Preparation of Benzene, Furan, and Thiophene Analogs of Duocarmycin SA Employing a Newly-Devised Phenol-Forming Reaction

Hideaki MURATAKE,* Aki HAYAKAWA, and Mitsutaka NATSUME*

Research Foundation Itsuu Laboratory, 2–28–10 Tamagawa, Setagaya-ku, Tokyo 158–0094, Japan.
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Five A-ring analogs of duocarmycin SA 9a—e were synthesized in racemic form modifying our second synthetic route toward duocarmycin SA. The problem encountered at the crucial phenol forming step to secure 17a, b from 16a, b under the conventionally used Kuwajima conditions was overcome by devising a more convenient method: simple heating of 16a—c in benzene in the presence of bis(triphenylphosphine)palladium(II) chloride (10 mol%), cesium carbonate (3 eq), and triphenylphosphine (0.3 eq) gave 17a—c in high yields of 86—91%. The intermediates 17a—e were readily led to the A-ring analogs (±)-9a—e almost according to the reported route.

Key words duocarmycin SA; analog synthesis; ketone α-arylation; antitumor antibiotic; palladium-catalyzed reaction; phenol-forming reaction

Duocarmycin SA (DSA, **1**) is an exceptionally potent antitumor antibiotic isolated from a culture broth of *Streptomyces* species in 1990 (Chart 1).[1] Among the several structurally related antibiotics, CC-1065,[2] duocarmycin A,[3,4] duocarmycins B_1,[4,5] B_2,[4,5] C_1[4,6] (=pyrindamycin B[7]), C_2[4,6] (=pyrindamycin A[7]), and D,[4] **1** is the newest and most promising member since it has proved to be the most potent and most stable.[8] We have already reported three independent synthetic routes toward **1**.[9—11] Two more total syntheses of **1** have been reported by Boger and his colleagues[12] and by Fukuda and Terashima.[13]

In our first route, (±)-**1** was synthesized starting from methyl 5-acetyl-4-bromo-1*H*-pyrrole-2-carboxylate (**2**) by way of pyrrolo[3,2-*f*]quinoline derivative **3** in 15 total steps, in 10% overall yield.[9] The second route also commenced from **2** involving two palladium-catalyzed carbon–carbon bond formation reactions to construct the tricyclic heteroaromatic intermediate **4**. (±)-**1** was prepared in 13 steps, in 22% overall yield from **2** by the second route.[10] In both routes, optical resolution was readily executed by the HPLC separation of (*R*)-*O*-methylmandelate of the pyrrolo[3,2-*f*]quinolinol intermediate **5**.[14] The separated unnatural (*R*)-**5** was converted to natural (*S*)-**5** by the inversion of the hydroxy group under the Mitsunobu reaction conditions. Thus, two enantioselective syntheses of **1** were established in an enantio-convergent manner. By the third route, optically pure **1** was synthesized starting from L-malic acid by way of the intermediate **6** in 19 steps, in 2% overall yield.[11] The absolute configuration of **1** was unequivocally shown to be 7b*R* for the first time by the third route.

The structure of the A-ring of **1** and its congeners has been proved to greatly influence the cytotoxic activity as well as the chemical stability, and some A-ring analogs have been selected as clinical candidates.[15] Furthermore, the simpler structure of DSA compared to those of taxol, mitomycin C, adriamycin *etc.* would permit a perpetual supply of the analogs by total synthesis. With this background in mind, we turned our attention to the preparation of A-ring analogs of **1** and earlier reported the synthesis of furan and thiophene analogs of DSA **7** and **8** applying our first synthetic route (Chart 2).[16] Among the above three routes, however, the second one[10] is the most suitable for analog synthesis, because it is the most practical from the viewpoints of number of steps, overall yield, and simple operations. Herein we describe the full details of our studies on the preparation of five A-ring analogs of DSA **9a—e**, modifying our second route.[17] The crucial palladium-catalyzed phenol-forming step (**10**→**11**) was revised and was much improved by the development of direct intramolecular α-arylation reaction of ketone instead of the Kuwajima conditions[18] which we had conventionally employed. Thus, as shown in Chart 4, Table 1 (*vide infra*), the direct cyclization of **16a—c** to **17a—c** (isolated after protection of phenol as methyl carbonate) was attained in high yields under novel palladium-catalyzed conditions: bis(triphenylphosphine)palladium(II) chloride [$PdCl_2(Ph_3P)_2$]–cesium carbonate (Cs_2CO_3)–triphenylphosphine (Ph_3P) in boiling benzene. The benzene [(±)-**9a**], furan [(±)-**9b**], thiophene [(±)-**9c**], and benzothiophene [(±)-**9d**] analogs of DSA lack methoxycarbonyl group at the 2-position which contributes to the chemical stability of the cyclopropanoindolinone pharmacophore. A preparation of (±)-**9e** bearing a bulky 3,4,5-trimethoxybenzyl group at the 2-position is also described, aiming for enhancement of the cytotoxic activity.

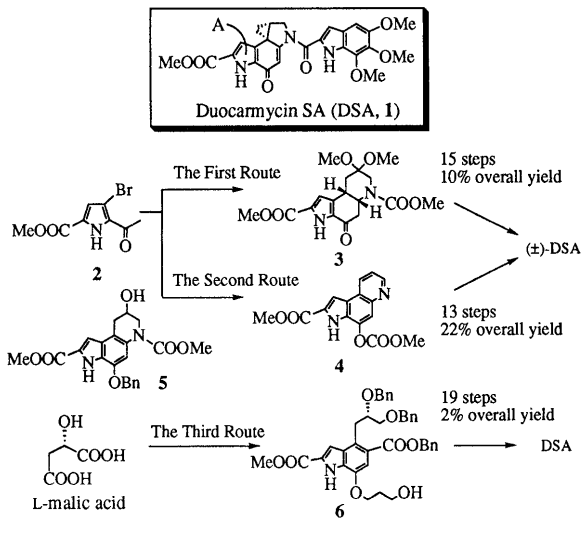

Chart 1

* To whom correspondence should be addressed.
Dedicated to the memory of Dr. Kyosuke Tsuda.

The transformation of **16a—c** to **17a—c** (Chart 4) is substantially regarded as an intramolecular version of the α-arylation reaction of aliphatic ketone. We have already reported an extension of the above palladium-catalyzed reaction conditions to the intramolecular α-arylation reaction of ketone,[19] aldehyde,[20] and nitro[20] groups as communications.

Preparation of Tricyclic Heteroaromatic Intermediates 17a—e At the outset, tricyclic aromatic intermediates **17a—e** corresponding to compound **4** were prepared according to our second route. The compounds **17a—d** were synthesized from the corresponding **12a—d** as shown in Chart 3. Compound **17e** was prepared later by substitution at 2-position of **17c** as shown in Chart 6.

i) Preparation of the Precursors **16a—d** for Cyclization: Among the starting materials **12a—d**, *o*-bromoacetophenone (**12a**) is commercially available (Chart 3). The yields of the known compounds **12b**,[21] **c**[22] were improved as follows. Treatment of 3-bromofuran in dichloromethane (CH_2Cl_2) with acetic anhydride (Ac_2O) and boron trifluoride etherate ($BF_3 \cdot OEt_2$) afforded **12b** in 76% yield accompanied by an isomer, 1-(4-bromo-2-furanyl)ethanone in 10% yield. The starting material, 1-(3-bromo-2-thienyl)ethanone (**12c**) prepared from 3-bromothiophene in 79% yield by treatment with Ac_2O and aluminum chloride ($AlCl_3$) in CH_2Cl_2 was found to contain an inseparable minor isomer, 1-(4-bromo-2-thienyl)ethanone in a ratio of 16 : 1 estimated by the ^{1}H-NMR integral values of the methyl signal observed at δ 2.67 (major) and δ 2.53 (minor). The same acylation procedure on 3-bromobenzo[*b*]thiophene with $AlCl_3$ readily gave **12d** in 78% yield.

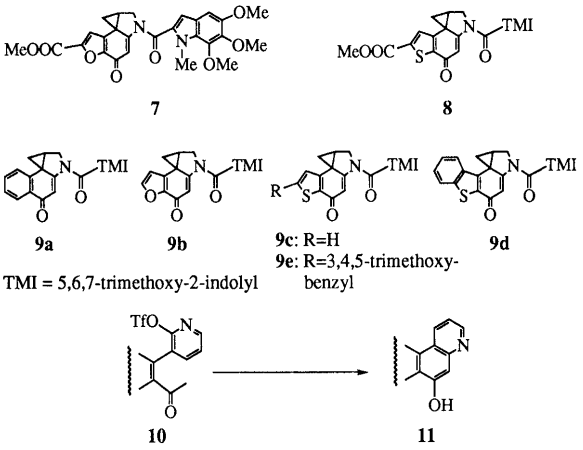

Chart 2

The Stille coupling reaction[23] of thus prepared **12a—d** with 2-fluoro-3-(trimethylstannyl)pyridine (**13**)[10] catalyzed by $PdCl_2(Ph_3P)_2$ proceeded as before without trouble affording **14a—d** in good to high yields (Chart 3). The yield of **14c** was calculated from used **13** because of the impurity of **12c**. Subsequent hydrolysis in 10% aqueous hydrochloric acid (HCl)–1,2-dimethoxyethane (DME) at 60 °C readily afforded pyridones **15a—d**, which were then transformed to the required precursors **16a—d** with trifluoromethanesulfonic anhydride (Tf_2O) and pyridine (Py) in CH_2Cl_2 at 0 °C to ambient temperature in high yields.

ii) Cyclization of **16a—d** to **17a—d** by the Conventional Method: The obtained triflates **16a—d** were subjected to the palladium-catalyzed cyclization under the Kuwajima conditions[18] following the conventional method of our second route (Chart 3).[10] First, the acetyl group was converted to enol silyl ether with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) and triethylamine (Et_3N). Then the crude product was heated in boiling xylene with 5 mol% of $PdCl_2(Ph_3P)_2$, 1.2 eq of tributyltin fluoride (Bu_3SnF), and 3 eq of lithium chloride (LiCl) to give a crude phenol derivative. At this stage, the xylene solution of the crude product from furan derivative **16b** contained some *tert*-butyldimethylsilyl ether judging from silica gel thin layer chromatography, and so it was treated with 10% aqueous HCl and methanol (MeOH) to liberate the phenol. Isolation of the products was executed after protection of the phenol group as methyl carbonate **17a—d** with methyl chloroformate (ClCOOMe) and sodium hydride (NaH) in tetrahydrofuran (THF)–*N*,*N*-dimethylformamide (DMF) (3 : 1). The respective yields for **17a** and **17b** were, however, only 24% and 27% accompanied by recovered **16a** and **16b** in 7% and 55%, respectively. In contrast, **17c**, **d** were obtained in good respective yields of 75% and 80%. It is unclear at present why the yields of **17a**, **b** were so low compared to those of **4** and **17c**, **d**. Since slight modification [increase of the palladium catalyst to 10 mol%, exchange of solvent to toluene, or exchange of TBDMSOTf to triisopropylsilyl trifluoromethanesulfonate] of the reaction conditions for **a** and **b** brought about no improvement, we decided to reinvestigate thoroughly the palladium-catalyzed cyclization conditions for **16a**, **b**, and **c**.

iii) Improved Palladium-Catalyzed Cyclization Conditions: At first, cyclization of the furan derivative **16b** was tried with various combinations of bases and solvents (at reflux) in the presence of a fixed palladium catalyst $PdCl_2(Ph_3P)_2$, and the resulting products were isolated as methyl carbonates as before (Chart 4) (Table 1). As can be

