Isopropenyldihydrofuran Derivatives. Preparation and Reactions of Some Isopropenyldihydrofurandicarboxylates

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Diethyl 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylate **1a** and methyl 5-isopropenyl-3-methoxycarbonyl-4,5-dihydrofuran-2-acetate **2a** were prepared by cylization of diethyl 2-oxosuccinate or dimethyl 3-oxoglutarate with (*E*)-1,4-dibromo-2-methyl-2-butene. Their chemical properties were studied.

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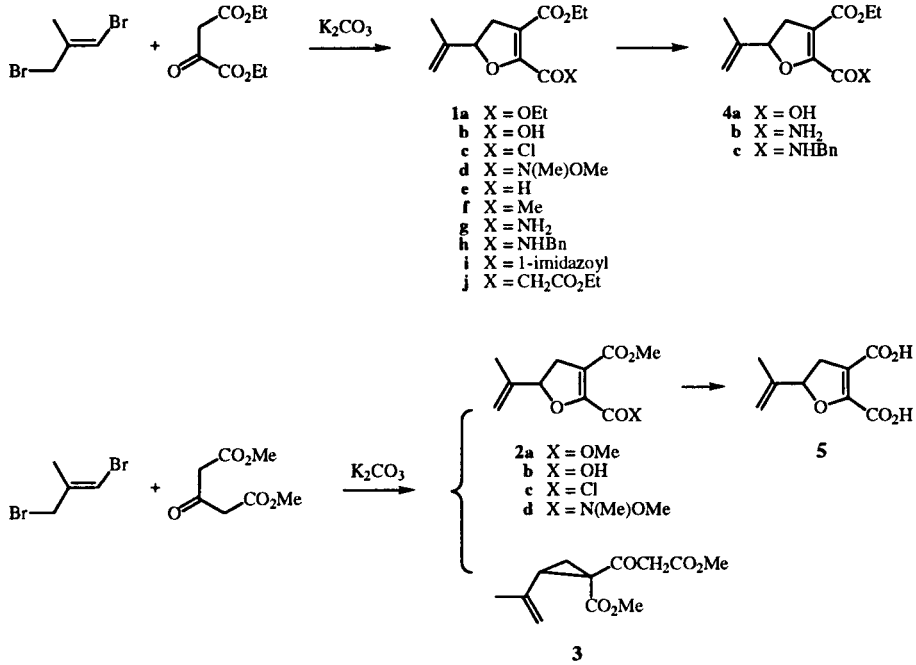
Many chiral 2-isopropenyl-2,3-dihydrobenzofurans have been isolated from various plants and fungi. Some of them were synthesized from the corresponding chiral 2,3-dihydrobenzofuran-2-carboxylic acids [1]. However, this method needs each chiral acid for each chiral isopropenyldihydrobenzofuran. Some chiral 2-isopropenyl-2,3-dihydrofuran derivatives were required as new chiral building blocks for natural chiral 2-isopropenyl-2,3-dihydrobenzofurans. Reports of the chemical properties of 2-isopropenyl-2,3-dihydrobenzofurans are not in the published literature. In this paper, the preparation and reactions of some 2-isopropenyl-2,3-dihydrofuran derivatives will be reported.

In the procedure reported by Nickl [2], diethyl 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylate **1a** was prepared in 58% yield by treating the sodium salt of diethyl 2-oxosuccinate [3] with (*E*)-1,4-dibromo-2-methyl-2-butene in acetone. A similar cyclization of dimethyl 3-oxoglutarate with (*E*)-1,4-dibromo-2-methyl-2-butene gave a mixture of the five-membered methyl 5-isopropenyl-3-methoxycarbonyl-4,5-dihydrofuran-2-acetate **2a** and the three-membered methyl 2-isopropenyl-1-methoxycarbonyl-β-oxo-1-cyclopropanepropionate 3 in 40% and 25% yields, respectively.

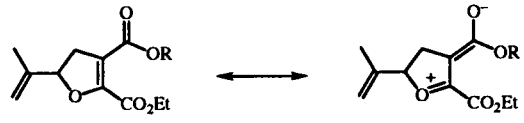
These diesters **1a** and **2a** were effectively hydrolyzed to the corresponding carboxylic acids by treating with alkali in a cool aqueous solution [4]. Hydrolyses of **1a** or **2a** with exess molar amounts of aqueous sodium hydroxide solution gave the corresponding diacids, 5-isopropenyl-4,5-dihydrofuran-2,3-dicarboxylic acid **4a** and 3-carboxy-5-isopropenyl-4,5-dihydrofuran-2-acetic acid **5** in 70% and 98% yields. Similar hydrolyses with equimolar amouts of aqueous sodium hydroxide solution gave the half-esters, 3-ethoxycarbonyl-5-isopropenyl-4,5-dihydrofuran-2-carboxylic acid **1b** and 5-isopropenyl-3-methoxycarbonyl-4,5-dihydrofuran-2-acetic acid **2b** in 81% yields. The structures of **1b** and **2b**



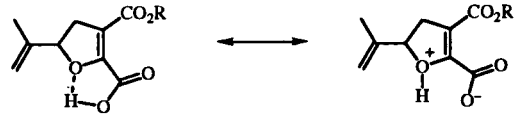
were confirmed by following the decarboxylation. Thermal decarboxylation of **1b** gave ethyl 5-isopropenyl-4,5-dihydrofuran-3-carboxylate **6a** (25%), which showed only a small coupling of the new olefinic proton signal in the pmr spectrum (Table 1). Thus, **6a** was assigned to a 3-carboxylate not to a 2-carboxylate, and the starting half-ester **1b** was therefore assigned as 3-ethoxycarbonyl-2-carboxylic acid. Hydrolysis of ester **6a** with an exess molar amount of aqueous sodium hydroxide solution also gave the corresponding acid **6b** (86%). A similar decarboxylation of **2b** gave methyl 5-isopropenyl-2-methyl-4,5-dihydrofuran-3-carboxylate **7** (81%), which was identified with the sample prepared by cyclization of methyl 3-oxobutanoate with (*E*)-1,4-dibromo-2-methyl-2-butene.

