

REMARKABLE DIASTEREOSELECTIVITY EXERTED BY
DIENOPHILE CONFIGURATION IN INTRAMOLECULAR
DIELS-ALDER REACTION OF ELECTRON DEFICIENT
HETERODIENES: NEW CHIRAL ENTRY INTO THE
SECOIRIDOID MONOTERPENES AND THE
HETEROYOHIMBINE INDOLE ALKALOIDS*

Seiichi Takano*, Shigeki Satoh, and Kunio Ogasawara

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980,
Japan

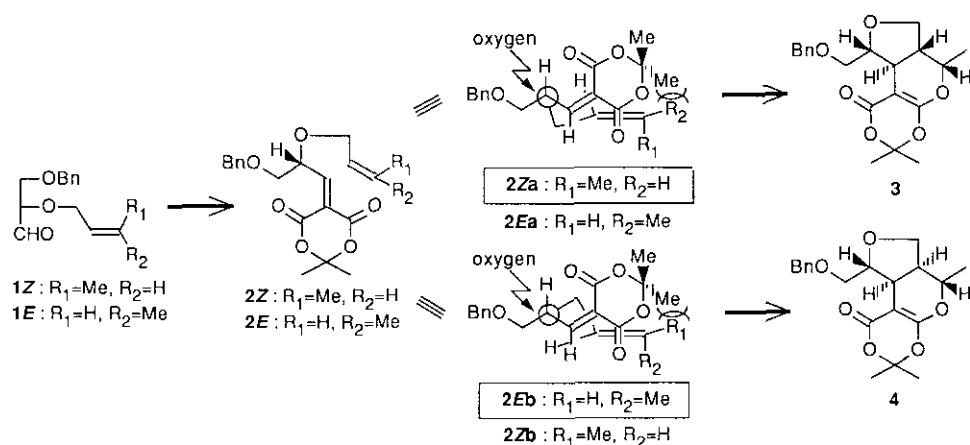
Keiichi Aoe

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co. Ltd., 2-2-
50, Kawagishi, Toda, Saitama 335, Japan

Abstract — Reaction between the optically active glyceraldehyde (1 $\mathbf{Z}$) carrying *Z*-olefin and Meldrum's acid furnished in one step the tricyclic adduct **3** with *trans* 5/6 ring juncture selectively under mild conditions by spontaneous condensation followed by the intramolecular Diels-Alder reaction. On the other hand, the *E*-olefin isomer (1 $\mathbf{E}$), under the same conditions, furnished the isomeric adduct **4** with *cis* 5/6 ring juncture selectively. The former gave a pair of the *cis*-fused bicyclic carbamates, (**22**) and (**25**), while the latter gave the *trans*-fused pair, (**23**) and (**26**), by the following transformations. Although these imply formal chiral route to the heteroyohimbine alkaloids, a new enantioselective route to a secoiridoid monoterpene, (–)-methyl elenolate (**37**), has also been developed.

We report here remarkable diastereoselectivity directed by the configuration of the dienophile in intramolecular Diels-Alder reaction involving electron deficient heterodienes. In relation to our recent project using chiral glycerol building blocks,¹ we attempted to prepare two isomeric

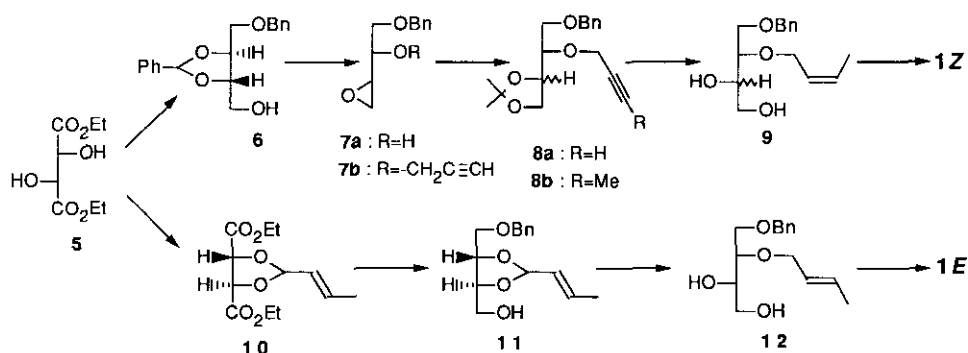
heterodiene substrates, **2Z** and **2E**, by condensing the isomeric chiral glyceraldehyde derivatives, **1Z** and **1E**, with Meldrum's acid, respectively. In the light of the well-established precedents, especially, extensive work of the Tietze's group² and our own observations,³ we expected that **2E** and **2Z** would generate the *trans*-fused Diels-Alder adducts isomeric at the secondary methyl group. Upon the condensation, facile, concurrent condensation and cycloaddition did occur in highly selective fashion to give a single adduct in each case. However, it was found that both adducts were not isomeric at the secondary methyl group, but at the ring juncture: thus, **2Z** carrying *Z*-olefin afforded exclusively the *trans*-5/6-adduct **3**, while **2E** carrying *E*-olefin afforded exclusively the *cis*-5/6-adduct **4** (Scheme 1).



Scheme 1

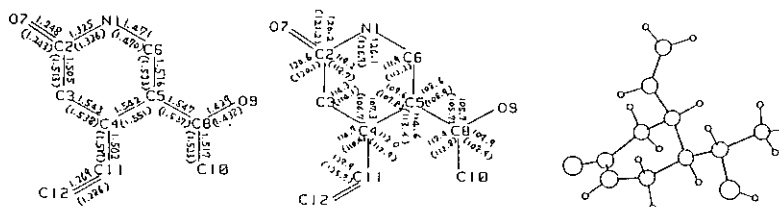
The starting glyceraldehydes **1Z** and **1E** were prepared, respectively, from diethyl (L)-tartrate (**5**) as outlined in Scheme 2. In these conversions, the former was prepared *via* oxidative cleavage of the benzylidene acetal^{4,5} (**6**) obtained from (**5**) by *N*-bromosuccinimide and the latter was prepared *via* reductive cleavage of the crotylidene acetal (**11**) obtained from (**5**) by diisobutylaluminum hydride,^{5,6} both in highly regioselective fashions.

When both of the aldehydes, (**1Z**) and (**1E**), were treated with Meldrum's acid⁷ smooth reaction took place at 0 °C - room temperature to give the corresponding adducts, **3** and **4**, respectively. Although we could not determine the stereochemistry of each adduct at this point, the following conversions revealed that they were not isomeric at the secondary methyl group, but at the ring

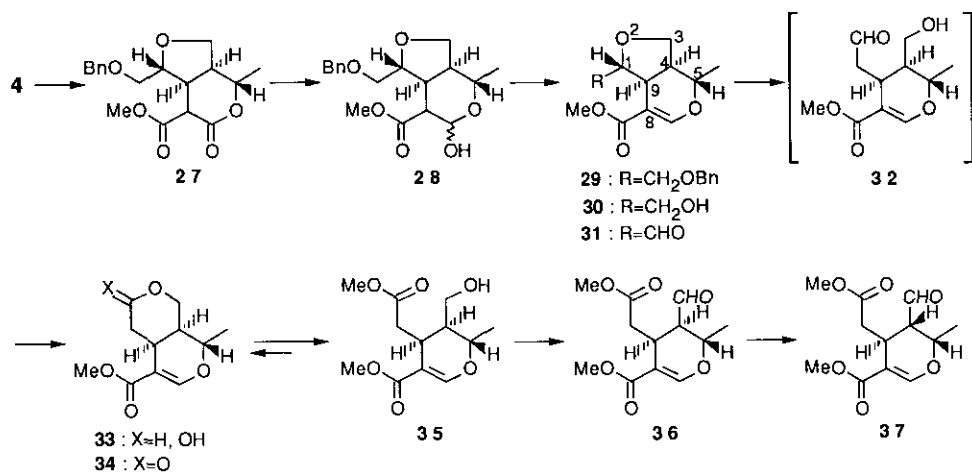


Scheme 2

juncture. Thus, refluxing both adducts in aqueous dioxane (2:1) allowed concurrent deketalization and decarboxylation to give the corresponding lactones (**13a** and **b**) which were converted into the corresponding olefin-alcohols (**17a** and **b**) by sequential debenzoylation, tosylation, halogen substitution, and reductive ring cleavage. Employing the Mitsunobu reaction,⁸ the alcohols (**17a** and **b**) were converted into the corresponding lactams (**20a**: X=O and **b**: X=O), respectively. Lactams (**20a**: X=O and **b**: X=O) were then transformed to the corresponding diols (**21a** and **b**) by sequential hydride reduction, acylation, and hydroboration-oxidation. Oxidation of diols (**21**) with silver carbonate on Celite (Fetizon reagent)⁹ afforded the corresponding lactones (**22** and **23**), respectively. Diols (**21**), after monobenzoylation at the primary center, were subjected to the Mitsunobu reaction⁸ to give the dibenzoates which on hydrolysis afforded the corresponding inverted diols (**24a** and **b**).¹⁰ Oxidation of the diols (**24a** and **b**) with Fetizon reagent furnished the corresponding lactones (**25** and **26**), respectively. Of these four isomeric lactones (**22**, **23**, **25**, and **26**), **25** originating from **1Z** was found to be identical in all respects, except the sign of optical rotation, with that obtained from 3-acetylpyridine by Uskokovic and co-workers¹¹ via microbial chiral reduction as key step. Consequently, by correlating to **25**, the structures of the remaining three other isomers as well as their progenitors, (**3**) and (**4**), could be deduced as shown. Thus, it was deduced that the *Z*-olefin (**2Z**) generated the adduct **3** with *trans* 5/6-ring juncture, while the *E*-olefin (**2E**) generated the adduct **4** with *cis*-5/6-ring juncture, both in highly diastereoselective fashions (Scheme 3). The stereochemical assignment could also be confirmed by X-ray crystallography of the crystalline intermediates **20a** and **23** which well supported the deduced structures (Figures 1, 2 and Tables 1,2).

