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SYNTHESIS OF TETRAHYDROFURO[2,3-*b*][1]BENZOPYRANONES BY THE RING-EXPANSION REACTION OF METHANOCHROMANONE WITH SYMMETRIC KETONES

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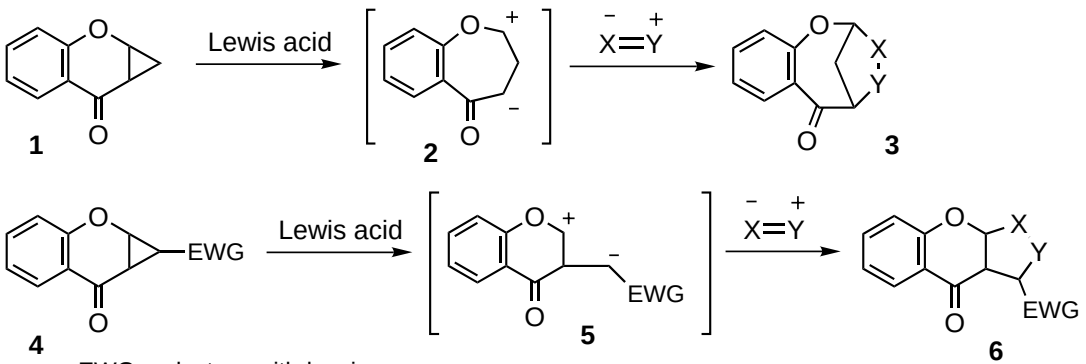
Abstract - In the presence of $SnCl_4$, 2,3-dimethoxycarbonylmethanochromanone (**8**) was transformed into a zwitterion which easily reacted with symmetric ketones to give the tetrahydrofuro[2,3-*b*][1]benzopyranone derivatives in good yields with high diastereoselectivity.

Cyclopropanes having an electron-withdrawing or -donating group are susceptible to ring-opening reactions.[1] Especially, cyclopropanes with donor and acceptor substituents at vicinal positions on the cyclopropane ring are the equivalent of a ring-opened 1,3-zwitterion,[2] which are expected to react with both nucleophiles[3] and electrophiles.[4]

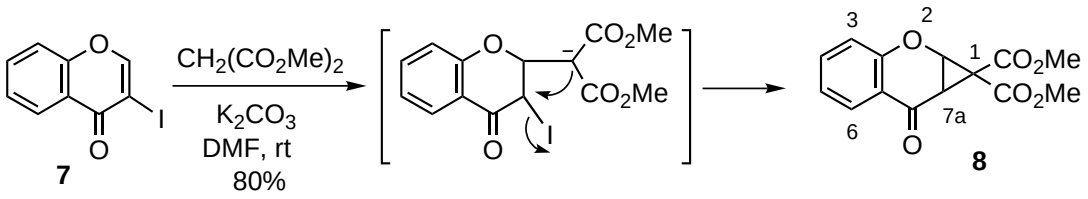
We have recently reported that 2,3-methanochromanone (**1**), readily prepared from the chromone and dimethyloxosulfonium methylide, was transformed into a zwitterionic intermediate (**2**) in the presence of a Lewis acid, and that **2** reacted with silyl enol ethers to give the ring-expanded product (**3**).[5] If methanochromanones having a strong electron-acceptor at the methano-position are employed instead of **1**, formation of a 1,3-zwitterionic intermediate (**5**) would be expected (Scheme 1). We report herein the synthesis of tetrahydrofuro[2,3-*b*][1]benzopyranone derivatives by the Lewis acid-promoted reaction of methanochromanone (**8**) having two ester groups at the methano-position with symmetric ketones.



