Domino Michael–*O*-alkylation reaction: one-pot synthesis of 2,4-diacylhydrofuran derivatives and its application to antitumor naphthofuran synthesis

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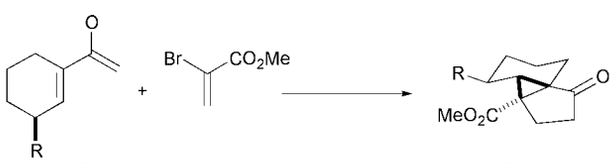
The reaction of enolates of 1,3-dicarbonyl compounds with α-halo-α,β-unsaturated carbonyl compounds affords 2,4-diacyldihydrofuran derivatives in the presence of DBU in THF. Chemical manganese dioxide oxidation of the hydrofurans leads to 2,4-diacylfuran derivatives. Application of the protocol enables short-step syntheses of antitumor naphthofuran natural products.

Introduction

Furans are important structural units as five-membered oxygen heterocycles in non-natural and natural organic compounds.[1] In particular, contributions of furans as versatile substrates for synthetic transformations are enormous. In addition, furan derivatives are widely distributed in Nature as polyketide (*e.g.*, compounds **1**[2] and **2**,[3] Fig. 1) or terpenoid (*e.g.*, compounds **3**[4] and **4**,[5] Fig. 1) constituents. Some of them have characteristic biological activities such as cytotoxic (*e.g.*, compound **1**), cardiotonic (*e.g.*, compound **2**), antiinflamatory (*e.g.*, compound **3**) or other prominent activities. Though hydrofurans are less common than furans, their importance is apparent as the precursors of (i) furans by oxidation, (ii) α-hydroxy carbonyl compounds by hydrolysis, or (iii) other useful oxygenated compounds by various manipulations. Among synthetic methodologies toward hydrofurans, non-ionic as well as ionic procedures have been exploited. Carbenoid,[6] radical[7] or photochemical[8] additions to olefins have been well utilised as non-ionic procedures. Among ionic reaction conditions,[9] Rodriguez and co-workers[9a–d] and subsequently Shioiri and co-workers[9e] presented a hydrofuran synthesis *via* a nucleophilic domino reaction during our study.

Although a number of methods are available as cited above, the search for newer methods for hydrofuran synthesis is continuously being pursued to develop efficient and short procedures. We previously reported the domino Michael–Michael-alkylation reaction of the kinetic enolate **5** (R = H) of acetylcyclohexene with methyl 2-bromopropenoate **6** leading to the tricyclo[4.4.0.0^{1,5}]decane framework **7** in a one-pot operation (bicycloannulation) (Scheme 1).[10] Our continuous efforts



5 **6** **7**

Scheme 1

to develop the nucleophilic domino reaction delineate herein a new entry toward 2,4-diacylhydrofuran synthesis.[11] The reaction was initiated by intermolecular Michael reaction between the thermodynamic enolate of 1,3-dicarbonyl compounds **8** or **12** and α-bromo-α,β-unsaturated carbonyl compound **6**, **9** or **10** followed by intramolecular *O*-alkylation (Scheme 2). Oxidation of the dihydrofurans **11** to furans **14** is also described (Scheme 3).

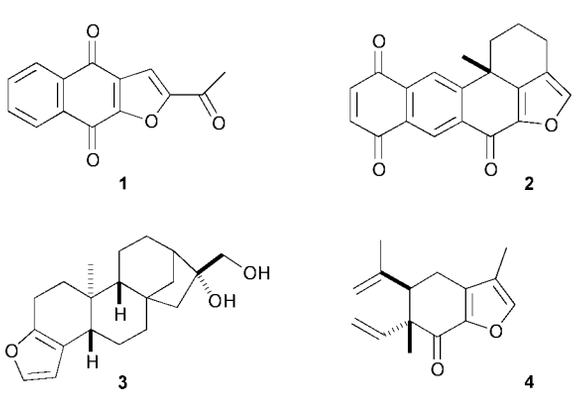
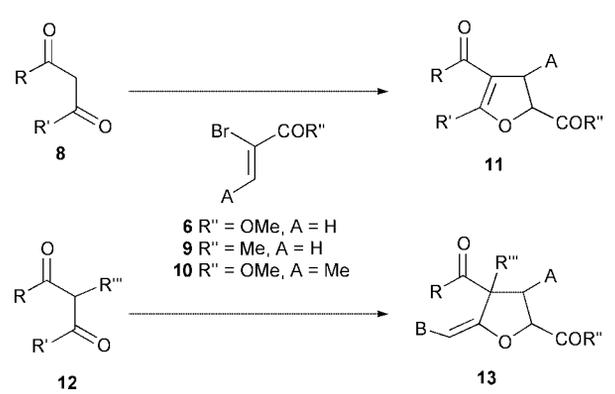


Fig. 1



Scheme 2

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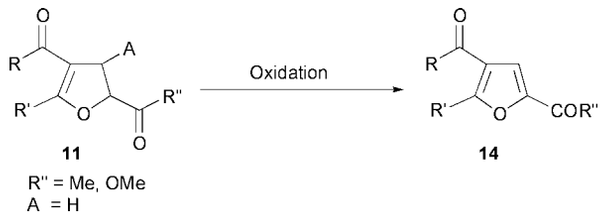
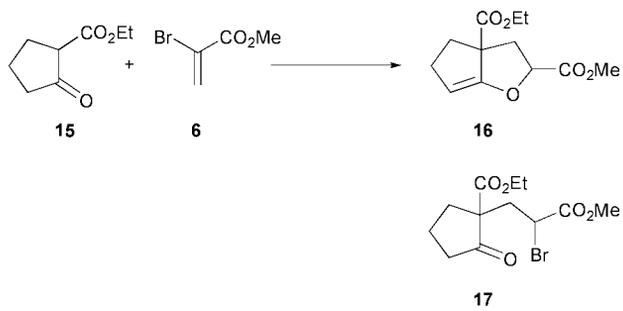


11 **14**

Scheme 3

Results and discussion

As an initial attempt, the reaction of the enolate of 2-(ethoxycarbonyl)cyclopentanone **15** with methyl 2-bromopropenoate **6** was employed to elucidate appropriate reaction conditions (Scheme 4).[11] The bromopropenoate **6** was easily prepared by



15 **6** **16** **17**

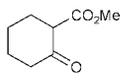
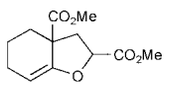
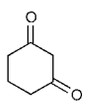
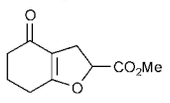
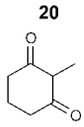
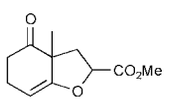
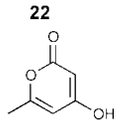
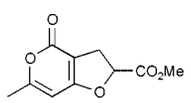
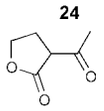
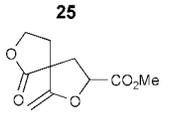
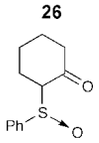
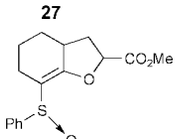
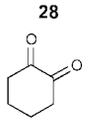
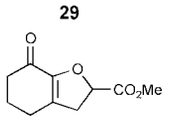
Scheme 4

addition of bromine in tetrachloromethane and subsequent careful distillation in the presence of triethylamine.[10] Since the bromopropenoate **6** is highly electrophilic, less nucleophilic bases could be used to generate the anion of the cyclopentanone **15**. The reaction with potassium carbonate in methanol provided a mixture of unidentified products. In the presence of diethylamino(trimethyl)silane[12] as an alternative non-nucleophilic base, the reaction resulted in Michael addition to give bromo ester **17**. After several attempts, it was found that the reaction proceeded readily in the presence of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in THF to give the desired hydrofuran derivative **16** in 86% yield as a single diastereomer (Scheme 4 and Table 1, entry 1). The results of the reaction of a variety of cyclic 1,3-dicarbonyl compounds are listed in Table 1, where the products were mixtures of diastereomers. No *O*-Michael reaction proceeded in entry 5 in spite of the predominant enol form of the pyrone **24**. In the reaction of α-(phenylsulfinyl)cyclohexanone **28**, the initial Michael reaction proceeded from the less substituted α-methylene carbon having less acidic protons (Table 1, entry 7) contrary to our anticipation. Not only 1,3-dicarbonyl but also 1,2-dicarbonyl compounds provided the dihydrofuran **31** as shown in Table 1, entry 8. The enolic hydrofuran products such as **19**, **23** or **27** were unstable.

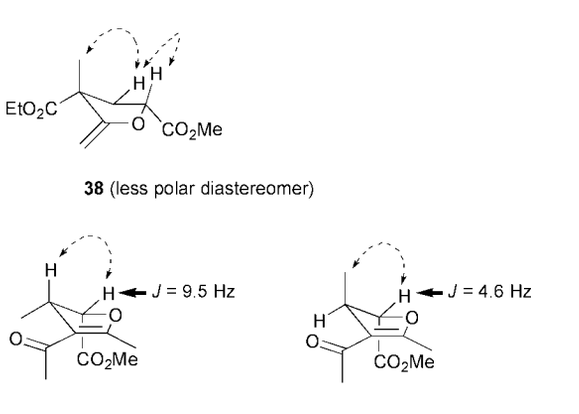
The present procedure was also applicable to various acyclic 1,3-dicarbonyl compounds and the results are listed in Table 2. In entry 2, a certain amount of cyclopropane derivative **36** was formed as a by-product. In entry 3, the product was a mixture of diastereomers. The relative stereochemistries of the less polar isomer of hydrofuran **38** and both diastereomers of the hydrofuran **40** were determined by NOESY experiments as shown in Fig. 2.

The reaction of methyl 3-oxobutanoate **32a** or pentane-2,4-dione **34** with methyl 2-bromobut-2-enoate **10** also provided hydrofuran derivatives **39** or **40** as a mixture of diastereomers in 23 and 35% yield respectively (Table 2, entries 4 and 5). Low yields might be due to steric hindrance in the initial Michael reaction. Attempted reaction of the 2-bromobut-2-enoate **10** with cyclic 1,3-dicarbonyl compounds did not give any hydrofuran products, though substrates disappeared rapidly by TLC monitoring.

Table 1 Synthesis of hydrofuran derivatives from cyclic 1,3-dicarbonyl compounds with methyl 2-bromopropenoate **6**

Entry	Substrate	Product	Yield (%)
1	**15**	**16**	**86**
2[a]	 **18**	 **19**	**87**[b]
3	 **20**	 **21**	83
4	 **22**	 **23**	92[b]
5	 **24**	 **25**	63
6	 **26**	 **27**	96[b]
7	 **28**	 **29**	33[b]
8	 **30**	 **31**	44

[a] Reactions were carried out at 0 °C, room temp. for 2 h except entry 6 in which reaction temp. was −78 to −50 °C. [b] A mixture of diastereomers was obtained.



38 (less polar diastereomer)

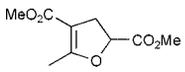
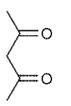
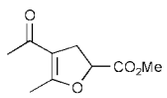
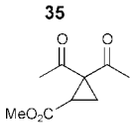
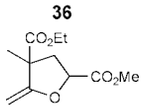
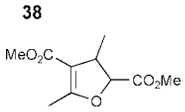
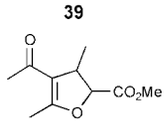
40 (more polar diastereomer) **40** (less polar diastereomer)

Fig. 2 Selected NOESY correlations of hydrofurans.

