The Birch Reduction of Heterocyclic Compounds. III. [1] Birch Reduction-Elimination Reaction of 2- and 3-Furancarboxylic Acid Derivatives

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Received December 8 1997

The Birch reduction of 2-(1-alkoxyalkyl)furan-3-carboxylic acids **1a-f** gave 2-alkyl-3-furancarboxylic acids **2a-f** with loss of the alkoxyl group in excellent isolated yields.

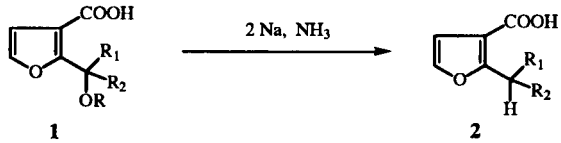
J. Heterocyclic Chem., **35**, 461 (1998).

Although Birch reductive elimination reactions of aromatic compounds [2] have been extensively studied, there are few reports [3] relating to heterocycles. Recently, we found that the Birch reduction of 2-(1-hydroxy or alkoxyalkyl)furan-3-carboxylic acids **1a-f** gave 2-alkyl-3-furancarboxylic acids **2a-f** with loss of the hydroxyl or alkoxyl group in good yields (Scheme 1). Derivatives **1** (R = H) are generally prepared in high yield from 3-furancarboxylic acid and carbonyl compounds using lithium diisopropylamide; however, the yield in alkylation to **2** with alkyl halides is not high (0-42%) [4]. The conversion from **1** (R = H) to the deoxy compound **2** has been carried out using some methods including (i) triethylsilane in trifluoroacetic acid [5], (ii) triphenylphosphine-iodine [6], followed by reduction or dehydrohalogenation and (iii) dehydration of the hydroxyl group or elimination of sulfonates, followed by hydrogenation. All of these methods gave either side products or low yield of the product.

The Birch reduction-elimination reaction of 2- and 3-furancarboxylic acid derivatives was performed with two equivalent atoms of sodium in liquid ammonia at -33°, and the results and the presumed reaction pathway are shown in the Table and Schemes 2-5.

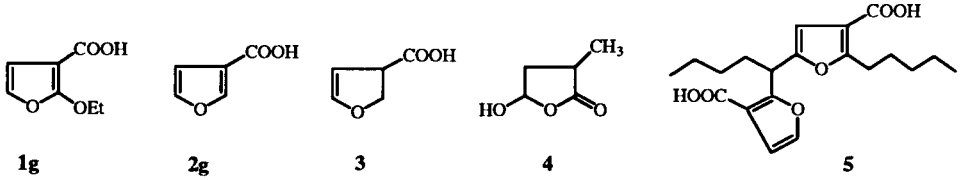
The reactions of 3-furancarboxylic acid derivatives **1a-f** afforded the elimination products **2a-f** in good yields, but 2-furancarboxylic acid derivatives **6** and **8** gave the products **7** and **9** in poor yields, and considerable amounts of the starting materials were recovered. Compound **1a** having a primary methoxyl group yielded a single product **2a** (entry 1). Compounds **1b,d** and **e** having a secondary methoxyl group also gave the products **2b-e** in excellent yields (entries 2-7), respectively. But in the case of hydroxyl group **1c** (R = H) the yields were lower and the recovered material increased. This is because the reactivity of the methoxyl group is superior to that of the hydroxyl group as a leaving group. The alkoxide formation by side reaction of sodium not only with the hydroxyl group (entries 3 and 4) but also with methanol as proton donor (entries 3 and 5) increased the recovered material. In the reduction of **1d** a small amount of dimer **5** was obtained.

