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ASYMMETRIC HALOLACTONISATION REACTION-2[1]

ELUCIDATION OF GENERAL APPLICABILITY AND MECHANISM OF THE ASYMMETRIC BROMOLACTONISATION REACTION[2]

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Abstract—Detailed studies on the asymmetric bromolactonisation were carried out by employing several structural types of α,β-unsaturated acids (2) as reaction substrates and various (*S*)-α-amino acids as chiral sources.

Following several novel aspects of the asymmetric bromolactonisation were uncovered by combining the results obtained in this study with those of the previous report. Thus, the bromolactonisation of (*S*)-N-(*cis*(E)-α,β-disubstituted-α,β-unsaturated) acylproline((*S*)-**3a,b**) proceeds more stereoselectively than that of the *trans*(Z)-α,β-disubstituted analogue ((*S*)-**3c**), to give the 6-membered bromolactone(**4A**) via the symmetrical and/or the carbocationic bromonium ions (**5AB** and/or **5AC**). While (*S*)-N-(*trans*(E)-β-monosubstituted-α,β-unsaturated)acylproline((*S*)-**3d**) undergoes no bromolactonisation, (*S*)-N-(β,β-disubstituted-α,β-unsaturated)acylproline((*S*)-**3e**) regiospecifically gives the 7-membered bromolactone(**11e**) via the carbocationic bromonium ion(**5AA**) when submitted to the bromolactonisation. (*S*)-Proline((*S*)-**8**) is found to the superior chiral source for the asymmetric bromolactonisation among those examined.

In the asymmetric synthesis of optically active α,α - disubstituted - α - hydroxy acids (**1a,b**) from α,β-unsaturated acids (**2a,b**) shown in Scheme 1, the bromolactonisations of (*S*)-N-(α,β-unsaturated)acylprolines (**3a,b**) with N-bromosuccinimide(NBS) in N,N-dimethylformamide(DMF) were found to occur highly stereoselectively and regiospecifically, giving mixtures of diastereomeric bromolactones (**4Aa,b** and **4Ba,b**) in which **4Aa,b** are predominant (**4Aa**:**4Ba** 94.5:5.5 and **4Ab**:**4Bb** 99:1).[1]

Although it is somewhat ambiguous whether heterolytic cleavage of NBS to bromonium ion(Br^+) occurs in an aprotic polar solvent such as DMF,[3] comparison of the design of the asymmetric synthesis and the experimental results[1] clearly uncovers that, as shown in Scheme 2, intervention of two types of the bromonium ions ((*S*)-**5A,C**) derivable from s-*trans*- and s-*cis*-conformers ((*S*)-**3A,C**), respectively, is only compatible with the first example of halolactonisation to conjugated double bond.[4]

In order to elucidate which conformer was responsible for the observed high stereoselectivity, the bromolactonisation of (*S*)-N-angeloylproline((*S*)-**3c**) was first attempted. Further studies on the applicability of this asymmetric bromolactonisation were also carried out by utilizing several kinds of **2** and by employing optically active (*S*)-α-amino acids other than (*S*)-proline((*S*)-**8**) as chiral sources.

This report deals with general applicability and mechanism of the asymmetric bromolactonisation which has been revealed by these studies.

RESULTS AND DISCUSSION

I. *Elucidation of the bromonium ion which predominantly participate in the asymmetric bromolactonisation*

As shown in Scheme 2, if **4Aa,b** can be formed via (*S*)-**5Ca,b**, exclusive formation of **4Ac** is reasonably expected for the asymmetric bromolactonisation of (*S*)-**3c** since the steric interaction between the carboxylate anion and the R^3 group should be the same in (*S*)-**5Ca,b** and (*S*)-**5Cc** because their R^3 groups are all Me. In contrast, when the formation of **4Aa,b** proceeds via (*S*)-**5Aa,b**, lower stereoselectivity should be observed for the asymmetric bromolactonisation of (*S*)-**3c** since steric interaction of the carboxylate anion and the R^2 groups are different.

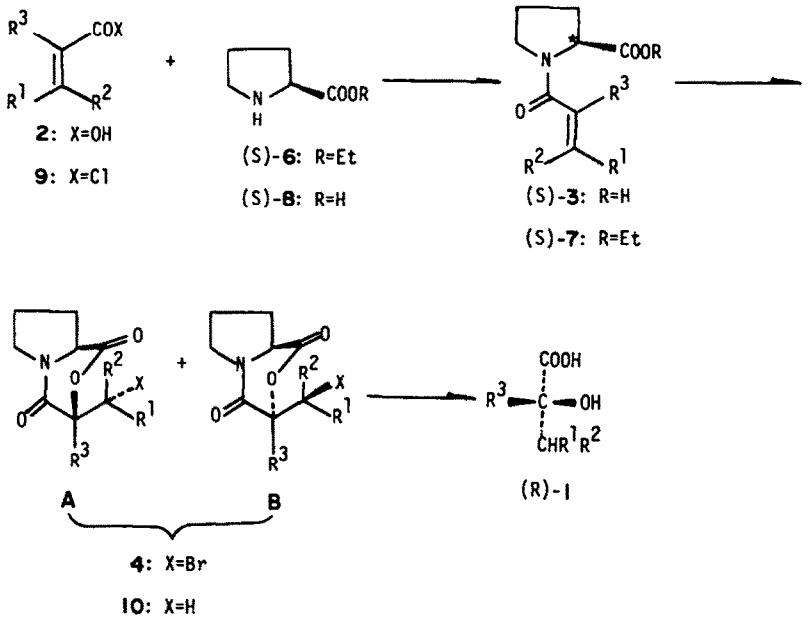
In order to discriminate these possibilities, the bromolactonisation of (*S*)-**3c** was attempted.

