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1,6-Dihydro-3(2*H*)-pyridinones. VIII.[1] Total Synthesis of (±)-Corynantheidol and Formal Synthesis of (±)-Quinine[2]

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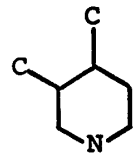
cis-3,4-Disubstituted piperidine compounds (**2** and **3**) were stereoselectively prepared from benzyl 3-(1,3-dioxolan-2-ylmethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (**13**) *via* the ketone (**17**). A total synthesis of (±)-corynantheidol (**4**) and a formal synthesis of (±)-quinine (**5**) have also been achieved from the piperidines **2** and **3**, respectively.

Keywords——oxymercuration–demercuration; *cis*-3,4-disubstituted piperidine; $A^{1,3}$-strain; alkaloid synthesis; meroquinene; corynantheidol; quinine

A piperidine moiety such as **1**, which involves carbon extensions at the 3- and 4-positions of the piperidine nucleus,exists as a partial structure of many kinds of alkaloids,*e.g.* Corynanthe alkaloids, Cinchona alkaloids, yohimbine, and reserpine. From the standpoint that a piperidine bearing suitable substituents at the 3- and 4-positions may serve as a key intermediate for synthesis of these alkaloids, it would be of great value to develop a general synthetic method for such piperidine compounds. As a part of our systematic studies on 1,6-dihydro-3(2*H*)-pyridinones, we now wish to describe preparations of *cis*-3-(1,3-dioxolan-2-ylmethyl)-piperidine-4-acetic acid derivatives (**2** and **3**) and their transformations into (±)-corynantheidol (**4**) and (±)-quinine (**5**), respectively.

Stereoselective Synthesis of Ethyl *cis*-3-(1,3-Dioxolan-2-ylmethyl)piperidine-4-acetates (2 and 3)

Previously, we reported that ethyl 3-(1,3-dioxolan-2-ylmethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate(**7**), derived from the allylic alcohol (**6**), gave the piperidin-3-ol (**8**) and 4-ol (**9**) in a ratio of 4:1 on hydroboration–oxidation, and that both alcohols (**8** and **9**) were oxidized with pyridinium chlorochromate (PCC) to afford the corresponding ketones (**10** and **11**).[3] The latter (**11**) seems to be a possible intermediate for the title compounds (**2** and **3**). In order to improve the yield of **9**, we started with a further examination of other hydration methods for the olefin **7**. Hydration of olefins by oxymercuration–demercuration is well known to proceed with opposite regioselectivity compared with that by hydroboration–oxidation.[4] Oxymercuration–demercuration of **7** under usual conditions,[5] however, afforded **8** and **9** in 40 and 38% yields, respectively. On the other hand, the initial reaction of **7** with *m*-chloroperbenzoic acid (MC-



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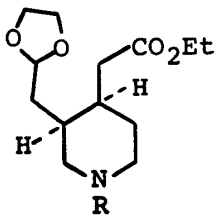
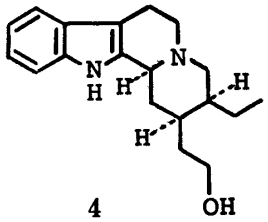


2: R=Cbz

3: R=H



4 OH

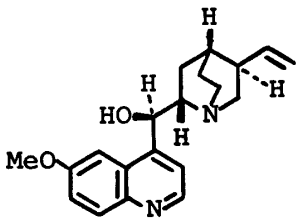


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Chart 1

TABLE I. Hydration of the Olefins **7** and **13**

Entry	Substrate	Conditions	Products	(Yield; %)
1[3]	**7**	1) B_2H_6/THF 0°C 3 h 2) H_2O_2, aq. NaOH 0°C 3 h	**8** (52)	**9** (13)
2	**7**	1) $Hg(OAc)_2$/THF-H_2O r.t. 13 h 2) $NaBH_4$, aq. NaOH r.t. 30 min	**8** (40)	**9** (38)
3	**7**	1) MCPBA/CH_2Cl_2 r.t. 15 h 2) B_2H_6, $NaBH_4$/THF r.t. 3 h	**8** (32)	**9** (49)
4	**7**	1) MCPBA/CH_2Cl_2 r.t. 15 h 2) H_2/PtO_2, EtOH r.t. 50 h[a]	**8** (26)	**9** (0)
5	**13**	1) MCPBA/CH_2Cl_2 r.t. 15 h 2) B_2H_6, $NaBH_4$/THF r.t. 3 h	**16** (34)	**15** (46)

a) The epoxide (**12**) was recovered (44%).

