mg, 0.09 mmol) was treated with chromium trioxide as in the preparation of **50** to yield, after chromatography (SiO_2, EtOAc/heptane, 1:2), **49** (21 mg, 59%): $[\alpha]^{25}_D$ −31.0° (*c* 1.3, MeOH) [lit.[30a] $[\alpha]^{25}_D$ −37° (*c* 0.15, $CHCl_3$), lit.[30b] $[\alpha]^{20}_D$ 10.2° (*c* 0.5, MeOH) and $[\alpha]^{20}_D$ −14.2° (*c* 1.3, MeOH)]; MS *m/e* (rel int) 384 (M^+, 8), 165 ($C_9H_9O_3$, 100), 135 ($C_8H_7O_2$, 63); ^1H NMR ($CDCl_3$) δ 6.70 (dd, 1 H, *J* = 7.0, 1.3 Hz, ArH), 6.47 (dd, 1 H, *J* = 7.0, 1.6 Hz, ArH), 6.46 (s, 1 H, ArH), 6.32 (d, 1 H, *J* = 1.5 Hz, ArH), 6.30 (d, 1 H, *J* = 1.5 Hz, ArH) 5.96–5.93 (m, 4 H, OCH_2O), 4.16 (dd, 1 H, *J* = 9.3, 6.8 Hz, H-5), 3.90–3.85 (1 H, H-5), 3.86 (s, 3 H, MeO), 2.95 (dd, 1 H, *J* = 14.0, 4.8 Hz, $ArCH_2$), 2.82 (dd, 1 H, *J* = 13.9, 6.8 Hz, $ArCH_2$), 2.62–2.46 (m, 4 H, H-3, H-4, $ArCH_2$); ^{13}C NMR ($CDCl_3$) δ 178.4 (CO), 149.0, 147.9, 146.4, 143.6, 134.1, 132.1, 131.6, 121.6, 108.8, 108.4, 108.3, 103.3 (Ar), 101.4, 101.1 (OCH_2O), 71.2 (C-5), 56.6 (MeO), 46.6, 41.2 (C-3 and C-4), 38.4, 35.2 ($ArCH_2$).

(−)-(3*R*,4*R*)-3,4-Bis[3,4-(methylenedioxy)benzyl]butyrolactone [(−)-Hinokinin, 50]. To a solution of chromium trioxide (0.291 g, 2.91 mmol) in dry pyridine[35] (0.459 g, 5.81 mmol) and dry dichloromethane (7.3 mL) was added a solution of **48** (0.148 g, 0.415 mmol) in dichloromethane (3 mL). After 10 min, the solution was decanted. The reaction flask was washed with dichloromethane (20 mL). The combined solutions were washed with aqueous sodium hydroxide (5 mL, 1 M), aqueous hydrochloric acid (5 mL, 5%), and saturated aqueous sodium hydrogen carbonate (2 × 5 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was chromatographed (SiO_2, dichloromethane) to give **50** (0.122 g, 83%) as an oil: $[\alpha]^{25}_D$ −34.7° (*c* 0.7, $CHCl_3$) [lit.[21b] $[\alpha]^{17}_D$ −34.0° (*c* 0.981); mp 64–65 °C (MeOH)]; ^1H NMR ($CDCl_3$) δ 6.75–6.69 (m, 2 H, ArH), 6.63–6.58 (m, 2 H, ArH), 6.48–6.45 (m, 2 H, ArH), 5.95–5.93 (m, 4 H, OCH_2O), 4.13 (dd, 1 H, *J* = 9.2, 6.9 Hz, H-5), 3.86 (dd, 1 H, *J* = 9.1, 7.0 Hz, H-5), 2.99 (dd, 1 H, *J* = 14.1, 4.9 Hz, $ArCH_2$), 2.84 (dd, 1 H, *J* = 14.1, 7.1 Hz, $ArCH_2$), 2.64–2.42 (m, 4 H, $ArCH_2$, H-3, H-4); ^{13}C NMR signals are in agreement with reported data (inter alia) δ 178.41 (CO), 34.87 ($ArCH_2$) (lit.[21h] δ 178.39, 34.78).

3-(2-Chloro-3,4,5-trimethoxybenzyl)-4-[3,4-(Methylenedioxy)benzyl]tetrahydrofuran (2″-Chloroburseran, 51). Treatment of **45** with $CDCl_3$ at room temperature for several days gave, after chromatography, a small amount of **51**: MS *m/e* (rel int) 422 (M^+, 3), 420 (M^+, 10), 216 (20), 215 (18), 182 (25), 181 (43), 136 (54), 135 (100); ^1H NMR ($CDCl_3$) δ 6.68 (d with further coupling, 1 H, *J* = 8.4 Hz, ArH), 6.54 (s, 1 H, ArH), 6.53 (dd, 1 H, *J* = 6.7, 1.7 Hz, ArH), 6.41 (s, 1 *H*, H-6″), 5.92 (q, 2 H, *J* = 1.3 Hz, OCH_2O), 3.96 (dd, 1 H, *J* = 8.8, 7.1 Hz, H-2 or H-5), 3.9 (1 H, H-2 or H-5), 3.90, 3.87, 3.81 (s, 3 H each, MeO), 3.57 (dd, 1 H, *J* = 8.7, 5.9 Hz, H-2 or H-5), 3.52 (dd, 1 H, *J* = 8.7, 6.0 Hz, H-2 or H-5), 2.83 (dd, 1 H, *J* = 13.6, 2.8 Hz, $ArCH_2$), 2.65–2.48 (m, 3 H, $ArCH_2$), 2.32–2.18 (m, 2 H, H-3, H-4).

Acknowledgments. We are grateful to Stefan Ahlfors for the synthesis of compounds **34r** and **43** and to Maria Levin and Mattias Svensson for technical assistance. This work was supported by the Swedish Natural Science Research Council and the Swedish National Board for Technical Development.

Synthesis of Highly Functionalized Flavones and Chromones Using Cycloacylation Reactions and C-3 Functionalization. A Total Synthesis of Hormothamnione

Lynda W. McGarry* and Michael R. Detty*

Corporate Research Laboratories, Eastman Kodak Company, Rochester, New York 14650-2115

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The cycloacylations of hydroxy- and methoxy-substituted phenols with aryl- and alkylpropiolic acids using Eaton's reagent (10% phosphorus pentoxide in methanesulfonic acid) gives highly substituted flavones and chromones in up to 63% yield. Styrylchromones were prepared from 2-methylchromones by condensation reactions of the 2-methyl group with various substituted benzaldehydes in sodium ethoxide and ethanol in almost quantitative yield. Methylation or hydroxylation at C-3 of these highly substituted flavones and styrylchromones was accomplished in a highly regioselective manner employing lithium diisopropylamide followed by quenching with an electrophile. Quenching of the initial anion with methyl triflate gave 3-methyl products while quenching of the initial anion with trimethylborate followed by oxidation gave 3-hydroxy products. A total synthesis of the naturally occurring styrylchromone hormothamnione, containing a 3-methyl substituent, is reported by use of these synthetic techniques.

The chromones, flavones, and related compounds are widely distributed in nature and have been found to play an important role in a number of biological processes.[1-4] In humans, naturally occurring chromones and flavones have shown biological effects as well. These are typified by the furochromone khellin (1), which has exhibited lipid-altering capabilities,[5] or by 3,4′,7-trihydroxyflavone (2), 5-hydroxy-4′,7-dimethoxyflavone (3), and 3,3′,4′,7-tetrahydroxyflavone (4), which have been shown to possess antiinflammatory activity.[6]

Other naturally occurring compounds that either are flavone-based or are flavones have been shown to be capable of mediating DNA strand cleavage in the presence of copper(II) and oxygen, presumably involving intercalation of the flavone.[7-9] These compounds, such as (−)-

(1) (a) Dean, F. M. *Naturally Occurring Oxygen Ring Compounds*; Butterworths: London, 1963. (b) *Heterocyclic Compounds: Chromenes, Chromanones, and Chromones*; Ellis, G. P., Ed.; Wiley: New York, 1977. (c) Swain, T. In *Chemistry and Biochemistry of Plant Pigments*; Goodwin, T. W., Ed.; Academic: London, 1976.

(2) For growth regulation: Mandava, N. B. In *Plant Growth Substances*; Mandava, N. B.; Ed.; ACS Symposium Series 136; American Chemical Society: Washington, DC, 1979; p 135.

(3) For indoleacetic acid oxidation: Thiman, K. V. In *Plant Physiology*; Steward, F. C., Ed.; Academic: New York, 1972; Vol. VIb.

(4) For dormancy inhibition: Isogi, Y.; Komoda, Y.; Okamoto, T. *Chem. Pharm. Bull.* **1970**, *18*, 1872.

(5) (a) Gamill, R. B.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1672. (b) Yamashita, A. *J. Am. Chem. Soc.* **1985**, *105*, 5823.

(6) (a) Gabor, M. *Prog. Clin. Bio. Res.* **1986**, *213*, 471. (b) Fourie, T. G.; Snyckers, F. O. *J. Nat. Prod.* **1984**, *47*, 1057.

(7) (a) Weinges, K.; Bahr, W.; Ebert, W.; Goritz, K.; Marx, H. D. In *Forschritte Chemie Organische Naturstuffe*; Zechmeister, L., Ed.; Springer-Verlag: New York, 1969; p 159. (b) Freudenberg, K.; Weinges, K. In *The Chemistry of Flavanoid Compounds*; Gessman, T. A., Ed.; Pergamon: Oxford, 1962; p 197.

