References and Notes

(1) Part 4 of a series on pheromone synthesis. For part 3 see P. J. Kocienski, J. M. Ansell, and R. W. Ostrow, *J. Org. Chem.*, **41**, 3625 (1976).
(2) D. F. Horler, *J. Chem. Soc. C*, 859 (1970).
(3) P. D. Landor, S. R. Landor, and S. Mukasa, *Chem. Comn.*, 1638 (1971).
(4) C. Descoins, C. A. Henrick, and J. B. Siddall, *Tetrahedron Lett.*, 3777 (1972).
(5) R. Baudouy and J. Gore, *Synthesis*, 573 (1974).
(6) D. Michelot and G. Linstrumelle, *Tetrahedron Lett.*, 275 (1976).
(7) The known alcohol **1** (see ref 3) was prepared in 78% yield from lithium acetylide and nonaldehyde: bp 81 °C (0.15 mm); IR (CCl_4) 3620, 3460, 3320, 660, and 630 cm^{-1}; NMR (CCl_4) δ 4.1 (m, 1 H), 4.0 (br s, 1 H), 2.25 (d, 1 H, J = 2 Hz), 1.8–0.9 (br, 14 H), 0.8 (distorted t, 3 H).
(8) J. K. Crandall and G. L. Tindell, *Chem. Commun.*, 1411 (1970).
(9) C. A. Henrick, W. E. Willy, D. R. McKean, E. Baggiolini, and J. B. Siddall, *J. Org. Chem.*, **40**, 8 (1975).
(10) Henrick (see ref 9) has noted a similar facile base-catalyzed rearrangement in analogous systems.
(11) D. K. Black, S. R. Landor, A. N. Pel, and P F. Whiter, *Tetrahedron Lett.*, 483 (1963).
(12) J. B. Lee and T. J. Nolan, *Can. J. Chem.*, **44**, 1331 (1966). For a review see R. Appel, *Angew. Chem., Int. Ed. Engl.*, **14**, 801 (1975).
(13) See, for example, E. E. van Tamelen and R. J. Anderson, *J. Am. Chem. Soc.*, **94**, 8225 (1972); J. B. Heather, R. S. D. Mittal, and C. J. Sih, *ibid.*, **98**, 3661 (1976).
(14) The formation of organometallic derivatives of bromide **4** provided to be unusually difficult. For example, in our hands, **4** failed to react with lithium wire in ether or hexane despite rigorous purification of reactants and solvents. The formation of the Grignard reagent in ether proved to be capricious; by using THF, however, we encountered little difficulty in initiating reaction. The corresponding homoallenic chloride would not react with lithium or magnesium under a variety of conditions.
(15) K. B. Sharpless, R. F. Lauer, and A. Y. Teranishi, *J. Am. Chem. Soc.*, **95**, 6137 (1973).
(16) The crude allenenic ester **6** was a single major component by TLC. Rapid chromatography on silica gel packed in CH_2Cl_2 was used to remove selenium-containing contaminents with little loss in material. The thermal instability of **6** precluded purification by vapor phase chromatography.

Stereospecific Synthesis of (2*S*,3*R*)-2-Amino-3-mercaptobutyric Acid—an Intermediate for Incorporation into β-Methyllanthionine-Containing Peptides

John L. Morell, Peter Fleckenstein, and Erhard Gross*

Section on Molecular Structure, Reproduction Research Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20014

