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Syntheses of Tetrahydrofurobenzofurans and Dihydromethanobenzodioxepines from 5-Hydroxy-3-methyl-3*H*-benzofuran-2-one. Rearrangement and Ring Expansion under Reductive Conditions on Treatment with Hydrides

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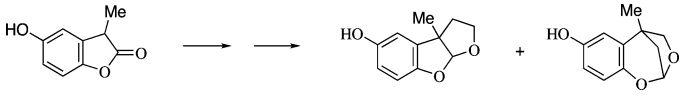

5-Hydroxy-3-methyl-3*H*-benzofuran-2-one, **5**, easily obtained from pyruvic acid and 1,4-cyclohexanedione, was used as a starting material to prepare (±)-5-hydroxy-3a-methyl-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran, **10**, and (±)-7-hydroxy-5-methyl-4,5-dihydro-2,5-methano-1,3-benzodioxepine, **14**. Reduced reactivity relative to 5-hydroxy-3-methoxycarbonylmethylene-3-methyl-3*H*-benzofuran-2-one, **6**, was preliminarily studied. Meanwhile, a plausible mechanism with regard to the formation of **10** and **14**, which included cyclization, rearrangement, and ring expansion of hemiacetal, **15**, is proposed. Specific carbamates of phenols, **10** and **14**, have shown impressive inhibitory activities against human acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) ex vivo.

Introduction

Physovenine, **1** (Figure 1), a minor alkaloid from *Physostigma venenosum*, has the *N*-methyl amino group at N^1 of physostigmine, **2**, replaced with an oxygen atom and still has potent anticholinesterase activity.[1] Compound **3**, prepared at Pfizer, whose structure has an indolinic amino group at N^8 of **2** replaced by a methylene group,[2] has likewise been reported to have potent anticholinesterase activity. In light of these findings, it seemed of interest to prepare carbamates of a tricyclic compound, **4**, where both amino groups of **2**, N^1, and $N,^8$ would be replaced by oxygen atoms (Figure 1). In this regard, some of the carbamates from **10** and its isomer, **14**, have recently been shown to possess impressive inhibitory activities against human acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) ex vivo.[3] The tricyclic moiety of such compounds chemically resembles

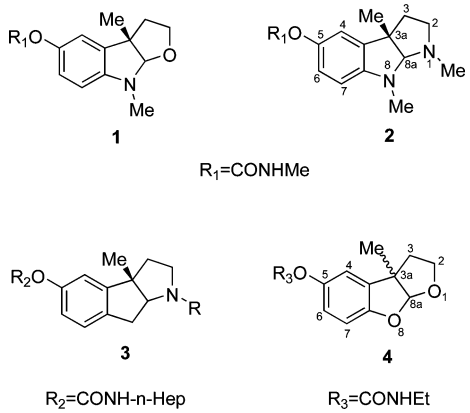

FIGURE 1. Compounds possessing potent anticholinesterase activity.

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(1) Yu, Q. S.; Liu, C.; Brzostowska, M.; Chrisey, L.; Brossi, A.; Greig, N. H.; Atack, J. R.; Soncrant, T. T.; Rapoport, S. I.; Randunz, H. E. *Helv. Chim. Acta* **1991**, *74*, 761.

(2) Chen, L.; Nielsen, J.; Hedberg, K.; Dunaiskis, A.; Jones, S.; Russo, L.; Johnson, J.; Ives, J.; Liston, D. *J. Med. Chem.* **1992**, *35*, 1429.

(3) Luo, W.; Yu, Q. S.; Zhan, M.; Parrish, D.; Deschamps, J. R.; Kulkarini, S.; Holloway, H. W.; Alley, G. M.; Lahiri, D. K.; Brossi, A.; Greig, N. H. *J. Med. Chem.* **2005**, *48*, 986.

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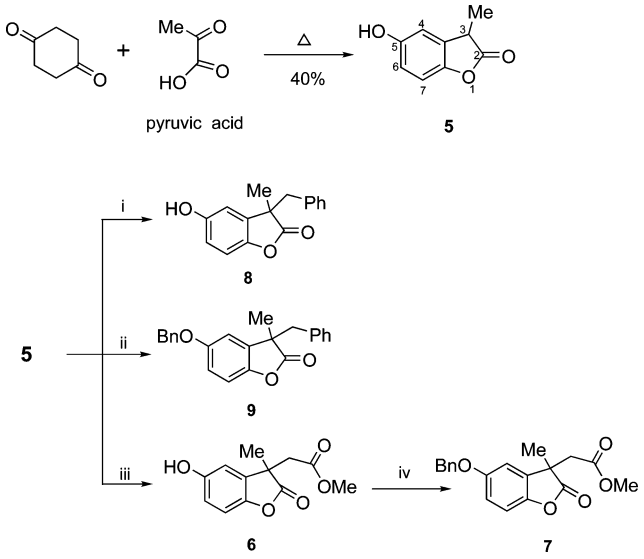
SCHEME 1. Preparations of Lactones 6 and 7[a]



[a] Reagents and conditions: (i) $ClCH_2Ph/CH_3COCH_3$, K_2CO_3, reflux 5 h, 94%; (ii) $BrCH_2Ph/C_2H_5OH$, NaOH, room temperature, 2 h; (iii) $ClCH_2CO_2Me$/DMF, NaH, 0 °C, 2 h, room temperature, overnight, 46%; (iv) $BrCH_2Ph/CH_3CN$, K_2CO_3, room temperature, 66 h, 99%.

