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ASYMMETRIC HALOLACTONISATION REACTION—1

ASYMMETRIC SYNTHESIS OF OPTICALLY ACTIVE α,α-DISUBSTITUTED-α-HYDROXY ACIDS FROM α,β-UNSATURATED ACIDS BY THE NOVEL USE OF HALOLACTONISATION REACTION[1]

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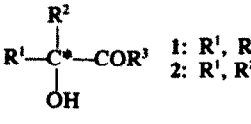
Abstract—Considering the usefulness of optically active α,α-disubstituted-α-hydroxy acids (1) and α,α-disubstituted-α-hydroxy ketones (2) readily accessible from 1, exploitation of a new asymmetric synthesis of 1 from α,β-unsaturated acids (3) which utilised halolactonisation reaction as its key step, was studied.

The asymmetric bromolactonisation of (*S*)-N-(α,β-unsaturated)acylproline((*S*)-5) derivable from 3 such as tiglic acid (3a) and *trans*-α-methylcinnamic acid (3b), with N-bromosuccinimide in N,N-dimethylformamide was found to proceed in a highly stereoselective and regiospecific manner, giving a mixture of the two diastereomeric bromolactones (8) in which one diastereomer (8A) was highly predominant. Debromination of 8 followed by acidic hydrolysis readily afforded (*R*)-1 being 89–98% optically pure.

Optically active α,α-disubstituted-α-hydroxy acids (1) and α,α-disubstituted-α-hydroxy ketones (2) readily accessible from 1, are considered quite useful as starting materials for preparation of several structural types of optically active natural products which involve 1 or 2 as their partial structural units. Thus, quinoline alkaloid camptothecin[2] and antifungal cryptosporiopsin[3] contain 1 in forms of lactone and ester, respectively, and anthracycline antibiotics adriamycin and daunorubicin,[4] which recently attract much attention because of their promising anticancer activity, involve 2 as their partial structures. Synthesis of one enantiomer of frontalin,[5] an aggregation pheromone of bark beetles, has been achieved by utilising lactonised 1 prepared by chemical resolution, as a starting material. The reported total synthesis of C-18 Cecropia juvenile hormone[6] clearly suggests that 1 and 2 are useful starting materials.



1: R^1, R^2 = alkyl or aryl, R^3 = OH
2: R^1, R^2, R^3 = alkyl or aryl

As methods for preparing 1 by asymmetric synthesis, addition reactions of Grignard reagents to chiral α-keto esters have been exclusively examined,[7] and high optical yields (max 93%) are achieved in the asymmetric synthesis of optically active atrolactic acid,[8] which has extensively been studied in connection with applicability of the so-called "Prelog rule".[7-9] Recently, it was reported that the use of conformationally rocked optically active 1,3-oxathine derivatives led to the asymmetric synthesis of highly optically active atrolactic acid methyl ether,[10] and that titanium chloride assisted addition of alkyl trimethyl silanes or silyl enol ethers to chiral α-keto esters could afford 1 in 55–68% optical yield.[11]

Although asymmetric synthesis of 1 seems to be thoroughly studied as mentioned above, structural variations of 1 accessible by asymmetric synthesis are limited because the asymmetric syntheses hitherto examined have solely utilised chiral esters of α-keto acids such as pyruvic acid and phenylglyoxylic acid, as reaction substrates. Considering wide applicability of 1 and 2 to synthesis of optically active natural products and limited numbers of methodologies available for asymmetric synthesis of 1, an effective method which would give 1 in high optical yields from achiral substrates other than α-keto acid derivatives, was sought.

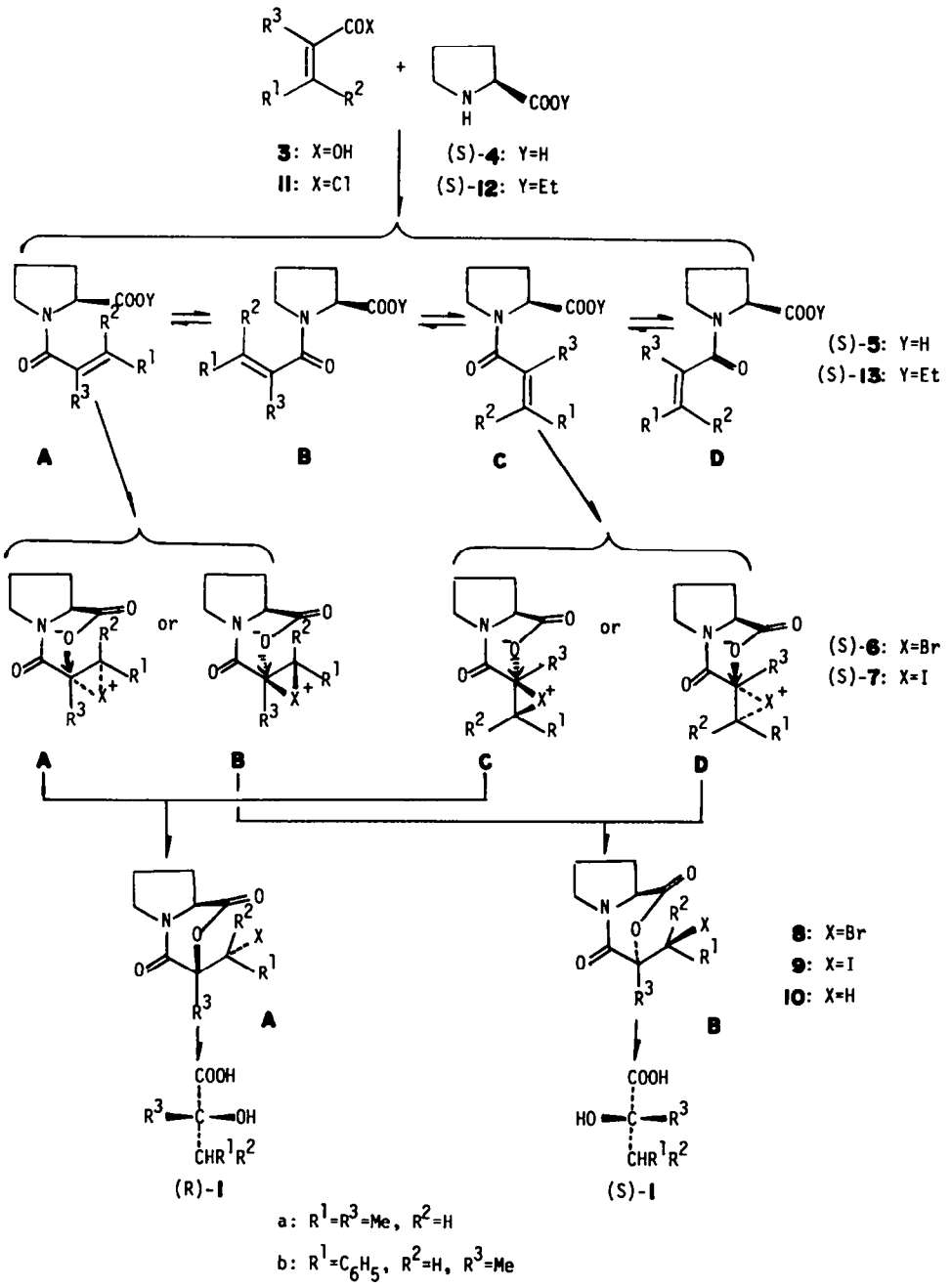
We have now succeeded in exploiting a novel asymmetric synthesis of 1 which utilises halolactonisation as its key step. This report concerns with strategy of the asymmetric synthesis and practical synthesis of 1 being 89–98% optically pure, by employing the designed reaction scheme.

