CONJUGATE ADDITION OF FURANS TO ENONES OR THEIR SYNTHETIC EQUIVALENTS +

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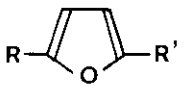
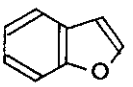
Abstract — Conjugate addition of furans 5 to enones 3 in the presence of an alcohol and boron trifluoride etherate is described. A same reaction product is obtained with hemiacetal vinylogs 1, synthetic equivalents of enones 3. Acidic treatment of adducts 6 and 7 leads to tri- and tetraketones 15 and 16.

The acid-mediated addition of simple furans to enone proceeds in modest yield since this reaction is limited by side reactions such as polymerization of the furans and/or enone. Kraus and Gootschalk[1] have described an elegant way to prepare some of these compounds using furans and γ-iodosilylenol ethers. Nevertheless, with the simplest enone, the methyl vinyl ketone, yields are modest even with the use of high pressure conditions.[2]

We have previously shown that Michaël reaction of enol ether to hemiacetal vinylogs 1 in the presence of boron trifluoride etherate gave 1,5-dicarbonyl compounds.[3] The delocalized cation 2 postulated as intermediate may be also produced by the reaction of a mixture of enone 3 and hydroxy compounds 4 in the presence of the same Lewis acid which gives high or quantitative yields.[4]

In this report, we describe the reaction of enones 3 and alcohol and of hemiacetal vinylogs 1 with furans 5a-f yielding adducts in good yields even with methyl vinyl ketone.





5f

5a R = R' = H

5b R = Me R' = H

5c R = OMe R' = H

5d R = R' = Me

5e R = C(OSiMe$_2$tBu) = CH_2; R' = H

+ Dedicated to Professor G. STORK for his 65th birthday.

With methyl vinyl ketone 3a and alcohol (ethanol or phenylethanol) the 2,5-disubstituted adduct 6a is obtained in high yield (entries 1, 2 table 1) from furan 5a. As previously observed[4] the yield is better than that obtained with hemiacetal vinylog 1a (entry 3).