Figure 1. X-ray Structural Analysis of Compound (20a: X=O)

dehydration, debenzoylation, and Swern oxidation,¹³ **28** provided the aldehyde (**31**) which was then converted to the lactol (**33**) via **32** by reductive cleavage. Oxidation of **33** with Fetizon reagent gave the lactone (**34**) which on methanolysis afforded an equilibrium mixture of the



Scheme 4

lactone (**34**) and the seco-ester (**35**). The mixture was sequentially neutralized, evaporated, and subjected to Swern oxidation¹³ in the same reaction flask to give the *cis*-aldehyde (**36**)¹⁴ (60%) and **34** (39%) which were separated by silica gel chromatography.

Upon stirring with silica gel in methylene chloride, **36** readily isomerized to the thermodynamically more stable *trans*-epimer, a biologically active secoiridoid monoterpene, (–)-methyl elenolate¹⁵ (**37**), in quantitative yield (**Scheme 4**). Since **37** has been converted into a heteroyohimbine alkaloid, (–)-ajmalicine (**15a**), it also constitutes a formal enantioselective synthesis of this medicinally important natural product.¹⁶

The remarkable diastereoselectivity in the intramolecular hetero-Diels-Alder reaction found in the present investigation could be successfully applied to the enantioselective synthesis of other physiologically active natural products, such as heteroyohimbine alkaloids,¹⁷ lignans,¹⁸ and kainoid amino acid.¹⁹

EXPERIMENTAL SECTION

All reactions except hydrogenation were carried out under argon. Ir spectra were measured with a JASCO A-102 spectrophotometer. ^1H Nmr spectra were recorded on JEOL-MX60, JEOL-FX90R and JEOL-JNM-GX500 spectrometers. Ms spectra were measured with Hitachi-M52 and JEOL-O1SG-2 instruments. Optical rotations were measured with a JASCO-DIP-4 automatic polarimeter.

(2S,3R/S)-1-Benzoyloxy-3,4-epoxy-2-(2-propynyl)butane (7b) ——— A suspension of the epoxide (**7a**)⁴ (411 mg, 2.12 mmol), benzyltriethylammonium chloride (323 mg, 1.42 mmol), and propargyl bromide (0.42 ml, 4.66 mmol) in benzene (5 ml) and 70% aq. NaOH (5 ml) was stirred vigorously at room temperature for 14 h. The mixture was extracted with ether and the extract was washed (H_2O , sat. NaCl), dried (MgSO_4), concentrated, and chromatographed (SiO_2 , 20% ether-hexane) to give **7b** (410 mg, 83%) as a colorless oil: $[\alpha]_{\text{D}}^{25} -16.9^\circ$ (c 1.18, CHCl_3). Ir (neat) ν_{max} : 3250, 2100 cm^{-1} ; ^1H nmr (CDCl_3) δ : 7.30 (s, 5H), 4.55 (s, 2H), 4.35 (d, 2H, $J=2.0$ Hz), 3.26-3.77 (m, 2H), 2.90-3.27 (m, 1H), 2.50-2.93 (m, 2H), 2.42 (t, 1H, $J=2.0$ Hz); ms (m/z): 232 (M^+), 91 (100%). Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$: 232.1098. Found: 232.1076 (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{16}\text{O}_3$: C 70.39, H 6.94. Found: C 70.51, H 6.78.

(2S,3R/S)-1-Benzoyloxy-3,4-isopropylidenedioxy-2-(2-propynyl)butane (8a) ——— A mixture of **7b** (37.46 g, 0.16 mol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (1.61 ml, 13.08 mmol) in acetone (180 ml) was stirred at 0°C for 0.5 h and at room temperature for 2 h. The reaction mixture was then neutralized with aq. NaHCO_3 and concentrated in vacuo. The residue was extracted with ether and the extract was washed (sat. NaHCO_3 , sat. NaCl), dried (MgSO_4), concentrated, and chromatographed (SiO_2 , 17% AcOEt -hexane) to give **8a** (44.44 g, 94%) as a colorless oil: $[\alpha]_{\text{D}}^{25} +1.25^\circ$ (c 0.96, CHCl_3). Ir (neat) ν_{max} : 3300, 2150 cm^{-1} ; ^1H nmr (CDCl_3) δ : 7.28 (s, 5H), 4.50 (s, 2H), 4.38 (d, 2H, $J=2.0$ Hz), 3.50-4.73 (m, 6H), 2.40 (t, 1H, $J=2.0$ Hz), 1.40 (s, 3H), 1.35 (s, 3H); ms (m/z): 290 (M^+), 91 (100%). Calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4$: 290.1517. Found: 290.1507 (M^+).

(2S,3R/S)-1-Benzoyloxy-3,4-isopropylidenedioxy-2-(2-butyryl)butane (8b) ——— To a stirred solution of **8a** (268 mg, 0.92 mmol) in THF (10 ml) was added NaH (60% w/w in oil, 540 mg, 10.16 mmol) at 0°C and, after 10 min at the same temperature, MeI (1.74 ml, 27.72 mmol) was added in one portion and the mixture was refluxed for 30 h. After cooling, the mixture

was treated with sat. NaHCO_3 and extracted with Et_2O . The extract was washed (H_2O , 5% $\text{Na}_2\text{S}_2\text{O}_3$, sat. NaHCO_3 , sat. NaCl), dried (MgSO_4), concentrated, and chromatographed (SiO_2 , 10% AcOEt -hexane) to give **8b** (279 mg, quant.) as a colorless oil: $[\alpha]_{\text{D}}^{23} +0.32^\circ$ (*c* 1.23, CHCl_3). Ir (neat) ν_{max} : 2250 cm^{-1} ; ^1H nmr (CDCl_3) δ : 7.27 (s, 5H), 4.52 (s, 2H), 4.33 (q, 2H, $J=2.0$ Hz), 3.48-4.55 (m, 6H), 1.82 (t, 3H, $J=2.0$ Hz), 1.40 (s, 3H), 1.33 (s, 3H); ms (*m/z*): 304 (M^+), 91 (100%). Calcd for $\text{C}_{18}\text{H}_{24}\text{O}_4$: 304.1672. Found: 304.1650 (M^+).

(2*S*,3*R*/*S*)-1-Benzoyloxy-2-[2(*Z*)-butenyl]-3,4-dihydroxybutane (9) — A solution of **8b** (9.37 g, 30.82 mmol) in ethanolic 1.5*N* H_2SO_4 (100 ml) was heated at 70 $^\circ\text{C}$ for 3 h. After cooling, the mixture was neutralized with aq. NaHCO_3 and extracted with CH_2Cl_2 . The extract was washed (H_2O , sat. NaCl), dried (MgSO_4), and chromatographed (SiO_2 , 3% MeOH - CHCl_3) to give (2*S*,3*R*/*S*)-1-benzoyloxy-2-(2-butynyl)-3,4-dihydroxybutane (9.10 g, quant.) as a colorless oil: $[\alpha]_{\text{D}}^{23} -49.9^\circ$ (*c* 0.91, CHCl_3). Ir (neat) ν_{max} : 3430, 1080 cm^{-1} ; ^1H nmr (CDCl_3) δ : 7.28 (s, 5H), 4.52 (s, 2H), 4.27 (q, 2H, $J=2.0$ Hz), 3.50-3.97 (m, 6H), 2.00-3.13 (br s, 2H, exchangeable with D_2O), 1.78 (t, 3H, $J=2.0$ Hz); ms (*m/z*): 265 (M^++1), 264 (M^+), 91 (100%). Calcd for $\text{C}_{15}\text{H}_{21}\text{O}_4$: 265.1436. Found: 265.1438 (M^++1).

A solution of the diol (4.61 g, 17.45 mmol) in EtOH (100 ml) was hydrogenated over Lindlar catalyst (230 mg, purchased from Aldrich) under atmospheric pressure at room temperature for 3 h and at 50 $^\circ\text{C}$ for 1 h. After removal of the catalyst by filtration, the filtrate was concentrated and chromatographed (SiO_2 , 1% MeOH - CHCl_3) to give **9** (4.45 g, 96%) as a colorless oil: $[\alpha]_{\text{D}}^{23} +31.3^\circ$ (*c* 1.04, CHCl_3). Ir (neat) ν_{max} : 3400 cm^{-1} ; ^1H nmr (CDCl_3) δ : 7.30 (s, 5H), 5.33-6.00 (m, 2H), 4.55 (s, 2H), 4.12-4.33 (m, 2H), 3.33-4.00 (m, 6H), 2.77-3.07 (m, 1H, exchangeable with D_2O), 2.23-2.63 (m, 1H, exchangeable with D_2O), 1.70 (d, 3H, $J=7.5$ Hz); ms (*m/z*): 267 (M^++1), 91 (100%). Calcd for $\text{C}_{15}\text{H}_{23}\text{O}_4$: 267.1591. Found: 267.1596 (M^++1).

Diethyl (2*R*,3*R*)-2,3-*O*-[(*E*)-Crotylidene]tartrate (10) — A mixture of L-(+)-diethyl tartrate (527 g, 2.56 mmol), crotonaldehyde diethyl acetal (454 g, 3.24 mol) and pyridinium *p*-toluenesulfonate (PPTS) (7.10 g, 28 mmol) in benzene (1.8 l) was refluxed for 14 h. After cooling, the mixture was washed (H_2O , sat. NaHCO_3 , sat. NaCl), dried (MgSO_4), concentrated, and distilled under vacuum to give **10** (469 g, 71%) as a pale yellow oil: bp 110-120 $^\circ\text{C}$ /0.3 torr; $[\alpha]_{\text{D}}^{17} -26.7^\circ$ (*c* 1.21, CHCl_3). Ir (neat) ν_{max} : 1745 cm^{-1} ; ^1H nmr (CDCl_3) δ : 5.40-6.50 (m, 3H), 4.77 (d, 1H, $J=7.0$ Hz), 4.67 (d, 1H, $J=7.0$ Hz), 4.28 (q, 4H, $J=8.0$ Hz), 1.78 (d, 3H, $J=6.0$ Hz), 1.32 (t, 6H, $J=8.0$ Hz); ms (*m/z*): 259 (M^++1), 185 (100%). Calcd for $\text{C}_{12}\text{H}_{19}\text{O}_6$: 259.1180. Found 259.1164 (M^++1). Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{O}_6$: C 55.80, H 7.03. Found: C 55.76, H 6.71.