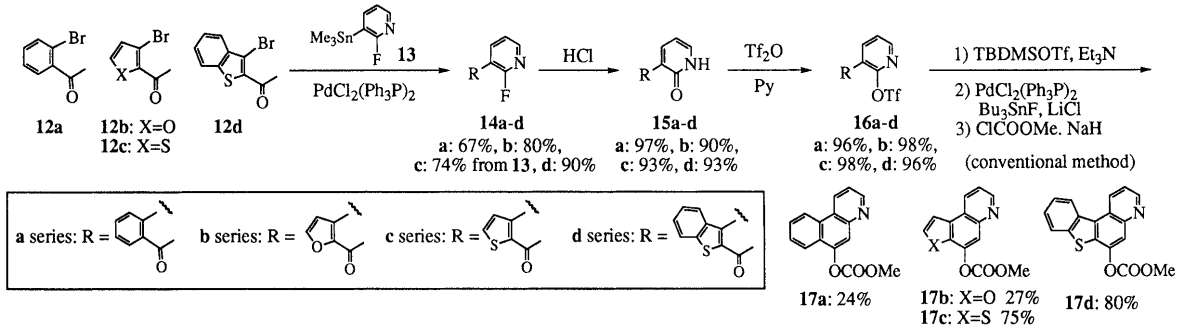

Chart 3

seen from Table 1, NaH and Cs_2CO_3 are preferable as base (run 2, 3, 7—10). Potassium *tert*-butoxide (*t*-BuOK) or potassium carbonate (K_2CO_3) gave a trace of or no desired **17b**, but afforded by-products **19**, **20** and recovery of starting material **16b** (run 4—6). Less polar solvent such as toluene was more suitable than polar THF; this is probably because a polar solvent tends to accelerate an intermolecular aldol reaction (run 1 *vs.* 2). The yield of **17b** was dramatically improved by the addition of a catalytic amount (0.3 eq) of Ph_3P (run 7 *vs.* 8). Eventually, the carbonate **17b** was obtained in 90% yield by stirring of **16b** with 10 mol% of $PdCl_2(Ph_3P)_2$, 3 eq of Cs_2CO_3, and 0.3 eq of Ph_3P in boiling benzene for 6 h (run 10). These reaction conditions of run 10 were also applicable to **16a** and **16c**, and the desired products **17a** and **17c** were readily isolated in 91 and 86% yields, respectively (run 11, 13). The addition of Ph_3P was pivotal, and without this the yield of **17a** dropped to only 6% accompanied by by-products **18** and the pyridone **15a** (run 12). It must be noted that the separation of the product is much easier than that in the conventionally employed Kuwajima conditions, because Bu_3SnF which causes considerable trouble at the separation step is not used under these novel conditions. Furthermore, the novel method requires no activation of the acetyl group as silyl enol ether prior to the palladium-catalyzed cyclization.

iv) On the Reaction Mechanism of the Improved Cyclization Conditions: The most probable mechanisms for the above novel palladium-catalyzed intramolecular cyclization reaction are shown in Chart 5, giving the run 7 in Table 1 as an example. After the oxidative addition of Pd(0) to the substrate **16b**, the acetyl group is partially deprotonated with Cs_2CO_3 to form an enolate **21** even in a less polar solvent, benzene, toluene, or xylene. Two pathways are possible from the intermediate **21**. Nucleophilic attack of the enolate on Pd(II) leads **21** to a palladacycle **22**, and the Heck type of insertion of the enolic olefin group to the aryl-Pd(II) bond affords a tricyclic hemiacetal-type compound **23**. Pd(0) is reductively eliminated from **22** to give a phenol **24**, which is converted to the desired product **17b** by the subsequent treatment with ClCOOMe–NaH. Coexisting starting material **16b** can behave as a trifluoromethanesulfonating agent, and by-product **19** is partially formed from **24** in the presence of Cs_2CO_3. On the other hand, a release of cesium hydroxide from **23** affords aromatic compound **25**, which is in turn transformed to the by-product **19**. Furthermore, the positional exchange of the palladium takes place from **23** to give **27** by way of **26**. Elimination of **28** from **27** furnishes deoxygenated product **20**. Usual reductive elimination from **23**, of course, gives cesium salt of **24**. The Ph_3P would play a role not only to reduce Pd(II) to Pd(0) but to increase the spatial congestion around the palladium of **21**, preventing the cyclization course toward **23** which is more congested than **22**.

v) Preparation of **17e** from **17c**: For the preparation of **17e**, the phenol protecting group of **17c** was first changed from methyl carbonate to benzyl ether **29**. Stirring of **17c** in MeOH–Et_3N (10 : 1) at room temperature (25 °C) readily afforded deprotected phenol, and after evaporation of volatile materials, introduction of benzyl group was effected under conditions A, B or C (Chart 6). The Mitsunobu reaction con-

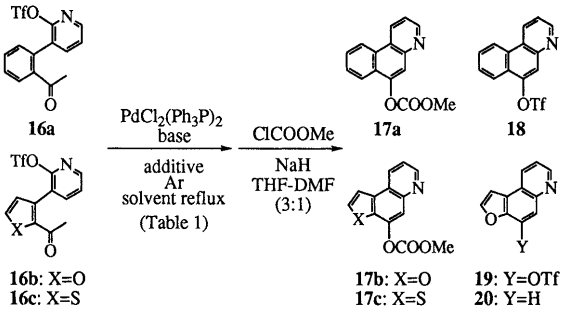

Chart 4

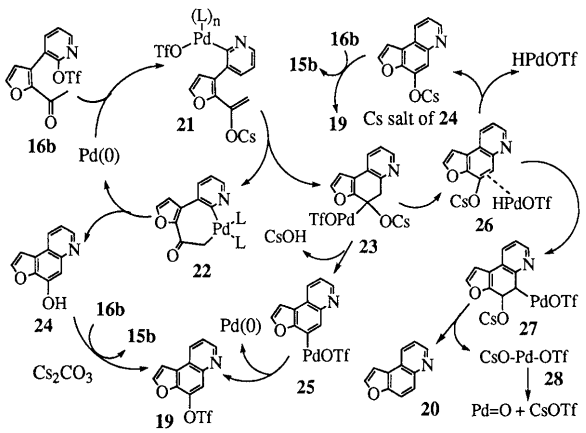

Chart 5

Table 1. Improved Palladium-Catalyzed Cyclization of **16a**, **b**, and **c** to Form **17a**, **b**, and **c**

Run	Starting material	Pd cat. (mol %)	Conditions				Product yield (%)		
			Base (eq)	Additive (eq)	Solvent	Time (h)	**17**	By-product	Recovery of **16**
1	**16b**	5	NaH (1.5)	—	THF	4	—	—	—
2	**16b**	5	NaH (3)	—	Xylene	16.5	**b**: 9	**19**: 11, **20**: 6, **15b**: 13	19
3	**16b**	20	NaH (3)	—	Xylene	5.5	**b**: 50	—	—
4	**16b**	5	*t*-BuOK (3)	—	Toluene	16	**b**: 1	**19**: 3	5
5	**16b**	5	K_2CO_3 (3)	—	THF	18.5	—	**19**: 6, **20**: 3	63
6	**16b**	5	K_2CO_3 (3)	—	Xylene	18	—	**19**: 18, **20**: 3, **15b**: 16	25
7	**16b**	5	CS_2CO_3 (3)	—	Xylene	4.5	**b**: 26	**19**: 6, **20**: 2	6
8	**16b**	5	CS_2CO_3 (3)	Ph_3P (0.3)	Xylene	5	**b**: 57	—	—
9	**16b**	10	CS_2CO_3 (3)	Ph_3P (0.3)	Xylene	2	**b**: 88	—	—
⑩	**16b**	10	CS_2CO_3 (3)	Ph_3P (0.3)	Benzene	6	**b**: 90	—	—
⑪	**16a**	10	CS_2CO_3 (3)	Ph_3P (0.3)	Benzene	1.5	**a**: 91	—	—
12	**16a**	10	CS_2CO_3 (3)	—	Benzene	5	**a**: 6	**18**: 16, **15a**: 38	—
⑬	**16c**	10	CS_2CO_3 (3)	Ph_3P (0.3)	Benzene	3	**c**: 86	—	—

ditions[24] A [benzyl alcohol (BnOH), diethyl azodicarboxylate (DEAD), Ph_3P in THF] gave desired **29** in 79% along with 5-benzyl by-product **30** and 5,5-dibenzyl-4-oxo by-product **31** in 11% and 1% respective yields. The yield of **29** was slightly improved to 86% employing conditions B [BnOH, 1,1′-(azodicarbonyl)dipiperidine (ADDP), tributylphosphine (Bu_3P)[25] in THF)]. These by-products were, however, increased under the basic conditions C [benzyl bromide (BnBr), K_2CO_3 in DMF]. After treatment of **29** with lithium diisopropylamide (LDA) in THF at −80——−75 °C, resulting lithium salt was trapped with 3,4,5-trimethoxybenzaldehyde to yield alcohol **32** in 76%. The benzylic alcohol **32** was easily reduced to the desired **17e** with triethylsilane (Et_3SiH) and $BF_3 \cdot OEt_2$ in CH_2Cl_2 at 0 °C in 92% yield.

Synthesis of DSA A-Ring Analogs 9a—e from 17a—e With the requisite quinolinol derivatives **17a—e** in hand, we then carried out further transformation to DSA A-ring analogs **9a—e** according to the reported procedure (Chart 7). Thus the heteroaromatic intermediates **17a—e** were subjected to reduction with sodium borohydride ($NaBH_4$) in the presence of ClCOOMe in THF–2-propanol (1 : 2) at room temperature to give a mixture of dihydroderivatives **33a—e** and **34a—e**. Without further purification due to their slight instability, these were oxidized with a catalytic amount of osmium tetroxide and trimethylamine *N*-oxide in acetone–H_2O (9 : 1) at room temperature. The resulting mixture of vicinal diol derivatives was then treated with Et_3SiH and $BF_3 \cdot OEt_2$ in CH_2Cl_2 to execute reductive cleavage of the hydroxy groups located at the benzylic and the α-carbamate positions. Desired **35a—e** were obtained in modest to good overall yields calculated from **17a—e** along with a slight amount of tetrahydro derivatives **36a—e**. The mechanism for the formation of the by-products **36a—e** through hydroboration and subsequent air oxidation reaction of **33a—e** or **34a—e** was reported previously.[10b] Methanesulfonates **37a—e** were obtained in high yields from **35a—e** in the usual way with methanesulfonyl chloride (MsCl) and Et_3N in CH_2Cl_2 at 0 °C. The compounds **37a—d** were readily cyclized to the cyclopropanoindolinone derivatives **38a—d** in high yields with K_2CO_3 in MeOH at room temperature. Among them, the compound **38a** was reported earlier by Boger *et al.*[26] For **37e**, hydrogenolysis of the benzyl protecting group on palladium hydroxide in MeOH–DME (5 : 1) was executed prior to the cyclization. Unexpectedly, the benzyl group strongly resisted the hydrogenolysis, and **38e** was obtained in 64% yield accompanied by recovered **37e** in 32% even after hydrogenolysis for 52 h under the atmospheric pressure of hydrogen. The final step, coupling of **38a—e** with imidazolide **39**[9] was carried out with K_2CO_3 in DMF at ambient temperature to complete the synthesis of DSA A-ring analogs (±)-**9a—e**. The low yield of (±)-**9b** is attributable to instability of the product. The above K_2CO_3 method[10] was found to be more conveniently applicable in these cases in better yields than the NaH in DMF method[9] employed in our first route toward DSA.

