4$
19d	H	H	CH_3O	H	H	$COCH_3$	**18b**	F[l]	88	49–51.5	$C_{12}H_{14}O_4$
19e	H	H	CH_3O	H	CH_3	CH_3	**18b (20, 15a)**	G[m] (H[n])	42 (13)	oil	$C_{12}H_{16}O_3$

[a] Yields of pure (^{1}H NMR, IR, UV, MS, TLC) chromatographed and/or recrystallized product. [b] Unless otherwise noted, C, H analyses were within ±0.4% of the calculated values. [c] Benzylation of the corresponding 6-hydroxychroman. [d] The starting material, *rac*-3,4-dihydro-2-methoxy-5,7,8-trimethyl-2*H*-1-benzopyran-6-ol (**9n**) is known: ref 3b. [e] Cyclocondensation of a hydroquinone with a vinyl ketone in acidic methanol as described in ref 7a. [f] Recrystallized from hexanes. [g] Recrystallized from toluene. [h] Recrystallized from acetonitrile. [i] Dibal reduction of the dihydrocoumarin. [j] Treatment of the chroman-2-ol with $SOCl_2$ followed by methanol. [k] Reaction of **20** with acrolein dimethyl acetal. [l] Treatment of the chroman-2-ol with acetic anhydride–pyridine. [m] Treatment of **18b** with methylmagnesium bromide; oxidation of the resulting alcohol with Jones reagent; treatment of the resulting chroman-2-ol with acidic methanol. [n] Reaction of **20** with methyl vinyl ketone in acidic methanol. [o] Compound gave a low microanalysis for carbon.

Table III. Reactions of 2-Methoxy-3,4-dihydro-2*H*-1-benzopyrans 9 with Cyanotrimethylsilane



9 10

sm	prod.	R	R^1	R^3	R^4	R^5	R^6	yield,[a] % $TiCl_4$	yield,[a] % BF_3·Et_2O	mp, °C	recrystd from	formula[b]
9a	**10a**	$C_6H_5CH_2$	CH_3	CH_3	CH_3	CH_3	CH_3	79[c]	43[d]	110–112	ether	$C_{21}H_{23}NO_2$
9b	**10b**	CH_3CO	CH_3	CH_3	CH_3	CH_3	CH_3	77[e]	78[e]	157–159[f]	ether	
9c	**10c**	H	CH_3	CH_3	CH_3	CH_3	CH_3	93	53	150–152[g]	ethyl acetate–hexanes	
9d	**10d**	$C_6H_5CH_2$	CH_3	CH_3	H	CH_3	CH_3	98[e]	42[e,h]	78–81	ethanol	$C_{20}H_{21}NO_2$
9e	**10e**	$C_6H_5CH_2$	CH_3	CH_3	CH_3	H	CH_3	trace[e]	29[e,i]	94–96	ethanol	$C_{20}H_{21}NO_2$
9f	**10f**	H	CH_3	OCH_3	OCH_3	CH_3	CH_3	68[j]		105–107	hexanes–ether	$C_{14}H_{17}NO_4$
9g	**10g**	H	CH_3	-CH=CHCH=CH-		CH_3	CH_3	75[j]		164–166	toluene	$C_{16}H_{15}NO_2$
9h	**10h**	H	H	*t*-C_4H_9	H	CH_3	CH_3	69[j]		179–181[k]	toluene	$C_{15}H_{19}NO_2$
9i	**10i**	H	CH_3	CH_3	CH_3	C_6H_5	CH_3	13[j,l]	trace	161–164	hexanes–ether	$C_{19}H_{19}NO_2$
9j	**10j**	H	CH_3	CH_3	CH_3	$(CH_2)_2C_6H_5$	CH_3	79[j]		139–140.5	toluene	$C_{21}H_{23}NO_2$
9k	**10k**	H	H	H	H	CH_3	CH_3	63[j]		136–137[n]	toluene	$C_{11}H_{11}NO_2$
9l	**10b**	CH_3CO	CH_3	CH_3	CH_3	CH_3	H	53[e]	71[e]	155–156[f]		
9n	**10n**	H	CH_3	CH_3	CH_3	H	CH_3	trace	68	151–151.5	ethyl acetate	$C_{13}H_{15}NO_2$
9o	**10n**	CH_3CO	CH_3	CH_3	CH_3	H	CH_3		19[o]			

[a] Yield of pure (^{1}H NMR, IR, UV, MS, TLC) chromatographed and/or recrystallized product. [b] C, H analyses were within ±0.4% of the calculated values. [c] In addition, 10% of **10c** was isolated by chromatography. [d] In addition 34% of **10c** was isolated by chromatography. [e] Procedures used were those described for conversion of **9a** to **10a**: see Experimental Section. [f] Lit.[3c] mp 157.5–159.5 °C. [g] Lit.[3c] mp 151–152 °C. [h] In addition, 49% of the corresponding 6-hydroxychroman, mp 137.5–139.5 °C (lit.[8b] mp 135 °C), was isolated by chromatography. [i] In addition, 39% of **10n** was isolated by chromatography. [j] Procedure used was that described for conversion of **9c** to **10c**: see Experimental Section. [k] Lit.[8b] mp 153–155 °C. [l] In addition, benzopyrylium salt **22** and chroman **23** were isolated: see Experimental Section. [m] Triturated. [n] Lit.[8b] mp 146–148 °C. [o] In addition, 53% of benzoxepinone **21** was isolated: see Experimental Section.

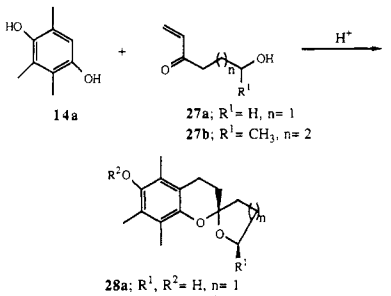
methyl substituent equatorially disposed. Upon treatment with cyanotrimethylsilane in the presence of either $TiCl_4$ or BF_3 etherate, both **28c** and **28d** underwent cleavage essentially exclusively at the chroman ring producing, stereospecifically, the cyanotetrahydropyrans **29c** and **29d**, respectively. This regiochemical result, as well as the relative configuration of the products, was confirmed by an X-ray analysis of the *p*-bromobenzoate **29f**. A view of this molecule, as shown in Figure 2 (supplementary material), reveals the axial disposition of the cyano group. A similar result was seen when spiro ketal **28a** was exposed to cyanotrimethylsilane–$TiCl_4$ in which case the cyanotetrahydrofuran hydroquinone **29a** was the exclusive product; however, the use of BF_3 etherate in this transformation provided the chroman-2-propanol **30a** in nearly 80% yield! Encouraged by this unexpected, Lewis acid mediated shift in regiochemistry, we returned to substrate **28b** and eventually discovered that stannic chloride–cya-

Table IV. Reactions of Sprio-Fused Ketals 28 with Cyanotrimethylsilane

sm	Lewis acid	prod. (yield, %)
28a	$TiCl_4$	**29a** (76)
28a	$BF_3{\cdot}OEt_2$	**30a** (77)[a]
28b	$TiCl_4$	**29b** (78),[b] **30c** (trace)
28b	$BF_3{\cdot}OEt_2$	**29b** (60),[b] **30c** (14)[c]
28b	$SnCl_4$	**29b** (trace), **30c** (83)[c]
28c	$TiCl_4$	**29c** (61)
28c	$SnCl_4$	complex mixture
28d	$TiCl_4$	**29d** (88)[b]
28d	$BF_3{\cdot}OEt_2$	**29d** (76)

[a] Isolated and purified as the diacetate **30b**. [b] Isolated and purified as the diacetate **29e**. [c] Isolated and purified as the diacetate **30d**.

notrimethylsilane treatment of this spiro ketal furnished the desired chromanol **30c** in 83% yield, isolated as the diacetate **30d**. This product was determined to consist of an approximately 1:1 mixture of epimers by ^1H NMR shift reagent studies carried out on the monobenzyl ether **30e**. Thus asymmetric induction was not observed in this cyanation, a result which testifies to the S_N1 nature of these substitution processes. It is interesting to note that exposure of tetrahydropyran **29b** to $SnCl_4$ or chroman **30c** to $TiCl_4$ led in both experiments to unchanged substrate. The failure to observe interconversion under the reaction conditions again demonstrates the irreversible nature of these cyanation reactions.