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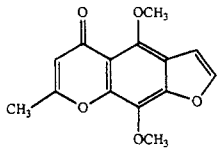

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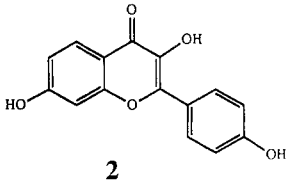

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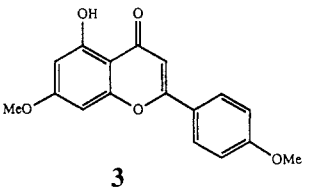

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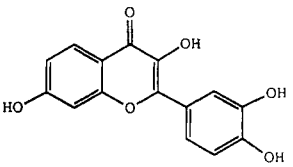
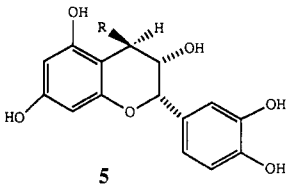


4

epicatechin (**5**), procyanidin B_2 (**6**), quercetin (**7**), and



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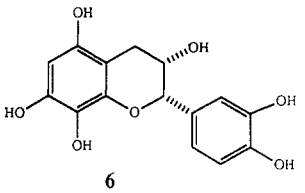

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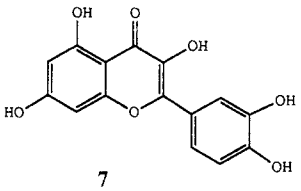

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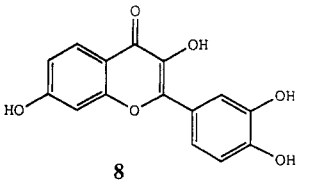
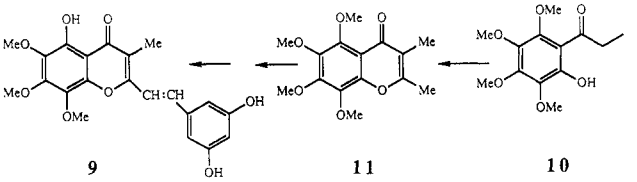


8

fisetin (**8**), bear a hydroxyl substituent at C-3 and possess a catechol group at the C-2 position. The presence of the catechol group appears to be critical for DNA strand cleavage since related compounds lacking the catechol moiety do not cleave DNA under the same conditions.[9]

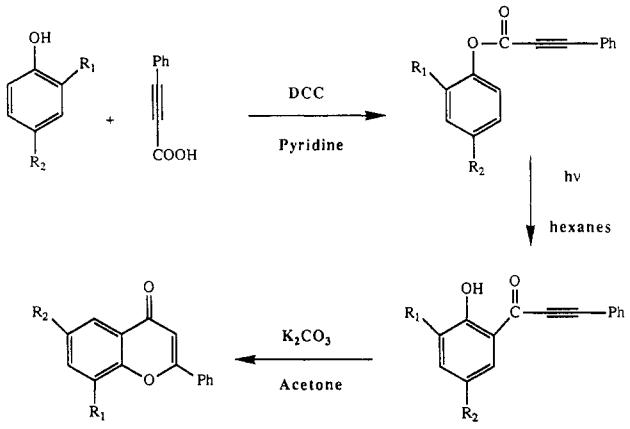
The styrylchromone hormothamnione (**9**) has been shown to be a potent cytotoxin to several human leukemia cell lines in vitro.[10] While the mechanism of its cytotoxic activity has not been fully characterized, it appears to operate via selective inhibition of RNA synthesis.[10] Hormothamnione lacks the catechol moiety characteristic of other flavone materials that break nuclear material. Furthermore, the 3-methyl substituent is rare in other naturally occurring chromones and flavones. Finally, hormothamnione is the first naturally occurring styrylchromone to be isolated.



9 11 10

Hormothamnione was isolated from the marine cryptophyte *Chrysophaeum taylori* in very small quantities.[10]

Scheme I



General synthetic routes to this structure would allow quantities of **9** to be produced for more extensive studies. The unusual structural features of **9** might be incorporated into related styrylchromones to seek greater activity if general synthetic routes were available. Alternatively, the incorporation of structural features found in other biologically active chromones and flavones (such as a 3-hydroxyl substituent or a catechol group in the styryl fragment) might provide other biological properties in styrylchromones. It would be highly desirable to develop synthetic routes to styrylchromones where both the C-3 substituent and the styryl aryl group could be introduced (and varied) at a late stage of the synthesis to produce "unnatural" analogues of hormothamnione.

The two reported syntheses of **9** utilize a common intermediate in propiophenone **10**, which was then converted to 2,3-dimethyl-5,6,7,8-tetramethoxychromone (**11**).[11,12] In these synthetic schemes, the C-3 substituent in the styrylchromone is set at a very early stage of the synthesis. Varying substituents at C-3 would not proceed through a "late" intermediate but would require a multistep synthetic strategy for each substituent.

The functionalization of C-3 in flavone[13,14] and in related sulfur, selenium, and tellurium analogues[14] has been accomplished via lithiation at C-3 with lithium diisopropylamide (LDA) and quenching with an appropriate electrophile. Lithiation of chromones and flavones containing methoxy substituents or other directing groups[15] might not give the regioselectivity observed in the lithiation of simple flavones. If regioselective metalation of highly oxygenated flavones and styrylchromones were observed, then a variety of C-3 substituents might be introduced at a late stage in the syntheses of complex flavones and styrylchromones.

This paper describes synthetic strategies for two aspects of syntheses of complex flavones and styrylchromones. The construction of flavones and chromones unsubstituted at C-3 can be accomplished in one or two steps from phenols and alkyl- or arylpropiolic acids with 10% phosphorus pentoxide in methanesulfonic acid (Eaton's reagent).[16] Flavones prepared in this manner as well as various

(8) (a) Roux, D. G. *Phytochemistry* **1972**, *11*, 1219. (b) Thompson, R. S.; Jacques, D.; Haslam, E.; Tanner, R. J. N. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1387. (c) Fletcher, A. C.; Porter, L. J.; Haslam, E.; Gupta, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1628. (d) Kolodziej, H. *Phytochemistry* **1986**, *25*, 1209.

(9) Chrisey, L. A.; Bonjar, G. H. S.; Hecht, S. M. *J. Am. Chem. Soc.* **1988**, *110*, 644.

(10) (a) Gerwick, W. H.; Lopez, A.; Van Duyne, G. D.; Clardy, J.; Ortiz, W.; Baez, A. *Tetrahedron Lett.* **1986**, *27*, 1979. (b) Gerwick, W. H. *J. Nat. Prod.* **1989**, *52*, 252.

(11) Alonso, R.; Brossi, A. *Tetrahedron Lett.* **1988**, *29*, 735.

(12) Ayyangar, N. R.; Khan, R. A.; Deshpande, V. H. *Tetrahedron Lett.* **1988**, *29*, 2347.

(13) Costa, A. M. B. S. R. C. S.; Dean, F. M.; Jones, M. A.; Varma, R. S. *J. Chem. Soc., Perkin Trans. 1* **1985**, *1*, 799.

(14) Detty, M. R.; McGarry, L. W. *J. Org. Chem.* **1988**, *53*, 1203.

(15) (a) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653. (b) Finnegan, R. A.; Altschuld, J. W. *J. Organomet. Chem.* **1967**, *9*, 193.

(16) Eaton, P. E.; Carlson, G. R.; Lee, J. T. *J. Org. Chem.* **1973**, *38*, 4071.

Table I. Product Distribution from Reaction of Phenols with Aryl- and Alkylpropiolic Acids Using Eaton's Reagent

entry	R	R_1	R_2	R_3	isolated yield of product, % a	b	c
12	Ph	OMe	OMe	OMe	63		
13	Ph	OMe	H	OMe	23	11	
14	Ph	OMe	H	H	5	36	3
15	Ph	OH	H	H	5	31	6
16	Me	OMe	OMe	OMe	5	11	54
17	Me	OMe	H	OMe		15	10
18	Me	OMe	H	H		4	16
19	3,4-$(MeO)_2C_6H_3$	OMe	OMe	OMe	26		
20	4-$(MeO)C_6H_4$	OMe	OMe	OMe	19	10	

styrylchromones can be functionalized at C-3 with LDA and appropriate electrophiles even in systems bearing numerous methoxy substituents. Both of these strategies were incorporated into a total synthesis of hormothamnione.

Results and Discussion

Synthesis of Chromones and Flavones. Flavones have been prepared typically from *o*-hydroxyacetophenones in three or more steps via either the Allan–Robinson method[17] or the Baker–Venkataraman procedure.[18,19] Several modifications of these procedures have been reported, which have decreased the number of steps, to obtain flavones in overall yields of up to 40%.[20,21] These procedures give decreasing yields as the number of hydroxy and methoxy substituents in the *o*-hydroxyacetophenone increases. Chromones have been prepared in similar fashion from *o*-hydroxyacetophenones and carboxylates.[1b]

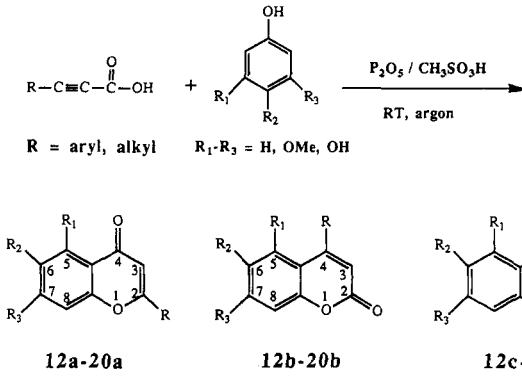
An alternative approach to the preparation of chromones[22] and flavones[23] involves the irradiation of aryl propynoates to give *o*-hydroxyaryl ethynyl ketones via a Photo–Fries rearrangement (Scheme I). The ketone can then be cyclized to the corresponding chromone or flavone in 10–25% overall yield.

