

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

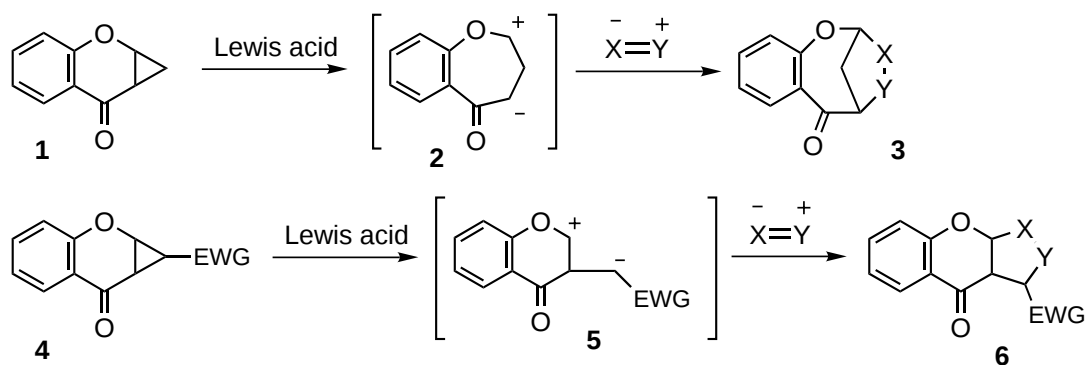
Yoshiaki Sugita,* Kazuyoshi Kawai, and Ichiro Yokoe

Faculty of Pharmaceutical Sciences, Josai University, Sakado, Saitama
350-0295, Japan

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.

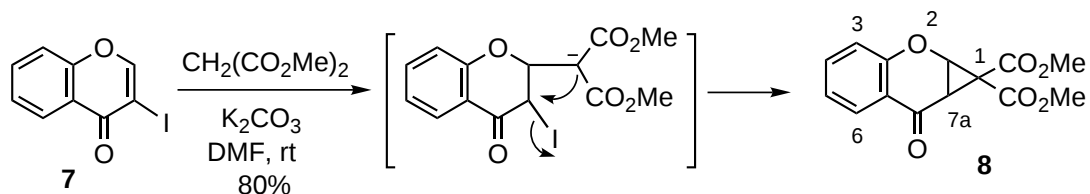
Cyclopropanes having an electron-withdrawing or -donating group are susceptible to ring-opening reactions.¹ Especially, cyclopropanes with donor and acceptor substituents at vicinal positions on the cyclopropane ring are the equivalent of a ring-opened 1,3-zwitterion,² which are expected to react with both nucleophiles³ 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.



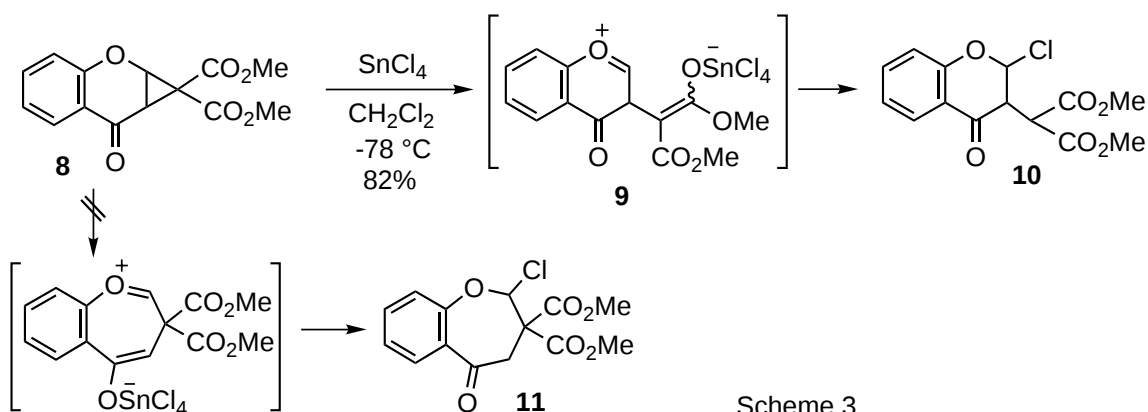
Scheme 1

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 reaction⁷ 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°C 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 ^1H -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 Et₃N in CH₂Cl₂ 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.

