Reactions of α- and β-Acylated Furans with Conjugated Dienes

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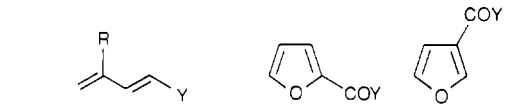
Cycloadditions of isoprene (and 1,3-butadiene and a 1,3-dioxy derivative thereof in one case each) with furfural, methyl α-furoate, β-furaldehyde, methyl β-furoate, methyl 2-methyl-3-furoate, dimethyl 2,4-furandicarboxylate, and 3-formylbenzofuran are described, and structure analysis of their products is presented. Determination of the reaction parameters has led to the conclusion of the β-acylfuran/1,3-diene reaction being an efficient process useful for organic synthesis.

In a recent study of cycloadditions of five-membered, aromatic heterocycles it was shown that β-acylfurans, acting as dienophiles, undergo the Diels–Alder reaction in product yields useful for organic synthesis.[1,2] Furthermore, the earlier observation[3] of the reaction of 1,3-butadiene (**1a**) with an α-acylfuran, i.e. furfural (**2a**), leading to a 2:1 adduct (albeit in low yield) was confirmed.[1] In view of the peculiarity of 2:1 cycloadduct formation a broader investigation of the chemistry of α-acylfurans and of the dissimilarity of behavior of α- and β-acylfurans was undertaken.

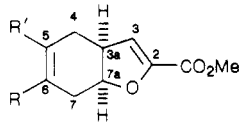


1a: R = Y = H
b: R = Me; Y = H
c: R = OSiMe$_3$; Y = OMe

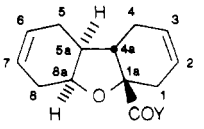
2 **3**

a: Y = H
b: Y = OMe

Despite the expenditure of much effort on the isolation of a 1:1 adduct in the furfural–butadiene reaction, none was observed.[1,4] In contrast, when now 1,3-butadiene (**1a**) (in excess) was caused to react with methyl α-furoate (**2b**) at 195 °C for 72 h, the 1:1 adduct **4a** and the 2:1 adduct **5b** were obtained in 3% yield each (59% of starting ester being recovered). In order to increase the 1:1/2:1 adduct ratio, the reaction was carried out with an excess of ester and under milder conditions (126 °C, 96 h).[3a] This change led to the isolation of esters **4a** and **5b** in 1 and 0.5% yield, respectively, and to the recovery of 94% of starting ester.

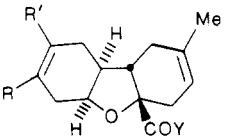


4a: R = R′ = H
b: R = Me; R′ = H
c: R = H; R = Me

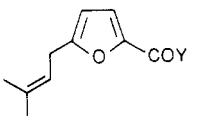


5a: Y = H
b: Y = OMe

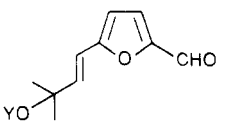
Exposure of methyl α-furoate (**2b**) to isoprene (**1b**) at the elevated temperature led to a ca. 2:1:2:1 mixture of esters **4b**, **4c**, **6a**, and **6b** in 10% yield and to recovery of 85% of furoic ester (**2b**). Under the milder reaction conditions and in the presence of an excess of ester (see above), the cycloaddition furnished recovered starting ester (94%), the aforementioned product mixture (1%), and methyl 5-prenyl-2-furoate (**7b**) (0.2%). Ester **7b** was synthesized independently by C(5)-prenylation of furfural (**2a**) with *N*-methylpiperazine, *n*-butyllithium, and prenyl bromide[5,6] and oxidation of the resultant 5-prenylfurfural (**7a**) (via its cyanhydrin) with manganese dioxide.[7] Intermediate **7a** was unstable in air and was transformed into hydroperoxide **8a**.[8]



6a: R = Me; R′ = H; Y = OMe
b: R = H; R′ = Me; Y = OMe
c: R = Me; R′ = Y = H
d: R = Y = H; R′ = Me

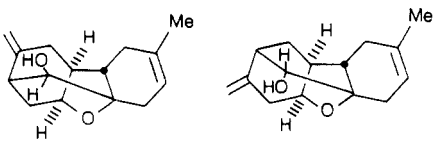


7a: Y = H
b: Y = OMe



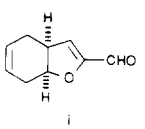
8a: Y = OH
b: Y = H

The two reactions of methyl α-furoate (**2b**) were then carried out with furfural (**2a**). At 195 °C (72 h) the aldehyde and isoprene (**1b**) underwent cycloaddition with the formation of tetracycles **9** (21%) and **10** (20%) (47% of starting aldehyde being recovered), i.e. products of intramolecular heteroene reactions of 2:1 adducts **6c** and **6d**. At 126 °C (96 h; excess aldehyde) the reaction led to a 1:1 mixture (3%) of aldehydes **6c** and **6d** and a 1:1 mixture (25%) of heteroene products **9** and **10** (71% of furfural being recovered). The intermediacy of the aldehyde pair **6c** and **6d** en route to the heteroene products could be proved by the formation of the latter in 87% yield on heating the tricycles at 126 °C (50 h).