EWG = electron-withdrawing group

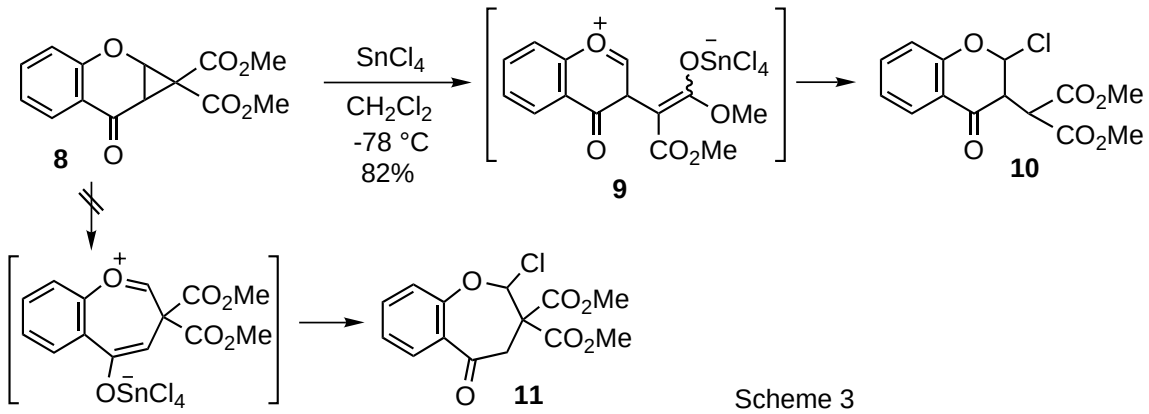
Scheme 1

Methanochromanone (**8**) was readily obtained in 80% yield by the reaction of 3-iodochromone (**7**)[6] with dimethyl malonate in the presence of potassium carbonate in DMF at room temperature (Scheme 2). The reaction pathway for the formation of cyclopropane ring involves the initial Michael reaction[7] of dimethyl malonate to the active site (2-position of the chromone ring) followed by cyclization of the resulting intermediate.



Scheme 2

At first, the reactivity of **8** by the action of a Lewis acid was examined. A solution of a stoichiometric amount of $SnCl_4$ in CH_2Cl_2 was added to a solution of **8** in CH_2Cl_2 at -78 ℃ to give the 2-chlorochromanone (**10**) in 82% yield and no 2-chloro-1-benzoxepinone (**11**)[5] was detected (Scheme 3). In this result, we considered that methanochromanone (**8**) is the equivalent of a ring-opened zwitterion (**9**).



Scheme 3

Next the reaction of **8** with symmetric ketones was undertaken. In the presence of $SnCl_4$ (10 mol%), **8** smoothly reacted with acetone in CH_2Cl_2 at -78 °C to afford the tetrahydrofuro[2,3-*b*][1]benzopyran-4-one (**12a**)[8] in quantitative yield with high *trans*-selectivity (*trans* : *cis* = >99 : 1, Table 1, Entry 1). The *trans/cis* ratio was determined by ^{1}H-NMR analysis of the reaction mixture. A similar tendency was observed in the [3+2] cycloaddition reaction of **8** with 3-pentanone and diphenyl ketone (Entries 2 and 3). Cyclic ketones such as cyclopentanone, cyclohexanone, and cycloheptanone also gave the corresponding cycloadducts in good yields with high *trans*-selectivity (Entries 4~6).

It was also found that the *trans*-adducts could be easily converted into *cis*-isomers by treatment with Et_3N.

Thus, treatment of the adduct (**12a**) with Et_3N in CH_2Cl_2 at room temperature gave the *cis*-isomer (**13a**) in 86% yield. The stereochemistry of the products was assigned based on NOE experiments. Thus, irradiation of H-9a in *cis*-isomer (**13a**) gave a 15.5% enhancement of the signal for H-3a supporting the *cis* stereochemistry. In comparison, irradiation of H-9a in *trans*-adduct (**12a**) resulted in only 3.5% enhancement of the signal for H-3a. The stereochemistry of cycloadducts (**12b~f**) was established by comparison of the coupling constants between H-3a and H-9a to those of **12a**. The adduct (**12a**) exhibited a coupling constant of 10.1 Hz, while values of 10.4, 10.4, 10.1, 10.1, and 10.1 Hz were observed for **12b**, **12c**, **12d**, **12e**, and **12f**, respectively.

