The Birch Reduction of Heterocyclic Compounds. 11. Birch Reduction and Reductive Alkylation of Furamides

Takamasa Kinoshita*, Daisuke Ichinari and Junko Sinya

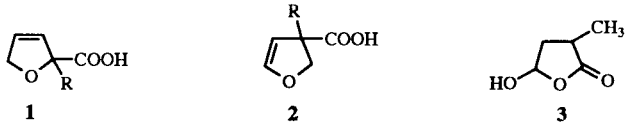
Department of Chemistry, Faculty of Science, Osaka City University, Sumiyoshi-ku, Osaka 558, Japan

Received October 23, 1995

The Birch reduction-alkylation of some *N,N*-dialkylfuramides and its application to the useful intermediates for the natural product synthesis are described.

J. Heterocyclic Chem., **33**, 1313 (1996).

In a previous paper [1], we reported the Birch reduction of 2- and 3-furancarboxylic acids to give 2,5-dihydro-2-furancarboxylic acid **1a** and 2,3-dihydro-3-furancarboxylic acid **2a**, respectively. Birch and Slobbe [2] have reported that the reduction of 2-furancarboxylic acid with lithium in liquid ammonia by the addition of an alkyl halide, instead of quenching by a proton donor, yields the reductive alkylation products **1b**. However, the same reaction of 3-furancarboxylic acid proceeded with β-elimination and ring opening to give a hydroxy lactone **3** in place of the alkylation product (Figure 1) [3].



1

a R = H
b R = alkyl

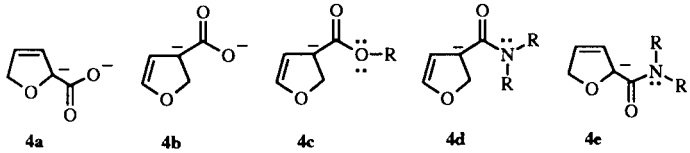
2

a R = H
b R = alkyl

3

Figure 1

Carbanion intermediates **4a-e** generated from two-electron reduction of furancarboxylic acid derivatives in the absence of a proton donor are shown in Figure 2. Differences in the stability of these carbanions can be explained by assuming a repulsive interaction between carbanion and carboxylate anion/lone-pair on the hetero atom. According to these considerations, the dianion **4b** is the most unstable one. As a result facile ring opening was observed because of the strong repulsion to the carboxylate anion (Birch's results). As the interaction with the lone-pairs on the oxygen atom in the anion **4c** is weaker, it is presumed that **4c** is more stable than **4b**. In the previous paper, we reported successful alkylation of intermediate **4c** obtained from methyl 2,3-dihydro-3-furoate with lithium diisopropylamide in tetrahydrofuran at -78° [4].



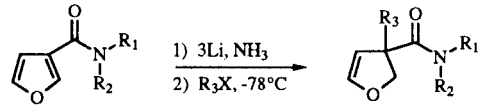
4a **4b** **4c** **4d** **4e**

Figure 2

The amide anion **4d** is evidently the most stable among these carbanions. In view of these observations and our interest in the reduction of heterocyclic compounds, we investigated the Birch reduction-alkylation of 2- and 3-furamides and the results are reported in this paper.

Birch reduction and reductive alkylation of *N,N*-dialkylfuramides were performed with lithium in ammonia-tetrahydrofuran at -78° (Scheme 1). Rapid addition of **5** to lithium (3 equivalents) in ammonia, followed by addition of an alkyl halide within 2 minutes gave *N,N*-dialkyl-3-alkyl-2,3-dihydro-3-furamide **6** in high yield. The reduction products of *N,N*-dimethylamide **5a** and *N,N*-diethylamide **5b** were too unstable to be purified. They decomposed during chromatographic purification. In contrast *N,N*-diisopropylamide **5c** gave a reduction product, isolated by recrystallization.

Scheme 1



5

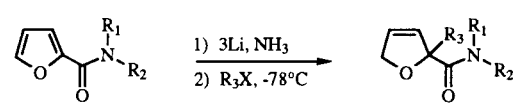
a $R_1 = R_2 = Me$
b $R_1 = R_2 = Et$
c $R_1 = R_2 = i\text{-Pr}$
d $R_1 = OMe$, $R_2 = Me$

6

a $R_1 = R_2 = Me$, $R_3 = H, Me$
b $R_1 = R_2 = Et$, $R_3 = H, Me$
c $R_1 = R_2 = i\text{-Pr}$, $R_3 = H, Me, Et, i\text{-Pr}$, allyl, $PhCH_2$

Reductive methylation of **5a**, **5b** and **5c** afforded 3-methyl-2,3-dihydro-3-furamide **6a** (52%), **6b** (77%) and **6c** (90%), respectively (Scheme 1 and the Table). The reductive alkylation of *N,N*-diisopropyl-2-furamides **7** under the same reaction conditions gave *N,N*-diisopropyl-2-alkyl-2,5-dihydro-2-furamides **8c** (Scheme 2 and the Table).

