AN ENANTIOSELECTIVE SYNTHESIS OF 1-(α-HYDROXYALKYL)-1,2,3,4-TETRAHYDRO-ISOQUINOLINES THROUGH OPTICALLY ACTIVE N-OXAACYLIMINIUM ION INTERMEDIATES

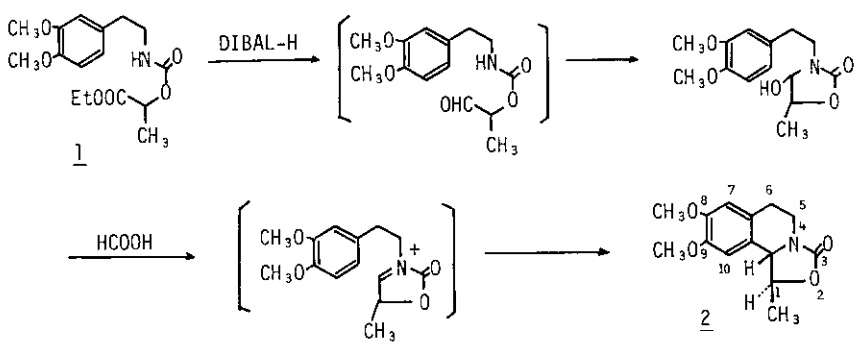
Shinzo Kano*, Yoko Yuasa, and Shiroshi Shibuya

Tokyo College of Pharmacy, 1432-1 Horinouchi, Hachioji, Tokyo 192-03, Japan

Abstract —— An enantioselective synthesis of 1S-(1'S-hydroxyethyl)-, 1S-(1'S-hydroxybenzyl)- and 1R-(1'R-hydroxybenzyl)-1,2,3,4-tetrahydroisoquinoline was achieved by reductive cleavage of the oxazolidinone ring of the corresponding 1-substituted oxazolo[4,3-a]isoquinolines, prepared by an application of N-oxaacyliminium ion cyclization with enantioselectivity.

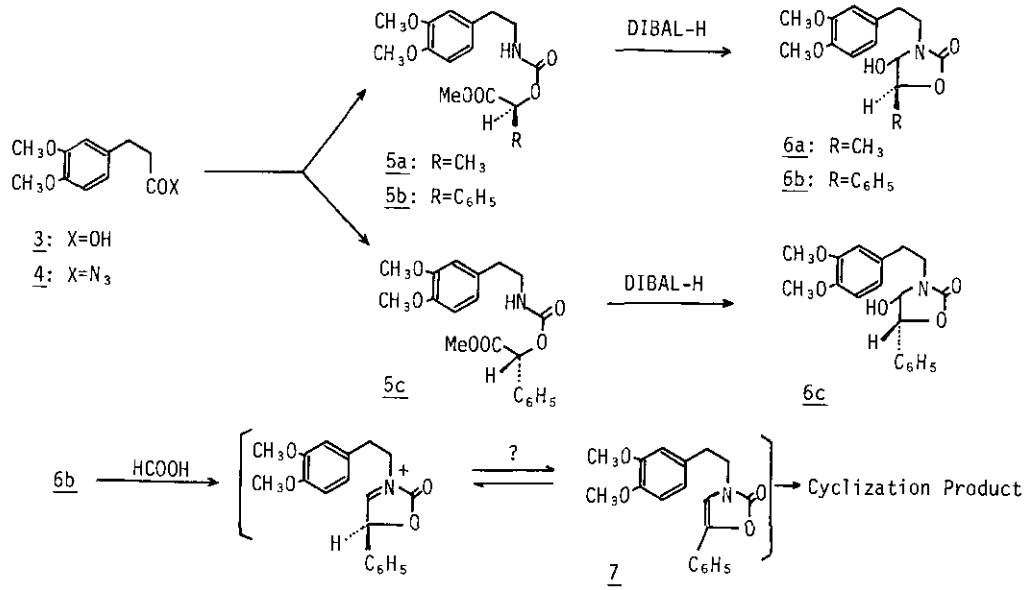
π-Cyclization of N-acyliminium ions has been documented as a potent tool in a synthesis of various kinds of heterocyclic systems[1]. From the pioneering work of Speckamp[1a-c] and the studies of others[1d-h], such cyclization have been found to achieve remarkable stereocontrol between proximate and remote chiral centers. N-Acyliminium ion cyclization onto aromatic ring have been used for a preparation of isoquinolines fused with heterocycles[1c,2-4]. Recently, we reported a diastereoselective synthesis of the 1-methyloxazolo[4,3-a]isoquinoline (2) starting with the carbamate (1) by an application of this method[2b]. (Scheme 1). We extensively investigated an enantioselective synthesis of 1-(α-hydroxyalkyl)-1,2,3,4-tetrahydroisoquinolines by reductive cleavage of the corresponding 1-substituted oxazolo[4,3-a]isoquinolines, obtained by cyclization of the optically active N-oxaacyliminium ion intermediates. The results of our studies are described in this paper.