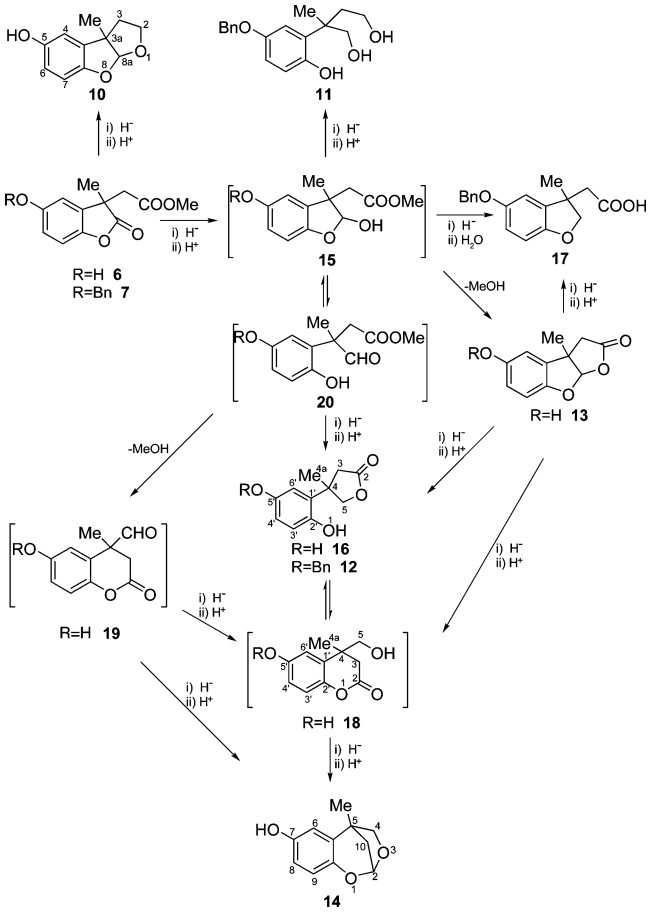
aflatoxins, fungal metabolites previously investigated in depth by Büchi,[4] Rapoport,[5] Townsend,[6] and others.

Although details concerning the construction of the desired tetrahydrofurobenzofuran moiety were discussed in the literature related to aflatoxins, its synthesis from the easily available lactone, **5** (Scheme 1), from 1,4-cyclohexanedione and pyruvic acid,[7] has not yet been reported. Combined with the knowledge that our group has accumulated in the syntheses of physostigmine analogues, we suggest an entirely new approach that focuses on lactone, **5**, and desired esters, **6** and **7** (Scheme 1).

Results and Discussion

When lactone **5** was treated with benzyl chloride in acetone in the presence of potassium carbonate, the 3C-alkylated product, **8** (Scheme 1), was obtained in excellent yield. Interaction with benzyl bromide in ethanol in the presence of sodium hydroxide afforded the C−O-dialkylated product, **9** (Scheme 1), indicating that there was an obvious competition in **5** between 3C- and 5O-alkylation. To avoid this problem, we first treated **5** with methyl chloroacetate in DMF and sodium hydride to obtain the lactone, **6**, in 46% yield. It was converted with benzyl bromide in acetonitrile in the presence of potassium carbonate into O-benzyl ether, **7**. The reduction of lactone, **6** or **7**, yielded, depending on the reducing

SCHEME 2. Synthesis and Possible Mechanism of Tetrahydrofurobenzofuran 10 and Dihydromethanobenzodioxepine 14



agent and experimental conditions, besides the desired tricyclic compound, **10**, (Scheme 2), a variety of intermediates that were isolated. Specific structures, which included **10**, **12**, **14**, **17**, and **22** (Scheme 3), were confirmed by single-crystal X-ray crystallography. Overnight from **7** with lithium aluminum hydride in ether at room temperature, the tetrol, **11**, (Scheme 2) was obtained, whereas reacting with lithium borohydride in dry ether at 0 °C for 30 min, the lactone, **12**, was the major product. With sodium borohydride in anhydrous ethanol at 0 °C for 10 min, the lactone carbonyl in **6** was reduced, first giving access to the tricyclic lactone, **13** (Scheme 2). Compound, **7**, could be reduced to acid, **17** (Scheme 2), with sodium borohydride in ethanol at room temperature for 17 h.

When lactone, **6**, was reduced with lithium aluminum hydride, reduction of both its lactone carbonyl to a hemiacetal and its ester group to an alcohol afforded the desired tricyclic diether, **10**. The results of reduction, leading to dioxepine, **14**, can be explained based on experimental details. These suggested that under the presence of minus hydrogen or hydride (such as lithium aluminum hydride, lithium borohydride, or sodium borohydride that can control the extent of different reductive processes), the carbonyl group of lactone, **6** or **7**, was reduced, respectively, first to hemiacetal, **15**, and then it was tautomerized to hydroquinone, **20**, with a 1,3 hydrogen shift. Further reduction of **15** followed by hydrolysis could provide acid **17**. The aldehyde, **20**, could

