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1,6-Dihydro-3(2*H*)-pyridinones. VII.[1] Stereoselective Total Synthesis of a Monoterpene Alkaloid, (±)-Tecomanine[2]

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The first total and stereoselective synthesis of (±)-tecomanine (**1**), one of the monoterpene alkaloids, was accomplished starting from ethyl 1,6-dihydro-3(2*H*)-oxopyridine-1-carboxylate (**2a**). The allylic alcohol (**8**), obtained as a major product on treatment of **2a** with methylmagnesium iodide, was subjected to the Claisen rearrangement using ethyl (1-propenyl)ether to afford the aldehyde (**30**) which was converted to the methyl ketone (**32**). The acetal (**33**) was stereoselectively hydrated by a hydroboration-oxidation process to give the alcohol (**34**) in an excellent yield. To prevent formation of the furan (**38**), the product (**34**) was initially hydrolyzed and then oxidized to afford the diketone (**36**). Although **36** is a mixture of two diastereoisomers due to the configuration of the side-chain methyl group, each isomer, **36a** and **36b**, provided solely the desired product (**40**) upon base-catalyzed intramolecular aldol reaction. The urethane (**40**) was easily converted into (±)-tecomanine (**1**) by $LiAlH_4$ reduction and subsequent PCC oxidation.

Keywords——dihydropyridinone; Claisen rearrangement; hydroboration-oxidation; intramolecular aldol reaction; pyrindine; monoterpene alkaloid; tecomanine; total synthesis

Many kinds of monoterpene alkaloids have been isolated and their structures have been elucidated.[3] All of them possess ten carbons and one nitrogen atom, and have a pyridine or piperidine unit in their structures. In spite of their simple frameworks, they show significant and various pharmacological activities. Among representative alkaloids of the family, tecomanine (**1**) was first isolated from *Tecoma stans* Juss. by Hammouda and Motawi,[4] and its salts show powerful hypoglycemic activities.[5] Tecomanine possesses a pyrindine framework, an enone structure, and three asymmetric centers in its structure, and has not hitherto been totally synthesized.[6]

Recently we prepared *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones (**2**)[7,8] for the first time, by an efficient method, and showed that the Claisen rearrangement of the alcohol (**3**) is potentially useful for new carbon-carbon bond formation on the piperidine ring.[9] In this paper, we describe the first total and stereoselective synthesis of (±)-tecomanine (**1**) starting from the dihydropyridinone (**2**) and utilizing the Claisen rearrangement reaction as a key reaction.

Our strategy for the synthesis of (±)-tecomanine (**1**) is based on the recognition that **1** is a 2-cyclopentenone derivative and the aldol condensation product of the *cis*-3,5-disubstituted piperidin-4-one **4** (R^1=Me). The diketone (**4**) should be stereoselectively obtainable *via* two alternative pathways from the aldehyde (**5**), which could be obtained by the Claisen rearrangement of the allylic alcohol (**6**) formed from the dihydropyridinone (**2**). The first route (path A) involves an initial introduction of the oxygen function at C-4 and subsequent one-carbon connection at the aldehyde carbon. In the second route (path B), the one-carbon connection is made prior to the introduction of the oxygen atom (Chart 1).

Synthesis of (±)-7-Demethyltecomanine [*rel*(4*R*, 7a*S*)-1,2,3,4,7,7a-Hexahydro-2,4-dimethyl-6*H*-2-pyrindin-6-one] (**7**)

In order to validate the above strategy for the synthesis of tecomanine, we first investigated the synthesis of its 7-demethyl analogue (**7**). The dihydropyridinone (**2a**) was treated with

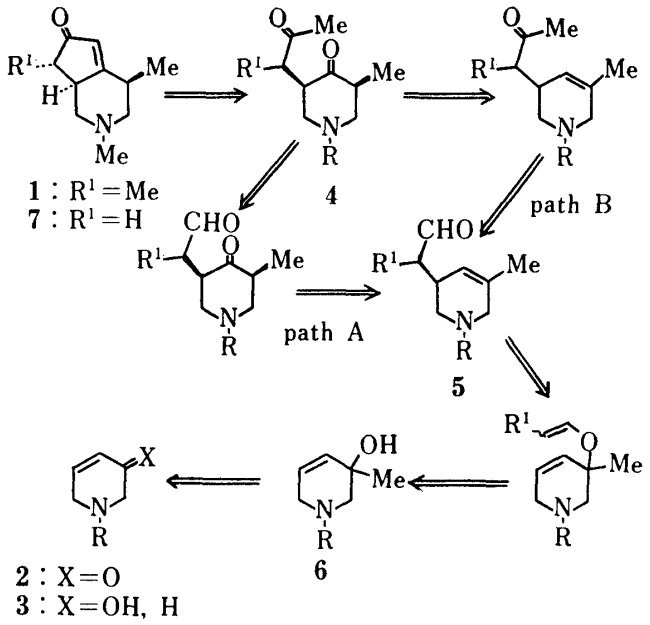

Chart 1

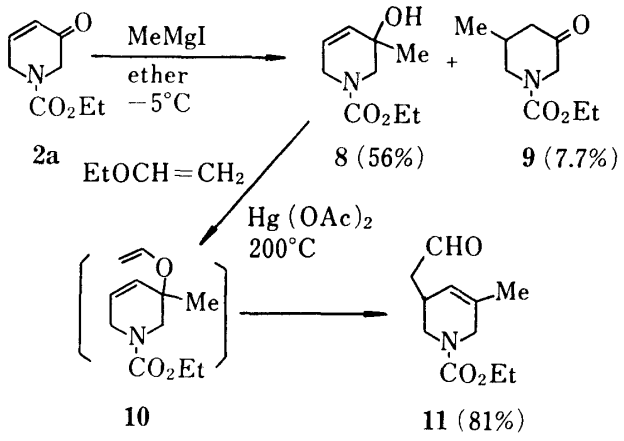

Chart 2

methylmagnesium iodide in ether at −5°C to provide the 1,2-adduct (**8**) as a major product along with a small amount of the 1,4-adduct (**9**). The allylic alcohol (**8**) was subjected to the Claisen rearrangement under the reported conditions[10] of heating with a large excess of ethyl vinyl ether containing mercuric acetate at 200°C in a sealed tube. The desired aldehyde (**11**) was obtained *via* the intermediate (**10**) in 81% yield (Chart 2). For preparation of the diketone (**4**; R^1=H) in Chart 1, we first examined path A.

