# Preparation of Alkyl-Substituted Indoles in the Benzene Portion. Part 14.[1] Synthesis of (±)-Duocarmycin SA, Natural (+)-Duocarmycin SA and Non-natural (−)-Duocarmycin SA

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**Total synthesis of duocarmycin SA (1), an extremely potent cytotoxic antibiotic, was achieved in the racemic form at first by effectively utilizing two reactions as key steps, (i) an intramolecular Heck reaction of the benzyl ether 21a, derived from a dihydropyridine 13a and a pyrrole derivative 11, to form tricyclic compounds 25a and 26a, and (ii) a modified Mitsunobu reaction on the diol derivative 40 for the construction of compound 41 having the pivotal pharmacophore of a cyclopropanoindolinone partial structure, which is critical for the high biological activities of 1. Next, optical resolution of an intermediary racemic secondary alcohol 50 was cleanly attained by derivatizing it to (*R*)-*O*-methylmandelates 52 and 53, and the resulting chiral alcohols (+)-50 and (−)-50 were respectively transformed into unnatural (−)-1 and natural (+)-1. Finally inversion of the secondary alcohol (+)-50 to the enantiomer (−)-50 was effected by using the Mitsunobu reaction. This constitutes an enantio-convergent total synthesis of natural duocarmycin SA (1) starting from a racemic compound.**

**Key words** total synthesis; duocarmycin SA; potent antitumor substance; Heck reaction; Mitsunobu reaction; enantio-convergent synthesis

Duocarmycin SA (**1**) is an extremely potent cytotoxic antibiotic, isolated from a culture broth of the *Streptomyces* species in 1990[2] (Chart 1). This product **1** is structurally related to other duocarmycins[3] and pyrindamycins,[4] and among these, **1** together with duocarmycin A (**2**) particularly resemble CC-1065 (**3**)[5] in that they carry an *N*-acylcyclopropanoindolinone partial structure **5** as a common pharmacophore responsible for the sequence-selective, reversible alkylation of DNA.[6] Duocarmycin SA (**1**) is a stable compound (SA meaning stable A) due to the presence of a methyl α-pyrrolecarboxylate moiety incorporated into the above pharmacophore, and exhibits high biological activities[2c,7b] relative to **2**, **3**, and other structurally related agents.

With the eventual aim of synthesizing more useful reagents, we initiated a total synthesis study of duocarmycin SA (**1**) and reported preliminarily a synthetic procedure of (±)-**1** in twelve steps.[8] Here we present the full details. The study was further extended to the optical resolution of a synthetic intermediate, and this lead to the preparation of both **1** having the natural absolute configuration and unnatural *ent*-**1**. A method was developed for inversion of a stereocenter in the resolved unnatural intermediate to the configuration of a natural enantiomer, and thus an efficient enantio-convergent synthesis of duocarmycin SA (**1**) was completed starting from a racemic compound. Boger *et al.* reported the first total synthesis of **1** in 1992,[7] and we described in preliminary form a second-generation synthesis of natural (+)-duocarmycin SA in 1995.[9]

**Total Synthesis of (±)-1** Our synthetic plan for **1** clearly differs from most previously reported syntheses of **1**,[7] **2**,[10] **3**,[11] and their synthetic analogues,[12] where the essential pharmacophore subunit **5** was constructed from an indolinol derivative **4**. By contrast, we envisioned that the formation of **5** would be possible in a stereospecific manner from a tetrahydroquinolinol derivative **6** carrying a hetero-atom X.[13] For the purpose of synthesizing duocarmycin SA (**1**), a tetrahydropyrroloquinolinol derivative **9** corresponding to the structural unit **6** was anticipated to be an important intermediate. The tricyclic derivative **9** would be obtainable from a compound such

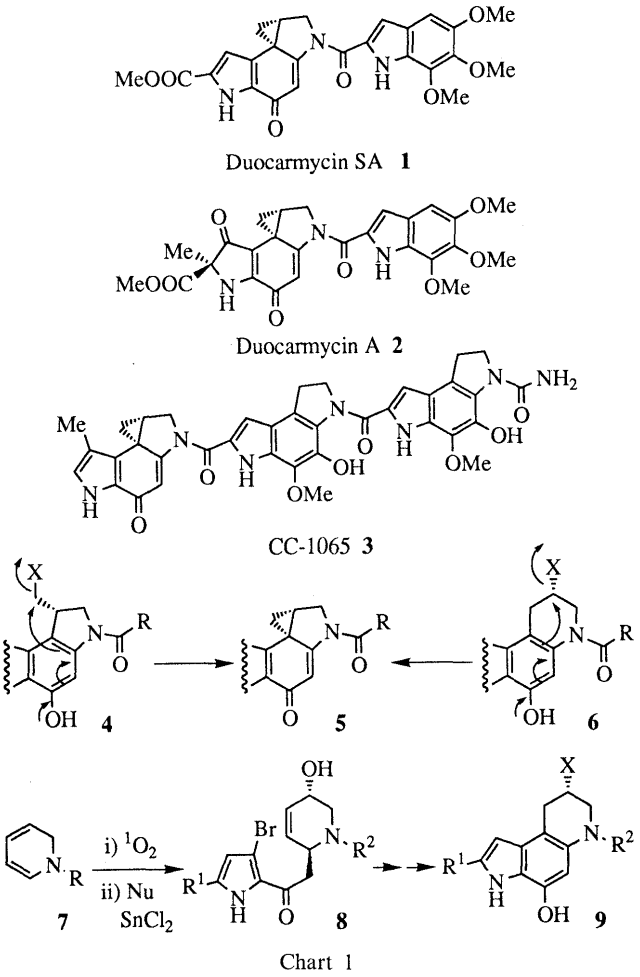


Chart 1

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as **8** by making the carbon–carbon bond connection *via* the intramolecular Heck reaction.[14] We planned to prepare the latter compound **8** by applying our synthetic method using singlet oxygen chemistry,[15] which consisted of a tin(II) chloride-mediated condensation reaction between an endoperoxide derived from 1,2-dihydropyridine **7** and a nucleophile (Nu). Our synthesis started with the preparation of this nucleophile from the known pyrrole derivative.

Methyl 4-bromopyrrole-2-carboxylate[16] (**10**) was acetylated by means of the Friedel-Crafts acylation using acetic anhydride and boron trifluoride–etherate in 1,2-dichloroethane to afford regioselectively the 5-acetyl derivative **11** in 93% yield (Chart 2). This was then treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMSOTf) in the presence of triethylamine[17] and the silyl enol ether **12** was obtained in 92% yield for use in the next condensation step. This compound **12** was slightly unstable on silica gel chromatography, and therefore it was used without further purification other than an extractive isolation. An attempted preparation of the corresponding trimethylsilyl enol ether was unsuccessful due to instability. According to the reported procedure,[15] the nucleophile **12** was condensed with a singlet oxygen adduct **14a** derived from 2 molar eq of 1-benzyloxycarbonyl-1,2-dihydropyridine (**13a**) in the presence of tin(II) chloride to provide *trans* **15a** and *cis* **16a** derivatives in 58% and 11% yields, calculated from **11**. Their stereochemistry was unequivocally determined on the basis of $^1$H-NMR data with reference to the literature.[15]

For the formation of tricyclic derivatives, the intramolecular Heck reaction on **15a**, **16a**, and their ether derivatives **17a**, **18a**, **19a**, **21a**, and **22a** was investigated under a variety of reaction conditions (Table 1).[18] The *N,O*-bismethoxymethyl derivatives **17a** and **18a** were prepared by the standard method, stirring **15a** and **16a** with chloromethyl methyl ether (MOMCl) and diisopropylethylamine in dichloromethane at room temperature, in 90% and 73% yields, respectively, accompanied with a by-product **20a** (10%) for the *cis* derivative **18a**. The *trans* *tert*-butyldimethylsilyl (TBDMS) ether **19a** was also prepared easily in 94% yield on treatment of **15a** with *tert*-butyldimethylchlorosilane and imidazole at room tempetature. On the other hand, conventional benzylation of **15a** under alkaline conditions, *i.e.* sodium hydride (3 molar eq) and benzyl (Bn) bromide (4 molar eq) in tetrahydrofuran (THF)–dimethylformamide (DMF) (5 : 1) at 0 °C to room temperature, afforded the benzyl ether **21a** in only 39% yield along with recovery of **15a** in 13% yield. The benzyl ethers **21a** and **22a** were therefore

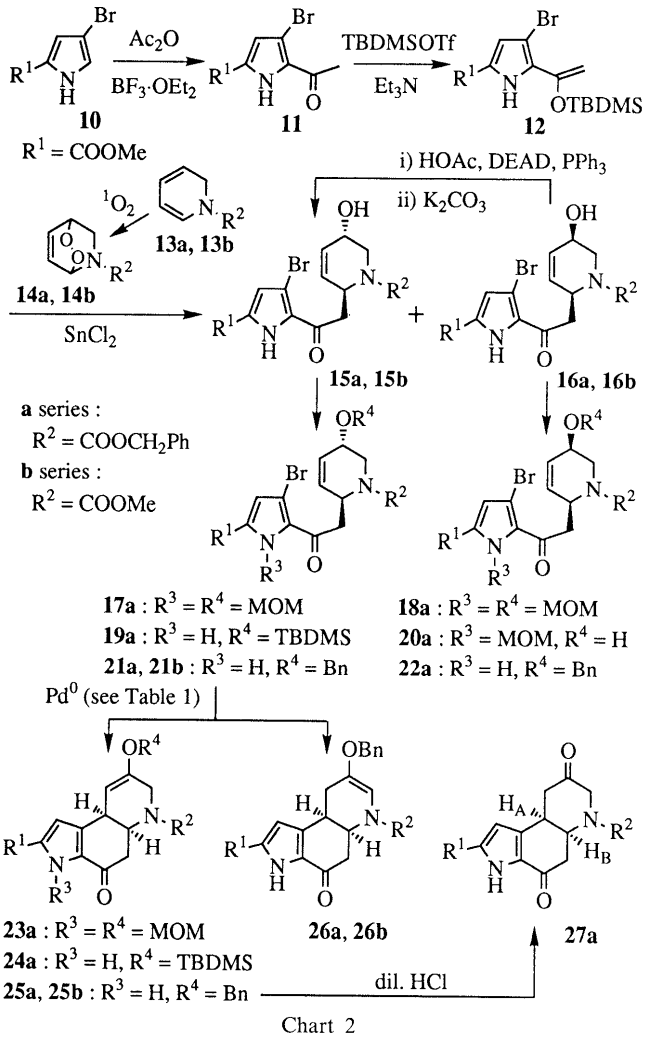



Chart 2

Table 1. Intramolecular Heck Reaction[a] of **15a**, **16a**, **17a**, **18a**, **19a**, **21a** and **22a** to Form Tricyclic Derivatives **23a**, **24a**, **25a**, **26a** and **27a**

| Run | Starting material | $Pd(OAc)_2$ (mol %) | Additive (molar eq) | Temperature (°C) | Time (h) | Product (% Yield) | Recovery of start. mat. (%) |
|---|---|---|---|---|---|---|---|
| 1 | **15a** | 20 | dppe (0.4), $Tl_2CO_3$ (1) | Reflux | 22.5 | — | 48 |
| 2 | **15a** | 30 | P(*o*-tol)$_3$ (0.75), $Et_3N$ (3) | 100 | 18 | **27a** (30) | 10 |
| 3 | **16a** | 30 | P(*o*-tol)$_3$ (0.75), $Et_3N$ (3) | 100 | 22 | — | 39 |
| 4 | **17a** | 30 | dppe (0.5), $Tl_2CO_3$ (2) | Reflux | 22 | **23a** (51) | 32 |
| 5 | **17a** | 30 | $PPh_3$ (0.6), KOAc (3), $Bu_4NBr$ (1.2) | Reflux | 20 | **23a** (61) | 34 |
| 6 | **17a** | 30 | P(*o*-tol)$_3$ (0.75), $Et_3N$ (3) | 100 | 22 | **23a** (83) | 9 |
| 7 | **18a** | 30 | $PPh_3$ (0.6), KOAc (3), $Bu_4NBr$ (1.2) | Reflux | 15 | — | 69 |
| 8 | **19a** | 30 | P(*o*-tol)$_3$ (0.75), $Et_3N$ (3) | 100 | 18 | **24a** (64), **27a** (4) | 24 |
| 9 | **21a** | 30 | dppe (0.5), $Tl_2CO_3$ (2) | 75—80 (DMF) | 22 | **25a** (27) | 11 |
| 10 | **21a** | 30 | P(*o*-tol)$_3$ (0.75), $Et_3N$ (3) | 100 | 17 | **25a** (79), **26a** (9) | — |
| 11 | **22a** | 30 | P(*o*-tol)$_3$ (0.75), $Et_3N$ (3) | 100 | 15 | — | 48 |
| 12 | **21a** | 15 | P(*o*-tol)$_3$ (0.38), $Et_3N$ (2) | 100 | 32 | **25a** (61), **26a** (7) | 29 |
| 13 | **21a** | 20 | P(*o*-tol)$_3$ (0.5), $Et_3N$ (2) | 110 | 17 | **25a** (81), **26a** (10) | — |
| 14 | **21a** | 5 | P(*o*-tol)$_3$ (0.13), $Et_3N$ (1) | 110 | 26 | **25a** (82), **26a** (11) | — |

*a*) The reaction was carried out in acetonitrile except for run 9.

prepared from **15a** and **16a** under acidic conditions using benzyl 2,2,2-trichloroacetimidate in the presence of a catalytic amount of trifluoromethanesulfonic acid[19] in respective yields of 72% and 68%.

The Heck reaction was carried out with a catalytic amount of palladium(II) acetate in acetonitrile (except for DMF at run 9) in the presence of various kinds of additives[20] (Table 1). In general, ether derivatives **17a**, **19a**, and **21a** afforded better yields of the reaction products than the alcohol **15a** (runs 1—2, 4—6, 8, 10, 12—14). The *cis* isomers **16a**, **18a**, and **22a** afforded none of reaction products, with recovery of the starting materials in moderate yields (runs 3, 7, and 11), while all the *trans* derivatives, *i.e.* **15a**, **17a**, **19a**, and **21a**, afforded the expected products **23a**, **24a**, **25a**, and **27a** respectively, together with the double bond regioisomer **26a** for the benzyl ether **21a** (runs 2, 4—6, 8—10, 12—14). In the case of the *trans* allyl alcohol **15a**, the product was a diketone **27a** (run 2). When the *tert*-butyldimethylsilyl ether **19a** was used as a substrate, **27a** was also formed as a by-product in 4% yield due to partial cleavage of the enol silyl ether moiety of **24a** (run 8). The enol ether **25a** was correlated with this diketone **27a** by hydrolysis with 2.5% hydrochloric acid in 1,2-dimethoxyethane (DME)–water (3 : 2) at room temperature in 89% yield.

The reaction conditions using bis(diphenylphosphino)-ethane (dppe) and thallium(I) carbonate[20b,21] gave inferior results to others (runs 1, 4, and 9). Among the reactions with tri-*o*-tolylphosphine and triethylamine, the benzyl ether **21a** afforded good results at elevated temperature (runs 10, 12—14), and finally the best reaction conditions were identified, *i.e.*, heating an acetonitrile solution of **21a** (*ca.* 60 mM) with palladium(II) acetate (5 mol%), tri-*o*-tolylphosphine (13 mol%), and triethylamine (1 molar eq) under an argon atmosphere at 110 °C for 26 h in a sealed tube, to yield **25a** (82%) and **26a** (11%) (run 14). In order to make use of the uncyclizable *cis* compound **16a**, it was converted to the *trans* isomer **15a** by Mitsunobu reaction[22] using acetic acid, diethyl azodicarboxylate (DEAD), and triphenylphosphine to afford the *O*-acetate of **15a** in 74% yield, followed by methanolysis of the latter with potassium carbonate in methanol in 93% yield (Chart 2). Another method, treatment of the mesylate of **16a** with cesium propionate in DMF followed by methanolysis as above of the resulting propionate,[23] also afforded the *trans* isomer **15a**, but in a lower yield of 48% from **16a**.

