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NEW ROUTES TO α -AMINO ACID β,γ -THIOENOL ETHER DERIVATIVES

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ABSTRACT

Racemic derivatives of α -amino acid β,γ -thioenol ethers have been synthesized from homoserine through a γ -elimination on a sulfoxide derived from aspartaldehyde. Optically active derivatives were efficiently prepared from *L*-methionine by a Pummerer like reaction.

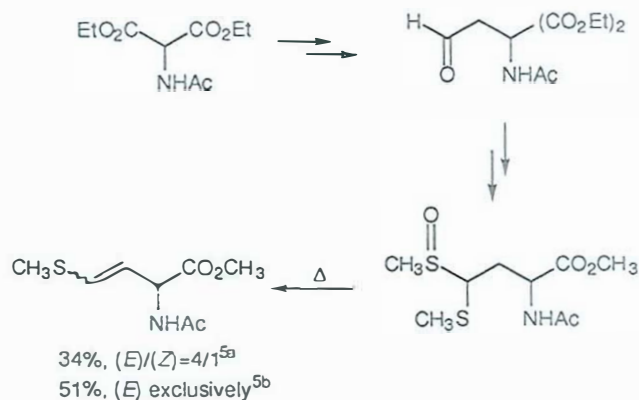
α -Amino acid β,γ -enol ethers **1** and their sulfur analogues **2** are compounds of biological interest: they are possible pyridoxal phosphate dependent enzyme inhibitors because of the presence of the double bond in the β,γ -position.¹

Indeed, the oxygen analogues **1** have shown antibiotic activity.² Both types of compounds exhibit some antiproliferative activity because they act as methionine analogues and inhibit *S*-adenosyl methionine transferase.³ (Scheme 1)



Scheme 1.

While several satisfactory synthetic solutions have been described for the α -amino acid β,γ -enol ether derivatives **1**,⁴ only two very similar pathways exist for the sulfur analogues **2** ($R=Me$). Starting from achiral diethyl acetamido malonate, the vinyl sulfide moiety is obtained by the elimination of a methylsulfinyl group in the γ -position (Scheme 2).⁵ Actually, various proportions of the α,β -unsaturated isomers are obtained in this step: unlike their oxygen analogues **1**, compounds **2** are highly prone to isomerisation into the more stable α,β -unsaturated analogues.^{5,6} The optically active derivatives are obtained through enzyme catalysed acid or amino group deprotections. Therefore, overall yields are very low. The problems experienced by the groups involved in the synthesis of derivatives **2** clearly show that it is a real synthetic challenge.^{5a}



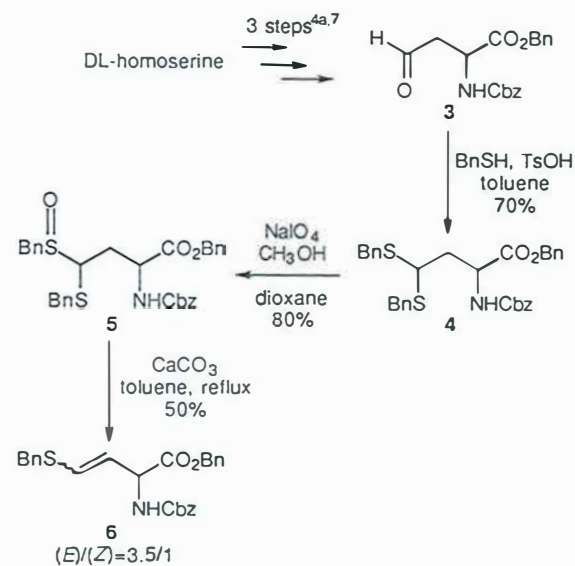
Scheme 2.

In this paper, we describe two new routes to derivatives **2** from the chiral pool: homoserine and methionine.

Racemic homoserine was first converted into the aspartaldehyde derivative **3** following the literature procedure.^{4a,7} The precursor sulfoxide **5** was obtained in good yield through dithioacetal formation⁸ followed by

sodium metaperiodate monooxidation. We have found optimal conditions to perform the thermal elimination of the sulfoxide⁹ leading to the formation of the desired β,γ -unsaturated α -amino acid derivatives **6** with a global yield of 50% without detecting the formation of the α,β -unsaturated isomers. (Scheme 3)

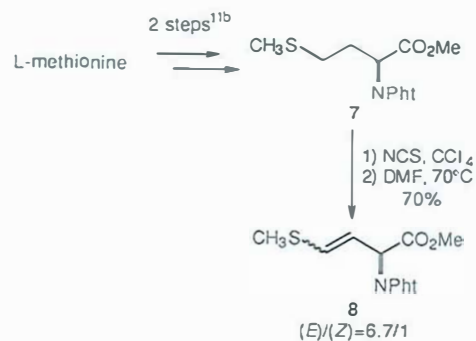
Nevertheless, the proceeding route, although successful, is still laborious.¹⁰



Scheme 3.