The aldehyde group in **11** was protected by acetalization with ethylene glycol and the acetal (**12**) was hydrated by means of the hydroboration–oxidation process.[11] The produced alcohol (**13**) was a single regioisomer but a stereoisomeric mixture because of the approach of diborane from both sides. Pyridinium chlorochromate (PPC) oxidation of **13** gave the ketone (**14**) which was ketalized to the bisacetal (**15**). Selective deacetalization of **15** was achieved by treatment with 1% hydrochloric acid in tetrahydrofuran (THF) to afford the aldehyde (**16**) in an almost quantitative yield. A one-carbon unit was introduced onto the aldehyde carbon by the reaction of **16** with methylmagnesium iodide to yield the alcohol (**17**), which was

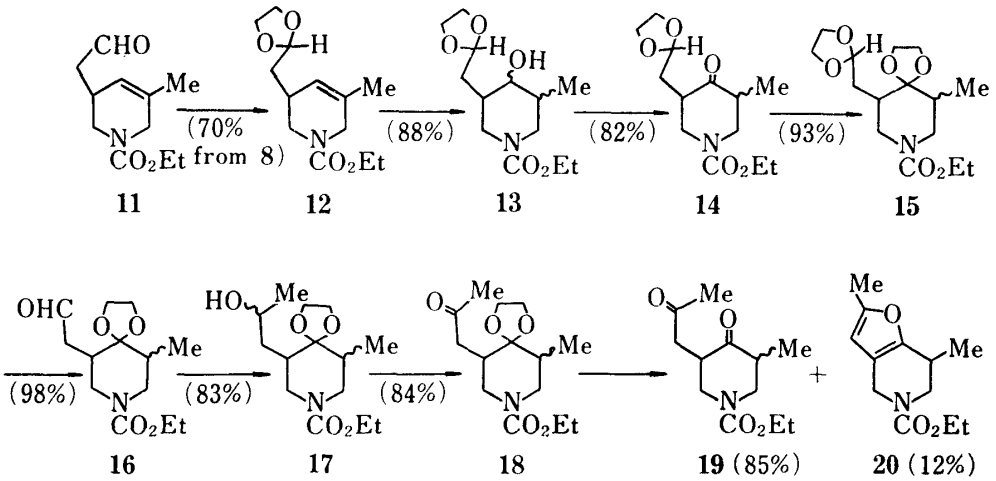

Chart 3

oxidized to the ketone (**18**). Hydrolysis of **18** was carried out with 10% hydrochloric acid in THF to give the diketone (**19**) as a diastereoisomeric mixture (*ca.* 1 : 8)[12] in 85% yield. As an overreaction product, the furan (**20**) was also isolated in 12% yield in this hydrolysis process.[13] The structure of **20** was easily confirmed from its proton nuclear magnetic resonance (^{1}H-NMR) spectrum, which exhibited a broad singlet at 5.69 ppm due to the proton at C-3. Thus, preparation of the diketone [**19**=**4**(R^1=H)] was achieved through path A, but the route was not wholly satisfactory in that **19** was obtained with poor stereoselectivity and the side product (**20**) was formed in the final step. Therefore, path B was examined next.

The aldehyde (**11**) was initially treated with methylmagnesium iodide to give the alcohol (**21**) as a 1 : 1 mixture of two diastereoisomers in 77% yield. PCC oxidation of **21** was followed by ketalization of the product (**22**) to afford the ethylene acetal (**23**) in 55% yield from **21**. Hydroboration-oxidation of **23** in a manner similar to that described for **13** resulted in exclusive formation of the desired product (**24**) as a single regio- and stereoisomer in 89% yield. The extremely high stereoselectivity is easily interpreted in terms of the bulkier alkyl pendant at C-3 in **23** than in **12**. The stereochemistry of **24** was not fully established but is well supported by the absence of formation of the hemiacetal (**25**) upon acidic hydrolysis of the acetal (**24**). The keto alcohol (**26**) obtained by the above hydrolysis was subjected to Jones oxidation[14] to afford the diketone (**27**) in 93% yield as a single isomer. Thus, path B was found to be preferable to path A, especially in terms of stereoselectivity.

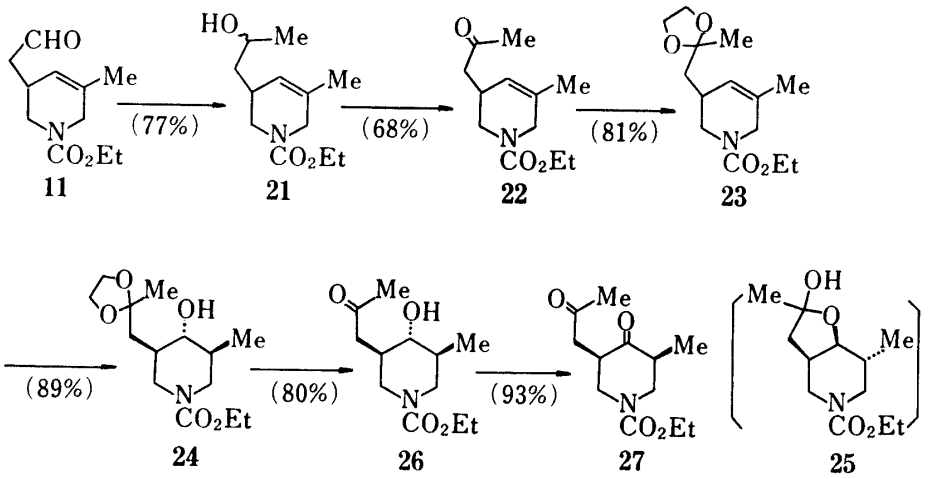

Chart 4

The intramolecular aldol condensation of **27** took place smoothly under the conditions of heating under reflux with anhydrous potassium carbonate in ethanol to provide the expected pyrindinone (**28**) in 87% yield. The position of the carbon-carbon double bond was determined by solvent shifts[15] of the signal of the methyl protons at C-4 in the ^{1}H-NMR spectra. Namely, the signal at 1.22 ppm in carbon tetrachloride shifted to 0.94 and 0.58 ppm in pyridine-d_5 and benzene-d_6, respectively. On the other hand, the same treatment of the diketone (**19**) also gave **28** as a sole product in a rather low yield (74%). The difference of yields from the diketones (**27** and **19**) may be attributable to the fact that the minor isomer of the diketone (**19**) gives no cyclization product but a polymerized resin.

Reduction of **28** with lithium aluminum hydride in ether gave the allylic alcohol (**29**), which was finally oxidized with PCC to furnish (±)-7-demethyltecomanine (**7**) as an oil.[16] Its spectral data were found to be similar to those reported for tecomanine.[17] The infrared (IR) spectrum showed a carbonyl band at 1715 cm^{-1} and a carbon-carbon double bond band at 1615 cm^{-1} in carbon tetrachloride, and the ^{1}H-NMR spectrum exhibited a broad singlet at

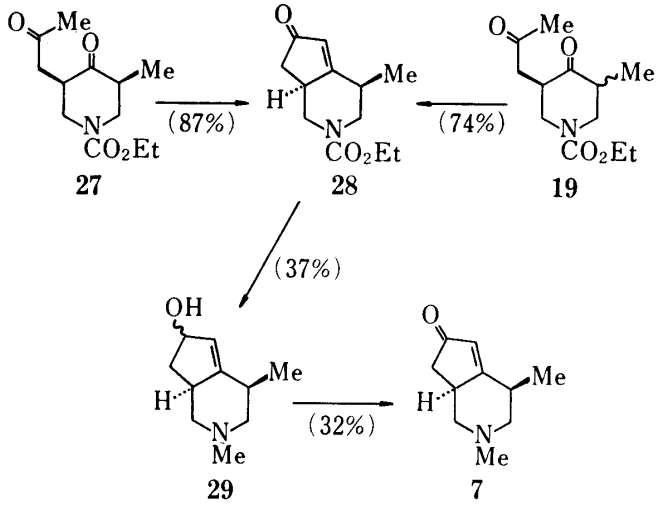

Chart 5

5.88 ppm due to the proton at C-5 and two methyl signals at 1.17 (doublet) and 2.34 ppm (singlet) owing to the C-4 and N-2 methyls, respectively.