In the ir spectra, two interesting effects were observed as following. The 3-carbonyl bands of diesters **1a**, **2a**, ester **6a**, and acid **6b** were observed lower than 1710 cm^{-1}, while the 2-carbonyl band of diester **1a** was observed higher at 1750 cm^{-1}. These lower shifts in the 3-carbonyl bands might be due to the conjugation with the lone paired electrons on the oxygen in the furan ring through a C=C bond. This conjugation might reversely disturb the other conjugation of the 2-carbonyl group with the C=C double bond, and therefore cause the higher shift in the 2-carbonyl band. While, the 2-carboxyl bands in **1b** and **4a** were observed at lower frequency, 1610 cm^{-1} and the 3-carbonyl bands in **1b** and **4a** were observed at a higher frequency, 1755 cm^{-1} (the ester carbonyl in **1b**) and 1710 cm^{-1} (the carboxyl in **4a**). These lower shifts might be due to the intramolecular hydrogen bonding between the 2-carboxyl group and the lone-paired electrons on the oxygen of a furan ring, and this intramolecular hydrogen bonding might reversely disturb the conjugation described above to shift the 3-carbonyl bands higher.

Conjugation



Intramolecular Hydrogen Bonding



Some alkylations and reductions on the 2- or 3-carbonyl groups were attempted to construct the benzene ring for the 2-isopropenyl-2,3-dihydrobenzofuran derivatives [4]. Grignard alkylation of diester **1a** with methylmagmesium

Table

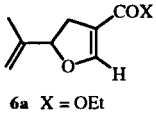
PMR Spectral Data of New Isopropenyldihydrofuran Derivatives, δ/ppm (J/Hx)

Compound	4-H_A	4-H_B	5 H_X	Other Protons [a]
1a	2.8 (dd, 15, 9)	3.1 (dd, 15, 10)	5.2 (dd, 10, 9)	1.3, 1.4 and 4.2, 4.4 (two OEt, 7)
1b	2.9 (dd, 17, 10)	3.3 (dd, 17, 11)	5.2 (dd, 11, 10)	1.4 and 4.3 (OEt, 7), 12.1 (CO_2H, br s)
1d	2.8 (dd, 15, 9)	3.2 (dd, 15, 10)	5.2 (dd, 10, 9)	1.3 and 4.2 (OEt, 7), 3.3 (NMe, s), 3.7 (OMe, s)
1e	2.8 (dd, 17, 10)	3.3 (dd, 17, 11)	5.1 (dd, 11, 10)	1.3 and4.3 (OEt, 7), 10.2 (CHO, s)
1f	2.8 (dd, 16, 9)	3.2 (dd, 16, 10)	5.2 (dd, 10, 9)	1.3 and 4.2 (OEt, 7), 2.5 (COMe, s)
1g	2.9 (dd, 16, 9)	3.3 (dd, 16, 10)	5.1 (dd, 10, 9)	1.3 and 4.6 (OEt, 7), 6.2 and 9.9 (two NH, two br s)
1h	2.9 (dd, 16, 10)	3.3 (dd, 16, 11)	5.3 (dd, 11, 10)	1.3 and 4.2 (OEt, 7), 4.6 (d, 5)
1i	2.9 (dd, 15, 9)	3.2 (dd, 15, 10)	5.2 (dd, 10, 9)	1.3, 1.4 and 4.2, 4.5 (two OEt, 7), 3.8 (CH_2 in keto, s), 5.7(C=CH in enol, br s), 12.3 (OH in enol, br s)
2a	2.7 (dd, 15, 8)	3.0 (dd, 15, 11)	5.0 (dd, 11, 8)	3.6 (OMe, s), 3.65 and 3.7 (CH_2, two d, 4)
2b	2.7 (dd, 15, 8)	3.1 (dd, 15, 10)	5.1 (dd, 10, 8)	3.7 (OMe, s), 3.7 (CH_2, s), 8.0 (CO_2H, s)
2d	2.8 (dd, 15, 9)	3.2 (dd, 15, 10)	5.2 (dd, 10, 9)	1.3 and 4.2 (OEt, 7), 3.3 (NMe, s), 3.7 (OMe, s)
4a	2.8 (dd, 16, 9)	3.1 (dd, 16, 11)	5.0 (dd, 11, 9)	12.4 (two CO_2H, br s)
4b	2.7 (dd, 16, 9)	3.2 (dd, 16, 11)	5.1 (dd, 11, 9)	7.2, 8.0, 8.3, and 9.2 (two NH_2, tetra br s)
4c	2.5 (dd, 15, 8)	2.6 (dd, 15, 4)	4.7 (dd, 8, 4)	4.1 and 5.6 (NH, two br m), 4.6 and 4,7 (two N-CH_2Ph, s and two d)
5	2.7 (dd, 16, 9)	3.1 (dd, 16, 12)	5.3 (dd, 12, 9)	3.7 and 3.8 (CH_2, two d, 4), 9.3 (CO_2H, br s)
6a	2.6 (ddd, 15, 9, 2)	3.0 (ddd, 15, 10, 2)	5.1 (dd, 10, 9)	1.2 and 4.1 (OEt, 7), 7.1 (2-H, t, 2)
6b	2.6 (ddd, 15, 9, 2)	3.0 (ddd, 15, 10, 2)	5.2 (dd, 10, 9)	7.4 (2-H, t, 2), 11.2 (CO_2H, br s)
6d	2.7 (ddd, 15, 9, 2)	3.1 (ddd, 15, 10, 2)	5.1 (dd, 10, 9)	3.2 (N-Me, s), 3.7 (OMe, s)
6e	2.7 (ddd, 15, 9, 2)	3.1 (ddd, 15, 10, 2)	5.2 (dd, 10, 9)	7.3 (2-H, t, 2), 9.6 (3-CHO, s)
7	2.6 (dd, 14, 8)	2.9 (dd, 14, 10)	5.1 (dd, 10, 8)	2.2 (2-Me, br s), 3.6 (OMe, s)
8	2.8 (dd, 17, 9)	3.3 (dd, 17, 11)	5.3 (dd, 11, 9)	8.7 and 8.9 (NH_2, two br s)
9	2.6 (dd, 15, 10)	2.7 (dd, 15, 5)	4.8 (dd, 10, 5)	1.3 and 4.2 (OEt, 7), 4.8 (NCH_2Ph, d, 8), 7.2-7.3 (ArH, m), 8.5 (NH, m)
11	2.7 (dd, 14, 9)	3.1 (dd, 14, 11)	5.1 (dd, 11, 9)	1.3 (two Me, s), 1.3 and 4.2(OEt, 7), (OH, br s)
12	2.8 (dd, 15, 9)	3.2 (dd, 15, 10)	5.2 (dd, 10, 9)	1.9 (C=CMe, d, 7), 3.8(OMe, s), 7.2(C=CH, q, 7), 10.7 (CO_2H, s)