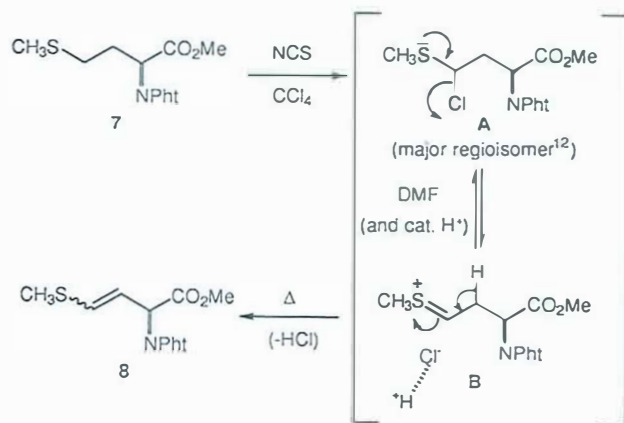
We have recently shown¹¹ that *L*-methionine is a possible precursor to optically active aspartaldehyde derivatives using a Pummerer like reaction¹² (a regioselective α -chlorination to the sulfide using *N*-chlorosuccinimide) followed by hydrolysis. Alternatively, we now report that optically active 2-amino-4-methylthio-3-butenic acid ("*3,4*-dehydro-*L*-methionine") derivatives can be efficiently obtained from *L*-methionine using the same reaction¹³ (Scheme 4).

Phthaloyl protection¹⁴ was chosen to avoid any amine participation.¹⁵ (*N,O*)-protected *L*-methionine **7** is treated with *N*-chlorosuccinimide in carbon tetrachloride. When the crude mixture of α -chlorosulfide intermediates is heated in dimethylformamide (70°C), the formation of the vinyl sulfide **8** is observed resulting from acid catalysed dehydrochlorination^{12b,13}



Scheme 4.

probably through the transient ionic species **B** in equilibrium with **A** in the polar solvent dimethylformamide (Scheme 5).



Scheme 5.

After purification by silica gel chromatography, major (*E*) isomer was shown to have 90–91% ee based on chiral HPLC analysis (see experimental part). The observed slight racemisation (compound 7 proved to be 96–98% ee^{11b}) might be due to the well-known stereochemical instability of these β,γ -unsaturated α -amino acid derivatives.

In conclusion, the procedures described herein allow the efficient synthesis of α -amino acids β,γ -thioether derivatives with optimized steps. The Pummerer strategy using *L*-methionine as starting material lead to the

protected optically active unsaturated analogue “*3,4-dehydro-L-methionine*” very quickly and efficiently without any detectable double bond isomerisation using cheap and easily handled reagents. Deprotection and variation study on the amino protecting groups as well as generalization to other thioether derivatives of commercially available optically active homocysteine are under investigations in our laboratory.

EXPERIMENTAL

All solvents and reagents were used as purchased. CCl_4 and DMF were stored over 4 Å molecular sieves before use. Purifications by flash column chromatography were performed using silica gel 60 0.04–0.063 mm (230–400 mesh) (Merck ref 9385), and TLC using silica gel 60F254, layer thickness 0.2 mm on aluminum sheets.

Melting points were determined on a Mettler FP 62 apparatus and are corrected. Optical rotations were measured on a Perkin Elmer 241 polarimeter in a 1 cm cell. IR spectra were obtained using a Nicolet 205 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 200 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane.

Chiral HPLC analysis was performed using a 25 cm \times 0.46 cm Chiracel OJ column from Daicel.

Benzyl (2*RS*)-2-Benzoyloxycarbonylamino-4,4-dibenzylthiobutanoate (4): Racemic aldehyde **3**^{4a,7} (16.3 g, 47 mmol), benzyl mercaptan (5.5 mL, 47 mmol) and TsOH (0.2 g, 1 mmol) in toluene (110 mL) are refluxed in a flask fitted with a Dean-Stark apparatus. After 12 h, the reaction mixture is washed with satd. aq. sodium carbonate then with water. The organic phase is dried (Na_2SO_4), filtered and evaporated to leave an oily residue. Purification by silica gel flash chromatography gives an oil (19 g, 70%). Crystallization of dithioacetal **4** occurs in Et_2O /pentane: mp = 65 °C.

^1H NMR (200 MHz, CDCl_3): δ = 2.10–2.50 (m, 2H, CH_2); 3.55 (br t, 1H, J = 7.6 Hz, SCHS); 3.65–3.90 (m, 4H, SCH_2); 4.6– (m, 1H, CHN); 5.00–5.30 (m, 5H, NH, OCH_2); 7.10–7.50 (m, 20H, H_{arom}).