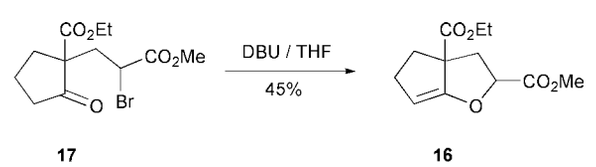
When the bromo ester **17** was treated with DBU in THF, the hydrofuran derivative **16** was obtained in 45% yield (Scheme 5).

Methyl 2-bromopropenoate **6** is an unstable compound and deteriorated in a few days even in the presence of hydroquinone in a freezer. Then we examined the hydrofuran synthesis by generating *in situ* the bromopropenoate **6** from the more stable methyl 2,3-dibromopropanoate **41** (Scheme 6), which was stable

Table 2 Synthesis of hydrofuran derivatives from acyclic 1,3-dicarbonyl compounds with methyl 2-bromopropenoate **6** or methyl 2-bromobutenoate **10**

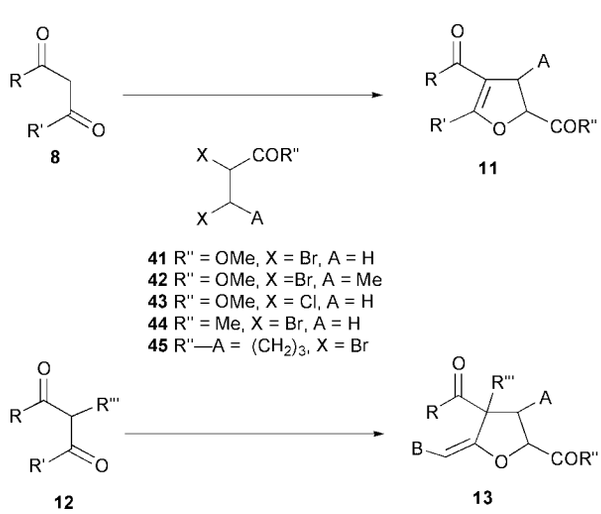
Entry[a]	Substrate	Product	Yield (%)
1	 **32a**	 **33**	62
2	 **34**	 **35**	61
		 **36**	27
3	 **37**	 **38**	74
4	**32a**	 **39**	23
5	**34**	 **40**	35

[a] Reactions were carried out at 0 °C–room temp. for 1–2 h.



17 **16**

Scheme 5



8 **11**

41 R'' = OMe, X = Br, A = H
42 R'' = OMe, X =Br, A = Me
43 R'' = OMe, X = Cl, A = H
44 R'' = Me, X = Br, A = H
45 R''—A = $(CH_2)_3$, X = Br

12 **13**

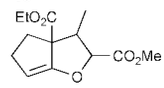
Scheme 6

enough to store in a refrigerator for a longer period of time. Improved or comparable results were obtained *via* the reactions of the bromopropenoate **6** as shown in Table 3, entries 1 and 2. Easy handling of the reagent and a 'clean' reaction without intractable material are the advantages of the present improved procedure. When sodium hydride was used as a base in the reaction of 2-(ethoxycarboxy)cyclopentanone **15**, only the Michael adduct **17** was obtained, in 63% yield. Methyl 2,3-dibromobutanoate **42** gave the hydrofuran derivatives in better yields than the reaction with methyl 2-bromobutenoate **10**, although yields were not satisfactory yet (Table 3, entries 6, 7 and 8).

In order to compare the differences caused by the halogen atoms, commercially available methyl 2,3-dichloropropanoate **43** was employed for the present reaction (Scheme 6 and Table 4). The results in entries 4 and 5 indicate that the dichloride **43** was less reactive towards subsequent *C*-alkylation.

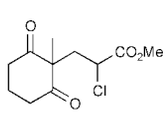
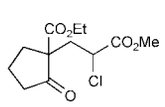
In order to expand the present protocol, we then examined the reactivity of 3-bromobut-3-en-2-one **9** as a domino partner. However, compound **9** is very unstable and we were unable to isolate it. Therefore, its precursor, 3,4-dibromobutan-2-one **44**, which is unstable also, was prepared by addition of bromine to but-3-en-2-one in pentane[13] at −15 °C and soon after careful work-up was subjected to the present hydrofuran synthesis. The reaction of various 1,3-dicarbonyl compounds with the dibromide **44** was carried out in THF using more than 2 equiv. of DBU as a base to afford 2-acetylhydrofuran derivatives in moderate to good yields (Scheme 6 and Table 5). Simple generation of 3-bromobut-3-en-2-one **9** was confirmed by NMR measurement after treating the dibromide **44** in $CDCl_3$ with

Table 3 Hydrofuran synthesis with methyl 2,3-dibromopropanoate **41** or 2,3-dibromobutanoate **42**

Entry	Substrate	Product	Yield (%)
1[a]	**32a**	**33**	89
2[a]	**34**	**35**	78
3[a]	**20**	**21**	82
4[a]	**15**	**16**	69[d]
5[a]	**37**	**38**	56
6[b,c]	**32a**	**39**	37[e] (1 : 1.7)
7[b,c]	**34**	**40**	37%[e] (1 : 1.4)
8[b,c]	**15**	 **46**	37[f] (2.1 : 1.5 : 1)

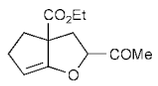
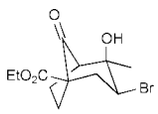
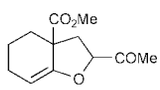
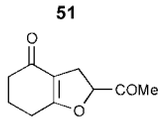
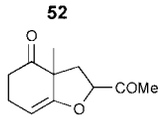
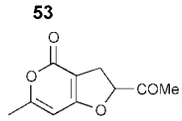
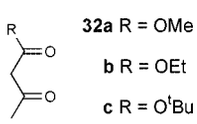
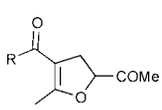
[a] Methyl 2,3-dibromopropanoate **41** was used and reactions were carried out at 0 °C–room temp. for 1–3 h. [b] Reaction was carried out at −30 °C–room temp. for 6–24 h. [c] Methyl 2,3-dibromobutanoate **42** was used as a domino partner. [d] A single diastereomer was obtained. [e] Two diastereomers were separated. [f] Three diastereomers were separated.

Table 4 Hydrofuran synthesis with methyl 2,3-dichloropropanoate **43**

Entry[a]	Substrate	Product	Yield (%)
1	**34**	**35** + **36**	**35** 85 **36** 9
2	**18**	**19**	93[b] (3.3 : 1)
3	**20**	**21**	69
4	**22**	**23**	38[c] (6 : 1)
		 **47**	31[e]
5	**15**	 **48**	100[c] (1.5 : 1)[d]

[a] Reactions were carried out at 0 °C for 0.5–3 h. [b] Two diastereomers were separated. [c] A mixture of two diastereomers was obtained. [d] Ratio was determined by ^{1}H NMR. [e] A single diastereomer was obtained.

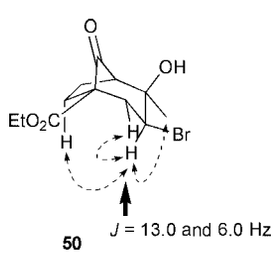
Table 5 Hydrofuran synthesis with 3,4-dibromobutan-2-one **44**

Entry	Substrate	Product	Yield (%)
1[a]	**15**	 **49**	55[c] (1 : 2)
		 **50**	38[c] (1 : 6)
2[b]	**15**	**49**	72[c] (7 : 3)
3[f]	**18**	 **51**	84[e] (1 : 2)
4[f]	**20**	 **52**	56
5[f]	**22**	 **53**	35[c] (1.7 : 1)
6[f]	**24**	 **54**	59
7[f]	**32a** R = OMe		**55a** R = OMe, 77
8[f]	 **32a** R = OMe **b** R = OEt **c** R = O^{t}Bu	 **55**	**55b** R = OEt, 57
9[f]			**55c** R = O^{t}Bu, 100
10[f]	**34** R = Me		**55d** R = Me, 93

[a] Reaction was carried out at 0 °C for 3.8 h. [b] Reaction was carried out at −25 °C to rt for 43 h. [c] A mixture of two diastereomers was obtained. [d] Ratio was determined by ^{1}H NMR. [e] Two diastereomers were separated. [f] Reaction was carried out at −30 °C to room temp. for 2–21 h.

an equivalent amount of DBU in an NMR tube. In the reaction of 2-(ethoxycarboxy)cyclopentanone **15**, in addition to the hydrofuran derivative **49**, domino Michael-aldol condensation product **50** was also produced. Prolonged reaction time enabled the equilibrium of the reaction to shift from aldol product **50** back to intermediary Michael addition product which cyclised to the desired hydrofuran **49** irreversibly (Table 5, entry 1). Though the dihydrofuran **49** was a separable mixture of diastereomers, relative stereochemistry could not be determined by NOESY experiments. On the other hand, relative stereochemistry of the major diastereomer of the aldol product **50** was determined by the coupling constants and NOESY experiments as shown in Fig. 3. The yield of dihydrofuran **53** was low due to its instability (Table 5, entry 5).

The success of generation of α-halo-α,β-unsaturated carbonyl compounds *in situ* from their corresponding α,β-dihalo carbonyl compounds prompted us to investigate the reaction of 2,3-dibromocyclohexanone **45** (Scheme 6) with pentane-2,4-dione **34** which provided the *trans*-hydrofuran derivative **56** in 49% yield (Table 6, entry 2). Results in entries 1 and 2 indicate that diethyl ether was a more suitable solvent than THF. As shown in Table 6, yields were moderate, probably due to the instability of 2,3-dibromocyclohexanone **45** and steric hindrance in Michael as well as *O*-alkylation steps. Relative stereochemistries of ring junctures of the products were evidently *trans* from the coupling constant (≈10 Hz) of the proton α to the ether oxygens.



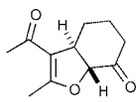
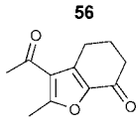
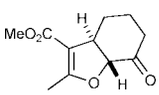
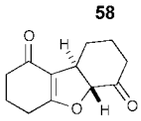
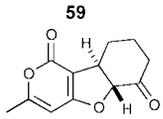
50

Fig. 3 Selected NOESY correlations of aldol product.

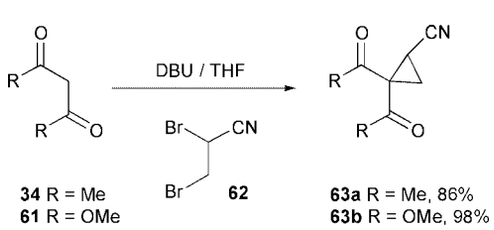
In the reaction of 2,3-dibromopropanonitrile **62**, only cyclopropane derivatives **63** were obtained in high yields as shown in Scheme 7. The sterically less congested cyano group may allow predominant *C*-alkylation.

After having established an efficient one-pot synthesis of hydrofuran derivatives by the domino Michael protocol, we then focused on transformation of the dihydrofuran derivatives into furan derivatives. Oxidation of dihydrofurans was at first attempted by using 2,3-dichlorodicyanobenzoquinone (DDQ) in refluxing 1,4-dioxane (Scheme 8). However, the dihydrofuran

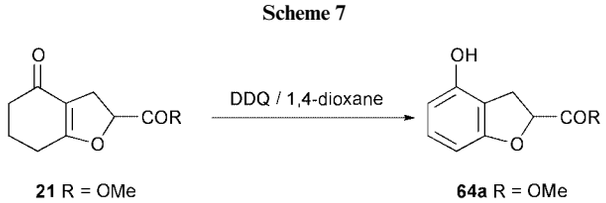
Table 6 Hydrofuran synthesis with 2,3-dibromocyclohexanone **45**

Entry[a]	Substrate	Product	Yield (%)
1[b]	**34**	 **56**	25
		 **57**	8
2[c]	**34**	**56** + **57**	**56** 49 **57** 5
3[c]	**32a**	 **58**	47[d]
4[e]	**20**	 **59**	47[d]
5[e]	**24**	 **60**	18[d]

[a] Reactions were carried at −24 °C to room temp. for 2–27 h. [b] THF was used as solvent. [c] Et_2O was used as solvent. [d] A single diastereomer was obtained. [e] A mixture of THF and Et_2O was used as solvent.

