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A Stereocontrolled Synthesis of (±)-Emetine and (±)-Protoemetinol by Intramolecular Michael Reaction[1)]

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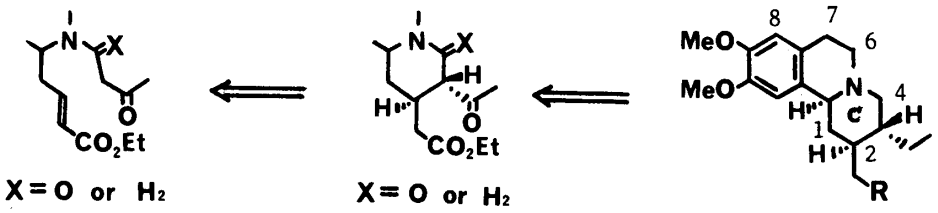
An intramolecular Michael reaction of **9** stereoselectively gave the tricyclic compound (**10**), which was converted to (±)-protoemetinol (**2**) and **13**. Compound **13** is an important intermediate for the synthesis of (±)-emetine. A simpler preparation of **13** was also carried out by the intramolecular Michael reaction of **14**, followed by reduction of the ketone moiety. Furthermore, the stereoselective formation of **26**, which is an intermediate for the synthesis of (±)-emetine, was achieved by the following sequence of reactions: intramolecular Michael reaction, reduction of the ketone moiety, and removal of the *N*-carbomethoxy group.

Keywords——(±)-emetine; (±)-protoemetinol; stereoselective synthesis; intramolecular Michael reaction; activated zinc powder; desulfurization

Intramolecular Michael reaction is an effective means for the stereoselective construction of a cyclic carbon skeleton.[2)] Thus, we have been interested in the application of this method to the syntheses of biologically active natural products such as emetine,[3)] one of the ipecac alkaloids, and ajmalicine and corynantheine, representative indole alkaloids. Our strategy for the synthesis of emetine was to apply the intramolecular Michael reaction to the stereocontrolled formation of ring C of emetine. Here we wish to report a stereoselective synthesis of (±)-emetine (**1**) and (±)-protoemetinol (**2**).

We have studied the synthesis of (±)-emetine by two different approaches. In the first



1 : R = emetine

2 : R = CH_2OH protoemetinol

Chart 1

approach, cyclization of **9** or **14** was examined. The iminium salt (**3**)[4] was condensed with ethyl 4-bromocrotonate in acetonitrile in the presence of activated zinc powder at room temperature for 20 h to give the tertiary amine (**4**) in 90% yield.[5] Although debenzylation of **4** was attempted by several methods, reduction of the double bond moiety preferentially occurred to give **6**. Then the conversion of **8** to **5** was carried out. The iminium salt (**7**), easily obtained in 90% yield from 3,4-dihydro-6,7-dimethoxyisoquinoline[6] and 2-(2-bromoethyl)-1,3-dioxolane, was condensed with ethyl 4-bromocrotonate under the same conditions described above to give **8** in 90% yield. A solution of **8** in a 20% solution of oxalic acid in aqueous ethanol was heated for 20 h to afford the secondary amine (**5**) in 82% yield. Contrary