Still another situation is posed by the linearly fused pyranochromans **34**. These substrates were prepared by cyclocondensation of diol ketal **33** with **14a** giving, in excellent yield, the phenol **34a** as a single epimer of unknown relative configuration.[22] When the corresponding acetate **34b** was treated with cyanotrimethylsilane–$TiCl_4$, and the crude product saponified, the chroman **35**, a mixture of epimers, was obtained cleanly. In this case, the regiochemistry of cleavage parallels that seen with the simple analogues **9** and compounds substituted at C-3 are available if desired.[23]

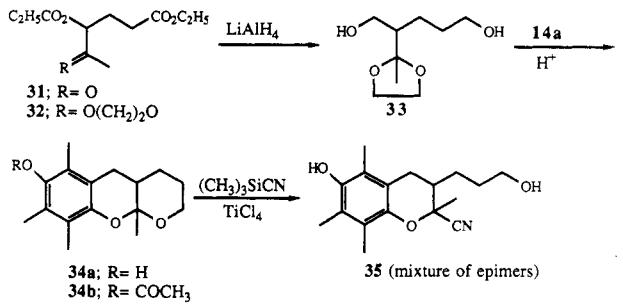
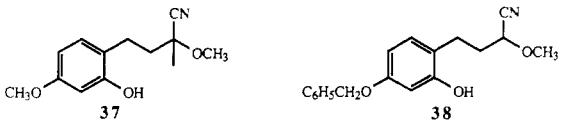


Table V presents our results with the 2,7-disubstituted chromans of interest regarding the leukotriene antagonist **3**. With the acetals **19a,b** only trace quantities of the desired nitriles **36a,b** were isolated. Instead, compound **38**, the endocyclic cleavage product, was isolated in 19% yield, along with 62% of recovered starting material, when **19a** was treated with cyanotrimethylsilane–$TiCl_4$. The use of BF_3 etherate was no more successful with these substrates. On the other hand, the 2-acetyloxy analogues **19c,d** afforded modest yields of the desired products when BF_3 etherate was employed. Conceivably, the efficiency of these cyanations could be further improved through the introduction of even better leaving groups at C-2 such as (trifluoroacetyl)oxy, *p*-nitrophenoxy, or (*p*-nitrobenzoyl)-oxy; however, these modifications were not explored since catalytic hydrogenation–hydrogenolysis of readily available chromone-2-carboxylates provides a facile and efficient alternative synthetic approach to 2-unsubstituted chroman-2-carboxylic acids and derivatives thereof.[4c,6] Treatment of the 2-methyl homologue **19e** with $TiCl_4$–cyanotrimethylsilane gave a mixture containing 43% of the desired nitrile **36c** and 34% of the endocyclic cleavage product **37**; however, with BF_3 etherate, **36c** was secured in over 80% yield. Thus the substrates in this series also exhibit dichotomous behavior, dictated in large part by the nature of the Lewis acid employed in the cyanation reaction.



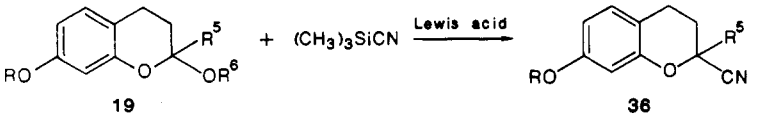
We have found that the most useful procedure for converting the chroman-2-carbonitriles to the corresponding acids involves treatment with potassium hydroxide in refluxing ethylene glycol–water. For example, by this method **36a** afforded the corresponding carboxylic acid in essentially quantitative yield.

In summary, our studies have revealed that a variety of chroman-2-carbonitriles and related compounds can be prepared via the reaction of 2-alkoxy-, 2-(acyloxy)-, and 2-hydroxychromans with cyanotrimethylsilane in the presence of Lewis acids. These processes are especially useful in the α-tocopherol structural series and make readily available substances with antioxidant properties. The regiochemistry of these reactions appears to be controlled by a subtle balance of factors, not the least of which involves the stability of the intermediate oxocarbonium species. Clearly the substrates bearing a substituent at C-2 react with much greater facility than those in which this position is unsubstituted. While stereoelectronic factors and the nature of the leaving group at C-2 certainly con-

(22) The conformational equilibrium of a related pyranochroman has been studied and found to favor the cis isomer: Lissac-Cahu, M.; Descotes, G.; Delmau, J.; Duplan, J. *C. R. Acad. Sci.* Paris, *Ser. C* **1971**, *272*, 1585–1587.

(23) Cf. Kirby, A. J.; Martin, R. J. *J. Chem. Soc., Chem. Commun.* **1978**, 803–804.

Table V. Reactions of 2-Methoxy- and 2-(Acetyloxy)-3,4-dihydro-2*H*-1-benzopyrans 19 with Cyanotrimethylsilane



19 36

					yield,[a] %			
sm	prod.	R	R^5	R^6	$TiCl_4$	$BF_3{\cdot}Et_2O$	mp, °C	formula[b]
19a	**36a**	$C_6H_5CH_2$	H	CH_3	trace[c]			
19b	**36b**	CH_3	H	CH_3		trace		
19c	**36a**	$C_6H_5CH_2$	H	$COCH_3$		44[f]	77–78.5[e]	$C_{17}H_{15}NO_2$
19d	**36b**	CH_3	H	$COCH_3$	0	41[g]	55–57[e]	$C_{11}H_{11}NO_2$
19e	**36c**	CH_3	CH_3	CH_3	43[d]	83	73.5–75[e]	$C_{12}H_{13}NO_2$

[a] Yield of pure (^{1}H NMR, IR, UV, MS, TLC) chromatographed and/or recrystallized product. [b] C, H analyses were within ±0.4% of the calculated values. [c] Compound **38** was isolated by chromatography in 19% yield along with 62% of starting material. [d] Compound **37** was isolated in 34% yield by chromoatography. [e] Recrystallized from ethanol. [f] Only 12 mol % Lewis acid used. [g] Only 12 mol % Lewis Acid used; a 47% yield was obtained when excess Lewis acid was used.

tribute to the regiochemical outcome of these reactions, the dramatic effect of the Lewis acid is most surprising and intriguing. Perhaps this aspect is best demonstrated with the spiro-fused ketal **28b**, in which case a nearly complete reversal of regiochemistry is observed upon changing from $TiCl_4$ to $SnCl_4$. To what degree and how these various factors contribute and interact is not readily apparent. Nonetheless, these processes seem to offer significant synthetic potential.

Experimental Section

General Information. "Hexanes" refers to the mixture of C_6 hydrocarbons supplied by Fisher Scientific. All of the reactions described below, except hydrogenations, were carried out under an atmosphere of argon. The "usual workup" conditions involve three extractions with the indicated solvent, washing the combined organic extracts with water and saturated brine, drying the organic solution over anhydrous magnesium sulfate, suction filtration, and concentration of the filtrate under water aspirator pressure using a rotary evaporator. The residue was then dried to constant weight under high vacuum. Column chromatography was performed using EM Silica Gel 60 (0.063–0.2 mm). Thin-layer chromatography was employed to monitor reactions and determine product purity and was performed using EM Silica Gel 60 F-254 precoated plates. Toluene–ethyl acetate or hexanes–ether mixtures were generally used as the mobile phases. Spots were detected with UV light and phosphomolybdic acid spray followed by heating. HPLC was performed using a Waters 500A instrument on silica gel columns. The IR, NMR, UV, and mass spectral data obtained for all compounds, if not reported, were consistent with the assigned structures. ^{1}H NMR spectra (200 or 400 MHz) were obtained in $CDCl_3$ solution. Chemical shifts are reported relative to tetramethylsilane as an internal standard. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected.

Synthesis of Chromans 9. Intermediates **9a–c,h,i,k,l,n,o** were prepared as previously described.[3,7] New compounds **9f,g,j,m** were prepared using the cyclocondensation method described by Scott et al.[7a] (method B). The data and results are presented in Table II. In the case of **9j**, equimolar quantities of vinyl ketone **15b**[12] and TMHQ (**14a**) were employed, whereas in the other examples, methyl vinyl ketone (**15a**) was used in excess.

***rac*-3,4-Dihydro-2-methoxy-2,5,7-trimethyl-6-(phenylmethoxy)-2*H*-1-benzopyran (9d) (Method A).** A mixture of 4.45 g (20 mmol) of chromanol **9m**, 5.75 mL (50 mmol) of benzyl chloride, 6.9 g (50 mmol) of anhydrous K_2CO_3, and 20 mL of *N,N*-DMF was stirred at room temperature for 42 h and then at 70–80 °C for 2 h. The resulting mixture was cooled, diluted with ether, and filtered with suction. The solids were washed with ether. The filtrate and washes were combined and processed in the usual manner. Column chromatography of the residue on 100 g of silica gel gave 5.72 g of benzyl ether **9d** as a pale-yellow oil, eluted with 49:1 toluene–ethyl acetate.