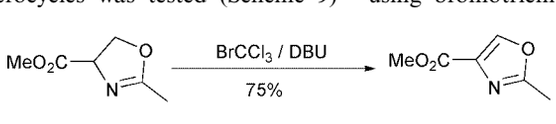


Scheme 7



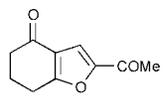
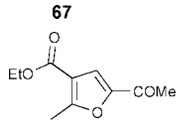
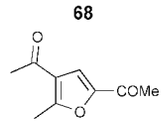
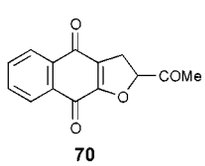
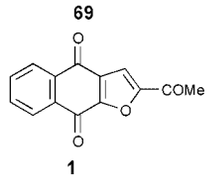
Scheme 8

21 or **52** provided the corresponding phenol **64a** or **64b** in 68 or 88% yield, respectively. Prolonged reaction time gave the corresponding quinone in low yield. The hydrofuran portion in **21** or **52** remained intact after DDQ oxidation. Switching the solvent to benzene also gave the phenol **64a**, in low yield. Preferential oxidation of the six-membered ring might be due to larger energy stabilisation by aromatisation. Then the protocol developed by Williams *et al.* for dehydrogenation of nitrogen heterocycles was tested (Scheme 9)[14] using bromotrichloromethane and DBU. Application of the reaction conditions successfully provided the desired furan derivatives as shown in Table 7.



Scheme 9 (Williams *et al.*[14]).

Table 7 Oxidation hydrofurans by procedure of Williams *et al.*

Entry[a]	Substrate	Product	Yield (%)
1	**52**	 **67**	63 (9)[b]
2	**55b**	 **68**	61
3	**55d**	 **69**	35 (12)[b]
4	 **70**	 **1**	43

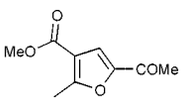
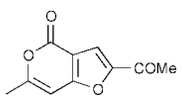
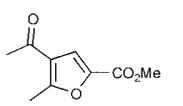
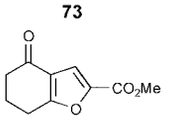
[a] Reactions were carried out with DBU and $BrCCl_3$ at 0 °C to room temp. for 7–21 h. [b] Amount of recovered dihydrofuran.

In our efforts to search for more efficient and less basic reaction conditions, attention was then paid to chemical manganese dioxide (CMD) oxidation (Scheme 10).[9c,15] At first, the effect of solvent was investigated by using cyclohexane, benzene, 1,2-dichloromethane, chloroform and so on. Among such efforts, refluxing a toluene solution of the dihydrofuran **55d** in the presence of 35 equiv. of CMD afforded the desired furan derivative **69** in 43% yield. Prolonged heating in the presence of toluene-*p*-sulfonic acid gave a better (59%) yield. Furthermore, the reaction was accelerated and the yield was improved to 68% when the reaction was carried out in methylcyclohexane (Table 8, entries 1, 2 and 3).[16] Representative results are shown in Table 8. No phenolic compound was produced as a by-product in entries 4, 5, and 10. The formation of thermodynamically less stable furan derivatives rather than phenolic compounds is interesting from a mechanistic point of view. Simplicity of operation is an attractive feature of the present CMD oxidation. In the case of oxidation of 2-(methoxycarbonyl)dihydrofuran, Williams' protocol or DDQ oxidation did not give satisfactory results. On the other hand, by tuning the solvent, CMD oxidations were successful in providing 2-(methoxycarbonyl)-furans **73** and **74** (Table 8, entries 9 and 10) indicating that the optimum solvent depends on the substrate employed.

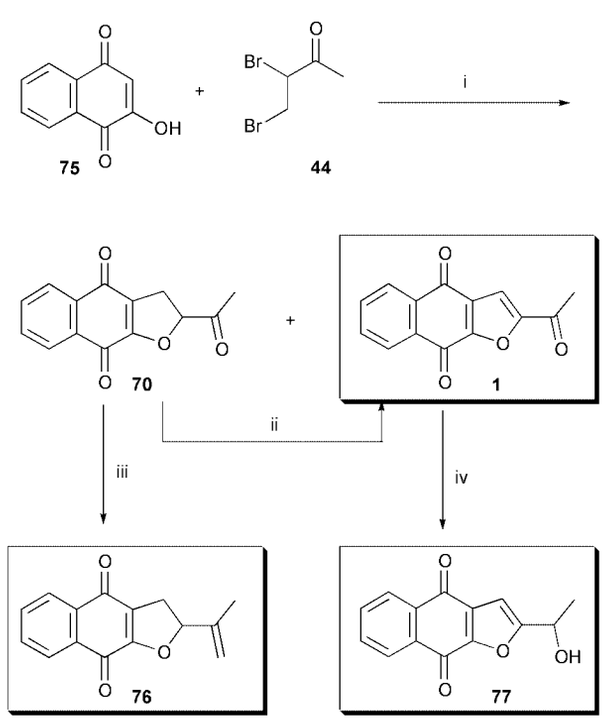
Scheme 10

The naphthofuran compound **1** was isolated from *Tabebuia cassinoides* (Lam.) DC. (Bignoniaceae) and has *in vitro* cytotoxic activity against KB cells (ED_{50} = 1.0 μg ml^{-1}).[2] In order to demonstrate the utility of our furan synthesis, we report a short-step synthesis of the naphthofuran compound **1**. The reaction of commercially available 2-hydroxy-1,4-naphthoquinone **75** with 3,4-dibromobutan-2-one **44** in the presence of DBU in THF furnished not only naphthodihydrofuran **70** in 37% yield but also the desired natural naphthofuran **1** in 28% yield (Scheme 11). Moderate combined yields of the products **70** and **1** might be due to the low solubility of the products **70** and

Table 8 CMD oxidation of hydrofurans

Entry[a]	Substrate	Product	Time/h	Yield (%)
1[b]	**55d**	**69**	42	43
2[b,c]	**55d**	**69**	44	59
3[d]	**55d**	**69**	3.5	68
4[d]	**52**	**67**	3.5	66
5[e]	**52**	**67**	22	55
6[d]	**55a**	 **71**	19.5	54
7[d]	**54**	 **72**	3	62
8[e]	**70**	**1**	19	60 (29)[h]
9[c,f]	**35**	 **73**	22	69 (20)[h]
10[g]	**21**	 **74**	23	43 (31)[h]

[a] Excess of CMD (35 equiv.) was used. [b] Toluene was used as solvent. [c] A catalytic amount of PTSA was added. [d] Methylcyclohexane was used as solvent. [e] Chloroform was used as solvent. [f] Benzene was used as solvent. [g] 1,2-Dichloroethane was used as solvent. [h] Amount of recovered dihydrofuran.



Scheme 11 *Reagents, conditions and yields*: i, DBU, THF, −25 °C to rt, 5.5 h, **1** 28%, **70** 37%; ii, MnO_2, $CHCl_3$, 60%; iii, methyltriphenylphosphonium bromide, *n*-BuLi, THF, rt, 20 h, 20%; iv, $NaBH_4$, MeOH, 79%.

1 which made isolation and purification difficult. Although DDQ oxidation of the dihydrofuran **70** resulted in complete recovery, dehydrogenation under Williams' protocol afforded the natural naphthofuran **1** in 43% yield (Table 7, entry 4). Furthermore the yield was improved by treatment of the dihydrofuran **70** with CMD in chloroform to provide the natural naphthofuran **1** in 60% yield (Table 8, entry 8) along with 29% recovery of the dihydrofuran **70**. The pathway of direct formation of the natural naphthofuran **1** under the present anionic domino reaction conditions is uncertain. An attempt of oxidation of the dihydrofuran **70** with bromine in the presence of DBU led only to recovery of the starting material **70**. Since attempted DDQ oxidation led only to recovery of the hydrofuran **70**, the naphthoquinone **75** could not be an oxidising reagent in the present synthesis. The present one-pot synthesis is superior to the previous 4-step synthesis in its simplicity of operation.[2,15] Sodium borohydride reduction of the natural naphthofuran **1** led in 79% yield to another natural naphthofuran **77** which is also cytotoxic (ED_{50} = 2.0 μg ml^{-1}).[2,17] Moreover, Wittig condensation of the dihydrofuran **70** provided in 20% yield *dl*-didehydroiso-α-lapachone **76**, a natural dihydrofuran isolated from heartwood of *Tabebuia rosea*.[18] The spectral data of the synthetic natural products, **1**, **76** and **77** were completely identical with those reported.

In summary, we have demonstrated that the domino nucleophilic reactions of both carbon and oxygen termini of the enolates of 1,3-dicarbonyl compounds to the α-halo-α,β-unsaturated carbonyl compounds furnish a variety of substituted hydrofuran derivatives **11** or **13** in satisfactory yields. The present protocol formally constitutes [3 + 2]heteroannulations of enolates to electron-deficient olefins. The utility was exemplified by CMD dehydrogenation to furan derivatives and application to the syntheses of natural antitumor naphthofurans.

Experimental

Mps were determined with a Yanaco MP hot-stage apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer. ^{1}H NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (200 MHz) and Unity 500plus (500 MHz) instruments with tetramethylsilane as internal standard. *J*-Values are in Hz. ^{13}C NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (50 MHz) and Unity 500plus (125 MHz) instruments with tetramethylsilane as internal standard. UV spectrum was measured with a JASCO V-530 spectrophotometer. Mass spectral data were obtained with a Hitachi M-4100 spectrometer. Medium-pressure liquid chromatography (MPLC) was carried out on a JASCO PRC-50 instrument with a silica gel-packed column. Microanalyses were carried out in the Instrumental Analysis Center for Chemistry, Tohoku University.

Methyl 3a-(ethoxycarbonyl)-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan-2-carboxylate 16

Procedure I with methyl 2-bromopropenoate 6. To a solution of 2-(ethoxycarbonyl)cyclopentanone **15** (148 μl, 1 mmol) and DBU (450 μl, 3 mmol) in THF (3 ml) was added methyl 2-bromopropenoate **6** (72 μl, 0.72 mmol) at −50 °C under nitrogen atmosphere. After the solution had been stirred for 5 h, more 2-bromopropenoate **6** (55 μ1, 0.55 mmol) was added. After 2 h, the reaction was quenched by addition of aq. ammonium chloride and the mixture was extracted with ethyl acetate twice. The combined organic layer was washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the mixture followed by silica gel column chromatography of the residue gave the dihydrofuran **16** (207 mg, 86%).