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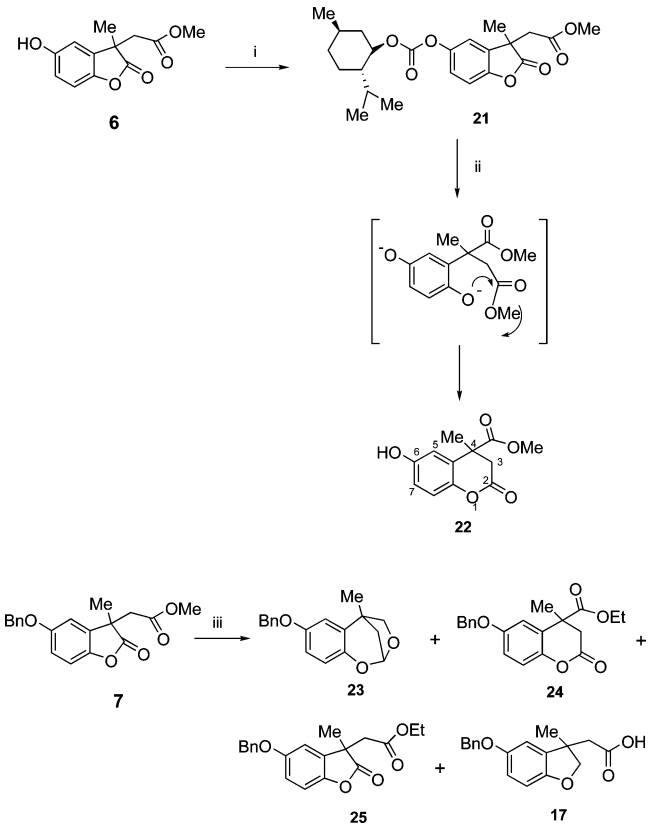
SCHEME 3. Formation of Lactones 22 and 24[a]



[a] Reagents and conditions: (i) (−)-menthylchloroformate, Et_3N, benzene, room temperature, 3 h, 76%; (ii) NaOH, MeOH, room temperature, 1.5 h, 20%; (iii) (a) $NaBH_4$, EtOH, room temperature, 17 h, (b) oxalic acid, room temperature, 0.5 h, 6% (**23**), 6% (**24**), 21% (**25**), and 62% (**17**).

be reduced and cyclized to lactone, **12** or **16**, or dealcoholized and cyclized to lactone, **19**.

Lactone, **16**, could be hydrolyzed and dehydrated or rearranged to **18**. **16**, **18**, and **19** can ultimately be reduced and dehydrated to form dioxepine, **14** (Scheme 2).

On the other hand, intermediates **15** and **20** can also afford a tricyclic lactone, **13**, with an intramolecular dealcoholization and cyclization (Scheme 2). When compound **13** was reduced under an alkaline condition, its acetal could be attacked by minus hydrogen or hydride, resulting in **16** and the phenol corresponding to **17**, and additionally, lactone **13** might also take place in a rearrangement and ring expansion, resulting in an intermediate, **19**, with a thermodynamically favorable six-membered ring. As a relative comparison, the steric energy and heat of formation (ΔH_f) of compound **13** and intermediate **19** have been calculated with CS Chem3D Molecular Modeling and Analysis.[8] The steric energy was computed after MM2 energy minimization, and the heat of formation was calculated by a regulated semiempirical method, AM1. The results in Table 1 clearly show that the steric energy of six-membered intermediate, **19**, is lower than that of lactone, **13**, and that the heat of formation of **19** ($\Delta H_f < 0$, exothermal reaction) is greater (absolute value) than that of **13**. Together, this suggests that **19** could be present as an active intermediate during the reduction. Additional and direct support is provided by ring-expansion products, **22** and **24** (Scheme 3), which possessed a similar 3,4-dihydro-2*H*-1-benzopyran-2-one structure and have been isolated on alkaline alcoholysis and reduction, respectively. Therefore, there could be three cleavage alternatives on alkaline reduction of **13**: the first provided hydroquinone, **16**, the second afforded the phenol corresponding to **17**, and the third resulted in intermediate **19**. Finally, **16** and **19** can all be reduced and dehydrated to form **14**.

The structure of compound **17** has been determined by its NMR and mass spectroscopy (MS) analyses and by single-crystal X-ray crystallography of its amide (to be published separately). The crucial structures of **10** and **14** were confirmed by single-crystal X-ray crystallography from their corresponding isopropylphenylcarbamate.[3]

When lactone **16** was dissolved in methanol it formed a mixture of tautomers, **16** and **18**, which can be compared with the fact that the same phenomenon occurs in pure lactone, **12**, whose structure has been confirmed by single-crystal X-ray crystallography (Supporting Information S22).

In addition, the structure of tautomer, **18**, was supported by its ^1H and ^{13}C NMR (Tables 2 and 3) and its molecular ion (*m/z* 209, MH^+), as determined from its mass spectrum. The data from Table 1 shows that the difference in both steric energy and heat of formation between **16** and **18** is relatively small. This suggests that the phenolic hydroxy in the 2′-position of **16** attacked the carbonyl group of its own five-membered lactone to give a six-membered lactone, **18**, and simultaneously, the carbinol group in the 5-position of **18** likely also attacked the carbonyl group of its own six-membered lactone to regenerate a five-membered lactone, **16**, in a polar proton solvent such as methanol. This equilibrium between **16** and **18** can be explained by a proton-shift of their tautomers. In our experiment, the equilibrium lies toward **16**, the ratio of which is 2.6 to 1.0, from ^1H NMR data in methanol at room temperature. One explanation underpinning this is that the steric energy of **16** (6.47 kcal/mol) is slightly lower than that of **18** (9.43 kcal/mol).