Synthesis of (±)-Tecomanine (1)

For the synthesis of tecomanine, it is necessary to introduce one more carbon unit at C-7 compared with that of **7**. A possible means for achieving this goal would be the Claisen rearrangement using ethyl 1-propenyl ether instead of ethyl vinyl ether. On heating with ethyl 1-propenyl ether[18] in a manner similar to that described in the foregoing section, the allylic alcohol (**8**) provided the aldehyde (**30**), which, without purification, was reacted with methylmagnesium iodide to give the alcohol (**31**) in 58% yield from **8** as a mixture of diastereoisomers. PCC oxidation of **31** afforded the ketone (**32**) as a 1:1 diastereoisomeric mixture. After protection of the ketone function as the ethylene acetal, the olefin (**33**) was subjected to the hydroboration–oxidation process. As the produced alcohol (**34**) was also a mixture of two stereoisomers, this hydration step proceeds with extremely high regio- and stereoselectivity. The mixture was separated by careful column chromatography on alumina into **34a** and **34b** in 41 and 49% yields, respectively. The relative configuration of the methyl

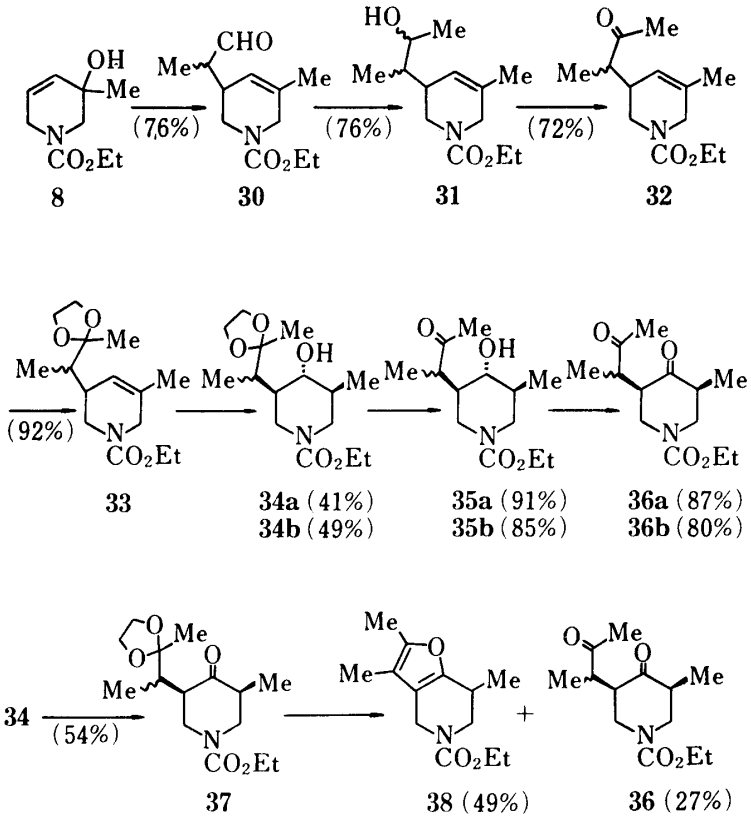

Chart 6

on the side chain in **34a** and **34b**, however, remains undetermined. Each isomer was hydrolyzed to the corresponding ketone (**35a** and **35b**) with 1% hydrochloric acid in THF and then the alcohol function in **35a** and **35b** was subjected to PCC oxidation, yielding the diketones (**36a** and **36b**, respectively). On the other hand, oxidation of **34** followed by acidic hydrolysis afforded the furan derivative (**38**) as a major product along with the diketone (**36**).

An attempt to cyclize the diketone (**36**) under the same conditions as used for **28** failed. The only isolated product was a tetrasubstituted olefin compound (**39**), which is presumably obtained from the expected compound (**40**) initially formed by the migration of the carbon-carbon double bond.[19] Then, the reaction was carried out at 45—50°C instead of at boiling point, and the desired product (**40**) was successfully obtained as a single stereoisomer in 88 or 87% yield from **36a** or **36b**, respectively. The fact that a single product (**40**) was obtained from both isomers of **36** can be interpreted as follows. In the basic medium employed, the isomers are interconvertible to each other and only **36′** can undergo intramolecular aldol reaction leading to **40**. For geometric reasons, the other isomer (**36″**) cannot cyclize.

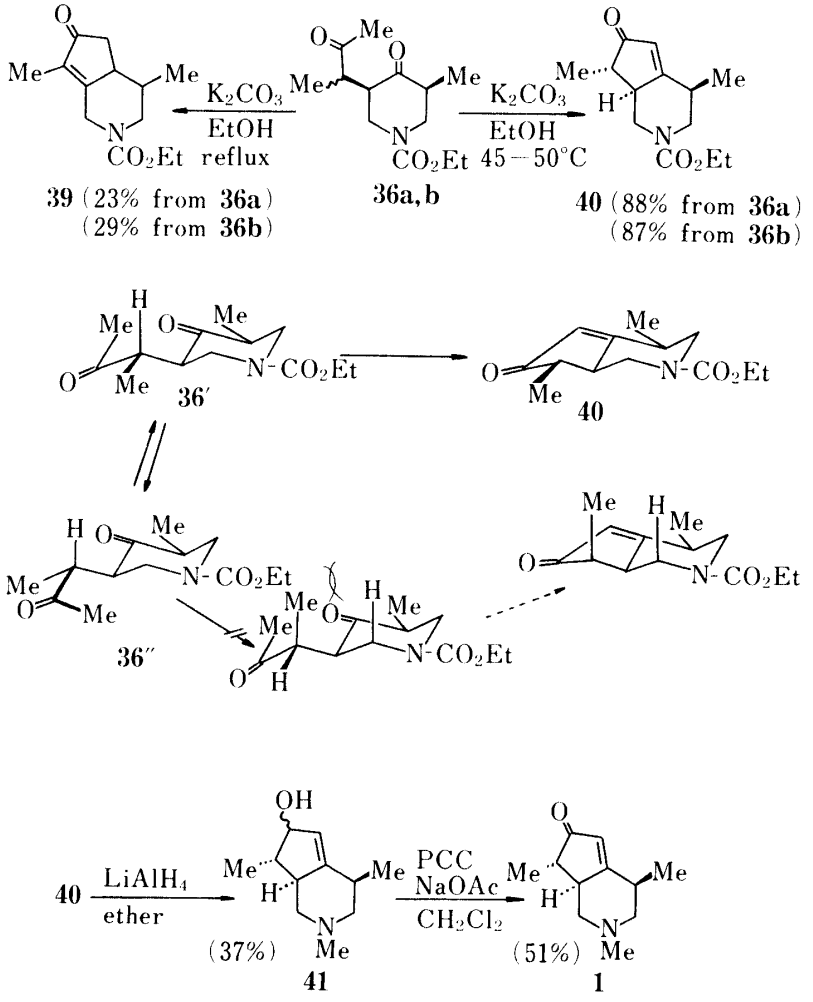

Chart 7

Lithium aluminum hydride reduction of **40** to the amino alcohol (**41**) followed by PCC oxidation furnished (±)-tecomanine (**1**), which was proved to be identical with natural tecomanine by means of thin-layer chromatography (TLC) and IR, ultraviolet (UV), and ^{1}H-NMR spectral comparisons.