Cycloacylation Reactions. The *o*-hydroxyaryl ethynyl ketones described above have been prepared from the acylation of phenols with phenylpropiolic acid in polyphosphoric acid (PPA) at 100 °C.[24] A basic workup of the PPA reaction mixtures gave flavones in 10–25% yields. The yields from this reaction compare favorably with those of other multistep procedures. However, PPA is difficult to work with and requires high temperatures for successful acylation.

Eaton's reagent (10% phosphorus pentoxide in methanesulfonic acid)[16] has been found to be superior to PPA in intramolecular acylation reactions. It can be used at ambient temperature or below, and organic substrates are much more soluble in this medium than in PPA. We have found that Eaton's reagent is an excellent medium for the cycloacylation reactions of phenols with alkyl- or arylpropiolic acids to give chromones or flavones, respectively.

A series of phenols and an equimolar amount of an alkyl- or arylpropiolic acid were added to Eaton's reagent. The resulting solution was stirred at ambient temperature under argon (Scheme II). Upon complete reaction of the phenol as monitored by thin-layer chromatography (TLC), the dark red reaction mixtures were poured into aqueous saturated sodium bicarbonate. The products of the reaction were isolated by extraction and chromatography on silica gel.

Scheme II



As shown in Scheme II, three types of products were isolated from these reactions: the flavone or chromone (**12a–20a**), the isomeric coumarin (**12b–20b**), and the uncyclized *o*-hydroxyaryl ethynyl ketone (**12c–20c**). The product ratios and isolated yields for these reactions are compiled in Table I.

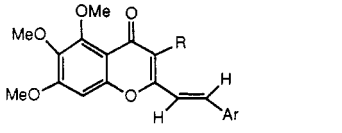
5,6,7-Trimethoxyflavone (**12a**) was obtained in 63% isolated yield from 3,4,5-trimethoxyphenol and phenylpropiolic acid. As the number of methoxy substituents on the phenol decreased, the yield of flavone decreased while the isolated yield of coumarin increased (Table I). The reaction of substituted arylpropiolic acids with 3,4,5-trimethoxyphenol gave flavones in yields of up to 26%.

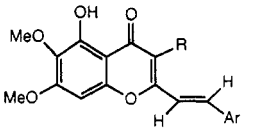
The use of alkylpropiolic acids gave product distributions quite different from those obtained from arylpropiolic acids. Very little chromone was isolated directly from the reaction mixtures. Instead, the *o*-hydroxylaryl ethynyl ketones were isolated. These materials were cyclized to the corresponding chromone with potassium carbonate in acetone. Alternatively, the crude reaction mixture can be stirred for longer periods of time over sodium bicarbonate. As was observed in the flavones, the amount of coumarin formed increased as the number of methoxy substituents on the phenol decreased.

Preparation of Styrylchromones. 3-Methyl-5,6,7-trimethoxychromone (**16a**) reacted with benzaldehyde derivatives in sodium ethoxide–ethanol to give styrylchromones in good yield. Thus, the condensation of **16a** with 3,5-dimethoxybenzaldehyde or with 3,5-bis(benzyloxy)benzaldehyde[25] gave styrylchromone **21** in 94% isolated yield or styrylchromone **22** in 91% isolated yield,

(17) Allan, J.; Robinson, R. *J. Chem. Soc.* **1924**, *125*, 2192.
(18) Baker, W. *J. Chem. Soc.* **1933**, 1381.
(19) Mahal, H. S.; Venkataraman, K. *Curr. Sci.* **1933**, *4*, 214.
(20) (a) Gupta, V. N.; Seshadri, T. R. *J. Sci. Ind. Res. (India)* **1957**, *16*, 116. (b) Srimannarayana, G.; Subba Rao, N. V. *Indian J. Chem.* **1968**, *6*, 696. (c) Hauteville, M.; Chadenson, M.; Chopin, J. *Bull. Soc. Chim.* **1975**, 1803. (d) Gaydou, E. M.; Bianchini, J. P. *Bull. Soc. Chim.* **1978**, II-43.
(21) Grover, S. K.; Jain, P. K.; Makrandi, J. K. *Synthesis* **1982**, 221.
(22) Alvaro, M.; Garcia, H.; Iborra, S.; Miranda, M. A.; Primo, J. *Tetrahedron* **1987**, *43*, 143.
(23) Miranda, M. A.; Garcia, H.; Iborra,, S.; Primo, J. *J. Org. Chem.* **1986**, *51*, 4432.
(24) Fozdar, B. I.; Khan, S. A.; Shamsuddin, K. M. *Chem. Ind.* **1986**, 586.
(25) Anand, R. A.; Ranjan, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1889.

respectively. Similarly, the condensation of **16a** with 3,4-bis(benzyloxy)benzaldehyde gave styrylchromone **23** in 89% isolated yield.





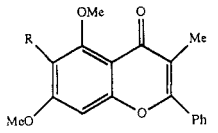
(Bn=CH_2Ph)

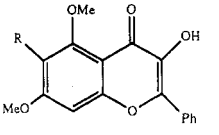
21; R=H, Ar=3,5-$(MeO)_2C_6H_3$
22; R=H, Ar=3,5-$(BnO)_2C_6H_3$
23; R=H, Ar=3,4-$(BnO)_2C_6H_3$
28; R=Me, Ar=3,5-$(MeO)_2C_6H_3$
29; R=Me, Ar=3,5-$(BnO)_2C_6H_3$
30; R=OH, Ar=3,5-$(BnO)_2C_6H_3$

31; R=H, Ar=3,5-$(HO)_2C_6H_3$
32; R=H, Ar=3,4-$(HO)_2C_6H_3$
33; R=Me, Ar=3,5-$(HO)_2C_6H_3$

Functionalization at C-3 in Highly Oxygenated Flavones and Styrylchromones. Many of the naturally occurring chromones and flavones, such as quercetin (**7**), fisetin (**8**), and hormothamnione (**9**), bear a non-hydrogen substituent at the C-3 position. Although metalation at C-3 of flavone with LDA followed by capture of an electrophile has yielded 3-substituted flavones,[13,14] functionalization of more highly substituted derivatives has not been reported. Since oxygen-containing substituents on an aryl ring can direct metalation,[15] we were concerned that lithiation of highly substituted flavones such as **12a** and **13a** might show poorer regioselectivity for C-3.

The reaction of 5,6,7-trimethoxyflavone with 1 equiv of LDA at −78 °C followed by quenching with methyl triflate gives 3-methyl-5,6,7-trimethoxyflavone (**24**) in 46% isolated yield. Similarly, 5,7-dimethoxyflavone (**13a**) is alkylated with 1 equiv of LDA and methyl triflate to give 3-methyl-5,7-dimethoxyflavone (**25**) in 51% isolated yield. Even in methoxy-substituted flavones, lithiation with LDA appears to be selective for C-3.





24, R = OMe
25, R = H

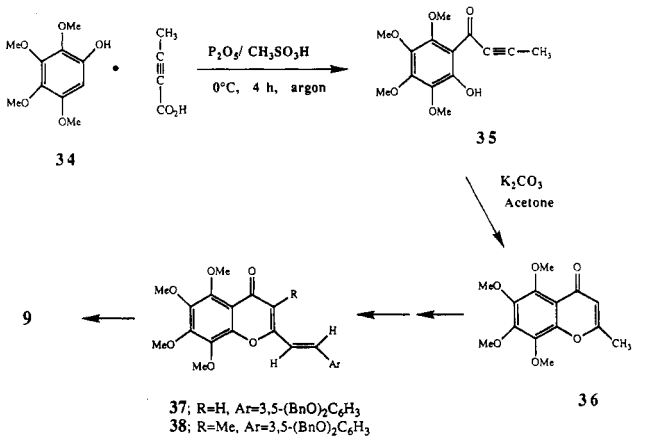
26, R = OMe
27, R = H

A 3-hydroxy substituent was introduced to both **12a** and **13a** by quenching the corresponding 3-lithioflavone with trimethylborate at −78 °C followed by oxidation with hydrogen peroxide in acetic acid.[26] 3-Hydroxy-5,6,7-trimethoxyflavone (**26**) was isolated in 51% yield and 3-hydroxy-5,7-dimethoxyflavone (**27**) was isolated in 64% yield with this procedure.

Functionalization of C-3 in styrylchromones was attempted next. The addition of a tetrahydrofuran (THF) solution of styrylchromone **21** to 1 equiv of LDA at −78 °C gave a deep orange-red solution. The resulting lithiated species was quenched with excess methyl triflate to give the 2-(3′,5′-dimethoxystyryl)-3-methyl-5,6,7-trimethoxychromone (**28**) in 44% isolated yield following workup and chromatography on silica gel. Treating the bis(benzyloxy)styryl derivative **22** with 1 equiv of LDA and an excess of methyl triflate gave 3-methylstyrylchromone **29** in 63% isolated yield following chromatography on silica gel. In a similar manner, treating lithiated **22** with trimethylborate followed by an oxidative workup with hydrogen peroxide gave 3-hydroxystyrylchromone **30** in 48% isolated yield.

