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A NEW CHIRAL GLYCINE-CATION EQUIVALENT. ASYMMETRIC SYNTHESIS OF OPTICALLY PURE β-AMINO ALCOHOLS AND α-AMINO ESTERS.

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Reaction of organometallic reagents with a chiral glycine template derived from glyoxal serves as a key step in asymmetric syntheses of the title products.

Among the different methods for synthesizing optically active α-amino acids, one of the most attractive involves the use of glycine-cation equivalents.[1] We report now the use of the substituted morpholine 1 as a chiral glycine template in the synthesis of β-amino alcohols and N-methyl α-amino esters. Homochiral synthon 1 was quantitatively obtained in a one-pot procedure from N-methyl (R)-phenylglycinol, thiophenol and an aqueous solution of glyoxal.[2] The crystal structure of 1 is shown in Figure 1;[4] of particular significance is the cis-arrangement of phenylthio and hydroxy groups, the phenylthio substituent being axially oriented.

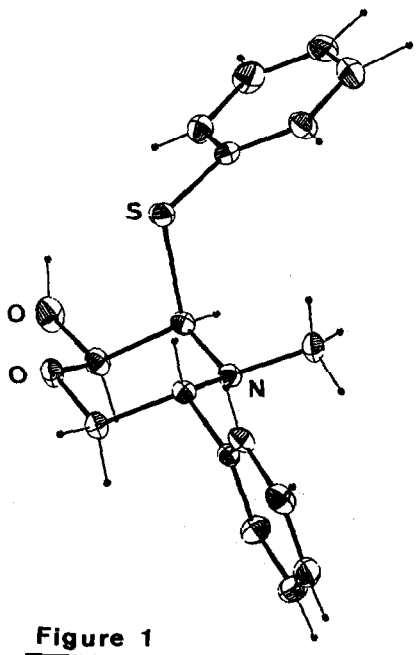
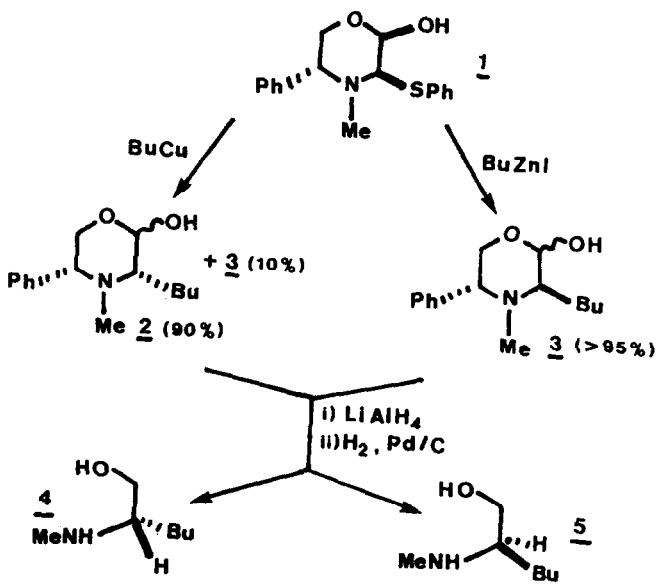


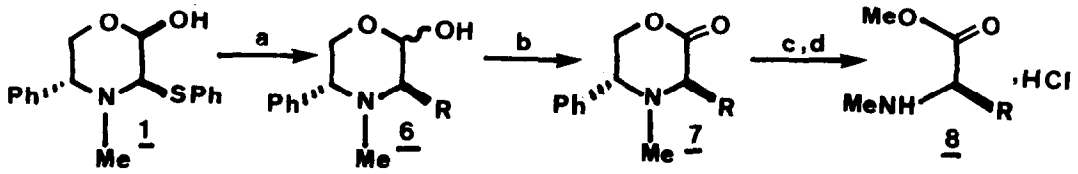
Figure 1



Scheme 1

Alkyl copper reagents are able to react with amino thioethers in order to afford substituted amines.[5] As outlined in Scheme 1, upon condensation with butyl copper (prepared from butyl lithium and CuBr) the heterocyclic amino thioether 1 gave rise to two diastereomeric products 2 and 3 resulting predominantly from inversion of stereochemistry. In marked contrast, butyl zinc iodide reacts exclusively with retention.[6] Reductive cleavage and N-debenzylation of hemiketals 2 and 3 led respectively to (S)-(+)- N-methyl 2-amino hexanol 4 (80% ee) and to its (R)-(−)-enantiomer 5 (>95% ee).[7]

The highly stereocontrolled condensation of an organozinc reagent with the amino thioether moiety of chiral synthon 1 seems particularly well suited for the synthesis of homochiral α-amino esters. As shown on Scheme 2, hemiketal 6 was first oxidized (Swern method) to lactone 7 ; formation of a carbamate by treatment of lactone 7 by vinyl chloroformiate was followed by an acid-catalyzed methanolysis resulting in the formation of the α-amino ester chlorhydrate 8 .



