

Large-Scale Preparation of (S) - α - Methylmethionine from the Parent Amino Acid **

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Abstract: The sodium salt of methionine is treated with pivalaldehyde to give an imine which is cyclized to an 1,3-oxazolidin-5-one by treatment with benzoyl chloride. The 2,4-*cis*-substituted heterocycle (6) is isolated by crystallization, methylated through the Li-enolate, and hydrolyzed to give the title compound with overall retention of configuration (ca. 10 g of title compound from 45 g of methionine).

The principle outlined in Scheme 1 allows a stereoselective substitution to be carried out at the one and only stereogenic center of simple chiral compounds (such as amino- and hydroxy-acids) through acetal intermediates.

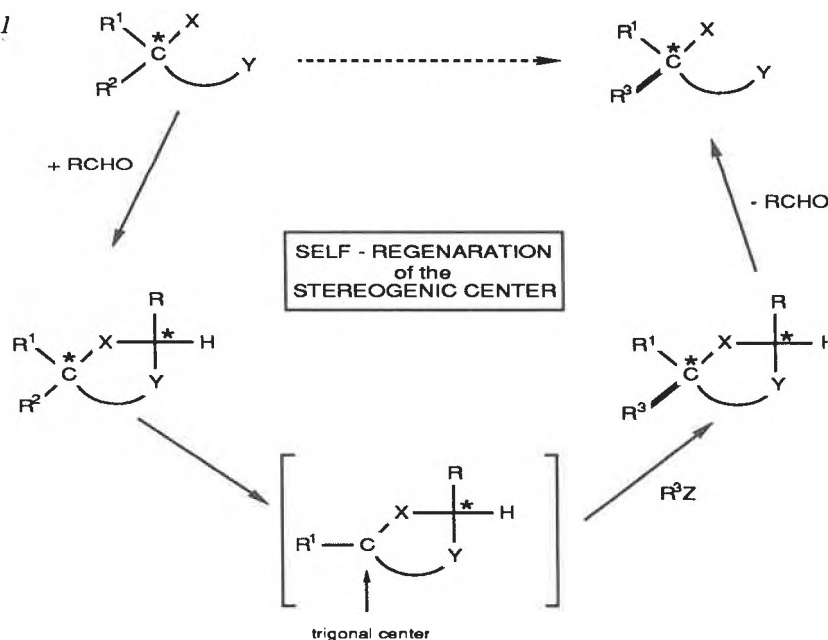
In this way, the original tetrahedral center can be temporarily rendered trigonal without producing racemic products, and without employing a chiral auxiliary. It has already been amply demonstrated^[1] that the intermediate trigonal center at the former site of the stereogenic center may be part of a C,C double bond which is hydrogenated^[2] and may have nucleophilic (anion)^[3], electrophilic (cation)^[4], or radical reactivity^[5].

The α -alkylation of amino acids **1** as exemplified by the procedure reported herein gives enantiomerically pure α -branched, i.e. α -persubstituted amino acids **2** or *ent*-**2**, depending upon whether the *cis*- (**3**) or the *trans*-substituted hetero-

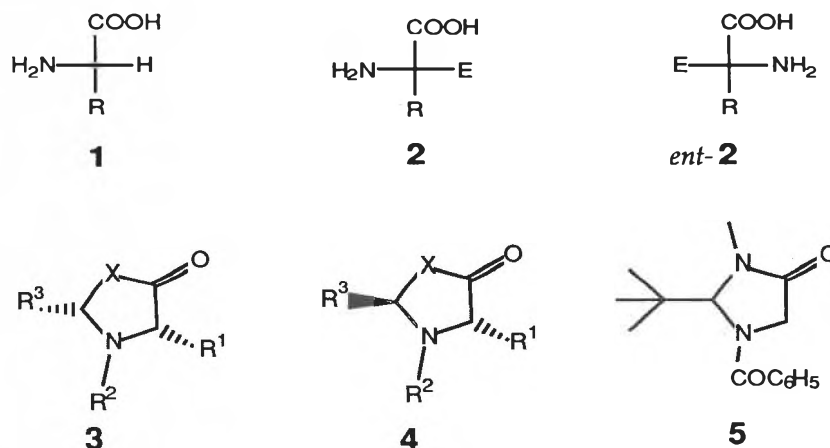
cycles (**4**) are used, see Scheme 2. The most generally useful heterocycles for the alkylation of simple amino acids by this method are the imidazolidinones (**3**, **4**: X = NCH₃)^[6]; the parent system **5**, a chiral glycine derivative (prepared by resolution)^[7] being commercially available. The oxazolidinones (**3**, **4**: X = O, R¹ \neq H)^[8] have the advantage of being much more readily hydrolyzed. On the other hand, their preparation is usually more tricky and their enolates are less stable and are poorer nucleophiles. Thus, in order to obtain the previously reported yields^[9] the conversion of each amino acid to the corresponding oxazolidinone may require painstaking optimization and elaboration of conditions^[10]. Also, only the more reactive electrophiles (methyl, allyl, benzyl halides, aldehydes, acid chlorides, nitroolefins) may be employed^[10].