9 **10**

(1) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.*, in press.
(2) Nesi, R.; Giomi, D.; Papaleo, S.; Quartara, L. *J. Chem. Soc., Chem. Commun.* **1986**, 1536.
(3) (a) Hillyer, J. C.; Swadesh, S.; Leslie, M. L.; Dunlop, A. P. *Ind. Eng. Chem.* **1948**, *40*, 2216. (b) Hillyer, J. C.; Edmonds, J. T., Jr. *J. Org. Chem.* **1952**, *17*, 600.
(4) In a 3:1:1 furfural–butadiene–water reaction at 204 °C the 2:1 adduct was accompanied by a side product, formulated as a α-hydroxy δ-lactone, whose structure suggested its derivation from 1:1 adduct i.[3b]

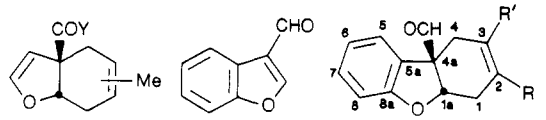


i

(5) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104.
(6) The C(5)-lithiation–prenylation of lithium α-furoate was avoided in view of the report of the lack of success in C(5)-lithiation–geranylation (Knight, D. W.; Nott, A. P. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1125).
(7) Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
(8) (a) Thomas, A. F.; Perret, C. *Tetrahedron* **1986**, *42*, 3311. (b) Wenkert, E.; Greenberg, R. S.; Kim, H.-S. *Helv. Chim. Acta* **1987**, *70*, 2159.

0022-3263/88/1953-5850$01.50/0

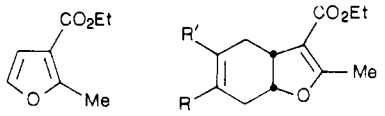
In contrast to the α-acylfurans, their β isomers—β-furaldehyde (**3a**) and methyl β-furoate (**3b**)—have been shown to be excellent dienophiles, e.g. yielding bicycles **11** (74 and 64% yields, respectively) on interaction with isoprene (**1b**).[1] In a similar behavior pattern the reaction (195 °C, 24 h) of 3-formylbenzofuran (**12**) and isoprene (**1b**) now gave a 2:1 mixture (67%) of cycloadducts **13a** and **13b**. In contrast to the β-acylfurans **3** and **12**, ester **14** proved to be a poor dienophile toward isoprene (**1b**), producing (195 °C, 72 h) a 2:1 mixture (10%) of esters **15a** and **15b** (83% of the starting furan being recovered). The blockage of cycloaddition on the acyl side of furan **14** by the methyl group makes this β-acylfuran behave like an α-acylfuran.[9]



11a: Y = H
b: Y = OMe

12

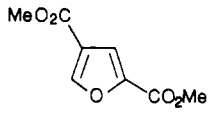
13a: R = Me; R' = H
b: R = H; R' = Me



14

15a: R = Me; R' = H
b: R = H; R' = Me

The most efficient Diels–Alder reaction was that of dimethyl 2,4-furandicarboxylate (**16**) and isoprene (**1b**) (195 °C, 72 h). It afforded a 1:1 mixture (73%) of bicycles **17a** and **17b** and a ca. 1:1 mixture (25%) of tricycles **18a** and **18b**.



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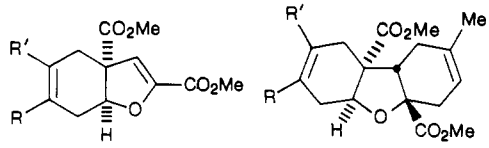


17 **18**

a: R = Me; R' = H. **b**: R = H; R' = Me

Product Structures. Being products of cycloaddition, bicycles **4**, **11**, **15**, and benzobicycles **13** are expected to be cis compounds, and, being products of two consecutive cycloadditions, tricycles **5** and **6** must encompass two sets of vicinal bridgehead cis arrays. The stereochemical relationship of the two bridgehead pairs with respect to each other would be expected to be anti on steric grounds, since the second cycloaddition leading to 2:1 adducts can be predicted to take place on the convex surface of the intermediate 1:1 adduct. This argument is substantiated by the formation of heteroene reaction products **9** and **10**, a reaction feasible only with cis–anti–cis precursors (**6c** and **6d**). Whereas the first reaction of the acylfurans has led to regioisomer mixtures, the tricycle-creating, second cycloaddition (i.e. a Diels–Alder reaction of isoprene with an α-alkoxycrotonaldehyde or α-alkoxycrotonate structure subunit) produced predominantly a single regioisomer with anticipated substitution pattern.[11] The stereochemistry of the hydroxy group in the heteroene addition products (**9** and **10**) is fixed by the steric constraints of the ene reaction. ^1H and ^{13}C NMR spectroscopy aided in the determination of the configuration of the cycloaddition products, with two-dimensional ^1H–^1H COSY[13] and ^1H–^{13}C correlated[13] spectral analysis being especially helpful in this connection.

