Chemoselective Cycloadditions of 3,4-Dialkoxyfurans and Alkyl Coumalates. Novel Loss of Aromaticity of Two Non-Benzenoid Aromatic Rings in a Mild Thermal Process[1]

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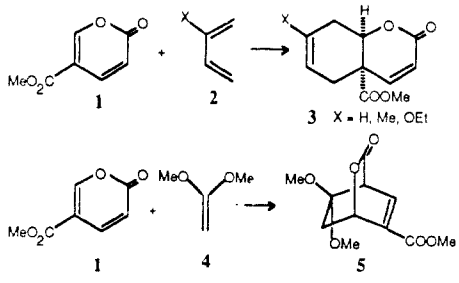
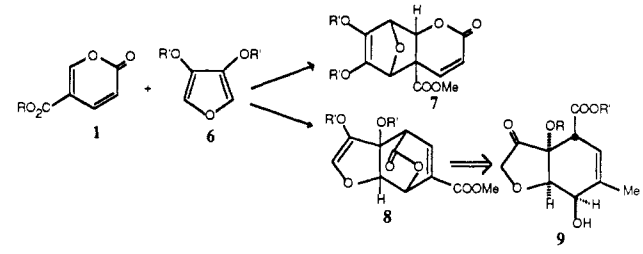
Alkyl coumalates **1** can serve as either dienes or dienophiles in cycloadditions depending on their reaction partners. They have often been used as dienophiles with simple substituted butadienes **2**, giving good yields of the Diels-Alder adducts **3** involving the 5,6-double bond of the pyrone as the dienophile, a useful process for trichothecane synthesis.[3] However, with highly electron-rich olefins, e.g., the ketene acetal **4**, they react as dienes in [4 + 2] cycloadditions affording good yields of the bicyclic lactones **5**.[4]

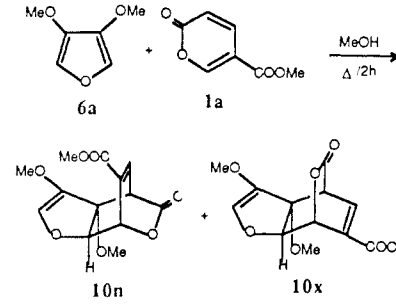


We now report that the reaction of the highly electron-rich dienes 3,4-dialkoxyfurans **6**, with alkyl coumalates **1**, which could proceed by either of two reaction pathways—furan as diene, pyrone as dienophile to give **7** or furan as dienophile, pyrone as diene to furnish **8**—occurs only by the latter route affording the bridged lactones in good yields and with extremely high regioselectivity. It is important to point out that in this reaction the aromaticity of two non-benzenoid aromatic systems are broken in a single thermal cycloaddition under mild conditions. A strong motivation for carrying out this chemistry is the structural similarity of the products, e.g., **8**, to the bottom half of the strongly antiparasitic and anthelmintic compound ivermectin[5] and the hope that a compound such as **8** might serve as a precursor in a short approach to the bottom half component **9**.[6]

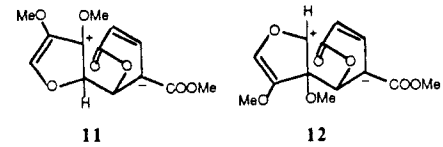
The components for the cycloaddition were easily prepared. 3,4-Dimethoxyfuran (**6a**) was prepared in five steps from diglycolic



acid[7] and methyl coumalate **1a** in two steps from malic acid[8] by the literature routes. Cycloaddition of **1a** and **6a** was effected by refluxing an equimolar solution of the two components in methanol for 2 h. Chromatography on silica gel afforded the two pure stereoisomers in approximately equal amounts in a combined yield of 52%.[9] The high-field ^{1}H NMR spectra of the isolated isomers (Table I) indicated clearly that the isomers possessed the same regiochemistry and only differed in their stereochemistry. This was obvious from the splitting patterns of H_c and H_e, the protons α to the oxygen and carbonyl of the lactone, respectively. H_c appeared as a doublet of doublets, coupled both to H_d and via allylic coupling to H_a, while H_e appeared as a simple doublet in each isomer. This could only be the case if the cycloaddition had occurred with the expected regiochemistry as shown. The stereochemistry of the adducts could not be determined simply from their NMR spectra. However, the less polar fraction from the chromatography, the exo isomer **10x**, proved to be nicely crystalline so that its structure could be assigned as exo by a single-crystal X-ray crystallographic analysis.[10]