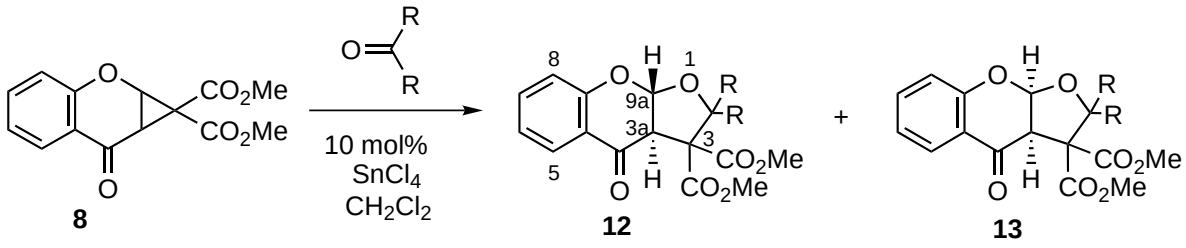


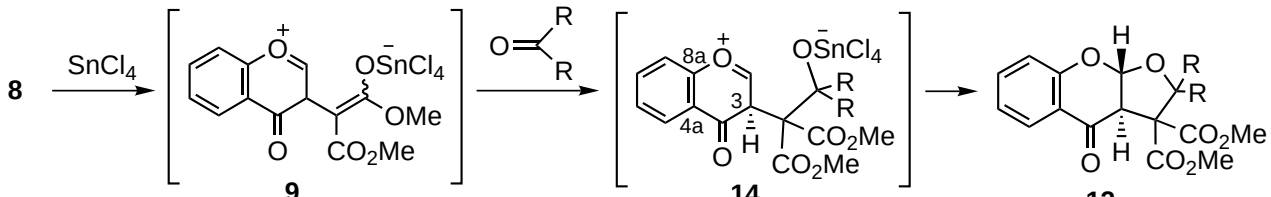
Table 1. Lewis acid-mediated [3+2] cycloaddition of **8** with symmetric ketones

Entry	Ketone	Temp (°C)	Time (h)	Product	Yield (%)[a]	*trans* : *cis*
1	acetone	-78	0.25	**12a**	99	>99 : 1
2	3-pentanone	-78→-30	4	**12b**	70	>99 : 1
3	diphenyl ketone	-78	0.4	**12c**	80	>99 : 1
4	cyclopentanone	-78→-50	2	**12d**	88	>50 : 1
5	cyclohexanone	-78→rt	3.5	**12e**	88	>99 : 1
6	cycloheptanone	-10	0.4	**12f**	67	>50 : 1

[a] Isolated yield

A plausible reaction mechanism is proposed in Schemes 4 and 5.

In the first step, **8** was initially transformed into a zwitterionic intermediate (**9**) by the action of a Lewis acid and the zwitterion reacted with ketones to form the intermediate (**14**). In the second step for the diastereoselective cycloaddition reaction, addition of a nucleophile can, in principle, occur at either face of the oxonium ion (**14**). In each case, either parallel or *anti*-parallel[9] (with respect to the axial hydrogen at C3) attack is possible. In general, the intramolecular 5-*exo*-trig ring closure of cyclohexane derivatives[10] leads to *cis*-fused products arising from *anti*-parallel addition *via* a chair-like transition state[11] (Figure 1). In the case of this reaction, C4-C4a, C4a-C8a, and C8a-O bonds in the intermediate (**14**) should be likely lied in the same plane (Figure 2). In the possible conformations of the intermediate (**14**), **14A** is favored over **14B** because of the unfavorable dipole-dipole interactions and/or the steric hindrance between the carbonyl and the ester groups. As a result, *trans*-fused products would be preferred.