Received July 6, 1976

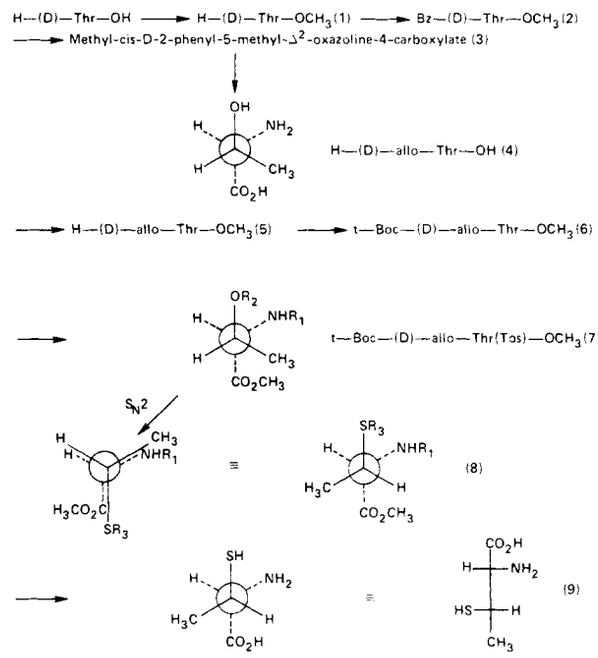
Access to the correct isomer[1] of β-methyllanthionine is a prerequisite for the synthesis of fragments of heterodetic polycyclic peptides, such as nisin.[2] A reasonable approach requires the preparation of *threo*-β-methyl-D-cysteine. Formation of the thioether bridge is anticipated to be accomplished by a substitution or addition reaction on a suitable alanine derivative before or after incorporation into the peptide chain.

Carter et al.[3] prepared the diastereoisomeric pairs of *S*-benzyl-β-methylcysteine which they called amino acids A and B and which have been assigned the threo and allo configurations, respectively.[1]

Hoogmartens et al.[4] began with the same method of preparation and by derivatization and crystallization with the aid of optically active bases resolved each of the pairs into the respective D and L amino acid.

This procedure is elaborate if only one of the four possible isomers is desired. Yields of the final product are low as the result of lack of stereospecificity in the synthesis.

We have devised a stereospecific synthesis outlined in the scheme (R_1 = *tert*-butyloxycarbonyl; R_2 = tosyl; R_3 = acetyl) below. Good yields of the desired isomer are obtained by a series of simple steps in a relatively short time. The crucial step involves an SN2 displacement of tosylate by thiolacetate anion. Although the products of such reactions are often mixtures resulting from elimination, O-alkylation of thiolacetate, or SN1 mechanisms, no evidence for these processes was observed here. Examination of the crude reaction mixture after hydrolysis and S-benzylation showed the only sulfur



containing product to be *threo*-*S*-benzyl-β-methyl-D-cysteine. A small amount of unreacted *allo*-*O*-tosyl-D-threonine was also present but had no effect on the subsequent steps.

The reactions were also applied to *allo*-DL-threonine and gave pure *allo*-β-methyl-DL-cysteine as determined by S-benzylation and amino acid analysis.

Experimental Section

Melting points are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of the National Institutes of Health. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter.

Amino acid analyses were performed on a modified Phoenix analyzer using the Moore, Stein, and Spackman system. *S*-Benzyl-β-methylcysteines were analyzed on a 60 × 0.9 cm column using pH 4.25, 0.2 N Na citrate buffer at a flow rate of 60 ml/h. Elution volumes of the threo and allo isomers of *S*-benzyl-β-methylcysteine are 163 and 187 ml, respectively.

Countercurrent distribution was run in a 200 tube Craig machine with lower and upper phase volumes of 10 ml each.

D-Threonine Methyl Ester Hydrochloride (1). D-Threonine, 180 g, $[\alpha]^{23}D$ +30.5° (*c* 1, water) [lit.[7] $[\alpha]^{26}D$ +28° (*c* 1–2, water)], obtained from Pierce, Rockford, Ill., was refluxed twice for 1 h in 1.5 l. of 2 N HCl in methanol to give 205 g (98%) of **1** as an oil which crystallized on standing under vacuum.