Requisite (*S*)-**3c**, $[\alpha]_D^{20} - 80.0°$ (MeOH), was prepared from (*S*)-ethyl prolinate ((*S*)-**6**)[6] and angelic acid (**2c**)[7] via (*S*)-ethyl N-angeloylprolinate ((*S*)-**7c**), $[\alpha]_D^{20} - 74.9°$ (EtOH), in a similar manner to those for (*S*)-**3a,b**.[1] While the bromolactonisation of (*S*)-**3c** with NBS in DMF was found to be very sluggish to give crude **4c** in 12% yield, the potassium salt of (*S*)-**3c** obtainable by treating (*S*)-**3c** with potassium t-butoxide, was successfully lactonised with NBS in DMF, affording crude **4c**, $[\alpha]_D^{20} - 53.5°$ (MeOH), as a mixture of the two diastereomers (**4Ac** and **4Bc**) in 76% yield.[8] The ratio of **4Ac** and **4Bc** could be calculated as 61:39 because (*R*)-**1a**,[9] $[\alpha]_D^{25} - 2.0°$ ($CHCl_3$), 22% optically pure,[11] was derived from crude **4c** via a diastereomeric mixture of the lactones (**10c**) by successive debromination[12] and acidic hydrolysis similar to those of **4a,b**.[1]

The use of (*S*)-**3c** in place of (*S*)-**3a,b** decreased the ratio of **4A** to **4B** from 94.5-99:5.5-1 to 69:39. This result clearly shows that the bromonium ions ((*S*)-**5Aa,b**) predominantly participate in the asymmetric bromolactonisation of (*S*)-**3a,b** which proceeds highly stereoselectively.

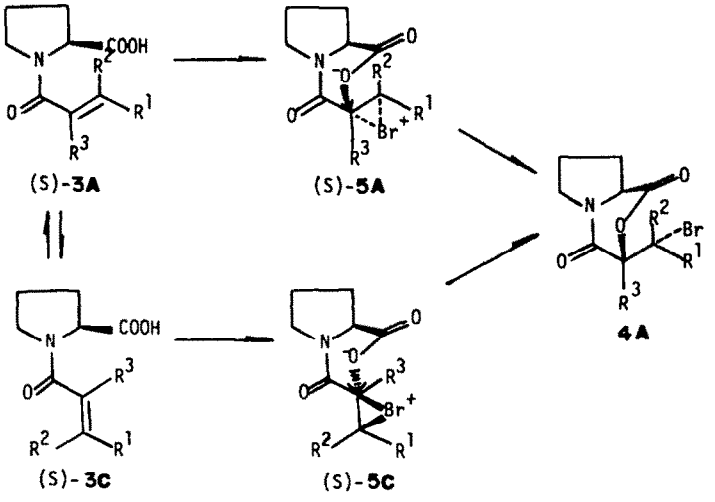
II. *Bromolactonisation reaction of (S)-N-(β-mono- or β,β-disubstituted-α,β-unsaturated)acylproline*

In order to obtain further information on the asymmetric bromolactonisation, the reaction of (*S*)-N-(β-mono- or β,β-disubstituted)acylproline was studied. (*S*)-N-crotonoyl, proline((*S*-**3d**), $[\alpha]_D^{20} - 102°$ (MeOH), and



	R^1	R^2	R^3
a:	Me	H	Me
b:	C_6H_5	H	Me
c:	H	Me	Me
d:	Me	H	H
e:	Me	Me	H

Scheme 1.



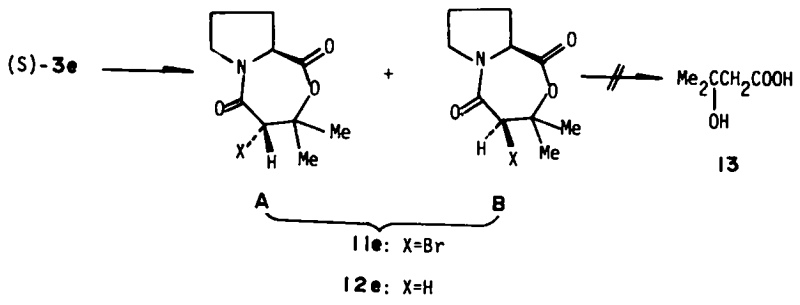
For R^1, R^2 and R^3, see Scheme 1.

Scheme 2.

(*S*)-N-(β-methylcrotonoyl)proline ((*S*)-3e), $[\alpha]_D^{20} - 92.8°$ (MeOH), were selected as reaction substrates, and were prepared by acylating (*S*)-proline((*S*)-8) with the corresponding acyl chlorides (9d,e)[13] according to the Schotten–Baumann procedure.

Attempted bromolactonisation of (*S*)-3d or its potassium salt with NBS in DMF completely failed to give the desired bromolactone (4d). This is conceivably due to lower electron density of the double bond of (*S*)-3d when compared with those of (*S*)-3a,b,c.[14]

On the other hand, treatment of (*S*)-3e with NBS (2 eq) in DMF afforded the crude 7-membered bromolactone



Scheme 3.

(11e) as a mixture of the two diastereomers (11Ae and 11Be), $[\alpha]_D^{20} - 79.3°$ ($CHCl_3$), in 89% yield as shown in Scheme 3. The yield of 11e decreased to 51% when one equivalent of NBS was used. Recrystallisation of crude 11e gave the predominantly formed diastereomer (11Ae or 11Be),[15] $[\alpha]_D^{20} - 90.3°$ ($CHCl_3$), in a pure state. Debromination of the purified bromolactone (11Ae or 11Be) with tri-n-butyltin hydride[12] gave the lactone (12a), $[\alpha]_D^{20} - 155°$ ($CHCl_3$), in 47% yield. The 7-membered structures of 11e and 12e were definitely established since the NMR spectrum of 12e exhibited its *gem*-dimethyl group as two singlets at 1.50 ppm and its α-methylene group as two doublets at 2.56 and 3.20 ppm (J = 18.8 Hz).

Exclusive formation of the 7-membered bromolactone has never been precedent for halolactonisation. While this observation seems quite different from the bromolactonisation of (*S*)-3a,b,c which solely affords the 6-membered bromolactones (4a,b,c), a change of electronic nature of the intermediary bromonium ion ((*S*)-5e) might account the observed result.

Attempted hydrolysis of 12e which might constitute another new asymmetric synthesis of optically active β-hydroxy-β,β-disubstituted acids from β,β-disubstituted-α,β-unsaturated acids, induced exclusive dehydration, and desired 3-hydroxy-3-methylbutyric acid (13) could not be obtained.

III. *Reaction mechanism and applicability of the asymmetric bromolactonisation*

Results for the asymmetric bromolactonisation of (*S*)-3 obtained in this and the previous studies,[1] are summarised in Table 1.