All cyclization products **23a**—**27a** possessed the *cis*-ring juncture. This was shown by inspection of the $^1$H-NMR spectrum of **27a**, where the coupling constant between $H_A$ at $\delta$ 3.64 (ddd, $J$=9.5, 5.5, 5 Hz) and $H_B$ at $\delta$ 4.97 (ddd, $J$=8.5, 5, 5 Hz) was 5 Hz. The above structural feature was reasonably explained by the well-known *syn*-1,2-addition during the Heck reaction[14] (Chart 3). Generally a substituent at the 2-position of *N*-alkoxycarbonyl-1,2,5,6-tetrahydropyridines takes axial orientation[15,24] to relieve the allylic 1,3-strain[25] between the substituent and the alkoxycarbonyl group on the nitrogen. Therefore, in the initial palladium adduct **28a**, generated from **21a** by oxidative addition of palladium(0), cyclization is restricted to occur from the $\beta$ side of the molecule, since the

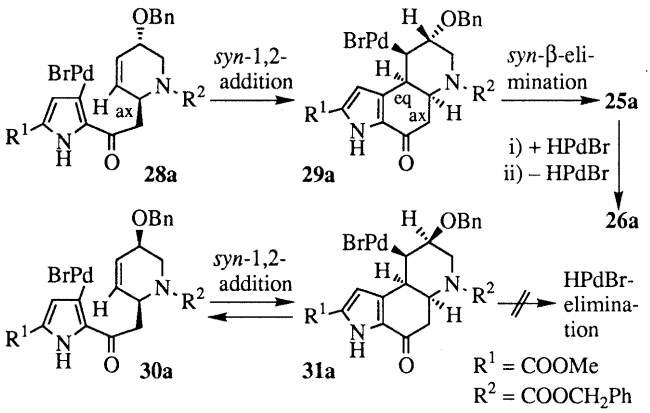



Chart 3

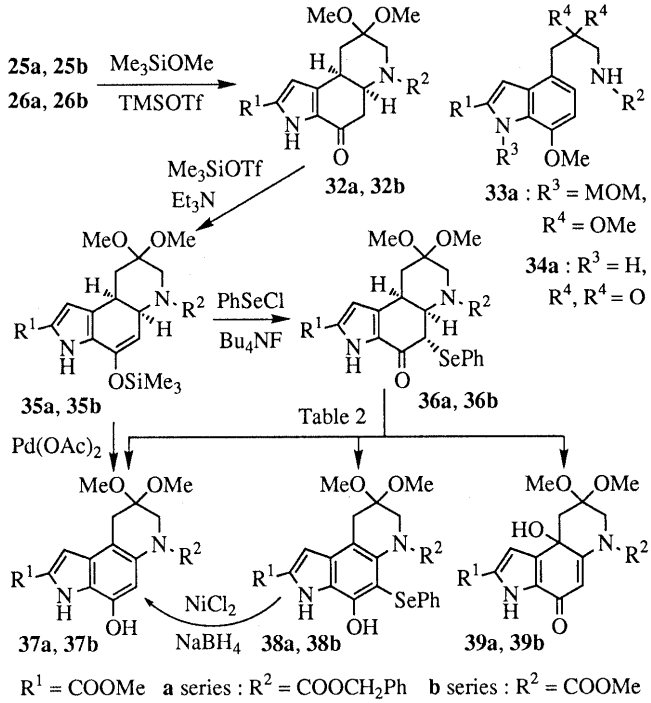



Chart 4

pyrrole-carrying side chain is situated axially, resulting in the formation of the *cis* cyclization product **29a**. Subsequent *syn* elimination of hydridopalladium(II) bromide[14] is possible with the neighboring benzyloxy group at the $\alpha$ side, furnishing the final product **25a** quite readily. Partial isomerization of the double bond in **25a** to **26a**, catalyzed by palladium(0), is common during the Heck reaction and is explained by the addition–elimination mechanism of hydridopalladium(II) bromide. On the other hand, in the case of the adduct **30a**, derived from the *cis* compound **22a**, cyclization reaction might take place to form **31a**, but this intermediate cannot split off the palladium species due to the unfavorable situation of the adjacent hydrogen atom. Therefore the reaction does not proceed further to the product, and the starting substrate is recovered according to the reverse process of **31a**→**30a**→**22a**.

Our next tasks were the acetalization of both enol ethers **25a** and **26a** to form a dimethyl acetal **32a** and its oxidative aromatization to obtain a tetrahydropyrroloquinolinol derivative **37a** (Chart 4). For the former process, a

Table 2. Oxidation of **36a** to Form the Indolol Derivative **37a**

| Run | Oxidizing agent (molar eq) | Solvent | Temperature (°C) | Time | **37a** % yield | **38a** % yield | **39a** % yield |
|---|---|---|---|---|---|---|---|
| 1 | $NaIO_4$ (10) (diethyl acetal) | THF–MeOH–$H_2O$ (1:1:1) | 20 | 18 h | — | — | — |
| 2 | *m*-CPBA (1.1) | $CH_2Cl_2$ | −20—−10 | 30 min | 21 | 48 | — |
| 3 | *m*-CPBA (1.08) | $Et_2O$ | 0 | 20 min | 25 | 42 | — |
| 4 | *m*-CPBA (1.07) | THF | 0 | 20 min | 68 | 11 | — |
| 5 | *m*-CPBA (1.05) | THF | −20 | 20 min | 71 | 20 | — |
| 6 | *m*-CPBA (1.07) | THF | −80 | 20 min | 56 | 26 | — |
| 7 | *m*-CPBA (1.08) | DME | 0 | 15 min | — | — | 19 |
| 8 | *m*-CPBA (1.08) | EtOAc | −20 | 20 min | 40 | 52 | — |
| 9 | $H_2O_2$ (10) | THF | 0 | 1.5 h | 68 | — | — |
| 10 | $H_2O_2$ (3)+Py (2.3) | $CH_2Cl_2$ | 0 | 30 min | — | — | 37 |

conventional operation such as refluxing **23a** for 30 min in a mixture of trimethyl orthoformate–methanol (4:1) containing 0.5% sulfuric acid afforded solely an unwanted indole derivative **33a** in 85% yield. In the structures of **23a**, **25a** and **26a**, the nitrogen atom at the piperidine ring is situated at the β-position to the ketone group, so that ready ring cleavage is inevitable under acidic conditions. After many trials with unsuccessful results, treatment of either **25a** or **26a** in dichloromethane with methoxytrimethylsilane in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) at low temperature was finally the reaction of choice,[26] and **32a** was produced in 86% or 76% yield, respectively, accompanied with the indole by-product **34a** in 7% yield from **26a**.

Next, dehydrogenation reaction was tried by two well-known methods. The Saegusa method[27] was examined first. Trimethylsilyl enol ether **35a**, prepared from **32a** by treatment with TMSOTf and triethylamine in dichloromethane,[28] was oxidized with 2 molar eq of $Pd(OAc)_2$ in acetonitrile at room temperature for 6 h. The result was disappointing, and the desired product **37a** was formed in only 19% yield, together with recovery of **32a** in 21% yield. Therefore, for the second trial, the phenylselenyl group was introduced into **32a** by stirring a THF solution of the above silyl enol ether **35a** with phenylselenenyl chloride and tetrabutylammonium fluoride[29] at 0 °C to room temperature for 13 h to afford stereoselectively **36a** in 83% yield. Oxidative elimination of the phenylselenyl group from **36a** was tried under various reaction conditions (Table 2). Usual oxidation with sodium metaperiodate or *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane afforded either no isolable product or a poor yield of **37a** with substantial formation of an oxidation product **38a** carrying the phenylselenyl group (runs 1, 2). With hydrogen peroxide, the result was fairly good, producing only **37a** in 68% yield (run 9), but in the presence of pyridine (Py), an over-oxidation product, hydroxydienone **39a**, was the sole isolable compound in 37% yield (run 10). Therefore, we re-examined the oxidation with *m*-CPBA using various kinds of solvents (runs 3—8). Among them, *m*-CPBA in THF gave reasonable results and the best conditions shown in run 5, *i.e.*, *m*-CPBA (1.05 molar eq) in THF at −20 °C for 20 min, furnished **37a** in 71% yield, along with the by-product **38a** in 20% yield. Fortunately the by-product **38a** was reusable by reductive dephenylselenylation with nickel boride,[30]

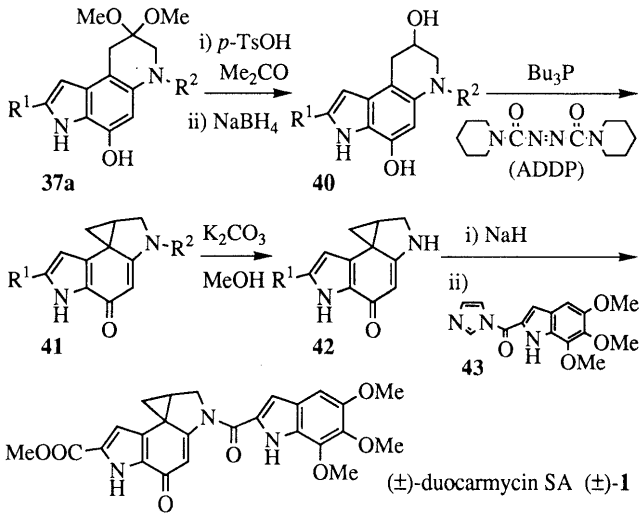
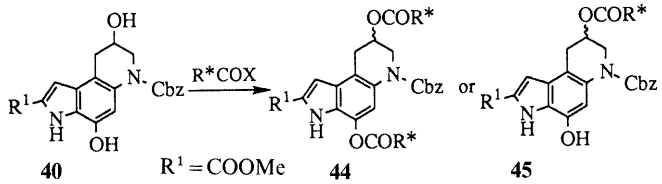



Chart 5

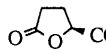
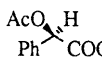
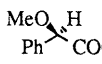
prepared *in situ* from nickel(II) chloride and sodium borohydride in THF–methanol (3:1) at 0 °C, giving additional **37a** in 85% yield. Thus, the preparation of **37a** was attained in a good overall yield from **25a** and **26a**. Deacetalization of **37a** was readily carried out by stirring it with a catalytic amount of *p*-toluenesulfonic acid in acetone at room temperature to afford an unstable ketone derivative, which was immediately reduced with sodium borohydride in methanol at −20 °C providing the diol derivative **40** in 79% yield, calculated from **37a** (Chart 5).

Now the stage was set for construction of the cyclopropane ring according to Chart 1, **6**→**5**. Fortunately, this transformation was directly achieved from the diol derivative **40** under Mitsunobu reaction conditions[22] to give the cyclopropanoindolinone derivative **41** in 68% yield. When this transformation was conducted by use of the modified Mitsunobu reaction with 1,1′-(azodicarbonyl)dipiperidine (ADDP) and tributylphosphine[31] in THF at room temperature, **41** was obtained in a more satisfactory yield of 88%. Since the nitrogen atom in **41** bearing the benzyloxycarbonyl (Cbz) group was involved in a vinylogous amide system, the Cbz group was readily cleaved under mild alkaline conditions, by stirring in methanol with potassium carbonate at room temperature, to afford the *N*-unprotected compound **42** in 95% yield. The sodium salt of **42** was condensed in

Table 3. Preparation of Diastereomers **44** and **45** from **40**, and Their Analytical HPLC Separation




**40** $R^1$ = COOMe **44** **45**

| Run | R*COX | Reaction conditions | Product (% yield) | HPLC[a] Solvent | α value[b] |
|---|---|---|---|---|---|
| 1 |  | Py, $CH_2Cl_2$; r.t., 14 h | **45** (90) | Hexane–$CH_2Cl_2$ (1:2) | 1 |
| 2 |  | DCC, DMAP, $CH_2Cl_2$; r.t., 50 min | **44a** (93) | Hexane–$CH_2Cl_2$ (2:3)<br>Hexane–EtOAc (3:1)<br>Benzene–EtOAc (4:1) | 1.09<br>1<br>1 |
| 3 |  | DCC, DMAP, $CH_2Cl_2$; r.t., 22 h | **44b** (22) | Hexane–$CH_2Cl_2$ (1:1) | 1.20 |
| 4 |  | DCC, DMAP, $CH_2Cl_2$; r.t., 30 min | **44c** (76) | Hexane–$CH_2Cl_2$ (3:4)<br>Hexane–EtOAc (1:1) | 1<br>1 |
| 5 |  | EDCI·HCl, DMAP, $CH_2Cl_2$; r.t., 3 h | **44d** (95) | Hexane–EtOAc (2:1)<br>Benzene–EtOAc (6:1)<br>1% THF–$CH_2Cl_2$<br>4% EtOAc–$CH_2Cl_2$<br>0.4% MeOH–$CH_2Cl_2$ | 1.10<br>1.20<br>1.39<br>1.47<br>1.50 |

*a*) Column: TOSOH $SiO_2$-60, 4.6 × 250 mm. *b*) $\alpha = t_2 - t_0 / t_1 - t_0$.

THF–DMF (2:1) at 0 °C for 4 h with the imidazolide **43**, prepared from 5,6,7-trimethoxyindole-2-carboxylic acid[6c,10c] and *N*,*N*′-carbonyldiimidazole in 91% yield, to achieve our total synthesis of (±)-duocarmycin SA (**1**) in 60% yield. Identity of the synthetic material with natural (+)-duocarmycin SA was confirmed by comparison of their IR (chloroform), $^1$H-NMR and $^{13}$C-NMR spectra.

**Optical Resolution as Well as Synthesis of Natural (+)- and Unnatural (−)-Duocarmycins SA** Next, we attempted an optical resolution of a racemic intermediate in the above synthesis for the purpose of preparing each enantiomer, *i.e.*, natural (+)- and unnatural (−)-duocarmycins SA. First, the diol **40** was esterified with several optically active carboxylic acids and separation of the resulting diastereomers was examined by HPLC using an analytical silica gel HPLC column (Table 3). The esterification was readily effected with a chiral acid chloride[32] using pyridine (run 1), and with chiral acids[33,34] using *N*,*N*′-dicyclohexylcarbodiimide (DCC) (runs 2—4), or 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl) (run 5) in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) to afford diastereomeric mixtures of **45** and **44a**—**44d** in good yields except for run 3, where the reaction proceeded only very slowly even after stirring for a long time. In run 1, the diester formed with (*S*)-5-oxo-2-tetrahydrofurancarboxylic acid was so unstable that partial hydrolysis took place during purification by silica gel chromatography, and only the monoester **45** was obtained in 90% yield. Although *O*-acetylmandelic acid served as an efficient auxiliary in precedent cases[7,10] passing through the precursor **4** (Chart 1), no separation on HPLC was observed in our case of **44c** (run 4), judging from the separation factor α, that is the ratio of the retention times of the two diastereomers. The best result was obtained by use of the ester **44d** with (*R*)-*O*-methylmandelic acid, affording high α values of 1.10—1.50 depending on the eluting solvents.

In extending the above analytical result to preparative HPLC separation, we encountered a serious problem. In the diester **44d**, the *O*-acyl bond between the phenol and (*R*)-*O*-methylmandelic acid was found to be unstable on a preparative HPLC column, and partial solvolytic cleavage of this bond occurred during separation, resulting in not only a loss of materials, but also a lowering the optical purity of the eventually obtained separated materials. Therefore we decided to protect this phenolic hydroxyl group with a benzyl group as in **46** (Chart 6) at an earlier stage in the above synthetic route. This decision had a severe effect on the protecting group $R^2$ of the nitrogen atom, which had been the Cbz group in the **a** series. This Cbz group had been adopted, at the outset of the synthesis, since it could be readily cleaved from the nitrogen atom at any time for condensation with 5,6,7-trimethoxyindole-2-carboxylic acid. Now that we had acquired a facile procedure (**41**→**42**) for removal of the $R^2$ protecting group based on the nature of the vinylogous amide acylate, the $R^2$ group could be changed to any acyl group other than Cbz. As the benzyl group was necessary for the phenolic protecting group, a methoxycarbonyl group was chosen for the nitrogen protecting group $R^2$ and all the synthetic steps up to the indole derivative **37** were repeated as the **b** series.