(a) RZnI (R = Pr, i-Bu) or RZnBr (R = $CH{=}CH_2$, $CH_2CH{=}CH_2$), 4 equiv, THF, rt (-20°C for R = $CH{=}CH_2$), 70-90%.

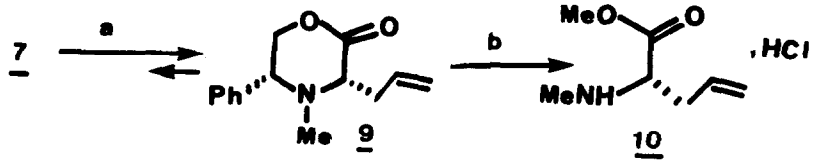
(b) $(COCl)_2$, DMSO, Et_3N, -50°C, 60-80%.

(c) $CH_2{=}CH{-}OCOCl$, CH_2Cl_2, reflux, 80-90%.

(d) HCl, saturated MeOH solution, reflux, 90%.

Scheme 2

With saturated alkyl zinc iodides (R = Pr, i-Bu), amino esters 8 are obtained in enantiomerically pure form.[8] In the case of vinyl zinc bromide, lactone 7 is diastereoisomerically pure but partial racemization occurs during the final acidic treatment leading to 8 with poor enantioselectivity (70% ee). Condensation of allyl zinc bromide with the amino thioether 1 proceeds without stereoselectivity and the lactone is produced as a 1:1 mixture of trans 7 (R = allyl) and cis 9 diastereoisomers.However nearly complete epimerization of the trans to the cis isomer can be easily performed in basic medium, leading ultimately to the corresponding α-amino ester chlorhydrate 10 with 90% ee (Scheme 3).

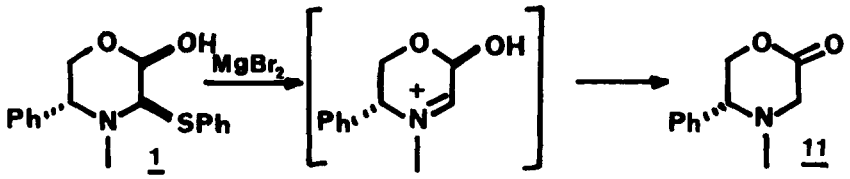


(a) t-BuOK, 0.1M t-BuOH solution, 40°C, 95%.

(b) cf (c) and (d) in Scheme 2

Scheme 3

We presume that reactions of synthon 1 with the organo zinc reagents are proceeding via an iminium ion intermediate (SN_1 process), as shown on Figure 2. Nucleophilic addition to this iminium ion leads to an axial anti adduct (with regard to the phenyl moiety).[9] The absence of stereoselectivity observed with allyl zinc bromide may be ascribed to the well known reversibility displayed by the addition of such reagents [10] (thermodynamic control). That synthon 1 is an iminium ion precursor is disclosed by its easy and quantitative transformation to lactone 11 when treated by magnesium bromide in THF solution :



On the other hand, the inversion of stereochemistry which was observed in the case of the alkyl copper reagent would result from an SN_2 pathway between nucleophilic butyl copper and synthon 1 (Figure 3).[11]

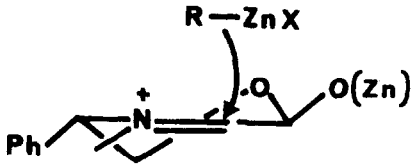


Figure 2

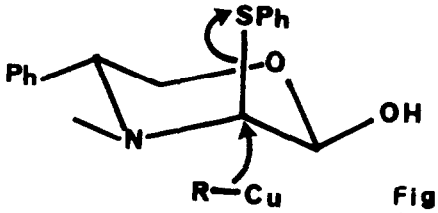


Figure 3

Acknowledgements : We are grateful to Dr. A. Alexakis for helpful discussions and to Roussel-Uclaf for a fellowship (F.C.).

