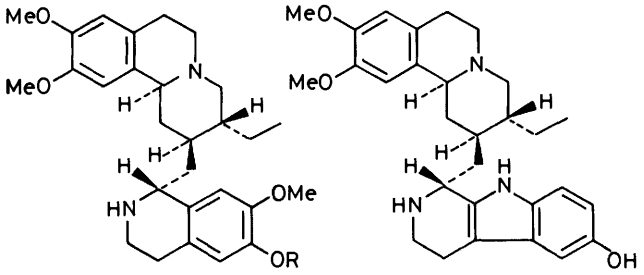
Asymmetric Total Synthesis of (−)-Protoemetinol, (−)-Protoemetine, (−)-Emetine, and (−)-Tubulosine by Highly Stereocontrolled Radical Cyclisations

Masataka Ihara, Ken Yasui, Nobuaki Taniguchi, and Keiichiro Fukumoto*
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

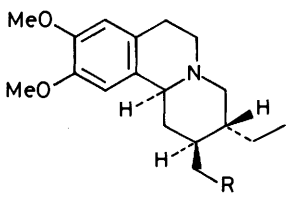
Both enantiomers of the menthyl half-esters (**10**) and (**23**) of ethylmalonic acid were converted into (+)-(4*S*,5*R*)-4-(2-benzyloxyethyl)-5-ethyl-3,4,5,6-tetrahydro-2-pyrone (**18**). A mixture of the *trans*-(**18**) and *cis*-lactones (**19**) in a ratio of *ca.* 4:1 was prepared by way of radical cyclisation of the (*E*)-α,β-unsaturated esters (**16**), while the former (**18**) was synthesised with high stereoselection by the cyclisation of the (*Z*)-esters (**26**). The lactone (**18**) was enantioselectively transformed into (−)-protoemetinol (**5**) and (−)-protoemetine (**4**), correlated to (−)-emetine (**1**) and (−)-tubulosine (**3**).

Although various approaches have been devised for the synthesis of emetine (**1**),[1,2] considerable attention is still paid to novel methodologies for the assembly of its ring system because both of its medicinal activity and structural similarity with indole alkaloids. We envisioned that the *trans*-substituted valerolactone (**6**) would be a potential synthetic intermediate of emetine (**1**) and a number of structurally related alkaloids. For example, the lactone (**6**) would be convertible, by standard manipulation, into protoemetinol (**5**) and protoemetine (**4**), and thence transformed into emetine (**1**),[3,4] cephaeline (**2**),[3] and tubulosine (**3**).[5] It was further considered that the lactone (**6**) could be constructed *via* the radical cyclisation of the bromoacetal (**7**), which could be derived from the chiral propane-1,3-diol derivative (**8**). Recently the enantioselective generation of the chiral building block (**8**) was developed by us[6] through crystallisation-induced asymmetric transformation of the chiral half-ester prepared from ethylmalonic acid (**9**). A highly stereocontrolled synthesis of the *trans*-substituted lactone (**6**) was realised by radical cyclisation of the (*Z*)-isomer



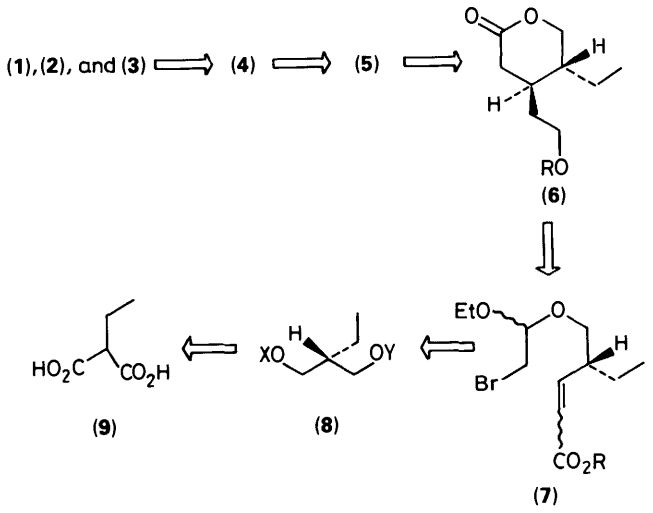
(**1**) R = Me
(**2**) R = H

(**3**)



(**4**) R = CHO
(**5**) R = CH_2OH

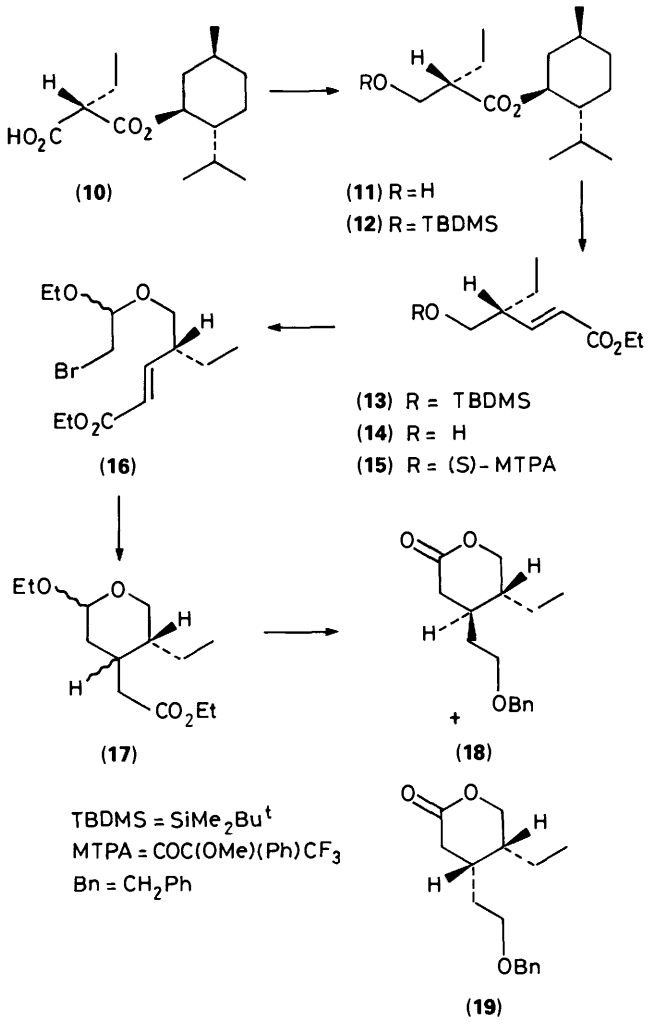
Scheme 1.



Scheme 2.

of (**7**) and we describe here an asymmetric synthesis of (−)-protoemetinol (**5**) and (−)-protoemetine (**4**), correlated to (−)-cephaeline (**2**),[3] (−)-emetine (**1**),[3,4] and (−)-tubulosine (**3**).[5,7]

The last decade has seen the emergence of free-radical-mediated cyclisation as a highly versatile and often indispensable method for bond formation.[8] Although the formation of five-membered rings has been utilized in the synthesis of a number of natural products, relatively few investigations[9] have been carried out on the formation of six-membered ring systems. We first examined 1,2-asymmetric induction in the construction of six-membered rings by radical cyclisation of the (*E*)-α,β-unsaturated esters (**16**). The substrates (**16**) of the crucial step were prepared starting from ethylmalonic acid (**9**). Condensation of ethylmalonic acid with (+)-menthol in the presence of dicyclohexylcarbodi-imide (DCC) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP)[10] gave a diastereoisomeric mixture of the half-esters as an oily product, which slowly solidified to provide the single stereoisomer (**10**).[6] The resulting half-ester (**10**) was converted into the t-butyldimethylsilyl (TBDMS) ether (**12**) *via* the primary alcohol (**11**) as described previously.[6] Reduction of the ester function of (**12**) using di-isobutylaluminium hydride (DIBAL) in dimethoxyethane (DME) at −78 °C, followed by Wittig reaction of the resulting aldehyde with (ethoxycarbonylmethylene)triphenylphosphorane provided the (*E*)-α,β-unsaturated ester (**13**) in



Scheme 3.