Here we describe modified, carefully optimized procedures for the preparation of (S)-(+)-2-methylmethionine from (S)-methionine via methylation of (2*S*,4*S*)-3-benzoyl-2-*tert*-butyl)-4-

Scheme 1



Scheme 2



[(R) or (S) configuration]

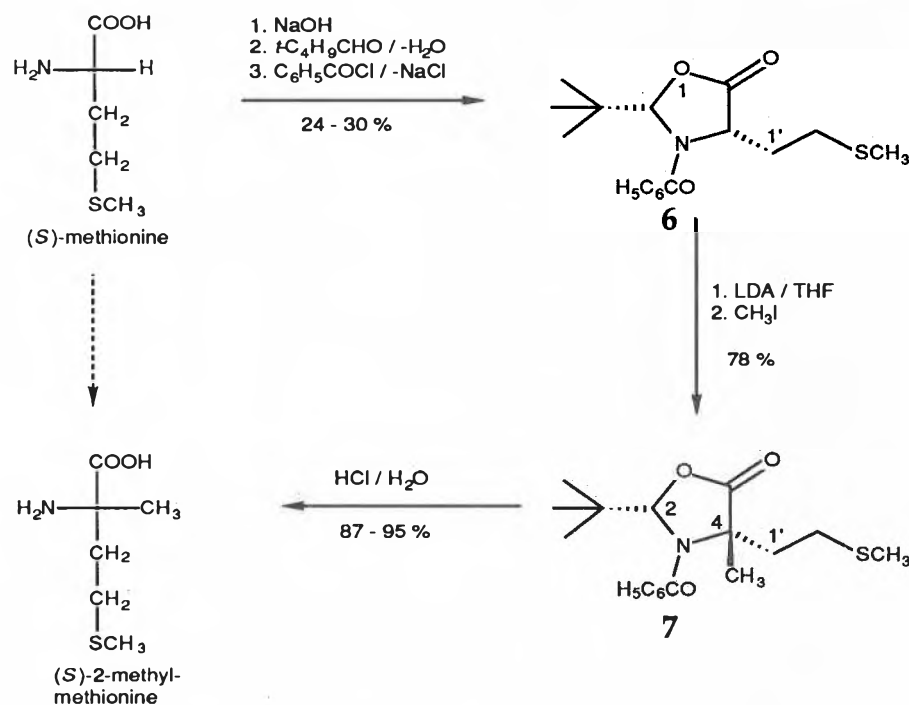
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Scheme 3



(3-thiabutyl)-1,3-oxazolidin-5-one (**6** \rightarrow **7**), a cyclic N,O-acetal of pivalaldehyde (Scheme 3).

Despite the rather modest yield in the cyclization step the present method allows the large-scale preparation of methionine (up to 10 g from 45 g of methionine). The facile isolation of the crystalline *cis*-oxazolidinone **6** obviates the need for chromatographic separation which would be scale-limiting. To the best of our knowledge, no preparation of enantiomerically pure α -methylmethionine has been published so far. For racemic mixtures, a patent, and reports about physiological activity see the references ^[11,12] and ^[13], respectively.

There are other published methods of preparing enantiomerically pure α -branched α -amino acids. In all cases either a resolution or an enantioselective synthesis using some sort of a chiral auxiliary (stoichiometric or catalytic) is applied^[14].

Experimental Part

General remarks: Melting points (uncorrected) were determined using a Büchi 510, or for over 200 °C a Culatti apparatus. The optical rotations were measured with a Perkin-Elmer 241 Polarimeter at room temperature. IR spectra (cm^{-1}) were taken with a Perkin-Elmer 983 spectrometer. ¹H-NMR spectra were recorded on a Varian EM-390 (90 MHz) and a Bruker WM 300-WB (300 MHz); chemical shifts are given in ppm (TMS was used as internal standard), coupling constants (*J*) in Hz. ¹³C-NMR spectra were measured with a Varian XL-300 (75 MHz).