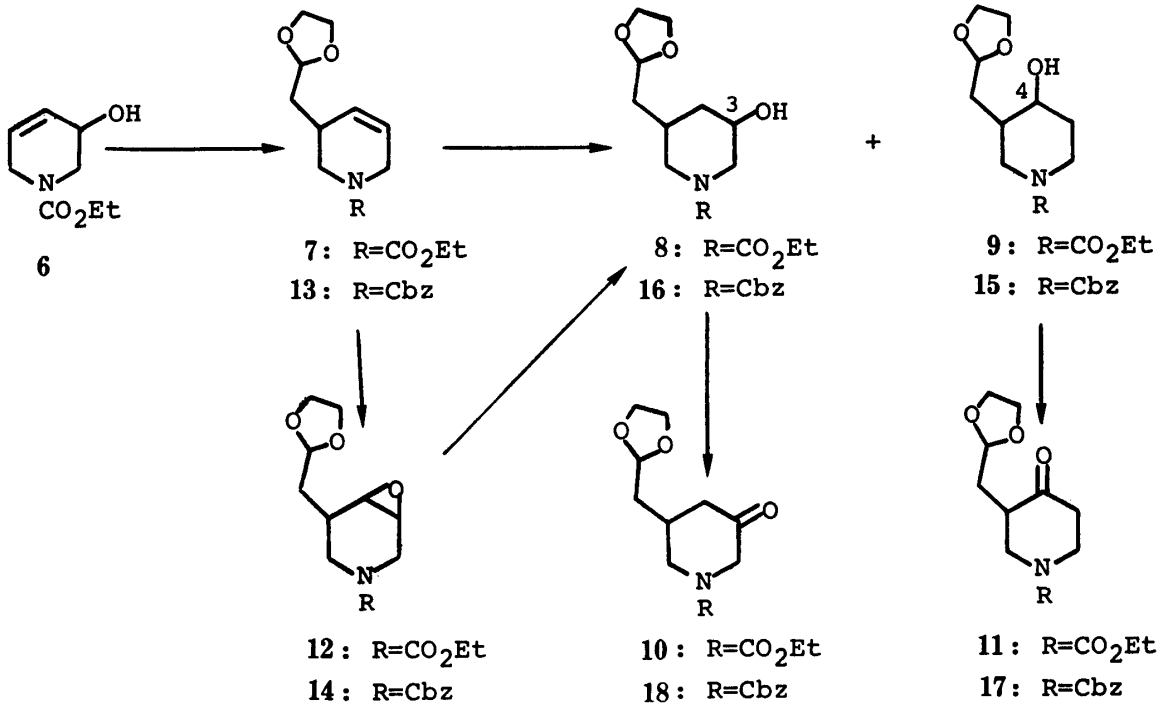

Chart 2

PBA) in dichloromethane yielded a stereoisomeric mixture of the epoxides (**12**), which was subsequently reduced with diborane in tetrahydrofuran (THF) to provide the desired 4-hydroxy derivative (**9**) in 49% yield along with the 3-hydroxy derivative (**8**; 32%). Catalytic hydrogenation of **12**, in contrast, was not effective, and **9** was not obtained (Table I). The hydration by epoxidation and subsequent reduction was also applicable to benzyl 3-(1,3-dioxolan-2-ylmethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (**13**), which was prepared from the ethyl urethane analogue (**7**) by exchange of the *N*-protecting group. Epoxidation of **13** with MCPBA and immediate reduction with diborane yielded two regioisomeric alcohols (**15** and **16**), in 46 and 34% yields, respectively. The position of the hydroxyl group in **15** or **16** was confirmed by the following chemical evidence. The main isomer (**15**) was found to be identical with the product obtained from the known alcohol (**9**)[3] by exchange of the *N*-substituent (–CO_2Et⟶–Cbz). The alcohols (**15** and **16**) were oxidized with PCC to afford the corresponding ketones (**17** and **18**).

Exposure of the ketone (**17**) to the ylid of triethyl phosphonoacetate[6] in benzene provided the unsaturated ester (**19**) in 60% yield. Catalytic hydrogenation of **19** over platinum oxide

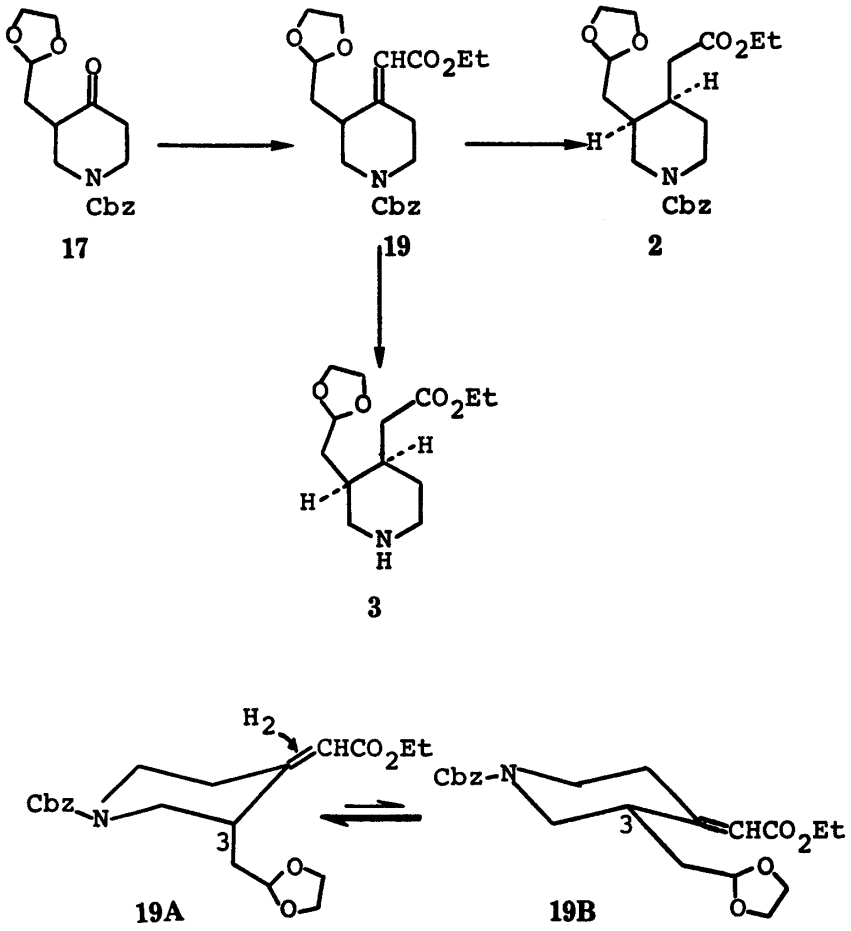

Chart 3

in ethyl acetate gave the saturated ester (**2**) in 93% yield, while that over 5% palladium on carbon in ethanol was accompanied with hydrogenolysis to afford the saturated amine (**3**) in 78% yield, both as single stereoisomers. The starting material (**19**) is expected to exist in the conformer **19A** rather than **19B** due to $A^{1,3}$-strain,[7] and therefore hydrogenation would occur exclusively from the side opposite the C-3 bulky substituent to give only the *cis*-3,4-disubstituted piperidine derivatives (**2** and **3**) as shown in Chart 3.

Total Synthesis of (±)-Corynantheidol

Corynantheidol (**4**) is a degradation product of an indole alkaloid, corynantheidine, isolated from *Pseudocinchona africana*,[8] and has now been synthesized from **2**.

On treatment with 1% hydrochloric acid in acetone, the acetal (**2**) afforded the aldehyde (**20**), which was then reduced with sodium borohydride in methanol to give the alcohol (**21**) in 91 % yield from **2**. Reductive removal of the hydroxyl group in **21** was achieved by the following stepwise sequence *via* the mesylate (**22**). The alcohol (**21**) was treated with methanesulfonyl chloride in pyridine to yield the mesylate (**22**), which was subsequently reduced with sodium iodide and zinc duct[9] in boiling 1,2-dimethoxyethane (DME) to afford the desired product (**23**) in 71% yield. Its proton nuclear magnetic resonance (^{1}H-NMR) spectrum exhibited a three-proton triplet at 0.90 ppm (J=5.5 Hz) due to the new terminal methyl protons. The benzoxycarbonyl group in **23** was removed by hydrogenolysis over 5% palladium on carbon in ethanol to give the secondary amine (**24**) in 84% yield. Since this product was found to be identical with an authentic sample of (+)-cincholoipon ethyl ester[10] by means of thin-layer chromatography (TLC) and infrared (IR) comparisons, the stereochemistry of **2** and **3** was unambiguously