Comparison of the chemical yields under the condition A clearly discloses that the (disubstituted-α,β-unsaturated)acyl groups involved in (*S*)-3a,b,c,e show a higher reactivity towards the bromolactonisation than the (monosubstituted-α,β-unsaturated)-acyl group of (*S*)-3d, and that the reactivity follows the order of *cis* ((E)-configuration) ((*S*)-3a) > *gem* ((*S*)-3e) > *trans* ((Z)-configuration) ((*S*)-3c) when compared in a range of the (dialkylsubstituted - α,β - unsaturated)acyl groups. The (disubstituted-α,β-unsaturated)acyl group of (*S*)-3b having a phenyl group at the β-position, exhibits the intermediate reactivity between *gem* ((*S*)-3e) and *trans* ((*S*)-3c) substitutions. Similar order of reactivity of the double bond which arises from a decrease of electron density, has been reported for the addition reaction of bromine to

Table 1. Results for the asymmetric bromolactonisation reactions of (*S*)-*N*-(α,β-unsaturated)acylproline((*S*)-3)

	(S)-3			Substitution Pattern of Double Bond(Confign.)	Reaction Condition[a]	Bromolactones Yield[b] (%)	Formation Ratio 4A	4B	11(11A+11B)
	R^1	R^2	R^3						
a	Me	H	Me	cis(E)	A	84	94.5	5.5	–[c]
b	C_6H_5	H	Me	cis(E)	A	24			
b	C_6H_5	H	Me	cis(E)	B	94	99	1	–[c]
c	H	Me	Me	trans(Z)	A	12			
c	H	Me	Me	trans(Z)	B	76	61	39	–[c]
d	Me	H	H	trans(E)	A	0			
e	Me	Me	H	gem	A	51	–[d]	–[d]	100[e]
e	Me	Me	H	gem	C	91	–[d]	–[d]	100[e]

a) A: NBS(1 eq) in DMF, rt, 20 hr; B: NBS(2 eq)-t-BuOK(1 eq) in DMF, -20°C, 2 hr, then rt 48 hr; C: NBS(2 eq) in DMF, rt, 20 hr. b) Based on the weight of the crude bromolactone obtained by the evaporation of the neutral organic extracts. c) Formation of the seven membered bromolactone was not observed. d) Formation of the six membered bromolactone was not observed. e) Formation ratio of the two diastereomeric bromolactones(11Ae and 11Be) was not determined.

substituted ethylenes.[14] Therefore, the rate determining step for the bromolactonisation might be the bromonium ion formation in complete the same manner as that for the bromine addition to substituted ethylenes.[14]

When the structures of the bromolactones (4 and 11) are compared, it is obvious that (*cis*(Z)- and *trans*(E) - α,β - disubstituted - α,β - unsaturated)acylprolines((*S*)-3a,b,c) give the 6-membered bromolactones (4a,b,c) wherein the former two (4a,b) can be produced more stereoselectively than the other (4c), and that (*gem* - β,β - disubstituted - α,β - unsaturaturated)acylproline ((*S*)-3e) affords exclusively the 7-membered bromolactone (11e). These results might be verified by the following explanation.

Thus, the bromonium ion ((*S*)-5A) which has been established to contribute to the predominant formation of 4A, might consist of an equilibrating mixture of three types of the bromonium ions ((*S*)-5AA, (*S*)-5AB and (*S*)-5AC). In the asymmetric bromolactonisation of (*S*)-3a,b,c, the symmetrical and/or the carbocationic bromonium ions ((*S*)-5AB and/or (*S*)-5AC) can be attacked regiospecifically at the α position by the intramolecular carboxylate anion in S_N2 and/or S_N1 like displacement processes, giving 4Aa,b,c as visualised in Scheme 4. Among two plausible brominium ions ((*S*)-5AB and (*S*)-5AC), the former will participate more preferentially since the amide CO group might destabilise the adjacent carbocation. In the case of (*S*)-3e, contribution of the other carbocationic bromonium ion ((*S*)-5AA) will predominate because the positive charge at the β position might be stabilized by the presence of the two Me groups. Therefore, in the latter instance, the lactonisation will occur regiospecifically at the β position in the S_N1 like process. The reason why the nucleophilic opening of the symmetric bromonium ion such as (*S*)-5AB occurs regiospecifically at the α-position is that the transition state where the leaving group and the intramolecular nucleophile are in a collinear relationship is energetically favoured in a similar manner to the backside collinear displacement of epoxide by the intramolecular carbanion.[16]

The observed regiospecific 6- or 7-membered bromolactone formation is also in agreement with the rule for ring closure proposed by Baldwin.[17]

IV. *The use of various chiral sources other than* (S)-*proline in the asymmetric synthesis*

Aiming to find out the chiral sources which are usable in place of (*S*)-8, the asymmetric synthesis was attempted by using (*S*)-phenylalanine((*S*)-14), (*S*)-N-benzylphenylalanine((*S*)-15),[18] and (*S*)-1,2,3,4 - tetrahydroisoquinoline - 3 - carboxylic acid((*S*)-16)[19] as chiral sources, and by employing 2a as a reaction substrate.

Acylation of (*S*)-14 and (*S*)-16 with 9a[20] by the Schotten–Baumann condition gave the corresponding (*S*)-N-tigloyl-α-amino acids ((*S*)-17 and (*S*)-18, $[\alpha]_D^{20}$ + 86.0° ($CHCl_3$) and $[\alpha]_D^{20}$ − 28.0° (2NNaOH). Treatment of (*S*)-ethyl N-benzylphenylalaninate((*S*)-19), $[\alpha]_D^{20}$ + 37.6° (EtOH), prepared from (*S*)-15, with 9a[20] in pyridine, followed by hydrolysis under alkaline condition, afforded (*S*)-N-benzyl-N-tigloylphenylalanine((*S*)-20), $[\alpha]_D^{20}$ − 152° (MeOH).

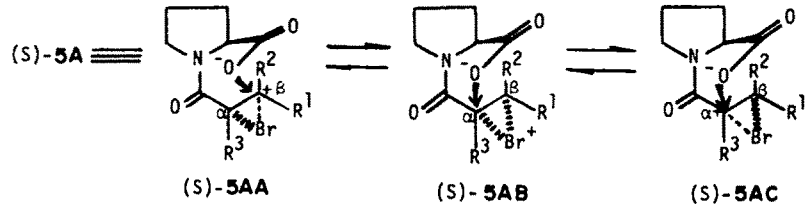
The asymmetric bromolactonisations of (*S*)-17 and (*S*)-20 or those of the potassium salts derived from (*S*)-17 and (*S*)-20, under the same condition as that for (*S*)-3a,[1] were found to give no trace amount of the desired bromolactones. These results might be rationalised by the fact that (*S*)-17 and (*S*)-20 are the straight chain δ,ϵ-unsaturated acids in which free rotation of the bond between the asymmetric center and the N atom is possible. These findings are in good accord with the unsuccessful iodolactonisation of δ,ϵ-hexeonic acid reported by van Tamelen.[5]

On the other hand, the reaction of (*S*)-18 with NBS in DMF after converting it into its potassium salt, successfully gave the crude bromolactone (21) as a mixture of the two diastereomers (21A and 21B), $[\alpha]_D^{20}$ − 141° ($CHCl_3$), in 33% yield. Transformation of crude 21 into (*R*)-1a,[9] $[\alpha]_D^{25}$ − 5.7° ($CHCl_3$), 64% optically pure,[11] was achieved by successive debromination[12] and acidic hydrolysis. The preparation of (*R*)-1a clearly determined the ratio of 21A to 21B as 82:18.