3,4-Dihydro-7-(phenylmethoxy)-2*H*-1-benzopyran-2-one (17a). A solution of 64.8 g (0.4 mol) of 7-hydroxycoumarin (umbelliferone, **16a**) in 800 mL of ethanol was hydrogenated at 40 psi, 60 °C, over 6 g of 10% palladium on carbon until gas uptake ceased. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo. The product (69.5 g) was a mixture of the desired dihydrocoumarin and ethyl 2,4-dihydroxybenzenepropanoate. The latter impurity could be converted to the desired lactone as follows: A solution of 55.5 g of this mixture, 0.5 g of *p*-toluenesulfonic acid monohydrate, and 1 L of toluene was heated to boiling. The resulting solution was distilled using a 10-in. Vigreux column until approximately 475 mL of distillate had been collected, bp 70–109 °C, over 45 min. The resulting solution was cooled, diluted with ethyl acetate, and washed with saturated sodium bicarbonate solution. Completion of the usual workup gave 7-hydroxydihydrocoumarin as a beige solid (45.7 g). A mixture of 54.1 g (0.33 mol) of material prepared in this way, 58 mL (0.5 mol) of benzyl chloride, 75.3 g (0.5 mol) of anhydrous sodium iodide, 87.5 mL (0.5 mol) of diisopropylethylamine, and 300 mL of dry acetonitrile was stirred and refluxed for 2 h. After being cooled, the resulting mixture was diluted with ether and filtered with suction. The solids were washed well with ether. The filtrate and washes were combined and concentrated in vacuo. The residue was taken up in ether–ethyl acetate, and the solution was washed with water, 1 N HCl, water, and aqueous sodium thiosulfate, and workup was completed in the usual manner, giving 89.8 g of an orange semisolid. This material was chromatographed on 1 kg of silica gel. Elution with 49:1 toluene–ethyl acetate afforded 54.7 g of solid, which was combined with 10.15 g of similarly produced material from a separate experiment. Recrystallization from 2:1 hexanes–ethyl acetate gave pure **17a** in 2 crops, 38.1 g, mp 79–80 °C, and 5.9 g, mp 77–79 °C (44.2% total yield) (lit.[13] oil).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55. Found: C, 75.55; H, 5.69.

***rac*-3,4-Dihydro-7-methoxy-2*H*-1-benzopyran-2-ol (18b) (Method C).** To a solution of 9.0 g (50.5 mmol) of dihydrocoumarin **17b**[14] in 80 mL of dry dichloromethane, cooled to −72 °C, was added dropwise, with stirring, 75 mL (75 mmol) of 1 M diisobutylaluminum hydride in hexane. After being stirred at −72 °C for 1.5 h, the reaction mixture was cautiously decomposed by the dropwise addition of 10 mL of methanol. After being stirred for an additional 20 min, the mixture was poured into 1 N sulfuric acid and worked up with ether in the usual manner. The residue was purified by HPLC (4:1 hexanes–ethyl acetate), giving 7.9 g of chromanol **18b** as a colorless oil.

***rac*-3,4-Dihydro-2-methoxy-7-(phenylmethoxy)-2*H*-1-benzopyran (19a) (Method D).** A solution of 0.256 g (1 mmol) of chromanol **18a**[4c] in 1 mL of dichloromethane was stirred with ice-bath cooling while 0.08 mL (1.1 mmol) of thionyl chloride was added dropwise, from a syringe. After being stirred in the cold for 15 min, the green solution was treated with 2 mL of dry methanol. The resulting bluish solution was stirred, in the cold for an additional 15 min, and then poured into saturated aqueous $NaHCO_3$. Workup with ether in the usual manner gave 0.298 g of a pale-yellow oil, which was chromatographed on 10 g of silica gel. Elution with 49:1 toluene–ethyl acetate afforded 0.25 g of chroman **19a** as a pale-yellow oil: ^{1}H NMR δ 5.14 (br s, 1,

$CHO(OCH_3)$), 5.04 (s, 2, $OCH_2C_6H_5$), 3.44 ppm (s, 3, OCH_3); MS m/z 270 (M^+).

***rac*-3,4-Dihydro-2,7-dimethoxy-2*H*-1-benzopyran (19b) (Method E).** A solution of 12.4 g (0.1 mol) of 3-methoxyphenol (**20**) in 100 mL of dichloromethane was stirred with ice-bath cooling, and 0.2 g (1.05 mmol) of *p*-toluenesulfonic acid monohydrate was added followed by the dropwise addition of 13 mL (0.11 mol) of acrolein dimethyl acetal, over 35–40 min. The addition of the acetal induced an exothermic reaction and a blue-green color. The temperature was kept below 10 °C. After being stirred with ice-bath cooling for 1 h, the reaction mixture was poured into saturated $NaHCO_3$ solution. Workup with dichloromethane in the usual manner gave 20.47 g of a viscous, red oil. This material was chromatographed on 200 g of silica gel. Elution with toluene afforded 5.65 g of **19b** as a mobile, pale-yellow liquid: ^1H NMR δ 3.80 (s, 3, $ArOCH_3$), 3.54 ppm (s, 3, OCH_3); MS m/z 194 (M^+).

***rac*-3,4-Dihydro-7-methoxy-2*H*-1-benzopyran-2-ol Acetate (19d) (Method F).** A solution of 2.7 g (15 mmol) of chromanol **18b** in 10 mL of acetic anhydride containing 5 drops of pyridine was kept at room temperature for 17 h and then concentrated at 40 °C/high vacuum. The oily residue was chromatographed on 100 g of silica gel. Elution with 4:1 and 1:1 hexanes–ether gave 2.93 g of acetate **19d** as a colorless oil, which crystallized on standing: ^1H NMR δ 3.77 (s, 3, $ArOCH_3$), 2.10 ppm (s, 3, $OCOCH_3$).

***rac*-3,4-Dihydro-2,7-dimethoxy-2-methyl-2*H*-1-benzopyran (19e) (Method G).** A 10-mL (28-mmol) sample of 2.8 M ethereal methylmagnesium bromide was stirred with ice-bath cooling while a solution of 1.8 g (10 mmol) of chromanol **18b** in 10 mL of anhydrous ether was added dropwise over 17 min. A dense, white precipitate formed. The resulting slurry was stirred at room temperature for 18 h and then cautiously poured into saturated ammonium chloride solution. Workup with ether in the usual manner gave 2.0 g of diol as a pink, viscous oil, which crystallized on standing: ^1H NMR δ 3.74 (s, 3, $ArOCH_3$), 1.21 ppm (d, 3, J = 7 Hz, CH_3CHO); MS m/z 196 (M^+). A solution of 1.52 g (7.75 mmol) of this diol in 60 mL of acetone was stirred with ice-bath cooling while 2.2 mL (8.8 mmol equiv) of Jones reagent was added dropwise from a syringe. The mixture was stirred in the cold for 5 min, decomposed by the addition of 12% aqueous $NaHSO_3$, and diluted with water. Workup in the usual manner with ether gave 1.2 g of an orange oil. This material was dissolved in 20 mL of methanol and 10 mL of trimethyl orthoformate. After the addition of 0.15 g of *p*-toluenesulfonic acid, the solution was stirred at room temperature for 17 h. The resulting purple solution was poured into saturated $NaHCO_3$, and workup with ether was carried out in the usual manner. There was obtained 1.2 g of an orange-brown oil. This material was combined with 0.255 g of similarly produced crude ketal and chromatographed on 25 g of silica gel. Elution with toluene gave 0.848 g of **19e** as a yellow oil: ^1H NMR δ 3.76 (s, 3, $ArOCH_3$), 3.29 (s, 3, OCH_3), 1.54 ppm (s, 3, $OCCH_3$); MS m/z 208 (M^+).

Method H. A solution of 2.48 g (20 mmol) of 3-methoxyphenol (**20**), 3 mL of trimethyl orthoformate, and 12 mL of methanol was stirred with ice-bath cooling, and 0.05 mL of concentrated sulfuric acid was added followed by the dropwise addition, over 12 min, of 1.9 mL of methyl vinyl ketone (**15a**). The resulting solution was stirred in the cold for 1.5 h and then at room temperature for 1 h before being poured into saturated $NaHCO_3$ solution. Workup with ether in the usual manner gave 4.8 g of a red-brown oil. This material was chromatographed on 50 g of silica gel. Elution with 49:1 toluene–ethyl acetate afforded 0.54 g of **19e** as an almost colorless oil.

General Procedure for Preparation of 3,4-Dihydro-2*H*-1-benzopyran-2-carbonitriles 10a,b,d,e and 36a–c. A solution of 3.27 mmol of the 2-methoxy-, 2-(acetyloxy)-, or 2-hydroxychroman **9** or **19** in 80 mL of dichloromethane was stirred at −40 °C (dry ice–acetone bath) (−20 °C for the BF_3 reactions) while 1.65 mL (12.4 mmol) of cyanotrimethylsilane was added in one portion followed by 0.56 mL (5.1 mmol) of titanium tetrachloride or 0.63 mL (5.1 mmol) of boron trifluoride etherate. The resulting, usually highly colored mixture from the $TiCl_4$ reaction was stirred at −40 °C for 1 h and then at −20 °C for 1 h. The BF_3 reactions were stirred at 0 °C for 2.5 h. The reactions were quenched by the addition of 7 mL of methanol and then poured into 1 N HCl (HCN evolution!). Workup with dichloromethane in the usual manner gave the crude product, which was purified by chromatography on 50 g of silica gel. The results are presented in Tables III and V. In the reactions of **19c,d**, only 0.05 mL (0.4 mmol) of BF_3 etherate was employed.