The singlet oxygen adduct **14b**, prepared from 1-

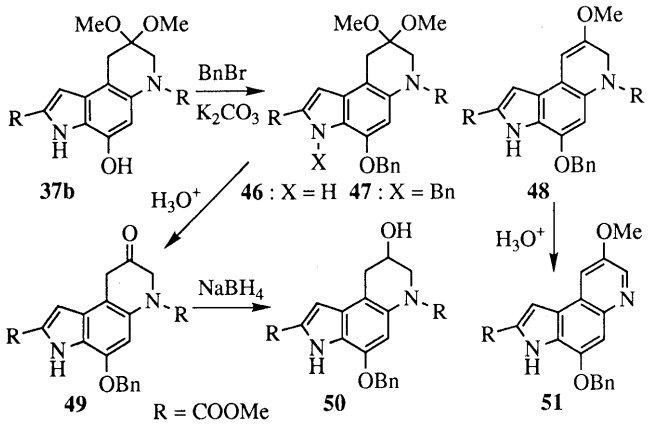


Chart 6

methoxycarbonyl-1,2-dihydropyridine (**13b**) was condensed with the silyl enol ether **12** to afford *trans* **15b** and *cis* **16b** in 64% and 8% yields, respectively (Chart 2). Conversion of the *cis* compound **16b** into the *trans* derivative **15b** was effected without difficulty in 70% overall yield, and the subsequent steps from **15b** to **37b** were carried out by way of **21b**, **25b** and **26b**, **32b**, **35b**, and **36b**, completely analogous to the **a** series (Chart 4). The resulting phenolic intermediate **37b** was benzylated by refluxing it in an acetone solution with benzyl bromide (1.06 molar eq) and potassium carbonate (2.0 molar eq) to afford the desired compound **46** in 80% yield, accompanied with the dibenzyl derivative **47** and recovery of **37b** in 4% yield each (Chart 6). Deacetalization of **46** was cleanly effected by treatment with a solution of 2.5% hydrochloric acid in THF–water (3 : 1) at room temperature to give the ketone **49** in 97% yield. When this deacetalization was carried out by another method such as stirring an acetone solution of **46** with *p*-toluenesulfonic acid at room temperature, a by-product **48** was obtained in 12% yield in addition to **49**, and further hydrochloric acid treatment of **48** afforded a fully aromatic compound **51** in 58% yield. Sodium borohydride reduction of **49** in THF–methanol (1 : 1) afforded the racemic alcohol **50** in 98% yield.

Taking into consideration the results in Table 3, the racemic alcohol **50** was converted into a mixture of diastereomeric esters with (*R*)-*O*-methylmandelic acid employing EDCI·HCl in the presence of a catalytic amount of DMAP in dichloromethane (Chart 7). This mixture was then separated by preparative HPLC (silica gel, 21.5 × 300 mm, 2% ethyl acetate–dichloromethane, 5 ml/min) to provide **52** ($t_R$ = 55 min) in 47% yield, and **53** ($t_R$ = 73 min) in 47% yield. The absolute configuration of their alcohol groups became clear after completion of the total synthesis. Separation was so good ($\alpha$ = 1.44) that each was readily obtained in >99.9% diastereomeric excess. Respective methanolysis of **52** and **53** using potassium carbonate in methanol at room temperature afforded (*R*)-(+)-**50** [$[\alpha]_D^{21}$ +10.3° (*c* = 0.66, chloroform)] and (*S*)-(−)-**50** [$[\alpha]_D^{21}$ −10.0° (*c* = 0.63, chloroform)] in 95 and 97% yields. Deprotection of (+)- and (−)-**50** was carried out easily on palladium hydroxide (Pearlman's catalyst) in methanol under hydrogen at an atmospheric pressure to give (+)- and (−)-**54** in 95% yield each. Subsequent cyclopropanoindolinone formation was effected as in the racemic series to obtain (−)- and (+)-**55** from (+)- and (−)-**54** in 84% and 82% yields. Removal of the methoxycarbonyl group from (−)- and (+)-**55** afforded as before (−)- and (+)-**42** in 95 and 96% yields, and the final coupling reaction of these with the imidazolide **43** derived from 5,6,7-trimethoxyindole-2-carboxylic acid completed the total synthesis of unnatural (−)-**1** [$[\alpha]_D^{21}$ −190° (*c* = 0.192, methanol)] and natural duocarmycin SA (+)-**1** [$[\alpha]_D^{21}$ +192° (*c* = 0.352, methanol)] in 66 and 74% yields; their specific rotational values were in good accordance with those reported in the literatures: $[\alpha]_D^{24}$ +180° (*c* = 0.1, methanol) for the natural specimen,[2] and $[\alpha]_D^{22}$ −189° (*c* = 0.02, methanol) and $[\alpha]_D^{22}$ +197° (*c* = 0.035, methanol) for Boger's synthetic (−)- and (+)-**1**.[7] Spectral data [$^1$H-NMR, IR (chloroform), and MS] of our synthetic (+)- and (−)-**1** were indistinguishable from those of the natural specimen.

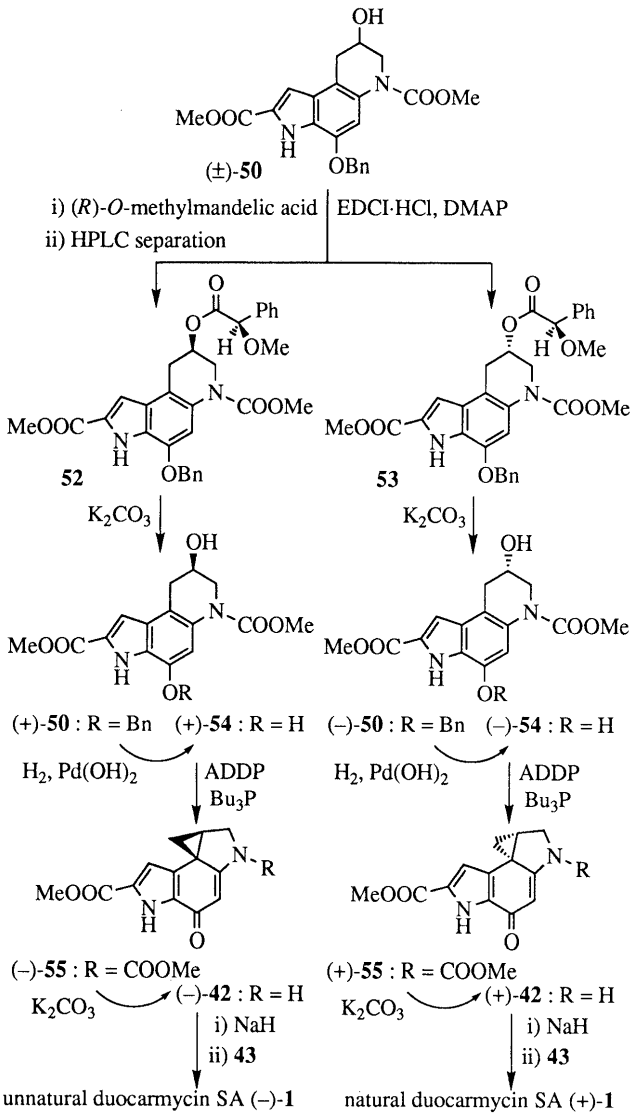
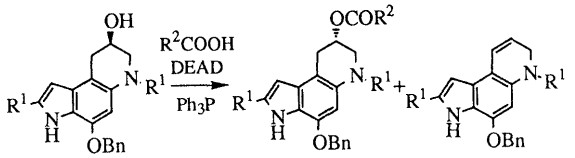


Chart 7

Finally configurational inversion of the secondary alcohol in (+)-**50** was tried by treating it with some carboxylic acids under the Mitsunobu conditions (Table 4). In each case, the desired inverted ester **56** was secured in a good yield, although formation of a dehydrated by-product **57** was unavoidable. Use of acetic acid afforded

Table 4. Mitsunobu Inversion of (*R*)-(+)-**50** to Form the (*S*)-Esters **56**




(*R*)-(+)-**50** **56** **57**

$R^1$ = COOMe $R^2$: **a** = Me, **b** = Ph, **c** = *p*-$NO_2$Ph

| Run | $R^2COOH$ (molar eq) | DEAD (molar eq) | $Ph_3P$ (molar eq) | Time (h) | **56** % yield | **57** % yield |
|---|---|---|---|---|---|---|
| 1 | MeCOOH (8) | 4 | 4 | 2 | 70 | 21 |
| 2 | PhCOOH (4) | 3 | 3 | 1 | 62 | 29 |
| 3 | *p*-$NO_2$PhCOOH (4) | 3 | 3 | 1 | 61 | 31 |

the best yield of **56a** (70%), along with **57** in 21% yield (run 1). Stirring a methanolic solution of **56a** with potassium carbonate gave in 95% yield (−)-**50** [$[\alpha]_D^{21}$ −9.6° (*c* = 0.25, chloroform)], whose enantiomeric exess was indicated to be >99.9% by an HPLC analysis of the (*R*)-*O*-methylmandelate derived from this (−)-**50**. Therefore the enantiomer (+)-**50** was efficiently changed to a useful chiral intermediate (−)-**50** for the synthesis of the natural product, and thus a total synthesis of natural duocarmycin SA (+)-**1** was accomplished starting from the pyrrole derivative **11** and a racemic singlet oxygen adduct **14b** of the dihydropyridine **13b**.

In summary, a novel synthetic route to (±)-**1** was developed, involving as pivotal reactions (i) the oxidative introduction of the nucleophile **12** into the dihydropyridine **13a**, (ii) the intramolecular Heck reaction of **21a** to produce tricyclic **25a** and **26a**, (iii) the oxidative aromatization of the acetal **32a** to **37a** by way of the selenide **36a**, and (iv) the dehydrative cyclization of the diol **40** to the cyclopropa[*c*]pyrrolo[3,2-*e*]indole skeleton **41** under modified Mitsunobu reaction conditions. Next, optical resolution of the secondary alcohol **50** was effected by derivatizing it to (*R*)-*O*-methylmandelates **52** and **53**. The resulting chiral alcohols (+)-**50** and (−)-**50** were transformed into unnatural (−)-**1** and natural (+)-**1**, respectively. Finally inversion of the secondary alcohol (+)-**50** to the enantiomer (−)-**50** was effected by using the Mitsunobu reaction. This constitutes an enantio-convergent total synthesis of natural duocarmycin SA (**1**) starting from a racemic compound.

## Experimental

Melting points were determined 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 at an ionizing voltage of 70 eV, and figures in parentheses indicate the relative intensities. IR spectra were measured on a Hitachi 215 spectrophotometer. $^1$H-NMR spectra were obtained on a Varian EM 390 (90 MHz) spectrometer, unless otherwise specified, in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference. $^1$H-NMR (400 MHz) and $^{13}$C-NMR (100 MHz) spectra were measured on a JEOL JNM-GX-400 spectrometer. Column chromatography was conducted on silica gel (Fuji Davison BW 200) or on aluminum oxide (Merck, activity grade II-III) and preparative TLC (PTLC) was carried out 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 layers with water or brine, drying over anhydrous $Na_2SO_4$, and evaporating off the solvents under reduced pressure.

**Methyl 5-Acetyl-4-bromo-1*H*-pyrrole-2-carboxylate (11)** $BF_3 \cdot OEt_2$ (0.85 ml, 6.9 mmol) was added to a solution of $Ac_2O$ (0.49 ml, 5.2 mmol) in 1,2-dichloroethane (4 ml) and the mixture was stirred at 0 °C for 5 min. A solution of **10** (350 mg, 1.72 mmol) in 1,2-dichloroethane (2 ml) was added dropwise to this and the whole was stirred for 2 h at 0 °C. $H_2O$ was added and the mixture was extracted with $CH_2Cl_2$. The organic layer was washed with saturated $NaHCO_3$–$H_2O$ and worked up as usual. Column chromatography over silica gel (15 g) using $CH_2Cl_2$ and recrystallization from $CH_2Cl_2$–hexane afforded **11** (392 mg, 93%) as colorless needles, mp 125.5—126 °C. *Anal.* Calcd for $C_8H_8BrNO_3$: C, 39.05; H, 3.28; Br, 32.47; N, 5.69. Found: C, 39.14; H, 3.30; Br, 32.69; N, 5.74. GC-HRMS Calcd for $C_8H_8BrNO_3$: 246.9668, 244.9688. Found: 246.9657, 244.9674. GC-MS *m/z*: 247, 245 ($M^+$; 60, 58), 232, 230 (40, 42), 216, 214 (13, 11), 200, 198 (95, 100), 43 (69). IR (KBr): 1718, 1660 cm$^{-1}$. $^1$H-NMR δ: 2.64 (3H, s), 3.88 (3H, s), 6.92 (1H, d, *J* = 3 Hz, changed to s with $D_2O$), 10.00 (1H, br s, NH).

**Methyl 4-Bromo-5-[1-[(*tert*-butyldimethylsilyl)oxy]ethenyl]-1*H*-pyrrole-2-carboxylate (12)** TBDMSOTf (112 μl, 0.487 mmol) was added to a solution of **11** (92 mg, 0.37 mmol) and $Et_3N$ (94 μl, 0.68 mmol) in $CH_2Cl_2$ (3 ml) at 0 °C under an Ar atmosphere and the mixture was stirred at 0 °C for 1.5 h. Saturated $NaHCO_3$–$H_2O$ was added and the whole was extracted with $CH_2Cl_2$. Usual work-up and purification by column chromatography over $Al_2O_3$ (15 g) using hexane–$CH_2Cl_2$ (2 : 1) gave **12** (124 mg, 92%) as a colorless syrup, along with recovery of **11** (5 mg, 5%). HRMS Calcd for $C_{14}H_{22}BrNO_3Si$: 361.0532, 359.0552. Found: 361.0542, 359.0527. IR ($CHCl_3$): 1708, 1619 cm$^{-1}$. MS *m/z*: 361, 359 ($M^+$; 14, 12), 304, 302 (76, 69), 290 (44), 288 (99), 286 (57), 272, 270 (22, 16), 246, 244 (29, 28), 230, 228 (22, 18), 223 (29), 198, 196 (25, 18), 75 (100), 73 (82), 57 (49). $^1$H-NMR δ: 0.25 (6H, s), 1.01 (9H, s), 3.86 (3H, s), 4.60 (1H, d, *J* = 2.5 Hz), 5.43 (1H, d, *J* = 2.5 Hz), 6.93 (1H, d, *J* = 3 Hz), 9.30 (1H, br s, NH).

***trans*-(±)- and *cis*-(±)-1-(Benzyloxycarbonyl)-2-[2-[3-bromo-5-(methoxycarbonyl)-1*H*-pyrrol-2-yl]-2-oxoethyl]-1,2,5,6-tetrahydro-5-hydroxypyridine (15a and 16a)** According to the reported procedure,[15] a solution of **13a** (880 mg, 4.09 mmol) and Methylene Blue (50 mg) in $CH_2Cl_2$ (150 ml) was photooxygenated at −65 °C for 2.5 h. A $CH_2Cl_2$ solution (5 ml) of the crude **12** (850 mg) prepared from **11** (502 mg, 2.04 mmol) as above was added to this at −70 °C, and an EtOAc solution (40 ml) of $SnCl_2$ (930 mg, 4.89 mmol) was added slowly during 10 min. After having been stirred at this temperature for 30 min and at 0 °C for 3 h, the mixture was treated as reported. Purification by column chromatography over silica gel (40 g) using benzene–EtOAc (2 : 1), followed by PTLC (1.5% MeOH–$CH_2Cl_2$) afforded **15a** (567 mg, 58%) as a more polar isomer and **16a** (108 mg, 11%) as a less polar isomer, along with recovery of **11** (23 mg, 4.5%). **15a**: Colorless glass. MS *m/z*: 460, 458 ($M^+ - H_2O$; 2, 2), 415, 413 (1, 1), 343, 341 (1, 1), 325, 323 (1, 1), 232, 230 (3, 3), 200, 198 (5, 6), 188 (7), 121 (4), 91 (100). IR ($CHCl_3$): 1719, 1692, 1654 cm$^{-1}$. $^1$H-NMR (60 °C) δ: 2.60 (1H, br s, OH), 3.06 (1H, dd, *J* = 15, 6 Hz), 3.19 (1H, d, *J* = 14 Hz), 3.37 (1H, dd, *J* = 15, 6.5 Hz), 3.84 (3H, s), 3.99—4.16 (1H, m), 4.33 (1H, d, *J* = 14 Hz), 4.96—5.27 (1H, m), 5.05 (2H, s), 5.78—6.14 (2H, m), 6.82 (1H, s), 7.23 (5H, s), 10.44 (1H, br s, NH). **16a**: Colorless glass. MS *m/z*: 460, 458 ($M^+ - H_2O$; 2, 2), 415, 413 (2, 1), 343, 341 (2, 2), 325, 323 (3, 3), 232, 230 (4, 4), 200, 198 (6, 6), 188 (5), 121 (4), 91 (100). IR ($CHCl_3$): 1718, 1695, 1653 cm$^{-1}$. $^1$H-NMR (60 °C) δ: 2.26 (1H, br s, OH), 2.61—2.98 (1H, m), 3.14 (1H, dd, *J* = 15, 6 Hz), 3.41 (1H, dd, *J* = 15, 6.5 Hz), 3.86 (3H, s), 4.15—4.53 (2H, m), 4.88—5.21 (1H, m), 5.06 (2H, s), 5.70—5.99 (2H, m), 6.85 (1H, s), 7.26 (5H, s), 10.09 (1H, br s, NH).