Thus, we have achieved the first total and stereoselective synthesis of (±)-tecomanine (**1**), by an 11-step sequence, as part of our continuing investigation on general alkaloid syntheses using a common synthon, the dihydropyridinone **2**.[1)]

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO A-102 spectrometer. A UV spectrum was recorded with a Hitachi 323 spectrophotometer in methanol. Mass spectra (MS) were obtained with a Hitachi M-80 mass spectrometer (direct inlet, at 75 eV). ^{1}H-NMR spectra were determined on a JEOL PMX-60 or FX-100 spectrometer using Me_4Si as an internal standard in $CDCl_3$ as a solvent unless otherwise mentioned. Organic extracts were dried over anhydrous Na_2SO_4 and the solvents were removed in a rotary evaporator under reduced pressure. Column chromatography was carried out with Silica gel 60 (Merck) or with alumina 90 (Merck). Preparative TLC was performed on Silica gel 60 GF_{254} (Merck).

Ethyl 3-Hydroxy-3-methyl-1,2,3,6-tetrahydropyridine-1-carboxylate (8) and Ethyl 5-Methyl-3-oxopiperidine-1-carboxylate (9)——A solution of **2a** (2.62 g) in abs. ether (20 ml) was added dropwise to a stirred solution of MeMgI in abs. ether (0.6 M; 60 ml) at −5°C over a period of 30 min. Stirring was continued for 10 min, then the reaction mixture was treated with sat. NH_4Cl aqueous solution. The organic layer was separated and the aqueous layer was extracted with ether (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 $CHCl_3$. The first fraction gave 222 mg (7.7%) of the 1,4-adduct (**9**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (CO), 1680 (NCOO). ^{1}H-NMR δ: 1.03 (3H, d, J=6 Hz, C_5–CH_3), 1.24 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.07 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 185 (90, M$^+$), 156 (75), 140 (100). The second fraction gave 1.62 g (56%) of the 1,2-adduct (**8**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1685 (NCOO). ^{1}H-NMR δ: 1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.29 (3H, s, C_3–CH_3), 2.66 (1H, s, OH), 3.29 and 3.69 (2H, AB-q, J=13 Hz, C_2–H), 3.75 (1H, dd, J=19 and 2 Hz, C_6–H), 4.09 (1H, d, J=19 Hz, C_6–H), 4.16 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.65 (1H, dd, J=10 and 2 Hz, C_5–H), 5.77 (1H, d, J=10 Hz, C_4–H). MS *m/e* (%): 185 (13, M$^+$), 140 (3), 102 (100).

Ethyl 5-Methyl-3-(2-oxoethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (11)——A mixture of **8** (2.4 g), $Hg(OAc)_2$ (1.4 g), and ethyl vinyl ether (25 ml) was heated at 200°C in a sealed tube for 36 h. Further $Hg(OAc)_2$ (0.5 g) was added, and the mixture was heated at 200°C for another 24 h. The inorganic compounds were filtered off and the filtrate was concentrated. The residue was taken up in C_6H_6 (150 ml) and the solution was washed with water, 2% HCl, and then water. Evaporation of the solvent left an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 2.22 g (81%) of the aldehyde (**11**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$cm^{-1}: 2720 (CHO), 1720 (CO), 1685 (NCOO). ^{1}H-NMR δ: 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.68 (3H, br s, C_5–CH_3), 3.75 (2H, br s, C_6–H), 4.05 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.40 (1H, m, C_4–H), 9.67 (1H, t, J=1.5 Hz, CHO). MS *m/e* (%): 211 (8, M$^+$), 183 (50), 167 (100).

Ethyl 3-(1,3-Dioxolan-2-ylmethyl)-5-methyl-1,2,3,6-tetrahydropyridine-1-carboxylate (12)——A mixture of the crude aldehyde **11** [prepared from **8** (507 mg) according to the foregoing procedure], ethylene glycol (0.5 ml), *p*-TsOH (trace), and C_6H_6 (40 ml) was refluxed with stirring for 1 h while the water formed was azeotropically removed using a Dean-Stark apparatus. The reaction mixture was washed with sat. $NaHCO_3$ and water, dried, and concentrated to leave an oil, which was chromatographed on alumina in C_6H_6 to afford 491 mg (70% from **8**) of the acetal (**12**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (NCOO), 1665 (C=C). ^{1}H-NMR δ: 1.26 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.67 (3H, s, C_5–CH_3), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.90 (1H, t, J=5 Hz, $CH\langle^{O}_{O}$), 5.45 (1H, m, C_4–H). MS *m/e* (%): 255 (10, M$^+$), 167 (55), 73 (100).

Ethyl 5-Methyl-4-oxo-3-(2-oxopropyl)piperidine-1-carboxylate (19) and Ethyl 2,7-Dimethyl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-5-carboxylate (20)——A solution of B_2H_6 in abs. THF (0.5 M; 10 ml) was added dropwise to a stirred solution of **12** (1.45 g) in abs. THF (20 ml) under ice cooling over a period of 10 min, and the mixture was further stirred under cooling for 2 h. After decomposition of excess B_2H_6 with water, 6 N NaOH (3 ml) and 30% aq. H_2O_2 (3 ml) were added to the mixture and the whole was allowed to stand in a refrigerator overnight. The organic solvent was evaporated off and the remainder was extracted with $CHCl_3$ (30 ml×3). The extract was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on alumina in $CHCl_3$ to afford 1.37 g (88%) of ethyl 3-(1,3-dioxolan-2-ylmethyl)-4-hydroxy-5-methylpiperidine-1-carboxylate (**13**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3450 (OH), 1675 (NCOO). ^{1}H-NMR δ: 0.94, 1.00 (total 3H, each d, J=6 Hz, C_5–CH_3), 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.09 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.83—5.07 (1H, m, $CH\langle^{O}_{O}$).

A solution of **13** (1.37 g) in CH_2Cl_2 (5 ml) was added to a stirred suspension of PCC (2.3 g) and NaOAc (750 mg) in CH_2Cl_2 (10 ml) over a period of 1 min. The mixture was further stirred at room temperature for 44 h and diluted with ether (60 ml). The resulting mixture was passed through a short column packed with Florisil and the column was thoroughly washed with ether. The combined eluates were concentrated to dryness and the residue was chromatographed on silica gel in $CHCl_3$ to afford 1.12 g (82%) of ethyl 3-(1,3-dioxolan-2-ylmethyl)-5-methyl-4-oxopiperidine-1-carboxylate (**14**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}:

1710 (CO), 1680 (NCOO). ^{1}H-NMR δ: 1.02, 1.07 (total 3H, each d, J=6.5 Hz, C_5-CH_3), 1.30 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.15 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.92, 4.95 (total 1H, each t, J=4.5 Hz, $CH\langle^{O}_{O}$).