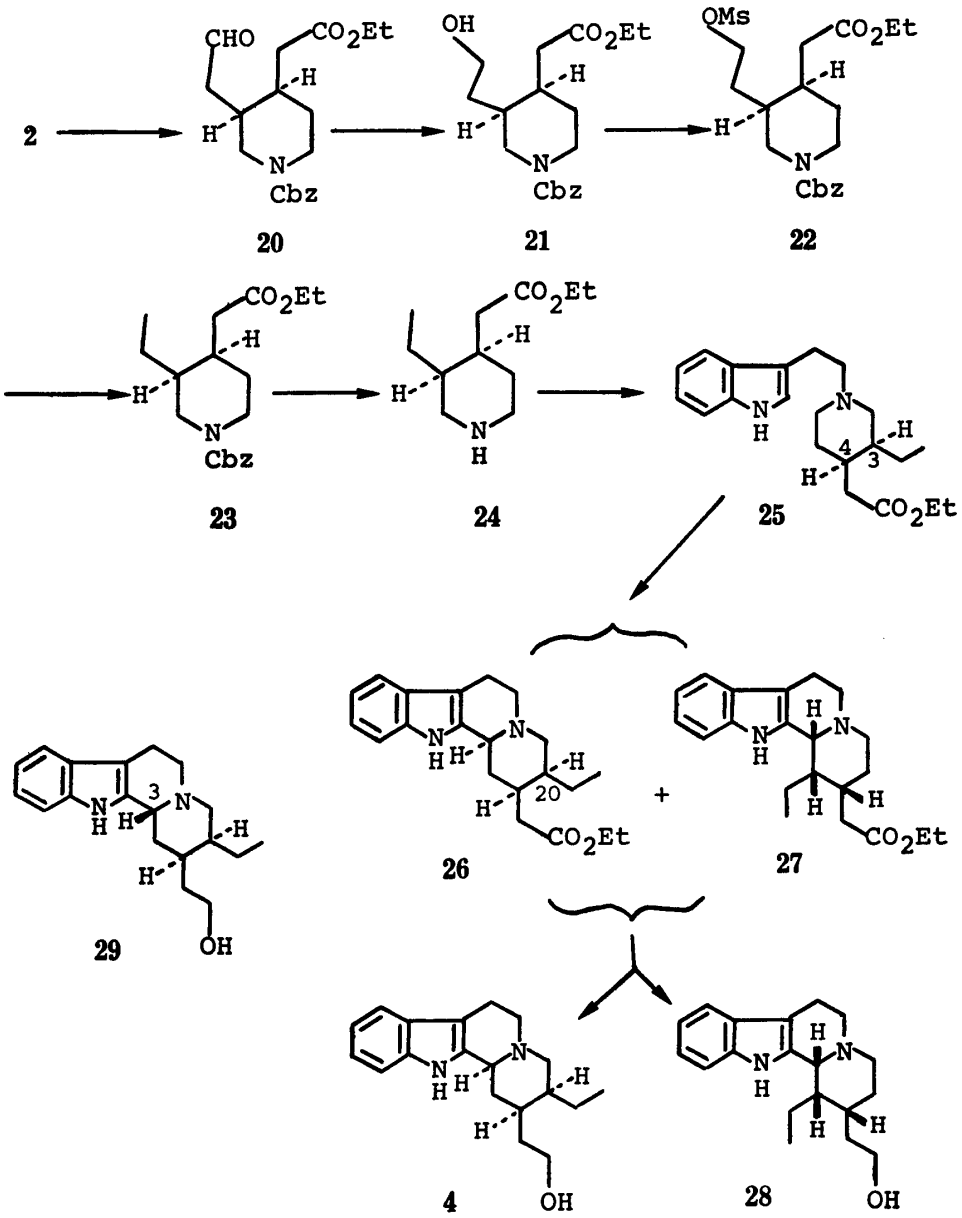

Chart 4

confirmed to be in accordance with earlier suggestions.

Condensation of the secondary amine (**24**) with tryptophyl bromide[11] in dioxane in the presence of potassium carbonate provided the tertiary amine (**25**) in 88% yield. Oxidative cyclization of *N*-[2-(3-indolyl)ethyl]piperidine derivatives into indolo[2,3-*a*]quinolizines has been well investigated with mercuric acetate as an oxidant.[12] This reaction in the presence of the disodium salt of ethylenediaminetetraacetic acid (EDTA·2Na), followed by reduction, is known to result in predominant formation of indolo[2,3-*a*]quinolizines with a *cis* relationship between the C_3- and C_{15}-hydrogens. When the indolylethylpiperidine (**25**) was treated with a 1 : 1 mixture of mercuric acetate and EDTA·2Na in refluxing 1% acetic acid for 4h, followed by reduction with sodium borohydride, a mixture of cyclized products (**26** and **27**) was obtained in 37% yield. Without separation, the mixture was further reduced with lithium aluminum hydride in ether to provide two hydroxy compounds. The main product (52% yield; mp 162—164°C) was found to be identical with (±)-corynantheidol (**4**)[13] by means of spectral comparisons. The minor product (32% yield; mp 137—140°C) has the same molecular formula

($C_{19}H_{26}N_2O$) as the main product and was assigned the structure **28** on the basis of the fact that this product was found to be not identical with (±)-3-epicorynantheidol (**29**)[13] and showed Bohlmann bands in the IR spectrum.

Formal Synthesis of (±)-Quinine

Uskoković *et al.* have reported a total synthesis of (±)-quinine (**5**) involving elaboration of (±)-*N*-benzoyl meroquinene methyl ester (**30**) from β-collidine.[14] Next, we describe an alternative synthesis of **30** from the aforementioned saturated amine (**3**).

Acylation of **3** with benzoyl chloride in a usual manner gave the benzamide (**31**; 99% yield), which was subjected to mild hydrolysis to provide the aldehyde (**32**). Treatment of **32** with sodium borohydride in ethanol was followed by chlorination with phosphorus oxychloride to yield the chloro ester (**34**). Attempts to dehydrochlorinate **34** resulted in the formation of only undefined resins. Thus, the ester (**34**) was hydrolyzed to the carboxylic acid (**35**), which was finally dehydrochlorinated according to the method of Uskoković[14] to provide the unsaturated acid, (±)-*N*-benzoyl meroquinene (**36**). Its methyl ester (**30**), prepared from **36** by treatment with diazomethane, was identical with an authentic sample of (+)-*N*-benzoyl meroquinene methyl ester, which was derived from (+)-meroquinene *tert*-butyl ester *d*-tartrate according to the known method,[15] on the basis of TLC, IR, and ^{1}H-NMR comparisons. Thus, an alternative synthesis of **30** was achieved and this synthesis also represents a formal synthesis of (±)-quinine (**5**).