Procedure II with methyl 2,3-dibromopropanoate 41 (representative procedure). To a stirred solution of 2-(ethoxycarbonyl)-cyclopentanone **15** (148 μl, 1.0 mmol) in THF (3 ml) was added DBU (300 μl, 2.0 mmol) at 0 °C under nitrogen atmosphere. After the mixture had been stirred for 30 min, a solution of 2,3-dibromopropanoate **41** (325 mg, 1.3 mmol) in THF (3 ml)

was added and the resulting solution was stirred for 2 h at room temperature. Then DBU (75 μl, 0.5 mmol) and 2,3-dibromopropanoate **41** (128 mg, 0.5 mmol) in THF (1 ml) was added. After being stirred for 1 h, the reaction mixture was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice and the combined organic layer was washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the mixture followed by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 2) provided the dihydrofuran **16** (167 mg, 69%); ν_{max}/cm^{-1} (neat) 2973, 1728 and 1680; δ_H (200 MHz) 1.29 (t, *J* 7.1, 3H), 1.78–1.95 (m, 2H), 2.39–2.57 (m, 2H), 2.80–3.0 (m, 2H), 3.80 (s, 3H), 4.20 (q, *J* 7.1, 2H), 4.78 (dd, *J* 3.5, 1.3, 1H) and 5.27 (dd, *J* 10.2, 6.4, 1H); δ_C (50 MHz) 13.00 (q), 34.07 (t), 35.56 (t), 38.39 (t), 52.25 (q), 61.17 (t), 85.28 (d), 95.14 (d), 161.51 (s), 171.26 (s) and 173.18 (s) (Found: C, 59.63; H, 6.52. Calc. for $C_{11}H_{16}O_5$: C, 59.99; H, 6.52%).

Methyl 2-bromo-3-[1-(ethoxycarbonyl)-2-oxocyclopentyl]-propanoate 17

To a solution of 2-(ethoxycarbonyl)cyclopentanone **15** (741 μl, 5.0 mmol) and diethylamino(trimethyl)silane (470 μl, 5.0 mmol) was added methyl 2-bromopropenoate **6** (741 μl, 5.0 mmol) at 0 °C and the resulting solution was stirred for 20 h at room temperature. Silica gel column chromatography followed by MPLC gave bromo ester **17** as a mixture of inseparable diastereomers (636 mg, 40%); ν_{max}/cm^{-1} ($CHCl_3$) 2957, 1750, 1728, 1439, 1365, 1273, 1155 and 1026; δ_H (200 MHz) 1.26 (t, *J* 6.4, 1.2H)[a], 1.28 (t, *J* 7.1, 1.8H)[a], 1.80–2.20 (m, 3H), 2.20–2.90 (m, 3H), 3.76 (s, 1.8H)[b], 3.78 (s, 1.2H)[b], 4.17 (q, *J* 7.2, 1.2H)[c], 4.20 (q, *J* 6.4, 0.8H)[c], 4.48 (dd, *J* 8.7, 7.0, 0.4H)[d] and 4.56 (dd, *J* 9.0, 4.4, 0.6H)[d] ([a]total 3H, [b]total 3H, [c]total 2H, [d]total 1H).

Dimethyl 2,3,3a,4,5,6-hexahydrobenzofuran-2,3a-dicarboxylate 19

Representative procedure with methyl 2-bromopropenoate 6. To a stirred solution of 2-(methoxycarbonyl)cyclohexanone **18** (156 mg, 1.0 mmol) in THF (3 ml) was added DBU (450 μl, 3.0 mmol) at 0 °C under nitrogen atmosphere. After the solution had been stirred for 20 min, methyl 2-bromopropenoate **6** (130 μl, 1.3 mmol) was added and stirring was continued for 50 min at room temperature. The reaction was quenched with aq. ammonium chloride and the product was extracted with ethyl acetate twice. The combined organic layer was washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solution followed by purification by MPLC (eluent ethyl acetate–*n*-hexane = 1 : 2) provided the less polar diastereomer of **19** (141 mg) and the more polar diastereomer of **19** (69 mg) in 87% combined yield.

The yield by the reaction with chloropropanoate **43** was 93%.

The less polar diastereomer had ν_{max}/cm^{-1} (neat) 2953, 1763, 1731, 1708, 1449 and 1215; δ_H (200 MHz) 1.22–1.66 (m, 2H), 2.04–2.17 (m, 2H), 2.39–2.57 (m, 2H), 2.45–2.55 (m, 1H), 2.73 (dd, *J* 12.8, 5.9, 1H), 3.75 (s, 3H), 3.78 (s, 3H), 4.71 (dd, *J* 10.7, 5.9, 1H) and 5.10 (t, *J* 3.7, 1H) (Found: C, 59.60; H, 6.71. Calc for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71%).

The more polar diastereomer had ν_{max}/cm^{-1} (neat) 2953, 1760, 1731, 1741, 1705, 1450 and 1221; δ_H (200 MHz) 1.12–1.42 (m, 1H), 1.62–1.85 (m, 1H), 2.01–2.28 (m, 3H), 2.45 (dt, *J* 12.8, 5.9, 1H), 2.73 (dd, *J* 12.3, 3.2, 1H), 2.92 (d, *J* 13.2, 1H), 3.66 (s, 3H), 3.76 (s, 3H), 4.71 (dd, *J* 9.8, 1.2, 1H) and 5.10 (t, *J* 3.7, 1H) (Found: C, 60.25; H, 6.71. Calc. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71%).

Methyl 4-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate 21

The yields of the reactions with bromopropenoate **6**, bromopropanoate **41** and dichloropropanoate **43** were 83, 82 and 69% respectively; ν_{max}/cm^{-1} (neat) 2953, 1760, 1763, 1731, 1708, 1449 and 1215; δ_H (200 MHz) 1.95–2.60 (m, 6H), 2.96 (ddt, *J* 14.9, 7.2, 2.0, 1H), 3.18 (ddt, *J* 14.9, 11.3, 2.0, 1H), 3.81 (s, 3H) and 5.18 (dd, *J* 11.3, 7.2, 1H); δ_C (50 MHz) 21.5, 23.6, 30.4, 36.3, 52.6, 80.0, 112.3, 170.3, 176.8 and 194.9 (Found: C, 60.95; H, 6.04. Calc. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16%).

Methyl 3a-methyl-4-oxo-2,3,3a,4,5,6-hexahydrobenzofuran-2-carboxylate 23

The yields of the reactions with bromopropenoate **6** and dichloropropanoate **43** were 92 and 31% respectively; ν_{max}/cm^{-1} (neat) 2953, 1759, 1714, 1695, 1439 and 1165; δ_H (200 MHz) 1.31 (s, 1H)[a], 1.37 (s, 2H)[a], 2.10–2.74 (m, 6H), 3.78 (s, 2H)[b], 3.81 (s, 1H)[b], 4.74 (dd, *J* 10.6, 2.2, 0.3H)[c], 4.84 (dd, *J* 9.0, 8.1, 0.7H)[c], 5.14 (dd, *J* 4.1, 2.2, 0.7H)[d] and 5.16 (t, *J* 2.2, 0.3H)[d] ([a]total 3H, [b]total 3H, [c]total 1H, [d]total 1H) (Found: C, 62.57; H, 6.62. Calc. for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71%).

Methyl 6-methyl-4-oxo-2,3-dihydro-4*H*-furo[3,2-*c*]pyran-2-carboxylate 25

Yield 63%; ν_{max}/cm^{-1} (neat) 2959, 1734, 1714, 1645, 1585 and 1261; δ_H (200 MHz) 2.28 (s, 3H), 3.16 (dd, *J* 15.1, 6.8, 1H), 3.39 (dd, *J* 15.1, 11.1, 1H), 3.83 (s, 3H), 5.31 (dd, *J* 15.1, 6.8, 1H) and 6.04 (s, 1H).

Methyl 1-methylene-6-oxo-2,7-dioxaspiro[4.4]nonane-3-carboxylate 27

Two diastereomers were separated to give 133 mg and 70 mg of dihydrofurans **27** (96% combined yield) in the following order of elution.

The less polar diastereomer had mp 60–63 °C; ν_{max}/cm^{-1} (CCl_4) 3119, 2953, 1786, 1743, 1680, 1439 and 1217; δ_H (200 MHz) 2.24 (dd, *J* 13.0, 5.7, 1H), 2.31–2.70 (m, 2H), 2.90 (dd, *J* 13.0, 8.1, 1H), 3.81 (s, 3H), 4.02 (d, *J* 3.2, 1H), 4.39 (d, *J* 5.5, 1H), 4.43 (d, *J* 5.5, 1H), 4.56 (d, *J* 3.2, 1H) and 5.03 (dd, *J* 13.0, 8.1, 1H) (Found: C, 56.42; H, 5.69. Calc. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%).

The more polar diastereomer had mp 58–62 °C; ν_{max}/cm^{-1} (CCl_4) 3119, 2953, 1786, 1743, 1680, 1439 and 1217; δ_H (200 MHz) 2.30–2.70 (m, 3H), 2.82 (dd, *J* 13.0, 7.9, 1H), 3.82 (s, 3H), 4.21 (d, *J* 3.2, 1H), 4.40 (d, *J* 5.5, 1H), 4.44 (d, *J* 5.5, 1H), 4.56 (d, *J* 3.2, 1H) and 4.82 (t, *J* 7.9, 1H) (Found: C, 56.48; H, 5.64. Calc. for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%).

Methyl 7-phenylsulfinyl-2,3,3a,4,5,6-hexahydrobenzofuran-2-carboxylate 29

Yield 33%; ν_{max}/cm^{-1} (CCl_4) 2941, 1780, 1680, 1442, 1209 and 1034; δ_H (200 MHz) 1.20–2.20 (m, 6H), 2.30–2.90 (m, *J* 13.0, 3H), 3.83 (s, 1.5H)[a], 3.84 (s, 1.5H)[a], 4.80–5.20 (m, 1H) and 7.35–7.80 (m, 5H) ([a]total 3H).

Peaks of major diastereomer: δ_C (50 MHz) 16.58 (t), 21.74 (t), 27.30 (t), 34.54 (t), 39.75 (d), 52.46 (q), 79.18 (d), 109.29 (s), 124.11 (d) (×2), 128.66 (d) (×2), 129.74 (d), 143.51 (s), 161.16 (s) and 170.14 (s).

Peaks of minor diastereomer: δ_C (50 MHz) 16.36 (t), 21.80 (t), 27.30 (t), 35.45 (t), 39.75 (d), 52.56 (q), 78.67 (d), 109.83 (s), 124.11 (d) (×2), 128.66 (d) (×2), 129.74 (d), 143.71 (s), 161.16 (s) and 170.77 (s) (Found: C, 63.03; H, 6.12. Calc. for $C_{16}H_{18}O_4S$: C, 62.73; H, 5.92%).

Methyl 7-oxo-2,3,4,5,6,7-hexahydrobenzofuran-2-carboxylate 31

Yield 44%; ν_{max}/cm^{-1} (neat) 2926, 1763, 1757 and 1678; δ_H (200 MHz) 2.00–2.18 (m, 2H), 2.34–2.54 (dd, 4H), 3.06 (ddt, *J* 18.0, 7.7, 2.0, 1H), 3.17 (ddt, *J* 18.0, 10.8, 2.0, 1H), 3.80 (s, 3H) and 5.04 (dd, *J* 10.8, 7.7, 1H) (Found: C, 60.88; H, 6.16. Calc. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16%).

Dimethyl 5-methyl-2,3-dihydrofuran-2,4-dicarboxylate 33

The yields by the reactions with bromopropenoate **6** and dibromopropanoate **41** were 62 and 89% respectively; ν_{max}/cm^{-1} (neat) 3536, 2955, 2464, 1732, 1440, 1386 and 1338; δ_H (200 MHz) 2.26 (dd, *J* 1.7, 3H), 3.02 (ddq, *J* 14.9, 7.3, 1.7, 1H), 3.23 (ddq, *J* 14.9, 11.6, 1.7, 1H), 3.71 (s, 3H), 3.80 (s, 3H) and 5.03 (dd, *J* 11.6, 7.3, 1H) (Found: C, 54.00; H, 6.04. Calc. for $C_9H_{12}O_5$: C, 53.97; H, 5.96%).