Scheme 4

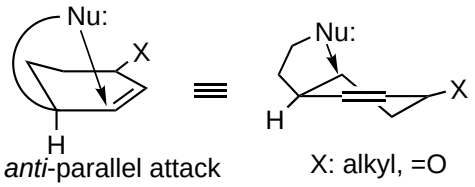


Figure 1

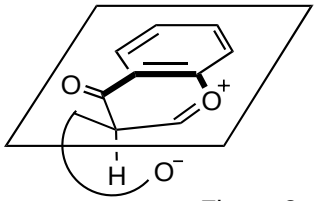
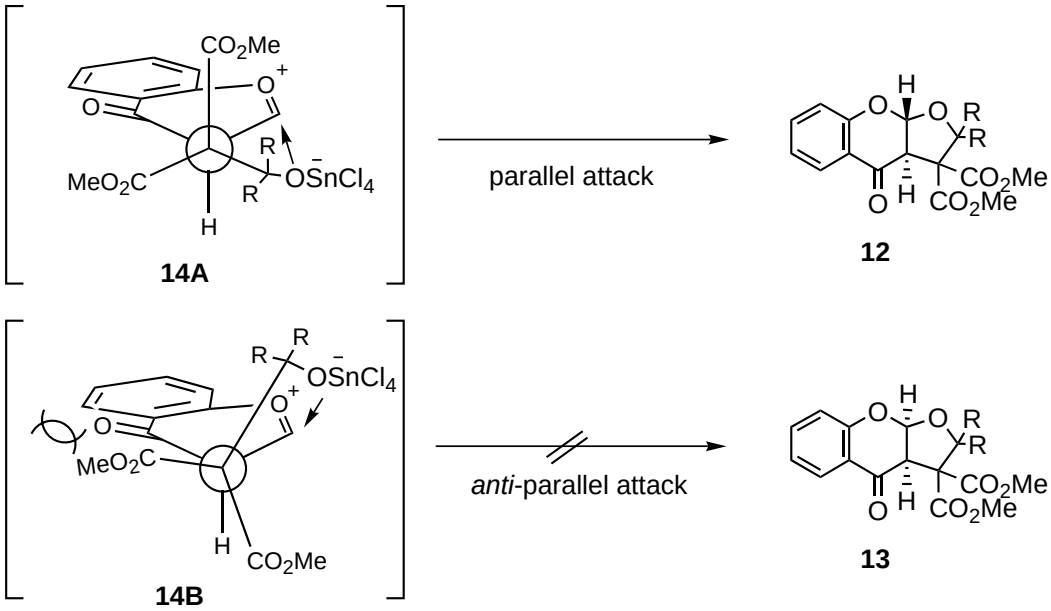


Figure 2



Scheme 5

In summary, we have demonstrated that the $SnCl_4$-catalyzed ring-opening addition reactions of **8** with symmetric ketones proceeded smoothly to afford the corresponding tetrahydrofuro[2,3-*b*][1]benzo-pyranones in high yields with high diastereoselectivity.

EXPERIMENTAL

All melting points were determined using a Yanagimoto micro-hot stage and are uncorrected. IR spectra were recorded using a JASCO IR-810 spectrophotometer and NMR spectra were measured using a JEOL JNM-A500 with tetramethylsilane as the internal standard. MS spectra were recorded using a JEOL JMS-700 spectrometer. Column chromatography was done on BW-820 MH (Fuji silysia).

Dimethyl 7,7a-dihydro-7-oxobenzo[*b*]cyclopropa[*e*]pyran-1,1-dicarboxylate (8)