Scheme 1

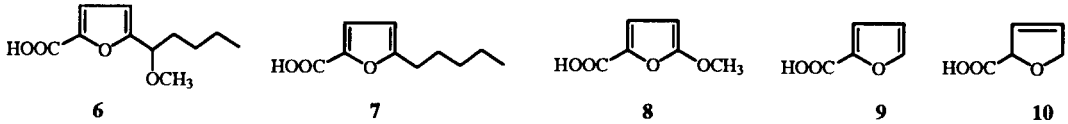


1 **2**

a: $R_1=R_2=H$, $R=CH_3$
b: $R_1=C_3H_7$, $R_2=H$, $R=CH_3$
c: $R_1=C_4H_9$, $R_2=H$, $R=H$
d: $R_1=C_4H_9$, $R_2=H$, $R=CH_3$
e: $R_1=Ph$, $R_2=H$, $R=CH_3$
f: $R_1=R_2=R_3=CH_3$



1g **2g** **3** **4** **5**



6 **7** **8** **9** **10**

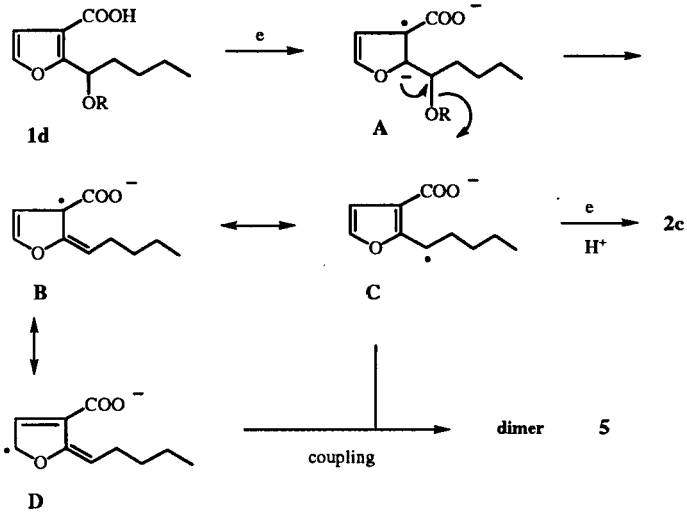
Table

Birch Reduction-elimination of **1a-g**, **6** and **8** with 2 Equivalent Atoms of Sodium

Entry	Compound (R)		Proton donor	Product	% [a]	Recovered% [a]	Others% [a]
1	**1a**	CH_3	none	**2a**	(80)	0	0
2	**1b**	CH_3	none	**2b**	(94)	0	0
3	**1c**	H	methanol	**2c**	(51)	(39)	0
4	**1c**	H	none	**2c**	(38)	(50)	0
5	**1d**	CH_3	methanol	**2d** [b]	82	15	(2) [c]
6	**1d**	CH_3	none	**2d** [b]	(86)	9	5 [c]
7	**1e**	CH_3	none	**2c**	(94)	0	0
8	**1f**	CH_3	none	**2f**	(92)	0	0
9	**1g**	C_2H_5	none	**2g**	20	30	31 [d]
10	**6**	CH_3	none	**7**	26	57	10 [e]
11	**8**	CH_3	none	**9**	8	92	0
12 [f]	**8**	CH_3	none	**9**	5	52	34 [g]

[a] Product compositions were determined by ^1H nmr; parentheses show isolated yields as methylester with diazomethane. [b] **2c** = **2d** [c] Dimer **5**. [d] Hydroxy lactone **4**. [e] Methyl 5-pentyl-2,5-dihydro-2-furancarboxylate (2%) + undetectable (~8%). [f] Lithium metal used. [g] 2,5-Dihydro-2-furancarboxylic acid **10**.

Scheme 2

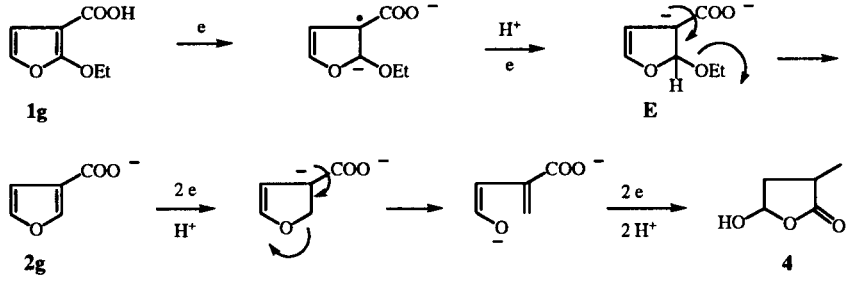


Compound **1f** having a tertiary methoxyl group afforded **2f** in 92% yield (entry 8). As shown in Scheme 2, the methoxyl group would be eliminated from the initial anion radical intermediate **A** to give products *via* the radical **B** and/or **C**, while the radical **C** couples with the radical **D** to produce dimer **5**.