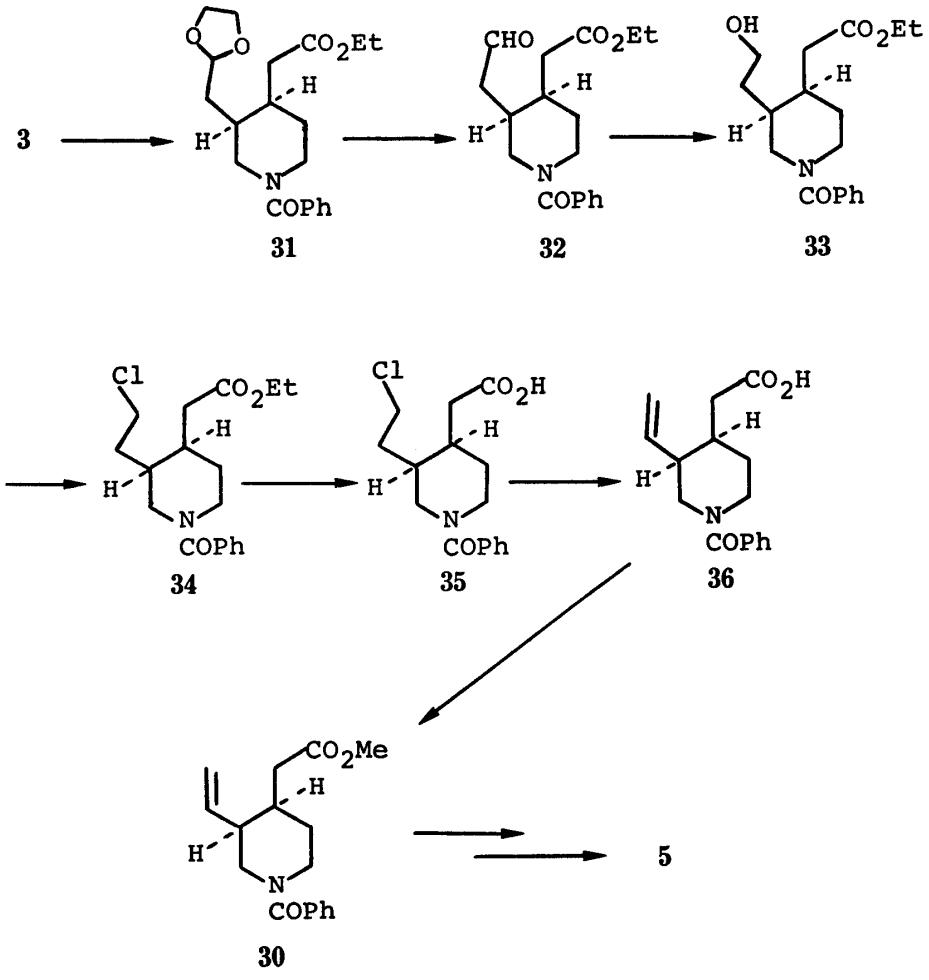

Chart 5

Further synthetic investigation using piperidines bearing functionalized alkyl substituents at the C-3 and C-4 positions, such as **2** and **3**, is in progress.

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO A-102 spectrometer. Mass spectra (MS) were taken with a Hitachi M-80 mass spectrometer (direct inlet, at 75 eV). ^{1}H-NMR spectra were recorded with a JEOL PMX-60 or FX-100 spectrometer in $CDCl_3$ using Me_4Si as an internal standard. All organic solutions were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator under reduced pressure. Column chromatography was carried out with Silica gel 60 (70—230 mesh, Merck) and alumina 90 (70—230 mesh, Merck).

Hydration of Ethyl 3-(1,3-Dioxolan-2-ylmethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (7)——a) Oxymercuration–demercuration Method: A solution of $Hg(OAc)_2$ (650 mg) in distilled water (4 ml) was added to a solution of the olefin (**7**; 418 mg) in THF (4 ml) and the mixture was stirred at room temperature for 13 h while the color of the solution changed from yellow to colorless. Then a solution of $NaBH_4$ (132 mg) in 10% NaOH (aq.) (6.5 ml) was added to the reaction mixture and the whole was further stirred at room temperature for 30 min. The resulting mixture was extracted with $CHCl_3$ (15 ml×3) and the extract was washed with brine, dried, and concentrated. The oily residue was chromatographed on alumina in $CHCl_3$. The first fraction afforded 170 mg (38%) of the 4-hydroxy compound (**9**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (OH), 1680 (NCOO). The second fraction afforded 181 mg (40%) of the 3-hydroxy compound (**8**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (OH), 1680 (NCOO). These products were found to be identical with authentic samples[3] by means of TLC and IR comparisons, respectively.

b) Epoxidation–reduction Method: A mixture of the olefin **7** (5.1 g), MCPBA (80%; 5.5 g), and CH_2Cl_2 (80 ml) was allowed to stand at room temperature for 15 h and was then diluted with $CHCl_3$ (100 ml). The resulting mixture was washed with a 1: 1 mixture of sat. $NaHCO_3$ and sat. $Na_2S_2O_3$, and then with brine. The dried organic layer was concentrated to give 5.5 g of crude ethyl 5-(1,3-dioxolan-2-ylmethyl)-3,4-epoxypiperidine-1-carboxylate (**12**) as a diastereoisomeric mixture. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (NCOO). ^{1}H-NMR δ: 1.20 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.85, 3.88 (total 4H, each s, OCH_2CH_2O), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.97, 5.00 (total 1H, each t, J=4.5 Hz, $CH\overset{O}{\underset{O}{}}$). MS m/e: 257 (M^+), 169 (base). A solution of B_2H_6 in THF (0.5 M; 20 ml) was added dropwise to a stirred solution of the above product (**12**; 3.34 g) in abs. THF (30 ml) under ice cooling over a period of 10 min. The reaction mixture was further stirred under cooling for 1 h then at room temperature for 3 h. Excess reagent was decomposed by addition of water, and the organic solvent was evaporated off. The residue was extracted with $CHCl_3$ (20 ml×4) and the extract was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on alumina in $CHCl_3$ to afford 1.65 g (49%) of **9** and 1.08 g (32%) of **8**.

c) *Via* Hydrogenolysis of the Epoxide (**12**): The epoxide **12** (0.080 g) was hydrogenated in EtOH (20 ml) over PtO_2 (15 mg) under atmospheric pressure of H_2 at room temperature for 50 h. The catalyst was filtered off and the filtrate was concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$. The first fraction yielded 35 mg (44%) of the starting material (**12**) and the second fraction afforded 21 mg (26%) of **8**.

Benzyl 3-(1,3-Dioxolan-2-ylmethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (13)——A mixture of the ethyl carbamate **7** (450 mg), 10% KOH (6 ml), and EtOH (10 ml) was refluxed with stirring for 90 h. Ethanol was evaporated off and the residue was diluted with water (10 ml) and $CHCl_3$ (10 ml). Carbobenzoxy chloride (0.50 g) was added to the resulting mixture and the whole was stirred under ice cooling for 4 h. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (10 ml×2). The combined $CHCl_3$ layer was washed with brine, dried, and concentrated. The oily residue was chromatographed on silica gel in $CHCl_3$ to afford 442 mg (78%) of the benzyl carbamate (**13**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (NCOO), 1650 (C=C). ^{1}H-NMR δ: 1.70 (2H, dd, J=7 and 5 Hz, $C\underline{H}_2CH\overset{O}{\underset{O}{}}$), 3.8—4.0 (4H, m, OCH_2CH_2O), 4.92 (1H, t, J=5 Hz, $CH\overset{O}{\underset{O}{}}$), 5.12 (2H, s, CH_2Ar), 5.70 (2H, m, C_4– and C_5–H), 7.32 (5H, s, Ar–H). MS m/e (%): 303 (6.4, M^+), 215 (100), 91 (76). High resolution MS. Calcd for $C_{17}H_{21}NO_4$: 303.1468. Found: 303.1467.