Discussion

The high reaction rate of the β-acylfurans vs the α-acyl isomers is in line with the much greater reactivity of the double bond adjacent to the electron-withdrawing group in a 1-acyl-1,3-butadiene. The (**2b**) → (**4b**, **4c**, **6a**, **6b**) and (**14**) → (**15a**, **15b**) reactions taking place at comparably low rates indicates that the acyl group on the nonreacting side of the furan ring may aid the reaction by even only an inductive effect. The higher reactivity and regioselectivity of 3-formylbenzofuran (**12**) than β-furaldehyde (**3a**) is in consonance with the difference of behavior between *N*-benzenesulfonylated β-acetylindole and β-acetylpyrrole[1] and suggests that the benzofuran derivative acts nearly as a benzene-decoupled β-oxyacrolein unit. The greater electron-withdrawing properties of the formyl group causes the furanaldehydes to be more reactive than the furancarboxylic esters, the diester **16** being the best substrate of the series (the site selectivity being enhanced by both carbomethoxy groups).

Applications

Whereas the use of the unprecedented diene reaction of β-acylfurans and benzofurans lies in the future, early glimpses of its potential in heterocyclic chemistry and natural product synthesis are discernible at this time. Thus, for example, the ready, high-yielding **12** → **13** conversion points the way to a new route of synthesis of the morphine alkaloids (e.g. morphine (**19**)). The following reaction of diester **16** illustrates the first two steps of a short reaction path to prephenic acid (**20**). Exposure of diester **16** to the dialkoxy diene **1c**[14] at 155 °C for 66 h, followed by silica gel hydrolysis, led to keto ester **22** in 94% yield (based on consumed diester).[15,16] It is noteworthy that there was obtained only a 1:1 adduct, whose structure and yield revealed extraordinary site selectivity, regioselectivity, and diastereoselectivity.[17]

Experimental Section

Infrared spectra of methylene chloride solutions were measured on a Perkin-Elmer 1330 spectrophotometer. ^1H and ^{13}C NMR spectra of deuteriochloroform solutions were recorded on a Nicolet QE-300 spectrometer operating at 300 and 75.5 MHz, respectively,

(9) The interference of the normal behavior of β-acylfurans on introduction of an α-methyl group is reminiscent of the disappearance of Diels–Alder reactivity of 2-cyclohexenones when C(3)-methylated.[10]

(10) Fringuelli, F.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 2802.

(11) Dienophilic acrolein and acrylic acid derivatives with hetero atom electron-donor α-substituents are known to undergo cycloaddition with isoprene (**1b**), yielding predominantly [3]-adducts[12] (Stella, L.; Boucher, J.-L. *Tetrahedron Lett.* **1982**, 953. Uneyama, K.; Takano, K.; Torii, S. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2867. Boucher, J.-L.; Stella, L. *Tetrahedron Lett.* **1985**, *26*, 875).

(12) Angell, E. C.; Fringuelli, F.; Minuti, L.; Pizzo, F.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 5177.

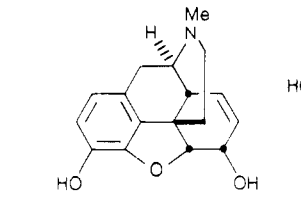
(13) (a) Benn, R.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 350. (b) Bax, A. *Two-Dimensional Nuclear Magnetic Resonance in Liquids*; Delft University: Dordrecht, Netherlands, 1984.

(14) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807.

(15) Fast chromatography of the crude cycloaddition product on silica gel permitted the isolation of enol ether **21** (see the Experimental Section).

(16) β-Elimination, reduction, and hydrolysis are required for conversion of keto ester **22** into prephenic acid (**20**).

(17) The stereochemistry of the methoxy group was based on an NOE experiment: irradiation of the ether *O*-methyl group causes 11% signal enhancement of the bridgehead oxymethine, 1,3-diaxial to it, with reference to the olefinic hydrogen signal.



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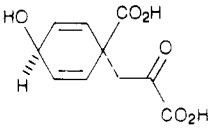

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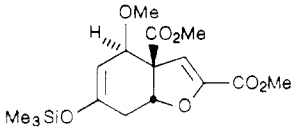
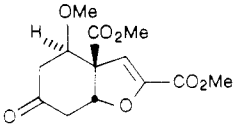


21



22

in the Fourier transform mode. The carbon shifts are in parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. All reactions were carried out in a nitrogen atmosphere. On workup all extracts were washed with brine and dried over magnesium sulfate. Column chromatography was executed on silica gel.