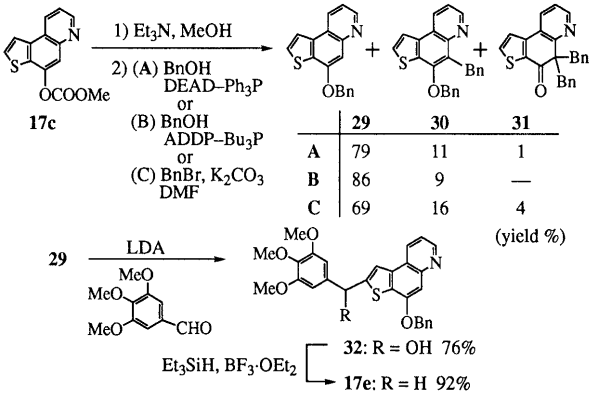

Chart 6

Summary Five DSA A-ring analogs (±)-**9a—e** were synthesized modifying our second synthetic route of DSA. We encountered a problem at the phenol forming step of securing **17a,b** from **16a,b** with the conventional palladium-catalyzed arylation reaction of enol silyl ether in the presence of Bu_3SnF and LiCl (the Kuwajima conditions). The arylation method lacks the generality affording **17a**, **17b** in low

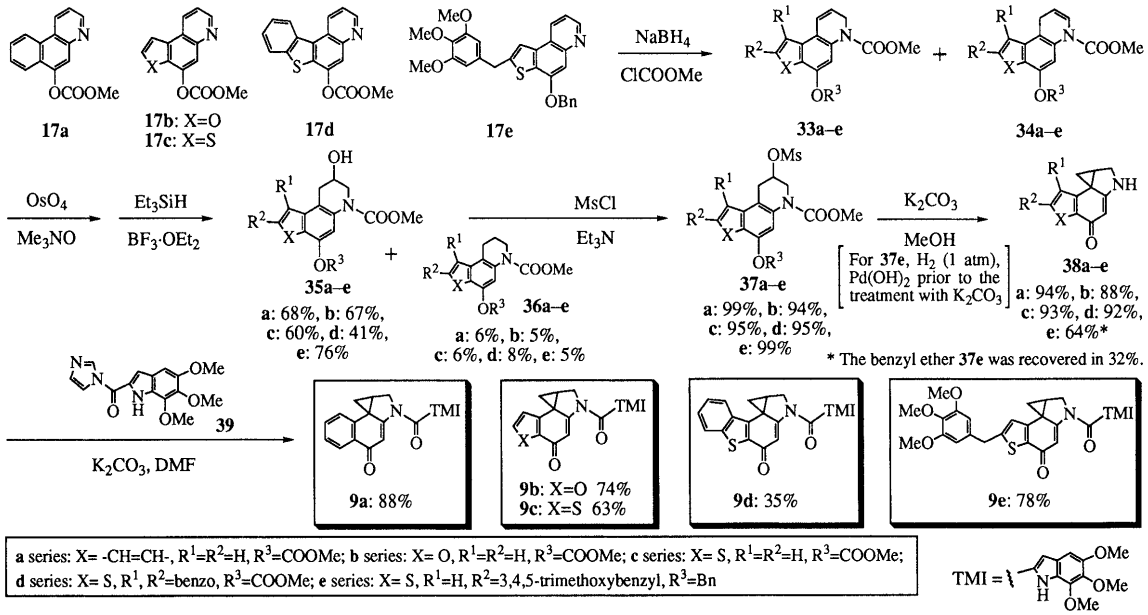

Chart 7

yields of 24% and 27%, respectively. This difficulty was, however, overcome by devising a more convenient method: simple heating of **16a—c** in benzene in the presence of $PdCl_2(Ph_3P)_2$ (10 mol%), Cs_2CO_3 (3 eq), and Ph_3P (0.3 eq) gave **17a—c** in 86—91% yields. The analogs (±)-**9a—e** were readily synthesized from the intermediates **17a—e** almost according to the reported route.

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 determined on a Hitachi 215 spectrophotometer. ^{1}H-NMR spectra were obtained on a Varian EM 390 (90 MHz) spectrometer in $CDCl_3$ unless otherwise specified with tetramethylsilane (TMS) 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 workup 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.

1-(3-Bromo-2-furanyl)ethanone (12b) A CH_2Cl_2 (20 ml) solution of 3-bromofuran (2.449 g, 16.7 mmol) was cooled to 0 °C, and Ac_2O (4.71 ml, 50.0 mmol) and $BF_3 \cdot OEt_2$ (2.25 ml, 18.3 mmol) were added to this. The mixture was stirred at 0 °C for 15 min, and at 21 °C for 4 h. The reaction was quenched by addition of H_2O and the whole was extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$–H_2O and then treated as usual to give a residue (4.54 g). Purification by silica gel column chromatography [hexane–EtOAc (19 : 1)] afforded 1-(4-bromo-2-furanyl)ethanone (0.320 g, 10%) as a less polar isomer and **12b** (2.406 g, 76%) as a more polar isomer. **12b**: Slightly yellow oil. GC-HRMS Calcd for $C_6H_5BrO_2$: 189.9453 and 187.9473. Found: 189.9459 and 187.9485. GC-MS *m/z*: 190, 188 (M^+, 50, 52); 175, 173 (100, 100); 148, 146 (4, 4); 147, 145 (4, 4); 119, 117 (14, 14); 84 (12). IR ($CHCl_3$): 1676 cm^{-1}. ^{1}H-NMR δ: 2.50 (3H, s), 6.63 (1H, d, J=2 Hz), 7.52 (1H, d, J=2 Hz). 1-(4-Bromo-2-furanyl)ethanone: Colorless scales, mp 65—66 °C (hexane). *Anal.* Calcd for $C_6H_5BrO_2$: C, 38.13; H, 2.67; Br, 42.28. Found: C, 37.87; H, 2.83; Br, 42.04. GC-HRMS Calcd for $C_6H_5BrO_2$: 189.9453 and 187.9473. Found: 189.9460 and 187.9498. GC-MS *m/z*: 190, 188 (M^+, 40, 42); 175, 173 (92, 100); 147, 145 (6, 4); 119, 117 (19, 22); 84 (31). IR (KBr): 1660 cm^{-1}. ^{1}H-NMR δ: 2.46 (3H, s), 7.17 (1H, s), 7.58 (1H, s).

Crude 1-(3-Bromo-2-thienyl)ethanone (12c) $AlCl_3$ (43.9 g, 0.330 mol) was added over 20 min to a cooled (−20 °C) solution of 3-bromothiophene (17.93 g, 0.110 mol) and Ac_2O (27.4 ml, 0.220 mol) in CH_2Cl_2 (200 ml). The mixture was vigorously stirred at this temperature for 30 min and at 0 °C for 2 h. The resulting mixture was poured into ice-water and the whole was extracted with CH_2Cl_2. After washing with saturated $NaHCO_3$–H_2O and usual workup, the residue was distilled to give recovered 3-bromothiophene [1.43 g, 8%, bp 43—46 °C (10 mmHg)] and crude **12c** [17.82 g, 79%, bp 121—124 °C (10 mmHg)]. The latter consists of **12c** and 1-(4-bromo-2-thienyl)ethanone in a ratio of 16 : 1. Crude **12c**: Colorless oil. GC-HRMS Calcd for C_6H_5BrOS: 205.9225 and 203.9245. Found: 205.9237 and 203.9265. GC-MS *m/z*: 206, 204 (M^+, 38, 36); 191, 189 (100, 96); 163, 161 (5, 5); 82 (35); 45 (29); 43 (46). IR ($CHCl_3$): 1658 cm^{-1}. ^{1}H-NMR δ: 2.67 (3H, s), 7.07 (1H, d, J=5.5 Hz), 7.50 (1H, d, J=5.5 Hz).

1-(3-Bromo-2-benzo[*b*]thienyl)ethanone (12d) In a similar way to the preparation of **12c**, 3-bromobenzo[*b*]thiophene (226 mg, 1.06 mmol) in CH_2Cl_2 (8 ml) was stirred with Ac_2O (0.30 ml, 3.18 mmol) and $AlCl_3$ (848 mg, 6.38 mmol) at 0—27 °C for 6 h. After the same workup as for **12c**, the residue was purified by PTLC [hexane–CH_2Cl_2 (3 : 1)] to give **12d** (210 mg, 78%) as colorless needles, mp 99.5—100 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{10}H_7BrOS$: C, 47.08; H, 2.77; Br, 31.32; S, 12.57. Found: C, 46.67; H, 2.95; Br, 31.55; S, 12.45. GC-HRMS Calcd for $C_{10}H_7BrOS$: 255.9381 and 253.9401. Found: 255.9406 and 253.9395. GC-MS *m/z*: 256, 254 (M^+, 57, 53); 241, 239 (100, 93); 213, 211 (23, 20); 132 (72); 93 (28); 43 (63). IR (KBr): 1635 cm^{-1}. ^{1}H-NMR δ: 2.76 (3H, s), 7.25—7.57 (2H, m), 7.62—7.97 (2H, m).

Stille Coupling Reaction of 12a—d with 13 to Form 14a—d Preparation of 1-[3-(2-fluoro-3-pyridinyl)-2-furanyl]ethanone (**14b**) is described as a typical example. A toluene solution of **12b** (144 mg, 0.762 mmol), **13** (239 mg, 0.916 mmol), and $PdCl_2(Ph_3P)_2$ (16 mg, 0.023 mmol) was stirred under reflux for 14 h. After the mixture had cooled, saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual workup and separation by PTLC [hexane–EtOAc (6 : 1)] afforded **14b** (125 mg, 80%) as colorless scales, mp 75.5—76.5 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{11}H_8FNO_2$: C, 64.39; H, 3.93; N, 6.83. Found: C, 64.58; H, 4.00; N, 6.75. GC-HRMS Calcd for $C_{11}H_8FNO_2$: 205.0539. Found: 205.0522. GC-MS *m/z*: 205 (M^+, 48), 190 (100), 134 (27), 107 (15). IR (KBr): 1668 cm^{-1}. ^{1}H-NMR δ: 2.51 (3H, s), 6.73 (1H, dd, J=2, 1.5 Hz), 7.22 (1H, ddd, J=7.5, 5, 1.5 Hz), 7.58 (1H, d, J=1.5 Hz), 8.06 (1H, ddd, J=9.5, 7.5, 2 Hz), 8.21 (1H, ddd, J=5, 2, 1.5 Hz).

Similarly, on treatment of **12a** (317 mg, 1.59 mmol) with **13** (456 mg, 1.75 mmol) and $PdCl_2(Ph_3P)_2$ (34 mg, 0.048 mmol) in boiling toluene (10 ml) for 8 h, 1-[2-(2-fluoro-3-pyridinyl)phenyl]ethanone (**14a**, 228 mg, 67%) was obtained as a colorless syrup. HRMS Calcd for $C_{13}H_{10}FNO$: 215.0746. Found: 215.0748. MS *m/z*: 215 (M^+, 35), 200 (100), 172 (40), 145 (17), 43 (41). IR (neat): 1692 cm^{-1}. ^{1}H-NMR δ: 2.46 (3H, s), 7.14—7.90 (6H, m), 8.13—8.34 (1H, m).

Similarly, on treatment of the crude **12c** (171 mg, 0.834 mmol) with **13** (189 mg, 0.724 mmol) and $PdCl_2(Ph_3P)_2$ (15 mg, 0.021 mmol) in toluene (5 ml) at 125—130 °C (sealed tube) for 5 h, 1-[3-(2-fluoro-3-pyridinyl)-2-thienyl]ethanone (**14c**, 118 mg, 74% from **13**) was obtained as colorless prisms, mp 83—84.5 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{11}H_8FNOS$: C, 59.71; H, 3.64; N, 6.33. Found: C, 59.61; H, 3.77; N, 6.35. GC-HRMS Calcd for $C_{11}H_8FNOS$: 221.0310. Found: 221.0309. GC-MS *m/z*: 221 (M^+, 39), 206 (100), 202 (7), 134 (17), 107 (9), 43 (24). IR (KBr): 1652 cm^{-1}. ^{1}H-NMR δ: 2.36 (3H, s), 7.08 (1H, d, J=5.5 Hz), 7.23 (1H, ddd, J=7.5, 5, 2 Hz), 7.58 (1H, d, J=5.5 Hz), 7.76 (1H, ddd, J=9, 7.5, 2 Hz), 8.23 (1H, ddd, J=5, 2, 1 Hz).

Similarly, on treatment of **12d** (65 mg, 0.255 mmol) with **13** (73 mg, 0.280 mmol) and $PdCl_2(Ph_3P)_2$ (9 mg, 0.013 mmol) in boiling toluene (5 ml) for 16 h, 1-[3-(2-fluoro-3-pyridinyl)-2-benzo[*b*]thienyl]ethanone (**14d**, 62 mg, 90%) was obtained as colorless prisms, mp 125—126 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{15}H_{10}FNOS$: C, 66.40; H, 3.72; N, 5.16. Found: C, 66.25; H, 3.86; N, 5.19. HRMS Calcd for $C_{15}H_{10}FNOS$: 271.0467. Found: 271.0452. MS *m/z*: 271 (M^+, 76), 256 (100), 228 (25), 209 (15), 184 (27), 43 (46). IR (KBr): 1664 cm^{-1}. ^{1}H-NMR δ: 2.37 (3H, s), 7.14—7.63 (4H, m), 7.81 (1H, ddd, J=9.5, 7, 2 Hz), *ca.* 7.81—8.02 (1H, m), 8.37 (1H, ddd, J=5, 2, 1 Hz).