This type of cycloaddition is probably not a concerted Diels-Alder reaction but rather the addition of the electron-rich olefin to the pyrone to generate a zwitterion which closes to give the bridged lactone in preference to the cyclobutane.[11] Thus the regiochemistry observed in this addition is that predicted by the expected stability of the regioisomeric zwitterions **11** and **12**. The cation in **11** should be much more stable than that in **12** due to an additional stable resonance contributor.[12]



(1) Presented at the 21st Reaction Mechanisms Conference, Austin, TX, June 1986.

(2) UCLA Gold Shield Faculty Awardee, 1986-1988.

(3) (a) Imagawa, T.; Kawanisi, M.; Sisido, K. *J. Chem. Soc., Chem. Commun.* **1971**, 1292-1293. (b) Imagawa, T.; Sueda, N.; Kawanisi, M. *J. Chem. Soc., Chem. Commun.* **1972**, 388. (c) Imagawa, T.; Sueda, N.; Kawanisi, M. *Tetrahedron* **1974**, *30*, 2227-2232. (d) Imagawa, T.; Nakagawa, T.; Kawanisi, M. Sisido, K. *Bull Chem. Soc. Jpn.* **1979**, *52*, 1506-1512. (e) Nakahara, Y.; Tatsuno, T. *Chem. Pharm. Bull.* **1980**, *28*, 1981-1985. (f) Kraus, G. A.; Frazier, K. *J. Org. Chem.* **1980**, *45*, 4820-4825. (g) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825-4830. (h) White, J. D.; Matsui, T.; Thomas, J. A. *J. Org. Chem.* **1981**, *46*, 3376-3378. (i) Matsui, T.; Inoue, T.; Nakayama, M. White, J. D. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 647-653.

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(5) For recent synthetic work on the avermectin and milbemycins, see: (a) Baker, R.; Swain, C. J.; Head, J. C. *J. Chem. Soc., Chem. Commun.* **1985**, 309-311. (b) Prashad, M.; Fraser-Reid, B. *J. Org. Chem.* **1985**, *50*, 1564-1566. (c) Crimmins, M. T.; Lever, J. G. *Tetrahedron Lett.* **1986**, *27*, 291-292. (d) Hanessian, S.; Ugolini, A.; Dubé, D.; Hodges, P. J.; André, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776-2778. (e) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Dubé, D. *Tetrahedron Lett.* **1986**, *27*, 2699-2702. For older work, see: Jung, M. E.; Street, L. J. *J. Am. Chem. Soc.* **1984**, *106*, 8327-8329 and references therein.

(6) Although the gross molecular skeleton of **8** is very similar to that of **9**, there are still challenges to be met in the conversion of **8** into **9**, especially in the manipulation of the functionality and control of the stereochemistry at C-5 (β-OH).

(7) (a) Iten, P. X.; Hofmann, A. A.; Eugster, C. H. *Helv. Chim. Acta* **1978**, *61*, 430-443. (b) McDonald, E.; Suksamrarn, A.; Wylie, R. D. *J. Chem. Soc., Perkin. Trans. 1* **1971**, 1893-1900.

(8) Methyl coumalate: Boyer, J. H.; Schoen, W. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, pp 532-534. Coumalic acid: Wiley, R. H.; Smith, N. R. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. 4, pp 201-202.

(9) All new compounds exhibited spectral data (500-MHz ^{1}H NMR, IR, MS, and elemental analysis) in full accord with their assigned structures.

(10) We thank Drs. Charles E. Strouse and Carolyn Knobler of the Department of Chemistry at UCLA for their great assistance in obtaining the X-ray crystallographic data, the details of which will be reported elsewhere.