Preparation of optically pure carbamate required a resolution, which was realized with menthylester, **21**, (Scheme 3). Alkaline alcoholysis of **21**, prepared from **6** with (−)-menthyl chloroformate, gave in addition to the desired enantiomers of **6** (to be published separately), an unexpected substituted dihydrocoumarin, **22**. Its structure has been confirmed by single-crystal X-ray crystallography (Supporting Information S33).

It can be proposed that the substituted dihydrocoumarin, **22**, was obtained by reacting the phenolate anion of **21** with the estercarbonyl by an intramolecular cyclization. The suggestion that the six-membered ring compound was thermodynamically more stable than its five-membered ring analogue was supported, again, with the rearrangement ring expansion of **7** with sodium borohydride in ethanol giving the ethyl ester **24** (Scheme 3).

In synopsis, the chemistry leading to tricyclic diether, **10**, and bridged-ring diether, **14**, from lactone **5** offers a wide field for theoretical chemists to explain the results we have reported herein based on experimental details.

(8) *Chem3D Molecular Modeling and Analysis*; CambridgeSoft Corporation, P113−164.

TABLE 1. Comparison of the Steric Energy Components and Heat of Formation for 13, 19, 16, and 18

energy term (kcal/mol)	lactone **13**	intermediate **19**	lactone **16**	tautomer **18**
stretch	1.32	0.93	1.35	1.11
bend	23.75	2.40	6.20	3.06
stretch-bend	−0.20	0.08	0.03	0.08
torsion	−6.36	−3.40	−10.22	−4.93
non-1,4 van der Waals	−2.78	−2.98	−1.45	−3.57
1,4 van der Waals	6.88	8.22	5.02	8.92
dipole/dipole	5.28	7.77	5.54	4.77
steric energy	**27.89**	**13.03**	**6.47**	**9.43**
heat of formation (ΔH_f)	**−86.86**	**−126.29**	**−148.18**	**−150.68**

TABLE 2. ^{1}H NMR Data of 16 and 18

proton	**16**/DMSO-d_6 δ found	**16**/CD_3OD δ found	**18**/CD_3OD δ found
Ar−H	∼6.56−6.30, m, 3H	∼6.54−6.40, m, 3H	∼6.80−6.48, m, 3H
5-H	4.38, 4.24; AB, *Jgem* = 5.04 Hz, 2H	4.52, 4.38; AB, *Jgem* = 5.40 Hz, 2H	3.50, 3.39; AB, *Jgem* = 12.6 Hz, 2H
3-H	2.87, 2.50; AB, *Jgem* = 16.6 Hz, 2H	2.97, 2.57; AB, *Jgem* = 18.1 Hz, 2H	2.69,2.49; AB, *Jgem* = 16.2 Hz, 2H
4a-H	1.23, s, 3H	1.39, s, 3H	1.22, s, 3H

TABLE 3. ^{13}C NMR Data of 16 and 18

carbon	**16**/DMSO-d_6 δ found (calcd[a])	**16**/CD_3OD δ found (calcd[a])	**18**/CD_3OD δ found (calcd[a])
2-C	176.7 (172.0)	180.0 (172.0)	171.4 (169.0)
2′-C	150.2 (149.5)	151.7 (149.5)	155.9 (153.7)
5-C	77.9 (86.1)	80.5 (86.1)	70.8 (75.1)
3-C	43.2 (53.0)	44.8 (53.0)	40.5 (44.5)
4-C	41.4 (21.9)	43.1 (21.9)	40.1 (30.2)

[a] From *CS ChemDraw Chemical Structure Drawing Standard*, CambridgeSoft Corporation.

The fact is that carbamates of tricyclic and bridged-ring moieties, as reported elsewhere,[3] showed potent anticholinesterase activities in a well-characterized ex vivo model, making them interesting molecules for further assessment in cell culture and animal models associated with Alzheimer's disease drug development.

Experimental Section

All reactions involving nonaqueous solutions were performed under an inert atmosphere.

5-Hydroxy-3-methyl-3*H*-benzofuran-2-one (5). Pyruvic acid (8.81 g, 0.10 mol) was added to 1,4-cyclohexanedione (11.2 g, 0.10 mol). The reaction was heated to 160−170 °C and then stirred for 3 h. The mixture began to crystallize at room temperature. After it was filtered and recrystallized with ethanol, a pale-yellow crystal product **5** (6.50 g, 40%) was afforded: mp 172.0−173.0 °C; ^{1}H NMR ($CDCl_3$) δ 6.80−6.51 (m, 3H, Ar−H), 4.69 (s, 1H, Ar−OH), 3.55 (q, 1H, C3−H), and 1.38 (d, 3H, C3−CH_3) ppm; CI-MS (CH_4), *m/z*: 165 (MH^+) and 137.