(2*S*,4*S*)-(+)-3-Benzoyl-2-*tert*-butyl-4-(3-thiabutyl)-1,3-oxazolidin-5-one (**6**) from (*S*)-methionine: A 1-L round-bottomed flask containing a large magnetic stirring bar, is charged

with (*S*)-methionine (44.8 g, 0.3 mol) and ethanol (95%, 100 mL). A solution of NaOH (12 g, 0.3 mol) in water (300 mL) is added to the stirred white suspension. After 10 min, the clear solution is evaporated to dryness under reduced pressure in a rotary evaporator. The white residue is dried for 14 h (room temperature / 0.1 Torr) to give 53 - 55 g of the methionine sodium salt.

The flask containing the salt is now equipped with a Claisen adapter. A Hershberg stirrer is introduced and a Dean-Stark trap carrying a reflux condenser with a drying tube is attached. Pentane (500 mL) and pivalaldehyde *p.a.* (52 mL, 0.47 mol) are added^[9], and the vigorously stirred mixture is heated at reflux. The water formed is azeotropically removed (8 - 10 mL). After 6 h no more water is separated, the solvent is removed in a rotary evaporator, and the residue is dried for 14 - 16 h (room temperature / 0.1 Torr) to give 69 - 70 g (96 - 99% yield) of the Schiff base salt. Some characteristic ¹H-NMR signals (90 MHz, d_6 - Me_2SO) of Schiff base sodium salt are: δ = 1.0 (s, *tert*-butyl), 2.0 (s, SCH_2), 7.4 (s, N=CH). This product is used without further purification.

The round-bottomed flask is equipped again with a Claisen adapter carrying a drying tube. After adding CH_2Cl_2 (600 mL) and benzoyl chloride *p.a.* (65 g, 0.46 mol) a Hershberg stirrer is introduced and the mixture is stirred at room temperature for 16 - 18 h. For workup, the mixture is poured into a 1-L separatory funnel containing half-saturated NaHCO_3 -solution (200 mL), the combined aqueous layers are then extracted with CH_2Cl_2 (200 mL). The combined organic layers are washed with half-saturated NaHCO_3 -solution (100 mL) and with H_2O (100 mL). After drying over MgSO_4 and removing the solvent in a rotary evaporator, the crude product is dried for 14 h (room temperature / oilpump vacuum) to yield 110 - 114 g of a brownish semi-solid. To this crude product, containing benzoyl chloride and a ca. 3:1 mixture of the *cis*- and *trans*-oxazolidinone (ratio by ¹H-NMR)^[9], is added ether (200 mL), and the mixture is stirred with a magnetic stirring bar for 1 h at room temperature. During this time, the coloured impurity goes into solution and filtration through a Buechner funnel with washing of the filter cake with ether (2x50 mL) gives ca.

40 g of colourless crystals containing the *cis*- and the *trans*-isomer in a ratio of ca. 6:1. In a 1-L round-bottomed flask, 39.0 g of an oxazolidinone sample consisting of a 5.8:1 mixture of diastereoisomers is heated at reflux with ether (280 mL)^[7] for 4 h. After decanting and washing the residue with ether (2x50 mL), the crystalline product is dried overnight at room temperature (ca. 0.1 Torr) to give 23 - 29 g (24 - 30% yield) of pure *cis*-diastereoisomer; $[\alpha]_D^{20} = +61.8^\circ$ ($c = 1$, CHCl_3); *m.p.* 126.4 - 127.2 °C. ¹H-NMR (300 MHz, CDCl_3): δ = 1.03 (s, *tert*-butyl), 1.88 (s, SCH_2), 2.08 and 2.22 (2m, $\text{H}_3\text{C}(1')$), 2.38 and 2.56 (2m, H_2CS), 4.18 (dxd, $J = 10.4$, $J = 3.4$ Hz, H-C(4)), 6.09 (s, HC(2)), 7.4 - 7.5 (m, 5H arom.). For other spectroscopic data and elemental analysis see ref.^[8].