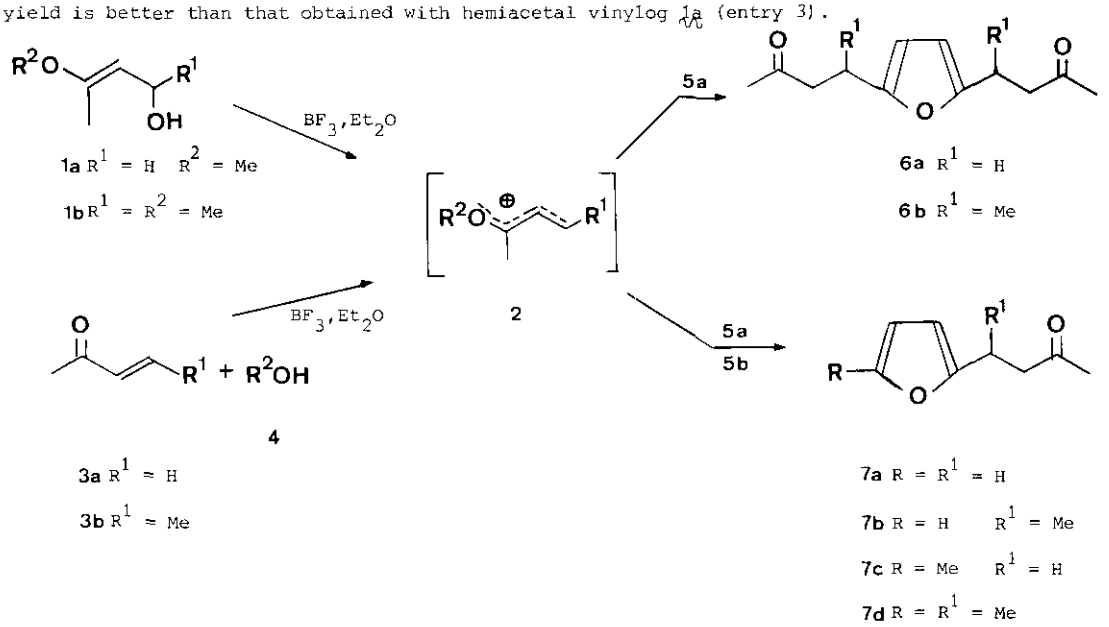


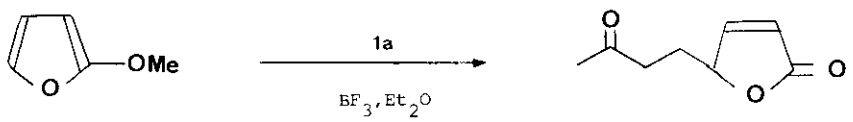
Table 1 : Reaction of furans 5 with hemiacetal vinylogs 1 or with enone 3 and alcohol 4 in the presence of BF_3,Et_2O [a]

Entry	R (in 2-substituted furan)	Reagents [b]	Reagent [c] / furan	Reaction products yield % [d]			
1	H	3a + EtOH	1/1	6a	80	7a	7
2	H	3a + Ph-CH(OH)-Me	1/1	6a	78	7a	7
3	H	1a	1/1	6a	62	7a	7
4	H	3a + EtOH	1/5	6a	48	7a	16
5	H	1a	1/5	6a	10	7a	21
6	Me	3a + EtOH	1/2			7c	79
7	Me	1a	1/2			7c	71
8	H	1b	3/2	6b	69	7b	11
9	Me	1b	1/2			7d	75
10	Me	3b + EtOH	1/2			7d	80
11	H	3b + EtOH	3/2	6b	22	7b	10
12	H	3b + MeOH	3/2	6b	38	7b	10

a : 0.2 eq. of BF_3,Et_2O versus enone 3 or hemiacetal vinylog 1.
b : Equimolar amount of enone 3 and alcohol 4.
c : Number of equivalents of reagents versus furan or 2-methylfuran.
d : Yield of isolated product purified by flash chromatography.

In all cases a small amount (7%) of monosubstituted product 7a (entries 1 - 3) is obtained. This product may be isolated by flash chromatography.[5] Attempts to produce the monoadduct 7a always give a mixture of the two compounds 6a and 7a even with the use of a large excess of furan (entries 4, 5) but in this case the total yield drops. The reagents enone 3a + alcohol 4 or hemiacetal vinylog 1a) also yield the adduct 7c with 2-methylfuran 5b (entries 6, 7). In the same reaction conditions, hemiacetal vinylog 1b gives the diadduct 6b with furan (entry 8) or to the monoadduct 7d with 2-methylfuran (entry 9) in good yields. A comparable yield of compound 7d is observed with the use of penten-3-one-2 3b, ethanol and 2-methylfuran 5b (entry 10). However this enone 3b and ethanol or methanol give lower yields with furan 5a (entries 11, 12). A tentative explanation was based on the rapidity of formation of the postutaled cation 2. From hemiacetal vinylog 1b, cation 2 seems to be produced faster than from enone 3b and alcohol 4. With the first reagent 1b a good reaction is obtained whichever of the two furans is used. However, enone 3b and alcohol 4 only give a good yield when the furan is sufficiently stable in the presence of the Lewis acid.

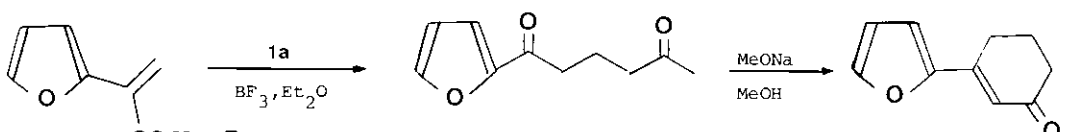
The butenolide 8 is obtained from 2-methoxyfuran 5c, in 48% yield.