***rac*-3,4-Dihydro-6-hydroxy-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carbonitrile (10c).** A solution of 15 g (63.5 mmol) of 2-methoxychroman **9c**[7a] in 300 mL of dichloromethane was stirred at −50 °C (dry ice–acetone bath) while 21.2 mL (159 mmol) of cyanotrimethylsilane was added in one portion followed by the dropwise addition of 17.4 mL (159 mmol) of titanium tetrachloride. The resulting mixture was stirred for 2.5 h during which time the temperature was allowed to rise to −20 °C. The reaction was quenched by the dropwise addition of 100 mL of methanol (HCN evolution!). After being stirred for 5 min, the solution was poured into ice–water (HCN evolution!). The dichloromethane layer was separated, and the aqueous phase was extracted twice more with dichloromethane. Usual processing of the dichloromethane extracts (which were additionally washed with saturated $NaHCO_3$ solution) gave 16.6 g of a beige solid. This material was recrystallized from 1:2 ethyl acetate–hexanes, giving pure chromanol **10c** in 2 crops, 12.1 g (82.4%) and 1.65 g (11.2%), both exhibiting mp 150–152 °C. This procedure was used to prepare the analogues **10f–k** as indicated in Table III.

***rac*-3,4-Dihydro-6-(phenylmethoxy)-2-(2-propenyl)-2,5,7,8-tetramethyl-2*H*-1-benzopyran (11).** A solution of 1.96 g (6 mmol) of **9a**,[3,7b] 3.4 mL (21.4 mmol) of allyltrimethylsilane, and 20 mL of dichloromethane was stirred at −78 °C (dry ice–acetone bath) while 0.66 mL (6 mmol) of titanium tetrachloride was added dropwise. The resulting dark-brown mixture was stirred at −78 °C for 3 h before being poured into water. Workup with ether in the usual manner gave an oily residue, which was chromatographed on 60 g of silica gel. Elution with 10:1 hexanes–ether afforded 1.4 g of **11** as a colorless oil: ^1H NMR δ 7.42 (m, 5, C_6H_5), 5.92 (m, 1, $CH{=}CH_2$), 5.11 (m, 2, $CH{=}CH_2$), 4.71 (s, 2, $PhCH_2O$), 2.61 (t, J = 7 Hz, 2, $ArCH_2$), 2.36 (d, J = 7.5 Hz, 2, $CH_2CH{=}CH_2$), 2.21, 2.16, 2.10 (3 s, 9, 3 $ArCH_3$), 1.80 (t, J = 7 Hz, 2, $ArCH_2CH_2$), 1.26 ppm (s, 3, CH_3CO); MS m/z 336 (M^+).

***rac*-3,4-Dihydro-2-ethyl-6-(phenylmethoxy)-2,5,7,8-tetramethyl-2*H*-1-benzopyran (12).** To a stirred solution of 4.56 g (14 mmol) of **9a**[3,7b] in 400 mL of dichloromethane, cooled to −75 °C, was added 3.1 mL (28.3 mmol) of titanium tetrachloride. After being stirred for 10 min, the mixture was treated with 10 mL (28 mmols) of 2.8 M ethereal ethylmagnesium bromide, dropwise, over a 20-min period. The reaction mixture was stirred at −75 °C for 1 h and then decomposed by the addition of 120 mL of 2:1 methanol–pyridine. After being warmed to room temperature, the mixture was poured into 3 N HCl and worked up with dichloromethane in the usual manner. The oily residue was chromatographed on silica gel. Elution with 16:1 hexanes–ether gave 1.55 g of **12** as a colorless oil: ^1H NMR δ 7.42 (m, 5, C_6H_5), 4.67 (s, 2, $PhCH_2O$), 2.59 (t, J = 7 Hz, 2, $ArCH_2$), 2.21, 2.16, 2.11 (3 s, 9, 3 $ArCH_3$), 1.23 (s, 3, CH_3CO), 0.96 ppm (t, 3, CH_3CH_2); MS m/z 324 (M^+).

***rac*-3,4-Dihydro-6-(phenylmethoxy)-*N*-(phenylmethyl)-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carboxamide (13).** A solution of 3.9 g (12 mmol) of **9a**[3,7b] and 1.47 mL (12 mmol) of benzyl isocyanide in 50 mL of dichloromethane was stirred with cooling from a dry ice–acetone bath while 1.47 mL (13.4 mmols) of titanium tetrachloride was added dropwise. The resulting mixture was stirred in the cooling bath for 2 h whereupon it was poured into saturated $NaHCO_3$ solution. Workup with dichloromethane in the usual manner gave an oily residue, which was chromatographed on 450 g of silica gel. Elution with 1:1 hexanes–ether gave 2.0 g of amide **13**. Recrystallization of a sample from hexanes gave colorless needles: ^1H NMR δ 6.71 (m, 1, NH), 2.20, 2.15, 2.10, 1.58 ppm (4 s, 12, 4 CH_3); IR 3425 (NH), 1668, 1518 cm^{-1} (amide); MS m/z 429 (M^+).

***rac*-4,5-Dihydro-7-hydroxy-3-methoxy-6,8,9-trimethyl-1-benzoxepin-2(3*H*)-one (21).** A solution of 9.5 g (36 mmol) of acetate **9o**[3c] in 880 mL of dichloromethane was stirred at −40 °C while 18.2 mL (0.136 mol) of cyanotrimethylsilane was added followed by 7 mL (56.7 mmol) of boron trifluoride etherate. The reaction mixture was stirred at −40 °C for 30 min and then at −10 to 0 °C for 2 h. The mixture was treated with 20 mL of methanol and cautiously poured into 1 N HCl. Workup with

dichloromethane and ethyl acetate in the usual manner gave a residue, which was taken up in 1:1 hexanes–ether. The resulting solution was filtered through a plug of silica gel and concentrated in vacuo. The residue (9.0 g) was separated into its components (**21**, more polar on TLC; **10n**, less polar on TLC) by HPLC (20:1 toluene–ether). There was obtained 4.65 g (52%) of benzoxepinone **21** and 1.45 g (19%) of chromanol **10n**. The analytical specimen of **21** was obtained by recrystallization from ethyl acetate as a colorless solid: mp 149–150 °C; ^{1}H NMR δ 4.64 (dd, 1, J = 3.5, 8 Hz, CHO), 4.27 (s, 1, OH), 3.78 (s, 3, OCH_3), 2.67 (m, 2, $ArCH_2$), 2.18, 2.16, 2.09 ppm (3 s, 9, 3 $ArCH_3$); MS m/z 250 (M^+).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.00; H, 7.28.

6-Hydroxy-5,7,8-trimethyl-2-phenyl-1-benzopyrylium Chloride Monohydrate (22) and *rac*-3,4-Dihydro-5,7,8-trimethyl-2-phenyl-2*H*-1-benzopyran-6-ol (23). A mixture of 2.0 g (6.7 mmol) of chromanol **9i**[3b] and 125 mL of dichloromethane was stirred at −30 °C while 2.3 mL (17.25 mmol) of cyanotrimethylsilane was added followed by 1.9 mL (17.3 mmol) of titanium tetrachloride. The mixture was stirred at −30 °C for 3 h at which point 15 mL of methanol was added, and this mixture was then poured into 150 mL of 1 N HCl. The resulting red mixture was filtered with suction, and the solid was washed with dichloromethane. Recrystallization of the solid from ethanol–ether gave 0.7 g (66%) of benzopyrylium salt **22** as a red solid: mp 170–172 °C; ^{1}H NMR δ (DMSO-d_6) 10.26 (s, 1, OH), 9.69 (d, 1, J = 9 Hz, CH), 8.93 (d, 1, J = 9 Hz, CH), 8.59 (d, 2, J = 9 Hz, phenyl), 7.91 (t, 1, J = 7.5 Hz, phenyl), 7.81 (t, 2, J = 7.5 Hz, phenyl), 2.75 (s, 3, $ArCH_3$), 2.65 (s, 3, $ArCH_3$), 2.56 ppm (s, 3, $ArCH_3$).

Anal. Calcd for $C_{18}H_{17}ClO_2 \cdot H_2O$: C, 67.82; H, 6.01; Cl, 11.12. Found: C, 67.48; H, 5.73; Cl, 11.22.