Scheme 2



7

a $R_1 = R_2 = Me$
b $R_1 = R_2 = Et$
c $R_1 = R_2 = i\text{-Pr}$
d $R_1 = OMe$, $R_2 = Me$

8

a $R_1 = R_2 = Me$, $R_3 = H, Me$
b $R_1 = R_2 = Et$, $R_3 = H, Me$
c $R_1 = R_2 = i\text{-Pr}$, $R_3 = H, Me, Et, i\text{-Pr}$, allyl, $PhCH_2$

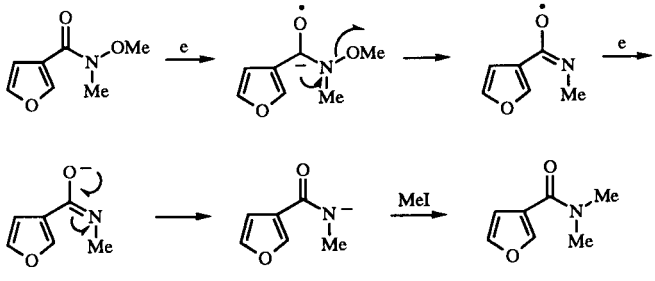
Table

Reductive Alkylation of *N,N*-Dialkyl-3-furamide **5** and *N,N*-Dialkyl-2-furamide **7**

Entry No.	R_3X	**6**	Product Yield (%)	**8**	(%)
1	MeI	a	52		
2	MeI	b	77		
3	MeI	c3	90	c3	76
4	EtI	c4	98	c4	71
5	*i*-Pr	c5	98	c5	62
6	allyl-Br	c6	85	c6	55
7	$PhCH_2I$	c7	92	c7	78
8	CH_3OH	c8	92	c8	41

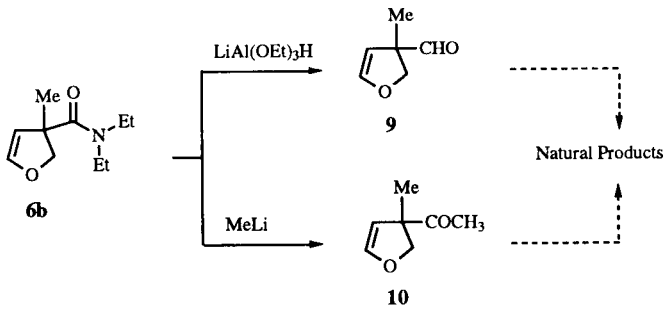
The reductive alkylation of *N*-methoxy-*N*-methyl-3-furamide **5d** proceeded unexpectedly with OMe elimination followed by *N*-alkylation to give *N,N*-dimethyl-3-furamide **5a** (Scheme 3). *N*-Methoxy-*N*-methyl-2-furamide **7d** was also alkylated to give the *N*-alkylation product.

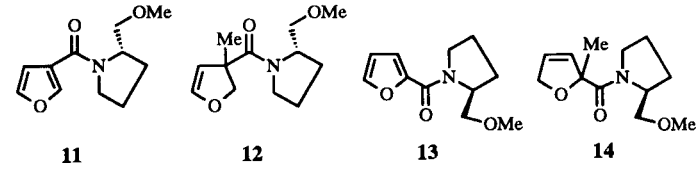
Scheme 3



All these results are in accordance with our expectations based on the considerations mentioned above. For further application of the alkylated 2,3- and 2,5-dihydrofurans obtained as synthetic units in natural product synthesis it was necessary to transform the amide group to other functional groups. Although the best results for reductive alkylations were obtained with *N,N*-diisopropylamides, the products were difficult to convert further. In the case of diethylamide **6b**, reduction with lithium triethoxyaluminium hydride gave aldehyde **9** in 60% yield and substitution with methyllithium gave ketone **10** in 44% yield (Scheme 4).

Scheme 4





11 **12** **13** **14**

Figure 3.

These compounds are versatile synthons for some natural products synthesis. Synthetic applications, *e.g.* hyperolactone (an antimicrobial compound isolated from *H. Chinense. L.* [5]) starting from **9** and **10** are currently under investigation and will be reported in due course.

For the construction of optically active dihydrofuran derivatives, we have studied the Birch reduction-alkylation of the *l*-prolinol derived furamides **11** and **13**. In accord with the literature-based expectation [6], **11** gave a mixture (68:32) of diastereoisomeric dihydrofuran **12** on alkylation with lithium and methyl iodide, while **13** gave a mixture (72:28) of **14**. The product mixture could not be isolated. The diastereomer distribution from each reductive alkylation was determined by gc analysis.

EXPERIMENTAL

All reagents were commercially available (reagent grade) and used without further purification. Diisopropylamine was distilled from calcium hydride. Tetrahydrofuran was dried by distillation from sodium benzophenone ketyl prior to use. Dichloromethane was distilled from phosphorus pentoxide. Melting points were determined on a micro hot-stage and are uncorrected. Column chromatography was performed with silica gel (Merck NO. 7734; 63-200 μm). Analyses gc were performed on a Shimadzu GC-9A chromatograph. The ir spectra were taken on a JASCO A-102 IR spectrophotometer. The nmr spectra (deuteriochloroform) were recorded with a JEOL FX-100 spectrometer.

N,N-Dimethyl-3-furamide **5a**.

A mixture of 3-furoylchloride (11.5 g, 87.8 mmoles) and *N,N*-dimethylformamide (13.5 g, 185 mmoles) were heated at 150° for four hours [7]. Excess dimethylformamide was evaporated, and the solidified residue was recrystallized from ethyl acetate-hexane (1:1, v/v) to give **5a** (9.15 g, 75%), mp 70-71°; ir (nujol): 3100, 1600, 1560, 1520, 1460, 1400, 1160, 870, 760 cm^{-1}; ^1H nmr: δ 3.11 (s, 6H), 6.62 (dd, 1H, J = 1.71 Hz, J = 0.73 Hz), 7.41 (dd, 1H), 7.73 (t, 1H, J = 0.73 Hz); ^{13}C nmr: δ 35.7, 38.5, 110.2 (d), 121.2 (s), 142.4 (d), 143.3 (d), 164.5 (s).