A mixture of **14** (1.12 g), ethylene glycol (1.0 ml), *p*-TsOH (trace), and C_6H_6 (50 ml) was refluxed for 16 h with stirring using a Dean–Stark apparatus. Work-up as usual gave an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 1.21 g (93%) of ethyl 6-(1,3-dioxolan-2-ylmethyl)-10-methyl-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**15**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (NCOO). ^{1}H-NMR δ: 0.85, 0.89 (total 3H, each d, J=7 Hz, C_{10}-CH_3), 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.89 (4H, m, OCH_2CH_2O), 4.09 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.89, 4.94 (total 1H, each t, J=5 Hz, $CH\langle^{O}_{O}$).

A solution of **15** (1.21 g) in THF (40 ml) containing 1% HCl (3 ml) was refluxed with stirring for 1.5 h and then the organic solvent was evaporated off. The remainder was extracted with $CHCl_3$ (20 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 1.02 g (98%) of ethyl 10-methyl-6-(2-oxoethyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**16**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2725 (CHO), 1715 (CO), 1680 (NCOO). ^{1}H-NMR δ: 0.86, 0.89 (total 3H, each d, J=6.5 Hz, C_{10}-CH_3), 1.22, 1.25 (total 3H, each t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.03, 4.06 (total 2H, each q, J=7 Hz, $OC\underline{H}_2CH_3$), 9.47—9.77 (1H, m, CHO).

A solution of **16** (1.02 g) in abs. ether (20 ml) was added dropwise to a stirred solution of MeMgI in abs. ether (0.6 M; 30 ml) over a period of 20 min at −10°C, and stirring was continued at the same temperature for another 2 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (50: 1) to afford 891 mg (83%) of ethyl 6-(2-hydroxypropyl)-10-methyl-1,4-dioxa-8-azaspiro[4.5]-decane-8-carboxylate (**17**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1675 (NCOO). ^{1}H-NMR δ: 0.86 (3H, d, J=6.5 Hz, C_{10}-CH_3), 1.18 (3H, d, J=7 Hz, CHOH-$C\underline{H}_3$), 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$).

A solution of **17** (891 mg) in CH_2Cl_2 (5 ml) was added to a stirred suspension of PCC (1.4 g) and NaOAc (0.50 g) in CH_2Cl_2 (15 ml) over a period of 1 min and the resulting mixture was further stirred at room temperature for 8 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 740 mg (84%) of ethyl 10-methyl-6-(2-oxopropyl)-1,4-dioxa-8-azaspiro[4.5]decane-8-carboxylate (**18**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1675 (NCOO). ^{1}H-NMR δ: 0.85 (3H, d, J=6.5 Hz, C_{10}-CH_3), 1.22, 1.25 (total 3H, each t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.13 (3H, s, $COCH_3$), 4.05, 4.08 (total 2H, each q, J=7 Hz, $OC\underline{H}_2CH_3$).

A mixture of **18** (740 mg), 10% HCl (6 ml), and THF (30 ml) was refluxed with stirring for 44 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$. The first fraction afforded 73 mg (12%) of the furan (**20**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (NCOO), 1580 (aromatic). ^{1}H-NMR δ: 1.17 (3H, d, J=6 Hz, C_7-CH_3), 1.24 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.22 (3H, s, C_2-CH_3), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.69 (1H, br s, C_3-H). MS *m/e* (%): 223 (17,M$^+$), 194 (16), 122 (100). The second fraction afforded 529 mg (85%) of the diketone (**19**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1705 (CO), 1685 (NCOO). ^{1}H-NMR δ: 1.02, 1.17 (8: 1, total 3H, each d, J=6 Hz, C_5-CH_3), 1.30 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.23 (3H, s, $COCH_3$), 4.20 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$).

Ethyl 3-(2-Hydroxypropyl)-5-methyl-1,2,3,6-tetrahydropyridine-1-carboxylate (**21**)——A solution of **11** (2.22 g) in abs. ether (20 ml) was added dropwise to a stirred solution of MeMgI in abs. ether (0.6 M; 60 ml) at −5°C over a period of 30 min and stirring was continued at the same temperature for another 30 min. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 1.83 g (77%) of **21** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1685 (NCOO). ^{1}H-NMR δ: 1.20 (3H, d, J=6 Hz, CHOH-$C\underline{H}_3$), 1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.68 (3H, br s, C_5-CH_3), 3.73 (2H, br s, C_6-H), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.42 (1H, m, C_4-H). MS *m/e* (%): 227 (60, M$^+$), 154 (44), 102 (43), 82 (100).

Ethyl 5-Methyl-3-(2-oxopropyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (**22**)——A solution of **21** (1.83 g) in CH_2Cl_2 (5 ml) was added to a stirred suspension of PCC (2.5 g) and NaOAc (0.85 g) in CH_2Cl_2 (15 ml) over a period of 2—3 min and the mixture was stirred at room temperature for 9 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 1.24 g (68%) of **22** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1680 (NCOO). ^{1}H-NMR δ: 1.26 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.66 (3H, br s, C_5-CH_3), 2.12 (3H, s, $COCH_3$), 3.34 (2H, d, J=4 Hz, C_2-H), 3.72 (2H, br s, C_6-H), 4.09 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.36 (1H, m, C_4-H). MS *m/e* (%): 225 (15, M$^+$), 167 (100), 138 (53).

Ethyl 3-(1,3-Dioxolan-2-ylmethyl)-5-methyl-1,2,3,6-tetrahydropyridine-1-carboxylate (**23**)——A mixture of **22** (1.18 g), ethylene glycol (2.0 ml), *p*-TsOH (trace), and C_6H_6 (50 ml) was refluxed with stirring using a Dean–Stark apparatus for 8 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 1.14 g (81%) of **23** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685 (NCOO). ^{1}H-NMR δ: 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.33 (3H, s, $CH_3C\langle^{O}_{O}$), 1.67 (3H, br s, C_5-CH_3), 3.92 (4H, s, OCH_2CH_2O), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.43 (1H, m, C_4-H). MS *m/e* (%): 269 (3, M$^+$), 167 (42), 87 (100).

Ethyl *rel*(3*R*,4*R*,5*S*)-3-(1,3-Dioxolan-2-ylmethyl)-4-hydroxy-5-methylpiperidine-1-carboxylate (**24**)——A solution of **23** (1.14 g) in abs. THF (10 ml) was added dropwise to a stirred solution of B_2H_6 in abs. THF (0.5 M; 30 ml) under ice cooling over a period of 10 min and the mixture was further stirred under cooling for

8 h. After decomposition of excess B_2H_6 with water (5 ml), a mixture of 6 N NaOH (4.5 ml) and 30% aq. H_2O_2 (4 ml) was added to the mixture and the whole was stirred under cooling overnight. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 1.08 g (89%) of **24** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1675 (NCOO). ^{1}H-NMR δ: 1.00 (3H, d, J=6 Hz, C_5–CH_3), 1.23 (3H, q, J=7 Hz, $OCH_2C\underline{H}_3$), 1.36 (3H, s, $CH_3C(=O)O$), 3.95 (4H, s, OCH_2CH_2O), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 287 (0.08, M^+), 185 (68), 156 (50), 87 (100).

