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ASYMMETRIC HALOLACTONISATION REACTION—4[1]

ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE α,β-EPOXYALDEHYDES FROM α,β-UNSATURATED ACIDS[2]

M. HAYASHI, S. TERASHIMA* and K. KOGA
Faculty of Pharmaceutical Sciences, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan

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Abstract—The bromolactones (**5**) stereoselectively produced by the asymmetric bromolactonisation of (S)-*N*-(α,β-unsaturated)acylprolines(**3**), were elaborated to highly optically active 2(*R*),3(*S*)-epoxyaldehydes(**8**)(84–98% ee) by successive epoxide formation and reductive cleavage of the proline moiety. The overall process constitutes a highly efficient asymmetric synthesis of **8** from α,β-unsaturated acids(**1**).

Much attention has been paid to optically active epoxides in recent years because of their importance in biochemistry[3,4] and synthetic organic chemistry.[5] Thus, optically active epoxides play pivotal roles in some biosynthetic and metabolic processes,[3] and natural products having optically active epoxides in their structural units exhibit various important physiological properties such as antibiotic, anti-cancer, and hormonal activities.[4] In total syntheses of natural products hitherto reported, various structural types of optically active epoxides have been utilized ingeniously as versatile synthetic blocks from which complex carbon frameworks can be elaborated.[5]

While three sorts of methods such as optical resolution, transformation from readily available optically active compound, and asymmetric synthesis, could produce optically active epoxide, preparation by the use of asymmetric synthesis is anticipated to be most efficient since asymmetric reaction could directly afford desired optically active epoxide in high optical and chemical yields if it proceeds in completely an ideal fashion.[6]

Due to these reasons mentioned above, various types of asymmetric syntheses including catalytic epoxidations by means of optically active transition metal complexes[7] and biological epoxidations with microorganisms,[8] have been developed as methods for preparing optically active epoxides.[9] Although high optical yields (*ca.* 100% ee) have been achieved in the preparation of simple unfunctionalized olefins,[7e,8] practical asymmetric syntheses of highly optically active functionalized epoxides whose absolute configurations can be mechanistically established, have not been exploited.[10]

We have previously described that the bromolactonisation of (S)-*N*-(α,β-unsaturated)acylprolines(**3**) readily obtainable from α,β-unsaturated acids(**1**) proceed stereoselectively by way of the bromonium ions(**4**) to give mixtures of the bromolactones (**5**) in which **5A** are highly predominant. Debromination of **5** followed by acidic hydrolysis was found to produce (*R*)-α-hydroxy acids((R)-**6**) of high enantiomeric purity(87–98% ee).[11,12]

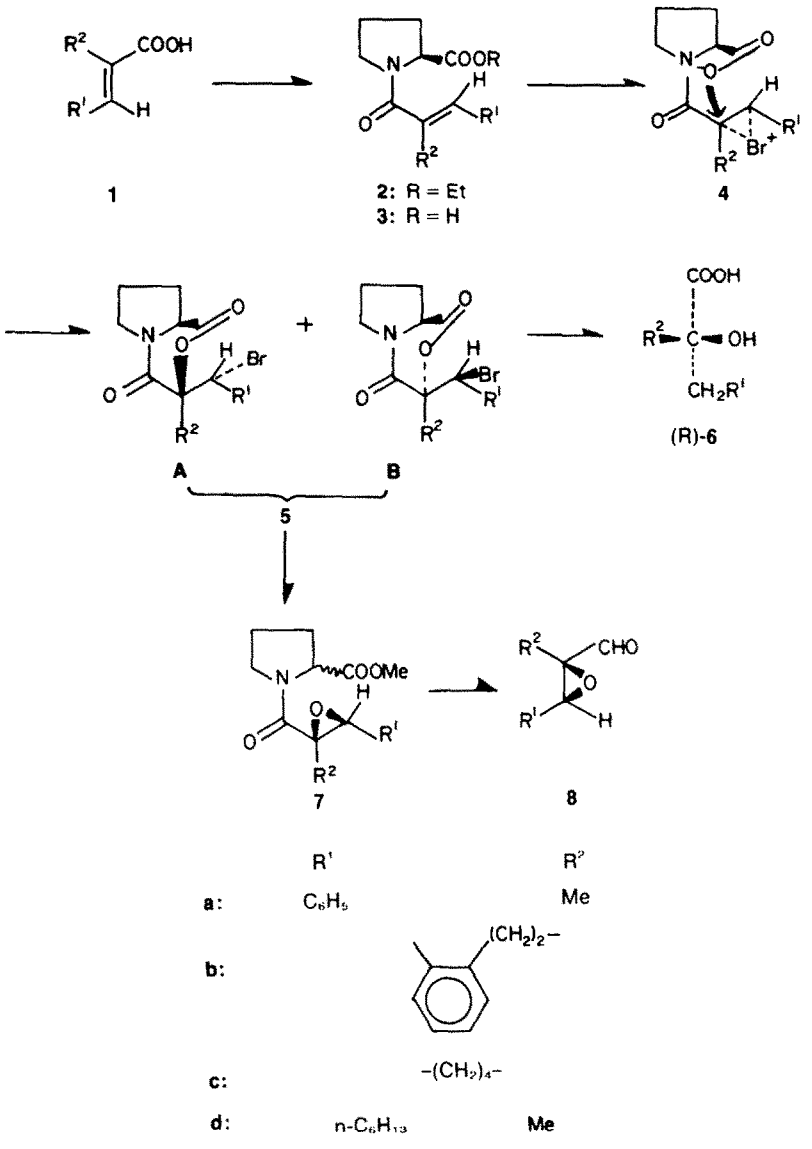
This paper deals with a novel application of the asymmetric reaction, developed for preparing (*R*)-**6**, to asymmetric synthesis of highly optically active α,β-epoxyaldehydes(**8**) whose absolute configurations can be definitely determined as 2(*R*),3(*S*) based on the established reaction mechanism of the asymmetric bromolactonisation reaction.[11] The exploited overall process constitutes a first practical asymmetric synthesis of **8** from **1**.

RESULTS AND DISCUSSION

As α,β-unsaturated acids(**1**) which can be utilized as reaction substrates, α-methylcinnamic acid(**1a**), 3,4-dihydro-2-naphthoic acid(**1b**), cyclohexene-1-carboxylic acid(**1c**), and 2-methyl-2(*E*)-nonenoic acid(**1d**) were chosen with an aim to cover a wide range of structural variation. While the former two kinds of acids(**1a,b**) were prepared following to the reported procedures,[11,12] preparations of the latter two types of acids(**1c,d**) were performed by using cycloheptene and n-heptanal as starting materials, respectively, and by employing the conventional synthetic methods which were detailed in experimental part.

