Synthesis of Furan and Thiophene Analogs of Duocarmycin SA

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Received October 23, 1996; accepted December 7, 1996

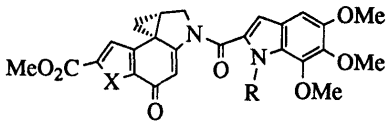
Total synthesis of furan and thiophene analogs 6 and 7 of duocarmycin SA was achieved in racemic forms, starting from methyl 4,5-dibromo-2-furan- and thiophenecarboxylates (15a and 15b). Lithio derivatives 12a (a series: X=O) and 12b (b series: X=S) were reacted with the aldehyde 22 for preparation of 25a and 25b, and successive synthetic operations, including Heck reaction of 25a and 25b to obtain 26a+27a and 26b+27b, and B ring aromatization, 28a and 28b→31a and 31b, based on our previous total synthesis of duocarmycin SA, afforded 36a and 36b. Treatment of 36a and 36b with potassium carbonate in methanol directly afforded cyclopropapyrroloindole derivatives 38a and 38b, whose condensation with the 5,6,7-trimethoxy-2-indolecarbonyl unit completed the synthesis of (±)-6 and (±)-7.

Key words total synthesis; duocarmycin SA furan analog; duocarmycin SA thiophene analog; potent antitumor substance; Heck reaction

Some time ago, we reported the first-generation total synthesis of duocarmycin SA (**1**),[1] an extremely potent cytotoxic antibiotic isolated from the *Streptomyces* species DO 113 in 1990 (Chart 1).[2] This antibiotic **1** is one of a new class of natural products having an *N*-acylcyclopropanoindolinone pharmacophore or its equivalent, which plays a pivotal role in the alkylation of double-stranded DNA in a sequence-selective manner.[3] Among these natural products, CC-1065[4] and duocarmycin A[5] have been well studied and their derivatives, adozelesin (**2**),[6] carzelesin (**3**)[7] and KW-2189 (**4**)[8] are now in clinical trials. Preparation of a variety of furan analogs **5** of CC-1065 was also reported.[9] As a continuation of our work on the total synthesis of **1**, we embarked on the synthesis of various kinds of analogs of **1**, with deep-seated core modifications, aiming at the development of compounds having more potent biological activities with reduced toxicities. Here we report syntheses of furan and thiophene analogs, (±)-**6** and (±)-**7**, of duocarmycin SA.

Synthesis was initially planned on the basis of our previous synthesis of (±)-duocarmycin SA (**1**),[1] according to route 1, *i.e.*, **8**→**9**→**10**→**11** (X=NH) in Chart 2. This synthesis includes three key steps: i) intramolecular Heck reaction of **9**, ii) followed by aromatization of ring B to afford **10**, and finally iii) formation of the cyclopropanoindolinone unit in **11**. However, in the cases of the furan and thiophene analogs, preparation of the starting compounds **8** (X=O and S) was found to be troublesome as described below, so that the actual synthesis was carried out according to route 2, where the important Heck substrates **9** (X=O and S) were prepared by condensation of lithium derivatives of *tert*-butyl esters **12** (X=O and S) with an aldehyde **13**.

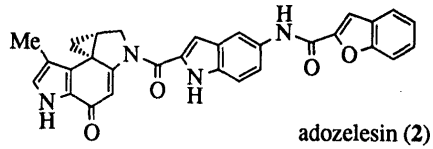
Attempted Synthesis of Methyl 5-Acetyl-4-bromo-2-furan- and thiophenecarboxylates (8a and 8b) The difficulty in route 1 stemmed from failure of the Friedel–Crafts acetylation of methyl 4-bromo-2-furan- and thiophenecarboxylates (**14a** and **14b**)[10,11] to afford **8a** and **8b**[12] (Chart 3), even though the reaction proceeded without trouble for preparation of the corresponding pyrrole derivative **8** (X=NH).[1] Therefore an alternative route to introduce the acetyl group into the C-5 position of **14a** and **14b** was studied utilizing lithium derivatives **12a** and **12b**, expected to be readily obtained from methyl 4,5-dibromo-2-furan- and thiophenecarboxylates (**15a** and **15b**).[13,14] First, the methyl ester in **15a** and **15b** was changed to the *tert*-butyl ester as in **16a**[15] and **16b** in



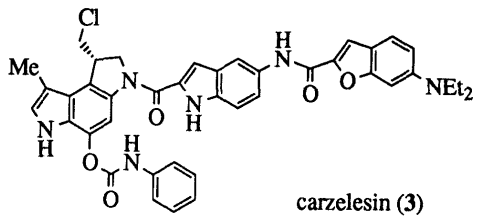
duocarmycin SA (**1**): X=NH, R=H

furan analog **6**: X=O, R=Me

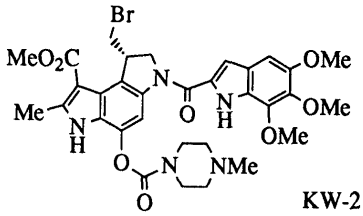
thiophene analog **7**: X=S, R=H



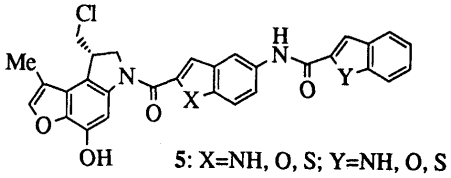
adozelesin (**2**)



carzelesin (**3**)



KW-2189 (**4**)



5: X=NH, O, S; Y=NH, O, S

Chart 1

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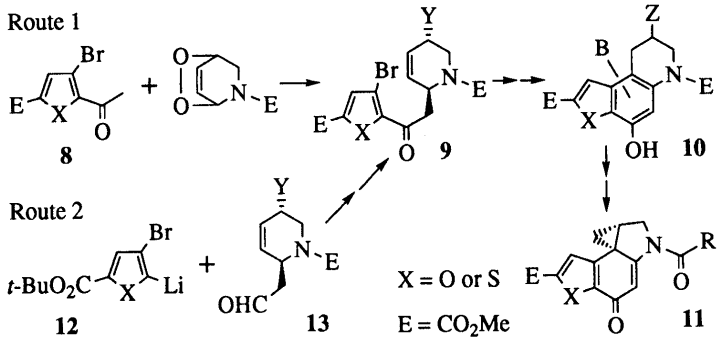

Chart 2

respective yields of 83% and 85% by alkaline hydrolysis, followed by condensation of the resulting carboxylic acid with *tert*-butanol using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) in the presence of 4-dimethylaminopyridine (DMAP).[16] In the dibromides **16a** and **16b**, the more reactive bromine atom was lithiated regioselectively by reaction with one equivalent of butyllithium at *ca.* −80 °C in tetrahydrofuran (THF) to generate **12a** and **12b**, which were allowed to react with *N*,*N*-dimethylformamide (DMF). The aldehydes **17a** and **17b**, obtained in 79% and 74% yields, were then treated with methylmagnesium iodide to afford in 89% and 98% yields **18a** and **18b**, and these were submitted to Swern oxidation[17] to obtain **19a** and **19b** in 94% and 91% yields, respectively. The *tert*-butyl ester **19a** was readily converted to the desired compound **8a** by treatment with trifluoroacetic acid (TFA), followed by esterification with diazomethane in 95% yield. Thus, the acetyl derivative **8** could be obtained through a multi-step pathway from **15a** and **15b**, though preparation of the Heck substrate **9** by this route proved to be rather tedious and unattractive. Therefore we examined the reaction of the lithium compound **12** with more elaborated electrophiles such as **13**, rather than DMF, to produce **9** in a more direct manner.

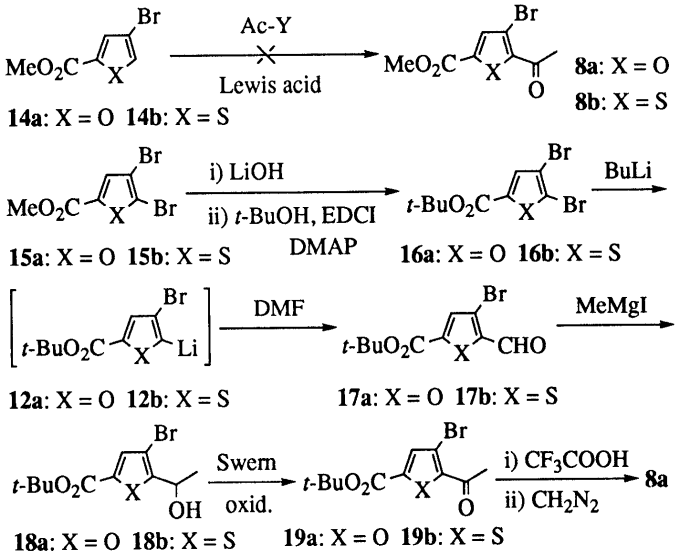

Chart 3

Synthesis of the Furan Analog 6 of Duocarmycin SA The synthesis was started with *O*-methylation of the known compound **20**[18] in 98% yield to obtain **21** by usual treatment with sodium hydride and iodomethane in a mixture of THF and DMF (3:1) (Chart 4). The acetal group in **21** was hydrolyzed in a 2.5% hydrochloric acid-containing solution of 1,2-dimethoxyethane (DME) and water (3:1) in 94% yield, and the resulting aldehyde **22** was allowed to react in a mixture of toluene and THF (*ca.* 2:1) with the lithiated compound **12a**, derived from the dibromofurancarboxylate **16a**, at *ca.* −80 °C to afford **23a** in 65% yield as a mixture of two diastereomeric isomers. Swern oxidation[17] of **23a** gave the ketone derivative **24a** in 96% yield, and the exchange reaction from the *tert*-butyl ester **24a** to the methyl ester **25a** was carried out in the same manner as before in 98% yield, providing the requisite Heck substrate in an efficient way.

Intramolecular Heck reaction[19] was carried out by heating an acetonitrile solution of **25a**, 10 mol% of palladium(II) acetate and 20 mol% of tri-*o*-tolylphosphine with tetrabutylammonium chloride[20] (1 eq) and triethylamine (2 eq) in a sealed tube at 105 °C for 1 h. Tricyclic derivatives **26a** and **27a** were obtained in 94% yield as an inseparable mixture (*ca.* 4:1) of two double bond isomers. The presence of a phase transfer catalyst, tetrabutylammonium chloride was essential for this reaction and without this reagent, the reaction required prolonged heating and gave much lower yields of reaction products. For dimethylacetal formation, this mixture of **26a** and **27a** was treated with trimethylsilyl (TMS) methoxide in the presence of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) in dichloromethane at −20 °C for 1 h to afford **28a** in 76.5% yield, along with recovery of **27a** and the formation of a by-product **41a** in 15% and 5% yields, respectively.[21] Both longer reaction time and higher reaction temperature resulted in an increased production of the undesired compound **41a**.