RESULTS AND DISCUSSION

I. *Design of the asymmetric synthesis of optically active α,α-disubstituted-α-hydroxy acids* (1) *by the use of halolactonisation reaction*

Based on the accumulated information regarding halolactonisation,[12-16] Scheme 1 was designed for the asymmetric synthesis of 1 from α,β-unsaturated acids (3) by employing commercially available (*S*)-proline ((*S*)-4) as a chiral source.

Thus, it is anticipated that (*S*)-N-(α,β-unsaturated)acylproline ((*S*)-5) readily obtainable from 3 and (*S*)-4, might exist as a mixture of four possible conformers ((*S*)-5A-D). Although s-*trans*- and s-*cis*-conformers ((*S*)-5B,D) are considered thermodynamically more stable than the others (s-*trans*- and s-*cis*-conformers)((*S*)-5A,C) due to their possible intramolecular H-bondings between the amide and the carboxyl groups, they would not participate in halolactonisation reaction because the double bonds involved in (*S*)-5B,D are remote from the carboxyl groups. Therefore, when (*S*)-5 is submitted to halolactonisation, the diastereomeric halolactones (8A,B or 9A,B) might be produced via two sets of the halonium ions ((*S*)-6A,C and (*S*)-6B,D or (*S*)-7A,C and (*S*)-7B,D), provided that attack of the intramolecular nucleophile, the carboxylate anion, promptly occurs before bond rotation and proceeds in a complete *trans* fashion.[13-15] In fact, the asymmetric halolactonisation might take place under an influence of the chiral center present in the (*S*)-proline moiety to give a mixture of 8A and 8B or 9A and 9B in which one diastereomer (8A, 9A or 8B, 9B) is predominant. Dehalogenation of 8 or 9



Scheme 1.

followed by hydrolysis would afford 1 which predominantly involves one enantiomer ((*R*)-1 or (*S*)-1), via the dehalogenated lactone (10).

Detailed studies on the designed synthetic scheme have clearly disclosed that the bromolactonisation of (*S*)-5 proceeds in a stereoselective and regiospecific manner, giving 8 in which 8A is highly predominant, and that successive debromination of 8 and acidic hydrolysis can furnish (*R*)-1 which has a high optical purity.

II. *Asymmetric synthesis of optically active α,α-disubstituted-α-hydroxy acids* (1) *from α,β-unsaturated acids* (3)

By selecting tiglic acid (3a) as 3, preparation and halolactonisation of (*S*)-5 were studied.

Acylation of (*S*)-4 with tigloyl chloride (11a) prepared from 3a,[17] under the usual Schotten–Baumann condition, gave (*S*)-N-tigloylproline ((*S*)-5a), $[\alpha]_D^{20}$ −72.7° (MeOH), in 86% yield. The same (*S*)-5a could be prepared in 90% yield by condensing (*S*)-ethyl prolinate ((*S*)-12)[18] with 3a in the presence of diethyl phosphorocyanidate (DEPC)[19] and triethylamine (TEA), followed by alkaline hydrolysis of crude (*S*)-ethyl N-tigloylprolinate((*S*)-13a).

Results of the halolactonisation examined by treating (*S*)-5a under various conditions are summarized in Table 1.

As expected, the double bond conjugating with a CO group undergoes no halolactonisation,[14] (*S*)-5a involving the double bond adjacent to the amide group, exhibited a similar tendency to halolactonisation. Thus, treatment of

Table 1. Halolactonisation reactions of (*S*)-N-tigloylproline ((*S*)-**5a**) under various conditions

Run	Reagents for Halolactonization Reaction[a]	Reaction Conditions Solv.	Temp. (°C)	Time (hr)	Halolactones (8 and 9) Structure[e]	Chemical Yield(%)[f]
1	KI(1)-I_2(1)-Na_2CO_3(1)	H_2O	70	13	9Aa+9Ba	35
2	Br_2(1.5)	$CHCl_3$	rt	2.5	8Aa+8Ba	47
3	Br_2(1.5)-TEA[b](1)	$CHCl_3$	rt	38	8Aa+8Ba	31
4	NBS[c](1)	$CHCl_3$	0	20	8Aa+8Ba	59
5	NBS[c](1)	DMF[d]	rt	20	8Aa+8Ba	84
6	NBS[c](2)-t-BuOK(1)	DMF[d]	rt	48	8Aa+8Ba	95

a) Numbers in parenthesis express equivalents of the reagent to (S)-5a. b) Triethylamine. c) N-Bromosuccinimide. d) N,N-Dimethylformamide. e) See ref. 20 and 23. f) This was calculated by the weight of the crude halolactone obtained by evaporation of the combined neutral organic extracts(See experimental).

