Tetrahedron Letters No. 11, pp 1005 - 1008, 1977. Pergamon Press. Printed in Great Britain.

ASYMMETRIC HALOLACTONIZATION REACTION: A HIGHLY EFFICIENT SYNTHESIS OF OPTICALLY ACTIVE α-HYDROXY ACIDS FROM α,β-UNSATURATED ACIDS

Shiro Terashima* and Sang-sup Jew
Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo, 113, Japan

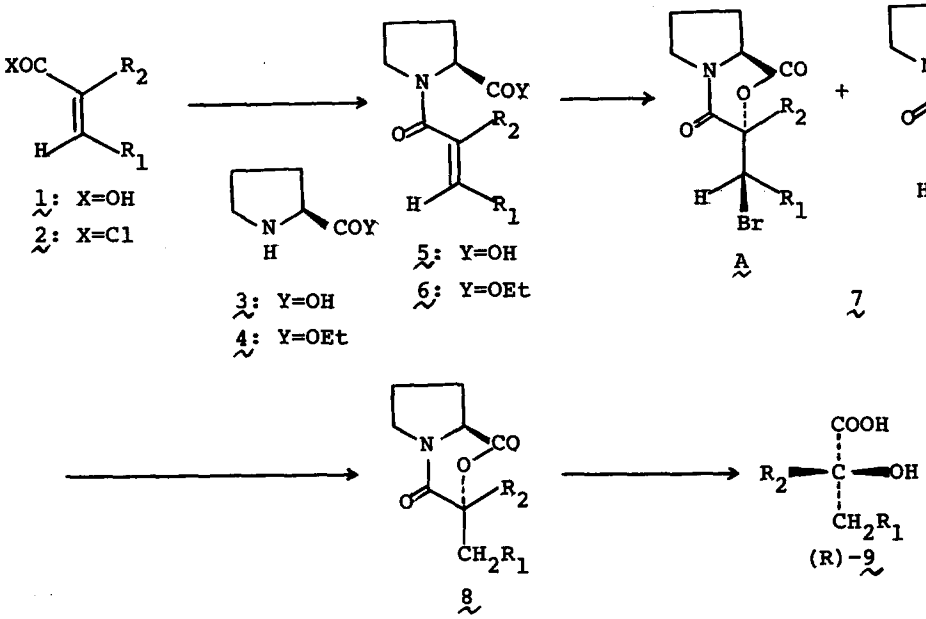
(Received in Japan 12 January 1977; received in UK for publiccation 4 February 1977)

There have been developed several kinds of asymmetric syntheses for preparing optically active α-hydroxy acids,1) and high optical induction(>80% e.e.) can be successfully achieved by selecting chiral sources1b) or by employing chiral catalysts.1c) However, since the asymmetric syntheses hitherto examined to obtain optically active α-hydroxy acids, have exclusively utilized α-keto acids or their esters as reaction substrates for Grignard addition and reduction of ketonic function, structural variations of optically active α-hydroxy acids, being accessible by the asymmetric syntheses, are quite limited.2)

In connection with the study of new approaches to the synthesis of optically active natural products, an effective method was sought which would give optically active α-hydroxy acids in high optical yields from achiral substrates other than α-keto acids or their esters. We have now found that halolactonization reaction of (S)-N-(α,β-unsaturated)carbonylprolines(5) readily prepared from α,β-unsaturated acids(1) and (S)-proline(3), proceeds almost stereospecifically, giving a mixture of the diastereomeric halolactones(7A and 7B) in which 7A is highly predominant, and that successive dehalogenation and hydrolysis of 7 can afford optically active (R)-α-hydroxy acids((R)-9) which have high optical purity(89-98% e.e.).

Acylation of 3 with tigloyl chloride(2a)3) prepared from tiglic acid(1a), under usual Schotten-Baumann condition, gave (S)(-)-tigloylproline(5a)4) (86%), mp 112.5-113.5°, $[\alpha]_D^{20}$-72.7°(c=1.00, MeOH), as colorless pillars. The same 5a was also prepared by condensing (S)(-)-ethyl prolinate(4)5) obtainable from 3, with 1a in the presence of diethyl phosphorocyanidate(DEPC) and triethylamine(TEA)(ca. 100%),6) followed by alkaline hydrolysis(KOH(1.3 eq)-aq. EtOH, rt, 1 hr)(90%) of the crude condensation product(6a).4a)