In both flavones and 2-styrylchromones bearing alkoxy substituents, LDA appears to lithiate the benzo[*b*]pyran ring system selectively at C-3. Such methodology allows the introduction of different substituents at C-3 at a late stage in the syntheses of certain flavones and styrylchromones.

Scheme III



37; R=H, Ar=3,5-$(BnO)_2C_6H_3$
38; R=Me, Ar=3,5-$(BnO)_2C_6H_3$

Selective Demethylation in Styrylchromones 22, 23, and 29. The selective dealkylation of 5-alkoxychromones and -flavones has been accomplished with boron trichloride at low temperature in dichloromethane.[27] The formation of a dichloroboronate between the C-4 carbonyl and the oxygen attached to C-5 presumably is responsible for the selective dealkylation observed. Treating styrylchromones **22**, **23**, and **29** with boron trichloride gives not only selective demethylation of the 5-methoxy substituent but also debenzylation of the 3′- and 5′-benzyloxy substituents to give styrylchromones **31**–**33** in 90, 93, and 71% isolated yields, respectively.

Styrylchromone **33** is an 8-desmethoxy analogue of hormothamnione (**9**). The synthesis of **33** suggests that the chemistry described for chromone ring formation, C-3 functionalization of styrylchromones, and 3′-, 5′-, and 5-alkoxy dealkylation should be applicable in a total synthesis of hormothamnione.

A Total Synthesis of Hormothamnione (9). A total synthesis of hormothamnione was accomplished by the sequence of reactions outlined in Scheme III. The synthesis of 5,6,7,8-tetramethoxy-substituted styrylchromones via a cycloacylation procedure would require 2,3,4,5-tetramethoxyphenol (**34**) as a starting material. Phenol **34** has been prepared in six steps with an overall yield of 40%.[28] The reaction of phenol **34** and an equimolar amount of 2-butynoic acid in Eaton's reagent at 0 °C gave *o*-hydroxyaryl ethynyl ketone **35** in 68% isolated yield. Cyclization of **35** in acetone with a catalytic amount of potassium carbonate gave 5,6,7,8-tetramethoxy-2-methylchromone (**36**) in 88% isolated yield.

Styrylchromone **37** was prepared by the condensation of 2-methylchromone **36** with 3,5-bis(benzyloxy)benaldehyde in sodium ethoxide–ethanol. The styrylchromone was isolated in 85% yield.

Methylation of **37** at C-3 was achieved via the addition of a THF solution of **37** to 2 equiv of LDA at −78 °C. The

(26) Kidwell, R. L.; Murphy, M.; Darling, S. D. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 918.

(27) Dean, F. M.; Goodchild, J.; Houghton, L. E.; Martin, J. A.; Morton, R. B.; Parton, B.; Price, A. W.; Samvichien, N. *Tetrahedron Lett.* **1966**, 4153.

(28) (a) Syper, L.; Kloc, K.; Lochowski, J. *Tetrahedron* **1980**, *36*, 123. (b) Brossi, A.; Sharma, P. N.; Takahashi, K.; Chiang, J. F.; Karle, I. L.; Seibert, G. *Helv. Chim. Acta* **1983**, *66*, 799.

3-lithio derivative was quenched with methyl triflate to give 3-methyl-2-[3',5'-bis(benzyloxy)styryl]-5,6,7,8-tetramethoxychromone (**38**) in 54% isolated yield. This intermediate has been prepared in both of the other routes to hormothamnione and completes a formal synthesis of the compound.[11,12]

The final step to hormothamnione consisted of treating a dichloromethane solution of **38** with boron trichloride at −15 °C. Selective demethylation of the methoxy substituent at C-5 and debenzylation gave hormothamnione in 89% isolated yield.

This synthetic route to hormothamnione gives an overall yield of 24% for the five steps of the reaction from tetramethoxyphenol **34**. The other two reported syntheses of **9** have similar overall yields from pentamethoxybenzene, which is an additional step removed from tetramethoxyphenol **34**.[11,12] In addition, styrylchromone **37** would serve as an advanced intermediate for the preparations of analogues of **9** in which the C-3 substituent is varied.

Summary and Conclusions

We have developed new synthetic routes to highly substituted flavones, chromones, and styrylchromones. The number and position of methoxy and/or hydroxy substituents in the benzo ring of such molecules are determined by an appropriate choice of phenol to participate in cycloacylation reactions with propiolic acids in Eaton's reagent. Unlike other methods to prepare such compounds, yields of flavones and chromones improve as the number of alkoxy substituents on the phenol increases. Functionalization of C-3 in flavones and styrylchromones is achieved with a high degree of regioselectivity with LDA to lithiate the C-3 position. Electrophilic capture of the 3-lithio derivatives with an appropriate electrophile gives various substituents at C-3. Through this chemistry, short synthetic paths to a variety of natural and "unnatural" products are available.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a General Electric QE-300 instrument. Infrared spectra were recorded on a Beckman IR 4250 instrument. Mass spectra were recorded on a Du Pont 21-491 instrument equipped for field desorption. Microanalyses were performed on a Perkin-Elmer 240 C, H, and N analyzer. THF was distilled from sodium benzophenone ketyl. Phenylpropiolic acid and butynoic acid were prepared from commercially available ethyl esters by saponification. (4-Methoxyphenyl)propiolic acid and (3,4-dimethoxyphenyl)propiolic acid were prepared from the methyl esters[29] by saponification. Phosphorus pentoxide, 3,4,5-trimethoxyphenol, 3,5-dimethoxyphenol, *m*-methoxyphenol, and resorcinol were used as received from commercial sources (Aldrich). 2,3,4,5-Tetramethoxyphenol was prepared in several steps via a literature procedure[28] from gallacetophenone. Diisopropylamine, methanesulfonic acid, boron trifluoride etherate, methyl triflate, and trimethylborate were distilled prior to use. ICN Silica 32-63, 60A, was used for flash chromatographic separations. Yields were not optimized. Compounds **9**,[10] **12a–20a**, **12b–15b**, **17b**, **26**, and **27** have been isolated from various plant sources.[1]

General Procedure for the Syntheses of Flavones and Chromones. For each 2 mmol of propiolic acid (and phenol), 1 g of phosphorus pentoxide was added to 10 g of methanesulfonic acid and the resultant mixture stirred at ambient temperature under argon until all of the phosphorus pentoxide was dissolved. The propiolic acid was then added. An equimolar amount of the phenol was added immediately following the addition of the propiolic acid. The mixture was degassed under argon and was then stirred at ambient temperature. The progress of the reaction was monitored by TLC on silica plates with 10% ethyl acetate–dichloromethane as the eluent. Upon complete consumption of the phenol, the dark red reaction mixture was poured slowly into saturated sodium bicarbonate solution (100 mL for every 10 g of methanesulfonic acid). The products were extracted with dichloromethane (3 × 100 mL/10 g of methanesulfonic acid). The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated under reduced pressure.

Preparation of 5,6,7-Trimethoxyflavone (12a). Phenylpropiolic acid (1.17 g, 8.00 mmol) and 3,4,5-trimethoxyphenol (1.47 g, 8.00 mmol) were treated as described with stirring for 24 h at room temperature in Eaton's reagent. Following workup, flavone **12a** crystallized from the crude reaction mixture in ethyl acetate. Pale yellow crystals of **12a** were collected: 1.60 g, 63%; mp 164–165 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 2 H), 7.53 (m, 3 H), 6.84 (s, 1 H), 6.69 (s, 1 H), 4.01 (s, 3 H), 4.00 (s, 3 H), 3.94 (s, 3 H); IR (KBr) 1625, 1485, 1450, 1410, 1350, 1270, 1200 cm^{-1}; FDMS, m/z 312 ($C_{18}H_{16}O_5$).

Preparation of 5,7-Dimethoxyflavone (13a) and 5,7-Dimethoxy-4-phenylcoumarin (13b). Phenylpropiolic acid (1.17 g, 8.00 mmol) and 3,5-dimethoxyphenol (1.23 g, 8.00 mmol) were treated as described with stirring for 16 h at room temperature. Following workup, the products were separated by chromatography on silica gel with 10% ethyl acetate–dichloromethane as the eluent. The coumarin **13b** was the faster moving component (R_f = 0.5) and was obtained in 0.21-g isolated yield (11%). The slower moving flavone **13a** (R_f = 0.1) was isolated in 0.52-g yield (23%).

13a: mp 148–149 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (m, 2 H), 7.52 (m, 3 H), 6.70 (s, 1 H), 6.59 (d, 1 H, J = 2 Hz), 6.39 (d, 1 H, J = 2 Hz), 3.97 (s, 3 H), 3.93 (s, 3 H); IR (KBr) 1650, 1605, 1485, 1450, 1345, 1210, 1200 cm^{-1}; FDMS, m/z 282 ($C_{17}H_{14}O_4$).

13b: mp 165–166 °C; ^{1}H NMR ($CDCl_3$) δ 7.39 (m, 3 H), 7.29 (m, 2 H), 6.55 (d, 1 H, J = 2 Hz), 6.25 (d, 1 H, J = 2 Hz), 6.02 (s, 1 H), 3.89 (s, 3 H), 3.44 (s, 3 H); IR (KBr) 1720, 1600, 1460, 1350, 1225, 1160 cm^{-1}; FDMS, m/z 282 ($C_{17}H_{14}O_4$).