Scheme 1



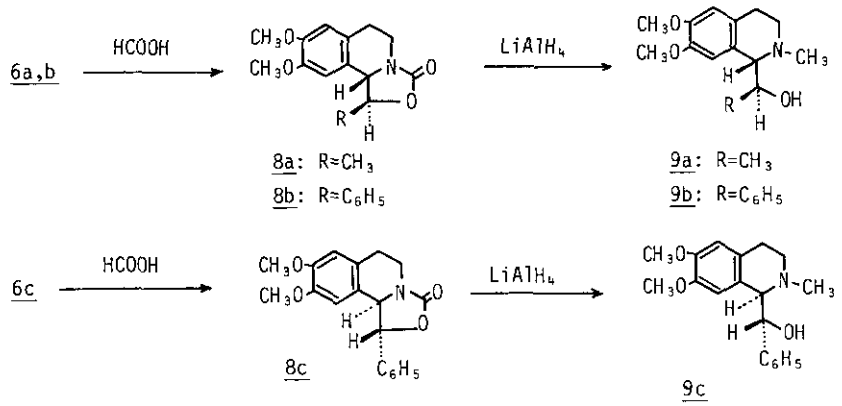
The precursors (6a-6c) for generation of the optically active N-oxaacyliminium ions were prepared as follows. The azide (4), derived from 3,4-dimethoxyphenylpropionic acid (3), was heated with methyl S-(+)-lactate[5] in toluene afforded the carbamate (5a)[6]. In this reaction, the use of methyl S-(+)-mandelate[5] and methyl R-(-)-mandelate[5] gave the corresponding carbamates (5b and 5b), respectively. Reduction of 5a-5c with diisobutylaluminum hydride yielded 6a-6c, respectively. Prior to examination of the optically active N-oxaacyliminium ion cyclization, one question is left to be answered. The question is whether or not the substituent has a substantial effect on an enantioselectivity of cyclization; i.e., will it direct the aromatic ring to attack predominantly one face of the acyliminium ion without isomerization to the oxazolone (7)? (Scheme 2). If the N-oxaacyliminium ion isomerizes to 7, even partially during cyclization, high enantioselectivity can not be expected because of racemization. For the proof of the cyclization pathway, cyclization of 7, prepared by dehydration of 6b with ammonium chloride, was examined. Treatment of 7 with formic acid resulted in only recovery of 7 without formation of any trace amount of cyclization product. This fact strongly indicates that the absolute configuration of the substituent at α-position of iminium carbon remains without racemization during cyclization. Therefore, 6a-6c were treated with formic acid at room temperature for 14 h to give the corresponding 1-substituted oxazolo[4,3-a]isoquinolines (8a-8c), respectively, ^{1}H NMR ($CDCl_3$) and IR ($CHCl_3$) spectra of which were identical with those of racemic compounds[2a]. Reduction of 8a-8c with lithium aluminum hydride yielded the corresponding 1-(α-hydroxyalkyl)-1,2,3,4-tetrahydroisoquinolines (9a-9c), respectively. ^{1}H NMR ($CDCl_3$) and IR ($CHCl_3$) spectral data were identical with those of racemic

Scheme 2



compounds[2a,b]. Thus, the first enantioselective synthesis of 1-(α-hydroxyalkyl)-1,2,3,4-tetrahydroisoquinolines was achieved.