(2S,3S)-1-O-Benzyl-2,3-O-[(E)-crotylidene]threitol (11) — To a stirred solution of **10** (254 g, 0.98 mol) in MeOH (1.6 l) was added NaBH₄ (55.8 g, 1.48 mol) portionwise at 0 °C. After stirring at the same temperature for 3.5 h, the reaction mixture was extracted successively with Et₂O and CH₂Cl₂. The combined extracts were washed (sat. NaCl), dried (MgSO₄), and concentrated to give the crude diol (129 g) as a colorless oil. This product was used without purification. Ir (neat) $\nu_{\max}$: 3400 cm⁻¹; ¹H nmr (CDCl₃) δ : 4.80-6.47 (m, 3H), 3.25-4.30 (m, 6H), 2.47-3.25 (br s, 2H, exchangeable with D₂O), 1.74 (d, 3H, *J*=6.0 Hz); ms (*m/z*): 174 (M⁺), 143 (100%).

To a stirred suspension of NaH (60% w/w in oil, 12.9 g, 0.32 mol, washed with hexane) in DMF (500 ml) was added dropwise the above diol (53.4 g, 0.31 mol) in THF (500 ml) at 0 °C and the mixture was kept stirring at 0 °C for 0.5 h and at room temperature for 1 h. The mixture was then cooled to -20 °C and BnBr (39.1 ml, 0.33 mol) in THF (40 ml) was added to the mixture. After stirring at 0 °C for 1 h and at room temperature for 1 h, sat. NaHCO₃ was added to the reaction mixture. The mixture was concentrated and the residue was extracted with Et₂O. The extract was washed (sat. NaCl), dried (MgSO₄), and chromatographed (SiO₂, 20% AcOEt-hexane) to give **11** (52.1 g, 42% from diester) as a colorless oil. Ir (neat) $\nu_{\max}$: 3325 cm⁻¹; ¹H nmr (CDCl₃) δ : 7.37 (s, 5H), 5.23-6.37 (m, 3H), 4.60 (s, 2H), 3.40-4.37 (m, 6H), 2.10 (br s, 1H, exchangeable with D₂O), 1.78 (d, 3H, *J*=6.0 Hz); Ms (*m/z*): 264 (M⁺), 91 (100%). Calcd for C₁₅H₂₀O₄: 264.1360. Found: 264.1343 (M⁺). Anal. Calcd for C₁₅H₂₀O₄: C 68.16, H 7.63. Found: C 67.75, H 7.55.

(2S,3S)-1-O-Benzyl-2-O-[(E)-2-butenyl]threitol (12) — To a stirred solution of **11** (115.3 g, 0.44 mol) in toluene (1400 ml) was added diisobutylaluminum hydride (311 ml, 1.75 mmol) at 0 °C and the stirring was continued at the same temperature for 1 h. 28% NH₄OH, THF, and MeOH were added at 0 °C, and the mixture was stirred at room temperature for 15 days. After filtration (Celite), the filtrate was concentrated and chromatographed (SiO₂, 25% AcOEt-hexane) to give **12** (86.3 g, 74%) as a colorless viscous oil: $[\alpha]_D^{26} +12.7^\circ$ (c 1.15, MeOH). Ir (neat) $\nu_{\max}$: 3420 cm⁻¹; ¹H nmr (CDCl₃) δ : 7.28 (s, 5H), 5.18-5.79 (m, 2H), 4.50 (s, 2H), 3.91-4.39 (m, 2H), 3.30-3.91 (m, 4H), 2.80 (s, 2H, exchangeable with D₂O), 1.68 (d, 3H, *J*=6.0 Hz); ms (*m/z*): 267 (M⁺+1), 91 (100%). Calcd for C₁₅H₂₃O₄: 267.1597. Found: 267.1619 (M⁺+1).

Formation of the *trans*-Adduct (3) from the *Z*-Diol (9) — To a stirred solution of the *Z*-1,2-diol (**9**) (8.85 g, 33.27 mmol) in MeOH (30 ml) was added a solution of aq. NaIO₄ (7.48 g, 34.93 mmol in H₂O 30 ml) dropwise at 0 °C and the reaction mixture was stirred at the same

temperature for 0.5 h. The mixture was extracted with Et₂O and the extract was washed (sat. NaCl), dried (MgSO₄), and concentrated below 20 °C to give the crude *Z*-glyceraldehyde (**1Z**) which was used without purification. A mixture of **1Z**, Meldrum's acid (6.23 g, 43.25 mmol), and ethylenediammonium diacetate (240 mg, 1.33 mmol) in 2-propanol (100 ml) was stirred at room temperature for 3.5 h. After removal of the solvent, the residue was extracted with Et₂O. The extract was washed (H₂O, sat. NaHCO₃, sat. NaCl), dried (MgSO₄), and concentrated to give the *trans*-adduct **3** (10.28 g) as a yellow oil. Since the product was too unstable to purify, the crude product was immediately used for the next reaction.

Formation of the *trans*-Lactone (13a) from the *trans*-Adduct (3) — The above **3** (10.28 g) was refluxed in aq. 1,4-dioxane (100 ml, 30%) for 19 h. After the mixture was extracted with Et₂O, the extract was washed (sat. NaHCO₃, sat. NaCl), dried (MgSO₄), concentrated, and chromatographed (SiO₂, 33% THF-hexane) to give the *trans*-lactone (**13a**) (6.14 g, 67%) as a colorless viscous oil which crystallized on standing. Recrystallization from Et₂O gave colorless needles: mp 79.5-81.5 °C; [α]_D²⁶ -79.1° (*c* 0.95, CHCl₃). *Ir* (Nujol) ν_{max} : 1720 cm⁻¹; ¹H nmr (CDCl₃) δ : 7.27 (s, 5H), 4.46-5.26 (m, 1H), 4.53 (s, 2H), 3.30-4.30 (m, 5H), 2.10-3.07 (m, 3H), 1.57-2.10 (m, 1H), 1.33 (d, 3H, *J*=7.0 Hz); *ms* (*m/z*): 276 (*M*⁺), 91 (100%). Calcd for C₁₆H₂₁O₄: 277.1439. Found 277.1439 (*M*⁺+1). *Anal.* Calcd for C₁₆H₂₀O₄: C 69.54, H 7.30. Found: C 69.29, H 7.52. In these conversions, a part of the product **13a** was transformed into the seco-acid which, however, was readily recovered and reverted to the lactone **13a** on reflux in toluene for 12 h in the presence of a catalytic amount of PPTS.

Formation of the *cis*-Adduct (4) from the *E*-Diol (12) — To a stirred solution of *E*-1,2-diol (**12**) (59.00 g, 0.22 mol) in MeOH (400 ml) was added a solution of aq. NaIO₄ (61.68 g, 0.29 mol in H₂O 400 ml) dropwise at 0 °C and the reaction mixture was stirred at the same temperature for 3 h. After filtration (Celite), the filtrate was extracted with Et₂O. The extract was washed (sat. NaCl), dried (MgSO₄), and concentrated below 20 °C to give the crude *E*-glyceraldehyde (**1E**) which was used without purification. A mixture of **1E**, Meldrum's acid (32.92 g, 0.23 mol), and ethylenediammonium diacetate (1.60 g, 8.87 mmol) in 2-propanol (500 ml) was stirred at 0 °C for 2 h and at room temperature for 13 h. After removal of the solvent in vacuo, the residue was extracted with Et₂O. The extract was washed (sat. NaHCO₃, sat. NaCl), dried (MgSO₄), and concentrated to give the crude adduct **4** (64.10 g). Since the product was too unstable to purify, the crude product was immediately used for the next reaction.

Formation of the *cis*-Lactone (13b) from the *cis*-Adduct (4) — The above **4** (64.10 g) was refluxed in aq. 1,4-dioxane (600 ml, 33%) for 3.5 h. After removal of the solvent, the residue was extracted with Et₂O. The extract was washed (sat. NaHCO₃, sat. NaCl), dried (MgSO₄), concentrated, and chromatographed (SiO₂, 25% AcOEt-hexane) to give *cis*-lactone (**13b**, 34.87 g, 57% overall from **12**) as a colorless viscous oil which crystallized on standing. Recrystallization from Et₂O-hexane gave colorless needles: mp 49.5–50.0 °C; [α]_D²⁵ –93.0° (*c* 1.00, CHCl₃). Ir (Nujol) $\nu_{\max}$: 1745 cm^{–1}; ¹H nmr (CDCl₃) δ : 7.29 (s, 5H), 4.56 (s, 2H), 3.29–4.30 (m, 6H), 2.11–2.71 (m, 4H), 1.33 (d, 3H, *J* = 6.9 Hz); ms (*m/z*): 227 (*M*⁺+1), 91 (100%). Calcd for C₁₆H₂₁O₄: 277.1438. Found 277.1411 (*M*⁺+1). *Anal.* Calcd for C₁₆H₂₀O₄: C 69.54, H 7.30. Found: C 69.29, H 7.52.

(3*R*,4*S*,5*S*)-5-Hydroxy-4-hydroxymethyl-3-vinylhexanoic Acid Lactone (17a) —

— A solution of the lactone (**13a**) (6.78 g, 21.06 mmol) in EtOH (70 ml) was hydrogenated over 10% palladized-carbon (680 mg) with a catalytic amount of conc. HCl under atmospheric pressure at room temperature for 3 h. After removal of the catalyst by filtration, the filtrate was concentrated to give ethyl (3*R*,4*S*,5*R*)-5-hydroxy-4-hydroxymethyl-3-vinylhexanoate (5.18 g, quant.) by concurrent ethanolysis of **14a**. Ir (neat) $\nu_{\max}$: 3400, 1720 cm^{–1}; ¹H nmr (CDCl₃) δ : 4.13 (q, 2H, *J* = 7.0 Hz), 3.27–4.37 (m, 6H), 1.67–3.07 (m, 6H, 2H exchangeable with D₂O), 1.23 (t, 3H, *J* = 7.0 Hz), 1.17 (d, 3H, *J* = 6.0 Hz); ms (*m/z*): 201 (*M*⁺–31), 109 (100%).