Diels–Alder Reactions. (a) A mixture of 50.0 mmol of acylfuran, 15.0 mmol of diene, and 288 mg (16 mmol) of water was cooled in an ampule at −196 °C, and the latter was sealed. It then was heated in an oil bath at 126 °C for 96 h. The ampule was opened at −196 °C, the unconsumed diene was evaporated, the excess acylfuran was distilled, and the residue was chromatographed.

1a–2b Reaction. Elution with 20:1 hexane–ethyl acetate gave 31 mg (1.1%, based on starting diene) of colorless, liquid ester **4a**: IR (C=O) 1755 (s) cm^{-1}; ^1H NMR δ 1.9–2.6 (m, 4, C-4 and C-7 H's), 3.2–3.4 (m, 1, H-3a), 3.82 (s, 3, OMe), 4.9–5.1 (m, 1 H-7a), 5.79 (d, 1, J = 3 Hz, H-3), 5.8–6.0 (m, 2, H-5, H-6); MS, m/e 180 (M^+, 8), 131 (36), 91 (39), 79 (base), 77 (47), 59 (32); exact mass 180.0796 (calcd for $C_{10}H_{12}O_3$ 180.0785).

Further elution yielded 15 mg (0.5%, based on starting diene) of colorless, liquid ester **5b**: bp 90–92 °C (0.05 Torr); IR (C=O) 1738 (s) cm^{-1}; ^1H NMR δ 1.9–2.6 (m, 10, methylenes, methines), 3.74 (s, 3, OMe), 4.2–4.4 (m, 1, H-8a), 5.7–5.8 (m, 4, olefinic H's); MS, m/e 234 (M^+, 1), 126 (38), 79 (base); exact mass 234.1250 (calcd for $C_{14}H_{18}O_3$ 234.1255).

1b–2b Reaction. Elution with 20:1 hexane–ethyl acetate furnished 5 mg (0.2%, based on starting diene) of colorless, liquid ester **7b**: IR (C=O) 1725 (s), (C=C) 1680 (m), 1598 (m) cm^{-1}; ^1H NMR δ 1.67, 1.76 (s, 3 each, methyls), 3.40 (d, 2, J = 7 Hz, CH_2), 3.87 (s, 3, OMe), 5.32 (t, 1, J = 7 Hz, olefinic H), 6.10 (d, 1, J = 3 Hz, H-4), 7.09 (d, 1, J = 3 Hz, H-3); MS, m/e 194 (M^+, base), 179 (60), 135 (35), 119 (56), 91 (47); exact mass 194.0933 (calcd for $C_{11}H_{14}O_3$ 194.0942).

Further elution afforded 30 mg (1.2%, based on starting diene) of a colorless, liquid 2:1:2:1 mixture of esters **4b**, **4c**, **6a**, and **6b**: IR (**6a,b**) (C=O) 1756 (s) cm^{-1}; (**4b,c**) (C=O) 1737 (s), (C=C) 1640 (m) cm^{-1}; ^1H NMR δ (**4b**) 1.72 (s, 3, Me), 1.8–2.5 (m, 4, C-4 and C-7 H's), 3.3–3.4 (m, 1, H-3a), 3.79 (s, 3, OMe), 4.9–5.1 (m, 1, H-7a), 5.50 (br s, 1, H-5), 5.77 (d, 1, J = 3 Hz, H-3); δ (**4c**) 1.72 (s, 3, Me), 1.8–2.5 (m, 4, C-4 and C-7 H's), 3.3–3.4 (m, 1, H-3a), 3.79 (s, 3, OMe), 5.0–5.1 (m, 1, H-7a), 5.57 (br s, 1, H-6), 5.77 (d, 1, J = 3 Hz, H-3); GC-MS, m/e (**4b,c**) 194 (M^+, 11), 126 (23), 95 (36), 68 (base); exact mass 194.0930 (calcd for $C_{11}H_{14}O_3$ 194.0943); GC–MS, m/e (**6a,b**) 262 (M^+, 1%), 203 (8), 194 (4), 126 (17), 93 (63), 68 (base); exact mass 262.1575 (calcd for $C_{16}H_{22}O_3$ 262.1568).

1b–2a Reaction. Elution with 9:1 hexane–ethyl acetate produced 43 mg (2.8%, based on starting diene) of a colorless, liquid, 1:1 mixture of aldehydes **6c** and **6d**: bp 70–72 °C (0.05 Torr); IR (CHO) 2715 (w), (C=O) 1734 (s) cm^{-1}; ^1H NMR δ 1.70 (s, 3, Me), 1.8–2.5 (m, 10, methylenes, methines), 4.3–4.5 (m, 1, H-8a), 5.40 (br s, 2, H-2, H-6 of **6c**, H-7 of **6d**), 9.54, 9.55 (s, 1, CHO); MS, m/e 232 (M^+, 4), 203 (15), 164 (7), 93 (base), 68 (83); exact mass 232.1445 (calcd for $C_{15}H_{20}O_2$ 232.1462).

