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# NOVEL ASPECTS OF ASYMMETRIC BROMOLACTONIZATION REACTION

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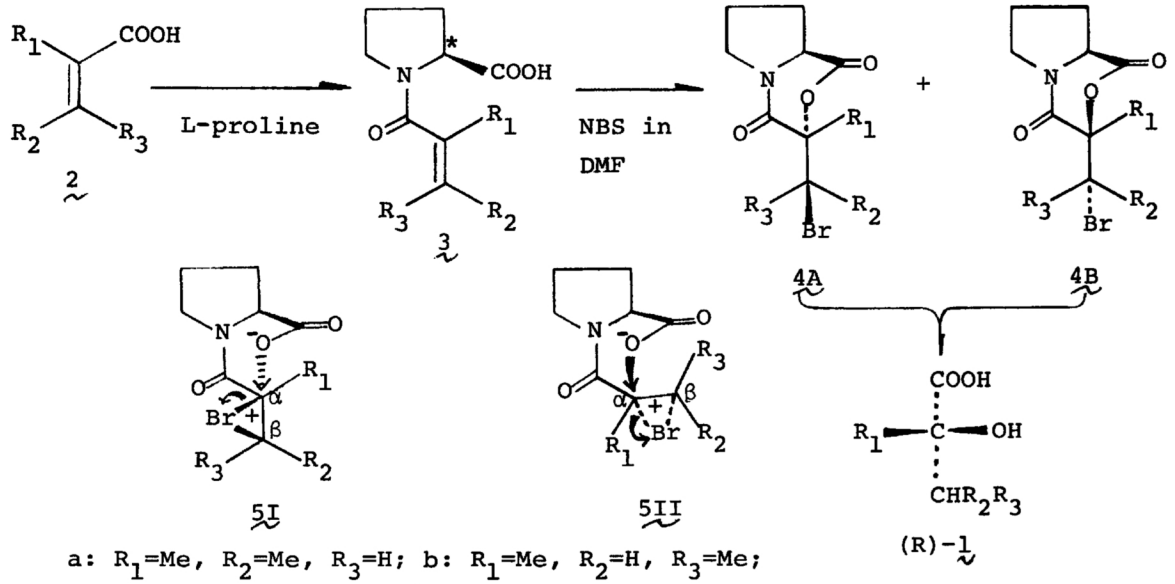
Asymmetric bromolactonization reaction was found to proceed highly stereo- and regiospecifically via the transition state such as 5II when (S)-N-(α,β-unsaturated acyl)-α-amino acid, where two alkyl groups are located at the α and β positions in a cis relationship and free rotation of the bond between asymmetric carbon and nitrogen is prohibited due to cyclic structure, is used as a reaction substrate.

In the asymmetric synthesis of optically active (R)-2-hydroxy-2-methylbutyric acid((R)-1a) from tiglic acid(2a),[1] the bromolactonization of (S)-(-)-N-tigloylproline(3a) with N-bromosuccinimide(NBS) in dimethylformamide(DMF) has been reported to proceed stereospecifically, giving a mixture of the diastereomeric lactones(4Aa and 4Ba) in which 4Aa is highly predominant(4Aa:4Ba 94.5:5.5). Although it is somewhat ambiguous whether heterolytic cleavage of NBS to bromonium ion($Br^+$) occurs in an aprotic polar solvent such as DMF,[2] two possible transition states(5Ia and 5IIa) have been set forth for this first example of halolactonization to conjugated double bond[1,3] since the α position of bromonium ion is the proper position for $S_N2$-like collinear displacement by the intramolecular carboxylate anion.[4]

In order to elucidate which transition state(5Ia or 5IIa) was responsible for the observed high stereospecificity, the bromolactonization of (S)-N-angeloylproline(3b) which was isomeric to 3a, was first attempted. Further studies on the applicability of this asymmetric halolactonization were also carried out by utilizing several kinds of α,β-unsaturated acids(2) and by employing optically active α-amino acids other than L-proline as chiral sources.

We wish to report here some novel aspects of this asymmetric synthesis which have been revealed by these studies.