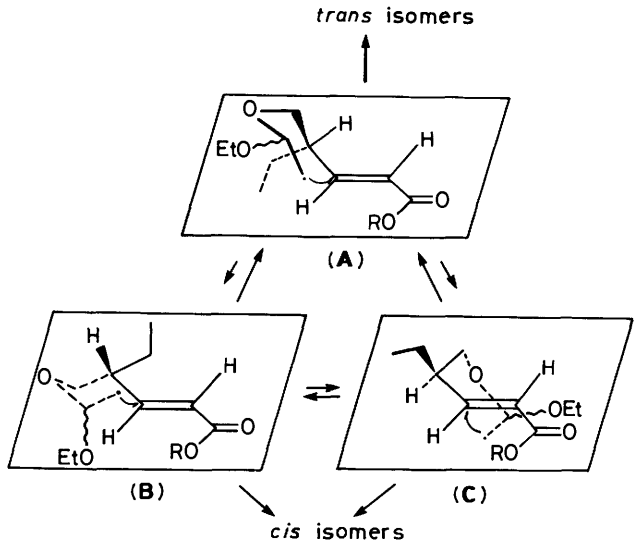
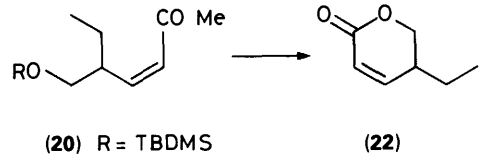


Figure 1. Transition states of radical cyclisation of the (*E*)-isomers (**16**).



Scheme 4.

73% overall yield for two steps. Deprotection of the TBDMS group of (**13**) was carried out with tetrabutylammonium fluoride to afford, in 98% yield, the alcohol (**14**), whose optical purity (>98% e.e) was determined by 500 MHz ^{1}H NMR spectroscopy after conversion into the (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetate (**15**). Treatment of the alcohol (**14**) with ethyl vinyl ether and *N*-bromosuccinimide [11] furnished the substrates (**16**) for the key reaction in 94% yield. The radical cyclisation was performed by heating the bromoacetals (**16**) in the presence of tributyltin hydride and α,α′-azoisobutyronitrile (AIBN) in benzene. The tetrahydropyran derivatives (**17**) were obtained in 96% yield as a mixture of four diastereoisomers. Reduction of the diasteroisomeric mixture of (**17**) with lithium aluminium hydride, followed by benzylation of the resulting alcohols using benzyl bromide in the presence of sodium hydride produced the corresponding benzyl ethers in 70% overall yield for two steps. A mixture of the two lactones (**18**) and (**19**) was gained in 70% overall yield in a ratio of *ca.* 4:1 by successive treatments; hydrolysis of the acetal function followed by Jones oxidation of the resulting cyclic hemiacetals. Separation of the two stereoisomers (**18**) and (**19**) was carried out using HPLC. It was supposed from a consideration of the reaction mechanism that the major product, $[\alpha]_D^{24}$ +17.46° (*c* 1.75 in $CHCl_3$), would be the desired *trans*-substituted lactone (**18**). Namely, three transition states (**A**,**B**,**C**) as shown in Figure 1 are possible for the radical cyclisation of the (*E*)-α,β-unsaturated esters (**16**). The transition state (**A**) leading to the *trans*-substituted pyrans would be favourable because considerable 1,3-allylic strain was expected for the other transition states (**B**) and (**C**) forming the *cis* isomers. However, the effect of the allylic strain would not be strong enough to achieve the complete stereoselection. We expected the selective formation of the *trans*-substituted isomers in the radical cyclisation of the (*Z*)-α,β-unsaturated esters as a result of energy differences, arising from allylic strain, in particular three conformations of the (*Z*)-isomers.

In order to prepare the (*Z*)-isomers of (**7**), 2-t-butyldimethylsiloxymethylbutan-1-ol was oxidised under Swern oxidation conditions to the corresponding aldehyde, which was then converted into the (*Z*)-α,β-unsaturated ester (**20**) in 80% overall yield for two steps according to the Still's method.[12] Formation of the lactone (**22**) readily occurred during the deblocking of the silyl group and none of the required alcohol (**21**) was formed. Therefore, the enantiomer (**23**)[6] of the half-ester was used as the starting material to prepare the correct enantiomers (**26**) of the (*Z*)-ester.

Reduction of the (−)-menthyl ester (**24**),[6] derived from (**23**), with DIBAL afforded the corresponding alcohol, which was subjected to reaction with 1,2-dibromoethyl ethyl ether in the presence of *N*,*N*-dimethylaniline,[13] followed by deprotection of the silyl group using tetrabutylammonium fluoride. The required alcohols (**25**), $[\alpha]_D^{26}$ +2.67° (*c* 2.36 in $CHCl_3$) were obtained in 89% overall yield for three steps. After Swern oxidation of the alcohols (**25**), the resulting aldehydes were transformed into the (*Z*)-α,β-unsaturated esters (**26**), $[\alpha]_D^{24}$ −30.38° (*c* 1.17 in $CHCl_3$) in 79% overall yield for two steps, according to the Still's procedure.[12] By the above conversion, the separable (*E*)-isomers were also obtained in 9.9% overall yield for two steps.

When the radical cyclisation was carried out using tributyltin hydride and irradiation with light at 254 nm at room

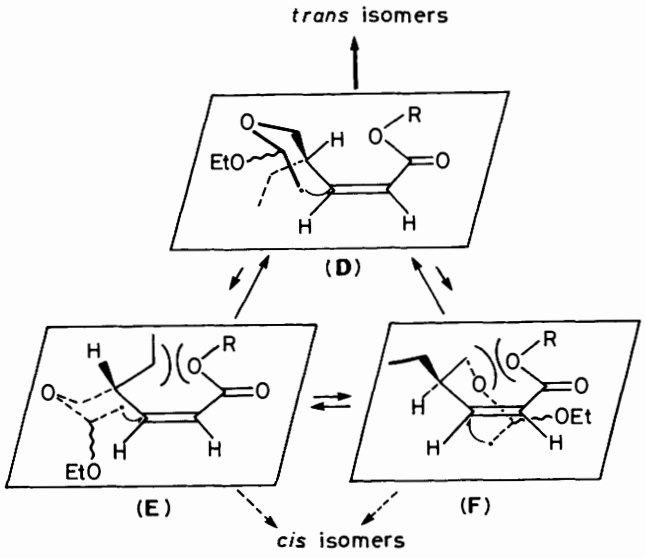
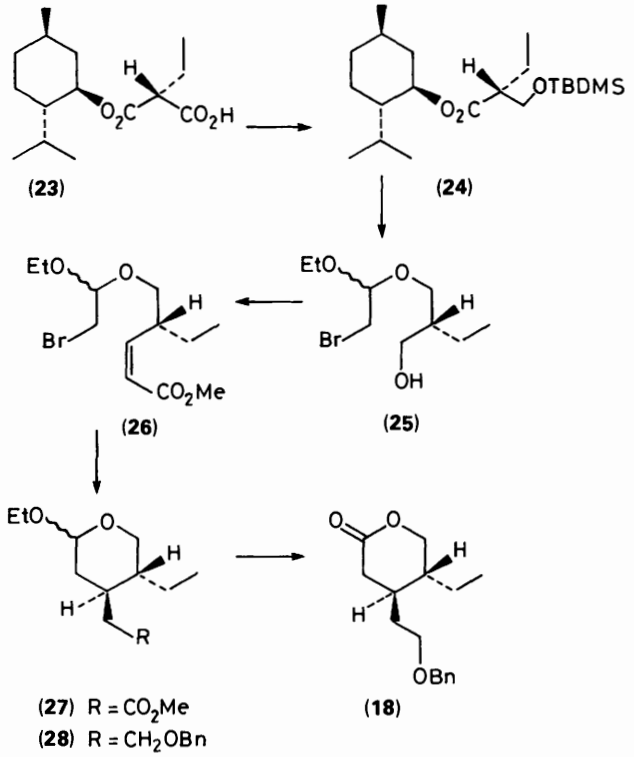