The dichloromethane–aqueous HCl filtrate from the above filtration was separated. The aqueous phase was extracted twice with dichloromethane, and the organic phases were combined and processed in the usual manner. The residue (1.2 g) was chromatographed on 150 g of silica gel, eluting with hexanes–ether mixtures. There was obtained 0.69 g (77%) of chromanol **23**[17] followed by 0.25 g (13%) of the 2-cyanochroman **10i**, both as solids. Recrystallization of **23** from toluene–hexanes gave colorless solid: mp 141–143 °C; ^{1}H NMR δ 7.45 (dd, 2, J_{meta} = 1.5 Hz, J_{ortho} = 7.5 Hz, phenyl), 7.39 (t, 2, J_{ortho} = 7.5 Hz, phenyl), 7.31 (tt, 1, J_{meta} = 1.5 Hz, J_{ortho} = 7.5 Hz, phenyl), 4.94 (dd, 1, J = 2, 10.5 Hz, CHO), 4.24 (s, 1, OH), 2.77 (m, 2, $ArCH_2$), 2.26 (m, 1, CH of CH_2), 2.19 (s, 6, 2 $ArCH_3$), 2.13 (s, 3, $ArCH_3$), 2.02 ppm (m, 1, CH of CH_2); MS m/z 268 (M^+).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.51; H, 7.29.

It was found that exposure of **9i** (0.1 g) to the above reaction conditions but omitting the cyanotrimethylsilane led to the formation of **22** and **23** (TLC). On the other hand, similar treatment of nitrile **10i** (20 mg) led to quantitative recovery of the nitrile. Results very similar to those described above were obtained when the cyanation of **9i** was performed using $BF_3 \cdot OEt_2$.

***rac*-2,3,4,4a,9,9a-Hexahydro-4a-methoxy-5,6,8-trimethyl-1*H*-xanthen-7-ol (25) (Cis–Trans Mixture).** A solution of 4.56 g (30 mmol) of TMHQ (**14a**) and 5.16 g (30 mmol) of hydroxy ketal **24**[18] in 30 mL of methanol was stirred with ice-bath cooling while 0.15 mL of concentrated sulfuric acid was added. The resulting solution was stirred at room temperature for 10 min, refluxed for 1 h, and stirred at room temperature for an additional 18 h. The orange-brown solution was poured into saturated $NaHCO_3$, and workup with ether was carried out in the usual manner. The crude, semicrystalline product was chromatographed on 100 g of silica gel. Elution with 9:1 hexanes–ether gave 5.13 g of a beige solid which was triturated with hexanes. The slurry was filtered, and the solid was washed with hexanes and dried under high vacuum. There was obtained 3.73 g (45%) of **25** as a pale-yellow solid: mp 110–143 °C; ^{1}H NMR δ 4.21 (s, 1, OH), 3.19 (s, 0.9, OCH_3 minor isomer), 3.12 ppm (s, 2.1, OCH_3 major isomer); MS m/z 276 (M^+).

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.87; H, 8.86.

***(rac*-4a*R*-*trans*)-2,3,4,4a,9,9a-Hexahydro-7-hydroxy-5,6,8-trimethyl-1*H*-xanthene-4a-carbonitrile (26).** The reaction of **25** with cyanotrimethylsilane–titanium tetrachloride was carried out as described above for the preparation of **10c**. Recrystallization of the crude product from toluene gave nitrile **26** in 69.4% yield as a colorless solid: mp 179–180 °C; ^{1}H NMR δ 4.32 (s, 1 OH), 2.17, 2.13, 2.11 ppm (3 s, 9, 3 $ArCH_3$), no OCH_3; MS m/z 271 (M^+).

Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.28; H, 7.84; N, 5.23.

The structure of **26** was determined by a single-crystal X-ray analysis. The crystal data are summarized in Table VI (supplementary material). The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, $\theta - 2\theta$ scans). The size of the crystal used for data collection was approximately 0.12 × 0.14 × 0.73 mm; the data were not corrected for absorption. Of the 2162 independent reflections for $\theta < 60°$, 1772 were considered observed [$I > 3.0\sigma(I)$]. The structure was solved by a multiple-solution procedure[24] and was refined by full-matrix least squares. In the final refinement, the non-hydrogen atoms were refined anisotropically. The hydrogen atoms, which correspond to peaks located on difference maps, were included in the structure-factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.052 and R_w = 0.072 for the 1772 observed reflections. The final difference map has no peaks greater than ±0.2 e Å^{-3}.

***rac*-3,4,4′,5′-Tetrahydro-5,7,8-trimethylspiro[2*H*-1-benzopyran-2,2′(3′*H*)-furan]-6-ol (28a).** A mixture of 5.3 g (46.5 mmol) of vinyl ketone **27a**,[19] 6.5 g (42.8 mmol) of TMHQ (**14a**), 0.5 g of *p*-toluenesulfonic acid monohydrate, and 100 mL of toluene was stirred and heated to reflux over 30 min. After being refluxed with water removal by means of a Dean–Stark trap for 15 min, the mixture was cooled and poured into saturated $NaHCO_3$ solution. Workup with toluene in the usual manner gave 6.4 g of crude product. Purification by HPLC (3:1 hexanes–ethyl acetate) and recrystallization from hexanes–ether at −70 °C afforded 2.9 g (27.3%) of **28a** as a colorless solid: mp 145–146 °C; ^{1}H NMR δ 4.22 (s, 1, OH), 3.99 (m, 2, CH_2O), 2.81 (m, 1, CH of $ArCH_2$), 2.69 (dt, 1, J = 5, 16.5 Hz, CH of $ArCH_2$), 2.15, 2.10 ppm (2 s, 9, 3 $ArCH_3$); MS m/z 248 (M^+).

***rac*-Tetrahydro-2-[2-(2,5-dihydroxy-3,4,6-trimethylphenyl)ethyl]-2-furancarbonitrile (29a).** The reaction of **28a** with cyanotrimethylsilane–titanium tetrachloride was carried out as described above for the preparation of **10c**. The crude product was purified by HPLC (3:2 hexanes–ethyl acetate), giving hydroquinone **29a** in 76.3% yield. Recrystallization from hexanes–ethyl acetate gave a colorless solid: mp 140–141 °C; ^{1}H NMR ($CDCl_3$–DMSO-d_6) δ 6.10 (s, 1, OH), 5.96 (s, 1, OH), 4.05 (t, 2, J = 6.5 Hz, CH_2O), 2.90 (m, 2, $ArCH_2$), 2.20 (s, 3, $ArCH_3$), 2.15 ppm (s, 6, 2 $ArCH_3$); MS m/z 275 (M^+).

***(rac*-2α,6′β)-3,4,3′,4′,5′,6′-Hexahydro-5,6′,7,8-tetramethylspiro[2*H*-1-benzopyran-2,2′-[2*H*]pyran]-6-ol (28b).** The reaction of 14.5 g (0.103 mol) of hydroxy vinyl ketone **27b**[20] and 13.7 g (0.09 mol) of TMHQ was carried out as described above for the preparation of **28a**. The crude product (37.3 g) was taken up in 1500 mL of boiling hexanes, and the mixture was filtered to remove some insoluble material. The filtrate was concentrated in vacuo, and the residue was chromatographed on 700 g of silica gel. Elution with 3:1 hexanes–ethyl acetate gave 18.2 g of solid. Recrystallization from hexanes afforded 10.8 g (43.5%) of pure **28b** as a colorless solid, mp 151–153 °C. The analytical specimen was obtained from another experiment: mp 155.5–156 °C; ^{1}H NMR δ 4.08 (s, 1, OH), 3.81 (m, 1, CHO), 2.18, 2.17, 2.11 (3 s, 9, 3 $ArCH_3$), 1.03 ppm (d, 3, J = 6.5 Hz, CH_3CHO).

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.97; H, 8.93.

***(rac*-2α,6′β)-3,4,3′,4′,5′,6′-Hexahydro-5,6′,7,8-tetramethyl-6-(phenylmethoxy)spiro[2*H*-1-benzopyran-2,2′-[2*H*]pyran] (28c).** A 9.7-g (35.1-mmol) sample of chromanol **28b** was benzylated as described above for the preparation of **9d**, with the modification that the reaction was stirred at room temperature for 66 h and not heated. The crude product was dissolved in boiling hexanes, and the solution was cooled in an ice-acetone bath. The precipitate was filtered with suction, washed with hexanes,

(24) Main, P.; Fiske, S.; Hull, S.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. MULTAN 11/82. University of York, England, and University of Louvain, Belgium, 1982.

and dried under high vacuum, giving 11.3 g (87.8%) of ether **28c** as a beige solid: mp 128–129 °C; ^{1}H NMR δ 4.73 (s, 2, $C_6H_5CH_2O$), 3.84 (m, 1, CHO), 2.24, 2.18 (2 s, 9, 3 $ArCH_3$), 1.05 ppm (d, 3, J = 6.5 Hz, CH_3CHO); MS m/z 366 (M^+).

Anal. Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.35. Found: C, 78.67; H, 8.29.