Ethyl *rel*(3*R*,4*R*,5*S*)-4-Hydroxy-5-methyl-3-(2-oxopropyl)piperidine-1-carboxylate (26)——A mixture of **24** (0.60 g), 1% HCl (10 ml), and THF (20 ml) was refluxed with stirring for 1 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 407 mg (80%) of **26** as colorless crystals. An analytical sample was obtained by recrystallization from C_6H_6–hexane as colorless needles, mp 73—75°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1705 (CO), 1675 (NCOO). ^{1}H-NMR δ: 0.98 (3H, d, J=6 Hz, C_5–CH_3), 1.24 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.17 (3H, s, $COCH_3$), 4.06 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 243 (0.6, M^+), 185 (55), 156 (100). *Anal.* Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.12; H, 8.70; N, 5.72.

Ethyl *rel*(3*R*,5*S*)-5-Methyl-4-oxo-3-(2-oxopropyl)piperidine-1-carboxylate (27)——The Jones reagent[14] (8 N; 0.8 ml) was added to a stirred solution of **26** (407 mg) in purified acetone (5 ml) under ice cooling over a period of 2 h. Excess reagent was decomposed with MeOH and the mixture was diluted with water and extracted with $CHCl_3$ (15 ml×3). The extract was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$ to afford 376 mg (93%) of **27** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1705 (CO), 1680 (NCOO). ^{1}H-NMR δ: 1.03 (3H, d, J=6 Hz, C_5–CH_3), 1.30 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.23 (3H, s, $COCH_3$), 4.20 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 241 (1.3, M^+), 184 (100).

Ethyl *rel*(4*R*,7a*S*)-1,2,3,4,7,7a-Hexahydro-4-methyl-6-oxo-6*H*-2-pyrindine-2-carboxylate (28)——a) From **27**: A mixture of **27** (262 mg), anhyd. K_2CO_3 (0.30 g), and abs. EtOH (50 ml) was refluxed with stirring in a stream of N_2 for 2.5 h. After neutralization with 10% HCl, the reaction mixture was concentrated and the residue was taken up in $CHCl_3$ (80 ml). The organic layer was washed with brine, dried, and concentrated to leave an oil, which was chromatographed on silica gel in $CHCl_3$ to afford 211 mg (87%) of **28** as a yellow oil. On standing overnight, the product solidified and recrystallization from ether afforded pale yellow prisms, mp 104.5—106°C. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1685 (NCOO), 1620 (C=C). ^{1}H-NMR δ: 1.20 (3H, d, J=6 Hz, C_4–CH_3), 1.29 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.19 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.93 (1H, br s, C_5–H); δ (in CCl_4): 1.22 (3H, d, J=6 Hz), 1.29 (3H, t, J=7 Hz), 4.13 (2H, q, J=7 Hz), 5.85 (1H, br s); δ (in C_5D_5N): 0.94 (3H, d, J=6 Hz), 1.22 (3H, t, J=7 Hz), 4.24 (2H, q, J=7 Hz), 5.92 (1H, br s); δ (in C_6D_6): 0.58 (3H, d, J=6 Hz), 1.04 (3H, t, J=7 Hz), 4.13 (2H, q, J=7 Hz), 5.59 (1H, br s). MS *m/e* (%): 223 (95, M^+), 194 (85), 166 (100). High resolution MS. Calcd for $C_{12}H_{17}NO_3$: 223.1207. Found: 223.1218.

b) From **19**: A mixture of **19** (416 mg), anhyd. K_2CO_3 (0.50 g), and abs. EtOH (80 ml) was treated in the same manner as described in a). Work-up as usual gave 284 mg (74%) of **28**.

***rel*(4*R*,7a*S*)-2,4-Dimethyl-1,2,3,4,7,7a-hexahydro-6*H*-2-pyrindin-6-ol (29)**——A solution of **28** (284 mg) in abs. ether (5 ml) was added to a suspension of $LiAlH_4$ (0.20 g) in abs. ether (30 ml) and the mixture was stirred at room temperature for 5 h then under reflux for 4 h. After decomposition of excess $LiAlH_4$ with AcOEt, sat. Rochelle salt solution was added to the mixture and the inorganic substances formed were filtered off. The filtrate was dried and concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (20: 1) to afford 78 mg (37%) of **29** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3575 (OH). ^{1}H-NMR δ: 1.17 (3H, d, J=7 Hz, C_4–CH_3), 2.28 (3H, s, NCH_3), 4.70—4.96 (1H, m, C_6–H), 5.37 (1H, d, J=1.5 Hz, C_5–H). MS *m/e* (%): 167 (80, M^+), 74 (100).

(±)-7-Demethyltecomanine[*rel*(4*R*,7a*S*)-1,2,3,4,7,7a-Hexahydro-2,4-dimethyl-6*H*-2-pyrindin-6-one] (7)——A solution of **29** (38 mg) in CH_2Cl_2 (5 ml) was added all at once to a suspension of PCC (60 mg) and NaOAc (30 mg) in CH_2Cl_2 (5 ml), and the mixture was stirred at room temperature for 1 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (12: 1) to afford 12 mg (32%) of **7** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (CO), 1615 (C=C). ^{1}H-NMR δ: 1.17 (3H, d, J=7 Hz, C_4–CH_3), 2.34 (3H, s, NCH_3), 5.88 (1H, br s, C_5–H). The picrate: mp 190.5—191.5°C (from EtOH). *Anal.* Calcd for $C_{10}H_{15}NO\cdot C_6H_3N_3O_7$: C, 48.73; H, 4.60; N, 14.21. Found: C, 48.55; H, 4.50; N, 14.02.

Ethyl 5-Methyl-3-(3-oxo-2-propyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (30)——A mixture of **8** (1.4 g), $Hg(OAc)_2$ (0.90 g), and ethyl 1-propenyl ether[18] (5 ml) was heated at 200°C in a sealed tube for 48 h. Further $Hg(OAc)_2$ (0.40 g) was added, and the mixture was heated for another 24 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 1.31 g (76%) of **30** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2710 (CHO), 1720 (CO), 1680 (NCOO). ^{1}H-NMR δ: 1.07, 1.12 (total 3H, each d, J=6.5 Hz, C_3–$CHC\underline{H}_3$), 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.67 (3H, s, C_5–CH_3), 3.70 (2H, br s, C_6–H), 4.05 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.35 (1H, br, C_4–H), 9.43, 9.44 (total 1H, each br s, CHO). MS *m/e* (%): 225 (10, M^+), 197 (80), 167 (61), 95 (100).