Hydrolysis of 14a—d with HCl to Form 15a—d Preparation of 3-(2-acetylphenyl)-2(1*H*)-pyridinone (**15a**) from **14a** is described as representative. A solution of **14a** (169 mg, 0.786 mmol) in DME (2 ml) and 10% HCl–H_2O (2 ml) was stirred at 55—60 °C for 2 h. After the mixture had cooled, saturated $NaHCO_3$–H_2O and NaCl powder were added and the whole was extracted with 10% MeOH–CH_2Cl_2. Usual workup afforded a crystalline residue, which was recrystallized from MeOH–CH_2Cl_2 to give **15a** (162 mg, 97%) as colorless prisms, mp 195—195.5 °C. *Anal.* Calcd for $C_{13}H_{11}NO_2$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.28; H, 5.25; N, 6.67. HRMS Calcd for $C_{13}H_{11}NO_2$: 213.0789. Found: 213.0782. MS *m/z*: 213 (M^+, 14), 198 (86), 195 (23), 170 (100), 115 (32), 43 (23). IR (KBr): 1679, 1640 cm^{-1}. ^{1}H-NMR δ: 2.48 (3H, s), 6.31 (1H, dd, J=7, 7 Hz), 7.11—7.75 (6H, m), 12.78 (1H, br s, NH).

In the same way, 3-(2-acetyl-3-furanyl)-2(1*H*)-pyridinone (**15b**, 86 mg, 90%) was obtained from **14b** (96 mg, 0.468 mmol) as colorless needles, mp 236—237 °C (MeOH–CH_2Cl_2). *Anal.* Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.90; H, 4.43; N, 6.86. HRMS Calcd for $C_{11}H_9NO_3$: 203.0582. Found: 203.0584. MS *m/z*: 203 (M^+, 64), 188 (100), 160 (28), 132 (41), 104 (35), 44 (65). IR (KBr): 1675, 1653, 1617 cm^{-1}. ^{1}H-NMR (10% CD_3OD–$CDCl_3$) δ: 2.50 (3H, s), 6.37 (1H, dd, J=7, 6.5 Hz), 6.90 (1H, d, J=1.5 Hz), 7.37 (1H, dd, J=6.5, 2 Hz), 7.58 (1H, d, J=1.5 Hz), 7.87 (1H, dd, J=7, 2 Hz).

In the same way, 3-(2-acetyl-3-thienyl)-2(1*H*)-pyridinone (**15c**, 77.5 mg, 93%) was obtained from **14c** (84 mg, 0.380 mmol) as colorless prisms, mp 208—209.5 °C (MeOH–CH_2Cl_2). *Anal.* Calcd for $C_{11}H_9NO_2S$: C, 60.25; H, 4.14; N, 6.39. Found: C, 60.21; H, 4.25; N, 6.42. HRMS Calcd for $C_{11}H_9NO_2S$: 219.0353. Found: 219.0344. MS *m/z*: 219 (M^+, 27), 204 (100), 201 (38), 176 (26), 121 (14), 104 (14), 45 (20), 43 (35). IR (KBr): 1659, 1639, 1617 cm^{-1}. ^{1}H-NMR (10% CD_3OD–$CDCl_3$) δ: 2.41 (3H, s), 6.36 (1H, dd, J=6.5, 6.5 Hz), 7.09 (1H, d, J=5 Hz), 7.37 (1H, dd, J=6.5, 1.5 Hz), 7.51 (1H, dd, J=6.5, 1.5 Hz), 7.56 (1H, d, J=5 Hz).

In the same way, 3-(2-acetyl-3-benzo[*b*]thienyl)-2(1*H*)-pyridinone (**15d**, 125 mg, 93%) was obtained from **14d** (135 mg, 0.498 mmol) as colorless needles, mp 280—283 °C (dec., MeOH–CH_2Cl_2). *Anal.* Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20. Found: C, 66.34; H, 4.30; N, 5.15. HRMS Calcd for $C_{15}H_{11}NO_2S$: 269.0510. Found: 269.0507. MS *m/z*: 269 (M^+, 67), 254 (93), 251 (26), 226 (100), 198 (20), 171 (31), 154 (25), 43

(75). IR (KBr): 1656, 1637, 1611 cm^{-1}. ^{1}H-NMR (10% CD_3OD–$CDCl_3$) δ: 2.46 (3H, s), 6.45 (1H, dd, J=7, 7 Hz), 7.21—7.63 (5H, m), 7.78—7.94 (1H, m).

Preparation of the Triflates 16a—d from 15a—d Formation of 3-(2-acetylphenyl)-2-pyridinyl trifluoromethanesulfonate (**16a**) is described as representative. Tf_2O (97 μl, 0.577 mmol) was added to a solution of **15a** (49 mg, 0.230 mmol) and pyridine (0.30 ml, 3.71 mmol) in CH_2Cl_2 (2.7 ml) at 0 °C. After stirring was continued at that temperature for 5 min and at 19 °C for 2 h, the reaction was quenched by addition of saturated $NaHCO_3$–H_2O. Extraction with CH_2Cl_2 followed by usual workup and separation by PTLC [hexane–EtOAc (3 : 1)] afforded **16a** (76 mg, 96%) as a colorless syrup. MS *m/z*: 196 (M^+–OTf, 100), 69 (24), 43 (25). IR (neat): 1693 cm^{-1}. ^{1}H-NMR δ: 2.50 (3H, s), 8.33 (1H, dd, J=5, 2 Hz), 7.23—7.99 (6H, m).

In the same way, **15b** (34 mg, 0.167 mmol) was allowed to react with Tf_2O (71 μl, 0.422 mmol) in CH_2Cl_2–pyridine (9 : 1, 3 ml) to afford 3-(2-acetyl-3-furanyl)-2-pyridinyl trifluoromethanesulfonate (**16b**, 55 mg, 98%) as colorless prisms, mp 60.5—61 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{12}H_8F_3NO_5S$: C, 42.99; H, 2.41; N, 4.18. Found: C, 43.00; H, 2.46; N, 4.24. GC-MS *m/z*: 186 (M^+–OTf, 100), 160 (11), 69 (24), 44 (55). IR (KBr): 1675 cm^{-1}. ^{1}H-NMR δ: 2.53 (3H, s), 6.74 (1H, d, J=2 Hz), 7.48 (1H, dd, J=8, 5 Hz), 7.70 (1H, d, J=2 Hz), 8.08 (1H, dd, J=8, 2 Hz), 8.46 (1H, dd, J=5, 2 Hz).

In the same way, **15c** (69 mg, 0.315 mmol) was allowed to react with Tf_2O (132 μl, 0.785 mmol) in CH_2Cl_2–pyridine (9 : 1, 3 ml) to afford 3-(2-acetyl-3-thienyl)-2-pyridinyl trifluoromethanesulfonate (**16c**, 108 mg, 98%) as colorless prisms, mp 64—65 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{12}H_8F_3NO_4S_2$: C, 41.02; H, 2.30; N, 3.99. Found: C, 41.02; H, 2.43; N, 4.21. GC-MS *m/z*: 202 (M^+–OTf, 100), 176 (7), 69 (21), 43 (36). IR (KBr): 1662 cm^{-1}. ^{1}H-NMR δ: 2.38 (3H, s), 7.06 (1H, d, J=5 Hz), 7.39 (1H, dd, J=7.5, 5 Hz), 7.60 (1H, d, J=5 Hz), 7.83 (1H, dd, J=7.5, 2 Hz), 8.34 (1H, dd, J=5, 2 Hz).

In the same way, **15d** (63 mg, 0.234 mmol) was allowed to react with Tf_2O (99 μl, 0.589 mmol) in CH_2Cl_2–pyridine (9 : 1, 3 ml) to afford 3-(2-acetyl-3-benzo[*b*]thienyl)-2-pyridinyl trifluoromethanesulfonate (**16d**, 90 mg, 96%) as a colorless syrup. HRMS Calcd for $C_{16}H_{10}F_3NO_4S_2$: 401.0003. Found: 400.9996. MS *m/z*: 401 (M^+, 2), 252 (100), 226 (11), 69 (20), 43 (38). IR ($CHCl_3$): 1676 cm^{-1}. ^{1}H-NMR δ: 2.44 (3H, s), 7.28—7.64 (3H, m), 7.50 (1H, dd, J=7.5, 4.5 Hz), *ca.* 7.80—8.01 (1H, m), 7.87 (1H, dd, J=7.5, 2 Hz), 8.49 (1H, dd, J=4.5, 2 Hz).

Palladium-Catalyzed Cyclization of 16a—d to Form 17a—d by the Conventional Method (Kuwajima Conditions) Preparation of Furo[3,2-*f*]quinoline-4-yl methyl carbonate (**17b**) is described as a typical example. A CH_2Cl_2 (3 ml) solution of **16b** (51 mg, 0.512 mmol) and Et_3N (85 μl, 0.611 mmol) was stirred with TBDMSOTf (87 μl, 0.379 mmol) under an Ar atmosphere at 0 °C for 1 h. Saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual workup left a residue (78 mg) which was dissolved in xylene (4 ml). $PdCl_2(Ph_3P)_2$ (5.5 mg, 7.83 μmol), Bu_3SnF (57 mg, 0.184 mmol), and LiCl (20 mg, 0.471 mmol) were added to this, and the resulting mixture was refluxed under an Ar atmosphere for 1 h. After the mixture had cooled in an ice bath, MeOH (4.5 ml) and 10% HCl–H_2O (0.5 ml) were added, and then the whole was stirred at 0 °C for 5 min and at 21 °C for 30 min. Saturated $NaHCO_3$–H_2O was added and the aqueous layer was saturated with NaCl. The whole was extracted with 10% MeOH–CH_2Cl_2 and then the organic layer was treated as usual. The residue was roughly purified by PTLC [benzene–EtOAc (5 : 1)] to give recovered **16b** (28 mg, 55%) and a crude phenolic material (39 mg). The crude phenol was dissolved in THF (3 ml) and DME (1 ml) and the solution was cooled at −18 °C. NaH (60% dispersion in mineral oil, 40 mg, 1.00 mmol) was added to this under an Ar atmosphere and the mixture was stirred for 5 min. A solution of ClCOOMe (77 μl, 1.00 mmol) in THF (1 ml) was added and the resulting mixture was stirred at −18—0 °C for 1.5 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual workup and separation by PTLC [benzene–EtOAc (2 : 1)] afforded **17b** (10 mg, 27%). ^{1}H-NMR of the crude silyl enol ether δ: −0.04 (6H, s), 0.72 (9H, s), 4.45 (1H, d, J=1.5 Hz), 4.84 (1H, d, J=1.5 Hz), 6.45 (1H, d, J=1.5 Hz), 7.34 (1H, dd, J=7.5, 4.5 Hz), 7.41 (1H, d, J=1.5 Hz), 7.85 (1H, dd, J=7.5, 21 Hz), 8.28 (1H, dd, J=4.5, 2 Hz). **17b**: Slightly yellow prisms, mp 69—70 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.05; H, 3.83; N, 5.90. HRMS Calcd for $C_{13}H_9NO_4$: 243.0531. Found: 243.0513. MS *m/z*: 243 (M^+, 50), 199 (42), 169 (25), 156 (100), 101 (22), 59 (24). IR ($CHCl_3$): 1772 cm^{-1}. ^{1}H-NMR δ: 4.01 (3H, s), 7.28 (1H, d, J=2 Hz), 7.48 (1H, dd, J=8.5, 4.5 Hz), 7.86 (1H, d, J=2 Hz), 7.90 (1H, s), 8.44 (1H, br d, J=8.5 Hz), 8.96 (1H, dd, J=4.5, 1.5 Hz).

In a similar way, benzo[*f*]quinolin-6-yl methyl carbonate (**17a**, 14 mg, 24%), along with recovered **16a** (5 mg, 7%), was obtained from **16a** (73 mg, 0.212 mmol) after separation by PTLC [hexane–CH_2Cl_2 (1 : 4)]. ^{1}H-NMR of the crude silyl enol ether δ: 0.03 (6H, s), 0.74 (9H, s), 4.29 (1H, d, J=1.5 Hz), 4.38 (1H, d, J=1.5 Hz), 7.15—7.63 (5H, m), 7.86 (1H, dd, J=7, 2 Hz), 8.32 (1H, dd, J=5, 2 Hz). **17a**: Colorless prisms, mp 107—108 °C (Et_2O–hexane). *Anal.* Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 71.08; H, 4.56; N, 5.49. HRMS Calcd for $C_{15}H_{11}NO_3$: 253.0738. Found: 253.0736. MS *m/z*: 253 (M^+, 44), 209 (38), 166 (100), 139 (36), 59 (30). IR (KBr): 1750 cm^{-1}. ^{1}H-NMR δ: 3.98 (3H, s), 7.46 (1H, dd, J=8.5, 4.5 Hz), 7.61—7.81 (2H, m), 7.91 (1H, s), 7.98—8.21 (1H, m), 8.44—8.69 (1H, m), 8.83 (1H, br d, J=8.5 Hz), 8.92 (1H, dd, J=4.5, 1.5 Hz).