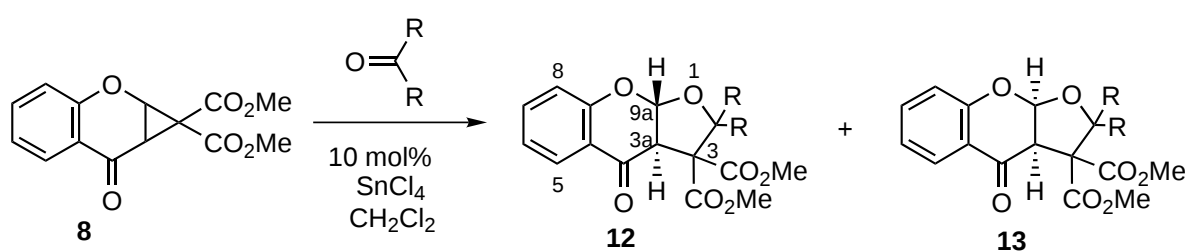


Table 1. Lewis acid-mediated [3+2] cycloaddition of **8** with symmetric ketones

Entry	Ketone	Temp (°C)	Time (h)	Product	Yield (%) ^a	<i>trans</i> : <i>cis</i>
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*-parallel⁹ (with respect to the axial hydrogen at C3) attack is possible. In general, the intramolecular 5-*exo*-trig ring closure of cyclohexane derivatives¹⁰ leads to *cis*-fused products arising from *anti*-parallel addition *via* a chair-like transition state¹¹ (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.

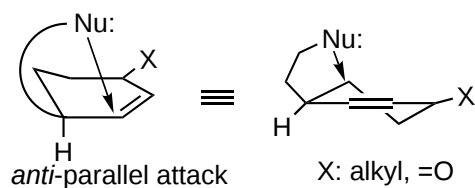
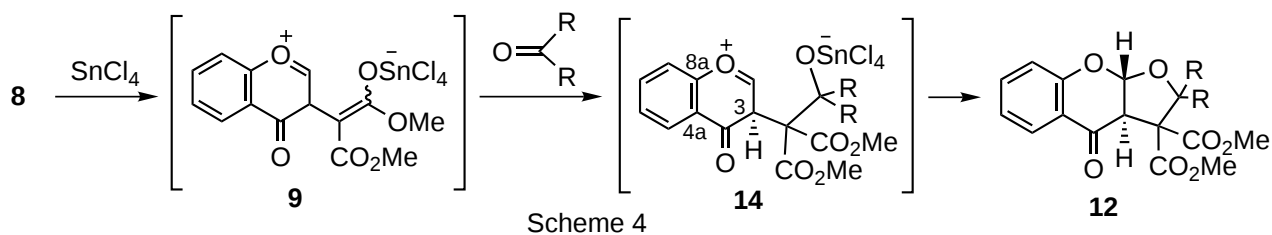


