Pergamon

Tetrahedron Letters, Vol. 35, No. 13, pp. 1999-2002, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0220-R

A Convenient Preparation of Optically Pure 3-Hydroxyglutaric Acid Derivatives

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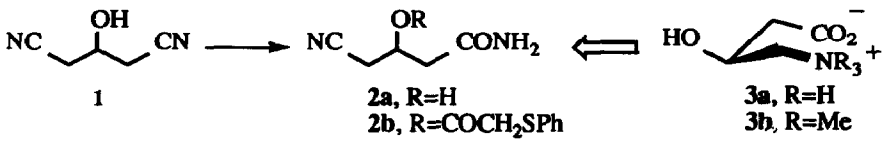
Abstract: *The diastereomeric monoamides resulting from condensation of (L)-cysteine with 3-hydroxyglutarodinitrile have been separated by chromatography then transformed in a few steps into either (+) or (-) methyl ester of 4-cyano-3-hydroxybutyric acid.*

Recently, we reported that nitrile **1** could be converted into the corresponding monoamide, **2a**, simply by treatment with MnO_2/SiO_2 for a few days at room temperature[1]. Since our main purpose was to prepare GABOB, **3a**, and its tris-*N*-methylated derivative -i.e. carnitine-, **3b**[2], we next attempted both to fractionate the racemic monoamide **2a** and to transform, preferably in a stereoconvergent manner, each resulting enantiomers into the targeted molecules.

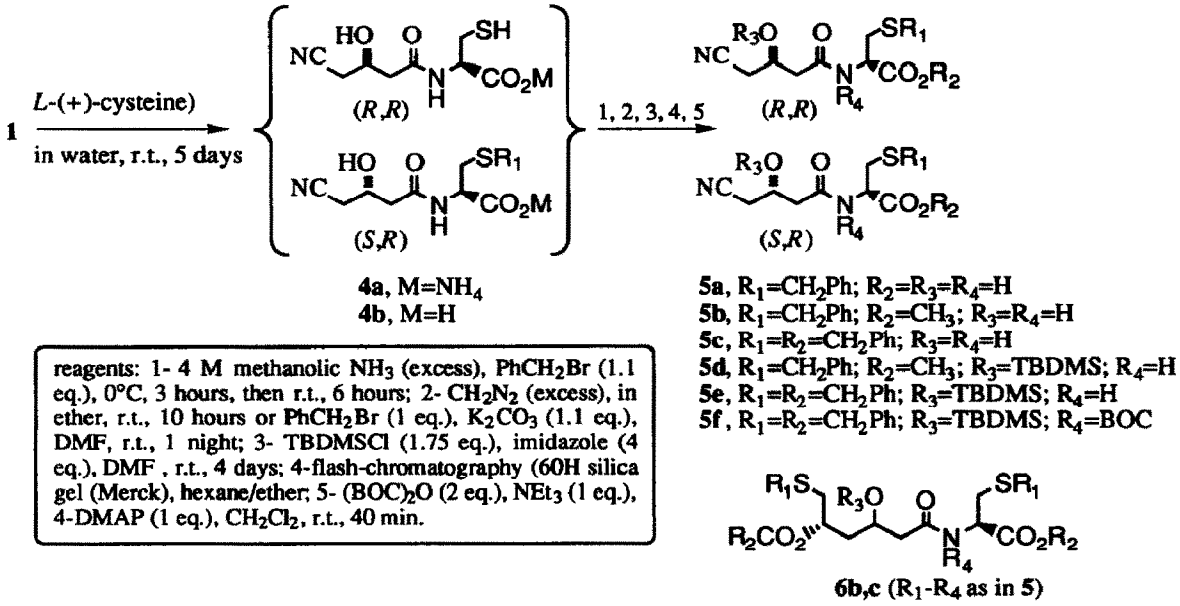


1 **2a**, R=H; **2b**, R=$COCH_2SPh$ **3a**, R=H; **3b**, R=Me

Kinetic resolution of β-hydroxynitriles has been achieved by using lipase-catalysed saponification of their *O*-acyl derivatives[3]. Among the various esters which have been tried, the phenylthioacetates proved to be the more satisfactory regarding the stereoselectivity of the process. Accordingly, we prepared ester **2b** from racemic **2a**[4]. Submitting this compound to hydrolytic conditions (*Pseudomonas fluorescens* lipase, pH 7 phosphate buffer) proved much disappointing. Though some optically active amide **2a** (14%; $[\alpha]_D$ -1.8, c=2, MeOH) was formed, the optical purity of either **2a** or the unreacted **2b** was low (less than 10%), therefore of no value for further synthetic applications. An entirely different approach based on the known ability of cysteine to give with nitriles the corresponding N-acylcysteine derivatives[5] was then experimented.

Stirring the dinitrile **1** with cysteine (1.05 eq.) in water for a while resulted in the disappearance of the nitrile. Evaporation of water left an oil whose ^1H NMR data (in D_2O) agreed with the expected acylcysteine structure. Detection of the diamide eventually resulting from a bis-condensation of **1** with cysteine was difficult at this stage. Acidification of the crude condensation product in order to liberate the acid from its ammonium salt, **4a**, proved impracticable due to the strong solubility in water of **4b**. Derivatisation of the salt was then attempted in order to render the material more tractable and, subsidiarily, to make possible the necessary separation of diastereomers.

