Synthesis of Duocarmycin SA by Way of Methyl 4-(Methoxycarbonyl)oxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate as a Tricyclic Heteroaromatic Intermediate

Hideaki MURATAKE,* Miyuki TONEGAWA, and Mitsutaka NATSUME*

Research Foundation Itsuu Laboratory, 2–28–10 Tamagawa, Setagaya-ku, Tokyo 158, Japan.
Received, September 11, 1997; accepted, October 23, 1997

Formal syntheses of (±)-duocarmycin SA, natural (+)-duocarmycin SA and unnatural (−)-duocarmycin SA were accomplished by way of a tricyclic heteroaromatic compound 10b. For the preparation of 10, an *N*-oxide route aiming at a process 20 in Chart 3 was first investigated by synthesizing 19, derived from Stille coupling products 13 between bromopyrrole 7a and 3-(tributylstannyl)pyridines 12, but without success. As the second approach, Stille coupling products 9a—c were prepared by condensation between 7a and 2-substituted 3-(trialkylstannyl)pyridines 8a—f. Both 9b and 35, derived from 9c, were converted to their silyl enol ethers and then subjected to a palladium-catalyzed methyl ketone-arylation reaction in the presence of tributyltin fluoride and lithium chloride, affording 10a and 10b in excellent yields, especially from 35. Application to 10b of three successive operations, *i.e.*, i) partial reduction of 10b to dihydropyridine derivatives 11a and 11b, ii) dihydroxylation of the double bonds formed to give 58 and 59, and iii) reductive elimination of the hydroxy groups adjacent to the nitrogen function and the aromatic ring, afforded 6 in fairly good yield. Compound 6 was readily converted to relay compounds 64 and 67, completing total syntheses of (±)-, (+)-, and (−)-duocarmycin SA. Both Sharpless asymmetric dihydroxylation (AD) and Jacobsen's asymmetric epoxidation were applied to 11a and 11b. At the best, 81% ee was observed in the AD reaction of 11a using 2,5-diphenyl-4,6-bis(9-*O*-dihydroquinyl)pyrimidine [(DHQ)$_2$PYR], but the resulting 58 possessed an unnatural absolute configuration.

Key words formal synthesis; duocarmycin SA; potent antitumor substance; Stille reaction; methyl ketone α-arylation; palladium-catalyzed reaction

In the previous two papers, we reported syntheses of duocarmycin SA (**1**),[1-3] and its furan and thiophene analogs **2** and **3**,[4] starting from bromopyrrole, bromofuran, and bromothiophene derivatives **4** (Chart 1). Palladium-catalyzed intramolecular Heck reaction of **4** played an important role in the construction of the tricyclic core structures **5**. While the reaction sequence leading to **1**, **2**, and **3** was not too long and each step proceeded in fairly good yield, we encountered some trouble at the aromatization step of **5**, in that i) supply of phenylselenenyl chloride in Japan was erratic, and ii) oxidative elimination of the α-phenylselenyl ketone occasionally failed for unknown reasons. Therefore, we planned an alternative synthetic pathway to avoid this step.

A new process stemmed from the idea that a fully aromatic compound **10** would afford dihydropyridine derivatives **11** on partial reduction, and by making use of the double bonds formed, a hydroxy group might be introduced at the required position either in a racemic or in an asymmetric way to give **6**. For the preparation of **10**, a Stille coupling product **9** of the bromide **7a** and stannylpyridine **8** (X=H and halogens) represents a potential precursor compound, and the pivotal bond connection between the methyl group and the α-pyridyl carbon in **9** has to be attained. For the first trial, a brief investigation using *N*-oxide derivatives of **9** (X=H) was carried out in the hope of α- and γ-activation of the pyridine nucleus for the nucleophic attack of enolates[5]; however, this attempt failed. Next, a halogen group was placed at X to start an intramolecular metal-mediated coupling reaction with the methyl ketone group. Here we report the details of these studies.[6]

N-Oxide of 9 (X=H) and Related Compounds According to the literature method of metallation,[7] 4-chloropyridine was treated with lithium diisopropylamide (LDA), followed by addition of tributyltin chloride to give 4-chloro-3-(tributylstannyl)pyridine (**12b**) in 84% yield (Chart 2). 5-Chloro-3-(tributylstannyl)pyridine (**12c**) was prepared by reaction of tributyltin lithium[8] with 3,5-dichloropyridine in 71% yield. These stannanes together with 3-(tributylstannyl)pyridine[9] (**12a**) were submitted to Stille coupling reaction[10] with the bromopyrrole **7a** using a catalytic amount of dichlorobis(triphenylphosphine)-palladium(II) in refluxing toluene or xylene (Table 1). 2-Bromoacetophenone (**17**) was similarly coupled with **12a**, and in entries 1, 3, and 4, the reaction proceeded cleanly, affording the expected products **13a**, **13c**, and **18** in very good yields. The sterically hindered stannane **12b**

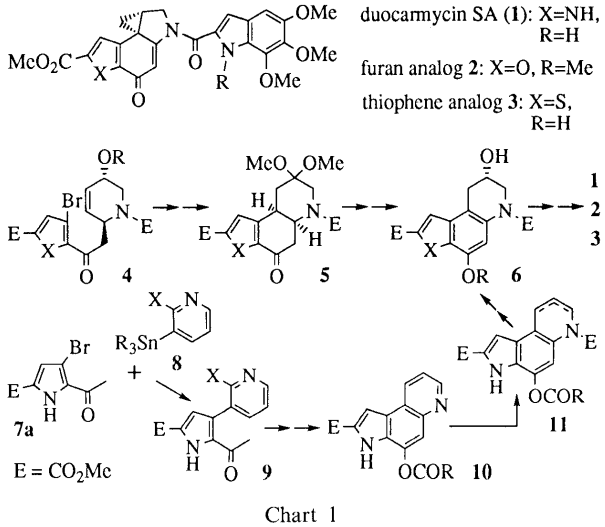

Chart 1

* To whom correspondence should be addressed.

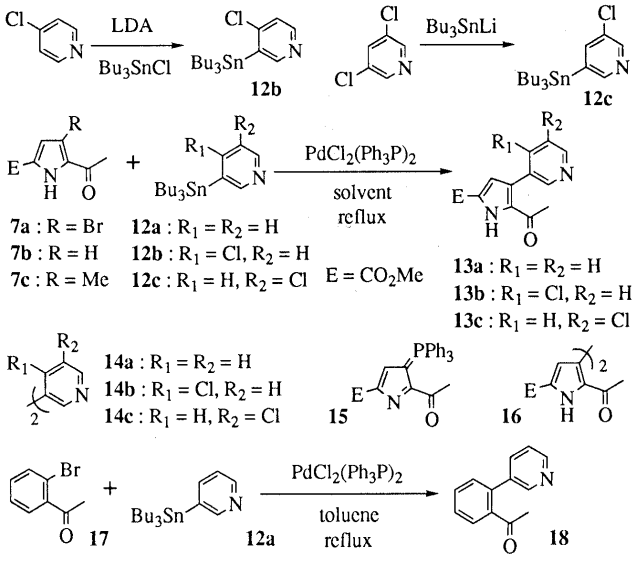

Chart 2

Table 1. Stille Coupling of **7a** and **17** with **12** to Form **13** and **18**

Entry	Material	Pd catalyst	Solvent	Time (h)	Product (yield %)	By-product (yield[a] %)
1	**7a**+**12a**	5 mol%	Toluene	7	**13a** (90)	**7b** (2), **14a** (14[b]), **15** (2)
2	**7a**+**12b**	10 mol%	Xylene	13	**13b** (27)	**7b** (38), **14b** (16[b]), **15** (4), **16** (10)
3	**7a**+**12c**	5 mol%	Toluene	4	**13c** (90)	**14c** (15[b])
4	**17**+**12a**	5 mol%	Toluene	4	**18** (86)	**14a** (12[b])

a) Calculated from **7a**. *b*) Calculated from **12a**—**c**.

(entry 2) required forcing reaction conditions, yet the coupling product **13b** was obtained in only 27% yield, along with a variety of by-products, **7b**,[11] **14b**,[12] **15**, and **16**, in considerable amounts. As the reaction was very slow, the bromopyrrole **7a** independently reacted with triphenylphosphine to give **15**, and the palladium complex derived from **7a** approached the unreacted **7a** to produce a dimer **16**.

The coupling products **13a**, **13c**, and **18**, obtained in quantity, were oxidized to their *N*-oxides **19a**, **19b**, and **21** in 94%, 79%, and 95% yields with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane (Chart 3). The *N*-oxide **19a** was converted to its silyl enol ether, and the latter was treated with various activating reagents such as acetic anhydride, trifluoroacetic anhydride, methanesulfonyl chloride, and *p*-toluenesulfonyl chloride in the presence of a base, in the expectation of nucleophilic substitution of the enolate onto the activated pyridine nucleus, as shown in **20**. However, no reaction product was detected.

In contrast, when **21** was submitted to the silylation reaction with *tert*-butyldimethylsilyl (TBDMS) triflate and triethylamine, an unexpected compound **22** was obtained in 65% yield, in addition to the silyl enol ethers of **21** and **18** in 21% and 10% yields, respectively. In the NMR spectrum of **22**, three olefinic protons were visible at 6.54 (dd, $J=10$, 10 Hz), 7.28 (d, $J=10$ Hz), and 8.13 (d, $J=10$ Hz) ppm, suggesting that a *Z* form double bond was situated in conjugation with an aldoxime group. The

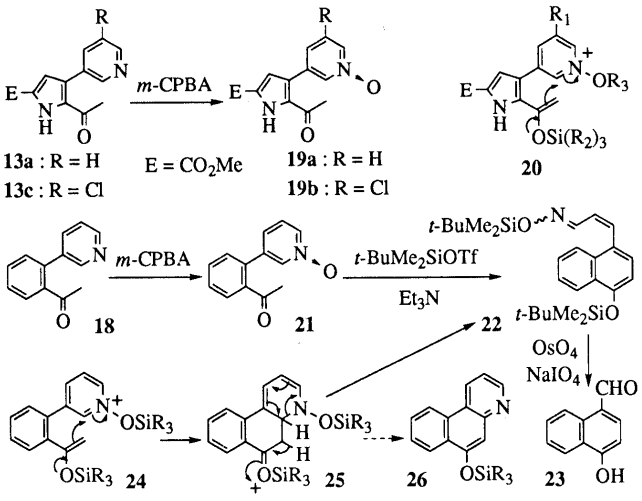

Chart 3

double bond in **22** was cleaved with a catalytic amount of osmium tetroxide and sodium metaperiodate to afford 4-hydroxy-1-naphthalenecarboxaldehyde[13] (**23**), mp 182—183 °C in 78% yield (lit., mp 183 °C,[13c] mp 181 °C[13d]). The reaction mechanism affording **22** was considered to be as follows: *tert*-butyldimethylsilyl triflate behaved as an activating reagent for the *N*-oxide, and the nucleophilic substitution reaction occurred as shown in **24**. If the *tert*-butyldimethylsilyloxy group was split off with the neighboring hydrogen atom as a silanol in **25**, the desired compound **26** might be formed. However, in fact, a retro-electrocyclic process occurred in the dihydropyridine part as shown by the arrows in **25**, resulting in the formation of the naphthalene derivative **22**.[14] In the case of **20**, the reaction might also proceed in an analogous manner, but the product would be a 7-hydroxyindole derivative bearing a conjugated unsaturated side chain, which could be too unstable to remain intact in the presence of strong activating reagents.

Synthesis of Tricyclic Heteroaromatic Compounds 10

Since the *N*-oxide route did not afford any cyclization product, we turned our attention to compound **9** having a halogen or relating leaving group at the α-position of the pyridine nucleus (Chart 1). Our plan was to make a carbon–carbon bond between this α-position and the terminal methyl group, and a search of the literature revealed a suitable report by Kuwajima and co-workers, describing a palladium-catalyzed arylation reaction of silyl enol ethers **27** of methyl ketones (2-oxoalkanes and acetophenone) with aryl bromides **28** (bromobenzene and its derivatives) (Chart 4).[15] This was immediately applied to a model compound, the *tert*-butyldimethylsilyl enol ether derived from the 4-chloropyridine **13b**. A xylene solution of the silyl enol ether, 20 mol% of dichlorobis(triphenylphosphine)palladium(II), and 2.5 eq of tributyltin fluoride was refluxed for 8 h, and the reaction mixture was treated with pivaloyl chloride in pyridine. The desired heteroaromatic compound **30** was isolated in 29% yield. Although the yield was still unsatisfactory, this result gave us a clue for the completion of this synthesis.

The next task was to prepare pyrrole-substituted 2-halogenopyridines **9** for the necessary tricyclic heteroaro-

matic compounds **10**. 2-Substituted pyridines **31a—d** were treated with *tert*-butyllithium or LDA, followed by addition of either trimethyltin chloride or tributyltin chloride to afford 2-substituted 3-(trialkylstannyl)pyridines **8a—f** in good yields (Table 2). These were coupled with the bromopyrrole **7a** by refluxing in xylene or toluene in the presence of dichlorobis(triphenylphosphine)palladium(II) or dichlorobis[tri(*o*-tolyl)phosphine]palladium(II) (Table 3). Judging from the yields, 3-(tributylstannyl)pyridines **8c** and **8e** and the 2-chloropyridine **8d** were not good substrates for the above Stille coupling reaction, probably due to steric hindrance to the approach to palladium complex derived from **7a** (entries 2, 4, and 3). The best result was obtained by a reaction between **7a** and 1.2 eq of 2-fluoro-3-(trimethylstannyl)pyridine **8f** with 5 mol% of dichlorobis[tri(*o*-tolyl)phosphine]palladium(II) in refluxing toluene for 14 h to afford **9c** in 65% yield, along with small amounts of by-products (entry 5).

As 2-chloro-3-iodopyridine **33** was a known compound,[16] the 3-stannylpyrrole **32** was prepared from **7a** in 33% yield by heating with 2 eq of bis(tributyltin) in the presence of 10 mol% of palladium(II) acetate and 0.2 eq of tri(*o*-tolyl)phosphine in acetonitrile (sealed tube) at 110 °C for 30 min.[17] Coupling reaction between **32** and **33** was carried out by refluxing a xylene solution in the presence of 10 mol% of palladium(II) acetate for 21 h, but unfortunately, the desired product **9b** was obtained only in 26% yield, together with **7b** in 38% yield.

With the requisite 2-halopyridines **9b** and **9c** in hand, their cyclization to the heteroaromatic compounds was studied at first by converting **9b** into its *tert*-butyldimethylsilyl ether as usual, followed by the palladium-catalyzed reaction, *i.e.* refluxing a xylene solution of the enol silyl ether with 20 mol% of dichlorobis(triphenylphosphine)palladium(II) and 2.5 eq of tributyltin fluoride for 10 h to afford **10a** in 59% yield after pivaloyl ester formation (Chart 5). As the same reaction did not start from the fluoride **9c**, this was hydrolyzed with 5% hydrochloric acid in a 1 : 1 mixture of dimethoxyethane (DME) and water at 60 °C for 2 h, and the resulting pyridone **34** (obtained in 96% yield) was transformed to a triflate **35** in 95% yield by treatment with trifluoromethanesulfonic anhydride and pyridine in dichloromethane at room temperature for 2 h. The triflate **35** was a very good substrate for the cyclization reaction, and a satisfactory result was obtained by refluxing a xylene solution of the *tert*-butyldimethylsilyl ether of **35**, 3 mol% of dichlorobis(triphenylphosphine)palladium(II), 1.1 eq of tributyltin fluoride, and 3 eq of lithium chloride under an atmosphere of Ar for 1 h. The resulting product was trapped with either pivaloyl chloride or methyl chloroformate in pyridine, and **10a** or **10b** was produced in 91% or 89% yield. For the substrate derived from the triflate **35**, addition of lithium chloride was essential to the reaction cycle just as in the case of the Stille coupling reaction.[10] The pivaloyl group was readily removed from **10a**, and subsequent treatment with tri(isopropyl)silyltriflate in the presence of Hünig base afforded the tri(isopropyl)silyl ether **36** in 92% yield.