The next task was the oxidative aromatization of ring B. For this purpose, compound **28a** was first converted into the silyl enol ether **29a** by treatment with TBDMSOTf in the presence of triethylamine in 93% yield, and then **29a** was treated with phenylselenenyl chloride in the presence of tetrabutylammonium fluoride in THF at 0 °C to give the α-phenylselenyl ketone **30a** in 71% yield, accompanied by the recovery of **28a** in 20% yield.[22] Oxidative elimination of the phenylselenyl group from **30a** was investigated under various conditions, using *m*-chloroperbenzoic acid (*m*-CPBA), sodium metaperiodate, and hydrogen peroxide (Table 1). Treatment of **30a** with hydrogen peroxide in THF at room temperature (20 °C) gave the expected hydroxybenzofuran derivative **31a** in 79% yield (run 4). The phenolic hydroxyl group in **31a**

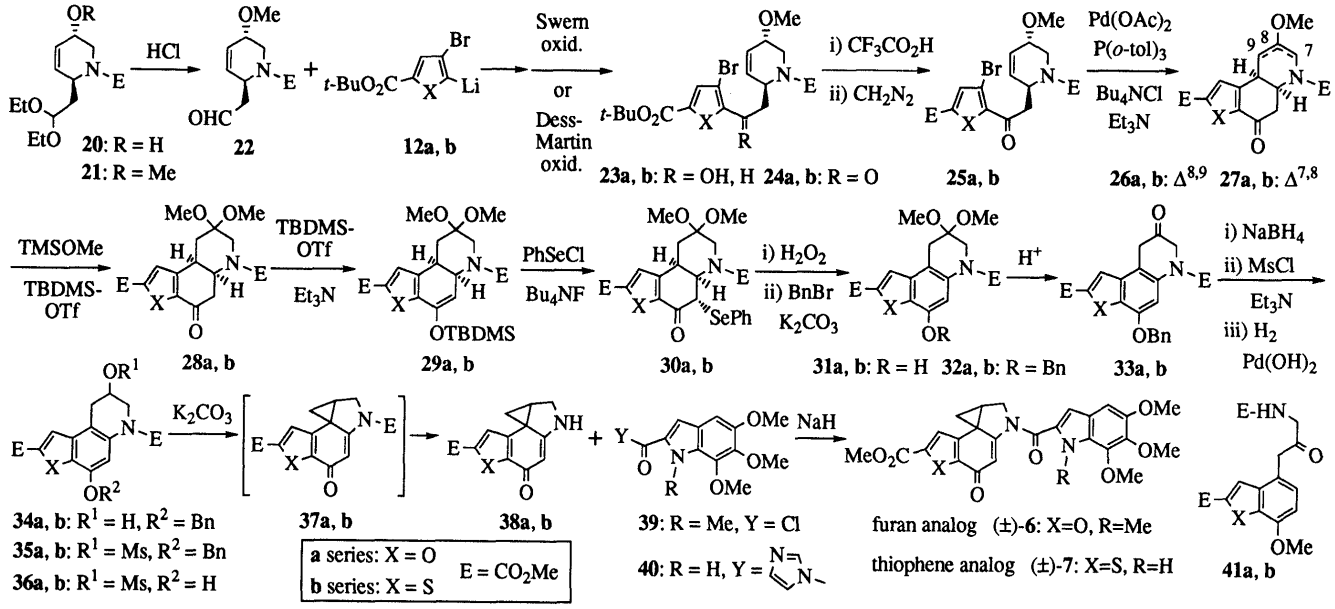

Chart 4

Table 1. Oxidative Aromatization of **30a** to Form **31a**

Run	Reagent	Solvent	Temperature (°C)	Time	Yield (%)
1	*m*-CPBA	THF	−20	30 min	57
2	$NaIO_4$	THF–MeOH–H_2O (1 : 1 : 1)	20	5.5 h	57
3	H_2O_2	CH_2Cl_2	0	25 min	48
4	H_2O_2	THF	20	70 min	79

was protected as its benzyl ether **32a** in 99% yield, and subsequent deacetalization of **32a** with perchloric acid in aqueous acetone afforded an unstable ketone **33a**, which was further reduced with sodium borohydride in a mixture of THF and methanol (1 : 1) at −20 °C to afford the hydroxy compound **34a** in 97% yield in two steps.

Next, cyclopropanoindolinone formation was studied by a new approach. The hydroxyl group in **34a** was activated as its methanesulfonate **35a** in 98% yield, and the benzyl group in **35a** was removed by catalytic hydrogenation over 20% palladium(II) hydroxide-carbon in a mixture of methanol and dichloromethane (4 : 1). The resulting rather unstable compound **36a** was directly submitted to base treatments under various conditions without further purification. Trials using bases such as sodium hydride, potassium *tert*-butoxide and triethylamine afforded unsatisfactory results, producing **37a** only in very poor yields. However, when **36a** was treated with potassium carbonate in a mixture of methanol and dichloromethane (5 : 1) at room temperature (20 °C) for 3 h, **38a** was directly obtained in 68.5% yield from **35a**. Fortunately potassium carbonate in methanol was effective enough for constructing the cyclopropanoindolinone skeleton, generating **37a** first as an intermediary compound. Then, ready cleavage of the methoxycarbonyl group on the nitrogen atom in **37a** occurred immediately under these reaction conditions to afford finally **38a** from **36a** in a single operation, since the methoxycarbonyl group was involved in the *N*-acyl vinylogous amide system.[23]

With the key compound **38a** in hand, the final stage called for the coupling reaction between **38a** and the 5,6,7-trimethoxyindole-2-carbonyl unit. In the light of our previous synthesis of duocarmycin SA,[1] coupling of **38a** with the imidazolide **40** was tried in the presence of sodium hydride. However, the reaction did not proceed as expected and no condensation product was isolated. After several fruitless attempts, coupling of **38a** with the acid chloride **39**, prepared from methyl 5,6,7-trimethoxy-1*H*-indole-2-carboxylate,[3c] was examined. The reaction was successful using sodium hydride, especially in a mixture of THF and DMF (4 : 1) at 0 °C. Thus, the synthesis of the furan analog (±)-**6** of duocarmycin SA was achieved in 80% yield.

Synthesis of the Thiophene Analog 7 of Duocarmycin SA Synthesis of the thiophene analog **7** was carried out in an analogous way. The lithiated derivative **12b** was prepared from *tert*-butyl 4,5-dibromo-2-thiophenecarboxylate **16b**, and reacted with the aldehyde **22** to produce **23b** in 71.5% yield. Dess–Martin oxidation[24] of **23b** afforded **24b** in 98% yield, and **24b** was converted to **25b** without difficulty in 96% yield. Heck reaction of **25b** was studied using a similar ratio of the same combination of reagents as in the case of the furan derivative, in solvents such as acetonitrile, toluene, DMF and THF. For the thiophene series, THF was the solvent of choice, and heating of **25b** with 15 mol% of palladium(II) acetate, 30 mol% of tri-*o*-tolylphosphine, 1 eq of tetrabutylammonium chloride, and 2 eq of triethylamine in a sealed tube at 120 °C for 2.5 h gave a mixture (*ca.* 2 : 1) of **26b** and **27b** in 66% yield. Compared to the case of the furan derivative, the reaction was a little sluggish, yielding intractable by-products, and required an elevated temperature and a longer heating time for completion even with a slightly larger amount of the catalyst. The dimethylacetalization of the mixture of **26b** and **27b** proceeded similarly to afford **28b** (64%), the by-product **41b** (6.5%), and recovery of the starting material (23.5%).

The next aromatization process was carried out in a similar manner, and **29b**, obtained from **28b** in 91% yield,

was converted into **31b** by way of **30b** in 38% yield (2 steps), along with the recovered **28b** in 36% yield. The benzyl ether **32b**, obtained from **31b** in 93.5% yield, was deacetalized with 5% hydrochloric acid in a mixture of DME and water (2 : 1) at room temperature (20 °C), and the ketone **33b** was directly reduced with sodium borohydride to give the hydroxy derivative **34b** in 91% yield in two steps. The methanesulfonate **35b** was prepared from **34b** in 99% yield, and **35b** was hydrogenated catalytically to afford **36b**, which was further treated with potassium carbonate in methanol to obtain the key compound **38b** in 86% yield from **35b**. In the case of the thiophene analog, coupling of **38b** with the imidazolide **40** was possible in modest yield, and (±)-**7** was obtained in 48% yield by using sodium hydride in a mixture of THF and DMF (3 : 1). Thus, we completed the synthesis of the thiophene analog (±)-**7** of duocarmycin SA as a slightly unstable compound. Both (±)-**6** and (±)-**7** are being subjected to biological tests.

In summary, furan and thiophene analogs, **6** and **7**, of duocarmycin SA were synthesized in racemic forms starting from methyl 4,5-dibromo-2-furan- and thiophenecarboxylates (**15a** and **15b**). In these syntheses, the lithio compounds **12a** and **12b** were condensed with the aldehyde **22** to obtain the Heck substrates **25a** and **25b**. Most of the other reaction steps conformed to the scheme used in the previous total synthesis of duocarmycin SA to reach **31a** and **31b**. Here a modification of the synthetic process was introduced to avoid the use of an expensive Mitsunobu reagent, 1,1′-(azodicarbonyl)dipiperidine, which had been particularly effective in the duocarmycin SA synthesis. This modification had the benefit of providing a shortcut from **36** directly to the key compounds **38**. Various kinds of acyl groups could be coupled with **38** for preparation of many biologically interesting compounds.

Experimental

Melting points were measured on a Yanagimoto micro-melting point apparatus and are not corrected. MS and high-resolution MS (HRMS) were recorded on a Hitachi M-80B spectrometer, and figures in parentheses indicate the relative intensities. IR spectra were taken on a Hitachi 215 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM 390 (90 MHz) spectrometer and a JEOL JNM-GX-400 (400 MHz) spectrometer in the stated solvents with tetramethylsilane as an internal reference. Column chromatography was carried out on silica gel, Fuji Davison BW 200 and preparative TLC (PTLC) was conducted on glass plates (20 × 20 cm) coated with Merck Silica gel 60 PF_{254} (1 mm thick). Usual work-up refers to washing of the organic layer with water or brine, drying over anhydrous Na_2SO_4, and evaporating off the solvents under reduced pressure.