5c 8

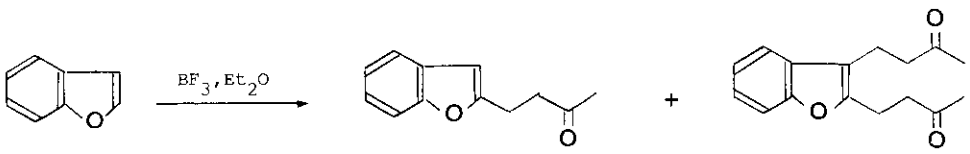
This product is similar to that observed by H. Takei and co-workers[6] from 2-butene-4-olide and methyl vinyl ketone in the presence of a base or from 2-trimethylsilyloxyfuran, methyl vinyl ketone and tin tetrachloride.

For the silylenol ether of 2-acetylfuran 5e two competing reaction centers were present. In the same conditions, the enol ether gives dicarbonyl compound 9 in 50% yield. This diketone is classically cyclized in basic medium in quantitative yield.



5e $OSiMe_2tBu$ 9 10

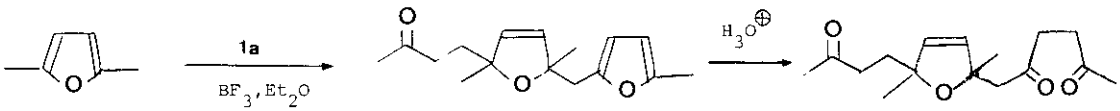
Benzofuran 5f with hemiacetal vinylog 1a or with methyl vinyl ketone 3a and ethanol always gives a mixture of 2- and 2,3-adducts 11a and 11b in quite the same proportion.



5f **11a** **11b**

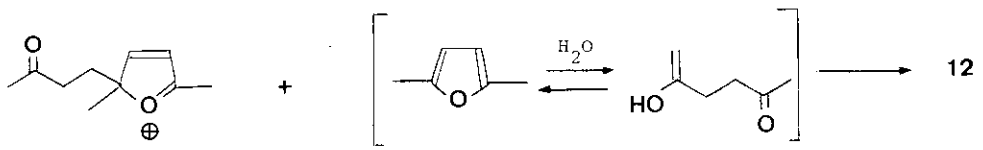
1a	Yield	26 %	31 %
3a + EtOH	Yield	22 %	25 %

With 2,5-dimethylfuran 5d, in which the two electron rich positions are substituted, the formation of compound 12 is observed.



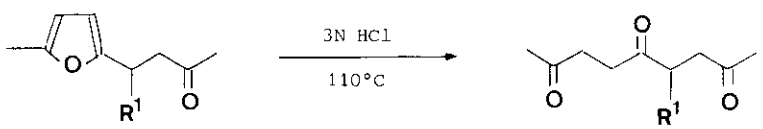
5d **12** **14**

The structure of compound 12 is fully compatible with spectral data and elementary analysis. This result may be explained by the formation of an intermediate oxonium 13 which reacts with the enol of the open form of 2,5-dimethylfuran. Acidic treatment of this compound yields ketone 14 which is in agrement with the proposed structure.



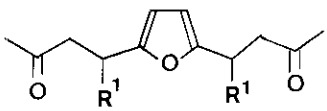
13 **5d**

Acidic treatment of compounds 7c-d leads to the corresponding triketone 15a,b.



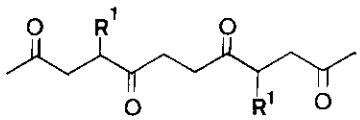
			Reaction time	Yield %
7c	R^1 = H	**15a**	1 h	91
7d	R^1 = Me	**15b**	1.5 h	68

In the same reaction conditions, tetraketone 16a is obtained in excellent yield from furan 6a.