Trapping of the intermediary phenol compound **37** as an acylate **10a**, a carbonate **10b**, and a silyl ether **36** proceeded without difficulty in high yield to afford a single

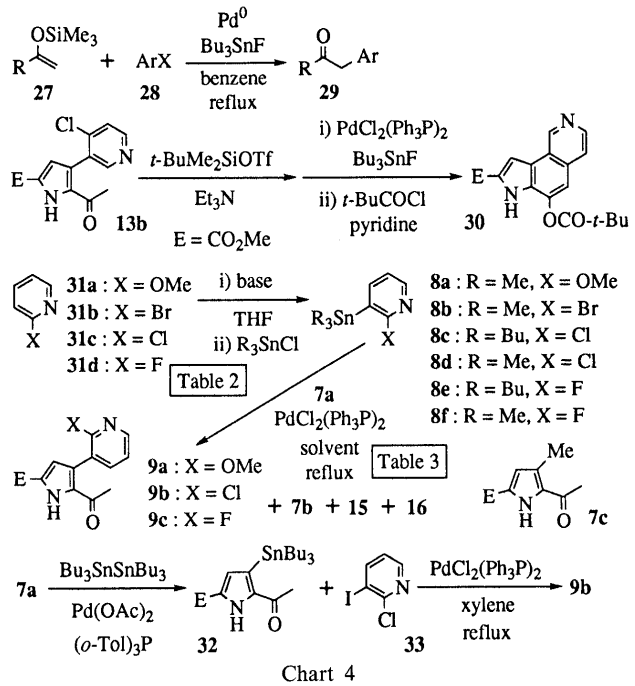

Chart 4

Table 2. Preparation of 2-Substituted 3-(Trialkylstannyl)pyridines **8** from 2-Substituted Pyridine **31**

Entry	Starting material	Base	Reagent	Product (yield %)	Recovery of **31**
1	**31a**	*tert*-BuLi	Me_3SnCl	**8a** (61)	8
2	**31b**	LDA	Me_3SnCl	**8b** (50)	43
3	**31c**	LDA	Bu_3SnCl	**8c** (52)	20
4	**31c**	LDA	Me_3SnCl	**8d** (50)	39
5	**31d**	LDA	Bu_3SnCl	**8e** (87)	—
6	**31d**	LDA	Me_3SnCl	**8f** (89)	—

Table 3. Stille Coupling of **7a** with **8** to Form **9**

Entry	Material	Catalyst	mol%	Solvent	Reflux time (h)	Product (yield %)	Recovery of **7a** (%)	By-product (yield %)
1	**8a**	$PdCl_2(Ph_3P)_2$	10	Xylene	8	**9a** (39)	—	**7b** (15), **7c** (23)
2	**8c**	$PdCl_2(Ph_3P)_2$	10	Xylene	10	**9b** (3)	18	**7b** (57), **15** (3), **16** (5)
3	**8d**	$PdCl_2(Ph_3P)_2$	10	Xylene	6	**9b** (21)	—	**7b** (12), **7c** (16), **15** (6), **16** (15)
4	**8e**	$PdCl_2[(o\text{-}Tol)_3P]_2$	5	Toluene	8	**9c** (21)	9	**7b** (61), bi-Py (11[a])
5	**8f**	$PdCl_2[(o\text{-}Tol)_3P]_2$	5	Toluene	14	**9c** (65)	—	**7b** (3), **7c** (8), **16** (6), bi-Py (14[a])

a) 2,2′-Difluoro-3,3′-bipyridine. Yield: calculated from **8e** or **8f**.

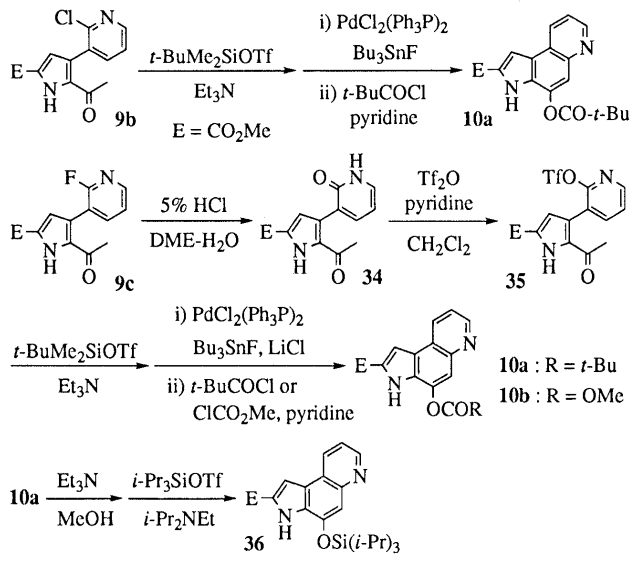

Chart 5

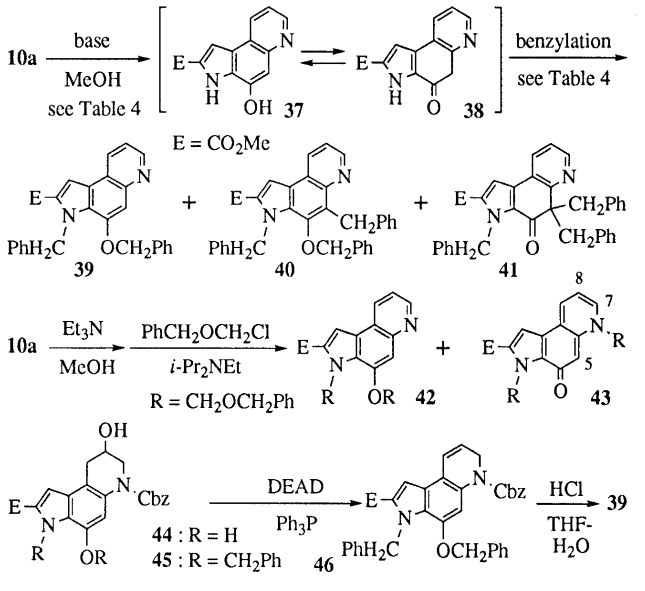

Chart 6

product. However, alkylation of the phenol **37** gave perplexing results (Chart 6). When **37** was submitted to benzylation reaction, the first site which accepted the benzyl group was the pyrrole nitrogen. Then introduction of the benzyl group occurred at either the phenol oxygen or the active methylene adjacent to the ketone form **38**. Three products were always obtained by benzylation reaction under varieties of conditions (Table 4); the yield of the *N,O*-dibenzyl derivative **39** was better than those of the others, but was still poor. Surprisingly, even under Mitsunobu conditions with diethyl azodicarboxylate (DEAD) and triphenylphosphine, *C*-benzylation products **40** and **41** were produced in considerable amounts (entry 4).

Trapping of **37** with benzyl chloromethyl ether and Hünig base[18] in dichloromethane at room temperature for 15 h afforded two products, **42** and **43**, in 23% and 42% yields, respectively. While the former was a usual *N,O*-disubstituted product, the latter was a hitherto unencountered compound, and exhibited an NMR pattern

Table 4. Conversion of Pivaloyl Ester **10a** to Benzyl Ethers

Entry	Reaction conditions for methanolysis	Reaction conditions for benzylation	Product (yield %) **39**	**40**	**41**
1	K_2CO_3, MeOH, r.t.	$PhCH_2Br$, NaH DMF, 0 °C	26	20	11
2	K_2CO_3, MeOH, r.t.	$PhCH_2Br$, K_2CO_3 acetone, reflux	44	21	30
3	Cs_2CO_3 MeOH, r.t.	$PhCH_2Br$, Cs_2CO_3 DMF, r.t.	35	25	20
4	Et_3N, MeOH, r.t.	$PhCH_2OH$, DEAD,Ph_3P, THF, r.t.	37	16	5

r.t. = room temperature.

(H_5: 6.53 ppm, s; H_7: 8.11 ppm, d, J=7 Hz; H_8: 6.66 ppm, dd, J=7, 7 Hz; H_9: 7.66 ppm, d, J=7 Hz) different from that of the pyridine derivative **42** (H_5: 7.65 ppm, s; H_7: 8.84 ppm, dd, J=4.5, 2 Hz; H_8: 7.38 ppm, dd, J=8.5, 4.5; H_9: 8.44 ppm, dd, J=8.5, 2 Hz). Therefore, compound **43** was deduced to be an N_a,N_b-disubstituted derivative of another valence tautomer of **37** and **38**.

The structure of **39** was firmly established by comparison with that of the compound derived from the previous work. Compound **44**[1] was converted to its dibenzyl derivative **45** in 84% yield by refluxing an acetone solution with benzyl bromide and potassium carbonate for 3 h. The hydroxy group in **45** was removed by dehydration under Mitsunobu conditions to give **46** in 78% yield. Treatment of **46** with *ca.* 3% hydrochloric acid in tetrahydrofuran (THF)–water (3 : 1) at room temperature for 40 h afforded **39** in 39% yield, accompanied by recovery of **46** in 35% yield. This clarified the structures of **10a** and **10b**, obtained by a novel palladium-catalyzed cyclization reaction.

Total Synthesis of Duocarmycin SA We now entered the final stage of the synthesis. The heteroaromatic compound **10a** was treated with potassium cyanide in the presence of either methyl chloroformate or benzyl chloroformate in a mixture of dichloromethane and water (4 : 1) at room temperature for 3 or 6 h (Chart 7).[19] The Reissert compound **47a** or **47b** was obtained in 92% or 93% yield along with the isomer **48a** or **48b** in 3% or 4% yield. As this reaction readily afforded **47a** and **47b** predominantly, conversion of these products to **53** was attempted in the hope that the cyano group would be instantaneously removed from **53** to give a suitable compound for further transformation. The diol derivative **49** was prepared as a single isomer from **47a** with a catalytic amount of osmium tetroxide and trimethylamine *N*-oxide in 76% yield, but the stereochemistry was not known. The hydroxy group at the benzylic position of **49** was eliminated by reduction with triethylsilane in the presence of boron trifluoride etherate to afford **50** in 89% yield, and this product was mesylated with methanesulfonyl chloride and triethylamine in dichloromethane. The unstable mesylate **52** was obtained in 76% yield together with **51** in *ca.* 10% yield. When this mesylate **52** was treated with potassium carbonate in methanol for preparation of **53**, the expected reaction did not occur, and formation of the fully aromatic compound **37** was detected on thin layer chromatography (TLC) of the crude reaction mixture.

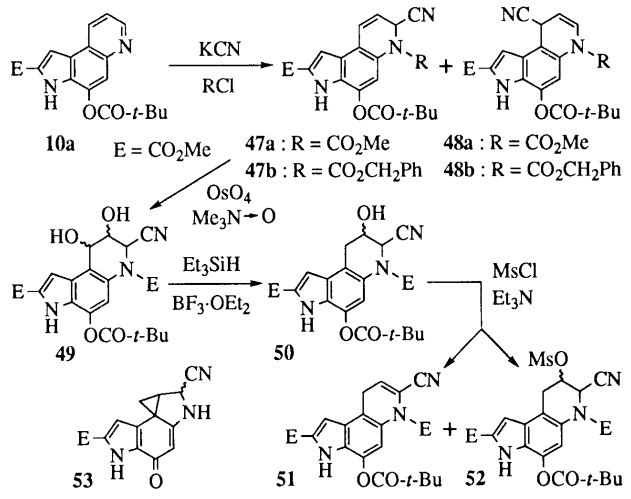

Chart 7

The dibenzyl derivative **39** was reduced with sodium borohydride in the presence of methyl chloroformate in a mixture of 2-propanol and THF (1 : 1) at room temperature (Chart 8). Immediately a single product was formed, but a separate experiment had revealed in advance that this was a borane adduct **56** of the starting compound. Without stopping the reaction at this point, the reaction mixture was stirred as it was for 4 h, and two products were obtained. However, the 1,4-dihydro compound **55** was so unstable that it was spontaneously converted back to the starting material during purification. Therefore, the 1,2-dihydro derivative **54** was isolated in 44% yield, along with recovered **39** in 25% yield.

The methyl carbonate **10b** was reduced with sodium borohydride and methyl chloroformate as above. In contrast to the dibenzyl case, the reaction proceeded very slowly and required a long stirring period (15 h) for completion. After work-up, the reaction mixture consisted of many products as seen on TLC, including the 1,2-dihydro derivative **11a** (52%), 1,4-dihydro derivative **11b** (21%), 9-hydroxytetrahydro derivative **57** (2%), and its 8-hydroxy isomer **6** (2%), together with the starting material **10b** (6%). Isolation of a borane adduct **56** in the reduction of **39** as stated above suggested that diborane was always produced in the reaction mixture, and this fact made possible to understand the formation of the by-products **57** and **6**, because the borane adducts of **11a** and **11b** might be oxidized by air to give alcohols as reported in the literature.[20] The dihydro derivatives **11a** and **11b** were separately oxidized to the diols **58** (89%) and **59**. The former was reduced with triethylsilane to afford **6** in 83% yield, while the latter, having a partial structure of α-carbinol carbamate, was directly subjected to reduction with triethylsilane to produce the same hydroxy compound **6** in 79% yield, calculated from **11b**.

These experiments meant that two products **11a** and **11b** among the four compounds derived from **10b** were readily convertible in good yield to **6**, which was itself another of the above four compounds. Therefore three operations, *i.e.*, i) dihydropyridine formation by treatment with sodium borohydride and methyl chloroformate, ii) diol formation with osmium tetroxide (a catalytic amount)

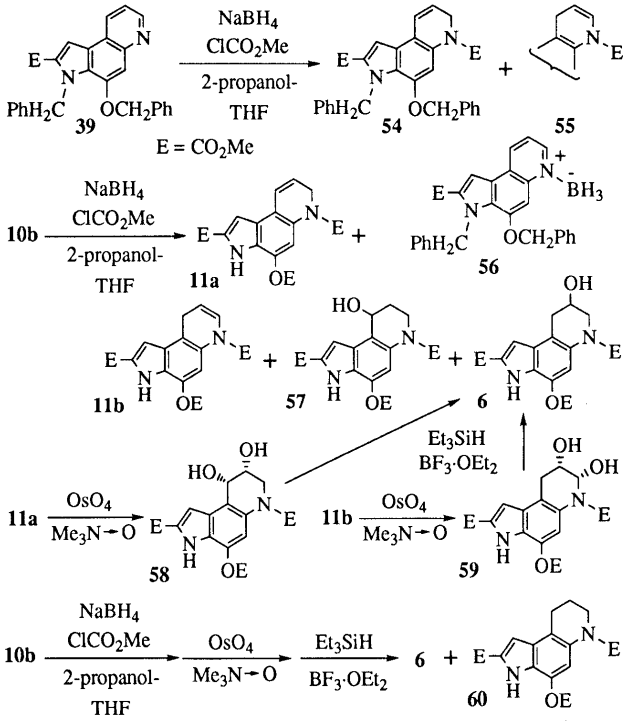

Chart 8

and trimethylamine *N*-oxide, and iii) reduction of hydroxy groups adjacent to the aromatic ring and the nitrogen atom using triethylsilane in the presence of boron trifluoride etherate, were successively applied to **10b**. The desired hydroxy compound **6** was obtained in 58% yield, accompanied by the formation of the tetrahydro derivative **60** originating from **57** in 6% yield.

For the completion of the total synthesis, **6** was mesylated to **61** in 97% yield, and **61** was treated with potassium carbonate in methanol at room temperature for 3 h (Chart 9). Methanolysis of the carbonate to **62**, formation of **63** of the cyclopropadienone structure,[21] and removal of the methoxycarbonyl group from the vinylogous amide nitrogen, proceeded successively during a single operation, and **64** was obtained in 93% yield. Previously we reported condensation of this compound with the imidazolide **65** using sodium hydride in *N*,*N*-dimethylformamide (DMF) and THF (2 : 1) to afford (±)-**1** in 60% yield.[1] This time, it was newly found that treatment of a DMF solution of **64** and **65** with potassium carbonate at room temperature was a suitable condition, affording (±)-**1** in 84% yield without recovery of the vinylogous amide **64**. Thus, our second-generation total synthesis of (±)-duocarmycin SA (**1**) was completed.

The hydroxy derivative **6** was converted to a dihydroxy compound **66** in 95% yield by treatment with triethylamine in methanol, and **66** was benzylated with benzyl bromide and potassium carbonate in refluxing acetone to afford **67** in 91% yield, accompanied by a by-product, the dibenzyl derivative **68** in 5% yield. The monobenzyl derivative **67** had been a key compound for optical resolution of the racemate, which had been accomplished by separation of the condensation product **69** between **67** and (*R*)-*O*-methylmandelic acid.[1b] As the separated compound **70** and its enantiomer had been transformed into natural

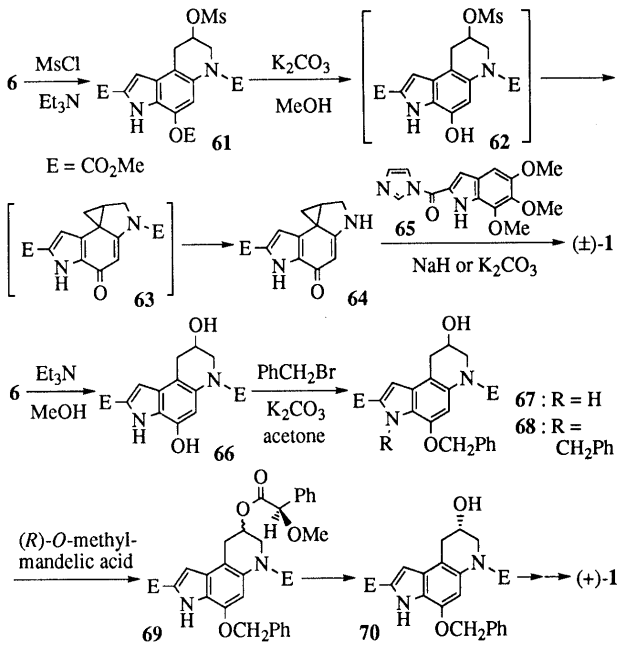

Chart 9

duocarmycin SA (+)-(**1**) and unnatural duocarmycin SA (−)-(**1**), preparation of **67** in this study constituted another total synthesis of (+)-**1** and (−)-**1**.