Although the bromolactonization of 3b,[5,6] mp 125-127°C, $[\alpha]_D^{20}$-80.0°(c=1.01, MeOH), with NBS(1.0 eq) in DMF was found to be very sluggish(r.t., 20 hr, 12% yield(4b)), the potassium salt of 3b obtainable by treating 3b with potassium t-butoxide(1.0 eq) in DMF, was successfully lactonized with NBS(2.0 eq) in DMF (-20°C, 1 hr, then r.t., 90 hr), yielding the crude bromolactone(4b)[5a] as a pale yellow caramel(76%), $[\alpha]_D^{20}$-53.5°(c=0.650, MeOH). The ratio of the two diastereomers(4Ab:4Bb) in the crude 4b could be calculated as 61:39 since (R)-(-)-1a, mp 58-64°C, $[\alpha]_D^{25}$-2.0°(c=1.21, $CHCl_3$), 22% optically pure,[7] was




a: $R_1$=Me, $R_2$=Me, $R_3$=H; b: $R_1$=Me, $R_2$=H, $R_3$=Me;
c: $R_1$=H, $R_2$=Me, $R_3$=H; d: $R_1$=H, $R_2$=Me, $R_3$=Me

derived from the crude 4b in a similar fashion to the case for 4a.[1)]

The use of 3b in place of 3a clearly decreased the ratio of 4A to 4B from 94.5:5.5 to 61:39. Steric interaction of the carboxyl group and the $R_1$ group should be the same in 5Ia and 5Ib because their $R_1$ group are both methyl. In contrast, in 5IIa and 5IIb, steric interaction of the carboxyl group and the $R_3$ group is clearly smaller in 5IIa than in 5IIb because their $R_3$ groups are different. Due to this reason, it is quite obvious that the highly stereospecific bromolactonization of 3a has occurred via 5IIa.

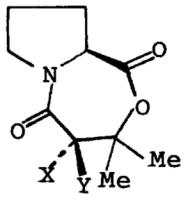
In order to obtain further information on the bromolactonization, the reactions of (S)-(-)-N-crotonoylproline(3c),[5,6)] mp 158-159°C, $[\alpha]_D^{20}$-102° (c=1.04, MeOH), and (S)-(-)-N-(β-methylcrotonoyl)proline(3d),[5,6)] mp 91-93°C, $[\alpha]_D^{20}$-92.8°(c=1.04, MeOH), with NBS were next examined.

Attempted bromolactonization of 3c or its potassium salt with NBS in DMF completely failed to give the expected bromolactones(4c).[8)] This result is conceivably due to lower electron density of the double bond of 3c when compared with that of 3a or 3b. Similar retardation of reaction speed arising from a decrease of electron density has been reported for the addition reaction of bromine to substituted ethylenes.[9)]

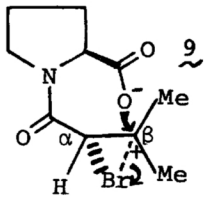
Unexpectedly, the treatment of 3d with NBS(2.0 eq) in DMF(r.t., 20 hr) afforded a mixture of the diastereomeric seven-membered lactones(7)[5a)] as colorless needles(89%) in which one diastereomer(7A or 7B) was highly predominant,[10)] mp 115-123°C, $[\alpha]_D^{20}$-79.3°(c=0.606, $CHCl_3$). Recrystallization of the crude 7 from ether gave one diastereomer(7A or 7B)[5)] as colorless needles in a pure state, mp 133-134°C, $[\alpha]_D^{20}$-90.3°(c=0.646, $CHCl_3$). Debromination of the crude 7 with tri-n-butyltin hydride(2.6 eq) in benzene(95°C, 24 hr) gave the lactone(8)[5)] in a good yield, colorless needles(from $CHCl_3$-ether), mp 124-125°C,

$[\alpha]_D^{20}$-155°(c=0.466, $CHCl_3$).

Exclusive formation of seven-membered lactone has never been reported for halolactonization.[3] While this observation seems quite different from the bromolactonization of 3a[1] or 3b which solely affords the six-membered lactone (4a or 4b), change of electronic nature in the intermediate bromonium ion might account for the observed result. The symmetric bromonium ion derived from 3a or 3b having two methyl groups at the α and β positions, can be opened regiospecifically at the α position by the intramolecular carboxylate anion in the $S_N2$-like displacement process as exemplified in 5IIa. On the other hand, in the bromonium ion produced from 3d which contains two methyl groups at the β position, the positive charge might be localized markedly at the β position by the presence of two methyl groups as visualized in 9. Therefore, in the latter case, the lactonization by the intramolecular carboxylate anion would occur regiospecifically at the β position.