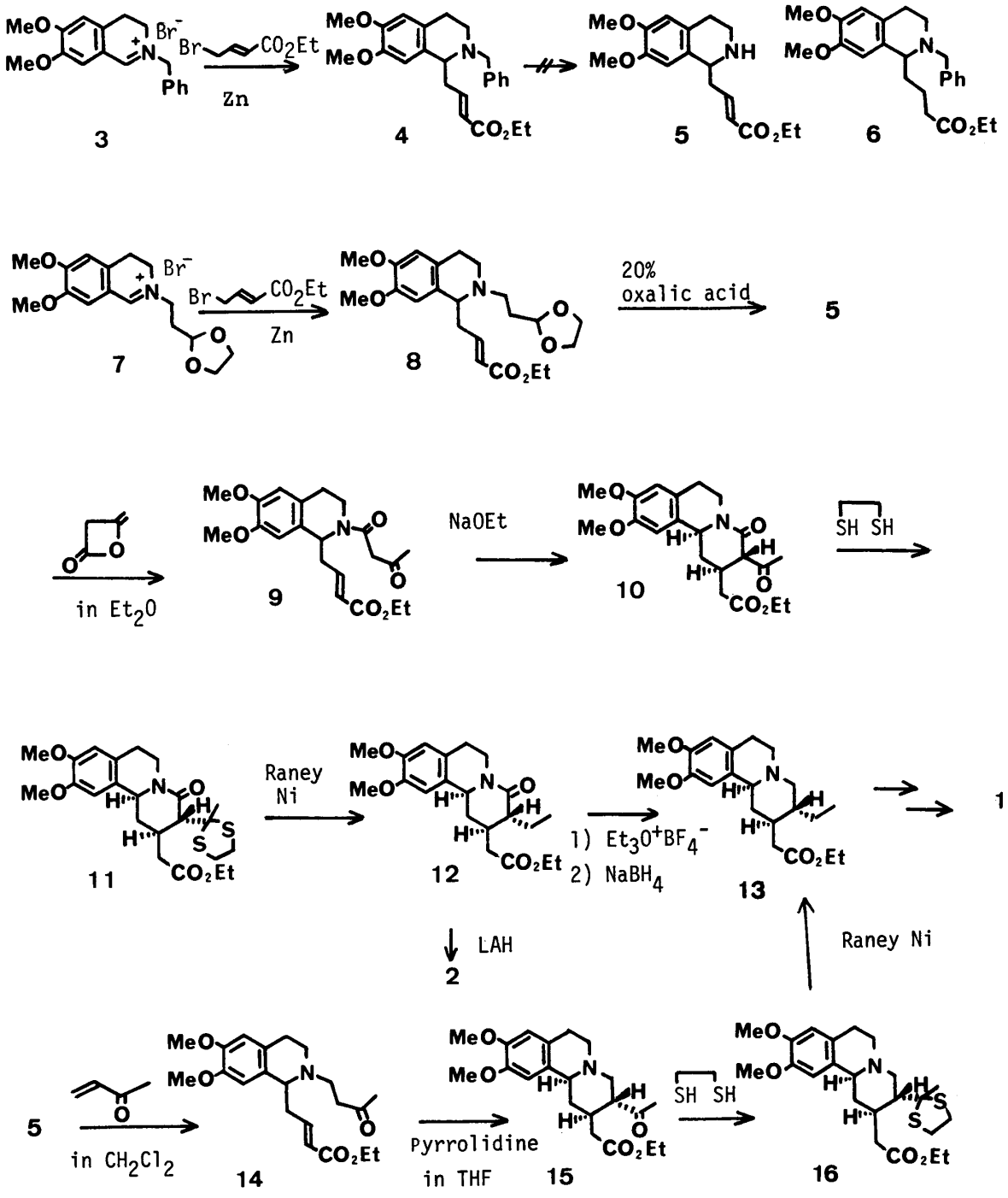


Chart 2

to expectation, no corresponding aldehyde was obtained. The secondary amine (**5**) would be formed from the corresponding aldehyde, which was produced by the hydrolysis of the acetal moiety of **8**, by a retro-Michael reaction. Treatment of **5** with diketene in dry ether at room temperature for 2 h afforded the ketoamide (**9**) in 84% yield. Cyclization reaction of **9** was carried out by the use of sodium ethoxide in dry ethanol at room temperature to yield the tricyclic compound (**10**) in 63% yield. In the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, the signal due to the proton on C_3 of **10** appeared at 3.5 as a doublet having the coupling constant $J=10$ Hz. This result suggests a *trans* relationship between C_2-H and C_3-H.[7] A mixture of **10** and ethanedithiol in trifluoroacetic acid was heated under reflux to afford the thioketal (**11**) in 71% yield. Desulfurization of **11** using Raney Ni (W-2) in ethanol gave the lactam ester (**12**) in 91% yield. Reduction of **12** with lithium aluminum hydride[8] afforded (±)-protoemetinol (**2**) (67% yield), which was identical [by infrared (IR, $CHCl_3$) and NMR ($CDCl_3$)] with an authentic sample.[9] Treatment of the lactam (**12**)