Preparation of 5-Methoxyflavone (14a), 5-Methoxy-4-phenylcoumarin (14b), and 1-(2-Hydroxy-4-methoxyphenyl)-3-phenylpropyn-1-one (14c). Phenylpropiolic acid (1.17 g, 8.00 mmol) and *m*-methoxyphenol (1.00 g, 8.00 mmol) were treated as described with stirring for 20 h at ambient temperature. Following workup, the products were separated by chromatography on silica gel with 10% ethyl acetate–dichloromethane as eluent. The fastest moving product (R_f = 0.9), isolated in 0.050-g yield (3%), was identified as propynone **14c**. The second product (R_f = 0.7), isolated in 0.72-g yield (36%), was identified as coumarin **14b**. The slowest moving product (R_f = 0.3), isolated in 0.10-g yield (5%), was identified as flavone **14a**.

14a: mp 107 °C; ^{1}H NMR ($CDCl_3$) δ 8.18 (dd, 1 H, J = 2.1, 8.3 Hz), 7.90 (m, 2 H), 7.55 (m, 3 H), 7.04 (d, 1 H, J = 8.3 Hz), 7.01 (d, 1 H, J = 2 Hz), 6.81 (s, 1 H), 3.98 (s, 3 H); IR (KBr) 1660, 1625, 1610, 1505, 1495, 1450 cm^{-1}; FDMS, m/z 252 ($C_{16}H_{12}O_3$).

Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.2; H, 4.8. Found: C, 75.9; H, 4.9.

14b: mp 92–94 °C; ^{1}H NMR ($CDCl_3$) δ 7.53 (m, 3 H), 7.47 (m, 2 H), 7.40 (d, 1 H, J = 9 Hz), 6.91 (d, 1 H, J = 2 Hz), 6.81 (dd, 1 H, J = 2, 9 Hz), 6.23 (s, 1 H), 3.90 (s, 3 H); IR (KBr) 1730 (br), 1620, 1550, 1505, 1445, 1370, 1280 cm^{-1}; FDMS, m/z 252 ($C_{16}H_{12}O_3$).

Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.2; H, 4.8. Found: C, 76.0; H, 4.9.

14c: mp 107–109 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 1 H, J = 8.5 Hz), 7.66 (d, 2 H, J = 8.5 Hz), 7.4 (m, 3 H), 6.52 (dd, 1 H, J = 2.3, 8.5 Hz), 6.42 (d, 1 H, J = 2.3 Hz), 3.91 (s, 3 H); IR (KBr) 2200, 1720, 1640, 1580, 1360, 1265, 1215, 1170 cm^{-1}; FDMS, m/z 252 ($C_{16}H_{12}O_3$).

Cyclization of 14c to 14a. Compound **14c** (0.050 g, 0.20 mmol) was dissolved in 10 mL of dry acetone. Anhydrous potassium carbonate (0.20 g) was then added. The resulting slurry was heated at reflux for 1 h. The carbonate was removed via filtration. The filtrate was concentrated in vacuo. The residue was recrystallized from ethyl acetate to give 0.04 g (80%) of **14a**.

Preparation of 7-Hydroxyflavone (15a), 7-Hydroxy-4-phenylcoumarin (15b), and 1-(2,4-Dihydroxyphenyl)-3-

(29) Detty, M. R.; Wadsworth, D. H.; Geer, S. M. *J. Org. Chem.* 1987, *52*, 3662.

phenylpropyn-1-one (15c). Phenylpropiolic acid (1.17 g, 8.00 mmol) and resorcinol (0.88 g, 8.0 mmol) were treated as described with stirring at ambient temperature for 16 h. Following workup, the products were separated via chromatography on silica gel with 10% ethyl acetate–dichloromethane as eluent. The first product from the column (R_f = 0.8), isolated in 0.114-g yield (6%), was identified as propynone **15c**. The second product (R_f = 0.7), isolated in 0.42-g yield (22%), was identified as coumarin **15b**. The final product from the column (R_f = 0.3), isolated in 0.095-g yield (5%), was identified a flavone **15a**.

15a: mp 239 °C; ^{1}H NMR (DMSO-d_6) δ 8.04 (m, 2 H), 7.87 (d, 1 H, J = 8.7 Hz), 7.56 (m, 3 H), 6.98 (d, 1 H, J = 2.1 Hz), 6.91 (dd, 1 H, J = 2.1, 8.7 Hz), 6.88 (s, 1 H); IR (KBr) 3000 (br), 1620, 1580, 1550, 1510, 1490, 1450, 1380, 1250 cm^{-1}; FDMS, m/z 238 ($C_{15}H_{10}O_3$).

15b: mp 247–248 °C; ^{1}H NMR (DMSO-d_6) δ 7.50 (m, 5 H), 7.25 (d, 1 H, J = 8.5 Hz), 6.78 (d, 1 H, J = 2 Hz), 6.75 (dd, 1 H, J = 2, 8.5 Hz), 6.13 (s, 1 H); IR (KBr) 1690, 1590, 1440, 1370, 1270, 1235 cm^{-1}; FDMS, m/z 238 ($C_{15}H_{10}O_3$).

Anal. Calcd for $C_{15}H_{10}O_3$: C, 75.6; H, 4.2. Found: C, 75.2; H, 4.5.

15c: mp 184–185 °C; ^{1}H NMR (DMSO-d_6) δ 7.54 (m, 7 H), 7.34 (d, 1 H, J = 9.6 Hz), 7.09 (d, 1 H, J = 3.5 Hz), 6.22 (s, 1 H); IR (KBr) 3000 (br), 2220, 1620, 1590, 1360, 1295, 1220, 1120 cm^{-1}; FDMS, m/z 238 ($C_{15}H_{10}O_3$).

Anal. Calcd for $C_{15}H_{10}O_3$: C, 75.6; H, 4.2. Found: C, 75.3; H, 4.5.

Cyclization of 15c to 15a. Compound **16c** (0.220 g, 0.90 mmol) was dissolved in 10 mL of dry acetone. Anhydrous potassium carbonate (0.20 g) was then added. The resulting slurry was heated at reflux for 1 h. The carbonate was removed via filtration. The filtrate was concentrated in vacuo. The residue was recrystallized from ethyl acetate to give 0.21 g (98%) of **15a**.

Preparation of 5,6,7-Trimethoxy-2-methylchromone (16a), 5,6,7-Trimethoxy-4-methylcoumarin (16b), and 1-(2-Hydroxy-4,5,6-trimethoxyphenyl)but-2-yn-1-one (16c). Butynoic acid (0.340 g, 4.00 mmol) and 3,4,5-trimethoxyphenol (0.740 g, 4.00 mmol) were treated as described with stirring at ambient temperature for 5 h. Following workup, the products were separated via chromatography on silica gel with 20% ethyl acetate–dichloromethane as eluent. The first product from the column (R_f = 0.8), isolated in 0.460-g yield (54%), was identified as **16c**. The second product from the column (R_f = 0.7), isolated in 0.090-g yield (17%), was identified as coumarin **16b**. The third product from the column (R_f = 0.3), isolated in 0.070-g yield (14%), was identified as chromone **16a**.

16a: mp 99 °C; ^{1}H NMR ($CDCl_3$) δ 6.70 (s, 1 H), 6.04 (s, 1 H), 3.99 (s, 3 H), 3.97 (s, 3 H), 3.93 (s, 3 H), 2.34 (s, 3 H); IR (KBr) 1660, 1605, 1490, 1465, 1410, 1390, 1350, 1260, 1195, 1115 cm^{-1}; FDMS, m/z 250 ($C_{13}H_{14}O_5$).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.0; H, 5.6.

16b: mp 176 °C; ^{1}H NMR ($CDCl_3$) δ 6.66 (s, 1 H), 6.06 (s, 1 H), 3.98 (s, 3 H), 3.93 (s, 3 H), 3.87 (s, 3 H), 2.57 (s, 3 H); IR (KBr) 1730, 1660, 1600, 1460, 1350, 1240, 1210 cm^{-1}; FDMS, m/z 250 ($C_{13}H_{14}O_5$).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.1; H, 5.7.

16c: mp 92 °C; ^{1}H NMR ($CDCl_3$) δ 6.26 (s, 1 H), 4.02 (s, 3 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 2.21 (s, 3 H); IR (KBr) 3000 (br), 2220, 1590, 1500, 1485, 1445, 1400, 1330, 1265, 1120, 1100 cm^{-1}; FDMS, m/z 250 ($C_{13}H_{14}O_5$).

Anal. Calcd for $C_{13}H_{14}O_5$: C, 62.4; H, 5.6. Found: C, 62.1; H, 5.7.

Cyclization of 16c to 16a. Compound **16c** (0.220 g, 0.88 mmol) was dissolved in 10 mL of dry acetone. Anhydrous potassium carbonate (0.20 g) was then added. The resulting slurry was heated at reflux for 1 h. The carbonate was removed via filtration. The filtrate was concentrated in vacuo. The residue was recrystallized from ethyl acetate to give 0.21 g (98%) of **16a**.

Preparation of 5,7-Dimethoxy-4-methylcoumarin (17b) and 1-(2-Hydroxy-4,6-dimethoxyphenyl)but-2-yn-1-one (17c). Butynoic acid (0.84 g, 10 mmol) and 3,5-dimethoxyphenol (1.54 g, 10.0 mmol) were treated as described with stirring at ambient temperature for 16 h. Following workup, the products were separated via chromatography on silica gel with 10% ethyl acetate–dichloromethane as eluent. The first product from the column (R_f = 0.8), isolated in 0.22-g yield (10%), was identified as **17c**. The second product (R_f = 0.6), isolated in 0.33-g yield (15%), was identified as **17b**.