***(rac*-2α,6′β)-3,4,3′,4′,5′,6′-Hexahydro-5,6′,7,8-tetramethylspiro[2*H*-1-benzopyran-2,2′-[2*H*]pyran]-6-ol Acetate (28d).** A solution of 15 g (54.3 mmols) of chromanol **28b** in 30 mL of pyridine and 45 mL of acetic anhydride was stirred at room temperature for 18 h and then poured into 400 mL of ice–water. After being stirred for 3 h, the slurry was filtered, and the solid was washed with water and then dissolved in dichloromethane. The solution was washed with 2 N NaOH, 1 N HCl, and brine and processed in the usual manner. The residue was dissolved in 50 mL of ether, and 200 mL of hexanes was added followed by Norit A. The mixture was filtered through a Celite pad, which was washed with hexanes. The filtrate and washes were combined and cooled to −75 °C. The resulting precipitate was isolated by filtration, washed with hexanes, and dried, giving 13.84 g (80.0%) of ester **28d** as a colorless solid, mp 121–123 °C.

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.55; H, 8.50.

***(rac*-2β,6α)-Tetrahydro-2-[2-[2-hydroxy-3,4,6-trimethyl-5-(phenylmethoxy)phenyl]ethyl]-6-methyl-2*H*-pyran-2-carbonitrile (29c).** A 1.76-g (4.8-mmol) sample of **28c** was treated with cyanotrimethylsilane–titanium tetrachloride by using the general procedure described above for the preparation of **10a,b,d,e** except that the temperature of the reaction was maintained at −10 °C instead of −20 °C. Chromatography of the crude product on 150 g of silica gel, eluting with hexanes–ethyl acetate mixtures, afforded 1.15 g (61%) of phenol **29c** as a solid. Recrystallization of a sample from acetonitrile gave colorless solid: mp 125–128 °C; ^{1}H NMR δ 5.51 (s, 1 OH), 4.67 (s, 2, $C_6H_5CH_2O$), 3.97 (m, 1, CHO), 2.88 (m, 2, $ArCH_2$) 2.25, 2.22, 2.16 (3 s, 9, 3 $ArCH_3$), 1.30 ppm (d, 3, J = 6.5 Hz, CH_3CHO); MS m/z 393 (M^+).

Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.02; H, 8.02; N, 3.54.

***(rac*-2β,6α)-2-[2-[3-(Acetyloxy)-6-hydroxy-2,4,5-trimethylphenyl]ethyl]tetrahydro-6-methyl-2*H*-pyran-2-carbonitrile (29d).** A solution of 1.23 g (3.87 mmol) of ester **28d** and 2.1 mL (15.8 mmol) of cyanotrimethylsilane in 100 mL of dichloromethane was stirred at −40 °C while 0.79 mL (7.2 mmol) of boron trifluoride etherate was added. After being stirred at −40 °C for 30 min, and at 0–5 °C for 3 h, the reaction mixture was poured into 1 N HCl and worked up with dichloromethane in the usual manner. The residue was purified by HPLC (4:1 hexanes–ethyl acetate), giving 1.01 g (75.6%) of phenol **29d** as a solid. Recrystallization from ether–hexanes afforded a colorless solid: mp 146–147 °C; ^{1}H NMR δ 5.64 (br s, 1, OH), 3.96 (m, 1, CHO), 2.87 (m, 2, CH_2), 2.33 (s, 3, OAc), 2.15 (s, 3, CH_3), 2.07 (s, 3, CH_3), 2.03 (s, 3, CH_3), 2.20–2.00 (m, 2, CH_2), 2.00–1.67 (m, 3, CH_2 and CH of CH_2), 1.71 (br d, 1, J_{gem} = 13 Hz, CH of CH_2), 1.55–1.44 (m, 1, CH of CH_2), 1.31–1.17 (m, 1, CH of CH_2), 1.29 ppm (d, 3, J = 6.5 Hz, CH_3).

Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.00; H, 8.08; N, 3.95.

***(rac*-2β,6α)-2-[2-[2-[(4-Bromobenzoyl)oxy]-3,4,6-trimethyl-5-(phenylmethoxy)phenyl]ethyl]tetrahydro-6-methyl-2*H*-pyran-2-carbonitrile (29f).** A mixture of 0.393 g (1 mmol) of phenol **29c**, 0.439 g (2 mmol) of 4-bromobenzoyl chloride, and 2 mL of dry pyridine was stirred at room temperature for 16 h. The resulting thick slurry was treated with water and stirred for a few minutes before being poured into 1 N HCl and worked up with dichloromethane in the usual manner (the combined organic extracts were additionally washed with saturated $NaHCO_3$ solution). The residue was chromatographed on 25 g of silica gel. Elution with 9:1 hexanes–ether gave 0.563 g of a colorless solid. Recrystallization from ethanol–dichloromethane afforded 0.519 g (90%) of diester **29f** as a colorless solid, mp 153–156 °C.

Anal. Calcd for $C_{32}H_{34}BrNO_4$: C, 66.67; H, 5.94; N, 2.43; Br, 13.86. Found: C, 66.56; H, 5.93; N, 2.45; Br, 13.96.

The structure of **29f** was determined by a single-crystal X-ray analysis. The crystal data are summarized in Table VII (supplementary material). The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (graphite-monochromated Cu Kα radiation, θ − 2θ scans). The size of the crystal used for data collection was approximately 0.04 × 0.18 × 0.18 mm; the data were corrected for absorption. Of the 3100 independent reflections for θ < 50°, 1225 were considered to be observed [$I < 2.0\sigma(I)$].

The structure was solved by a multiple-solution procedure[24] and was refined by full-matrix least squares. In the final refinement, anisotropic thermal parameters were used for the non-hydrogen atoms, and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.076 and R_w = 0.068 for the 1225 observed reflections. The final difference map has no peaks greater than ±0.3 e Å^{-3}.

***rac*-6-(Acetyloxy)-2-[3-(acetyloxy)propyl]-3,4-dihydro-5,7,8-trimethyl-2*H*-1-benzopyran-2-carbonitrile (30b).** A solution of 0.68 g (2.74 mmol) of spiroketal **28a** in 65 mL of dichloromethane was stirred at −20 °C while 1.35 mL (10.1 mmol) of cyanotrimethylsilane was added followed by 0.55 mL (4.45 mmol) of boron trifluoride etherate. The resulting mixture was stirred at −20 °C for 1 h and allowed to warm to 0 °C over an additional 1 h before being quenched with 5 mL of methanol. The mixture was poured into 1 N HCl, and workup was carried out in the usual manner with dichloromethane. The residue of diol **30a** was dissolved in 20 mL of acetic anhydride and 10 mL of pyridine. After being stirred at room temperature for 2 h, the solution was treated with ice–water and worked up with ether in the usual manner. Recrystallization of the residue from toluene–hexanes afforded 0.75 g (76%) of diester **30b** as a colorless solid: mp 113–114 °C; ^{1}H NMR δ 4.20 (m, 2, CH_2OAc), 2.93 (ddd, 1, J_{vic} = 6, 11.5 Hz, J_{gem} = 16 Hz, CH of $ArCH_2$), 2.77 (dd, 1, J_{vic} = 5 Hz, J_{gem} = 16 Hz, CH of $ArCH_2$), 2.34 (s, 3, ArOAc), 2.09 (s, 3, OAc), 2.11, 2.04, 2.00 ppm (3 s, 9, 3 $ArCH_3$).

Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.84; H, 7.01; N, 3.90. Found: C, 66.69; H, 7.24; N, 3.82.

***(rac*-2β,6α)-2-[2-[2,5-Bis(acetyloxy)-3,4,6-trimethylphenyl]ethyl]tetrahydro-6-methyl-2*H*-pyran-2-carbonitrile (29e). (a) Using $TiCl_4$.** To a solution of 1.6 g (5 mmol) of acetate **28d** in 120 mL of dichloromethane, stirred and cooled to −40 °C, was added 2.3 mL (17.2 mmol) of cyanotrimethylsilane followed by 1.6 mL (14.6 mmol) of titanium tetrachloride. The reaction mixture was stirred at −40 °C for 4.5 h and kept at −35 °C overnight before being quenched by the addition of 10 mL of methanol. The mixture was poured into 1 N HCl and worked up in the usual manner. The residue was dissolved in 25 mL of acetic anhydride and 10 mL of pyridine, and the solution was stirred at room temperature for 4 h. The resulting solution was poured into ice–water, and the mixture was stirred for 2 h. The solid that precipitated was isolated by suction filtration, washed well with water, and dried, giving 1.71 g (88%) of diacetate **29e** as a colorless solid.