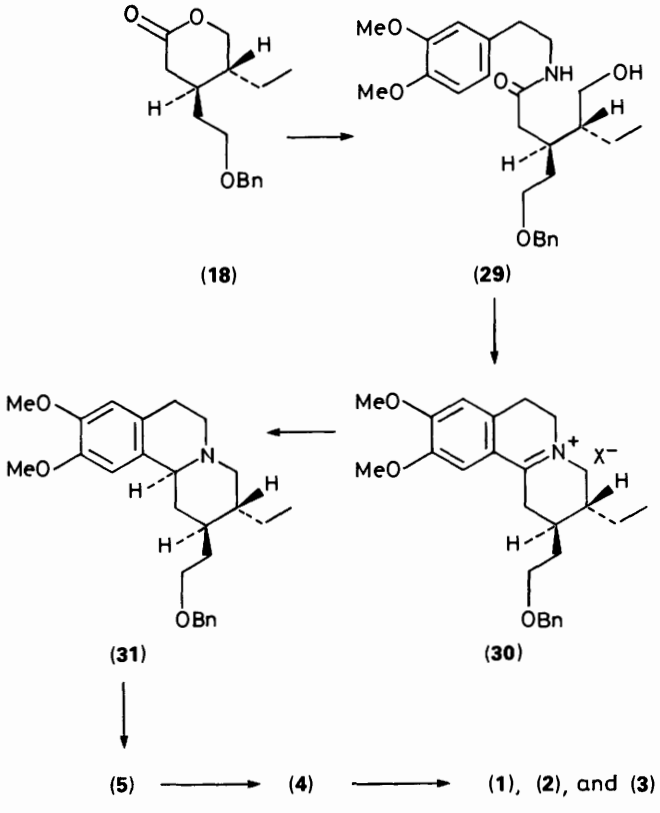
Figure 2. Transition states of radical cyclisation of the (*Z*)-isomers (**26**).

temperature or using tributyltin hydride in the presence of triethylborane[14] at 0 °C, the cyclic products (**27**) were obtained in 75 or 70% yield as a mixture of two diastereoisomers; however, there was considerable formation of by-products such as the debrominated compounds (**26**; Br = H). The (*Z*)-esters (**26**) when heated in the presence of tributyltin hydride and AIBN in benzene gave the best result and a mixture of the two diasteroisomers of (**27**) was formed in 97% yield. Reduction of the mixture of (**27**) with DIBAL, followed by benzylation of the resulting alcohols, provided the benzyl ethers (**28**) in 85% overall yield. Hydrolysis of (**28**) with dilute acetic acid at 60 °C gave the cyclic hemiacetals, which were oxidised using Fetizon reagent to give the lactone (**18**) in 78% overall yield for two steps. The product was a single stereoisomer, whose physical properties including specific rotation, $[\alpha]_D^{25}$ +16.80° (*c* 0.50 in $CHCl_3$), were consistent with those of the major product (**18**) derived from the (*E*)-isomers (**16**). Thus it was confirmed that no significant racemisation occurred during the above transformation. The highly selective formation of the *trans*-substituted pyrans (**27**) could be accounted for by the instability, as a result of allylic strain, in the transition states (**E**) and (**F**) which would lead to the *cis* isomers (see Figure 2).

Since the required *trans*-substituted valerolactone (**18**) is available as an optically pure form by a highly enantioselective synthesis, our attention focussed on the conversion of the lactone (**18**) into ipecacuanha alkaloids. The lactone (**18**) was heated with 3,4-dimethoxyphenethylamine at 155–165 °C to afford quantitatively the amide (**29**), $[\alpha]_D^{23}$ +6.04° (*c* 3.82 in $CHCl_3$), which was treated with hot phosphorus oxychloride. After conversion of the cyclised product into its perchlorate, catalytic hydrogenation of the resulting iminium salt (**30**) using Adams catalyst[4,15] provided the *trans*-quinolizidine (**31**) in 36% overall yield for two steps as a single diastereoisomer. Debenzylation of (**31**) using palladium(II) chloride in methanol–chloroform under a hydrogen atmosphere formed in 41% yield (−)-protoemetinol (**5**),[16] whose spectral data were identical with those of the authentic racemate.[2c] Hydrogenation of the above iminium salt (**30**) using the palladium catalyst furnished the mixture of (−)-protoemetinol (**5**) and its epimer at the 11b-position. Conversion of (**5**) into the perchlorate gave crystals, $[\alpha]_D^{24}$ −15.27° (*c* 0.26 in MeOH), m.p. 202–204 °C (lit.,[4] m.p. 199–200 °C). Transformation of (−)-protoemetinol (**5**) into (−)-protoemetine (**4**)[4] was accomplished in 51% yield by oxidation using dimethyl sulphoxide, trifluoroacetic anhydride, and triethylamine.[17] Spectral data for the labile product, $[\alpha]_D^{28}$ −14.38° (*c* 0.57 in EtOH) well supported the structure of (**4**). Since (−)-protoemetine (**4**) had been transformed into (−)-emetine (**1**),[3,4] (−)-cephaeline (**2**),[3] and (−)-tubulosine (**3**),[5] total synthesis of these alkaloids was also achieved in a formal sense.



Scheme 5.



Scheme 6.

Experimental

General Methods.—M.p.s were measured on a Yanako micromelting-point apparatus and are uncorrected. IR spectra were recorded for $CHCl_3$ solutions on a Hitachi 260-10 spectrophotometer. NMR spectra were measured for $CDCl_3$ solutions on JEOL JNM-PMX-60, JEOL-FX-90A, JEOL-PS-100, and JNM-GX-500 spectrometers. Chemical shifts are reported as δ_H relative to internal $SiMe_4$. Mass spectra were taken on JEOL-JMS-01SG-2 and JEOL-DX-300 spectrometers. Optical rotations were determined on a JASCO-DIP-340 polarimeter. All new compounds described in the Experimental section were homogeneous on TLC and HPLC. HPLC was carried out using a Gilson system and monitored by UV absorptions and refractive-index measurements.

(+)-(1S,3S,4R)-p-*Menthan*-3-*yl Hydrogen* (S)-*Ethylmalonate* (**10**).—To a stirred solution of ethylmalonic acid (10.0 g, 75.8 mmol), (+)-menthol (11.8 g, 75.8 mmol), and DMAP (100 mg, 0.82 mmol) in a mixture of MeCN (150 ml) and CH_2Cl_2 (150 ml) at −40 °C was added a solution of DCC (16.7 g, 81.1 mmol) in CH_2Cl_2 (150 ml) during 40 min. The mixture was stirred for 6 h at −40 °C and then for 10 h at room temperature. After evaporation, the residue was taken up into ether and the solution was filtered through Celite. The filtrate was evaporated to give a residue, which was partitioned between a small excess of dilute aqueous $NaHCO_3$ and Et_2O. The aqueous layer was further washed with Et_2O and then acidified with conc. HCl under ice cooling. After extraction with Et_2O several times, the combined extracts were dried (Na_2SO_4) and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with benzene–acetone (85:15, v/v) afforded the epimeric half-esters as an oil. The oily product was then set aside for 5 days at room temperature when it became crystalline and afforded (2S)-*half-ester* (**10**) (15.1 g, 74%), m.p. 67–70 °C (Found: C, 66.35; H, 9.95. $C_{15}H_{26}O_4$ requires C, 66.65; H, 9.7%); $[\alpha]_D^{25}$ + 43.57° (*c* 1.59 in $CHCl_3$); $\nu_{max.}$ 2 800–2 350 (OH) and 1 720 cm^{-1} (C=O); δ_H(500 MHz) 0.75 (3 H, d, *J* 7.4 Hz, CH*Me*), 0.89 (3 H, d, *J* 7.4 Hz, CH*Me*), 0.91 (3 H, d, *J* 7.4 Hz, CH*Me*), 1.00 (3 H, t, *J* 7.4 Hz, CH_2Me), 3.31 (1 H, t, *J* 7.4 Hz, OCOCH), and 4.75 (1 H, dt, *J* 4.3 and 11.3 Hz, 3-H); *m/z* 271 (M^+ + 1).

(+)-(1S,3S,4R)-p-*Menthan*-3-*yl* (2S)-2-*Hydroxymethylbutyrate* (**11**).—A mixture of the half-ester (**10**) (210 mg, 0.778 mmol) and oxalyl chloride (0.7 ml, 8.02 mmol) in dry CH_2Cl_2 (8 ml) was heated under reflux for 2 h and then evaporated with protection from moisture. A solution of the resulting residue in dry CH_2Cl_2 (2 ml) was added dropwise to a stirred solution of tetrabutylammonium borohydride (210 mg, 0.817 mmol) in dry CH_2Cl_2 (2 ml) at −78 °C and the mixture was stirred for 30 min at the same temperature. The same work-up and purification as in the case of the enantiomer[6] gave the (2S)-*alcohol* (**11**) (86.0 mg, 43%) as needles, m.p. 64–65 °C (Found: C, 70.0; H, 11.2. $C_{15}H_{28}O_3$ requires C, 70.25; H, 11.0%); $[\alpha]_D^{25}$ +60.12° (*c* 1.04 in $CHCl_3$); $\nu_{max.}$ 3 545 (OH) and 1 710 cm^{-1} (C=O); δ_H(100 MHz) 0.73 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.90 (4 H, d, *J* 7.2 Hz, 2 × CH*Me*), 0.94 (3 H, t, *J* 7.3 Hz, CH_2Me), 2.35–2.60 (1 H, m, OCOCH), 3.59–3.90 (2 H, m, OCH_2), and 4.68 (1 H, dt, *J* 4.5 and 10.6 Hz, 3-H); *m/z* 101 (M^+ − menthyloxy).