A mixture of the above seco-ester (417 mg, 1.79 mmol) and *p*-toluenesulfonyl chloride (586 mg, 3.06 mmol) in pyridine (10 ml) was stirred at room temperature for 40 h. After removal of the solvent using a vacuum pump, the residue was extracted with Et₂O. The extract was washed (H₂O, 5% HCl, sat. NaHCO₃, sat. NaCl), dried (MgSO₄), concentrated, and chromatographed (SiO₂, 50% AcOEt-hexane) to give ethyl (3*R*,4*S*,5*S*)-5-hydroxy-4-(*p*-toluenesulfonyloxymethyl)-3-vinylhexanoate (**15a**: seco-ethyl ester) (485 mg, 70%) as a colorless oil: [α]_D²⁸ –17.5° (*c* 0.84, CHCl₃). Ir (neat) $\nu_{\max}$: 3500, 1730 cm^{–1}; ¹H nmr (CDCl₃) δ : 7.82 (d, 2H, *J* = 8.0 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 4.13 (q, 2H, *J* = 6.0 Hz), 3.56–4.40 (m, 6H), 2.42 (s, 3H), 1.67–2.67 (m, 5H, 1H exchangeable with D₂O), 1.25 (t, 3H, *J* = 6.0 Hz), 1.13 (d, 3H, *J* = 6.0 Hz); ms (*m/z*): 370 (*M*⁺–16), 202 (100%).

A mixture of the above tosylate (108 mg, 0.22 mmol) and NaI (259 mg, 1.73 mmol) in 2-butanone (2 ml) was refluxed for 17 h. After removal of the solvent, the residue was extracted with Et₂O. The extract was washed (H₂O, 5% Na₂S₂O₃, sat. NaCl), dried (MgSO₄), and concentrated to give the iodide (**16a**: seco-ethyl ester) (96 mg, 97%) as a colorless oil. Ir (neat) $\nu_{\max}$: 3450,

1725 cm^{-1} ; ^1H nmr (CDCl_3) δ : 4.20 (q, 2H, $J=7.0$ Hz), 3.10-4.47 (m, 6H), 1.77-2.77 (m, 5H, 1H exchangeable with D_2O), 1.32 (t, 3H, $J=7.0$ Hz), 1.28 (d, 3H, $J=6.0$ Hz); ms (m/z): 343 (M^++1), 216 (100%).

A suspension of the above iodide (4.14 g, 12.11 mmol) and activated zinc dust (3.96 g, 60.55 mmol) in 95% aqueous EtOH (70 ml) was refluxed for 1.5 h. After removal of the solvent, the residue was extracted with CH_2Cl_2 . The extract was washed (sat. NaCl), dried (MgSO_4), and concentrated to give a mixture of the lactone (**17a**) and its seco-ester which was refluxed in toluene (60 ml) for 12 h. After removal of the solvent, the residue was chromatographed (SiO_2 , 75% Et_2O -hexane) to give the desired *trans*-vinyl alcohol (**17a**) as a colorless oil accompanied by a minor amount of the inseparable isomeric by-product (ca. 5:1) generated by lactone exchange (1.64 g, 80% overall from **13a**). Ir (neat) ν_{max} : 3450, 1720 cm^{-1} ; ^1H nmr (CDCl_3) δ : 5.50-6.17 (m, 1H), 4.50-5.43 (m, 3.33H), 3.73 (d, 1.67 H, $J=7.0$ Hz), 1.67-3.03 (m, 5H, 1H exchangeable with D_2O), 1.40 (d, 2.51 H, $J=7.0$ Hz), 1.30 (d, 0.49 H, $J=6.0$ Hz); ms (m/z): 171 (M^++1), 43 (100%). Calcd for $\text{C}_9\text{H}_{15}\text{O}_3$: 171.1019. Found: 171.1008 (M^++1). Anal. Calcd for $\text{C}_9\text{H}_{14}\text{O}_3$: C 63.51, H 8.29. Found: C 63.03, H 8.65.

(4S,5R)-5-[(1S)-Hydroxyethyl]-4-vinylpiperidin-2-one (20a: X=O) — A mixture of the above lactone (**17a**) (1.64 g, 9.64 mmol), triphenylphosphine (3.28 g, 12.53 mmol), and phthalimide (1.84 g, 12.53 mmol) in THF (50 ml) was stirred with diisopropyl azodicarboxylate (2.47 ml, 12.53 mmol) at 0 °C for 0.5 h and at room temperature for 0.5 h. After removal of the solvent, the residue was chromatographed (SiO_2 , 67% Et_2O -hexane) to give the imide (**18a**) (2.85 g). In these conversion the contaminated secondary alcohol was decomposed presumably by prevailed elimination reaction. The imide (**18a**) (61 mg, 0.204 mmol) was then refluxed with 90% hydrazine hydrate (20.4 mg, 0.41 mmol) in EtOH (2 ml) for 0.5 h. After removal of the solvent, CHCl_3 was added to the residue and the mixture was filtered. The filtrate was evaporated and chromatographed (SiO_2 , 1% MeOH- CH_2Cl_2) to give the lactam (**20a: X=O**) (30 mg, 84% overall from the vinyl alcohol) as a colorless solid which was recrystallized from Et_2O to give colorless needles: mp 182.5-183.5 °C; $[\alpha]_{\text{D}}^{23} +14.9^\circ$ (c 0.94, MeOH). Ir (Nujol) ν_{max} : 3450, 3200, 1660 cm^{-1} ; ^1H nmr (CDCl_3 , CD_3OD) δ : 6.90 (br s), 4.89-6.13 (m, 3H), 2.97-4.01 (m, 4H), 2.30-2.93 (m, 3H), 1.53-2.23 (m, 1H), 1.27 (d, 3H, $J=7.0$ Hz); ms (m/z): 170 (M^++1), 169 (M^+), 121 (100%). Calcd for $\text{C}_9\text{H}_{16}\text{NO}_2$: 170.1179. Found: 170.1166 (M^++1). Anal. Calcd for $\text{C}_9\text{H}_{15}\text{NO}_2$: C 63.88, H 8.94, N 8.28. Found: C 63.75, H 9.07, N 8.12.

(3S,4S)-1-Carbomethoxy-4-[2-hydroxyethyl]-3-[(1S)-hydroxyethyl]piperidine

(21a) — A mixture of **20a** (X=O) (151 mg, 0.89 mmol) and LiAlH₄ (170 mg, 4.47 mmol) in THF (4 ml) was refluxed for 16 h. After quenching the reaction by addition of 28% NH₄OH, the reaction mixture was filtered (Celite). The filtrate was concentrated to give the amine (**20a**: X=H₂) (143 mg, 100%) as a colorless oil. Ir (neat) $\nu_{\max}$: 3350, 3300, 1640 cm⁻¹; ¹H nmr (CDCl₃) δ : 5.53-6.43 (m, 1H), 4.87-5.40 (m, 2H), 1.22 (d, 3H, *J*=6.0 Hz).

A mixture of **20a** (X=H₂) (770 mg, 4.97 mmol), Et₃N (2.18 ml, 15.6 mmol), and ClCO₂Me (0.40 ml, 5.20 mmol) in CH₂Cl₂ (20 ml) was stirred at room temperature for 0.5 h. The mixture was extracted with CH₂Cl₂ and the extract was washed (5% aq. HCl, sat. NaHCO₃, sat. NaCl), dried (MgSO₄), and concentrated, and chromatographed (SiO₂, Et₂O-hexane 1:1 v/v) to give the vinyl-carbamate (860 mg, 72%) as a colorless oil: $[\alpha]_D^{24}$ -43.7° (c 1.06, CHCl₃). Ir (neat) $\nu_{\max}$: 3400, 1670 cm⁻¹; ¹H nmr (CDCl₃) δ : 5.80-6.47 (m, 1H), 4.90-5.33 (m, 2H), 2.88-4.40 (m, 5H), 3.72 (s, 3H), 2.37-2.88 (m, 1H), 2.12 (br s, 1H, exchangeable with D₂O), 1.46-2.03 (m, 3H), 1.23 (d, 3H, *J*=6.0 Hz); ms (*m/z*): 214 (M⁺+1), 213 (M⁺), 88 (100%). Calcd for C₁₁H₂₀O₃N: 214.1442. Found 214.1417 (M⁺+1). Anal. Calcd for C₁₁H₁₉O₃N: C 61.94, H 8.98, N, 6.57. Found: C 61.66, H 8.98, N 6.30.

To a stirred solution of the carbamate (827 mg, 3.88 mmol) in THF (20 ml) was added 0.5 M dicyclohexylborane in THF (19.41 ml, 9.71 mmol) and the reaction mixture was stirred at room temperature for 2.5 h. After cooling to 0 °C, MeOH (5.0 ml), 3N NaOH (3.4 ml), and 30% H₂O₂ (3.3 ml) were added successively to the reaction mixture and the mixture was heated at 50 °C for 1 h. After removal of the solvent, the residue was extracted with Et₂O and the extract was washed (sat. NaCl), dried (MgSO₄), concentrated, and chromatographed (SiO₂, 3% MeOH-Et₂O) to give the diol (**21a**) (950 mg, quant.) as a colorless oil: $[\alpha]_D^{24}$ -20.0° (c 1.30, MeOH). Ir (neat) $\nu_{\max}$: 3400, 1675 cm⁻¹; ¹H nmr (CDCl₃) δ : 3.70 (s, 3H), 2.97-4.20 (m, 7H), 2.37-2.93 (br s, 2H, exchangeable with D₂O), 1.30-2.33 (m, 6H), 1.30 (d, 3H, *J*=7.0 Hz); ms (*m/z*): 231 (M⁺), 88 (100%). Calcd for C₁₁H₂₂NO₄: 232.1548. Found: 232.1538 (M⁺+1). Anal. Calcd for C₁₁H₂₁NO₄: C 57.12, H 9.15, N 6.06. Found: C 56.65, H 9.17, N 5.77.