Figure 1

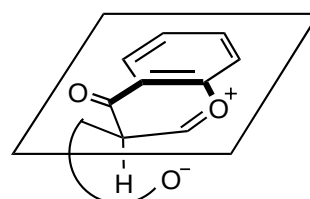
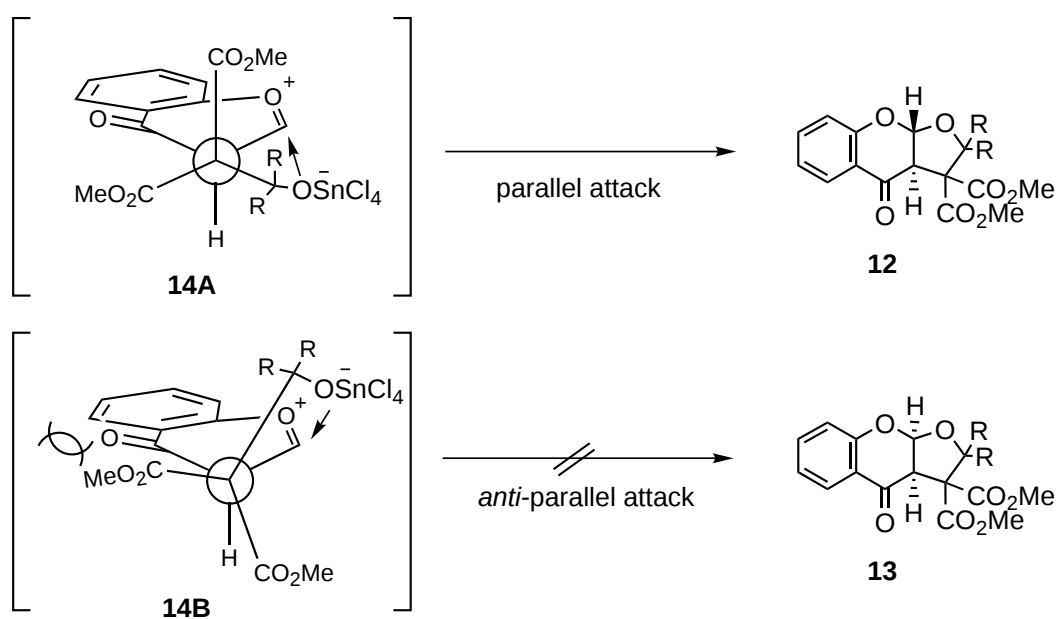


Figure 2



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]benzopyranones 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} ; 1H -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-4H-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 mixture 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} ; 1H -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 mixture was stirred vigorously for 10 min and allowed to rt. The mixture was extracted with

CH₂Cl₂ (30 mL x 3) and the combined organic layers were dried over Na₂SO₄. 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-4H-furo[2,3-b][1]benzopyran-

3,3-dicarboxylate (12a): colorless prism (from AcOEt-hexane), mp 115-117 °C; IR (CHCl₃) 1750, 1730, 1610 cm⁻¹; ¹H-NMR (CDCl₃) 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 C₁₇H₁₈O₇: 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-4H-furo[2,3-b][1]benzopyran-

3,3-dicarboxylate (12b): colorless prism (from AcOEt-hexane), mp 108-110 °C; IR (CHCl₃) 1750, 1720, 1620 cm⁻¹; ¹H-NMR (CDCl₃) 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, CH₂CH₃), 1.92 (2H, q, *J* = 7.3 Hz, CH₂CH₃), 1.94 (1H, dq, *J* = 14.6, 7.3 Hz, CH₂CH₃), 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 C₁₉H₂₂O₇: 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-4H-furo[2,3-b][1]benzopyran-

3,3-dicarboxylate (12c): colorless prism (from AcOEt-hexane), mp 260-262 °C; IR (CHCl₃) 1745, 1725, 1600 cm⁻¹; ¹H-NMR (CDCl₃) 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 C₂₇H₂₂O₇: C, 70.74; H, 4.84. Found: C, 70.53; H, 4.92.

Dimethyl trans-2,3,3a,9a-tetrahydro-4-oxo-4H-furo[2,3-b][1]benzopyran-2-spirocyclo-

pentane-3,3-dicarboxylate (12d): colorless prism (from Et₂O-hexane), mp 124-126 °C; IR (CHCl₃) 1740, 1610 cm⁻¹; ¹H-NMR (CDCl₃) 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 C₁₉H₂₀O₇: C, 63.33; H, 5.59. Found: C, 63.05; H, 5.63.