5-Hydroxy-3-methoxycarbonylmethylene-3-methyl-3*H*-benzofuran-2-one (6). Under a nitrogen atmosphere, sodium hydride (0.24 g, 0.01 mol) was added to a solution of compound **5** (1.64 g, 0.01 mol) and methyl chloroacetate (1.19 g, 0.01mol) in 6 mL of dry DMF at 0 °C in portions over 1 h. The mixture was stirred for another 1 h at 0 °C and then overnight at room temperature. The reaction mixture then was poured onto 25 g of ice and extracted with ether (3 × 20 mL). The extract was washed with brine (2 × 20 mL) and dried over magnesium sulfate. After filtering and removing solvents, 2.16 g of crude product was afforded. It was recrystallized with ethyl acetate to give white crystals of **6** (1.09 g, 46%): mp 153.5−155.0 °C; ^{1}H NMR ($CDCl_3$) δ 6.92−6.61 (m, 3H, Ar−H), 5.07 (s, 1H, Ar−OH), 3.44 (s, 3H, OCH_3), 3.02, 2.84 (AB, *Jgem* = 18.0 Hz, 2H, C3−CH_2COO), and 1.41 (s, 3H, C3−CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 179.7, 170.0, 154.0, 144.9, 132.1, 114.6, 110.6, 110.2, 51.5, 44.5, 40.9, and 24.7 ppm; CI-MS(CH_4), *m/z* 237 (MH^+), 205, and 177; HRMS *m/z* calcd for $C_{12}H_{12}O_5$, 236.0685; found 236.0673.

5-Benzyloxy-3-methoxycarbonylmethylene-3-methyl-3*H*-benzofuran-2-one (7). Benzyl bromide (1.06 g, 6.20 mmol) was added into a solution of compound **6** (1.46 g, 6.20 mmol) in 17 mL of acetonitrile in the presence of potassium carbonate (0.86 g, 6.22 mmol). The mixture was reacted for 66 h at room temperature and then was filtered to remove salt. After removing solvents, the residue was dissolved into ethyl acetate, washed with brine, and dried over sodium sulfate. Crude product then was chromatographed on silica gel (EtOAc/Hexane = 1/2.5) to give white crystals of **7** (2.01 g, 99%): mp 88.8−91.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.36−6.75 (m, 8H, Ar−H), 4.94 (s, 2H, C5−OCH_2Ph), 3.44 (s, 3H, OCH_3), 3.01, 2.85 (AB, *Jgem* = 19.8 Hz, 2H, C3−CH_2COO), and 1.41 (s, 3H, C3−CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 180.2, 170.1, 156.2, 147.5, 137.0, 132.5, 129.0, 128.5, 128.0, 115.0, 111.7, 110.6, 71.2, 52.3, 45.5, 42.4, and 25.4 ppm; CI-MS(CH_4), *m/z* 327 (MH^+), 295, 267, and 91; HRMS *m/z* calcd for $C_{19}H_{18}O_5$, 326.1154; found, 326.1147.

3-Benzyl-5-hydroxy-3-methyl-3*H*-benzofuran-2-one (8). Potassium carbonate (1.38 g, 0.01 mol) was added to a solution of compound **5** (1.64 g, 0.01mol) and benzyl chloride (1.27 g, 0.01mol) in 10 mL of acetone containing a small amount of triethylamine. The mixture was refluxed for 5 h. After removing the acetone, the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over sodium sulfate and repeated to remove any remaining solvent. The residue was recrystallized with ethyl acetate to give white crystals of **8** (2.4 g, 94%): mp 165.5−169.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.06−6.58 (m, 8H, Ar−H), 4.81 (s, 1H, OH), 3.10, 3.00 (AB, *Jgem* = 16.2 Hz, 2H, C3−CH_2Ph), 1.50 (s, 3H, C3−CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 179.4, 151.3, 145.3, 134.0, 131.3, 128.9, 127.1, 126.1, 114.1, 110.2, 110.1, 48.8, 43.9, and 22.9 ppm; CI-MS(CH_4), *m/z* 255 (MH^+), 227, 209, and 91; HRMS *m/z* calcd for $C_{16}H_{14}O_3$, 254.0943; found, 254.0944.

3-Benzyl-5-benzyloxy-3-methyl-3*H*-benzofuran-2-one (9). A mixture of compound **5** (82 mg, 0.5 mmol), sodium hydroxide (20 mg, 0.5 mmol), benzyl bromide (86 mg, 0.5 mmol), and 0.5 mL of ethanol was stirred for 2 h at room temperature. After filtration, drying, and removal of solvent, the residue was chromatographed on silica gel (AcOEt/Hexane = 1/2.5) to give product **9** as a gum (65 mg): ^{1}H NMR ($CDCl_3$) δ 7.39−6.68 (m, 13H, Ar−H), 4.97 (s, 2H, C5−OCH_2Ph), 3.11, 2.98 (AB, J*gem* = 15.3 Hz, 2H, C3−CH_2Ph), and 1.49 (s, 3H, C3−CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 180.5, 155.8, 147.0, 137.1, 135.5, 132.4, 130.3, 129.0, 128.5, 128.4, 128.3, 128.1, 128.0, 115.3, 111.4, 71.2, 50.1, 45.3, and 24.3 ppm; CI-MS(CH_4), *m/z* 345 (MH^+), 317, 299, 267, and 91; HRMS *m/z* calcd for $C_{23}H_{20}O_3$, 344.1412; found, 344.1426.