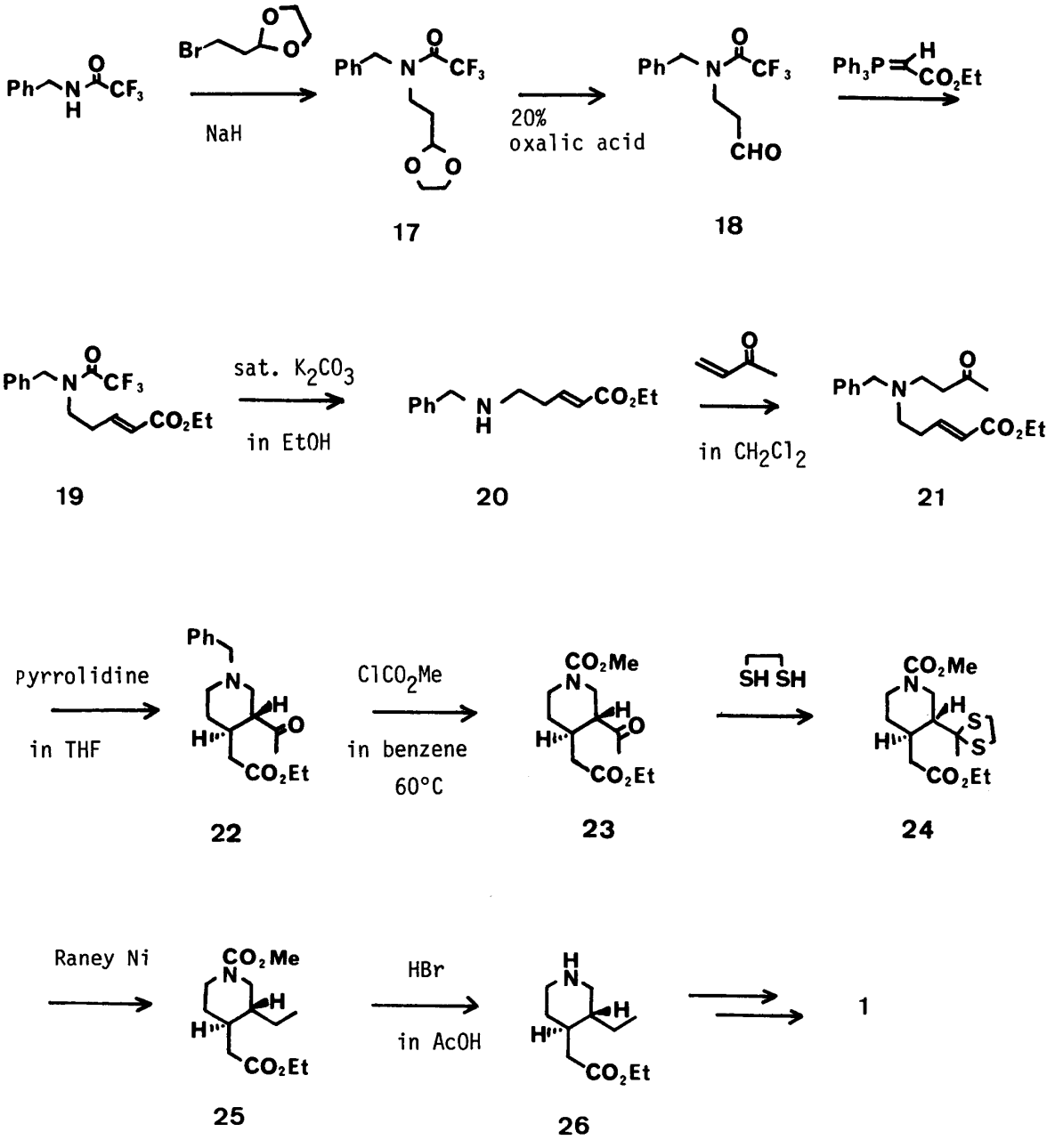


Chart 3

with triethyloxonium fluoroborate[10] in dry CH_2Cl_2 at room temperature, followed by sodium borohydride reduction, afforded the emetine precursor (**13**) in 54% yield. The structure of **13** was established by direct comparison with an authentic sample.[11] As **13** has already been converted to (±)-emetine,[12] this constitutes a formal synthesis of (±)-emetine (**1**).

A simpler preparation of **13** was further examined. Treatment of **5** with methyl vinyl ketone in dry CH_2Cl_2 at room temperature gave **14** in 92% yield. The tertiary amine (**14**) was cyclized smoothly on treatment with pyrrolidine in tetrahydrofuran (THF) at room temperature to afford the tricyclic compound (**15**) in 80% yield.[13] A mixture of **15** and ethanedithiol in trifluoroacetic acid was heated under reflux to give the thioketal (**16**) (68% yield), which was treated with Raney Ni (W-2) in ethanol at 78 °C for 2 h to furnish **13** in 76% yield.[14]

In the second approach, cyclization of the acyclic compound (**21**) was investigated. Condensation of *N*-benzyltrifluoroacetamide with 2-(2-bromoethyl)-1,3-dioxolane using sodium hydride in benzene–*N*,*N*-dimethylformamide (DMF) (5 : 1) gave the amide (**17**) in 89% yield. Partial hydrolysis of **17** with a 20% solution of oxalic acid in aqueous THF afforded the aldehyde (**18**) in 68% yield. Treatment of **18** with ethyl (triphenylphosphoranylidene)-acetate[15] in CH_2Cl_2 at room temperature afforded the unsaturated ester (**19**) in 85% yield. Hydrolysis of **19** with 5% aqueous potassium carbonate gave the secondary amine (**20**) (92% yield), which was condensed with methyl vinyl ketone in dry CH_2Cl_2 at room temperature to furnish **21** in 99% yield. Cyclization reaction of **21** was carried out using pyrrolidine in dry THF at room temperature to give the cyclic compound (**22**)[16] in 80% yield as the sole product. No corresponding stereoisomer of **22** was detected. Treatment of **22** with methyl chloroformate in dry benzene at 60 °C gave the carbamate (**23**) in 93% yield.[17] The carbamate (**23**) was converted to **25** in 68% yield *via* its thioketal (**24**) by the same method as that in the case of **11** or **16** described above. Selective removal of the *N*-carbomethoxy group was effected by treatment of **25** with glacial acetic acid saturated with hydrogen bromide at room temperature for 18 h to give the secondary amine (**26**) in 94% yield.[18] This compound (**26**) is an important intermediate for the synthesis of (±)-emetine.[19]

In conclusion, stereoselective syntheses of (±)-emetine (**1**) and (±)-protoemetinol (**2**) were achieved by the intramolecular Michael reaction of **9**, **14**, and **21**. The use of this reaction in the synthesis of other alkaloids is now being examined.

Experimental

IR spectra were determined with a JASCO A-102 spectrophotometer, and ^{1}H-NMR spectra, with a JEOL PMX-60 or JX-270 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL JMS-D200 spectrometer at 70 eV. Column chromatography was performed on silica gel (100—200 mesh, from Nakarai Chemical Co., Inc.) throughout the present study.

Ethyl 4-(2-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl)crotonate (4)——Ethyl 4-bromocrotonate (5.15 g, 26.7 mmol) was dissolved in a solution of 2-benzyl-6,7-dimethoxy-3,4-dihydroisoquinolium bromide (**3**)[4] (3.22 g, 8.09 mmol) in dry acetonitrile (30 ml). The solution was cooled in an ice bath, then activated zinc powder (2.09 g, 44.5 mmol) was added under an argon. After the temperature had been gradually raised to room temperature, the reaction mixture was allowed to stand for 2 d with stirring. Then, the reaction mixture was poured into saturated aqueous $NaHCO_3$, filtered, and extracted with CH_2Cl_2. The extract was dried over anhydrous K_2CO_3. After removal of the solvent, the residue was subjected to column chromatography on SiO_2 [benzene–CH_2Cl_2 (9 : 1)] to afford **4** (3.17 g, 90% yield) as a yellow oil. MS *m/z*: 395 (M^+). IR (film): 1710 (ester CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, t, J = 7 Hz, $OCH_2\underline{Me}$), 2.10—3.30 (6H, m), 3.76 (2H, s, $ArC\underline{H}_2$), 3.80 (3H, s, OMe), 3.85 (3H, s, OMe), 4.20 (2H, q, J = 7 Hz, $OC\underline{H}_2Me$), 5.77 (1H, br d, J = 16 Hz, $=C\underline{H}CO_2Et$), 6.48 (1H, s, ArH), 6.59 (1H, s, ArH), 7.02 (1H, dt, J = 7, 16 Hz, $C\underline{H}=CHCO_2Et$), 7.30 (5H, s, ArH). High-resolution MS Calcd for $C_{24}H_{29}NO_9$: 395.2095. Found: 395.2166.