Hydration of 13——A mixture of the olefin **13** (2.9 g), MCPBA (80%; 2.47 g), and CH_2Cl_2 (30 ml) was allowed to stand at room temperature for 15 h. Work-up as usual gave 3.2 g of crude benzyl 5-(1,3-dioxolan-2-ylmethyl)-3,4-epoxypiperidine-1-carboxylate (**14**). A solution of B_2H_6 in THF (0.5 M; 20 ml) was added dropwise to a stirred solution of the above product (**14**; 3.2 g) in abs. THF (20 ml) and the resulting mixture was stirred under ice cooling for 1 h then at room temperature for 3 h. Work-up as usual gave an oily residue, which was chromatographed on alumina in $CHCl_3$. The first fraction afforded 1.40 g (46%) of benzyl 3-(1,3-dioxolan-2-ylmethyl)-4-hydroxypiperidine-1-carboxylate (**15**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (OH), 1680 (NCOO). ^{1}H-NMR δ: 3.6—4.0 (4H, m, OCH_2CH_2O), 4.88 (1H, t, J=4.5 Hz, $CH\overset{O}{\underset{O}{}}$), 5.02 (2H,

s, CH_2Ar), 7.18 (5H, s, Ar–H). MS *m/e* (%): 321 (1.4, M^+), 216 (21), 91 (100). High resolution MS. Calcd for $C_{17}H_{23}NO_5$: 321.1574. Found: 321.1568. The second fraction afforded 1.03 g (34%) of benzyl 5-(1,3-dioxolan-2-ylmethyl)-3-hydroxypiperidine-1-carboxylate (**16**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1680 (NCOO). ^{1}H-NMR δ: 3.90 (4H, m, OCH_2CH_2O), 4.83 (1H, t, J=4.5 Hz, $CH\overset{O}{\underset{O}{}}$), 5.05 (2H, s, CH_2Ar), 7.23 (5H, s, Ar–H). MS *m/e* (%): 321 (4.2, M^+), 233 (59), 230 (74), 91 (100). High resolution MS. Calcd for $C_{17}H_{23}NO_5$: 321.1574. Found: 321.1557.

An Alternative Synthesis of 15——A mixture of **9** (1.08 g), KOH (1.2 g), water (15 ml), and EtOH (15 ml) was refluxed with stirring for 93 h. Ethanol was evaporated off and the residue was diluted with water (60 ml). The resulting aqueous solution was washed with ether (10 ml) in order to remove a small amount of the starting material (**9**). Chloroform (30 ml) and carbobenzoxy chloride (0.70 ml) was added to the aqueous solution and the whole was stirred under ice cooling for 1 h. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (30 ml×2). The combined organic layer was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$–MeOH (20: 1) to afford 1.21 g (90%) of **15**. This product was found to be identical with the sample (**15**) obtained as mentioned above.

Benzyl 3-(1,3-Dioxolan-2-ylmethyl)-4-oxopiperidine-1-carboxylate (17)——A mixture of the alcohol **15** (1.37 g), PCC (1.84 g), NaOAc (0.70 g), and CH_2Cl_2 (20 ml) was stirred at room temperature for 5 h. The reaction mixture was diluted with ether (20 ml) and the resulting mixture was passed through a short column packed with Florisil. The column was washed thoroughly with ether. The combined eluate was concentrated and the residue was chromatographed on silica gel in $CHCl_3$ to afford 1.08 g (79%) of the ketone (**17**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710 (CO), 1680 (NCOO). ^{1}H-NMR δ: 3.7—3.8 (4H, m, OCH_2CH_2O), 4.91 (1H, t, J=5 Hz, $CH\overset{O}{\underset{O}{}}$), 5.13 (2H, s, CH_2Ar), 7.28 (5H, s, Ar–H). MS *m/e* (%): 319 (0.11, M^+), 91 (100), 73 (42). High resolution MS. Calcd for $C_{17}H_{21}NO_5$: 319.1418. Found: 319.1419.

Benzyl 5-(1,3-Dioxolan-2-ylmethyl)-3-oxopiperidine-1-carboxylate (18)——A mixture of the alcohol **16** (98 mg), PCC (138 mg), NaOAc (52 mg), and CH_2Cl_2 (3 ml) was stirred at room temperature for 8 h. Work-up as usual gave an oil, which was chromatographed on silica gel in $CHCl_3$ to afford 65 mg (66%) of the ketone (**18**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (COO), 1680 (NCOO). ^{1}H-NMR δ: 3.7—3.9 (4H, m, OCH_2CH_2O), 4.85 (1H, t, J=4.5 Hz, $CH\overset{O}{\underset{O}{}}$), 5.08 (2H, s, CH_2Ar), 7.26 (5H,s, Ar–H). MS *m/e*(%): 319 (28, M^+), 184 (24), 91 (100), 73(26). High resolution MS. Calcd for $C_{17}H_{21}NO_5$: 319.1418. Found: 319.1407.

Benzyl 3-(1,3-Dioxolan-2-ylmethyl)-4-ethoxycarbonylmethylenepiperidine-1-carboxylate (19)——A solution of triethyl phosphonoacetate (641 mg) in dry C_6H_6 (5 ml) was added dropwise to a stirred suspension of NaH (50% in oil; 1.43 g) in dry C_6H_6 (15 ml) under ice cooling over a period of 2—3 min, and the mixture was further stirred at room temperature for 1 h. A solution of the ketone **17** (760 mg) in dry C_6H_6 (10 ml) was added to the mixture and the whole was stirred at room temperature for another 1 h. The reaction mixture was washed with water and brine, dried, and concentrated to leave an oil, which was chromatographed on alumina in C_6H_6 and C_6H_6–$CHCl_3$ (1: 1) to afford 730 mg (79%) of the unsaturated ester (**19**) as colorless prisms, mp 78—80°C (from C_6H_6–hexane). IR ν_{max}^{KBr} cm^{-1}: 1700 sh (COO), 1680 (NCOO), 1640 (C=C). ^{1}H-NMR δ: 1.25 (3H, t, J=7 Hz, OCH_2CH_3), 3.7—3.9 (4H, m, OCH_2CH_2O), 4.10 (2H, q, J=7 Hz, OCH_2CH_3), 4.80 (1H, t, J=4.5 Hz, $CH\overset{O}{\underset{O}{}}$), 5.07 (2H, s, CH_2Ar), 5.68 (1H, s, CH=), 7.25 (5H, s, Ar–H). *Anal.* Calcd for $C_{21}H_{27}NO_6$: C, 64.76; H, 6.99; N, 3.60. Found: C, 64.53; H, 6.87; N, 3.58.

Benzyl *rel*(3*S*,4*R*)-3-(1,3-Dioxolan-2-ylmethyl)-4-ethoxycarbonylmethylpiperidine-1-carboxylate (2)——The unsaturated ester **19** (1.13 g) was hydrogenated in AcOEt (10 ml) over PtO_2 (50 mg) under atmospheric pressure at room temperature for 3 h. The catalyst was filtered off and the filtrate was concentrated to leave an oil, which was chromatographed on alumina in $CHCl_3$ to afford 1.05 g (93%) of the saturated ester (**2**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (COO), 1680 (NCOO). ^{1}H-NMR δ: 1.23 (3H, t, J=7 Hz, OCH_2CH_3), 2.23 (2H, br, C_4–CH_2), 3.7—3.9 (4H, m, OCH_2CH_2O), 4.07 (2H, q, J=7 Hz, OCH_2CH_3), 4.96 (1H, t, J=5 Hz, $CH\overset{O}{\underset{O}{}}$), 5.03 (2H, s, CH_2Ar), 7.20 (5H, s, Ar–H). MS *m/e* (%): 391 (0.36, M^+), 91 (100), 73 (39). High resolution MS. Calcd for $C_{21}H_{29}NO_6$: 391.1992. Found: 391.1989.