Scheme 3



EXPERIMENTAL

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 instrument. Mass spectra were taken at an ionizing voltage of 70 eV on a Hitachi RMU-7L instrument. IR spectra were recorded on a JASCO IRA-1 spectrometer, and $[\alpha]_D$ was determined on a JASCO DIP-4 instrument.

General Procedure for a Synthesis of the Carbamates (5a-5c) To a stirred mixture of 3,4-dimethoxyphenylpropionic acid (4.2 g, 20 mmol), Et_3N (4.04 g, 40 mmol) and acetone (50 ml) was added ClCOOEt (2.40 g, 22 mmol) under ice-cooling. After 0.5 h, a solution of NaN_3 (1.95 g, 30 mmol) in H_2O (3 ml) was added to this solution. After the stirring had been continued for 1 h at room temperature, the mixture was diluted with H_2O and extracted with toluene. The extract was dried (Na_2SO_4) and evaporated to 30-40 ml. A mixture of this solution and optically active α-hydroxycarboxylate[5] (25 mmol) was heated at 110°C for 14 h. The solvent was evaporated and the remaining residue was chromatographed on silica gel (30 g). Elution with benzene-hexane (1:1) afforded 5 as an oil. 5a: 78 % yield, ^{1}H NMR ($CDCl_3$) δ 1.46 (3H, d, J=7 Hz), 2.78 (2H, t, J=7 Hz), 3.32-3.56 (2H, m), 3.77, 3.87, 3.90 (each 3H, each s), 5.11 (1H, q, J=7 Hz), 6.79-6.85 (3H, m), IR ($CDCl_3$) cm^{-1} 3438 (NH), 1760, 1725 (C=O), MS m/e 311 (M^+), $[\alpha]_D^{22}$=+10.73° ($CHCl_3$, c=0.0878); 5b: 75 % yield, ^{1}H NMR ($CDCl_3$) δ 2.80 (2H, t, J=7 Hz), 3.37-3.60 (2H, m), 3.75 (3H, s), 3.88 (6H, s), 5.98 (1H, s), 6.73-6.84 (3H, m), 7.46 (5H, broad s), IR ($CHCl_3$) cm^{-1} 3460 (NH), 1770, 1750 (C=O), MS m/e 357 (M^+), $[\alpha]_D^{22}$=+64.79 ($CHCl_3$, c=0.099); 5c: 75 % yield, $[\alpha]_D^{22}$=-64.36° ($CHCl_3$, c=0.0257).

General Procedure for a Synthesis of 8a-8c To a stirred solution of 5 (5 mmol) in toluene (20 ml) was added diisobutylaluminum hydride (1.42 g, 10 mmol, 6.7 ml of 25 % toluene solution) at -78°C. After the stirring had been continued for 40 min at the same temperature, the mixture was decomposed with 5 % H_2SO_4 (30 ml) and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and

evaporated. The resulting residue (6a-6c) was treated with formic acid (10 ml) at room temperature for 14 h. The mixture was made basic with 28 % ammonia and extracted with $CHCl_3$. The extract was washed with H_2O, dried (Na_2SO_4) and evaporated to give 8, ^1H NMR ($CDCl_3$) and IR ($CHCl_3$) spectra of which were identical with those of racemic compounds[2a]. 8a: 72 % yield, mp 140-141°C, $[\alpha]_D^{22}$= +147.96° ($CHCl_3$, c=0.1028). 8b: 68 % yield, mp 163-164°C, $[\alpha]_D^{22}$=+1.25° ($CHCl_3$, c=0.03-4). 8c: 70 % yield, $[\alpha]_D^{22}$=-1.17° ($CHCl_3$, c=0.1171).