1. R.M. Williams, "Synthesis of Optically Active α-Amino Acids", Pergamon Press, Oxford, 1989, p.95.

2. (a) N-Methyl (R)-phenylglycinol (7.7 g) was added into a 10% wt glyoxal aqueous solution (29 ml). After the reaction mixture was stirred for 3 h (room temperature), water (150 ml) and thiophenol (5.6 g) were successively added. The produced precipitate was extracted with methylene chloride. The organic layer was dried over $MgSO_4$ and the removal of the solvent afforded crude 1 which was washed with diethyl ether; 12.5 g, Mp : 119°C, $[\alpha]_D^{20}$ = +322° (c 1.2, $CHCl_3$) (H)NMR (200 MHz, $CDCl_3$): 2.14 (s;N-Me), 3.47-3.73 (m; $^DCH_2$), 3.82 (dd;J=1.7; 9.5;Ph-CH), 4.49 (d;J=13.5;OH), 4.64 (d; J=1.5;N-CH-S), 5.09 (dd;J=1.5,13.5; O-CH-O), 7.2-7.6 (m;Ph).
(b) Le Rouzic et al.[3] described an analogous reaction from N-methyl ethanolamine which led to an achiral morpholine derivative via an intermediate 2,3,5,6-dioxazinodioxane (two-step procedure).

3. A. Le Rouzic, D. Raphalen, D. Papillon and M. Kerfanto, Tetrahedron Lett., 1985, 26, 1853.

4. Crystal data : $C_{17}H_{19}NO_2S$, M=301, monoclinic, space group $P2_1$, a = 10.052(2), b = 6.669(5), c = 12.113(2) A, Beta = 107.13(1). Vol = 776(3) A, Dc = 1.290 g/cm^3 for Z = 4, mu(Mo-Kalpha) = 42.94 cm^{-1}. 1556 data were collected on a MONIUS CAD4 diffractometer. The structure was solved by using SHELXS program (G.M. Sheldrick, Program for Crystal Structure Solution, University of Gottingen, Gottingen, FRG, 1986). The structure was refined by least-squares techniques using CRYSTALS (D.J. Watkin, J.R. Carruthers and P.W. Betteridge, "Crystals User Guide", Chemical Crystallography Laboratory, University of Oxford, Oxford, UK, 1986). Figure 2 shows an Ortep view of the molecular structure and ellipsoids represent 30% of probability. Atomic co-ordinates, bond lenghts and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

5. C. Germon, A. Alexakis and J.F. Normant, Tetrahedron Lett., 1980, 21, 3763.
For reactions of Grignard reagents with amino thioethers, see : I.E. Pollak, A.E. Trifunac and G.F. Grillot, J. Org. Chem., 1967, 32, 272.

6. All new compounds described here gave satisfactory spectroscopic and analytical data.

7. The enantiomeric excess and the abolute configurations of these compounds wer established by chemical correlation with the amino alcohol obtained by reduction with $LiAlH_4$ of N-formyl L-norleucine.

8 Determinations of the enantiomeric excesses and of the absolute configurations were performed as follows. (i) R = Pr, i-Bu : chemical correlation with the corresponding N-methyl α-amino esters made from commercially available amino acids: both polarimetric measurement and NMR spectroscopy (on Mosher amides) show that compounds 8 are enantiomerically pure. (ii) R = vinyl, allyl) : chemical correlations of the hydrogenated derivatives (H_2, Pd/C) with the corresponding N-methyl α-amino esters ; enantiomeric excesses were determined by NMR measurements on the Mosher derivatives.

9 For some related stereoselective additions to iminium ions, see:
(a) L.E. Overman and R.L. Freerks, J. Org. Chem., 1981, 46, 2833;
(b) L. Guerrier, J. Royer, D.S. Grierson and H.P. Husson, J. Am. Chem. Soc., 1983, 105, 7754; (c) R.V. Stevens, Acc. Chem. Res., 1984, 17, 289;
(d) R.M. Williams, P.J. Sinclair , D. Zhai and D. Chen, J. Am. Chem. Soc., 1988, 110, 1547.

10. J.L. Moreau, Bull Soc. Chim. Fr., 1975, 1248.

11. Alkyl copper reagents are not basic enough to deprotonate hydroxyl moieties see : J.F. Normant and A. Alexakis, Synthesis, 1981, 841.

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