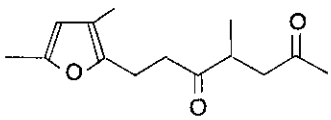
6a R^1 = H

6b R^1 = Me

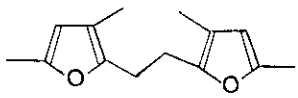


16a R^1 = H

16b R^1 = Me



17



18

Starting material				16	17	18
6a	115°C	0.5 h	%	94		
6b	120°C	6 h	%	10	17	68
6b	20°C	5 d	%	57	15	13

The adduct 6b in similar conditions gives a little tetraketone 16b accompanied by substituted furans 17 and 18. Furan 18 is the major product.

On the other hand, acidic treatment at room temperature (5 days) inverses the proportion of tetraketone 16b and furan 18. No starting material is observed in either case.

The three products 16-18 are easily separated by flash chromatography.[5] With these two conditions furan 17 is always present in the same proportions. In the reaction conditions the tetraketone 16b is cyclized in two steps yielding first furan 17 and then 18. Thus, in this reaction 2,3,5-trisubstituted furan 17 and 18 may be prepared from simple furan.

The synthetic possibilities of these reactions are now in progress.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Perkin Elmer 60 MHz R 12 spectrometer and ^{13}C on a Varian CFT 20 spectrometer. All chemical shifts are reported in δ units downfield from internal TMS in $CDCl_3$ solution otherwise noted. IR spectra (film) were obtained with a Perkin Elmer 237 instrument. Nitromethane is dried on molecular sieves and distilled prior to use. All reactions were conducted under an argon atmosphere.

Example : Reaction of 2-methylfuran 5b with methyl vinyl ketone 3a (entry 6)

To 10 mmol of furan 5b (0.82 g, 2 eq) in 10 ml of nitromethane were added 5 mmol of methyl vinyl ketone (0.35 g) in 5 ml of nitromethane. The mixture was cooled to -20°C and 1 mmol of boron trifluoride etherate solution (123 µl, 0.2 eq.) in 5 mmol of ethanol (0.23 g) were added via syringe with stirring. Stirring was continued for 1 h. The reaction mixture was allowed to warm to -10°C and 5 ml of an aqueous saturated solution of sodium hydrogencarbonate were added.

The mixture was extracted with methylene chloride (4 x 10 ml), dried ($MgSO_4$) and evaporated. Adduct 7c was purified by flash chromatography (ether/petroleum ether : 5/100). Yield : 79 %.

Reaction of 2-methylfuran 5b with hemiacetal vinylog 1a[8] (entry 7)

To 10 mmol of furan 5b (0.82 g, 2 eq) in 10 ml of nitromethane were added 5 mmol of hemiacetal vinylog 1a (0.51 g) in 5 ml of nitromethane. The solution was cooled to -20°C. Boron trifluoride etherate (1 mmol, 123 µl, 0.2 eq) mixed with 31 µl of diethyl ether[8] (BF_3,Et_2O/Et_2O = 4/1 volumic ratio) were introduced via syringe. Stirring was continued for 1 h. Work up was the same as above.

All the experiments are as described above except for some molecular ratios (furan/reagents) which are defined when necessary.

2,5-Di(3-oxobutyl)furan 6a

IR : 1720 cm^{-1} (C=O). ^1H NMR : 2.13 (6 H, s), 2.78 (8 H, s), 5.88 (2 H, s). ^{13}C NMR (C_6D_6): 22.2 (2 x C'_1), 29.2 (2 x C'_4), 41.2 (2 x C'_2), 105.7 (C_3, C_4), 153.3 (C_2, C_5), 206.0 (2 x C'_3).

2,5-Di(1-methyl-3-oxobutyl)furan 6b

IR : 1720 cm^{-1} (C=O). ^1H NMR : 1.22 (6 H, d), 2.13 (6 H, s), 2.7 (4 H, m), 3.30 (2 H, m), 5.90 (2 H, s). ^{13}C NMR : 18.1 (CH_3 at C'_1), 28.2 (C'_1), 29.4 (C'_4), 48.4 (C'_2), 103.4 (C_3 and C_4), 156.5 (C_2 and C_5), 206.0 (C'_3).