3,4-Dihydro-6,7-dimethoxy-2-(3,3-ethylenedioxypropyl)isoquinolinium Bromide (7)——2-(2-Bromoethyl)-1,3-dioxolane (1.9 g, 10.47 mmol) was added to a solution of 3,4-dihydro-6,7-dimethoxyisoquinoline[6] (2 g, 10.47 mmol) in dry ether–ethanol (30 ml, 2 : 1). The solution thus obtained was heated under reflux for 20 h. The precipitated iminium salt was collected by filtration, washed with ether, and dried over silica gel under reduced pressure. The yield was 3.5 g (90%). This iminum salt (**7**) was very hygroscopic and was used in the subsequent reaction without further

purification. IR (Nujol): 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.8 (2H, m, $NCH_2C\underline{H}_2$), 3.83 (3H, s, OMe), 3.93 (3H, s, OMe), 4.26 (2H, t, J=6 Hz, $NC\underline{H}_2CH_2$), 5.0 (1H, t, J=3.2 Hz, $-C\underline{H}<^{O}_{O}$]), 6.90 (1H, s, ArH), 7.67 (1H, s, ArH), 9.70 (1H, s, –CH=N).

Ethyl 4-[6,7-Dimethoxy-2-(3,3-ethylendioxypropyl)-1,2,3,4-tetrahydro-1-isoquinolyl]crotonate (8)——Ethyl 4-bromocrotonate (5.48 g, 28.2 mmol) was dissolved in a solution of **7** (3.5 g, 9.4 mmol) in dry acetonitrile (30 ml), then activated zinc powder (3.05 g, 47.05 mmol) was added under an argon atmosphere at 0 °C. The temperature was gradually raised to room temperature and stirring was continued for 2 d. The reaction mixture was poured into saturated aqueous $NaHCO_3$, filtered, and extracted with CH_2Cl_2. The extract was dried over anhydrous K_2CO_3. After removal of the solvent, the residue was purified by column chromatography on SiO_2 (benzene–CH_2Cl_2 (9 : 1)) to give **8** (3.4 g, 90%) as a yellow oil. MS m/z: 405 (M^+). IR (film): 1715 (ester CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.67—2.07 (2H, m), 2.40—3.03 (8H, m), 3.86 (6H, s, OMe), 3.90 (4H, s, $OC\underline{H}_2C\underline{H}_2O$), 4.22 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.00 (1H, t, J=5 Hz, $\underline{H}\times^{O}_{O}$]), 5.85 (1H, br d, J=16 Hz, $=C\underline{H}CO_2Et$), 6.52 (1H, s, ArH), 6.59 (1H, s, ArH), 7.13 (1H, dt, J=7, 16 Hz, $C\underline{H}=CHCO_2Et$). High-resolution MS Calcd for $C_{22}H_{31}NO_6$: 405.2150. Found: 405.2106.

Ethyl 4-(6,7-Dimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl)crotonate (5)——Aqueous oxalic acid (20%, 4 ml) was added to a solution of **8** (0.101 g, 0.25 mmol) in ethanol (2 ml), and the mixture was heated under reflux with stirring for 20 h. The reaction mixture was basified with saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2. The extract was dried over anhydrous K_2CO_3. After removal of the solvent, the residue was subjected to column chromatography on SiO_2(CH_2Cl_2) to afford **5** (0.062 g, 82%) as a yellow oil. MS m/z: 305 (M^+). IR (film): 3325 (NH), 1710 (ester CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 2.50—3.30 (6H, m), 1.83 (1H, br s, NH), 3.83 (6H, s, OMe×2), 4.20 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.93 (1H, br d, J=16 Hz, $=C\underline{H}CO_2Et$), 6.60 (2H, br s, ArH), 7.03 (1H, dt, J=16, 7 Hz, $C\underline{H}=CHCO_2Et$). High-resolution MS Calcd for $C_{17}H_{23}NO_4$: 305.1626. Found: 305.1616.

Ethyl 4-(2-Acetoacetyl-6,7-dimethoxy-1,2,3,4-tetrahydro-1-isoquinolyl)crotonate (9)——Diketene (0.29 g, 3.48 mmol) was added to a solution of **5** (1.06 g, 3.48 mmol) in dry Et_2O (50 ml) with stirring at 0 °C. After standing for 2 h at room temperature, the solvent was evaporated off. The residue was subjected to column chromatography on SiO_2 (CH_2Cl_2–benzene (1 : 1)) to afford **9** (1.14 g, 84%) as a yellow oil. MS m/z: 389 (M^+). IR (film): 1720 (ester CO), 1640 (amide CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 2.25 (3H, s, COMe), 2.50—3.00 (4H, m), 3.60 (2H, s, $COC\underline{H}_2COMe$), 3.85 (6H, s, OMe×2), 4.15 (2H, q, J=7 Hz, OCH_2Me), 5.75 (1H, br d, J=16 Hz, $=C\underline{H}CO_2Et$), 6.60 (2H, br s, ArH), 7.06 (1H, dt, J=7, 16 Hz, $C\underline{H}=CHCO_2Et$). High-resolution MS Calcd for $C_{21}H_{27}NO_6$: 389.1837. Found: 389.1849.