(3R,4R,5S)-5-Hydroxy-4-hydroxymethyl-3-vinylhexanoic Acid Lactone (17b) —

The *cis*-lactone (**13b**) (6.51 g, 23.59 mmol) was hydrogenated over 10% palladized carbon (610 mg) in EtOH (150 ml) containing a catalytic amount of conc. HCl under atmospheric pressure at room temperature for 5.5 h. After removal of the catalyst by filtration, the filtrate was concentrated to give the alcohol (**14b**) (4.20 g) as a colorless oil. Ir (neat) $\nu_{\max}$: 3450, 1735

cm⁻¹; ¹H nmr (CDCl₃) δ: 3.33-4.63 (m, 6H), 1.83-2.87 (m, 5H, 2H exchangeable with D₂O), 1.37 (d, 3H, *J*=6.0 Hz); ms (*m/z*): 187 (*M*⁺+1), 81 (100%). A mixture of **14b** (4.20 g) and *p*-toluenesulfonyl chloride (5.95 g, 31.20 mmol) in pyridine (120 ml) was stirred at room temperature for 10 h. After removal of the solvent using a vacuum pump, the residue was extracted with Et₂O. The extract was washed (5% HCl, sat. NaHCO₃, sat. NaCl), dried (MgSO₄), and concentrated to give the tosylate (**15b**) (6.94 g) as colorless needles which was used without purification. For the analytical purpose, a small amount of the product was purified by tlc (silica gel, AcOEt) followed by recrystallization (CH₂Cl₂-Et₂O) to give a pure sample: mp 156-157 °C; [α]_D¹⁸ -81.10° (*c* 1.05, CHCl₃). Ir (Nujol) ν_{max}: 1740, 1355, 1180 cm⁻¹; ¹H nmr (CDCl₃) δ: 7.77 (d, 2H, *J*=10 Hz), 7.33 (d, 2H, *J*=10 Hz), 3.33-4.55 (6H, m), 2.13-2.90 (m, 7H), 1.33 (d, 3H, *J*=6.0 Hz); ms (*m/z*): 341 (*M*⁺+1), 155 (100%). Calcd for C₁₆H₂₁O₆S: 341.1057. Found: 341.1016 (*M*⁺+1). *Anal.* Calcd for C₁₆H₂₁O₆S: C 56.46, H 5.92, S 9.42. Found: C 56.52, H 6.05, S 9.65. A mixture of **15b** (6.94 g) and sodium iodide (14.15 g, 94.36 mmol) in 2-butanone (150 ml) was refluxed for 12 h. After removal of the solvent, the residue was extracted with Et₂O. The extract was washed (H₂O, 5% Na₂S₂O₃, sat. NaCl), dried (MgSO₄), and concentrated to give the iodide (**16b**) (5.44 g) as colorless needles which were used without purification. Recrystallization (CH₂Cl₂-Et₂O) gave an analytically pure sample: mp 125.5-126.5 °C; [α]_D²⁵ -76.80° (*c* 0.66, CHCl₃). Ir (Nujol) ν_{max}: 1720 cm⁻¹; ¹H nmr (CDCl₃) δ: 3.40-4.57 (m, 4H), 3.23 (d, 2H, *J*=7.0 Hz), 2.10-3.10 (m, 4H), 1.37 (d, 3H, *J*=7.0 Hz); ms (*m/z*): 297 (*M*⁺+1), 296 (*M*⁺), 155 (100%). Calcd for C₉H₁₃O₃I: 295.9907. Found: 295.9907 (*M*⁺). *Anal.* Calcd for C₉H₁₃O₃I: C 36.51, H 4.43. Found: C 36.67, H 4.50.

A mixture of **16b** (5.44 g) and activated zinc dust (11.62 g, 0.18 mol) in 95% aqueous EtOH (200 ml) was heated at 60 °C for 2 h, and at reflux for 0.5 h. After filtration (Celite), the filtrate was concentrated and chromatographed (SiO₂, Et₂O) to give the desired **17b** as a colorless oil accompanied by the inseparable isomeric by-product generated by lactone exchange (2.90 g, 72% overall from the benzyl ether). Ir (neat) ν_{max}: 3450, 1740, 1640 cm⁻¹; ¹H nmr (CDCl₃) δ: 5.50-6.17 (m, 1H), 4.87-5.30 (m, 2H), 4.47 (dq, 0.6H, *J*=7.9, 6.0 Hz), 4.11-4.39 (m, 1.2H), 3.94 (dq, 0.4H, *J*=6.0, 3.6 Hz), 3.54-3.85 (m, 0.8H), 2.13-3.09 (m, 3H), 1.69-2.06 (m, 1H), 1.61 (s, 1H, exchangeable with D₂O), 1.40 (d, 1.2H, *J*=6.0 Hz), 1.24 (d, 1.8H, *J*=6.0 Hz); ms (*m/z*): 171 (*M*⁺+1), 43 (100%). Calcd for C₉H₁₅O₃: 171.1021. Found: 171.1031.

(4*S*,5*S*)-5-[(1*S*)-Hydroxyethyl]-4-vinylpiperidin-2-one (20b: X=O) — A mixture of the lactone (**17b**) (2.66 g, 15.65 mmol), triphenylphosphine (6.15 g, 23.47 mmol), and phthal-

imide (3.45 g, 23.47 mmol) in THF (75 ml) was stirred with diisopropyl azodicarboxylate (4.62 ml, 23.47 mmol) at 0 °C for 10 min and then at room temperature for 0.5 h. After removal of the solvent, the residue was chromatographed (SiO₂, 67% Et₂O-hexane) to give the imide (**18b**) (3.90 g) which was then refluxed with 90% hydrazine hydrate (1.29 ml, 26.58 mmol) in EtOH (40 ml) for 0.5 h. After removal of the solvent, CHCl₃ was added to the residue and the mixture was filtered. The filtrate was evaporated and chromatographed (MPLC, SiO₂, 1% MeOH-CH₂Cl₂) to give the lactam isomer (4*S*,5*R*,6*R*)-3-hydroxymethyl-6-methyl-4-vinylpiperidin-2-one (260 mg, 10% overall from the lactone **17b** from the contaminated lactone by-product) as the less polar fraction as a colorless viscous oil: $[\alpha]_D^{22} -9.6^\circ$ (*c* 0.85, CHCl₃). Ir (neat) $\nu_{\max}$: 3230, 1655 cm⁻¹; ¹H nmr (CDCl₃) δ : 5.63-6.63 (m, 3H), 4.87-5.43 (m, 2H), 3.47-4.50 (m, 3H), 1.73-3.27 (m, 4H), 1.28 (d, 3H, *J*=7.0 Hz); ms (*m/z*): 170 (*M*⁺+1), 169 (*M*⁺), and the desired lactam (**20b**: X=O) (680 mg, 26% from the lactone (**17b**)) as the more polar fraction as colorless plates which was recrystallized from CHCl₃: mp 123-124.5 °C; $[\alpha]_D^{21} -93.6^\circ$ (*c* 1.03, CHCl₃). Ir (Nujol) $\nu_{\max}$: 3400, 3300, 1655 cm⁻¹; ¹H nmr (CDCl₃) δ : 6.85-7.49 (br s, 1H), 5.40-6.10 (m, 1H), 4.90-5.40 (m, 2H), 3.97 (dq, 1H, *J*=6.6, 6.0 Hz), 2.91-3.73 (m, 3H), 1.56-2.90 (m, 4H), 1.18 (d, 3H, *J*=6.6 Hz); ms (*m/z*): 170 (*M*⁺+1), 123 (100%). Calcd for C₉H₁₆NO₂: 170.1181. Found: 170.1776 (*M*⁺+1). Anal. Calcd for C₉H₁₅NO: C 63.88, H 8.94, N 8.28. Found: C 63.73, H 9.16, N 8.28.

(3*R*,4*S*)-1-Carbomethoxy-4-(2-hydroxyethyl)-3-[(1*S*)-hydroxyethyl]piperidine

(21b) — A mixture of the lactam (**20b**: X=O) (300 mg, 1.78 mmol) and LiAlH₄ (202 mg, 5.33 mmol) in THF (7 ml) was refluxed for 3 h. After quenching the reaction by addition of 28% NH₄OH, the reaction mixture was filtered (Celite). The filtrate was concentrated to give the amine (**20b**: X=H₂) (254 mg) as a colorless amorphous solid. Ir (neat) $\nu_{\max}$: 3330, 1645 cm⁻¹; ¹H nmr (CDCl₃) δ : 5.40-6.10 (m, 1H), 4.80-5.37 (m, 2H), 3.93 (dq, 1H, *J*=6.0, 4.0 Hz), 1.08 (d, 3H, *J*=6.0 Hz), 0.70-3.63 (m, 10 Hz); ms (*m/z*): 155 (*M*⁺), 31 (100%).

A mixture of **20b** (X=H₂) (254 mg), Et₃N (0.69 ml, 4.91 mmol), and ClCO₂Me (0.17 ml, 2.13 mmol) in CH₂Cl₂ (5 ml) was stirred at room temperature for 0.5 h. The mixture was extracted with CH₂Cl₂ and the extract was washed (5% aq. HCl, sat. NaHCO₃, sat. NaCl), dried (MgSO₄), and concentrated to give the vinyl-carbamate (340 mg) as a pale yellow oil. Ir (neat) $\nu_{\max}$: 3350, 1700 cm⁻¹; ¹H nmr (CDCl₃) δ : 4.87-5.10 (m, 3H), 3.68 (s, 3H), 3.57-4.50 (m, 3H), 1.25-3.30 (m, 8H), 1.97 (s, 1H, exchangeable with D₂O), 1.16 (d, 3H, *J*=7.0 Hz); ms (*m/z*): 213 (*M*⁺), 89 (100%).

To a stirred solution of the carbamate (340 mg) in THF (8 ml) was added 0.5 M dicyclohexylborane in THF (8.38 ml, 4.19 mmol) and the reaction mixture was stirred at room temperature for 2.5 h. After cooling to 0 °C, EtOH (3.3 ml), 3N NaOH (2.2 ml), and 30% H₂O₂ (2.3 ml) were added successively to the reaction mixture and the mixture was heated at 50 °C for 1 h. After removal of the solvent, the residue was extracted with Et₂O and the extract was washed (sat. NaCl), concentrated, and chromatographed (SiO₂, 5% MeOH-CHCl₃) to give the diol (**21b**) (405 mg, 99% overall from **20b** (X=H₂)) as a colorless viscous oil: [α]_D²¹ -13.0° (c 0.63, MeOH). Ir (neat) $\nu_{\max}$: 3400, 1680 cm⁻¹; ¹H nmr (CDCl₃) δ : 3.34-4.24 (m, 5H), 3.64 (s, 3H), 2.54-3.31 (m, 2H), 2.79 (s, 2H, exchangeable with D₂O), 0.84-2.17 (m, 6H), 1.22 (d, 3H, *J*=7.0 Hz); ms (*m/z*): 231 (M⁺), 89 (100%). Calcd for C₁₁H₂₁O₄N: 231.1469. Found: 231.1461 (M⁺).