Methyl 4-acetyl-5-methyl-2,3-dihydrofuran-2-carboxylate 35

The yields by the reactions with bromopropenoate **6**, dibromopropanoate **41** and dichloropropanoate **43** were 61, 78 and 85% respectively; ν_{max}/cm^{-1} (neat) 2939, 1759, 1678, 1626 and 1213; δ_H (200 MHz) 2.23 (s, 3H), 2.29 (t, *J* 1.5, 3H), 3.08 (ddq, *J* 14.7, 7.3, 1.5, 1H), 3.29 (ddq, *J* 14.7, 11.4, 1.5, 1H), 3.80 (s, 3H) and 5.03 (dd, *J* 11.4, 7.3, 1H) (Found: C, 58.39; H, 6.37. Calc. for $C_9H_{12}O_4$: C, 58.69; H, 6.57%).

Methyl 2,2-diacetylcyclopropanecarboxylate 36

Yield 27%; ν_{max}/cm^{-1} (neat) 2935, 1736, 1703, 1442 and 1208; δ_H (200 MHz) 1.66 (dd, *J* 8.7, 4.6, 1H), 1.93 (dd, *J* 6.5, 4.6, 1H), 2.23 (s, 3H), 2.36 (s, 3H), 2.60 (dd, *J* 8.7, 6.5, 1H) and 3.70 (s, 3H) (Found: C, 58.86; H, 6.47. Calc. for $C_9H_{12}O_4$: C, 58.69; H, 6.57%).

Methyl 4-(ethoxycarbonyl)-4-methyl-5-methylenetetrahydrofuran-2-carboxylate 38

The yields by the reactions with bromopropenoate **6** and dibromopropanoate **41** were 74 and 56% respectively.

The less polar diastereomer had ν_{max}/cm^{-1} (neat) 2935, 1736, 1680, 1441, 1269 and 1219; δ_H (500 MHz) 1.27 (t, *J* 7.0, 3H), 1.48 (s, 3H), 1.99 (dd, *J* 13.0, 9.0, 1H), 2.91 (dd, *J* 13.0, 7.0, 1H), 3.80 (s, 3H), 4.09 (d, *J* 2.5, 1H), 4.13–4.24 (m, 2H), 4.50 (d, *J* 2.5, 1H) and 4.89 (dd, *J* 9.0, 7.0, 1H).

The more polar diastereomer had ν_{max}/cm^{-1} (neat) 2936, 1741, 1690, 1441, 1259 and 1232; δ_H (200 MHz) 1.25 (t, *J* 7.1, 3H), 1.48 (s, 3H), 2.24 (dd, *J* 13.1, 8.7, 1H), 2.94 (dd, *J* 13.1, 5.2, 1H), 3.80 (s, 3H), 4.12 (d, *J* 2.4, 1H), 4.15 (q, *J* 7.1, 2H), 4.50 (d, *J* 2.4, 1H) and 4.76 (dd, *J* 8.7, 5.2, 1H).

Dimethyl 3,5-dimethyl-2,3-dihydrofuran-2,4-dicarboxylate 39

Representative procedure with methyl 2,3-dibromobutanoate 42. To a stirred solution of methyl 3-oxobutanoate **32a** (100 µl, 1.0 mmol) in THF (3 ml) was added DBU (330 µl, 2.2 mmol) at 0 °C under nitrogen atmosphere. After the solution had been stirred for 20 min, a solution of methyl 2,3-dibromobutanoate **42** (340 mg, 1.32 mmol) in THF (3 ml) was added at −20 °C and the temperature was raised gradually to room temperature during 5 h. DBU (149 µl, 1.0 mmol) was added and after 50 min the reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice, and the extract was washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solution followed by MPLC of the residue (eluent ethyl acetate–*n*-hexane = 1 : 2) afforded the less polar (30 mg) and the more polar diastereomer of the dihydrofuran **39** (42 mg) in 37% combined yield. The yield by the reaction with bromobutenoate **10** was 23%.

The less polar diastereomer had ν_{max}/cm^{-1} (neat) 2933, 1761, 1743, 1705, 1651, 1439, 1358 and 1217; δ_H (200 MHz) 1.33 (d, *J* 6.7, 3H), 2.26 (d, *J* 1.3, 3H), 3.34 (dqq, *J* 6.7, 5.2, 1.3, 1H), 3.71 (s, 3H), 3.78 (s, 3H) and 4.55 (d, *J* 5.2, 1H).

The more polar diastereomer had ν_{max}/cm^{-1} (neat) 2935, 1765, 1703, 1651, 1439, 1358 and 1207; δ_H (200 MHz) 1.08 (d, *J* 6.8, 3H), 2.25 (d, *J* 1.2, 3H), 3.50 (dqq, *J* 9.8, 6.8, 1.2, 1H), 3.73 (s, 3H), 3.81 (s, 3H) and 5.06 (d, *J* 9.8, 1H) (Found: C, 55.76; H, 6.49. Calc. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59%).

Methyl 4-acetyl-3,5-dimethyl-2,3-dihydrofuran-2-carboxylate 40

The yields of the reactions with bromobutenoate **10** and dibromobutanoate **42** were 35 and 37% respectively.

The less polar diastereomer had ν_{max}/cm^{-1} (neat) 2933, 1750, 1672, 1626, 1439 and 1209; δ_H (200 MHz) 1.32 (d, *J* 6.8, 3H), 2.25 (s, 3H), 2.30 (d, *J* 1.2, 3H), 3.40 (dqq, *J* 6.8, 4.6, 1.2, 1H), 3.78 (s, 3H) and 4.54 (d, *J* 4.6, 1H) (Found: C, 60.29; H, 6.98. Calc. for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12%).

The more polar diastereomer had ν_{max}/cm^{-1} (neat) 2935, 1769, 1745, 1676, 1630, 1603, 1439 and 1201; δ_H (200 MHz) 1.07 (d, *J* 6.8, 3H), 2.28 (s, 3H), 2.29 (d, *J* 1.0, 3H), 3.53 (dqq, *J* 9.5, 6.8, 1.0, 1H), 3.83 (s, 3H) and 5.04 (d, *J* 9.5, 1H) (Found: C, 60.37; H, 6.94. Calc. for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12%).

Ethyl 2-(methoxycarbonyl)-3-methyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan-3a-carboxylate 46

Three diastereomers were separated by MPLC and spectral data are described in their order of elution.

Diastereomer I had 17% yield; ν_{max}/cm^{-1} (neat) 2933, 1761, 1720, 1680, 1441 and 1226; δ_H (200 MHz) 1.14 (d, *J* 6.9, 3H), 1.31 (t, *J* 7.1, 3H), 1.64–1.84 (m, 1H), 2.22–2.50 (m, 2H), 2.58–2.80 (m, 2H), 3.81 (s, 3H), 4.10–4.38 (m, 2H), 4.67 (dd, *J* 3.5, 1.4, 1H) and 4.98 (d, *J* 10.1, 1H).

Diastereomer II had 12% yield; ν_{max}/cm^{-1} (neat) 2933, 1763, 1726, 1684, 1441 and 1228; δ_H (200 MHz) 0.89 (d, *J* 7.3, 3H), 1.29 (t, *J* 7.2, 3H), 1.85–3.00 (m, 5H), 3.81 (s, 3H), 4.21 (q, *J* 7.2, 2H), 4.78 (dd, *J* 3.3, 1.3, 1H) and 5.36 (d, *J* 5.5, 1H).

Diastereomer III had 8% yield; ν_{max}/cm^{-1} (neat) 2933, 1760, 1726, 1682, 1441 and 1244; δ_H (200 MHz) 1.15 (d, *J* 7.4, 3H), 1.25 (t, *J* 7.1, 3H), 1.90–2.10 (m, 2H), 2.35–2.55 (m, 1H), 2.75–3.00 (m, 1H), 3.08 (qd, *J* 7.4, 1.6, 1H), 3.76 (s, 3H), 4.14 (qd, *J* 7.1, 1.1, 2H), 4.59 (d, *J* 1.6, 1H) and 4.80 (dd, *J* 3.7, 1.8, 1H).

Methyl 2-chloro-3-(1-methyl-2,6-dioxocyclohexyl)propanoate 47

To a stirred solution of 2-methylcyclohexane-1,3-dione **22** (63 mg, 0.5 mmol) in THF (3 ml) was added DBU (194 µl, 1.3 mmol) at 0 °C under nitrogen atmosphere. After the mixture had been stirred for 20 min, methyl 2,3-dichloropropanoate **43** (77 µl, 0.65 mmol) was added and stirring was continued for 40 min. The reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice and the extracts were washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solution followed by MPLC separation of the residue gave chloride **47** (33 mg, 31%) along with the dihydrofuran **23** (47 mg, 38%); ν_{max}/cm^{-1} (neat) 2953, 1751, 1712, 1555, 1437, 1412, 1281, 1172 and 1022; δ_H (200 MHz) 1.33 (s, 3H), 1.97–2.14 (m, 2H), 2.63 (d, *J* 7.8, 2H), 2.66–2.78 (m, 4H), 3.73 (s, 3H) and 4.46 (t, *J* 7.8, 1H).

Methyl 2-chloro-3-[1-(ethoxycarbonyl)-2-oxocyclopentyl]-propanoate 48

Yield 100%; ν_{max}/cm^{-1} (neat) 2959, 1750, 1728, 1441, 1263 and 1173; δ_H (200 MHz) 1.26 (t, *J* 7.0, 1.8H)[a], 1.28 (t, 1.2H)[a], 1.80–2.10 (m, 3H), 2.15–2.81 (m, 5H), 3.78 (s, 1.8H)[b], 3.79 (s, 1.2H)[b], 4.36 (q, *J* 7.0, 2H), 4.48 (t, *J* 6.6, 0.4H)[c] and 4.59 (t, *J* 6.6, 0.6H)[c] ([a]total 3H, [b]total 3H, [c]total 1H).

Ethyl 2-acetyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*b*]furan-3a-carboxylate 49

Representative procedure with 3,4-dibromobutan-2-one 44. To a stirred solution of but-3-en-2-one (110 µl, 1.3 mmol) in pentane (1.5 ml) was added a solution of bromine (72 µl, 1.4 mmol) in pentane (1 ml) at −15 °C. After being stirred for 10 min, the solvent was evaporated *in vacuo*.

To a stirred solution of 2-(ethoxycarbonyl)cyclopentanone **15** (148 µl, 1.0 mmol) in THF (3 ml) was added DBU (360 µl,

2.4 mmol) at 0 °C under nitrogen atmosphere. After the mixture had been stirred for 20 min, a solution of 3,4-dibromobutan-2-one **44** (prepared above) in THF (3 ml) was added at 0 °C and the resulting solution was stirred for 3.8 h at room temperature. The reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice and the extracts were washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by MPLC separation of the residue (eluent ethyl acetate–*n*-hexane = 1 : 3) provided a mixture of diastereomers of **49** (122 mg, 55%) along with bicyclic ketone **50** (117 mg, 38%) as crystals.

The dihydrofuran **49** had ν_{max}/cm^{-1} (CCl_4) 2941, 1722, 1680, 1444 and 1203; δ_H (200 MHz) 1.23 (t, *J* 7.0, 2H)[a], 1.29 (t, *J* 7.1, 1H)[a], 1.60–2.20 (m, 2H), 2.25 (s, 1H)[b], 2.27 (s, 2H)[b], 2.35–2.65 (m, 2H), 2.80–3.00 (m, 2H), 4.11 (qd, *J* 7.0, 1.1, 1.3H)[c], 4.20 (q, *J* 7.1, 0.7H)[c], 4.76 (dd, *J* 3.4, 1.3, 1H), 4.81 (dd, *J* 10.5, 1.7, 0.65H)[d] and 5.14 (dd, *J* 10.2, 6.7, 0.35H)[d] ([a]total 3H, [b]total 3H, [c]total 2H, [d]total 1H); *m*/*z* 224 (M^+, 12%), 181 ($M^+ - CH_3CO$, 4), 154 (55), 151 ($M^+ - CO_2Et$, 21), 108 (59), 79 (29), 55 (51) and 43(100) (Found: M^+, 224.1046. Calc. for $C_{12}H_{16}O_4$: *M*, 224.1048).