As shown in *Scheme* 1, bromolactonisation of **3a**, prepared from **1a** by way of (*S*)-ethyl *N*-(α,β-unsaturated)acylprolinate (**2a**) according to the reported procedure,[11] gave the same mixture of **5Aa** and **5Ba**, $[\alpha]_D^{20}$ −105°(MeOH), in 95% yield as that obtained previously.[11] Since this sample had been converted to (*R*)-**6a**, 98% ee,[11] the ratio of **5Aa** to **5Ba** could be definitely determined as 99:1. While stereospecific transformations of halolactones to epoxy esters[13] or epoxy acids[5b] have recently reported, we have also found that the mixture of **5Aa** and **5Ba** is effectively transformed to the crude epoxy ester(**7a**) in 90% yield by treating with sodium methoxide in methanol. The product(**7a**) showed its methyl ester as two singlets at 3.72 and 3.80 ppm in its NMR spectrum. This spectral feature clearly disclosed that epimerization of the methyl ester occurred during the epoxide formation. The ratio of two epimers involved in **7a** could be roughly estimated as 2:1 by the peak intensity. Without further purification, crude **7a** was subjected to reductive cleavage of the epimerized proline moiety using sodium *bis*(2-methoxyethoxy)aluminum hydride(Vitride), affording optically active (+)-2-methyl-3-phenyl-2(*R*),3(*S*)-epoxypropanal((+)-**8a**), $[\alpha]_D^{20}$ +182°($CHCl_3$), in 72% yield.[14] The structure of (+)-**8a** was definitely confirmed by spectral comparisons with the corresponding racemic α,β-epoxyaldehyde(dl-**8a**) which was prepared from **1a**[11] by successive esterification, reduction, epoxidation, and oxidation(see Experimental).[15] The optical yield of (+)-**8a** could be calculated as 98% ee since the diastereomeric mixture of **5Aa** and **5Ba**(99:1) was subjected to the sequential reactions.[16]

In completely the same manner, the crude bromo-



Scheme 1.

lactone(**5b**), $[\alpha]_D^{20}$ −72.0°($CHCl_3$), was prepared in 88% yield from **3b** which was derived from **1b**.[12] The ratio of the two diastereomers (**5Ab** and **5Bb**) involved in crude **5b** was rigorously estimated as 96:4 by the fact that crude **5b** had already been converted to (*R*)-**6b**, 92% ee.[12] Similarly to **5a**, crude **5b** was transformed to (−)-**8b**, $[\alpha]_D^{20}$ − 189°($CHCl_3$), 92% ee, by way of crude **7b**. The chemical yields for the epoxide formation in a mixture of MeOH and THF and the reductive cleavage were both found to be 85%. The NMR spectrum showed that crude **7b** consisted of two epimeric esters in a ratio of 1:1. Optically active α,β-epoxyaldehyde((−)-**8b**) exhibited the same spectral properties as those of the corresponding racemic compound(dl-**8b**) which was independently prepared from ethyl 3,4-dihydro-2-naphthoate[12] (see Experimental).

The synthetic scheme developed with **1a,b** was further applied to **1c,d** to explore generality of the asymmetric synthesis. (S)-*N*-(α,β-Unsaturated)acylprolines(**3c,d**), $[\alpha]_D^{20}$ −49.8°(EtOH) and $[\alpha]_D^{20}$ −44.6°(EtOH), were similarly prepared from **1c,d** by way of **2c,d**. The asymmetric bromolactonisation of **3c,d** by the same procedure as that reported,[11,12] afforded the crude crystalline bromolactones(**5c,d**), $[\alpha]_D^{20}$ −99.4°(EtOH) and $[\alpha]_D^{20}$ −15.3°(EtOH), in 78% and 93% yields, respectively. Being different from the cases for **5a,b** in which the ratios of **5Aa,b** to **5Ba,b** had been established by the previous studies,[11,12] the predominantly formed bromolactones(**5Ac,d**), $[\alpha]_D^{20}$ −112°(EtOH) and $[\alpha]_D^{20}$ −19.5°(EtOH), were isolated in pure states by repeated recrystallizations of crude **5c,d**. When pure **5Ac,d** were successively treated by the reaction conditions for the epoxide formation in a mixture of MeOH and THF, and for the reductive removal of the proline moiety, there could be obtained optically pure (+)-**8c,d**, $[\alpha]_D^{20}$ + 44.7°($CHCl_3$) and $[\alpha]_D^{20}$ + 115°($CHCl_3$), in good yields by way of the mixtures of two epimeric esters(**7c,d**). The same sequential treatments of crude **5c,d**(mixtures of **5Ac,d** and **5Bc,d**) gave partially optically active (+)-**8c,d**, $[\alpha]_D^{20}$ + 43.6°($CHCl_3$) and $[\alpha]_D^{20}$ + 96.9°($CHCl_3$), respec-

tively. Comparisons of optical rotations clearly demonstrated that the optical yields of (+)-**8c,d** and the formation ratios of **5Ac,d** to **5Bc,d** were 98% ee, 84% ee, and 99:1, 92:8, respectively.

In summary, the reaction course shown in *Scheme* 1 is found to allow for the synthesis of highly optically active **8**(84–98% ee) from **1**. Moreover, in cases where **5** are obtained as crystalline solids and separation of the predominantly formed bromolactones(**5A**) can be readily accomplished by repeated recrystallizations, optically pure **8** can be also synthesized by subjecting purified **5A** to the established reaction scheme.

Considering operational simplicity and high optical yields, the exploited asymmetric synthesis might have wide practical values. It is also worth noting that functionalities involved in **8** are quite useful for further chemical elaborations including nucleophilic epoxide opening and carbon chain elongation from the aldehyde group. Along these lines, application of the overall process to synthesis of optically active natural products, especially anthracycline antibiotics being of current interest due to their promising anticancer activity,[17] is in progress in this laboratory.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra measurements were carried out using a JASCO Spectrometer Model DS-402G and a JASCO IRA-1 Grating IR Spectrometer. NMR spectra were measured with a Hitachi R-24 High Resolution Spectrometer. All signals are expressed by the ppm downfield from TMS used as an internal standard(δ value). The following abbreviations are used: singlet(s), doublet(d), triplet(t), quartet(q), multiplet(m), broad(br). Measurements of optical rotations were performed with a YANACO OR-50 Automatic Polarimeter and a JASCO DIP-181 Digital Polarimeter. Mass spectra were taken with a JEOL JMS SG-2 Mass Spectrometer. All reactions were carried out using anhydrous solvents, and the combined organic extracts obtained in each experiments were dried over Na_2SO_4 or $MgSO_4$ before successive filtration and evaporation *in vacuo* by a rotary evaporator.