Anal. Calcd. for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.43; H, 6.54; N, 10.01.

N,N-Diethyl-3-furamide **5b**.

To a stirred solution of diethylamine (25 ml, 0.244 mole) and triethylamine (60 ml) in dry dichloromethane (120 ml) at -10° was added a fleshly distilled 3-furoylchloride (15.96 g, 0.122 mole) in dry dichloromethane (30 ml). After stirring overnight at room temperature, the mixture was poured onto ice-water containing hydrochloric acid. The product was extracted with

dichloromethane (3 x 100 ml), then washed with saturated sodium hydrogen carbonate and brine, and concentrated *in vacuo* to give a yellow oil which was purified by distillation to afford **5b** (18.7 g, 91%) as a colourless oil, bp 77-78°/5 mm Hg; ir (neat): 3150, 1620, 1510, 1430, 1220, 880 cm^{-1}; ^1H nmr: δ 1.21 (t, 6H, J = 7.0 Hz), 3.48 (q, 4H, J = 7.0 Hz), 6.59 (bs, 1H), 7.41 (t, 1H, J = 1.8 Hz, J = 1.2 Hz), 7.70 (bs, 1H); ^{13}C nmr: δ 12.5, 14.0, 40.0, 42.5, 110.1 (d, C-4), 121.8 (s, C-3), 142.6 (d, C-2 and C-5), 164.1 (s, C=O).

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.64; H, 7.83; N, 8.37. Found: C, 64.19; H, 7.83; N, 8.33.

N,N-Diisopropyl-3-furamide **5c**.

3-Furoyl chloride (11.7 g) was treated as in the preparation of diethylfuramide **5b** to give **5c** (90% yield) as a colourless crystal, bp 130°/10 mm Hg, mp 44-45° (*n*-hexane); ir (nujol): 3100, 1620, 1570, 1450, 1380, 1340, 1210, 1155, 1040, 875, 750 cm^{-1}; ^1H nmr: δ 1.35 (d, 12H, J = 7.0 Hz), 3.70-4.10 (bs, 2H), 6.51 (bs, 1H), 7.40 (d, 1H, J = 2.0 Hz), 7.62 (bs, 1H); ^{13}C nmr: δ 20.8 (q), 48.2 (d), 109.7 (d), 123.3 (s), 141.9 (d), 142.5 (d), 164.1 (s).

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.72; H, 8.79; N, 7.16.

N-Methoxy-*N*-methyl-3-furamide **5d**.

Pyridine (13.4 g, 0.17 mole) was added dropwise at 0° to a stirred solution of 3-furoylchloride (20.0 g, 0.153 mole) and *N,O*-dimethylhydroxylamine hydrochloride (16.4 g, 0.167 mole) in dry dichloromethane (500 ml). After stirring overnight at room temperature, the reaction mixture was washed with 3*N* hydrochloric acid and then saturated sodium hydrogen carbonate and dried. The solvent was evaporated, and the residue was distilled to give **5d** (17.6 g, 74%) as a colourless oil, bp 75-78°/8 mm Hg, mp 41-42°; ir (nujol): 3180, 3150, 1620, 1560, 1150, 990, 880, 740 cm^{-1}; ^1H nmr: δ 3.34 (s, 3H), 3.71 (s, 3H), 6.87 (s, 1H), 7.42 (s, 1H), 8.03 (s, 1H); ^{13}C nmr: δ 32.7 (q), 61.0 (q), 111.3 (d), 119.7 (s), 142.6 (d), 146.4 (d), 163.1 (s).

Anal. Calcd. for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03: Found: C, 54.21; H, 5.81; N, 9.02.

N,N-Dimethyl-2-furamide **7a**.

This compound was prepared according to the literature [8], mp 45-46° ; ir (nujol): 3100, 1620, 1570, 1500, 1390, 1270, 1160, 1090, 750 cm^{-1}; ^1H nmr: δ 3.19 (s, 6H), 6.47 (t, 1H, J = 0.7 Hz, J = 1.8 Hz), 6.98 (d, 1H, J = 1.8 Hz), 7.50 (d, 1H, J = 0.7 Hz); ^{13}C nmr: δ 37.1, 110.0 (d), 115.8 (d), 143.0 (d), 157.2 (s), 160.1 (s).

N,N-Diisopropyl-2-furamide **7c**.

2-Furoyl chloride 38 g was treated as in the preparation of **6** to give **7c** (53 g, 90%) as viscous oil, bp 86°/3 mm Hg; ir (neat): 3100, 1625, 1570, 1435, 1330, 1200, 1035, 810, 750 cm^{-1}; ^1H nmr: δ 1.37 (d, 12H, J = 7.0 Hz), 3.80-4.10 (bs, 2H), 6.42 (bd, 1H), 6.81 (d, 1H), 7.41 (bs, 1H); ^{13}C nmr: δ 20.6 (q), 47.8 (d), 110.6 (d), 113.6 (d), 142.6 (d), 149.2 (s), 160.0 (s).

Anal. Calcd. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.55; H, 8.75; N, 7.10.