These results obviously disclose that prohibition of free rotation of the C*–N bond which can locate the α,β-unsaturated acyl moiety in the vicinity of the carboxyl group, is inevitable for effecting successful bromolactonisation. The same fixation of the C*–N bond is also attained in (*S*)-3a,b,c,e.

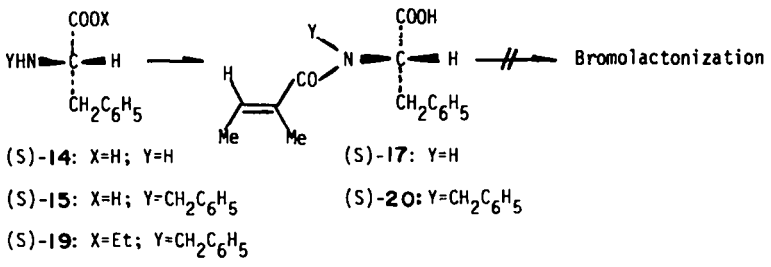
Comparison of the result obtained for (*S*)-18 with that for (*S*)-1a[1] also uncovers that the reactivity and stereoselectivity of (*S*)-18 for the asymmetric bromolactonisation are fairly lower than those of (*S*)-3a, and that (*S*)-8 is the most superior chiral source among those studied. The reason for the lowered formation ratio of 21A and 21B is still obscure, but a delicate structural change near the reaction site might be reflected for the observed result.

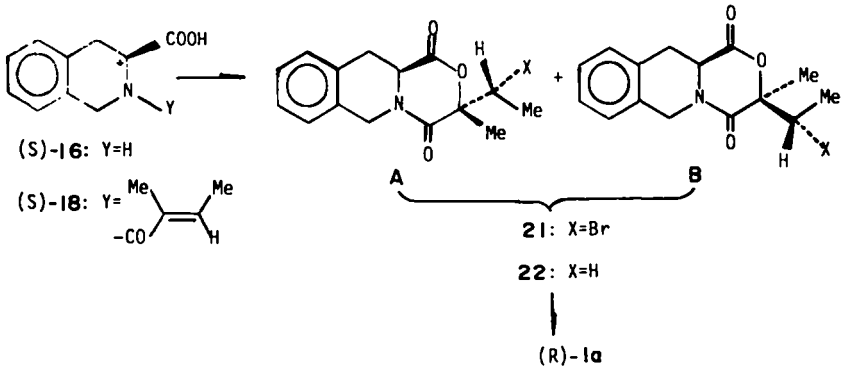
Summing up the results obtained in this and the previous studies, it is clearly established that (*S*) - N - (*cis*(E) - α,β - disubstituted - α,β - unsaturated)acylproline derivable from the corresponding α,β-unsaturated acids and (*S*)-8 is submitted to the asymmetric bromolactonisation, the reaction can proceed in a highly stereoselective and regiospecific manner via the symmetrical and/or the carbocationic bromonium ions ((*S*)-5AB and/or (*S*)-5AC) to give bromolactone (4) in which 4A is highly predominant. This conclusion is successfully visualised by the asymmetric synthesis of optically active anthracyclinones, aglycones of anthracyclinone antibiotics.[21]



For R^1, R^2 and R^3, see Scheme 1.

Scheme 4.





Scheme 5.

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 Infrared 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 anhydrous 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-Angeloylproline*((S)-3c)

(a) (S)(−)-*Ethyl N-angeloylprolinate*((*S*)-7c). Treatments of 2c[7] (m.p. 45–47°) (200 mg, 2.00 mmole) and (*S*)-6[6] ($[\alpha]_D^{20}$ − 42.6° (*c* = 2.01, EtOH)) (320 mg, 2.24 mmole) similar to those for the preparation of (*S*)-3a,b[1] gave crude (*S*)-7c as a pale yellow oil (427 mg, quantitative yield) after evaporation of the combined organic extracts (benzene–ethyl acetate, 1:2). Purification of this sample by column chromatography (silica gel, solvent hexane–ether, 1:1) gave pure (*S*)-7c as a pale yellow oil (327 mg, 73%), $[\alpha]_D^{20}$ − 74.9° (*c* = 1.08, EtOH); IR ν_{max}^{film} cm^{-1}: 1750 (ester), 1630 (amide); NMR (in $CDCl_3$): 1.27 (3H, t, J = 7 Hz, CH_3CH_2), 1.47–2.67 (10H, m, $CH_3CH{=}C(CH_3)$ and $CH_2CH_2CH_2N$), 3.17–3.77 (2H, m, CH_2N), 4.12 (2H, q, J = 7 Hz, CH_3CH_2), 4.17–4.67 (1H, m, NCHCO), 5.17–5.67 (1H, m, $CH_3CH{=}$).

(b) (S)(−)-*N-angeloylproline*((S)-3c). Treatment of (*S*)-7c ($[\alpha]_D^{20}$ − 74.9° (*c* = 1.08, EtOH)) (323 mg, 1.43 mmole) similar to those for the preparations of (*S*)-3a,b[1] afforded crude (*S*)-3c as a colorless powder (250 mg, 91%), m.p. 123–125°, after evaporation of the combined EtOAc extracts. Recrystallisation of this sample from hexane–ether gave pure (*S*)-3c as colorless plates, m.p. 125–127°, $[\alpha]_D^{20}$ − 80.0° (*c* = 1.01, MeOH); IR ν_{max}^{Nujol} cm^{-1}: 1750 (acid), 1674 (amide); NMR (in $CDCl_3$): 1.36–2.56 (10H, m, $CH_3CH{=}C(CH_3)$ and $CH_2CH_2CH_2N$), 3.16–3.86 (2H, m, CH_2N), 4.16–4.86 (1H, m, NCHCO), 5.06–5.86 (1H, m, $CH_3CH{=}$), 10.04 (1H, s, COOH). (Found: C, 60.64; H, 7.75; N, 7.39. Calc. for $C_{10}H_{15}O_3N$: C, 60.91; H, 7.61; N, 7.11%).