(11) With a 1,1-diarylethylene as the dienophile, the major product is the 6-(2,2-diarylvinyl)-5,6-dihydropyrone-5-carboxylate, the product of internal deprotonation of a zwitterionic intermediate such as **11**.[4a]

(12) Another way to describe the reaction is that it is an electrophilic substitution by the coumalate on the dialkoxyfuran, a process which would certainly occur predominately at the more reactive 2-position of the furan.

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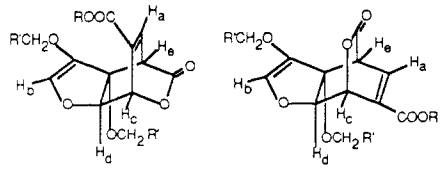
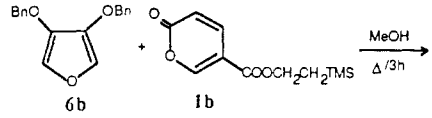
Table I. Selected ^{1}H NMR Data for Cycloadducts[16]



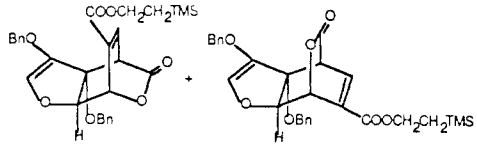
n x

	compound			
	10n	**10x**	**13n**	**13x**
R	Me	Me	$(CH_2)_2Me_3Si$	$(CH_2)_2Me_3Si$
R′	H	H	Ph	Ph
H_a	7.26	7.35	7.17	7.30
H_b	5.95	6.20	6.01	6.25
H_c	5.79	5.84	5.78	5.84
H_d	4.77	4.33	4.81	4.39
H_e	4.00	4.12	4.17	4.27
J_{ae}	6.75	6.1	6.85	6.2
J_{cd}	4.7	2.0	4.7	2.2
J_{ac}	2.4	1.75	2.3	~1.0

In order to test the generality of this novel cycloaddition and to produce compounds more amenable for conversion to the ivermectin bottom half, we prepared two analogous components for additional cycloadditions. A slight modification of the literature route[7] allowed the preparation of 3,4-bis(benzyloxy)furan (**6b**) from diglycolic acid in five steps. Conversion of coumalic acid to its acid chloride ($SOCl_2/\Delta$/6 h/80%) followed by reaction with 2-(trimethylsilyl)ethanol (pyr/Et_2O–THF/−5 to 25 °C/3 h/65%) gave the silylethyl coumalate **1b**. Cycloaddition of **1b** with **6b** as before (MeOH/Δ/3 h) gave a 1:1 mixture of **13n**/**13x** in 38%

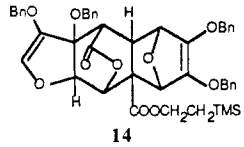


6b 1b



13n 13x

yield with approximately 20% of a 2:1 furan/pyrone adduct being formed for which the structure **14** has been assigned.[13] However,



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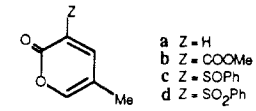
modification of the reaction conditions as follows permitted us to overcome this obstacle. Refluxing a methanol solution containing 10 equiv of **1b** and 1 equiv of **6b** for 3 h followed by silica gel chromatography afforded an 86% yield of **13n** and **13x** in a ratio of 53:47 with only a trace of **14** being produced. In addition this simple chromatography returned 86% of the unreacted coumalate **1b** in pure form for use in further cycloadditions. The strutures of the endo and exo adducts **13n**/**13x** were assigned by the close similarity of their ^{1}H NMR spectra to those of **10n** and **10x**, respectively, especially the coupling constants of H_c and H_e (Table I).

Further attempted cycloadditions of 5-substituted pyrone derivatives highlight the necessity that C-5 not bear an electron-donating group, even a methyl group. For example, 5-methylpyrone and its 2-substituted derivatives **15a–d**[14] were all prepared



a Z = H
b Z = COOMe
c Z = SOPh
d Z = SO_2Ph

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but did not add to **1a** or **1b** under normal conditions (MeOH or $PhCH_3$ at reflux).[15] The use of catalytic Lewis acids in these reactions gave back the coumalates but decomposed the electron-rich furans.