Ethyl 3-bromo-4-hydroxy-4-methyl-8-oxobicyclo[3.2.1]octane-carboxylate 50. This compound had mp 104–106 °C; ν_{max}/cm^{-1} (CCl_4) 3571, 2953, 1772, 1734, 1680, 1273 and 1217; δ_H (500 MHz) 1.28 (t, *J* 7.0, 2H), 1.36 (s, 2.6H)[a], 1.39 (s, 0.4H)[a], 1.67–1.75 (m, 1H), 1.96–2.00 (m, 1H), 2.04–2.19 (m, 1H), 2.34 (s, 1H), 2.46 (dd, *J* 13.0, 6.0, 0.15H)[b], 2.49 (dd, *J* 13.0, 6.0, 0.85H)[b], 2.55 (d, *J* 7.5, 1H), 2.57–2.62 (m, 1H), 2.87 (t, *J* 13.0, 1H), 4.23 (q, *J* 7.0, 0.3H)[c], 4.24 (q, *J* 7.0, 1.7H)[c], 4.35 (dd, *J* 12.5, 6.0, 0.85H)[d] and 4.42 (dd, *J* 13.0, 6.0, 0.15H)[d] ([a]total 3H, [b]total 1H, [c]total 2H, [d]total 1H); δ_C (125 MHz) peaks of minor diastereomer: 14.10 (s), 17.07 (t), 26.03 (t), 26.87 (q), 40.42 (t), 54.49 (d), 56.34 (d), 57.67 (s), 61.66 (t), 79.45 (s), 169.56 (s) and 206.97 (s); peaks of major diastereomer; 14.10 (s), 18.62 (t), 25.50 (t), 26.87 (q), 42.24 (t), 54.49 (d), 55.89 (d), 57.26 (s), 61.55 (t), 79.45 (s), 169.56 (s) and 206.40 (s) (Found: C, 47.23; H, 5.6. Calc. for $C_{12}H_{17}BrO_4$: C, 47.29; H, 5.50%).

Methyl 2-acetyl-2,3,3a,4,5,6-hexahydrobenzofuran-3a-carboxylate 51

The less polar diastereomer was obtained in 28% yield; ν_{max}/cm^{-1} 3568, 3072, 2960, 2496, 1720, 1682, 1449 and 1359; δ_H (200 MHz) 1.26 (t, *J* 7.1, 3H), 1.60–1.90 (m, 2H), 2.22 (s, 3H), 2.35–2.55 (m, 2H), 2.70–3.00 (m, 2H), 4.20 (q, *J* 7.1, 2H), 4.76 (dd, *J* 3.4, 1.3, 1H) and 5.14 (dd, *J* 10.2, 6.7, 1H).

The more polar diastereomer was obtained in 56% yield; ν_{max}/cm^{-1} 3568, 3072, 2960, 2496, 1720, 1682, 1449 and 1359; δ_H (200 MHz) 1.22 (t, *J* 7.1, 3H), 1.65–1.91 (m, 1H), 2.00–2.15 (m, 1H), 2.26 (s, 3H), 2.38–2.68 (m, 2H), 2.75–2.93 (m, 2H), 4.11 (qd, *J* 7.0, 1.1, 2H), 4.76 (dd, *J* 3.4, 1.3, 1H) and 4.91 (dd, *J* 10.5, 1.7, 1H); *m*/*z* 224 (M^+, 12%), 181 ($M^+ - CH_3CO$, 4), 154 (55), 151 ($M^+ - CO_2Et$, 21), 108 (59), 79 (29), 55 (51) and 43 (100) (Found: M^+, 224.1046. Calc. for $C_{12}H_{16}O_4$: *M*, 224.1048).

2-Acetyl-2,3,4,5,6,7-hexahydrobenzofuran-4-one 52

Yield 56%; crystals; mp 52–55 °C; ν_{max}/cm^{-1} ($CHCl_3$) 3030, 1726, 1641, 1456, 1402, 1359, 1196 and 1178; δ_H (200 MHz) 1.95–2.20 (m, 2H), 2.25 (s, 3H), 2.3–2.4 (m, 2H), 2.45–2.60 (m, 2H), 2.88 (ddt, *J* 14.9, 7.6, 2.0, 1H), 3.11 (ddt, *J* 14.9, 11.6, 2.0, 1H) and 5.09 (dd, *J* 11.6, 7.6, 1H) (Found: C, 66.63; H, 6.72. Calc. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%).

2-Acetyl-3a-methyl-2,3,3a,4,5,6-hexahydrobenzofuran-4-one 53

Yield 35%; ν_{max}/cm^{-1} (CCl_4) 2974, 1722, 1695, 1458, 1358, 1234 and 1163; δ_H (200 MHz) 2.20 (s, 1.9H)[a], 2.30 (s, 1.1H)[a], 2.35–2.80 (m, 9H), 4.57 (dd, *J* 10.5, 2.3, 0.37H)[b], 4.69 (dd, *J* 10.9, 6.7, 0.63H)[b] and 5.05–5.20 (m, 1H) ([a]total 3H, [b]total 1H); *m*/*z* 194 (M^+, 24%), 152 (48), 133 (55), 109 (71), 81 (30), 55 (28) and 43 (100) (Found: M^+, 194.0947. $C_{11}H_{14}O_3$ requires *M*, 194.0942).

2-Acetyl-6-methyl-2,3-dihydro-4*H*-furo[3,2-*c*]pyran-4-one 54

Yield 59%; crystals; mp 84–86 °C; ν_{max}/cm^{-1} ($CHCl_3$) 3030, 1726, 1643, 1588, 1452, 1417, 1359, 1167, 1103 and 1024; δ_H (200 MHz) 2.28 (s, 6H), 3.09 (dd, *J* 15.3, 7.2, 1H), 3.31 (dd, *J* 15.3, 11.3, 1H), 5.21 (dd, *J* 11.3, 7.2, 1H) and 6.03 (s, 1H) (Found: C, 62.00; H, 5.34. Calc. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19%).

Methyl 5-acetyl-2-methyl-4,5-dihydrofuran-3-carboxylate 55a

Yield 77%; ν_{max}/cm^{-1} (neat) 2953, 1712, 1653, 1439, 1385, 1332, 1255, 1224, 1190, 1140 and 1089; δ_H (200 MHz) 2.24 (s, 3H), 2.26 (d, *J* 1.7, 3H), 2.94 (ddq, *J* 15.0, 7.6, 1.3, 1H), 3.16 (ddq, *J* 15.0, 11.8, 1.3, 1H), 3.71 (s, 3H) and 4.90 (dd, *J* 11.8, 7.6, 1H) (Found: C, 58.46; H, 6.40. Calc. for $C_9H_{12}O_4$: C, 58.69; H, 6.57%).

Ethyl 5-acetyl-2-methyl-4,5-dihydrofuran-3-carboxylate 55b

Yield 57%; ν_{max}/cm^{-1} (neat) 2954, 1724, 1702, 1653, 1385, 1251, 1224, 1145 and 1086; δ_H (200 MHz) 1.27 (t, *J* 7.2, 3H), 2.24 (s, 3H), 2.26 (t, *J* 1.6, 3H), 2.94 (ddq, *J* 15.0, 7.5, 1.6, 1H), 3.17 (ddq, *J* 15.0, 11.8, 1.6, 1H), 4.17 (q, *J* 7.2, 2H) and 4.89 (dd, *J* 11.8, 7.5, 1H); *m*/*z* 198 (M^+, 4%), 183 ($M^+ - CH_3$, 7), 153 (20), 109 (14) and 83 (22) (Found: M^+, 198.0870. $C_{10}H_{14}O_4$ requires *M*, 198.0891).

tert-Butyl 5-acetyl-2-methyl-4,5-dihydrofuran-3-carboxylate 55c

Yield 100%; ν_{max}/cm^{-1} ($CHCl_3$) 3552, 2932, 2480, 1720, 1657 and 1385; δ_H (200 MHz) 1.48 (s, 9H), 2.22 (t, *J* 1.7, 3H), 2.24 (s, 3H), 2.89 (ddq, *J* 15.0, 7.5, 1.7, 1H), 3.13 (ddq, *J* 15.0, 11.8, 1.7, 1H) and 4.86 (dd, *J* 11.8, 7.5, 1H).

2,4-Diacetyl-5-methyl-2,3-dihydrofuran 55d

Yield 93%; ν_{max}/cm^{-1} ($CHCl_3$) 2926, 1716, 1684, 1634, 1421, 1383, 1359, 1290 and 1221; δ_H (200 MHz) 2.21 (s, 3H), 2.25 (s, 3H), 2.29 (t, *J* 1.5, 3H), 3.02 (ddq, *J* 14.7, 7.4, 1.5, 1H), 3.23 (ddq, *J* 14.7, 11.7, 1.5, 1H) and 4.91 (dd, *J* 11.7, 7.4, 1H); *m*/*z* 168 (M^+, 6%), 125 ($M^+ - CH_3CO$, 48), 83 (6) and 43 (100) (Found: M^+, 168.0791. Calc. for $C_9H_{12}O_3$: *M*, 168.0786).

3-Acetyl-2-methyl-3a,4,5,6,7,7a-hexahydrobenzofuran-7-one 56

Representative experimental procedure with 2,3-dibromocyclohexanone 45. To a stirred solution of cyclohex-2-enone (145 µl, 1.32 mmol) in diethyl ether (1.5 ml) was added a solution of bromine (62 µl, 1.2 mmol) in diethyl ether (1.0 ml) at −20 °C under nitrogen atmosphere. After being stirred for 10 min, the solution was diluted with diethyl ether (5 ml). To the resulting solution was added pentane-2,4-dione **34** (102 µl, 1.0 mmol) and subsequently DBU (450 µl, 3.0 mmol) at −20 °C and the reaction mixture was warmed gradually to room temperature over a period of 5 h. The reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice and the extract was washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the mixture followed by MPLC separation of the residue (eluent ethyl acetate–*n*-hexane = 2 : 1) provided the dihydrofuran **56** (102 mg, 49%) as crystals along with the furan **57** (10 mg, 5%) as crystals. The dihydrofuran **56** had mp 77–79 °C; ν_{max}/cm^{-1} (CCl_4) 2947, 1730, 1676, 1628, 1603, 1556, 1452, 1386, 1223, 1136 and 949; δ_H (200 MHz) 1.40–1.60 (m, 1H), 1.80–1.95 (m, 2H), 2.99–2.20 (m, 1H), 2.28 (s, 3H), 2.29 (d, *J* 1.3, 3H), 2.40–2.60 (m, 2H), 3.70–3.90 (m, 1H) and 4.74 (d, *J* 10.3, 1H).

2-Acetyl-2-methyl-4,5,6,7-tetrahydrobenzofuran-7-one 57. This compound had mp 65–68 °C; ν_{max}/cm^{-1} ($CHCl_3$) 2955, 1726, 1673, 1622, 1578, 1531, 1437, 1413, 1358, 1130 and 951; δ_H (200 MHz) 2.19 (quint, *J* 6.0, 2H), 2.50 (s, 3H), 2.58 (t, *J* 6.0, 2H), 2.69 (s, 3H) and 3.00 (t, *J* 6.0, 2H).