Further elution led to 196 mg (12%, based on starting diene) of colorless, oily alcohol **10**: IR (OH) 3516 (m), (C=C) 1643 (m) cm^{-1}; ^1H NMR δ 1.64 (s, 3, Me), 1.7–1.8 (m, 2, C-5 H's), 1.8–1.9 (m, 1, H-4a), 1.9–2.1 (m, 2, C-4 H's), 2.1–2.3 (m, 1, H-5a), 2.2–2.4 (m, 2, C-1 H's), 2.3–2.5 (m, 1, H-8), 2.62 (dd, 1, J = 16, 4 Hz, H-8), 2.76 (br s, 1, H-6), 3.39 (dd, 1, J = 12, 6 Hz, OCH), 4.47 (t, 1, J = 5 Hz, H-8a), 4.98, 5.05 (br s, 1 each, olefinic H's), 5.30 (br s, 1, H-2); ^{13}C NMR δ 23.4 (Me), 28.7 (C-5), 28.9 (C-1), 31.0 (C-4), 33.7 (C-8), 40.7 (C-5a), 44.6 (C-6), 45.2 (C-4a), 73.8 (C-8a), 76.0 (OCH), 82.6 (C-1a), 114.4 (7-CH_2), 117.9 (C-2), 131.1 (C-3), 143.9 (C-7); MS, m/e 232 (M^+, 28), 214 (13), 209 (19), 147 (base), 93 (84); exact mass 232.1454 (calcd for $C_{15}H_{23}O_2$ 232.1462).

Yet further elution liberated 199 mg (13%, based on starting diene) of colorless, oily alcohol **9**: IR (OH) 3512 (w), (C=C) 1645 (w) cm^{-1}; ^1H NMR δ 1.56 (dd, 1, J = 10, 7 Hz, H-4a), 1.66 (s, 3, Me), 1.76 (dt, 1, J = 14, 2 Hz, H-8), 1.8–2.0 (m, 1, H-4), 1.9–2.1 (m, 1, H-8), 2.0–2.1 (m, 1, H-1), 2.17 (d, 1, J = 12 Hz, H-5), 2.1–2.3 (m, 1, H-4), 2.2–2.4 (m, 2, H-5, H-5a), 2.61 (d, 1, J = 19 Hz, H-1), 2.80 (br s, 1, H-7), 3.48 (dd, 1, J = 10, 6 Hz, OCH), 4.3–4.5 (m, 1, H-8a), 4.92, 5.09 (s, 1 each, olefinic H's), 5.34 (br s, 1, H-3); ^{13}C NMR δ 22.9 (Me), 30.4 (C-8), 30.5 (C-4), 31.7 (C-5), 34.5 (C-1), 39.9 (C-4a), 41.8 (C-7), 42.6 (C-5a), 71.8 (OCH), 72.2 (C-8a), 83.2 (C-1a), 113.6 (6-CH_2), 118.7 (C-3), 132.2 (C-2), 145.4 (C-6); MS, m/e 232 (M^+, base), 214 (7), 203 (23), 109 (34), 93 (63); exact mass 232.1460 (calcd for $C_{15}H_{20}O_2$ 232.1462).

A solution of 15 mg (0.061 mmol) of a 1:1 mixture of aldehydes **6c** and **6d** in 0.3 mL of toluene was heated at 126 °C for 50 h and then evaporated. Rapid chromatography and elution with 4:1 hexane–ethyl acetate yielded 13 mg (87%) of a colorless, oily, 1:1 mixture of alcohols **9** and **10**.

(b) A mixture of 5.0 mmol of acylfuran and 60.0 mmol of diene in 1 mL of dry benzene was cooled in an ampule at −196 °C, and the latter was sealed. It then was heated in a phosphoric acid bath at 195 °C for 72 h. The ampule was opened at −196 °C, the excess diene was evaporated, the unconsumed acylfuran was distilled, and the residue was chromatographed.

1a–2b Reaction. Elution with 20:1 hexane–ethyl acetate gave 43 mg (6%, based on consumed **2b**) of colorless, liquid ester **4a** and 64 mg (7%, based on consumed **2b**) of colorless, liquid ester **5b**.

1b–2b Reaction. Elution with 20:1 hexane–ethyl acetate furnished a 2:1:2:1 mixture of 92 mg (63%, based on consumed **2b**) of colorless, liquid esters **4b**, **4c**, **6a**, and **6b**.