***trans*-(±)-2-[2-[3-Bromo-5-(methoxycarbonyl)-1*H*-pyrrol-2-yl]-2-oxoethyl]-1,2,5,6-tetrahydro-5-hydroxy-1-(methoxycarbonyl)pyridine (15b)** Colorless glass. MS *m/z*: 384, 382 ($M^+ - H_2O$; 17, 16), 232, 230 (19, 20), 200, 198 (34, 34), 156 (100), 138 (53), 124 (46), 59 (32). IR ($CHCl_3$): 1721, 1694, 1659 cm$^{-1}$. $^1$H-NMR (60 °C) δ: 2.53 (1H, br s, OH), 3.10 (1H, dd, *J* = 15.5, 6.5 Hz), 3.18 (1H, dd, *J* = 14, 2.5 Hz), 3.40 (1H, dd, *J* = 15.5, 7.5 Hz), 3.63 (3H, s), 3.88 (3H, s), 3.99—4.20 (1H, m), 4.29 (1H, br d, *J* = 14 Hz), 5.06 (1H, dd, *J* = 7.5, 6.5 Hz), 5.84—6.17 (2H, m), 6.91 (1H, s), 10.48 (1H, br s, NH).

***cis*-(±)-2-[2-[3-Bromo-5-(methoxycarbonyl)-1*H*-pyrrol-2-yl]-2-oxoethyl]-1,2,5,6-tetrahydro-5-hydroxy-1-(methoxycarbonyl)pyridine (16b)** Colorless glass. MS *m/z*: 384, 382 ($M^+ - H_2O$; 22, 22), 232, 230 (36, 40), 200, 198 (50, 51), 156 (100), 138 (79), 124 (52), 59 (46). IR ($CHCl_3$): 1720, 1698, 1655 cm$^{-1}$. $^1$H-NMR (60 °C) δ: 2.78 (1H, dd, *J* = 15, 12 Hz), *ca.* 2.78—3.44 (1H, br m, OH), 3.16 (1H, dd, *J* = 15.5, 6 Hz), 3.44 (1H, dd, *J* = 15.5, 7 Hz), 3.64 (3H, s), 3.89 (3H, s), 4.14—4.50

(2H, m), 4.93 (1H, dd, $J=7$, 6 Hz), 5.69—6.00 (2H, m), 6.91 (1H, s), 10.47 (1H, br s, NH).

***trans*-(±)-1-(Benzyloxycarbonyl)-2-[2-[3-bromo-5-(methoxycarbonyl)-1-(methoxymethyl)-1*H*-pyrrol-2-yl]-2-oxoethyl]-1,2,5,6-tetrahydro-5-[(methoxymethyl)oxy]pyridine (17a)** MOMCl (0.20 ml, 2.6 mmol) was added to an ice-cooled solution of **15a** (71 mg, 0.15 mmol) and iso-$Pr_2NEt$ (0.70 ml, 4.0 mmol) in $CH_2Cl_2$ (1.5 ml), and the mixture was stirred at 0 °C for 1 h and then at 21 °C for 2 h. $H_2O$ was added and the whole was extracted with $CH_2Cl_2$. The organic layer was successively washed with 0.1 N citric acid–$H_2O$ and saturated $NaHCO_3$–$H_2O$. Usual work-up and purification by PTLC [hexane–EtOAc (2 : 1)] afforded **17a** (76 mg, 90%) as a colorless glass. MS *m/z*: 504, 502 ($M^+$ – MOMOH; 3, 3), 453 (2), 379 (2), 337, 335 (3, 3), 276, 274 (7, 6), 232 (6), 170 (5), 91 (100), 45 (77). IR ($CHCl_3$): 1720, 1695 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 2.96—3.60 (3H, m), 3.20 (3H, s), 3.32 (3H, s), 3.84 (3H, s), 3.91—4.09 (1H, m), 4.43 (1H, d, $J=14$ Hz), 4.58 (1H, d, $J=7$ Hz), 4.69 (1H, d, $J=7$ Hz), 4.94—5.28 (1H, m), 5.10 (2H, s), 5.79—6.23 (2H, m), 5.94 (2H, s), 6.93 (1H, s), 7.28 (5H, s).

***cis*-(±)-1-(Benzyloxycarbonyl)-2-[2-[3-bromo-5-(methoxycarbonyl)-1-(methoxymethyl)-1*H*-pyrrol-2-yl]-2-oxoethyl]-1,2,5,6-tetrahydro-5-[(methoxymethyl)oxy]pyridine (18a)** Similarly, a solution of **16a** (66 mg, 0.14 mmol) and iso-$Pr_2NEt$ (1.05 ml, 6.04 mmol) in $CH_2Cl_2$ (1.5 ml) was stirred with MOMCl (0.30 ml, 4.0 mmol) at 0 °C for 1 h and then at 21 °C for 20 h. The same work-up as above and purification by PTLC [hexane–EtOAc (5 : 2)] gave **18a** (57 mg, 73%) and **20a** (7 mg, 10%) in order of increasing polarity. **18a**: Colorless glass. MS *m/z*: 504, 502 ($M^+$ – MOMOH; 3, 3), 379 (3), 369, 367 (3, 3), 337, 335 (5, 3), 276, 274 (11, 10), 232 (5), 170 (5), 91 (100), 45 (84). IR ($CHCl_3$): 1721, 1692 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 2.82 (1H, dd, $J=12.5$, 10 Hz), 3.08—3.63 (2H, m), 3.20 (3H, s), 3.36 (3H, s), 3.84 (3H, s), 4.03—4.30 (1H, m), 4.47 (1H, dd, $J=12.5$, 6 Hz), 4.69 (2H, s), 4.90—5.19 (1H, m), 5.10 (2H, s), 5.71—6.04 (2H, m), 5.96 (2H, s), 6.92 (1H, s), 7.29 (5H, s). **20a**: Colorless glass. MS *m/z*: 504, 502 ($M^+ - H_2O$; 1.5, 1.5), 399, 397 (2, 2), 369, 367 (2, 2), 355, 353 (2, 2), 337, 335 (2, 2), 276, 274 (6, 7), 232 (3), 200, 198 (2, 2), 188 (7), 91 (100), 45 (58). IR ($CHCl_3$): 1719, 1688 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 1.70 (1H, br s, OH), 2.56—2.94 (1H, m), 3.10—3.62 (4H, m), 3.20 (3H, s), 3.84 (3H, s), 4.89—5.23 (1H, m), 5.10 (2H, s), 5.69—6.08 (2H, m), 5.96 (2H, s), 6.93 (1H, s), 7.30 (5H, s).

***trans*-(±)-1-(Benzyloxycarbonyl)-2-[2-[3-bromo-5-(methoxycarbonyl)-1*H*-pyrrol-2-yl]-2-oxoethyl]-5-[(*tert*-butyldimethylsilyl)oxy]-1,2,5,6-tetrahydropyridine (19a)** TBDMSCl (28 mg, 0.19 mmol) was added to a solution of **15a** (68 mg, 0.14 mmol) and imidazole (24 mg, 0.35 mmol) in $CH_2Cl_2$ (1.5 ml), and the mixture was stirred at 20 °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–EtOAc (2 : 1)] afforded **19a** (79 mg, 94%) as a colorless glass. MS *m/z*: 535, 533 ($M^+$ – *tert*-Bu; 3, 3), 232, 230 (4, 5), 200, 198 (6, 11), 197 (8), 154 (28), 91 (100), 75 (23), 73 (34). IR ($CHCl_3$): 1720, 1692, 1653 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 0.03 (6H, s), 0.82 (9H, s), *ca.* 2.99—3.26 (1H, m), 3.07 (1H, dd, $J=15$, 6.5 Hz), 3.33 (1H, dd, $J=15$, 7.5 Hz), 3.85 (3H, s), 4.04—4.20 (1H, m), 4.20 (1H, d, $J=14.5$ Hz), 4.98 and 5.13 (AB, $J=11.5$ Hz), 4.98—5.26 (1H, m), 5.70—6.06 (2H, m), 6.85 (1H, s), 10.10 (1H, br s, NH).

***trans*-(±)- and *cis*-(±)-5-Benzyloxy-1-(benzyloxycarbonyl)-2-[2-[3-bromo-5-(methoxycarbonyl)-1*H*-pyrrol-2-yl]-2-oxoethyl]-1,2,5,6-tetrahydropyridines (21a and 22a)** TfOH (5 $\mu$l, 0.06 mmol) was added to a solution of **15a** (125 mg, 0.262 mmol) and benzyl 2,2,2-trichloroacetimidate (107 $\mu$l, 0.576 mmol) in cyclohexane–$CH_2Cl_2$ (2 : 1) (4.5 ml) under an Ar atmosphere at 0 °C, and the mixture was stirred at the same temperature for 20 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 ($CH_2Cl_2$) afforded **21a** (107 mg, 72%) together with the recovered **15a** (9 mg, 7%). **21a**: Colorless glass. MS *m/z*: 487 ($M^+$ – Br, 0.4), 460, 458 (3, 3), 415, 413 (1, 1), 278 (3), 215 (7), 170 (4), 91 (100). IR ($CHCl_3$): 1720, 1697, 1658 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 3.08 (1H, dd, $J=15$, 6.5 Hz), 3.09 (1H, dd, $J=14.5$, 3 Hz), 3.37 (1H, dd, $J=15$, 7 Hz), 3.73—3.99 (1H, m), 3.86 (3H, s), *ca.* 4.43—4.67 (1H, m), 4.43 and 4.64 (AB, $J=11.5$ Hz), 5.00—5.30 (1H, m), 5.07 (2H, s), 5.80—6.19 (2H, m), 6.84 (1H, s), 7.22 (5H, s), 7.25 (5H, s), 10.03 (1H, br s, NH).

Similarly **22a** (34 mg, 68%) was obtained from **15a** (42 mg), accompanied with recovery of **15a** (8 mg, 19%). **22a**: Colorless glass. MS *m/z*: 460, 458 ($M^+$ – BnOH; 3, 3), 325, 323 (2, 2), 232, 230 (2, 2), 200, 198 (3, 3), 91 (100), 65 (5). IR ($CHCl_3$): 1720, 1695, 1653 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 2.84 (1H, dd, $J=12$, 9 Hz), 3.13 (1H, dd, $J=15$, 7 Hz), 3.40 (1H, dd, $J=15$, 6 Hz), 3.86 (3H, s), 3.86—4.17 (1H, m), 4.31—4.60 (1H, m), 4.60 (2H, s), 4.88—5.20 (1H, m), 5.04 (2H, s), 5.71—6.04 (2H, m), 6.84 (1H, d, $J=1$ Hz, changed to s with $D_2O$), 7.24 (5H, s), 7.28 (5H, s), 9.91 (1H, br s, NH).

***trans*-(±)-5-Benzyloxy-2-[2-[3-bromo-5-(methoxycarbonyl)-1*H*-pyrrol-2-yl]-2-oxoethyl]-1,2,5,6-tetrahydro-1-(methoxycarbonyl)pyridine (21b)** Compound **21b** (106 mg, 71%) was obtained from **16b** (122 mg) as a colorless solid, together with recovery of **16b** (9 mg, 7%). MS *m/z*: 384, 382 ($M^+$ – BnOH; 6, 6), 232, 230 (4, 5), 200, 198 (7, 8), 139 (15), 91 (100), 59 (5). IR ($CHCl_3$): 1722, 1700, 1658 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 3.06 (1H, dd, $J=15$, 2 Hz), 3.10 (1H, dd, $J=15.5$, 6.5 Hz), 3.38 (1H, dd, $J=15.5$, 7.5 Hz), 3.63 (3H, s), 3.76—3.97 (1H, m), 3.86 (3H, s), 4.46 and 4.66 (AB, $J=11.5$ Hz), 4.49 (1H, br d, $J=15$ Hz), 5.10 (1H, ddd, $J=7.5$, 6.5, 3 Hz), 5.92 (1H, dd, $J=10.5$, 4 Hz), 6.08 (1H, dd, $J=10.5$, 3 Hz), 6.89 (1H, s), 7.14—7.43 (5H, m), 10.34 (1H, br s, NH).

**Methyl *cis*-(±)-8-Benzyloxy-6-(benzyloxycarbonyl)-3,4,5,5a,7,9a-hexahydro-4-oxo-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (25a) and Methyl *cis*-(±)-8-Benzyloxy-6-(benzyloxycarbonyl)-3,4,5,5a,9,9a-hexahydro-4-oxo-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (26a)** (Table 1, run 14) An MeCN solution (3 ml) of **21a** (103 mg, 0.182 mmol), $Pd(OAc)_2$ (2 mg, 9 $\mu$mol), (*o*-tol)$_3$P (7 mg, 0.02 mmol), and $Et_3N$ (25 $\mu$l, 0.18 mmol) was heated at 110 °C with stirring in a sealed tube under an Ar atmosphere for 26 h. 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 separation by PTLC [benzene–EtOAc (6 : 1)] gave **25a** (72 mg, 82%) and **26a** (10 mg, 11%) in order of decreasing polarity. **25a**: Colorless glass. HRMS Calcd for $C_{28}H_{26}N_2O_6$: 486.1789. Found: 486.1804. MS *m/z*: 486 ($M^+$, 1), 395 (1), 351 (10), 91 (100), 65 (5). IR ($CHCl_3$): 1700, 1667 $cm^{-1}$. $^1$H-NMR (400 MHz, 60 °C) $\delta$: 2.47 (1H, dd, $J=16$, 4 Hz), 2.87 (1H, dd, $J=16$, 12.5 Hz), 3.65 (1H, d, $J=17$ Hz), 3.84—3.91 (1H, m), 3.90 (3H, s), 4.39 (1H, br d, $J=17$ Hz), 4.66 (1H, s), 4.71 and 4.77 (AB, $J=12$ Hz), 4.94—5.05 (1H, m), 5.17 (2H, s), 6.80 (1H, d, $J=2$ Hz), 7.25—7.36 (10H, m), 9.49 (1H, br s, NH). **26a**: Colorless glass. HRMS Calcd for $C_{28}H_{26}N_2O_6$: 486.1789. Found: 486.1797. MS *m/z*: 486 ($M^+$, 2), 351 (9), 91 (100), 65 (4). $^1$H-NMR of major and minor rotamers (400 MHz) $\delta$: 2.27 (1H, ddd, $J=18$, 11.5, 2 Hz), 2.56 (1H, dd, $J=18$, 6 Hz), 2.61—2.77 (2H, m), 3.26—3.35 (1H, m), 3.90 (3H, s), 4.78 and 4.72, 4.76 (total 2H, s and AB, $J=11$ Hz), 4.92 and *ca.* 4.72—4.82 (total 1H, ddd and m, $J=12$, 5, 5 Hz), 5.18, 5.24 and 5.20, 5.23 (total 2H, AB each, $J=12.5$ Hz each), 6.55 and 6.40 (total 1H, br s each), 6.77 and 6.77—6.78 (total 1H, d and m, $J=2$ Hz), 7.28—7.42 (10H, m), 9.75 (1H, br s, NH).