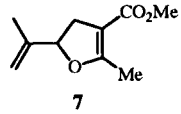
[a] Isopropenyl signals are the almost same in all sample; 1.7-1.8 (s, Me), 4.8-4.9 and 4.9-5.1 (two br s, two olefinic).

bromide gave tertiary alcohol **11** even with an equimolar amount, and none of the alkylated products was obtained in similar alkylations of **6a** and **7** even with excess molar amounts of methylmagnesium bromide. Reduction of diester **1a** and ester **6a** with lithium aluminium hydride caused the decomposion of the furan-ring and similar reductions of **1a** and **6a** with diisobutylaluminum hydride recovered the starting ester. The 3-carbonyl groups might be deactivated by the conjugation descibed above. Thus, *N*-methoxy-*N*-methylcarboxamides **1d**, **2d**, and **6d**, active for metal hydride or alkyl metal to give the corresponding aldehydes or monoalkylations [5], were prepared by treating the corresponding furancarbonyl chlorides with *N*-methoxy-*N*-methylamine. Reduction of **1d** or **6d** with diisobutylaluminum hydride gave ethyl 2-formyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylate **1e** (65%) or 5-isopropenyl-4,5-dihydrofuran-3-carbaldehyde **6e** (25%).

Alkylation of **1d** with methylmagnesium bromide gave 2-acetyl-3-carboxylate **1f** (62%). However, a similar reduction and alkylation of *N*-methoxy-*N*-methylcarboxamide **2d** showed only recovery of starting materials, probably because the methylene group might be acidic enough to decompose the reagents. Condensation of diester **2a** with acetaldehyde in the presence of sodium methylate gave α-ethylidene-5-isopropenyl-3-methoxycarbonyl-4,5-dihydrofuran-2-acetic acid **12** (40%). Brooks *et al.* also reported that some 1-imidazolylcarboxamides were active in alkylations [6]. 1-Imidazolylcarboxamide **1i** was similarly prepared by treating half-ester **1b** with 1,1'-carbonyldiimidazole. Alkylation of 1-imidazolylcarboxamide **1i** with magnesium salt of ethyl hydrogen malonate [7] gave ethyl 3-ethoxycarbonyl-5-isopropenyl-β-oxo-4,5-dihydrofuran-2-propionate **1j**.