In a similar way, methyl thieno[3,2-*f*]quinolin-4-yl carbonate (**17c**, 342 mg, 75%) was obtained from **16c** (617 mg, 1.76 mmol) after separation by PTLC [benzene–EtOAc (5 : 1)]. ^{1}H-NMR of the crude silyl enol ether δ: 0.10 (6H, s), 0.84 (9H, s), 4.27 (1H, d, J=2 Hz), 4.31 (1H, d, J=2 Hz), 6.93 (1H, d, J=5.5 Hz), 7.24 (1H, d, J=5.5 Hz), 7.34 (1H, dd, J=7.5, 5 Hz), 7.84 (1H, dd, J=7.5, 2 Hz), 8.29 (1H, dd, J=5, 2 Hz). **17c**: Slightly yellow prisms, mp 122—123 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50; N, 5.40. Found: C, 60.00; H, 3.68; N, 5.42. GC-HRMS Calcd for $C_{13}H_9NO_3S$: 259.0303. Found: 259.0312. GC-MS *m/z*: 259 (M^+, 45), 215 (31), 186 (14), 172 (100), 145 (15), 59 (19). IR (KBr): 1759 cm^{-1}. ^{1}H-NMR δ: 3.99 (3H, s), 7.49 (1H, dd, J=8.5, 4.5 Hz), 7.67 (1H, d, J=5.5 Hz), 7.95 (1H, s), 7.96 (1H, d, J=5.5 Hz), 8.58 (1H, dd, J=8.5, 2 Hz), 8.93 (1H, dd, J=4.5, 2 Hz).

In a similar way, [1]benzothieno[3,2-*f*]quinolin-6-yl methyl carbonate (**17d**, 44 mg, 80%) was obtained from **16d** (71 mg, 0.177 mmol) after separation by PTLC [benzene–EtOAc (3 : 1)]. ^{1}H-NMR of the crude silyl enol ether δ: 0.12 (3H, s), 0.16 (3H, s), 0.76 (9H, s), 4.22 (1H, d, J=2.5 Hz), 4.30 (1H, d, J=2.5 Hz), *ca.* 6.98—7.35 (3H, m), 7.30 (1H, dd, J=7.5, 5 Hz), *ca.* 7.50—7.74 (1H, m), 7.74 (1H, dd, J=7.5, 2 Hz), 8.26 (1H, dd, J=5, 2 Hz). **17d**: Slightly yellow needles, mp 180.5—181.5 °C (dec., CH_2Cl_2–hexane). *Anal.* Calcd for $C_{17}H_{11}NO_3S$: C, 66.00; H, 3.58; N, 4.53. Found: C, 66.02; H, 3.73; N, 4.62. HRMS Calcd for $C_{17}H_{11}NO_3S$: 309.0459. Found: 309.0448. MS *m/z*: 309 (M^+, 50), 265 (27), 222 (100), 195 (11), 59 (19). IR (KBr): 1759 cm^{-1}. ^{1}H-NMR δ: 4.01 (3H, s), 7.38—7.69 (3H, m), 7.86—8.11 (1H, m), 8.11 (1H, s), 8.56—8.79 (1H, m), 8.96 (1H, dd, J=4.5, 1.5 Hz), 9.21 (1H, br d, J=8.5 Hz).

Improved Palladium-Catalyzed Cyclization of 16a—c to Form 17a—c Among runs 10, 11, and 13 of Table 1 carried out under the optimized conditions, preparation of **17b** (run 10) is described as a typical example. A slurry of **16b** (64 mg, 0.191 mmol), $PdCl_2(Ph_3P)_2$ (13.5 mg, 0.019 mmol), Ph_3P (15 mg, 0.057 mmol), and Cs_2CO_3 (187 mg, 0.574 mmol) in benzene (4 ml) was refluxed with stirring under an Ar atmosphere for 6 h. After the mixture had cooled in an ice bath, citric acid monohydrate (121 mg, 0.630 mmol) and H_2O (5 ml) were added and the whole was stirred for 5 min. The whole was adjusted to pH 6—7 by addition of several drops of saturated $NaHCO_3$–H_2O, then thoroughly extracted with 10% MeOH–CH_2Cl_2. Usual workup gave a crystalline material (72 mg) which was then dissolved in THF (3 ml) and DMF (1 ml). NaH (60% dispersion in mineral oil, 38 mg, 0.950 mmol) was added to the solution at −18 °C under an Ar atmosphere and the mixture was stirred at that temperature for 15 min. A THF (1 ml) solution of ClCOOMe (74 μl, 0.958 mmol) was added and the whole was stirred at −18—0 °C for 1 h. The reaction was quenched by addition of saturated NH_4Cl—H_2O and the whole was extracted with CH_2Cl_2. Usual workup and purification by PTLC [benzene–EtOAc (2 : 1)] afforded **17b** (42 mg, 90%) as slightly yellow prisms, mp 69—70 °C (CH_2Cl_2–hexane), whose spectral data were identical with those of the specimen prepared above by the conventional method.

In the same way, **17a** (40 mg, 91%), colorless prisms, mp 107—108 °C (Et_2O–hexane), was obtained from **16a** (60 mg, 0.174 mmol). The spectral data of **17a** were described above.

In the same way, **17c** (43 mg, 86%), slightly yellow prisms, mp 120—122 °C (CH_2Cl_2–hexane), was obtained from **16c** (68 mg, 0.194 mmol). The spectral data of **17c** were described above.

The following by-products were isolated from the other runs carried out under the conditions shown in Table 1. Benzo[*f*]quinolin-6-yl trifluoromethanesulfonate (**18**, Table 1, run 12): Colorless glass. HRMS Calcd for $C_{14}H_8F_3NO_3S$: 327.0176. Found: 327.0166. MS *m/z*: 327 (M^+, 22), 194 (29), 166 (100), 139 (24), 69 (29). ^{1}H-NMR δ: 7.63 (1H, dd, J=8.5, 4.5 Hz), *ca.* 7.71—7.96 (2H, m), 8.04 (1H, s), 8.12—8.37 (1H, m), 8.56—8.82 (1H, m), 8.95 (1H, dd, J=8.5, 1.5 Hz), 9.03 (1H, dd, J=4.5, 1.5 Hz). Furo[3,2-*f*]quinolin-4-yl trifluoromethanesulfonate (**19**, Table 1, runs 2, 4—7): Colorless prisms, mp 59—59.5 °C (hexane). *Anal.* Calcd for $C_{12}H_6F_3NO_4S$: C, 45.43; H, 1.91; N, 4.42. Found: C, 45.34; H, 2.14; N, 4.47. GC-HRMS

Calcd for $C_{12}H_6F_3NO_4S$: 316.9969. Found: 316.9981. GC-MS *m/z*: 317 (M^+, 28), 253 (4), 184 (14), 156 (100), 101 (15), 69 (31). ^{1}H-NMR δ: 7.36 (1H, d, J=2.5 Hz), 7.59 (1H, dd, J=8.5, 4.5 Hz), 7.96 (1H, d, J=2.5 Hz), 8.00 (1H, s), 8.49 (1H, dd, J=8.5, 2 Hz), 9.02 (1H, dd, J=4.5, 2 Hz). Furo[3,2-*f*]quinoline (**20**, Table 1, runs 2, 5—7): Colorless syrup. GC-HRMS Calcd for $C_{11}H_7NO$: 169.0527. Found: 169.0553. GC-MS *m/z*: 169 (M^+, 100), 140 (23), 114 (22), 87 (11), 63 (18). ^{1}H-NMR δ: 7.18 (1H, d, J=2 Hz), 7.38 (1H, dd, J=8.5, 4.5 Hz), 7.76 (1H, d, J=2 Hz), 7.82 (1H, d, J=9 Hz), 8.00 (1H, d, J=9 Hz), 8.35 (1H, dd, J=8.5, 1.5 Hz), 8.85 (1H, dd, J=4.5, 1.5 Hz).

Benzyl Thieno[3,2-*f*]quinolin-4-yl Ether (29) (i) Condition A: Et_3N (0.20 ml, 1.44 mmol) was added to a solution of **17c** (27 mg, 0.104 mmol) in MeOH (2 ml) and the mixture was stirred at 25 °C for 1.5 h. The volatile materials were evaporated off, and benzene (5 ml) was added to the residue. The solvent was again evaporated to dryness to leave a crystalline residue. BnOH (43 μl, 0.416 mmol), Ph_3P (82 mg, 0.313 mmol), and DEAD (49 μl, 0.311 mmol) were added in this order to a cooled (0 °C) slurry of the residue in THF (3 ml) under an Ar atmosphere, and the mixture was stirred at 0 °C for 10 min, then at 21 °C for 1.5 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual workup and purification by PTLC [benzene–EtOAc (14 : 1)] afforded crude **30** (5.5 mg), 5,5-dibenzyl-4,5-dihydrothieno[3,2-*f*]quinolin-4-one (**31**, 0.5 mg, 1%), and crude **29** (69 mg, contaminated with Ph_3PO) in order of increasing polarity. The crude **30** was further separated by PTLC [hexane–CH_2Cl_2 (3 : 2)] to give benzyl 5-benzylthieno[3,2-*f*]quinolin-4-yl ether (**30**, 4.5 mg, 11%). The crude **29** was purified by PTLC [hexane–EtOAc (4 : 1)] to afford **29** (24 mg, 79%) as colorless prisms, mp 116—117 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{18}H_{13}NOS$: C, 74.20; H, 4.50; N, 4.81. Found: C, 73.90; H, 4.47; N, 5.10. HRMS Calcd for $C_{18}H_{13}NOS$: 291.0717. Found: 291.0698. MS *m/z*: 291 (M^+, 24), 262 (4), 186 (5), 172 (8), 91 (100), 65 (11). ^{1}H-NMR δ: 5.39 (2H, s), 7.22—7.63 (7H, m), 7.63 (1H, d, J=5.5 Hz), 7.92 (1H, d, J=5.5 Hz), 8.49 (1H, br d, J=8 Hz), 8.83 (1H, dd, J=4.5, 1.5 Hz). **30**: Colorless prisms, mp 154—155 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{25}H_{19}NOS$: C, 78.71; H, 5.02; N, 3.67. Found: C, 78.72; H, 5.09; N, 3.75. HRMS Calcd for $C_{25}H_{19}NOS$: 381.1186. Found: 381.1192. MS *m/z*: 381 (M^+, 5), 290 (100), 262 (9), 260 (9), 91 (83), 65 (12). ^{1}H-NMR δ: 4.79 (2H, s), 5.08 (2H, s), 7.04—7.60 (6H, m), 7.60 (1H, d, J=5.5 Hz), 7.97 (1H, d, J=5.5 Hz), 8.58 (1H, dd, J=8, 1.5 Hz), 8.97 (1H, dd, J=4.5, 1.5 Hz). **31**: Colorless needles, mp 159—161 °C (CH_2Cl_2–hexane). HRMS Calcd for $C_{25}H_{19}NOS$: 381.1186. Found: 381.1192. MS *m/z*: 381 (M^+, 2), 290 (100), 260 (8), 91 (67), 65 (16). IR (KBr): 1636 cm^{-1}. ^{1}H-NMR δ: 3.65 (2H, d, J=11.5 Hz), 3.81 (2H, d, J=11.5 Hz), 6.54—6.93 (10H, m), 7.04 (1H, d, J=5 Hz), 7.20 (1H, dd, J=8, 4.5 Hz), 7.48 (1H, d, J=5 Hz), 7.63 (1H, dd, J=8, 2 Hz), 8.80 (1H, dd, J=4.5, 2 Hz).

(ii) Condition B: The deprotected phenol prepared from **17c** (30 mg, 0.116 mmol) as above was dissolved in THF (4 ml). BnOH (48 μl, 0.464 mmol), ADDP (88 mg, 0.349 mmol), and Bu_3P (87 μl, 0.350 mmol) were successively added to this at 21 °C under an Ar atmosphere. After stirring for 1 h, the mixture was treated and purified by PTLC as above to yield **29** (29 mg, 86%) and **30** (4 mg, 9%).