Methyl 2-methyl-7-oxo-3a,4,5,6,7,7a-hexahydrobenzofuran-3-carboxylate 58

Yield 47%; ν_{max}/cm^{-1} (CCl_4) 2951, 1730, 1709, 1649, 1555, 1439, 1383, 1209, 1190, 1091 and 991; δ_H (200 MHz) 1.50–2.15 (m, 4H), 2.26 (d, *J* 1.3, 3H), 2.35–2.65 (m, 2H), 3.65–3.85 (m, 1H), 3.73 (s, 3H) and 4.76 (d, *J* 10.5, 1H); δ_C (50 MHz) 15.2, 20.4, 26.5, 29.4, 37.2, 45.6, 83.8, 117.2, 167.7, 193.5 and 207.1.

1,2,3,4,5,6,7,8,9,9a-Decahydrodibenzofuran-1,6-dione 59

Yield 47%; crystals; mp 47–50 °C; ν_{max}/cm^{-1} (CCl_4) 2951, 1730, 1658, 1641, 1454, 1398, 1223, 1180, 1136 and 981; δ_H (200 MHz) 1.50–2.25 (m, 6H), 2.25–2.40 (m, 2H), 2.40–2.70 (m, 4H), 3.70–3.95 (m, 1H) and 4.95 (d, *J* 10.7, 1H) (Found: C, 69.58; H, 6.93. Calc. for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84%).

3-Methyl-5a,6,7,8,9,9a-hexahydro-1*H*-benzo[1′,2′ : 4,5]furo-[3,2-*c*]pyran-1,6-dione 60

Yield 18%; crystals; mp 121–124 °C; ν_{max}/cm^{-1} (CCl_4) 2955, 1738, 1643, 1587, 1451, 1415 and 1226; δ_H (200 MHz) 1.75–2.25 (m, 4H), 2.28 (s, 3H), 2.45–2.70 (m, 2H), 3.90–4.15 (m, 1H), 5.09 (d, *J* 10.3, 1H) and 6.06 (s, 1H) (Found: C, 65.16; H, 5.68. Calc. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49%).

2,2-Diacetylcyclopropanecarbonitrile 63a

To a stirred solution of acrylonitrile (86 μl, 1.3 mmol) and a small amount of hydroquinone in pentane (1.5 ml) was added a solution of bromine (72 μl, 1.4 mmol) in pentane (1 ml) at −15 °C under nitrogen atmosphere. After the mixture had been stirred for 10 min, the solvent was evaporated off *in vacuo*.

To a solution of pentane-2,4-dione **34** (103 μl, 1.0 mmol) in THF (3 ml) was added DBU (344 μl, 2.3 mmol) at 0 °C under nitrogen atmosphere. Subsequently a solution of 2,3-dibromopropionitrile **62** (prepared above) in THF (2 ml) was added and the resulting solution was stirred at room temperature for 2 h, when DBU (75 μl, 0.5 mmol) was added and stirring was continued for 2 h. Again DBU (75 μl, 0.5 mmol) was added. After being stirred for 20 min, the reaction mixture was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice and the extract was washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solution followed by MPLC separation of the residue (eluent ethyl acetate–*n*-hexane = 1 : 3) provided the cyclopropanenitrile **63a** (131 mg, 86%); ν_{max}/cm^{-1} (neat) 2935, 2245, 1701, 1423 and 1363; δ_H (200 MHz) 1.56 (dd, *J* 9.2, 5.1, 1H), 2.05 (dd, *J* 6.8, 5.1, 1H), 2.23 (s, 3H), 2.45 (s, 3H) and 2.54 (dd, *J* 9.2, 6.8, 1H); δ_C (50 MHz) 11.5, 20.1, 28.9, 29.3, 48.1, 116.6, 198.7 and 199.0.

2,2-Bis(methoxycarbonyl)cyclopropanecarbonitrile 63b

Yield 98%; ν_{max}/cm^{-1} (neat) 2935, 2249, 1738, 1437 and 1331; δ_H (200 MHz) 1.74 (dd, *J* 9.5, 5.1, 1H), 2.09 (dd, *J* 7.1, 5.1, 1H), 2.50 (dd, *J* 9.5, 7.1, 1H), 3.81 (s, 3H) and 3.88 (s, 3H) (Found: C, 52.28; H, 4.87; N, 7.44. Calc. for $C_8H_9NO_4$: C, 52.46; H, 4.95; N, 7.64%).

2-Acetyl-4,5,6,7-tetrahydrobenzofuran-4-one 67

Representative procedure of CMD oxidation of the dihydrofuran 52. A stirred solution of the dihydrofuran **52** (180 mg, 1.0 mmol) in methylcyclohexane (10 ml) was heated with CMD (3.0 g, 35 mmol) at reflux under nitrogen atmosphere for 3.5 h. The mixture was passed through a silica gel short column and evaporated to dryness. The residue was purified by silica gel column chromatography (eluent ethyl acetate–*n*-hexane = 10 : 1) to give the furan **67** (117 mg, 66%) as crystals.

Representative procedure by Williams protocol. To a stirred solution of the dihydrofuran **52** (90 mg, 0.5 mmol) in dichloromethane (5 ml) was added DBU (90 μl, 0.6 mmol) at 0 °C under nitrogen atmosphere. After the mixture had been stirred for 5 min, bromotrichloromethane (64 μl, 0.65 mmol) was added and stirring was continued for 5.5 h at 0 °C and at room temperature for 15 h. The reaction was quenched by addition of aq. ammonium chloride. The organic layer was extracted with ethyl acetate twice and the extract was washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the mixture followed by silica gel column chromatography of the residue (eluent ethyl acetate–*n*-hexane = 2 : 1) provided the furan **67** (56 mg, 63%) and recovered dihydrofuran **52** (9 mg, 9%); compound **67** had mp 69–70 °C; ν_{max}/cm^{-1} ($CHCl_3$) 2936, 1692, 1678, 1585, 1458, 1358 and 1136; δ_H (200 MHz) 2.25 (m, 2H), 2.48 (s, 3H), 2.56 (m, 2H), 2.98 (t, *J* 6.1, 2H) and 7.39 (s, 1H); δ_C (50 MHz) 22.0, 23.4, 25.9, 37.5, 113.6, 122.4, 151.7, 167.0, 186.1 and 193.6 (Found: C, 67.79; H, 5.99. Calc. for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66%).

Methyl 4-hydroxy-2,3-dihydrobenzofuran-2-carboxylate 64a

A solution of the dihydrofuran **21** (100 mg, 0.51 mmol) and DDQ (149 mg, 0.66 mmol) in 1,4-dioxane (4 ml) was stirred at room temperature for 1.5 h under nitrogen atmosphere and then warmed gradually to 100 °C for 18 h. The resulting solution was passed through a silica gel short column and evaporated to dryness. The residue was purified by silica gel column chromatography (eluent ethyl acetate–*n*-hexane = 1 : 4) to give the phenol **64a** (66 mg, 68%) and recovered dihydrofuran **21** (10 mg, 11%). Compound **64a** had mp 88–92 °C; ν_{max}/cm^{-1} 3607, 1768, 1743, 1635, 1630, 1466 and 1288; δ_H (200 MHz) 3.34 (dd, *J* 15.4, 6.8, 1H), 3.53 (dd, *J* 15.4, 10.4, 1H), 3.81 (s, 3H), 4.80 (s, 1H), 5.25 (dd, *J* 10.4, 6.8, 1H), 6.34 (d, *J* 8.1, 1H), 6.52 (d, *J* 8.1, 1H) and 7.02 (t, *J* 8.1, 1H); δ_C (50 MHz) 31.2, 52.7, 79.3, 102.6, 108.5, 110.6, 129.5, 152.4, 160.6 and 171.8.

1-(4-Hydroxy-2,3-dihydrobenzofuran-2-yl)ethanone 64b

A solution of the dihydrofuran **52** (90 mg, 0.5 mmol) and DDQ (148 mg, 0.65 mmol) in 1,4-dioxane (7 ml) was stirred at room temperature for 3.5 h and then warmed gradually to 100 °C for 8 h. The resulting solution was passed through a silica gel short column and evaporated to dryness. Silica gel column chromatography of the residue provided the phenol **64b** (78 mg, 88%); ν_{max}/cm^{-1} ($CHCl_3$) 3605, 3427, 2984, 1741, 1630, 1604, 1466 and 1238; δ_H (200 MHz) 2.30 (s, 3H), 3.25 (dd, *J* 16.0, 6.9, 1H), 3.44 (dd, *J* 16.0, 10.8, 1H), 5.08 (dd, *J* 10.7, 6.8, 1H), 6.36 (d, *J* 8.3, 1H), 6.50 (d, *J* 8.0, 1H) and 7.03 (t, *J* 8.1, 1H).

Ethyl 5-acetyl-2-methylfuran-3-carboxylate 68

Yield 61% by Williams' protocol; crystals; mp 87–88 °C; ν_{max}/cm^{-1} (CCl_4) 2984, 1724, 1688, 1599, 1431, 1246 and 1103; δ_H (200 MHz) 1.37 (t, *J* 7.2, 3H), 2.46 (s, 3H), 2.67 (s, 3H), 4.32 (q, *J* 7.2, 2H) and 7.41 (s, 1H) (Found: C, 61.04; H, 6.04. Calc. for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16%).

3,5-Diacetyl-2-methylfuran 69

The yields by Williams' protocol and CMD oxidation were 35 and 68% respectively; crystals; mp 89–91 °C; ν_{max}/cm^{-1} ($CHCl_3$) 3011, 2953, 1674, 1579, 1531, 1410, 1361, 1252 and 1165; δ_H (200 MHz) 2.46 (s, 3H), 2.48 (s, 3H), 2.69 (s, 3H) and 7.39 (s, 1H) (Found: C, 64.82; H, 5.94. Calc. for $C_9H_{10}O_3$: C, 65.05; H, 6.07%).

2-Acetyl-2,3,4,9-tetrahydronaphtho[2,3-*b*]furan-4,9-dione 70

To a stirred solution of but-3-en-2-one (210 μl, 2.5 mmol) in pentane (2 ml) was added a solution of bromine (134 μl, 2.6 mmol) in pentane (1 ml) at −15 °C. After being stirred for 10 min, the mixture was evaporated *in vacuo*.

To a stirred solution of 2-hydroxy-1,4-naphthoquinone **75** (174 mg, 1.0 mmol) in THF (5 ml) was added DBU (550 μl, 3.7 mmol) and the resulting red solution was stirred for 20 min under nitrogen atmosphere. A solution of 3,4-dibromobutan-2-one **44** in THF (2 ml) was added at 0 °C and the resulting solution was stirred at room temperature for 4.3 h. DBU (75 μl, 0.52 mmol) was added again and stirring was continued for 2.6 h. The reaction was quenched by addition of aq. ammonium chloride and the product was extracted with chloroform twice. The extracts were washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the solution *in vacuo* followed by preparative TLC separation (developer ethyl acetate–chloroform = 1 : 12) afforded naphthodihydrofuran **70** (90 mg, 37%) and the natural naphthofuran **1** (68 mg, 28%) as yellow crystals.

2-Acetyl-2,3,4,5-tetrahydronaphtho[2,3-*b*]furan-4,9-dione 70. Compound **70** had mp 170–175 °C; ν_{max}/cm^{-1} (CCl_4) 2940, 1726, 1682, 1652, 1633, 1597, 1390 and 1362; δ_H (200 MHz) 2.39 (s, 3H), 3.40 (dd, *J* 17.7, 8.5, 1H), 3.44 (dd, *J* 17.7, 11.0, 1H), 5.27 (dd, *J* 11.0, 8.5, 1H), 7.70–7.80 (m, 2H) and 8.05–8.19 (m, 2H).