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

Treatments of (*S*)-3c($[\alpha]_D^{20}$ − 77.8° (*c* = 0.996, MeOH)) similar to the bromolactonisation of (*S*)-3b[1] gave crude 4c (a mixture of 4Ac and 4Bc) as a pale yellow oil (461 mg, 76%), $[\alpha]_D^{20}$ − 53.5° (c = 0.650, MeOH), after evaporation of the combined EtOAc extracts; IR ν_{max}^{film} cm^{-1}: 1750 (lactone), 1680 (amide); NMR (in $CDCl_3$): 1.40–2.40 (4H, m, $CH_2CH_2CH_2N$), 1.60 (3H, s, CH_3COO), 1.75 (3H, d, J = 7 Hz, CH_3CHBr), 3.25–3.95 (2H, m, CH_2N), 4.05–4.85 (2H, m, CH_3CHBr and NCHCO). Since this sample gives (*R*)-1a[9] being 22% optically pure,[11] the formation ratio of the two diastereomeric bromolactones (4Ac and 4Bc) can be calculated as 61:39. This crude sample (4c) was directly submitted to the next debromination.

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

Treatment of crude 4c($[\alpha]_D^{20}$ − 53.5° (*c* = 0.650, MeOH)) (409 mg, 1.48 mmole) similar to the debromination of crude 4a[1] gave crude 10c (a mixture of 10Ac and 10Bc) as colorless needles (212 mg, 73%), m.p. 69–80°, $[\alpha]_D^{20}$ − 80.5° (*c* = 0.852, MeOH), after evaporation of the combined ethereal eluates from a silica gel column. IR and NMR spectra of this sample were almost identical with those of pure 10Aa obtained in the previous study.[1] This sample was immediately used for the next hydrolysis.

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

(a) *Hydrolysis of* 10c *prepared from* 4c. Treatment of crude 10c (m.p. 69–80°, $[\alpha]_D^{20}$ − 80.5° (*c* = 0.852, MeOH) (180 mg, 0.912 mmole) similar to those previously described,[1] gave partially optically active (*R*)-1a[9] in a pure state (88 mg, 82%), colorless needles, m.p. 58–64°, $[\alpha]_D^{25}$ − 2.0° (*c* = 1.21, $CHCl_3$), after evaporation of the combined EtOAc extracts. Spectral (IR and NMR) properties of this sample were identical with those of authentic optically pure (*R*)-1a.[1] Since optically pure (*R*)-1a shows $[\alpha]_D^{25}$ − 8.9° (*c* = 2.97, $CHCl_3$),[1] the formation ratio of the two diastereomeric bromolactones (4Ac and 4Bc) and the optical purity of (*R*)-1a, can be calculated as 61:39 and 22%, respectively.

(b) *Hydrolysis of* 22 *prepared from* 21. A mixture of crude 21 (m.p. 118–132°, $[\alpha]_D^{20}$ – 120° (c = 0.512, MeOH)) (1.15 g, 4.44 mmole) and 36% HCl (18 ml) was refluxed for 20 hr, then was evaporated *in vacuo*. The evaporation residue was dissolved in MeOH (10 ml), to which was added KOH (85% pure) (1.32 g, 20.0 mmole) aq. The mixture was stirred at 80–90° (bath temp.) for 1 hr, and was evaporated *in vacuo*. The evaporation residue was treated as previously described,[1] giving partially optically active (*R*)-1a[9] in a pure state (410 mg, 78%), colorless needles, m.p. 69–73°, $[\alpha]_D^{25}$ – 5.7° (c = 3.17, $CHCl_3$), after evaporation of the combined EtOAc extracts. Spectral (IR and NMR) properties of this sample were identical with those of authentic optically pure (*R*)-1a.[1] Since optically pure (*R*)-1a shows $[\alpha]_D^{25}$ – 8.9 (c = 2.97, $CHCl_3$),[1] the formation ratio of the two diastereomeric bromolactones (21A and 21B) and the optical purity of (*R*)-1a, can be calculated as 82:18 and 64%, respectively.

(S) (−)-N-*Crotonoylproline*((S)-3d)

Acylation of (*S*)-8 ($[\alpha]_D^{20}$ – 85.5° (c = 4.00, H_2O)) (22.9 g, 0.20 mole) with 9d (25.0 g, 0.24 mole) according to the Schotten–Baumann procedure similar to that for the preparation of (*S*)-3a,[1] gave crude (*S*)-3d as a colorless solid (30.5 g, 84%), after evaporation of the combined EtOAc extracts. Recrystallisation from acetone afforded pure (*S*)-3d as colorless pillars (23.8 g, 67%), m.p. 158–159° $[\alpha]_D^{20}$ – 102° (c = 1.04, MeOH); $IR\nu_{max}^{Nujol}$ cm^{-1}: 1720 (acid), 1660 (olefin), 1590 (amide); NMR (in CD_3OD): 1.87 (3H, Br d, J = 7 Hz, CH_3CH=), 1.57–2.47 (4H, m, $CH_2CH_2CH_2N$), 3.52 (32H, m, CH_2N), 4.17–4.67 (1H, m, NCHCO), 5.77–7.17 (2H, m, CH_3CH=CH). (Found: C, 58.95; H, 7.18; N, 7.61. Calc. for $C_9H_{13}O_3N$: C, 59.00; H, 7.15; N, 7.65%).