Asymmetric Induction Asymmetric dihydroxylation (AD) as reported by Sharpless and co-workers[22] was applied to the dihydropyridine derivatives **11a** and **11b** (Chart 10). When **11a** was treated with 3 mol% of osmium tetroxide, 6 eq of potassium ferricyanide(III), 5 mol% of 2,5-diphenyl-4,6-bis(9-*O*-dihydroquinyl)pyrimidine [$(DHQ)_2PYR$] (**71**), 4 eq of methanesulfonamide, and 3 eq of sodium bicarbonate in a mixture of *tert*-butanol and water (1 : 1) at 0—22 °C for 16 h, a dihydroxylated compound was produced in 69% yield, and the product was later determined to be (8*S*,9*R*)-**58**, obtained in 81% ee. This absolute configuration corresponds to that of unnatural (−)-duocarmycin SA. Next the chiral reagent was changed to 2,5-diphenyl-4,6-bis(9-*O*-dihydroquinidyl)pyrimidine [$(DHQD)_2PYR$], and the AD reaction of **11a** was carried out with 6 mol% of this reagent in the presence of the same amounts of other materials as above for 23 h. The product obtained in 75% yield was shown to be (8*R*,9*S*)-**58** having the correct absolute configuration, but unfortunately, in a rather low optical yield (58% ee).

Both AD products, (8*S*,9*R*)-**58** and (8*R*,9*S*)-**58**, were separately reduced with triethylsilane and boron trifluoride etherate to afford (8*R*)-**6** and (8*S*)-**6**, whose *O*-methyl carbonate was removed by treatment with triethylamine in methanol, and the resulting hydroxy-phenol derivatives were treated with 1,1′-(azodicarbonyl)dipiperidine (ADDP) in the presence of tributylphosphine as reported previously.[1] Compounds (7b*S*)-**63** and (7b*R*)-**63** obtained here were subjected to HPLC analysis using a chiral column. Optically pure (7b*R*)-**63**, synthesized previously from L-malic acid,[3c] was utilized as a standard sample, and the optical purity of the (7b*S*)-**63** and (7b*R*)-**63** samples, derived from the AD reaction, was determined as shown above.

Another dihydropyridine derivative **11b** was similarly

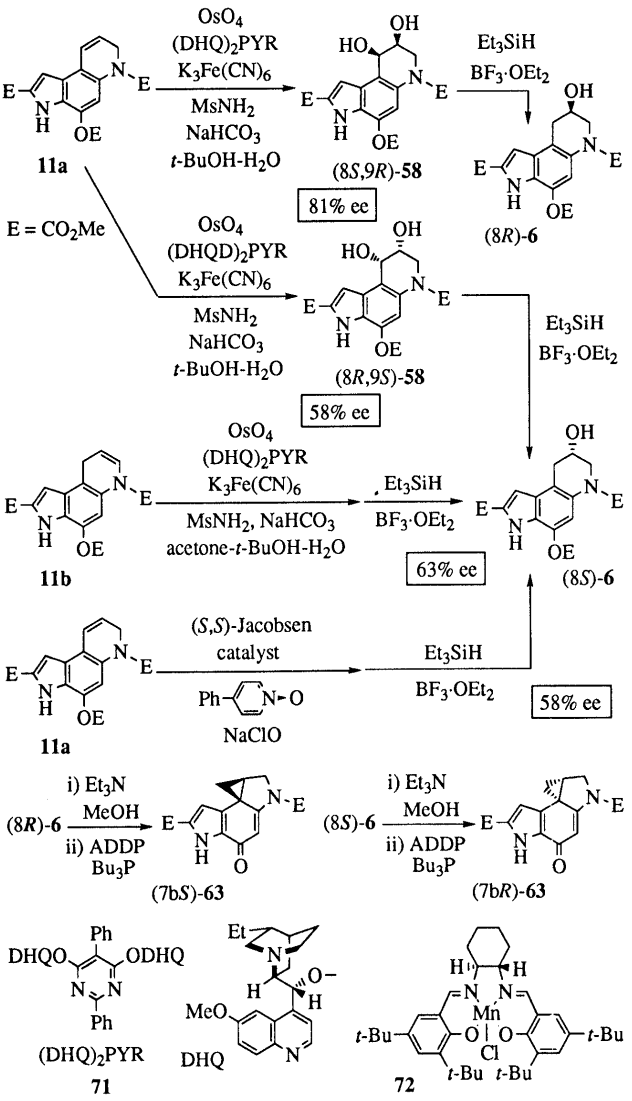

Chart 10

submitted to the AD reaction using $(DHQ)_2PYR$ in a mixture of acetone, *tert*-butanol, and water (1 : 2 : 2) for 19 h. Without purification, the crude product was reduced with triethylsilane as usual to give (8*S*)-**6** of 63% ee in 76% yield. As a whole, the Sharpless AD reaction did not give a satisfactory result; we therefore turned our attention to the asymmetric epoxidation reported by Jacobsen and co-workers.[23] Compound **11a** was treated with 10 mol% of (*S*,*S*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride [(*S*,*S*)-Jacobsen catalyst] (**72**), 0.25 eq of 4-phenylpyridine *N*-oxide, and 1.5 eq of sodium hypochlorite in dichloromethane at 0 °C for 30 min. The resulting crude product was reduced with triethylsilane to afford (8*S*)-**6** of 58% ee in 30% yield, along with the formation of **10b** in 10% yield. Thus, asymmetric induction of either **11a** or **11b** was unsuccessful. The Sharpless and Jacobsen reactions leading to (8*S*)-**6**, the compound of the desired correct absolute configuration, both proceeded in poor optical yields.[24] Therefore, for asymmetric synthesis of duocarmycin SA, a total synthesis starting from an optically active compound[3c] seemed to be required. The details will be reported in the near future.

Summary Stille coupling reaction between **7** and **8** was

investigated in detail, and 2-fluoro-3-(trimethylstannyl)-pyridine (**8f**) was concluded to be the best substrate for condensation with **7a** (Chart 4). The most important finding was an application of the palladium-catalyzed methyl ketone-arylation reaction reported by Kuwajima to the construction of heteroaromatic phenol derivatives (Chart 5). The α-pyridyltriflate **35** rather than the chloride **9b** was a suitable compound for this reaction, and brief treatment with a palladium catalyst in the presence of tin fluoride and lithium chloride afforded **10a** and **10b** in excellent yields. Conversion of **10b** to **6** was carried out by application of three operations without isolation of intermediary reaction products (Chart 8). Thus i) partial reduction of **10b** to dihydropyridine derivatives, ii) dihydroxylation of the double bonds formed, and iii) reductive elimination of one of the hydroxy groups, afforded **6** in fairly good yield. Compound **6** was readily converted to relay compounds **64** and **67** of the previous paper,[1b] thus completing total syntheses of (±)-, (+)-, and (−)-duocarmycin SA (Chart 9).

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 in $CDCl_3$ unless otherwise specified 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.

4-Chloro-3-(tributylstannyl)pyridine (12b) A hexane solution of BuLi (1.64 M, 7.09 ml, 11.6 mmol) was added to a THF solution (30 ml) of iso-Pr_2NH (1.85 ml, 13.2 mmol) at −18 °C, and the mixture was stirred under an Ar atmosphere at that temperature for 20 min. The mixture was then cooled to −81 °C, and a THF solution (5 ml) of 4-chloropyridine (1.20 g, 10.6 mmol) was added dropwise to it. The whole was stirred at −81—−76 °C for 30 min, and then Bu_3SnCl (3.05 ml, 11.2 mmol) was slowly added. Stirring was continued at −76—−65 °C for 30 min and at 21 °C for 30 min. Saturated NH_4Cl–H_2O was added, and the mixture was extracted with EtOAc, then worked up as usual. The crude product was purified by column chromatography using SiO_2 (80 g) and hexane–EtOAc (9 : 1) as an eluent to give **12b** (3.57 g, 84%) as a colorless oil. GCMS *m/z*: 350 (14), 348 (29), 346 (75), 345 (29), 344 (53), 343 (17) and 342 (26) ($M^+ - Bu$); 294 (7), 292 (14), 290 (39), 289 (14), 288 (29), 287 (9) and 286 (14); 238 (10), 236 (21), 234 (55), 233 (18), 232 (54), 231 (17) and 230 (33); 155 (46); 57 (100). ^{1}H-NMR δ: 0.67—2.14 (27H, m), 7.26 (1H, d, *J* = 5 Hz), 8.41 (1H, d, *J* = 5 Hz), 8.50 (1H, s).

5-Chloro-3-(tributylstannyl)pyridine (12c) A hexane solution of BuLi (1.64 M, 2.41 ml, 3.95 mmol) was added to a cooled (−18 °C) solution of hexabutylditin (2.29 g, 3.95 mmol) in THF (12 ml) under an Ar atmosphere, and the solution was stirred at that temperature for 10 min and at 0 °C for 30 min. The solution was cooled again at −83 °C, and a THF solution (3 ml) of 3,5-dichloropyridine (615 mg, 4.16 mmol) was added in one portion. The mixture was stirred at −83—−75 °C for 40 min and at 0 °C for 30 min, then poured into saturated NH_4Cl–H_2O. Extraction with EtOAc, usual work-up and purification by SiO_2 column chromatography [50 g, hexane–EtOAc (39 : 1)] afforded **12c** (1.13 g, 71% from hexabutylditin) as a colorless oil. GCMS *m/z*: 350 (14), 348 (28), 346 (69), 345 (27), 344 (51), 343 (18) and 342 (25) ($M^+ - Bu$); 294 (11), 292 (25), 290 (57), 289 (22), 288 (44), 287 (16) and 286 (24); 238 (20), 236 (41), 234 (100), 233 (34), 232 (98), 231 (31) and 230 (62). ^{1}H-NMR δ: 0.68—1.79 (27H, m), 7.65-7.79 (1H, m), 8.35—8.63 (2H, m).

Stille Coupling of 7a and 17 with 12 Preparation of methyl 5-acetyl-4-(3-pyridinyl)-1*H*-pyrrole-2-carboxylate (**13a**) is described as a typical example. A toluene solution (6 ml) of **7a** (160 mg, 0.650 mmol), **12a** (264 mg, 0.717 mmol), and $PdCl_2(Ph_3P)_2$ (23 mg, 0.033 mmol) was stirred under reflux for 7 h. After the mixture had cooled, 2 N HCl–H_2O was added and the whole was extracted with CH_2Cl_2. The organic layer was washed with saturated $NaHCO_3$–H_2O and treated as usual to give a neutral residue (248 mg). The aqueous layer was made basic with powdered $NaHCO_3$ and the mixture was extracted with CH_2Cl_2, then worked up as usual. The resulting crystalline basic residue (162 mg) was recrystallized from CH_2Cl_2–hexane, followed by PTLC separation (3% MeOH–CH_2Cl_2) of the residue obtained from the mother liquor of the above recrystallization to afford **13a** (143 mg, 90%) as colorless prisms, mp 189—190 °C, and **14a**[25] (8 mg, 14% from **12a**). **13a**: *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 63.87; H, 5.04; N, 11.45. HRMS Calcd for $C_{13}H_{12}N_2O_3$: 244.0847. Found: 244.0841. MS *m/z*: 244 (M^+, 74), 229 (11), 212 (10), 211 (11), 197 (100), 184 (13), 141 (22), 43 (39). IR (KBr) cm^{-1}: 1707, 1654. ^{1}H-NMR δ: 2.12 (3H, s), 3.92 (3H, s), 6.89 (1H, d, *J* = 2.5 Hz, changed to s with D_2O), 7.38 (1H, dd, *J* = 8, 5 Hz), 7.74 (1H, ddd, *J* = 8, 2, 2 Hz), 8.59—8.82 (2H, m), 10.17 (1H, br s, NH). The neutral residue was purified by PTLC [hexane–EtOAc (5 : 2)] to afford **7b**[11] (2 mg, 2%), colorless needles, mp 112—113 °C (CH_2Cl_2–hexane), and methyl 5-acetyl-4-(triphenylphosphoranylidene)pyrrole-2-carboxylate (**15**) (2 mg, 1%). HRMS Calcd for $C_{26}H_{22}NO_3P$: 427.1336. Found: 427.1343. MS *m/z*: 427 (M^+, 100), 412 (27), 369 (40), 262 (18), 183 (53), 108 (23), 77 (18), 43 (47). IR ($CHCl_3$) cm^{-1}: 1695, 1636. ^{1}H-NMR δ: 2.52 (3H, s), 3.87 (3H, s), 6.91 (1H, d, *J* = 4.5 Hz), 7.27—7.85 (15H, m).

Similarly, **7a** (50 mg, 0.20 mmol) was reacted with **12b** (90 mg, 0.22 mmol) in the presence of $PdCl_2(Ph_3P)_2$ (14 mg, 0.020 mmol) in boiling xylene (5 ml) for 13 h to afford methyl 5-acetyl-4-(4-chloro-3-pyridinyl)-1*H*-pyrrole-2-carboxylate (**13b**) (15.5 mg, 27%), **7b** (13 mg, 38%), **14b**[12] (4 mg, 16% from **12b**), **15** (3.5 mg, 4%), and dimethyl 5,5′-diacetyl-4,4′-bi-1*H*-pyrrole-2,2′-dicarboxylate (**16**) (3.5 mg, 10%). **13b**: Colorless prisms, mp 143—144 °C (CH_2Cl_2–hexane). HRMS Calcd for $C_{13}H_{11}{}^{37}ClN_2O_3$ and $C_{13}H_{11}{}^{35}ClN_2O_3$: 280.0428 and 278.0457. Found: 280.0417 and 278.0453. MS *m/z*: 280 (3) and 278 (8) (M^+), 243 (99), 233 (14) and 231 (40), 211 (100), 43 (49). IR (KBr) cm^{-1}: 1724, 1660. ^{1}H-NMR δ: 2.06 (3H, s), 3.92 (3H, s), 6.89 (1H, br s), 7.49 (1H, d, *J* = 5 Hz), 8.62 (1H, d, *J* = 5 Hz), 8.66 (1H, s), 10.68 (1H, br s, NH). **16**: Colorless prisms, mp 233—235 °C (MeOH–CH_2Cl_2). *Anal.* Calcd for $C_{16}H_{16}N_2O_6$: C, 57.83; H, 4.85; N, 8.43. Found: C, 57.56; H, 4.88; N, 8.45. HRMS Calcd for $C_{16}H_{16}N_2O_6$: 332.1007. Found: 332.1012. MS *m/z*: 332 (M^+, 4), 289 (74), 257 (100), 225 (57), 43 (58). IR (KBr) cm^{-1}: 1735, 1653. ^{1}H-NMR δ: 2.06 (6H, s), 3.91 (6H, s), 6.84 (2H, s), 10.04 (2H, br s, NH).

Similarly, **7a** (155 mg, 0.630 mmol) was reacted with **12c** (280 mg, 0.694 mmol) in the presence of $PdCl_2(Ph_3P)_2$ (22 mg, 0.031 mmol) in boiling toluene (6 ml) for 4 h to afford methyl 5-acetyl-4-(5-chloro-3-pyridinyl)-1*H*-pyrrole-2-carboxylate (**13c**) (157.5 mg, 90%) and 5,5′-dichloro-3,3′-bipyridine (**14c**) (12 mg, 15% from **12c**). **13c**: Colorless needles, mp 176—177 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{13}H_{11}ClN_2O_3$: C, 56.02; H, 3.98; N, 10.05. Found: C, 55.76; H, 4.01; N, 10.04. HRMS Calcd for $C_{13}H_{11}{}^{37}ClN_2O_3$ and $C_{13}H_{11}{}^{35}ClN_2O_3$: 280.0428 and 278.0457. Found: 280.0404 and 278.0457. MS *m/z*: 280 (25) and 278 (75) (M^+), 265 (5) and 263 (15), 248 (6) and 246 (15), 233 (34) and 231 (100), 177 (9) and 175 (20), 43 (52). IR (KBr) cm^{-1}: 1720, 1662. ^{1}H-NMR δ: 2.17 (3H, s), 3.92 (3H, s), 6.89 (1H, d, *J* = 2.5 Hz, changed to s with D_2O), 7.75 (1H, dd, *J* = 2, 2 Hz), 8.57 (1H, br d, *J* = 2 Hz), 8.64 (1H, br d, *J* = 2 Hz), 10.23 (1H, br s, NH). **14c**: Colorless prisms, mp 180—181 °C (CH_2Cl_2–hexane). HRMS Calcd for $C_{10}H_6{}^{37}Cl_2N_2$, $C_{10}H_6{}^{37}Cl^{35}ClN_2$ and $C_{10}H_6{}^{35}Cl_2N_2$: 227.9849, 225.9878 and 223.9908. Found: 227.9835, 225.9869 and 223.9922. MS *m/z*: 228 (12), 226 (72) and 224 (100) (M^+); 191 (10) and 189 (30); 164 (5) and 162 (12). ^{1}H-NMR δ: 7.88 (2H, dd, *J* = 2, 1.5 Hz), 8.66 (2H, d, *J* = 2 Hz), 8.73 (2H, d, *J* = 1.5 Hz).