(b) Using BF_3 Etherate. To a stirred solution of 1.5 g (5.4 mmol) of chromanol **28b** in 130 mL of dichloromethane, cooled to −20 °C, was added 2.7 mL (20.2 mmol) of cyanotrimethylsilane followed by 1.1 mL (9 mmol) of boron trifluoride etherate. The reaction mixture was stirred for 1 h at −20 °C and 3 h at 0 °C before being quenched with 5 mL of methanol. The mixture was poured into 1 N HCl and worked up with dichloromethane in the usual manner. The residue was acetylated as described in the preceding experiment. The resulting mixture of acetates (1.74 g) was chromatographed on 200 g of silica gel. Elution with toluene–ether mixtures gave 1.26 g (60.3%) of hydroquinone diacetate **29e** followed by 0.3 g (14.4%) of the chroman diacetate **30d**. The analytical specimen of **29e** was obtained by recrystallization from ether–hexanes, giving colorless solid: mp 118–120 °C; ^{1}H NMR δ 3.87 (m, 1, CHO), 2.37, 2.35 (2 s, 6, 2 ArOAc), 2.09, 2.05, 2.03 (3 s, 9, 3 $ArCH_3$), 1.21 ppm (d, 3, J = 6 Hz, CH_3CHO); MS m/z 387 (M^+).

Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 67.98; H, 7.44; N, 3.61.

***rac*-6-(Acetyloxy)-2-[4-(acetyloxy)pentyl]-3,4-dihydro-5,7,8-trimethyl-2*H*-1-benzopyran-2-carbonitrile (Mixture of Epimers) (30d).** A solution of 1.35 g (4.9 mmol) of chromanol **28b** in 120 mL of dichloromethane was stirred at −40 °C while 2.4 mL (18 mmol) of cyanotrimethylsilane was added followed by 2.1 mL (18 mmol) of stannic chloride. The resulting mixture

was stirred at −40 to −20 °C for 2.5 h and then treated with 5 mL of methanol. The mixture was poured into 1 N HCl and worked up with dichloromethane in the usual manner. The residual 1.7 g consisting mainly of diol **30c** was acetylated as described above. Chromatography of the crude diacetate on 40 g of silica gel and recrystallization from ether afforded 1.57 g (83%) of the epimeric mixture of diesters **30d** as a colorless solid. The analytical specimen was obtained from another experiment: mp 75–77 °C; ^{1}H NMR δ 4.97 (m, 1, C*H*OAc), 2.91 (ddd, 1, J_{vic} = 6, 11.5 Hz, J_{gem} = 16 Hz, CH of CH_2), 2.76 (dd, 1, J_{vic} = 5 Hz, J_{gem} = 16 Hz, CH of CH_2), 2.34 (s, 3, ArOAc), 2.27 (m, 1, CH of CH_2), 2.05 (s, 3, OAc), 2.04 (s, 3, $ArCH_3$), 2.00 (s, 3, $ArCH_3$), 2.20–1.55 (br m, 8, 3 CH_2, CH, CH of CH_2), 1.27 ppm (d, 3, J = 6 Hz, CH_3CHOAc); MS m/z 387 (M^+).

Anal. Calcd for $C_{22}H_{29}NO_5$: C, 68.20; H, 7.54; N, 3.61. Found: C, 67.79; H, 7.68; N, 3.61.

***rac*-6-(Phenylmethoxy)-2-(4-hydroxypentyl)-3,4-dihydro-5,7,8-trimethyl-2*H*-1-benzopyran-2-carbonitrile (Mixture of Epimers) (30e).** A 0.5-g (1.8-mmol) sample of chromanol **28b** was treated with cyanotrimethylsilane–stannic chloride as described in the preceding experiment. The crude diol **30c** (0.5 g) was benzylated by using the procedure described above (method A). The crude product was purified by thick-layer chromatography on silica gel plates using 3:1 toluene–ether as the mobile phase. There was obtained 0.52 g (73.5%) of mono benzyl ether **30e** as a colorless solid, mp 108–112 °C. The Eu(fod)$_3$-shifted, 400-MHz ^{1}H NMR spectrum of this sample revealed it to be an approximately 56:44 mixture of epimers. The epimeric mixture could not be detected in the unshifted spectrum. The analytical specimen of **30e** was obtained from a separate experiment by recrystallization from toluene (which did not appear to alter the epimer ratio), mp 108–112° C; ^{1}H NMR δ 7.49 (d, 2, J = 7 Hz, phenyl), 7.39 (m, 3, phenyl), 4.70 (s, 2, $OCH_2C_6H_5$), 3.89 (m, 1, C*H*OH), 2.90 (ddd, 1, J_{vic} = 6, 11.5 Hz, J_{gem} = 16 Hz, CH of CH_2), 2.75 (dd, 1, J_{vic} = 5 Hz, J_{gem} = 16 Hz, CH of CH_2), 2.22 (s, 3, $ArCH_3$), 2.17 (s, 3, $ArCH_3$), 2.11 (s, 3, $ArCH_3$), 1.39 (br s, 1, OH), 1.25 ppm (d, 3, J = 6 Hz, CH_3CHOH). Addition of Eu(fod)$_3$ caused downfield shifts of the CH_3CHOH doublet and one of the aromatic methyl singlet resonances.

Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 75.99; H, 7.96; N, 3.52.

Attempted Interconversion of 29b and 30c. A solution of 0.65 g (2.14 mmol) of hydroquinone **29b** in 100 mL of dichloromethane was stirred at −40 °C while 0.9 mL of stannic chloride was added. The mixture was stirred at −40 °C for 2 h and then poured into 1 N HCl. Workup with dichloromethane in the usual manner gave 0.65 g of residue. TLC analysis revealed none of chroman **30c** to be present. The major components were the starting hydroquinone and the corresponding benzoquinone. In a similar manner, a solution of 0.1 g (0.33 mmol) of chromanol **30c** in 7 mL of dichloromethane was treated at −40 °C with 0.1 mL of titanium tetrachloride. The mixture was stirred at −40 °C for 4 h and then worked up as usual. TLC analysis of the product revealed it to be unchanged starting material, with no trace of **29b** being discernable.

***rac*-3,4,4a,10a-Tetrahydro-6,8,9,10a-tetramethyl-2*H*,5*H*-pyrano[2,3-*b*][1]benzopyran-7-ol (34a).** A mixture of 23 g (0.1 mol) of diethyl acetylglutarate (**31**), 7.5 g (0.12 mol) of ethylene glycol, 50 mg of *p*-toluenesulfonic acid monohydrate, and 100 mL of benzene was stirred and refluxed for 5 h, using a Dean–Stark trap to remove water. The resulting solution was cooled and washed with saturated $NaHCO_3$ solution, and workup was completed in the usual manner. The oily product was found by NMR and TLC to be a 2:1 mixture of the desired ketal (**32**) and starting ketone, respectively. This material was treated with 8 g of ethylene glycol, 20 mL of triethyl orthoformate, and 0.1 g of *p*-toluenesulfonic acid monohydrate, and the mixture was stirred at room temperature for 22 h. At the end of this time, the reaction mixture was poured into saturated $NaHCO_3$ solution, and workup was carried out with ether in the usual manner, giving 26.53 g of a pale-yellow oil, which was now mainly (85–90%) the desired ketal. Without further purification, this material was dissolved in 50 mL of anhydrous ether, and the solution was added dropwise, over 55 min, to a stirred slurry of 8 g (0.2 mmol) of lithium aluminum hydride in 200 mL of anhydrous ether. A vigorous reaction was noted during the addition as the ether refluxed and a thick slurry developed. The resulting mixture was stirred at room temperature for 21 h before being cautiously decomposed by the dropwise addition, with ice-bath cooling, of 16 mL of water followed by 12.8 mL of 10% NaOH. After being stirred at room temperature for 4.5 h, the mixture was treated with some anhydrous sodium sulfate and filtered with suction. The filter cake was washed thoroughly with ether. Concentration in vacuo of the combined filtrate and washes gave 15.8 g (83.1%) of diol ketal **33** as a colorless oil: ^{1}H NMR δ 4.01 (s, 4, OCH_2CH_2O), 3.70 (m, 4, CH_2OH), 3.13 (t, 1, J = 6 Hz, OH), 1.34 ppm (s, 3, CH_3).

A mixture of this diol (83.2 mmol), 11.4 g (75 mmol) of TMHQ (**14a**), 1.08 g of *p*-toluenesulfonic acid monohydrate, and 333 mL of toluene was stirred and refluxed, with water removal by means of a Dean–Stark trap, for 3.25 h. The resulting red solution was cooled and washed with saturated $NaHCO_3$ solution, and workup was completed in the usual manner (some difficulty was noted in filtering the magnesium sulfate drying agent, since, at this point, the product began to precipitate from the dried toluene solution), giving an extremely insoluble solid residue. This material was triturated with hot methanol. The mixture was cooled, and the solid was isolated by suction filtration, washed with methanol, and dried. There was obtained 13.47 g of **34a** as an off-white solid, mp 191–193 °C. From the filtrate, an additional 2.86 g of **34a** was obtained: mp 191–193 °C (total yield, 16.33 g, 83.1%); ^{1}H NMR δ 4.22 (s, 1, OH), 4.04 (ddd, 1, J_{gem} = 11.5 Hz, J_{vic} = 2, 12 Hz, CH of CH_2O), 3.75 (dd, 1, J_{gem} = 11.5 Hz, J_{vic} = 5 Hz, CH of CH_2O), 2.40, 2.91 (AB of ABX, 2, J_{gem} = 17 Hz, J_{vic} = <1, 6 Hz, $ArCH_2$), 2.17 (s, 6, 2 CH_3), 2.10 (s, 3, CH_3), 1.96 (dt, 1, J_{gem} = 12 Hz, J_{vic} = 6 Hz, CH of CH_2), 1.74 (tq, 1, J_{gem} = 12.5 Hz, J_{vic} = 5.5, 12.5, 12.5 Hz, CH of CH_2), 1.55 (br m, 1, CH of CH_2), 1.47 (br m, 1, CH), 1.44 (dt, 1, J_{gem} = 12 Hz, J_{vic} = 4, 12 Hz, CH of CH_2), 1.36 ppm (s, 3, CH_3); MS m/z 262 (M^+).

Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.10; H, 8.49.

***rac*-3,4,4a,10a-Tetrahydro-6,8,9,10a-tetramethyl-2*H*,5*H*-pyrano[2,3-*b*][1]benzopyran-7-ol Acetate (34b).** A solution of 2.62 g (10 mmol) of **34a** in 5 mL of acetic anhydride and 10 mL of pyridine was kept at room temperature for 18 h and then concentrated at 50 °C/high vacuum. The residue was dissolved in ether, the solution was washed with 1 N HCl, water, and saturated $NaHCO_3$ solution, and workup was completed in the usual manner, giving 3.01 g of a solid. Recrystallization from ethanol afforded 2.77 g (91.1%) of ester **34b** as a colorless solid; mp 130–133 °C; ^{1}H NMR δ 2.34, 2.16, 2.04, 1.97, 1.38 ppm (5 s, 15, 5 CH_3); MS m/z 304 (M^+).

Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.00; H, 7.99.

***rac*-3,4-Dihydro-6-hydroxy-3-(3-hydroxypropyl)-2,5,7,8-tetramethyl-2*H*-1-benzopyran-2-carbonitrile (35) (Mixture of Epimers).** A 2.43-g (8-mmol) sample of ester **34b** was treated with cyanotrimethylsilane–titanium tetrachloride using the procedure described above for the preparation of **10c**. The crude product was chromatographed on 50 g of silica gel. Elution with 1:1 toluene–ethyl acetate gave 2.33 g of the acetate of **35** as a colorless glass. The ^{1}H NMR spectrum of this material indicated an approximately 2:1 mixture of epimers. A mixture of this material, 3.52 g of anhydrous potassium carbonate, 35 mL of methanol, and 3.5 mL of water was stirred and refluxed for 3.5 h. The resulting mixture was cooled and poured into water. Workup with ether in the usual manner gave a crystalline residue, which was chromatographed on 50 g of silica gel. Elution with 1:1 toluene–ethyl acetate gave a solid, which was triturated with toluene. There was obtained 1.3 g (56.2%) of **35** as a colorless solid: mp 111–155 °C; ^{1}H NMR δ 4.33, 4.32 (s, 1, OH of 2:1 epimers), 3.68, 3.73 (br q, 2, J = 5 Hz, CH_2O of 2:1 epimers), 3.02, 2.52 (AB of ABX, 1.33, J_{gem} = 17 Hz, J_{vic} = 4.5, 6 Hz, $ArCH_2$ of major epimer), 2.85, 2.47 (AB of ABX, 0.67, J_{gem} = 16.5 Hz, J_{vic} = 5, 11 Hz, $ArCH_2$ of minor epimer), 2.16, 2.12, 2.11 (s, 9, 3 CH_3), 1.82, 1.69 (s, 3, CH_3 of 2:1 epimers), 1.96–1.54 (br m, 3, CH and CH_2), 1.36, 1.31 (br t, 1, J = 5 Hz, OH of 2:1 epimers), 1.42, 1.23 ppm (m, 1, CH of CH_2 of 2:1 epimers); MS m/z 289 (M^+).

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.34; H, 7.99; N, 4.91.

***rac*-2-Hydroxy-α,4-dimethoxy-α-methylbenzenebutanenitrile (37).** This compound was isolated, in 34% yield, by chromatography, on silica gel, of the reaction mixture obtained

upon treatment of **19e** with cyanotrimethylsilane–titanium tetrachloride (eluting with 1:1 hexanes–ether), as a yellow oil: ^{1}H NMR δ 7.02 (d, 1, J = 8 Hz, C-6 H), 6.42 (m, 2, C-3, C-5 H), 5.30 (s, 1, OH), 3.80 (s, 3, OCH_3), 3.54 (s, 3, OCH_3), 2.76 (m, 2, CH_2), 2.08 (m, 2, CH_2), 1.60 ppm (s, 3, CH_3); MS m/z 235 (M^+).

***rac*-2-Hydroxy-α-methoxy-4-(phenylmethoxy)benzenebutanenitrile (38).** This compound was isolated, in 19% yield, by chromatography, on silica gel, of the reaction mixture obtained upon treatment of **19a** with cyanotrimethylsilane–titanium tetrachloride (eluting with 1:1 hexanes–ether) as an oil which crystallized on standing: ^{1}H NMR δ 7.40 (m, 5, $C_6H_5CH_2$), 7.00 (d, 1, J = 8 Hz, C-6 H), 6.47 (m, 2, C-3, C-5 H), 5.13 (s, 1, OH), 5.02 (s, 2, $C_6H_5CH_2O$), 4.01 (dd, 1, J = 2,6 Hz, CHCN), 3.54 (s, 3, OCH_3), 2.76 (t, 2, J = 7 Hz, CH_2), 2.16 ppm (m, 2, CH_2); MS m/z 297 (M^+).

Typical Procedure for Hydrolysis of the 3,4-Dihydro-2*H*-1-benzopyran-2-carbonitriles: *rac*-3,4-Dihydro-7-(phenylmethoxy)-2*H*-1-benzopyran-2-carboxylic Acid. A mixture of 0.265 g (1 mmol) of nitrile **36a**, 0.5 g (7.68 mmol) of pulverized 86% potassium hydroxide, 4 mL of ethylene glycol, and 0.3 mL of water was stirred and heated (150 °C oil bath) for 4.5 h. The resulting solution was cooled, diluted with water, and extracted twice with ether (the ether extracts were discarded). The aqueous alkaline solution was acidified with 3 N HCl, leading to the formation of a white precipitate, which was isolated by workup with ether in the usual manner. There was obtained 0.283 g (99.6%) of the acid as a colorless solid: mp 127–129 °C; ^{1}H NMR δ 5.03 (s, 2, OCH_2Ph), 4.70 (dd, 1, J = 4,8 Hz, CHO); MS m/z 284 (M^+). The analytical specimen was obtained from a separate experiment as a colorless solid, mp 129–130.5 °C (from ethyl acetate–hexanes).

Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 72.00; H, 5.65.

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Supplementary Material Available: Tables of crystal data, final atomic parameters, final anisotroic thermal parameters, bond lengths and angles, and perspective drawings of **26** and **29f** and elemental analyses (13 pages). Ordering information is given on any current masthead page.

Palladium(0)-Catalyzed Azidation of Allyl Esters. Selective Synthesis of Allyl Azides, Primary Allylamines, and Related Compounds

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Palladium(0)-catalyzed reaction of allyl esters such as phosphates, carbonates, and carboxylates with sodium azide gives allyl azides. The azidation proceeds with retention of configuration at the allylic carbon. Optically active (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl azide (**19**) is obtained from (*R*)-(*E*)-(+)-4-phenyl-3-buten-2-yl acetate (**18**) stereoselectively. Sequential substitution of (*Z*)-4-acetoxy-2-buten-1-yl diethyl phosphate (**24**) with nucleophiles and subsequently azide ion gives (*E*)-4-substituted-2-buten-1-yl azides **27**. The reaction of allyl azides with triphenylphosphine gives iminotriphenylphosphoranes, which are versatile synthetic intermediates of primary allylamines, *N*-allylimines, and *N*-allylamides. Treatment of allyl azides with triphenylphosphine and subsequently with aqueous ammonium solution gives primary allylamines. Other synthetic applications of allyl azides are also described.

The growing importance of primary allylamines as enzyme inhibitors[1] and biologically active substances has led to the development of new synthetic methods for primary allylamines.[2,3]

Palladium-catalyzed amination of allylic compounds with secondary amines has been extensively studied and proved to be efficient for the synthesis of tertiary amines,[4] and various nitrogen-containing biologically active compounds such as alkaloids have been synthesized.[5] However, the palladium-catalyzed reactions with ammonia or primary amines cannot be applied to the synthesis of primary or secondary allylamines, because polyallylation results in contamination of secondary and tertiary allylamines. Therefore, for the synthesis of primary allylamines, preparation of N-protected primary allylamines, such as 4,4′-dimethoxybenzhydrylamine,[6] *p*-toluenesulfonamide,[7] phthalimide,[8] and di-*tert*-butyl iminodi-

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