(3*S*,4*S*)-1-Carbomethoxy-3-[(1*S*)-hydroxyethyl]piperidine-4-carboxylic Acid

Lactone (22) — A suspension of **21a** (39 mg, 0.17 mmol) and Fetizon reagent (200 mg) in benzene (3.5 ml) was azeotropically refluxed for 9.5 h. After removal of the reagent by filtration (Celite), the filtrate was concentrated to give the lactone (**22**) (19 mg, 50%) as a colorless viscous oil: [α]_D²⁶ -76.1° (c 0.42, MeOH). Ir (neat) $\nu_{\max}$: 1730, 1695 cm⁻¹; ¹H nmr (CDCl₃) δ : 3.75-4.83 (m, 3H), 3.75 (s, 3H), 2.07-3.40 (m, 4H), 1.45 (d, 3H, *J*=6.0 Hz), 1.23-2.34 (m, 4H); ms (*m/z*): 227 (M⁺), 140 (100%). Calcd for C₁₁H₁₇NO₄: 227.1156. Found: 211.1145 (M⁺).

(3*S*,4*S*)-1-Carbomethoxy-4-(2-hydroxyethyl)-3-[(1*S*)-hydroxyethyl]piperidine

(24a) — A mixture of the diol (**21a**) (145 mg, 0.63 mmol) and benzoyl chloride (0.09 ml, 0.76 mmol) in pyridine (5 ml) was stirred at room temperature for 35 h. After removal of the solvent under vacuum, the residue was extracted with Et₂O. The extract was washed (5% HCl, sat. NaHCO₃, sat. NaCl), dried (MgSO₄), and chromatographed (SiO₂, 80% Et₂O-hexane) to give (3*S*,4*S*)-4-(2-benzoyloxyethyl)-1-carbomethoxy-3-[(1*S*)-hydroxyethyl]piperidine (149 mg, 71%, 83% based on the consumed starting material): [α]_D²⁸ -15.3° (c 0.98, CHCl₃). Ir (neat) $\nu_{\max}$: 3425, 1700 cm⁻¹; ¹H nmr (CDCl₃) δ : 7.93-8.27 (m, 2H), 7.33-7.73 (m, 3H), 2.93-4.60 (m, 7H), 3.70 (s, 3H), 2.43 (br s, 1H, exchangeable with D₂O), 1.28 (d, 3H, *J*=6.0 Hz), 1.10-2.27 (m, 6H); ms (*m/z*): 335 (M⁺), 105 (100%). Calcd for C₁₈H₂₅NO₅: 335.1732. Found: 335.1737 (M⁺).

A mixture of the above benzoate (193 mg, 0.58 mmol), tri-*n*-butylphosphine (0.57 ml, 2.30 mmol), and benzoic acid (281 mg, 2.30 mmol) in THF (7 ml) was stirred with diisopropyl azodicarboxylate (0.45 ml, 2.30 mmol) at 0 °C for 1 h and then at room temperature for 11 h. After removal of the solvent, the residue was chromatographed (SiO₂, 67% Et₂O-hexane) to give the dibenzoate which was treated with K₂CO₃ (400 mg) in MeOH (5 ml) at room temperature for

15 h followed by 3N NaOH (1.5 ml) at room temperature for 1.5 h with stirring. The mixture was extracted with CH_2Cl_2 and the extract was washed (sat. NaCl), dried (MgSO_4), and chromatographed (SiO_2 , 67% Et_2O -hexane) to give the elimination product, (4*S*)-1-carbomethoxy-3(*Z*)-ethylidene-4-(2-hydroxyethyl)piperidine (69 mg, 56%) as the less polar fraction as a colorless oil: $[\alpha]_{\text{D}}^{25} -18.1^\circ$ (*c* 1.89, MeOH). Ir (neat) ν_{max} : 3430, 1690 cm^{-1} ; ^1H nmr (CDCl_3) δ : 5.35 (q, 1H, $J=9.0$ Hz), 4.03 (br s, 2H), 3.70 (s, 3H), 3.40-3.93 (m, 4H), 2.13 (s, 1H, exchangeable with D_2O), 1.74 (d, 3H, $J=9.0$ Hz), 1.00-2.67 (m, 5H); ms (*m/z*): 214 (M^++1), 213 (M^+), 168 (100%). Calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_3$: 213.1365. Found: 213.1368 (M^+) and the desired diol (**24a**) (52 mg, 39%) as the more polar fraction as a colorless oil: $[\alpha]_{\text{D}}^{26} -18.0^\circ$ (*c* 0.95, MeOH). Ir (neat) ν_{max} : 3400, 1680 cm^{-1} ; ^1H nmr (CDCl_3) δ : 3.60 (s, 3H), 3.33 (br s, 2H, exchangeable with D_2O), 1.27 (d, 3H, $J=6.0$ Hz), 1.10-4.07 (m, 13 H); ms (*m/z*): 231 (M^+), 88 (100%). Calcd for $\text{C}_{11}\text{H}_{22}\text{NO}_4$: 232.1547. Found: 232.1532 (M^++1).

(3*R*,4*S*)-1-Carbomethoxy-3-[(1*S*)-hydroxyethyl]piperidine-4-carboxylic Acid

Lactone (25) — A suspension of the above diol (**24a**) (51 mg, 0.22 mmol) and Fetizon reagent (700 mg) in benzene (10 ml) was refluxed as described for the lactone **22** to give the lactone **25** (34 mg, 68%) as colorless prisms (Et_2O) whose spectral data (ir, nmr, and ms) were identical with those of the known antipode: mp 78.5-81.5 $^\circ\text{C}$ (lit.¹¹: mp 78-80 $^\circ\text{C}$); $[\alpha]_{\text{D}}^{25} -36.2^\circ$ (*c* 0.68, MeOH) [lit.¹¹: $[\alpha]_{\text{D}}^{25} +32.2^\circ$ (*c* 1.0, MeOH)].

(3*R*,4*S*)-1-Carboxymethyl-3-[(1*S*)-hydroxyethyl]piperidine-4-carboxylic Acid

Lactone (23) — A suspension of **21b** (410 mg, 1.78 mmol) and Fetizon reagent (1435 mg) in benzene (15 ml) was azeotropically refluxed for 9.5 h. After filtration (Celite), the filtrate was concentrated to give crude **23** which on recrystallization (Et_2O) gave pure **23** (380 mg, 94%) as colorless needles: mp 144-145 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{22} +10.8^\circ$ (*c* 1.02, MeOH). Ir (Nujol) ν_{max} : 3400, 1690 cm^{-1} ; ^1H nmr (CDCl_3) δ : 3.93-4.43 (m, 2H), 4.08 (dq, 1H, $J=6.4$, 11 Hz), 3.68 (s, 3H), 1.40 (d, 3H, $J=6.4$ Hz), 0.73-3.17 (m, 8H); ms (*m/z*): 228 (M^++1), 227 (M^+), 140 (100%). Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_4\text{N}$: 228.1234. Found: 228.1201 (M^++1). Anal. Calcd for $\text{C}_{11}\text{H}_{17}\text{NO}_4$: C 58.13, H 7.54, N 6.16. Found: C 58.15, H 7.65, N 6.16.

(3*R*,4*S*)-1-Carbomethoxy-4-(2-hydroxyethyl)-3-[(1*R*)-hydroxyethyl]piperidine

(24b) — A mixture of **21b** (254 mg, 1.10 mmol) and benzoyl chloride (0.16 ml, 1.33 mmol) in pyridine (5 ml) was stirred at room temperature for 23 h. After removal of the solvent using a vacuum pump, the residue was extracted with Et_2O . The extract was washed (5% HCl, sat. NaHCO_3 , sat. NaCl), dried (MgSO_4), and chromatographed (SiO_2 , 80% Et_2O -hexane) to give

(3*R*,4*S*)-4-(2-benzoyloxyethyl)-1-carbomethoxy-3-[(1*S*)-hydroxyethyl]piperidine (280 mg, 76%) as a colorless oil. Ir (neat) $\nu_{\max}$: 3425, 1695 cm^{-1} ; ^1H nmr (CDCl_3) δ : 7.88-8.23 (m, 2H), 7.33-7.73 (m, 3H), 3.67-4.67 (m, 5H), 3.67 (s, 3H), 2.67-3.37 (m, 2H), 2.17 (s, 1H, exchangeable with D_2O), 1.20 (d, 3H, $J=6.0$ Hz), 1.06-2.57 (m, 6H); ms (m/z): 336 (M^++1), 335 (M^+), 105 (100%). Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_5$: 335.1733. Found 335.1754 (M^+).

A mixture of the above benzoate (64 mg, 0.19 mmol), triphenylphosphine (55 mg, 0.21 mmol), and benzoic acid (26 mg, 0.21 mmol) was stirred with diisopropyl azodicarboxylate (0.04 ml, 0.21 mmol) at room temperature for 2.5 h. After removal of the solvent, the residue was chromatographed (SiO_2) to give crude (3*R*,4*S*)-3-[(1*R*)-benzoyloxyethyl]-4-(2-benzoyloxy)-1-carbomethoxypiperidine which was refluxed with 10% aq. NaOH in THF (50%, 3 ml) for 13 h. After cooling, the mixture was extracted with CH_2Cl_2 and the extract was washed (sat. NaCl), dried (MgSO_4), and chromatographed (SiO_2 , 10% MeOH-Et $_2\text{O}$) to give **24b** (40 mg, 69% overall from **21b**) as a colorless oil: $[\alpha]_{\text{D}}^{26} -1.6^\circ$ (c 0.42, MeOH). Ir (neat) $\nu_{\max}$: 3300, 1680 cm^{-1} ; ^1H nmr (CDCl_3) δ : 3.57-4.37 (m, 5H), 3.70 (s, 3H), 2.67-3.33 (m, 4H, 2H exchangeable with D_2O), 1.27 (d, 3H, $J=6.0$ Hz), 0.90-2.30 (m, 6H); ms (m/z): 232 (M^++1), 231 (M^+), 168 (100%). Calcd for $\text{C}_{11}\text{H}_{22}\text{NO}_4$: 232.1547. Found: 232.1530 (M^++1).