1b–2a Reaction. Elution with 9:1 hexane–ethyl acetate produced 232 mg (38%, based on consumed **2a**) of colorless, oily alcohol **10** and 244 mg (40%, based on consumed **2a**) of colorless, oily alcohol **9**.

1b–12[18] Reaction. Elution with 100:1 hexane–ethyl acetate afforded 1.60 g (67%) of a colorless, liquid, 2:1 mixture of **13a** and **13b**: IR (CHO) 2720 (w), (C=O) 1728 (s), (C=C) 1601 (m), cm^{-1}; ^1H NMR δ (**13a**) 1.75 (s, 3, Me), 2.34 (dd, 1, J = 16, 5 Hz, H-4), 2.4–2.5 (m, 2, C-1 H's), 2.6–2.7 (m, 1, H-4), 5.34 (t, 1, J = 5 Hz, H-1a), 5.50 (br s, 1, H-3), 6.77 (d, 1, J = 8 Hz, H-5), 6.88 (m, 1, H-7), 7.07 (d, 1, J = 7 Hz, H-8), 7.18 (m, 1, H-6), 9.66 (s, 1, CHO); δ (**13b**) 1.68 (s, 3, Me), 2.28 (d, 1, J = 15 Hz, H-4), 2.4–2.5 (m, 2, C-1 H's), 2.67 (d, 1, J = 15 Hz, H-4), 5.27 (t, 1, J = 5 Hz, H-1a), 5.50 (br s, 1, H-2), 6.77 (d, 1, J = 8 Hz, H-5), 6.88 (m, 1, H-7), 7.07 (d, 1, J = 7 Hz, H-8), 7.18 (m, 1, H-6), 9.65 (s, 1, CHO); MS, m/e 214 (M^+, 4), 185 (38), 145 (44), 43 (base); exact mass 214.1005 (calcd for $C_{14}H_{14}O_2$ 214.0992).

1b–14[19] Reaction. Elution with 50:1 hexane–ethyl acetate led to 105 mg (56%, based on consumed **14**) of a colorless, liquid, 2:1 mixture of esters **15a** and **15b**: IR (C=O) 1741 (s), (C=C) 1643 (s) cm^{-1}; ^1H NMR δ (**15a**) 1.39 (t, 3, J = 7 Hz, ester Me), 1.71 (s, 3, Me), 2.0–2.4 (m, 4, C-4 and C-7 H's), 2.15 (s, 3, olefinic Me), 3.3–3.4 (m, 1, H-3a), 4.1–4.4 (m, 2, OCH_2), 4.8–4.9 (m, 1, H-7a), 5.44 (br s, 1, H-5); δ (**15b**) 1.38 (t, 3, J = 7 Hz, ester Me), 1.68 (s, 3, Me), 2.0–2.4 (m, 4, C-4 and C-7 H's), 2.14 (s, 3, olefinic Me), 3.2–3.4 (m, 1, H-3a), 4.1–4.4 (m, 2, OCH_2), 4.9–5.0 (m, 1, H-7a), 5.58 (br s, 1, H-6); MS, m/e 222 (M^+, 31), 154 (base), 126 (30), 125 (32), 93 (54); exact mass 222.1246 (calcd for $C_{13}H_{18}O_3$ 222.1254).

1b–16[20] Reaction. Elution with 6:1 hexane–ethyl acetate gave 400 mg (25%) of colorless liquid, 1:1 mixture of esters **18a** and **18b**: IR (C=O) 1732 (s) cm^{-1}; ^1H NMR δ (**18a**) 1.64, 1.67 (s, 3 each, methyls), 2.0–2.6 (m, 8, C-1, C-5 and C-8 H's), 2.6–2.7 (m,

(18) For the preparation of 3-formylbenzofuran (**12**) see: Shafiee, A.; Mohamadpour, M. *J. Heterocycl. Chem.* **1978**, *15*, 481.
(19) Bernary, E. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 493.
(20) Feist, F. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 1992.

1, H-4a), 3.68, 3.74 (s, 3 each, methoxyls), 4.6–4.7 (m, 1, H-8a), 5.2–5.4 (m, 1, H-3), 5.5–5.6 (m, 1, H-6); δ (**18b**) 1.64, 1.67 (s, 3 each, methyls), 2.0–2.6 (m, 8, C-1, C-4, C-5, and C-8 H's), 2.7–2.9 (m, 1, H-4a), 3.70, 3.74 (s, 3 each, methoxyls), 4.6–4.7 (m, 1, H-8a), 5.2–5.4 (m, 1, H-3), 5.4–5.5 (m, 1, H-7); MS, *m/e* 320 (M^+, 1), 261 (10), 152 (base), 151 (65), 68 (53); exact mass 320.1633 (calcd for $C_{18}H_{24}O_5$ 320.1621).