N-Methoxy-*N*-methyl-2-furamide **7d**.

2-Furoyl chloride 8.65 g was treated as in the preparation of **5c** to give **7d** (9.36 g, 92%) as a colourless oil, bp 85-87°/8 mm Hg; mp 38°; ir (nujol): 3160, 3140, 1630, 1560, 1390, 1290, 1165, 980, 930, 770 cm^{-1}; ^1H nmr: δ 3.35 (s, 3H), 3.77 (s, 3H), 6.51 (dd, 1H, J = 3.6 Hz, J = 1.8 Hz), 7.15 (d, 1H, J = 1.8 Hz), 7.60 (bs, 1H); ^{13}C nmr: δ 33.1 (q), 61.3 (q), 111.5 (d), 117.3 (d), 145.1 (d), 145.7 (s), 159.1 (s).

Anal. Calcd. for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.08; H, 5.80; N, 8.99.

Reductive Alkylation of *N,N*-Dialkylfuramides **5a-d** and **7c-d**. General Procedure.

Lithium (210 mg, 3 equivalents) was added to the stirred liquid ammonia (100 ml) in small pieces at -70°. *N,N*-Dialkylfuramide **5** or **7** (10 mmoles) in dry THF (5 ml) was added to the blue solution, followed by alkyl halide (15 mmoles) within 2 minutes, and the resulting yellow solution was stirred for 0.5 hour at -70°. After removal of cooling bath, the mixture was warmed slowly to room temperature while the ammonia was removed with a stream of nitrogen. Saturated ammonium chloride solution (30 ml) was added, and the mixture was extracted with dichloromethane (3 x 40 ml). The combined organic extracts were washed with water (3 x 40 ml) and brine (40 ml) and dried with sodium sulfate. Removal of solvent *in vacuo* afforded the crude product. Silica gel chromatography (hexane-ethyl acetate 4:1) or vacuum distillation gave **6a-c** or **8c** (Table).

N,N-Dimethyl-3-methyl-2,3-dihydro-3-furamide **6a**.

This compound had bp 62° /5 mm Hg; ir (neat): 2950, 1630, 1395, 1115, 1035, 940 cm^{-1}; ^1H nmr: δ 1.42 (s, 3H), 3.00 (bs, 6H), 4.09 (d, 1H, J = 9.2 Hz), 4.78 (d, 1H, J = 9.2 Hz), 5.22 (d, 1H, J = 2.4 Hz), 6.12 (d, 1H, J = 2.4 Hz); ^{13}C nmr: δ 25.7 (q), 37.2 (bq), 53.1 (C-3), 79.4 (C-2), 106.3 (C-4), 145.8 (C-5), 173.8 (C=O).

N,N-Diethyl-3-methyl-2,3-dihydro-3-furamide **6b**.

This compound had bp 73°/5 mm Hg; ir (neat): 2900, 1630, 1420, 1120, 840 cm^{-1}; ^1H nmr: δ 1.07 (s, 3H), 1.15 (s, 3H), 1.35 (s, 3H), 3.2-3.5 (m, 4H), 4.04 (d, 1H, J = 9.2 Hz), 4.73 (d, 1H, J = 9.2 Hz), 5.13 (d, 1H, J = 3.1 Hz), 6.28 (d, 1H, J = 3.1 Hz); ^{13}C nmr: δ 12.5, 14.1, 26.3 (CH_3), 40.5, 41.3, 53.4 (C-3), 79.5 (C-2), 106.6 (C-4), 146.0 (C-5), 173.3 (C=O).

Anal. Calcd. for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.15; H, 9.59; N, 7.36.

N,N-Diisopropyl-2,3-dihydro-3-furamide **6c8**.

This compound had mp 73-74°; ^1H nmr: δ 1.21 (d, 3H, J = 6.6 Hz), 1.25 (d, 3H, J = 6.6 Hz), 1.38 (d, 6H, J = 6.8 Hz), 3.44 (quint, 1H), 3.80-4.19 (m, 2H), 4.36 (t, 1H, J = 10.0 Hz), 4.85 (m, 2H), 6.40 (t, 1H, J = 2.0 Hz); ^{13}C nmr; δ 20.4, 20.6, 20.9, 21.0, 45.9 (C-3), 46.6, 48.1, 71.8 (C-2), 99.1 (C-4), 147.5 (C-5), 170.0 (C=O).

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.95; H, 9.78; N, 7.08.

N,N-Diisopropyl-3-methyl-2,3-dihydro-3-furamide **6c3**.

This compound had mp 34-35°; ^1H nmr: δ 1.22 (d, 6H, J = 6.6 Hz), 1.39 (d, 6H, J = 6.6 Hz), 1.39 (s, 3H, CH_3), 3.32 (quint, 1H), 3.93 (quint, 1H), 4.07 (d, 1H, J = 9.0 Hz), 4.73 (d, 1H, J = 9.0 Hz), 5.17 (d, 1H, J = 2.7 Hz), 6.31 (d, 1H, J = 2.7 Hz); ^{13}C nmr: δ 20.6, 25.9 (CH_3), 46.3, 48.1, 54.2 (C-3), 79.1 (C-2), 106.7 (C-4), 145.6 (C-5), 172.8 (C=O).

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.28; H, 10.02; N, 6.59.

N,N-Diisopropyl-3-ethyl-2,3-dihydro-3-furamide **6c4**.