^{13}C NMR (50.3 MHz, CDCl_3): δ = 34.7; 35.1; 37.8 (CH_2 , SCH₂); 46.5 (SCHS); 52.3 (CHN); 66.9; 67.3 (OCH_2); 127.0–137.0 (C_{arom}); 155.6 (NHCO₂Bn); 171.2 (CO₂Bn).

MS (DCI, NH_3): m/z = 589 ($\text{M} + \text{NH}_4$)⁺, 497 ($\text{M} - \text{PhCH}_3 + \text{NH}_4$)⁺, 480 ($\text{M} - \text{PhCH}_3 + \text{H}$)⁺, 465 ($\text{M} - \text{BnSH} + \text{NH}_4$)⁺, 448 ($\text{M} - \text{BnSH} + \text{H}$)⁺.

Analysis: calcd $\text{C}_{33}\text{H}_{33}\text{NO}_4\text{S}_2$: C: 69.32; H: 5.82; N: 2.45; found: C: 69.11; H: 5.88; N: 2.51.

5:1) to give **8** (2.0 g, 69%, (*E*)/(*Z*) ~ 6.7/1 by ¹H NMR analysis) as a colorless oil.

Crystallisation of major (*E*) isomer resulted in a mixture of hexanes-Et₂O at 0 °C, mp = 74–76 °C, [α]_D²⁰ = +11 (c = 1.2, CHCl₃).

Optical purity of the major (*E*) isomer is 90–91% ee based on HPLC analysis over a 25 cm × 0.46 cm Chiralcel OJ column using hexane-isopropyl alcohol (70:30) as eluent and a flow rate of approximately 1 mL min⁻¹. The peak assignment was confirmed by co-injections of the *R*-isomer synthesized by the same method. The *S*-isomer elutes with a retention time of 38 min while the *R*-isomer has a retention time of 52 min.

8E: ¹H NMR (200 MHz, CDCl₃): δ = 2.29 (s, 3H, CH₃S), 3.78 (s, 3H, CO₂CH₃), 5.46 (d, 1H, *J* = 8.5 Hz, CHN), 5.87 (dd, 1H, *J* = 8.5 Hz, 15 Hz, CH=C*H*-CHN), 6.49 (d, 1H, *J* = 15 Hz, S-C*H*=CH), 7.70–7.90 (m, 4H, Ph1).

¹³C NMR (50.3 MHz, CDCl₃): δ = 14.2 (CH₃S), 53.0, 53.7 (CHN, CO₂CH₃), 115.6 (SCH=CH), 123.5 (CH_{arom}), 131.8 (C_{arom}), 133.0 (SCH=CH), 134.1 (CH_{arom}), 166.9, 168.6 (CO).

MS (DCI, NH₃): *m/z* 292 (M + H)⁺, 309 (M + NH₄)⁺.

IR (KBr, cm⁻¹): 3070, 3040, 2960, 2920, 2900, 1775, 1740, 1735, 1630, 1620, 1470, 1420, 1390.

Analysis: calcd C₁₄H₁₃NO₄S: C:57.72; H:4.50; N:4.81; found: C:57.55; H:4.56; N:4.73

For comparison and (*E*)/(*Z*) ratio determination: ¹H NMR: **8Z**: 5.75 (d, *J* = 8 Hz), 6.14 (dd, *J* = 8, 9.4 Hz), 6.33 (d, *J* = 9.4 Hz). **8Z** was fully described previously by us, see ref.^{13a}