2-Acetyl-4,9-dihydronaphtho[2,3-*b*]furan-4,9-dione 1. Compound **1** had mp 224–225 °C; ν_{max}/cm^{-1} (CCl_4) 2940, 1689, 1678, 1595, 1583 and 1359; δ_H (200 MHz) 2.67 (s, 3H), 7.62 (s, 1H), 7.75–7.85 (m, 2H) and 8.19–8.45 (m, 2H); *m*/*z* 240 (M^+, 60%), 226 (15), 225 ($M^+ - CH_3$, 100), 157 (10), 113 (18), 76 (10), 105 (38), 53 (15) and 43 (29); λ_{max} (EtOH) nm (log ε), 254 (4.38), 271 (4.28) and 340 (3.54) (Found: C, 69.67; H, 3.63. Calc. for $C_{14}H_8O_4$: C, 70.00; H, 3.36%).

The yields by Williams' protocol and CMD oxidation were 43 and 60% respectively.

Methyl 5-acetyl-2-methylfuran-3-carboxylate 71

Yield 54% by CMD oxidation; crystals; mp 46–47 °C; ν_{max}/cm^{-1} ($CHCl_3$) 3030, 2955, 1726, 1682, 1583, 1545, 1439, 1315, 1259, 1172, 1116 and 951; δ_H (200 MHz) 2.45 (s, 3H), 2.68 (s, 3H), 3.86 (s, 3H) and 7.40 (s, 1H); δ_C (50 MHz) 14.2, 25.8, 51.7, 115.6, 118.4, 150.0, 163.1, 163.2 and 185.9 (Found: C, 59.60; H, 5.86. Calc. for $C_9H_{10}O_4$: C, 59.34; H, 5.53%).

2-Acetyl-6-methyl-4*H*-furo[3,2-*c*]pyran-4-one 72

Yield 62% by CMD oxidation; yellow crystals; mp 245–247 °C; ν_{max}/cm^{-1} (CCl_4) 2940, 1689, 1678, 1595, 1583 and 1359; δ_H (200 MHz) 2.39 (s, 3H), 2.54 (s, 3H), 6.49 (s, 1H) and 7.55 (s, 1H); δ_C (50 MHz) 20.2, 25.8, 28.5, 87.4, 95.2, 98.3, 161.1, 165.6, 170.4 and 204.2.

Methyl 4-acetyl-5-methylfuran-2-carboxylate 73

Yield 69% by CMD oxidation; crystals; mp 145–146 °C; ν_{max}/cm^{-1} ($CHCl_3$) 2955, 1726, 1682, 1587, 1541, 1439, 1334, 1239 and 1172; δ_H (200 MHz) 2.44 (s, 3H), 2.68 (s, 3H), 3.91 (s, 3H) and 7.40 (s, 1H); δ_C (50 MHz) 14.7, 29.0, 52.1, 111.8, 118.1, 122.8, 141.9, 162.1 and 193.2 (Found: C, 59.34; H, 5.59. Calc. for $C_9H_{10}O_4$: C, 59.34; H, 5.53%).

Methyl 4-oxo-4,5,6,7-tetrahydrobenzofuran-2-carboxylate 74

Yield 43% by CMD oxidation; crystals; mp 74–76 °C; ν_{max}/cm^{-1} ($CHCl_3$) 3007, 2955, 1728, 1688, 1591, 1547, 1458, 1319, 1294, 1147 and 1005; δ_H (200 MHz) 2.22 (quint, *J* 6.3, 2H), 2.54 (m, 2H), 2.97 (t, *J* 6.3, 2H), 3.91 (s, 3H) and 7.39 (s, 1H) (Found: C, 61.87; H, 5.24. Calc. for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19%).

2-(Methylvinyl)-2,3,4,9-tetrahydronaphtho[2,3-*b*]furan-4,9-dione 76

To a stirred suspension of methyltriphenylphosphonium bromide (235 mg, 0.66 mmol) in THF (10 ml) was added *n*-butyllithium (0.42 ml, 0.66 mmol; 1.57 M in *n*-hexane) at 0 °C under nitrogen atmosphere. After being stirred for 10 min, the dihydrofuran **70** (80 mg, 0.33 mmol) as a solution in THF (10 ml) was added at −78 °C. The resulting solution was stirred for 20 h with gradual warming to room temperature. The reaction was quenched by addition of aq. ammonium chloride and the product was extracted with chloroform twice. The combined organic layer was washed successively with water and brine and dried over anhydrous sodium sulfate. Evaporation of the mixture followed by silica gel column chromatography of the residue (eluent chloroform–ethyl acetate = 10 : 1) afforded the naphthofuran **76** (16 mg, 20%) as yellow crystals; mp 60–64 °C; ν_{max}/cm^{-1} ($CHCl_3$) 2957, 1726, 1685, 1657, 1628, 1597, 1390, 1197 and 960; δ_H (200 MHz) 1.81 (d, *J* 1.2, 3H), 3.04 (dd, *J* 17.1, 8.3, 1H), 3.36 (dd, *J* 17.4, 11.0, 1H), 5.01 (q, *J* 1.4, 1H), 5.14 (q, *J* 1.0, 1H), 5.45 (dd, *J* 10.9, 9.0, 1H), 7.70 (m, 2H) and 8.07 (m, 2H).

2-(Hydroxyethyl)-2,3,4,9-tetrahydronaphtho[2,3-*b*]furan-4,9-dione 77

To a stirred solution of the naphthofuran **1** (20 mg, 0.083 mmol) in chloroform (2 ml) and methanol (0.5 ml) was added sodium borohydride (3.3 mg, 0.042 mmol) at 0 °C. After being stirred for 20 min, the reaction mixture was quenched by addition of brine. The organic layer was extracted with chloroform twice and the extract was washed successively with water and brine. Evaporation of the mixture followed by silica gel column chromatography (eluent ethyl acetate–*n*-hexane = 1 : 2) provided alcohol **77** (16 mg, 79%) as yellow crystals; mp 138–141 °C; ν_{max}/cm^{-1} ($CHCl_3$) 3616, 2874, 1674, 1597, 1537, 1437, 1371, 1224 and 958; δ_H (200 MHz) 1.66 (d, *J* 6.6, 3H), 2.17–2.38 (m, 1H), 4.90–5.20 (m, 1H), 6.86 (s, 1H), 7.65–7.85 (m, 2H) and 8.10–8.30 (m, 2H).

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References

1 (*a*) A. J. Sargent and T. M. Cresp, in *Comprehensive Organic Chemistry*, ed. P. G. Sammes, Pergamon Press, Oxford, 1979, vol. 4, pp. 693–744; (*b*) C. W. Bird and G. W. H. Cheeseman, in *Comprehensive Heterocyclic Chemistry*, ed. G. W. H. Cheeseman, Pergamon Press, Oxford, 1984, Vol. 4, pp. 89–153; (*c*) C. J. Burns, *Contemp. Org. Synth.*, 1994, **1**, 23; (*d*) A. R. Katritzky and A. F. Pozharskii, *Handbook of Heterocyclic Chemistry*, Pergamon Press, Oxford, 2nd edn., 2000.
2 M. M. Rao and D. G. I. Kingston, *J. Nat. Prod.*, 1982, **45**, 600; C. L. Lopes, R. S. C. Lopes, A. V. Pinto and P. R. R. Costa, *J. Heterocycl. Chem.*, 1984, **21**, 621.
3 H. Nakamura, J. Kobayashi, M. Kobayashi, Y. Ohizumi and Y. Hirata, *Chem. Lett.*, 1985, 713.
4 C. Djerassi, M. Cais and L. A. Mitsher, *J. Am. Chem. Soc.*, 1959, **81**, 2386.
5 J. Endo, *Yakugaku Zasshi (J. Pharm. Soc. Jpn.)*, 1975, **95**, 1321.
6 J. Yoshida, S. Yano, T. Ozawa and N. Kawabata, *J. Org. Chem.*, 1985, **50**, 3467; E. A. Lund, I. A. Kennedy and A. G. Fallis, *Can. J. Chem.*, 1996, **74**, 2401; C. Anac and A. Daut, *Liebigs Ann. Chem.*, 1997, 1249; Y. R. Lee, *Synth. Commun.*, 1998, **28**, 865; H. M. L. Davies, G. Ahmed, R. L. Calvo, M. R. Churchill and D. G. Churchill, *J. Org. Chem.*, 1998, **63**, 2641; M. C. Pirrung and F. Blume, *J. Org. Chem.*, 1999, **64**, 3692; Y. R. Lee, J. Y. Suk and B. S. Kim, *Tetrahedron Lett.*, 1999, **40**, 6603.

7 K. Kobayashi, M. Mori, T. Uneda, O. Morikawa and H. Konishi, *Chem. Lett.*, 1996, 451; Y. R. Lee and B. S. Kim, *Tetrahedron Lett.*, 1997, **38**, 2095; Y. R. Lee, N. S. Kim and B. S. Kim, *Tetrahedron Lett.*, 1997, **38**, 5671; V.-H. Nguyen, H. Nishino and K. Kurosawa, *Synthesis*, 1997, 899; G. Bar, A. F. Parsons and C. B. Thomas, *Tetrahedron Lett.*, 2000, **41**, 7751.
8 K. Kobayashi, H. Shimizu, A. Sasaki and H. Suginome, *J. Org. Chem.*, 1991, **56**, 3204.
9 (*a*) T. Lavoisier and J. Rodriguez, *Synlett*, 1996, 339; (*b*) T. Lavoisier-Gallo and J. Rodriguez, *J. Org. Chem.*, 1997, **62**, 3787; (*c*) J.-P. Dulcere and E. Dumez, *J. Chem. Soc., Chem. Commun.*, 1997, 971; (*d*) E. Dumez, J. Rodriguez and J.-P. Dulcere, *J. Chem. Soc., Chem. Commun.*, 1997, 1831; (*e*) S. Arai, K. Nakayama, Y. Suzuki, K. Hatano and T. Shioiri, *Tetrahedron Lett.*, 1998, **39**, 9739; (*f*) K. C. Nicolaou, J. A. Pfefferkorn, Q.-Q. Cao, S. Kim and J. Kessabi, *Org. Lett.*, 1999, **1**, 807; (*g*) R. Antonioletti, G. Right, L. Oliveri and P. Bovicelli, *Tetrahedron Lett.*, 2000, **41**, 10127.
10 H. Hagiwara, F. Abe and H. Uda, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2651 and references cited therein.
11 (*a*) H. Hagiwara, K. Sato, T. Suzuki and M. Ando, *Heterocycles*, 1999, **51**, 497; (*b*) H. Hagiwara, K. Sato, T. Suzuki and M. Ando, *Tetrahedron Lett.*, 1997, **38**, 2103.
12 H. Hagiwara, N. Komatsubara, H. Ono, T. Okabe, T. Hoshi, T. Suzuki, M. Ando and M. Kato, *J. Chem. Soc., Perkin Trans. 1*, 2001, 316.
13 E. R. Buchman and H. Sargent, *J. Am. Chem. Soc.*, 1945, **67**, 400.
14 D. R. Williams, P. D. Lowder, Y.-G. Gu and D. A. Brooks, *Tetrahedron Lett.*, 1997, **38**, 331.
15 T. Aoyama, N. Sonoda, M. Yamauchi, K. Toriyama, M. Anzai, A. Ando and T. Shioiri, *Synlett*, 1998, 35.
16 E. J. Corey and S. E. Lazerwith, *J. Am. Chem. Soc.*, 1998, **120**, 12777.
17 K. Kobayashi, T. Uneda, M. Kawakita, O. Morikawa and H. Konishi, *Tetrahedron Lett.*, 1997, **38**, 837.
18 W. Sandermann, M. H. Simatupang and W. Wendelborn, *Naturwissenschaften*, 1968, **55**, 38; K. Inoue, C.-C. Chen, H. Inouye and K. Kuriyama, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2764.