(iii) Condition C: The deprotected phenol prepared from **17c** (35 mg, 0.135 mmol) as above was dissolved in DMF (2.5 ml). K_2CO_3 (93 mg, 0.674 mmol) and BnBr (21 μl, 0.177 mmol) were added to this and the mixture was stirred at 22 °C for 14 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with EtOAc. Usual workup and separation by PTLC [hexane–CH_2Cl_2 (2 : 3)] afforded **29** (27 mg, 69%), **30** (8 mg, 16%), and **31** (2 mg, 4%).

4-Benzyloxy-α-(3,4,5-trimethoxyphenyl)thieno[3,2-*f*]quinoline-2-methanol (32) Butyllithium (1.65 M in hexane, 0.33 ml, 0.545 mmol) was added to a THF (2 ml) solution of diisopropylamine (0.12 ml, 0.858 mmol) at −18 °C and the mixture was stirred for 10 min. The mixture was cooled to −81 °C, and a THF (2 ml) solution of **29** (40 mg, 0.137 mmol) was added dropwise to this. The stirring was continued at −81—67 °C for 2 h. The resulting solution was again cooled to −80 °C and 3,4,5-trimethoxybenzaldehyde (67 mg, 0.342 mmol) was added portionwise to this. After the stirring was continued at −80—75 °C for 30 min, saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual workup and purification by PTLC (2% MeOH–CH_2Cl_2) afforded **32** (51 mg, 76%) as colorless fine needles, mp 190—191 °C (MeOH–CH_2Cl_2). *Anal.* Calcd for $C_{28}H_{25}NO_5S$: C, 68.97; H, 5.17; N, 2.87. Found: C, 68.93; H, 5.18; N, 3.00. HRMS Calcd for $C_{28}H_{25}NO_5S$: 487.1452. Found: 487.1447. MS *m/z*: 487 (M^+, 19), 195 (5), 172 (7), 91 (100), 65 (7). IR (KBr): 1600 cm^{-1}. ^{1}H-NMR δ: 3.86 (9H, s), 4.00 (1H, br s, OH), 5.30 (2H, s), 6.13 (1H, s), 6.77 (2H, s), 7.19—7.59 (7H, m), 7.59 (1H, s), 8.33 (1H, br d, J=8.5 Hz), 8.76 (1H, dd, J=4.5, 1.5 Hz).

Benzyl 2-(3,4,5-Trimethoxybenzyl)thieno[3,2-*f*]quinolin-4-yl Ether (17e) $BF_3 \cdot OEt_2$ (35 μl, 0.284 mmol) was added to a solution of **32** (56 mg, 0.115 mmol) and Et_3SiH (64 μl, 0.402 mmol) in CH_2Cl_2 (5 ml) under an Ar atmosphere at 0 °C and the mixture was stirred at that temperature for 30 min. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual workup and separation by PTLC [benzene–EtOAc (4 : 1)] provided **17e** (50 mg, 92%) as a colorless foam. HRMS Calcd for $C_{28}H_{25}NO_4S$: 471.1503. Found: 471.1511. MS *m/z*: 471 (M^+ 29), 366 (4), 352 (4), 185 (4), 181 (3), 91 (100), 65 (7). ^{1}H-NMR δ: 3.85 (9H, s), 4.28 (2H, s), 5.40 (2H, s), 6.57 (2H, s), 7.28—7.75 (7H, m), 7.66 (1H, s), 8.49 (1H, d, J=8 Hz), 8.88 (1H, br d, J=4.5 Hz).

Transformation of 17a—e to 35a—e by Way of 33a—e and 34a—e Preparation of methyl (±)-8,9-dihydro-8-hydroxy-4-[(methoxycarbonyl)oxy]furo[3,2-*f*]quinoline-6(7*H*)-carboxylate (**35b**) from **17b** is described as a typical example. $NaBH_4$ (53 mg, 1.39 mmol) was added to a solution of **17b** (34 mg, 0.140 mmol) and ClCOOMe (108 μl, 1.40 mmol) in 2-PrOH–THF (2 : 1, 4.5 ml) at 0 °C under an Ar atmosphere and the mixture was stirred at 0 °C for 5 min, then at 22 °C for 19 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual workup left a mixture of **33b** and **34b** (50 mg), which was dissolved in acetone–H_2O (9 : 1, 4 ml). $Me_3NO \cdot 2H_2O$ (23 mg, 0.207 mmol) and OsO_4 (1.5 mg, 0.006 mmol) were added to the solution at 0 °C and the mixture was stirred at 21 °C for 1 h. The solvent was evaporated off at an ambient temperature and the resulting residue was dried over P_2O_5 for 2 h. The residue was dissolved in CH_2Cl_2 (4 ml), and the solution was cooled in an ice bath. Et_3SiH (134 μl, 0.841 mmol) and $BF_3 \cdot OEt_2$ (52 μl, 0.423 mmol) were successively added to this and the mixture was stirred under an Ar atmosphere at 0 °C for 5 min and at 25 °C for 3 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual workup and purification by PTLC [benzene–EtOAc (2 : 1)] gave **35b** (30 mg, 67%) and methyl 8,9-dihydro-4-[(methoxycarbonyl)oxy]furo[3,2-*f*]quinoline-6(7*H*)-carboxylate (**36b**, 2 mg, 5%) in order of decreasing polarity. **35b**: Colorless foam. HRMS Calcd for $C_{15}H_{15}NO_7$: 321.0847. Found: 321.0858. MS *m/z*: 321 (M^+, 100), 303 (6), 302 (6), 263 (16), 228 (18), 202 (29), 200 (30), 186 (26), 89 (20), 59 (91). IR ($CHCl_3$): 1768, 1689 cm^{-1}. ^{1}H-NMR δ: 2.30 (1H, br s, OH), 2.85 (1H, dd, J=17, 5 Hz), 3.22 (1H, dd, J=17, 5 Hz), *ca.* 3.64—4.04 (2H, m), 3.79 (3H, s), 3.94 (3H, s), 4.17—4.49 (1H, m), 6.72 (1H, d, J=2 Hz), 7.54 (1H, s), 7.61 (1H, d, J=2 Hz). **36b**: Colorless glass. HRMS Calcd for $C_{15}H_{15}NO_6$: 305.0898. Found: 305.0883. MS *m/z*: 305 (M^+, 100), 260 (14), 246 (16), 202 (33), 186 (21), 174 (22), 158 (23), 130 (23), 59 (73). IR ($CHCl_3$): 1771, 1698 cm^{-1}. ^{1}H-NMR δ: 1.88—2.17 (2H, m), 2.94 (2H, t, J=6.5 Hz), 3.80 (3H, s), 3.84 (2H, t, J=6.5 Hz), 3.96 (3H, s), 6.73 (1H, d, J=2 Hz), 7.56 (1H, s), 7.60 (1H, d, J=2 Hz).

In the same way, starting from **17a** (44 mg, 0.174 mmol), methyl (±)-2,3-dihydro-2-hydroxy-6-[(methoxycarbonyl)oxy]benzo[*f*]quinoline-4(1*H*)-carboxylate (**35a**, 39 mg, 68%) and methyl 2,3-dihydro-6-[(methoxycarbonyl)-oxy]benzo[*f*]quinoline-4(1*H*)-carboxylate (**36a**, 3.5 mg, 6%) along with recovered **17a** (4 mg, 9%) were obtained after separation by PTLC [benzene–EtOAc (3:1)]. **35a**: Colorless needles, mp 189—190 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{17}H_{17}NO_6$: C, 61.62; H, 5.17; N, 4.23. Found: C, 61.31; H, 5.14; N, 4.17. HRMS Calcd for $C_{17}H_{17}NO_6$: 331.1055. Found: 331.1046. MS *m/z*: 331 (M^+, 100), 212 (22), 196 (16), 184 (17), 167 (18), 127 (25), 59 (88). IR (KBr): 1757, 1672 cm^{-1}. ^{1}H-NMR δ: 1.99 (1H, br s, OH), 3.09 (1H, dd, J=17.5, 5 Hz), 3.46 (1H, dd, J=17.5, 6 Hz), *ca.* 3.74—4.03 (2H, m), 3.84 (3H, s), 3.97 (3H, s), 4.33—4.57 (1H, m), 7.38—7.69 (2H, m), 7.78 (1H, s), 7.78—8.05 (2H, m). **36a**: Colorless glass. HRMS Calcd for $C_{17}H_{17}NO_5$: 315.1106. Found: 315.1101. MS *m/z*: 315 (M^+, 100), 271 (8), 256 (16), 212 (17), 196 (25), 168 (30), 141 (19), 115 (19), 59 (72). IR ($CHCl_3$): 1764, 1696 cm^{-1}. ^{1}H-NMR δ: 1.95—2.29 (2H, m), 3.14 (2H, t, J=7 Hz), *ca.* 3.74—4.00 (2H, m), 3.82 (3H, s), 3.94 (3H, s), 7.37—7.67 (2H, m), 7.79 (1H, s), 7.85—8.06 (2H, m).

In the same way, starting from **17c** (41 mg, 0.158 mmol), methyl (±)-8,9-dihydro-8-hydroxy-4-[(methoxycarbonyl)oxy]thieno[3,2-*f*]quinoline-6(7*H*)-carboxylate (**35c**, 32 mg, 60%) and methyl 8,9-dihydro-4-[(methoxycarbonyl)oxy]thieno[3,2-*f*]quinoline-6(7*H*)-carboxylate (**36c**, 3 mg, 6%) were obtained by way of dihydroderivatives **33c** and **34c** (*ca.* 4.5 : 1) after purification by PTLC [benzene–EtOAc (2 : 1)]. ^{1}H-NMR of the crude **33c** δ: 3.78 (3H, s), 3.92 (3H, s), 4.42 (2H, dd, J=4.5, 1.5 Hz), 6.08 (1H, dt, J=9.5, 4.5 Hz), 6.89 (1H, br d, J=9.5 Hz), 7.37 (1H, d, J=5 Hz), 7.45 (1H, d, J=5 Hz), 7.59 (1H, s). **35c**: Colorless foam. HRMS Calcd for $C_{15}H_{15}NO_6S$: 337.0619. Found: 337.0624. MS *m/z*: 337 (M^+, 100), 319 (5), 279 (16), 218 (22), 216 (25), 202 (25), 190 (18), 173 (18), 89 (16), 59 (77). IR ($CHCl_3$): 1768, 1699 cm^{-1}. ^{1}H-NMR δ: 2.67 (1H, br s, OH), 2.92 (1H, dd, J=17, 5 Hz), 3.28 (1H, dd, J=17, 6 Hz), *ca.* 3.66—3.89 (2H, m), 3.78 (3H, s), 3.93 (3H, s), 4.13—4.40 (1H, m), 7.23 (1H, d, J=5 Hz), 7.44 (1H, d, J=5 Hz), 7.65 (1H, s). **36c**:

Colorless glass. HRMS Calcd for $C_{15}H_{15}NO_5S$: 321.0670. Found: 321.0667. MS *m/z*: 321 (M^+, 100), 262 (15), 218 (24), 202 (24), 174 (38), 147 (25), 59 (72). IR ($CHCl_3$): 1767, 1695 cm^{-1}. ^{1}H-NMR δ: 1.89—2.23 (2H, m), 3.05 (2H, t, J=6.5 Hz), 3.79 (3H, s), 3.84 (2H, t, J=7 Hz), 3.94 (3H, s), 7.32 (1H, d, J=5 Hz), 7.46 (1H, d, J=5 Hz), 7.68 (1H, s).