3(*S*)[1′(*R*) - *Bromophenylmethyl*] - 3(*S*) - *methyl* - 1,4 - *dioxo* - 3, 4, 6, 7, 8*a*(*S*) - *hexahydro* - 1*H* - *pyrrolo*[2,1 - *c*][1,4]*oxazine*(**5Aa**) *and its* 1′(*S*),3(*R*) - *isomer*(**5Ba**). According to the reported procedure,[11a,c] **3a**(m.p. 114.5–115.5°, $[\alpha]_D^{20}$ − 13.3° (c = 1.01, MeOH)) (lit.,[11a,c] m.p. 116–117°, $[\alpha]_D^{20}$ − 11.8° (c = 1.00, MeOH)) (4.80 g, 18.5 mmole) was subjected to the bromolactonisation, giving crude **5a**(a mixture of **5Aa** and **5Ba**) as a pale yellow unstable caramel(5.94 g, 95%), $[\alpha]_D^{20}$ − 105° (c = 1.30, MeOH) (lit.,[11a,c] $[\alpha]_D^{20}$ − 102°(c = 0.934, MeOH)), after evaporation of the EtOAc extracts. Spectral (IR and NMR) properties of this sample were superimposable on those reported.[11a,c] Since crude **5a** had been converted to (*R*)-**6a**, 98% ee, in the previous study,[11a,c] the formation ratio of **5Aa** and **5Ba** could be determined as 99:1.

1(*R*) - *Bromo* - 1′,4′ - *dioxo* - 3, 4, 6′, 7′, 8′, 8′*a*(*S*) - *hexahydro* - *spiro*[*naphthalene* - 2(*S*)(1*H*), 3′(*S*)(4′*H*) - 1*H* - *pyrrolo*[2,1-*c*][1,4] *oxazine*](**5Ab**) *and its* 1(*S*), 2(*R*), 3′(*R*) - *isomer*(**5Bb**). The same bromolactonisation of **3b**(m.p. 136–137.5°, $[\alpha]_D^{20}$ − 102.5°(c = 1.07, $CHCl_3$))(lit.,[12a,c] oil, $[\alpha]_D^{20}$ − 93.3° (c = 2.16, $CHCl_3$))(2.00 g, 7.37 mmole) as that reported,[12a,c] afforded crude **5b**(a mixture of **5Ab** and **5Bb**) as pale yellow needles (2.26 g, 88%), m.p. 162–164°, $[\alpha]_D^{20}$ − 72.0° (c = 0.640, $CHCl_3$)(lit.,[12a,c] m.p. 166–170°, $[\alpha]_D^{20}$ − 68.6°(c = 1.01, $CHCl_3$)), after evaporation of the EtOAc extracts. This sample showed the same spectral (IR and NMR) properties as those reported.[12a,c] The previous study[12a,c] had disclosed that crude **5b** contained **5Ab** and **5Bb** in a ratio of 96:4 since (*R*)-**6b**, 92% ee, was prepared from this sample.

Cyclohexene - 1 - *carboxylic acid*(**1c**)

(a) trans-*Cycloheptane*-1,2-*diol*.[18] Cycloheptene(17.3 g, 0.18 mole) was added to a stirred mixture of 30% H_2O_2aq(33 ml) and 85% HCOOHaq(150 ml) at 40–50° over 30 min. After stirring at 50° for 1 hr, then at room temp. for 24 hr, 10% $Na_2S_2O_3$aq was added to the reaction mixture to decompose the excess peroxide, and the aqueous mixture was concentrated *in vacuo*. The evaporation residue was diluted with NaOHaq (NaOH(15 g) in H_2O(30 ml)) and extracted with EtOAc. The combined organic extracts were washed with sat. NaClaq, filtered, and evaporated *in vacuo*, to afford the crude diol as a pale yellow solid (18.3 g, 78%). This was recrystallized from toluene, giving a pure sample as colorless needles (11.6 g, 50%), m.p. 59–64°(lit.,[19] m.p. 63°).

(b) *Cyclohexene* - 1 - *carbaldehyde*.[20] Conc. HNO_3(24 ml) was added to a suspension of $NaIO_4$(119 g, 0.56 mole) in H_2O (1.12 l), and the whole mixture was stirred until a clear solution formed. After the pH of the soln. was adjusted to 4 by adding 20% NaOHaq, the crude diol(44.0 g, 0.34 mole) was gradually added to the aqueous mixture at *ca.* 20° with stirring, and the whole mixture was stirred at room temp. for 44 hr. Et_2O (500 ml) and 20% NaOHaq(160 ml) were successively added to the reaction mixture, and the two layer soln was stirred at room temp for 6 hr. The upper Et_2O layer was separated, and the lower aqueous phase was further extracted with Et_2O. The Et_2O extracts were combined and washed with sat. NaClaq. Filtration and evaporation *in vacuo* gave the curde aldehyde as a yellow oil (28.0 g, 75%). Fractional distillation of this oil afforded the pure sample as a pale yellow oil(12.9 g, 35%), b.p. 45°(4.5 mmHg)(Lit.,[21] b.p. 70°(13 mmHg)).

(c) *Cyclohexene* - 1 - *carboxylic acid*(**1c**). Jones reagent(120 ml, 0.33 mole) was added over 30 min to a stirred soln of the aldehyde(12.0 g, 0.11 mole) in Me_2CO (180 ml) cooled in an ice–water bath, and the whole mixture was stirred at room temp for 2 hr. The reaction was quenched by adding i-PrOH(35 ml), and the mixture was concentrated to one-fourth of the original volume. The residual solution was diluted with sat. NaClaq, and extracted with EtOAc. The organic extracts were combined and re-extracted with sat. $NaHCO_3$aq. The bicarbonate extracts was acidified with conc HCl, and extracted with EtOAc. The combined EtOAc extracts were washed with sat.NaClaq. Filtration and evaporation *in vacuo* gave crude **1c** as a pale yellow solid of low melting point(8.9 g, 65%). This was subjected to fractional distillation, giving pure **1c** as a colorless oil which gradually solidified on standing at room temp, b.p. 102–105° (4mmHg) (lit.,[22] b.p. 133–134° (11 mmHg), m.p. 38–39°). IR ν_{max}^{nujol} cm^{-1}: 1690(COOH). NMR(in $CDCl_3$): 1.3–2.2(4H, m, $CH_2\underline{CH_2}CH_2CH_2$), 1.8–2.8(4H, m, $CH_2\underline{C}H{=}\underline{C}H\underline{CH_2}$), 6.90(1H, br, s, C$\underline{H}$=), 10.45(1H, br s, COO$\underline{H}$).