Similarly, 2-bromoacetophenone (**17**) (209 mg, 1.05 mmol) was reacted with **12a** (425 mg, 1.15 mmol) in the presence of $PdCl_2(Ph_3P)_2$ (37 mg, 0.053 mmol) in boiling toluene (6 ml) for 4 h to afford 3-(2-acetylphenyl)pyridine (**18**) (178 mg, 86%) and **14a** (10.5 mg, 12% from **12a**). **18**: Colorless syrup. HRMS Calcd for $C_{13}H_{11}NO$: 197.0840. Found: 197.0840. MS *m/z*: 197 (M^+, 11), 182 (100), 154 (14), 127 (26), 43 (19). IR (neat) cm^{-1}: 1691. ^{1}H-NMR δ: 2.19 (3H, s), 7.24—7.80 (6H, m), 8.53—8.76 (2H, m).

***N*-Oxidation of 13a, 13c, and 18 to Form 19a, 19b, and 21** Preparation of **19a** is described as a typical example. *m*-CPBA (56 mg, 0.32 mmol) was added to a CH_2Cl_2 solution (5 ml) of **13a** (53 mg, 0.22 mmol) at

0 °C, and the mixture was stirred at 0 °C for 5 min and at 21 °C for 2 h. Saturated $NaHCO_3$–H_2O and NaCl were successively added to this and the whole was thoroughly extracted with 10% MeOH–CH_2Cl_2. Usual work-up followed by purification by PTLC (5% MeOH–CH_2Cl_2) afforded methyl 5-acetyl-4-(1-oxido-3-pyridinyl)-1*H*-pyrrole-2-carboxylate (**19a**) (53 mg, 94%) as colorless needles, mp 199—200 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.87; H, 4.72; N, 10.79. HRMS Calcd for $C_{13}H_{12}N_2O_4$: 260.0796. Found: 260.0800. MS *m/z*: 260 (M^+, 100), 244 (48), 213 (24), 197 (70), 191 (39), 141 (27), 43 (79). IR (KBr) cm^{-1}: 1724, 1665. ^{1}H-NMR (10% CD_3OD–$CDCl_3$) δ: 2.37 (3H, s), 3.93 (3H, s), 6.95 (1H, s), 7.31—7.65 (2H, m), 8.28 (1H, ddd, J=5, 1.5, 1.5 Hz), 8.41 (1H, dd, J=1.5, 1.5 Hz).

Similarly, oxidation of **13c** (27 mg, 0.097 mmol) with *m*-CPBA (42 mg, 0.24 mmol) at 17 °C for 18 h afforded 5-acetyl-4-(5-chloro-1-oxido-3-pyridinyl)-1*H*-pyrrole-2-carboxylate (**19b**) (22.5 mg, 79%) as colorless prisms, mp 234—236 °C (MeOH–CH_2Cl_2). HRMS Calcd for $C_{13}H_{11}{}^{37}ClN_2O_4$ and $C_{13}H_{11}{}^{35}ClN_2O_4$: 296.0377 and 294.0407. Found: 296.0393 and 294.0418. MS *m/z*: 296 (2) and 294 (6) (M^+), 280 (7) and 278 (18), 249 (6) and 247 (22), 233 (18) and 231 (35), 191 (48), 176 (28), 43 (100). IR (KBr) cm^{-1}: 1723, 1672. ^{1}H-NMR (10% CD_3OD–$CDCl_3$) δ: 2.40 (3H, s), 3.92 (3H, s), 6.92 (1H, s), 7.48 (1H, dd, J=1.5, 1.5 Hz), 8.22—8.36 (2H, m).

Similarly, **18** (82 mg, 0.42 mmol) was oxidized with *m*-CPBA (108 mg, 0.626 mmol) at 24 °C for 2 h to afford 3-(2-acetylphenyl)pyridine 1-oxide (**21**) (84 mg, 95%) as a colorless syrup. HRMS Calcd for $C_{13}H_{11}NO_2$: 213.0789. Found: 213.0790. MS *m/z*: 213 (M^+, 100), 181 (39), 144 (40), 129 (58), 43 (49). IR (neat) cm^{-1}: 1692. ^{1}H-NMR δ: 2.42 (3H, s), 7.10—7.89 (6H, m), 8.14—8.34 (2H, m).

3-[[(4-*tert*-Butyldimethylsilyl)oxy]-1-naphthalenyl]-(*Z*)-propenecarboxaldehyde *O*-(*tert*-Butyldimethylsilyl)oxime (22) TBDMSOSO$_2$CF$_3$ (TBDMSOTf) (0.26 ml, 1.1 mmol) was added to a CH_2Cl_2 solution (4 ml) of **21** (40 mg, 0.19 mmol) and Et_3N (0.31 ml, 2.2 mmol) at 0 °C under an Ar atmosphere. The solution was stirred at 0 °C for 5 min and at 23 °C for 2.5 h, then saturated $NaHCO_3$–H_2O was added to it. Extraction with CH_2Cl_2, usual work-up, and purification by PTLC [hexane–EtOAc (39 : 1)] afforded **22** (54 mg, 65%), 3-[[2-(1-*tert*-butyldimethylsilyloxy)-ethenyl]phenyl]pyridine (silyl enol ether of **18**) (6 mg, 10%), and 3-[[2-(1-*tert*-butyldimethylsilyloxy)ethenyl]phenyl]pyridine 1-oxide (silyl enol ether of **21**) (13 mg, 21%) in order of increasing polarity. **22**: Colorless glass. HRMS Calcd for $C_{25}H_{39}NO_2Si_2$: 441.2517. Found: 441.2531. MS *m/z*: 441 (M^+, 21), 384 (8), 357 (28), 310 (27), 283 (17), 252 (16), 102 (19), 75 (50), 73 (100). IR ($CHCl_3$) cm^{-1}: 1583. ^{1}H-NMR δ: 0.17 (6H, s), 0.28 (6H, s), 0.91 (9H, s), 1.08 (9H, s), 6.54 (1H, dd, J=10, 10 Hz), 6.83 (1H, d, J=8.5 Hz), 7.25 (1H, d, J=8.5 Hz), 7.28 (1H, d, J=10 Hz), 7.35—7.62 (2H, m), 7.74—7.99 (1H, m), 8.13 (1H, d, J=10 Hz), 8.13—8.38 (1H, m). Silyl enol ether of **18**: Colorless glass. HRMS Calcd for $C_{19}H_{25}NOSi$: 311.1704. Found: 311.1684. MS *m/z*: 311 (M^+, 26), 254 (69), 180 (94), 75 (100), 73 (31), 57 (14). IR ($CHCl_3$) cm^{-1}: 1619. ^{1}H-NMR δ: −0.04 (6H, s), 0.68 (9H, s), 4.42 (2H, s), 7.18—7.60 (5H, m), 7.81 (1H, ddd, J=8, 1.5, 1.5 Hz), 8.48—8.63 (1H, m), 8.68—8.83 (1H, m). Silyl enol ether of **21**: Colorless glass. HRMS Calcd for $C_{19}H_{25}NO_2Si$: 327.1653. Found: 327.1658. MS *m/z*: 327 (M^+, 89), 310 (21), 270 (28), 252 (78), 196 (26), 180 (33), 75 (86), 73 (100). IR ($CHCl_3$) cm^{-1}: 1622. ^{1}H-NMR δ: 0.02 (6H, s), 0.72 (9H, s), 4.48 (2H, s), 7.13—7.60 (6H, m), 8.17 (1H, ddd, J=5.5, 1.5, 1.5 Hz), 8.32—8.45 (1H, m).

4-Hydroxy-1-naphthalenecarboxaldehyde (23) OsO_4 (1 mg, 4 μmol) and $NaIO_4$ (112 mg, 0.523 mmol) were added to a solution of **22** (23 mg, 0.052 mmol) in THF (3 ml) and H_2O (1 ml), and the mixture was stirred at 23 °C for 40 h. Saturated $Na_2S_2O_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [benzene–EtOAc (3 : 1)] afforded **23** (7 mg, 78%) as colorless prisms, mp 182—183 °C (Et_2O–hexane). HRMS Calcd for $C_{11}H_8O_2$: 172.0524. Found: 172.0527. MS *m/z*: 172 (M^+, 98), 171 (100), 143 (26), 115 (57), 89 (13), 63 (13). IR (KBr) cm^{-1}: 1647, 1620. ^{1}H-NMR (10% CD_3OD–$CDCl_3$) δ: 6.96 (1H, d, J=8 Hz), *ca.* 7.44—7.85 (2H, m), 7.85 (1H, d, J=8 Hz), 8.28—8.49 (1H, m), 9.19—9.39 (1H, m), 10.13 (1H, s).

Methyl 6-(Pivaloyloxy)-1*H*-pyrrolo[2,3-*h*]isoquinoline-8-carboxylate (30) TBDMSOTf (39 μl, 0.17 mmol) was added to a cooled (0 °C) solution of **13b** (19 mg, 0.068 mmol) and Et_3N (38 μl, 0.27 mmol) in CH_2Cl_2 (3 ml) under an Ar atmosphere, and the mixture was stirred at 0 °C for 1 h. Saturated $NaHCO_3$–H_2O was added, and the whole was extracted with CH_2Cl_2, then worked up as usual to give a residue (32 mg). A xylene solution (3 ml) of this, Bu_3SnF (53 mg, 0.17 mmol), and $PdCl_2(Ph_3P)_2$ (10 mg, 0.014 mmol) was stirred under reflux for 8 h. The solvent was evaporated *in vacuo*, and the residue was dissolved in pyridine (2 ml). Pivaloyl chloride (50 μl, 0.41 mmol) was added at 0 °C, and the mixture was stirred at 23 °C for 3 h. Addition of saturated $NaHCO_3$–H_2O, extraction with CH_2Cl_2, usual work-up, and purification by PTLC [benzene–EtOAc (2 : 1)] afforded a crude product (21 mg), which was further purified by PTLC (CH_2Cl_2) to give **30** (6.5 mg, 29%) as colorless needles, mp 217—219 °C (dec.) (CH_2Cl_2–hexane). HRMS Calcd for $C_{18}H_{18}N_2O_4$: 326.1265. Found: 326.1259. MS *m/z*: 326 (M^+, 18), 242 (21), 210 (25), 57 (100). IR (KBr) cm^{-1}: 1748, 1726. ^{1}H-NMR δ: 1.47 (9H, s), 3.98 (3H, s), 7.50 (1H, s), 7.67 (1H, d, J=5.5 Hz), 7.81 (1H, d, J=2 Hz, changed to s with D_2O), 8.59 (1H, d, J=5.5 Hz), 9.34 (1H, br s, NH), 9.61 (1H, s).

Preparation of 2-Substituted 3-(Trialkylstannyl)pyridines (8a—f) Preparation of 2-fluoro-3-(trimethylstannyl)pyridine (**8f**) is described as a typical example. BuLi (1.69 M in hexane, 20.3 ml, 34.3 mmol) was added to a cooled (−20 °C) solution of iso-Pr_2NH (5.23 ml, 37.4 mmol) in THF (50 ml) under an Ar atmosphere. This solution was stirred at the same temperature for 20 min and cooled to −78 °C. A THF solution (5 ml) of **31d** (3.02 g, 31.1 mmol) was added dropwise to the above solution, and stirring was continued at −78—−70 °C for 2.5 h. Then a THF solution (10 ml) of Me_3SnCl (6.50 g, 32.7 mmol) was added, and the whole was stirred at −74—−60 °C for 45 min and at 0 °C for 45 min. The mixture was poured into saturated NH_4Cl–H_2O, and extraction with EtOAc followed by usual work-up and purification by SiO_2 (100 g) column chromatography [hexane–EtOAc (9 : 1)] afforded **8f** (7.27 g, 89%) as a colorless oil. GCHRMS Calcd for $C_8H_{12}FNSn$: 260.9974. Found: 260.9974. GCMS *m/z*: 265 (0.3), 263 (0.8), 261 (1.9), 260 (0.8), 259 (1.1), 258 (0.3) and 257 (0.5) (M^+); 250 (18), 248 (14), 246 (100), 245 (32), 244 (74), 243 (27) and 242 (44); 235 (3), 233 (3), 231 (18), 230 (7), 229 (13), 228 (6) and 227 (8); 220 (3), 218 (2), 216 (18), 215 (7), 214 (14), 213 (6) and 212 (9); 143 (14), 141 (13), 139 (77), 138 (20), 137 (58), 136 (19) and 135 (62); 92 (36); 65 (11). ^{1}H-NMR δ: 0.36 (9H, s), 7.12 (1H, ddd, J=7, 5, 3.5 Hz), 7.83 (1H, ddd, J=7, 7, 2 Hz), 8.18 (1H, dd, J=5, 2 Hz).

Similarly, **31a** (1.00 g, 9.17 mmol) in THF (30 ml) was lithiated with a 1.7 M pentane solution of *tert*-BuLi (7.02 ml, 11.9 mmol) under an Ar atmosphere at −78—−72 °C for 1 h, followed by addition of a THF solution (5 ml) of Me_3SnCl (1.92 g, 9.65 mmol) at −72 °C. The same treatment as above afforded 2-methoxy-3-(trimethylstannyl)pyridine (**8a**) (1.53 g, 61%), along with the recovered **31a** (80 mg, 8%). **8a**: Colorless oil. GCHRMS Calcd for $C_9H_{15}NOSn$: 273.0174. Found: 273.0166. GCMS *m/z*: 277 (0.3), 275 (0.5), 273 (1.9), 272 (0.4), 271 (1.2), 270 (0.4) and 269 (0.9) (M^+); 262 (19), 260 (15), 258 (100), 257 (31), 256 (76), 255 (28) and 254 (44); 232 (12), 230 (8), 228 (53), 227 (18), 226 (41), 225 (14) and 224 (25); 202 (5), 200 (4), 198 (21), 197 (8), 196 (17), 195 (7) and 194 (10); 139 (4), 137 (3), 135 (18), 134 (8), 133 (15), 132 (6) and 131 (9). ^{1}H-NMR δ: 0.27 (3H, s), 3.90 (3H, s), 6.82 (1H, dd, J=6.5, 5 Hz), 7.63 (1H, dd, J=6.5, 2 Hz), 8.13 (1H, dd, J=5, 2 Hz).

Treatment of **31b** (1.05 g, 6.65 mmol) with LDA in the same manner as described for the preparation of **8f**, followed by reaction with Me_3SnCl (1.45 g, 7.29 mmol) afforded 2-bromo-3-(trimethylstannyl)pyridine (**8b**) (1.07 g, 50%) and recovered **31b** (0.45 g, 43%). **8b**: Colorless oil. GCMS *m/z*: 312 (10), 310 (18), 308 (65), 307 (23), 306 (100), 305 (34), 304 (68), 303 (16) and 302 (27) (M^+ − Me); 297 (2), 295 (4), 293 (13), 292 (5), 291 (19), 290 (8), 289 (13), 288 (4) and 287 (6); 205 (7), 203 (13), 201 (44), 200 (10), 199 (66), 198 (19), 197 (47), 196 (10) and 195 (18); 139 (7), 137 (6), 135 (41), 134 (14), 133 (33), 132 (12) and 131 (19); 92 (42). ^{1}H-NMR δ: 0.40 (9H, s), 7.20 (1H, dd, J=7, 5 Hz), 7.63 (1H, dd, J=7, 2 Hz), 8.29 (1H, dd, J=5, 2 Hz).

Similarly, **31c** (2.20 g, 19.4 mmol) and Bu_3SnCl (5.78 ml, 21.3 mmol) afforded 2-chloro-3-(tributylstannyl)pyridine (**8c**) (4.08 g, 52%) and recovered **31c** (0.44 g, 20%). **8c**: Colorless oil. GCMS *m/z*: 273 (19), 271 (35), 269 (100), 268 (39), 267 (73), 266 (23) and 265 (39) (M^+ − Cl − Bu − CH_2 = $CHCH_3$); 217 (7), 215 (10), 213 (26), 212 (11), 211 (20), 210 (8) and 209 (13); 181 (7), 179 (8), 177 (37), 176 (13), 175 (27), 174 (10) and 173 (15); 159 (10), 157 (19), 155 (49), 154 (15), 153 (35), 152 (11) and 151 (22); 57 (67). ^{1}H-NMR δ: 0.68—2.10 (27H, m), 7.13 (1H, dd, J=7.5, 5 Hz), 7.71 (1H, dd, J=7.5, 2 Hz), 8.31 (1H, dd, J=5, 2 Hz).