3α-Acetyl-9,10-dimethoxy-2β-ethoxycarbonylmethyl-1,2,3,6,7,11bα-hexahydrobenzo[*a*]quinolizin-4-one (10)——Sodium (0.052 g, 2.26 mmol) was dissolved in dry EtOH (30 ml), and to this solution was added a solution of **9** (0.84 g, 2.16 mmol) in dry EtOH (10 ml) at 0 °C. The mixture was stirred for 1.5 h at room temperature, then the solvent was evaporated off. The residue was triturated with H_2O (20 ml) and extracted with benzene. After removal of the solvent, the residue was subjected to column chromatography on SiO_2 (CH_2Cl_2) to afford **10** (0.526 g, 63%) as a pale yellow oil. MS m/z: 389 (M^+). IR (film) 1728 (ester CO), 1630 (amide CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 2.43 (3H, s, COMe), 3.53 (1H, d, J=10 Hz, $COC\underline{H}CO$), 3.89 (6H, s, OMe×2), 4.18 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.72 (2H, m, C_{11b}-H and C_6-H_{eq}), 6.80 (1H, s, ArH), 6.82 (1H, s, ArH). High-resolution MS Calcd for $C_{21}H_{27}NO_6$: 389.1837. Found: 389.1782.

9,10-Dimethoxy-3α-(1,1-ethylenedithioethyl)-2β-ethoxycarbonylmethyl-1,2,3,6,7,11bα-hexahydrobenzo[*a*]quinolizin-4-one (11)——A mixture of **10** (0.1 g, 0.257 mmol) and ethanedithiol (0.5 ml, 3.74 mmol) in trifluoroacetic acid (3 ml) was heated under reflux for 3 h. After removal of the solvent, the residue was subjected to column chromatography on SiO_2 (CH_2Cl_2–benzene (3 : 1)) to give **11** (0.085 g, 71%) as a pale yellow oil. MS m/z: 465 (M^+). IR (film): 1730 (ester CO), 1632 (amide CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.98 (3H, s, CMe), 2.10—3.00 (8H, m), 3.48 (1H, d, J=10 Hz, $COCH<$), 3.80 (6H, s, OMe×2), 4.20 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.67—5.08 (2H, m, C_6-H_{eq} and C_{11b}-H), 6.70 (1H, s, ArH), 6.72 (1H, s, ArH). High-resolution MS Calcd for $C_{23}H_{31}NO_5S_2$: 465.1642. Found: 465.1675.

9,10-Dimethoxy-2β-ethoxycarbonylmethyl-3α-ethyl-1,2,3,6,7,11bα-hexahydrobenzo[*a*]quinolizin-4-one (12)——A mixture of a solution of **11** (0.12 g, 0.258 mmol) in dry EtOH (30 ml) and Raney nickel (W-2, 3.0 g) was heated under reflux. After 2 h, the Raney nickel was filtered off through celite. The filtrate was concentrated *in vacuo* and the residue was subjected to column chromatography on SiO_2 (CH_2Cl_2–benzene (3 : 1)) to afford **12** (0.088 g, 91%) as a colorless oil. MS m/z: 375 (M^+). IR (film): 1730 (ester CO), 1632 (amide CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.28 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.95—3.10 (11H, m), 3.88 (6H, s, OMe×2), 4.19 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 4.60—4.94 (2H, m, C_6-H_{eq} and C_{11b}-H), 6.62 (1H, s, ArH), 6.64 (1H, s, ArH). High-resolution MS Calcd for $C_{21}H_{29}NO_5$: 375.2044. Found: 375.2027.

9,10-Dimethoxy-2β-ethoxycarbonylmethyl-3α-ethyl-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizine (13)——A mixture of **12** (0.1 g, 0.26 mmol) and triethyloxonium fluoroborate[10] (0.788 g, 1.6 mmol) was heated under reflux for 24 h. After removal of the solvent, the residue was dissolved in dry EtOH (6 ml). To this solution, $NaBH_4$ (0.066 g, 1.76 mmol) was added in small portions at 0 °C and stirring was continued for 24 h at room temperature. The mixture was diluted with H_2O and then extracted with CH_2Cl_2. The extract was washed with brine, dried over K_2CO_3, and

concentrated *in vacuo* to leave an oil which was subjected to column chromatography on SiO_2 with AcOEt–benzene (3 : 2) as an eluent. From the early part of the eluate, **12** (0.01 g, 16%) was recovered. From the later part, **13** (0.51 g, 54%) was obtained. All spectral data for **13** were identical with those of an authentic sample.[11]

(±)-Protoemetinol (2)——A solution of **12** (0.122 g, 0.325 mmol) in dry Et_2O–dioxane (1 : 1) (10 ml) was added dropwise to a stirred, ice-cooled suspension of $LiAlH_4$ (0.17 g, 4.48 mmol) in dry ether (10 ml). After the mixture had been heated under reflux for 2.5 h, 10% aqueous NaOH was added under ice-cooling. The supernatant ethereal solution was separated from the resulting insoluble inorganic materials by decantation, dried over anhydrous K_2CO_3, and concentrated to afford **2** (0.08 g, 67%) as a pale yellow oil. All spectral data were identical with those of an authentic sample.[9]

Ethyl 4-[6,7-Dimethoxy-2-(3-oxobutyl)-1,2,3,4-tetrahydro-1-isoquinolyl]crotonate (14)——Methyl vinyl ketone (0.012 g, 0.17 mmol) was dissolved in a solution of **5** (0.05 g, 0.16 mmol) in dry Et_2O (3 ml) with stirring at 0 °C. After standing for 2 h at room temperature, the solvent was evaporated off. The residue was subjected to column chromatography on SiO_2 (AcOEt–benzene (2 : 3)) to give **14** (0.057 g, 92%) as a pale yellow oil. MS *m/z*: 375 (M^+). IR (film): 1710 (ester and ketone CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 2.26 (3H, s, COMe), 2.41—3.40 (10H, m), 3.50—3.80 (1H, m, C_{11b}-H), 3.83 (6H, s, OMe × 2), 4.18 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.79 (1H, br d, J=16 Hz, $C\underline{H}$=$CHCO_2Et$), 6.48 (1H, s, ArH), 6.56 (1H, s, ArH). High-resolution MS Calcd for $C_{21}H_{29}NO_5$: 375.2044. Found: 375.2075.

