Tetrahedron Letters,Vol.26,No.51,pp 6345-6348,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

ASYMMETRIC SYNTHESIS VII[1] : ENANTIOSPECIFIC PREPARATION OF β -AMINOALCOHOLS FROM THE N-CYANOMETHYL-4-PHENYL-1,3-OXAZOLIDINE SYNTHON

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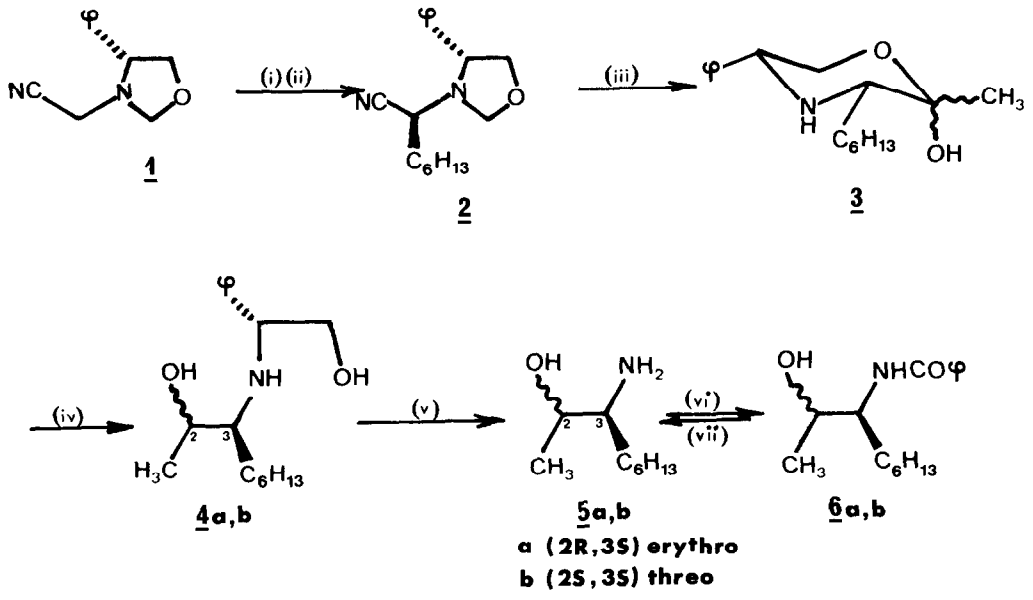
Abstract :

(-)-N-cyanomethyl-4-phenyl-1,3-oxazolidine 1 has been investigated as chiral template for the enantiospecific synthesis of β -aminoalcohols. (-)-2(R)-hydroxy-3(S)-nonylamine 5a was chosen as a target molecule of the new method.

In continuation of our current work on the possibility of using chiral synthons derived from (-)-(R)-phenylglycinol[1-3] for the asymmetric preparation of nitrogen-containing natural products we now report a new approach for the synthesis of β-amino-alcohols. Due to the biological interest of many compounds containing this functionality, various methods have appeared in the literature for their preparation in optically active form.

For a long time the most widely used technique was resolution of racemic intermediates. More recent approaches have involved classical chemical transformations of chiral α-hydroxy epoxides[4], the asymmetric reduction of α-aminoketones[5] and the reduction of chiral α-aminoalkyl arylketones[6]. In connection with the promising synthetic potential of chiral aliphatic α-aminoketones[7], it seemed quite interesting to investi-gate α-aminonitriles as intermediates for their preparation. Indeed, we have recently demonstrated[3] that a large variety of optically pure α -aminonitriles could be obtained from the readily available N-cyanomethyl-4-phenyl-1,3-oxazolidine synthon 1.

It has been shown that organolithium reagents gave addition reactions to the nitrile group of the α-aminonitrile function whereas Grignard reagents led to substitu-tion[8]. However these organometallics are also basic reagents which could afford a carbanion responsible for the racemization of the optically active centers and the formation of byproducts. Nevertheless, we have found that the addition of 1.1 equivalent of methyllithium to the α -aminonitrile 2 occurred largely as it does with simple nitriles and that optical purity was preserved.



1 2 3 4a,b 5a,b 6a,b

a (2R,3S) erythro
b (2S,3S) threo

Reagents : (i) : LDA-HMPT, THF, - 78°C. (ii) : $nC_6H_{13}Br$, 1h. (iii) : CH_3Li (1.1 equiv., 1.6M in ether), THF, - 78°C, 1h ; 20 % HCl, rt, 3h. (iv) : $NaBH_4$, CH_3OH, rt, 3h. (v) : H_2, Pd $(OH)_2$, CH_3OH, rt, 1 atm., 12h. (vi) : PhCOCl, DMAP, CH_2Cl_2, rt, 30 min. (vii) : conc. HCl, 2-propanol, Δ , 24h.