In the same way, starting from **17d** (27 mg, 0.087 mmol), methyl (±)-2,3-dihydro-2-hydroxy-6-[(methoxycarbonyl)oxy][1]benzothieno[3,2-*f*]quinoline-4(1*H*)-carboxylate (**35d**, 14 mg, 41%) and methyl 2,3-dihydro-6-[(methoxycarbonyl)oxy][1]benzothieno[3,2-*f*]quinoline-4(1*H*)-carboxylate (**36d**, 2.5 mg, 8%) along with recovered **17d** (2 mg, 7%) were obtained after purification by PTLC [hexane–CH_2Cl_2 (1 : 3)]. **35d**: Colorless glass. HRMS Calcd for $C_{19}H_{17}NO_6S$: 387.0775. Found: 387.0775. MS *m/z*: 387 (M^+, 100), 328 (5), 266 (12), 223 (14), 184 (12), 139 (12), 59 (53). IR ($CHCl_3$): 1769, 1692 cm^{-1}. ^{1}H-NMR δ: 2.51 (1H, br s, OH), 3.29 (1H, dd, J=17, 5 Hz), 3.67 (1H, dd, J=17, 6 Hz), *ca.* 3.67—4.09 (2H, m), 3.80 (3H, s), 3.96 (3H, s), 4.24—4.53 (1H, m), 7.24—7.58 (2H, m), 7.66—7.97 (1H, m), 7.73 (1H, s), 8.12—8.40 (1H, m). **36d**: Colorless glass. HRMS Calcd for $C_{19}H_{17}NO_5S$: 371.0826. Found: 371.0835. MS *m/z*: 371 (M^+, 100), 312 (9), 284 (14), 224 (29), 197 (19), 59 (54). IR ($CHCl_3$): 1771, 1698 cm^{-1}. ^{1}H-NMR δ: 1.99—2.35 (2H, m), 3.43 (2H, t, J=7 Hz), 3.73—4.03 (2H, m), 3.81 (3H, s), 3.96 (3H, s), 7.31—7.57 (2H, m), 7.71—7.98 (1H, m), 7.77 (1H, s), 8.21—8.46 (1H, m).

In the same way, starting from **17e** (45 mg, 0.096 mmol), methyl (±)-4-(benzyloxy)-8,9-dihydro-8-hydroxy-2-(3,4,5-trimethoxybenzyl)thieno[3,2-*f*]quinoline-6(7*H*)-carboxylate (**35e**, 40 mg, 76%) and methyl 4-(benzyloxy)-8,9-dihydro-2-(3,4,5-trimethoxybenzyl)thieno[3,2-*f*]quinoline-6(7*H*)-carboxylate (**36e**, 2.5 mg, 5%) along with recovered **17e** (2 mg, 4%) were isolated after separation by PTLC [benzene–EtOAc (5 : 2)]. **35e**: Colorless glass. HRMS Calcd for $C_{30}H_{31}NO_7S$: 549.1819. Found: 549.1806. MS *m/z*: 549 (M^+, 38), 458 (4), 430 (5), 181 (20), 91 (100), 65 (8), 59 (11). IR ($CHCl_3$): 1691 cm^{-1}. ^{1}H-NMR δ: 2.09 (1H, br s, OH), 2.91 (1H, dd, J=17.5, 5.5 Hz), 3.29 (1H, dd, J=17.5, 6 Hz), *ca.* 3.61—4.03 (2H, m), 3.76 (3H, s), 3.87 (9H, s), 4.20 (2H, s), 4.23—4.52 (1H, m), 5.27 (2H, s), 6.56 (2H, s), 7.06 (1H, s), 7.27 (1H, s), 7.27—7.65 (5H, m). **36e**: Colorless glass. HRMS Calcd for $C_{30}H_{31}NO_6S$: 533.1870. Found: 533.1860. MS *m/z*: 533 (M^+, 56), 473 (5), 442 (13), 414 (15), 354 (12), 181 (22), 91 (100). IR ($CHCl_3$): 1687 cm^{-1}. ^{1}H-NMR δ: 1.87—2.20 (2H, m), 2.96 (2H, t, J=6.5 Hz), 3.67—3.94 (2H, m), 3.75 (3H, s), 3.86 (9H, s), 4.17 (2H, s), 5.24 (2H, s), 6.55 (2H, s), 7.06 (1H, s), 7.26 (1H, s), 7.26—7.62 (5H, m).

Mesylation of 35a—e to Form 37a—e Preparation of methyl (±)-2,3-dihydro-6-[(methoxycarbonyl)oxy]-2-[(methylsulfonyl)oxy]benzo[*f*]quinoline-4(1*H*)-carboxylate (**37a**) from **35a** is described as representative. MsCl (13 μl, 0.168 mmol) was added to a cooled (0 °C) solution of **35a** (27 mg, 0.082 mmol) and Et_3N (45 μl, 0.323 mmol) in CH_2Cl_2 (2.5 ml) under an Ar atmosphere. After having been stirred at 0 °C for 30 min, the reaction was quenched by addition of saturated $NaHCO_3$–H_2O and the mixture was extracted with CH_2Cl_2. The organic layer was successively washed with saturated $CuSO_4$–H_2O and then with saturated $NaHCO_3$–H_2O. Usual workup followed by purification by PTLC [benzene–EtOAc (3 : 1)] provided **37a** (33 mg, 99%) as a colorless foam. HRMS Calcd for $C_{18}H_{19}NO_8S$: 409.0830. Found: 409.0830. MS *m/z*: 409 (M^+, 35), 313 (15), 312 (19), 254, (21), 238 (51), 210 (57), 167 (38), 59 (100). IR ($CHCl_3$): 1766, 1708 cm^{-1}. ^{1}H-NMR δ: 3.04 (3H, s), 3.33 (1H, dd, J=18, 4.5 Hz), 3.57 (1H, dd, J=18, 5.5 Hz), 3.81 (1H, dd, J=13.5, 2.5 Hz), 3.84 (3H, s), 3.96 (3H, s), 4.36 (1H, dd, J=13.5, 5.5 Hz), 5.20—5.47 (1H, m), 7.40—7.68 (2H, m), 7.74 (1H, s), *ca.* 7.74—8.06 (2H, m).

In the same manner, **35b** (29 mg, 0.090 mmol) was mesylated to afford methyl (±)-8,9-dihydro-4-[(methoxycarbonyl)oxy]-8-[(methylsulfonyl)oxy]-furo[3,2-*f*]quinoline-6(7*H*)-carboxylate (**37b**, 34 mg, 94%) as a colorless foam. HRMS Calcd for $C_{16}H_{17}NO_9S$: 399.0623. Found: 399.0614. MS *m/z*: 399 (M^+, 41), 302 (29), 258 (18), 244 (19), 228 (89), 200 (88), 185 (38), 59 (100). IR ($CHCl_3$): 1769, 1706 cm^{-1}. ^{1}H-NMR δ: 3.03 (3H, s), 3.16 (1H, dd, J=17.5, 4 Hz), 3.40 (1H, dd, J=17.5, 5 Hz), 3.80 (3H, s), 3.80 (1H, dd, J=14, 3 Hz), 3.95 (3H, s), 4.31 (1H, dd, J=14, 6 Hz), 5.15—5.41 (1H, m), 6.72 (1H, d, J=2.5 Hz), 7.54 (1H, s), 7.63 (1H, d, J=2.5 Hz).

In the same manner, **35c** (30 mg, 0.089 mmol) was mesylated to afford methyl (±)-8,9-dihydro-4-[(methoxycarbonyl)oxy]-8-[(methylsulfonyl)oxy]-thieno[3,2-*f*]quinoline-6(7*H*)-carboxylate (**37c**, 35 mg, 95%) as a colorless glass. HRMS Calcd for $C_{16}H_{17}NO_8S_2$: 415.0394. Found: 415.0370. MS *m/z*: 415 (M^+, 38), 318 (23), 306 (12), 274 (12), 244 (53), 216 (62), 201 (38), 173 (40), 59 (100). IR ($CHCl_3$): 1767, 1710 cm^{-1}. ^{1}H-NMR δ: 3.02 (3H, s), 3.26 (1H, dd, J=17.5, 4 Hz), 3.48 (1H, dd, J=17.5, 5.5 Hz), 3.80 (1H, dd, J=13.5, 2.5 Hz), 3.81 (3H, s), 3.93 (3H, s), 4.32 (1H, dd, J=13.5, 5.5 Hz), 5.29 (1H, dddd, J=5.5, 5.5, 4, 2.5 Hz), 7.25 (1H, d, J=5.5 Hz), 7.48 (1H, d, J=5.5 Hz), 7.65 (1H, s).

In the same manner, **35d** (14 mg, 0.033 mmol) was mesylated to afford methyl (±)-2,3-dihydro-6-[(methoxycarbonyl)oxy]-2-[(methylsulfonyl)oxy]-[1]benzothieno[3,2-*f*]quinoline-4(1*H*)-carboxylate (**37d**, 16 mg, 95%) as a colorless glass. HRMS Calcd for $C_{20}H_{19}NO_8S_2$: 465.0551. Found: 465.0555. MS *m/z*: 465 (M^+, 69), 369 (14), 368 (15), 310 (20), 294 (27), 266 (41), 223 (44), 59 (100). IR ($CHCl_3$): 1768, 1710 cm^{-1}. ^{1}H-NMR δ: 3.08 (3H, s), 3.47—4.07 (3H, m), 3.84 (3H, s), 3.97 (3H, s), 4.34 (1H, dd, J=13.5, 6 Hz), 5.24—5.54 (1H, m), 7.33—7.60 (2H, m), 7.75 (1H, s), 7.75—7.97 (1H, m), 8.09—8.32 (1H, m).

In the same manner, **35e** (40 mg, 0.073 mmol) was mesylated to afford methyl (±)-4-(benzyloxy)-8,9-dihydro-8-[(methylsulfonyl)oxy]-2-(3,4,5-trimethoxybenzyl)thieno[3,2-*f*]quinoline-6(7*H*)-carboxylate (**37e**, 45 mg, 99%) as a colorless glass. HRMS Calcd for $C_{31}H_{33}NO_9S_2$: 627.1595. Found: 627.1603. MS *m/z*: 627 (M^+, 13), 531 (9), 518 (6), 471 (9), 440 (13), 181 (21), 91 (100), 79 (5), 65 (7), 59 (9). IR ($CHCl_3$): 1704, 1596 cm^{-1}. ^{1}H-NMR δ: 3.04 (3H, s), 3.18 (1H, dd, J=17, 4.5 Hz), 3.43 (1H, dd, J=17, 6 Hz), 3.63—3.96 (1H, m), 3.73 (3H, s), 3.82 (9H, s), 4.13 (2H, s), 4.25 (1H, dd, J=13.5, 5 Hz), 5.11—5.40 (1H, m), 5.19 (2H, s), 6.47 (2H, s), 6.96 (1H, s), 7.13 (1H, s), 7.23—7.57 (5H, m).

Cyclization of 37a—d to Form the Precursors 38a—d Preparation of (8b*RS*,9a*SR*)-2,4,9,9a-tetrahydro-1*H*-benzo[*e*]cycloprop[*c*]indol-4-one[26] (**38a**) from **37a** is described as a typical example. K_2CO_3 (39 mg, 0.283 mmol) was added to a solution of **37a** (33 mg, 0.081 mmol) in MeOH (3 ml). After having been stirred at 17 °C for 4 h, the mixture was cooled in an ice bath. CH_2Cl_2 (5 ml), citric acid monohydrate (59 mg, 0.281 mmol), and H_2O (5 ml) were successively added to the mixture and the whole was extracted with 10% MeOH–CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$–H_2O and then treated as usual. Purification by PTLC (4% MeOH–CH_2Cl_2) provided **38a** (15 mg, 94%) as a colorless glass. HRMS Calcd for $C_{13}H_{11}NO$: 197.0840. Found: 197.0832. MS *m/z*: 197 (M^+, 100), 180 (32), 168 (42), 154 (18), 139 (32), 115 (20), 83 (21). IR ($CHCl_3$): 1620, 1596 cm^{-1}. ^{1}H-NMR δ: 1.35 (1H, dd, J=4, 4 Hz), 1.54 (1H, dd, J=7.5, 4 Hz), 2.36—2.95 (1H, m), 3.63 (1H, d, J=10.5 Hz), 3.84 (1H, dd, J=10.5, 5 Hz), 5.76 (1H, s), 6.34 (1H, br s, NH), 6.73—6.91 (1H, m), 7.22—7.53 (2H, m), 8.11—8.30 (1H, m).