2-(3-Oxobutyl)furan 7a

IR : 1720 cm^{-1} (C=O). ^1H NMR : 2.13 (3 H, s), 2.82 (4 H, 2 t), 5.96 (1 H, m), 6.24 (1 H, m), 7.26 (1 H, d). ^{13}C NMR (C_6D_6) : 21.8 (C'_1), 29.4 (C'_4), 41.3 (C'_2), 104.8 (C_3), 109.9 (C_4), 140.7 (C_5), 154.2 (C_2), 206.7 (C'_3).

2-(1-Methyl-3-oxobutyl)furan 7b

IR : 1720 cm^{-1} (C=O). ^1H NMR : 1.27 (3 H, d), 2.10 (3 H, s), 2.72 (2 H, t), 3.3 (1 H, m), 5.98 (1 H, m), 6.25 (1 H, m), 7.29 (1 H, s broad). ^{13}C NMR : 18.7 (CH_3 at C'_1), 28.7 (C'_1), 30.0 (C'_4), 49.0 (C'_2), 103.6 (C_3), 109.8 (C_4), 140.7 (C_5), 158.7 (C_2), 207.0 (C'_3).

5-Methyl-2-(3-oxobutyl)furan 7c

IR : 1720 cm^{-1} (C=O). ^1H NMR : 2.12 (3 H, s), 2.22 (3 H, s), 2.80 (4 H, s), 5.82 (2 H, s). ^{13}C NMR : 12.5 (CH_3 at C_5), 21.5 (C'_1), 28.8 (C'_4), 40.9 (C'_2), 105.0 and 105.3 (C_3 and C_4), 149.5 (C_5), 152.0 (C_2), 206.0 (C'_3).

2-(1-Methyl-3-oxobutyl)5-methylfuran 7d

IR : 1720 cm^{-1} (C=O). ^1H NMR : 1.22 (3 H, d), 2.10 (3 H, s), 2.22 (3 H, s), 2.69 (2 H, m), 3.30 (1 H, m), 5.86 (2 H, s). ^{13}C NMR : 12.6 (CH_3 at C_5), 18.3 (CH_3 at C'_1), 28.3 (C'_1), 29,4 (C'_4), 48.6 (C'_2), 103.8 (C_4), 105.2 (C_3), 149.5 (C_5), 156.5 (C_2), 206.1 (C'_3).

7-Oxo-2-octene-4-olide 8 (Molar ratio 5c/1a = 1.2/1)

IR : 1750-1770, 1720 cm^{-1} (C=O), 1605 cm^{-1} (C=C). ^1H NMR : 2,0 (2 H, m), 2.17 (3 H, s), 2.68 (2 H, m), 5.15 (1 H, m), 6.16 (1 H, dd), 7.66 (1 H, dd). ^{13}C NMR : 25.8 (C_5), 29,0 (C_8), 37.1 (C_6), 81.5 (C_4), 120.4 (C_2), 156.1 (C_3), 172.1 (C_1), 206.3 (C_7).

2-(1,5-Dioxohexyl)furan 9

IR : 1715, 1680 cm^{-1} (C=O). ^1H NMR : 2.0 (3 H, t), 2.15 (3 H, s), 2.58 (2 H, t), 2.88 (2 H, t), 6.62 (1 H, m), 7.3 (1 H, m), 7.68 (1 H, m). ^{13}C NMR : 17.6 (C'_3), 29.4 (C'_6), 36.7 (C'_2), 41.9 (C'_4), 111.7 (C_4), 116.7 (C_3), 146.0 (C_5), 152.0 (C_2), 188.3 (C'_1), 207.7 (C'_5).