3α-Acetyl-9,10-dimethoxy-2β-ethoxycarbonylmethyl-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizine (15)——A mixture of **14** (0.26 g, 0.7 mmol) and pyrrolidine (0.05 g, 0.7 mmol) in dry THF was stirred for 15 h at room temperature. After removal of the solvent, the residue was subjected to column chromatography on SiO_2 (AcOEt–benzene (1 : 1)) to afford **15** (0.2 g, 80%) as a colorless powder, mp 95—98 °C. MS *m/z*: 375 (M^+). IR (film): 1728 (ester CO), 1710 (ketone CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.19 (3H, s, COMe), 1.80—3.05 (11H, m), 3.22 (1H, d, J=10 Hz, C_{11b}-H), 3.54 (6H, s, OMe × 2), 3.84 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 6.27 (1H, s, ArH), 6.33 (1H, s, ArH). *Anal.* Calcd for $C_{21}H_{29}NO_5$: C, 67.18; H, 7.79; N, 3.37. Found: C, 66.91; H, 7.72; N, 3.56.

9,10-Dimethoxy-2β-ethoxycarbonylmethyl-3α-(1,1-ethylenedithioethyl)-1,3,4,6,7,11bα-hexahydro-2*H*-benzo[*a*]quinolizine (16)——A mixture of **15** (0.1 g, 0.27 mmol), and ethanedithiol (0.5 ml, 3.74 mmol) in trifluoroacetic acid was heated under reflux for 4 h. After removal of the solvent, the residue was basified with 10% aqueous NaOH and then extracted with benzene. The organic solution was washed with brine, dried over anhydrous K_2CO_3, and concentrated to leave an oil, which was subjected to column chromatography on SiO_2 (AcOEt–benzene (1 : 4)) to give **16** (0.083 g, 69%) as a pale yellow oil. MS *m/z*: 451 (M^+). IR (film): 2840 and 2760 (*trans*-quinolizidine ring),[20] 1720 (ester CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.77 (3H, s, $\underset{S}{\overset{S}{>}}C$–Me), 1.95—3.60 (17H, m), 3.82 (6H, s, OMe × 2), 4.22 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 6.60 (1H, s, ArH), 6.64 (1H, s, ArH). High-resolution MS Calcd for $C_{23}H_{33}NO_4S_2$: 451.1849. Found: 451.1823.

Desulfurization of 16——A mixture of **16** (0.066 g, 0.146 mmol) and Raney nickel (W-2, 0.9 g) in EtOH (15 ml) was heated under reflux for 2 h. The Raney nickel was filtered off through celite and the filtrate was concentrated *in vacuo*. The residue was chromatographed on SiO_2 (CH_2Cl_2) to give **13** (0.04 g, 76%) as a colorless oil. All spectral data were identical with those of an authentic sample.[11]

2-[2-(*N*-Benzyltrifluoroacetamido)ethyl]-1,3-dioxolane (17)——2-(2-Bromoethyl)-1,3-dioxolane (21.4 g, 0.12 mol) was added to a solution of NaH (60% oil suspension) (5.12 g) and *N*-benzyltrifluoroacetamide (20 g, 0.099 mol) in dry benzene–DMF (5 : 1, 120 ml) under an argon atmosphere with stirring at 60 °C. The mixture was heated under reflux for 20 h, and then cautiously poured into ice-water and extracted with benzene. The organic phase was washed with saturated brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by distillation, 155—170 °C/0.1 mmHg, to afford **17** (28.3 g, 89% yield). MS *m/z*: 304 (M^+ + 1). IR (film): 1690 (amide CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.17 (2H, m, $NCH_2C\underline{H}_2$), 3.33—3.67 (2H, m, $NC\underline{H}_2CH_2$), 3.76—4.03 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 4.68 (2H, s, $NC\underline{H}_2Ar$), 4.90 (1H, t, J=4.2 Hz, $\underset{O}{\overset{O}{>}}CH$–), 7.17—7.57 (5H, m, ArH). *Anal.* Calcd for $C_{14}H_{16}F_3NO_3$: C, 55.45; H, 5.32; N, 4.62. Found: C, 55.52; H, 5.37; N, 4.70.

3-(*N*-Benzyltrifluoroacetamido)propionaldehyde (18)——Aqueous oxalic acid (20%, 30 ml) was added to a solution of **17** (10 g, 3.3 mmol) in THF (100 ml) and the reaction mixture was heated under gentle reflux for 48 h. The reaction mixture was concentrated under reduced pressure and extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was subjected to column chromatography on SiO_2 (CH_2Cl_2–benzene (1 : 1)) to give **18** (5.8 g, 68%) as a colorless oil. MS *m/z*: 259 (M^+). IR (film): 1690 (amide CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.72 (2H, t, J=6 Hz, $NCH_2C\underline{H}_2$), 3.56 (2H, t, J=6 Hz, $NC\underline{H}_2CH_2$), 4.67 (2H, br d, J=4.5 Hz, NCH_2Ar), 7.07—7.53 (5H, m, ArH). High resolution MS Calcd for $C_{12}H_{12}F_3NO_2$: 259.08193. Found: 259.0811.