(2*S*,4*S*)-(+)-3-Benzoyl-2-*tert*-butyl-4-methyl-4-(3-thiabutyl)-1,3-oxazolidinone (**7**): A dry 1-L two-necked-round-bottomed flask, containing a magnetic stirring bar, equipped with a three-way stopcock (on the NS 29 joint) and a rubber septum on the side arm (NS 14.5) is charged with the oxazolidinone **6** (19.26 g, 60 mmol) and flushed with argon^[11]. Tetrahydrofuran (400 mL), freshly distilled from LAH under argon, is added by syringe and the resulting clear solution is cooled to -78 °C internal temperature^[9]. In a 250 mL two-necked round-bottomed flask, equipped the same way as described above, a lithium diisopropylamide solution is prepared in the following way: Under argon, diisopropylamine (10 mL, 74.1 mmol) is diluted with THF (100 mL), cooled with a dry-ice bath to -78 °C, and combined with BuLi (45 mL, 71.4 mmol, 1.59 M solution in hexane). The cooling bath is then removed for 30 min allowing the mixture to warm. After this period, the clear yellow solution is again cooled to -78 °C internal temperature. The cold LDA solution is now transferred dropwise via a Teflon[®] cannula (2 mm diameter) to the stirred cold oxazolidinone solution. During this addition, the internal temperature in the 1L flask is monitored and the rate of addition should be such that the temperature does not rise above -75 °C. At the addition of the first drop of LDA solution to the reaction mixture, a dark-yellow colour develops. After 30 min the addition is complete, the 250 mL flask is rinsed with THF (10 mL) which is also added to the oxazolidinone solution. When the temperature returns to -78 °C, the now dark-orange clear solution of the lithium enolate is stirred for 1 h. At this point is added, dropwise by syringe neat, freshly distilled iodomethane (7.0 mL, 112.4 mmol). The internal temperature of the reaction mixture does not change. Stirring at -78 °C is continued for 4 h, then the solid dry ice is spooned from the cooling bath and the reaction is permitted to warm to room temperature during ca. 16 h (overnight). The now slightly yellow, cloudy mixture is transferred into a 2-L separatory funnel containing CH_2Cl_2 (500 mL) and half-saturated NH_4Cl solution (500 mL). After separation of the two phases, the aqueous phase is extracted with CH_2Cl_2 (2x250 mL). The combined yellow organic phases are washed with half-saturated NaCl solution (3x200 mL), and most of the impurity causing the yellow colour is extracted into the aqueous phases. Drying over MgSO_4 , evaporating the solvents, and freeing of last solvent traces (overnight at room temperature / 0.1 Torr) gives 19.0 - 19.4 g (94-96 % yield) of a yellow solid. This product is mixed with ethanol *p.a.* (50 mL) and stirred for 30 min at room temperature. During this time, the coloured impurity dissolves. Filtration through a Buechner funnel and washing of the filter cake with ethanol (50 mL) in several small portions affords 15.1 g (75 % yield) of colourless crystals; $[\alpha]_D^{20} = +68.4^\circ$ ($c = 1$, CHCl_3); *m.p.* 131 - 132 °C. Concentration of

the mother liquor gives a brownish semi-solid residue which is again treated with 10 mL ethanol *p.a.* (following the above described procedure, i.e. stirring for 30 min and filtering) and washed with ethanol (10 mL) to produce another 0.7 g (3.5 % yield) of colourless crystals; $[\alpha]_D = +68.3^\circ$ ($c = 1$, CHCl_3); *m.p.* 131 - 132 °C. The total amount thus isolated is 15.8 g (78.5 % yield) of pure *cis*-isomer 7. For spectroscopic data and elemental analysis see ref.^[9].