(*S*)-**5a** with a mixture of potassium iodide, iodine, and sodium bicarbonate, being the most popular reagent for iodolactonisation,[13–15] was found to afford a 20% yield of the crude iodolactone (**9a**).[20] Modification of this condition could only improve the yield of **9a**[20] up to 35% (Table 1, run 1). From crude **9a**, predominantly formed **9Aa**,[21] $[\alpha]_D^{20}$ −58° (MeOH), was isolated in a pure state by recrystallisation.

Next, the condition which induced successful bromolactonisation of *cis*- and *trans*-stilbene-2-carboxylic acid,[22] was applied to (*S*)-**5a**. Treatment of (*S*)-**5a** with bromine in chloroform afforded the crude bromolactone (**8a**)[23] in 47% yield (Table 1, run 2). Addition of TEA (1 eq) to increase a population of the carboxylate anion present in the medium, and prolonged reaction time were shown to be useless for improving the yield of **8a**[23] (Table 1, run 3).

Bromolactonisation of (*S*)-**5a** was further attempted by employing the condition for bromoether formation of linalool.[24] Although the reaction of (*S*)-**5a** with N-bromosuccinimide (NBS) in chloroform or in carbon tetrachloride increased the yield of crude **8a**[23] up to 59% (Table 1, run 4), the purity of crude **8a** definitely decreased more than that observed before (Table 1, run 1–3) due to possible side reactions including allylic bromination.

While homolytic cleavage of NBS in a polar solvent is well known,[25] it is somewhat ambiguous whether heterolytic cleavage of NBS to bromonium ion (Br^+) and succinimide anion occurs in a polar solvent.[26] However, if NBS occurs heterolytic cleavage in a polar solvent as exemplified by the conversion of olefin to *vicinal*-dibromide by the use of NBS in a polar solvent,[27] succinimide anion can be produced as a counter anion of bromonium ion in the reaction medium. In the case of bromo lactonisation, the succinimide anion having a lower nucleophilicity and stronger basicity than the bromide anion,[28] might assist the bromolactone formation by converting the carboxyl group into carboxylate anion more effectively than the bromide anion. Due to this reason, it seems quite promising that the yield of **8a** can be much improved when (*S*)-**5a** is treated with NBS in a polar solvent. This expectation was found to be the case.

Thus, the asymmetric bromolactonisation of (*S*)-**5a** with NBS in N,N-dimethylformamide (DMF) successfully afforded crude **8a**, $[\alpha]_D^{20}$ −77.2° (MeOH), in 84% yield (Table 1, run 5). In this experiment, purified anhydrous DMF was used as the solvent because of the presence of a small amount of water,[29] aliphatic alcohol,[30] or catechols[31] released bromine from NBS in a polar aprotic solvent.[25a]

In order to further improve the yield of **8a**, the bromolactonisation was carried out after converting (*S*)-**5a** to its potassium salt with t-BuOK. This operation was performed by expecting that t-butoxide anion could produce the carboxylate anion more strictly than succinimide anion. While improvement of the yield for crude **8a**[23] could be achieved by submitting the preliminary formed potassium salt of (*S*)-**5a** to the bromolactonisation with NBS, the purity of crude **8a**[23] clearly decreased due to the formation of many side products (Table 1, run 6).[32]

Since crude **8a**, $[\alpha]_D^{20}$ −77.2° (MeOH), can be transformed to (*R*)-2-hydroxy-2-methylbutyric acid ((*R*)-**1a**) being 89% optically pure (*vide infra*) and halolactonisation is well established to proceed in a complete *trans* fashion,[13–15] it is evident that crude **8a** contains the two diastereomers (**8Aa** and **8Ba**) in a ratio of 94.5:5.5. When crude **8a** was once recrystallised, the predominantly formed diastereomer (**8Aa**), $[\alpha]_D^{20}$ −83.2° (MeOH), could be obtained in a pure state in 63% yield based on (*S*)-**5a**.

Debromination of crude **8a**, $[\alpha]_D^{20}$ −77.2° (MeOH), with tri-n-butyltin hydride[33] in benzene yielded the crude lactone (**10a**) as a mixture of the two diastereomers (**10Aa** and **10Ba**), $[\alpha]_D^{20}$ −107° (MeOH), in 94% yield. Hydrolysis of crude **10a** was effected by refluxing a mixture of crude **10a** and 36% hydrochloric acid, giving (*R*)-**1a**,[34] $[\alpha]_D^{25}$ −7.9° ($CHCl_3$), in 97% yield. The *levo* rotatory acid ((*R*)-**1a**), exhibited the same spectral properties as those of the racemic acid ((±)-**1a**) prepared from 2-butanone.[36] On the other hand, when pure **8Aa**, $[\alpha]_D^{20}$ −83.6° (MeOH), was similarly debrominated and hydrolysed,[37] and the acidic product was recrystallised, optically pure (*R*)-**1a**,[34] $[\alpha]_D^{25}$ −8.9° ($CHCl_3$), could be obtained via pure **10Aa**, $[\alpha]_D^{20}$ −112° (MeOH).

Therefore, it is obvious that the formation ratio of the two diastereomeric bromolactones (**8Aa** and **8Ba**) and the optical purity of (*R*)-**1a** directly prepared from crude **8a** can be calculated as 94.5:5.5 and 89%, respectively.

Next, the scheme developed with **3a** was applied to

readily available *trans*-α-methylcinnamic acid (**3b**)[38] which had the same substitution pattern as for **3a**. Analogous acylation of (*S*)-**12** with **3b** in the presence of DEPC[19] and TEA followed by alkaline hydrolysis gave (*S*)-**5b**, $[\alpha]_D^{20}$ −11.8° (MeOH), via the (*S*)-ethyl ester ((*S*)-**13b**), $[\alpha]_D^{20}$ −30.3° (EtOH).