6a X = OEt
b X = OH
c X = Cl
d X = N(Me)OMe
e X = H



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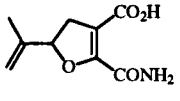

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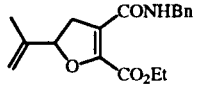

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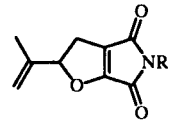
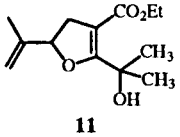


10a R = H
b R = Bn



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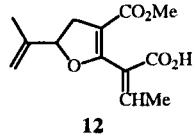

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In our previous paper, chiral 1-phenylethylamine was the most effective base for the optical resolution of 2,3-dihydrobenzofuran-2-carboxylic acid [1]. For the optical resolutions of acids **1b**, **2b**, **4a**, **5**, and **6b**, the formation of stable salts with chiral 1-phenylethylamine were, however, all unsuccessful. The formation of stable amides was then attempted by aminolysis of diester **1a** with benzylamine, instead of chiral 1-phenylethylamine. Aminolysis of **1a** with an excess molar amount of benzylamine gave diamide **4c** in 23% yield. A similar aminolysis of **1a** with equimolar amounts of benzylamine gave a half-amide **1h** in low (7%) yield, but, very interestingly, a similar aminolysis of **1a** in the presence of *p*-toluenesulfonic acid monohydrate as an acid-catalyst gave the other halfamide **9** in 18% yield. The half-amide prepared from **1b** (by treating the 2-chloroformyl-3-carboxylate derivative **1c** with benzylamine) was identical with the former half-amide **1h**. Therefore, it was confirmed that the half-amide **1h** was a 2-carbamoyl-3-carboxylate and the other half-amide **9** was a 3-carbamoyl-2-carboxylate. These might be explained as follows. The aminolysis on the 2-carbonyl group was usually preferential because of the deactivation of the 3-carbonyl by the conjugation as descriced above. The protonation on the ring oxygen of furan might disturb this conjugation and change the preference of conjugation with C=C from the 3-carbonyl to the 2-carbonyl group. Ammonolysis of diester **1a** with aqueous ammonia gave a mixture of diamide **4b** and carbamoylcarboxylic acid **8**. Carbamoylcarboxylic acid **8** did not show intramolecular hydrogen-bonding in the ir spectrum. The sample pepared from half-ester **1b** (by treating the 2-chloroformyl-3-carboxylate **1c** with ammonia followed by hydrolysis) was identical with **8** and the structure of **8** was confirmed to be a 2-carbamoyl-3-carboxylic acid. The low yields in the aminolyses and ammonolyses might be due to the competitive decomposition of a furan ring. In aminolyses and ammonolysis, none of the formation of the corresponding five-membered imides **10a,b** was observed. These might be due to the ring strain of two five-membered condensed ring systems.

EXPERIMENTAL

The melting points and boiling points were uncorrected. The ir spectra were recorded on a JASCO WS/IR-7300 spectrometer in liquid films or potassium bromide disks. Mass spectra were measured on a JEOL JMS-OISG-2 mass spectrometer. The pmr spectra were measured on a JEOL PMX-60Si or FX-90Q nmr spectrometer in carbon tetrachloride or deuteriochloroform, solution, and the data were summarized in the Table.

Preparation of Diethyl 5-Isopropenyl-4,5-dihydrofuran-2,3-dicarboxylate **1a**.

To a suspension of the sodium enolate of diethyl 2-oxosuccinate [3] (41.5 g, 197 mmol) in acetone (300 ml) was added potassium carbonate (56.0 g, 405 mmoles) and (*E*)-1,4-dibromo-2-methyl-2-butene (67.1 g, 294 mmoles), and the mixture was stirred at room temepature for 8 hours. The organic layer was collected by decantation and concentrated under reduced pressure, then extracted with ether. The resiual solids were treated with water and extracted with ether. The combined mixture was

extracted with ether. The combined ether extracts were washed with 5% aqueous sodium hydroxide solution and saturated sodium chloride solution, and dried over anhydrous sodium sulfate. After removal of the solvent, the oily residue was distilled under reduced pressure to give **1a** (29.0 g, 58%), bp 120-137° (4 mm Hg), ir: 1750 and 1710 cm^{-1}, ms: m/z 254 (M^+).

Anal. Calcd. for $C_{13}H_{18}O_5$: (**1a**): C, 61.40; H, 7.14. Found: C, 61.36; H, 7.10.

Preparation of Methyl 5-Isopropenyl-3-methoxycarbonyl-4,5-dihydrofuran-2-acetate **2a**.

To a suspension of dimethyl 3-oxoglutarate (12.9 g, 74.2 mmoles) in acetone (200 ml) was added anhydrous potassium carbonate (20.2 g, 146 mmoles) and (*E*)-1,4-dibromo-2-methyl-2-butene (16.8 g, 73.2 mmoles). The mixture was stirred under ice-cooling for 7 hours. After a similar treatment described above for **1a**, the oily residue obtained was distilled, and the fractions boiling at 135-140° (4 mm Hg) was chromatographed on a silica-gel column. The fractions eluted with benzene gave **2a** (7.21 g, 40%), bp *ca.* 140° (4 mm Hg) (bath temperature); ir: 1750 and 1710 cm^{-1}; ms: m/z 240 (M^+). Alkaline washings gave methyl 2-isopropenyl-1-methoxycarbonyl-β- oxocyclopropane-1-propionata **3** (4.43 g, 25%), bp *ca.* 140° (4 mm Hg) (bath temperature); ir: 1740 and 1700 cm^{-1}, pmr (ppm): 1.6 (1H, dd, J = 9 and 4 Hz, 3-Ha), 1.7 (3H, br s, Me in isopropenyl), 1.9 (1H, dd, J = 8 and 4 Hz, 3-Hb), 2.5 (1H, dd, J = 9 and 8 Hz, 2-H), 3.6 (3H, s, OMe), 3.7 (3H, s, OMe), 3.8 (2H, s, CH2), 4.8 (1H, br s, C=CH in isopropenyl), 4.9 (1H, br s, C=CH in isopropenyl); hrms: M^+ 240.100. Found: M for $C_{12}H_{16}O_5$: 240.099.