Ethyl 3-(3-Hydroxy-2-butyl)-5-methyl-1,2,3,6-tetrahydropyridine-1-carboxylate (31)——A solution of **30** (1.31 g) in abs. ether (20 ml) was added dropwise to a stirred solution of MeMgI in abs. ether (0.6 M; 30 ml) at −5°C over a period of 10 min and the mixture was further stirred at the same temperature for 2 h. Work-

up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 1.06 g (76%) of **35** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380 (OH), 1680 (NCOO). ^{1}H-NMR δ: 0.75—1.00 (3H, m, C_3–CHC$\underline{H}_3$), 1.16 (3H, d, J=7 Hz, CHOH–C$\underline{H}_3$), 1.24 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.68 (3H, br s, C_5–CH_3), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.47, 5.63 (total 1H, each m, C_4–H). MS *m/e* (%): 241 (36, M^+), 194 (21), 168 (52), 102 (62), 96 (100).

Ethyl 5-Methyl-3-(3-oxo-2-butyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (**32**)——A solution of **31** (830 mg) in CH_2Cl_2 (5 ml) was added to a suspension of PCC (1.0 g) and NaOAc (380 mg) in CH_2Cl_2 (30 ml) at room temperature over a period of 10 min and the mixture was further stirred at room temperature for 7 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 591 mg (72%) of **32** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1685 (NCOO). ^{1}H-NMR δ: 1.05, 1.13 (total 3H, each d, J=6 Hz, C_3–CHC$\underline{H}_3$), 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.67 (3H, s, C_5–CH_3), 2.11, 2.15 (total 3H, each s, $COCH_3$), 4.11 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.37 (1H, m, C_4–H). MS *m/e* (%): 239 (3, M^+), 196 (6), 167 (100).

Ethyl 3-(1-(2-Methyl-1,3-dioxolan-2-yl)ethyl)-5-methyl-1,2,3,6-tetrahydropyridine-1-carboxylate (**33**)——A mixture of **32** (591 mg), ethylene glycol (1.0 ml), *p*-TsOH (trace), and C_6H_6 (50 ml) was refluxed with stirring using a Dean–Stark apparatus for 12 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 644 mg (92%) of **33** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (NCOO). ^{1}H-NMR δ: 0.88, 0.90 (total 3H, each d, J=7 Hz, C_3–CHC$\underline{H}_3$), 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.27, 1.28 (total 3H, each s, $CH_3C\langle^{O}_{O}$), 1.68 (3H, s, C_5–CH_3), 3.89 (4H, s, OCH_2CH_2O), 4.09 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.27, 5.50 (total 1H, each m, C_4–H). MS *m/e* (%): 283 (7, M^+), 194 (14), 167 (98), 87 (100).

Ethyl *rel*(3*R*,4*R*,5*S*)-3-(1-(2-Methyl-1,3-dioxolan-2-yl)ethyl)-4-hydroxy-5-methylpiperidine-1-carboxylate (34a and 34b)——A solution of **33** (847 mg) in abs. THF (10 ml) was added dropwise to a stirred solution of B_2H_6 in abs. THF (0.5 M; 20 ml) under ice cooling over a period of 10 min and the mixture was further stirred for 3 h under cooling. Work-up similar to the procedure described for **24** gave an oily residue, which was chromatographed on alumina in $CHCl_3$. The first fraction afforded 367 mg (41%) of **34a** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1670 (NCOO). ^{1}H-NMR δ: 1.01 (3H, d, J=5 Hz, C_5–CH_3 or C_3–CHC$\underline{H}_3$), 1.02 (3H, d, J=7 Hz, C_3–CHC$\underline{H}_3$ or C_5–CH_3), 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.34 (3H, s, $CH_3C\langle^{O}_{O}$), 3.97 (4H, s, OCH_2CH_2O), 4.07 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.53 (1H, s, OH). MS *m/e* (%): 301 (0.4, M^+), 286 (3), 239 (11), 185 (87), 156 (87), 116 (100), 87 (100). High resolution MS. Calcd for $C_{15}H_{27}NO_5$: 301.1888. Found: 301.1891. The second fraction afforded 442 mg of the isomer (**34b**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (OH), 1670 (NCOO). ^{1}H-NMR δ: 0.94 (3H, d, J=7 Hz, C_3–CHC$\underline{H}_3$ or C_5–CH_3), 1.01 (3H, d, J=5 Hz, C_5–CH_3 or C_3–CHC$\underline{H}_3$), 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.31 (3H, s, $CH_3C\langle^{O}_{O}$), 3.93 (4H, s, OCH_2CH_2O), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 301 (1.6, M^+), 286 (3), 257 (23), 185 (70), 156 (68), 116 (100), 87 (100). High resolution MS. Calcd for $C_{15}H_{27}NO_5$: 301.1888. Found: 301.1883.

Ethyl *rel*(3*R*,4*R*,5*S*)-4-Hydroxy-5-methyl-3-(3-oxo-2-butyl)piperidine-1-carboxylate (35a and 35b)——a) From **34a**: A mixture of **34a** (181 mg), 1% HCl (3 ml), and THF (6 ml) was refluxed for 1 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (20: 1) to afford 140 mg (91%) of **39a** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1700 (CO), 1680 (NCOO). ^{1}H-NMR δ: 1.00 (3H, d, J=6 Hz, C_3–CHC$\underline{H}_3$ or C_5–CH_3), 1.09 (3H, d, J=5.5 Hz, C_5–CH_3 or C_3–CHC$\underline{H}_3$), 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.21 (3H, s, $COCH_3$), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). High resolution MS. Calcd for $C_{13}H_{23}NO_4$: 257.1626. Found: 257.1623.

b) From **34b**: A mixture of **34b** (379 mg), 1% HCl (3 ml), and THF (13 ml) was refluxed for 1 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (20: 1) to afford 275 mg (85%) of **35b** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1700 (CO), 1680 (NCOO). ^{1}H-NMR δ: 1.00 (3H, d, J=6 Hz, C_5–CH_3 or C_3–CHC$\underline{H}_3$), 1.05 (3H, d, J=7 Hz, C_3–CHC$\underline{H}_3$ or C_5–CH_3), 1.24 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.18 (3H, s, $COCH_3$), 4.07 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 257 (3, M^+), 185 (57), 168 (70), 156 (100). High resolution MS. Calcd for $C_{13}H_{23}NO_4$: 257.1626. Found: 257.1645.