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REFERENCES

1. a) Walsh, C. *Tetrahedron* **1982**, *38*, 871; b) Rando, R.R. *Pharmacol. Rev.* **1984**, *36*, 111; c) Turner, W.L.; Pallett, K.E.; Lea, P.J. *Phytochemistry* **1998**, *47*, 189.
2. a) Pruess, D.L.; Scannel, J.P.; Kellet, H.A.; Ax, H.A.; Janecek, J.; Williams, T.H.; Stempel, A.; Berger, J.J. *J. Antibiot.* **1974**, *27*, 229; b) Scannel, J.P.; Pruess, D.L.; Demny, T.H.; Sello, L.H.; Williams, T.H.; Stempel, A. *J. Antibiot.* **1972**, *25*, 122.
3. a) Porter, C.W.; Sufrin, J.R. *Anticancer Res.* **1986**, *6*, 525; b) Sufrin, J.R.; Lombardini, J.B.; Kramer, D.L.; Alks, V.; Bernacki, R.J.; Porter, C.W. In: *Biological Methylation and Drug Design*, Borchardt, R.T.; Creveling, C.R.; Ueland, P.M. Ed.; Humana, Clifton: New Jersey, 1986, pp. 373; c) Sufrin, J.R.; Lombardini, J.B.; Alks, V. *Biochim. Biophys. Acta* **1993**, *1202*, 87.
4. a) Keith, D.D.; Tortora, J.A.; Ineichen, K.; Leimgruber, W. *Tetrahedron* **1975**, *31*, 2633; b) Keith, D.D.; Tortora, J.A.; Yang, R. *J. Org. Chem.* **1978**, *43*, 3711; c) Keith, D.D.; Yang, R.; Tortora, J.A.; Weigle, M. *J. Org. Chem.* **1978**, *43*, 3713; d) Hoppe, I.; Schöllkopf, U. *Synthesis* **1982**, 129; e) Sufrin, J.R.; Lombardini, J.B.; Keith, D.D. *Biochem. Biophys. Res. Commun.* **1982**, *106*, 251; f) Daumas, M.; Vo-Quang, L.; Vo-Quang, Y.; Le Goffic, F. *Tetrahedron Lett.* **1989**, *30*, 5121; g) Alks, V.; Sufrin, J.R. *Synth. Commun.* **1989**, *19*, 1479; h) Alks, V.; Sufrin, J.R. *Tetrahedron Lett.* **1990**, *31*, 5257; i) Daumas, M.; Vo-Quang, L.; Le Goffic, F. *Tetrahedron* **1992**, *48*, 2373; j) Coulter, C.V.; Gerrand, J.A.; Kraunsoe, J.A.E.; Moore, D.J.; Pratt, A. *J. Tetrahedron* **1996**, *52*, 7127; k) Kobayashi, K.; Akamatsu, H.; Irisawa, S.; Takahashi, M.; Marikawa, O.; Konishi, H. *Chem. Lett.* **1997**, 503.
5. a) Alks, V.; Keith, D.D.; Sufrin, J. R. *Synthesis* **1992**, 623; b) Balenovic, K.; Deljac, A. *Rec. Trav. Chim. Pays-Bas* **1973**, *92*, 117; c) Deljac, A.; Deljac, V.; Vela, V.; Balenovic, K. *Rad. Jugosl. Akad. Znan. Umjet. Kem.* **1990**, [448]8, 15; *Chem. Abstr.* **1990**, *115*, 279721.
6. a) Hine, J.; Skoglung, M.J. *J. Org. Chem.* **1982**, *47*, 4766; b) Hine, J.; Flachskam, N.W. *J. Am. Chem. Soc.* **1973**, *95*, 1179.
7. Fushiya, S.; Maeda, K.; Funayama, T.; Nozoe, S. *J. Med. Chem.* **1988**, *31*, 480.
8. Change of methylsulfinyl to benzylsulfinyl was motivated by the search of a sulfoxide more labile to thermal elimination.
9. Meffre, P.; Vo-Quang, L.; Vo-Quang, Y.; Le Goffic, F. *Synth. Commun.* **1989**, *19*, 3457.
10. We first reconsidered the original approach^{5b} from diethyl acetamido malonate with minor variations but obtained low yields especially in the sulfoxide thermolysis step: high amounts of more stable conjugated isomer were formed, and a tedious separation was needed. When thermolysis was stopped before the isomerization was detected by TLC, formation of the vinyl sulfide was observed with a maximum yield of 39% ((*E*)/(*Z*) = 12/1). Although it proved to be more successful, the route described here from racemic homoserine was not considered to

be efficient enough to be transposed to expensive optically active material.

11. a) Meffre, P.; Durand, P.; Le Goffic, F. *Synthesis* **1995**, 1111-1114; b) Meffre, P.; Durand, P.; Le Goffic, F. *Org. Synth.* **1999**, *76*, 123-132; c) Meffre, P. *Amino Acids* **1999**, *16*, 251-272.
12. a) De Lucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157; b) Wilson Jr., G.E. *Tetrahedron* **1982**, *38*, 2597; c) Dilworth, B.M.; McKervey, M.A. *Tetrahedron* **1986**, *42*, 3731.
13. Formation of vinylsulfides from sulfides in the same reaction conditions and in the presence of a catalytic quantity of acid was previously observed by us (but in very low yield) and others: a) Meffre, P.; Lhermitte, H.; Vo-Quang, L.; Vo-Quang, Y.; Le Goffic, F. *Tetrahedron Lett.* **1991**, *32*, 4717; b) Tsai, Y.-M.; Chang, F.-C.; Huang, J.; Shiu, C.-L. *Tetrahedron Lett.* **1989**, *30*, 2121.
14. Easton, C.J.; Hutton, C.A. *Synlett* **1998**, 457.
15. Lambeth, D.O.; Swank, D.W. *J. Org. Chem.* **1979**, *44*, 2632.