To a mixture of 3-iodochromone (5.4 g, 20 mmol) and K_2CO_3 (11 g, 80 mmol) in DMF (80 mL) was added methyl malonate (2.8 g, 21 mmol) at rt. After being stirred for 3 h, the reaction mixture was deluted with water and extracted with Et_2O. The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane -AcOEt = 4 : 1) to give **8** (4.4 g, 80%), mp 104-105 °C (from AcOEt-hexane). IR ($CHCl_3$) 1740, 1690, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.04 (1H, d, *J* = 7.0 Hz, H-7a), 3.31 (3H, s, OMe), 3.81 (3H, s, OMe), 4.92 (1H, d, *J* = 7.0 Hz, H-1a), 7.01 (1H, dd, *J* = 8.5, 0.9 Hz, H-3), 7.07 (1H, ddd, *J* = 8.2, 7.9, 0.9 Hz, H-5), 7.50 (1H, ddd, *J* = 8.5, 8.2, 1.5 Hz, H-4), 7.87 (1H, dd, *J* = 7.9, 1.5 Hz, H-6); ^{13}C-NMR ($CDCl_3$) δ 33.98, 35.24, 52.83, 53.68, 63.70, 117.59, 119.15, 122.71, 126.28, 136.16, 157.52, 162.69, 167.83, 183.35; MS *m/z* 276 (M^+). *Anal*. Calcd for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38. Found: C, 60.72; H, 4.46.

Dimethyl (2-chloro-2,3-dihydro-4*H*-1-benzopyran-3-yl)malonate (10)

To a stirred solution of **8** (138 mg, 0.5 mmol) in CH_2Cl_2 (6 mL) was dropwise a solution of $SnCl_4$ (1.0 *M* solution in CH_2Cl_2, 0.6 mL, 0.6 mmol) at -78 °C under argon atmosphere. After being stirred for 30 min, the reaction was quenched at the same temperature by adding phosphate buffer (Ph 7). The mixure was stirred vigorously for 10 min and allowed to rt. The mixture was extracted with CH_2Cl_2 (30 mL x 3) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was recrystallized from Et_2O-hexane to give **10** (128 mg, 82%), mp 104-106 °C. IR ($CHCl_3$) 1760, 1740, 1700, 1650, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.65 (1H, dd, *J* = 8.5, 2.8 Hz, H-3), 3.72 (3H, s, OMe), 3.74 (3H, s, OMe), 3.81 (1H, d, *J* = 8.5 Hz, COCHCO), 6.72 (1H, d, *J* = 2.8 Hz, H-2), 7.06 (1H, dd, *J* = 8.2, 0.9 Hz, H-8), 7.21 (1H, ddd, *J* = 8.2, 7.9, 0.9 Hz, H-6), 7.59 (1H, td, *J* = 8.2, 8.2, 1.5 Hz, H-7), 7.94 (1H, dd, *J* = 7.9, 1.5 Hz, H-5); High-resolution MS *m/z* Calcd for $C_{14}H_{13}O_6{}^{35}Cl$ (M^+); 312.0401, Found: 312.0371.

General Procedure for [3+2] Cycloaddition Reaction of Methanochromanone (8) with Symmetric Ketones.

To a stirred solution of **8** (138 mg, 0.5 mmol) and a ketone (1 mmol) in CH_2Cl_2 (4 mL) was dropwise a solution of $SnCl_4$ (0.2 *M* solution in CH_2Cl_2, 0.25 mL, 0.05 mmol) at -78~-10 °C under argon atmosphere. After being stirred for 0.2~4 h at -78 °C~rt, the reaction was quenched by saturated aqueous $NaHCO_3$. The mixure was stirred vigorously for 10 min and allowed to rt. The mixture was extracted with

CH_2Cl_2 (30 mL x 3) and the combined organic layers were dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography (hexane / AcOEt) to afford the cycloadduct (**12a-f**). The yield is given in Table 1.

Dimethyl *trans*-2,3,3a,9a-tetrahydro-2,2-dimethyl-4-oxo-4*H*-furo[2,3-*b*][1]benzopyran-3,3-dicarboxylate (12a): colorless prism (from AcOEt-hexane), mp 115-117 °C; IR ($CHCl_3$) 1750, 1730, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.49 (3H, s, Me), 1.56 (3H, s, Me), 3.82 (3H, s, OMe), 3.83 (3H, s, OMe), 3.98 (1H, d, *J* = 10.1 Hz, H-3a), 5.98 (1H, d, *J* = 10.1 Hz, H-9a), 7.10 (1H, ddd, *J* = 8.5, 7.3, 1.0 Hz, H-6), 7.12 (1H, dd, *J* = 8.5, 1,0 Hz, H-8), 7.54 (1H, ddd, *J* = 8.5, 7.3, 1.8 Hz, H-7), 7.89 (1H, dd, *J* = 7.9, 1.8 Hz, H-5); MS *m/z* 334 (M^+). *Anal*. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43. Found: C, 60.95; H, 5.36.