(+)-(1S,3S,4R)-p-*Menthan*-3-*yl* (2S)-2-(*t-Butyldimethylsiloxymethyl*)*butyrate* (**12**).—To a solution of the alcohol (**11**) (430 mg, 1.68 mmol), TBDMSCl (410 mg, 2.72 mmol), and DMAP (5.5 mg, 0.045 mmol) in a mixture of dry CH_2Cl_2 (5 ml) and dry DMF (4 ml) at 0 °C was added Et_3N (0.57 ml, 4.10 mmol), and the mixture was stirred for 10 h at room temperature. The same work-up and purification as for the enantiomer[6] gave the *ether* (**12**) (622 mg, 100%) as an oil (Found: C, 68.2; H, 11.35. $C_{21}H_{42}O_3Si$ requires C, 68.1; H, 11.35%); $[\alpha]_D^{27}$ +39.59° (*c* 1.45 in $CHCl_3$); $\nu_{max.}$ 1 720 cm^{-1} (C=O); δ_H(100 MHz) 0.02 (6 H, s, $SiMe_2$), 0.77 (3 H, d, *J* 7.2 Hz, CH*Me*), 0.85 (9 H, s, Bu^t), 0.87 (6 H, d, *J* 7.1 Hz, 2 × CH*Me*), 0.90 (3 H, t, *J* 7.2 Hz, CH_2Me), 2.30–2.57 (1 H, m, OCOCH), 3.67 (1 H, dd, *J* 9.8 and 19.9 Hz, C*H*HOTBDMS), 3.75 (1 H, dd, *J* 8.4 and 19.9 Hz, CH*H*OTBDMS), and 4.68 (1 H, dt, *J* 4.5 and 10.6 Hz, 3-H); *m/z* 371 (M^+ + 1).

(−)-*Ethyl* (4R)-(E)-4-*t-Butyldimethylsiloxymethylhex*-2-*enoate* (**13**).—To a stirred solution of the ester (**12**) (323 mg, 0.873 mmol) in a mixture of dry CH_2Cl_2 (2.5 ml) and DME (2.5 ml) at −78 °C was added dropwise 1M DIBAL in hexane (1.05 ml, 1.05 mmol), and the stirring was continued for 0.5 h at the same temperature. After addition of water (1.05 ml), the cooling bath was removed and then the resulting mixture was further stirred for 30 min at room temperature. The mixture was filtered through Celite and the filtrate, including the washings with Et_2O, was dried (Na_2SO_4) and evaporated to give a crude aldehyde; δ_H(60 MHz) 0.02 (6 H, s, $SiMe_2$), 0.81 (9 H, s, Bu^t), 3.75 (2 H, d, *J* 5.6 Hz, CH_2OTBDMS), and 9.52 (1 H, d, *J* 1.8 Hz, CHO), which was used for the next reaction without further purification.

A mixture of the above aldehyde and (ethoxycarbonylmethylene)triphenylphosphorane (304 mg, 0.874 mmol) in dry MeCN (6.7 ml) was stirred at room temperature for 10 h and heated under reflux for 2 h. After dilution with benzene, the mixture was washed successively with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4) and evaporated. Silica gel column chromatography of the residue with hexane–Et_2O (95:5, v/v) as eluant afforded the *ester* (**13**) (183 mg, 73% for two steps) (Found: C, 62.75; H, 10.75. $C_{15}H_{30}O_3Si$ requires C, 62.9; H, 10.55%); $[\alpha]_D^{29}$ −4.20° (*c* 1.57 in $CHCl_3$); $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ_H(90 MHz) 0.01 (6 H, s, $SiMe_2$), 0.86 (9 H, s, Bu^t), 0.73–0.95 (3 H, m, CH_2Me), 1.26 (3 H, t, *J* 7.4 Hz, OCH_2Me), 2.09–2.37 (1 H, m, C*H*Et), 3.55 (2 H, d, *J* 5.9 Hz, CH_2OTBDMS), 4.17 (2 H, q, *J* 6.9 Hz, OCH_2Me), 5.80 (1 H, dd, *J* 1.1 and 15.8 Hz, CHCH=C*H*), and 6.79 (1 H, dd, *J* 8.6 and 15.8 Hz, CHC*H*=CH); *m/z* 286 (M^+).

(−)-*Ethyl* (4R)-(E)-4-*Hydroxymethylhex*-2-*enoate* (**14**).—To a stirred solution of the above ester (**13**) (1.96 g, 6.85 mmol) in dry THF (20 ml) at 0 °C was added dropwise 1M Bu_4NF in THF (13.7 ml, 13.7 mmol), and the mixture was stirred for 1 h at room temperature. After evaporation of the solvent, the residue was subjected to silica gel column chromatography. Elution with hexane–AcOEt (7:3, v/v) afforded the *alcohol* (**14**) (1.16 g, 98%) as an oil (Found: C, 62.5; H, 9.55. $C_9H_{16}O_3$ requires C, 62.75; H, 9.35%); $[\alpha]_D^{26}$ −8.29° (*c* 1.01 in $CHCl_3$); $\nu_{max.}$ 1 710 cm^{-1} (C=O); δ_H(90 MHz) 0.94 (3 H, t, *J* 7.1 Hz, CH_2Me), 1.34 (3 H, t, *J* 7.4 Hz, OCH_2Me), 1.54–1.83 (1 H, br s, OH), 2.09–2.59 (1 H, m, C*H*Et), 3.43–3.84 (2 H, m, CH_2OH), 4.20 (2 H, q, *J* 7.1 Hz, OCH_2Me), 5.90 (1 H, dd, *J* 1.4 and 15.8 Hz, CHCH=C*H*), and 6.81 (1 H, dd, *J* 8.8 and 15.8 Hz, CHC*H*=CH); *m/z* 142 (M^+ − 1 − Et).

Ethyl (4R)-(E)-4-[(S)-1-*Methoxy*-1-(*trifluoromethyl*)*phenylacetoxymethyl*]*hex*-2-*enoate* (**15**).—To a stirred solution of the above alcohol (**14**) (12.1 mg, 0.070 mmol), (−)-(S)-MTPA (25.6 mg, 0.109 mmol), and DMAP (19.6 mg, 0.160 mmol) in dry CH_2Cl_2 (1 ml) at 0 °C was added dropwise a solution of DCC (19.4 mg, 0.094 mmol) in dry CH_2Cl_2 (1 ml), and the mixture was stirred for 10 h at room temperature. After dilution with a mixture of hexane and Et_2O, the mixture was filtered through Celite. The filtrate was washed successively with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated to give a residue, which was purified by silica gel column chromatography. Elution with hexane–

AcOEt (9:1, v/v) afforded the *MTPA ester* (**15**) (7.0 mg, 26%) (Found: M^+, 388.1520. $C_{19}H_{23}O_5F_3$ requires M, 388.1498); δ_H(500 MHz) 0.92 (3 H, t, J 7.6 Hz, CH_2Me), 1.28 (3 H, t, J 7.2 Hz, OCH_2Me), 3.52 (3 H, s, OMe), 4.18 (2 H, q, J 7.2 Hz, OCH_2Me), 4.25 (1 H, dd, J 7.2 and 11.6 Hz, CHHOMPTA), 4.34 (1 H, dd, J 5.4 and 11.6 Hz, CHHOMPTA), 5.81 (1 H, dd, J 1.3 and 16.3 CHCH=CH), 6.71 (1 H, dd, J 8.8 and 16.3 Hz, CHCH=CH), and 7.37–7.51 (5 H, m, Ph).