(*S*)(−) - *Ethyl N* - (*cyclohexene* - 1 - *carbonyl*)*prolinate*(**2c**). A DMF soln(24 ml) of diethyl phosphorocyanidate(DEPC)[23] (4.06 g, 24.9 mmole) and a DMF soln(24 ml) of Et_3N (2.29 g, 22.6 mmole) were successively added to a stirred mixture of **1c** (2.85 g, 22.6 mmole) and (*S*)(−)-ethyl prolinate[24] ($[\alpha]_D^{20}$ − 39.6° (c = 2.68, EtOH)) (3.57 g, 24.9 mmole) in DMF (30 ml) at 0° under an Ar. The mixture was stirred at 0° for 1 hr, then at room temp. for 48 hr. The soln was diluted with a mixture of C_6H_6 and EtOAc (1:2), and the resulted soln. was washed successively with 5%HClaq, H_2O, sat. NaClaq,sat $NaHCO_3$aq, H_2O, and sat. NaClaq. Filtration and evaporation *in vacuo* gave almost pure **2c** as a yellow viscous oil (5.55 g, 98%), $[\alpha]_D^{20}$ − 49.8° (c = 1.15, EtOH). IR ν_{max}^{film} cm^{-1}: 1740(COOEt), 1655(CON), 1620(C=C). NMR (in $CDCl_3$): 1.25(3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 1.1–2.7(12H, m, $NCH_2\underline{CH_2}$–CH_2 and $CH_2\underline{CH_2}CH_2\underline{CH_2}$), 3.62(2H, t, J = 6.5 Hz, NCH_2), 4.14(2H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 4.3–4.7(1H, m, NC$\underline{H}$CO), 6.00(1H, br, s, C$\underline{H}$=). Mass: *m/e*: 251[M^+], 206, 178.

(*S*)(−) - *N* - (*Cyclohexene* - 1 - *carbonyl*)*proline*(**3c**). An aqueous soln(35 ml) of KOH(85% pure) (1.87 g, 28.4 mmole) was added to an EtOH soln (45 ml) of **2c**($[\alpha]_D^{20}$ − 49.8° (c = 1.15, EtOH)) (5.50 g, 21.9 mmole). After stirring for 45 hr at room temp, the mixture was concentrated below 45° to one-third of the original volume, diluted with H_2O, and washed with Et_2O. The alkaline aqueous soln was acidified (pH = 2) with conc. HCl, saturated with NaCl, and extracted with EtOAc. The EtOAc extracts were combined and washed with sat. NaClaq. Filtration and evaporation *in vacuo* afforded crude **3c** as a colorless powder (3.92 g, 80%), m.p. 123–124°. A part of this powder (3.88 g)

was recrystallized from C_6H_6-hexane to give pure **3c** as colorless needles (3.44 g, 71%), m.p. 123–124°, $[\alpha]_D^{20}$ – 54.8° (c = 1.13, EtOH). IR ν_{max}^{nujol} cm^{-1}: 1720 (COOH), 1650(CON). NMR (in $CDCl_3$): 1.1–2.6 (12H, m, NCH_2CH_2–CH_2 and $CH_2CH_2CH_2CH_2$), 3.3–3.9 (2H, br t, J = 6.5 Hz, NCH_2), 4.3–4.8 (1H, br t, J = 6.5 Hz, NCHCO), 6.00(1H, br s, CH=), 11.28 (1H, s, COOH). (Found: C, 64.77; H, 7.55; N, 6.04. Calc. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27%).

2(*R*) - *Bromo* - 1′,4-*dioxo* - 6′, 7′, 8′, 8′*a*(*S*) - *tetrahydro* - *spiro*[*cyclohexane* - 1(*S*), 3′(*S*)(4′*H*) - 1*H* - *pyrrolo*[2,1 - *c*]-[1,4]*oxazine*] (**5Ac**) *and its* 1(*R*), 2(*S*), 3′(*R*) - *isomer*(**5Bc**). A DMF soln (48 ml) of KOt-Bu(1.73 g, 15.3 mmole) and a DMF soln (32 ml) of NBS (5.49 g, 30.8 mmole) were successively added to a cooled (– 20°), stirred soln of **3c**($[\alpha]_D^{20}$ – 54.8° (c = 1.13, EtOH)) (3.44 g, 15.4 mmole) in DMF(30 ml) under an Ar. After stirring at – 20° for 2 hr, then at room temp. for 40 hr, the reaction mixture was diluted with EtOAc. The organic soln. was washed successively with 5% $NaHCO_3$aq, H_2O, and sat. NaClaq. Filtration and evaporation *in vacuo* gave crude **5c** (a mixture of **5Ac** and **5Bc**) as pale yellow needles (3.62 g, 78%), m.p. 129–135°, $[\alpha]_D^{20}$ – 99.4°(c = 1.04, EtOH). Spectral (IR and NMR) properties of this sample were identical with those of pure **5Ac** prepared as described below. Since this sample gave (+)-**8c**, 98% ee, the formation ratio of **5Ac** to **5Bc** could be calculated as 99 : 1.

Recrystallization of a part of crude **5c**(1.80 g) from Et_2O afforded predominantly formed **5Ac** in a pure state (1.09 g, 61% recovery), m.p. 141.5–142.5°, $[\alpha]_D^{20}$ – 112° (c = 1.03, EtOH). IR ν_{max}^{nujol} cm^{-1}: 1735(COO), 1640(CON). NMR (in $CDCl_3$): 1.0–3.2 (12H, m, $NCH_2CH_2CH_2$ and $CH_2CH_2CH_2CH_2$), 3.3–4.2(2H, m, NCH_2), 4.15–4.7(2H, m, NCHCO and CHBr). (Found: C, 47.79; H, 5.30; N, 4.37. Calc. for $C_{12}H_{16}O_3NBr$: C, 47.70; H, 5.34; N, 4.64%).