(±)-5-Hydroxy-3a-methyl-2,3,3a,8a-tetrahydrofuro[2,3-*b*]benzofuran (10) and (±)-7-hydroxy-5-methyl-4,5-dihydro-2,5-methano-1,3-benzodioxepine (14). Under a nitrogen atmosphere, a solution of compound **6** (1.04 g, 4.40 mmol) in 20 mL of THF was dropwise added to lithium aluminum hydride (0.33 g, 8.70 mmol) at room temperature. The mixture was stirred for 1 h at room temperature, and then oxalic acid (1.97 g, 21.90 mmol) was added and stirred for another 0.5 h at room temperature. The mixture was filtered and concentrated. Resulting residues were chromatographed on silica gel (EtOAc/Hexane = 1/3) to give a mixture of **10** and **14** as a gum (84.8 mg): ^{1}H NMR ($CDCl_3$) δ 6.75−6.60 (m, 6H, Ar−H), 5.83 (s, 1H, C8a−H of **10**), 5.77 (d, *J* = 1.80 Hz, 1H, C2−H of **14**), 4.21−3.61 (m, 4H, C4−CH_2 of **14** and C2−CH_2 of **10**), 2.22−1.96 (m, 4H, C10−CH_2 of **14** and C3−CH_2 of **10**), 1.53 (s, 3H, C3a-CH_3 of **10**), and 1.50 (s, 3H, C5−CH_3 of **14**) ppm; GC-MS(CI) two peaks (1:1 ca.), *m/z* 193 (MH^+), respectively. This was directly used as a reactant in the following reactions without separation.[3]

2-(5′-Benzyloxyphenyl-2′-hydroxy)-2-methyl-1,4-butanediol (11). Under a nitrogen atmosphere, lithium aluminum hydride (184.8 mg, 4.869 mmol) was added in portions to a solution of compound **7** (310.0 mg, 0.950 mmol) in 27 mL of dry ether in an ice bath. The mixture was stirred for 1 h at 0 °C and at room temperature overnight. Hydrochloric acid (1 N) was added to the reaction system up to pH 6. The formed precipitate was removed, and solvent was also removed by evaporation. The residue was dissolved in 30 mL of ethyl acetate and washed with brine (2 × 20 mL). After the organic layer was dried over sodium sulfate, filtered, and evaporated, 289 mg of crude product was afforded. This then was recrystallized with chloroform to give white crystals of **11** (186 mg, 65%): mp 112.3−114.5 °C; ^{1}H NMR (DMSO-d_6) δ 9.50 (s, 1H, ArO−H), 7.51−6.70 (m, 8H, Ar−H), 5.01 (s, 2H, CH_2Ph), 4.80, 4.31(2s, 2H, C1, C4−2OH), 3.69 (d, 2H, C4−2H), 3.32−3.09 (m, 2H, C1−2H), 2.33−1.81 (m, 2H, C3−2H), and 1.31 (s, 3H, C2−CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ 151.2, 150.2, 138.0, 132.5, 128.7, 128.1, 128.0, 116.6, 116.5, 112.2, 70.0, 68.5, 58.4, 42.5, 38.4, and 23.1 ppm; CI-MS(CH_4), *z/m*: 267 (MH^+ − 36), 251, 211, and 193; HRMS *m/z* calcd for $C_{18}H_{22}O_4$, 302.1518; found, 302.1508. Anal. Calcd for $C_{18}H_{24}O_5$ (M+H_2O): C, 67.48; H, 7.55. Found: C, 67.10; H, 7.19.

4-(5′-Benzyloxyphenyl-2′-hydroxy)-4,5-dihydro-4-methyl-3*H*-furan-2-one (12). Under a nitrogen atmosphere, lithium borohydride (4.56 mg, 0.209 mmol) was added to a solution of compound **7** (68.0 mg, 0.208 mmol) in 4 mL of dry ether at 0 °C. The mixture was reacted for 0.5 h. Placed in an ice bath, 2.5 g of ice was added to the above reaction system, which was stirred for 5 min. After filtering, the residue was extracted with ethyl acetate (2 × 10 mL). The combined organic layer was dried over sodium sulfate and then evaporated to remove solvents. The residue was recrystallized with AcOEt/CH_2Cl_2(1/6) to give white crystals of **12** (40.3 mg, 65%): mp 162.0−164.0 °C; ^{1}H NMR (DMSO-d_6) δ 9.41 (s, 1H, ArO−H), 7.65−6.84 (m, 8H, Ar−H), 5.13 (s, 2H, CH_2Ph), 4.68, 4.52 (AB, J*gem* = 11.7 Hz, 2H, C5−H), 3.17, 2.80 (AB, J*gem* = 18.9 Hz, 2H, C3−H), and 1.51 (s, 3H, C4−CH_3) ppm; ^{13}C NMR (DMSO-d_6) δ 176.7, 151.6, 149.1, 137.8, 131.5, 128.7, 128.2, 128.1, 116.4, 114.8, 113.7, 77.8, 70.1, 43.3, 41.4, and 25.7 ppm; CI-MS(CH_4), *m/z* 299 (MH^+), 283, and 239; HRMS *m/z* calcd for $C_{18}H_{18}O_4$, 298.1205; found, 298.1211. Anal. Calcd for $C_{18}H_{22}O_6$ (M + $2H_2O$): C, 64.66; H, 6.63. Found: C, 64.71; H, 6.27.