***tert*-Butyl 4,5-Dibromo-2-furancarboxylate (16a)** A solution of **15a** (3.34 g, 11.8 mmol) and LiOH·H_2O (988 mg, 23.5 mmol) in a mixture of DME (20 ml) and H_2O (10 ml) was stirred at 20 °C for 1 h. After evaporation of the solvents under reduced pressure at room temperature, 7% HCl–H_2O (18 ml) was added, and the whole was extracted with CH_2Cl_2. Usual work-up gave the crude acid (3.18 g), which was dissolved in CH_2Cl_2 (65 ml) and *tert*-BuOH (23 ml). After addition of DMAP (1.44 g, 11.8 mmol) and EDCI·HCl (4.51 g, 23.5 mmol), the mixture was stirred under an Ar atmosphere at 20 °C for 14 h. Quenching with H_2O was followed by extraction with CH_2Cl_2. After successive washing of the CH_2Cl_2 solution with 3.5% HCl–H_2O and saturated $NaHCO_3$–H_2O, usual work-up gave a residue (3.66 g), which was separated by silica gel column chromatography [hexane–CH_2Cl_2 (3 : 1)] to afford **16a** (3.19 g, 83%) as a colorless syrup. HRMS Calcd for $C_9H_{10}{}^{81}Br_2O_3$, $C_9H_{10}{}^{81}Br^{79}BrO_3$ and $C_9H_{10}{}^{79}Br_2O_3$: 327.8958, 325.8977 and 323.8997. Found: 327.8931, 325.8973 and 323.8999. MS *m/z*: 328 (5), 326 (10) and 324 (5) (M^+); 272 (50), 270 (100) and 268 (50); 255 (14), 253 (27) and 251 (14); 199 (6), 197 (11) and 195 (6); 118 (17) and 116 (18); 57 (63); 41 (48); 29 (27). IR ($CHCl_3$) cm^{-1}: 1732, 1720. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.55 (9H, s), 7.05 (1H, s).

***tert*-Butyl 4,5-Dibromo-2-thiophenecarboxylate (16b)** Similarly, **15b** (2.124 g, 7.08 mmol) was hydrolyzed with LiOH·H_2O (595 mg, 14.2 mmol) to afford the crude acid (*ca.* 2 g), which was reacted with *tert*-BuOH (23 ml) using DMAP (865 mg, 7.09 mmol) and EDCI·HCl (2.72 g, 14.2 mmol) to afford **16b** (2.053 g, 85%) as a colorless syrup. HRMS Calcd for $C_9H_{10}{}^{81}Br_2O_2S$, $C_9H_{10}{}^{81}Br^{79}BrO_2S$ and $C_9H_{10}{}^{79}Br_2O_2S$: 343.8729, 341.8749 and 339.8769. Found: 343.8767, 341.8769 and 339.8752. GC-MS *m/z*: 344 (3), 342 (5) and 340 (3) (M^+); 288 (28), 286 (56) and 284 (27); 271 (12), 269 (22) and 267 (12); 162 (12) and 160 (12); 81 (43); 57 (58); 56 (46); 41 (100). IR ($CHCl_3$) cm^{-1}: 1700. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.57 (9H, s), 7.48 (1H, s).

***tert*-Butyl 4-Bromo-5-formyl-2-furancarboxylate (17a)** A THF (20 ml) solution of **16a** (724.5 mg, 2.22 mmol) was cooled at −80 °C, and BuLi in hexane (1.64 M, 1.35 ml, 2.21 mmol) was added. The mixture was stirred under an Ar atmosphere at −80 °C for 4 min, DMF (0.34 ml, 4.39 mmol) was added, and the whole was stirred under an Ar atmosphere at −80—−70 °C for 20 min. Quenching with saturated NH_4Cl–H_2O, extraction with Et_2O and usual work-up gave a residue (608 mg), which was separated by column chromatography over silica gel [hexane–EtOAc (13 : 1)] to afford **17a** (481.5 mg, 79%) as a colorless syrup. MS *m/z*: 276 (3) and 274 (3) (M^+), 220 (42) and 218 (42), 219 (38) and 217 (31), 203 (14) and 201 (14), 57 (29), 56 (84), 41 (100), 39 (49). IR ($CHCl_3$) cm^{-1}: 1727, 1689. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.58 (9H, s), 7.20 (1H, s), 9.84 (1H, s).

***tert*-Butyl 4-Bromo-5-formyl-2-thiophenecarboxylate (17b)** Similarly, **16b** (118 mg, 0.345 mmol) was reacted with BuLi in hexane (1.68 M, 0.21 ml, 0.35 mmol), followed by reaction with DMF (54 μl, 0.70 mmol) to afford **17b** (74.5 mg, 74%) as a colorless syrup. GC-MS *m/z*: 292 (2) and 290 (2) (M^+), 236 (15) and 234 (15), 235 (22) and 233 (14), 219 (10) and 217 (10), 191 (6) and 189 (6), 109 (6), 82 (32), 81 (20), 57 (72), 56 (100), 41 (84), 39 (41). IR ($CHCl_3$) cm^{-1}: 1710, 1675. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.61 (9H, s), 7.65 (1H, s), 10.02 (1H, s).

***tert*-Butyl 4-Bromo-5-(1-hydroxyethyl)-2-furancarboxylate (18a)** A solution of **17a** (111 mg, 0.404 mmol) in Et_2O (7 ml) was cooled at −20 °C, and MeMgI in Et_2O (0.6 M, 2.7 ml, 1.6 mmol) was added dropwise. The mixture was stirred under an Ar atmosphere at −20 °C for 15 min, then the reaction was quenched with saturated NH_4Cl–H_2O. Extraction with Et_2O followed by usual work-up gave a residue (121 mg), which was purified by PTLC [hexane–DME (8 : 1)] to afford **18a** (104.5 mg, 89%) as a colorless syrup. MS *m/z*: 236 (6) and 234 (6) ($M^+ - Me_2C{=}CH_2$), 221 (23) and 219 (29), 218 (36) and 216 (36), 203 (14) and 201 (15), 193 (7) and 191 (22), 191 (22) and 189 (15), 145 (14) and 143 (14), 56 (48), 41 (100), 39 (68). IR ($CHCl_3$) cm^{-1}: 1721. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.54 (9H, s), 1.58 (3H, d, J = 7 Hz), 2.60 (1H, br s, OH), 5.00 (1H, br q, J = 7 Hz), 7.02 (1H, s).

***tert*-Butyl 4-Bromo-5-(1-hydroxyethyl)-2-thiophenecarboxylate (18b)** Similarly, **17b** (70 mg, 0.24 mmol) was reacted with MeMgI in Et_2O (0.6 M, 1.6 ml, 0.96 mmol) to afford **18b** (72.5 mg, 98%) as a colorless syrup. HRMS Calcd for $C_{11}H_{15}{}^{81}BrO_3S$ and $C_{11}H_{15}{}^{79}BrO_3S$: 307.9905 and 305.9925. Found: 307.9901 and 305.9920. GC-MS *m/z*: 308 (5) and 306 (5) (M^+), 252 (10) and 250 (12), 237 (47) and 235 (56), 209 (14) and 207 (15), 171 (18), 84 (37), 57 (37), 44 (100), 42 (96), 40 (83). IR ($CHCl_3$) cm^{-1}: 1700. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.55 (3H, d, J = 7 Hz), 1.56 (9H, s), 3.22 (1H, br s, OH), 5.16 (1H, q, J = 7 Hz), 7.47 (1H, s).

***tert*-Butyl 5-Acetyl-4-bromo-2-furancarboxylate (19a)** Dimethyl sulfoxide (DMSO) (0.46 ml, 6.48 mmol) was added to a cooled (−80 °C) solution of oxalyl chloride (0.19 ml, 2.18 mmol) in CH_2Cl_2 (6 ml). The mixture was stirred under an Ar atmosphere at that temperature for 5 min, a solution of **18a** (156 mg, 0.536 mmol) in CH_2Cl_2 (8 ml) was added, and the whole was stirred at −80—−75 °C for 30 min. Then Et_3N (1.49 ml, 10.7 mmol) was added, and stirring was continued at −75 °C for 5 min and at −20 °C for 25 min. Quenching with saturated $NaHCO_3$–H_2O, extraction with Et_2O and usual work-up gave a residue (177 mg), which was purified by PTLC [hexane–CH_2Cl_2 (1 : 1)] to afford **19a** (146 mg, 94%) as a colorless syrup. HRMS Calcd for $C_{11}H_{13}{}^{81}BrO_4$ and $C_{11}H_{13}{}^{79}BrO_4$: 289.9977 and 287.9997. Found: 289.9994 and 287.9996. MS *m/z*: 290 (5) and 288 (5) (M^+), 234 (40) and 232 (39), 219 (87) and 217 (95), 217 (95) and 215 (10), 175 (12) and 173 (14), 93 (17), 56 (61), 43 (90), 41 (100). IR ($CHCl_3$) cm^{-1}: 1728, 1690. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.59 (9H, s), 2.57 (3H, s), 7.13 (1H, s).

***tert*-Butyl 5-Acetyl-4-bromo-2-thiophenecarboxylate (19b)** Similarly, **18b** (69.5 mg, 0.23 mmol) was oxidized using DMSO (0.32 ml, 4.5 mmol), oxalyl chloride (0.20 ml, 2.3 mmol) and Et_3N (0.79 ml, 5.7 mmol) to afford **19b** (63 mg, 91%) as colorless prisms, mp 74—75 °C (hexane). *Anal.* Calcd for $C_{11}H_{13}BrO_3S$: C, 43.29; H, 4.29. Found: C, 43.12; H, 4.39. HRMS Calcd for $C_{11}H_{13}{}^{81}BrO_3S$ and $C_{11}H_{13}{}^{79}BrO_3S$: 305.9749 and 303.9769. Found: 305.9742 and 303.9793. GC-MS *m/z*: 306 (15) and 304 (15) (M^+), 251 (21) and 249 (21), 250 (26) and 248 (24), 235 (85) and 233 (100), 233 (100) and 231 (23), 191 (18) and 189 (20), 109 (17), 82 (20), 81 (24), 57 (72), 56 (49), 43 (80), 41 (62), 39 (25). IR ($CHCl_3$) cm^{-1}: 1710, 1663. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.58 (9H, s), 2.68 (3H, s), 7.62 (1H, s).