When (*S*)-**5b** was submitted to the asymmetric bromolactonisation as for (*S*)-**5a** (Table 1, run 5), the yield of crude **8b** was found to be very low (24%) even after 66 hrs' reaction at room temperature. This is conceivably due to lowered electron density of the double bond brought about by the additional conjugation with benzene ring. Therefore, the bromolactonisation of (*S*)-**5b** was carried out by first converting (*S*)-**5b** to its potassium salt. Although this operation was ineffective for the bromolactonisation of (*S*)-**5a** because of decreased purity of crude **8a**,[32] reaction of the potassium salt of (*S*)-**5b** with NBS in DMF successfully afforded crude **8a** as a mixture of the two diastereomers (**8Ab** and **8Bb**, 99:1) (*vide infra*), $[\alpha]_D^{20}$ − 102° (MeOH), in 91% yield.

Debromination of crude **8b** followed by acidic hydrolysis in the same manner as for crude **8a**, gave (*R*)-2-hydroxy-2-methyl-3-phenylpropionic acid ((*R*)-**1b**),[39] $[\alpha]_D^{17}$ +16.7° (dioxane), in a good yield. Since the highest reported optical rotation of (*R*)-**1b** is $[\alpha]_D$ +17.0° (dioxane),[41] the ratio of the two diastereomers (**8Ab** and **8Bb**) involved in crude **8b** and the optical purity of (*R*)-**1b**, can be calculated as 99:1 and 98%, respectively.

As exemplified in the preparations of (*R*)-**1a,b**, this asymmetric synthesis can afford **1** by the hitherto reported method, not being accessible in high optical yields from **3**. Due to this reason in addition to its operational simplicity, the overall process might have wide practical values.

Taking into account the design of the asymmetric synthesis shown in Scheme 1 and the experimental results, it appears that intervention of two types of the bromonium ions ((*S*)-**6A** and (*S*)-**6C**) derivable from s-*trans*- and s-*cis*-conformers ((*S*)-**5A** and (*S*)-**5C**), respectively, is only compatible with the exclusive formation of **8A**.

Studies on discrimination of the two possible bromonium ions ((*S*)-**6A** and (*S*)-**6C**) and on general applicability and detailed reaction mechanism of the asymmetric bromolactonisation are the subject of the accompanying paper.[42]

EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra measurements were performed with 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 (60 MHz) and a JEOL JNM-PS-100 Spectrometer (100 MHz). All signals are expressed by the ppm downfield from TMS used as an internal standard (δ value). Following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). Measurements of optical rotations were carried out using a YANACO OR-50 Automatic Polarimeter. All reactions were performed by using anhyd solvents, and the combined organic extracts obtained in each experiment, were dried over Na_2SO_4 or $MgSO_4$ before successive filtration and evaporation *in vacuo*.

(S)(−)-N-*Tigloylproline*((S)-5a)

(A) *Preparation of* (S)-**5a** *according to the Schotten–Baumann procedure.* (*S*)-**4** ($[\alpha]_D^{20}$ − 85.5° (*c* = 4.00, H_2O)(10.4 g, 0.090 mole) was dissolved in 2N NaOH (53 ml, 0.106 mole) cooled in an ice bath, and the resulting alkaline soln was diluted with acetone (53 ml). An acetone soln (53 ml) of **11a**[17] (16.0 g, 0.135 mole) and the 2N NaOH soln (80 ml, 0.160 mole) were simultaneously added over 70 min to the aqueous soln of (*S*)-**4** with stirring in an ice bath. The pH of the mixture was kept at 10–11 during the addition of the acylating agent. After the stirring was continued for 2 hr at room temp, the mixture was submitted to evaporation *in vacuo* to remove the acetone. The residual soln was washed with ether, and acidified (pH ≒ 2) with conc HCl. The acidic mixture was extracted with EtOAc after being saturated with NaCl, and the combined EtOAc extracts were washed with sat NaClaq. Filtration and evaporation *in vacuo* gave crude (*S*)-**5a** as a colorless solid (19.5 g, quantitative yield). Recrystallisation from hexane–benzene (2:3) gave pure (*S*)-**5a** as colorless pillars (15.3 g, 86%), m.p. 112.5–113.5°, $[\alpha]_D^{20}$ − 72.7° (*c* = 1.00, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1740 (acid), 1582 (amide). NMR (in $CDCl_3$): 1.78 (3H, s, CH_3CH=), 1.81 (3H, s, =$C(CH_3)CO$), 1.50–2.50 (4H, m, $CH_2CH_2CH_2N$), 3.35–3.75 (2H, m, CH_2N), 4.53 (1H, t, J = 7 Hz, NCHCO), 5.75 (1H, br s, CH=), 11.0 (1H, s, COOH). (Found: C, 60.70; H, 7.64; N, 7.13. Calc for $C_{10}H_{15}O_3N$: C, 60.91; H, 7.61; N, 7.11%).

(B) *Preparation of* (*S*)-**5a** *by the use of DEPC.* (a) (*S*)-Ethyl N-tigloylprolinate ((*S*)-**13b**). A soln of DEPC[19] (558 mg, 3.42 mmole) in DMF (10 ml) was added to a cooled (0°), stirred mixture of **3a** (311 mg, 3.11 mmole) and (S)-**12**[18] ($[\alpha]_D^{20}$ −42.6° (*c* = 2.01, EtOH)) (500 mg, 3.49 mmole) in DMF (10 ml). A DMF soln of TEA (315 mg, 3.11 mmole) was further added over 5 min and the whole mixture was stirred at 0° for 2 hr, then at room temp. for 2 days. After dilution with benzene–EtOAc (1:2), the mixture was successively washed with 5% HCl, H_2O, sat NaClaq, sat $NaHCO_3$aq, H_2O, and sat NaClaq. Filtration and evaporation *in vacuo* gave crude (*S*)-**13a** as a pale yellow oil (695 mg, quantitative yield), which was immediately used for the next step. IR ν_{max}^{film} cm^{-1}: 1750 (ester), 1630 (amide). NMR (in $CDCl_3$): 1.32 (3H, t, J = 7 Hz, CH_2CH_3), 1.10–2.90 (4H, m, $CH_2CH_2CH_2N$), 1.76 (3H, s, CH_3CH=), 1.78 (3H, s, =$C(CH_3)CO$), 3.54 (2H, t, J = 7 Hz, CH_2N), 4.13 (2H, q, J = 7 Hz, CH_2CH_3), 4.40 (1H, m, NCHCO), 5.65 (1H, br m, CH=).