This compound had bp 80-82°/5 mm Hg; ^1H nmr: δ 0.90 (t, 3H, J = 7.4 Hz), 1.21 (d, 6H, J = 6.6 Hz), 1.40 (d, 6H, J = 6.6

Hz), 1.70 (q, 2H, J = 7.4 Hz), 3.33 (quint, 1H), 3.88 (quint, 1H), 4.14 (d, 1H, J = 9.3 Hz), 4.69 (d, 1H, J = 9.3 Hz), 5.16 (d, 1H, J = 3.0 Hz), 6.33 (d, 1H, J = 3.0 Hz); ^{13}C nmr: δ 9.0 (CH_3), 20.5, 20.6, 31.4 (CH_2), 46.2, 48.1, 59.3 (C-3), 77.0 (C-2), 104.6 (C-4), 145.7 (C-5), 172.1 (C=O).

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.30; H, 10.29; N, 6.22. Found: C, 69.18; H, 10.21; N, 6.19.

N,N-Diisopropyl-3-isopropyl-2,3-dihydro-3-furamide **6c5**.

This compound had mp 68-69°; ^{1}H nmr: δ 0.89 (d, 3H, J = 6.6 Hz), 0.90 (d, 3H, J = 6.6 Hz), 1.20 (d, 6H, J = 6.6 Hz), 1.41 (d, 6H, J = 6.6 Hz), 1.94 (quint, 1H), 3.33 (quint, 1H), 3.80 (quint, 1H), 4.27 (d, 1H, J = 9.5 Hz), 4.54 (d, 1H, J = 9.5 Hz), 5.08 (d, 1H, J = 2.7 Hz), 6.33 (d, 1H, J = 2.7 Hz); ^{13}C nmr: δ 17.3 (*i*-Pr), 18.0 (*i*-Pr), 20.4, 20.6, 20.8, 33.0 (CH), 46.5, 48.2, 63.7 (C-3), 74.5 (C-2), 101.9 (C-4), 145.5 (C-5), 173.0 (C=O).

Anal. Calcd, for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.25; H, 10.50; N, 5.81.

N,N-Diisopropyl-3-allyl-2,3-dihydro-3-furamide **6c6**.

This compound had bp 105-106°/5 mm Hg; ^{1}H nmr: δ 1.23 (d, 6H, J = 6.6 Hz), 1.39 (d, 6H, J = 6.6 Hz), 2.42 (d, 2H, J = 7.1 Hz, CH_2), 3.33 (quint, 1H), 3.91 (quint, 1H), 4.21 (d, 1H, J = 9.3 Hz), 4.63 (d, 1H, J = 9.3 Hz), 4.95-5.90 (m, 3H, CH_2=CH), 5.17 (d, 1H, J = 2.9 Hz), 6.34 (d, 1H,J = 2.9 Hz); ^{13}C nmr: δ 20.6, 20.8, 42.9 (CH_2), 46.6, 48.2, 58.4 (C-3), 76.5 (C-2), 104.8 (C-4), 118.4 (CH_2=CH), 133.1 (CH_2=CH), 146.2 (C-5), 171.7 (C=O).

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.61; H, 9.69; N, 5.85.

N,N-Diisopropyl-3-benzyl-2,3-dihydro-3-furamide **6c7**.

This compound had bp 142-143°/5 mm Hg; ^{1}H nmr: δ 1.16 (d, 3H, J = 6.6 Hz), 1.22 (d, 3H, J = 6.6 Hz), 1.41 (d, 6H, J = 6.6 Hz), 2.99 (q, 2H, J = 5.9 Hz, $PhCH_2$), 3.33 (quint, 1H), 3.95 (quint, 1H), 4.30 (d, 1H, J = 9.3 Hz), 4.56 (d, 1H, J = 9.3 Hz), 5.12 (d, 1H, J = 2.9 Hz), 6.25 (d, 1H, J = 2.9 Hz), 7.21 (m, 5H, arom); ^{13}C nmr: δ 20.5, 20.7, 44.3 ($PhCH_2$), 46.6, 48.2, 59.8 (C-3), 76.8 (C-2), 105.2 (C-4), 126.7, 128.0, 130.1, 136.6, 146.0 (C-5), 172.1 (C=O).

Anal. Calcd. for $C_{18}H_{25}NO_2$ C, 75.22; H, 8.77; N, 4.87. Found: C, 75.24; H, 8.73; N, 4.84.

N,N-Diisopropyl-2,5-dihydro-2-furamide **8c8**.

This compound had mp 89-90 ; ^{1}H nmr: δ 1.22 (d, 6H, J = 6.6 Hz), 1.40 (d, 6H, J = 6.8 Hz), 3.44 (quint, 1H), 4.22 (quint, 1H), 4.73 (m, 2H), 5.41 (m, 1H), 5.90 (m, 1H), 6.02 (m, 1H); ^{13}C nmr: δ 20.5, 20.9, 46.0, 48.0, 76.2 (C-5), 85.1 (C-2), 125.7 (C-3), 128.4 (C-4), 169.5 (C=O).

Anal. Calcd. for $C_{11}H_{19}NO_2$ C, 66.97; H, 9.71; N, 7.10. Found: C, 67.07; H, 9.68; N, 7.07.

N,N-Diisopropyl-2-methyl-2,5-dihydro-2-furamide **8c3**.