3a,8a-Dihydro-5-hydroxy-3a-methyl-furo[2,3-*b*]benzofuran-2(3*H*)-one (13) and 4-(2′,5′-dihydroxyphenyl)-4,5-dihydro-4-methyl-3*H*-furan-2-one (16). Sodium borohydride (0.12 g, 3.17 mmol) was added to a solution of compound **6** (0.71 g, 3.01 mmol) in 3 mL of ethanol at 0 °C. The reaction mixture was stirred for another 10 min at this temperature, and then hydrogen chloride in dry ether (1 N) was added until a pH value of 7.5−8.0 was reached. Thereafter direct chromatography on silica gel (EtOAc/Hexane = 1/3) afforded product **13** as a gum (0.12 g): ^{1}H NMR ($CDCl_3$) δ 6.72−6.56 (m, 3H, Ar−H), 6.03 (s, 1H, C8a−H), 2.90, 2.72 (AB, J*gem* = 18.0 Hz, 2H, C3−H), and 1.49 (s, 3H, C3a-CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 173.9, 152.2, 150.7, 132.8, 116.9, 113.6, 111.9, 110.7, 50.7, 41.9, and 24.2 ppm; CI-MS(CH_4), *m/z* 207 (MH^+), 189, 177, 161, and 149; HRMS *m/z* calcd for $C_{11}H_{10}O_4$, 206.0579; found, 206.0582. Other white crystals of **16** (0.30 g, 48%): mp 182.5−184.0 °C; ^{1}H NMR (CD_3OD) δ 6.54−6.40 (m. 3H, Ar−H), 4.79 (s, 2H, Ar−OH), 4.52, 4.38 (AB, J*gem* = 5.40 Hz, 2H, C5−H), 2.97, 2.57 (AB, J*gem* = 18.1 Hz, 2H, C3−H), and 1.39 (s, 3H, C4a−H) ppm; ^{13}C NMR (CD_3OD) δ 180.0, 151.7, 149.6, 132.7, 118.0, 115.8, 115.1, 80.5, 44.8, 43.1, and 26.4 ppm; CI-MS(CH_4), *m/z* 209 (MH^+), 191, 177, 164, and 149; HRMS *m/z* calcd for $C_{11}H_{13}O_4$, 209.0814; found, 209.0817.

5-Benzyloxy-3-carboxymethylene-3-methyl-2,3-dihydrobenzofuran (17), 7-Benzyloxy-5-methyl-4,5-dihydro-2,5-methano-1,3-benzodioxepine (23), 6-Benzyloxy-3,4-dihydro-4-ethoxycarbonyl-4-methyl-2*H*-1-benzopyran-2-one (24), and 5-Benzyloxy-3-ethoxycarbonylmethylene-3-methyl-3*H*-benzofuran-2-one (25). Sodium borohydride (71.4 mg, 1.887 mmol) was added to a solution of compound **7** (405.0 mg, 1.241 mmol) in 24 mL of ethanol at room temperature and was stirred for 17 h at the same temperature. Oxalic acid (428.0 mg, 4.753 mmol) was added to this reaction system and then continuously reacted for 0.5 h at room temperature. Thereafter, direct chromatography on silica gel (EtOH/CH_2Cl_2 = 1/155) gave white crystals of **17** (228 mg, 62%): mp 130.0−132.5 °C; ^{1}H NMR ($CDCl_3$) δ 10.3 (s, br, 1H, COOH), 7.39−6.60 (m, 8H, Ar−H), 4.91 (s, 2H, CH_2Ph), 4.51, 4.22 (AB, J*gem* = 9.0 Hz, 2H, C2−H), 2.63 (s, 2H, C3−CH_2COOH), and 1.38 (s, 3H, C3−CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 175.6, 153.9, 153.7, 137.6, 135.4, 128.9, 128.3, 128.0, 115.1, 110.8, 110.3, 82.9, 71.5, 44.4, 43.9, and 25.1 ppm; CI-MS(CH_4), *m/z* 297 (M^+ − 1), 281, 269, 251, 235, 219, 207, 177, 166, 153, 136, 121, 112, 100, 91, and 55; HRMS *m/z* calcd for $C_{18}H_{18}O_4$, 298.1205; found, 298.1210. Anal. Calcd for $C_{18}H_{20.6}O_{5.3}$ (M + $1.3H_2O$): C, 67.19; H, 6.45. Found: C, 66.88; H, 5.68. The second product **23** (21 mg, 6%): ^{1}H NMR ($CDCl_3$) δ 7.46−6.71 (m, 8H, Ar−H), 5.73 (d, *J* = 1.80 Hz, 1H, C2−H), 5.01 (s, 2H, CH_2Ph), 4.18, 3.76 (AB, J*gem* = 6.3 Hz, 2H, C4−H), 2.21, 2.00 (AB, J*gem* = 14.9 Hz, 2H, C10−H), and 1.51 (s, 3H, C5−CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 152.9, 145.7, 137.2, 132.7, 128.6, 128.0, 127.6, 116.6, 113.7, 111.3, 100.4, 84.4, 70.8, 39.9, 39.7, and 16.9 ppm; CI-MS(CH_4), *m/z*: 282 (M^+), 265, 239, 205, 191, 175, 161, 149, 119, 100, and 91; HRMS *m/z* calcd for $C_{18}H_{19}O_3$, 283.1334; found, 283.1327. The third product **24** (25 mg, 6%): ^{1}H NMR ($CDCl_3$) δ 7.42−6.82 (m, 8H, Ar−H), 5.06 (s, 2H, CH_2Ph), 4.12 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 3.11, 2.60 (AB, J*gem* = 16.2 Hz, 2H, C3−H), 1.58 (s, 3H, C4−CH_3), and 1.21 (t, *J* = 7.2 Hz, 3H, CH_3CH_2O) ppm; ^{13}C NMR ($CDCl_3$) δ 173.1, 166.0, 156.0, 145.4, 136.9, 129.0, 128.6, 127.9, 118.6, 115.7, 113.0, 110.0, 71.0, 62.5, 44.6, 39.6, 23.3, and 14.2 ppm; CI-MS(CH_4) *m/z* 341 (MH^+), 313, 295, 281, 267, 253, and 91; HRMS *m/z* calcd for $C_{20}H_{21}O_5$, 341.1389; found, 341.1402. Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.37; H, 6.20. The fourth product **25** (90 mg, 21%): ^{1}H NMR ($CDCl_3$) δ 7.47−6.76 (m, 8H, Ar−H), 5.02 (s, 2H, CH_2Ph), 3.94 (q, *J* = 8.1 Hz, 2H, OCH_2CH_3), 3.10, 2.85 (AB, J*gem* = 18.0 Hz, 2H, C3−