Methyl 5-Acetyl-4-bromo-2-furancarboxylate (8a) A solution of **19a** (380.5 mg, 1.32 mmol) in TFA (5 ml) was stirred at 20 °C for 1 h. After evaporation of TFA *in vacuo* at room temperature, two operations of CH_2Cl_2 (3 ml) addition followed by evaporation of the solvent were carried out. The residue was dissolved in Et_2O (10 ml), and CH_2N_2 in Et_2O was added to the solution. After decomposition of excess CH_2N_2 with AcOH, saturated $NaHCO_3$–H_2O was added. The whole was extracted with Et_2O and worked up as usual to give a residue (327.5 mg). Separation by silica gel column chromatography [hexane–EtOAc (5 : 1)], followed by recrystallization from CH_2Cl_2–hexane gave **8a** (308 mg, 95%) as colorless prisms, mp 81—82 °C. *Anal.* Calcd for $C_8H_7BrO_4$: C, 38.90; H, 2.86. Found: C, 38.71; H, 3.01. HRMS Calcd for $C_8H_7{}^{81}BrO_4$ and $C_8H_7{}^{79}BrO_4$: 247.9508 and 245.9528. Found: 247.9489 and 245.9506. MS *m/z*: 248 (39) and 246 (39) (M^+), 233 (100) and 231 (98), 175 (18) and 173 (20), 93 (22), 59 (18), 51 (18), 43 (76). IR (KBr) cm^{-1}: 1720, 1670. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.59 (3H, s), 3.93 (3H, s), 7.24 (1H, s).

Methyl (2*RS*,5*RS*)-2-(2,2-Diethoxyethyl)-1,2,5,6-tetrahydro-5-methoxy-1-pyridinecarboxylate (21) A solution of **20** (121 mg, 0.443 mmol) in a mixture of THF (4.5 ml) and DMF (1.5 ml) was cooled at 0 °C, and 60% NaH (39 mg, 0.98 mmol) was added. After subsequent addition of iodomethane (55 μl, 0.88 mml), the mixture was stirred under an Ar atmosphere at 0 °C for 5 min and at 20 °C for 3.5 h. Quenching with saturated NH_4Cl–H_2O, extraction with Et_2O and usual work-up gave a residue (161.5 mg). Purification by silica gel column chromatography [hexane–EtOAc (3 : 2)] afforded **21** (125 mg, 98%) as a colorless syrup. MS *m/z*: 241 (M^+ – EtOH, 4), 209 (38), 180 (25), 170 (52), 154 (23), 138 (41), 125 (29), 103 (56), 59 (45), 45 (100), 31 (75). IR ($CHCl_3$) cm^{-1}: 1693. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 1.10 (3H, t, J=7 Hz), 1.19 (3H, t, J=7 Hz), 1.59—2.05 (2H, m), 2.93 (1H, dd, J=15, 3 Hz), 3.27—3.89 (5H, m), 3.36 (3H, s), 3.71 (3H, s), 4.41 (1H, br d, J=15 Hz), *ca.* 4.54—4.81 (1H, m), 4.58 (1H, dd, J=6, 6 Hz), 5.75—6.10 (2H, m).

Methyl (2*RS*,5*RS*)-1,2,5,6-Tetrahydro-5-methoxy-2-oxoethyl-1-pyridinecarboxylate (22) A solution of **21** (367 mg, 1.28 mmol) in DME (6 ml) containing 10% HCl–H_2O (2 ml) was stirred at 20 °C for 1 h, then cooled to 0 °C, saturated $NaHCO_3$–H_2O was added, and the whole was extracted with CH_2Cl_2. Usual work-up and purification by column chromatography over silica gel [hexane–EtOAc (2 : 3)] gave **22** (270 mg, 99%) as a colorless syrup. MS *m/z*: 181 (M^+ – MeOH, 11), 170 (21), 138 (15), 126 (57), 97 (100), 45 (60). IR ($CHCl_3$) cm^{-1}: 1728, 1693. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 2.61 (2H, dd, J=7, 2 Hz), 2.91 (1H, dd, J=14, 2.5 Hz), 3.36 (3H, s), 3.55—3.78 (1H, m), 3.71 (3H, s), 4.39 (1H, br d, J=14 Hz), 4.87—5.15 (1H, m), 5.80—6.14 (2H, m), 9.78 (1H, t, J=2 Hz).

Methyl (2*RS*,5*RS*)-2-[2-[3-Bromo-5-(*tert*-butoxycarbonyl)-2-furyl]-2-hydroxyethyl]-1,2,5,6-tetrahydro-5-methoxy-1-pyridinecarboxylate (23a) BuLi in hexane (1.66 M, 0.85 ml, 1.41 mmol) was added to a cooled (*ca.* −80 °C) solution of **16a** (507 mg, 1.56 mmol) in THF (15 ml), and the mixture was stirred under an Ar atmosphere at that temperature for 3 min. After addition of a solution of the aldehyde **22** (207 mg, 0.972 mmol) in toluene (8.5 ml), stirring was continued at −77—−75 °C for 25 min. Quenching with saturated NH_4Cl–H_2O, extraction with CH_2Cl_2, and usual work-up gave a residue (665 mg). Separation by silica gel column chromatography [hexane–EtOAc (4 : 5→1 : 3)] afforded crude **23a** (330.5 mg) and crude **22** (52 mg). The former was purified by PTLC [hexane–DME (3 : 1)] to give **23a** (290.5 mg, 65%) as a colorless syrup. Purification of the latter by PTLC [hexane–EtOAc (4 : 5)] recovered **22** (47 mg, 23%). **23a**: MS *m/z*: 405 (2) and 403 (2) [$M^+ - Me_2C{=}CH_2$], 221 (7) and 219 (8), 203 (3) and 201 (3), 170 (79), 139 (66), 98 (47), 97 (100), 57 (33), 45 (65), 41 (47). IR ($CHCl_3$) cm^{-1}: 1714. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 1.56 (9H, s), *ca.* 1.75—2.53 (2H, m), 2.93 and 2.97 (1H, dd each, J=15, 2.5 Hz and 15, 3 Hz), 3.35 and 3.38 (3H, s each), 3.53—3.73 (1H, m), 3.70 and 3.77 (3H, s each), 4.36 (1H, br d, J=15 Hz), 4.56—5.13 (2H, m), 5.78—6.15 (2H, m), 7.01 (1H, s).

Methyl (2*RS*,5*RS*)-2-[2-[3-Bromo-5-(*tert*-butoxycarbonyl)-2-thienyl]-2-hydroxyethyl]-1,2,5,6-tetrahydro-5-methoxy-1-pyridinecarboxylate (23b) Similarly, the lithio derivative prepared from **16b** (1.039 g, 3.04 mmol) with BuLi in hexane (1.68 M, 1.70 ml, 2.86 mmol) was allowed to react with the aldehyde **22** (404.5 mg, 1.90 mmol) to give **23b** (646 mg, 71.5%) and recovered **22** (90 mg, 22%). **23b**: colorless syrup. MS *m/z*: 420 (4) and 418 (4) [M^+ – *tert*-Bu], 404 (3) and 402 (3), 170 (100), 155 (12), 139 (21), 138 (16), 98 (40), 97 (71), 57 (24), 45 (43), 41 (42), 39 (19). IR ($CHCl_3$) cm^{-1}: 1704. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: *ca.* 1.41—2.37 (2H, m), 1.53 (9H, s), 2.85 and 3.04 (1H, dd each, J=14.5, 2.5 Hz and 14.5, 2.5 Hz), 3.39 and 3.41 (3H, s each), 3.56—3.76 (1H, m), 3.75 and 3.81 (3H, s each), 4.37 and 4.44 (1H, br d each, J=14.5 and 14.5 Hz), 4.59—5.35 (2H + OH, m), 5.75—6.21 (2H, m), 7.49 (1H, s).

Methyl (2*RS*,5*RS*)-2-[2-[3-Bromo-5-(*tert*-butoxycarbonyl)-2-furyl]-2-oxoethyl]-1,2,5,6-tetrahydro-5-methoxy-1-pyridinecarboxylate (24a) DMSO (0.87 ml, 12 mmol) was added to a cooled (−76 °C) solution of oxalyl chloride (0.36 ml, 4.13 mmol) in CH_2Cl_2 (12 ml), and the solution was stirred under an Ar atmosphere at that temperature for 5 min. A solution of **23a** (471 mg, 1.02 mmol) in CH_2Cl_2 (15 ml) was added, and the mixture was stirred at −76—−71 °C for 30 min. After addition of Et_3N (2.85 ml, 20.5 mmol), stirring was continued at −71 °C for 5 min and −20 °C for 30 min. Quenching with saturated $NaHCO_3$–H_2O, extraction with Et_2O and usual work-up gave a residue (600 mg), which was separated by silica gel column chromatography [hexane–EtOAc (3 : 2)] to afford **24a** (452 mg, 96%) as a colorless syrup. MS *m/z*: 427 (1) and 425 (1) (M^+ – MeOH), 372 (4) and 370 (11), 370 (11) and 368 (8), 219 (5) and 217 (5), 170 (52), 138 (41), 97 (100), 45 (22), 41 (42). IR ($CHCl_3$) cm^{-1}: 1730, 1693. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 1.59 (9H, s), 3.05 (1H, dd, J=14.5, 2.5 Hz), 3.14 (2H, d, J=7 Hz), 3.37 (3H, s), 3.54—3.79 (1H, m), 3.63 (3H, s), 4.44 (1H, br d, J=14.5 Hz), 4.93—5.20 (1H, m), 5.84—6.20 (2H, m), 7.14 (1H, s).

Methyl (2*RS*,5*RS*)-2-[2-[3-Bromo-5-(*tert*-butoxycarbonyl)-2-thienyl]-2-oxoethyl]-1,2,5,6-tetrahydro-5-methoxy-1-pyridinecarboxylate (24b) Dess–Martin reagent (834 mg, 1.97 mmol) was added to a solution of **23b** (117 mg, 0.246 mmol) in CH_2Cl_2 (12 ml), and the mixture was stirred under an Ar atmosphere at 65—75 °C for 2 h. The whole was poured into a mixed solution of saturated $NaHCO_3$–H_2O (50 ml) and saturated $Na_2S_2O_3$–H_2O (50 ml). Extraction with Et_2O followed by usual work-up gave a residue (135 mg). Separation and purification by PTLC [hexane–DME (9 : 2)] gave **24b** (114 mg, 98%) as a colorless syrup. MS *m/z*: 443 (9) and 441 (8) (M^+ – MeOH), 402 (4) and 400 (4), 388 (5) and 386 (6), 387 (4) and 385 (4), 306 (3), 291 (5) and 289 (4), 235 (24) and 233 (24), 170 (62), 138 (32), 97 (100), 45 (57), 41 (82), 39 (33). IR ($CHCl_3$) cm^{-1}: 1713, 1700, 1660. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 1.59 (9H, s), 3.02 (1H, dd, J=14.5, 3 Hz), 3.12 (1H, dd, J=16, 6 Hz), 3.39 (3H, s), 3.40 (1H, dd, J=16, 7 Hz), 3.57—3.83 (1H, m), 3.67 (3H, s), 4.93—5.26 (1H, m), 4.46 (1H, br d, J=14.5 Hz), 5.85—6.24 (2H, m), 7.62 (1H, s).