Protection of the thiol moiety was achieved in treating the crude ammonium salt, **4a**, with benzyl bromide



4a, M=NH_4
4b, M=H

reagents: 1- 4 M methanolic NH_3 (excess), $PhCH_2Br$ (1.1 eq.), 0°C, 3 hours, then r.t., 6 hours; 2- CH_2N_2 (excess), in ether, r.t., 10 hours or $PhCH_2Br$ (1 eq.), K_2CO_3 (1.1 eq.), DMF, r.t., 1 night; 3- TBDMSCl (1.75 eq.), imidazole (4 eq.), DMF , r.t., 4 days; 4-flash-chromatography (60H silica gel (Merck), hexane/ether; 5- $(BOC)_2O$ (2 eq.), NEt_3 (1 eq.), 4-DMAP (1 eq.), CH_2Cl_2, r.t., 40 min.

5a, R_1=CH_2Ph; R_2=R_3=R_4=H
5b, R_1=CH_2Ph; R_2=CH_3; R_3=R_4=H
5c, R_1=R_2=CH_2Ph; R_3=R_4=H
5d, R_1=CH_2Ph; R_2=CH_3; R_3=TBDMS; R_4=H
5e, R_1=R_2=CH_2Ph; R_3=TBDMS; R_4=H
5f, R_1=R_2=CH_2Ph; R_3=TBDMS; R_4=BOC

6b,c (R_1-R_4 as in **5**)

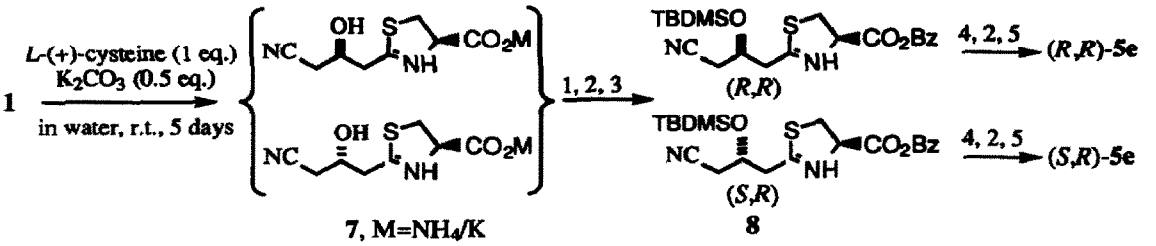
in methanolic ammonia[6]. After acidification, and extraction with butanol, esterification was performed using either diazomethane in ether or benzyl bromide in DMF and in presence of K_2CO_3. Column chromatography (silica gel, MeOH/CH_2Cl_2) then afforded, respectively, the methyl esters **5b** (57%) and the benzyl esters **5c** (64%). Trace amounts of diamide **6b** (resp. **6c**) were also isolated. In each case, the monoamide fraction was a 1/1 mixture of two diastereomers (NMR), which behave similarly in TLC whatever the eluting system we used. Fortunately, silylation of the hydroxyl group with TBDMSCl (100%) induced a net dichotomy in Rf and a clean separation of each diastereomeric monoamide resulted from flash-chromatography of either amidoesters **5d** or **5 e**, what afforded, respectively: *i*) (*S,R*)-**5d** ($[\alpha]_D$ +8.7, c=4, $CHCl_3$; Rf=0.1, 1:1 hexane/ether) and (*R,R*)-**5d** ($[\alpha]_D$ +4.4, c=5, $CHCl_3$; Rf=0.05, 1:1 hexane/ether), from the methyl ester derivatives; *ii*) (*S,R*)-**5e** ($[\alpha]_D$ +1, c=4, $CHCl_3$; Rf=0.4, 1:3 hexane/ether) and (*R,R*)-**5e** ($[\alpha]_D$ -3, c=5, $CHCl_3$; Rf=0.35, 1:3 hexane/ether), from the corresponding benzyl ester derivatives. Cleavage of the secondary amide functionality in either (*R,R*)-**5e** or (*S,R*)-**5e** was smoothly realised in first converting these two compounds into their BOC derivatives[7] -i.e. respectively (*R,R*)-**5f** (98%) and (*S,R*)-**5f** (93%)- . Methanolysis (2 M MeONa in MeOH, r.t., 20 min) then furnished the two enantiomers of 4-cyano-3-hydroxybutanoic acid, methyl ester, respectively (*R*)-**9** and (*S*)-**9**, in good yield (93-94%). The optical purity of both (*R*)-**9** and (*S*)-**9**, as deduced from either comparison of optical rotation with literature data[8] or ^1H NMR experiments with camphoratoeuropium, was fairly good (≥96%)[9].