Ethyl 5-(*N*-Benzyltrifluoroacetamido)-2-pentenoate (19)——Ethyl (triphenylphosphoranylidene)acetate[15] (13 g, 37.3 mmol) was added to a solution of **18** (9.67 g, 37.3 mmol) in dry CH_2Cl_2 (100 ml) in one portion with stirring at 0 °C. After being stirred for 2 h at room temperature, the reaction mixture was concentrated to leave a syrup, which

was subjected to column chromatography on SiO_2 (benzene) to give **19** (10.45 g, 85%) as a colorless oil. MS *m/z*: 329 (M^+). IR (film): 1720 and 1655 (unsaturated ester CO), 1690 (amide CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J= 7.5 Hz, $OCH_2\underline{Me}$), 2.30—2.72 (2H, m, $NCH_2C\underline{H}_2$), 3.30—3.67 (2H, m, $NC\underline{H}_2CH_2$), 4.25 (2H, q, J=7.5 Hz, $OC\underline{H}_2Me$), 4.73 (2H, d, J=6 Hz, $NC\underline{H}_2Ar$), 5.85 (1H, dt, J=16.5, 1.5 Hz, CH=C$\underline{H}$CO), 6.91 (1H, dt, J=16.5, 6 Hz, C$\underline{H}$=CHCO), 7.20—7.62 (5H, m, ArH). High-resolution MS Calcd for $C_{16}H_{18}F_3NO_3$: 329.12376. Found: 329.1207.

Ethyl 5-Benzylamino-2-pentenoate (20)——Aqueous K_2CO_3 (5%, 10 ml) was added to a solution of **19** (2.25 g, 6.84 mmol) in ethanol (30 ml), and the reaction mixture was stirred for 6 h at room temperature, then concentrated under reduced pressure below room temperature and extracted with CH_2Cl_2. The organic solution was washed with brine, dried over anhydrous K_2CO_3, and concentrated *in vacuo*. The residue was subjected to column chromatography on SiO_2 to give **20** (1.7 g, 92%) as a pale yellow oil. MS *m/z*: 234 (M^++1). IR (film): 1720 and 1640 (unsaturated ester CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.5 Hz, $OCH_2\underline{Me}$), 1.47 (1H, s, NH), 2.23—2.63 (2H, m, $C\underline{H}_2CH$=), 2.82 (2H, t, J=6 Hz, $NCH_2C\underline{H}_2$), 3.86 (2H, s, $ArC\underline{H}_2$), 4.25 (2H, q, J=7.5 Hz, $OC\underline{H}_2Me$), 5.95 (1H, dt, J=16, 1.5 Hz, CHC=C$\underline{H}$CO), 7.03 (1H, dt, J=16, 6 Hz, C$\underline{H}$=CHCO), 7.40 (5H, br s, ArH). *Anal.* Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21: N, 6.00. Found: C, 71.81, H, 8.07; N, 6.30.

Ethyl 5-(*N*-Benzyl-3-oxo-butylamino)-2-pentenoate (21)——Methyl vinyl ketone (0.4 g, 6.8 mmol) was added to a solution of **20** (1.32 g, 5.67 mmol) in dry CH_2Cl_2 (20 ml) with stirring at room temperature and the stirring was continued for 2 h. The solution was concentrated to leave **21** (1.7 g, 99%), which was subjected to the next reaction without further purification. MS *m/z*: 304 (M^++1). IR (film): 1710 and 1650 (unsaturated ester CO), 1690 (amide CO and ketone CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 2.06 (3H, s, COMe), 2.23—2.96 (8H, m), 3.53 (2H, s, $ArC\underline{H}_2$), 4.15 (2H, q, J=7 Hz, $OC\underline{H}_2Me$), 5.75 (1H, dt, J=16, 1.5 Hz, CH=C$\underline{H}$CO), 6.80 (1H, dt, J=16, 6 Hz, C$\underline{H}$=CHCO), 7.20 (5H, br s, ArH). High-resolution MS Calcd for $C_{18}H_{25}NO_3$: 303.1833. Found: 303.1768.

Ethyl *trans*-3-Acetyl-1-benzyl-4-piperidineacetate (22)——A mixture of **21** (0.67 g, 2.21 mmol) and pyrrolidine (0.16 g, 2.21 mmol) in THF (10 ml) was stirred at room temperature for 12 h. After removal of the solvent, the residue was subjected to column chromatography on SiO_2 (CH_2Cl_2) to afford **22** (0.537 g, 80%) as a colorless oil. MS *m/z*: 303 (M^+). IR (film): 1730 (ester CO), 1710 (ketone CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, J=7.1 Hz, $CO_2CH_2\underline{Me}$), 1.3—1.5 (1H, m, C_5-H_{ax}), 1.7—1.9 (2H, m), 2.06—2.23 (1H, m), 2.13 (3H, s, COMe), 2.31 (1H, dd, J=18.5, 8.2 Hz, C(H)$\underline{H}CO_2Et$), 2.64 (1H, dt, J=10.3, 4.1 Hz), 2.8—2.9 (1H, m, C_6-H_{eq}), 2.95 (1H, dq, J=11.0, 2.7 Hz, C_2-H_{eq}), 3.50 (2H, s, $ArC\underline{H}_2$), 4.10 (2H, q, J=7.1 Hz, $OC\underline{H}_2Me$), 7.2—7.3 (5H, m, ArH). *Anal.* Calcd for $C_{18}H_{25}NO_5$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.14; H, 8.35; N, 4.64.