(−)-*Ethyl* (4R)-(E)-4-(2-*Bromo*-1-*ethoxyethoxymethyl*)*hex*-2-*enoate* (**16**).—To a stirred solution of the alcohol (**14**) (100 mg, 0.581 mmol) in ethyl vinyl ether (10 ml) at 0 °C was slowly added *N*-bromosuccinimide (497 mg, 2.79 mmol), and the mixture was stirred for 6 h at the same temperature. After filtration, the filtrate was diluted with Et_2O. The mixture was washed with brine, dried (Na_2SO_4), and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (97:3, v/v) afforded the *bromoacetals* (**16**) (177 mg, 94%) as an oil (Found: C, 48.5; H, 7.2; Br, 24.95. $C_{13}H_{23}BrO_4$ requires C, 48.3; H, 7.15; Br, 24.7%); $[\alpha]_D^{24}$ −5.80° (*c* 0.97 in $CHCl_3$); $\nu_{max.}$ 1 718 cm^{-1} (C=O); δ_H(90 MHz) 0.90 (3 H, t, J 6.8 Hz, CH_2Me), 2.16–2.61 (1 H, m, CHEt), 3.34 (2 H, d, J 5.6 Hz, CH_2Br), 3.42–3.93 (4 H, m, 2 × OCH_2), 4.18 (2 H, q, J 7.3 Hz, OCH_2Me), 4.65 (1 H, t, J 5.6 Hz, EtOCH), 5.88 (1 H, dd, J 0.6 and 15.8 Hz, CHCH=CH), and 6.83 (1 H, dd, J 8.4 and 15.8 Hz, CHCH=CH); m/z 323 (M^+).

(+)-(5R)-2-*Ethoxy*-4-*ethoxycarbonylmethyl*-5-*ethyl*-3,4,5,6-*tetrahydro*-2H-*pyran* (**17**).—A mixture of the above bromoacetals (**16**) (29 mg, 0.090 mmol), AIBN (1 mg, 0.006 mmol), and Bu_3SnH (0.027 ml, 0.099 mmol) in dry benzene (20 ml) was heated under reflux for 8 h. After being cooled, the mixture was evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (9:1, v/v) afforded the *tetrahydropyrans* (**17**) (21 mg, 96%) as an oily mixture of four diastereoisomers (Found: C, 63.15; H, 10.15. $C_{13}H_{24}O_4 \cdot 0.25H_2O$ requires C, 62.75; H, 9.85%); $[\alpha]_D^{26}$ +12.14° (*c* 1.17 in $CHCl_3$); $\nu_{max.}$ 1 723 cm^{-1}; δ_H(90 MHz) 0.73–1.09 (3 H, m, CH_2Me), 4.13 (2 H, q, J 7.5 Hz, OCH_2Me), 4.33–4.56 (0.5 H, m, 2-H), and 4.66–4.86 (0.5 H, m, 2-H); m/z 244 (M^+).

(±)-*Methyl* (Z)-4-*t*-*Butyldimethylsiloxymethylhex*-2-*enoate* (**20**).—To a stirred solution of DMSO (0.062 ml, 0.875 mmol) in dry CH_2Cl_2 (1 ml) at −78 °C was added $(COCl)_2$ (0.047 ml, 0.538 mmol). After the mixture had been stirred for 10 min at −78 °C, a solution of the (±)-alcohol (**8**; X and/or Y = H and/or TBDMS) (48.0 mg, 0.220 mol) in dry CH_2Cl_2 (1 ml) was added dropwise. After being stirred for 15 min at −78 °C, to the mixture was added Et_3N (0.18 ml, 1.29 mmol). The cooling bath was then removed and the reaction mixture was allowed to stand at room temperature for 1 h. After addition of water, the mixture was extracted with hexane. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated to afford a crude aldehyde, which was used for the following reaction without purification.

To a stirred suspension of KH (19.8 mg, 0.495 mmol) in dry DME (1.5 ml) at 0 °C was added methyl bis(2,2-trifluoroethyl)-phosphonoacetate (141 mg, 0.442 mmol) and the mixture was stirred for 0.5 h at the same temperature. After a dropwise addition of a solution of the above aldehyde in dry DME (0.5 ml) at −78 °C, the reaction mixture was slowly brought to room temperature during 10 h whilst being stirred. The reaction mixture was poured into saturated aqueous NH_4Cl and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated. Silica gel column chromatography of the residue with hexane–AcOEt (24:1, v/v) as eluant afforded the *ester* (**20**) (47.8 mg, 80% for two steps) as an oil (Found: M^+ − OMe, 241.1640. $C_{13}H_{25}O_2Si$ requires m/z 241.1624); $\nu_{max.}$ 1 722 cm^{-1} (C=O); δ_H(90 MHz) 0.01 (6 H, s, $SiMe_2$), 0.84 (9 H, s, Bu^t), 0.72–0.98 (3 H, m, CH_2Me), 3.30–3.62 (2 H, m, CH_2OTBDMS), 3.68 (3 H, s, OMe), 5.81 (1 H, d, J 11.6 Hz, CHCH=CH), and 6.08 (1 H, dd, J 9.3 and 11.6 Hz, CHCH=CH).

(±)-5-*Ethyl*-5,6-*dihydro*-2-*pyrone* (**22**).—To a stirred solution of the TBDMS ether (**20**) (40.0 mg, 0.147 mmol) in dry THF (3 ml) at 0 °C was added 1M Bu_4NF in THF (0.30 ml, 0.30 mmol). After the mixture had been stirred for 6 h at room temperature, evaporation of the solvent gave a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (7:3, v/v) afforded the *lactone* (**22**) (17 mg, 92%) as an oil; $\nu_{max.}$ 1 732 cm^{-1} (C=O); δ_H(90 MHz) 0.78–1.19 (3 H, m, CH_2Me), 4.14 (1 H, dd, J 7.4 and 11.3 Hz, OCHH), 4.43 (1 H, dd, J 5.4 and 11.3 Hz, OCHH), 6.00 (1 H, dd, J 2.3 and 11.3 Hz, CH=CHCO), and 6.87 (1 H, dd, J 3.7 and 11.3 Hz, CH=CHCO).

(+)-(2R)-(2-*Bromo*-1-*ethoxyethoxymethyl*)*butan*-1-*ol* (**25**).—To a stirred solution of the (−)-menthyl ester (**24**)[6] (979 mg, 2.65 mmol) in dry THF (25 ml) at −20 °C was added dropwise 1M DIBAL in hexane (6.70 ml, 6.70 mmol), and the mixture was stirred for 1 h at −20 °C. After addition of water (8.85 ml), the resulting mixture was further stirred for 0.5 h and then filtered through Celite. The filtrate, including the washings with Et_2O, was dried (Na_2SO_4) and evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (9:1, v/v) afforded the corresponding alcohol (951 mg) contaminated with (−)-menthol.

To a stirred solution of the above product in dry CH_2Cl_2 (20 ml) at 0 °C were added *N*,*N*-dimethylaniline (0.70 ml, 5.52 mmol) and a solution of 1,2-dibromoethyl ethyl ether (1.41 g, 6.06 mmol) in dry CH_2Cl_2 (5 ml), and the mixture was stirred for 12 h at room temperature. After dilution with hexane, the mixture was washed successively with 5% aqueous $KHSO_4$, saturated aqueous $NaHCO_3$, water, and brine, dried (Na_2SO_4), and evaporated. The residue was subjected to silica gel column chromatography with hexane–AcOEt (24:1, v/v) to give the corresponding acetals (1.93 g) contaminated with (−)-menthyl bromoacetals.

To a stirred solution of the above product in dry THF (30 ml) at 0 °C was added dropwise 1M Bu_4NF in THF (4.5 ml, 4.50 mmol) and the mixture was stirred for 3 h at room temperature. After evaporation of the solvent, the residue was purified by silica gel column chromatography. Elution with hexane–AcOEt (7:3, v/v) gave the *alcohols* (**25**) (604 mg, 89% for three steps) as an oil (Found: C, 42.15; H, 7.6; Br, 31.25. $C_9H_{19}BrO_3$ requires C, 42.35; H, 7.5; Br, 31.35%); $[\alpha]_D^{26}$ +2.67° (*c* 2.36 in $CHCl_3$); $\nu_{max.}$ 3 550 cm^{-1} (OH); δ_H(90 MHz) 0.74–1.19 (3 H, m, CH_2Me), 1.22 (3 H, t, J 7.2 Hz, OCH_2Me), 3.37 (2 H, d, J 5.6 Hz, CH_2Br), 3.35–3.83 (6 H, m, 3 × CH_2O), and 4.46 (1 H, t, J 5.6 Hz, EtOCH); m/z 209 and 211 (M^+ − OEt).