In the same way, (7b*RS*,8a*SR*)-1,2,8,8a-tetrahydro-4*H*-cyclopropa[*c*]furo-[3,2-*e*]indol-4-one (**38b**, 14 mg, 88%) was obtained from **37b** (34 mg, 0.085 mmol) after separation by PTLC (5% MeOH–CH_2Cl_2). **38b**: Colorless foam. HRMS Calcd for $C_{11}H_9NO_2$: 187.0633. Found: 187.0630. MS *m/z*: 187 (M^+, 100), 170 (11), 158 (18), 130 (68), 77 (30), 63 (29), 52 (29). IR ($CHCl_3$): 1624, 1560 cm^{-1}. ^{1}H-NMR δ: 1.30 (1H, dd, J=5, 4 Hz), 1.58 (1H, dd, J=8, 4 Hz), 2.76 (1H, ddd, J=8, 6, 5 Hz), 3.63 (1H, d, J=11 Hz), 3.84 (1H, br dd, J=11, 6 Hz), 5.56 (1H, s), 6.16 (1H, d, J=2 Hz), 6.40 (1H, br s, NH), 7.50 (1H, d, J=2 Hz).

In the same way, (7b*RS*,8a*SR*)-1,2,8,8a-tetrahydro-4*H*-cyclopropa[*c*]thieno[3,2-*e*]indol-4-one (**38c**, 15.5 mg, 93%) was obtained from **37c** (34 mg, 0.082 mmol) after separation by PTLC (5% MeOH–CH_2Cl_2). **38c**: Colorless foam. HRMS Calcd for $C_{11}H_9NOS$: 203.0404. Found: 203.0403. MS *m/z*: 203 (M^+, 100), 188 (13), 186 (15), 174 (44), 160 (18), 147 (14), 145 (14), 121 (10), 102 (13), 63 (15), 45 (16). IR ($CHCl_3$): 1607, 1581 cm^{-1}. ^{1}H-NMR δ: 1.32 (1H, dd, J=5, 4 Hz), 1.60 (1H, dd, J=8, 4 Hz), 2.81 (1H, ddd, J=8, 5, 5 Hz), 3.61 (1H, d, J=10.5 Hz), 3.83 (1H, dd, J=10.5, 5 Hz), 5.61 (1H, s), 6.62 (1H, d, J=5 Hz), 6.64 (1H, br s, NH), 7.42 (1H, d, J=5 Hz).

In the same way, (9c*RS*,10a*SR*)-1,2,10,10a-tetrahydro-4*H*-cyclopropa[*c*]-[1]benzothieno[3,2-*e*]indol-4-one (**38d**, 7.5 mg, 92%) was obtained from **37d** (15 mg, 0.032 mmol) after purification by PTLC (4% MeOH–CH_2Cl_2). **38d**: Slightly yellow glass. HRMS Calcd for $C_{15}H_{11}NOS$: 253.0561. Found: 253.0553. MS *m/z*: 253 (M^+, 100), 224 (40), 210 (16), 197 (14), 195 (16), 152 (12), 63 (11), 44 (11). IR ($CHCl_3$): 1612, 1581 cm^{-1}. ^{1}H-NMR δ: 1.32 (1H, dd, J=4.5, 4.5 Hz), 2.09 (1H, dd, J=8, 4.5 Hz), 3.18—3.46 (1H, m), 3.74 (1H, d, J=10.5 Hz), 3.93 (1H, dd, J=10.5, 5 Hz), 5.74 (1H, s), 6.44 (1H, br s, NH), 7.23—7.47 (3H, m), 7.77—7.96 (1H, m).

(7b*RS*,8a*SR*)-1,2,8,8a-tetrahydro-6-(3,4,5-trimethoxybenzyl)-4*H*-cyclopropa[*c*]thieno[3,2-*e*]indol-4-one (38e) A slurry of **37e** (14 mg, 0.022 mmol) and 20% $Pd(OH)_2$ on carbon (10 mg) in MeOH (5 ml) and DME (1 ml) was hydrogenated under H_2 atmosphere (1 atm) at 19 °C for 52 h. The mixture was filtered and the filtrate was evaporated to give a residue (16 mg). The residue was dissolved in MeOH (3 ml) and K_2CO_3 (11 mg, 0.080 mmol) was added to this with stirring at 21 °C. The stirring was continued at this temperature for 2.5 h, then the mixture was treated as for the preparation of **38a** from **37a**. Purification by PTLC (3% MeOH–CH_2Cl_2) afforded **38e** (5.5 mg, 64%) and recovered **37e** (4.5 mg, 32%). **38e**: Colorless glass. HRMS Calcd for $C_{21}H_{21}NO_4S$: 383.1190. Found: 383.1175. MS *m/z*: 383

(M^+, 15), 381 (14), 368 (6), 366 (6), 352 (4), 57 (51), 56 (55), 42 (100). IR ($CHCl_3$): 1608, 1593 cm^{-1}. ^1H-NMR δ: 1.36 (1H, dd, J=5, 4 Hz), 1.61 (1H, dd, J=8, 4 Hz), 2.67—2.92 (1H, m), 3.59 (1H, d, J=10.5 Hz), 3.81 (1H, dd, J=10.5, 5 Hz), 3.83 (9H, s), 4.06 (2H, s), 5.29 (1H, br s, NH), 5.62 (1H, s), 6.39 (1H,s), 6.49 (2H, s).

Duocarmycin SA A-Ring Analogs 9a—e The coupling reaction to prepare (8b*RS*,9a*SR*)-1,2,9,9a-tetrahydro-2-[(5,6,7-trimethoxy-1*H*-indol-2-yl)-carbonyl]-4*H*-benzo[*e*]cycloprop[*c*]indol-4-one (**9a**) is described as a typical example. K_2CO_3 (91 mg, 0.659 mmol) was added to a solution of **38a** (13 mg, 0.066 mmol) and the imidazolide **39** (40 mg, 0.133 mmol) in DMF (2.5 ml) under an Ar atmosphere and the mixture was stirred at 27 °C for 3 h. CH_2Cl_2 (5 ml), citric acid monohydrate (151 mg, 0.719 mmol), and H_2O (10 ml) were successively added and the whole was thoroughly extracted with 10% MeOH–CH_2Cl_2. After washing with saturated $NaHCO_3$–H_2O, the organic layer was worked-up as usual. The resulting residue was separated by PTLC (0.7% MeOH–CH_2Cl_2) to afford crude **9a** (29 mg). The crude **9a** was further purified by PTLC [benzene–EtOAc (5 : 2)] to yield **9a** (25 mg, 88%) as a slightly yellow powder. HRMS Calcd for $C_{25}H_{22}N_2O_5$: 430.1527. Found: 430.1514. MS *m/z*: 430 (M^+, 73), 413 (34), 234 (100), 204 (19), 179 (18). IR ($CHCl_3$): 1648, 1627, 1604 cm^{-1}. ^1H-NMR δ: 1.55 (1H, dd, J=5, 4.5 Hz), 1.71 (1H, dd, J=7.5, 4.5 Hz), 2.74—3.00 (1H, m), 3.89 (3H, s), 3.94 (3H, s), 4.07 (3H, s), *ca.* 4.27—4.61 (2H, m), 6.79 (1H, s), 6.79—7.02 (1H, m), 6.96 (1H, d, J=2 Hz, changed to s with D_2O), 7.14 (1H, s), 7.27—7.64 (2H, m), 8.25 (1H, dd, J=7, 2 Hz), 9.37 (1H, br s, NH).

Similarly, **38b** (9 mg, 0.048 mmol) was allowed to react with **39** (29 mg, 0.096 mmol) in the presence of K_2CO_3 (66 mg, 0.478 mmol) in DMF (1.5 ml) to yield (7b*RS*,8a*SR*)-1,2,8,8a-tetrahydro-2-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-4*H*-cyclopropa[*c*]furo[3,2-*e*]indol-4-one (**9b**, 15 mg, 74%) as a colorless powder. HRMS Calcd for $C_{23}H_{20}N_2O_6$: 420.1320. Found: 420.1306. MS *m/z*: 420 (M^+, 34), 234 (100), 186 (37), 185 (43). IR (KBr): 1631, 1592 cm^{-1}. ^1H-NMR δ: 1.59 (1H, dd, J=5.5, 4.5 Hz), 1.78 (1H, dd, J=7.5, 4.5 Hz), 2.69—2.94 (1H, m), 3.89 (3H, s), 3.94 (3H, s), 4.07 (3H, s), *ca.* 4.27—4.61 (2H, m), 6.26 (1H, d, J=2.5 Hz), 6.79 (1H, s), 6.93 (1H, d, J=2 Hz, changed to s with D_2O), 6.97 (1H, s), 7.63 (1H, d, J=2.5 Hz), 9.28 (1H, br s, NH).

Similarly, **38c** (7 mg, 0.034 mmol) was allowed to react with **39** (21 mg, 0.070 mmol) in the presence of K_2CO_3 (48 mg, 0.348 mmol) in DMF (1.5 ml) to provide (7b*RS*,8a*SR*)-1,2,8,8a-tetrahydro-2-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-4*H*-cyclopropa[*c*]thieno[3,2-*e*]indol-4-one (**9c**, 9.5 mg, 63%) as a slightly yellow powder. HRMS Calcd for $C_{23}H_{20}N_2O_5S$: 436.1092. Found: 436.1086. MS *m/z*: 436 (M^+, 20), 234 (100), 203 (34), 191 (10), 173 (13), 160 (10), 77 (11). IR ($CHCl_3$): 1645, 1617 cm^{-1}. ^1H-NMR δ: 1.61 (1H, dd, J=5, 4.5 Hz), 1.82 (1H, dd, J=7.5, 4.5 Hz), 2.73—2.99 (1H, m), 3.88 (3H, s), 3.94 (3H, s), 4.07 (3H, s), *ca.* 4.27—4.60 (2H, m), 6.74 (1H, d, J=5 Hz), 6.80 (1H, s), 6.96 (1H, d, J=2 Hz, changed to s with D_2O), 7.02 (1H, s), 7.61 (1H, d, J=5 Hz), 9.36 (1H, br s, NH).

Similarly, **38d** (4.5 mg, 0.018 mmol) was allowed to react with **39** (11 mg, 0.037 mmol) in the presence of K_2CO_3 (25 mg, 0.181 mmol) in DMF (1.5 ml) to give (9c*RS*,10a*SR*)-1,2,10,10a-tetrahydro-2-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-4*H*-cyclopropa[*c*][1]benzothieno[3,2-*e*]indol-4-one (**9d**, 3 mg, 35%) as a slightly yellow powder. HRMS Calcd for $C_{27}H_{22}N_2O_5S$: 486.1248. Found: 486.1250. MS *m/z*: 486 (M^+, 34), 253 (49), 251 (65), 234 (100). IR ($CHCl_3$): 1643, 1610 cm^{-1}. ^1H-NMR (10% CD_3OD–$CDCl_3$) δ: 1.68 (1H, dd, J=4.5, 4.5 Hz), 2.39 (1H, dd, J=8.5, 4.5 Hz), *ca.* 3.31—3.52 (1H, m), 3.90 (3H, s), 3.94 (3H, s), 4.09 (3H, s), *ca.* 4.39—4.74 (2H, m), 6.84 (1H, s), 7.02 (1H, s), 7.13 (1H, s), 7.33—7.67 (3H, m), 7.87—8.10 (1H, m).

Similarly, **38e** (6 mg, 0.016 mmol) was allowed to react with **39** (10 mg, 0.033 mmol) in the presence of K_2CO_3 (22 mg, 0.159 mmol) in DMF (1.5 ml) to give (7b*RS*,8a*SR*)-1,2,8,8a-tetrahydro-6-(3,4,5-trimethoxybenzyl)-2-[(5,6,7-trimethoxy-1*H*-indol-2-yl)carbonyl]-4*H*-cyclopropa[*c*]thieno[3,2-*e*]indol-4-one (**9e**, 7.5 mg, 78%) as a slightly yellow glass. HRMS Calcd for $C_{33}H_{32}N_2O_8S$: 616.1877. Found: 616.1894. MS *m/z*: 616 (M^+, 30), 452 (27), 383 (100), 234 (88). IR ($CHCl_3$): 1644, 1613 cm^{-1}. ^1H-NMR δ: 1.58 (1H, dd, J=5, 5 Hz), 1.76 (1H, dd, J=7.5, 5 Hz), 2.67—2.93 (1H, m), 3.84 (9H, s), 3.87 (3H, s), 3.93 (3H, s), 4.07 (5H, s), *ca.* 4.22—4.58 (2H, m), 6.42 (1H, s), 6.47 (2H, s), 6.79 (1H, s), 6.93 (1H, d, J=2.5 Hz, changed to s with D_2O), 6.97 (1H, s), 9.31 (1H, br s, NH).

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