This compound had mp 34-35°; ^{1}H nmr: δ 1.16 (d, 3H, J = 6.4 Hz), 1.19 (d, 3H, J = 6.6 Hz), 1.36 (d, 3H, J = 6.6 Hz), 1.40 (d, 3H, J = 6.6 Hz), 1.50 (s, 3H, CH_3), 3.35 (quint, 1H), 4.66 (bs, 2H), 4.80 (quint, 1H), 5.81 (d, 1H, J = 6.0 Hz), 6.10 (dt, 1H, J = 6.0 Hz, J = 2.0 Hz); ^{13}C nmr: δ 20.5, 25.4 (CH_3), 46.3, 48.1, 75.6 (C-5), 93.1 (C-2), 124.5 (C-3), 133.7 (C-4), 172.6 (C=O).

Anal. Calcd. for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 67.94; H, 9.95; N, 6.55.

N,N-Diisopropyl-2-ethyl-2,5-dihydro-2-furamide **8c4**.

This compound had bp 58-60°/5 mm Hg; ^{1}H nmr: δ 0.88 (t, 3H, J = 7.3 Hz, CH_3), 1.16 (d, 6H, J = 6.4 Hz), 1.36 (d, 3H, J = 6.6 Hz), 1.40 (d, 3H, J = 6.6 Hz), 1.82 (q, 2H, J = 7.3 Hz, CH_2), 3.41 (quint, 1H), 4.65 (bs, 2H), 4.85 (quint, 1H), 5.90 (d, 1H, J = 6.3 Hz), 6.07 (dt, 1H, J = 2.0 Hz); ^{13}C nmr: δ 7.75 (CH_3), 20.4, 20.7, 30.9 (CH_2), 46.2, 47,8, 76.3 (C-5), 96.5 (C-2), 125.3 (C-3), 131.4 (C-4), 172.4 (C=O).

Anal. Calcd. for $C_{13}H_{23}NO_2$: C, 69.30; H, 10.29; N, 6.22. Found: C, 69.01; H, 10.23; N, 6.14.

N,N-Diisopropyl-2-isopropyl-2,5-dihydro-2-furamide **8c5**.

This compound had mp 43-44°; ^{1}H nmr: δ 0.86 (d, 3H, J = 6.6 Hz, *i*-Pr), 0.95 (d, 3H, J = 6.6 Hz, *i*-Pr), 1.13 (d, 3H, J = 6.6 Hz), 1.17 (d, 3H, J = 6.6 Hz), 1.38 (d, 3H, J = 6.6 Hz), 1.41 (d, 3H, J = 6.6 Hz), 2.13 (quint, 1H, CH), 3.36 (quint, 1H), 4.65 (dd, 2H, J = 2.2 Hz), 4.91 (quint, 1H), 5.94 (d, 1H, J = 6.0 Hz), 6.05 (dt, 1H, J = 2.2 Hz); ^{13}C nmr: δ 16.4 (*i*-Pr), 17.8 (*i*-Pr), 20.5, 20.7, 34.8 (CH), 46.3, 47.7, 76.6 (C-5), 99.8 (C-2), 125.9 (C-3), 129.1 (C-4), 172.1 (C=O).

Anal. Calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.19; H, 10.55; N, 5.80.

N,N-Diisopropyl-2-allyl-2,5-dihydro-2-furamide **8c6**.

This compound had bp 84-85°/5 mm Hg; ^{1}H nmr: δ 1.17 (d, 3H, J = 6.6 Hz), 1.21 (d, 3H, J = 6.6 Hz), 1.38 (d, 3H, J = 6.6 Hz), 1.40 (d, 3H, J = 6.6 Hz), 2.58 (d, 2H, J = 6.8 Hz, CH_2), 3.37 (quint, 1H), 4.66 (dd, 2H, J = 2.0 Hz), 4.96 (quint, 1H), 5.07 (bd, 2H, J = 12.0 Hz, CH_2=CH), 5.58-5.92 (m, 1H, CH_2=CH), 5.91 (dd, 1H, J = 6.4 Hz, J = 1.5 Hz), 6.11 (dt, 1H, J = 6.4 Hz); ^{13}C nmr: δ 20.5, 43.0 (CH_2), 46.3, 47.8, 76.3 (C-5), 95.5 (C-2), 118.2 (CH_2=CH), 125.3 (C-3), 131.7 (C-4), 132.3 (CH_2=CH), 171.6 (C=O).

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.55; H, 9.74; N, 5.85.

N,N-Diisopropyl-2-benzyl-2,5-dihydro-2-furamide **8c7**.

This compound had mp 69-70°; ^{1}H nmr: δ 1.03 (d, 3H, J = 6.6 Hz), 1.13 (d, 3H, J = 6.6 Hz), 1.36 (d, 3H, J = 6.6 Hz), 1.42 (d, 3H, J = 6.6 Hz), 3.10 (q, 2H, J = 13.7 Hz, $PhCH_2$), 3.34 (quint, 1H), 4.44 (q, 2H, J = 12.5 Hz, J = 2.4 Hz), 4.91 (quint, 1H), 5.72 (d, 1H, J = 6.1 Hz), 6.08 (dt, 1H, J = 6.1 Hz, J = 2.4 Hz), 7.21 (s, 5H, arom); ^{13}C nmr: δ 20.4, 20.7, 21.0, 44.6 ($PhCH_2$), 46.5, 48.1, 76.6 (C-5), 96.8 (C-2), 125.6 (C-3), 126.5, 127.9, 130.7, 132.2 (C-4), 136.4, 171.9 (C=O).