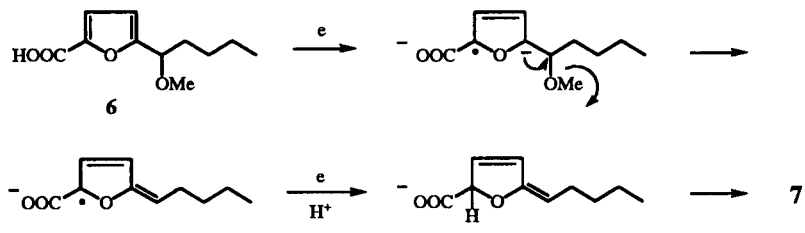
In the case of 2-ethoxy-3-furancarboxylic acid **1g**, the ethoxyl group was removed at the stage of the anion E to give furancarboxylic acid which proceeded with β-elimination and ring opening to afford a hydroxy lactone **4** as a further reduction product. This result shows that the reaction (**2g** → **4**) is faster than the reaction (**1g** → **2g**) (Scheme 3). Since six electrons are consumed in the reduction of **1g** to **4**, the starting material **1g** in some amount is recovered.

On the other hand, **2**-furancarboxylic acid derivatives resist reduction along with by-products. The reaction of **6** gave a complex mixture and a large amount of recovered starting material (Scheme 4, entry 10). Compound **8** was not reduced by sodium, but it was reduced by lithium to give 2,5-dihydro-2-furancarboxylic acid **10** as a further reduction product (entries 11 and 12). The result is also interpreted in the same way mentioned above. Differences in the reduction between 3- and 2-furancarboxylic acids can be explained by assuming the reduction potential [7] of the substrates. In conclusion, the Birch reduction-elimination

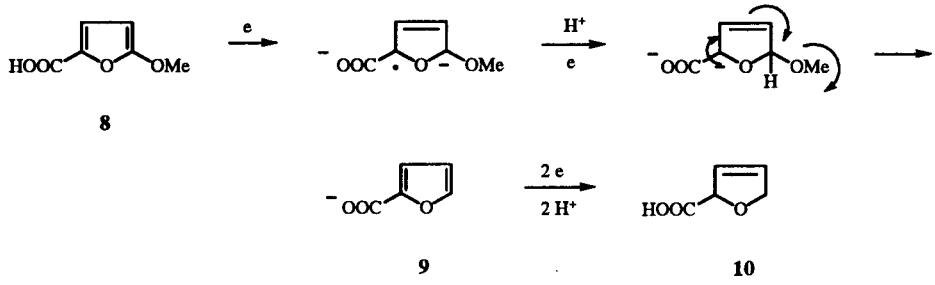
Scheme 3



Scheme 4



Scheme 5



reaction is more advantageous for 3-furancarboxylic acid derivatives than for 2-furancarboxylic acids.

This method is useful for the synthesis of some natural products. Synthetic applications, *e.g.*, methylenolactocin [8] (antitumor antibiotic from *penicillium sp.*) and *trans*-cognac lactone [9] isolated from oak barrels, are currently under investigation and will be reported in due course.

EXPERIMENTAL

Column chromatography was performed with silica gel (Merck NO. 7734; 63-200 μm), and thin-layer chromatography (tlc) was performed on a glass plate coated with Kieselgel 60 GF254 (Merck), followed by detection by uv light. The ir spectra were taken on a JASCO A-102 IR spectrophotometer. The ^1H and ^{13}C nmr (deuteriochloroform), and mass spectra were recorded on JEOL LA-300 (300 MHz) and JEOL AX-500 spectrometers, respectively.