**Methyl *cis*-(±)-8-Benzyloxy-3,4,5,5a,7,9a-hexahydro-6-(methoxycarbonyl)-4-oxo-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (25b) and Its Double Bond Isomer 26b** An inseparable mixture of **25b** and **26b** (5.7 : 1) (340 mg, 95%) was obtained from **21b** (429 mg). HRMS Calcd for $C_{22}H_{22}N_2O_6$: 410.1476. Found: 410.1468. MS *m/z*: 410 ($M^+$, 5), 319 (5), 91 (100), 65 (5). IR ($CHCl_3$): 1710, 1672 $cm^{-1}$. $^1$H-NMR of **25b** (400 MHz, 60 °C) $\delta$: 2.46 (1H, dd, $J=16$, 4.5 Hz), 2.87 (1H, dd, $J=16$, 12.5 Hz), 3.63 (1H, d, $J=17.5$ Hz), 3.74 (3H, s), 3.84—3.90 (1H, m), 3.90 (3H, s), 4.36 (1H, br d, $J=17.5$ Hz), 4.67 (1H, s), 4.72 and 4.78 (AB, $J=11.5$ Hz), 4.90—5.02 (1H, m), 6.81 (1H, s), 7.25—7.35 (5H, m), 9.83 (1H, br s, NH). $^1$H-NMR of **26b** (400 MHz, 60 °C) $\delta$: 2.28 (1H, ddd, $J=17$, 11.5, 2 Hz), 2.55 (1H, dd, $J=17$, 6 Hz), 2.62—2.73 (2H, m), 3.28 (1H, ddd, $J=11.5$, 6, 5 Hz), 3.78 (3H, s), 3.89 (3H, s), 4.78 (2H, s), 4.90—5.02 (1H, m), 6.77 (1H, s), 7.25—7.35 (6H, m), 9.83 (1H, br s, NH). The ratio of **25b** and **26b** was estimated from the integral values of the $\delta$ 6.81 and 6.77 signals.

**Methyl *cis*-(±)-6-(Benzyloxycarbonyl)-3,4,5,5a,7,9a-hexahydro-3-(methoxymethyl)-8-[(methoxymethyl)oxy]-4-oxo-6*H*-pyrrolo[3,2-*f*]-quinoline-2-carboxylate (23a)** Colorless glass. HRMS Calcd for $C_{25}H_{28}N_2O_8$: 484.1844. Found: 484.1837. MS *m/z*: 484 ($M^+$, 3), 408 (4), 317 (10), 216 (17), 91 (100), 45 (94). IR ($CHCl_3$): 1720, 1698, 1664 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 2.44 (1H, dd, $J=16$, 5 Hz), 2.92 (1H, dd, $J=16$, 12.5 Hz), 3.31 (3H, s), 3.38 (3H, s), 3.58 (1H, d, $J=18$ Hz), 3.76—3.97 (1H, m), 3.87 (3H, s), 4.33 (1H, d, $J=18$ Hz), 4.80—5.11 (4H, m), 5.17 (2H, s), 6.11 (2H, s), 7.34 (5H, s).

**Methyl *cis*-(±)-6-(Benzyloxycarbonyl)-8-[(*tert*-butyldimethylsilyl)-oxy]-3,4,5,5a,7,9a-hexahydro-4-oxo-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (24a)** Colorless solid. HRMS Calcd for $C_{27}H_{34}N_2O_6Si$: 510.2184. Found: 510.2193. MS *m/z*: 510 ($M^+$, 6), 375 (46), 343 (4), 91 (100), 73 (39). IR ($CHCl_3$): 1700, 1667 $cm^{-1}$. $^1$H-NMR $\delta$: 0.09 (3H, s), 0.13 (3H, s), 0.88 (9H, s), 2.44 (1H, dd, $J=17$, 5 Hz), 2.88 (1H, dd, $J=17$, 13 Hz), 3.51 (1H, d, $J=18$ Hz), 3.74—4.01 (1H, m), 3.89 (3H, s),

4.24 (1H, d, $J$=18 Hz), 4.73 (1H, s), *ca.* 4.73—5.17 (1H, m), 5.17 (2H, s), 6.79 (1H, d, $J$=1.5 Hz), 7.34 (5H, s), 9.78 (1H, br s, NH).

**Methyl *cis*-(±)-6-(Benzyloxycarbonyl)-3,4,5,5a,7,8,9,9a-octahydro-4,8-dioxo-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (27a)** A solution of **25a** (9 mg, 0.02 mmol) in 4% HCl-containing DME–$H_2O$ (3 : 2) (2.5 ml) was stirred at 20 °C for 6 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 **27a** (6.5 mg, 89%) as a colorless glass. HRMS Calcd for $C_{21}H_{20}N_2O_6$: 396.1320. Found: 396.1336. MS *m/z*: 396 ($M^+$, 2), 305 (2), 290 (20), 91 (100), 65 (7). IR ($CHCl_3$): 1700, 1670 $cm^{-1}$. $^1$H-NMR (400 MHz, 60 °C) $\delta$: 2.68 (1H, dd, $J$=16.5, 9.5 Hz), 2.79 (1H, dd, $J$=16.5, 5 Hz), 2.81 (1H, dd, $J$=16.5, 5.5 Hz), 3.03 (1H, dd, $J$=16.5, 8.5 Hz), 3.47 (1H, d, $J$=18.5 Hz), 3.64 (1H, ddd, $J$=9.5, 5.5, 5 Hz), 3.89 (3H, s), 4.48 (1H, d, $J$=18.5 Hz), 4.97 (1H, ddd, $J$=8.5, 5, 5 Hz), 5.17 (2H, s), 6.70 (1H, d, $J$=2.5 Hz), 7.28—7.38 (5H, m), 9.61 (1H, br s, NH).

**Conversion of 16a to 15a** i) A THF solution (1.5 ml) of DEAD (44 mg, 0.25 mmol) was added dropwise to a solution of **16a** (60 mg, 0.13 mmol), $Ph_3P$ (66 mg, 0.25 mmol), and HOAc (36 $\mu$l, 0.63 mmol) in THF (1.5 ml) at 0 °C. The mixture was stirred at 0 °C for 5 min and at 22 °C for 1.5 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 [benzene–EtOAc (8 : 1)], gave *trans*-(±)-5-acetoxy-1-(benzyloxycarbonyl)-2-[2-[3-bromo-5-(methoxycarbonyl)-1*H*-pyrrol-2-yl]-2-oxoethyl]-1,2,5,6-tetrahydropyridine (*O*-acetate of **15a**) (48 mg, 74%) as a colorless foam. MS *m/z*: 460, 458 ($M^+$ – HOAc; 3, 2), 200, 198 (4, 5), 170 (7), 91 (100) 43 (14). IR ($CHCl_3$): 1721, 1700 (sh), 1653 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 1.90 (3H, s), 3.11 (1H, dd, $J$=15.5, 6.5 Hz), 3.23 (1H, dd, $J$=15, 3 Hz), 3.39 (1H, dd, $J$=15.5, 7 Hz), 3.87 (3H, s), 4.42 (1H, d, $J$=15 Hz), 4.97—5.33 (2H, m), 5.10 (2H, s), 5.93 (1H, br dd, $J$=10, 4.5 Hz), 6.14 (1H, dd, $J$=10, 3.5 Hz), 6.84 (1H, d, $J$=2.5 Hz), 7.25 (5H, s), 9.91 (1H, br s, NH). This *O*-acetate of **15a** (61 mg) in 1.5% $K_2CO_3$–MeOH (3 ml) was stirred at 19 °C for 2 h. Saturated $NH_4Cl$–$H_2O$ was added and the mixture was extracted with $CH_2Cl_2$. Usual work-up and purification by PTLC [benzene–EtOAc (3 : 1)] afforded **15a** (52 mg, 93%).

ii) MsCl (26 $\mu$l, 0.34 mmol) was slowly added to a cooled (−20 °C) solution of **16a** (63 mg, 0.13 mmol) and $Et_3N$ (0.18 ml, 1.3 mmol) in $CH_2Cl_2$ (3 ml) under an Ar atmosphere. The mixture was stirred at −20 °C for 40 min, then 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 $NaHCO_3$–$H_2O$, and then treated as usual to leave a residue (80 mg). CsOCOEt (41 mg, 0.20 mmol) was added to a solution of this residue in DMF (2 ml), and the mixture was stirred under an Ar atmosphere at 21 °C for 15 h. Saturated $NH_4Cl$–$H_2O$ was added and the whole was extracted with $Et_2O$, and then worked up as usual to give the crude propionate of **15a**. This was treated with 1.5% $K_2CO_3$–MeOH (3 ml) at 20 °C for 5 h. The same work-up as above afforded **15a** (30 mg, 48%).

***trans*-(±)-5-Acetoxy-2-[2-[3-bromo-5-(methoxycarbonyl)-1*H*-pyrrol-2-yl]-2-oxoethyl]-1,2,5,6-tetrahydro-1-(methoxycarbonyl)pyridine (*O*-acetate of 15b)** Colorless glass. MS *m/z*: 384, 382 ($M^+$ – HOAc; 16, 14), 325, 323 (4, 5), 232, 230 (13, 14), 200, 198 (20, 39), 156 (36), 138 (94), 94 (32), 59 (24), 43 (100). IR ($CHCl_3$): 1720, 1700 (sh), 1657 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 1.99 (3H, s), 3.11 (1H, dd, $J$=16, 6.5 Hz), 3.19 (1H, dd, $J$=15, 3 Hz), 3.40 (1H, dd, $J$=16, 7 Hz), 3.65 (3H, s), 3.88 (3H, s), 4.36 (1H, d, $J$=15 Hz), 4.98—5.28 (2H, m), 5.93 (1H, br dd, $J$=10, 4.5 Hz), 6.15 (1H, dd, $J$=10, 4 Hz), 6.91 (1H, s), 10.14 (1H, br s, NH).

**Methyl 4-[[3-(Benzyloxycarbonyl)amino]-2,2-dimethoxypropyl]-7-methoxy-1-(methoxymethyl)-1*H*-indole-2-carboxylate (33a)** A solution of **23a** (8 mg, 0.02 mmol) in a 0.5% $H_2SO_4$-containing mixture (2 ml) of MeOH and $HC(OMe)_3$ (4 : 1) was heated for 30 min under reflux. After the mixture had cooled, saturated $NaHCO_3$–$H_2O$ was added and the whole was extracted with $CH_2Cl_2$, and then worked up as usual. Purification by PTLC (0.3% MeOH–$CH_2Cl_2$) gave **33a** (7 mg, 85%) as a colorless glass. HRMS Calcd for $C_{26}H_{32}N_2O_8$: 500.2157. Found: 500.2163. MS *m/z*: 500 ($M^+$, 2), 468 (3), 437 (1), 392 (2), 360 (3), 336 (4), 262 (5), 238 (43), 130 (29), 91 (100), 45 (29). IR ($CHCl_3$): 1712 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 3.21 (5H, s), *ca.* 3.21—3.38 (2H, m), 3.31 (6H, s), 3.86 (3H, s), 3.93 (3H, s), 4.46—4.76 (1H, m, NH), 4.94 (2H, s), 6.24 (2H, s), 6.71 (1H, d, $J$=8.5 Hz), 7.03 (1H, d, $J$=8.5 Hz), 7.27 (5H, s), 7.42 (1H, s).

**Methyl *cis*-(±)-6-(Benzyloxycarbonyl)-3,4,5,5a,7,8,9,9a-octahydro-8,8-dimethoxy-4-oxo-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (32a)** From **25a**: $Me_3SiOTf$ (48 $\mu$l, 0.25 mmol) was added to a cooled (−20 °C) solution of **25a** (60 mg, 0.12 mmol) and $Me_3SiOMe$ (0.17 ml, 1.24 mmol) in $CH_2Cl_2$ (4 ml) and the mixture was stirred under an Ar atmosphere at −20 °C for 4 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–EtOAc (1 : 1)] afforded **32a** (47 mg, 86%) as a colorless glass. HRMS Calcd for $C_{23}H_{26}N_2O_7$: 442.1738. Found: 442.1739. MS *m/z*: 442 ($M^+$, 6), 277 (75), 223 (22), 91 (100), 65 (11). IR ($CHCl_3$): 1694, 1669 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 1.53 (1H, dd, $J$=13, 13 Hz), 2.26 (1H, ddd, $J$=13, 4.5, 3 Hz), 2.46 (1H, dd, $J$=17, 5.5 Hz), 2.76 (1H, d, $J$=15 Hz), 2.93 (1H, dd, $J$=17, 13 Hz), *ca.* 3.13—3.44 (1H, m), 3.22 (6H, s), 3.88 (3H, s), 4.39 (1H, br d, $J$=15 Hz), 4.75—5.13 (1H, m), 5.16 (2H, s), 6.75 (1H, s), 7.33 (5H, s), 9.61 (1H, br s, NH).

From **26a**: Similarly a solution of **26a** (18 mg, 0.037 mmol) and $Me_3SiOMe$ (51 $\mu$l, 0.37 mmol) in $CH_2Cl_2$ (2 ml) was treated with $Me_3SiOTf$ (14 $\mu$l, 0.073 mmol) at −20 °C for 2 h and at 0 °C for 1.5 h. Work-up as above and purification by PTLC (1% MeOH–$CH_2Cl_2$) afforded **32a** (12.5 mg, 76%) and methyl 4-[[3-(benzyloxycarbonyl)-amino]-2-oxopropyl]-7-methoxy-1*H*-indole-2-carboxylate (**34a**) (1 mg, 7%) in order of decreasing polarity. **34a**: Colorless syrup. HRMS Calcd for $C_{22}H_{22}N_2O_5$: 410.1476. Found: 410.1476. MS *m/z*: 410 ($M^+$, 11), 302 (67), 218 (89), 186 (100), 108 (59), 91 (40), 79 (70), 51 (28). IR ($CHCl_3$): 1709 $cm^{-1}$. $^1$H-NMR $\delta$: 3.90 (2H, s), 3.93 (3H, s), 3.95 (3H, s), 4.07 (2H, d, $J$=5 Hz), 5.05 (2H, s), 5.38 (1H, br s, NH), 6.66 (1H, d, $J$=8 Hz), 6.92 (1H, d, $J$=8 Hz), 7.14 (1H, d, $J$=2 Hz), 7.31 (5H, s), 9.18 (1H, br s, indole NH).

**Methyl *cis*-(±)-3,4,5,5a,7,8,9,9a-Octahydro-8,8-dimethoxy-6-(methoxycarbonyl)-4-oxo-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (32b)** Compound **32b** (39 mg, 84%) was obtained as a colorless glass from a mixture of **25b** and **26b** (52 mg) at −20 °C for 5 h. HRMS Calcd for $C_{17}H_{22}N_2O_7$: 366.1426. Found: 366.1436. MS *m/z*: 366 ($M^+$, 15), 335 (9), 334 (7), 277 (100), 223 (39), 208 (28), 59 (33), 43 (19). IR ($CHCl_3$): 1700, 1667 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 1.54 (1H, dd, $J$=13, 13 Hz), 2.27 (1H, ddd, $J$=13, 4.5, 3 Hz), 2.45 (1H, dd, $J$=16.5, 5.5 Hz), 2.76 (1H, d, $J$=14.5 Hz), 2.94 (1H, dd, $J$=16.5, 13 Hz), 3.11—3.43 (1H, m), 3.25 (3H, s), 3.27 (3H, s), 3.73 (3H, s), 3.89 (3H, s), 4.36 (1H, br d, $J$=14.5 Hz), 4.69—5.07 (1H, m), 6.74 (1H, s), 10.11 (1H, br s, NH).