***N*-Benzoyl-D-threonine Methyl Ester (2).** **1** (205 g) was benzoylated without further purification by the dropwise addition of 175 ml of benzoyl chloride (1.5 mol) to a solution in 1.5 l. of water–dioxane (2:1) over 1 h using 5 N NaOH to maintain a pH of 8.5–9.0 and an ice bath to keep the temperature at 30 °C. The dioxane was removed under reduced pressure and the aqueous phase extracted with ethyl acetate. Evaporation of the solvent yielded 285 g (80%) of crude **2**. Recrystallization from benzene gave 220 g (63%) of pure **2**, mp 92–94 °C, $[\alpha]^{22}D$ −22.0° (*c* 8, ethanol) [lit.[5] mp 96.0 °C, $[\alpha]^{26}D$ −23.2° (*c* 6, ethanol)].

Methyl *cis*-D-2-Phenyl-5-methyl-Δ²-oxazoline-4-carboxylate (3). **3** (205 g, 0.875 mol) was prepared by treating **2** with thionyl chloride (twice distilled from triphenyl phosphite[6]) according to the literature.[5]

***allo*-D-Threonine (4).** Crude crystalline **3** (205 g) was hydrolyzed in 1 l. of 6 N HCl at 90 °C for 5 h. Workup according to the literature[5] yielded 76 g (65% based on **2**) of pure **4**, $[\alpha]^{27}D$ −32.5° (*c* 8, 1 N HCl in water) [lit.[5] *allo*-L-threonine $[\alpha]^{27}D$ +32.5° (*c* 8.2, 1 N HCl in water)].

***allo*-D-Threonine Methyl Ester Hydrochloride (5).** **4** (75 g, 0.625 mol) was esterified in the same manner as D-threonine. The yield

was 103 g (97%) of crude crystalline material from which 1 g was recrystallized from methanol–ether to give 0.9 g of pure product, $[\alpha]^{23}D$ −23.1° (c 5, methanol), mp 115 °C. Anal. Calcd for $C_5H_{12}NO_3Cl$: C, 35.41; H, 7.13; N, 8.26; Cl, 20.91. Found: C, 35.33; H, 7.39; N, 8.45; Cl, 20.70.

***allo*-Boc-D-threonine Methyl Ester (6).** Crude **5** (103 g, 0.61 mol) was dissolved in 1 l. of dry (Linde 4A) dimethyl sulfoxide and 170 ml (1.22 mol) of triethylamine was added with vigorous stirring. After the addition of 90 ml (0.67 mol) of *tert*-butyloxycarbonyl azide the mixture was stirred for 48 h at room temperature. The volume was reduced to 200 ml under vacuum before 1 l. of ice water was added. Following acidification to pH 2.5 with citric acid the solution was extracted with five 200-ml portions of ethyl acetate. The combined extracts were washed with $NaHCO_3$ solution. Evaporation of the solvent after drying over Na_2SO_4 gave 124 g (87%) of a pale yellow oil, $[\alpha]^{23}D$ +14.4° (c 5.0, ethanol). Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.49; H, 8.21; N, 6.00. Found: C, 50.80; H, 8.53; N, 5.80.

***allo*-Boc-*O*-tosyl-D-threonine Methyl Ester (7). 6** (124 g, 0.53 mol) was dissolved in 400 ml of pyridine (distilled and stored over 4A sieves) and cooled to 0 °C. Tosyl chloride (133 g, 0.70 mol, recrystallized from petroleum ether) was added in portions over 10 min to maintain a temperature of 0–5 °C. The solution stood at 5 °C for 30 h and was then poured onto 1 l. of crushed ice and stirred for 0.5 h. The oily precipitate was extracted into 1.5 l. of ether and washed with ice-cold 0.01 N HCl (5–6 l.) to an acid reaction and finally with water to neutrality. Evaporation of the ether after drying over Na_2SO_4 yielded 189 g (91%) of crude **7**. Although the racemic compound crystallized readily, **7** resisted and was purified by extraction into cyclohexane–petroleum ether (1:1) at 37 °C and precipitation in the cold. Final yield of purified product 147 g (71%); homogeneous by TLC and showing the same R_f as the crystalline racemate; $[\alpha]^{19}D$ +4.2° (c 8, ethanol). Anal. Calcd for $C_{17}H_{25}NO_7S$: C, 52.70; H, 6.50; N, 3.62; S, 8.28. Found: C, 53.48; H, 6.58; N, 3.53; S, 9.33.[8]

***threo*-Boc-*S*-acetyl-β-methyl-D-cysteine Methyl Ester (8).** **7** (90.8 g, 0.227 mol) was dissolved in 300 ml of DMF (purified by passage over a column of acidic Al_2O_3 Brockman activity I and stored over 4A sieves). The solution was divided equally among five 100-ml Kjeldahl flasks.