17b: mp 169 °C; ^{1}H NMR ($CDCl_3$) δ 6.44 (d, 1 H, J = 2 Hz), 6.37 (d, 1 H, J = 2 Hz), 6.04 (s, 1 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 2.30 (s, 3 H); IR (KBr) 1660, 1610, 1570, 1450, 1390, 1340, 1255, 1155 cm^{-1}; FDMS, m/z 220 ($C_{12}H_{12}O_4$).

17c: 82–85 °C; ^{1}H NMR ($CDCl_3$) δ 6.03 (d, 2 H, J = 2 Hz), 5.90 (d, 2 H, J = 2 Hz), 3.85 (s, 3 H), 3.82 (s, 3 H), 2.14 (s, 3 H); IR (KBr) 3250, 2240, 2210, 1605, 1580, 1492, 1478, 1450, 1425, 1350, 1300 cm^{-1}; FDMS, m/z 220 ($C_{12}H_{12}O_4$).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.4; H, 5.5. Found: C, 65.0; H, 5.8.

Preparation of 7-Methoxy-4-methylcoumarin (18b) and 1-(2-Hydroxy-4-methoxyphenyl)but-2-yn-1-one (18b). Butynoic acid (1.01 g, 12 mmol) and 3-methoxyphenol (1.5 g, 12 mmol) were treated as described with stirring at ambient temperature for 16 h. Following workup, the products were separated via chromatography on silica gel with 10% ethyl acetate–dichloromethane as eluent. The first product from the column (R_f = 0.8), isolated in 0.34-g yield (16%), was identified as **18c**. The second product (R_f = 0.6), isolated in 0.10-g yield (4%), was identified as **18b**.

18b: mp 158–160 °C (lit.[30] mp 158–160 °C); ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 1 H), 6.83 (m, 2 H), 6.14 (q, 1 H, J < 1 Hz), 3.88 (s, 3 H), 2.40 (d, 3 H, J < 1 Hz); IR (KBr) 1730, 1620, 1610, 1390 cm^{-1}; FDMS, m/z 190 ($C_{11}H_{10}O_3$).

18c: oil; ^{1}H NMR ($CDCl_3$) δ 8.06 (d, 1 H), 7.45 (m, 2 H), 3.89 (s, 3 H), 2.10 (s, 3 H); IR (KBr) 3300, 2220, 1615, 1570, 1500 cm^{-1}; FDMS, m/z 190 ($C_{11}H_{10}O_3$).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3. Found: C, 69.4; H, 5.3.

Preparation of 1-(2-Hydroxy-3,4,5,6-tetramethoxyphenyl)but-2-yn-1-one (35). 2,3,4,5-Tetramethoxyphenol (4.00 g, 18.7 mmol) and butynoic acid (1.68 g, 20.0 mmol) were treated as described at 0 °C for 4.5 h. Following workup, chromatography on silica gel with 5% ethyl acetate–dichloromethane as eluent gave **35** (R_f = 0.8) in 3.69-g yield (68%): oil; ^{1}H NMR ($CDCl_3$) δ 6.415 (s, 1 H), 3.945 (s, 3 H), 3.87 (s, 3 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 2.08 (s, 3 H); IR (KBr) 2900 (br), 2250, 1725, 1605, 1490, 1470, 1430, 1410, 1260, 1090 cm^{-1}; FDMS, m/z 280 ($C_{14}H_{16}O_6$).

Anal. Calcd for $C_{14}H_{16}O_6$: C, 60.0; H, 5.8. Found: C, 60.1; H, 5.8.

Cyclization of 35 to 5,6,7,8-Tetramethoxy-2-methylchromone (36). Compound **35** (1.85 g, 6.35 mmol) was dissolved in 20 mL of acetone. Potassium carbonate (1.0 g) was added, and the resulting mixture was heated at reflux for 1 h. The potassium carbonate was removed by filtration, and the filtrate was concentrated in vacuo. The residue was partitioned between water and dichloromethane. The dichloromethane layer was dried over sodium sulfate and concentrated to give 1.55 g (88%) of **36** as an oily solid (lit.[31] oil) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 6.01 (s, 1 H), 4.05 (s, 3 H), 3.93 (s, 3 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 2.34 (s, 3 H); FDMS, m/z 280 ($C_{14}H_{16}O_6$).

Preparation of 3',4',5,6,7-Pentamethoxyflavone (19a). (3,4-Dimethoxyphenyl)propiolic acid (0.100 g, 0.50 mmol) and 3,4,5-trimethoxyphenol (0.092 g, 0.50 mmol) were treated as described with stirring for 4 h at ambient temperature. Following workup, chromatography on silica gel with 50% ethyl acetate–dichloromethane as eluent gave 0.032 g (26%) of **16a** (R_f = 0.35): mp 160 °C; ^{1}H NMR ($CDCl_3$) δ 8.00 (d, 1 H, J = 2 Hz), 7.28 (m, 2 H), 6.90 (dd, 1 H, J = 2, 8), 6.67 (s, 1 H), 4.07 (s, 3 H), 3.945 (s, 3 H), 3.94 (s, 3 H), 3.935 (s, 3 H), 3.89 (s, 3 H); IR (KBr) 1640, 1600, 1510, 1450, 1420, 1350, 1180 cm^{-1}; FDMS, m/z 372 ($C_{20}H_{20}O_7$).

Preparation of 4',5,6,7-Tetramethoxyflavone (20a) and 5,6,7-Trimethoxy-4-(4-methoxyphenyl)coumarin (20b). (4-Methoxyphenyl)propiolic acid (0.352 g, 2.00 mmol) and 3,4,5-trimethoxyphenol (0.370 g, 2.00 mmol) were treated as described with stirring at ambient temperature for 12 h. Following workup,

(30) Brubaker, A. N.; DeRuiter, J.; Whitmer, W. L. *J. Med. Chem.* **1986**, *29*, 1094.

(31) Ahluwalia, V. K.; Kumar, D.; Gupta, M. C. *Indian J. Chem., Sect. B.* **1978**, *16B*, 216.

the products were separated via chromatography on silica gel with 25% ethyl acetate–dichloromethane as eluent. The first product from the column (R_f = 0.6), isolated in 0.050-g yield (10%), was identified as coumarin **20b**. The second product from the column (R_f = 0.35), isolated in 0.132-g yield (19%), was identified as flavone **20a**.

20a: mp 160 °C; ^{1}H NMR ($CDCl_3$) δ 7.81 (d, 2 H, J = 8 Hz), 6.99 (d, 2 H, J = 8 Hz), 6.80 (s, 1 H), 6.60 (s, 1 H), 3.98 (s, 3 H), 3.97 (s, 3 H), 3.91 (s, 3 H), 3.88 (s, 3 H); IR (KBr) 1640, 1600, 1510, 1450, 1420, 1350, 1260, 1210 cm^{-1}; FDMS, m/z 342 ($C_{19}H_{18}O_6$).

20b: mp 92–95 °C; ^{1}H NMR ($CDCl_3$) δ 7.28 (d, 2 H, J = 8 Hz), 6.93 (d, 2 H, J = 8 Hz), 6.73 (s, 1 H), 6.07 (s, 1 H), 3.95 (s, 3 H), 3.88 (s, 3 H), 3.82 (s, 3 H), 3.29 (s, 3 H); IR (KBr) 1720, 1610, 1460, 1360, 1225 cm^{-1}; FDMS, m/z 342 ($C_{19}H_{18}O_6$).

Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.7; H, 5.3. Found: C, 66.4; H, 5.5.

General Procedure for the Preparation of Styrylchromones. A 2-methylchromone and 2 equiv of either 3,5-dimethoxybenzaldehyde or 3,5-bis(benzyloxy)benzaldehyde[28] were stirred with 2 equiv of sodium methoxide in methanol (10 mL/mmol) at reflux for 4 h. The reaction mixture was cooled to ambient temperature, precipitating the styrylchromone, which was collected by filtration. Compound **21** was used without further purification while compounds **22**, **23**, and **37** were purified via chromatography on silica gel with 10% ethyl acetate–dichloromethane as eluent.

5,6,7-Trimethoxy-2-[2-(3,5-dimethoxyphenyl)ethenyl]chromone (21): 89%; mp 148.5–151 °C; ^{1}H NMR ($CDCl_3$) δ 7.43 (d, 1 H, J = 16.0 Hz), 6.78 (s, 1 H), 6.68 (d, 1 H, J = 16.0 Hz), 6.70 (d, 2 H, J = 2.1 Hz), 6.485 (t, 1 H, J = 2.1 Hz), 6.18 (s, 1 H), 3.98 (s, 3 H), 3.97 (s, 1 H), 3.91 (s, 3 H), 3.84 (s, 6 H); IR (KBr) 1635, 1610, 1585, 1455, 1205, 1115 cm^{-1}; FDMS, m/z 398 ($C_{22}H_{22}O_7$).

Anal. Calcd for $C_{22}H_{22}O_7$: C, 66.3; H, 5.6. Found: C, 66.3; H, 5.5.