Ethyl *rel*(3*S*,4*R*)-3-(1,3-Dioxolan-2-ylmethyl)piperidine-4-acetate (3)——The unsaturated ester **19** (670 mg) was hydrogenated in EtOH (15 ml) over 5% Pd-C (300 mg) under atmospheric pressure at room temperature for 2 h. The catalyst was filtered off and the filtrate was concentrated to leave an oil, which was chromatographed on alumina in $CHCl_3$ and $CHCl_3$–MeOH (99: 1) to afford 340 mg (78%) of the saturated amine (**3**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 1720 (COO). ^{1}H-NMR δ: 1.23 (3H, t, J=7 Hz, OCH_2CH_3), 3.7—3.9 (4H, m, OCH_2CH_2O), 4.07 (2H, q, J=7 Hz, OCH_2CH_3), 4.85 (1H, t, J=3 Hz, $CH\overset{O}{\underset{O}{}}$). MS *m/e* (%): 257 (12, M^+), 212 (90), 82 (82), 73 (98), 70 (100). High resolution MS. Calcd for $C_{13}H_{23}NO_4$: 257.1625. Found: 257.1622.

Benzyl *rel*(3*S*,4*R*)-4-Ethoxycarbonylmethyl-3-(2-hydroxyethyl)piperidine-1-carboxylate (21)——A mixture of the acetal **2** (410 mg), 1% HCl (5 ml), and acetone (12 ml) was refluxed for 50 min, then the organic solvent was evaporated off. The residue was diluted with water and extracted with $CHCl_3$ (20 ml×3). The

extract was washed with brine, dried, and concentrated to leave 360 mg of crude aldehyde (**20**). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2700 (CHO), 1720 (COO, CO), 1680 (NCOO). ^{1}H-NMR δ: 1.22 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 4.07 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 5.05 (2H, s, CH_2Ar), 7.25 (5H, s, Ar–H), 9.60 (1H, br, CHO). MS *m/e* (%): 347 (0.1, M^+), 184 (27), 91 (100). Sodium borohydride (50 mg) was added to a stirred solution of the crude aldehyde (**20**; 360 mg) in MeOH (5 ml) under ice cooling and the mixture was further stirred for 10 min. Methanol was evaporated off and the residue was diluted with water and extracted with $CHCl_3$ (20 ml×3). The extract was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$–MeOH (20: 1) to afford 332 mg (91% from **2**) of the alcohol (**21**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1720 (COO), 1680 (NCOO). ^{1}H-NMR δ: 1.23 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 4.08 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 5.06 (2H, s, CH_2Ar), 7.24 (5H, s, Ar–H). MS *m/e* (%): 349 (0.5, M^+), 214 (100), 91 (83). High resolution MS. Calcd for $C_{19}H_{27}NO_5$: 349.1888. Found: 349.1911.

Benzyl *rel*(3*S*,4*R*)-4-Ethoxycarbonylmethyl-3-(2-methanesulfonyloxyethyl)piperidine-1-carboxylate (22)——Methanesulfonyl chloride (0.5 ml) was added to a solution of the alcohol **21** (660 mg) in dry pyridine (5 ml), and the mixture was allowed to stand at room temperature for 14 h. The reaction mixture was then poured into a mixture of conc. HCl (4 ml) and ice, and the resulting mixture was extracted with $CHCl_3$ (20 ml×3). The extract was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$–MeOH (97: 3) to afford 603 mg (74%) of the mesylate (**22**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (COO), 1680 (NCOO), 1355, 1170 (SO_2). ^{1}H-NMR δ: 1.23 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.20 (2H, d, J=1.5 Hz, C_4–CH_2), 2.85 (3H, s, SCH_3), 4.08 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 5.05 (2H, s, CH_2Ar), 7.25 (5H, s, Ar–H). MS *m/e* (%): 427 (1.1, M^+), 292 (100), 91 (64). High resolution MS. Calcd for $C_{20}H_{29}NO_7S$: 427.1662. Found: 427.1646.

Benzyl *rel*(3*S*,4*R*)-4-Ethoxycarbonylmethyl-3-ethylpiperidine-1-carboxylate (23)——Sodium iodide (1.05 g) and zinc dust (917 mg) were added to a solution of the mesylate **22** (0.60 g) in DME (12 ml) and the mixture was refluxed with stirring for 1 h. Inorganic substances were filtered off and the filtrate was concentrated to give an oil, which was chromatographed on silica gel in $CHCl_3$ to afford 449 mg (96%) of **23** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (COO), 1680 (NCOO). ^{1}H-NMR δ: 0.90 (3H, t, J=5.5 Hz, C_3–$CH_2\underline{CH_3}$), 1.23 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.23 (2H, d, J=1.5 Hz, C_4–CH_2), 4.08 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 5.05 (2H, s, CH_2Ar), 7.22 (5H, s, Ar–H). MS *m/e* (%): 333 (0.3, M^+), 242 (47), 198 (100), 91 (22). High resolution MS. Calcd for $C_{19}H_{27}NO_4$: 333.1938. Found: 333.1930.

Ethyl *rel*(3*S*,4*R*)-3-Ethylpiperidine-4-acetate [(±)-Cincholoipon Ethyl Ester] (24)——The benzyl urethane **23** (449 mg) was hydrogenated in EtOH (12 ml) over 5% Pd-C (230 mg) under atmospheric pressure at room temperature for 2 h. Work-up as usual gave an oily residue, which was chromatographed on alumina in $CHCl_3$–MeOH (19: 1) to afford 227 mg (84%) of the amine (**24**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3300 (NH), 1720 (COO). ^{1}H-NMR δ: 0.90 (3H, t, J=6 Hz, C_3–$CH_2\underline{CH_3}$), 1.23 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 2.00 (1H, s, NH), 2.23 (2H, d, J=1.5 Hz, C_4–CH_2), 4.06 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$). MS *m/e* (%): 199 (76, M^+), 170 (100), 126 (33), 112 (48), 110 (34), 44 (40). High resolution MS. Calcd for $C_{11}H_{21}NO_2$: 199.1570. Found: 199.1567. This product (**24**) was found to be identical with an authentic sample of (+)-cincholoipon ethyl ester[10] by means of TLC, IR ($CHCl_3$), and ^{1}H-NMR ($CDCl_3$) comparisons.

Ethyl *rel*(3*S*,4*R*)-3-Ethyl-1-[2-(3-indolyl)ethyl]piperidine-4-acetate (25)——A mixture of the amine **24** (270 mg), tryptophyl bromide (293 mg), anhydrous K_2CO_3 (253 mg), and dry dioxane (15 ml) was refluxed with stirring for 66 h, then inorganic substances were filtered off. Concentration of the filtrate gave an oil, which was chromatographed on alumina in $CHCl_3$ to afford 412 mg (88%) of **25** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 1720 (COO). ^{1}H-NMR δ: 0.92 (3H, t, J=7 Hz, C_3–$CH_2\underline{CH_3}$), 1.26 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 4.13 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 7.0—7.8 (5H, m, Ar–H), 7.9—8.3 (1H, br, NH). MS *m/e* (%): 342 (0.67, M^+), 212 (100). High resolution MS. Calcd for $C_{21}H_{30}N_2O_2$: 342.2305. Found: 342.2320.