(b) (*S*)(−)-N-Tigloylproline ((*S*)-**5a**). A soln of (*S*)-**13a** (598 mg, 2.48 mmole) and KOH (85% pure) (209 mg, 3.16 mmole) in a mixture of EtOH (2 ml) and H_2O (2 ml) was stirred at room temp. for 1 hr, then was concentrated *in vacuo* to one tenth of the original volume below 45°. After evaporation, the residue was diluted with H_2O (52 ml). The aqueous soln was washed with ether, acidified (pH ≒ 2) with conc HCl, and then extracted with EtOAc after saturation with NaCl. The combined organic extracts were washed with sat NaClaq. Filtration and evaporation *in vacuo* gave crude (*S*)-**5a** as a colorless solid (440 mg, 90%). Recrystallization from hexane–benzene (2:3) gave pure (*S*)-**5a** as colorless pillars, m.p. 111–113°, $[\alpha]_D^{20}$ −71.9° (*c* = 1.04, MeOH), whose spectral (IR and NMR) properties were identical with those of (*S*)-**5a** obtained in A).

3(S)[1'(R)-*Iodoethyl*]-3(S)-*methyl*-1,4-*dioxo*-3, 4, 6, 7, 8, 8a(S)-*hexahydro*-1*H*-*pyrrolo*[2,1-c] [1, 4]*oxazine* (**5Aa**) *and its* 1'(S), 3(R)-*isomer* (**9Ba**) (*iodolactonisation of* (S)-**5a**)

Table 1, *run* 1. KI (7.58 g, 45.6 mmole) and I_2 (3.86 g, 15.2 mmole) was added to a soln of (*S*)-**5a**($[\alpha]_D^{20}$ − 72.9° (*c* = 1.00, MeOH)) (1.00 g, 5.07 mmole) and Na_2CO_3 (537 mg, 5.07 mmole) in H_2O (16 ml). The mixture was stirred at 70° for 9 hr. Since the pH of the mixture changed from 6.5 to 4.5, sat $NaHCO_3$aq was added to adjust the pH to 6.5. After the stirring was further continued for 4 hr, the dark color of the mixture was decolorised by the addition of solid $Na_2S_2O_3$. The aqueous mixture was extracted with EtOAc after saturation with NaCl. The combined EtOAc extracts were successively washed with sat $NaHCO_3$aq and sat NaClaq. Filtration and evaporation *in vacuo* gave crude **9a**[20] as a pale yellow thick oil (580 mg, 35%). Tlc (silica gel, solvent ether) analysis of this oil showed an almost single spot whose R_f value (0.33) was the same as that of **9Aa**. IR spectrum of this sample was almost identical with that of **9Aa**. The oily residue was dissolved in hexane–ether, and the organic soln was cooled in an ice bath to crystallise the predominantly formed **9Aa**[21] in a pure state (289 mg, 17%), colorless needles, m.p. 109°, $[\alpha]_D^{20}$ −58° (*c* = 1.00, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1765 (lactone), 1675 (amide). NMR (in $CDCl_3$): 1.75 (3H, s, CH_3CCON), 2.05 (3H, d, J = 7.2 Hz, CH_3CHI), 1.20–2.80 (4H, m, $CH_2CH_2CH_2N$), 3.40–3.90

(2H, m, CH_2N), 4.10–4.70 (2H, m, NCHCO and CH_3CHI). (Found: C, 37.18; H, 4.38; N, 4.14. Calc. for $C_{10}H_{14}O_3NI$: C, 37.17; H, 4.37; N, 4.33%).

When the same iodolactonisation was performed by adding KI (3.72 g, 22.8 mmole) and I_2 (1.93 g, 7.59 mmole) to a soln of (*S*)-**5a** (500 mg, 2.53 mmole) and $NaHCO_3$ (212 mg, 2.53 mmole) in H_2O (8 ml), crude **9a**[20] could be obtained as a yellow caramel (135 mg, 20%) after evaporation of the combined EtOAc extracts. Specral (IR and NMR) behavior of this sample were identical with those of crude **9a** obtained above.

3(S)[1'(R)-*Bromoethyl*]-3(S) - *methyl* - 1,4 - *dioxo* - 3,4,6,7,8,8a(S) - *hexahydro* - 1*H* - *pyrrolo*[2,1-c][1,4]*oxazine* (**8Aa**) *and its* 1'(S), 3(R) - *isomer* (**8Ba**) (*bromolactonisation of* (S)-**5a**)

(a) *Table* 1, *run* 2. A chloroform soln (2 ml) of Br_2 (237 mg, 1.5 mmole) was added to a soln of (*S*)-**5a**($[\alpha]_D^{20}$ −72.7° (*c* = 1.00, MeOH)) (197 mg, 1.00 mmole) in $CHCl_3$ (2 ml), and the whole was stirred at room temp for 2.5 hr. The red soln was evaporated *in vacuo* at room temp to give a residue, which was dissolved in EtOAc (20 ml). The EtOAc soln was successively washed with sat $NaHCO_3$aq and sat NaClaq. Filtration and evaporation *in vacuo* gave crude **8a**,[23] as a pale yellow solid (130 mg, 47%), m.p. 97–108°. Spectral (IR and NMR) properties of this sample was identical with those of pure **8Aa** obtained below. Tlc analysis (silica gel, solvent ether) of this solid showed a single spot whose R_f value was 0.36. Recrystallisation of this sample from hexane–ether gave predominantly formed **8Aa** in a pure state. (80 mg, 30%), colorless needles, m.p. 111.5–112.5°, $[\alpha]_D^{20}$ −81.8° (*c* = 0.756, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1760 (lactone), 1670 (amide). NMR (in $CDCl_3$): 1.70 (3H, s, CH_3CCON), 1.93 (3H, d, J = 7.2 Hz, CH_3CHBr), 1.40–2.70(4H, m, $CH_2CH_2CH_2N$), 3.37–3.92 (2H, m, CH_2N), 3.92–4.72 (2H, m, NCHCO and CH_3CHBr). (Found: C, 43.32; H, 5.00; N, 4.90. Calc for $C_{10}H_{14}O_3NBr$: C, 43.51; H, 5.07; N, 5.07%).