3-(2-Furanyl)-2-cyclohexenone 10

IR : 1660 cm^{-1} (C=O). ^1H NMR : 2.5 (6 H, m), 6.5 (2 H, m), 6.80 (1 H, m), 7.60 (1 H, s broad). ^{13}C NMR : 22.1 (C_5), 25.0 (C_4), 37.2 (C_6), 112.0 and 112.3 (C'_3 and C'_4), 120.6 (C_2), 144.7 (C'_5), 146.9 (C'_2), 151.9 (C_3), 199.1 (C_1).

2-(3-Oxobutyl)benzofuran 11a

IR : 1720 cm^{-1} (C=O). ^1H NMR : 2.15 (3 H, s), 2.95 (4 H, m), 6.4 (1 H, s), 7.1-7.65 (4 H, m). ^{13}C NMR : 22.8 (C'_1), 29.9 (C'_4), 42,0 (C'_2), 102.6 (C_3), 111,0, 120.7, 122.8 and 123.6 (C_{4-7}) 129.2 (C_8), 155.0 (C_9), 158.1 (C_2), 206.7 (C'_3). Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; Found : C, 77.0; H, 6.4.

2,3-Di(3-oxobutyl)benzofuran 11b

IR : 1720 cm^{-1} (C=O). ^1H NMR : 2.11 (3 H, s), 2.15 (3 H, s), 2.88 (8 H, m), 7.15-7.6 (4 H, m). ^{13}C NMR : 16.9 and 19.84 (C'_1 and C''_1), 29.2 and 29.4 (C'_4 and C''_4), 40.7 and 42.4 (C'_2 and C''_2), 112.1 (C_3), 110.9, 118.2, 121.6 and 122.8 (C_{4-7}), 128.5 (C_8), 152.4 (C_9), 153.4 (C_2), 206.3 and 207.0 (C'_3 and C''_3). Anal. Calcd for $C_{16}H_{18}O_3$: C, 74.40; H, 7.02; Found C 74.1; H, 6.8.

2,5-Dimethyl-2-(3-oxobutyl)-5-[methylene-5(methyl-2-furanyl)]dihydrofuran 12

IR : 1725 cm^{-1} (C=O), 1570 cm^{-1} (C=C). ^1H NMR : 1.23 (6 H), 1.80 (2 H, m), 2.10 (3 H, s), 2.26 (3 H, s), 2.47 (2 H, m), 2.84 (2 H, s), 5.76 (2 H, m), 5.90 (2 H, m). ^{13}C NMR: 13.25 (CH_3 on furan at C''_5), 26.6 and 27.3 (CH_3 at C_2 and C_5), 29.6 (C'_4), 34.5 (C'_1), 38.9 (C'_2), 41.4 (CH_2 at C_5), 88.7 and 38.9 (C_2 and C_5), 105.8 and 108.0 (C''_3 and C''_4 of furan), 132.2 and 132.8 (C_3 and C_4), 150.2 (C''_2 and C''_5 of furan), 208.4 (C'_3). Anal.Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45; Found C, 73.14; H, 8.55.

2,5-Dimethyl-2-(3-oxobutyl)-5-(2,5-dioxohexyl)dihydrofuran 14

IR : 1720 cm^{-1}. ^1H NMR (CCl_4) : 1.28 (6 H, s), 1.75 (2 H, t), 2.1 (6 H, s broad), 2.4 (2 H, m), 2.62 (6 H, s broad), 5.75 (2 H, m). ^{13}C NMR : 26.3 and 27.4 (CH_3 at C_2 and C_5), 29.5 (C''_6 and C'_4), 34.1 (C'_1), 36.3, 37.7 and 38.6 (C''_3, C''_4, C'_2), 54.9 (C''_1), 87.2 and 88.7 (C_2 and C_5), 132.1 and 132.6 (C_3 and C_4), 206.3 and 206.6 (C''_2 and C''_5), 208.2 (C'_3). Anal.Calcd for $C_{14}H_{24}O_4$: C, 68,54,

H, 8.62; Found C, 68.41; H, 8.58.