N-(3,4-Dimethoxyphenethyl)-5-phenyloxazolidin-2-one (7) A mixture of 6b (obtained from 1.87 g, 5 mmol of 5b according to the method as above), $CHCl_3$ (30 ml) and NH_4Cl (1.06 g, 20 mmol) was stirred at room temperature for 14 h. The mixture was washed with H_2O, dried (Na_2SO_4) and evaporated. The resulting residue was chromatographed on silica gel (20 g). Elution with AcOEt-hexane (1:2) (25 ml) afforded 7 (0.3 g, 18.5 %) as an oil. ^1H NMR ($CDCl_3$) δ 2.80 (2H, t, J=7 Hz), 3.53 (2H, t, J=7 Hz), 3.87 (3H, s), 3.90 (3H, s), 6.79 (3H, s), 6.82 (3H, broad s), 7.40 (5H, broad s), MS m/e 325.1295 (M^+, Calcd for $C_{19}H_{19}NO_4$: 325.1297). Successive elution with the same solvent (70 ml) gave 8b (0.4 g, 25 %).

General Procedure for a Synthesis of 9a-9c To a stirred solution of $LiAlH_4$ (0.38 g, 10 mmol) in THF was added a solution of 8 (3 mmol) in THF (10 ml) under ice-cooling. After the stirring had been continued for 14 h at room temperature, the mixture was worked up as usual to give 9. 9a: 93 % yield, an oil, ^1H NMR ($CDCl_3$) δ 1.29 (3H, d, J=6 Hz), 2.47 (3H, s), 3.84 (6H, s), 6.66 (1H, s), 6.68 (1H, s), MS m/e (M^+-45) [M^+ was not observed on EI MS, but CI MS gave m/z 252 (MH^+)], $[\alpha]_D^{22}$=+26.58° ($CHCl_3$, c=0.0060). 9b: 95 % yield, mp 148-149°C, $[\alpha]_D^{22}$=+1.10° ($CHCl_3$, c= 0.04335). 9c: 93 % yield, mp 147-149°C, $[\alpha]_D^{22}$=-1.17° ($CHCl_3$, c=0.0154).

REFERENCES AND NOTES

1. (a) For a review: W. N. Speckamp, Recl. Trav. Chim., Pays-Bas, 100, 345 (1981). (b) J. A. M. Hamersma and W. N. Speckamp, Tetrahedron Lett., 23, 3811 (1982), and references cited therein. (c) J. A. M. Hamersma and W. N. Speckamp, Tetrahedron, 38, 3255 (1982), and references cited therein. (d) D. J. Hart, J. Org. Chem., 46, 367 (1981). (e) D. J. Hart and K.Kanai, J. Am. Chem. Soc., 105, 1255 (1983). (f) A. R. Chamberlin and J. Y. L. Chung, J. Am. Chem. Soc., 105, 3653 (1983). (g) M. S. Hadley, F. D. King, and R. T. Martin, Tetrahedron Lett., 24, 91 (1983). (h) B. E. Maryanoff, D. E. McComsey, and B. A. D.-Emswiller, J. Org. Chem., 48, 5062 (1983).
2. (a) S. Kano, Y. Yuasa, T. Yokomatsu, and S. Shibuya, J. Org. Chem., 48, 3835 (1983). (b) S. Kano, Y. Yuasa, T. Yokomatsu, and S. Shibuya, Chem. Lett., 1983, 1475.
3. H. Kohn and Z.-K. Liao, J. Org. Chem., 47, 2787 (1982).
4. D. Freher and J.-P.. Maffarand, Heterocycles, 20, 1731 (1983).
5. Commercially available materials were used.
6. In some cases, the corresponding oxazolidine-2,4-diones were formed during heating.

Received, 5th November, 1984