(b) *Table* 1, *run* 3. A chloroform soln (2 ml) of Br_2 (237 mg, 1.5 mmole) and a chloroform soln (0.5 ml) of TEA (101 mg, 1.0 mmole) were successively added to a soln of (*S*)-**5a**($[\alpha]_D^{20}$ −72.7° (*c* = 1.00, MeOH)) (197 mg, 1.0 mmole) in $CHCl_3$ (2 ml). The mixture was treated in a similar manner to that described in (a), to give crude **8a**[23] as a colorless solid (86.5 mg, 31%) after evaporation of the combined EtOAc extracts. This sample was identified as crude **8a** obtained in (a) by spectral (IR and NMR) and chromatographic (tlc) comparisons.

(c) *Table* 1, *run* 5. A DMF soln (22.5 ml) of NBS (2.67 g, 15 mmole) was added to a stirred soln of (*S*)-**5a**($[\alpha]_D^{20}$ −72.7° (*c* = 1.00, MeOH)) (2.96 g, 15 mmole) in DMF (22.5 ml) under N_2. After stirring at room temp. for 20 hr, the mixture was diluted with EtOAc (1.4 l). The EtOAc soln was successively washed with 5%$NaHCO_3$aq, H_2O, and sat NaClaq. Filtration and evaporation *in vacuo* gave crude **8a** as colorless needles (3.49 g, 84%), m.p. 98–108°, $[\alpha]_D^{20}$ −77.2° (*c* = 0.740, MeOH). IR and NMR spectra of this sample was identical with pure **8Aa** obtained in (a). Tlc analysis (silica gel, solvent ether) of this sample exhibited a single spot whose R_f value was identical with that of pure **8Aa** (0.36). Since this sample can be transformed to (*R*)-**1a** being 98% optically pure, it is evident that this crude sample contains the two diastereomeric bromolactones (**8Aa** and **8Ba**) in a ratio of 94.5:5.5.

Recrystallisation of a part of crude **8a** (242 mg) from ether or hexane–ether afforded predominantly formed **8Aa** in a pure state (182 mg, 63% based on (*S*)-**5a**), colorless needles, m.p. 111.5–112.5°C, $[\alpha]_D^{20}$ −83.2° (*c* = 0.754, MeOH). This sample showed complete the same spectral (IR and NMR) behavior as those of an analytical sample of **8Aa** obtained in (a).

(d) *Table* 1, *run* 6. A DMF soln (4 ml) of t-BuOK (224 mg, 2.0 mmole) and a DMF soln (2 ml) of NBS (712 mg, 4.0 mmole) was successively added to a stirred soln of (*S*)-**5a**($[\alpha]_D^{20}$ −72.7° (*c* = 1.00, MeOH)) (395 mg, 2.0 mmole) in DMF (2 ml) at −20°C under N_2. The mixture was stirred at −20° for 2 hr, then at room temp. for 48 hr. Extractive isolation with EtOAc followed by evaporation *in vacuo*, gave crude **8a**[23] as a yellow thick oil (562 mg, 95%). Tlc analysis (silica gel, solvent ether) of this oil showed the presence of three impurities (R_f = 0.47, 0.28 and 0.22) in addition to the desired **8a** (R_f = 0.36).

3(R) - *Ethyl* - 3(R) - *methyl* - 1,4 - *dioxo* - 3,4,6,7,8,8a(S) - *hexahydro*-1H-*pyrrolo*[2,1-*c*][1,4]*oxazine* (**10Aa**) *and its* 3(S) - *isomer* (**10Ba**)

A benzene soln (7 ml) of tri-n-butyltin hydride[33] (4.22 g, 14.5 mmole) was added dropwise over 1 min to a stirred soln of crude **8a** (m.p. 98–108°, $[\alpha]_D^{20}$ −77.2° (*c* = 0.740, MeOH)) (2.00 g, 7.25 mmole) in benzene (10 ml) at 70° under N_2. The mixture was stirred at 90–100° for 15 hr, and was evaporated *in vacuo* to afford a mixture of pale yellow needles and oil, which was submitted to column chromatography (silica gel, solvent, first hexane, then ether). After organotin compounds were eluted from the column by the use of hexane, elution with ether gave the fractions containing desired **10a**. The ethereal fractions were combined and evaporated *in vacuo* to give crude **10a** (a mixture of **10Aa** and **10Ba**) as a colorless solid (1.34 g, 94%), m.p. 94–97°, $[\alpha]_D^{20}$ −107° (*c* = 0.706, MeOH). This sample showed the same spectral (IR and NMR) properties as those of pure **10Aa** obtained as follows.

Debromination of pure **8Aa** (m.p. 111.5–112.5°, $[\alpha]_D^{20}$ −83.6° (*c* = 0.691, MeOH)) (1.70 g, 6.16 mmole) with tri-n-butyltin hydride[33] (2.33 g, 8.00 mmole) in benzene (12 ml) in the same manner, gave a mixture of crystals and oil after evaporation of the benzene solution *in vacuo*. Addition of hexane to the evaporation residue, followed by cooling at −70°, precipitated crude **10Aa** as colorless crystals (1.29 g, quantitative yield), m.p. 99–101°. Recrystallisation of crude **10Aa** from hexane–ether gave pure **10Aa** as colorless needles (1.03 g, 85%), m.p. 105–106°, $[\alpha]_D^{20}$ −112° (*c* = 0.760, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1740 (lactone), 1683 (amide). NMR (in $CDCl_3$): 1.00 (3H, t, J = 7 Hz, CH_3CH_2), 1.57 (3H, s, CH_3CCO), 1.92 (2H, q, J = 7 Hz, CH_3CH_2), 1.80–2.70 (4H, m, $CH_2CH_2CH_2N$), 3.40–3.90 (2H, m, CH_2N), 4.10–4.50 (1H, m, NCHCO). (Found: 61.20; H, 7.71; N, 7.28. Calc for $C_{10}H_{15}O_3N$: C, 60.90; H, 7.67; N, 7.10%).