Similarly, **31e** (1.20 g, 10.6 mmol) and Me_3SnCl (2.20 g, 11.1 mmol) afforded 2-chloro-3-(trimethylstannyl)pyridine (**8d**) (1.46 g, 50%) and recovered **31e** (0.47 g, 39%). **8d**: Colorless oil. GCMS *m/z*: 266 (18), 264

(38), 262 (100), 261 (32), 260 (70), 259 (21) and 258 (35) ($M^+ - Me$); 251 (4), 249 (8), 247 (23), 246 (8), 245 (16), 244 (6) and 243 (8); 155 (78); 135 (39); 92 (52). ^{1}H-NMR δ: 0.40 (9H, s), 7.15 (1H, dd, J=7, 5 Hz), 7.72 (1H, dd, J=7, 2 Hz), 8.31 (1H, dd, J=5, 2 Hz).

Similarly, **31d** (1.00 g, 10.3 mmol) and Bu_3SnCl (2.94 ml, 10.8 mmol) afforded 2-fluoro-3-(tributylstannyl)pyridine (**8e**) (3.48 g, 87%) as a colorless oil. GCMS m/z: 334 (10), 332 (9), 330 (61), 329 (23), 328 (46), 327 (18) and 326 (25) ($M^+ - Bu$); 278 (14), 276 (11), 274 (74), 273 (27), 272 (57), 271 (22) and 270 (34); 220 (13), 218 (44), 216 (66), 215 (22), 214 (45), 213 (11) and 212 (18); 57 (100). ^{1}H-NMR δ: 0.69—1.98 (27H, m), 7.13 (1H, ddd, J=7, 5, 3.5 Hz), 7.83 (1H, ddd, J=7, 7, 2 Hz), 8.19 (1H, dd, J=5, 2 Hz).

Stille Coupling Reaction of 7a and 8 to Form 9 Preparation of methyl 5-acetyl-4-(2-fluoro-3-pyridinyl)-1*H*-pyrrole-2-carboxylate (**9c**) is described as a typical example. A toluene solution (10 ml) of **7a** (299 mg, 1.22 mmol), **8f** (365 mg, 1.40 mmol), and $PdCl_2[(o\text{-}Tol)_3P]_2$ (45 mg, 0.060 mmol) was refluxed under an Ar atmosphere for 14 h. Saturated $NaHCO_3$–H_2O was added, and the whole was extracted with CH_2Cl_2. Usual work-up followed by purification by PTLC [benzene–EtOAc (4 : 1)] afforded 2,2′-difluoro-3,3′-bipyridine (185 mg, 14% from **8f**), a mixture of **7b** and **7c**, **9c** (206 mg, 65%), and **16** (12.5 mg, 6%) in order of increasing polarity. The mixture of **7b** and **7c** was separated by PTLC [hexane–THF (7 : 1)] to give **7b** (6.5 mg, 3%) as a less polar substance and 5-acetyl-4-methyl-1*H*-pyrrole-2-carboxylate (**7c**) (18 mg, 8%) as a more polar substance. **9c**: Colorless prisms, mp 121—122 °C ($MeOH$–CH_2Cl_2). *Anal.* Calcd for $C_{13}H_{11}FN_2O_3$: C, 59.54; H, 4.23; N, 10.09. Found: C, 59.45; H, 4.28; N, 10.89. HRMS Calcd for $C_{13}H_{11}FN_2O_3$: 262.0753. Found: 262.0755. MS m/z: 262 (M^+, 65), 247 (12), 230 (8), 215 (100), 159 (26), 43 (34). IR (KBr) cm^{-1}: 1708, 1653. ^{1}H-NMR δ: 2.17 (3H, s), 3.93 (3H, s), 6.91 (1H, d, J=2.5 Hz, changed to s with D_2O), 7.31 (1H, ddd, J=7.5, 5, 2 Hz), 7.83 (1H, ddd, J=9, 7.5, 2 Hz), 8.31 (1H, ddd, J=5, 2, 1 Hz), 10.33 (1H, br s, NH). 2,2′-Difluoro-3,3′-bipyridine: Colorless needles, mp 153—154 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{10}H_6F_2N_2$: C, 62.50; H, 3.15; N, 14.58. Found: C, 62.61; H, 3.27; N, 14.68. HRMS Calcd for $C_{10}H_6F_2N_2$: 192.0499. Found: 192.0491. MS m/z: 192 (M^+, 100), 165 (6), 146 (6), 121 (6). ^{1}H-NMR δ: 7.31 (2H, dd, J=7.5, 5 Hz), 7.76—8.07 (2H, m), 8.30 (2H, dd, J=5, 2 Hz). **7c**: Colorless prisms, mp 98—99 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.67; H, 6.12; N, 7.81. HRMS Calcd for $C_9H_{11}NO_3$: 181.0738. Found: 181.0731. MS m/z: 181 (M^+, 59), 166 (24), 150 (14), 134 (100), 121 (32), 78 (12), 43 (24). IR (KBr) cm^{-1}: 1728, 1635. ^{1}H-NMR δ: 2.38 (3H, s), 2.49 (3H, s), 3.87 (3H, s), 6.71 (1H, d, J=2 Hz, changed to s with D_2O), 9.79 (1H, br s, NH).

Similarly, **7a** (60 mg, 0.24 mmol) was allowed to react with **8a** (81 mg, 0.30 mmol) and $PdCl_2(Ph_3P)_2$ (17 mg, 0.024 mmol) in boiling xylene (4 ml) for 8 h to yield methyl 5-acetyl-4-(2-methoxy-3-pyridinyl)-1*H*-pyrrole-2-carboxylate (**9a**) (26 mg, 39%), **7c** (12 mg, 23%), and **7b** (6 mg, 15%) in order of decreasing polarity after purification by PTLC [hexane–EtOAc (5 : 2)]. **9a**: Colorless prisms, mp 177—179 °C ($MeOH$–CH_2Cl_2). HRMS Calcd for $C_{14}H_{14}N_2O_4$: 274.0953. Found: 274.0952. MS m/z: 274 (M^+, 100), 243 (29), 227 (43), 199 (79), 171 (47), 43 (55). IR (KBr) cm^{-1}: 1698, 1656. ^{1}H-NMR δ: 2.08 (3H, s), 3.91 (3H, s), 3.94 (3H, s), 6.84 (1H, br s), 6.98 (1H, dd, J=7.5, 5 Hz), 7.56 (1H, dd, J=7.5, 2 Hz), 8.25 (1H, dd, J=5, 2 Hz), 10.03 (1H, br s, NH).

Similarly, **7a** (60 mg, 0.24 mmol) was allowed to react with **8d** (75 mg, 0.27 mmol) and $PdCl_2(Ph_3P)_2$ (17 mg, 0.024 mmol) in boiling xylene (4 ml) for 6 h to afford **7b** (5 mg, 12%), **7c** (7 mg, 16%), methyl 5-acetyl-4-(2-chloro-3-pyridinyl)-1*H*-pyrrole-2-carboxylate (**9b**) (14.5 mg, 21%), **16** (6 mg, 15%), and **15** (6 mg, 6%) in order of increasing polarity after separation by PTLC [benzene–EtOAc (3 : 1)]. **9b**: Colorless prisms, mp 171—172 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{13}H_{11}ClN_2O_3$: C, 56.02; H, 3.98; N, 10.05. Found: C, 55.82; H, 3.99; N, 10.15. HRMS Calcd for $C_{13}H_{11}{}^{37}ClN_2O_3$ and $C_{13}H_{11}{}^{35}ClN_2O_3$: 280.0428 and 278.0457. Found: 280.0433 and 278.0459. MS m/z: 280 (0.4) and 278 (1) (M^+), 243 (93), 233 (4) and 231 (11), 211 (100), 177 (6) and 175 (15), 43 (59). IR (KBr) cm^{-1}: 1728, 1657. ^{1}H-NMR δ: 2.07 (3H, s), 3.93 (3H, s), 6.85 (1H, d, J=2.5 Hz, changed to s with D_2O), 7.33 (1H, dd, J=7.5, 5 Hz), 7.71 (1H, dd, J=7.5, 2 Hz), 8.49 (1H, dd, J=5, 2 Hz), 10.19 (1H, br s, NH).

Methyl 5-Acetyl-4-(tributylstannyl)-1*H*-pyrrole-2-carboxylate (32) An MeCN solution (3 ml) of **7a** (60 mg, 0.24 mmol), $(Bu_3Sn)_2$ (170 mg, 0.29 mmol), $Pd(OAc)_2$ (5.5 mg, 0.025 mmol), and $(o\text{-}Tol)_3P$ (15 mg, 0.049 mmol) was heated in a sealed tube with stirring under an Ar atmosphere at 110 °C for 30 min. After the mixture had cooled, saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [benzene–EtOAc (8 : 1)] gave **32** (36.5 mg, 33%), together with **7b** (8 mg, 20%) and **16** (13 mg, 32%). **32**: Colorless syrup. MS m/z: 404 (18), 402 (16), 400 (100), 399 (38), 398 (75), 397 (32) and 396 (43) ($M^+ - Bu$); 372 (11), 370 (9), 368 (58), 367 (21), 366 (43), 365 (18) and 364 (25); 258 (10), 256 (11), 254 (60), 253 (20), 252 (43), 251 (17) and 250 (26); 57 (14). IR ($CHCl_3$) cm^{-1}: 1713, 1660. ^{1}H-NMR δ: 0.61—1.98 (27H, m), 2.52 (3H, s), 3.89 (3H, s), 6.96 (1H, s), 10.26 (1H, br s, NH).

Alternative Preparation of 9b from 32 A xylene solution (5 ml) of **32** (32 mg, 0.070 mmol), **33** (25 mg, 0.10 mmol), and $PdCl_2(Ph_3P)_2$ (5 mg, 7 μmol) was refluxed for 21 h. After the mixture had cooled, saturated $NaHCO_3$–H_2O was added. Extraction with CH_2Cl_2, usual work-up, and separation by PTLC [benzene–EtOAc (6 : 1)] afforded **9b** (5 mg, 26%) and **7b** (4.5 mg, 38%).

Methyl 4-Pivaloyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (10a) from 9b TBDMSOTf (47 μl, 0.20 mmol) was added to a solution of **9b** (23 mg, 0.083 mmol) and Et_3N (46 μl, 0.33 mmol) in CH_2Cl_2 (3 ml) under an Ar atmophere at 0 °C. The mixture was stirred 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 gave a crude silyl enol ether (43 mg). This was dissolved in xylene (4 ml), and Bu_3SnF (64 mg, 0.21 mmol) and $PdCl_2(Ph_3P)_2$ (12 mg, 0.017 mmol) were added. The resulting mixture was refluxed under an Ar atmosphere for 10 h. The solvent was evaporated *in vacuo*, and pyridine (2 ml) was added to the residue. Pivaloyl chloride (61 μl, 0.50 mmol) was added to the cooled (0 °C) pyridine solution, and the mixture was stirred at 0—24 °C for 3 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by purification by PTLC [benzene–EtOAc (4 : 1)] afforded crude **10a**, which was further purified by PTLC [hexane–CH_2Cl_2 (1 : 4)] to give **10a** (16 mg, 59%) as colorless prisms, mp 135—136 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.59. Found: C, 66.30; H, 5.60; N, 8.58. HRMS Calcd for $C_{18}H_{18}N_2O_4$: 326.1265. Found: 326.1274. MS m/z: 326 (M^+, 19), 242 (38), 210 (41), 181 (10), 154 (12), 57 (100). IR ($CHCl_3$) cm^{-1}: 1753, 1712. ^{1}H-NMR δ: 1.46 (9H, s), 3.94 (3H, s), 7.43 (1H, dd, J=8, 4.5 Hz), 7.69 (1H, d, J=2 Hz, changed to s with D_2O), 7.73 (1H, s), 8.46 (1H, dif. d, J=8 Hz), 8.86 (1H, dd, J=4.5, 1.5 Hz), 9.48 (1H, br s, NH). ^{1}H-NMR of crude TBDMS enol ether of **9b** δ: 0.19 (6H, s), 0.87 (9H, s), 3.86 (3H, s), 4.18 (1H, d, J=2.5 Hz), 4.33 (1H, d, J=2.5 Hz), 6.87 (1H, d, J=2.5 Hz), 7.25 (1H, dd, J=8, 5 Hz), 7.68 (1H, dd, J=8, 2 Hz), 8.39 (1H, dd, J=5, 2 Hz), 9.38 (1H, br s, NH).

Methyl 5-Acetyl-4-(1,2-dihydro-2-oxo-3-pyridinyl)-1*H*-pyrrole-2-carboxylate (34) A solution of **9c** (180 mg, 0.687 mmol) in 5% HCl/DME–H_2O (1 : 1) (4 ml) was stirred at 60 °C for 2 h. After the mixture had cooled, saturated $NaHCO_3$–H_2O and NaCl powder were added, and the whole was thoroughly extracted with 10% $MeOH$–CH_2Cl_2. Usual work-up afforded a crystalline residue, which was recrystallized from $MeOH$–CH_2Cl_2 to give **34** (171 mg, 96%) as slightly yellow prisms, mp 227—229 °C. *Anal.* Calcd for $C_{13}H_{12}N_2O_4$: C, 59.99; H, 4.65; N, 10.77. Found: C, 59.57; H, 4.78; N, 10.88. HRMS Calcd for $C_{13}H_{12}N_2O_4$: 260.0796. Found: 260.0799. MS m/z: 260 (M^+, 65), 245 (27), 213 (100), 185 (30), 129 (27), 43 (57). IR (KBr) cm^{-1}: 1715, 1609. ^{1}H-NMR (10% CD_3OD–$CDCl_3$) δ: 2.30 (3H, s), 3.88 (3H, s), 6.39 (1H, dd, J=7, 6.5 Hz), 6.86 (1H, s), 7.42 (1H, dd, J=6.5, 2 Hz), 7.56 (1H, dd, J=7, 2 Hz).

Methyl 5-Acetyl-4-[2-[(trifluoromethanesulfonyl)oxy]-3-pyridinyl]-1*H*-pyrrole-2-carboxylate (35) Tf_2O (179 μl, 1.06 mmol) was added to a cooled (0 °C) solution of **34** (111 mg, 0.427 mmol) in CH_2Cl_2 (3.6 ml) and pyridine (0.4 ml). The mixture was stirred at 0 °C for 5 min and at 25 °C for 2 h. Saturated $NaHCO_3$–H_2O was added, and the whole was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [hexane–CH_2Cl_2 (1 : 4)] afforded **35** (159 mg, 95%) as colorless prisms, mp 119—120 °C (dec.) (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{14}H_{11}F_3N_2O_6S$: C, 42.86; H, 2.83; N, 7.14. Found: C, 42.62; H, 2.91; N, 7.09. HRMS Calcd for $C_{14}H_{11}F_3N_2O_6S$: 392.0289. Found: 392.0279. MS m/z: 392 (M^+, 1), 361 (2), 281 (2), 243 (100), 211 (51), 185 (38), 69 (30), 43 (59). IR (KBr) cm^{-1}: 1707, 1653. ^{1}H-NMR δ: 2.10 (3H, s), 3.90 (3H, s), 6.90 (1H, d, J=2.5 Hz, changed to s with D_2O), 7.47 (1H, dd, J=7.5, 5 Hz), 7.88 (1H, dd, J=7.5, 2 Hz), 8.45 (1H, dd, J=5, 2 Hz), 10.13 (1H, br s, NH).

Methyl 4-Pivaloyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (10a) from 35 TBDMSOTf (0.59 ml, 2.6 mmol) was added to a cooled (0 °C) CH_2Cl_2 solution (8 ml) of **35** (460 mg, 1.17 mmol) and Et_3N (0.65 ml,

4.7 mmol) under an Ar atmosphere. The mixture was stirred at that temperature for 1 h, and treated according to the procedure from **9b** to give a crude silyl enol ether (1.124 g). This was dissolved in xylene (12 ml), and $PdCl_2(Ph_3P)_2$ (25 mg, 0.036 mmol), Bu_3SnF (399 mg, 1.29 mmol), and LiCl (150 mg, 3.53 mmol) were added. The resulting mixture was refluxed under an Ar atmosphere for 1 h. The solvent was evaporated *in vacuo*, and CH_2Cl_2 (5 ml) and pyridine (2 ml) were added to the residue. Pivaloyl chloride (0.58 ml, 4.7 mmol) was then added to the cooled (0 °C) solution, and the mixture was stirred at 18 °C for 5 h. After the solvent had been removed *in vacuo*, 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 (8 : 1)], followed by recrystallization from CH_2Cl_2–hexane afforded **10a** (349 mg, 91%) as colorless prisms, mp 135—136.5 °C.