2-*Methyl*-2(*E*)-*nonenoic acid*(**1d**)

(a) *Ethyl* 2 - *methyl* - 2(E) - *nonenoate*. A DME soln (17.5 ml) of ethyl 2-(diethylphosphinyl)propionate[25] (8.28 g, 34.9 mmole) was added over 5 min to a suspension of NaH(840 mg, 34.9 mmole) in DME (35 ml) at 15–20° under an Ar. The mixture was stirred at 15° for 1 hr, then at 35° for 5 min. After cooling to 15°, a DME soln (17.5 ml) of n-heptanal (3.99 g, 34.9 mmole) was added over 15 min to the stirred soln of the sodium salt prepared above. After the stirring was continued at room temp. for 20 min, ice (23 g) was added to the reaction mixture. The whole was extracted with Et_2O and the combined Et_2O extracts were washed with sat NaClaq. Filtration and evaporation *in vacuo* gave an oily residue (6.70 g, 97%). NMR spectrum disclosed that this oily product consisted of 2(*E*)- and 2(*Z*)-isomers in a ratio of 87 : 13. This was repeatedly purified by column chromatography (silica gel, solvent C_6H_6), giving the pure 2(*E*)-isomer as a colorless oil (3.61 g, 52%). IR ν_{max}^{film} cm^{-1}: 1700 (COOEt). NMR (in $CDCl_3$): 0.86(3H, br t, J = 5 Hz, $CH_3CH_2CH_2$), 1.26(3H, br t, J = 7 Hz, OCH_2CH_3), 1.0–1.8(8H, m, $CH_3CH_2CH_2CH_2CH_2CH_2$), 1.82(3H, br s, CH_3C=), 2.10(2H, br t, J = 6 Hz, CH_2CH=), 4.17(2H, q, J = 7 Hz, OCH_2CH_3), 6.73(1H, br t, J = 7 Hz, CH=). Mass: *m/e*: 198[M^+].

(b) 2 - *Methyl* - 2(*E*) - *nonenoic acid*(**1d**). KOHaq(KOH(85% pure (910 mg, 13.8 mmole) in H_2O(12 ml)) was added to an EtOH soln (12 ml) of the ethyl ester (1.82 g, 9.18 mmole), and the mixture was stirred at room temp. for 15 hr. After concentration *in vacuo* to one-fourth of the original volume, the residue was diluted with H_2O (40 ml) and washed with Et_2O. The aqueous phase was acidified (pH ≒ 1) by adding conc HCl, saturated with NaCl, then extracted with Et_2O. The Et_2O extracts were combined and washed with sat. NaClaq. Filtration and evaporation *in vacuo* gave almost pure **1d** as a pale yellow oil (1.39 g, 89%). IR ν_{max}^{film} cm^{-1}: 1690(COOH). NMR (in $CDCl_3$): 0.89(3H, br t, J = 5 Hz, $CH_3CH_2CH_2$), 0.9–1.8(8H, m, $CH_3CH_2CH_2CH_2CH_2CH_2$), 1.83 (3H, br s, CH_3C=), 2.14 (2H, br t, J = 6 Hz, CH_2CH=), 6.92(1H, br t, J = 7 Hz, CH_2CH=), 11.92(1H, br s, COOH). Mass: *m/e*: 170[M^+], 152, 113, 100.

(*S*)(–) - *Ethyl N* - (2 - *methyl* - 2(*E*) - *nonenoyl*)*prolinate*(**2d**). A DMF soln (12 ml) of DEPC[23] (1.25 g, 7.66 mmole) and a DMF soln (12 ml) of Et_3N(705 mg, 6.96 mmole) were successively added to a mixture of **1d** (1.19 g, 6.96 mmole) and (*S*)(–)-ethyl prolinate[24] ($[\alpha]_D^{22}$ – 39.6° (c = 2.68, EtOH)) (1.10 g, 7.66 mmole) in DMF (20 ml) at 0° under an Ar. After stirring at 0° for 1 hr, then at room temp. for 24 hr, the mixture was worked up in a similar manner to that for **2c**, giving crude **2d** as a yellow oil (2.32 g, quantitative yield). This was purified by column chromatography (silica gel, solvent Et_2O) to afford pure **2d** as a pale yellow oil (1.73 g, 84%), $[\alpha]_D^{20}$ – 44.6° (c = 1.8, EtOH). IR ν_{max}^{film} cm^{-1}: 1740 (COOEt), 1600 (CON). NMR (in $CDCl_3$): 0.87 (3H, br t, J = 5 Hz, $CH_3CH_2CH_2$), 1.25 (3H, t, J = 7 Hz, OCH_2CH_3), 1.0–1.8(8H, m, $CH_3CH_2CH_2CH_2CH_2$), 1.82(3H, br s, CH_3C=), 1.8–2.55(6H, m, $NCH_2CH_2CH_2$ and CH_2C=), 3.60(2H, br t, J = 6 Hz, NCH_2), 4.17(2H, q, J = 7 Hz, OCH_2CH_3), 4.41(1H, br t, J = 6 Hz, NCHCO), 5.4–6.0(1H, m, CH=). Mass: *m/e*: 295[M^+], 250, 222.

(*S*)(–) - *N* - (2 - *Methyl* - 2(*E*) - *nonenoyl*)*proline*(**3d**). An aqueous soln (15 ml) of KOH (85% pure)(420 mg, 6.38 mmole) was added to an EtOH soln (15 ml) of **2d**($[\alpha]_D^{20}$ – 44.6° (c = 1.8, EtOH)) (1.72 g, 5.82 mmole), and the mixture was stirred at room temp. for 38 hr. The aqueous mixture was worked up in a similar manner to that for **3c**, to give crude **3d** as a pale yellow oil (1.30 g, 84%). $[\alpha]_D^{20}$ – 39.8° (c = 1.03, EtOH), after evaporation of the EtOAc extracts. IR ν_{max}^{film} cm^{-1}: 1725(COOH), 1575(CON). NMR (in $CDCl_3$): 0.91(3H, br t, J = 5 Hz, $CH_3CH_2CH_2$), 1.0–1.8(8H, m, $CH_3CH_2CH_2CH_2CH_2$), 1.85(3H, br s, CH_3C=), 1.9–2.5(6H, m, $NCH_2CH_2CH_2$ and CH_2CH=), 3.63(2H, t, J = 6 Hz, NCH_2), 4.3–4.8(1H, m, NCHCO), 5.79(1H, br t, J = 6 Hz, CH_2CH=), 10.2(1H, br s, COOH). Mass: *m/e*: 267[M^+], 223. This oily acid(**3d**) was directly used for the next bromolactonisation reaction.

3(*S*)(1′(*R*) - *Bromoheptyl*) - 3(*S*) - *methyl* - 1,4 - *dioxo* - 3,4,6,7,8, 8*a*(*S*) - *hexahydro* - 1*H* - *pyrrolo*[2,1 - *c*][1,4]*oxazine*(**5Ad**) *and its* 1′(*S*),3(*R*) - *isomer*(**5Bd**). A DMF soln (16 ml) of KOt-Bu(540 mg, 4.79 mmole) and a DMF soln(10 ml) of NBS(1.71 g, 9.58 mmole) were successively added to a cooled(– 20°), stirred soln of **3d**($[\alpha]_D^{20}$ – 39.8°(c = 1.03, EtOH)) (1.72 g, 5.82 mmole) in DMF (10 ml) under an Ar. After stirring at – 20° for 2 hr, then at room temp for 44 hr, the reaction mixture was worked up in the same manner as that for **5c**, giving crude **5d** (a mixture of **5Ad** and **5Bd**) as a pale yellow caramel after evaporation of the combined EtOAc extracts (1.48 g, 93%). This sample gradually solidified when kept at room temp, and showed m.p. 64–71° and $[\alpha]_D^{20}$ – 15.3° (c = 1.00, EtOH). Spectral (IR and NMR) properties of this sample were identical with those of pure **5Ad** prepared as described below. Since this sample afforded (+)-**8d**, 84% ee, the formation ratio of **5Ad** to **5Bd** could be calculated as 92 : 8.