(−)-*Methyl* (4R)-(Z)-4-(2-*Bromo*-1-*ethoxyethoxymethyl*)-*hex*-2-*enoate* (**26**).—To a stirred solution of dry DMSO (0.87 ml, 12.3 mmol) in dry CH_2Cl_2 (25 ml) at −78 °C was added $(COCl)_2$ (0.86 ml, 9.85 mmol). After the mixture had been stirred for 10 min at −78 °C, a solution of the above alcohols (**25**) (1.25 g, 4.90 mmol) in dry CH_2Cl_2 (5 ml) was added dropwise. The resulting mixture was stirred for 15 min at −78 °C, after which Et_3N (2.4 ml, 17.3 mmol) was added. The cooling bath was then removed and the reaction mixture was allowed to stand at room temperature for 1 h. After addition of water, the mixture was extracted with hexane. The extract was washed with water and brine, dried ($MgSO_4$), and evaporated to afford the corresponding aldehydes as a yellowish oil (1.25 g),

which were used for the next reaction without further purification (Found: M^+ – OEt, 206.9996 and 209.0041. $C_7H_{12}BrO_2$ requires *m/z* 207.0020 and 209.0000); $\nu_{max.}$ 1 730 cm^{-1} (C=O); δ_H(60 MHz) 0.77–1.13 (3 H, m, CH_2Me), 1.22 (3 H, t, *J* 7.2 Hz, OCH_2Me), 3.30 (2 H, d, *J* 5.4 Hz, CH_2Br), 3.47–3.84 (4 H, m, 2 × CH_2O), 4.65 (1 H, t, *J* 5.4 Hz, EtOC*H*), and 9.67 (1 H, d, *J* 2.0 Hz, CHO).

To a stirred solution of methyl bis(2,2,2-trifluoroethyl)-phosphonoacetate (1.77 g, 5.59 mmol) and 18-crown-6 (5.18 g, 19.6 mmol) in dry THF (20 ml) at −78 °C were added dropwise 0.5M potassium bis(trimethylsilyl)amide in toluene (10.8 ml, 5.40 mmol) and a solution of the above aldehyde (1.25 g) in dry THF (5 ml). After having been stirred for 2 h at −78 °C, the reaction mixture was poured into saturated aqueous NH_4Cl. After extraction with CH_2Cl_2, the combined extracts were washed with brine, dried (Na_2SO_4), and evaporated to afford a residue, which was purified by silica gel column chromatography. Elution with hexane–AcOEt (97:3, v/v) gave the (*Z*)-*esters* (**26**) (1.19 g, 79% for two steps) as an oil (Found: C, 46.65; H, 6.95; Br, 25.9. $C_{12}H_{21}BrO_4$ requires C, 46.6; H, 6.85; Br, 25.85%); $[\alpha]_D^{24}$ −30.38° (*c* 1.17 in $CHCl_3$); $\nu_{max.}$ 1 724 cm^{-1} (C=O); δ_H(90 MHz) 0.90 (3 H, t, *J* 7.3 Hz, CH_2Me), 1.23 (3 H, t, *J* 7.3 Hz, OCH_2Me), 3.35 (2 H, d, *J* 5.6 Hz, CH_2Br), 3.70 (3 H, s, OMe), 3.42–3.84 (4 H, m, 2 × CH_2O), 4.66 (1 H, t, *J* 5.6 Hz, EtOC*H*), 5.85 (1 H, d, *J* 11.9 Hz, C*H*=CHCH), and 6.13 (1 H, dd, *J* 9.0 and 11.9 Hz, CH=C*H*CH); *m/z* 263 and 265 (M^+ − OEt).

Further elution gave the (*E*)-isomers (149 mg, 9.9% for two steps) as an oil; $\nu_{max.}$ 1 714 cm^{-1} (C=O); δ_H(60 MHz) 0.73–1.06 (3 H, m, CH_2Me), 1.23 (3 H, t, *J* 7.5 Hz, OCH_2Me), 3.37 (2 H, d, *J* 5.4 Hz, CH_2Br), 3.77 (3 H, s, OMe), 3.47–3.97 (4 H, m, 2 × CH_2O), 4.63 (1 H, t, *J* 5.4 Hz, EtOC*H*), 5.85 (1 H, d, *J* 16.0 Hz, C*H*=CHCH), and 6.83 (1 H, dd, *J* 8.4 and 16.0 Hz, CH=C*H*CH).

(−)-(4R,5R)-2-*Ethoxy*-5-*ethyl*-4-*methoxycarbonylmethyl*-3,4,5,6-*tetrahydro*-2H-*pyran* (**27**).—A mixture of the bromoacetals (**26**) (549 mg, 1.78 mmol), AIBN (30.3 mg, 0.185 mmol), and Bu_3SnH (0.65 ml, 2.42 mmol) in dry benzene (12 ml) was heated under reflux for 1 h and then evaporated under reduced pressure. Silica gel column chromatography of the crude product with hexane–AcOEt (92:8, v/v) as eluant gave the *tetrahydropyrans* (**27**) (395 mg, 97%) as an oily mixture of two diasteroisomers (Found: C, 62.6; H, 9.7. $C_{12}H_{22}O_4$ requires C, 62.6; H, 9.65); $[\alpha]_D^{25}$ −7.98° (*c* 0.43 in $CHCl_3$); $\nu_{max.}$ 1 732 cm^{-1} (C=O); δ_H(500 MHz) 0.73 −1.06 (3 H, m, CH_2Me), 2.51 (1 H, dd, *J* 3.8 and 15.2 Hz, C*H*HCO$_2$Me), 2.61 (1 H, dd, *J* 4.2 and 15.2 Hz, CH*H*CO$_2$Me), 3.68 (3 H, s, OMe), 3.40–4.44 (4 H, m, 2 × CH_2O), 4.66–4.69 (0.4 H, m, EtOC*H*), and 4.77–4.80 (0.6 H, m, EtOC*H*); *m/z* 215 (M^+ − Me).

(+)-(4S,5R)-(2-*Benzyloxyethyl*)-2-*ethoxy*-5-*ethyl*-3,4,5,6-*tetrahydro*-2H-*pyran* (**28**).—To a stirred solution of the esters (**27**) (834 mg, 3.63 mmol) in dry THF (20 ml) at −20 °C was added dropwise 1M DIBAL in hexane (9.0 ml, 9.0 mmol), and the mixture was stirred for 1 h at −20 °C. After addition of water (9.0 ml), the resulting mixture was further stirred for 0.5 h and then filtered through Celite. The filtrate, including the washings with Et_2O, was dried (Na_2SO_4) and evaporated to give crude alcohols as an oil; $\nu_{max.}$ 3 620 cm^{-1} (OH), which was used for the next reaction without further purification.

To a suspension of 60% oily dispersion of NaH (294 mg, 7.35 mmol) in dry THF (12 ml) was added a solution of the above alcohols in dry THF (3 ml) with ice cooling. The mixture was heated under reflux for 30 min and cooled to room temperature. After addition of benzyl bromide (0.74 ml, 6.22 mmol), the mixture was heated under reflux for 12 h and then poured into saturated aqueous NH_4Cl. The resulting mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and evaporated. Silica gel column chromatography of the residue with benzene–acetone (98:2, v/v) as eluant gave the *benzyl ethers* (**28**) (900 mg, 85% for two steps) as an oil (Found: C, 71.6; H, 9.5. $C_{18}H_{28}O_3 \cdot 0.5H_2O$ requires C, 71.7; H, 9.5%); $[\alpha]_D^{25}$ +12.09° (*c* 1.15 in $CHCl_3$); δ_H(90 MHz) 0.73–1.10 (3 H, m, CH_2Me), 1.22 (3 H, t, *J* 7.2 Hz, OCH_2Me), 4.24–4.45 (0.4 H, m, 2-H), 4.49 (2 H, s, OCH_2Ph), 4.69–4.82 (0.6 H, m, 2-H), and 7.04–7.57 (5 H, m, Ph); *m/z* 292 (M^+).