Preparation of **1a-e** and **6**. General Procedure.

The reaction was carried out using a modification of the procedure reported by Knight and Nott [4]. A solution of lithium diisopropylamide was prepared by the addition of *n*-butyllithium (1.6 *N* in *n*-hexane, 35 ml) to a stirred and cooled solution of diisopropylamine (8 ml) in dry tetrahydrofuran (60 ml) at -78° under nitrogen. To this was added a solution of furancarboxylic acid (3.1 g, 27.3 mmoles) in dry tetrahydrofuran (10 ml). The solution was stirred at -78° for 30 minutes. Then electrophile (50 mmoles) was added dropwise during 5 minutes. After stirring for 30 minutes followed by warming to room temperature, the mixture was quenched by the addition of water, and extracted with ether. The water layer was acidified with hydrochloric acid, and extracted with ether. The ether solution was washed with water and brine, dried with sodium sulfate, and concentrated *in vacuo* to give the hydroxy acid. The resulting hydroxy acid was methylated with iodomethane in dimethylsulfoxide in the presence of powdered potassium hydroxide [10]. The methoxymethyl ester thus obtained as above was hydrolyzed with sodium hydroxide in dioxane-water to give the methoxy acid.

2-Methoxymethyl-3-furancarboxylic Acid **1a**.

This compound was prepared from 3-furancarboxylic acid and methoxymethyl chloride in 83% yield, mp 79-80°; ir (nujol); 1680 cm^{-1}; ^1H nmr: δ 3.44 (s, 3H), 4.75 (s, 2H), 6.74 (d, 1H, J = 2.0 Hz), 7.39 (d, 1H, J = 2.0 Hz); ^{13}C nmr: δ 58.6 (q), 64.9 (t), 111.1 (d), 115.9 (s), 142.6 (d), 158.1 (s), 168.4 (s).

Anal. Calcd. for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 54.10; H, 5.17.

2-(1-Methoxybutyl)-3-furancarboxylic Acid **1b**.

This compound was prepared from 3-furancarboxylic acid and 1-butanal in 52% yield, mp 61-62°; ir (nujol): 1680 cm^{-1}; ^1H nmr: δ 0.93 (t, 3H, J = 7.4 Hz), 1.19-1.45 (m, 2H), 1.73-1.98 (m, 2H), 3.31 (s, 3H), 5.01 (t, 1H, J = 7.4 Hz), 6.75 (d, 1H, J = 2.0 Hz), 7.41 (d, 1H, J = 2.0 Hz); ^{13}C nmr: δ 13.8 (q), 18.6 (t), 36.0 (t), 57.0 (q), 74.7 (d), 110.8 (d), 116.0 (s), 142.2 (d), 161.0 (s), 168.8 (s).

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.76; H, 7.11.

2-(1-Hydroxypentyl)-3-furancarboxylic Acid **1c**.

This compound was prepared from 3-furancarboxylic acid and 1-pentanal in 78% yield, mp 50-51°; ^1H nmr: δ 0.89 (t, 3H, J = 6.7 Hz), 1.34 (m, 4H), 1.86 (m, 2H), 5.05 (t, 1H, J = 7.9 Hz), 6.71 (d, 1H, J = 1.8 Hz), 7.31 (d, 1H, J = 1.8 Hz); ^{13}C nmr: δ 14.0 (q), 22.5 (t), 27.6 (t), 35.3 (t), 67.9 (d), 111.4 (d), 113.3 (s), 141.1 (d), 165.1 (s), 169.3 (s).

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H. 7.12. Found: C, 60.31; H, 7.20.

2-(1-Methoxypentyl)-3-furancarboxylic Acid **1d**.