In summary we have demonstrated that two non-benzenoid aromatic systems can lose aromaticity in a single thermal cycloaddition under mild conditions. Further we have shown that a 3,4-dialkoxyfuran prefers to react as a dienophile rather than a diene with alkyl coumalates in a completely regioselective manner. Finally the conversion of some of these intermediates, e.g., **13n**, into compounds, e.g., **9**, which might serve as components for the bottom half of ivermectin is under way and will be reported in due course.

Acknowledgment. We thank the Agricultural Research Division of the American Cyanamid Co. for financial support of the early stages of this work and the National Institutes of Health (GM-31349) for continuing support.

Registry No. 1a, 6018-41-3; **1a** (acid chloride), 23090-18-8; **1a** (acid), 500-05-0; **1b**, 104213-65-2; **6a**, 58928-51-1; **6b**, 53996-40-0; **10n**, 104213-64-1; **10x**, 104319-19-9; **13n**, 104213-66-3; **13x**, 104319-20-2; **14**, 104239-86-3; $HO(CH_2)_2TMS$, 2916-68-9.

(13) Compound **14** is a mixture of stereoisomers, presumably formed by initial reaction in the desired sense to give **13n** and **13x**, followed by Diels–Alder addition of the electron-rich furan to the strained acrylate unit of the product.

(14) 5-Methylpyrone (**15a**) was prepared by a modification of the known route: Takeuchi, Y.; Makino, Y.; Maruyama, K.; Yoshii, E. *Heterocycles* **1980**, *14*, 163–168. The other pyrones, **15b–d**, were all prepared by new routes which will be described in detail elsewhere.

(15) At temperatures much higher than refluxing benzene, elimination of carbon dioxide and a mole of alcohol occurs to produce the alkoxy-substituted benzoate.[4a,c,e] Therefore, the use of higher temperatures was precluded.

(16) Chemical shift data is given in parts per million downfield from internal tetramethylsilane and coupling constants are in hertz. The spectra were recorded at 500 MHz. Other resonances in the spectra are as follows: **10n**, 3.82 (3 H, s), 3.57 (3 H, s), 3.35 (3 H, s); **10x**, 3.83 (3 H, s), 3.61 (3 H, s), 3.24 (3 H, s); **13n**, 7.40–7.26 (10 H, m), 4.69 (2 H, AB q, J = 11.2 Hz), 4.65 (2 H, s), 4.30 (2 H, m), 1.05 (2 H, m), 0.06 (9 H, s); **13x**, 7.40–7.24 (10 H, m), 4.74 (2 H, s), 4.55 (2 H, d, J = 11.5 Hz), 4.46 (2 H, d, J = 11.5 Hz), 4.31 (2 H, m), 1.05 (2 H, m), 0.06 (9 H, s).

Additivity in Complex CD Curves of Multichromophoric Systems

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Interaction of the transition moments of two or more chromophores within a chiral molecule constitutes a coupled oscillator, which gives rise to a split CD curve. The closer the λ_{max} of interacting chromophores, the more efficient the coupling, yet a split CD is observed even when the λ_{max} values differ by as much as 80 nm.[1,2]

In hexopyranoside[3] and trichothecene[4] tri- and tetrabenzoates, and more recently pyranoside benzylates,[5] the amplitudes of split

(1) (a) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257. (b) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy—Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983; p 550ff. (c) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590.

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(3) Lui, H. W.; Nakanishi, K. *J. Am. Chem. Soc.* **1982**, *104*, 1178.

(4) Oltz, E. M.; Nakanishi, K.; Yagen, B.; Corley, D. G.; Rottinghaus, G. E.; Tempesta, M. S. *Tetrahedron* **1986**, *42*, 2615.

(5) Takeda, R.; Nakanishi, K., unpublished results.

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