Hydrolysis : To 2 mmol of adduct 6 or 7 was added 5 ml of 3N HCl . The reaction mixture was heated to 110°C. The reaction was monitored by TLC. After cooling, ketone was extracted with CH_2Cl_2 (4 x 20 ml). The solution was dried ($MgSO_4$) and ketones 15 and 16 were purified by flash chromatography.

2,5,8- Nonanetrione 15a[7]

IR : 1720 cm^{-1} (C=O). ^1H NMR : 2.11 (6 H, s), 2.67 (8 H, s). ^{13}C NMR : 29.0 (C_1 and C_9), 35.3, 36.2 (C_3, C_4, C_6 and C_7), 206.3 (C_2 and C_8), 207.1 (C_5).

4- Methyl-2,5,8-nonanetrione 15b

IR : 1715 cm^{-1} (C=O). ^1H NMR (CCl_4) : 1.0 (3 H, d), 1.98 (3 H, s), 2.03 (3 H, s), 2.6 (4 H, s broad), 2.6 (3 H, m). ^{13}C NMR (C_6D_6): 16.5 (CH_3 at C_4), 29.4 (C_1 and C_9), 34.9 and 36.7 (C_6 and C_7), 41.0 (C_4), 46.43 (C_3), 206.0 (C_8 or C_2), 206.1 (C_2 or C_8), 211.2 (C_5).

2,5,8,11- Dodecanetetrone 16a[7]

IR : 1715 cm^{-1} (C=O). ^1H NMR : 2.12 (6 H, s), 2.68 (8 H, s); 2.70 (4 H, s). ^{13}C NMR : 29.4 (C_1 and C_{12}), 35.6 (C_4, C_6, C_7 and C_9), 36.5 (C_3 and C_{10}), 206.6 (C_2 and C_{11}), 207.4 (C_5 and C_8).

4,9- Dimethyl-2,5,8,11-dodecanetetrone 16b

IR : 1715 cm^{-1} (C=O). ^1H NMR : 1.10 (6 H, d), 2.11 (6 H, s); 2.2-3.2 (10 H, m). ^{13}C NMR : 16.2 (2 CH_3 at C_4 and C_9), 29.4 (C_1 and C_{12}), 34.1 (C_6 and C_7), 40.5 (C_4 and C_9), 46.1 (C_3 and C_{10}), 206.6 (C_2 and C_{11}), 211.5 (C_5 and C_8).

2-(4-Methyl-3,6-dioxoheptyl)-3,5-dimethylfuran 17

IR : 1715 cm^{-1} (C=O), 1585 cm^{-1} (C=C). ^1H NMR : 1.04 (3 H, d), 1.86 (3 H, s), 2.11 (3 H, s), 2.18 (3 H, s), 2.8 (4 H, s), 2.4-3.1 (3 H, m), 5.7 (1 H, s). ^{13}C NMR : 9.4 (CH_3 at C_3), 13.0 (CH_3 at C_5), 16.1 (CH_3 at C_4'), 19.7 (C_1'), 29.5 (C_7'), 39.4 (C_2'), 40.9 (C_4'), 46.0 (C_5'), 108.5 (C_4), 114.4 (C_3), 147.3 (C_2 or C_5), 148.9 (C_2 or C_5), 206.8 (C_6'), 212.0 (C_3').

1,2-{Di(3,5-dimethyl-2-furanyl)}ethane 18

IR : 1585 cm^{-1} (C=C). ^1H NMR : 1.79 (6 H, s), 2.22 (6 H, s), 2.78 (4 H, s), 5.78 (2 H, s). ^{13}C NMR : 9.2 (CH_3 on C_3' of furan), 13.1 (CH_3 on C_5' on furan), 25.1 (C_1 and C_2), 108.5 (2 C_3'), 114.8 (2 C_4'), 148.0 (C_2' or C_5'), 148.9 (C_2' or C_5').

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