Anal. Calcd. for $C_{12}H_{16}O_5$: (**2a**): C, 59.99; H, 6.71. Found: C, 59.69; H, 6.68.

Hydrolysis of Diester **1a** and **2a** or Half-ester **1b** to Diacid **4a** and **5**.

Diester **1a**, **2a** or half-ester **1b** (*ca.* 10 mmoles) was stirred with 5% aqueous sodium hydroxide solution (50 ml) at room temperature for 5 hours. After washing with ether, the aqueous layer was acidified with 10% hydrochloric acid and extracted with ether by the salting-out techniques. The ether layer was washed with saturated sodium chloride solution and was dried over anhydrous sodium sulfate. After removal of the solvent, the yellow solids were crystallized from hexane-ether to give diacid **4a** (64% from **1a**, 70% from **1b**), mp 165.5-166°; ir: 1710 and 1615 cm^{-1}; ms: m/z 210 (M^+), or **5** (98%), mp 134.5-135°; ir: 1710 and 1680 cm^{-1}; ms: m/z 124 (M^+-CO_2).

Anal. Calcd. for $C_9H_{10}O_5$: (**4a**): C, 54.54; H, S.O9. Found: C, 54.49; H, 5.21.*Anal.* Calcd. for $C_{10}H_{12}O_5$ **5**: C, 56.60; H, 5.70. Found: C, 56.86; H, 5.79.

Partial Hydrolysis of Di-ester **1a** or **2a** to Half-ester **1b** or **2b**.

Diester **1a** or **2b** (*ca.* 10.0 mmoles) was stirred with 1.4% aqueous sodium hydroxide solution (28.5 ml, 10.0 mmoles) at room temperature for 24 hours. After washing with ether, the aqueous layer was acidified with 10% hydrochloric acid and extracted with ether. The ether layer was washed with saturated sodium chloride solution and was dried over anhydrous sodium sulfate. After removal of the solvent, the oily residue was chromatographed on a silica gel column. The fractions eluted with chloroform gave half-ester **1b** (81%, conversion yield 100%), bp *ca.* 160° (4 mm Hg) (bath temperature); ir: 1750 and 1615 cm^{-1}; ms: m/z 226 (M^+), or **2b** (81%, conversion yield 93%) [8]; ir: 1705 and 1650 cm^{-1}; hrms: M^+ 226.086. Found M for $C_{12}H_{16}O_5$-CO_2: 226.08. Starting diester **1a** (21%) and **2a** (13%) were recovered from the ether washings.

*Anal.*Calcd. for $C_{11}H_{14}O_5$: (**1b**): C, 58.40; H, 6.24. Found: C, 58.68; H, 6.33.

Anal. Calcd. for $C_{12}H_{14}O_7$-CO_2 **2b**: C, 58.40; H, 6.24. Found: C, 58.32; H, 6.55 .

Thermal Decarboxylation of Half-ester **1b** or **2b** to Ester **6a** and **7**.

In a glass tube in the oven, half-ester **1b** or **2b** was heated to around 200°, and then the pressure was graduately reduced and then held at 100 mm Hg. The distillate was chromatographed on a silica-gel column. The fractions eluted with benzene-cyclohexane (1:1) gave ethyl 5-isopropenyl-4,5-dihydrofuran-3-carboxylate **6a** (25%), bp *ca.* 150° (16 mm Hg) (bath temperature); ir: 1705 cm^{-1}; ms: m/z 182 (M^+), or methyl 5-isopropenyl-2-methyl-4,5-dihydrofuran-3-carboxylate **7** (81%), bp 110° (18 mm Hg) (bath temperature); ir: 1710 cm^{-1}; ms: m/z 182 (M^+), hrms: M^+ 182.095. Found for M $C_{10}H_{14}O_3$: 182.094.

Anal. Calcd. for $C_{10}H_{14}O_3$: (**6a**): C, 65.91; H, 7.74. Found: C, 65.62; H, 7.83.

Hydrolysis of Ester **6a** to 5-Isopropenyl-4,5-dihydrofuran-3-carboxylic Acid **6b**.

Ester **6a** (260 mg, 1.44 mmoles) was treated with 5% aqueous sodium hydroxide solution (13 ml) at room temperature for 20 hours. After washing with ether, the aqueous layer was acidified with 10% hydrochloric acid and extracted with ether by using the salting-out techniques. The ether layer was washed with saturated sodium chloride solution and was dried over anhydrous sodium sulfate. After removal of the solvent, the white crystals were recrystallized from hexane-ether to give acid **6b** (191 mg, 86%), mp 106-107° dec; ir: 1635 cm^{-1}; ms: m/z 154 (M^+).

Anal. Calcd. for $C_8H_{10}O_3$ (**6b**): C, 62.32; H, 6.54. Found: C, 62.26; H, 6.60.

Alkylation of Diester **1a** with Excess Molar Amount of Methylmagnesium Bromide.