(S) (−)-N-(*β-Methylcrotonoyl*)*proline* ((S)-3e)

In a manner similar to the case for (*S*)-3a,[1] this compound was prepared by acylating (*S*)-8 ($[\alpha]_D^{20}$ – 85.5° (c = 4.00, H_2O)) (16.2 g, 0.14 mole) with 9e[13] (b.p. 60–64° (34 mmHg)) (20.0 g, 0.17 mole) according to the Schotten–Baumann procedure. The crude product ((*S*)-3e) obtained as yellow needles by evaporation of the combined EtOAc extracts, weighed 27.2 g (98%). Decolorisation of this sample with charcoal followed by two successive recrystallisations from hexane–ether, gave pure (*S*)-3e as colorless needles (18.0 g, 64%), m.p. 91–93°, $[\alpha]_D^{20}$ – 92.8° (c = 1.04, MeOH); $IR\nu_{max}^{Nujol}$ cm^{-1}: 1720 (acid), 1665 (olefin), 1590 (amide); NMR (in $CDCl_3$): 1.90 (3H, br s, CH_3CH=), 2.90 (3H, br s, CH_3C=), 1.44–2.54 (4H, m, $CH_2CH_2CH_2N$), 3.36–3.76 (2H, m, CH_2N), 4.26–4.76 (1H, m, NCHCO), 5.59, 5.61 (1H, two br s, =CHCO). (Found: C, 60.84; H, 7.57; N, 6.98. Calc. for $C_{10}H_{15}O_3N$: C, 60.91; H, 7.61; N, 7.11%).

4(S) - *Bromo* - 3,3 - *dimethyl* - 1,5 - *dioxo* - 4,5,7,8,9,9a(S) - 1H,3H - *pyrrolo*[2,1-c][1, 4] *oxazepine* (11*Ae*) *and its* 4(R)-*Isomer* (11*Be*) (*Bromolactonisation of* (S)-3e)

A DMF soln (1.5 ml) of NBS (356 mg, 2.00 mmole) was added to a stirred soln of (*S*)-3e (m.p. 91–93°, $[\alpha]_D^{20}$ – 92.8° (c = 1.04, MeOH)) (197 mg, 1.00 mmole) in DMF (1.5 ml) at room temp. under N_2. After being stirred at room temp. for 20 hr, the mixture was diluted with EtOAc (90 ml), and was worked up as for the bromolactonisation of (*S*)-3a[1] to give crude 11e (a mixture of 11Ae and 11Be) as colorless needles (254 mg, 89%), m.p. 115–123°, $[\alpha]_D^{20}$ – 79.3° (c = 0.606, $CHCl_3$), after evaporation of the combined EtOAc extracts. Recrystallisation of crude 11e from chloroform–ether gave pure sample (11Ae or 11Be)[15] as colorless needles (137 mg, 50%), m.p. 133–134° (dec), $[\alpha]_D^{20}$ – 90.3° (c = 0.646, $CHCl_3$). $IR\nu_{max}^{Nujol}$ cm^{-1}: 1740, 1730 (lactone), 1675 (amide); NMR (in $CDCl_3$): 1.56 (3H, s, CH_3), 1.72 (3H, s, CH_3), 1.82–2.12 (2H, m, $CH_2CH_2CH_2N$), 2.12–2.72 (2H, m, $CH_2CH_2CH_2N$), 3.61 (2H, t, J = 7.2 Hz, CH_2N), 4.47 (1H, br t, J = 7.5 Hz, NCHCO), 4.98 (1H, s, $CHBr$). (Found: C, 43.50; H, 5.20; N, 5.16, Calc. fo $C_{10}H_{14}O_3NBr$: C, 43.51; H, 5.07; N, 5.07%).

Similar bromolactonisation of (*S*)-3e (98.6 mg, 0.50 mmole) with NBS (89 mg, 0.50 mmole) in DMF (1 ml) at room temp. for 23 hr afforded crude 11e (a mixture of 11Ae and 11Be) (70 mg, 51%). This was identified with crude 11e obtained above by tlc (silica gel, solvent ether, Rf 0.45) comparison.

3,3 - *Dimethyl* - 1,5 - *dioxo* - 4,5,7,8,9,9a(S) - 1*H*,3*H* - *pyrrolo*[2,1-c] [1,4]*oxazepine*(12e)

A benzene soln (1 ml) of tri-n-butyl-tin hydride[12] (754 mg, 2.6 mmole) was added over 1 min to a stirred soln of purified (11Ae or 11Be) (m.p. 133–134° (dec), $[\alpha]_D^{20}$ – 90.3° (c = 0.646, bromolactone $CHCl_3$)) (276 mg, 1.0 mmole) at 50° under N_2, and the mixture was stirred at 90–100° for 24 hr. Evaporation of the mixture *in vacuo* gave a mixture of crystals and oil. Addition of hexane to residue gave crude 12e as colorless crystals (92 mg, 47%), m.p. 122–124°, $[\alpha]_D^{20}$ – 146° (c = 0.492, $CHCl_3$). Recrystallisation from chloroform–ether gave pure 12e as colorless needles (75 mg, 27%), m.p. 124–125°, $[\alpha]_D^{20}$ – 155° (c = 0.466, $CHCl_3$), $IR\nu_{max}^{Nujol}$ cm^{-1}: 1715 (lactone), 1660 (amide); NMR (in $CDCl_3$): 1.50 (6H, br s, two CH_3), 1.68–1.98 (2H, m, $CH_2CH_2CH_2N$), 1.98–2.40 (2H, m, $CH_2CH_2CH_2N$), 2.56(1H, d, J = 18.8 Hz, one of $NCOCH_2$), 3.20 (1H, J = 18.8 Hz, one of $NCOCH_2$), 3.40–3.76 (2H, m, CH_2N), 4.46 (1H, doubled d, J = 7.5 and 4.5 Hz, NCHCO). (Found: C, 60.93: H, 7.66; N, 6.81. Calc. for $C_{10}H_{15}O_3N$: C, 60.90; H, 7.61; N, 7.11%).

(S)(+)-N-*Tigloylphenylalanine*((S)-17)

Acylation of (*S*)-14 (2.77 g, 16.8 mmole) with 9a[20] (2.40 g, 20.2 mmole) according to the Schotten-Baumann procedure similar manner to the preparation of (*S*)-3a,[1] gave crude (*S*)-17 as a colorless caramel (4.64 g, quantitative yield) after evaporation of the combined EtOAc extracts. Crude (*S*)-17 was converted to the corresponding methyl ester by treating with an excess amount of diazomethane in ether. The crude methyl ester obtained as a pale yellow oil (5.32 g, quantitative yield) by evaporation of the ethereal soln *in vacuo*, was purified by column chromatography (silica gel, solvent hexane–ether, 1 : 1), giving the pure ester as a colorless oil (3.96 g, 89%), $[\alpha]_D^{20}$ – 28.4° (c = 0.854, MeOH). $IR\nu_{max}^{film}$ cm^{-1}: 1750 (ester), 1665 (olefin), 1630 (amide); NMR (in $CDCl_3$): 1.62–1.92 (6H, m, two CH_3), 3.18 (2H, d, J = 6.6 Hz, $C_6H_5CH_2CH$), 3.72 (3H, s, CO_2CH_3), 4.62–5.07 (1H, m, $C_6H_5CH_2CHCO$), 5.92–6.42 (2H, m, CH_3CH= and NH), 6.82–7.32 (5H, m, C_6H_5).