Recrystallization of a part of crude **5d** (570 mg) from hexane gave predominantly formed **5Ad** in a pure state (495 mg, 66% recovery), m.p. 77.5–78.5°, $[\alpha]_D^{20}$ – 19.5° (c = 1.01, EtOH). IR ν_{max}^{nujol} cm^{-1}: 1760(COO), 1660(CON). NMR (in $CDCl_3$): 0.88 (3H, br t, J = 5 Hz, $CH_3CH_2CH_2$), 1.0–1.7(8H, m, $CH_3CH_2CH_2CH_2CH_2$), 1.70(3H, s, CH_3), 1.6–3.0(6H, m, $NCH_2CH_2CH_2$ and CH_2CHBr), 3.25–4.0(2H, m, NCH_2), 4.0–4.4(1H, m, CHBr), 4.4–4.8(1H, m, NCHCO). (Found: C, 51.85; H, 6.95; N, 4.00. Calc. for $C_{15}H_{24}O_3NBr$: C, 52.03; H, 6.99; N, 4.05%).

Methyl N - (2 - *methyl* - 3 - *phenyl* - 2(*R*),3(*S*) - *epoxypropionyl*)*prolinate*(**7a**). A soln of NaOMe(935 mg, 17.3 mmole) in MeOH (52 ml) was added over 5 min to a stirred MeOH soln (52 ml) of crude **5a**($[\alpha]_D^{20}$ – 105°(c = 1.30, MeOH))(5.84 g, 17.3 mmole) at – 78° under an Ar. After stirring at – 78° for 4 hr, the MeOH solution was concentrated *in vacuo* below 0°, giving an oily residue which was dissolved in Et_2O, and dried. Filtration and evaporation *in vacuo* gave crude **7a** as a pale yellow oil (4.51 g, 90%). IR ν_{max}^{film} cm^{-1}: 1740 (COOMe), 1630(CON). NMR (in $CDCl_3$): 1.26, 1.29 (3H, two s, CH_3C), 1.5–2.6 (4H, m, $NCH_2CH_2CH_2$), 3.3–4.1 (2H, m, NCH_2), 3.72, 3.80 (3H, two s, $COOCH_3$), 3.95–4.3(1H, m, CHC_6H_5), 4.3–5.1(1H, m, NCHCO), 7.27, 7.30(5H, two s, C_6H_5). Mass:*m/e*: 289[M^+], 258, 230. The NMR spectrum clearly disclosed that epimerization of the methyl ester occurred during the epoxide formation. Ratio of the two epimers could be roughly estimated as 2 : 1 by the peak integration. This sample was immediately subjected to the next reduction.

Methyl N - (1(*S*),2(*R*) - *epoxy* - 1, 2, 3, 4 - *tetrahydro* - 2 - *naphthoyl*)*prolinate*(**7b**). A soln of NaOMe (329 mg, 6.09 mmole) in MeOH (40 ml) was added to a stirred soln of crude

5b($[\alpha]_D^{20}$ − 72.0° (c = 0.640, $CHCl_3$)) (2.15 g, 6.14 mmole) in a mixture of MeOH (20 ml) and THF (20 ml) at −78° under an Ar. After stirring at −78° for 3 hr, the mixture was worked up in the same manner as that for **7a**, to afford crude **7b** as a pale yellow caramel (1.57 g, 85%) after evaporation of the Et_2O soln. IR ν_{max}^{film} cm^{-1}: 1740 (COOMe), 1630 (CON). NMR (in $CDCl_3$): 1.62–2.5(4H, m, $NCH_2CH_2CH_2$), 2.3–3.2(6H, m, NCH_2 and $C_6H_4CH_2CH_2$), 3.70, 3.73(3H, two s, $COOCH_3$), 3.88, 4.00(1H, two s, C_6H_4CH), 4.35–5.05(1H, m, NCHCO), 6.6–7.65(4H, m, C_6H_4). Mass:*m/e*: 301[M^+], 285, 270, 242. The NMR spectrum showed that this sample contained two epimers of the methyl esters in a ratio of 1:1. This sample was directly subjected to the next reaction.

Methyl N - (1(R),2(S)-epoxycyclohexane - 1 - carbonyl)prolinate(**7c**). A soln of NaOMe(150 mg, 2.78 mmole) in MeOH(10 ml) was added to a soln of **5Ac**(m.p. 141.5–142.5°, $[\alpha]_D^{20}$ − 112° (c = 1.03, EtOH)) (840 mg, 2.78 mmole) in a mixture of MeOH(10 ml) and THF (10 ml) at −78° under an Ar. After stirring at −78° for 4 hr, similar treatments of the reaction mixture to those for the preparation of **7a** gave crude **7c** as a yellow viscous oil(675 mg, 96%). IR ν_{max}^{film} cm^{-1}: 1740(COOMe), 1630 (CON). NMR(in $CDCl_3$): 1.1–2.8(12H, m, $NCH_2CH_2CH_2$ and CH_2CH_2–CH_2CH_2), 3.0–3.9(3H, m, NCH_2 and CHO), 3.73, 3.78(3H, two s, $COOCH_3$), 4.3–5.1(1H, m, NCHCO). Mass:*m/e*: 253[M^+], 222, 194. The NMR spectrum clearly showed that this sample contained two epimers of the methyl esters in a ratio of 2:1.

When crude **5c**(a mixture of **5Ac** and **5Bc**) (m.p. 129–135°, $[\alpha]_D^{20}$ − 99.4° (c = 1.04, EtOH)) (840 mg, 2.78 mmole) was similarly treated, there could be obtained crude **7c** as a pale yellow viscous oil (670 mg, 95%). Spectral(IR and NMR) properties of this sample were identical with those described above.

Two lots of **7c** were separately utilized for the next reduction.