5,6,7-Trimethoxy-2-[2-[3,5-bis(benzyloxy)phenyl]ethenyl]chromone (22): 91%; mp 165–165.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.3–7.5 (m, 11 H), 6.82 (d, 2 H, J = 2 Hz), 6.79 (s, 1 H), 6.68 (d, 1 H, J = 16 Hz), 6.66 (t, 1 H, J = 2 Hz), 6.18 (s, 1 H), 5.10 (s, 4 H), 4.01 (s, 3 H), 3.99 (s, 3 H), 3.93 (s, 3 H); IR (KBr) 1630, 1610, 1580, 1480, 1450, 1410, 1370, 1250, 1200, 1120 cm^{-1}; FDMS, m/z 550 ($C_{34}H_{30}O_7$).

Anal. Calcd for $C_{34}H_{30}O_7$: C, 74.17; H, 5.49. Found: C, 74.41; H, 5.37.

5,6,7-Trimethoxy-2-[2-[3,4-bis(benzyloxy)phenyl]ethenyl]chromone (23): 89%; mp 155 °C; ^{1}H NMR ($CDCl_3$) δ 7.3–7.5 (m, 11 H), 7.0–7.2 (m, 3 H), 6.80 (s, 1 H), 6.50 (d, 1 H, J = 8 Hz), 6.16 (s, 1 H), 5.25 (s, 4 H), 4.01 (s, 3 H), 4.00 (s, 3 H), 3.94 (s, 3 H); IR (KBr) 1650, 1590, 1510, 1480, 1450, 1410, 1370, 1250, 1200, 1120 cm^{-1}; FDMS, m/z 550 ($C_{34}H_{30}O_7$).

Anal. Calcd for $C_{34}H_{30}O_7$: C, 74.2; H, 5.5. Found: C, 74.2; H, 5.5.

5,6,7,8-Tetramethoxy-2-[2-[3,5-bis(benzyloxy)phenyl]ethenyl]chromone (37): 85%; mp 119 °C; ^{1}H NMR ($CDCl_3$) δ 7.36–7.48 (m, 14 H), 6.82 (d, 2 H, J = 2 Hz), 6.79 (s, 1 H), 6.67 (t, 1 H, J = 2 Hz), 6.20 (s, 1 H), 5.11 (s, 4 H), 4.12 (s, 3 H), 4.04 (s, 3 H), 3.96 (s, 3 H), 3.95 (s, 3 H); IR (KBr) 1630, 1580, 1460, 1420, 1410, 1375, 1160, 1110 cm^{-1}; FDMS, m/z 580 ($C_{35}H_{32}O_8$).

Anal. Calcd for $C_{35}H_{32}O_8$: C, 72.40; H, 5.56. Found: C, 72.61; H, 5.44.

General Procedure for Functionalization at C-3 of Flavones and Styrylchromones. One equivalent of *n*-butyllithium was added to 1 equiv of diisopropylamine in dry THF (5 mL/mmol) cooled to −78 °C under an argon atmosphere. The LDA solution was warmed to 0 °C for 0.5 h and was recooled to −78 °C. The flavone or styrylchromone in dry THF (10 mL/mmol) was added dropwise via syringe to the LDA. The resulting solution was stirred for 1 h at −78 °C before addition of the electrophile.

To introduce a methyl substituent at C-3, the reaction mixture was quenched by the addition of 2 equiv of methyl trifluoromethanesulfonate to the reaction mixture. The resulting solution was warmed to ≈−20 °C and was then poured into water. The product was extracted with ethyl acetate. The extracts were dried over sodium sulfate and concentrated in vacuo. Chromatography on silica gel eluting with 10% ethyl acetate–dichloromethane as eluent gave the methylated products.

5,6,7-Trimethoxy-3-methylflavone (24): 46%; mp 114 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (m, 2 H), 7.53 (m, 3 H), 6.72 (s, 1 H), 4.04 (s, 3 H), 3.96 (s, 1 H), 3.94 (s, 3 H), 2.14 (s, 3 H); IR (KBr) 1620, 1605, 1480, 1460, 1420, 1350, 1250, 1210 cm^{-1}; FDMS, m/z 326 ($C_{19}H_{18}O_5$).

Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.9; H, 5.6. Found: C, 69.8, H, 5.6.

5,7-Dimethoxy-3-methylflavone (25): 73%; 178 °C; ^{1}H NMR ($CDCl_3$) δ 7.65 (m, 2 H), 7.54 (m, 3 H), 6.47 (d, 1 H, J = 2 Hz), 6.38 (d, 1 H, J = 2 Hz), 3.92 (s, 3 H), 3.86 (s, 3 H), 2.09 (s, 3 H); IR (KBr) 1625, 1570, 1490, 1470, 1425, 1350, 1205 cm^{-1}; FDMS, m/z 296 ($C_{18}H_{16}O_4$).

Anal. Calcd for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 72.8; H, 5.6.

5,6,7-Trimethoxy-2-[2-(3,5-dimethoxyphenyl)ethenyl]-3-methylchromone (28): 44%; mp 143.5–145 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (d, 1 H, J = 15.8 Hz), 7.07 (d, 1 H, J = 15.8 Hz), 6.74 (s, 1 H), 6.73 (d, 2 H, J = 2.1 Hz), 6.48 (t, 1 H, J = 2.1 Hz), 3.98 (s, 6 H), 3.90 (s, 3 H), 3.85 (s, 6 H), 2.18 (s, 3 H); IR (KBr) 1625, 1608, 1583, 1460, 1420, 1208 cm^{-1}; FDMS, m/z 412 ($C_{23}H_{24}O_7$).

Anal. Calcd for $C_{23}H_{24}O_7$: C, 66.98; H, 5.87. Found: C, 66.53; H, 5.62.

5,6,7-Trimethoxy-2-[2-[3,5-bis(benzyloxy)phenyl]ethenyl]-3-methylchromone (29): 63%; mp 143 °C; ^{1}H NMR ($CDCl_3$) δ 7.30–7.50 (m, 11 H), 7.05 (d, 1 H, J = 16 Hz), 6.82 (d, 2 H, J = 2 Hz), 6.73 (s, 1 H), 6.65 (s, 1 H), 5.1 (s, 4 H), 3.98 (s, 3 H), 3.978 (s, 3 H), 3.90 (s, 3 H), 2.17 (s, 3 H); IR (KBr) 1620, 1460, 1420, 1380, 1350, 1300, 1280, 1255 cm^{-1}; FDMS, m/z 564 ($C_{35}H_{32}O_7$).

Anal. Calcd for $C_{35}H_{32}O_7$: C, 74.45; H, 5.71. Found: C, 74.82; H, 5.60.

5,6,7,8-Tetramethoxy-2-[2-[3,5-bis(benzyloxy)phenyl]ethenyl]-3-methylchromone (38): 54%; mp 113–115 °C (lit.[11] mp 118 °C); ^{1}H NMR ($CDCl_3$) δ 7.36–7.50 (m, 14 H), 7.04 (d, 1 H, J = 16 Hz), 6.84 (d, 2 H, J = 2 Hz), 6.67 (s, 1 H), 5.11 (s, 4 H), 4.12 (s, 3 H), 4.04 (s, 3 H), 3.97 (s, 3 H), 3.95 (s, 3 H), 2.20 (s, 3 H); IR (KBr) 1620, 1580, 1460, 1420, 1380, 1350, 1210, 1155 cm^{-1}; FDMS, m/z 594 ($C_{36}H_{34}O_8$).

To introduce a 3-hydroxy substituent, the reaction mixture was quenched with a solution of trimethylborate (0.115 mL/mmol) in THF (5 mL/mmol). The resulting solution was stirred 0.5 h at −78 °C. The reaction mixture was acidified with glacial acetic acid (90 mg/mmol), was stirred for 15 min, and was then oxidized with 30% hydrogen peroxide (0.15 mL/mmol). The solution was allowed to warm slowly to room temperature and was then shaken with aqueous saturated sodium bicarbonate solution (50 mL/mmol). The aqueous mixture was extracted with ethyl acetate (4 × 20 mL/mmol). The combined organic extracts were dried over sodium sulfate and concentrated. Chromatography on silica gel with 10% ethyl acetate–dichloromethane as eluent gave the pure 3-hydroxy products.

5,6,7-Trimethoxy-3-hydroxyflavone (26): 51%; mp 164–166 °C; ^{1}H NMR ($CDCl_3$) δ 8.24 (d, 2 H, J = 7.4 Hz), 7.5 (m, 3 H), 7.36 (s, 1 H), 6.82 (s, 1 H), 4.05 (s, 3 H), 4.01 (s, 3 H), 3.94 (s, 3 H); IR (KBr) 3280, 1605, 1480, 1460, 1430, 1390, 1370, 1300, 1260, 1210 cm^{-1}; FDMS, m/z 328 ($C_{18}H_{16}O_6$).

Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.46; H, 4.73.

5,7-Dimethoxy-3-hydroxyflavone (27): 64%; mp 172–174 °C; ^{1}H NMR ($CDCl_3$) δ 8.20 (d, 2 H, J = 8.6 Hz), 7.5 (m, 3 H), 7.42 (d, 1 H, J = 2 Hz), 6.56 (d, 1 H, J = 2 Hz), 3.98 (s, 3 H), 3.91 (s, 3 H); IR (KBr) 3300, 1610, 1560, 1490, 1430, 1370, 1300, 1230, 1210, 1150 cm^{-1}; FDMS, m/z 298 ($C_{17}H_{14}O_5$).

Anal. Calcd for $C_{17}H_{14}O_5$ C, 68.45; H, 4.73. Found: C, 68.16; H, 4.91.