(+)-(4S,5R)-4-(2-*Benzyloxyethyl*)-5-*ethyl*-3,4,5,6-*tetrahydro*-2-*pyrone* (**18**).—(*a*) A solution of the above benzyl ethers (**28**) (310 mg, 1.06 mmol) in a mixture of acetic acid (8 ml) and water (2 ml) was warmed at 60 °C for 1.5 h and then evaporated to afford crude hemiacetals; $\nu_{max.}$ 3 600 cm^{-1} (OH), which was used for the next reaction without further purification.

Ag_2CO_3 on Celite (Fetizon reagent; 2.12 g, 2.12 mmol) had been dried beforehand by azeotropic distillation using benzene. To a suspension of Fetizon reagent in dry benzene (5 ml) was added a solution of the above hemiacetals in dry benzene (5 ml), and the mixture was heated under reflux for 12 h. After being cooled, the oxidant was removed by filtration through Celite and the filtrate was evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with hexane–AcOEt (4:1, v/v) afforded the trans-*lactone* (**18**) (216 mg, 78% for two steps) as an oil (Found: C, 73.0; H, 8.6. $C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45%); $[\alpha]_D^{25}$ +16.80° (*c* 0.50 in $CHCl_3$); $\nu_{max.}$ 1 740 cm^{-1} (C=O); δ_H(500 MHz) 0.92 (3 H, t, *J* 6.6 Hz, CH_2Me), 2.25 (1 H, dd, *J* 6.8 and 15.9 Hz, 3-H), 2.65 (1 H, dd, *J* 6.0 and 15.9 Hz, 3-H), 3.51 (2 H, t, *J* 5.8 Hz, CH_2OBn), 3.99 (1 H, dd, *J* 7.7 and 11.5 Hz, 6-H), 4.31 (1 H, dd, *J* 5.0 and 11.5 Hz, 6-H), 4.49 (2 H, s, OCH_2Ph), and 7.21–7.50 (5 H, m, Ph); *m/z* 262 (M^+).

(*b*) To a stirred suspension of $LiAlH_4$ (46.3 mg, 1.22 mmol) in dry Et_2O (4 ml) at 0 °C was added a solution of the tetrahydropyrans (**17**) (365 mg, 1.50 mmol), prepared from the (*E*)-esters (**16**), in dry Et_2O (4 ml). The mixture was stirred for 1 h at 0 °C. After addition of water (0.05 ml), 10% aqueous NaOH (0.05 ml), water (1.32 ml), and Et_2O (10 ml), the mixture was further stirred for 1 h. After filtration through Celite, the filtrate was dried (Na_2SO_4) and evaporated to give the corresponding alcohols as an oil, which were benzylated as above to afford the benzyl ethers (97.0 mg, 70% for two steps) as a mixture of four diastereoisomers. To a solution of the benzyl ethers (97.0 mg, 0.332 mmol) in dry THF (2 ml) at 0 °C was added dropwise 1M HCl (1 ml), and the mixture was stirred at room temperature for 7 h. After addition of CH_2Cl_2, the resulting mixture was washed with water and brine, dried (Na_2SO_4), and evaporated to give the crude hemiacetals. To a stirred solution of the product in freshly distilled acetone (6.8 ml) at 0 °C was added dropwise Jones reagent (0.25 ml, 0.369 mmol), and the stirring was continued for 20 min at the same temperature. After addition of Pr^iOH until the colour of the reaction mixture turned to green, the mixture was partitioned between saturated aqueous $NaHCO_3$ and $CHCl_3$. The combined $CHCl_3$ layers were washed with water, dried (Na_2SO_4), and evaporated. Silica gel column chromatography of the residue with benzene–AcOEt (97:3, v/v) afforded the diastereoisomeric mixture of lactones (**18**) and (**19**) (60.8 mg, 70% for two steps) as an oil. HPLC using Microsorb Si (10 × 250 mm, 5 μm) with hexane–AcOEt (4:1, v/v; 4 ml min^{-1}) as eluant determined the ratio (*ca.* 4:1) of the two isomers (**18**) and (**19**). Separation using HPLC gave the *trans*-isomer (**18**) as the faster running product, $[\alpha]_D^{24}$ +17.46° (*c* 1.75 in $CHCl_3$), whose spectral data were identical with those of the compound, prepared by the method (*a*).

The slower running fraction gave the *cis*-isomer (**19**), $\nu_{max.}$ 1 740 cm^{-1} (C=O); δ_H(500 MHz) 0.97 (3 H, t, *J* 7.4 Hz, CH_2Me), 2.38 (1 H, dd, *J* 8.6 and 18.2 Hz, 3-H), 2.58 (1 H, dd, *J* 6.0 and

18.2 Hz, 3-H), 3.47–3.56 (2 H, m, CH_2OBn), 4.25–4.28 (2 H, m, 6-H), 4.50 (2 H, s, OCH_2Ph), and 7.23–7.38 (5 H, m, Ph).

(+)-(3S,4R)-3-(2-*Benzyloxyethyl*)-N-(3,4-*dimethoxyphenethyl*)-4-*hydroxymethylhexacarboxamide* (**29**).—A mixture of the lactone (**18**) (22.6 mg, 0.086 mmol) and 3,4-dimethoxyphenethylamine (0.10 ml, 0.593 mmol) was heated at 155–165 °C for 6 h. After dilution with benzene, the mixture was washed successively with 5% aqueous $KHSO_4$ (× 2), saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated. Silica gel column chromatography of the crude product with benzene–acetone (7:3, v/v) as eluant gave the *amide* (**29**) (38 mg, 100%) as a viscous oil (Found: M^+, 443.2646. $C_{26}H_{37}NO_5$ requires 443.2671); $[\alpha]_D^{23}$ +6.04° (*c* 3.82 in $CHCl_3$); ν_{max} 3 455 (OH), 3 385 (NH), and 1 660 cm^{-1} (C=O); δ_H(90 MHz) 0.78–1.01 (3 H, m, CH_2Me), 2.66 (2 H, t, *J* 7.1 Hz, CH_2Ar), 3.29–3.63 (6 H, m, 2 × CH_2O and CH_2N), 3.84 and 3.85 (each 3 H, each s, 2 × OMe), 4.45 (2 H, s, OCH_2Ph), 5.86–6.08 (1 H, m, NH), 6.60–6.85 (3 H, m, 3 × ArH), and 7.19–7.41 (5 H, m, Ph).

(−)-(2R,3R,11bS)-2-(2-*Benzyloxyethyl*)-3-*ethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizidine* (**31**).—A mixture of the amide (**29**) (21.3 mg, 0.048 mmol) and freshly distilled $POCl_3$ (2.0 ml, 21.5 mmol) was heated under reflux for 4 h. After concentration under a reduced pressure, the residue was rinsed with hexane and then partitioned between saturated aqueous $NaHCO_3$ and CH_2Cl_2. The organic layer was dried (K_2CO_3) and evaporated to give a residue, which was dissolved in CH_2Cl_2 (5 ml). The mixture was heated under reflux for 3 h. After addition of 2M aqueous $LiClO_4$ (5 ml), the resulting mixture was stirred at room temperature for 1 h. The organic layer was washed with 0.1M aqueous $LiClO_4$, dried ($MgSO_4$), and evaporated to give the crude perchlorate (**30**; X = ClO_4) as a yellowish solid, which was used for the next reaction without further purification.

The above perchlorate in ethanol (5 ml) was stirred with PtO_2 (11.8 mg, 0.052 mmol) at room temperature under a hydrogen atmosphere (1 atm) for 2 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give a residue, which was dissolved in CH_2Cl_2. The mixture was washed with 10% ammonium hydroxide and brine, dried (K_2CO_3), and evaporated. Silica gel column chromatography of the residue with $CHCl_3$–MeOH (98:2, v/v) as eluant afforded the trans-*quinolizidine* (**31**) (7.1 mg, 36% for two steps) as a viscous oil (Found: M^+, 409.2587. $C_{26}H_{35}NO_3$ requires 409.2617); $[\alpha]_D^{25}$ −20.16° (*c* 1.11 in $CHCl_3$); ν_{max} 2 800–2 700 cm^{-1} (*trans*-quinolizidine bands); δ_H(90 MHz) 0.81–0.98 (3 H, m, CH_2Me), 3.78 and 3.85 (each 3 H, each s, 2 × OMe), 4.44 and 4.60 (each 1 H, each d, each *J* 11.3 Hz, OCH_2Ph), 6.55 and 6.60 (each 1 H, each s, 2 × ArH), and 7.20–7.41 (5 H, m, Ph).