To a methanolic soln (10 ml) of the pure methyl ester (1.15 g, 4.4 mmole) was added KOH (85% pure) (0.35 g, 5.3 mmole) aq (10 ml). The mixture was stirred at room temp. for 3 hr, then was concentrated *in vacuo*. The evaporation residue was diluted with H_2O, washed with ether, and acidified (pH ÷ 2) with conc HCl. After saturation with NaCl, the acidic aqueous soln was extracted with EtOAc. The combined EtOAc extracts were washed with sat. NaCl aq. Filtration and evaporation *in vacuo* gave pure (*S*)-17 as a colorless caramel (1.10 g, quantitative yield), $[\alpha]_D^{20}$ + 86.0° (c = 1.79, $CHCl_3$); $IR\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (acid), 1670 (olefin), 1638 (amide); NMR (in $CDCl_3$): 1.60–1.80 (6H, m, two CH_3), 3.10 (2H, br d, J = 5.4 Hz, $C_6H_5CH_2CH$), 4.72–4.98 (1H, m, $C_6H_5CH_2CH$), 6.20–6.52 (2H, m, CH_3CH= and NH), 7.00–7.28 (5H, m, C_6H_5), 9.67 (1H, m, COOH).

(S)(−)-N-*Benzyl*-N-*tigloylphenylalanine*((S)-2b)

(a)(S)(+)-N-*Benzylphenylalanine* (*S*)-15). Prepared from (*S*)-14 in 78% yield according to the reported procedure,[18] m.p. 236–237°, $[\alpha]_D^{22}$ + 25.0° (c = 1.01, 0.2N-NaOH) (lit.,[18a] m.p. 255° (dec), $[\alpha]_D^{22}$ + 18.09° (0.2N-NaOH)).

(b) (S)(+)-*Ethyl* N-*benzylphenylalaninate hydrochloride* ((S)-19). This was prepared in 94% yield by treating (*S*)-15 with thionyl chloride in EtOH, m.p. 149–151° (recrystallised from acetone–ether), $[\alpha]_D^{20}$ + 37.6° (c = 2.04, EtOH); $IR\nu_{max}^{Nujol}$ cm^{-1}: 1757 (ester).

(c) (S)(−)-*Ethyl* N-*benzyl*-N-*tigloylphenylalaninate*. A mixture of (*S*)-19 (3.58 g, 11.2 mmole) and 9a[20] (1.99 g, 16.8 mmole) in pyridine (22 ml) was stirred at room temp. for 2.5 hr, then was poured onto an ice-water (110 ml). The aqueous mixture was extracted with EtOAc, and the combined EtOAc extracts were successively washed with 10% HCl, sat. NaCl, sat $CuSO_4$, H_2O, sat $NaHCO_3$, and sat NaCl aq. Filtration and evaporation *in vacuo* gave the crude product as a pale yellow oil (4.41 g, quantitative yield), which was purified by column chromatography (silica gel, solvent hexane–ether, 1 : 1), to afford the pure ester as a pale yellow caramel (2.55 g, 62%), $[\alpha]_D^{20}$ – 159° (c = 1.09, EtOH). $IR\nu_{max}^{film}$ cm^{-1}: 1743 (ester), 1640 (amide); NMR (in

$CDCl_3$): 1.20 (3H, t, J = 7 Hz, CH_3CH_2), 1.50–1.90 (6H, m, $CH_3CH=C(CH_3)$), 3.28 (2H, d, J = 7.6 Hz, $C_6H_5CH_2CH$), 3.80–4.20 (1H, m, $C_6H_5CH_2CH$), 4.00 (2H, q, J = 7 Hz, CH_3CH_2), 3.95 (1H, d, J = 15 Hz, one of $C_6H_5CH_2N$), 4.55 (1H, d, J = 15 Hz, one of $C_6H_5CH_2N$), 5.30–5.70 (1H, m, $CH_3CH=$), 7.18 (10H, s, two C_6H_5).

(d) (S)(−)-N-*Benzyl*-N-*tigloylphenylalanine*((S)-**20**). Hydrolysis of (*S*)(−)-ethyl N-benzyl-N-tigloylphenylalaninate (2.46 g, 6.74 mmole) in KOH, (85% pure) (0.58 g, 8.76 mmole) aq (14 ml) similar to that for preparation of (*S*)-**17** afforded crude (*S*)-**20** as a colorless caramel (2.46 g, quantitative yield), $[\alpha]_D^{20}$ − 151° (*c* = 1.32, MeOH), which gradually solidified when kept in a freezer (−20°) for 2 months, m.p. 50–58°. Recrystallisation of crude (*S*)-**20** from hexane–ether gave pure (*S*)-**20** as colorless pillars (1.93 g, 85%), m.p. 59–61°C, $[\alpha]_D^{20}$ − 152° (*c* = 1.31, MeOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 (acid), 1625 (amide); NMR (in $CDCl_3$): 1.35–1.85 (6H, m, $CH_3CH=C(CH_3)$), 3.30 (2H, d, J = 8.4 Hz, $C_6H_5CH_2CH$), 3.84 (1H, d, J = 15 Hz, one of $C_6H_5CH_2N$), 4.58 (1H, d, J = 15 Hz, one of $C_6H_5CH_2N$), 3.65–4.35 (1H, m, $C_6H_5CH_2CH$), 6.65–7.35 (10 H, m, two C_6H_5). (Found: C, 74.44; H, 6.75; N, 4.18. Calc. for $C_{21}H_{23}O_3N$: C, 74.75; H, 6.87; N, 4.15%).