**Methyl (5α,5aα,9aα)-(±)-6-(Benzyloxycarbonyl)-3,4,5,5a,7,8,9,9a-octahydro-8,8-dimethoxy-4-oxo-5-(phenylseleno)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (36a)** $Me_3SiOTf$ (0.20 ml, 1.0 mmol) was added to a solution of **32a** (155 mg, 0.351 mmol) and $Et_3N$ (0.39 ml, 2.8 mmol) in $CH_2Cl_2$ (6 ml) and the mixture was stirred under an Ar atmosphere at 0 °C for 10 min and at 22 °C for 1.5 h. Saturated $NaHCO_3$–$H_2O$ was added and the whole was extracted with $CH_2Cl_2$, and then worked up as usual to afford crude **35a** (222 mg) as a colorless syrup. This was dissolved in THF (6 ml), and PhSeCl (81 mg, 0.42 mmol) and 1 N $Bu_4NF$–THF (0.18 ml, 0.18 mmol) were successively added to this under an Ar atmosphere at 0 °C, then the mixture was stirred at 0—22 °C for 13 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–EtOAc (2 : 1)] gave **36a** (174 mg, 83%) and recovered **32a** (8 mg, 5%). **36a**: Colorless glass. HRMS Calcd for $C_{29}H_{30}N_2O_7Se$: 598.1217. Found: 598.1223. MS *m/z*: 600, 598, 596, 595, 594 ($M^+$; 0.6, 4, 2, 0.5, 0.5), 441 (3), 409 (3), 318 (24), 91 (100). IR ($CHCl_3$): 1700, 1668 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 1.54 (1H, dd, $J$=13, 13 Hz), 2.22 (1H, dif. d, $J$=13 Hz), 2.41 (1H, d, $J$=15 Hz), 3.15 (3H, s), *ca.* 3.15—3.57 (1H, m), 3.18 (3H, s), 3.87 (3H, s), 4.26 (1H, br d, $J$=15 Hz), 4.39 (1H, d, $J$=12 Hz), 4.95 (1H, dd, $J$=12, 4.5 Hz), 5.20 (2H, s), 6.75 (1H, d, $J$=2 Hz, changed to s with $D_2O$), 7.10—7.53 (8H, m), 7.53—7.80 (2H, m), 9.65 (1H, br s, NH).

**Methyl (5α,5aα,9aα)-(±)-3,4,5,5a,7,8,9,9a-Octahydro-8,8-dimethoxy-6-(methoxycarbonyl)-4-oxo-5-(phenylseleno)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (36b)** Compound **36b** (249 mg, 85%) was obtained from **32b** (205 mg) as a colorless glass, along with the recovered **32b** (11 mg, 5%) by way of **35b**. HRMS Calcd for $C_{23}H_{26}N_2O_7Se$: 522.0903. Found: 522.0893. MS *m/z*: 524, 522, 520, 519, 518 ($M^+$; 7, 28, 13, 7, 7), 365 (45), 333 (68), 301 (48), 273 (60), 159, 157, 155, 154, 153 (18, 47, 23, 16, 13), 77 (50), 59 (100). IR ($CHCl_3$): 1700, 1663 $cm^{-1}$. $^1$H-NMR (60 °C) $\delta$: 1.54 (1H, dd, $J$=13.5, 13.5 Hz), 2.23 (1H, ddd, $J$=13.5, 4.5, 3 Hz), 2.41 (1H, d, $J$=15 Hz), 3.18 (3H, s), *ca.* 3.18—3.46 (1H, m), 3.23 (3H, s), 3.72 (3H, s), 3.88 (3H, s), 4.22 (1H, br d, $J$=15 Hz), 4.39 (1H, d, $J$=12 Hz), 4.90 (1H, dd, $J$=12, 4.5 Hz), 6.70 (1H, s), 7.07—7.38 (3H, m), 7.48—7.80 (2H, m), 9.89 (1H, br s, NH).

**Methyl 6-(Benzyloxycarbonyl)-3,7,8,9-tetrahydro-4-hydroxy-8,8-dimethoxy-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (37a)** (Table 2, run

5) *m*-CPBA (7 mg, 0.04 mmol) was added to a cooled (−20 °C) solution of **36a** (23 mg, 0.038 mmol) in THF (3 ml) under an Ar atmosphere and the mixture was stirred at the same temperature for 20 min. Saturated $NaHCO_3$–$H_2O$ was added and the whole was extracted with $CH_2Cl_2$. Usual work-up and separation by PTLC (1.5% MeOH–$CH_2Cl_2$) afforded **37a** (12 mg, 71%) and crude **38a** (5.5 mg) in order of decreasing polarity. The latter was further purified by PTLC [hexane–EtOAc (2 : 1)] to give methyl 6-(benzyloxycarbonyl)-3,7,8,9-tetrahydro-4-hydroxy-8,8-dimethoxy-5-(phenylseleno)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**38a**) (4.5 mg, 20%). **37a**: Colorless glass. HRMS Calcd for $C_{23}H_{24}N_2O_7$: 440.1582. Found: 440.1581. MS *m/z*: 440 ($M^+$, 24), 273 (9), 231 (16), 199 (15), 91 (100), 75 (44). IR ($CHCl_3$): 1700, 1670 (sh) $cm^{-1}$. $^1$H-NMR (400 MHz) $\delta$: 3.13 (2H, s), 3.29 (6H, s), 3.88 (2H, s), 3.95 (3H, s), 5.27 (2H, s), 6.62 (1H, br s, OH), 7.12 (1H, d, $J$=2 Hz), 7.30—7.44 (6H, m), 9.43 (1H, br s, NH). **38a**: Colorless glass. HRMS Calcd for $C_{29}H_{28}N_2O_7Se$: 596.1060. Found: 596.1041. MS *m/z*: 598, 596, 594, 593, 592 ($M^+$; 2, 4, 3, 1, 1), 440 (13), 231 (10), 91 (100), 77 (13), 75 (32), 51 (10). IR ($CHCl_3$): 1710 $cm^{-1}$. $^1$H-NMR $\delta$: 2.86 (1H, d, $J$=13.5 Hz), 3.17 (2H, s), 3.27 (3H, s), 3.30 (3H, s), 3.94 (3H, s), 4.46—4.80 (1H, m), 4.86—5.36 (2H, m), 6.76 (1H, br s, OH), 6.99—7.56 (11H, m), 9.36 (1H, br s, NH).

**Methyl 3,7,8,9-Tetrahydro-4-hydroxy-8,8-dimethoxy-6-(methoxycarbonyl)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (37b)** Compound **37b** (16 mg, 74%) and its 5-phenylselenyl derivative **38b** (6 mg, 19%) were obtained by oxidation of **36b** (31 mg) with *m*-CPBA at 0 °C. **37b**: Colorless glass. HRMS Calcd for $C_{17}H_{20}N_2O_7$: 364.1269. Found: 364.1273. MS *m/z*: 364 ($M^+$, 100), 333 (37), 59 (58). IR ($CHCl_3$): 1714 (sh), 1693 $cm^{-1}$. $^1$H-NMR $\delta$: 3.10 (2H, s), 3.33 (6H, s), 3.83 (3H, s), 3.84 (2H, s), 3.92 (3H, s), 7.09 (1H, d, $J$=2.5 Hz), 7.18 (1H, s), 7.54 (1H, br s, OH), 9.73 (1H, br s, NH). **38b**: Colorless glass. HRMS Calcd for $C_{23}H_{24}N_2O_7Se$: 520.0747. Found: 520.0746. MS *m/z*: 522, 520, 518, 517, 516 ($M^+$; 13, 49, 29, 12, 11), 363 (100), 331 (32), 78 (71), 59 (84). IR ($CHCl_3$): 1709 $cm^{-1}$. $^1$H-NMR $\delta$: 2.86 (1H, d, $J$=13.5 Hz), *ca.* 2.94—3.39 (2H, m), 3.31 (6H, s), 3.56 (3H, s), 3.94 (3H, s), 4.65 (1H, d, $J$=13.5 Hz), 6.77 (1H, br s, OH), 7.13 (5H, s), 7.17 (1H, d, $J$=2.5 Hz, changed to s with $D_2O$), 9.36 (1H, br s, NH).

**Methyl 6-(Benzyloxycarbonyl)-3,4,7,8,9,9a-hexahydro-9a-hydroxy-8,8-dimethoxy-4-oxo-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (39a)** Colorless glass. HRMS Calcd for $C_{23}H_{24}N_2O_8$: 456.1531. Found: 456.1526. MS *m/z*: 456 ($M^+$, 2), 440 (1), 365 (6), 324 (4), 233 (21), 201 (7), 91 (100), 65 (5). IR ($CHCl_3$): 1713, 1660 $cm^{-1}$. $^1$H-NMR $\delta$: 1.82 (1H, d, $J$=14 Hz), 2.80 (1H, dd, $J$=14, 2.5 Hz), 2.97 (1H, d, $J$=14 Hz), 3.28 (3H, s), 3.35 (3H, s), 3.89 (3H, s), 4.72 (1H, dd, $J$=14, 2.5 Hz), 5.02 (1H, s, OH), 5.13 and 5.28 (AB, $J$=13 Hz), 6.21 (1H, s), 7.03 (1H, d, $J$=2 Hz, changed to s with $D_2O$), 7.33 (5H, s), 9.76 (1H, br s, NH).

**Nickel Boride Reduction of 38a, b to 37a, b** $NiCl_2 \cdot 6H_2O$ (21 mg, 0.088 mmol) and $NaBH_4$ (10 mg, 0.26 mmol) were successively added to a solution of **38a** (27 mg, 0.045 mmol) in THF (3 ml) and MeOH (1 ml) at 0 °C and the mixture was vigorously stirred at the same temperature for 30 min. Another portion of $NiCl_2 \cdot 6H_2O$ (21 mg) and $NaBH_4$ (10 mg) was further added and stirring was continued at 0 °C for 30 min. Saturated $NH_4Cl$–$H_2O$ was added and the whole was extracted with $CH_2Cl_2$, and then worked up as usual. Purification by PTLC (1% MeOH–$CH_2Cl_2$) afforded **37a** (17 mg, 85%). Similarly reduction of **38b** to **37b** proceeded in 87% yield.

**Methyl (±)-6-(Benzyloxycarbonyl)-3,7,8,9-tetrahydro-4,8-dihydroxy-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (40)** *p*-TsOH·$H_2O$ (3 mg, 0.02 mmol) was added to an acetone solution (2 ml) of **37a** (24 mg, 0.055 mmol) and the mixture was stirred at 24 °C for 2.5 h. Saturated $NaHCO_3$–$H_2O$ was added and the whole was extracted with $CH_2Cl_2$, and then worked up as usual to give a crude, unstable ketone derivative (24 mg). A solution of this in MeOH (3 ml) was cooled to −20 °C and treated with $NaBH_4$ (8 mg, 0.2 mmol) at the same temperature for 20 min. 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 (4% MeOH–$CH_2Cl_2$), gave **40** (17 mg, 79%) as colorless prisms, mp 175—176 °C ($CH_2Cl_2$). *Anal.* Calcd for $C_{21}H_{20}N_2O_6$: C, 63.63; H, 5.09; N, 7.07. Found: C, 63.32; H, 5.13; N, 6.99. HRMS Calcd for $C_{21}H_{20}N_2O_6$: 396.1320. Found: 396.1321. MS *m/z*: 396 ($M^+$, 21), 261 (18), 229 (19), 91 (100). IR (KBr): 1713, 1678 $cm^{-1}$. $^1$H-NMR (10% $CD_3OD$–$CDCl_3$) $\delta$: 2.81 (1H, dd, $J$=17.5, 6 Hz), 3.24 (1H, dd, $J$=17.5, 6 Hz), 3.70 (1H, dd, $J$=13, 6 Hz), 3.90 (3H, s), 3.93 (1H, dd, $J$=13, 3.5 Hz), 4.26 (1H, dddd, $J$=6, 6, 6, 3.5 Hz), 5.20 (2H, s), 7.06 (1H, s), 7.09 (1H, s), 7.22—7.51 (5H, m).

**Methyl (±)-2-(Benzyloxycarbonyl)-1,2,4,5,8,8a-hexahydro-4-oxocyclopropa[*c*]pyrrolo[3,2-*e*]indole-6-carboxylate (41)** ADDP (130 mg, 0.516 mmol) was added to a solution of **40** (37 mg, 0.093 mmol) and $Bu_3P$ (128 $\mu$l, 0.515 mmol) in THF (3 ml), and the mixture was stirred under an Ar atmosphere at 0 °C for 10 min and at 26 °C for 4 h. Saturated $NaHCO_3$–$H_2O$ was added and the whole was extracted with $CH_2Cl_2$, and then worked up as usual. Purification by PTLC [benzene–EtOAc (3 : 1)] gave **41** (31 mg, 88%) as a colorless amorphous solid. *Anal.* Calcd for $C_{21}H_{18}N_2O_5$: C, 66.66; H, 4.80; N, 7.41. Found: C, 66.52; H, 4.87; N, 7.39. HRMS Calcd for $C_{21}H_{18}N_2O_5$: 378.1215. Found: 378.1206. MS *m/z*: 378 ($M^+$, 3), 334 (4), 243 (11), 211 (6), 91 (100), 65 (8). IR ($CHCl_3$): 1719, 1620 $cm^{-1}$. $^1$H-NMR (400 MHz) $\delta$: 1.43 (1H, dd, $J$=4.5, 4.5 Hz), 1.64 (1H, dd, $J$=7.5, 4.5 Hz), 2.69 (1H, ddd, $J$=7.5, 4.5, 4.5 Hz), 3.89 (3H, s), 4.03 (1H, dd, $J$=11, 4.5 Hz), 4.08 (1H, d, $J$=11 Hz), 5.25 and 5.28 (AB, $J$=12.5 Hz), 6.55 (1H, d, $J$=2 Hz), 6.88 (1H, br s), 7.33—7.43 (5H, m), 9.87 (1H, br s, NH).

**Methyl (±)-1,2,4,5,8,8a-Hexahydro-4-oxocyclopropa[*c*]pyrrolo[3,2-*e*]indole-6-carboxylate (42)** A slurry of **41** (31 mg, 0.082 mmol) in 1% $K_2CO_3$–MeOH (4 ml) was stirred at 23 °C for 80 min, during which time the mixture became clear. Saturated $NH_4Cl$–$H_2O$ was added and the whole was extracted with 10% MeOH–$CH_2Cl_2$, and then worked up as usual. Purification by PTLC (5% MeOH–$CH_2Cl_2$) afforded **42** (19 mg, 95%) as a colorless powder. HRMS Calcd for $C_{13}H_{12}N_2O_3$: 244.0847. Found: 244.0850. MS *m/z*: 244 ($M^+$, 100), 212 (59). IR (KBr): 1687 $cm^{-1}$. $^1$H-NMR (10% $CD_3OD$–$CDCl_3$) $\delta$: 1.27 (1H, dd, $J$=4.5, 4 Hz), 1.60 (1H, dd, $J$=7.5, 4 Hz), 2.84 (1H, ddd, $J$=7.5, 4.5, 4.5 Hz), 3.62 (1H, d, $J$=10.5 Hz), 3.84 (1H, dd, $J$=10.5, 4.5 Hz), 3.89 (3H, s), 5.54 (1H, s), 6.54 (1H, s).

**1-[(5,6,7-Trimethoxy-1*H*-indol-2-yl)carbonyl]-1*H*-imidazole (43)** *N*,*N*′-Carbonyldiimidazole (77 mg, 0.48 mmol) was added to a solution of 5,6,7-trimethoxy-1*H*-indole-2-carboxylic acid (108 mg, 0.430 mmol) in DMF (2 ml) and the mixture was stirred under an Ar atmosphere at 23 °C for 5 h. $H_2O$ was added and the whole was extracted with EtOAc, and then worked up as usual to leave a crystalline material. Recrystallization from $CH_2Cl_2$–hexane gave **43** (118 mg, 91%) as slightly yellow prisms, mp 187.5—189.5 °C. *Anal.* Calcd for $C_{15}H_{15}N_3O_4$: C, 59.79; H, 5.02; N, 13.95. Found: C, 59.65; H, 5.05; N, 13.93. HRMS Calcd for $C_{15}H_{15}N_3O_4$: 301.1062. Found: 301.1064. MS *m/z*: 301 ($M^+$, 61), 234 (100). IR (KBr): 1680 $cm^{-1}$. $^1$H-NMR $\delta$: 3.89 (3H, s), 3.94 (3H, s), 4.09 (3H, s), 6.84 (1H, s), 7.17 (1H, d, $J$=2.5 Hz, changed to s with $D_2O$), 7.17—7.27 (1H, m), 7.66—7.77 (1H, m), 8.36—8.49 (1H, m), 9.73 (1H, br s, NH).