Dimethyl *trans*-2,2-diethyl-2,3,3a,9a-tetrahydro-4-oxo-4*H*-furo[2,3-*b*][1]benzopyran-3,3-dicarboxylate (12b): colorless prism (from AcOEt-hexane), mp 108-110 °C; IR ($CHCl_3$) 1750, 1720, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.00 (3H, t, *J* = 7.3 Hz, Me), 1.04 (3H, t, *J* = 7.3 Hz, Me), 1.68 (1H, dq, *J* = 14.6, 7.3 Hz, C*H*$_2$CH$_3$), 1.92 (2H, q, *J* = 7.3 Hz, C*H*$_2$CH$_3$), 1.94 (1H, dq, *J* = 14.6, 7.3 Hz, C*H*$_2$CH$_3$), 3.81 (6H, s, OMe), 3.93 (1H, d, *J* = 10.4 Hz, H-3a), 6.00 (1H, d, *J* = 10.4 Hz, H-9a), 7.10 (1H, ddd, *J* = 7.9, 7.3, 1.0 Hz, H-6), 7.13 (1H, dd, *J* = 8.5, 1.0 Hz, H-8), 7.54 (1H, ddd, *J* = 8.5, 7.3, 1.8 Hz, H-7), 7.88 (1H, dd, *J* = 7.9, 1.8 Hz, H-5); MS *m/z* 361 (M^+-1). *Anal*. Calcd for $C_{19}H_{22}O_7$: C, 62.98; H, 6.12. Found: C, 62.75; H, 6.06.

Dimethyl *trans*-2,3,3a,9a-tetrahydro-4-oxo-2,2-diphenyl-4*H*-furo[2,3-*b*][1]benzopyran-3,3-dicarboxylate (12c): colorless prism (from AcOEt-hexane), mp 260-262 °C; IR ($CHCl_3$) 1745, 1725, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.37 (3H, s, OMe), 3.47 (3H, s, OMe), 4.46 (1H, d, *J* = 10.4 Hz, H-3a), 6.28 (1H, d, *J* = 10.4 Hz, H-9a), 7.14 (1H, ddd, *J* = 7.9, 7.3, 1.0 Hz, H-6), 7.20-7.29 (4H, m), 7.32 (1H, m), 7.41 (2H, m), 7.48 (2H, m), 7.61 (1H, ddd, *J* = 8.3, 7.3, 1.8 Hz, H-7), 7.89 (1H, dd, *J* = 7.9, 1.8 Hz, H-5), 7.90 (2H, m); MS *m/z* 458 (M^+). *Anal*. Calcd for $C_{27}H_{22}O_7$: C, 70.74; H, 4.84. Found: C, 70.53; H, 4.92.

Dimethyl *trans*-2,3,3a,9a-tetrahydro-4-oxo-4*H*-furo[2,3-*b*][1]benzopyran-2-spirocyclopentane-3,3-dicarboxylate (12d): colorless prism (from Et_2O-hexane), mp 124-126 °C; IR ($CHCl_3$) 1740, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.66-2.07 (8H, m), 3.81 (3H, s, OMe), 3.83 (3H, s, OMe), 3.95 (1H, d, *J* = 10.1 Hz, H-3a), 5.92 (1H, d, *J* = 10.1 Hz, H-9a), 7.10 (1H, ddd, *J* = 7.9, 7.3, 1.0 Hz, H-6), 7.12 (1H, dd, *J* = 8.5, 1.0 Hz, H-8), 7.53 (1H, ddd, *J* = 8.5, 7.3, 1.8 Hz, H-7), 7.88 (1H, dd, *J* = 7.9, 1.8 Hz, H-5); MS *m/z* 360 (M^+). *Anal*. Calcd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found: C, 63.05; H, 5.63.