Methyl (2*RS*,5*RS*)-2-[2-[3-Bromo-5-(methoxycarbonyl)-2-furyl]-2-oxoethyl]-1,2,5,6-tetrahydro-5-methoxy-1-pyridinecarboxylate (25a) A solution of **24a** (842 mg, 1.84 mmol) in TFA (12 ml) was stirred at 20 °C for 30 min. After evaporation of TFA *in vacuo* at ambient temperature, addition of CH_2Cl_2 (5 ml) followed by evaporation of the solvents was carried out twice. The residue was dissolved in Et_2O (12 ml), and a solution of CH_2N_2 in Et_2O was added. After decomposition of excess CH_2N_2 with AcOH, saturated $NaHCO_3$–H_2O was added. Extraction with Et_2O and usual work-up gave a residue (769 mg), which was purified by silica gel column chromatography [hexane–EtOAc (3 : 2)] to afford **25a** (750 mg, 98%) as a colorless syrup. MS *m/z*: 385 (3) and 383 (3) (M^+ – MeOH), 330 (7) and 328 (7), 326 (4) and 324 (4), 233 (7) and 231 (7), 170 (47), 138 (43), 97 (100), 59 (21), 45 (51). IR ($CHCl_3$) cm^{-1}: 1740, 1693. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 3.05 (1H, dd, J=14, 3 Hz), 3.15 (2H, d, J=7 Hz), 3.37 (3H, s), 3.60—3.80 (1H, m), 3.64 (3H, s), 3.94 (3H, s), 4.44 (1H, br d, J=14 Hz), 4.92—5.20 (1H, m), 5.83—6.20 (2H, m), 7.23 (1H, s).

Methyl (2*RS*,5*RS*)-2-[2-[3-Bromo-5-(methoxycarbonyl)-2-thienyl]-2-oxoethyl]-1,2,5,6-tetrahydro-5-methoxy-1-pyridinecarboxylate (25b) Similarly, **24b** (635.5 mg, 1.34 mmol) was treated with TFA (8.5 ml), followed by esterification with CH_2N_2 to afford **25b** (558 mg, 96%) as a colorless syrup. MS *m/z*: 401 (12) and 399 (11) (M^+ – MeOH), 346 (7) and 344 (7), 249 (22) and 247 (23), 170 (45), 138 (17), 97 (100), 59 (21), 45 (51), 41 (22). IR ($CHCl_3$) cm^{-1}: 1720, 1696. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 3.02 (1H, dd, J=14.5, 3 Hz), 3.13 (1H, dd, J=15.5,

6 Hz), 3.38 (3H, s), 3.40 (1H, dd, J=15.5, 7 Hz), 3.61—3.78 (1H, m), 3.65 (3H, s), 3.92 (3H, s), 4.45 (1H, br d, J=14.5 Hz), 4.93—5.25 (1H, m), 5.78—6.24 (2H, m), 7.68 (1H, s).

Dimethyl (5a*RS*,9a*SR*)-4,5,5a,6,7,9a-Hexahydro-8-methoxy-4-oxofuro[3,2-*f*]quinoline-2,6-dicarboxylate (26a) and Dimethyl (5a*RS*,9a*SR*)-4,5,5a,6,9,9a-Hexahydro-8-methoxy-4-oxofuro[3,2-*f*]quinoline-2,6-dicarboxylate (27a) An acetonitrile (6 ml) solution of **25a** (106 mg, 0.255 mmol) containing $Pd(OAc)_2$ (6 mg, 0.03 mmol), P(*o*-tol)$_3$ (16 mg, 0.05 mmol), Bu_4NCl (71 mg, 0.26 mmol) and Et_3N (71 μl, 0.51 mmol) was heated under an Ar atmosphere in a sealed tube at *ca.* 105 °C for 1 h. After the mixture had cooled, H_2O was added, and the whole was extracted with CH_2Cl_2. Usual work-up gave a residue (162 mg), which was separated and purified by PTLC [hexane–EtOAc (3 : 2) and 1% MeOH–CH_2Cl_2] to afford a *ca.* 4 : 1 mixture of **26a** and **27a** (80.5 mg, 94%) as a colorless foam. HRMS Calcd for $C_{16}H_{17}NO_7$: 335.1004. Found: 335.0990. MS *m/z*: 335 (M^+, 100), 304 (16), 288 (34), 276 (34), 219 (16), 207 (20), 206 (19), 192 (22), 179 (19), 144 (56), 59 (93). IR ($CHCl_3$) cm^{-1}: 1684. ^{1}H-NMR (400 MHz, 60 °C, $CDCl_3$) δ: for **26a**: 2.54 (1H, dd, J=16, 4.5 Hz), 2.91 (1H, dd, J=16, 13 Hz), 3.53—3.61 (1H, m), 3.55 (3H, s), 3.75 (3H, s), 3.84—3.89 (1H, m), 3.93 (3H, s), 4.29 (1H, br d, J=17.5 Hz), 4.49—4.54 (1H, m), 7.20 (1H, s); for **27a**: 2.24 (1H, ddd, J=17, 11.5, 2 Hz), 2.48—2.58 (1H, m), 2.64—2.84 (2H, m), 3.29 (1H, ddd, J=11.5, 6.5, 5 Hz), 3.58 (3H, s), 3.79 (3H, s), 3.93 (3H, s), *ca.* 4.70—4.94 (1H, m), *ca.* 6.10—6.55 (1H, m), 7.16 (1H, s).

Dimethyl (5a*RS*,9a*SR*)-4,5,5a,6,7,9a-Hexahydro-8-methoxy-4-oxothieno[3,2-*f*]quinoline-2,6-dicarboxylate (26b) and Dimethyl (5a*RS*,9a*SR*)-4,5,5a,6,9,9a-Hexahydro-8-methoxy-4-oxothieno[3,2-*f*]quinoline-2,6-dicarboxylate (27b) A THF (7 ml) solution of **25b** (107.5 mg, 0.249 mmol) containing $Pd(OAc)_2$ (8.5 mg, 0.04 mmol), P(*o*-tol)$_3$ (23 mg, 0.08 mmol), Bu_4NCl (69 mg, 0.25 mmol) and Et_3N (69 μl, 0.50 mmol) was heated under an Ar atmosphere in a sealed tube at 120 °C for 2.5 h. Similar treatment to that described above afforded a 2.2 : 1 mixture of **26b** and **27b** (57.5 mg, 66%) as a yellow glass. HRMS Calcd for $C_{16}H_{17}NO_6S$: 351.0775. Found: 351.0786. MS *m/z*: 351 (M^+, 100), 320 (15), 304 (15), 292 (20), 260 (22), 208 (36), 144 (50), 59 (78). IR ($CHCl_3$) cm^{-1}: 1714, 1679. ^{1}H-NMR (400 MHz, 60 °C, $CDCl_3$) δ: for **26b**: 2.57 (1H, dd, J=16, 4.5 Hz), 2.92 (1H, dd, J=16, 13 Hz), 3.54 (3H, s), 3.58 (1H, ddd, J=17.5, 3, 1 Hz), 3.75 (3H, s), 3.92 (3H, s), 3.92—3.98 (1H, m), 4.29 (1H, br d, J=17.5 Hz), 4.48—4.54 (1H, m), 4.90—5.10 (1H, m), 7.71 (1H, s); for **27b**: 2.24 (1H, ddd, J=17, 11.5, 2 Hz), 2.50 (1H, dd, J=17, 6 Hz), 2.64—2.85 (2H, m), 3.38 (1H, ddd, J=11, 6, 5 Hz), 3.59 (3H, s), 3.79 (3H, s), 3.92 (3H, s), 4.70—4.94 (1H, m), 6.11—6.57 (1H, m), 7.67 (1H, s).

Dimethyl (5a*RS*,9a*SR*)-4,5,5a,6,7,8,9,9a-Octahydro-8,8-dimethoxy-4-oxofuro[3,2-*f*]quinoline-2,6-dicarboxylate (28a) and Methyl 7-Methoxy-4-[3-(methoxycarbonyl)amino-2-oxopropyl]benzofuran-2-carboxylate (41a) TBDMSOTf (0.15 ml, 0.64 mmol) was added to a cooled (−20 °C) solution of a mixture of **26a** and **27a** (108 mg, 0.322 mmol) and TMSOMe (0.67 ml, 4.86 mmol) in CH_2Cl_2 (9 ml). The mixture was stirred under an Ar atmosphere at that temperature for 1 h, then saturated $NaHCO_3$–H_2O was added, and the whole was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [hexane–EtOAc (2 : 1)] gave **28a** (90.5 mg, 76.5%) along with **41a** (5.5 mg, 5%) and the recovered **27a** (16.5 mg, 15%). **28a**: Colorless glass. HRMS Calcd for $C_{17}H_{21}NO_8$: 367.1266. Found: 367.1284. MS *m/z*: 367 (M^+, 14), 336 (14), 278 (100), 252 (82), 224 (58), 167 (28), 165 (35), 144 (24), 105 (21), 88 (32), 59 (75), 43 (45). IR ($CHCl_3$) cm^{-1}: 1727, 1688. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 1.55 (1H, dd, J=13.5, 13.5 Hz), 2.31 (1H, ddd, J=13.5, 5.5, 2.5 Hz), 2.52 (1H, dd, J=16.5, 5 Hz), 2.74 (1H, d, J=15 Hz), 2.99 (1H, dd, J=16.5, 13 Hz), 3.05—3.54 (1H, m), 3.27 (6H, s), 3.74 (3H, s), 3.91 (3H, s), 4.35 (1H, br d, J=15 Hz), 4.70—5.17 (1H, m), 7.13 (1H, s). **41a**: Colorless prisms, mp 174—175 °C (CH_2Cl_2–MeOH). *Anal.* Calcd for $C_{16}H_{17}NO_7$: C, 57.31; H, 5.11; N, 4.18. Found: C, 57.20; H, 5.12; N, 4.19. HRMS Calcd for $C_{16}H_{17}NO_7$: 335.1004. Found: 335.1009. MS *m/z*: 335 (M^+, 15), 219 (100), 173 (10), 88 (16). IR (KBr) cm^{-1}: 1710. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.68 (3H, s), 3.90 (2H, s), 3.97 (3H, s), 4.02 (3H, s), 4.09 (2H, d, J=4.5 Hz), 5.30 (1H, br s), 6.86 (1H, d, J=8 Hz), 7.07 (1H, d, J=8 Hz), 7.51 (1H, s).