**(±)-Duocarmycin SA (1)** A solution of **42** (8.5 mg, 0.035 mmol) in THF (1 ml) and DMF (0.5 ml) was stirred with 60% NaH (7 mg, 0.18 mmol) under an Ar atmosphere at 0 °C for 20 min. The imidazolide **43** (21 mg, 0.070 mmol) was added and the mixture was stirred at 0 °C for 4 h. Saturated $NH_4Cl$–$H_2O$ was added and the whole was extracted with EtOAc. The extract was worked up as usual. Separation by PTLC (4% MeOH–$CH_2Cl_2$) afforded crude (±)-**1** (11 mg) and recovered **42** (2 mg, 24%). The former was purified by PTLC [benzene–EtOAc (3 : 4)] to give (±)-duocarmycin SA (**1**) (10 mg, 60%) as a slightly yellow amorphous solid. HRMS Calcd for $C_{25}H_{23}N_3O_7$: 477.1534. Found: 477.1533. MS *m/z*: 477 ($M^+$, 20), 244 (17), 234 (100). IR ($CHCl_3$): 3455 (m), 3005 (w), 2955 (w), 2840 (w), 1713 (s), 1642 (s), 1620 (s), 1518 (m), 1493 (s), 1467 (m), 1443 (w), 1431 (w), 1401 (s), 1386 (s), 1304 (s), 1267 (s), 1255 (sh), 1238 (sh), 1209 (sh), 1154 (w), 1137 (w), 1109 (m), 1044 (m), 1019 (w), 1002 (m), 938 (w), 907 (w), 889 (w), 860 (w), 827 (w) $cm^{-1}$. $^1$H-NMR (400 MHz) $\delta$: 1.57 (1H, dd, $J$=4.5, 4.5 Hz), 1.76 (1H, dd, $J$=7.5, 4.5 Hz), 2.79 (1H, ddd, $J$=7.5, 5, 4.5 Hz), 3.89 (3H, s), 3.91 (3H, s), 3.94 (3H, s), 4.07 (3H, s), 4.39 (1H, d, $J$=10.5 Hz), 4.47 (1H, dd, $J$=10.5, 5 Hz), 6.61 (1H, br s), 6.78 (1H, s), 6.95 (1H, d, $J$=2 Hz), 7.03 (1H, s), 9.30 (1H, br s, NH), 9.95 (1H, br s, NH). $^{13}$C-NMR $\delta$: 23.5, 25.9, 31.3, 52.1, 54.8, 56.2, 61.2, 61.5, 97.5, 107.5, 107.7, 112.5, 123.2, 126.3, 126.7, 128.3, 129.9, 131.5, 138.8, 141.0, 150.4, 160.9, 161.1, 161.5, 177.9.

**Methyl (8*S*)- and (8*R*)-6-(Benzyloxycarbonyl)-4,8-bis[(*S*)-3-*tert*-butoxycarbonyl-2,2-dimethyl-4-oxazolinecarbonyloxy]-3,7,8,9-tetrahydro-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylates (44a)** Colorless glass. MS *m/z*: 623 ($M^+ - C_{11}H_{17}NO_4$, 2), 568 (1), 492 (1), 490 (1), 378 (9), 243 (18), 211 (17), 91 (100), 57 (45). $^1$H-NMR of two diastereomers $\delta$: 1.38, 1.48, 1.57, 1.64 and 1.66 (total 30H, s each), 2.84—3.74 (3H, m), 3.74—4.46 (6H, m), 3.90 (3H, s), 4.56—4.76 (1H, m), 5.21 (2H, s), 5.27—5.54 (1H, m), 7.06—7.18 (1H, m), 7.22—7.52 (6H, m), 10.57 (1H, br s, NH).

**Methyl (8*S*)- and (8*R*)-6-(Benzyloxycarbonyl)-3,7,8,9-tetrahydro-4,8-**

**bis[(*S*)-1-triphenylmethyl-2-aziridinecarbonyloxy]-6*H*-pyrrolo[3,2-*f*]-quinoline-2-carboxylates (44b)** Colorless glass. MS *m/z*: 731 ($M^+ - Tr - CO_2$, 0.1), 584 (2), 341 (9), 243 (100), 165 (73), 77 (8), 51 (8). IR ($CHCl_3$): 1740 (sh), 1714 $cm^{-1}$. $^1$H-NMR of two diastereomers $\delta$: 1.20—1.91 (3H, m), 2.11—2.30 (2H, m), 2.43—2.58 (1H, m), 2.90—3.26 (1H, m), 3.26—3.60 (1H, m), 3.63—4.01 (1H, m), 3.92 (3H, s), 4.12—4.48 (1H, m), 5.11 and 5.14 (total 2H, s each), 5.36—5.61 (1H, m), 6.96—7.86 (37H, m), 8.70 (1H, br s, NH).

**Methyl (8*S*)- and (8*R*)-4,8-Bis[(*R*)-α-(Acetoxy)phenylacetoxy]-6-(benzyloxycarbonyl)-3,7,8,9-tetrahydro-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylates (44c)** Colorless foam. HRMS Calcd for $C_{41}H_{36}N_2O_{12}$: 748.2266. Found: 748.2277. MS *m/z*: 748 ($M^+$, 4), 614 (5), 572 (2), 378 (9), 243 (41), 211 (23), 91 (100), 44 (49). IR ($CHCl_3$): 1741, 1711 $cm^{-1}$. $^1$H-NMR of two diastereomers $\delta$: 2.02 and 2.12 (total 3H, s each), 2.29 (3H, s), 2.66—3.48 (2H, m), 3.53—3.81 (1H, m), 3.91 (3H, s), 3.98—4.40 (1H, m), 4.89, 5.10 and 5.16 (total 2H, AB and s, $J$ = 12 Hz), 5.24—5.49 (1H, m), 5.73 and 5.78 (total 1H, s each), 6.03 (1H, s), 6.96 and 7.09 (total 1H, d each, $J$ = 2 Hz), 7.09—7.72 (16H, m), 9.31 (1H, br s, NH).

**Methyl (8*S*)- and (8*R*)-6-(Benzyloxycarbonyl)-3,7,8,9-tetrahydro-4,8-bis[(*R*)-α-(methoxy)phenylacetoxy]-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylates (44d)** EDCI·HCl (19.5 mg, 0.102 mmol) was added to a solution of **40** (9 mg, 0.02 mmol), (*R*)-*O*-methylmandelic acid (12.5 mg, 0.075 mmol) and DMAP (0.5 mg, 4 μmol) in $CH_2Cl_2$ (2 ml) under an Ar atmosphere, and the mixture was stirred at 26 °C for 3 h. The reaction was quenched by addition of 0.1 N citric acid–$H_2O$ and the whole was extracted with $CH_2Cl_2$. Usual work-up and purification by column chromatography using silica gel (8 g) and hexane–EtOAc (3 : 2) gave **44d** (15 mg, 95%) as a colorless glass. HRMS Calcd for $C_{39}H_{36}N_2O_{10}$: 692.2368. Found: 692.2348. MS *m/z*: 692 ($M^+$, 2), 378 (2), 243 (3), 211 (4), 121 (100), 91 (35), 77 (11). IR ($CHCl_3$): 1772 (sh), 1749, 1713 $cm^{-1}$. $^1$H-NMR of two diastereomers $\delta$: 2.57—3.31 (2H, m), 3.31 (3H, s), 3.46—3.80 (1H, m), 3.52 (3H, s), 3.88 (3H, s), 4.02—4.42 (1H, m), 4.50 and 4.61 (total 1H, s each), 5.03 and 5.26 (AB, $J$ = 10.5 Hz), 5.09 and 5.20 (total 1H, s each), 6.87 and 7.02 (total 1H, d each, $J$ = 2 Hz), 7.02—7.75 (17H, m), 8.22 (1H, br s, NH). HPLC analysis using 0.4% MeOH–$CH_2Cl_2$ of flow rate, 1 ml per min, afforded $t_0$ = 3.13 min, $t_1$ = 8.77 min, and $t_2$ = 11.58 min, meaning $\alpha$ = 1.50.

**Methyl (8*S*)- and (8*R*)-6-(Benzyloxycarbonyl)-3,7,8,9-tetrahydro-8-[(*S*)-tetrahydro-5-oxo-2-furancarbonyloxy]-4-hydroxy-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylates (45)** Colorless glass. HRMS Calcd for $C_{26}H_{24}N_2O_9$: 508.1480. Found: 508.1494. MS *m/z*: 508 ($M^+$, 2), 396 (2), 378 (3), 334 (2), 243 (10), 211 (10), 91 (100), 85 (30). IR ($CHCl_3$): 1792, 1754, 1707 $cm^{-1}$. $^1$H-NMR of two diastereomers $\delta$: 1.84—2.59 (4H, m), 2.78—3.44 (2H, m), 3.53 (1H, br d, $J$ = 14.5 Hz), 3.89 (3H, s), 4.43 (1H, dd, $J$ = 14.5, 4 Hz), 4.51—4.79 (1H, m), 5.19 (2H, s), 5.30—5.56 (1H, m), 7.03 (1H, br s), 7.12 (1H, br s), 7.18—7.47 (5H, m), 9.74 (1H, br s, NH).

**Methyl 4-Benzyloxy-3,7,8,9-tetrahydro-8,8-dimethoxy-6-(methoxycarbonyl)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (46)** An acetone solution (5 ml) of **37b** (60 mg, 0.16 mmol) containing BnBr (21 μl, 0.18 mmol) and $K_2CO_3$ (46 mg, 0.33 mmol) was heated for 8 h under reflux. After cooling in an ice bath, saturated $NH_4Cl$–$H_2O$ was added and the whole was extracted with $CH_2Cl_2$, and then worked up as usual. Separation by PTLC [benzene–EtOAc (9 : 1)] afforded the *N*-benzylated by-product **47** (3.5 mg, 4%), **46** (60 mg, 80%) and recovered **37b** (2.5 mg, 4%) in order of increasing polarity. **46**: Colorless glass. HRMS Calcd for $C_{24}H_{26}N_2O_7$: 454.1738. Found: 454.1739. MS *m/z*: 454 ($M^+$, 39), 422 (6), 363 (13), 331 (24), 91 (100), 59 (16). IR ($CHCl_3$): 1707 $cm^{-1}$. $^1$H-NMR $\delta$: 3.11 (2H, s), 3.33 (6H, s), 3.76 (3H, s), 3.85 (2H, s), 3.90 (3H, s), 5.15 (2H, s), 7.11 (1H, d, $J$ = 2.5 Hz), 7.19 (1H, br s), 7.27—7.56 (5H, m), 9.17 (1H, br s, NH). Methyl 3-benzyl-4-benzyloxy-3,7,8,9-tetrahydro-8,8-dimethoxy-6-(methoxycarbonyl)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (**47**): Colorless glass. HRMS Calcd for $C_{31}H_{32}N_2O_7$: 544.2208. Found: 544.2206. MS *m/z*: 544 ($M^+$, 27), 512 (5), 453 (11), 421 (20), 361 (6), 121 (52), 91 (100), 65 (12). IR ($CHCl_3$): 1702 $cm^{-1}$. $^1$H-NMR $\delta$: 3.11 (2H, s), 3.32 (6H, s), 3.72 (3H, s), 3.80 (3H, s), 3.84 (2H, s), 5.00 (2H, s), 6.13 (2H, s), 6.71—6.92 (2H, m), 7.19 (1H, br s), 6.97—7.37 (10H, m).

**Methyl 4-Benzyloxy-3,7,8,9-tetrahydro-6-(methoxycarbonyl)-8-oxo-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (49)** i) A solution of **46** (222 mg, 0.489 mmol) in 2.5% HCl-containing THF–$H_2O$ (3 : 1) (6 ml) was stirred at 20 °C for 10 h. Saturated $NaHCO_3$–$H_2O$ was added and the whole was extracted with 10% MeOH–$CH_2Cl_2$. Usual work-up gave a crystalline residue, which was purified by recrystallization from $CH_2Cl_2$–MeOH and PTLC ($CH_2Cl_2$) to yield **49** (194 mg, 97%) as colorless needles, mp 198—200 °C. *Anal.* Calcd for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.74; H, 5.01; N, 6.94. HRMS Calcd for $C_{22}H_{20}N_2O_6$: 408.1320. Found: 408.1318. MS *m/z*: 408 ($M^+$, 21), 348 (2), 289 (10), 257 (9), 91 (100), 65 (8), 59 (16). IR ($CHCl_3$): 1708 $cm^{-1}$. $^1$H-NMR $\delta$: 3.71 (2H, s), 3.77 (3H, s), 3.92 (3H, s), 4.31 (2H, s), 5.20 (2H, s), 7.03 (1H, br s), 7.13 (1H, d, $J$ = 2 Hz, changed to s with $D_2O$), 7.30—7.59 (5H, m), 9.26 (1H, br s, NH).

ii) An acetone solution (2.5 ml) of **46** (27 mg, 0.059 mmol) and *p*-TsOH·$H_2O$ (3 mg, 0.02 mmol) was stirred at 21 °C for 2.5 h. Treatment as above and separation by PTLC ($CH_2Cl_2$) afforded **48** (3 mg, 12%) and **49** (20.5 mg, 84%) in order of increasing polarity. Methyl 4-benzyloxy-3,7-dihydro-8-methoxy-6-(methoxycarbonyl)-6*H*-pyrrolo-[3,2-*f*]quinoline-2-carboxylate (**48**): Colorless glass. HRMS Calcd for $C_{23}H_{22}N_2O_6$: 422.1476. Found: 422.1472. MS *m/z*: 422 ($M^+$, 34), 362 (8), 331 (81), 299 (17), 255 (37), 91 (100), 65 (18), 59 (22). IR ($CHCl_3$): 1702, 1648 $cm^{-1}$. $^1$H-NMR $\delta$: 3.72 (3H, s), 3.74 (3H, s), 3.90 (3H, s), 4.37 (2H, s), 5.16 (2H, s), 5.79 (1H, s), 7.21 (1H, d, $J$ = 2.5 Hz, changed to s with $D_2O$), 7.10 (1H, br s), 7.27—7.58 (5H, m), 9.02 (1H, br s, NH).

**Methyl 4-Benzyloxy-8-methoxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (51)** A solution of **48** (6 mg, 0.01 mmol) in 2.5% HCl-containing THF–$H_2O$ (3 : 1) (2 ml) was stirred at 20 °C for 18 h. The same work-up as above and purification by PTLC ($CH_2Cl_2$) afforded **51** (3 mg, 58%) as a colorless glass. HRMS Calcd for $C_{21}H_{18}N_2O_4$: 362.1265. Found: 362.1272. MS *m/z*: 362 ($M^+$, 39), 302 (6), 271 (28), 239 (20), 211 (16), 91 (100), 65 (11). IR ($CHCl_3$): 1711 $cm^{-1}$. $^1$H-NMR $\delta$: 3.94 (3H, s), 3.97 (3H, s), 5.29 (2H, s), 7.28—7.64 (6H, m), 7.64 (1H, d, $J$ = 2 Hz, changed to s with $D_2O$), 7.76 (1H, d, $J$ = 2.5 Hz), 8.55 (1H, d, $J$ = 2.5 Hz), 9.49 (1H, br s, NH).

**Methyl (±)-4-Benzyloxy-3,7,8,9-tetrahydro-8-hydroxy-6-(methoxycarbonyl)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (50)** $NaBH_4$ (12 mg, 0.32 mmol) was added to a cooled (0 °C) solution of **49** (32 mg, 0.078 mmol) in THF–MeOH (1 : 1) (3 ml) and the mixture was stirred at 0 °C for 10 min and at 20 °C for 30 min. Saturated $NH_4Cl$–$H_2O$ was added and the whole was extracted with $CH_2Cl_2$, and then worked up as usual. Purification by PTLC [benzene–EtOAc (2 : 1)] gave **50** (31.5 mg, 98%) as a colorless glass. HRMS Calcd for $C_{22}H_{22}N_2O_6$: 410.1476. Found: 410.1474. MS *m/z*: 410 ($M^+$, 44), 319 (15), 225 (12), 91 (100), 65 (14), 59 (13). IR ($CHCl_3$): 1700 $cm^{-1}$. $^1$H-NMR $\delta$: 2.20 (1H, br s, OH), 2.83 (1H, dd, $J$ = 17.5, 5 Hz), 3.22 (1H, dd, $J$ = 17.5, 6 Hz), 3.72 (3H, s), 3.81 (2H, d, $J$ = 5 Hz), 3.88 (3H, s), 4.16—4.44 (1H, m), 5.13 (2H, s), 7.07 (1H, d, $J$ = 2 Hz, changed to s with $D_2O$), 7.16 (1H, s), 7.25—7.55 (5H, m), 9.17 (1H, br s, NH).