This compound had mp 55-57°; ^1H nmr: δ 0.89 (t, 3H, J = 7.3 Hz), 1.20 (m, 1H), 1.34 (m, 3H), 1.82 (m, 1H), 1.93 (m, 1H), 3.32

(s, 3H), 4.94 (t, 1H, J = 7.0 Hz), 6.76 (d, 1H, J = 1.8 Hz), 7.40 (d, 1H, J = 1.8 Hz); ^{13}C nmr: δ 14.0 (q), 22.5 (t), 27.5 (t), 33.8 (t), 57.2 (q), 75.4 (d), 111.1 (d), 115.9 (s), 142.2 (d), 160.8 (s), 167.8 (s).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.98; H, 7.62.

2-(1-Methoxy-1-phenylmethyl)-3-furancarboxylic Acid **1e**.

This compound was prepared from 3-furancarboxylic acid and benzaldehyde in 66% yield, mp 116-117°; ir (nujol): 1670 cm^{-1}; ^{1}H nmr: δ 3.45 (s, 3H), 6.08 (s, 1H), 6.75 (d, 1H, J = 2.0 Hz), 7.37 (d, 1H, J = 2.0 Hz), 7.28-7.49 (m, 5H); ^{13}C nmr: δ 57.3 (q), 76.7 (d), 110.9 (d), 115.3 (s), 127.0 (d), 128.2 (d), 128.5 (d), 138.1 (s), 142.6 (d), 158.7 (s), 168.6 (s).

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.22; H, 5.20.

2-(1-Methoxy-1-methylethyl)-3-furancarboxylic Acid **1f**.

This compound was prepared from 3-furancarboxylic acid and acetone in 51% yield as an oil; ^{1}H nmr: δ 1.67 (s, 6H), 3.37 (s, 3H), 6.89 (d, 1H, J = 1.8 Hz), 7.32 (d, 1H, J = 1.8 Hz); ^{13}C nmr: δ 25.2 (q), 51.2 (q), 96.1 (s), 113.9 (d), 116.0 (s), 141.0 (d), 159.1 (s), 162.6 (s). ms (m/z): 183 (65, M-CH_3), 166 (45, M-CH_3OH), 151 (70), 135 (100); hrms of methyl ester: Calcd. for $C_9H_{11}O_4$ (M-CH_3)$^+$ 183.0657. Found: m/z 183.0671.

2-Ethoxy-3-furancarboxylic Acid **1g**.

This compound was prepared by Diels-Alder reaction [11] of ethyl propiolate with 5-ethoxy-4-methyloxazole [12] in over all yield of 34%, mp 121-122°; ir (nujol): 3400, 1630, 1130 cm^{-1}; ^{1}H nmr: δ 1.47 (t, 3H, J = 7.1 Hz), 4.48 (q, 2H, J = 7.1 Hz), 6.63 (d, 1H, J = 2.4 Hz), 6.84 (d, 1H, J = 2.4 Hz); ^{13}C nmr: δ 15.0 (q), 67.9 (t), 91.5 (s), 111.8 (d), 132.3 (d), 162.8 (s), 168.1 (s).

Anal. Calcd. for $C_7H_8O_4$: C, 53.85; H, 5.16. Found: C, 53.78; H, 5.14.

5-(1-Methoxypentyl)-2-furancarboxylic Acid **6**.

This compound was prepared from 2-furancarboxylic acid and 1-pentanal in 71% yield as a syrupy oil; ^{1}H nmr: δ 0.89 (t, 3H, J = 7.0 Hz), 1.32 (m, 4H), 1.84 (m, 2H), 3.32 (s, 3H), 4.27 (t, 1H, J = 6.7 Hz), 6.43 (d, 1H, J = 3.7 Hz), 7.28 (d, 1H, J = 3.7 Hz); ^{13}C nmr: δ 13.9 (q), 22.4 (t), 27.4 (t), 34.2 (t), 57.1 (q), 77.0 (d), 109.1 (d), 120.5 (d), 143.1 (s), 161.2 (s), 162.6 (s); hrms: Calcd for $C_{11}H_{16}O_4$: (M$^+$) 212.1048. Found: m/z 212.1048.

5-Methoxy-2-furancarboxylic Acid **8**.