Methyl N - (2 - methyl - 2(R),3(S) - epoxynonenoyl)prolinate(**7d**). A soln of NaOMe(54.0 mg, 1.00 mmole) in MeOH(4 ml) was added to a stirred soln of **5Ad**(m.p. 77.5–78.5°, $[\alpha]_D^{20}$ − 19.5° (c = 1.01, EtOH)) (346 mg, 1.00 mmole) in a mixture of MeOH (3.5 ml) and THF (3.5 ml) at −78° under an Ar. After stirring at −78° for 5 hr, the reaction mixture was worked up similarly to the case for **7a**, giving crude **7d** as a pale yellow oil (315 mg, quantitative yield). IR ν_{max}^{film} cm^{-1}: 1740 (COOMe), 1620(CON). NMR (in $CDCl_3$): 0.89 (3H, br t, J = 5 Hz, $CH_3CH_2CH_2$), 1.0–1.9(10H, m, $CH_3CH_2CH_2CH_2CH_2CH_2$), 1.51(3H, s, CH_3C), 1.8–2.5(4H, m, $NCH_2CH_2CH_2$), 2.8–3.4(1H, m, CHO), 3.3–3.85(2H, m, NCH_2), 3.72, 3.78(3H, two s, $COOCH_3$), 4.4–5.1(1H, NCHCO). Mass:*m/e*: 297[M^+], 266, 238. The NMR spectrum clearly showed that this sample consisted of the two epimeric methyl esters in a ratio of 5:3.

When crude **5d**(a mixture of **5Ad** and **5Bd**) (m.p. 64–71°, $[\alpha]_D^{20}$ − 15.3° (c = 1.00, EtOH)) (346 mg, 1.00 mmole) was treated in a similar manner, crude **7d** could be obtained as a pale yellow oil (240 mg, 87%). Spectral (IR and NMR) properties of this sample were identical with those described above. Two lots of **7d** were separately subjected to the next reduction.

(+) - 2 - *Methyl* - 3 - *phenyl* - 2(*R*),3(*S*) - *epoxypropanal*((+) - **8a**). A soln of $NaAlH_2(OCH_2CH_2OMe)_2$ (70% benzene soln) (9.16 ml, 32.7 mmole) in ether (9.2 ml) was added dropwise over 5 min to an Et_2O soln (130 ml) of crude **7a**(4.30 g, 14.9 mmole) at 0° under an Ar. After stirring at 0° for 1 hr, satd NH_4Cl(34 ml) was added to the reaction mixture. The whole mixture was further stirred at 0° for 30 min, filtered through a pad of celite, and diluted with Et_2O. The Et_2O soln was washed successively with 20%NH_4Claq and satd NaClaq. Filtration and evaporation *in vacuo* gave crude (+)-**8a** as a pale brown oil (2.89 g, 89%), which was purified by column chromatography (silica gel, solvent Et_2O) to give (+)-**8a** as a pale yellow oil (1.73 g, 72%), $[\alpha]_D^{20}$ + 167° (c = 1.01, $CHCl_3$). Distillation of this sample afforded completely pure (+)-**8a** as a colorless oil, b.p. 75–82° (0.9 mmHg), $[\alpha]_D^{20}$ + 182° (c = 2.00, $CHCl_3$). Based on the formation ratio of **5Aa** to **5Ba**, the optical purity of this sample could be calculated as 98%. IR $\nu_{max}^{CHCl_3}$ 3 cm^{-1}: 1730(CHO), 890, 850 (epoxide). NMR (in $CDCl_3$): 1.22 (3H, s, CH_3), 4.27(1H, s, CH), 7.30(5H, s, C_6H_5), 9.00(1H, s, CHO). mass:*m/e*: 162 [M^+], 145, 133. These spectral(IR and NMR) features were identical with those of dl-**8a**.

(−) - 1(*S*),2(*R*) - *Epoxy* - 1, 2, 3, 4 - *tetrahydronaphthalene* - 2 - *carbaldehyde*((−) - **8b**). Similar treatments of crude **7b**(1.40 g, 4.65 mmole) to those of **7a** gave crude **7b** as a viscous oil (890 mg, quantitative yield), which was subjected to column chromatography (silica gel, solvent Et_2O), affording pure (−)-**8b** as pale yellow needles (570 mg, 76%), m.p. 72.5–76°, $[\alpha]_D^{20}$ − 189° (c = 1.00, $CHCl_3$). The optical purity of this sample could be calculated as 92% ee based on the formation ratio of **5Ab** to **5Bb**. Repeated recrystallizations of this sample from hexane afforded an analytical sample as colorless needles, m.p. 79–79.5°, $[\alpha]_D^{20}$ − 222° (c = 1.04, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730(CHO), 825(epoxide). NMR(in $CDCl_3$): 1.6–3.0(4H, m, $C_6H_4CH_2CH_2$), 4.10(1H, s, CH), 6.9–7.5(4H, m, C_6H_4), 9.18 (1H, s, CHO). These spectral(IR and NMR) properties were identical with those of dl-**8b**. (Found: C, 75.79; H, 5.80. Calc. for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79%).

(+) - 1(*R*),2(*S*) - *Epoxycyclohexane* - 1 - *carbaldehyde*((+) - **8c**). Similar treatments of crude **7c**(675 mg, 2.66 mmole) prepared from **5Ac**, to those of **7a** gave crude **7c** as a pale yellow oil (310 mg, 92%), which was purified by column chromatography (silica gel, solvent Et_2O) to give optically pure (+)-**8c** as a pale yellow oil (195 mg, 58%), $[\alpha]_D^{20}$ + 44.7° (c = 1.01, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$3 cm^{-1}: 1730(CHO), 875, 840(epoxide). NMR (in $CDCl_3$): 0.7–2.75(8H, m, $CH_2CH_2CH_2CH_2$), 3.20(1H, br t, J = 3 Hz, CH), 8.78(1H, s, CHO). Mass:*m/e*: 126[M^+], 88.

When crude **7c**(670 mg, 2.65 mmole) prepared from crude **5c** (a mixture of **5Ac** and **5Bc**) was treated in the same manner as that described above, (+)-**8c** showing $[\alpha]_D^{20}$ + 43.6° (c = 6.0, $CHCl_3$), could be obtained as a pale yellow oil (200 mg, 60%), after purification by column chromatography. This sample exhibited the same spectral properties as those cited above. The optical purity of the latter sample could be calculated as 98% ee by assuming that (+)-**8c** having $[\alpha]_D^{20}$ + 44.7° (c = 1.01, $CHCl_3$) was optically pure.