Further elution yielded 920 mg (73%) of a colorless, liquid, 1:1 mixture of esters **17a** and **17b**: IR (C=O) 1742 (s), 1728 (s), (C=C) 1644 (m), 1598 (w) cm^{-1}; ^1H NMR δ (**17a**) 1.79 (s, 3, Me), 2.2–2.4 (m, 3, H-4, C-7 H's), 2.52 (dd, 1, J = 16, 3 Hz, H-4), 3.76, 3.79 (s, 3 each, methoxyls), 5.38 (t, 1, J = 4 Hz, H-7a), 5.5–5.6 (m, 1, H-5), 5.75 (s, 1, H-3); δ (**17b**) 1.73 (s, 3, Me), 2.2–2.4 (m, 1, H-7), 2.22 (d, 1, J = 15 Hz, H-4), 2.35 (d, 1, J = 15 Hz, H-4), 2.5–2.7 (m, 1, H-7), 3.76, 3.79 (s, 3 each, methoxyls), 5.33 (t, 1, J = 4 Hz, H-7a), 5.5–5.6 (m, 1, H-6), 5.75 (s, 1, H-3); MS, *m/e* 252 (M^+, 12), 193 (23), 184 (30), 153 (67), 68 (base); exact mass 252.0991 (calcd for $C_{13}H_{16}O_5$ 252.0996).

(c) 1c–16 Reaction. A mixture of 184 mg (1.0 mmol) of dimethyl 2,4-furandicarboxylate (**16**) and 2.07 g (12.0 mmol) of 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (**1c**) was heated at 150 °C for 66 h and then subjected to Kugelrohr distillation (at 70 °C (0.05 Torr)) for removal of the excess diene. Chromatography of the residue on 50 g of silica gel and elution over a 5-min period with 4:1 hexane–ethyl acetate furnished 92 mg (50%) of starting ester and then 134 mg (94%, based on consumed **16**) of colorless, oily keto ester **22**: IR (C=O) 1742 (s), 1730 (s), (C=C) 1676 (m) cm^{-1}; ^1H NMR δ 2.38 (dd, 1, J = 18, 2 Hz, H-5), 2.79 (dd, 1, J = 18, 4 Hz, H-5), 2.82 (dd, 1, J = 18, 4 Hz, H-7), 2.93 (dd, 1, J = 18, 2 Hz, H-7), 3.27 (s, 3, ether OMe), 3.82, 3.83 (s, 3 each, ester methoxyls), 3.94 (br s, 1, H-4), 5.64 (m, 1, H-7a), 5.92 (s, 1, H-3); MS, *m/e* (M^+, 2), 253 (2), 225 (8), 184 (46), 169 (25), 139 (47), 131 (49), 100 (base), 58 (81); exact mass 284.0878 (calcd for $C_{13}H_{16}O_7$ 284.0893).

Chromatography of 36 mg (0.1 mmol) of diester **21** (see below) on 10 g of silica gel and elution over a 5-min period with 4:1 hexane–ethyl acetate afforded 27 mg (95%) of keto ester **22**.

After repetition of the above **1c–16** reaction the crude reaction mixture was subjected to Kugelrohr distillation (at 70 °C (0.05 Torr)) over a 4-h period, thereby permitting the removal of excess diene (some unconsumed furan diester undergoing sublimation). A solution of the distillation residue in 15 mL of dry hexane was kept at −18 °C for 12 h and then filtered, leading to the recovery of 90 mg (combined precipitate and sublimate) (49%) of diester **16**. Evaporation of the filtrate, rapid chromatography of the residue, and elution with 4:1 hexane–ethyl acetate gave 452 mg of impure ester **21**. Kugelrohr distillation (70 °C (0.05 Torr)) for 5 h removed the impurities and distillation of the residue led to 135 mg (74%, based on consumed **16**) of colorless, oily diester **21**: bp 110–114 °C (0.05 Torr); IR (C=O) 1740 (s), 1730 (s), (C=C) 1652 (m) cm^{-1}; ^1H NMR δ 0.21 (s, 9, $SiMe_3$), 2.44 (d, 1, J = 16 Hz, H-7), 2.80 (ddd, 1, J = 16, 4, 3 Hz, H-7), 3.18 (s, 3, ether OMe), 3.77, 3.78 (s, 3 each, ester methoxyls), 4.10 (d, 1, J = 7 Hz, H-4), 5.0–5.1 (m, 1, H-5), 5.67 (dd, 1, J = 4, 2 Hz, H-7a), 5.72 (s, 1, H-3).

Further elution led to 31 mg (21%, based on consumed **16**) of colorless liquid diester **22**.