After several unsuccessful attempts, it was found that halolactonization reaction of 5a could be efficiently carried out by stirring a mixture of 5a



a: $R_1=R_2=Me$; b: $R_1=C_6H_5$, $R_2=Me$

and N-bromosuccinimide(NBS)(1.0 eq) in dimethylformamide(DMF) at room temperature for 20 hr. Usual extractive isolation of the neutral fraction with ethyl acetate gave the crude bromolactone(7a)[4a] (84%), colorless needles, mp 98-108°, $[\alpha]_D^{20}-77.2^\circ$(c=0.740, MeOH), as the sole reaction product. As crude 7a can be converted to (R)(-)-2-hydroxy-2-methylbutyric acid((R)(-)-9a) which is 89% optically pure(*vide infra*), and halolactonization is well known to generally proceed in a *trans* fashion,[7] it is evident that crude 7a thus obtained, contains two diastereomers(7aA and 7aB) in a ratio of 94.5:5.5.[8] When crude 7a was once recrystallized from a mixture of ether and hexane, the predominantly formed diastereomer(7aA) could be obtained in a pure state(64%) as colorless needles,[4] mp 111.5-112.5°, $[\alpha]_D^{20}-81.8^\circ$(c=0.756, MeOH).

Debromination[9] of crude 7a with tri-n-butyltin hydride(2.0 eq) in benzene at 90-100° for 15 hr, followed by removing organotin compounds with a silica gel column(solvent, first hexane, then ether), yielded the crude lactone(8a)[4a] (94%), mp 94-97°, $[\alpha]_D^{20}-107^\circ$(c=0.706, MeOH). Hydrolysis of crude 8a was effected by refluxing a mixture of crude 8a and 36% hydrochloric acid for 8 hr. Extraction of the acidic fraction with ethyl acetate, and evaporation *in vacuo*, afforded (R)(-)-9a,[4a,10] mp 72-74°, $[\alpha]_D^{25}-7.9^\circ$(c=2.97, $CHCl_3$).

When pure 7aA was similarly debrominated and hydrolyzed, and the acidic reaction product was recrystallized from hexane, optically pure (R)(-)-9a,[4,10] mp 78-79°, $[\alpha]_D^{25}-8.9^\circ$(c=2.97, $CHCl_3$), was obtained as colorless needles *via* optically pure 8a,[4] mp 105-106°, $[\alpha]_D^{20}-112^\circ$(c=0.760, MeOH). From these experiments, it became evident that the optical purity of (R)(-)-**9a**10) prepared from crude **7a**, could be calculated as 89%.

Next, the reaction scheme exploited with **1a** was applied to <u>trans</u>-α-methylcinnamic acid(**1b**).11) Analogous acylation of **4** with **1b** in the presence of DEPC and TEA, and subsequent hydrolysis, gave **5b**4)(86%), mp 116-117°, $[\alpha]_{D}^{20}-11.8^{\circ}$(c=1.00, MeOH), as colorless needles <u>via</u> **6b**.4)

When **5b** was submitted to halolactonization reaction under the same condition as for **5a**, the yield of crude **7b** was found to be very low(24%) even after 66 hrs' reaction at room temperature. Therefore, the halolactonization of **5b** was carried out after first converting **5b** into its potassium salt with potassium t-butoxide(1.0 eq) in DMF. This operation was performed by expecting that potassium t-butoxide could produce the carboxylate anion more strictly than succinimide anion derived from NBS. Stirring a mixture of the potassium salt of **5b** and NBS(2.0 eq) in DMF at -20° for 1 hr, then at room temperature for 48 hr, gave crude **7b**(**7bA**:**7bB** 99:1)(<u>vide infra</u>)4a)(91%), $[\alpha]_{D}^{20}-102^{\circ}$(c=0.934, MeOH), as a yellow caramel, after extractive isolation similar to the case for **7a**.

Debromination(71%) of crude **7b**, followed by acidic hydrolysis(91%), in the same manner as that for crude **7a**, afforded (R)(+)-2-hydroxy-2-methyl-3-phenylpropionic acid((R)(+)-**9b**),4a,12) mp 115-117°, $[\alpha]_{D}^{17}+16.7^{\circ}$(c=5.71, dioxane), by way of the crude lactone(**8b**),4a,13) mp 135-141°, $[\alpha]_{D}^{20}-69.7^{\circ}$ (c=0.633, $CHCl_3$).