(*R*)-**9**, $[\alpha]_D$ -21 (c=1.8, CH_2Cl_2)
lit.[8]: $[\alpha]_D$ -20.5(c=1,CH_2Cl_2)

(*S*)-**9**, $[\alpha]_D$ +19.5 (c+=1.8, CH_2Cl_2)

The amides (*R,R*)-**5e** and (*S,R*)-**5e** were also obtained with comparable yields from the thiazolines **7**, which

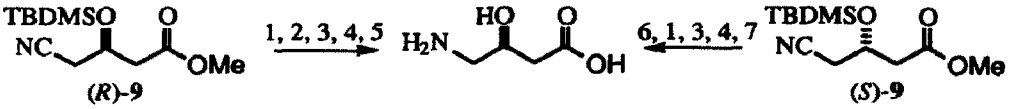
were readily formed on treatment of nitrile **1** with cysteine as above but in maintaining the pH at a higher value (pH 9) by initial addition of a small amount (0.5 eq.) of K_2CO_3 as recommended in related cases[5]. Esterification of the resulting mixture with benzyl bromide in DMF (16 hours, r.t.) was followed by column



reagents: 1- $PhCH_2Br$ (1 eq.), r.t., 16 hours; 2-TBDMSCl (1.5 eq.), imidazole (3eq.), DMF, r.t., 2 days; 3- flash-chromatography on 60H silica gel (Merck), hexane/ether; 4- 1:1 1 N aqueous HCl/MeOH, r.t., 2 hours; 5- n-BuLi (1.1 eq.), THF, -78°C, then $PhCH_2Br$, r.t., overnight.

chromatography (silica gel, $MeOH/CH_2Cl_2$), what afforded the monothiazoline derivatives as a mixture of diastereomers (53%). As observed with the amides, silylation (TBDMSCl (1.1 eq.), imidazole (2.5 eq.), DMF, r.t., 2days; 91%) made possible the separation by flash-chromatography of the two diastereomeric *O*-protected derivatives (*S,R*)-**8** ($[\alpha]_D$ +2, c=1.5 in MeOH) and(*R,R*)-**8** ($[\alpha]_D$ +0.4, c=8 in MeOH). Treatment of each diastereomers with 1 N aqueous HCl in methanol, silylation with TBDMSCl (desilylation occured during the acidic hydrolysis of the thiazolines), followed by benzylation of the thiol functionality finally gave, respectively, the amides (*S,R*)-**5e** and (*R,R*)-**5e** with optical properties as above.

Conversion of both esters (*R*)-**9** and (*S*)-**9** into GABOB, **3a**, could then be performed convergently as shown below. Deprotection of the hydroxyl group (1:9 40% aqueous HF/CH_3CN) in (*R*)-**9** allowed the hydration of the nitrile moiety to take place in using MnO_2/SiO_2 in hexane[1] (some saponification of the ester was also observed). Acetylation of the crude hydroxyamide was followed by Hofmann degradation with *I,I*-bis-trifluoroacetyloxy-iodobenzene[10]. Full saponification then afforded, after purification by ion-exchange chromatography[2], the targeted aminoacid (24%).



reagents: 1- 1:9 40% HF/CH_3CN, r.t., 2 days; 2- MnO_2/SiO_2, hexane, r.t., 6 days; 3- acetyl chloride (1.1 eq.), pyridine (1.1 eq.), ether, r.t., 14 hours; 4- $PhI(OCOCF_3)_2$, (1 eq.), CH_3CN/H_2O, r.t., 3 hours; 5- K_2CO_3 (3 eq.), MeOH, r.t., 8 hours; 6-liq. NH_3, overnight; 7- conc. HCl, reflux, 5 hours.

The same product was obtained from the (*S*)-**9** isomer in converting first the ester into an amido group by treatment with liquid ammonia. Exchange of the silyl protecting group for an acetoxy residue was followed by Hofmann rearrangement as above. Finally, acidic hydrolysis gave **3a** (17%) with similar optical properties.

In conclusion, conversion of the *meso* dinitrile **1** into either (*R*) or (*S*) methyl ester of 4-cyano-3-hydroxybutyric acid has been achieved in making use of cysteine as a chiral auxiliary agent. The usefulness of the resulting synthons -i.e. (*R*)-**9** and (*S*)-**9**- has been illustrated by the preparation of GABOB, a biologically interesting aminoacid. Since (*R*)-**9** has also been used to synthesize HMG-CoA-reductase inhibitors[8], it appears that the set of very simple chemical events presented herein allows to prepare various useful optically

active compounds in starting from such common raw materials as epichlorhydrin and potassium cyanide.

Recently, the conversion of nitrile **1** into optically pure 4-cyano-3-hydroxybutyric acid has been shown to be mediated by microorganisms[11,12]. It is interesting noting that only the last step -i.e., the amide-acid conversion- of the involved enzymatic process occurs in a stereoselective manner (the first one -i.e. the nitrile-amide conversion- is generally considered as being devoid of any steroselectivity) and, furthermore, that a cysteine residue is probably involved at the active site of the enzyme complex[13]. Further investigations on a possible biomimetic development for our process are now being pursued.

Acknowledgements: Thanks are due to "Ministère de la Recherche et de la Technologie" for a grant (to R.L.).

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(*Received in France* 3 *January* 1994; *accepted* 25 *January* 1994)