(R)(−)-2-*Hydroxy*-2-*methylbutylic acid*((R)-**1a**)

A mixture of crude **10a** (m.p. 94–97°, $[\alpha]_D^{20}$ −107° (*c* = 0.706, MeOH))(985 mg, 5.00 mmole) and 36% HCl (10.3 ml) was refluxed for 8 hr. The acidic mixture was diluted with sat NaCl (20 ml), and extracted with EtOAc. The combined organic layers were extracted with sat $NaHCO_3$aq after being washed with sat NaClaq. The bicarbonate extracts were combined, acidified (pH ≒ 2) with conc HCl, and extracted with EtOAc. The combined EtOAc layers were washed with sat NaClaq. Filtration and evaporation *in vacuo* gave partially optically active (*R*)-**1a**[34] in a pure state (572 mg, 97%), colorless needles, m.p. 72–74°, $[\alpha]_D^{25}$ −7.9° (*c* = 2.97, $CHCl_3$). Spectral (IR and NMR) properties of this sample were identical with those of optically pure (*R*)-**1a** obtained as described below. Since optically pure (*R*)-**1a** prepared from pure **10Aa**, shows $[\alpha]_D^{25}$ −8.9° (*c* = 2.97, $CHCl_3$), the formation ratio of the two diastereomeric bromolactones (**8Aa** and **8Ba**) and the optical purity of (*R*)-**1a** can be calculated as 94.5:5.5 and 89%, respectively.

The same treatment of pure **10Aa** (m.p. 105–106°, $[\alpha]_D^{20}$ −113° (*c* = 3.01, $CHCl_3$))(985 mg, 5.00 mmole) as those described gave optically pure (*R*)-**1a**[34] as colorless needles (535 mg, 91%), m.p. 72–74°, $[\alpha]_D^{20}$ −8.5° (*c* = 3.01, $CHCl_3$), after evaporation of the EtOAc extracts. Recrystallisation of this sample from hexane afforded optically pure (*R*)-**1a**, colorless needles, m.p. 78–79°, $[\alpha]_D^{25}$ −8.9° (*c* = 2.97, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (acid). NMR (in $CDCl_3$): 0.94 (3H, t, J = 6 Hz, CH_3CH_2), 1.45 (3H, s, CH_3CCO), 1.42–2.02 (2H, m, CH_3CH_2), 6.12–7.12 (2H, br s, COOH and OH). These spectra were identical with those of the racemic acid ((±)-**1a**) prepared from 2-butanone according to the reported procedure,[36] m.p. 71–72° (lit.,[36] m.p. 72.5°).

Conversion of pure **10Aa** into (*R*)-**1a** was also carried out by successive acidic and alkaline hydrolyses.[37] Thus, a mixture of pure **10Aa** (m.p. 105–106°, $[\alpha]_D^{20}$ −113° (*c* = 0.672, MeOH)) (985 mg, 5.00 mmole) and 36% HCl (10.3 ml) was refluxed for 3 hr, then was evaporated *in vacuo*. The evaporation residue was dissolved in MeOH (10.5 ml), to which was added an aqueous soln (10.5 ml) of KOH (85% pure) (1.05 g, 15.9 mmole). The whole was stirred at room temp. for 45 hr, and was evaporated *in vacuo*. The evaporation residue was dissolved in H_2O, and the aqueous soln was extracted with ether. The aqueous layer was

acidified (pH ≈ 2) with conc. HCl, saturated with NaCl, and extracted with EtOAc. The combined EtOAc layers were washed with sat NaClaq. Filtration and evaporation *in vacuo* gave optically pure (*R*)-**1a** as colorless needles (525 mg, 90%), m.p. 74.5–76.5°, $[\alpha]_D^{25}$ −9.1° (*c* = 3.09, $CHCl_3$). Recrystallisation from hexane gave optically pure (*R*)-**1a**, colorless needles, m.p. 78–79°, $[\alpha]_D^{25}$ −8.9° (*c* = 3.06, $CHCl_3$). This sample showed the same spectral (IR and NMR) properties as those of optically pure (*R*)-**1a** obtained above.

(S)(−)-N-trans-*α*-*Methylcinnamoylproline* ((S)-**5b**

(a) (S)(−)-*Ethyl* N-trans-*α*-*methylcinnamoylprolinate* ((S)-**13b**). Condensation of **3b**[38] (3.24 g, 0.020 mole) and (*S*)-**12**[18] ($[\alpha]_D^{20}$ −42.5° (*c* = 2.01, EtOH)) (3.21 g, 0.022 mole) in a manner similar to the preparation of (*S*)-**13a** gave crude (*S*)-**13b** as a pale yellow caramel (6.18 g, quantitative yield) after evaporation of the combined organic extracts (benzene–ethyl acetate (1:2) (1.8 l)). Purification of crude (*S*)**13b** by column chromatography (silica gel, solvent petr. ether–ether 1:2) afforded pure (*S*)-**13b** as a colorless caramel (5.16 g, 90%), $[\alpha]_D^{20}$ −30.3° (*c* = 1.07, EtOH). IR ν_{max}^{film} cm^{-1}: 1730 (ester), 1620 (amide). NMR (in $CDCl_3$): 1.22 (3H, t, J = 8 Hz, CH_3CH_2), 2.09 (3H, d, J = 1.4 Hz, CH_3C=), 1.63–2.53 (4H, m, $CH_2CH_2CH_2N$), 3.67 (2H, t, J = 6 Hz, CH_2N), 4.18 (2H, q, J = 8 Hz, CH_3CH_2), 4.43–4.63 (1H, m, NCHCO), 6.70 (1H, br s, C_6H_5CH=), 7.30 (5H, s, C_6H_5).