CH_2COO), 1.48 (s, 3H, C3−CH_3), and 1.08 (t, J = 8.1 Hz, 3H, CH_3CH_2O) ppm; ^{13}C NMR ($CDCl_3$) δ 179.9, 169.1, 155.8, 147.2, 136.6, 132.1, 128.6, 128.1, 127.6, 114.6, 111.3, 110.2, 70.9, 61.0, 45.2, 42.4, 25.1, and 13.8 ppm; CI-MS(CH_4), *m/z* 341 (MH^+), 313, 295, 281, 267, 253, and 91; HRMS *m/z* calcd for $C_{20}H_{21}O_5$, 341.1389; found, 341.1383.

3-Methoxycarbonylmethylene-3-methyl-3*H*-benzofuran-2-one-5yl O-Menthyl-carbonate (21). Under a nitrogen atmosphere, a solution of compound **6** (116 mg, 0.491 mmol) and triethylamine (0.06 mL) in 1.5 mL of benzene was dropwise added to (−)-menthyl chloroformate (118 mg, 0.539 mmol) in 1.5 mL of benzene. The mixture was stirred for 3.0 h at room temperature, and then hydrochloric acid (1 N, 2.7 g) was added. The mixture was extracted by ethyl acetate. The extract was washed by water and then was dried over sodium sulfate. The concentrate was recrystallized by hexane or ethanol to afford white crystals of **21** (157 mg, 76%): mp 127.4−128.1 °C; ^1H NMR ($CDCl_3$) δ 7.20−7.02 (m, 3H, Ar−H), 4.68−4.52 (m, 1H, CHOC=O), 3.53 (s, 3H, CH_3O), 3.10, 2.96 (AB, J*gem* = 17.6 Hz, 2H, C3−CH_2COO), 2.21−2.11 (m, 1H, CH−^{i}Pr), 2.10−1.98 (m, 1H, $CHMe_2$), 1.80−1.65 (m, 1H, CHMe), 1.51 (s, 3H, C3−CH_3), 1.59−1.41 (m, 2H, CH_2COC=O), 1.26−0.80 (m, 4H, CH_2CH_2), 0.97 (d, 6H, CH_3CCH_3), and 0.85 (d, 3H, CH_3CCCOC=O) ppm; ^{13}C NMR ($CDCl_3$) δ 177.7, 168.0, 151.7, 148.9, 146.1, 130.4, 120.1, 114.5, 109.9, 78.3, 50.5, 45.5, 43.5, 40.5, 39.1, 32.5, 29.9, 24.7, 23.3, 21.9, 20.4, 19.2, and 14.9 ppm; CI-MS (CH_4), *m/z* 419 (MH^+), 418, 417, 371, 237, 181, 153, and 109; HRMS *m/z* calcd for $C_{23}H_{34}NO_7(MNH_4^+)$, 436.2335; found, 436.2326.

3,4-Dihydro-6-hydroxy-4-methoxycarbonyl-4-methyl-2*H*-1-benzopyran-2-one (22). A mixture of compound **21** (0.69 g, 1.649 mmol) and sodium hydroxide (0.28 g, 7.0 mmol) in 25 mL of methanol was stirred for 1.5 h at room temperature. The mixture was neutralized with hydrochloric acid (1 N) and then was evaporated to remove methanol. The residue was extracted with ethyl acetate and washed by brine. After drying over sodium sulfate, its concentrate was chromatographed on silica gel ($EtOH/CH_2Cl_2$ = 1/100) to afford white crystals of **22** (77.9 mg, 20%): mp 147.0−149.0 °C; ^1H NMR ($CDCl_3$) δ 6.99−6.78 (m, 3H, Ar−H), 4.92 (s, br, 1H, Ar−OH), 3.71 (s, 3H, OCH_3), 3.18, 2.61 (AB, J*gem* = 16.2 Hz, 2H, C3−H), and 1.65 (s, 3H, C4−CH_3) ppm; ^{13}C NMR ($CDCl_3$) δ 173.4, 167.0, 152.9, 145.4, 126.2, 118.8, 116.7, 113.0, 53.5, 44.5, 39.5, and 23.4 ppm; CI-MS (CH_4), *m/z* 237 (MH^+), 205, 177, and 163; HRMS *m/z* calcd for $C_{12}H_{13}O_5$, 237.0763; found, 237.0767.

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Supporting Information Available: NMR spectra for all new compounds described herein and crystallographic data for some key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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