Anal. Calcd. for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.19; H, 8.74; N, 4.86.

3-Methyl-2,3-dihydro-3-furancarboxaldehyde **9**.

To a stirred and cooled (0°) solution of 1*N* lithium aluminium hydride in ether (17.5 ml, 7.5 mmoles) was added dropwise a solution of dry ethanol (2.4 g, 52.5 mmoles) in dry ether (10 ml) and the reaction mixture was stirred for 30 minutes. The reagent, lithium triethoxyaluminium hydride, prepared in this manner was added dropwise slowly to a solution of **6b** (2.95 g, 16.1 mmoles) in ether (10 ml) and stirred for an additional one hour at 0°. After the reaction mixture was quenched with water, inorganic by-products were removed by filtration through Celite. The filtrate was neutralized with 1*N* hydrochloric acid. The ether layer was washed with water, dried and distilled to give aldehyde **9** (1.08 g, 60%) as a viscous oil, bp 140°; ir (neat): 2950, 1720, 1600, 1150, 1040 cm^{-1}; ^{1}H nmr:

δ 1.27 (s, 3H, CH_3), 3.99 (d, 1H, J = 9.5 Hz, H-2), 4.69 (d, 1H, J = 9.5 Hz, H-2), 4.78 (d, 1H, J = 2.4 Hz, H-4), 6.44 (d, 1H, J = 2.4 Hz, H-5), 9.53 (s, 1H, CHO); ^{13}C nmr; 19. 7 (CH_3), 57.9 (C-3), 75. 5 (C-2), 102.5 (C-4), 148.9 (C-5), 199.3 (CHO).

3-Methyl-2,3-dihydro-3-furyl Methyl Ketone **10**.

To a stirred solution of **6b** (1.0 g, 5.5 mmoles) in dry ether (20 ml) was added a solution of 1.5*N* methyllithium in ether (4 ml, 6.0 mmoles) at - 20° under a nitrogen atmosphere. After stirring for one hour at 0° and additional 3 hours at room temperature, the reaction mixture was quenched by addition of water and neutralyzed with dilute hydrochloric acid. The extract with ether, after evaporation, chromatographed with pentane-ether (10:1) to give **10**; bp 63-65° /16 mm Hg (295 mg, 44%); ir (neat): 2950, 1600, 1450, 1350, 1140, 1015, 945, 725 cm^{-1}; ^1H nmr: δ 1.32 (s, 3H, CH_3), 2.20 (s, 3H, $COCH_3$), 3.94 (d, 1H, J = 9.5 Hz, H-2), 4.75 (d, 1H, J = 9.5 Hz, H-2), 4.99 (d, 1H, J = 2.8 Hz, H-4), 6.38 (d, 1H, J = 2.8 Hz, H-5); ^{13}C nmr: δ 23.1 (CH_3), 25.5 ($COCH_3$), 59.6 (C-3), 77.4 (C-2), 105.3 (C-4), 140.1 (C-5), 209.4 (C=O).

(2'*S*)-3{[2'-(Methoxymethyl)pyrrodinyl]carbonyl}furan **11**.

To a stirred solution of *l*-prolinol (9.1 g, 90.1 mmoles) and triethylamine (30 ml) in dry dichloromethane (150 ml) at -10° was added 3-furoyl chloride (11.7 g, 89.3 mmoles) in dichloromethane (50 ml). After stirring overnight at room temperature, the mixture was washed with 3*N* hydrochloric acid and then saturated sodium hydrogen carbonate, dried (magnesium sulfate), and concentrated to give (2'*S*)-3-{[2'-(hydroxymethyl)-pyrrodinyl]carbonyl}furan (12.2 g, 70%) as a viscous oil, which was chromatographed with benzene-ethyl acetate (1:2), $[\alpha]_D$ -92.6° (c = 1.3, methanol); ^1H nmr: δ 1.70-2.20 (m, 4H), 3.67 (bs, 3H), 4.38 (t, 2H, J = 5.0 Hz), 4.57 (bs, 1H, OH), 6.74 (bs, 1H), 7.43 (bs, 1H), 7.83 (s, 1H); ^{13}C nmr: δ 24.8 28.0, 49.7, 61.7, 66.5, 110.5, 122.3, 142.8, 144.6, 165.3.

A solution of the oil (11.0 g, 56.4 mmoles) in dry THF (50 ml) was added to a suspension of sodium hydride (50% mineral oil; 2.78 g, 56.4 mmoles) in dry THF (150 ml). After stirring for one hour at room temperature, methyl iodide (12.0 g, 85 mmoles) was added to the reaction mixture, and stirred overnight. The mixture was poured onto ice-water, and extracted with dichloromethane, washed with water and dried. The solvent was evaporated, and the residue was chromatographed with benzene-ethyl acetate (2:1, v/v) to give **11** (10.0 g, 85%), mp 47°; $[\alpha]_D$ -97.9° (c = 1.0, methanol); ir (nujol): 3150, 1600, 1560, 1520, 1440, 1160, 1120, 880 cm^{-1}; ^1H nmr: δ 1.98 (bs, 4H), 3.36 (s, 3H), 3.60 (bd, 4H), 4.39 (bs, 1H), 6.75 (bs, 1H), 7.40 (bs, 1H), 7.82 (bs, 1H); ^{13}C nmr: δ 27.4, 27.6, 49.2, 57.4, 59.1, 72.6, 110.7, 122.9, 142.7, 144.3, 162.8.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.08; H, 7.21; N, 6.68.