This compound was prepared from methyl 5-bromo-2-furancarboxylate [13] using a modification of the procedure by Maumy *et al* [14] in 49% yield, mp 136-137° (lit [9] mp 136-138° dec); ir (nujol): 1660 cm^{-1}; ^{1}H nmr: δ 3.97 (s, 3H), 5.39 (d, 1H, J = 3.7 Hz), 7.29 (d, 1H, J = 3.7 Hz).

Birch Reduction of Substituted Methoxy Furancarboxylic Acids. General Procedure.

To a solution of the methoxy furancarboxylic acid (5 mmoles in tetrahydrofuran 5 ml) in liquid ammonia (*ca.* 10 ml per mmole of substrate) was added 2 equivalent atoms of sodium little by little with constant stirring under reflux. The mixture was stirred for an additional hour and excess of ammonium chloride was added. After evaporation of liquid ammonia at room temperature, the residue was acidified with hydrochloric acid and extracted with ether (3 x 40 ml). The combined organic extracts were washed with water and brine, and dried with sodium sulfate. Removal of solvent *in vacuo* afforded the product. Some of them, **2a-f**, were isolated as the methyl ester with diazomethane.

2-Methyl-3-furancarboxylic Acid **2a**.

This compound had mp 102° (lit [15] mp 102°), and was identified with the authentic sample prepared from ethyl acetoacetate and chloroacetaldehyde according to the literature [15]; ^{1}H nmr: δ 2.54 (s, 3H), 6.62 (d, 1H, J = 2.0 Hz), 7.19 (d, 1H, J = 2.0 Hz).

2-Butyl-3-furancarboxylic Acid **2b**.

This compound was obtained as a syrupy oil; ^{1}H nmr: δ 0.93 (t, 3H, J = 7.3 Hz), 1.37 (sep, 2H, J = 7.5 Hz), 1.67 (quint, 2H, J = 7.5 Hz), 3.03 (t, 2H, J = 7.5 Hz), 6.68 (d, 1H, J = 2.0 Hz), 7.27 (d, 1H, J = 2.0 Hz); ^{13}C nmr: δ 13.8 (q), 22.3 (t), 27.4 (t), 30.0 (t), 110.9 (d), 112.6 (s), 140.6 (d), 165.0 (s), 170.1 (s); hrms: Calcd. for $C_9H_{12}O_3$: (M+) 168.0786. Found: m/z 168.0801.

2-Pentyl-3-furancarboxylic Acid **2c**.

This compound had mp 34°.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.95; H, 7.80.

Spectral data for the methyl ester of **2c**.

This compound had ^{1}H nmr: δ 0.89 (t, 3H, J = 6.7 Hz), 1.33 (m, 4H), 1.67 (m, 2H), 2.98 (t, 2H, J = 7.9 Hz), 3.81 (s, 3H), 6.62 (d, 1H, J = 1.8 Hz), 7.23 (d, 1H, J = 1.8 Hz); ^{13}C nmr: δ 13.9 (q, C-5'), 22.3 (t, C-4'), 27.5 (t, C- 1'), 27.6 (t, C-2'), 31.3 (t, C-3'), 51.2 (q, CH_3), 110.6 (d, C-4), 112.8 (s, C-3), 140.3 (d, C-5), 163.4 (s, C-2), 164.4 (s, C=O).

2-Benzyl-3-furancarboxylic Acid **2e**.

This compound had mp 104-105°; ir (Nujol): 1670 cm^{-1}; ^{1}H nmr: δ 4.38 (s, 2H), 6.71 (d, 1H, J = 2.0 Hz), 7.30 (d, 1H, J = 2.0 Hz), 7.20-7.35 (m, 5H); ^{13}C nmr: δ 33.6 (t), 110.9 (d), 113.1 (s), 126.7 (d), 128.6 (d), 128.8 (d), 137.0 (s), 141.3 (d), 162.0 (s), 169.3 (s).

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 70.94; H, 4.95.

2-Isopropyl-3-furancarboxylic Acid **2f**.