Potassium thiolacetate was prepared by the addition of a 10% excess of thiolacetic acid to a methanolic solution of KOH. The solvent was removed on a rotary evaporator and excess thiolacetic acid under high vacuum. A water solution of the salt had a pH of 5.5.

After cooling to 0 °C, the Kjeldahl flasks were cleared of oxygen by alternate application of vacuum and nitrogen; 7.8 g (0.07 mol) of potassium thiolacetate was added, and each flask was again flushed, and prior to sealing under vacuum equipped with a magnetic stirring bar. The reaction was allowed to proceed with stirring at room temperature for 36 h although a copious precipitate of potassium tosylate appeared within 0.5 h. The contents of the reaction vessels were combined and the DMF removed in vacuo. The residue was extracted with 250 ml of ethyl acetate and washed with three 150-ml portions of water. Upon evaporation of the ethyl acetate 53 g (75%) of an orange oil was obtained, $[\alpha]^{23}D$ −55.6° (c 5, ethanol). Examination of an analytical amount by amino acid analysis after hydrolysis and oxidation with performic acid revealed the presence of 90% of the expected amount of β-methylcysteic acid and 10% of threonine. The product was considered pure enough for the subsequent steps in the synthesis. For the purpose of characterization 3 g was subjected to 1250 transfers in a countercurrent distribution machine [solvent system chloroform–benzene–methanol–water (1:1:1.5:0.5)] to yield 2.2 g of a pale yellow oil, K = 0.105, 99% pure by amino acid analysis, $[\alpha]^{23}D$ −66.1° (c 5, ethanol). Anal. Calcd for $C_{12}H_{21}NO_5S$: C, 49.47; H, 7.26; N, 4.80; S, 11.01. Found: C, 49.38; H, 7.57; N, 4.74; S, 12.63.[8] **7** (100 mg), K = 0.092, was also isolated. A fraction comprising the intersection of the incompletely resolved thiol ester and tosylate accounted for another 500 mg. Amino acid analysis showed this fraction to be 70% thiol ester.

***threo*-2-Amino-3-mercapto-D-butyric Acid (9).** Crude **8** (50 g, 0.172 mol) was exposed for 0.5 h to 100 ml of trifluoroacetic acid at room temperature. The acid was evaporated in vacuo and the product dissolved in 150 ml of 12 N HCl and heated to 65 °C for 5 h. Evaporation of the solution gave a yellow oil which solidified on lyophilization. The material was dissolved in 900 ml of ethanol and treated with 1 equiv of NH_4OH. Upon cooling 12.4 g of a white, crystalline product was obtained. A further 2 g remained in the mother liquor, overall yield 65%. The product (300 mg) was allowed to react with benzyl bromide in liquid ammonia to give in 80% yield (2*S*,3*R*)-2-amino-3-benzylthiolbutyric acid on precipitation from neutral aqueous solution and crystallization from ethanol. The compound was pure by amino acid analysis, $[\alpha]^{22}D$ −76.2° (c 1, 1 N HCl) [lit.[3] $[\alpha]^{25}D$ −72.0° (c 1, 1 N HCl)]. The disulfide desired for the preparation of derivatives was obtained by air oxidation of 7.0 g of **9** over a period of 4 days in 200 ml of aqueous ammonia at pH 8.6. After recrystallization from water–ethanol 5.6 g (80%) of a white hemihydrate was obtained. The product was homogeneous by amino acid analysis, $[\alpha]^{19}D$ −414° (c 1, 1 N HCl). Anal. Calcd for $C_8H_{17}N_2O_{5.5}S_2$: C, 34.77; H, 6.20; N, 10.14; S, 23.20. Found: C, 34.69; H, 6.10; N, 10.06; S, 22.64.[8]