Oxidative Cyclization of 25——A mixture of **25** (103 mg), $Hg(OAc)_2$ (191 mg), EDTA·2Na (175 mg), and 1% AcOH (12 ml) was refluxed with stirring for 4 h. After cooling, the mixture was adjusted to pH 6 with $NaHCO_3$, and EtOH (12 ml) was added to the mixture. Sodium borohydride (30 mg) was added portionwise to the resulting mixture and the whole was stirred under ice cooling for 20 min. A precipitate was filtered off and the filtrate was concentrated. The residue was extracted with $CHCl_3$ (25 ml×2) and the extract was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on alumina in $CHCl_3$–C_6H_6 (1: 1) to afford 38 mg (37%) of a mixture of the cyclized products (**26** and **27**) as a pale brown oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 2820, 2720 (Bohlmann bands), 1720 (COO). ^{1}H-NMR δ: 0.8—1.0 (3H, C–$CH_2\underline{CH_3}$), 1.26 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 4.10 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 6.9—7.4 (4H, m, Ar–H), 7.67 (1H, br, NH). MS *m/e* (%): 340 (100, M^+), 339 (51), 311 (13), 253 (17).

(±)-Corynantheidol (4) and Its Isomer (28)——A mixture of the esters **26** and **27** (61 mg), $LiAlH_4$ (40 mg), and dry ether (15 ml) was refluxed with stirring for 1 h. Excess $LiAlH_4$ and the complex were decomposed with AcOEt and aqueous sat. Rochelle salt solution. The inorganic salts were filtered off and washed with ether. The combined ethereal layer was dried and concentrated to leave an oil, which was chromatographed on silica gel. The fraction eluted with ether afforded 28 mg (52%) of (±)-corynantheidol (**4**) as pale yellow crystals, mp 162—164°C (from ether). IR ν_{max}^{KBr} cm^{-1}: 3470 (NH), 3300 (OH), 2790, 2730 (Bohlmann bands). ^{1}H-NMR δ: 0.92 (3H, t, J=6 Hz, C_{20}–$CH_2\underline{CH_3}$), 3.75 (2H, t, J=7 Hz, $C\underline{H_2}OH$), 7.0—7.5 (4H, m, Ar–H), 7.88 (1H, br, NH). MS *m/e* (%): 298 (91, M^+), 297 (100), 225 (16), 184 (15), 170 (32), 169 (29). High

resolution MS. Calcd for $C_{19}H_{26}N_2O$: 298.2043. Found: 298.2025. The synthetic product **4** was proved to be identical with an authentic sample of **4** by means of spectral comparisons. The fraction eluted with ether–MeOH (99: 1) afforded 18 mg (34%) of **28** as pale yellow crystals, mp 137—140°C (from C_6H_6–hexane). IR ν_{max}^{KBr} cm^{-1}: 3460 (NH), 3300 (OH), 2800, 2760 (Bohlmann bands). ^{1}H-NMR δ: 0.83 (3H, t, J=7 Hz, CH_2CH_3), 3.47 (1H, s, OH), 3.78 (2H, t, J=7 Hz, CH_2OH), 7.0—7.5 (4H, m, Ar–H), 7.59 (1H, br, NH). MS *m/e* (%): 298 (85, M^+), 297 (100), 253 (29), 197 (55), 184 (27), 170 (39). High resolution MS. Calcd for $C_{19}H_{26}N_2O$: 298.2043. Found: 298.2034.

Ethyl *rel*(3*S*,4*R*)-1-Benzoyl-3-(1,3-dioxolan-2-ylmethyl)piperidine-4-acetate (31)——Benzoyl chloride (130 mg) and a solution of anhydrous K_2CO_3 (130 mg) in water (1 ml) were added to a solution of the amine **3** (205 mg) in $CHCl_3$ (10 ml), and the mixture was stirred at room temperature for 5 min. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (10 ml×2). The combined $CHCl_3$ layer was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$–MeOH (99: 1) to afford 285 mg (99%) of the amide (**31**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (COO), 1620 (NCO). ^{1}H-NMR δ: 1.23 (3H, t, J=7 Hz, OCH_2CH_3), 2.30 (2H, br, C_4–CH_2), 3.77 (4H, m, OCH_2CH_2O), 4.10 (2H, q, J=7 Hz, OCH_2CH_3), 4.6—4.9 (1H, m, $CH\overset{O}{\underset{O}{}}$), 7.33 (5H, s, Ar–H). MS *m/e* (%): 361 (10, M^+), 288 (38), 273 (25), 184 (30), 105 (100). High resolution MS. Calcd for $C_{20}H_{27}NO_5$: 361.1887. Found: 361.1885.

Ethyl *rel*(3*S*,4*R*)-1-Benzoyl-3-(2-hydroxyethyl)piperidine-4-acetate (33)——A mixture of the acetal **31** (275 mg), 1% HCl (3 ml), and acetone (12 ml) was refluxed for 1.5 h. The acetone was evaporated off and the residue was diluted with water (10 ml). The resulting mixture was extracted with $CHCl_3$ (15 ml×3) and the extract was washed with brine. Concentration of the dried extract left 260 mg of crude ethyl *cis*-(3*H*,4*H*)-1-benzoyl-3-(2-oxoethyl)piperidine-4-acetate (**32**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2725 (CHO), 1720 (CO, COO), 1620 (NCO). ^{1}H-NMR δ: 1.23 (3H, t, J=7 Hz, OCH_2CH_3), 4.07 (2H, q, J=7 Hz, OCH_2CH_3), 7.25, 7.28 (total 5H, each s, Ar–H), 9.67 (1H, br, CHO). Sodium borohydride (25 mg) was added to a solution of the above crude aldehyde (**32**; 210 mg) in EtOH (5 ml) and the resulting mixture was stirred under ice cooling for 20 min. The reaction mixture was neutralized with AcOH and then concentrated. After dilution with water, the residue was extracted with $CHCl_3$ (15 ml×3) and the extract was washed with brine, dried, and concentrated. The oily residue was chromatographed on silica gel in $CHCl_3$–EtOH (49: 1) to afford 190 mg (97%) of the alcohol (**33**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1720 (COO), 1615 (NCO). ^{1}H-NMR δ: 1.25 (3H, t, J=7 Hz, OCH_2CH_3), 2.03 (1H, s, OH), 2.31 (2H, m, C_4–CH_2), 4.13 (2H, q, J=7 Hz, OCH_2CH_3), 7.39 (5H, s, Ar–H). MS *m/e* (%): 319 (25, M^+), 274 (19), 214 (32), 122 (29), 105 (100). High resolution MS. Calcd for $C_{18}H_{25}NO_4$: 319.1782. Found: 319.1816.