(S)(−) - N - *Tigloyl* - 1,2,3,4 - *tetrahydroisoquinoline* - 3 - *carboxylic acid*((S)-**18**)

This was prepared by acylating (*S*)-**16**[19] (m.p. 295–298° (sublime), $[\alpha]_D^{20}$ − 158° (*c* = 1.94, 1.4N-NaOH)) (5.0 g, 28.2 mmole) with **9a**[20] (5.02 g, 42.3 mmole) following the Schotten–Baumann procedure similar to that for the preparation of (*S*)-**3a**.[1] Evaporation of the combined EtOAc extracts afforded crude (*S*)-**18** as a colorless solid (7.2 g, 99%), which on recrystallisation from EtOH gave pure (*S*)-**18** as colorless needles (6.5 g, 89%), *m.p.* 189–190°, $[\alpha]_D^{20}$ − 28.0° (*c* = 2.05, 2N-NaOH). IR ν_{max}^{Nujol} cm^{-1}: 1735 (acid), 1580 (amide); NMR (in CD_3OD): 1.50–1.90 (6H, m, $CH_3CH=C(CH_3)$), 3.10–3.40 (2H, m, $CH_2CHCOOH$), 4.65 (2H, br d, J = 7 Hz, CH_2N), 5.05 (1H, t, J = 5 Hz, NCHCO), 5.50–5.90 (1H, m, $CH_3CH=$), 7.12 (4H, s, C_6H_4). (Found: C, 69.37; H, 6.69; N, 5.36. Calc. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40%).

7,8 - *Benzo* - 3(S)[1'(R) - *bromoethyl*] - 3(S) - *methyl* - 1,4 - *dioxo* - 1,3,4,6,9,9a(S) - *hexahydropyrido*[2,1-c][1,4] *oxazine*(**21A**) *and its* 1'(S), 3(R) - *Isomer*(**21B**) (*bromolactonisation of* (S)-**18**)

A DMF soln (15 ml) of t-BuOK (2.07 g, 18.5 mmole) and a DMF soln (15 ml) of NBS (6.59 g, 18.5 mmole) were successively added to a stirred, cooled (−20°) soln of (*S*)-**18** (m.p. 189–190°, $[\alpha]_D^{20}$ − 28.0° (*c* = 2.05, 2N-NaOH)) (4.80 g, 18.5 mmole) in DMF (37 ml) under N_2. After being stirred at −20° for 30 min, then at 60° for 92 hr, the mixture was worked up as in the case for the bromolactonisation of (*S*)-**3b**[1] to give crude **21** (a mixture of **21A** and **21B**) as a yellow caramel (3.38 g, 54%) after evaporation of the combined EtOAc extracts. Purification of crude **21** by column chromatography (silica gel, solvent hexane–ether, 1:1) afforded almost pure **21** (a mixture of **21A** and **21B**) as yellow needles (2.05 g, 33%), m.p. 115–142°, $[\alpha]_D^{20}$ − 141° (*c* = 0.610, $CHCl_3$). Since this sample gives (*R*)-**1a**[9] being 67% optically pure,[11] the formation ratio of **21A** and **21B** can be calculated as 83.5:16.5.

A part of almost pure **21** (450 mg, 1.33 mmole) was successively purified by recrystallisation from ether, preparative tlc (silica gel, solvent hexane–ether, 1:2), and further recrystallisation from ether, giving pure **21A**[22] as colorless needles (167 mg, 37% recovery from almost pure **21**), m.p. 149–151°, $[\alpha]_D^{20}$ − 159° (*c* = 0.462, $CHCl_3$). IR ν_{max}^{Nujol} cm^{-1}: 1750 (lactone), 1660 (amide). NMR (in $CDCl_3$): 1.75 (3H, s, CH_3CCO), 1.87 (3H, d, J = 7 Hz, CH_3CHBr), 2.72–3.92 (2H, m, CH_2CHCOO), 4.12–4.62 (2H, m, NCHCO and CH_3CHBr), 4.35 (1H, d, J = 17 Hz, one of CH_2N), 5.25 (1H, d, J = 17 Hz, one of CH_2N), 7.15 (4H, s, C_6H_4). (Found: C, 53.37; H, 4.84; N, 3.98. Calc. for $C_{15}H_{16}O_3NBr$: C, 53.27; H, 4.77; N, 4.14%).

7,8 - *Benzo* - 3(R) - *ethyl* - 3(R) - *methyl* - 1,4 - *dioxo* - 1,3,4,6,9,9a(S) - *hexahydropyrido*[2,1-c][1,4]*oxazine*(**22A**) *and its* 3(S) - *isomer*(**22B**)

A benzene soln (7 ml) of tri-n-butyltin hydride[12] (4.79 g, 16.3 mmole) was added dropwise to a stirred soln of crude **21**(m.p. 115–142°, $[\alpha]_D^{20}$ − 141° (*c* = 0.610, $CHCl_3$)) (1.82 g, 5.38 mmole) in benzene (10 ml) at 90° under N_2. The mixture was stirred at 90–100° for 2 hr, and was evaporated *in vacuo* to give a mixture of crystals and oil. The evaporation residue was purified as in the case for the debromination of **4a**,[1] giving crude **22** as pale yellow needles (1.22 g, 87%), m.p. 118–132°, $[\alpha]_D^{20}$ − 120° (*c* = 0.512, MeOH), after evaporation of the combined ethereal eluates from the silica gel column. Spectral (IR and NMR) properties of this sample were identical with those of pure **22** prepared as described below.

Similar debromination of pure **21A** (m.p. 144–151°, $[\alpha]_D^{20}$ − 155° (*c* = 0.495, $CHCl_3$)) (85 mg, 0.25 mmole) as gave a mixture of crystals and oil when the mixture was evaporated *in vacuo*. Removal of the organotin compounds from the evaporation residue by the addition of hexane, followed by purification with preparative tlc (silica gel, solvent hexane–ether, 1:2), gave crude **22A** as colorless needles (34 mg, 52%), m.p. 115–130°. Further recrystallisation of this sample from ether afforded pure **22A** as colorless needles (29 mg, 44%), m.p. 137–138°, $[\alpha]_D^{20}$ − 138° (*c* = 0.538, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1740 (lactone), 1658 (amide). NMR (in $CDCl_3$): 0.95 (3H, t, J = 7 Hz, CH_3CH_2), 1.65 (3H, s, CH_3CCO), 1.77–2.37 (2H, m, CH_3CH_2), 3.07 (1H, doubled d, J = 11 and 16 Hz, one of CH_2CHCOO), 3.47 (1H, doubled d, J = 5 and 16 Hz, one of CH_2CHCOO), 4.32 (1H, doubled d, J = 5 and 11 Hz, CH_2CHCOO), 4.42 (1H, d, J = 16 Hz, one of CH_2N), 5.08 (1H, d, J = 16 Hz, one of CH_2N), 7.20 (4H, s, C_6H_4). (Found: C, 69.39; H, 6.60; N, 5.45. Calc. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40%).

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