7 A: X=H, Y=Br
B: X=Br, Y=H
8 X=Y=H



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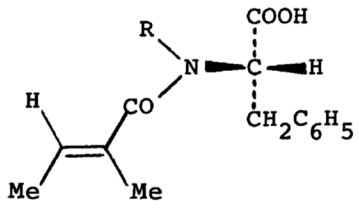
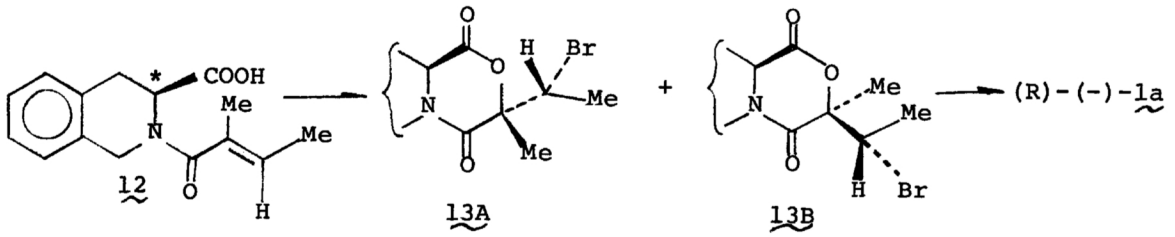
Finally, three kinds of (S)-N-tigloyl-α-amino acids(10, 11, 12) were prepared to examine the utility of optically active α-amino acids other than L-proline as chiral sources. Although the bromolactonizations of 10,[5,6] mp 59-61°C, $[\alpha]_D^{20}$-151°(c=1.32, MeOH), and 11,[5a,6] colorless caramel, $[\alpha]_D^{20}$+86.0°(c=1.79, $CHCl_3$), or those of the potassium salts derived from 10 and 11, afforded no trace amount of the desired lactones,[8] the reaction of 12,[5,6] mp 189-190°C, $[\alpha]_D^{20}$-28.0°(c=2.05, 2N-NaOH), with NBS(2.0 eq) in DMF(60°C, 90 hr) after converting it into its potassium salt, successfully gave a mixture of the diastereomeric lactones(13A and 13B),[5a] mp 115-142°C, $[\alpha]_D^{20}$-141°(c=0.610, $CHCl_3$), as pale yellow needles(33%). Transformation of the mixture of 13A and 13B into (R)-(-)-1a, mp 69-73°C, $[\alpha]_D^{25}$-5.7°(c=3.17, $CHCl_3$), 64% optically pure,[7] similarly determined the ratio of 13A to 13B as 82:18.



10: R=$CH_2C_6H_5$
11: R=H

Although the ratio of the diastereomeric lactones



12 13A 13B (R)-(-)-1a

(13A:13B) is clearly smaller than that of 4Aa to 4Ba[1] produced from 3a, only the bromolactonization of 12 has occurred successfully. This result obviously discloses 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 bromolactonization. The same fixation of the C*-N bond is also attained in 3a.

Combining the results obtained here with those of the previous report,[1] it is evident that when (S)-N-(α,β-unsaturated acyl)-α-amino acid, where two alkyl groups are located at the α and β positions in a cis relationship and free rotation of the bond between asymmetric carbon and nitrogen is prohibited due to cyclic structure, is submitted to the bromolactonization, the reaction can proceed highly stereo- and regiospecifically via the transition state such as 5II.

Although this conclusion has already been visualized with (S)-N-(α-methylcinnamoyl)proline,[1] studies on the asymmetric bromolactonization with (S)-N-(α,β-unsaturated acyl)-α-amino acids which fulfil the above-mentioned structural requirements, are still under progress.

## References and Notes

1) S. Terashima and S-s. Jew, Tetrahedron Letters, 1977, 1005.
2) a) V.L. Heasley, R.A. Skidgel, G.E. Heasley, and D. Strickland, J. Org. Chem., 39, 3953(1974). b) I. Mecev, N. Christova, R. Pomakova, B. Panajotova, and A. Jovtscheff, Z. Chem., 15, 191(1975).
3) E.E. van Tamelen and M. Shamma, J. Am. Chem. Soc., 76, 2315(1954).
4) For a similar backside collinear displacement of epoxide by the intramolecular carbanion, see G. Stork and J.F. Cohen, J. Am. Chem. Soc., 96, 5270 (1974).
5) a) Infrared(ir) and nuclear magnetic resonance(nmr) spectra were in agreement with the assigned structure. b) Satisfactory analytical data were obtained for this compound.
6) This was prepared from the corresponding α,β-unsaturated acid(2) and optically active α-amino acid in a similar manner to 3a(see ref. 1).
7) Identified with authentic (R)-(-)-1a by spectral(ir and nmr) and chromatographic(tlc) comparison. (R)-(-)-1a showing $[\alpha]_D^{25}$-8.9°(c=2.97, $CHCl_3$) was assumed to be 100% optically pure(see ref. 1).
8) This was ascertained by spectral(ir and nmr) analyses of the crude neutral reaction products.
9) J-E. Dubois and G. Mouvier, Bull. Soc. Chim. Fr., 1968, 1426.
10) Determined by spectral(nmr) and chromatographic(tlc) analyses.

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