(b) (S)(−)-N-trans-*α*-*Methylcinnamoylproline* ((S)-**5b**). Similar alkaline hydrolysis of pure (*S*)-**13b**($[\alpha]_D^{20}$ −30.3° (*c* = 1.07, EtOH)) (5.00 g, 17.4 mmole) gave crude (*S*)-**5b** as a colorless solid (4.35 g, 96%), m.p. 114–116°, after evaporation of the combined EtOAc extracts. Recrystallisation from hexane–benzene afforded pure (*S*)-**5b** as colorless needles (3.92 g, 87%), m.p. 116–117°, $[\alpha]_D^{20}$ −11.8° (*c* = 1.00, MeOH) and $[\alpha]_D^{20}$ −26.2° (*c* = 0.980, Me_2CO). IR ν_{max}^{Nujol} cm^{-1}: 1725 (acid), 1587 (amide). NMR (in $CDCl_3$): 1.57–2.47 (4H, m, $CH_2CH_2CH_2N$), 2.07 (3H, d, J = 1 Hz, =$C(CH_3)$CO), 3.67 (2H, t, J = 6 Hz, CH_2N), 4.62 (1H, br t, J = 6 Hz, NCHCO), 6.67 (1H, br s, C_6H_5CH=), 7.30 (5H, s, C_6H_5), 8.92 (1H, s, COOH). (Found: C, 69.71; H, 6.73; N, 5.43. Calc for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40%).

3(S)[1'(R) - *Bromophenylmethyl*] - 3(S) - *methyl* - 1,4 - *dioxo* - 3,4,6,7,8,8a(S) - *hexahydro* - 1*H* - *pyrrolo*[2,1-c][1,4]*oxazine* (**8Ab**) *and its* 1'(S),3(R) - *isomer* (**8Bb**) (*bromolactonisation of* (S)-**5b**)

A DMF soln (16 ml) of t-BuOK (0.898 g, 8.00 mmole) was added over 5 min to a stirred soln of (*S*)-**5b** ($[\alpha]_D^{20}$ −11.8° (*c* = 1.00, MeOH)) (2.07 g, 8.00 mmole) in DMF (8 ml) at −20° under N_2. A soln of NBS (2.85 g, 16.0 mmole) in DMF (24 ml) was further added over 5 min to the soln, and the whole was stirred at −20° for 2 hr, then at room temp. for 48 hr. The mixture was diluted with EtOAc (1.6 l), and the EtOAc soln was successively washed with 5%$NaHCO_3$, H_2O and sat NaClaq. Filtration and evaporation *in vacuo* gave crude **8b** (a mixture of **8Ab** and **8Bb**) as a pale yellow unstable caramel (2.46 g, 91%), $[\alpha]_D^{20}$ −102° (*c* = 0.934, MeOH). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (lactone), 1673 (amide). NMR (in $CDCl_3$): 1.47–2.57 (4H, $CH_2CH_2CH_2N$), 1.87 (3H, s, CH_3CCO), 2.57–3.97 (3H, m, CH_2NCHCO), 5.34 (1H, s, CHBr), 7.32 (5H, m, C_6H_5). This unstable caramel was directly used for the next debromination. Since this sample can be converted to 98% optically pure (*R*)-**1b**, the ratio of the two diastereomeric bromolactones (**8Ab** and **8Bb**) involved in this caramel, can be calculated as 99:1.

When the same bromolactonisation was attempted at room temp. for 66 hr by using NBS (1 eq) in the absence of t-BuOK, a 24% yield of crude **8b** could be obtained after extractive isolation.

3(R) - *Benzyl* - 3(R) - *methyl* - 1,4 - *dioxo* - 3,4,6,7,8,8a(S) - *hexahydro* - 1H - *pyrrolo*[2,1-c][1, 4]*oxazine* (**10Ab**) *and its* 3(S) - *isomer* (**10Bb**)

The same treatment of crude **8b**($[\alpha]_D^{20}$ −102° (*c* = 0.934, MeOH)) (2.36 g, 6.96 mmole) as for the debromination of **8a** gave crude **10b** as a pale yellow needles (1.28 g, 71%), m.p. 135–141°, $[\alpha]_D^{20}$ −69.7° (*c* = 0.633, $CHCl_3$), after evaporation of the combined eluates from the silica gel column. This sample showed the same spectral (IR and NMR) properties as those of pure **10Ab** prepared as mentioned below.

Successive purifications of a part of crude **10b** by recrystallisation from ether–chloroform, preparative tlc (silica gel, solvent ether), and further recrystallisation from ether–chloroform, afforded pure **10Ab** as colorless needles, m.p. 144–145°, $[\alpha]_D^{20}$ −79.3° (*c* = 0.640, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1745 (lactone), 1675 (amide). NMR (in $CDCl_3$): 1.17–2.47 (4H, m, $CH_2CH_2CH_2N$), 1.70 (3H, s, CH_3CCO), 2.10–3.80 (2H, m, CH_2N), 2.70–3.80 (1H, m, NCHCO), 3.00 (1H, d, J = 15.6 Hz, one of $C_6H_5CH_2$), 3.24 (1H, d, J = 15.6 Hz, one of $C_6H_5CH_2$), 7.23 (5H, s, C_6H_5). (Found: C, 69.30; H, 6.71; N, 5.23. Calc. for $C_{15}H_{17}O_3N$: C, 69.43; H, 6.61; N, 5.40%).

(R)(+) - 2 - *Hydroxy* - 2 - *methyl* - 3 - *phenylpropionic acid* ((R) - **1b**)

Reflux of a mixture of crude **10b** ($[\alpha]_D^{20}$ −69.7° (*c* = 0.663, $CHCl_3$)) (1.00 g, 3.86 mmole) and 36% HCl (8 ml) for 8 hr, followed by the same workup as that for the preparation of (*R*)-**1a**, gave partially optically active (*R*)-**1b** in a pure state (631 mg, 91%), colorless needles, m.p. 115–117°, $[\alpha]_D^{17}$ +16.7° (*c* = 5.71, dioxane). IR and NMR spectra of this sample were identical with those of authentic (*R*)-**1b**[40] (lit.,[40] m.p. 117.5–119°, $[\alpha]_D^{17}$ +16.4° (*c* = 5.658, dioxane)). The formation ratio of the two diastereomeric bromolactones (**8Ab** and **8Bb**) and the optical purity of (*R*)-**1b**, can be calculated as 99:1 and 98%, respectively, by assuming that the highest reported optical rotation[41] of (*R*)-**1b**, $[\alpha]_D$ +17.0° (*c* = 5.595, dioxane), is optically pure.

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