**Methyl (*R*)- and (*S*)-4-Benzyloxy-3,7,8,9-tetrahydro-8-[(*R*)-*O*-methylmandelyl]oxy-6-(methoxycarbonyl)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylates (52 and 53)** EDCI·HCl (42 mg, 0.22 mmol) was added to a $CH_2Cl_2$ solution (3 ml) of (±)-**50** (30 mg, 0.073 mmol), (*R*)-*O*-methylmandelic acid (24 mg, 0.14 mmol), and DMAP (1 mg, 8 μmol), and the mixture was stirred under an Ar atmosphere at 20 °C for 2 h. The reaction was quenched by addition of 0.1 N citric acid–$H_2O$ and the mixture was extracted with $CH_2Cl_2$. The organic layer was washed with saturated $NaHCO_3$–$H_2O$ and worked up as usual, and then the residue was separated by PTLC [benzene–EtOAc (2 : 1)] to give a mixture of **52** and **53** (40 mg). This was further separated by HPLC using TOSOH $SiO_2$-60 (21.5 × 300 mm), 2% EtOAc–$CH_2Cl_2$ at a flow rate of 5 ml per min, with UV detection at 285 nm, providing **52** (19 mg, 47%, $t_R$ = 55 min, >99.9% de) and **53** (19 mg, 47%, $t_R$ = 73 min, >99.9% de). **52**: Colorless glass. HRMS Calcd for $C_{31}H_{30}N_2O_8$: 558.2000. Found: 558.1991. $[\alpha]_D^{21}$ +0.79° ($c$ = 1.2, $CHCl_3$). MS *m/z*: 558 ($M^+$, 15), 392 (19), 301 (32), 269 (6), 225 (27), 121 (45), 91 (100), 77 (16), 59 (12). IR ($CHCl_3$): 1747, 1702 $cm^{-1}$. $^1$H-NMR (400 MHz) $\delta$: 3.04 (1H, dd, $J$ = 18, 3 Hz), 3.31 (1H, dd, $J$ = 18, 6 Hz), 3.37 (3H, s), 3.59 (3H, s), 3.61 (1H, br d, $J$ = 14 Hz), 3.93 (3H, s), 4.12 (1H, dd, $J$ = 14, 5.5 Hz), 4.72 (1H, s), 5.17 and 5.21 (AB, $J$ = 11.5 Hz), 5.37—5.43 (1H, m), 7.09 (1H, d, $J$ = 2.5 Hz), 7.32—7.51 (11H, m), 9.10 (1H, br s, NH). **53**: Colorless glass. HRMS Calcd for $C_{31}H_{30}N_2O_8$: 558.2000. Found: 558.2000. $[\alpha]_D^{21}$ −49.9° ($c$ = 0.766, $CHCl_3$). MS *m/z*: 558 ($M^+$, 13), 392 (18), 301 (34), 269 (6), 225 (26), 121 (45), 91 (100), 77 (15), 59 (13). IR ($CHCl_3$): 1747, 1702 $cm^{-1}$. $^1$H-NMR (400 MHz) $\delta$: 2.80 (1H, dd, $J$ = 18, 3.5 Hz), 3.18 (1H, dd, $J$ = 18, 6 Hz), 3.40 (3H, s), 3.66 (1H, dd, $J$ = 13.5, 2.5 Hz), 3.76 (3H, s), 3.92 (3H, s), 4.32 (1H, dd, $J$ = 13.5, 5 Hz), 4.67 (1H, s), 5.18 and 5.22 (2H, AB, $J$ = 11.5 Hz), 5.35—5.41 (1H, m), 7.00 (1H, d, $J$ = 2.5 Hz), 7.25—7.51 (11H, m), 9.08 (1H, br s, NH).

**(*R*)-50 and (*S*)-50** A solution of **52** (25 mg) in 1% $K_2CO_3$–MeOH

(2.5 ml) was stirred at 18 °C for 1 h. Saturated $NH_4Cl$–$H_2O$ was added and the mixture was extracted with $CH_2Cl_2$, and then worked up as usual. Purification by PTLC [benzene–EtOAc (2:1)] gave (*R*)-(+)-**50** (17.5 mg, 95%) as a colorless glass. HRMS Calcd for $C_{22}H_{22}N_2O_6$: 410.1476. Found: 410.1472. $[\alpha]_D^{21}$ +10° ($c$=0.66, $CHCl_3$). In the same manner, (*S*)-(−)-**50** (13.5 mg, 97%) was obtained from **53** (19 mg) as a colorless glass. HRMS Calcd for $C_{22}H_{22}N_2O_6$: 410.1476. Found: 410.1471. $[\alpha]_D^{21}$ −10° ($c$=0.63, $CHCl_3$).

**Methyl (*R*)-(+)- and (*S*)-(−)-3,7,8,9-Tetrahydro-4,8-dihydroxy-6-(methoxycarbonyl)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylates [(+)-54 and (−)-54]** A solution of (+)-**50** (17.5 mg) in MeOH (5 ml) was hydrogenated (1 atm $H_2$) over 20% $Pd(OH)_2$–C (2 mg) at 10 °C for 4 h to give, after purification by PTLC [benzene–EtOAc (2:3)], (+)-**54** (13 mg, 95%) as a colorless amorphous solid. HRMS Calcd for $C_{15}H_{16}N_2O_6$: 320.1007. Found: 320.1010. $[\alpha]_D^{21}$ +4.1° ($c$=0.53, MeOH). MS $m/z$: 320 ($M^+$, 93), 288 (100), 59 (55). IR ($CHCl_3$): 1695 $cm^{-1}$. $^1$H-NMR (10% $CD_3OD$–$CDCl_3$) $\delta$: 2.81 (1H, dd, $J$=18, 5.5 Hz), 3.24 (1H, dd, $J$=18, 6 Hz), *ca.* 3.54—4.00 (2H, m), 3.77 (3H, s), 3.92 (3H, s), 4.13—4.46 (1H, m), 6.99 (1H, s), 7.06 (1H, s). Similarly (−)-**54** (10 mg, 95%) was obtained from (−)-**50** (13.5 mg) as a colorless amorphous solid. HRMS Calcd for $C_{15}H_{16}N_2O_6$: 320.1007. Found: 320.1004. $[\alpha]_D^{21}$ −4.1° ($c$=0.59, MeOH).

**Methyl (7b*S*)-(−)- and (7b*R*)-(+)-1,2,4,5,8,8a-Hexahydro-2-(methoxycarbonyl)-4-oxocyclopropa[*c*]pyrrolo[3,2-*e*]indole-6-carboxylates [(−)-55 and (+)-55]** In the same manner as described for the preparation of (±)-**41**, (+)-**54** (12 mg, 0.038 mmol) in THF (2.5 ml) was treated with $Bu_3P$ (28 $\mu$l, 0.11 mmol) and ADDP (28 mg, 0.11 mmol) to give (−)-**55** (9.5 mg, 84%) as a colorless amorphous solid after PTLC (0.7% MeOH–$CH_2Cl_2$). HRMS Calcd for $C_{15}H_{14}N_2O_5$: 302.0902. Found: 302.0908. $[\alpha]_D^{21}$ −179° ($c$=0.354, 10% MeOH–$CH_2Cl_2$). MS $m/z$: 302 ($M^+$, 100), 270 (28), 211 (75), 155 (33), 59 (51). IR ($CHCl_3$): 1713, 1618 $cm^{-1}$. $^1$H-NMR (400 MHz) $\delta$: 1.42 (1H, dd, $J$=4.5, 4.5 Hz), 1.65 (1H, dd, $J$=7.5, 4.5 Hz), 2.70 (1H, ddd, $J$=7.5, 4.5, 4.5 Hz), 3.86 (3H, s), 3.90 (3H, s), 4.01 (1H, dd, $J$=11.5, 4.5 Hz), 4.07 (1H, d, $J$=11.5 Hz), 6.56 (1H, d, $J$=2 Hz), 6.83 (1H, s), 9.76 (1H, br s, NH). Similarly (+)-**55** (10 mg, 82%) was obtained from (−)-**54** (13 mg) as a colorless amorphous solid. HRMS Calcd for $C_{15}H_{14}N_2O_5$: 302.0902. Found: 302.0904. $[\alpha]_D^{21}$ +181° ($c$=0.606, 10% MeOH–$CH_2Cl_2$).

**Methyl (7b*S*)-(−)- and (7b*R*)-(+)-1,2,4,5,8,8a-Hexahydro-4-oxocyclopropa[*c*]pyrrolo[3,2-*e*]indole-6-carboxylates [(−)-42 and (+)-42]** According to the same procedure as used for the preparation of (±)-**42**, (−)-**42** (6.5 mg, 95%) was obtained from (−)-**55** (8.5 mg) as a colorless powder. HRMS Calcd for $C_{13}H_{12}N_2O_3$: 244.0847. Found: 244.0856. $[\alpha]_D^{21}$ −167° ($c$=0.239, MeOH). Likewise (+)-**42** (8.5 mg, 96%) was obtained from (+)-**55** (11 mg) as a colorless powder. HRMS Calcd for $C_{13}H_{12}N_2O_3$: 244.0847. Found: 244.0849. $[\alpha]_D^{21}$ +165° ($c$=0.425, MeOH).

**Unnatural (−)- and Natural (+)-Duocarmycins SA [(−)-1 and (+)-1]** In the same way as described for the preparation of (±)-**1**, (−)-**1** (6.5 mg, 66%) was obtained from (−)-**42** (5 mg) as a slightly yellow powder, accompanied with recovered (−)-**42** (1.5 mg, 30%). HRMS Calcd for $C_{25}H_{23}N_3O_7$: 477.1534. Found: 477.1534. $[\alpha]_D^{21}$ −190° ($c$=0.192, MeOH). Natural (+)-**1** (11.5 mg, 74%) was prepared from (+)-**42** (8 mg) as a slightly yellow powder, accompanied with recovered (+)-**42** (1.5 mg, 19%). HRMS Calcd for $C_{25}H_{23}N_3O_7$: 477.1534. Found: 477.1537. $[\alpha]_D^{21}$ +192° ($c$=0.352, MeOH).

**Methyl (*S*)-(−)-8-Acetoxy-4-benzyloxy-3,7,8,9-tetrahydro-6-(methoxycarbonyl)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (56a)** DEAD (23 $\mu$l, 0.15 mmol) was added to a cooled (0 °C) solution of (+)-**50** (15 mg, 0.037 mmol), $Ph_3P$ (38 mg, 0.15 mmol), and HOAc (17 $\mu$l, 0.30 mmol) in THF (2.5 ml), and the mixture was stirred under an Ar atmosphere at 0 °C for 30 min and at 19 °C for 1.5 h. Saturated $NaHCO_3$–$H_2O$ was added and the whole was extracted with $CH_2Cl_2$. Usual work-up and separation by PTLC [benzene–EtOAc (14:1)] gave **56a** (11.5 mg, 70%) and methyl 4-benzyloxy-3,7-dihydro-6-(methoxycarbonyl)-6*H*-pyrrolo-[3,2-*f*]quinoline-2-carboxylate (**57**) (3 mg, 21%) in order of decreasing polarity. **56a**: Colorless glass. HRMS Calcd for $C_{24}H_{24}N_2O_7$: 452.1582. Found: 452.1584. $[\alpha]_D^{21}$ −34.8° ($c$=0.500, $CHCl_3$). MS $m/z$: 452 ($M^+$, 14), 392 (17), 301 (37), 225 (39), 91 (100), 59 (18), 43 (22). IR ($CHCl_3$): 1738, 1707 $cm^{-1}$. $^1$H-NMR $\delta$: 2.01 (3H, s), 2.94 (1H, dd, $J$=17.5, 3.5 Hz), 3.31 (1H, dd, $J$=17.5, 6 Hz), 3.59 (1H, dd, $J$=13.5, 2.5 Hz), 3.75 (3H, s), 3.90 (3H, s), 4.28 (1H, dd, $J$=13.5, 5.5 Hz), 5.17 (2H, s), 5.17—5.46 (1H, m), 7.09 (1H, d, $J$=2 Hz, changed to s with $D_2O$), 7.14 (1H, s), 7.23—7.60 (5H, m), 9.15 (1H, br s, NH). **57**: Colorless glass. HRMS Calcd for $C_{22}H_{20}N_2O_5$: 392.1371. Found: 392.1370. MS $m/z$: 392 ($M^+$, 2), 332 (17), 91 (100), 65 (12). IR ($CHCl_3$): 1697 $cm^{-1}$. $^1$H-NMR $\delta$: 3.72 (3H, s), 3.90 (3H, s), 4.38 (2H, dd, $J$=4.5, 2 Hz), 5.18 (2H, s), 5.97 (1H, dt, $J$=9.5, 4.5 Hz), 6.79 (1H, br d, $J$=9.5 Hz), 7.13 (1H, s), 7.20 (1H, d, $J$=2 Hz, changed to s with $D_2O$), 7.29—7.58 (5H, m), 9.03 (1H, br s, NH).

**Methyl (*S*)-(−)-8-Benzoyloxy-4-benzyloxy-3,7,8,9-tetrahydro-6-(methoxycarbonyl)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (56b)** Colorless glass. HRMS Calcd for $C_{29}H_{26}N_2O_7$: 514.1738. Found: 514.1757. $[\alpha]_D^{21}$ −54.3° ($c$=0.312, $CHCl_3$). MS $m/z$: 514 ($M^+$, 4), 392 (16), 301 (22), 225 (22), 105 (33), 91 (100), 77 (37), 51 (18). IR ($CHCl_3$): 1713 $cm^{-1}$. $^1$H-NMR $\delta$: 3.17 (1H, dd, $J$=18, 3.5 Hz), 3.45 (1H, dd, $J$=18, 5.5 Hz), 3.60 (3H, s), 3.66 (1H, dd, $J$=12.5, 1.5 Hz), 3.94 (3H, s), 4.56 (1H, dd, $J$=12.5, 5 Hz), 5.22 (2H, s), 5.54—5.75 (1H, m), 7.07—7.18 (2H, m), 7.18—7.63 (8H, m), 7.84—8.07 (2H, m), 9.11 (1H, br s, NH).

**Methyl (*S*)-8-(4-Nitrobenzoyl)oxy-4-benzyloxy-3,7,8,9-tetrahydro-6-(methoxycarbonyl)-6*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylate (56c)** Colorless glass. HRMS Calcd for $C_{29}H_{25}N_3O_9$: 559.1589. Found: 559.1597. MS $m/z$: 559 ($M^+$, 8), 392 (11), 301 (25), 225 (24), 91 (100), 59 (16). IR ($CHCl_3$): 1722 (sh), 1710 $cm^{-1}$. $^1$H-NMR $\delta$: 3.15 (1H, dd, $J$=18, 3 Hz), 3.46 (1H, dd, $J$=18, 5.5 Hz), 3.57 (3H, s), 3.60 (1H, dd, $J$=13.5, 1.5 Hz), 3.91 (3H, s), 4.61 (1H, dd, $J$=13.5, 5 Hz), 5.19 (2H, s), 5.55—5.80 (1H, m), 7.05—7.20 (2H, m), 7.29—7.59 (5H, m), 8.10 and 8.25 ($A_2B_2$, $J$=9.5 Hz).

**Methanolysis of 56a to (−)-50** In the same manner as described for the preparation of (+)-**50** from **52**, (−)-**50** (9.5 mg, 95%) was obtained from **56a** (11 mg) after PTLC [benzene–EtOAc (2:1)]. $[\alpha]_D^{21}$ −9.6° ($c$=0.25, $CHCl_3$).

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