Methyl 4-(Methoxycarbonyl)oxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (10b) from 9b The phenol derivative **37**, prepared from **35** (230 mg, 0.587 mmol) in the same manner as described above, was dissolved in pyridine (2 ml), and the solution was cooled to −18 °C under an Ar atmosphere. $ClCO_2Me$ (272 μl, 3.52 mmol) was slowly added dropwise to the above solution, and the mixture was stirred at that temperature for 30 min and then at 20 °C for 3 h. Pyridine was removed under reduced pressure at 20 °C, saturated $NaHCO_3$–H_2O was added, and the whole was thoroughly extracted with CH_2Cl_2. Usual work-up followed by purification by SiO_2 (20 g) column chromatography (CH_2Cl_2) afforded **10b** (157 mg, 89%) as colorless needles, mp 166—167 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.03; N, 9.33. Found: C, 59.90; H, 3.96; N, 9.54. HRMS Calcd for $C_{15}H_{12}N_2O_5$: 300.0745. Found: 300.0743. MS *m/z*: 300 (M^+, 100), 224 (29), 213 (28), 195 (55), 181 (61), 168 (27), 153 (53), 127 (24), 59 (47). IR (KBr) cm^{-1}: 1747, 1716. ^{1}H-NMR δ: 3.90 (3H, s), 3.96 (3H, s), 7.47 (1H, dd, *J*=8.5, 4.5 Hz), 7.72 (1H, br s), 7.92 (1H, s), 8.49 (1H, dd, *J*=8.5, 1.5 Hz), 8.90 (1H, dd, *J*=4.5, 1.5 Hz), 10.33 (1H, br s, NH).

Methyl 4-Tri(isopropyl)silyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (36) A MeOH solution (2 ml) of **10a** (20 mg, 0.061 mmol) and Et_3N (0.20 ml, 1.4 mmol) was stirred at 20 °C for 2 h. The volatile materials were removed *in vacuo*, and the residue in CH_2Cl_2 (2 ml) was stirred with iso-Pr_2NEt (213 μl, 1.23 mmol) and iso-Pr_3SiOTf (66 μl, 0.25 mmol) under an Ar atmosphere at 0 °C for 15 min and at 20 °C for 15 h. Saturated $NaHCO_3$–H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up followed by purification by PTLC [hexane–EtOAc (2 : 1)] afforded **36** (22.5 mg, 92%) as colorless needles, mp 138—139 °C (CH_2Cl_2–hexane). HRMS Calcd for $C_{22}H_{30}N_2O_3Si$: 398.2024. Found: 398.2035. MS *m/z*: 398 (M^+, 86), 355 (100), 323 (28), 311 (55), 211 (25), 59 (23), 43 (29). IR (KBr) cm^{-1}: 1715. ^{1}H-NMR δ: 1.18 (18H, d, *J*=6.5 Hz), *ca.* 1.18—1.71 (3H, m), 3.99 (3H, s), 7.36 (1H, s), 7.38 (1H, dd, *J*=8, 4.5 Hz), 7.72 (1H, d, *J*=2.5 Hz, changed to s with D_2O), 8.45 (1H, dd, *J*=8, 1.5 Hz), 8.83 (1H, dd, *J*=4.5, 1.5 Hz), 9.39 (1H, br s, NH).

Benzylation of 37 to Form 39, 40, and 41 The run given under entry 2 in Table 4 is shown as an example. A MeOH solution (2 ml) of **10a** (21 mg, 0.064 mmol) and K_2CO_3 (89 mg, 0.64 mmol) was stirred at 19 °C for 20 min. MeOH was removed *in vacuo*, and the residue in acetone (3 ml) was heated with benzyl bromide (BnBr) (38 μl, 0.32 mmol) under reflux for 1 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 followed by purification by PTLC [hexane–CH_2Cl_2 (1 : 3)] afforded methyl 3,5-dibenzyl-4-benzyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**40**) (7 mg, 21%), methyl 3,5,5-tribenzyl-4,5-dihydro-4-oxo-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**41**) (10 mg, 30%), and methyl 3-benzyl-4-benzyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**39**) (12 mg, 44%) in order of increasing polarity. **39**: Colorless prisms, mp 167—168 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{27}H_{22}N_2O_3$: C, 76.76; H, 5.25; N, 6.63. Found: C, 76.81; H, 5.39; N, 6.62. HRMS Calcd for $C_{27}H_{22}N_2O_3$: 422.1629. Found: 422.1629. MS *m/z*: 422 (M^+, 23), 363 (2), 345 (4), 331 (6), 317 (2), 299 (2), 181 (3), 121 (37), 91 (100), 65 (12). IR (KBr) cm^{-1}: 1713. ^{1}H-NMR δ: 3.85 (3H, s), 5.17 (2H, s), 6.28 (2H, s), 6.66—6.94 (2H, m), 7.03—7.44 (10H, m), 7.86 (1H, s), 8.42 (1H, dd, *J*=8, 1.5 Hz), 8.76 (1H, dd, *J*=4.5, 1.5 Hz). **40**: Colorless prisms, mp 157—159 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{34}H_{28}N_2O_3$: C, 79.66; H, 5.51; N, 5.47. Found: C, 79.64; H, 5.65; N, 5.51. HRMS Calcd for $C_{34}H_{28}N_2O_3$: 512.2098. Found: 512.2100. MS *m/z*: 512 (M^+, 7), 453 (2), 421 (58), 393 (3), 361 (3), 297 (3), 271 (3), 255 (3), 243 (3), 121 (11), 91 (100), 65 (9). IR (KBr) cm^{-1}: 1707. ^{1}H-NMR δ: 3.84 (3H, s), 4.77 (2H, s), 4.80 (2H, s), 6.23 (2H, s), 6.70—6.97 (2H, m), 6.97—7.42 (13H, m), 7.42 (1H, dd, *J*=8.5, 4.5 Hz), 7.93 (1H, s), 8.50 (1H, dd, *J*=8.5, 1.5 Hz), 8.88 (1H, dd, *J*=4.5, 1.5 Hz). **41**: Colorless needles, mp 168—169 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{34}H_{28}N_2O_3$: C, 79.66; H, 5.51; N, 5.47. Found: C, 79.62; H, 5.61; N, 5.45. HRMS Calcd for $C_{34}H_{28}N_2O_3$: 512.2098. Found: 512.2086. MS *m/z*: 512 (M^+, 3), 453 (1), 421 (82), 393 (2), 361 (2), 297 (3), 272 (3), 242 (4), 121 (27), 91 (100), 65 (12). IR (KBr) cm^{-1}: 1724, 1640. ^{1}H-NMR δ: 3.55 (2H, d, *J*=13 Hz), 3.73 (3H, s), 3.76 (2H, d, *J*=13 Hz), 6.16 (2H, s), 6.37—6.67 (4H, m), 6.67—7.08 (9H, m), 7.18 (1H, dd, *J*=8, 5 Hz), *ca.* 7.18—7.43 (3H, m), 7.57 (1H, dd, *J*=8, 1.5 Hz), 8.76 (1H, dd, *J*=5, 1.5 Hz).

Benzyloxymethylation of 37 to Form 42 and 43 Benzyl chloromethyl ether (70 μl, 0.50 mmol) was added to a cooled (0 °C) CH_2Cl_2 solution (1 ml) of iso-Pr_2NEt (0.5 ml) and **37**, prepared from **10a** (33 mg, 0.10 mmol) as above. The mixture was stirred at 0 °C for 30 min and at 20 °C for 15 h. Saturated $NaHCO_3$–H_2O was added, and the whole was extracted with CH_2Cl_2. Usual work-up followed by purification by PTLC (2% MeOH–CH_2Cl_2) afforded methyl 3-(benzyloxymethyl)-4-(benzyloxymethyl)oxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**42**) (11 mg, 23%) and methyl 3,6-bis(benzyloxymethyl)-4,6-dihydro-4-oxo-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**43**) (20.5 mg, 42%) in order of increasing polarity. **42**: Colorless glass. HRMS Calcd for $C_{29}H_{26}N_2O_5$: 482.1840. Found: 482.1840. MS *m/z*: 482 (M^+, 4), 452 (5), 346 (5), 333 (4), 254 (13), 121 (14), 91 (100), 65 (8). IR ($CHCl_3$) cm^{-1}: 1711. ^{1}H-NMR δ: 3.96 (3H, s), 4.52 (2H, s), 4.77 (2H, s), 5.50 (2H, s), 6.51 (2H, s), 7.20 (5H, s), 7.30 (5H, s), 7.38 (1H, dd, *J*=8.5, 4.5 Hz), 7.65 (1H, s), 7.84 (1H, s), 8.44 (1H, dd, *J*=8.5, 2 Hz), 8.84 (1H, dd, *J*=4.5, 2 Hz). **43**: Slightly yellow prisms, mp 206—208 °C (MeOH–CH_2Cl_2). HRMS Calcd for $C_{29}H_{26}N_2O_5$: 482.1840. Found: 482.1837. MS *m/z*: 482 (M^+, 2), 452 (4), 346 (4), 333 (4), 301 (3), 254 (12), 121 (13), 91 (100), 65 (8). IR (KBr) cm^{-1}: 1695, 1627. ^{1}H-NMR δ: 3.94 (3H, s), 4.65 (4H, s), 5.52 (2H, s), 6.53 (1H, s), 6.66 (1H, dd, *J*=7, 7 Hz), 6.84 (2H, s), 7.09—7.43 (5H, m), 7.34 (5H, s), 7.62 (1H, s), 7.66 (1H, br d, *J*=7 Hz), 8.11 (1H, br d, *J*=7 Hz).

Methyl 3-Benzyl-4-benzyloxy-6-benzyloxycarbonyl-6,7,8,9-tetrahydro-8-hydroxy-3*H*-pyrrolo[3,2-f]quinoline-2-carboxylate (45) BnBr (42 μl, 0.35 mmol) was added to a slurry of **44** (23 mg, 0.058 mmol) and K_2CO_3 (64 mg, 0.46 mmol) in acetone (4 ml), and the mixture was heated under reflux for 3 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 followed by purification by PTLC [benzene–EtOAc (3 : 1)] afforded **45** (28 mg, 84%) as a colorless foam. HRMS Calcd for $C_{35}H_{32}N_2O_6$: 576.2258. Found: 576.2256. MS *m/z*: 576 (M^+, 10), 485 (2), 461 (4), 423 (2), 394 (2), 351 (3), 181 (3), 121 (15), 91 (100), 65 (8). IR ($CHCl_3$) cm^{-1}: 1712. ^{1}H-NMR δ: 2.31 (1H, d, *J*=4 Hz, OH), 2.87 (1H, dd, *J*=18, 5 Hz), 3.26 (1H, dd, *J*=18, 6 Hz), 3.79 (1H, dd, *J*=12.5, 3.5 Hz), 3.80 (3H, s), 4.01 (1H, d, *J*=12.5 Hz), 4.20—4.50 (1H, m), 4.80 (2H, s), 5.14 (1H, d, *J*=11.5 Hz), 5.30 (1H, d, *J*=11.5 Hz), 6.13 (2H, s), 6.69—6.96 (2H, m), 6.96—7.53 (15H, m).

Methyl 3-Benzyl-4-benzyloxy-6-benzyloxycarbonyl-6,7-dihydro-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (46) Ph_3P (29 mg, 0.11 mmol) and DEAD (17 μl, 0.11 mmol) were successively added to a THF solution (2.5 ml) of **45** (12.5 mg, 0.022 mmol) under an Ar atmosphere at 0 °C. The mixture was stirred at 0 °C for 10 min and at 22 °C for 2 h. Then H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by purification by PTLC [hexane–CH_2Cl_2 (1 : 3)] afforded **46** (9.5 mg, 78%) as a colorless glass. HRMS Calcd for $C_{35}H_{30}N_2O_5$: 558.2153. Found: 558.2136. MS *m/z*: 558 (M^+, 8), 523 (8), 422 (6), 331 (2), 255 (3), 181 (3), 121 (14), 91 (100), 65 (8). IR ($CHCl_3$) cm^{-1}: 1712, 1694. ^{1}H-NMR δ: 3.83 (3H, s), 4.47 (1H, dd, *J*=4.5, 1.5 Hz), 4.83 (2H, s), 5.23 (2H, s), 6.01 (1H, dt, *J*=10, 4.5 Hz), 6.14 (2H, s), 6.71—6.98 (3H, m), 6.98—7.53 (15H, m).

HCl Treatment of 46 to Form 39 A solution of **46** (8.5 mg, 0.015 mmol) in 2.5% HCl/THF–H_2O (3 : 1) (2 ml) was stirred at 22 °C for 40 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by separation by PTLC [hexane–CH_2Cl_2 (1 : 3)] afforded **39** (2.5 mg, 39%) as colorless prisms, mp 167—169 °C (CH_2Cl_2–hexane), along with recovered **46** (3 mg, 35%).

Methyl 7-Cyano-6,7-dihydro-6-(methoxycarbonyl)-4-(pivaloyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (47a) $ClCO_2Me$ (75 μl, 0.97 mmol) was added to a suspension of KCN (85 mg, 1.3 mmol) and **10a** (53 mg, 0.16 mmol) in CH_2Cl_2 (4 ml) and H_2O (1 ml), and the mixture was stirred at 20 °C for 3 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by purification by PTLC [benzene–EtOAc (6 : 1)] afforded **47a** (61.5 mg,

92%) and methyl 9-cyano-6,9-dihydro-6-(methoxycarbonyl)-4-(pivaloyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**48a**) (2 mg, 3%) in order of decreasing polarity. **47a**: Colorless prisms, mp 139—140 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{21}H_{21}N_3O_6$: C, 61.30; H, 5.15; N, 10.22. Found: C, 61.11; H, 5.20; N, 10.38. HRMS Calcd for $C_{21}H_{21}N_3O_6$: 411.1429. Found: 411.1406. MS *m/z*: 411 (M^+, 8), 327 (10), 268 (12), 242 (13), 210 (14), 85 (7), 57 (100), 41 (18). IR (KBr) cm^{-1}: 1740, 1706. ^{1}H-NMR δ: 1.43 (9H, s), 3.90 (3H, s), 3.96 (3H, s), 6.06 (1H, dd, J=9, 6.5 Hz), 6.23 (1H, d, J=6.5 Hz), 7.19 (1H, d, J=9 Hz), 7.31 (1H, d, J=2.5 Hz, changed to s with D_2O), 7.55 (1H, s), 8.97 (1H, br s, NH). **48a**: Colorless glass. HRMS Calcd for $C_{21}H_{21}N_3O_6$: 411.1429. Found: 411.1426. MS *m/z*: 411 (M^+, 10), 327 (16), 295 (8), 85 (7), 57 (100), 41 (18). IR ($CHCl_3$) cm^{-1}: 1716, 1680. ^{1}H-NMR δ: 1.44 (9H, s), 3.93 (3H, s), 3.97 (3H, s), 4.94 (1H, d, J=5 Hz), 5.30 (1H, dd, J=7.5, 5 Hz), 7.34 (1H, d, J=2.5 Hz, changed to s with D_2O), 7.34 (1H, d, J=7.5 Hz), 8.13 (1H, s), 8.90 (1H, br s, NH).

Methyl 6-(Benzyloxycarbonyl)-7-cyano-6,7-dihydro-4-(pivaloyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (47b) Similarly, **10a** (56 mg, 0.17 mmol) was allowed to react with KCN (89 mg, 1.4 mmol) and $ClCO_2CH_2Ph$ (147 μl, 1.03 mmol) in CH_2Cl_2 (4 ml) and H_2O (1 ml) at 20 °C for 6 h to afford **47b** (78 mg, 93%) and methyl 6-(benzyloxycarbonyl)-9-cyano-6,9-dihydro-4-(pivaloyloxy)-3*H*-pyrrolo[3,2-*f*]-quinoline-2-carboxylate (**48b**) (3.5 mg, 4%) after PTLC [hexane–CH_2Cl_2 (1 : 2)]. **47b**: Colorless prisms, mp 188—189 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{27}H_{25}N_3O_6$: C, 66.52; H, 5.17; N, 8.62. Found: C, 66.00; H, 5.16; N, 8.73. HRMS Calcd for $C_{27}H_{25}N_3O_6$: 487.1742. Found: 487.1727. MS *m/z*: 487 (M^+, 2), 443 (1), 351 (3), 326 (9), 242 (19), 210 (19), 91 (37), 57 (100), 41 (17). IR (KBr) cm^{-1}: 1744, 1699. ^{1}H-NMR δ: 1.38 (9H, s), 3.94 (3H, s), 5.17 (1H, d, J=12 Hz), 6.04 (1H, dd, J=9, 6.5 Hz), 6.26 (1H, d, J=6.5 Hz), 6.41 (1H, d, J=12 Hz), 7.09 (1H, d, J=9 Hz), 7.29 (1H, d, J=2 Hz, changed to s with D_2O), 7.38 (5H, s), 7.50 (1H, s), 8.94 (1H, brs, NH). **48b**: Colorless glass. HRMS Calcd for $C_{27}H_{25}N_3O_6$: 487.1742. Found: 487.1723. MS *m/z*: 487 (M^+, 5), 443 (1), 351 (2), 326 (3), 268 (7), 242 (6), 210 (6), 91 (71), 57 (100), 41 (15). IR ($CHCl_3$) cm^{-1}: 1713. ^{1}H-NMR δ: 1.41 (9H, s), 3.97 (3H, s), 4.94 (1H, d, J=5 Hz), 5.30 (1H, dd, J=7.5, 5 Hz), 5.33 (2H, s), 7.27—7.58 (7H, m), 8.12 (1H, s), 8.87 (1H, br s, NH).