(+) - 2 - *Methyl* - 2(*R*),3(*S*) - *epoxynonanal*((+)-**8d**). The same treatments of crude **7d** (310 mg, 1.10 mmole) obtained from pure **5Ad**, as those of **7a** afforded optically pure (+)-**8d** as a pale yellow oil (130 mg, 76% based on **5Ad**) after purification with column chromatography (silica gel, solvent pentane: Et_2O 2:1), $[\alpha]_D^{20}$ + 115° (c = 0.90, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730(CHO). NMR (in $CDCl_3$): 0.93(3H, br t, J = 5 Hz, $CH_3CH_2CH_2$), 1.0–1.9(10H, m, $CH_3CH_2CH_2CH_2CH_2CH_2$), 3.21 (1H, br t, J = 5.5 Hz, CH), 8.79(1H, s, CHO). Mass:*m/e*: 170[M^+], 141.

When crude **7d**(240 mg, 0.81 mmole) prepared from crude **5d** (a mixture of **5Ad** and **5Bd**), was treated in a similar manner to that described above, pure (+)-**8d** showing $[\alpha]_D^{20}$ + 96.9° (c = 0.80, $CHCl_3$), could be obtained as a pale yellow oil (115 mg, 68% based on **5d**). Spectral (IR and NMR) properties of this sample were identical with those obtained above. The optical purity of this sample could be calculated as 84% by assuming that (+)-**8d** having $[\alpha]_D^{20}$ + 115° (c = 0.90, $CHCl_3$) was optically pure.

dl - 2 - Methyl - 3 - phenyl - 2,3 - epoxypropanal(*dl*-**8a**)

(a) trans - α - *Methylcinnamyl alcohol*. Usual esterification of **1a**[11a,c] with EtOH-conc H_2SO_4 (catalytic amount) (84%), followed by reduction with $LiAlH_4$(79%), gave the pure product as a colorless oil, b.p. 99–100° (3 mmHg) (lit.,[26] b.p. 96–97° (1.5 mmHg)).

(b) *dl - 2 - Methyl - 3 - phenyl - 2,3 - epoxypropanol*. A CH_2Cl_2 soln (20 ml) of the pure alcohol (2.70 g, 18.2 mmole) was added over 5 min to a cooled (0°), stirred soln of m-Cl-$C_6H_4CO_3H$ (85% pure) (5.55 g, 27.3 mmole) in CH_2Cl_2 (40 ml) under an Ar. After stirring at 0° for 30 min, then at room temp. for 2.5 hr, the reaction mixture was filtered. The filtrate was washed successively with 10%$NaHCO_3$aq, 5%Na_2CO_3aq, and sat. NaClaq. Filtration and evaporation *in vacuo* gave a pale yellow oil which was subjected to fractional distillation to afford the pure product as a colorless oil (1.98 g, 66%), b.p. 110° (4.5 mmHg). IR ν_{max}^{film} cm^{-1}: 3400(OH), 845(epoxide). NMR (in $CDCl_3$): 1.12 (3H, s, CH_3), 3.75(1H, s, OH), 3.82(2H, s, CH_2OH), 4.21(1H, s, CH), 7.32(5H, s, C_6H_5). Mass:*m/e*: 164[M^+].

(c) *dl - 2 - Methyl - 3 - phenyl - 2,3 - epoxypropanal*(*dl*-**8a**). A CH_2Cl_2 soln(2.25 ml) of the alcohol(100 mg, 0.61 mmole) was added to a cooled(0 ~ −5°), stirred suspension of CrO_3–$2C_5H_5N$ (1.34 g, 5.19 mmole) and celite(2.7 g) in CH_2Cl_2(14 ml), and the

whole mixture was stirred at the same temp for 1 hr. After $NaHSO_4$–H_2O(2.7 g) was added to the reaction mixture and the stirring was continued for 20 min, the mixture was filtered through a pad of anhyd. $MgSO_4$. Evaporation *in vacuo* gave a brown oil which was purified by column chromatography (silica gel, solvent C_6H_6) to afford pure dl-**8a** as a colorless oil(35 mg, 35%). Spectral(IR and NMR) properties of this sample were identical with those recorded on optically active (+)-**8a**.

dl - 2,3 - *Epoxy* - 1,2,3,4 - *tetrahydronaphthalene* - 2 - *carbaldehyde* (*dl*-**8b**)

(a) *dl* - *Ethyl* 1,2 - *epoxy* - 1,2,3,4 - *tetrahydro* - 2 - *naphthoate*. A CH_2Cl_2 soln (2.0 ml) of ethyl 3,4 - dihydro - 2 - naphthoate[12a,c] (200 mg, 0.99 mmole) was added to a cooled (0°), stirred soln of m-Cl-$C_6H_4CO_3H$ (85% pure) (300 mg, 1.48 mmole) in CH_2Cl_2(3.0 ml) under an Ar. After stirring at 0° for 1 hr, then at room temp. for 24 hr, the mixture was filtered. The filtrate was washed successively with 10% $NaHCO_3$aq, 5%Na_2CO_3aq, and sat NaClaq after being diluted with CH_2Cl_2(30 ml). Filtration and evaporation *in vacuo* followed by purification with column chromatography (silica gel, solvent C_6H_6), afforded the pure product as a colorless oil (145 mg, 67%). This oil gradually solidified as colorless needles, m.p. 34-35°. IR ν_{max}^{film} cm^{-1}: 1730(COOEt), 880, 855, 830(epoxide). NMR (in $CDCl_3$): 1.31(3H, t, J = 7 Hz, OCH_2CH_3), 2.05–3.05 (4H, m, $C_6H_4CH_2CH_2$), 4.05(1H, s, CH), 4.25(2H, q, J = 7 Hz, OCH_2CH_3), 6.75–7.6(4H, m, C_6H_4). Mass: *m/e*: 218[M^+].

(b) *dl* - 1,2 - *Epoxy* - 1,2,3,4 - *tetrahydronaphthalene* - 2 - *carbaldehyde*(*dl*-**8b**). A soln of diisobutylaluminum hydride (DIBAL) in hexane (1.75M soln) (15.6 ml, 27.4 mmole) was added over 8 min to a cooled (−78°), stirred soln of the ester (4.98 g, 22.8 mmol) in toluene (100 ml). After stirring at −78° for 3 hr, the reaction was quenched by adding MeOH (10 ml). The whole mixture was further stirred at −78° for 10 min. Sat. NaCl aq and Et_2O were successively added to the reaction mixture. After filtration, the upper Et_2O phase was separated and the lower aqueous phase was extracted with Et_2O. The organic extracts were combined and washed with sat. NaClaq. Filtration and evaporation *in vacuo* gave crude dl-**8b** as a pale yellow viscous oil (3.77 g, 95%), a part of which (480 mg) was further purified by column chromatography (silica gel, solvent Et_2O) to give pure dl-**8b** as a colorless solid (210 mg, 42%), m.p. 41–44.5°. This sample showed identical spectral (IR and NMR) properties with those recorded on optically active (−)-**8b**.

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