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RESOLUTION OF 2-AMINO-5-THIOMETHYL PENTANOIC ACID (HOMOMETHIONINE) WITH AMINOPEPTIDASE FROM PSEUDOMONAS PUTIDA OR CHIRAL PHOSPHORIC ACIDS.

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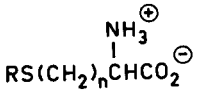
Summary: Both enantiomers of homomethionine have been obtained very readily by either of two newly developed resolution methods. The absolute configuration of homomethionine has been established with the aid of circular dichroic (CD) measurements.

Homomethionine (1a) is a naturally occurring amino acid that serves apparently as the precursor of the aglycone of sinigrin (2), found in black mustard seed and horseradish root.[1] It is a member of a family of homologs, starting with methionine (1c), which is the



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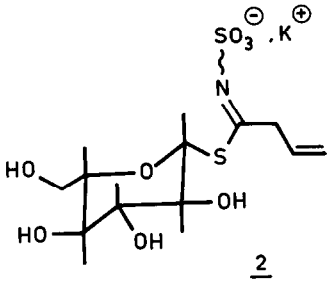
a) n=3;R=CH_3
b) n=1;R=H
c) n=2;R=CH_3



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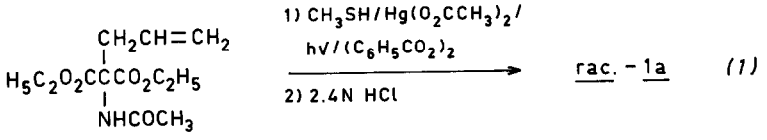
biosynthetic precursor of 1a.[2] The lengthening of the chain by one methylene unit (1c to 1a) involves a complex sequence of reactions that begins with deamination, followed by addition of acetate, decarboxylation, and adjustment of oxidation levels.[3]

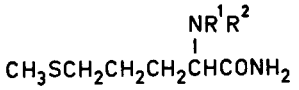
Homomethionine is also of potential interest as a precursor of various chiral intermediates for synthetic purposes.[4] For our own ends, in conjunction with work on the

synthesis of new chiral sulfur-containing ligands for transition metals, we desired multigram quantities of 1a in optically pure form. Methods for transformation of L-cysteine (1b) and L-methionine (1c) to chiral ligands have already been developed.[5] We were surprised to find, however, that 1a, to our knowledge, has been described only once in optically active form. All other work has been carried out on racemic material. By extraction of 20 kg of fresh cabbage it was possible to isolate 50 mg of 1a, $[\alpha]_D^{25.5}$ +21.0° (c 0.3, 6N HCl), which was assumed to be the L-enantiomer.[6] We describe here two efficient routes to optically pure 1a, and present evidence for confirmation of the suggested absolute configuration.

Racemic 1a was conveniently prepared on a large scale (300 mmol) analogously to the literature procedure,[7,8] although the free radical addition of methane thiol (eq 1) required long irradiation times and appreciable excesses of thiol. Resolution was achieved by use of a newly developed enzymic method.[9] The amide ($SOCl_2/CH_3OH$, then NH_3) of 1a (200 mmol) was

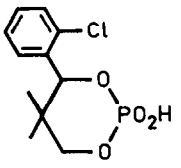


suspended in H_2O (300 mL), and held for 20 hr at 40° with the amino peptidase from Pseudomonas putida (0.75 g). Benzaldehyde (12 mL) was then added, the reaction mixture was stirred for 3 hr at 30°, and the insoluble Schiff base (3) of unreacted amide (19.5 g, 78 mmol), $[\alpha]_D^{20}$ +26.0° (c 1, CH_3OH)) was filtered off.[10] The filtrate was evaporated, and then stirred with CH_3OH (200 mL). Homomethionine (1a) (15.2 g, 93 mmol, 93% yield), $[\alpha]_D^{25}$ +24.7° (c 0.3, 6N HCl)) was isolated by filtration. The amino acid was shown to be >98% enantiomerically



3) $R^1, R^2 = =CHC_6H_5$

4) $R^1, R^2 = H$



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pure by thin layer chromatography on silica gel impregnated with a chiral phase (CHIRALPLATE, Macherey-Nagel, Dueren) against racemic 1a.

The insoluble Schiff base (3) (18 g, 72 mmol) was hydrolyzed (27 mL 96% H_2SO_4 in 300 mL H_2O). There was obtained 8g (49 mmol, 68% yield) of D-acid 1a, $[\alpha]_D^{25}$ -25.9° (c 0.3, 6N HCl), which is >99% enantiomerically pure as judged by tlc.

Chemical resolution was also carried out with the aid of newly developed chiral phosphoric acid (5).[11] A solution of (+)-5 (54 mmol) and 1a (54 mmol) was made in 150 mL warm H_2O/C_2H_5OH (2.7:1 v:v). The solution after 3 days stirring was filtered to remove solid salt, which was washed with H_2O and dried. This salt then was stirred for 20 hr with 130 mL 2.4N

HCl solution. The solid 5 was removed by filtration, and filtrate was evaporated to dryness and then dissolved in 30mL H_2O/C_2H_5OH (1:1 v:v) and neutralized with NaOH solution. The precipitate of 1a was isolated by filtration, washed, and dried to give pure 1a (10 mmol, 37% yield, $[\alpha]_D^{25}$ -23.9° (c 0.3, 6N HCl). No attempt was made to isolate more 1a from solution.

On the basis of biochemical considerations, (+)-1a should have the S (equivalent to L) configuration.[6,9] Confirmation of this anticipation is necessary, however. The N-dithiocarbethoxy derivatives of (-)-1a and L-(+)-1c (for comparison purposes) were prepared.[12] Both exhibited n-π* absorptions in CH_3OH at 330 nm (ε 1a 92). These bands gave rise to Cotton effects with maxima at 340 nm in the CD spectra, $[\theta]_{339}$ 1a -3575, and $[\theta]_{340}$ for 1c +2670 in CH_3OH. In accord with well established literature precedent (-)-1a must indeed have a configuration opposite to that of (+)-1c.[13] (-)-Homomethionine has therefore the R configuration and belongs to the D series.

These simple resolutions on a multigram scale of 1a demonstrate the efficacy of these two new methods, one enzymic and the other chemical. An advantage of the enzymic process is the obtainment of both optically pure enantiomers in a single resolution operation. A general process for the resolution of amino acids, based on the enzymic approach described here, has been developed at DSM, where it is now being operated on a pilot plant scale.[9]

An application of resolved homomethionine in organometallic chemistry is described in the following publication.[14]

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