Methyl 7-Cyano-6,7,8,9-tetrahydro-8,9-dihydroxy-6-(methoxycarbonyl)-4-(pivaloyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (49) OsO_4 (1 mg, 4 μmol) was added to a solution of **47a** (22 mg, 0.054 mmol) and $Me_3NO \cdot 2H_2O$ (12 mg, 0.11 mmol)) in acetone (2.7 ml) and H_2O (0.3 ml), and the mixture was stirred at 20 °C for 1 h. Saturated $Na_2S_2O_3$–H_2O was added and the whole was extracted with 10% MeOH–CH_2Cl_2. Usual work-up and purification by PTLC [benzene–EtOAc (2 : 3)] gave **49** (18 mg, 76%) as a colorless glass. HRMS Calcd for $C_{21}H_{23}N_3O_8$: 445.1484. Found: 445.1492. MS *m/z*: 445 (M^+, 13), 361 (20), 329 (5), 85 (9), 57 (100), 41 (15). IR ($CHCl_3$) cm^{-1}: 1757, 1713. ^{1}H-NMR δ: 1.41 (9H, s), 3.59—4.20 [3H, m, changed to δ 4.04 (1H, dd, J=6, 4 Hz) with D_2O], 3.80 (3H, s), 3.90 (3H, s), 5.09 (1H, br d, J=4 Hz), 5.36 (1H, d, J=6 Hz), 7.38 (2H, s), 8.94 (1H, br s, NH).

Methyl 7-Cyano-6,7,8,9-tetrahydro-8-hydroxy-6-(methoxycarbonyl)-4-(pivaloyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (50) $BF_3 \cdot OEt_2$ (10 μl, 0.081 mmol) was added to a cooled (0 °C) solution of **49** (7 mg, 0.02 mmol) and Et_3SiH (25 μl, 0.16 mmol) in CH_2Cl_2 (1.5 ml), and the mixture was stirred at that temperature for 15 min and at 20 °C for 3 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [benzene–EtOAc (3 : 2)] gave **50** (6 mg, 89%) as a colorless foam. HRMS Calcd for $C_{21}H_{23}N_3O_7$: 429.1534. Found: 429.1531. MS *m/z*: 429 (M^+, 21), 345 (41), 313 (27), 57 (100), 41 (14). IR ($CHCl_3$) cm^{-1}: 1711. ^{1}H-NMR δ: 1.42 (9H, s), 2.91 (1H, br s, OH), 3.02 (1H, dd, J=17.5, 2.5 Hz), 3.46 (1H, dd, J=17.5, 5 Hz), 3.84 (3H, s), 3.93 (3H, s), 4.40—4.62 (1H, m), 5.50 (1H, d, J=4 Hz), 7.16 (1H, d, J=2 Hz, changed to s with D_2O), 7.49 (1H, s), 8.86 (1H, br s, NH).

Methyl 7-Cyano-6,7,8,9-tetrahydro-8-(methanesulfonyloxy)-6-(methoxycarbonyl)-4-(pivaloyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (52) MsCl (9 μl, 0.12 mmol) was added to a cooled (0 °C) solution of **50** (5 mg, 0.01 mmol) and Et_3N (32 μl, 0.23 mmol) in CH_2Cl_2 (1.5 ml) under an Ar atmosphere, and the mixture was stirred at that temperature for 1 h. Saturated $NaHCO_3$–H_2O was added and the whole was extracted with CH_2Cl_2. The organic layer was successively washed with saturated $CuSO_4$–H_2O and saturated $NaHCO_3$–H_2O, then treated as usual. Purification by PTLC [benzene–EtOAc (5 : 1)] afforded **52** (4.5 mg, 76%) and methyl 7-cyano-6,9-dihydro-6-(methoxycarbonyl)-4-(pivaloyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**51**) (0.5 mg, *ca.* 10%). **52**: Unstable colorless glass. HRMS Calcd for $C_{22}H_{25}N_3O_9S$: 507.1310. Found: 507.1319. MS *m/z*: 507 (M^+, 8), 423 (10), 327 (8), 268 (12), 250 (8), 85 (8), 57 (100), 41 (14). IR ($CHCl_3$) cm^{-1}: 1709. ^{1}H-NMR δ: 1.43 (9H, s), 3.08 (3H, s), 3.30 (1H, dd, J=18.5, 3 Hz), 3.70 (1H, dd, J=18.5, 5.5 Hz), 3.90 (3H, s), 3.97 (3H, s), 5.35—5.55 (1H, m), 5.99 (1H, d, J=4 Hz), 7.20 (1H, d, J=2 Hz, changed to s with D_2O), 7.53 (1H, s), 8.87 (1H, br s, NH). **51**: Colorless glass. HRMS Calcd for $C_{21}H_{21}N_3O_6$: 411.1429. Found: 411.1419. MS *m/z*: 411 (M^+, 14), 327 (22), 282 (6), 250 (12), 85 (8), 57 (100), 41 (17). IR ($CHCl_3$) cm^{-1}: 2230, 1711. ^{1}H-NMR δ: 1.44 (9H, s), 3.62 (2H, d, J=5 Hz), 3.93 (3H, s), 3.94 (3H, s), 6.58 (1H, t, J=5 Hz), 7.21 (1H, d, J=2 Hz, changed to s with D_2O), 7.55 (1H, s), 8.77 (1H, br s, NH).

Methyl 3-Benzyl-4-(benzyloxy)-6,7-dihydro-6-(methoxycarbonyl)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (54) $NaBH_4$ (8.5 mg, 0.22 mmol) and a THF solution (0.5 ml) of $ClCO_2Me$ (16.5 μl, 0.21 mmol) were successively added to a cooled (0 °C) solution of **39** (6 mg, 0.01 mmol) in THF (1 ml) and 2-propanol (1 ml) under an Ar atmosphere, and the mixture was stirred at 0 °C for 30 min and at 20 °C for 4 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by purification by PTLC [hexane–CH_2Cl_2 (1 : 3)] gave unstable **55** (2 mg) and **54** (3 mg, 44%) in order of increasing polarity. When **55** was subjected to purification by PTLC (CH_2Cl_2), it was completely converted back to **39** (1.5 mg, 25%). **54**: Colorless glass. HRMS Calcd for $C_{29}H_{26}N_2O_5$: 482.1840. Found: 482.1841. MS *m/z*: 482 (M^+, 18), 422 (5), 391 (26), 331 (2), 255 (4), 121 (28), 105 (10), 91 (100), 65 (10), 59 (6). IR ($CHCl_3$) cm^{-1}: 1712, 1695. ^{1}H-NMR δ: 3.73 (3H, s), 3.84 (3H, s), 4.44 (2H, dd, J=4, 1 Hz), 5.08 (2H, s), 6.02 (1H, dt, J=10, 4 Hz), 6.18 (2H, s), 6.76—7.03 (3H, m), 7.03—7.42 (9H, m), 7.42 (1H, s). **56**: Colorless glass. MS *m/z*: 422 ($M^+ - BH_3$, 21), 363 (3), 345 (4), 331 (6), 317 (2), 299 (2), 181 (3), 121 (37), 91 (100), 65 (11). IR ($CHCl_3$) cm^{-1}: 2350 (B-H), 1720. ^{1}H-NMR δ: 3.89 (3H, s), 5.31 (2H, s), 6.30 (2H, s), 6.69—6.95 (2H, m), 7.08—7.57 (9H, m), 7.88 (1H, s), 8.20 (1H, s), 8.66 (1H, d, J=8 Hz), 9.01 (1H, d, J=5.5 Hz).

Reduction of 10b to Form 11a, 11b, 57, and 6 $NaBH_4$ (63 mg, 1.7 mmol) was added portion-wise to a cooled (0 °C) solution of **10b** (50 mg, 0.17 mmol) and $ClCO_2Me$ (129 μl, 1.7 mmol) in THF (2 ml) and 2-propanol (4 ml) under an Ar atmosphere. The mixture was stirred at 22 °C for 15 h. Saturated NH_4Cl–H_2O was added and the whole was extracted with CH_2Cl_2. Usual work-up followed by separation by PTLC (CH_2Cl_2) afforded methyl 6,9-dihydro-6-(methoxycarbonyl)-4-(methoxycarbonyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**11b**) (12.5 mg, 21%), methyl 6,7-dihydro-6-(methoxycarbonyl)-4-(methoxycarbonyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**11a**) (31 mg, 52%), and a mixture of **57**, **6** and the recovered **10b** in order of increasing polarity. The mixture was further separated by PTLC [benzene–EtOAc (5 : 2)] to give methyl 6,7,8,9-tetrahydro-9-hydroxy-6-(methoxycarbonyl)-4-(methoxycarbonyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**57**) (1.5 mg, 2%), recovery of **10b** (3 mg, 6%), and methyl 6,7,8,9-tetrahydro-8-hydroxy-6-(methoxycarbonyl)-4-(methoxycarbonyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**6**) (1.5 mg, 2%) in order of increasing polarity. **11a**: Colorless glass. HRMS Calcd for $C_{17}H_{16}N_2O_7$: 360.0956. Found: 360.0950. MS *m/z*: 360 (M^+, 80), 301 (34), 285 (48), 269 (22), 225 (69), 154 (32), 127 (23), 59 (100). IR ($CHCl_3$) cm^{-1}: 1768, 1713, 1697. ^{1}H-NMR δ: 3.81 (3H, s), 3.96 (3H, s), 3.98 (3H, s), 4.46 (2H, dd, J=4, 1.5 Hz), 6.14 (1H, dd, J=10, 4 Hz), 6.89 (1H, br d, J=10 Hz), 7.30 (1H, d, J=2 Hz, changed to s with D_2O), 7.59 (1H, s), 9.04 (1H, br s, NH). **11b**: Colorless glass. HRMS Calcd for $C_{17}H_{16}N_2O_7$: 360.0956. Found: 360.0954. MS *m/z*: 360 (M^+, 100), 301 (13), 300 (18), 283 (17), 225 (30), 181 (21), 154 (27), 127 (23), 59 (91). IR ($CHCl_3$) cm^{-1}: 1767, 1713. ^{1}H-NMR δ: 3.57 (2H, br d, J=4 Hz), 3.88 (3H, s), 3.97 (3H, s), 3.98 (3H, s), 5.36 (1H, dt, J=8.5, 4 Hz), 7.05 (1H, br d, J=8.5 Hz), 7.22 (1H, d, J=2.5 Hz), 8.09 (1H, s), 9.02 (1H, br s, NH). **57**: Colorless glass. HRMS Calcd for $C_{17}H_{18}N_2O_8$: 378.1062. Found: 378.1064. MS *m/z*: 378 (M^+, 57), 360 (61), 301 (39), 285 (44), 225 (54), 154 (27), 59 (100). IR ($CHCl_3$) cm^{-1}: 1766, 1712, 1700. ^{1}H-NMR δ: 1.94 (1H, br s, OH), 2.01—2.27 (2H, m), 3.41—3.79 (1H, m), 3.79 (3H, s), 3.95 (3H, s), 3.97 (3H, s), 4.17—4.49 (1H, m), 5.07—5.23 (1H, m), 7.41 (1H, d, J=2 Hz, changed to s with D_2O), 7.82 (1H, s), 9.11 (1H, br s, NH). **6**: Colorless glass. HRMS Calcd for $C_{17}H_{18}N_2O_8$: 378.1062. Found: 378.1058. MS *m/z*: 378 (M^+, 100), 360 (20), 320 (28), 302 (24), 288 (31), 225 (30), 59 (99). IR (KBr) cm^{-1}: 1768, 1713, 1700. ^{1}H-NMR δ: 2.87 (1H, dd, J=17, 5 Hz), 2.91 (1H, br s, OH), 3.24 (1H, dd, J=17, 5.5 Hz), *ca.* 3.69—4.01 (2H, m), 3.80 (3H, s), 3.90 (3H, s), 3.92 (3H, s), 4.18—4.48 (1H, m), 7.10

(1H, d, $J=2$ Hz, changed to s with D_2O), 7.60 (1H, s), 9.59 (1H, br s, NH).

Methyl (8*R,9*S**)-6,7,8,9-Tetrahydro-8,9-dihydroxy-6-(methoxycarbonyl)-4-(methoxycarbonyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (58)** In a similar manner to that described for the preparation of **49**, **11a** (17 mg, 0.047 mmol) was allowed to react with OsO_4 (0.5 mg, 2 μmol) and $Me_3NO\cdot 2H_2O$ (7 mg, 0.06 mmol) in acetone–H_2O (9 : 1) (2 ml) at 20 °C for 1 h. The same work-up, followed by purification by PTLC [benzene–EtOAc (2 : 3)], gave **58** (16.5 mg, 89%) as a colorless glass. HRMS Calcd for $C_{17}H_{18}N_2O_9$: 394.1011. Found: 394.1007. MS *m/z*: 394 (M^+, 36), 376 (38), 318 (29), 258 (24), 59 (78), 44 (100). IR ($CHCl_3$) cm^{-1}: 1767, 1706. ^{1}H-NMR δ: 3.44 (2H, br s, OH), 3.56—4.19 (3H, m), 3.77 (3H, s), 3.88 (3H, s), 3.91 (3H, s), 4.96 (1H, d, $J=4.5$ Hz), 7.37 (1H, d, $J=2$ Hz, changed to s with D_2O), 7.66 (1H, s), 9.53 (1H, br s, NH).

Reductive Dehydroxylation of 58 to Form 6 A solution of **58** (12 mg, 0.030 mmol) and Et_3SiH (24 μl, 0.15 mmol) in CH_2Cl_2 (2.5 ml) was stirred with $BF_3\cdot OEt_2$ (11 μl, 0.089 mmol) under an Ar atmosphere at 0 °C for 1 h. The same work-up as described for the preparation of **50** followed by purification by PTLC [benzene–EtOAc (2 : 3)] gave **6** (9.5 mg, 83%).

Preparation of 6 from 11b by Way of 59 In a similar manner to the above two operations, **11b** (6 mg, 0.02 mmol) was allowed to react with OsO_4 (0.5 mg, 2 μmol) and $Me_3NO\cdot 2H_2O$ (3 mg, 0.03 mmol) in acetone–H_2O (9 : 1) (2 ml) at 20 °C for 1.5 h. The solvents were removed *in vacuo*, and the residue was dried over P_2O_5 for 30 min under reduced pressure. It was dissolved in CH_2Cl_2 (2 ml), and Et_3SiH (21 μl, 0.13 mmol) and $BF_3\cdot OEt_2$ (8 μl, 0.07 mmol) were successively added under an Ar atmosphere at 0 °C. The solution was stirred at the same temperature for 1 h, and then saturated $NaHCO_3$–H_2O was added. The whole was extracted with CH_2Cl_2, and usual work-up followed by purification by PTLC [benzene–EtOAc (2 : 1)] afforded **6** (5 mg, 79%).

Preparation of 6 from 10b through Three Successive Steps A solution of **10b** (118 mg, 0.393 mmol) in THF (3 ml) and 2-propanol (6 ml) was treated as above with $ClCO_2Me$ (304 μl, 3.93 mmol) and $NaBH_4$ (150 mg, 3.95 mmol) for 17 h. Work-up as before gave a residue (156 mg), which was oxidized with OsO_4 (2 mg, 8 μmol) and $Me_3NO\cdot 2H_2O$ (52 mg, 0.47 mmol) in acetone–H_2O (9 : 1) (5 ml) at 0 °C for 15 min and at 18 °C for 1.5 h. The mixture was worked up as above, and the residue in CH_2Cl_2 (5 ml) was treated with Et_3SiH (0.38 ml, 2.4 mmol) and $BF_3\cdot OEt_2$ (0.15 ml, 1.2 mmol) under an Ar atmosphere at 0 °C for 30 min and at 20 °C for 6 h. The same work-up as above followed by purification by PTLC [CH_2Cl_2–EtOAc (5 : 1)] afforded **6** (86 mg, 58% overall yield) and methyl 6,7,8,9-tetrahydro-6-(methoxycarbonyl)-4-(methoxycarbonyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**60**) (9 mg, 6%) in order of decreasing polarity. **60**: Colorless prisms, mp 184—186 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{17}H_{18}N_2O_7$: C, 56.35; H, 5.01; N, 7.73. Found: C, 56.07; H, 5.14; N, 7.22. HRMS Calcd for $C_{17}H_{18}N_2O_7$: 362.1113. Found: 362.1117. MS *m/z*: 362 (M^+, 100), 330 (13), 303 (10), 271 (18), 59 (54). IR ($CHCl_3$) cm^{-1}: 1766, 1712, 1694. ^{1}H-NMR δ: 1.86—2.23 (2H, m), 2.99 (2H, t, $J=6.5$ Hz), *ca.* 3.71—3.95 (2H, m), 3.80 (3H, s), 3.95 (3H, s), 3.97 (3H, s), 7.20 (1H, d, $J=2.5$ Hz, changed to s with D_2O), 7.66 (1H, s), 9.03 (1H, br s, NH).