As a target molecule we chose 2-hydroxy-3-nonylamines[9] which are part of the immuno-potentiator erythro-9-(2-hydroxy-3-nonyl) hypoxanthine[10]. Alkylation of the anion derived from 1[3] with n-hexyl bromide afforded a diastereomeric mixture (74 : 26 ratio) from which the major S isomer 2[11] was easily separated in its pure form by flash chromatography (SiO_2, hexane-AcOEt, 90 : 10 ; Y : 53 %). Treatment of a THF solution of 2 with methyllithium (1.1 equivalent, 1.6 M ether) followed by acid hydrolysis (20 % aqueous HCl) led in a one pot reaction to the formation of 3[12] as a mixture of α -and β -anomers (90:10 ratio respectively, determined by ^{13}C NMR analysis ; overall yield 35 %). Compound 3 likely comes from cyclisation of the hydroxy ketone formed by the acid hydrolysis of the intermediate imine with simultaneous cleavage of the oxazolidine ring with loss of CH_2O. The assigned structure as depicted for 3 was based on the assumption that this compound exists in the most stable chair conformation with equatorial substituents and on its following conversion to the β -aminoalcohols 5 having the 3(S) absolute configuration of the starting material 2 preserved (vide infra). Indeed, $NaBH_4$-CH_3OH reduction of compound 3 gave the alcohols 4a and 4b in nearly quantitative yield as an inseparable mixture of erythro and threo isomers respectively. Diastereomeric excess (60 %) was determined in the crude product by integration of the ^{13}C NMR spectrum[13]. The stereochemical outcome of the reduction is in agreeement with previous results for methyl ketones[14]. The chiral appendage

of the mixture 4a and 4b was quantitatively removed by hydrogenolysis. No separation of the diastereomers 5a and 5b could be achieved ; they were in turn transformed into the benzamides 6a and 6b. The major isomer 6a was crystallized from hexane-ethyl acetate (96 % pure as determined by HPLC analysis). Analytically pure 6a was obtained by preparative HPLC [normal phase, CH_2Cl_2- CH_3OH 95:5 ; mp 133-135°C ; $(\alpha)_D^{25}$-45.3° ($CHCl_3$, c 0.5)] . The facile purification of β -aminoalcohols as their benzamides is interesting to note since the free primary amine derivatives are quite unstable and difficult to handle.

Finally, acid hydrolysis of 6a afforded 5a [oil, $(\alpha)_D^{25}$-14.2° (EtOH, c 1.2)] which proved to be identical to 2(R)-hydroxy-3(S)-nonylamine[4]. The optical purity of 5a was confirmed by preparation of Mosher's amide[15] (ee $\geqslant$ 98 %, checked by ^1H NMR and HPLC analysis).

The most notable feature of the chiral synthesis outlined herein is that the β -aminoalcohols 5a and 5b were formed with complete retention of configuration at the α position of the amine function showing that addition of methyllithium and acid hydrolysis occurred without racemization. The same observations have been recently made in the α-aminoacid series[16,17].

On consideration that enantiomeric (+) synthon 1 is also available, the present strategy can be extended to the synthesis of enantiomeric β -aminoalcohols.

Acknowledgements : We would like to thank Dr. BESSODES for providing us with an authentic sample of (-)-2(R)-hydroxy-3(S)-nonylamine.

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11 All new compounds showed satisfactory analytical and spectroscopic data.

12 3 : oil ; IR (neat) : 3400-3000 cm^{-1}, no carbonyl absorption ; MS m/z : CI 278 (M+1), EI m/z (relative intensity) 246 (M-31, 18), 234 (72), 168 (14), 164 (18), 148 (18), 146 (14), 121 (36), 114 (100), 106 (27), 104 (91) ; anal. calcd. for $C_{17}H_{27}NO_2$, C 73.64, H 9.74, N 5.05, found C 73.53, H 9.63, N 5.12 ; ^{13}C NMR (50.3 MHz, $CDCl_3$) δ (ppm) : 139.9 - 128.6 - 128.0 - 127.1 (aromatic), 95.3 (s), 66.6 (t), 63.8 (d), 61.4 (d), 31.7 (t), 30.6 (t), 29.3 (t), 26.1 (t), 22.5 (t), 23.4 (q), 14.0 (q). Minor signals for the β anomer at : 67.5 (t), 65.2 (d), 32.8 (t), 29.1 (t), 25.7 (t).

13 4a and 4b : oil ; IR (neat) : 3500-3000, 2900, 1415, 1050 cm^{-1}. ^{13}C NMR (50.3 MHz, $CDCl_3$) δ ppm : erythro : 142.1 - 128.6 - 127.6 - 127.4 (aromatic), 67.3 (t), 67.0 (d), 62.5 (d), 59.7 (d), 31.7 (t), 29.7 (t), 29.3 (t), 26.4 (t), 22.6 (t), 17.9 (q), 14.0 (q). Threo : 69.7 (t), 64.4 (d), 32.2 (t), 25.5 (t), 10.1 (q). MS m/z (relative intensity) : 248 (M-31, 40), 234 (100), 218 (9), 204 (11), 121 (30), 114 (91), 91 (27). Anal. calcd. for $C_{17}H_{29}NO_2$: C, 73.03, H, 10.38, N, 5.01. Found : C, 72.92, H, 10.43, N, 5.34.

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(Received in France 25 September 1985)