Dimethyl *trans*-2,3,3a,9a-tetrahydro-4-oxo-4*H*-furo[2,3-*b*][1]benzopyran-2-spirocyclohexane-3,3-dicarboxylate (12e): colorless prism (from Et_2O-hexane), mp 134-136 °C; IR ($CHCl_3$) 1750, 1730, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.23 (1H, m), 1.54 (1H, m), 1.65-1.90 (8H, m), 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 4.00 (1H, d, *J* = 10.1 Hz, H-3a), 5.99 (1H, d, *J* = 10.1 Hz, H-9a), 7.10 (1H, ddd, *J* = 7.9, 7.0, 1.0 Hz, H-6), 7.14 (1H, dd, *J* = 8.2, 1.0 Hz, H-8), 7.53 (1H, ddd, *J* = 8.2, 7.0, 1.8 Hz, H-7), 7.89 (1H, dd, *J* = 7.9, 1.8 Hz, H-5); MS *m/z* 374 (M^+). *Anal*. Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 64.01; H, 6.01.

Dimethyl *trans*-2,3,3a,9a-tetrahydro-4-oxo-4*H*-furo[2,3-*b*][1]benzopyran-2-spirocyclo-heptane-3,3-dicarboxylate (12f): colorless prism (from AcOEt-hexane), mp 132-134 °C; IR ($CHCl_3$) 1750, 1730, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.44 (1H, m), 1.55-2.08 (11H, m), 3.80 (3H, s, OMe), 3.83 (3H, s, OMe), 3.92 (1H, d, *J* = 10.1 Hz, H-3a), 6.00 (1H, d, *J* = 10.1 Hz, H-9a), 6.99 (1H, ddd, *J* = 8.2, 7.0, 1.0 Hz, H-6), 7.13 (1H, dd, *J* = 8.2, 1.0 Hz, H-8), 7.53 (1H, ddd, *J* = 8.5, 7.0, 1.8 Hz, H-7), 7.88 (1H, dd, *J* = 7.9, 1.8 Hz, H-5); MS *m/z* 388 (M^+). *Anal.* Calcd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23. Found: C, 64.75; H, 6.28.

Dimethyl *cis*-2,3,3a,9a-tetrahydro-2,2-dimethyl-4-oxo-4*H*-furo[2,3-*b*][1]benzopyran-3,3-dicarboxylate (13a): To a solution of **12a** (66.8 mg, 0.2 mmol) in CH_2Cl_2 (2 mL) was added Et_3N (101 mg, 1 mmol) at rt. After being stirred for 6 h, 10% HCl was added to the mixture and the whole was extracted with CH_2Cl_2 (20 mL x 3). The organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane-AcOEt = 10 : 1) to give **13a** (57 mg, 86%) as a colorless oil. IR ($CHCl_3$) 1750, 1690, 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.31 (3H, s, Me), 1.62 (3H, s, Me), 3.48 (3H, s, OMe), 3.86 (3H, s, OMe), 4.18 (1H, d, *J* = 6.7 Hz, H-3a), 6.12 (1H, d, *J* = 6.7 Hz, H-9a), 7.04 (1H, dd, *J* = 8.2, 1.0 Hz, H-8), 7.05 (1H, ddd, *J* = 7.9, 7.3, 1.0 Hz, H-6), 7.52 (1H, ddd, *J* = 8.2, 7.3, 1.8 Hz, H-7), 7.82 (1H, dd, *J* = 7.9, 1.8 Hz, H-5); ^{13}C-NMR ($CDCl_3$) δ 25.05, 26.96, 52.13, 53.10, 54.00, 68.73, 85.48, 100.33, 118.27, 120.24, 122.00, 126.52, 136.50, 157.37, 166.95, 168.12, 188.80; High-resolution MS *m/z* Calcd for $C_{17}H_{18}O_7$ (M^+): 334.1052, Found: 334.1034.

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