Registry No.—**1**, 60538-15-0; **2**, 60538-16-1; **3**, 60538-17-2; **4**, 24830-94-2; **5**, 60538-18-3; **6**, 60538-19-4; **7**, 60538-20-7; **8**, 60538-21-8; **9**, 43083-49-4, D-threonine, 632-20-2; benzoyl chloride, 98-88-4; thionyl chloride, 7719-09-7; *tert*-butyloxycarbonyl azide, 1070-19-5; tosyl chloride, 98-59-9; potassium thiolacetate, 10387-40-3; β-methylcysteic acid, 60538-22-9; (2*S*,3*S*)-2-amino-3-benzylthiolbutyric acid, 60538-23-0.

References and Notes

(1) J. L. Morell and E. Gross, *J. Am. Chem. Soc.*, **95**, 6480 (1973).
(2) E. Gross and J. L. Morell, *J. Am. Chem. Soc.*, **93**, 4634 (1971).
(3) H. E. Carter, C. M. Stevens, and L. F. Ney, *J. Biol. Chem.*, **139**, 247 (1941).
(4) J. Hoogmartens, P. J. Claes, and H. Vanderhaeghe, *J. Org. Chem.*, **39**, 425 (1974).
(5) D. F. Elliot, *J. Chem. Soc.*, 62 (1950).
(6) L. Friedman and W. P. Wetter, *J. Chem. Soc. A*, 36 (1967).
(7) H. D. West and H. E. Carter, *J. Biol. Chem.*, **119**, 103, 109 (1937).
(8) The percentage figures given for sulfur are from single first determinations. In view of satisfactory C, H, and N data, additional purity criteria provided, and a likely greater margin of error for sulfur values, analyses were not repeated.

Prostaglandins and Congeners.[1] 11. Synthesis of *dl*-13-Hydroxyprostanoic Acids

Allan Wissner

Metabolic Disease Therapy Research Section, Lederle Laboratories, American Cyanamid Company, Pearl River, New York 10965

Received August 4, 1976

In an effort to prepare biologically more selective prostaglandin congeners, a program was initiated in our laboratory involving the synthesis of congeners in which the 15-hydroxy function was shifted to other positions in the β chain. In a previous report we have described the synthesis and biological properties of prostaglandin analogues wherein the 15-hydroxy group is moved to the C_{16}, C_{17}, and C_{20} position or is replaced by a hydroxymethyl group.[2] Another group has reported compounds wherein the hydroxy group is placed at C_{14}.[3] We now describe a convenient synthesis of prostaglandin congeners wherein the hydroxy function has been shifted to the C_{13} position. After this work was completed, two reports appeared concerning the synthesis of 13-hydroxyprostanoic acids which do not contain the 11-hydroxy substituent.[4] Our synthesis, which is different, is also applicable to the synthesis of 13-hydroxyprostaglandins which contain this biologically important 11-hydroxy group.

dl-9-Oxo-13-hydroxyprostanoic acid (**2**) is conveniently obtained by the benzophenone sensitized photoaddition of 1-octanol to the cyclopentenone **1**[5] using a 350-nm light source and a Pyrex reaction vessel.[6] Since 1-octanol also serves as the solvent, the product is isolated by sodium hydroxide extraction, which also serves to epimerize any 8-iso isomers to the corresponding 8-normal isomers, followed by silica gel chromatography. 13-Hydroxyprostaglandin **2** is obtained as two C_{13} epimers, separable by thin layer chromatography. The major side product of this reaction has been identified as the conjugate reduction product **3**.

In a similar manner photoaddition of 1-octanol to 4-hydroxycyclopentenone **4**[7] gives, after extraction with sodium bicarbonate solution and silica gel chromatography, *dl*-9-