Dimethyl (5a*RS*,9a*SR*)-4,5,5a,6,7,8,9,9a-Octahydro-8,8-dimethoxy-4-oxothieno[3,2-*f*]quinoline-2,6-dicarboxylate (28b) and Methyl 7-Methoxy-4-[3-(methoxycarbonyl)amino-2-oxopropyl]benzothiophene-2-carboxylate (41b) Similarly, reaction of a mixture of **26b** and **27b** (108.5 mg, 0.309 mmol) with TMSOMe (0.64 ml, 4.6 mmol) and TBDMSOTf (0.14 ml, 0.61 mmol) afforded **28b** (75.5 mg, 64%) along with **41b** (7 mg, 6.5%), with recovery of **26b**+**27b** (25.5 mg, 23.5%). **28b**: Colorless prisms, mp 171—173 °C (CH_2Cl_2–MeOH). *Anal.* Calcd for $C_{17}H_{21}NO_7S$: C, 53.25; H, 5.52; N, 3.65. Found: C, 53.12; H, 5.47; N, 3.69. HRMS Calcd for $C_{17}H_{21}NO_7S$: 383.1037. Found: 383.1047. MS *m/z*: 383 (M^+, 15), 352 (16), 351 (8), 294 (100), 268 (91), 240 (69), 225 (31), 209 (17), 149 (16), 144 (18), 121 (17), 88 (17), 59 (52), 43 (27). IR (KBr) cm^{-1}: 1700, 1667. ^{1}H-NMR (400 MHz, 60 °C, $CDCl_3$) δ: 1.59 (1H, dd, J=13, 13 Hz), 2.29 (1H, ddd, J=13, 5, 2 Hz), 2.58 (1H, br dd, J=16.5, 4 Hz), 2.76 (1H, br d, J=14 Hz), 2.97 (1H, br dd, J=16.5, 13 Hz), 3.25 (3H, s), 3.26 (3H, s), 3.37 (1H, ddd, J=13, 5, 5 Hz), 3.74 (3H, s), 3.91 (3H, s), 4.11—4.61 (1H, m), 4.68—5.20 (1H, m), 7.65 (1H, s). **41b**: Colorless prisms, mp 140—141 °C (CH_2Cl_2–MeOH). *Anal.* Calcd for $C_{16}H_{17}NO_6S$: C, 54.69; H, 4.88; N, 3.99. Found: C, 54.45; H, 4.95; N, 4.14. HRMS Calcd for $C_{16}H_{17}NO_6S$: 351.0775. Found: 351.0784. MS *m/z*: 351 (M^+, 17), 319 (16), 287 (8), 235 (100), 189 (19), 88 (14), 59 (12). IR (KBr) cm^{-1}: 1700. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.66 (3H, s), 3.94 (3H, s), 4.01 (5H, s), 4.09 (2H, d, J=5 Hz), 5.17—5.53 (1H, m, NH), 6.82 (1H, d, J=8 Hz), 7.21 (1H, d, J=8 Hz), 8.04 (1H, s).

Dimethyl (5a*RS*,9a*SR*)-4-(*tert*-Butyldimethylsilyloxy)-5a,6,7,8,9,9a-hexahydro-8,8-dimethoxyfuro[3,2-*f*]quinoline-2,6-dicarboxylate (29a) TBDMSOTf (0.71 ml, 3.03 mmol) was added to a solution of **28a** (149.5 mg, 0.407 mmol) in the presence of Et_3N (0.85 ml, 6.11 mmol) in CH_2Cl_2 (10 ml), and the mixture was stirred under an Ar atmosphere at 25 °C for 30 min. Addition of saturated $NaHCO_3$–H_2O, extraction with CH_2Cl_2 and usual work-up gave a residue (360.5 mg). Purification by silica gel column chromatography [hexane–EtOAc (3 : 1)] afforded **29a** (181.5 mg, 93%) as a colorless glass. HRMS Calcd for $C_{23}H_{35}NO_8Si$: 481.2130. Found: 481.2118. MS *m/z*: 481 (M^+, 6), 450 (26), 449 (54), 392 (55), 360 (60), 249 (23), 162 (84), 89 (38), 73 (100), 59 (51), 43 (24). IR ($CHCl_3$) cm^{-1}: 1700, 1620. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 0.21 (6H, s), 1.00 (9H, s), 1.48 (1H, dd, J=13, 13 Hz), 1.94 (1H, ddd, J=13, 4.5, 2.5 Hz), 2.76 (1H, d, J=14 Hz), 2.95 (1H, ddd, J=13, 7.5, 4.5 Hz), 3.20 (3H, s), 3.24 (3H, s), 3.74 (3H, s), 3.87 (3H, s), 4.10—4.51 (1H, m), 4.74 (1H, d, J=2.5 Hz), 5.19—5.56 (1H, m), 7.04 (1H, s).

Dimethyl (5a*RS*,9a*SR*)-4-(*tert*-Butyldimethylsilyloxy)-5a,6,7,8,9,9a-hexahydro-8,8-dimethoxythieno[3,2-*f*]quinoline-2,6-dicarboxylate (29b) Similarly, **28b** (31 mg, 0.081 mmol) was treated with TBDMSOTf (0.14 ml, 0.61 mmol) and Et_3N (0.17 ml, 1.2 mmol) to afford **29b** (36.5 mg, 91%) as a colorless glass. HRMS Calcd for $C_{23}H_{35}NO_7SSi$: 497.1901. Found: 497.1929. MS *m/z*: 497 (M^+, 4), 465 (87), 450 (12), 434 (14), 376 (20), 265 (30), 162 (61), 89 (34), 73 (100), 59 (39). IR ($CHCl_3$) cm^{-1}: 1692. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 0.24 (6H, s), 1.00 (9H, s), 1.56 (1H, dd, J=13, 13 Hz), 1.92 (1H, dd, J=13, 4.5 Hz), 2.78 (1H, d, J=14 Hz), 3.08 (1H, ddd, J=13, 7, 4.5 Hz), 3.19 (3H, s), 3.23 (3H, s), 3.74 (3H, s), 3.86 (3H, s), 4.12—4.86 (1H, m), 4.68 (1H, d, J=2 Hz), 5.25—5.61 (1H, m), 7.55 (1H, s).

Dimethyl (5*RS*,5a*SR*,9a*SR*)-4,5,5a,6,7,8,9,9a-Octahydro-8,8-dimethoxy-4-oxo-5-(phenylseleno)furo[3,2-*f*]quinoline-2,6-dicarboxylate (30a) PhSeCl (95%, 145 mg, 0.719 mmol) was added to a cooled (0 °C) solution of **29a** (103 mg, 0.214 mmol) in THF (8.5 ml). The mixture was stirred under an Ar atmosphere at 0 °C for 6 min, Bu_4NF in THF (1 M, 0.86 ml, 0.86 mmol) was added, and the whole was stirred at that temperature for 10 min. Addition of saturated $NaHCO_3$–H_2O, extraction with Et_2O and usual work-up gave a residue (179 mg), which was separated by PTLC (CH_2Cl_2) to afford crude **30a** (84 mg) and crude **28a** (16.5 mg). Purification of the former by PTLC [hexane–EtOAc (2 : 1)] provided **30a** (79 mg, 71%) as a colorless glass. HRMS Calcd for $C_{23}H_{25}NO_8Se$: 523.0744. Found: 523.0733. MS *m/z*: 525 (7), 524 (8), 523 (27), 522 (4), 521 (14), 520 (6) and 519 (6) (M^+); 434 (3), 433 (4), 432 (12), 431 (2), 430 (7), 429 (3) and 428 (3); 366 (100); 334 (69); 302 (87); 274 (86); 260 (84); 162 (26); 157 (42); 155 (22); 144 (32); 77 (32); 59 (81); 45 (84); 43(38). IR ($CHCl_3$) cm^{-1}: 1728, 1690. ^{1}H-NMR (90 MHz, 60 °C, $CDCl_3$) δ: 1.56 (1H, dd, J=13, 13 Hz), 2.25 (1H, ddd, J=13, 4.5, 2.5 Hz), 2.44 (1H, d, J=15 Hz), 3.21 (3H, s), *ca.* 3.21—3.56 (1H, m), 3.25 (3H, s), 3.76 (3H, s), 3.93 (3H, s), 4.24 (1H, dd, J=15, 2.5 Hz), 4.35 (1H, d, J=12 Hz), 4.89 (1H, dd, J=12, 5 Hz), 7.07 (1H, s), 7.15—7.44 (3H, m), 7.44—7.86 (2H, m). The latter was purified by PTLC [hexane–EtOAc (3 : 2)] to recover **28a** (15.5 mg, 20%).

Dimethyl 6,7,8,9-Tetrahydro-4-hydroxy-8,8-dimethoxyfuro[3,2-*f*]-quinoline-2,6-dicarboxylate (31a) A solution of **30a** (157.5 mg, 0.302 mmol) in THF (11.5 ml) containing 31% H_2O_2–H_2O (0.33 ml, 3.01 mmol) was stirred at 20 °C for 70 min. After quenching of the reaction with saturated $Na_2S_2O_3$–H_2O, the whole was extracted with 10% MeOH–CH_2Cl_2, and worked up as usual to give a mixture (116 mg).

Purification by PTLC (2.5% MeOH–CH_2Cl_2) afforded crude **31a** (89 mg), which was recrystallized from CH_2Cl_2–MeOH to provide **31a** (87 mg, 79%) as colorless prisms, mp 264—265 °C. *Anal.* Calcd for $C_{17}H_{19}NO_8$: C, 55.89; H, 5.24; N, 3.83. Found: C, 55.97; H, 5.26; N, 4.00. HRMS Calcd for $C_{17}H_{19}NO_8$: 365.1109. Found: 365.1105. MS *m/z*: 365 (M^+, 100), 350 (18), 334 (60), 274 (24), 246 (18), 173 (16), 89 (18), 88 (18), 75 (21), 59 (52), 45 (68). IR (KBr) cm^{-1}: 1686. ^{1}H-NMR (90 MHz, 10% CD_3OD–$CDCl_3$) δ: 3.09 (2H, s), 3.34 (6H, s), 3.82 (3H, s), 3.84 (2H, s), 3.95 (3H, s), 7.26 (1H, s), 7.47 (1H, s).