(−)-(2R,3R,11bS)-3-*Ethyl*-2-(2-*hydroxyethyl*)-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizidine* (*Protoemetinol*; **5**).—A solution of the benzyl ether (**31**) (17.0 mg, 0.042 mmol) in a mixture of MeOH (5 ml) and $CHCl_3$ (0.2 ml) was stirred with $PdCl_2$ (11.3 mg, 0.064 mmol) at room temperature under a hydrogen atmosphere (1 atm) for 12 h. The catalyst was filtered off and the filtrate was evaporated to give a residue, which was dissolved in CH_2Cl_2. The mixture was washed with 10% ammonium hydroxide and brine, dried (K_2CO_3), and evaporated. Silica gel column chromatography of the residue with $CHCl_3$–MeOH (96:4, v/v) as eluant gave (−)-protoemetinol (**5**) (5.5 mg, 41%) (Found: M^+, 319.2133. $C_{19}H_{29}NO_3$ requires 319.2148), which was converted into the perchlorate and recrystallized from EtOH–AcOEt to give crystals, m.p. 202–204 °C (lit.,[4] m.p. 199–200 °C); $[\alpha]_D^{24}$ −15.27° (*c* 0.26 in MeOH); ν_{max} 2 800–2 700 cm^{-1} (*trans*-quinolizidine bands); δ_H(90 MHz) 0.78–1.02 (3 H, m, CH_2Me), 3.85 and 3.86 (each 3 H, each s, 2 × OMe), and 6.57 and 6.68 (each 1 H, each s, 2 × ArH).

(−)-(2R,3R,11bS)-3-*Ethyl*-2-*formylmethyl*-1,2,3,4,6,7-*hexahydro*-9,10-*dimethoxy*-11bH-*benzo*[a]*quinolizidine* (*Protoemetine*; **4**).—To a stirred solution of DMSO (0.030 ml, 0.423 mmol) in dry CH_2Cl_2 (1.5 ml) at −78 °C was added freshly distilled $(CF_3CO)_2O$ (0.015 ml, 0.106 mmol) in dry CH_2Cl_2 (0.1 ml). After the mixture had been stirred for 10 min at −78 °C, a solution of (−)-protoemetinol (**5**) (11.3 mg, 0.035 mmol) in dry CH_2Cl_2 (1.5 ml) and a solution of DMSO (0.006 ml, 0.085 mmol) in dry CH_2Cl_2 (0.3 ml) was added to it. The resulting mixture was stirred for 50 min at −78 °C after which Et_3N (0.060 ml, 0.43 mmol) was added dropwise. The cooling bath was then removed and the reaction mixture was stirred at room temperature for 1 h. Water and 10% aqueous ammonium hydroxide were added to the mixture which was then extracted with CH_2Cl_2. The combined extracts were washed with brine, dried (K_2CO_3), and evaporated to give a residue, which was chromatographed on silica gel using $CHCl_3$–MeOH (98:2, v/v) as eluant to afford (−)-protoemetine (**4**) (5.7 mg, 51%) (Found: M^+, 317.1973. $C_{19}H_{27}NO_3$ requires 317.1991); $[\alpha]_D^{28}$ −14.38° (*c* 0.57 in EtOH); ν_{max} 2 800–2 700 (*trans*-quinolizidine bands) and 1 730 cm^{-1} (C=O); δ_H(500 MHz) 0.82–1.00 (3 H, m, CH_2Me), 3.84 (6 H, s, 2 × OMe), 6.57 and 6.64 (each 1 H, each s, 2 × ArH), and 9.90 (1 H, s, CHO).

Acknowledgements

This work was supported in part by Grant in Aid for Scientific Research on Priority Areas, 01607002, Advanced Molecular Conversion From the Ministry of Education, Science and Culture of Japan. We thank Mr. Kawamura, Mrs. A. Satoh, Miss K. Mushiake, Miss M. Inada, and Miss H. Ohnuma of this Institute for microanalysis, spectral measurements, and preparation of the manuscript.

References

1 T. Fujii and M. Ohba, 'The Alkaloids,' Vol. XXII, ed. by A. Brossi, Academic Press, New York, 1983, pp. 1–50.
2 Leading references of synthesis of emetine: (*a*) A. R. Battersby and J. C. Turner, *J. Chem. Soc.*, 1960, 717; (*b*) E. E. van Tamelen, C. Placeway, G. P. Schiemenz, and I. G. Wright, *J. Am. Chem. Soc.*, 1969, **91**, 7359; (*c*) T. Kametani, Y. Suzuki, H. Terasawa, and M. Ihara, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1211; (*d*) S. Takano, S. Sasaki, H. Kanno, K. Shishido, and K. Ogasawara, *J. Org. Chem.*, 1978, **43**, 4169; (*e*) T. Fujii and S. Yoshifuji, *Chem. Pharm. Bull.*, 1979, **27**, 1486; (*f*) R. T. Brown and M. F. Jones, *Tetrahedron Lett.*, 1984, **25**, 3127; (*g*) T. Kametani, S. A. Surgenor, and K. Fukumoto, *J. Chem. Soc., Perkin Trans. 1*, 1981, 920; (*h*) T. Naito, N. Kojima, O. Miyata, and I. Ninomiya, *Chem. Pharm. Bull.*, 1986, **34**, 3530; (*i*) Y. Hirai, T. Terada, A. Hagiwara, and T. Yamazaki, *Chem. Pharm. Bull.*, 1988, **36**, 1343.
3 C. Szántay, L. Töke, and P. Kolonits, *J. Org. Chem.*, 1966, **31**, 1447.
4 A. R. Battersby and B. J. T. Harper, *J. Chem. Soc.*, 1959, 1748.
5 C. Szántay and G. Kalaus, *Chem. Ber.*, 1969, **102**, 2270.
6 M. Ihara, M. Takahashi, N. Taniguchi, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1987, 619; M. Ihara, M. Takahashi, N. Taniguchi, K. Yasui, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1989, 897.
7 Part of this work has been published as preliminary communications: M. Ihara, N. Taniguchi, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Chem. Commun.*, 1987, 1438; M. Ihara, K. Yasui, N. Taniguchi, K. Fukumoto, and T. Kametani, *Tetrahedron Lett.*, 1988, **29**, 4963.
8 B. Giese, 'Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds,' Pergamon, Oxford, 1986, and references cited therein.
9 Leading references on recent six-membered ring formation: G. Stork, R. Mook, Jr., S. A. Biller, and S. D. Rychnovsky, *J. Am. Chem. Soc.*, 1983, **105**, 3741; M. Ladlow and G. Pattenden, *Tetrahedron Lett.*,

1985, **26**, 4413; A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, 1985, **41**, 3925; A. L. J. Beckwith and D. M. O'Shea, *Tetrahedron Lett.*, 1986, **27**, 4525; M. Koreeda and I. A. George, *J. Am. Chem. Soc.*, 1986, **108**, 8098.
10 B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.
11 Y. Ueno, K. Chino, M. Watanabe, O. Moriya, and M. Okawara, *J. Am. Chem. Soc.*, 1982, **104**, 5564; Y. Ueno, O. Moriya, K. Chino, M. Watanabe, and M. Okawara, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1351.
12 W. C. Still and C. Gennari, *Tetrahedron Lett.*, 1983, **24**, 4405; K. Shishido, Y. Sukegawa, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, 1987, 993.
13 D. C. Rowlands, K. W. Greenlee, J. M. Derber, and C. E. Boord, *J. Org. Chem.*, 1952, **17**, 807; G. Stork and R. Mook, Jr., *J. Am. Chem. Soc.*, 1983, **105**, 3720.
14 H. Nozaki, K. Oshima, and K. Utimoto, *J. Am. Chem. Soc.*, 1987, **109**, 2547.
15 T. Fujii, S. Yoshifuji, and K. Yamada, *Tetrahedron*, 1980, **36**, 965.
16 A. R. Battersby, R. S. Kapil, S. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar, *Tetrahedron Lett.*, 1966, 4965.
17 K. Omura, A. K. Sharm, and D. Swern, *J. Org. Chem.*, 1976, **41**, 957.

Paper 9/04314D
Received 9*th October* 1989
Accepted 14*th November* 1989