To a solution of diester **1a** (1.60 g, 6.30 mmoles) in dry ether (40 ml) was added 1.0*M* methylmagnesium bromide tetrahydrofuran solution (6.4 ml, 6.4 mmoles) at -10°. The mixture was stirred at room temperature for 1 hour. After treating with saturated aqueous ammonium chloride solution, the mixture was diluted with ether. The ether layer was dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on a silica-gel column. The fractions eluted with hexane-ethyl acetate (100:1) gave ethyl 5-isopropenyl-2-(1-hydroxy-1-methylethyl)-4,5-dihydrofuran-3-carboxylate **11** (41%, conversion yield 80%), bp *ca.* 110° (18 mm Hg) (bath temperature); ir: 3350 and 1670 cm^{-1}; pmr (ppm): 1.3 (6H, s, Me x 2), 1.3 (3H, t, J = 7 Hz, Me in ethyl), 1.8 (3H, broad s, Me in isopropenyl), 2.7 (1H, dd, J = 14 and 9 Hz, 4-Ha), 3.1 (1H, dd, J = 14 and 11 Hz, 4-Hb), 4.2 (2H, q, J = 7 Hz, CH_2 in ethyl), 4.8 (1H, broad s, C=CH in isopropenyl), 5.0 (1H, broad s, C=CH in isopropenyl), 5.0 (1H, dd, J = 11 and 9 Hz), 6.2 (1H, broad s, OH); ms: (m/z) 240 (M^+). The fractions eluted with hexane-ethyl acetate (10:1) were recovered diester **1a** (32%).

Anal. Calcd. for $C_{13}H_{20}O_4$ (**11**): C, 64.98; H, 8.39. Found: C, 64.75; H, 8.24.

Preparation of *N*-Methoxy-*N*-methylamides **1d**, **2d**, and **6d**.

The acid chloride **1c**, **2c**, or **6c** was prepared from acid **1b**, **2b** or **6b**, thionyl chloride (20 ml), and dry benzene (10 ml), dissolved in in dry chloroform (40 ml). Following the procedure described by

Nahm and Weinreb [5], *N,O*-dimethylhydroxylamine hydrochloride (500 mg, 5.10 mmoles) was added to the solution of the acid chloride, then dry pyridine (0.82 ml) was added with ice-water cooling. The mixture was stirred at room temperature for 17 hours. The solvent was removed under reduced pressure and the residue was diluted with ether. The ether layer was washed with 10% hydrochloric acid, saturated sodium hydrogencarbonate solution, and saturated sodium chloride solution, then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on a silica-gel column. The fractions eluted with benzene-chloroform (1:1) gave corresponding *N*-metoxy-*N*-methylamide **1d** (67%), bp 150° (5 mm Hg) (bath temperature); ir: 1705 and 1680 cm^{-1}; ms: m/z 269 (M^+), **2d** (56%), bp *ca.* 170° (5 mm Hg) (bath temperature); ir: 1745 and 1700 cm^{-1}; ms: m/z 269 (M^+), or **6d** (%), bp *ca.* 130° (5 mm Hg) (bath temperature); ir: 1625 cm^{-1}; ms: m/z 197 (M^+).

Anal. Calcd. for $C_{13}H_{19}NO_5$ (**1d**): C, 57.98; H, 7.11; N, 5.20. Found: C, 58.10; H, 7.08; N, 5.34.

Anal. Calcd. for $C_{13}H_{19}NO_5$ **2d**: C, 57.98; H, 7.11; N, 5.20. Found: C, 57.70; H, 7.07; N, 5.27.

Anal. Calcd. for $C_{10}H_{15}NO_3$: **6d**: C, 60.89; H, 7.67; N, 7.10. Found: C, 60.67; H, 7.76; N, 6.86.

Reduction of *N*-Methoxy-*N*-methylamides **1d**, **2d**, and **6d** with diisobutylaluminum Hydride.

To a solution of *N*-methoxy-*N*-methylamide **1d**, **2d**, or **6d** (5.52 mmoles) in dry tetrahydrofuran (20 ml) was slowly added 1.0*M* heptane solution of diisobutylaluminum hydride (8.00 ml, 8.00 mmoles) at -80° under an Argon atmosphere. The mixture was stirred at the temperature for 2 hours. After treating with methanol (1.5 ml) and then with saturated aqeous ammonium chloride solution with cooling, the mixture was diluted with saturated sodium chloride solution and then concentrated under reduced pressure. The residue was extracted with ether, the ether layer was washed with 10% hydrochloric acid, saturated sodium hydrogen carbonate solution, and then saturated sodium chloride solution, followed by drying over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on a silica-gel column. The fractions eluted with benzene gave ethyl 2-formyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylate **1e** (65%), bp *ca.* 120° (4 mm Hg) (bath temperature); ir: 1705 and 1680 cm^{-1}; ms: m/z 269 (M^+), or 5-isopropenyl-4,5-dihydrofuran-3-carboaldehyde **6e** (25%), bp *ca.* 110° (5 mm Hg) (bath temperature); ir: 1660 cm^{-1}, hrms: M^+ 138.0674. Found: M for $C_8H_{10}O_2$: 138.0678). In a similar reduction of **2d** with diisobutylaluminum hydride the starting amide was recovered (90%).

Anal. Calcd. for $C_{11}H_{14}O_4$ (**1f**): C, 62.84; H, 6.71. Found: C, 62.92; H, 6.86.

Aklylation of *N*-Methoxy-*N*-methylamides **1d** and **2d** with Methylmagnesium Bromide.