5,6,7-Trimethoxy-3-hydroxy-2-[2-[3,5-bis(benzyloxy)phenyl]ethenyl]chromone (30): 48%; mp 206–208 °C; ^{1}H NMR ($CDCl_3$) δ 7.2–7.5 (m, 12 H), 6.85 (d, 2 H, J = 2 Hz), 6.78 (s, 1 H), 6.62 (t, 1 H, J = 2 Hz), 5.09 (s, 4 H), 4.01 (s, 3 H), 3.99 (s, 3 H), 3.92 (s, 3 H); IR (KBr) 3300, 1600, 1480, 1420, 1360, 1290, 1260, 1200, 1150, 1100 cm^{-1}; FDMS, m/z 566 ($C_{34}H_{34}O_8$).

Anal. Calcd for $C_{34}H_{30}O_8$: C, 72.07; H, 5.34. Found: C, 72.26; H, 5.21.

General Procedure for the C-5 Demethylation and Debenzylation of Styrylchromones 22, 23, 29, and 38. Prepa-

ration of 9 and 34–36. The styrylchromone was dissolved in dichloromethane (5 mL/mmol), and 1.1 equiv of 1.0 M boron trichloride in dichloromethane was added dropwise at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and was then warmed to ambient temperature. The reaction mixture was poured into water, and the products were extracted with either dichloromethane or ethyl acetate. The combined organic extracts were dried over sodium sulfate and concentrated. The products were purified via chromatography on silica gel with 20% methanol–dichloromethane as eluent. The styrylchromones were recrystallized from methanol.

9 (hormothamnione): 89%; mp 268–270 °C (lit.[11] mp 271 °C); ^{1}H NMR ($CDCl_3$, acetone-d_6) δ 12.70 (s, 1 H), 8.04 (s, 2 H), 7.6 (d, 1 H, J = 15.8 Hz), 7.10 (d, 1 H, J = 15.8 Hz), 6.75 (d, 2 H, J = 2 Hz), 6.51 (t, 1 H, J = 2 Hz), 4.11 (s, 3 H), 4.00 (s, 3 H), 3.94 (s, 3 H), 2.17 (s, 3 H) [lit.[11] ^{1}H NMR (THF-d_8) δ 12.8 (s, 1 H), 11.00 (s, 1 H), 8.70 (s, 1 H), 7.55 (d, 1 H, J = 15.7 Hz), 7.17 (d, 1 H, J = 15.7 Hz), 6.58 (d, 2 H, J = 2 Hz), 6.29 (t, 1 H, J = 2 Hz), 4.03 (s, 3 H), 3.93 (s, 3 H), 3.85 (s, 3 H), 2.16 (s, 3 H)]; FDMS, m^+/z 400 ($C_{21}H_{20}O_8$).

6,7-Dimethoxy-5-hydroxy-2-[2-(3,5-dihydroxyphenyl)ethenyl]chromone (31): mp 233–237 °C; ^{1}H NMR ($CDCl_3$, acetone-d_6) δ 12.44 (s, 1 H), 7.92 (s, 1 H), 6.8–7.2 (m, 3 H), 5.8–6.5 (m, 5 H), 3.64 (s, 3 H), 3.51 (s, 3 H); IR (KBr) 3400, 1600, 1490, 1460, 1370, 1290 cm^{-1}; FDMS, m/z 356 ($C_{19}H_{16}O_7$).

6,7-Dimethoxy-5-hydroxy-2-[2-(3,4-dihydroxyphenyl)ethenyl]chromone (32): mp 188–191 °C; ^{1}H NMR ($CDCl_3$, acetone-d_6) δ 12.54 (s, 1 H), 7.8 (br s, 1 H), 7.5 (br s, 1 H), 7.20 (d, 1 H, J = 16 Hz), 6.80 (d, 1 H, J = 2 Hz), 6.68 (dd, 1 H, J = 2, 10 Hz), 6.30 (d, 1 H, J = 16 Hz), 6.297 (s, 1 H), 5.83 (s, 1 H), 3.66 (s, 3 H), 3.54 (s, 3 H); IR (KBr) 3400, 1650, 1600, 1490, 1460, 1370, 1290 cm^{-1}; FDMS, m/z 356 ($C_{19}H_{16}O_7$).

6,7-Dimethoxy-5-hydroxy-2-[2-(3,5-dihydroxyphenyl)ethenyl]-3-methylchromone (33): mp 244–247 °C; ^{1}H NMR ($CDCl_3$, acetone-d_6) δ 12.51 (s, 1 H), 7.9 (br s, 1 H), 7.40 (d, 1 H, J = 16 Hz), 7.00 (d, 1 H, J = 16 Hz), 6.5–6.9 (m, 3 H), 6.15 (s, 1 H), 3.47 (s, 3 H), 3.33 (s, 3 H), 1.65 (s, 3 H); IR (KBr) 3400, 1650, 1600, 1490, 1460, 1350, 1300 cm^{-1}; FDMS, m/z 370 ($C_{20}H_{18}O_7$).

Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.9; H, 4.9. Found: C, 64.8; H, 4.9.

Diels–Alder Cycloaddition Reactions of Isobenzofuran and *o*-Quinodimethane with 1,2-Diheteroethylenes

Stan V. D'Andrea, Jeremiah P. Freeman, and Jacob Szmuszkovicz*

Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556

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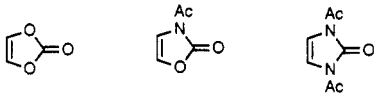
2,3-Diheterotetrahydronaphthalenes are produced efficiently and stereoselectively by the [4 + 2] cycloaddition of *o*-quinodimethane and isobenzofuran with various 1,2-diheteroethylenes.

Isobenzofuran (IBF)[1] and *o*-quinodimethane (QDM)[2] have found extensive use as reactive dienes in intermolecular and intramolecular Diels–Alder reactions for the rapid construction of polycyclic ring systems. The obvious synthetic utility of these highly reactive substrates has prompted research into new methods for their generation and novel usage in [4 + 2] cycloadditions.[3] Although examples of [4 + 2] cycloadditions of these dienes (IBF and QDM) with "electron-poor" and "electron-neutral" dienophiles are abundant, we have uncovered few examples employing "electron-rich" dienophiles, specifically 1,2-diheteroethylenes.[4]

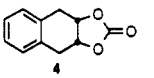
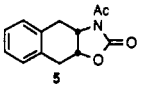
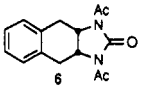
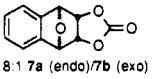
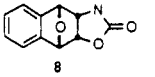
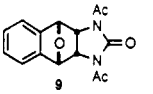
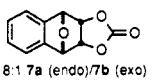
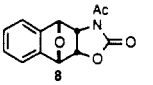
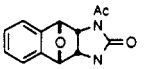
1,2-Diheteroethylenes such as vinylene carbonate (**1**),[5] 4-oxazolin-2-one (**2**),[6] and 1,3-diacetylimidazolin-2-one (**3**)[7]



1 **2** **3**

have been shown to undergo Diels–Alder cycloadditions with substrates such as cyclopentadiene (endo), hexa-

Table I

entry	dienophile	diene or precursor	conditions	product	yield
1			48h, 230°C, Toluene	 **4**	70%
2			48h, 230°C, Toluene	 **5**	90%
3			48h, 230°C, Toluene	 **6**	74%
4			60°C, PhH, 23h	 8:1 **7a** (endo)/**7b** (exo)	79%
5			60°C, PhH, 23h	 **8**	98%
6			100°C, PhH, 18h	 **9**	100%
7			xylenes, 135°, Ac_2O, 24h	 8:1 **7a** (endo)/**7b** (exo)	89%
8			xylenes, 135°, AcOH, 48h	 **8**	93%
9			xylenes, 135°, AcOH, 36h	 **9**	81%

(1) (a) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093. (b) Rickborn, B. *Advances in Theoretically Interesting Molecules*; Thummel, R. P., ed.; JAI Press Inc.: Greenwich, CN, 1989; Vol. I, pp 1–134. (c) Friedrichsen, W. *Adv. Heterocycl. Chem.* **1980**, *26*, 135. (d) Haddadin, M. J. *Heterocycles* **1978**, *9*, 865.

(2) For recent reviews, see: (a) Charlton, J. L.; Alaudin, M. M. *Tetrahedron* **1987**, *43*, 2873. (b) Wong, H. N. C.; Lau, K.-L.; Tam, K.-F. *Top. Curr. Chem.* **1986**, *133*, 85.

(3) (a) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4061. (b) Jung, M. E.; Lam, Y.-S. P.; Mansuri, M.; Speltz, L. M. *J. Org. Chem.* **1985**, *50*, 1087. (c) Carre, M.-C.; Gregoire, B.; Caubere, P. *J. Org. Chem.* **1984**, *49*, 2050. (d) Meegalla, S. K.; Rodrigo, R. *Synthesis* **1989**, 942. (e) Choy, W.; Yang, H. *J. Org. Chem.* **1988**, *53*, 5796.

(4) For one isolated example, see: Newman, M. S. *J. Org. Chem.* **1961**, *26*, 2630.

(5) (a) Scharf, H.; Seidler, H. *Chem. Ber.* **1971**, *104*, 3030. (b) Scharf, H.; Kusters, W. *Chem. Ber.* **1972**, *105*, 564. (c) Russell, G.; Schmitt, K.; Mattox, J. *J. Am. Chem. Soc.* **1975**, *95*, 1882. (d) Hartmann, W. *Chem. Ber.* **1968**, *101*, 1643.

0022-3263/90/1955-4356$02.50/0