(3*R*,4*S*)-1-Carboxymethyl-3-[(1*R*)-hydroxyethyl]piperidine-4-carboxylic Acid

Lactone (26) — A suspension of the diol (**24b**) (47 mg, 0.20 mmol) and Fetizon reagent (670 mg) in benzene (6 ml) was refluxed as described for the lactone (**23**) for 12 h. After filtration (Celite), the filtrate was concentrated and chromatographed (SiO_2 , Et $_2\text{O}$) to give the lactone (30 mg, 65%) as a colorless oil: $[\alpha]_{\text{D}}^{26} +41.7^\circ$ (c 0.59, MeOH). Ir (neat) $\nu_{\max}$: 1730, 1695 cm^{-1} ; ^1H nmr (CDCl_3) δ : 4.69 (dq, 1H, $J=6.6, 4.4$ Hz), 3.91-4.47 (m, 2H), 3.69 (s, 3H), 1.20-2.94 (m, 8H), 1.30 (d, 3H, $J=6.6$ Hz); ms (m/z): 228 (M^++1), 227 (M^+), 88 (100%). Calcd for $\text{C}_{11}\text{H}_{18}\text{NO}_4$: 228.1235. Found: 228.1200 (M^++1).

Formation of the *cis*-Lactone Ester (27) from the *E*-Diol (12) — To a stirred solution of **12** (29.83 g, 0.11 mol) in MeOH (300 ml) was added NaIO_4 (28.80 g, 0.14 mol) in H_2O (200 ml) at 0 $^\circ\text{C}$ and the mixture was stirred at the same temperature for 2 h. After filtration (Celite), the filtrate was extracted with Et $_2\text{O}$. The extract was washed (sat. NaCl), dried (MgSO_4), and concentrated to give the aldehyde (**1E**) (26.09 g) as a pale yellow oil. A mixture of **1E** (26.09 g), Meldrum's acid (16.14 g, 0.11 mol), and ethylenediammonium diacetate (403 mg, 2.24 mmol) in MeOH (250 ml) was stirred at room temperature for 20 h. After removal of the solvent, the residue was extracted with Et $_2\text{O}$. The extract was washed (sat. NaHCO_3 , sat. NaCl),

dried (MgSO_4), and evaporated to give the unstable adduct **4** (36.47 g) as a pale yellow oil which was refluxed in MeOH (300 ml) for 4.5 h. After removal of the solvent, the residue was extracted with Et_2O . The extract was washed (sat. NaHCO_3 , sat. NaCl), dried (MgSO_4), concentrated, and chromatographed (SiO_2 , 50% AcOEt -hexane) to give the methyl ester (**27**) (18.53 g, 50% overall) as a colorless viscous oil: $[\alpha]_{\text{D}}^{28} -57.30^\circ$ (c 1.41, CHCl_3). Ir (neat) ν_{max} : 1740, 1730 cm^{-1} ; ^1H nmr (CDCl_3) δ : 7.27 (s, 5H), 4.52 (s, 2H), 3.68 (s, 3H), 3.40-4.47 (m, 7H), 2.20-3.27 (m, 2H), 1.33 (d, 3H, $J=6.0$ Hz); ms (m/z): 334 (M^+), 91 (100%). Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_6$: 334.1415. Found: 334.1395 (M^+). Anal. Calcd for $\text{C}_{18}\text{H}_{22}\text{O}_6$: C 64.65, H 6.63. Found: C 64.64, H 6.47.

(1R,4S,8R,9S)-1-Benzylloxymethyl-7-carbomethoxy-4-methyl-4,5,8,9-tetrahydro-2,5-dioxaindane (29) — To a stirred solution of **27** (10.44 g, 31.26 mmol) in THF (400 ml) was added LiEt_3BH (1M in THF, 46.9 ml, 46.9 mmol) and the mixture was stirred at -70°C for 1 h and at -30°C for 1 h. Then another portion of LiEt_3BH (1M in THF, 9.4 ml, 9.40 mmol) was added to the mixture. After stirring at -30°C for 11 h, the mixture was quenched with 5% HCl (30 ml). The mixture was extracted (Et_2O), washed (sat. NaCl), dried (MgSO_4), concentrated, and chromatographed (SiO_2 , 50% AcOEt -hexane) to give a mixture of the lactol (**28**) and the starting **27**. The mixture (10.03 g) in toluene (150 ml) was refluxed azeotropically with a catalytic amount of *p*-toluenesulfonic acid monohydrate for 1.5 h. After removal of the solvent, the mixture was extracted with Et_2O . The extract was washed (sat. NaHCO_3 , sat. NaCl), dried (MgSO_4), and chromatographed (SiO_2 , 20-50% AcOEt -hexane) to give the recovered **27** (6.77 g, 65%) and **29** (2.78 g, 28%, 80% based on the consumed starting material) as a colorless viscous oil which was crystallized from Et_2O and petr. ether to give colorless plates: mp $71.5-73.0^\circ\text{C}$; $[\alpha]_{\text{D}}^{27} -61.23^\circ$ (c 0.97, CHCl_3). Ir (neat) ν_{max} : 1700, 1625 cm^{-1} ; ^1H nmr (CDCl_3) δ : 7.67 (s, 1H), 7.20-7.50 (br s, 5H), 4.60 (s, 2H), 3.70-4.27 (m, 5H), 4.07 (dd, 1H, $J=9, 6$ Hz), 3.66 (s, 3H), 2.93 (dd, 1H, $J=7, 7$ Hz), 1.80-2.30 (m, 1H), 1.40 (d, 3H, $J=6$ Hz); ms (m/z): 318 (M^+), 197 (100%). Calcd for $\text{C}_{18}\text{H}_{23}\text{O}_5$: 319.1545. Found: 319.1515 (M^++1). Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{O}_5$: C 67.91, H 6.97. Found: C 67.86, H, 6.87.

(1R,4S,8R,9S)-7-Carbomethoxy-1-hydroxymethyl-4-methyl-4,5,8,9-tetrahydro-2,5-dioxaindane (30) — A solution of **29** (522 mg, 1.64 mmol) in MeOH (15 ml) was hydrogenated over 10% palladized carbon (50 mg) containing a catalytic amount of conc. HCl under atmospheric pressure at room temperature for 45 min. After filtration (Celite), the filtrate was concentrated to give **30** (376 mg, quant.) as a colorless oil which was used without purification.

For the analytical purpose a small amount of the product was purified by chromatography (SiO₂, 80% Et₂O-hexane) to give pure **30**: [α]_D -24.70° (c 1.07, CHCl₃). Ir (neat) $\nu_{\max}$: 3470, 1705, 1630 cm⁻¹; ¹H nmr (CDCl₃) δ : 7.73 (s, 1H), 4.14 (dd, 1H, *J*=9, 6 Hz), 3.50-4.10 (m, 5H), 2.80-3.20 (m, 2H, 1H exchangeable with D₂O), 1.90-2.30 (m, 1H), 1.43 (d, 3H, *J*=7.5 Hz); ms (*m/z*): 229 (*M*⁺+1), 228 (*M*⁺), 197 (100%). Calcd for C₁₁H₁₆O₅: 228.0998. Found 228.1005 (*M*⁺). Anal. Calcd for C₁₁H₁₆O₅: C 57.88, H 7.07. Found: C 57.93, H 7.30.

(1*R*,4*S*,8*R*,9*S*)-7-Carbomethoxy-1-formyl-4-methyl-4,5,8,9-tetrahydro-2,5-

dioxaindane (31) — To a stirred solution of oxalyl chloride (0.37 ml, 3.28 mmol) in CH₂Cl₂ (15 ml) was added DMSO (0.47 ml, 19.70 mmol) dropwise at -62 °C and, after 15 min, a solution of **30** (376 mg, 1.64 mmol) in CH₂Cl₂ (18 ml) followed by, after 30 min, Et₃N (1.83 ml, 13 mmol) were added at the same temperature. After raising gradually to room temperature, 1% HCl was added to the mixture. The mixture was extracted with Et₂O and the extract was washed (sat. NaHCO₃, sat. NaCl), dried (MgSO₄), concentrated, and chromatographed (SiO₂, Et₂O) to give the aldehyde (**31**) (370 mg) as a yellow oil which was used without further purification. Ir (neat) $\nu_{\max}$: 3350, 1725, 1695, 1665, 1625 cm⁻¹; ¹H nmr (CDCl₃) δ : 9.78 (d, 1H, *J*=1.7 Hz), 7.73 and 7.28 (each br s, total 1H), 3.77 and 3.73 (each s, total 3H), 3.62-4.46 (m, 3H), 3.03-3.55 (m, 1H), 1.84-2.36 (m, 1H), 1.42 and 1.40 (each d, total 3H, each *J*=6.9 Hz); ms (*m/z*): 227 (*M*⁺+1), 197 (100%).

Reductive Cleavage of the Aldehyde (31) — To a stirred solution of **31** (370 mg, 1.64 mmol) and conc. HCl (10 drops) in THF (10 ml) was added activated zinc dust (4.30 g) portionwise at room temperature for 1 h. After filtration (Celite), the filtrate was extracted with Et₂O. The extract was washed (sat. NaHCO₃, sat. NaCl), dried (MgSO₄), and chromatographed (SiO₂, 25% Et₂O-hexane) to give the lactol (**33**) (357 mg) as a colorless oil. Ir (neat) $\nu_{\max}$: 3425, 1700, 1630 cm⁻¹; ¹H nmr (CDCl₃) δ : 5.23 (m, 0.4H), 4.82 (ddd, 0.6H, *J*=8.5, 6.8, 2.4 Hz), 3.84-4.52 (m, 3H), 3.71 (s, 3H), 3.34 (d, 1H, *J*=6.8 Hz, exchangeable with D₂O), 2.25-3.25 (m, 3H), 1.96-2.46 (m, 1H), 1.41 (d, 3H, *J*=6.2 Hz); ms (*m/z*): 229 (*M*⁺+1), 288 (*M*⁺), 29 (100%). Calcd for C₁₁H₁₆O₅: 228.1014. Found: 228.0994 (*M*⁺). Anal. Calcd for C₁₁H₁₆O₅: C 57.88, H 7.07. Found: C 57.73, H 6.87.