(S)-(+)-α-Methylmethionine by Hydrolysis of the Oxazolidinone 7: A 500 mL round-bottomed flask equipped with a condenser and a magnetic stirring bar is charged with the oxazolidinone 7 (13.42 g, 40 mmol) and 6N HCl (250 mL). The mixture is heated at vigorous reflux and the crystals slowly dissolve. After 2.5 h all solids are dissolved, the refluxing is continued for another 1.5 h. The clear colourless solution is then cooled to room temperature (crystals precipitate) and the whole transferred into a 1-L separatory funnel. The mixture is extracted with CH_2Cl_2 (4x80 mL). The combined organic layers are washed with H_2O (80 mL). The combined water layers are evaporated at 60 °C bath temperature / ca. 30 Torr. The colourless crystalline residue is dried overnight (0.1 Torr) to give 7.35 - 7.45 g (92 - 93 % yield) of the *(S)-(+)-α*-methylmethionine hydrochloride; $[\alpha]_D = +12.5^\circ$ ($c = 1$, H_2O); *m.p.* 207 - 211 °C (dec.). The hydrochloride salt is dissolved in water (50 mL) and adsorbed on Dowex® 50Wx8 (H^+ form, 300 g)^[10] in a 35x450 mm column. The resin is now eluted with H_2O (dist.), and after ca. 150 mL of eluent, the pH changes to ca. pH 2, after another 250 mL eluent the pH is again neutral. Now the column is eluted with 1.3 N aqueous NH_3 . During this process a warm zone is observed to move down the column and arrives at the outlet of the column after ca. 400 mL ammonia eluent. A 1 L fraction is collected and this is evaporated in a rotary evaporator. After drying for 4 h (70 °C / 0.1 Torr) 5.2 - 5.6 g (87 - 92 % yield) α -methyl methionine is isolated as a colourless solid; $[\alpha]_D = +21.0^\circ$ ($c = 1$, 0.2 N HCl); *m.p.* 278 - 280 °C (dec., in a sealed tube). If after the 1L fraction another 800 mL fraction is collected and evaporated at 60 °C / 30 Torr an additional 0.22 g of almost colourless product of $[\alpha]_D = +19^\circ$ ($c = 1$, 0.2 N HCl) is isolated. This raises the yield to 95.6 %. - IR (KBr): $\nu = 3050, 1600, 1455, 1435, 1400, 1365, 1345, 1305, 1250, 1230, 550, 410$. ¹H-NMR (90 MHz, D_2O , ref. HOD peak at $\delta = 4.8$): $\delta = 1.65$ (s, $\text{CH}_2\text{-C}(2)$), 2.20 (s, CH_2S), 2.1-2.8 (m, 2 CH_2). ¹³C-NMR (75 MHz D_2O): $\delta = 16.70$ (CH_2), 25.08 (SCH_2), 30.17 (CH_2), 39.01 (CH_2), 63.96 (CNH_2), 178.59 (COOH). - Anal. calc. for $\text{C}_6\text{H}_{13}\text{NO}_2\text{S}$ (163.24): C 44.15, H 8.03, N 8.58, O 19.60, S 19.64; found C 44.30, H 8.01, N 8.63.

The isolated methylmethionine was compared with commercial (+)-2-methylmethionine by TLC analysis using Chiralplate[®] [22]. Solutions containing 1% of the amino acid

in $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ (1:1) were applied. An acetonitrile/ $\text{CH}_3\text{OH}/\text{H}_2\text{O}$ mixture (100: 25: 25) was used for the chromatography, the spots were developed by spraying with ninhydrin (Merck) and heated to 110 °C for 10 min. According to this analysis, our material contains less than 1% of the (-)-enantiomer.

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- [15] Practical grade pivalaldehyde (ca. 75%) can be used; the yield will drop by ca. 5%.
- [16] ¹H-NMR of the *cis*-isomer see procedure. - The pure *trans*-isomer can be isolated by flash chromatography of the *cis/trans* mixture (silica gel, pentane / ether / CH_2Cl_2 5: 2: 1). It has the following properties: *m.p.* 155.8 - 156.4 °C (from ether); $[\alpha]_D = +132.1^\circ$ ($c = 1$, CHCl_3); ¹H-NMR (300 MHz, CDCl_3): $\delta = 1.03$ (s, *t*-butyl), 1.84 (s, SCH_2), 2.0 (m, $\text{H}_2\text{C}(1')$), 2.3 (m, H_2CS), 4.51 (dxd, $J = 6.5$, $J = 2.2$ Hz, HC(4)), 6.19 (s, HC(2)) and 7.45 - 7.70 (m, 5H arom.).
- [17] The volume X of ether (mL) can be calculated in the following way: the amount of *trans*-isomer (Y grams) in the sample to be purified, as determined by NMR-analysis, is multiplied by a factor of 44.5 ($X = 44.5 Y$). This procedure was discovered when we found that a 1:1 diastereomeric mixture is more soluble in ether than the pure *cis*-isomer.
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- [19] A Pt100 thermometer with digital recorder for measurement of the temperature was used.
- [20] Dowex® 50Wx8 Na⁺ form - as purchased from Fluka AG or recovered from a previous use - is stirred for 30 min with ca. 6 N HCl, washed to nearly neutral, stirred with ca. 6 N NH_4OH , washed again with water, then stirred a second time with ca. 6 N HCl and washed to neutral (pH 7). The resin thus obtained is used directly.
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