5-Prenylfurfural (7a). A solution of 4.12 mL (6.60 mmol) of a 1.6 M hexane solution of *n*-butyllithium was added to a stirring solution of 734 mg (7.34 mmol) of *N*-methylpiperazine in 20 mL of dry tetrahydrofuran at −78 °C. After 0.5 h, 576 mg (0.60 mmol) of furfural (**2a**) (distilled freshly from potassium carbonate) was added, and the mixture was stirred for another 0.5 h. A 1.6 M hexane solution of *n*-butyllithium (3.75 mL, 6.0 mmol) was added, and the mixture was stirred at −35 °C for 6 h (a copious amount of solid precipitating during this time). Prenyl bromide (1.19 g, 8.00 mmol) was added dropwise at −78 °C, and stirring was continued for 1 h. The mixture was allowed to warm to room temperature, poured into 40 mL of vigorously stirring, cold brine, and extracted with methylene chloride. The extract was dried and evaporated. Chromatography of the residue and elution with 20:1 hexane–ethyl acetate led in late fractions to the recovery of 472 mg (82%) of furfural (**2a**) and in early eluates to 118 mg (67%, based on consumed **2a**) of colorless, liquid aldehyde **7a**: bp 65–68 °C (0.05 Torr); IR (CHO) 2724 (w), (C=O) 1676 (s), (C=C) 1585 (m) cm^{-1}; ^1H NMR δ 1.69, 1.76 (s, 3 each, methyls), 3.43 (d, 2, J = 7 Hz, CH_2), 5.32 (m, 1, olefinic H), 6.22 (d, 1, J = 4 Hz, H-4), 7.17 (d, 1, J = 4 Hz, H-3), 9.52 (s, 1, CHO); MS, *m/e* 164 (M^+, 67), 149 (31), 135 (19), 95 (17), 69 (32), 41 (base); exact mass 164.0852 (calcd for $C_{10}H_{12}O_2$ 164.0836).

When kept in an open flask for 72 h aldehyde **7a** (40 mg) underwent a chemical change. Chromatography of the resultant mixture and elution with 1:1 hexane–ethyl acetate yielded 3 mg (7%) of starting aldehyde, 1.5 mg (3%, based on consumed **7a**) of colorless, liquid hydroperoxide **8a** [^1H NMR δ 1.44 (s, 6, methyls), 6.46 (d, 1, J = 4 Hz, H-4), 6.49, 6.66 (d, 1 each, J = 16 Hz, olefinic Hs), 7.22 (d, 1, J = 4 Hz, H-3), 9.58 (s, 1, CHO)], and 6 mg (14%, based on consumed **7a**) of colorless, liquid alcohol **8b**: IR (OH) 3587 (w), (CHO) 2723 (w), (C=O) 1680 (s), (C=C) 1609 (w), 1570 (w) cm^{-1}; ^1H NMR δ 1.42 (s, 6, methyls), 6.41 (d, 1, J = 4 Hz, H-4), 6.52, 6.70 (d, 1 each, J = 16 Hz, olefinic Hs), 7.22 (d, 1, J = 4 Hz, H-3), 9.56 (s, 1, CHO); MS, *m/e* 180 (M^+, 10), 165 (16), 162 (6), 151 (11), 137 (base); exact mass 180.0783 (calcd for $C_{10}H_{12}O_3$ 180.0784).

Methyl 5-Prenyl-2-furoate (7b). A mixture of 33 mg (0.20 mmol) of aldehyde **7a**, 52 mg (1.06 mmol) of sodium cyanide, 19 mg (0.32 mmol) of glacial acetic acid, and 364 mg (4.20 mmol) of manganese dioxide in 1 mL of methanol was stirred at room temperature for 2 h. It was poured into 5 mL of water and extracted with methylene chloride. The extract was dried and evaporated, yielding 35 mg (90%) of ester **7b**, identical in all respects with the above **1b–2b** reaction product.

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Registry No. **1a**, 106-99-0; **1b**, 78-79-5; **1c**, 59414-23-2; **2a**, 98-01-1; **2b**, 611-13-2; **4a**, 117252-27-4; **4b**, 117252-37-6; **4c**, 117252-41-2; **5b**, 117252-38-7; **6a**, 117252-28-5; **6b**, 117252-39-8; **6c**, 117252-42-3; **6d**, 117252-43-4; **7a**, 117252-29-6; **7b**, 117269-19-9; **8a**, 117252-30-9; **8b**, 117252-40-1; **9**, 117269-18-8; **10**, 117269-17-7; **12**, 4687-25-6; **13a**, 117252-31-0; **13b**, 117252-44-5; **14**, 28921-35-9; **15a**, 117252-32-1; **15b**, 117252-45-6; **16**, 1710-13-0; **17a**, 117252-33-2; **17b**, 117252-46-7; **18a**, 117252-34-3; **18b**, 117252-47-8; **20**, 87664-40-2; **21**, 117252-35-4; **22**, 117252-36-5; prenyl bromide, 870-63-3.