Ethyl *rel*(3*S*,4*R*)-1-Benzoyl-3-(2-chloroethyl)piperidine-4-acetate (34)——A mixture of the alcohol **33** (215 mg), $POCl_3$ (0.40 ml), and dry pyridine (4 ml) was allowed to stand at room temperature for 1 h and then acidified with conc. HCl. The resulting mixture was extracted with $CHCl_3$ (15 ml×3) and the extract was washed with brine, dried, and concentrated. The oily residue was chromatographed on silica gel in $CHCl_3$ to afford 180 mg (79%) of the chloro ester (**34**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (COO), 1615 (NCO). ^{1}H-NMR δ: 1.23 (3H, t, J=7 Hz, OCH_2CH_3), 2.28 (2H, br, C_4–CH_2), 4.07 (2H, q, J=7 Hz, OCH_2CH_3), 7.25 (5H, s, Ar–H). MS *m/e* (%): 339 [16, M^+ (^{37}Cl)], 337 [45, M^+ (^{35}Cl)], 302 (25), 274 (23), 232 (55), 105 (100). High resolution MS. Calcd for $C_{18}H_{24}NO_3{}^{35}Cl$: 337.1442. Found: 337.1431.

***rel*(3*S*,4*R*)-1-Benzoyl-3-(2-chloroethyl)piperidine-4-acetic Acid (35)**——A mixture of the ester **34** (130 mg), 1 N NaOH (5 ml), and MeOH (5 ml) was stirred at room temperature for 3 h and then the MeOH was evaporated off. The residue was diluted with water, acidified to pH 1 with 10% HCl, and extracted with $CHCl_3$ (10 ml×3). Concentration of the dried extract afforded 124 mg (quant.) of the carboxylic acid (**35**) as colorless prisms, mp 110—114°C (from ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600—2400 (COOH), 1705 (COO), 1615 (NCO). ^{1}H-NMR δ: 2.27 (2H, br, C_4–CH_2), 7.27 (5H, s, Ar–H), 9.91 (1H, s, COOH). MS *m/e* (%): 311 [19, M^+ (^{37}Cl)], 309 [55, M^+ (^{35}Cl)], 274 (72), 246 (40), 105 (100). *Anal.* Calcd for $C_{16}H_{20}NO_3Cl$: C, 62.03; H, 6.51; N, 4.52. Found: C, 61.89; H, 6.25; N, 4.58.

(±)-*N*-Benzoylmeroquinene Methyl Ester (30)——According to the known procedure,[14] a mixture of **35** (95 mg), *tert*-BuOK (172 mg), dry DMSO (2 ml), and dry C_6H_6 (2 ml) was heated with stirring at 70°C for 1 h. After evaporation of the C_6H_6, the mixture was treated with 1 N NaOH (10 ml) and washed with CH_2Cl_2 in order to remove DMSO. The aqueous layer was acidified with conc. HCl and then extracted with C_6H_6–ether (1: 1) (10 ml×5). The extract was dried and concentrated to give 78 mg of crude (±)-*N*-benzoylmeroquinene (**36**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500—2400 (COOH), 1705 (COOH), 1615 (NCO). ^{1}H-NMR δ: 4.9—5.8 (3H, m, $CH{=}CH_2$), 7.25 (5H, s, Ar–H), 8.5—8.8 (1H, br, COOH). A solution of CH_2N_2 in ether (*ca.* 2% solution; 8 ml) was added dropwise to a stirred solution of the above crude product (78 mg) in MeOH (5 ml) under ice cooling over a period of 2—3 min and stirring was continued for another 10 min under cooling. The solvent was evaporated off and the residue was chromatographed on silica gel in $CHCl_3$ to afford 49 mg (56%) of **30** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1725 (COO), 1615 (NCO). ^{1}H-NMR δ: 2.26 (2H, br, C_4–CH_2), 3.66 (3H, s, OCH_3), 4.9—5.2 (2H, m, $CH{=}CH_2$), 5.79 (1H, ddd, J=16, 11, and 9 Hz, $CH{=}CH_2$), 7.34 (5H, s, Ar–H). MS *m/e* (%): 287 (30, M^+), 182 (21), 105 (100). High resolution MS. Calcd

for $C_{17}H_{21}NO_3$: 287.1520. Found: 287.1511. This product was proved to be identical with an authentic sample of (+)-*N*-benzoylmeroquinene methyl ester[15] by means of TLC, IR ($CHCl_3$), and ^{1}H-NMR ($CDCl_3$) comparisons.

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References and Notes

1) Part VII: T. Imanishi, N. Yagi, and M. Hanaoka, *Chem. Pharm. Bull.*, **31**, 1243 (1983).
2) Preliminary report of this study: T. Imanishi, M. Inoue, Y. Wada, and M. Hanaoka, *Chem. Pharm. Bull.*, **30**, 1925 (1982).
3) T. Imanishi, N. Yagi, H. Shin, and M. Hanaoka, *Chem. Pharm. Bull.*, **30**, 4052 (1982).
4) *Cf.* H.C. Brown and P. Geogheagan, Jr., *J. Am. Chem. Soc.*, **89**, 1522 (1967); *idem*, *J. Org. Chem.*, **35**, 1844 (1970).
5) H.O. House and D.G. Melillo, *J. Org. Chem.*, **38**, 1398 (1973).
6) W.S. Wadsworth and W.D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).
7) F. Johnson, *Chem. Rev.*, **68**, 375 (1968).
8) M.-M. Janot, R. Goutarel, and J. Chabasse-Massoneau, *Bull. Soc. Chim. Fr.*, **1953**, 1033; C. Vamvacas, W.v. Phillipsborn, E. Schlittler, H. Schmid, and P. Karrar, *Helv. Chim. Acta*, **40**, 1793 (1957).
9) Y. Fujimoto and T. Tatsuno, *Tetrahedron Lett.*, **1976**, 3325.
10) V. Prelog and E. Zalan, *Helv. Chim. Acta*, **27**, 535 (1944); T. Fujii, S. Yoshifuji, and M. Tai, *Chem. Pharm. Bull.*, **23**, 2094 (1975).
11) J.L. Neumeyer, U.V. Moyer, and J.E. Leonard, *J. Med. Chem.*, **12**, 450 (1969).
12) *Cf.* J. Gutzwiller, G. Pozzolato, and M. Uskoković, *J. Am. Chem. Soc.*, **93**, 5907 (1971); P.A. Wender, J.M. Schaus, and A.W. White, *ibid.*, **102**, 6157 (1980).
13) S. Takano, K. Masuda, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, **1980**, 887.
14) M. Uskoković, C. Reese, H.L. Lee, G. Grethe, and J. Gutzwiller, *J. Am. Chem. Soc.*, **93**, 5902 (1971); G. Grethe, H.L. Lee, T. Mitt, and M.R. Uskoković, *ibid.*, **93**, 5904 (1971).
15) M.R. Uskoković, D.L. Pruess, C.W. Despreaux, S. Shiuey, G. Pizzolato, and J. Gutzwiller, *Helv. Chim. Acta*, **56**, 2834 (1973).