To a solution of *N*-methoxy-*N*-methylamide **1d** (666 mg, 2.48 mmoles) in dry tetrahydrofuran (20 ml), was added at 0° 1.0*M* methylmagnesium bromide tetrahydrofuran solution (3.00 ml, 3.00 mmoles) under an Argon atmosphere. The mixture was stirred at room temperature for 2 hours. After treating with 10% hydrochloric acid with ice-cooling, the mixture was extracted with ether. The ether layer was washed with 10% hydrochloric acid and saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on a silica-gel column. The fractions eluted with benzene gave ethyl 2-acetyl-5-isopropenyl-4,5-dihydrofuran-3-carboxylate **1f** (343 mg, 62%), bp *ca.* 100° (6 mm Hg) (bath temperature); ir: 1705 cm^{-1}; ms: m/z 224 (M^+). In a similar allcylation of **2d** with methylmagnesium bromide the starting amide (61%) was recovered.

Anal. Calcd. for $C_{12}H_{16}O_4$ (**1f**): C, 64.27; H, 7.19. Found: C, 64.03; H, 7.27.

Condensation of Diester **2a** with Acetaldehyde.

To a solution of sodium methylalte, prepared from sodium metal (80 mg, *ca.* 4 mmoles) and absolute metanol (10 ml), was added diester **2a** (745 mg, 3.10 mmoles) and acetaldehyde (440 mg, 10 mmoles). The mixture was stirred for 1 hour. After treating with 10% hydrochloric acid, the mixture was extracted with ether. The ether layer was washed with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, then dried over anhydrous sodium sulfate. After removal of the ether the residue was chromatogramed on a silica-gel to recover diester **2a** (247 mg, 33%). Acidification of the sodium hydrogencarbonate solution gave 2-ethylidene-5-isopropenyl-3-methoxycarbonyl-4,5-dihydrofuran-2-acetic acid **12** (316 mg, 40%) as a colorless precipitate, mp 108-109°; ir: 1725 and 1650 cm^{-1}; ms: m/z 252 (M^+).

Anal. Calcd. for $C_{13}H_{16}O_5$ **12**: C, 61.89; H, 6.39. Found: C, 61.98; H, 6.47.

Alkylation of 1-Imidazolylcarboxamide **1i** with the Magnesium Salt of Ethyl Hydrogen Malonate.

To a solution of half-ester **1b** (1.38 g, 6.11 mmoles) in tetrahydrofuran (25 ml) was added 1,1'-carbonyldiimidazole (940 mg, 5.80 mmoles). The mixture was stirred for 8 hours. The solution of 1-imidazolylcarboxamide **1i** thus prepared was added to a suspension of magnesium ethyl hydrogen malonate [7], prepared from magnesium ethoxide (4.50 mmoles) and ethyl hydrogenmalonate (1.20 g, 9.10 mmoles), and dry tetrahydrofuran (20 ml). The mixture was refluxed for 16 hours under an Argon atmosphere. After removal of the solvent under reduced pressure, the residue was treated with 10% hydrochloric acid and extracted with ether. The ether layer was washed with saturated sodium hydrogencarbonate solution and saturated sodium chloride solution, then dried over anhydrous sodium sulfate. After removal of the ether, the residue was chromatographed on silica-gel. The fractions eluted with chloroform gave ethyl 3-ethoxycarbonyl-5-isopropenyl-β-oxo-4,5-dihydrofuran-2-propionate **1j** (300 mg, 17%, conversion yield 31%), bp *ca.* 170-180° (17 mm Hg); ir: 1710 and 1590 cm^{-1}; ms: m/z 296 (M^+). The starting acid **1b** (45%) was recovered from the sodium hydrogencarbonate washings.

Anal. Calcd. for $C_{15}H_{20}O_6$ (**1j**): C, 60.79; H, 6.82. Found: C, 60.88; H, 6.89.

Aminolysis of Diester **1a** with Benzylamine.

With an Excess Molar Amount of Benzylamine.

To a solution of diester **1a** (1.07 g, 4.21 mmoles) in benzene (15 ml) was added benzylamine (2.26 g, 21.0 mmoles). The mixture was refluxed for 37 hours. After cooling, the mixture was diluted with ether, the organic layer washed with 10% hydrochloric acid, then with saturated sodium hydrogencarbonate solution, followed by a sodium chloride solution, then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatogramed on a silica-gel column. The fractions eluted with hexane-ethyl acetate (2:1) was crystallized from hexane-ether to give diamide **4c** (366 mg, 23%), mp 89.5-90.5°; ir: 1690 and 1650 cm^{-1}; ms: m/z 376 (M^+).

Anal. Calcd. for $C_{23}H_{24}N_2O_3$ (**4c**): C, 73.38; H, 6.43; N, 7.44. Found: C, 73.08; H, 6.27; N, 7.35.

With an Equimolar Amount of Benzylamine.

To a solution of diester **1a** (1.09 g, 4.29 mmoles) in benzene (10 ml) was added benzylamine (465 mg, 4.34 mmoles), and the mixture was refluxed for 9 hours. After cooling, the mixture was diluted with ether, and the organic layer was washed with 10% hydrochloric acid, saturated sodium hydrogencarbonate solution, and sodium chloride solution, and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was chromatographed on a silica-gel column. The fractions eluted with hexane-ethyl acetate gave oily 2-carbamoyl-3-carboxylate **1h** (100 mg, 7%, conversion yield 10%); ir: 1680 and 1605 cm^{-1}; ms: m/z 315 (M^+). The fractions eluted with benzene gave starting diester **1a** (308 mg, 28%).