Oxidation of the Lactol (33) — A suspension of **33** (357 mg) and Fetizon reagent (3.57 g) in benzene (40 ml) was refluxed for 1 h. After filtration (Celite), the filtrate was concentrated and chromatographed (SiO₂, AcOEt-hexane, 60%) to give the lactone (**34**) (304 mg 82% overall from **29**) as a colorless solid which was recrystallized (Et₂O) to give colorless needles: mp 94.5-

95.5 °C; $[\alpha]_D^{29} -8.60^\circ$ (c 1.09, CHCl_3). Ir (neat) ν_{max} : 1740, 1700, 1630 cm^{-1} ; ^1H nmr (CDCl_3) δ : 7.61 (s, 1H), 4.46 (dd, 1H, $J=12$, 4.4 Hz), 4.25 (dd, 1H, $J=12$, 4.4 Hz), 3.94 (dq, 1H, $J=9.4$, 6.1 Hz), 3.74 (s, 3H), 3.11 (dd, 1H, $J=19$, 6.7 Hz), 2.91-3.25 (m, 1H), 2.36 (dd, 1H, $J=19$, 11 Hz), 1.80-2.18 (m, 1H), 1.43 (d, 3H, $J=6.1$ Hz); ms (m/z): 227 (M^{++1}), 226 (M^+), 167 (100%). Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_5$: 226.0842. Found: 226.0855 (M^+). Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_5$: C 58.40, H 6.24. Found: C 58.21, H 6.07.

Sequential Methanolysis and Oxidation of the Lactone (34) — A mixture of the lactone (**34**) (46 mg, 0.20 mmol) and p-toluenesulfonic acid monohydrate (2 mg, 0.01 mmol) in MeOH (5 ml) was stirred at room temperature for 10 h. After adding Et_3N (0.03 ml, 0.20 mmol), the mixture was evaporated and the residue containing the seco-ester in CH_2Cl_2 (5 ml) was added to a stirred solution of oxalyl chloride (0.07 ml, 0.61 mmol) and DMSO (0.09 ml, 1.22 mmol) in CH_2Cl_2 (2 ml) at -62°C . After 30 min, the mixture was treated with Et_3N (0.34 ml, 2.44 mmol) at the same temperature and was gradually raised to room temperature. The mixture was treated with sat. NaHCO_3 and extracted with Et_2O . The extract was washed (sat. NaCl), dried (MgSO_4), concentrated, and chromatographed (SiO_2 , Et_2O -hexane, 20% then 33%) to give a mixture of the aldehyde (**36**) and (–)-methyl elenolate (**37**) (31 mg, 60%, 98% based on the consumed lactone) and the recovered lactone (**34**) (18 mg, 39%).

(–)-Methyl Elenolate (37) — A solution of the mixture of **36** and **37** (31 mg, mmol) in CH_2Cl_2 (4 ml) was stirred with silica gel (600 mg) at room temperature for 4 h. After filtration the mixture was evaporated and chromatographed (SiO_2 , Et_2O) to give (–)-methyl elenolate (**37**) (31 mg, quant.) as a colorless oil: $[\alpha]_D^{25} -121^\circ$ (c 0.68, CHCl_3) [lit.^{15d}: $[\alpha]_D -117.0^\circ$ (CHCl_3)].

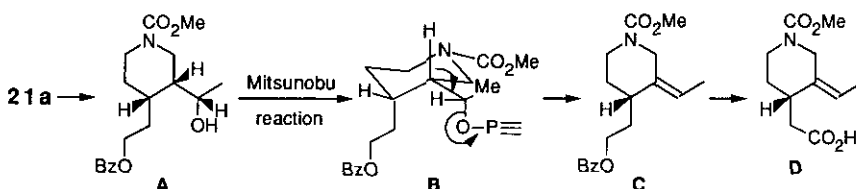
Spectral data (ir, nmr, and ms) were identical with those of an authentic material.^{15c}

ACKNOWLEDGMENTS

We are greatly indebted to Dr. Nobuo Shimma, Nippon Roche Co. Ltd., for providing spectra (^1H nmr, ir, and ms) of the compound **25** and Dr. Seiichi Saito, Tanabe Pharmaceutical Co. Ltd., for performing X ray analysis. We also thank the Ministry of Education, Science and Culture, Japan, for generous support of this research (Grant-in-Aid for Scientific Research on Priority Areas: 01607002) and Fellowships of the Japan Society for the Promotion of Science for Japanese Junior Scientists (S. S.).

REFERENCES AND NOTES

- + Taken from Dissertation of Shigeki Satoh, Tohoku University, March 1988. Part of the work was presented at 27 th Symposium on the Chemistry of Natural Products, Oct. 15 - 18, 1985, Hiroshima, Japan: S. Takano, S. Satoh, and K. Ogasawara, *Tennen Yuki Kagobutsu Koen Yoshishu*, 1985, **27**, pp. 236 - 243.
1. (a) S. Takano and K. Ogasawara, *J. Synth. Org. Chem. Jpn.*, 1982, **40**, 1037. (b) *idem*, *ibid.*, 1987, **45**, 1157. (c) *idem*, *ibid.*, 1989, **47**, 813. (d) S. Takano, *Pure Appl. Chem.*, 1987, **59**, 353.
2. (a) L. -F. Tietze, G. von Kiedrowski, K. Harms, W. Clegg, and G. Sheldrick, *Angew. Chem. Int. Ed. Engl.*, 1980, **19**, 134. (b) L. -F. Tietze and G. von Kiedrowski, *Tetrahedron Lett.*, 1981, **22**, 219. (c) L. -F. Tietze, 'Selectivity - A Goal for Synthetic Efficiency,' Verlag Chemie, Weinheim, 1984, pp. 299-316. (d) L. -F. Tietze, T. Brumby, M. Pretor, and G. Remberg, *J. Org. Chem.*, 1988, **53**, 810, and references cited therein.
3. S. Takano, S. Satoh, and K. Ogasawara, *Heterocycles*, 1985, **23**, 41.
4. R. M. Wenger, *Helv. Chim. Acta*, 1983, **66**, 2308.
5. (a) S. Takano, A. Kurotaki, Y. Sekiguchi, S. Satoh, M. Hiram, and K. Ogasawara, *Synthesis*, 1986, 403. (b) E. Hungerbuhler, D. Seebach, and D. Wasmuth, *Angew. Chem. Int. Ed. Engl.*, 1979, **18**, 958.
6. (a) S. Takano, M. Akiyama, S. Sato, and K. Ogasawara, *Chemistry Lett.*, 1983, 1593. (b) S. Takano, M. Akiyama, and K. Ogasawara, *Chem. Pharm. Bull.*, 1984, **32**, 791.
7. L. -F. Tietze and T. Eicher, 'Reaktionen und Synthesen,' Thieme Verlag, Stuttgart, 1981, pp. 387-389.
8. O. Mitsunobu, *Synthesis*, 1981, 1.
9. M. Fetizon, M. Golfier, and J. -M. Louis, *Tetrahedron*, 1975, **31**, 171.
10. Even tri-*n*-butylphosphine (Cf. T. G. Back and D. J. McPhee, *J. Org. Chem.*, 1984, **49**, 3842.) was used in place of triphenylphosphine in the Mitsunobu reaction of the primary benzoate (A) obtained from **21a**, a formation of (*S*)-2(*Z*)-ethylidene-4-(2-benzoyloxyethyl)-1-methoxy-carboxypiperidine (C) was overwhelmed (56%) presumably via a rigid conformation (B) suited for E2 elimination. The structure of the olefin (C) was determined by converting it into (*S*)-4-carboxymethyl-3(*Z*)-ethylidene-1-methoxycarbonylpiperidine (D), $[\alpha]_D^{25} -19.3^\circ$ (c 0.80, MeOH), of which enantiomer (ent-D), $[\alpha]_D^{25} +13.4^\circ$ (c 1.0, MeOH), was already known.¹¹



11. (a) M. R. Uskokovic, R. L. Lewis, J. J. Partridge, C. W. Despreaux, and D. L. Pruess, *J. Am. Chem. Soc.*, 1979, **101**, 6742. (b) N. Shimma, I. Kompis, V. J. Gruenman, and M. R. Uskokovic, *Tennen Yuki Kagobutsu Koen Yoshishu*, 1982, **25**, pp. 172-179.
12. Reduction of **27** with diisobutylaluminum hydride followed by acid catalyzed dehydration could afford **29** in 61% yield. However, it was accompanied by the α,β -unsaturated aldehyde (**29**: $\text{CO}_2\text{Me}=\text{CHO}$) in 14% yield.
13. A. J. Mancuso and D. Swern, *Synthesis*, 1981, 165.
14. The *cis*-aldehyde (**36**) could not be isolated in pure state owing to its ready isomerization to the *trans*-isomer (**37**) during isolation stage.
15. (a) F. A. Mackellar, R. C. Kelly, E. E. van Tamelen, and C. Dorschel, *J. Am. Chem. Soc.*, 1973, **95**, 7155. (b) R. C. Kelly and I. Schletter, *Ibid.*, 1973, **95**, 7156. (c) S. Hatakeyama, K. Saijo, and S. Takano, *Tetrahedron Lett.*, 1985, **26**, 865. (d) S. Hatakeyama, N. Ochi, H. Numata, and S. Takano, *J. Chem. Soc., Chem. Commun.*, 1988, 1202.
16. Cf. J. Gutzwiller, G. Pizzolato, and M. R. Uskokovic, *Helv. Chim. Acta*, 1981, **64**, 1663.
17. S. Takano, S. Satoh, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1988, 59.
18. S. Takano, T. Ohkawa, S. Tamori, S. Satoh, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 1988, **189**, 19.
19. S. Takano, T. Sugihara, S. Satoh, and K. Ogasawara, *J. Am. Chem. Soc.*, 1988, **110**, 6467.

Received, 31st August, 1989