(3*R*/*S*,2'*S*)-3-Methyl-2,3-dihydro-3-[{3'-(methoxymethyl)-pyrrodinyl}carbonyl]furan **12**.

This compound was obtained as syrup in 30% yield; ^1H nmr: δ 1.39 (s, 3H, CH_3), 1.90 (bs, 4H, H-3', H-4'), 3.33 (s, 3H, OMe), 3.45 (bs, 3H, H-2', H-5'), 4.05 (d, 1H, J = 9.0 Hz, H-2), 4.30 (bs, 2H, H-6'), 4.78 (d, 1H, J = 9.0 Hz, H-2), 5.19 (d, 1H, J = 2.9 Hz, H-4), 6.33 (d, 1H, J = 2.9 Hz, H-5); ^{13}C nmr: δ 13.1 (CH_3), 24.8 (C-4'), 27.6 (C-3'), 49.3 (C-5'), 56.6 (OMe), 58.9 (C-3, C-2'), 72.6 (C-2, C-6'), 109.7 (C-4), 139.8 (C-5)

(2'*S*)-2-{[2'-(Methoxymethyl)pyrrodinyl]carbonyl}furan **13**.

2-Furoyl chloride was treated as in the preparation of **11** to give (2'*S*)-2-{[2'(hydroxymethyl)pyrrodinyl]carbonyl}furan in 75% yield as hygroscopic oil, $[\alpha]_D$ -80.5° (c = 1.0, methanol); ir (neat): 3400, 3140, 1730, 1600, 1565, 1480, 1420, 1240, 1040, 880, 760 cm^{-1}; ^1H nmr: δ 1.95 (bs, 4H), 3.71 (t, 2H, J = 5.3 Hz), 3.89 (d, 2H, J = 5.1 Hz), 4.87 (bd, 1H, J = 5.1 Hz), 6.49 (dd, 1H, J = 3.4 Hz, J = 1.0 Hz), 7.09 (d, 1H, J = 3.4 Hz), 7.53 (d, 1H, J = 1.0 Hz).

The product was analyzed as the *p*-nitrobenzoate, mp 105-106°.

Anal. Calcd. for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.40; H, 4.68; N, 8.09.

Compound **13** was obtained in 69% yield as an oil, bp 110-112°/4 mm Hg; $[\alpha]_D$ -93.5° (c = 1.2, methanol); ir (neat): 3100, 1620, 1580, 1480, 1410, 1120, 1010, 760 cm^{-1}; ^1H nmr: δ 2.00 (bs, 4H), 3.35 (s, 3H), 3.58 (bs, 2H), 3.82 (bs, 2H), 4.43 (bs, 1H), 6.48 (s, 1H), 7.08 (s, 1H), 7.51 (s, 1H); ^{13}C nmr: δ 24.6, 26.3, 48.2, 57.4, 58.9, 72.2, 111.3, 116.0, 143.9, 148.6, 158.2.

Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.07; H, 7.21; N,6.69.

(2*R*/*S*,2'*S*)-2-Methyl-2,5-dihydro-2-[{2'-(methoxymethyl)pyrrodinyl}carbonyl]furan **14**.

This compound was obtained as syrup 67% yield; ir (neat): 3000, 2920, 2875, 1620, 1520, 1430, 1010, 900 cm^{-1}; ^1H nmr: δ 1.50 (s, 3H, CH_3), 1.90 (bd, 4H, H-3', H-4'), 3.34 (bs, 3H, OMe), 3.50-3.75 (m, 3H, H-2', H-5'), 4.25 (bs, 2H, H-6'), 4.68 (bs, 2H, H-5), 5.88 (d, 1H, J = 6.2 Hz, H-3), 5.96 (dd, 1H, J = 6.2 Hz, J = 2.0 Hz, H4); ^{13}C nmr: δ 24.7 (CH_3), 25.0 (C-4'), 26.5 (C-3'), 47.5 (C-5'), 57.8 (OMe), 58.9 (C-2'), 72.1 (C-6'), 75.1 (C-5), 93.1 (C-2), 125.7 (C-3), 132.5 (C-4), 172.1 (C=O).

Acknowledgement.

We thank Mr. Junichi Goda and Miss Rika Tanaka for the microanalyses and Dr. Kazuo Yoshihara of Suntory Institute for Bioorganic Research for helpful discussions.

REFERENCES AND NOTES

[1] T. Kinoshita, K. Miyano and T. Miwa, *Bull. Chem. Soc. Japan*, **48**, 1865 (1975).

[2] A. Birch and J. Slobbe, *Tetrahedron Letters*, 627 (1975).

[3] J. Slobbe, *J. Aust. Chem.*, **29**, 2553 (1976).

[4] T. Kinoshita, M. Hirano and N. Yoshida, *Synthesis*, 384 (1991).

[5] M. Tada, M. Nagai, C. Okumura, Y. Osano and T. Matsuzaki, *Chem. Letters*, 683 (1989).

[6] A. G. Schultz, *Acc. Chem. Res.*, **23**, 207 (1990) and references cited therein.

[7] G. M. Coppingher, *J. Am. Chem. Soc.*, **76**, 1372 (1954).

[8] R. I. Meltzer, A. D. Lewis and J. A. King, *J. Am. Chem. Soc.*, **73**, 4062 (1955).