This compound had mp 78-79° (lit [16] mp 79°); ir (nujol): 1720 cm^{-1}; ^{1}H nmr: δ 1.28 (d, 6H, J = 7.0 Hz), 3.81 (sep, 1H, J = 7.0 Hz), 6.68 (d, 1H, J = 2.0 Hz), 7.27 (d, 1H, J = 2.0 Hz); ^{13}C nmr: δ 20.7 (q), 27.3 (d), 110.8 (d), 111.0 (s), 140.4 (d), 168.8 (s), 170.1 (s).

3-Formyl-2-methylpropanoic Acid: Hydroxy Lactone **4**.

This compound [3b] was isolated as 3-methoxycarbonylbutyraldehyde dimethylacetal by treatment with acetyl chloride in methanol; ir (neat): 1710, 1425, 1170, 1050 cm^{-1}; ^{1}H nmr: δ 1.19 (d, 3H, J = 6.9 Hz), 1.64 (dt, 1H, J = 5.8 Hz, J = 13.9 Hz), 2.03 (dddd, 1H, J = 5.7 Hz, J = 5.8 Hz, J = 13.9 Hz), 2.58 (m, 1H), 3.31 (s, 6H), 3.68 (s, 3H), 4.39 (t, 1H, J = 5.7 Hz), ^{13}C nmr: δ 17.6 (q), 35.5 (d), 36.5 (t), 51.6 (q), 52.9 (q), 53.0 (q), 102.9 (d), 176.6 (s); hrms: Calcd. for $C_7H_{13}O_3$: (M-CH_3O)$^+$ 145.0865. Found: m/z 145.0867.

Methyl 2-Pentyl-5-[1-(3-methoxycarbonylfuran-2-yl)pentyl]-3-furancarboxylate **5**. (Dimer).

This compound had the following spectral data; ^{1}H nmr: δ 0.88 (t, 6H, J = 7.3 Hz), 1.30 (m, 8H), 1.63 (m, 2H), 2.04 (m, 2H), 2.93 (t, 2H, J = 7.3 Hz), 3.78 (s, 3H), 3.84 (s, 3H), 4.93 (t, 1H, J = 7.9

Hz), 6.33 (s, 1H), 6.65 (d, 1H, J = 1.8 Hz), 7.29 (d, 1H, J = 1.8 Hz); ^{13}C nmr: δ 13.9 (q), 14.0 (q), 22.31 (t), 22.33 (t), 27.4 (t), 27.7 (t), 29.4 (t), 31.3 (t), 31.9 (t), 36.9 (d), 51.1 (q), 51.4 (q), 106.5 (d), 110.5 (d), 113.1 (s), 113.7 (s), 141.2 (d), 152.4 (s), 160.4 (s), 162.4 (s), 164.0 (s), 164.5 (s); ms (m/z): 390 (20, M^+), 358(40, M-CH_3O), 333 (100, M-C_4H_9); hrms: Calcd. for $C_{22}H_{30}O_6$: $(M)^+$ 390.2042. Found: m/z 390.2068.

5-Pentyl-2-furancarboxylic Acid **7**.

Spectral data for the methyl ester of **7** are; ^{1}H nmr: δ 0.90 (t, 3H, J = 6.7 Hz), 1.33 (m, 4H), 1.69 (m, 2H), 2.68 (t, 2H, J = 7.6 Hz), 3.87 (s, 3H), 6.11 (d, 1H, J = 3.7 Hz), 7.09 (d, 1H, J = 3.7 Hz); hrms: Calcd. for $C_{11}H_{16}O_3$: (M^+) 196.1099. Found: m/z 196.1093.

2,5-Dihydro-2-furancarboxylic Acid **10**.

This compound was identified with the authentic sample prepared [17] by the Birch reduction of 2-furancarboxylic acid; ^{1}H nmr: δ 4.80 (m, 2H), 5.25 (m, 1H), 5.90 (m, 1H), 6.08 (m, 1H); ^{13}C nmr: δ 76.7 (t), 83.8 (d), 124.1 (d), 129.2 (d), 175.6 (s).

Acknowledgement.

We are grateful to Professor Akio Ichimura (Osaka City University) for the measurements of Cyclic Voltammetry.

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