Methyl (±)-6,7,8,9-Tetrahydro-8-(methanesulfonyloxy)-6-(methoxycarbonyl)-4-(methoxycarbonyloxy)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (61) MsCl (15 μl, 0.19 mmol) was added to a cooled (0 °C) solution of **6** (36 mg, 0.095 mmol) and Et_3N (53 μl, 0.38 mmol) in CH_2Cl_2 (3 ml) under an Ar atmosphere, 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. The organic layer was successively washed with saturated $CuSO_4$–H_2O and saturated $NaHCO_3$–H_2O, then treated as usual. Purification by PTLC [benzene–EtOAc (2 : 1)] afforded **61** (42 mg, 97%) as a colorless glass. HRMS Calcd for $C_{18}H_{20}N_2O_{10}S$: 456.0837. Found: 456.0831. MS *m/z*: 456 (M^+, 56), 425 (5), 360 (28), 359 (34), 347 (24), 301 (37), 285 (37), 225 (48), 59 (100). IR ($CHCl_3$) cm^{-1}: 1768, 1710. ^{1}H-NMR δ: 3.06 (3H, s), 3.20 (1H, dd, $J=18$, 4 Hz), 3.47 (1H, dd, $J=18$, 5 Hz), 3.83 (3H, s), 3.84 (1H, dd, $J=13.5$, 3 Hz), 3.95 (6H, s), 4.32 (1H, dd, $J=13.5$, 5.5 Hz), 5.20—5.46 (1H, m), 7.16 (1H, d, $J=2.5$ Hz, changed to s with D_2O), 9.43 (1H, br s, NH).

Methyl (±)-1,2,4,5,8,8a-Hexahydro-4-oxocyclopropa[*c*]pyrrolo[3,2-*e*]-indole-6-carboxylate (64) A MeOH solution (4 ml) of **61** (42 mg, 0.092 mmol) and K_2CO_3 (45 mg, 0.33 mmol) was stirred under an Ar atmosphere at 21 °C for 3 h. Saturated NH_4Cl–H_2O was added and the whole was thoroughly extracted with 10% MeOH–CH_2Cl_2. Usual work-up followed by purification by PTLC (5% MeOH–CH_2Cl_2) afforded **64** (21 mg, 93%) as a colorless powder, whose spectral data were identical with those previously reported.[1b]

(±)-Duocarmycin SA [(±)-1] A DMF solution (1.5 ml) of **64** (7 mg, 0.03 mmol), **65** (17 mg, 0.056 mmol), and K_2CO_3 (40 mg, 0.29 mmol) was stirred under an Ar atmosphere at 21 °C for 4.5 h. CH_2Cl_2 (5 ml) was added and the mixture was cooled to 0 °C. Citric acid monohydrate (67 mg, 0.32 mmol) was added portion-wise, and H_2O was further added with stirring. After the mixture had been stirred at 0 °C for 2 min, the whole was thoroughly extracted with 10% MeOH–CH_2Cl_2, and the organic layer was washed with saturated $NaHCO_3$–H_2O. Usual work-up followed by purification by PTLC (2% MeOH–CH_2Cl_2) gave a crude product, which was further purified by PTLC [benzene–EtOAc (3 : 4)] to afford (±)-**1** (11.5 mg, 84%) as a slightly yellow powder, whose spectral data were identical with those previously reported.[1b]

Methyl (±)-6,7,8,9-Tetrahydro-4,8-dihydroxy-6-(methoxycarbonyl)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (66) A solution of **6** (113 mg, 0.299 mmol) in MeOH–Et_3N (9 : 1) (4 ml) was stirred at 23 °C for 1 h. The volatile materials were removed *in vacuo*, and the crystalline residue was recrystallized from MeOH–CH_2Cl_2 to afford **66** (91 mg, 95%) as colorless prisms, mp 243—244 °C. *Anal.* Calcd for $C_{15}H_{16}N_2O_6$: C, 56.24; H, 5.04; N, 8.75. Found: C, 56.13; H, 5.10; N, 8.74. Spectral data were identical with those of optically resolved compounds.[1b]

Methyl (±)-4-(Benzyloxy)-6,7,8,9-tetrahydro-8-hydroxy-6-(methoxycarbonyl)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (67) BnBr (10 μl, 0.084 mmol) was added to a slurry of **66** (25 mg, 0.078 mmol) and K_2CO_3 (27 mg, 0.20 mmol) in acetone (4 ml) and the mixture was stirred under reflux for 4 h. After it had cooled, saturated NH_4Cl–H_2O was added and the whole was extracted with 10% MeOH–CH_2Cl_2. Usual work-up followed by purification by PTLC (CH_2Cl_2) afforded **67** (29 mg, 91%), together with methyl (±)-3-benzyl-4-(benzyloxy)-6,7,8,9-tetrahydro-8-hydroxy-6-(methoxycarbonyl)-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**68**) (2 mg, 5%). Although **67** had been reported as a colorless glass previously,[1b] it was obtained this time as colorless prisms, mp 138—140 °C (CH_2Cl_2–hexane). *Anal.* Calcd for $C_{22}H_{22}N_2O_6$: C, 64.38; H, 5.40; N, 6.83. Found: C, 63.99; H, 5.53; N, 6.90. Spectral data were identical with those reported.[1b] **68**: Colorless glass. HRMS Calcd for $C_{29}H_{28}N_2O_6$: 500.1946. Found: 500.1935. MS *m/z*: 500 (M^+, 30), 409 (38), 121 (82), 91 (100), 65 (11). IR ($CHCl_3$) cm^{-1}: 1712. ^{1}H-NMR δ: 2.90 (1H, dd, $J=18$, 4.5 Hz), 3.29 (1H, dd, $J=18$, 6 Hz), 3.63—4.02 (2H, m), 3.73 (3H, s), 3.82 (3H, s), 4.25—4.49 (1H, m), 5.02 (2H, s), 6.13 (2H, s), 6.73—6.93 (2H, m), 7.03—7.38 (10H, m).

AD Reaction on 11a with (DHQ)$_2$PYR to Form (8*S*,9*R*)-58 (81% ee) OsO_4 (1% w/v) in *tert*-BuOH–H_2O (1 : 1) (50 μl, 2.0 μmol) was added to a slurry containing $(DHQ)_2PYR$ (3 mg, 3 μmol), $MsNH_2$ (26 mg, 0.27 mmol), $NaHCO_3$ (17 mg, 0.20 mmol), and $K_3Fe(CN)_6$ (132 mg, 0.40 mmol) in *tert*-BuOH–H_2O (1 : 1) (1 ml) at 0 °C. After the mixture had been stirred at 0 °C for 15 min and at 21 °C for 10 min, it was added dropwise to a solution of **11a** (24 mg, 0.067 mmol) in *tert*-BuOH–H_2O (1 : 1) (2 ml) at 0 °C, and the resulting mixture was stirred at 0 °C for 2 h and at 21 °C for 16 h. Saturated $Na_2S_2O_3$–H_2O and NaCl powder were added, and the whole was extracted with CH_2Cl_2. Usual work-up and purification by PTLC [benzene–EtOAc (2 : 3)] afforded (8*S*,9*R*)-**58** (18 mg, 69%), whose optical purity was confirmed by HPLC analysis after transformation to **63** through three steps: i) dehydroxylation to (8*R*)-**6** with Et_3SiH and $BF_3\cdot OEt_2$ as above, ii) methanolysis to (8*R*)-**66** with Et_3N in MeOH as above, and iii) cyclization to (7b*S*)-**63** with ADDP and Bu_3P.[1b] HPLC analysis of **63** using a ChiralCel OD column (0.46 × 25 cm) and hexane–2-propanol (2 : 1) (1 ml/min flow rate) showed t_R (7b*S*) = 14.3 min, t_R (7b*R*) = 19.8 min and $t_0 = 3.5$ min ($\alpha = 1.51$), and revealed that the compound **63** obtained here showed 81% ee in favor of the unnatural (7b*S*)-enantiomer.

AD Reaction on 11a with (DHQD)$_2$PYR to Form (8*R*,9*S*)-58 (58% ee) Similarly, **11a** (17 mg, 0.047 mmol) was dihydroxylated with $(DHQD)_2PYR$ (2.5 mg, 2.8 μmol), 1% w/v OsO_4 in *tert*-BuOH–H_2O (1 : 1) (36 μl, 1.4 μmol), $K_3Fe(CN)_6$ (94 mg, 0.29 mmol), $MsNH_2$ (18 mg, 0.20 mmol), and $NaHCO_3$ (12 mg, 0.14 mmol) and in *tert*-BuOH–H_2O (1 : 1) (3 ml) at 0—21 °C for 23 h to afford (8*R*,9*S*)-**58** (14 mg, 75%), whose ee value was determined to be 58% as above.

AD Reaction on 11b with (DHQ)$_2$PYR Similarly, **11b** (20 mg, 0.056 mmol) was dihydroxylated with $(DHQ)_2PYR$ (3 mg, 3 μmol), 1% w/v OsO_4 in *tert*-BuOH–H_2O (1 : 1) (42 μl, 1.7 μmol), $K_3Fe(CN)_6$ (147 mg, 0.447 mmol), $MsNH_2$ (21 mg, 0.22 mmol), and $NaHCO_3$ (14 mg, 0.17 mmol) and in acetone–*tert*-BuOH–H_2O (1 : 2 : 2) (5 ml) at 0—22 °C for 22 h to afford the crude diol (37 mg). This was treated with Et_3SiH

(53 μl, 0.33 mmol) and $BF_3 \cdot OEt_2$ (21 μl, 0.17 mmol) in CH_2Cl_2 (2 ml) under an Ar atmosphere at 0 °C for 30 min and at 22 °C for 1 h to afford (8*S*)-**6** (16 mg, 76%) after purification as above. Its optical purity was determined to be 63% ee by HPLC analysis after conversion to **63** as above.

Asymmetric Epoxidation of 11a with (*S,S*)-Jacobsen Catalyst NaOCl–H_2O (5%, 186 μl, 0.125 mmol) was added to a cooled (0 °C) CH_2Cl_2 solution (3 ml) of **11a** (30 mg, 0.083 mmol), **72** (5 mg, 8 μmol), and 4-phenylpyridine *N*-oxide (7 mg, 0.04 mmol), and the mixture was stirred at 0 °C for 30 min. Saturated $Na_2S_2O_3$–H_2O and saturated NH_4Cl–H_2O were added, and the whole was extracted with CH_2Cl_2. Usual work-up gave a residue (45 mg), which was treated with Et_3SiH (106 μl, 0.665 mmol) and $BF_3 \cdot OEt_2$ (41 μl, 0.33 mmol) in CH_2Cl_2 (3 ml) under an Ar atmosphere at 0—20 °C for 3 h. The same work-up as above and purification by PTLC [benzene–EtOAc (2 : 3)] afforded **10b** (2.5 mg, 10%) and (8*S*)-**6** (9.5 mg, 30%), whose optical purity value was determined to be 58% ee by HPLC analysis after conversion to **63** as above.

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.

References and Notes

1) *a*) Muratake H., Abe I., Natsume M., *Tetrahedron Lett.*, **35**, 2573—2576 (1994); *b*) *Idem*, *Chem. Pharm. Bull.*, **44**, 67—79 (1996).
2) Isolation and Structure Determination: *a*) Ichimura M., Ogawa T., Takahashi K., Kobayashi E., Kawamoto I., Yasuzawa T., Takahashi I., Nakano H., *J. Antibiot.*, **43**, 1037—1038 (1990); *b*) Yasuzawa T., Saitoh Y., Ichimura M., Takahashi I., Sano H., *ibid.*, **44**, 445—447 (1991); *c*) Ichimura M., Ogawa T., Katsumata S., Takahashi K., Takahashi I., Nakano H., *ibid.*, **44**, 1045—1053 (1991).
3) Other Syntheses: *a*) Boger D. L., Machiya K., *J. Am. Chem. Soc.*, **114**, 10056—10058 (1992); *b*) Boger D. L., Machiya K., Hertzog D. L., Kitos P. A., Holmes D., *ibid.*, **115**, 9025—9036 (1993); *c*) Muratake H., Matsumura N., Natsume M., *Chem. Pharm. Bull.*, **43**, 1064—1066 (1995). Reviews: *a*) Boger D. L., *Acc. Chem. Res.*, **28**, 20—29 (1995); *b*) Boger D. L., Johnson D. S., *Angew. Chem. Int., Ed. Engl.*, **35**, 1438—1474 (1996); *c*) Boger D. L., Boyce, C. W., Garbaccio R. M., Goldberg, J. A., *Chem. Rev.*, **97**, 787—828 (1997).
4) Muratake H., Okabe K., Takahashi M., Tonegawa M., Natsume M., *Chem. Pharm. Bull.*, **45**, 799—806 (1997).
5) *a*) Hamana M., Noda H., *Chem. Pharm. Bull.*, **13**, 912—920 (1965); *b*) *Idem*, *ibid.*, **14**, 762—769 (1966); *c*) *Idem*, *ibid.*, **15**, 474—480 (1967); *d*) *Idem*, *ibid.*, **18**, 26—31 (1970).
6) Part of this paper was reported as a communication. Muratake H., Tonegawa M., Natsume M., *Chem. Pharm. Bull.*, **44**, 1631—1633 (1996).
7) Comins D. L., Myoung Y. C., *J. Org. Chem.*, **55**, 292—298 (1990).
8) *a*) Still W. C., *J. Am. Chem. Soc.*, **99**, 4836—4838 (1977); *b*) *Idem*, *ibid.*, **100**, 1481—1487 (1978).
9) Sundberg R. J., Hamilton G., Trindle C., *J. Org. Chem.*, **51**, 3672—3679 (1986).
10) Reviews: *a*) Stille J. K., *Angew. Chem.*, **98**, 504—519 (1986); *Angew. Chem., Int. Ed. Engl.*, **25**, 508—524 (1986); *b*) Mitchell T. N., *Synthesis*, **1992**, 803—815; *c*) Ritter K., *ibid.*, **1993**, 735—762.
11) Anderseon H. J., Huang C. W., *Can. J. Chem.*, **45**, 897—902 (1967).
12) Kosuge T., Zenda H., Suzuki Y., *Chem. Pharm. Bull.*, **18**, 1068—1071 (1970).
13) *a*) Gattermann L., Holacher T., *Ber.*, **32**, 284 (1899); *b*) Adams R., Levine I., *J. Am. Chem. Soc.*, **45**, 2373 (1923); *c*) Creamer L. K., Fischer A., Mann B. R., Packer J., Richards R. B., Vaughan J., *J. Org. Chem.*, **26**, 3148—3152 (1961); *d*) Gross H., Rieche A., Matthey G., *Chem. Ber.*, **96**, 308—313 (1963).
14) Reaction of nitromethane with 1-methoxypyridinium iodide in the presence of sodium methoxide in ethanol at room temperature gave 1-methoxyimino-6-*aci*-nitrohexa-2,4-diene in 60% yield. Okamoto T., Takayama H., private communication, 1961.
15) Kuwajima I., Urabe H., *J. Am. Chem. Soc.*, **104**, 6831—6833 (1982).
16) Sakamoto T., Kondo Y., Yamanaka H., *Chem. Pharm. Bull.*, **33**, 4764—4768 (1985).
17) Kosugi M., Shimizu K., Ohtani A., Migita T., *Chem. Lett.*, **1981**, 829—830.
18) Stork G., Isobe M., *J. Am. Chem. Soc.*, **97**, 6260—6261 (1975).
19) Popp F. D., Katz L. E., Klinowski C. W., Wefer J. M., *J. Org. Chem.*, **33**, 4447—4450 (1968).
20) Brown H. C., Midland M. M., Kabalka G. W., *J. Am. Chem. Soc.*, **93**, 1024—1025 (1971).
21) *a*) Winstein S., Baird R., *J. Am. Chem. Soc.*, **79**, 756—757 (1957); *b*) Baird R., Winstein S., *ibid.*, **85**, 567—578 (1963).
22) *a*) Sharpless K. B., Amberg W., Bennani Y. L., Crispino G. A., Hartung J., Jeong K.-S., Kwong H.-L., Morikawa K., Wang Z.-M., Xu D., Zhang X.-L., *J. Org. Chem.*, **57**, 2768—2771 (1992); *b*) Crispino G. A., Jeong K.-S., Kolb H. C., Wang Z.-M., Xu D., Sharpless K. B., *ibid.*, **58**, 3785—3786 (1993). Review: Kolb H. C., VanNieuwenhze M. S., Sharpless K. B., *Chem. Rev.*, **94**, 2483—2547 (1994).
23) *a*) Zhang W., Loebach J. L., Wilson S. R., Jacobsen E. N., *J. Am. Chem. Soc.*, **112**, 2801—2803 (1990); *b*) Jacobsen E. N., Zhang W., Muci A. R., Ecker J. R., Deng L., *ibid.*, **113**, 7063—7064 (1991); *c*) Deng L., Jacobsen E. N., *J. Org. Chem.*, **57**, 4320—4323 (1992).
24) Boger and co-workers reported a similar Jacobsen epoxidation of a benzene analog related to our dihydropyridine derivative, which gave an optically active epoxide of 92% ee in 70% yield. Boger D. L., McKie J. A., Boyce C. W., *Synlett*, **1997**, 515—517.
25) Smith C. R., *J. Am. Chem. Soc.*, **50**, 1936—1938 (1928).