Ethyl *rel*(3*R*,5*S*)-5-Methyl-3-(3-oxo-2-butyl)-4-oxopiperidine-1-carboxylate (36a and 36b)——a) From **35a**: The Jones reagent (8 N; 0.5 ml) was added dropwise to a stirred solution of **35a** (241 mg) in purified acetone (5 ml) under ice cooling over a period of 2 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 209 mg (87%) of **36a** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1680 (NCOO). ^{1}H-NMR δ: 1.03 (3H, d, J=7 Hz, C_3–CHC$\underline{H}_3$ or C_5–CH_3), 1.22 (3H, d, J=7.5 Hz, C_5–CH_3 or C_3–CHC$\underline{H}_3$), 1.30 (3H, t, J=7 Hz, $OC\underline{H}_2CH_3$), 2.23 (3H, s, $COCH_3$), 4.19 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS (CI) *m/e* (%): 256 (100, M^++1), 238 (45), 184 (39).

b) From **35b**: The Jones reagent (8 N; 0.6 ml) was added dropwise to a stirred solution of **35b** (275 mg) in purified acetone (5 ml) under ice cooling over a period of 2 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 218 mg (80%) of **36b** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1680 (NCOO). ^{1}H-NMR δ: 0.99 (3H, d, J=6 Hz, C_3–CHC$\underline{H}_3$ or C_5–CH_3), 1.08 (3H, d, J=7 Hz, C_5–CH_3 or C_3–CHC$\underline{H}_3$), 1.31 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.31 (3H, s, $COCH_3$), 4.21 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS (CI) *m/e* (%): 256 (100, M^++1), 238 (72), 184 (60).

Ethyl 2,3,7-Trimethyl-4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-5-carboxylate (38)——The Jones reagent (8 N; 0.3 ml) was added dropwise to a stirred solution of **34** (*ca.* 1: 1 mixture of **34a** and **34b**; 156 mg) in purified acetone (3 ml) under ice cooling over a period of 2 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 80 mg (54%) of ethyl *rel*(3*R*,5*S*)-3-(1-(2-methyl-1,3-dioxolan-2-yl)ethyl)-5-methyl-4-oxopiperidine-1-carboxylate (**37**), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1680 (NCOO), which was used for the next step without further purification. A mixture of **37** (102 mg), 10% HCl (2 ml), and THF (10 ml) was refluxed with stirring for 3 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$. The first fraction afforded 40 mg (49%) of **38** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670 (NCOO), 1600 (aromatic). ^{1}H-NMR δ: 1.18 (3H, d, J=6.5 Hz, C_7–CH_3), 1.28 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.85 (3H, s, C_3–CH_3), 2.17 (3H, s, C_2–CH_3), 4.17 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 237 (56, M^+), 208 (59), 136 (100). The second fraction afforded 22 mg (27%) of **36** as a diastereoisomeric mixture. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1705 (CO), 1680 (NCOO).

Ethyl 4,7-Dimethyl-6-oxo-1,2,3,4,4a,5-hexahydro-6*H*-2-pyrindine-2-carboxylate (39)——a) From **36a**: A mixture of **36a** (108 mg), anhyd. K_2CO_3 (0.10 g), and abs. EtOH (20 ml) was refluxed with stirring in a stream of N_2 for 1 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 23 mg (23%) of **39** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (CO), 1680 (NCOO), 1620 (C=C). ^{1}H-NMR δ: 1.02 (3H, d, J=6 Hz, C_4–CH_3), 1.28 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.75 (3H, m, C_7–CH_3), 4.14 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 3.48 and 5.06 (2H, AB-q, J=15 Hz, C_1–H). MS *m/e* (%): 237 (91, M^+), 208 (100), 194 (57), 164 (59).

b) From **36b**: A mixture of **36b** (187 mg), anhyd. K_2CO_3 (150 mg), and abs. EtOH (30 ml) was treated in the same manner as described in a) to afford 0.050 g (29%) of **39**.

Ethyl *rel*(4*R*,7*S*,7a*S*)-4,7-Dimethyl-6-oxo-1,2,3,4,7,7a-hexahydro-6*H*-2-pyrindine-2-carboxylate (40)——a) From **36a**: A mixture of **36a** (67 mg), anhyd. K_2CO_3 (20 mg), and abs. EtOH (20 ml) was heated at 45—50°C with stirring in a stream of N_2 for 1.3 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 55 mg (88%) of **40** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685 (CO), 1680 (NCOO), 1615 (C=C). ^{1}H-NMR δ: 1.20 (3H, d, J=4.5 Hz, C_4–CH_3 or C_7–CH_3), 1.21 (3H, d, J=7.5 Hz, C_7–CH_3 or C_4–CH_3), 1.30 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.19 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.91 (1H, s, C_5–H). MS *m/e* (%): 237 (86, M^+), 208 (100), 180 (54). High resolution MS. Calcd for $C_{13}H_{19}NO_3$: 237.1364. Found: 237.1370.

b) From **36b**: A mixture of **36b** (176 mg), anhyd. K_2CO_3 (50 mg), and abs. EtOH (20 ml) was treated in the same manner as described in a) to afford 142 mg (87%) of **40**, which was proved to be identical with the sample obtained in a) by means of TLC, IR, and ^{1}H-NMR comparisons.

***rel*(4*R*,7*S*,7a*S*)-2,4,7-Trimethyl-1,2,3,4,7,7a-hexahydro-6*H*-2-pyrindin-6-ol (41)**——A solution of **40** (35 mg) in abs. ether (5 ml) was added all at once to a suspension of $LiAlH_4$ (30 ml) in abs. ether (10 ml) and the mixture was stirred at room temperature for 5.5 h. Work-up as usual gave an oily residue, which was chromatographed on alumina in $CHCl_3$ to afford 0.010 g (37%) of **41** as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3575 (OH). ^{1}H-NMR δ: 1.06 (3H, d, J=6.5 Hz, C_4–CH_3 or C_7–CH_3), 1.17 (3H, d, J=6.5 Hz, C_7–CH_3 or C_4–CH_3), 2.25, 2.31 (total 3H, each s, NCH_3), 4.41 (1H, br s, C_6–H), 5.35 (1H, d, J=1 Hz, C_5–H). MS *m/e* (%): 181 (22, M^+), 163 (8), 74 (100). High resolution MS. Calcd for $C_{11}H_{19}NO$: 181.1465. Found: 181.1462.

(±)-Tecomanine (1)——A solution of **41** (24 mg) in CH_2Cl_2 (3 ml) was added all at once to a suspension of PCC (30 mg) and NaOAc (30 ml) in CH_2Cl_2 (5 ml) and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with MeOH (3 ml) and inorganic substances were filtered off. The filtrate was concentrated and the oily residue was subjected to preparative TLC in $CHCl_3$–MeOH (50: 1) to afford 12 mg (51%) of (±)-tecomanine (**1**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (CO), 1620 (C=C). ^{1}H-NMR δ: 1.16 (3H, d, J=6.5 Hz, C_4–CH_3 or C_7–CH_3), 1.19 (3H, d, J=7.5 Hz, C_7–CH_3 or C_4–CH_3), 2.35 (3H, s, NCH_3), 5.86 (1H, s, C_5–H). MS *m/e* (%): 179 (100, M^+), 164 (23), 111 (38), 93 (29), 57 (99). UV λ_{max}: 225.5 nm; λ_{max} (in the presence of acid): 221.5 nm. The picrate: mp 184.5—185.5°C (from EtOH). *Anal.* Calcd for $C_{11}H_{17}NO \cdot C_6H_3N_3O_7$: C, 50.00; H, 4.94; N, 13.72. Found: C, 50.22; H, 4.96; N, 13.47. The synthetic product was proved to be identical with natural tecomanine by means of TLC, UV, IR, and ^{1}H-NMR comparisons.

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