Anal. Calcd. for $C_{18}H_{21}NO_4$ (**1h**): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.45; H, 6.83; N, 4.56.

With Excess Molar Amount of Benzylamine in Presence of *p*-Toluenesulfonic Acid.

To a solution of diester **1a** (540 mg, 2.21 mmoles) in benzene (10 ml) was added benzylamine (770 mg, 7.13 mmoles) and a catalytic amount of *p*-toluenesulfonic acid mono-hydrate. The mixture was refluxed for 8 hours. After cooling, the mixture was diluted with ether, and the organic layer was washed with 10% hydrochloric acid, saturated sodium hydrogencarbonate solution, and sodium chloride solution, and then dried over anhydrous sodium sulfate. After removal the solvent, the residue was chromatogramed on a silica-gel column. The fractions eluted with hexane-ether (20:1) was crystallized from hexane-ether to give 3-carbamoyl-2-carboxylate **9** (57 mg, 9%), mp 39-40°; ir: 1680 and 1605 cm^{-1}; ms: m/z 315 (M^+). The fractions eluted with hexane-ether (10:1) was crystallized from cyclohexaneas to give diamide **4c** (57 mg, 9%).

Anal. Calcd. for $C_{18}H_{21}NO_4$ (**9**): C, 68.55; H, 6.71; N, 4.44. Found: C, 68.31; H, 6.82; N, 4.63.

Ammonolysis of Diester **1a**.

Diester **1a** (2.85 g, 11.2 mmoles) was treated with ammonia (20 ml) at 55-60° for 2.5 hours. The precipitate was collected by filtration and recrystallized from cyclohexane-ethanol to give diamide **4b** (390 mg, 18%), mp 220-223°; ir: 1705 and 1625 cm^{-1}; ms: m/z 196 (M^+).

Anal. Calcd. for $C_9H_{12}N_2O_3$ (**4b**): C, 55.09; H, 6.17; N, 14.28. Found: C, 55.28; H, 6.23; N, 13.98.

Acidification of the alkaline filtrate also gave a precipitate, which was recrystallized from cyclohexane-chloroform to give 2-carbamoyl-3-carboxylic acid **8** (300 mg, 14%), mp 183-184°; ir: 1650 and 1615 cm^{-1}; ms: m/z 197 (M^+).

Anal. Calcd. for $C_9H_{11}NO_4$ (**8**): C, 54.82; H, 5.62; N, 7.10. Found: C, 54.75; H, 5.72; N, 7.05.

Preparation of 2-Carbamoyl-3-carboxylate **1g** and **1h** from Half-ester **1b**.

To a solution of acid chloride **1c**, prepared from half-ester **1b** (678 mg, 3.00 mmoles) and thionyl chloride (13 g, 110 mmoles), in benzene (30 ml) was added benzylamine (660 mg, 6.17 mmoles) or ammonia (5 ml), and the mixture was stirred at room temperature for a night. After the reaction the mixture was diluted with ether and the organic layer was washed with 10% hydrochloric acid, saturated sodium hydrogencarbonate solution, and saturated sodium chloride solution, and was dried over anhydrous sodium sulfate. After removal of the benzene, the residue was purified on a silica-gel column or recrystallization. Oily yellow amide **1h** was obtained as the fractions eluted with hexane-chloroform (3:1) in 81%, and was identical with the sample, obtained by aminolysis of **1a** with benzylamine, previuously described. Crystalline 3-ethoxycarbonyl-5-isopropenyl-4,5-dihydrofuran-2-carboxamide **1g** was obtained by recrystallization from hexane-chloroform in 82%, mp 73-74°; ir: 1690 and 1600 cm^{-1}; ms: 225 (M^+).

Anal. Calcd. for $C_{11}H_{15}NO_4$ (**1g**): C, 58.65; H, 6.71; N, 6.22. Found: C, 58.59; H, 6.64; N, 6.19.

Hydrolysis of 2-Carbamoyl-3-carboxylate **1g** to 2-Carbamoyl-3-carboxylic Acid **8**.

2-Carbamoyl-3-carboxylate **1g** (616 mg, 2.73 mmoles) was stirred with 5% aqueous solution (12 ml) of sodium hydroxide at room temperature for 3 hours. After washing with ether, the aqueous layer was acidified with 10% hydrochloric acid and reextracted with ethyl acetate using the salting-out technic. The ethyl acetate layer was washed with saturated sodium chloride solution and was dried over anhydrous sodium sulfate. After removal of the solvent, the crude crysrals were crystallized from cyclohexane chloroform to give 2-carbamoyl-3-carboxylic acid **8** (443 mg, 82%).

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[2] J. Nickl, *Chem, Ber.*, **91**, 553 (1958); in this paper, the product in the cyclization of 3-oxobutate with 1,4-dibromo-2-methyl-2-butene was described as 2-isopropenyl-1-acetylcyclopropane-1-carboxylate, but this might be revised to the 4-isopropenyl-2-methyl-4,5-dihydrofuran-3-carboxylate.

[3] Diethyl 2-oxosuccinate was used as the commercially available sodium enolate (diethyl oxalacetate, sodium salt).

[4] Hydrolyses in warm alkaline solution might cause a decomposition of the furan ring, especially in 2,3-diester **1a**.

[5] Diels-Alder reactions of diester **1a** with some dienes were unsuccessful.

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[9] Half-ester **2b** was readily decarboxylated in the thermal analyses.