Ethyl *trans*-3-Acetyl-1-methoxycarbonyl-4-piperidineacetate (23)——A mixture of **22** (0.058 g, 0.19 mmol) and methyl chloroformate (0.022 g, 0.23 mmol) in dry benzene (5 ml) was heated at 60 °C for 12 h. After removal of the solvent, the residue was subjected to column chromatography on SiO_2 (benzene) to give **23** (0.048 g, 93%) as a colorless oil. MS *m/z*: 272 (M^++1). IR (film) 1730 (ester CO), 1700 (carbamate CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7.1 Hz, $CO_2CH_2\underline{Me}$), 1.13—1.36 (1H, m, C_5-H_{ax}), 1.81 (1H, dq, J=13.4, 2.9 Hz, C_5-H_{eq}), 2.15 (1H, dd, J= 15.6, 9.2 Hz, C(H)$\underline{H}CO_2Et$), 2.25 (3H, s, COMe), 2.32 (1H, dd, J=15.6, 4.2 Hz, C(H)$\underline{H}CO_2Et$), 2.57 (1H, dt, J=10.4, 3.4 Hz, C_3-H), 2.6—2.9 (2H, m, C_2-H_{ax} and C_6-H_{ax}), 3.73 (3H, s, NCO_2Me), 4.13 (2H, q, J=7.1 Hz, $CO_2C\underline{H}_2Me$), 4.1—4.4 (2H, br, C_2-H_{eq} and C_6-H_{eq}). *Anal.* Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.44; H, 7.86; N, 4.89.

Ethyl *trans*-3-(1,1-Ethylenedithio)ethyl-1-methoxycarbonyl-4-piperidineacetate (24)——A mixture of **23** (0.1 g, 0.37 mmol) and ethanedithiol (0.23 g, 3.67 mmol) in trifluoroacetic acid (3 ml) was heated under reflux for 3 h. After removal of the solvent, the residue was subjected to column chromatography on SiO_2 (benzene) to afford **24** (0.105 g, 81%) as a colorless oil. MS *m/z*: 347 (M^+). IR (film): 1725 (ester CO), 1700 (carbamate CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7 Hz, $CO_2CH_2\underline{Me}$), 1.48—1.62 (1H, m, C_5-H_{ax}), 1.78 (3H, s, >CMe), 1.85—2.05 (2H, m), 2.3—2.5 (2H, m), 2.6—2.8 (1H, m), 3.2—3.4 (4H, m, $SC\underline{H}_2C\underline{H}_2S$), 3.5—3.7 (1H, m, C_6-H_{eq}), 3.71 (3H, s, CO_2Me), 3.95—4.15 (1H, m, C_2-H_{eq}), 4.14 (2H, q, J=7 Hz, $CO_2C\underline{H}_2Me$). *Anal.* Calcd for $C_{15}H_{25}NO_4S_2$: C, 51.71; H, 7.18; N, 3.88. Found: C, 51.85; H, 7.25; N, 4.03.

Ethyl *trans*-3-Ethyl-1-methoxycarbonyl-4-piperidineacetate (25)——A mixture of **24** (0.05 g, 0.144 mmol) and Raney nickel (W-2, 1.53 g) in dry ethanol (20 ml) was heated under reflux for 2 h. The Raney nickel was filtered off through celite and the filtrate was evaporated *in vacuo*. The residue was subjected to column chromatography on SiO_2 (CH_2Cl_2) to afford **25** (0.031 g, 84%) as a colorless oil. MS *m/z*: 257 (M^+). IR (film) 1730 (ester CO), 1700 (carbamate CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=7 Hz, $CCH_2\underline{Me}$), 1.1—1.15 (3H, m), 1.26 (3H, t, J=7 Hz, $OCH_2\underline{Me}$), 1.50—1.65 (1H, m), 1.7—1.8 (1H, m), 2.07 (1H, dd, J=15, 8 Hz, C(H)$\underline{H}CO_2Et$), 2.56 (1H, dd, J=15, 4 Hz, C(H)$\underline{H}CO_2Et$), 2.75—2.90 (1H, m), 3.68 (3H, s, NCO_2Me), 3.9—4.1 (1H, m, C_2-H_{eq}), 4.13 (2H, q, J=7 Hz). *Anal.* Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.52; H, 9.06; N, 5.38.

Ethyl *trans*-3-Ethyl-4-piperidineacetate (26)——Compound **25** (19 mg, 0.074 mmol) was dissolved in acetic acid saturated with hydrogen bromide (1 ml). A mixture was stirred at room temperature for 18 h. The reaction mixture was made alkaline with saturated aqueous K_2CO_3 and concentrated to leave an orange oil. The oil was purified by vacuum distillation, giving **26** (13.8 mg, 94%) as a colorless oil, bp 90—95 °C (bath) (0.5 mmHg) (lit.[19] bp 87 °C (2 mmHg)). MS *m/z*: 199 (M^+). IR (film): 1730 (ester CO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, t, J=7.1 Hz,

$CHCH_2\underline{Me}$), 1.26 (3H, t, $J=7.1$ Hz, $COCH_2\underline{Me}$), 4.13 (2H, q, $J=7.1$ Hz, $COC\underline{H}_2Me$).

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References and Notes

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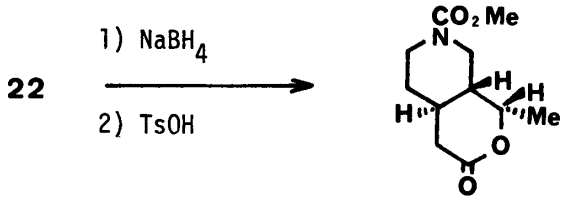

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