Dimethyl 6,7,8,9-Tetrahydro-4-hydroxy-8,8-dimethoxythieno[3,2-*f*]-quinoline-2,6-dicarboxylate (31b) Similarly, **29b** (284.5 mg, 0.572 mmol) was treated with PhSeCl (95%, 381 mg, 1.89 mmol) and Bu_4NF in THF (1 M, 2.29 ml, 2.29 mmol) to afford crude **30b** (269 mg). This α-phenylselenylketone was oxidized with 31% H_2O_2–H_2O (1.0 ml, 9.1 mmol) in THF (25 ml) to afford **31b** (83 mg, 38%) as colorless prisms, mp 221—222 °C (dec.). *Anal.* Calcd for $C_{17}H_{19}NO_7S$: C, 53.53; H, 5.02; N, 3.67. Found: C, 53.48; H, 5.07; N, 3.86. HRMS Calcd for $C_{17}H_{19}NO_7S$: 381.0881. Found: 381.0875. MS *m/z*: 381 (M^+, 100), 350 (65), 291 (18), 290 (22), 276 (16), 262 (17), 189 (25), 89 (15), 88 (18), 75 (20), 59 (57), 45 (53). IR (KBr) cm^{-1}: 1708, 1673. ^{1}H-NMR (90 MHz, 10% CD_3OD–$CDCl_3$) δ: 3.21 (2H, s), 3.35 (6H, s), 3.83 (3H, s), 3.85 (2H, s), 3.94 (3H, s), 7.23 (1H, s), 8.00 (1H, s).

Dimethyl 4-Benzyloxy-6,7,8,9-tetrahydro-8,8-dimethoxyfuro[3,2-*f*]-quinoline-2,6-dicarboxylate (32a) A solution of **31a** (42 mg, 0.12 mmol) and benzyl bromide (55 μl, 0.46 mmol) in acetone (10 ml) was refluxed in the presence of K_2CO_3 (48 mg, 0.35 mmol) for 2 h. After the mixture had cooled, saturated NH_4Cl–H_2O was added, and the whole was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [hexane–EtOAc (3 : 1)] gave **32a** (52 mg, 99%) as a colorless glass. HRMS Calcd for $C_{24}H_{25}NO_8$: 455.1579. Found: 455.1595. MS *m/z*: 455 (M^+, 22), 424 (5), 423 (5), 364 (21), 332 (7), 274 (10), 91 (100), 65 (7), 59 (10). IR ($CHCl_3$) cm^{-1}: 1703. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.07 (2H, s), 3.31 (6H, s), 3.72 (3H, s), 3.84 (2H, s), 3.93 (3H, s), 5.26 (2H, s), 7.24—7.61 (5H, m), 7.36 (1H, s), 7.45 (1H, s).

Dimethyl 4-Benzyloxy-6,7,8,9-tetrahydro-8,8-dimethoxythieno[3,2-*f*]-quinoline-2,6-dicarboxylate (32b) Similarly, **31b** (31 mg, 0.081 mmol) was benzylated with benzyl bromide (29 μl, 0.24 mmol) and K_2CO_3 (56 mg, 0.41 mmol) to afford **32b** (37.5 mg, 98%) as a colorless glass. HRMS Calcd for $C_{24}H_{25}NO_7S$: 471.1350. Found: 471.1368. MS *m/z*: 471 (M^+, 18), 439 (8), 380 (9), 348 (14), 290 (7), 91 (100), 65 (10), 59 (12). IR ($CHCl_3$) cm^{-1}: 1710. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.22 (2H, s), 3.35 (6H, s), 3.78 (3H, s), 3.87 (2H, s), 3.93 (3H, s), 5.24 (2H, s), 7.22—7.63 (6H, m), 8.03 (1H, s).

Dimethyl (8*RS*)-4-Benzyloxy-6,7,8,9-tetrahydro-8-hydroxyfuro[3,2-*f*]-quinoline-2,6-dicarboxylate (34a) A solution of **32a** (64 mg, 0.14 mmol) in a mixture of acetone (5 ml) and H_2O (2 ml) containing 70% $HClO_4$ (1.2 ml, 8.4 mmol) was stirred at 20 °C for 50 min. After addition of H_2O, the mixture was extracted with CH_2Cl_2. Washing of the CH_2Cl_2 solution with saturated $NaHCO_3$–H_2O followed by usual work-up gave crude **33a** (60 mg), which was used for the next reaction without purification. A solution of the above material **33a** in a mixture of THF (2.5 ml) and MeOH (2.5 ml) was cooled at −20 °C, and $NaBH_4$ (27 mg, 0.71 mmol) was added. The reaction mixture was stirred under an Ar atmosphere at −20 °C for 25 min, the reaction was quenched with saturated NH_4Cl–H_2O, and the whole was extracted with CH_2Cl_2. Usual work-up gave a residue (61 mg), which was purified by PTLC [hexane–EtOAc (1 : 1)] to afford **34a** (56 mg, 97%) as a colorless glass. HRMS Calcd for $C_{22}H_{21}NO_7$: 411.1317. Found: 411.1307. MS *m/z*: 411 (M^+, 16), 91 (100). IR ($CHCl_3$) cm^{-1}: 1700. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.48 (1H, br d, *J* = 3 Hz, OH), 2.81 (1H, dd, *J* = 17.5, 5 Hz), 3.17 (1H, dd, *J* = 17.5, 6 Hz), *ca.* 3.65—4.06 (2H, m), 3.71 (3H, s), 3.95 (3H, s), 4.13—4.50 (1H, m), 5.27 (2H, s), 7.25—7.61 (5H, m), 7.35 (1H, s), 7.45 (1H, s).

Dimethyl (8*RS*)-4-Benzyloxy-6,7,8,9-tetrahydro-8-hydroxythieno[3,2-*f*]quinoline-2,6-dicarboxylate (34b) A solution of **32b** (34 mg, 0.072 mmol) in 5% HCl-containing DME–H_2O (2 : 1) (3 ml, 1.37 mmol) was stirred at 20 °C for 2 h. Saturated $NaHCO_3$–H_2O was added, and the whole was extracted with 10% MeOH–CH_2Cl_2. Usual work-up gave crude **33b** (31 mg). A solution of this in a mixture of THF (2 ml) and MeOH (2 ml) was cooled at 0 °C, and $NaBH_4$ (11 mg, 0.29 mmol) was added. The reaction mixture was stirred at 0 °C for 30 min, saturated NH_4Cl–H_2O was added, and the whole was extracted with 10% MeOH–CH_2Cl_2. Usual work-up gave a residue (37 mg), which was purified by PTLC [1% MeOH–CH_2Cl_2] to afford **34b** (28 mg, 91%) as a colorless glass. HRMS Calcd for $C_{22}H_{21}NO_6S$: 427.1088. Found: 427.1078. MS *m/z*: 427 (M^+, 16), 91 (100), 65 (8), 59 (9). IR ($CHCl_3$) cm^{-1}: 1707. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.59 (1H, br s, OH), 2.92 (1H, dd, *J* = 15.5, 5.5 Hz), 3.28 (1H, dd, *J* = 15.5, 6 Hz), 3.59—4.10 (2H, m), 3.75 (3H, s), 3.94 (3H, s), 4.14—4.34 (1H, m), 5.24 (2H, s), 7.19—7.66 (5H, m), 7.36 (1H, s), 7.98 (1H, s).

Dimethyl (8*RS*)-4-Benzyloxy-6,7,8,9-tetrahydro-8-(methanesulfonyl-oxy)furo[3,2-*f*]quinoline-2,6-dicarboxylate (35a) Methanesulfonyl chloride (60 μl, 0.78 mmol) was added to a cooled (0 °C) solution of **34a** (39.5 mg, 0.096 mmol) in CH_2Cl_2 (5 ml) and Et_3N (0.21 ml, 1.51 mmol). The mixture was stirred under an Ar atmosphere at 0 °C for 25 min, then saturated $NaHCO_3$–H_2O was added. Extraction with CH_2Cl_2 and usual work-up gave a residue (62 mg), which was purified by PTLC [hexane–CH_2Cl_2 (1 : 6)] to afford **35a** (46 mg, 98%) as a colorless glass. HRMS Calcd for $C_{23}H_{23}NO_9S$: 489.1092. Found: 489.1096. MS *m/z*: 489 (M^+, 10), 393 (4), 380 (5), 302 (7), 91 (100), 65 (6), 59 (6). IR ($CHCl_3$) cm^{-1}: 1710. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.04 (3H, s), 3.10 (1H, dd, *J* = 17.5, 4 Hz), 3.36 (1H, dd, *J* = 17.5, 6 Hz), 3.74 (3H, s), 3.77 (1H, dd, *J* = 14, 2 Hz), 3.95 (3H, s), 4.27 (1H, dd, *J* = 14, 6 Hz), 5.13—5.40 (1H, m), 5.26 (2H, s), 7.23—7.62 (5H, m), 7.32 (1H, s), 7.43 (1H, s).

Dimethyl (8*RS*)-4-Benzyloxy-6,7,8,9-tetrahydro-8-(methanesulfonyl-oxy)thieno[3,2-*f*]quinoline-2,6-dicarboxylate (35b) Similarly, reaction of **34b** (27 mg, 0.063 mmol) with methanesulfonyl chloride (15 μl, 0.19 mmol) and Et_3N (53 μl, 0.38 mmol) gave **35b** (31.5 mg, 99%) as a colorless glass. HRMS Calcd for $C_{23}H_{23}NO_8S_2$: 505.0864. Found: 505.0870. MS *m/z*: 505 (M^+, 10), 409 (4), 396 (6), 318 (7), 274 (3), 91 (100), 65 (7), 59 (8). IR ($CHCl_3$) cm^{-1}: 1712. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.03 (3H, s), *ca.* 3.10—3.60 (2H, m), 3.67—4.03 (1H, m), 3.75 (3H, s), 3.90 (3H, s), 4.28 (1H, dd, *J* = 13.5, 5.5 Hz), 5.13—5.41 (1H, m), 5.23 (2H, s), 7.24—7.61 (5H, m), 7.33 (1H, s), 7.97 (1H, s).