Dimethyl trans-2,3,3a,9a-tetrahydro-4-oxo-4H-furo[2,3-b][1]benzopyran-2-spirocyclo-

hexane-3,3-dicarboxylate (12e): colorless prism (from Et₂O-hexane), mp 134-136 °C; IR (CHCl₃) 1750, 1730, 1610 cm⁻¹; ¹H-NMR (CDCl₃) 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 C₂₀H₂₂O₇: 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-spirocycloheptane-3,3-dicarboxylate (12f): colorless prism (from AcOEt-hexane), mp 132-134 °C; IR (CHCl₃) 1750, 1730, 1610 cm⁻¹; ¹H-NMR (CDCl₃) 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 C₂₁H₂₄O₇: 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 CH₂Cl₂ (2 mL) was added Et₃N (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 CH₂Cl₂ (20 mL x 3). The organic layer was dried over Na₂SO₄ 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 (CHCl₃) 1750, 1690, 1610 cm⁻¹; ¹H-NMR (CDCl₃) 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); ¹³C-NMR (CDCl₃) 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 C₁₇H₁₈O₇ (M⁺): 334.1052, Found: 334.1034.

REFERENCE AND NOTES

1. Review: H. N. C. Wong, M.-U. Hon, C.-W. Tse, and Y.-C. Yip, *Chem. Rev.*, 1989, **89**, 165.
2. Review: H.-U. Reißig, *Top. Curr. Chem.*, 1988, **144**, 73.
3. K. Saigo, S. Shimada, T. Shibasaki, and M. Hasegawa, *Chem. Lett.*, **1990**, 1093; b) M. Komatsu, I. Suehiro, Y. Horiguchi, and I. Kuwajima, *Synlett*, **1991**, 771.
4. a) K. Saigo, S. Shimada, Y. Hashimoto, and M. Hasegawa, *Chem. Lett.*, **1989**, 1293; b) K. Saigo, S. Shimada, and M. Hasegawa, *Chem. Lett.*, **1990**, 905; c) K. Saigo, S. Shimada, Y. Hashimoto, T. Nagashima, and M. Hasegawa, *Chem. Lett.*, **1990**, 1101; d) S. Shimada, Y. Hashimoto, A. Sudo, M. Hasegawa, and K. Saigo, *J. Org. Chem.*, 1992, **57**, 7126; e) S. Shimada, Y. Hashimoto, and K. Saigo, *J. Org. Chem.*, 1993, **58**, 5226; f) S. Shimada, Y. Hashimoto, T. Nagashima, M. Hasegawa, and K. Saigo, *Tetrahedron*, 1993, **49**, 1589.
5. Y. Sugita, K. Kawai, H. Hosoya, and I. Yokoe, *Heterocycles*, 1999, **51**, 2029.
6. R. B. Gammill, *Synthesis*, **1979**, 901.
7. a) Y. Sugita and I. Yokoe, *Heterocycles*, 1996, **43**, 2503; b) S. T. Saengchantara and T. W. Wallace, *Tetrahedron*, 1990, **46**, 3029; c) P. D. Clarke, A. O. Fitton, H. Suschitzky, T. W. Wallace, H. A.

- Dowlatshahi, and J. L. Suschitzky, *Tetrahedron Lett.*, 1986, **27**, 91; d) T. W. Wallace, *Tetrahedron Lett.*, 1984, **25**, 4299.
8. a) P. J. Cremins, R. Hayes, and T. W. Wallace, *Tetrahedron*, 1991, **47**, 9431; b) P. J. Cremins and T. W. Wallace, *J. Chem. Soc., Chem. Commun.*, **1984**, 1698.
9. J. Valls and E. Toromanoff, *Bull. Soc. Chim. France*, **1961**, 758.
10. a) G. Majetich, J. Defauw, K. Hull, and T. Shawe, *Tetrahedron Lett.*, 1985, **26**, 4711; b) R. E. Ireland and P. Maienfisch, *J. Org. Chem.*, 1988, **53**, 640; c) P. A. Bartlett and C. F. Pizzo, *J. Org. Chem.*, 1981, **46**, 3896; d) R. C. Cambie, P. S. Rutledge, R. F. Somerville, and P. D. Woodgate, *Synthesis*, **1988**, 1009; e) J.-E. Bäckvall, P. G. Andersson, and O. Vågberg, *Tetrahedron Lett.*, 1989, **30**, 137.
11. D. A. Oare and C. H. Heathcock, in E. L. Eliel and S. H. Wilen (eds), "Topics in Stereochemistry", Wiley, New York, 1989, pp. 372-374.