Since the highest optical rotation of optically active **9b** among those reported, was found to be $[\alpha]_{D}+17.0^{\circ}$(c=5.60, dioxane),14) the optical purity of (R)(+)-**9b** prepared from crude **7b**, and the ratio of the two diastereomers (**7bA** and **7bB**) being present in crude **7b**, could be calculated as 98% and 99:1, respectively.

As exemplified above, the asymmetric reaction developed here, can afford optically active α-hydroxy acids, being not accessible in high optical yields by the hitherto reported asymmetric syntheses. Due to this reason in addition to its operational simplicity, this overall process might have wide practical values.

Studies on a full scope of this asymmetric synthesis, and on an application of optically active α-hydroxy acids thus obtained, to natural product synthesis, are under progress in these laboratories.

<u>Acknowledgement</u>: The authors thank Prof. Kenji Koga, University of Tokyo, for his encouragement and advice throughout this work.

<u>References</u>

1) a) J.D. Morrison and H.S. Mosher,"Asymmetric Organic Reactions", Prentice-

Hall, inc., Englewood Cliffs, New Jersey, 1971, pp 50-83; b) J.A. Berson and M.A. Greenbaum, J. Am. Chem. Soc., 80, 445, 653(1958); c) I. Ojima, T. Kogure, and Y. Nagai, Tetrahedron Letters, 1974, 1889; T. Hayashi, T. Mise, and M. Kumada, Ibid., 1976, 4351.

2) Optically active α-hydroxy acids which have been mainly prepared by asymmetric syntheses, are atrolactic acid, mandelic acid, lactic acid, etc.

3) G. Barger, W.F. Martin, and W. Mitchell, J. Chem. Soc., 1937, 1820.

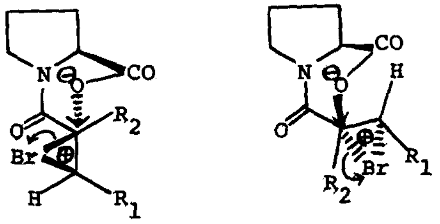
4) a) Infrared and nuclear magnetic resonance spectra were in agreement with the assigned structure. b) Satisfactory analytical data were obtained for this compound.

5) M. Shibasaki, S. Terashima, and S. Yamada, Chem. Pharm. Bull.(Tokyo), 23, 279(1975).

6) S. Yamada, Y. Kasai, and T. Shioiri, Tetrahedron Letters, 1973, 1595.

7) H.O. House,"Modern Synthetic Reactions", 2nd Ed., W.A. Benjamin, Inc., Melono Park, California, 1972, p 441.

8) Exclusive formation of one of the two diastereomers in this asymmetric halolactonization might be verified by assuming that the intramolecular attack of the carboxylate anion to the incipiently formed halonium ion occurs predominantly from the α-side in the s-cis-conformer(I) or from the β-side in the s-trans-conformer(II). Studies to discriminate which conformer is responsible for the observed high stereoselectivity, is under progress by changing the α,β-unsaturated carbonyl group of 5.



I II

9) H.G. Kuivila, Synthesis, 1970, 499.

10) Absolute configuration of (-)-9a showing $[\alpha]_{D}^{25}-8.5^{\circ}$(c=3.0, $CHCl_3$), has been determined to belong to (R)-series by chemical correlation(BO W. Christensen and A. Kjaer, Acta Chem. Scad., 16, 2466(1962).).

11) J.R. Johnson,"The Perkin Reaction and Related Reactions", in "Organic Reactions", John Wiley & Sons, Inc., New York, 1942, Vol. 1, p 251.

12) (+)-9b showing $[\alpha]_{D}^{17}+16.4^{\circ}$(c=5.66, dioxane), has been reported to have (R)-configuration(M. Kobayashi, K. Koga, and S. Yamada, Chem. Pharm. Bull. (Tokyo), 20, 1898(1972).).

13) When crude 8b was purified by a combination of preparative thin layer chromatography(silica gel, solvent ether) and recrystallization from ether-$CHCl_3$, pure 8b,[4] mp 144-145°, $[\alpha]_{D}^{20}-79.3^{\circ}$(c=0.640, $CHCl_3$), was obtained as colorless needles.

14) A.G. Davies, F.M. Ebeid, and J. Kenyon, J. Chem. Soc., 1957, 3154.