Methyl (7a*RS*,8a*SR*)-6,7,7a,8-Tetrahydro-4-oxo-4*H*-cyclopropa[*c*]-furo[3,2-*e*]indole-2-carboxylate (38a) A solution of **35a** (86 mg, 0.18 mmol) in a mixture of MeOH (20 ml) and CH_2Cl_2 (5 ml) was hydrogenated over 20% $Pd(OH)_2$–C (36 mg) under H_2 (1 atm) at 19 °C for 30 min. The catalyst was filtered off through a Celite bed, and the Celite was washed with MeOH. Concentration of the filtrate gave a residue (75.5 mg), which was purified by PTLC (2% MeOH–CH_2Cl_2) to afford crude **36a** (68 mg). A solution of **36a** in a mixture of MeOH (12.5 ml) and CH_2Cl_2 (2.5 ml) was stirred in the presence of K_2CO_3 (303 mg, 2.20 mmol) at 20 °C for 3 h. After quenching with 0.5 N citric acid (15 ml), the whole was extracted with CH_2Cl_2 and worked up as usual to give a residue (43 mg). Purification by PTLC (4% MeOH–CH_2Cl_2) afforded **38a** (29.5 mg, 68.5%) as a yellow powder. HRMS Calcd for $C_{13}H_{11}NO_4$: 245.0687. Found: 245.0686. MS *m/z*: 245 (M^+, 53), 244 (46), 243 (100), 212 (53), 156 (36). IR ($CHCl_3$) cm^{-1}: 1720, 1620. ^{1}H-NMR (400 MHz, 10% CD_3OD–$CDCl_3$) δ: 1.36 (1H, dd, *J* = 5, 4 Hz), 1.70 (1H, dd, *J* = 8, 4 Hz), 2.92 (1H, ddd, *J* = 8, 5.5, 5 Hz), 3.70 (1H, d, *J* = 11 Hz), 3.86 (1H, dd, *J* = 11, 5.5 Hz), 3.92 (3H, s), 5.60 (1H, s), 6.97 (1H, s).

Methyl (7a*RS*,8a*SR*)-6,7,7a,8-Tetrahydro-4-oxo-4*H*-cyclopropa[*c*]-thieno[3,2-*e*]indole-2-carboxylate (38b) Similarly, **35a** (28 mg, 0.055 mmol) was hydrogenated over 20% $Pd(OH)_2$–C (10 mg) to afford crude **36b** (25 mg), which was treated with K_2CO_3 (77 mg, 0.56 mmol) to afford **38b** (12.5 mg, 86%) as a light yellow powder. HRMS Calcd for $C_{13}H_{11}NO_3S$: 261.0459. Found: 261.0457. MS *m/z*: 261 (M^+, 100), 228 (21), 202 (20), 173 (23), 145 (13), 59 (15). IR ($CHCl_3$) cm^{-1}: 1713, 1604. ^{1}H-NMR (90 MHz, 10% CD_3OD–$CDCl_3$) δ: 1.35 (1H, dd, *J* = 5, 4 Hz), 1.70 (1H, dd, *J* = 7.5, 4 Hz), 2.82—3.08 (1H, m), 3.67 (1H, d, *J* = 11 Hz), 3.89 (1H, dd, *J* = 11, 5 Hz), 3.86 (3H, s), 5.72 (1H, s), 7.34 (1H, s).

5,6,7-Trimethoxy-1-methyl-1*H*-indole-2-carbonyl Chloride (39) (i) Preparation of Methyl 5,6,7-Trimethoxy-1-methyl-1*H*-indole-2-carboxylate. A THF (0.5 ml) suspension of mineral oil-free NaH, prepared by rinsing of 60% NaH (7.5 mg, 0.19 mmol) with pentane (0.5 ml) twice, was added to a cooled (0 °C) solution of methyl 5,6,7-trimethoxy-1*H*-indole-2-carboxylate[24] (13 mg, 0.049 mmol) in a mixture of THF (1.5 ml) and DMF (0.4 ml). After subsequent addition of MeI (16 μl, 0.26 mmol), stirring was continued under an Ar atmosphere at 0 °C for 20 min. Quenching with saturated NH_4Cl–H_2O, extraction with Et_2O and usual work-up gave a residue (14.5 mg). Purification by PTLC [hexane–EtOAc (7 : 1)] afforded the *N*-methylindole derivative (13.5 mg, 99%) as a colorless syrup. HRMS Calcd for $C_{14}H_{17}NO_5$: 279.1106. Found: 279.1118. MS *m/z*: 279 (M^+, 100), 264 (84), 221 (27), 206 (21). IR ($CHCl_3$) cm^{-1}: 1710. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.86 (6H, s), 3.90 (3H, s), 3.98 (3H, s), 4.29 (3H, s), 6.78 (1H, s), 7.14 (1H, s). (ii) Preparation of 5,6,7-Trimethoxy-1-methyl-1*H*-indole-2-carboxylic acid. A solution of

the above methyl ester (60 mg, 0.22 mmol) and $LiOH \cdot H_2O$ (27 mg, 0.64 mmol) in a mixture of DME (4 ml) and H_2O (2 ml) was stirred at 40 °C for 1.5 h. After acidification with 10% HCl–H_2O (1 ml), the whole was extracted with 10% MeOH–CH_2Cl_2. Usual work-up gave a crystalline residue (59.5 mg), which was recrystallized from CH_2Cl_2–MeOH to afford the carboxylic acid (53.5 mg, 94%) as colorless prisms, mp 215.5—216 °C. *Anal.* Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.76; H, 5.73; N, 5.37. HRMS Calcd for $C_{13}H_{15}NO_5$: 265.0949. Found: 265.0962. MS *m/z*: 265 (M^+, 100), 250 (82), 207 (30), 192 (22). IR (KBr) cm^{-1}: 2930, 1660. ^{1}H-NMR (90 MHz, 10% CD_3OD–$CDCl_3$) δ: 3.84 (3H, s), 3.90 (3H, s), 3.96 (3H, s), 4.24 (3H, s), 6.76 (1H, s), 7.18 (1H, s). (iii) Preparation of **39**. Oxalyl chloride (29 μl, 0.33 mmol) was added to a cooled (0 °C) solution of the carboxylic acid (19.5 mg, 0.074 mmol) in CH_2Cl_2 (3 ml) containing DMF (7 μl, 0.09 mmol), and stirring was continued at 0 °C for 1 h. Addition of H_2O, extraction with Et_2O, and usual work-up gave a residue (20 mg). Purification by silica gel column chromatography [hexane–EtOAc (6 : 1)] followed by recrystallization from CH_2Cl_2–hexane afforded the acid chloride **39** (17 mg, 81.5%) as yellow prisms, mp 96—97 °C. *Anal.* Calcd for $C_{13}H_{14}ClNO_4$: C, 55.04; H, 4.97; N, 4.94. Found: C, 55.06; H, 4.92; N, 4.99. HRMS Calcd for $C_{13}H_{14}{}^{37}ClNO_4$ and $C_{13}H_{14}{}^{35}ClNO_4$: 285.0581 and 283.0610. Found: 285.0595 and 283.0611. MS *m/z*: 285 (33) and 283 (100) (M^+), 270 (22) and 268 (61), 248 (52). IR (KBr) cm^{-1}: 1725. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.88 (3H, s), 3.93 (3H, s), 3.98 (3H, s), 4.21 (3H, s), 6.79 (1H, s), 7.52 (1H, s).

Methyl (7a*RS*,8a*SR*)-6,7,7a,8-Tetrahydro-4-oxo-6-[(5,6,7-trimethoxy-1-methyl-1*H*-indol-2-yl)carbonyl]-4*H*-cyclopropa[*c*]furo[3,2-*e*]indole-2-carboxylate (6) A THF (0.5 ml) suspension of mineral oil-free NaH, prepared by rinsing of 60% NaH (10 mg, 0.25 mmol) with pentane, was added to a cooled (0 °C) solution of **38a** (5 mg, 0.02 mmol) in a mixture of THF (2 ml) and DMF (0.5 ml). The mixture was stirred under an Ar atmosphere at 0 °C for 3 min, the acid chloride **39** (5.5 mg, 0.02 mmol) was added, and stirring was continued at the same temperature for 40 min. Quenching with 0.5 N citric acid (8 ml), extraction with CH_2Cl_2, washing of the CH_2Cl_2 solution with saturated $NaHCO_3$–H_2O and usual work-up gave a residue (11 mg). Purification by PTLC (1% MeOH–CH_2Cl_2) afforded **6** (8 mg, 80%) as a yellow powder. HRMS Calcd for $C_{26}H_{24}N_2O_8$: 492.1531. Found: 492.1547. MS *m/z*: 492 (M^+, 14), 257 (13), 248 (100), 179 (14). IR ($CHCl_3$) cm^{-1}: 1723, 1637. ^{1}H-NMR (400 MHz, 10% CD_3OD–$CDCl_3$) δ: 1.78 (1H, dd, J=5, 5 Hz), 1.96 (1H, dd, J=8, 5 Hz), 2.88 (1H, ddd, J=8, 5, 5 Hz), 3.87 (3H, s), 3.94 (6H, s), 4.02 (3H, s), 4.10 (3H, s), 4.21 (1H, d, J=11.5 Hz), 4.37 (1H, dd, J=11.5, 5 Hz), 6.26 (1H, s), 6.75 (2H, s), 7.05 (1H, s).

Methyl (7a*RS*,8a*SR*)-6,7,7a,8-Tetrahydro-4-oxo-6-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-4*H*-cyclopropa[*c*]thieno[3,2-*e*]indole-2-carboxylate (7) NaH (60%, 5 mg, 0.1 mmol) was added to a cooled (0 °C) solution of **38b** (11 mg, 0.042 mmol) in THF (2 ml) and DMF (0.5 ml), and the mixture was stirred under an Ar atmosphere at 0 °C for 3 min. The imidazolide **40**[1] (26 mg, 0.086 mmol) was added, and stirring was continued at the same temperature for 2 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with EtOAc. Usual work-up gave a residue (50 mg), which was purified by PTLC [benzene–EtOAc (1 : 1) and 1% MeOH–$CHCl_3$] to afford **7** (10 mg, 48%) as a light yellow powder. HRMS Calcd for $C_{25}H_{22}N_2O_7S$: 494.1146. Found: 494.1159. MS *m/z*: 494 (M^+, 21), 273 (32), 234 (100), 50 (27). IR ($CHCl_3$) cm^{-1}: 1712, 1612. ^{1}H-NMR (90 MHz, 10% CD_3OD–$CDCl_3$) δ: 1.66 (1H, dd, J=4.5, 4.5 Hz), 1.89 (1H, dd, J=7.5, 4.5 Hz), *ca.* 2.78—3.09 (1H, m), 3.86 (3H, s), 3.91 (6H, s), 4.05 (3H, s), 4.41 (1H, d, J=10 Hz), 4.51 (1H, dd, J=10, 5 Hz), 6.81 (1H, s), 6.96 (1H, s), 7.02 (1H, s), 7.46 (s).

Acknowledgment We are grateful to the Research Laboratories, Shionogi & Co., Ltd., for elemental analysis. Thanks are due to the Ministry of Education, Science, Sports and Culture of Japan for financial support.

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