Pergamon

Tetrahedron 58 (2002) 9765–9767

TETRAHEDRON

Efficient synthesis of (*S*,*S*)-ethambutol from L-methionine

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Received 9 September 2002; accepted 16 October 2002

Abstract—Starting from readily available amino acid L-methionine, an efficient synthesis of the tuberculostatic agent (*S*,*S*)-ethambutol has been developed. The key steps in the synthetic sequence involve: dimerization of methionine methyl ester through oxalyl diamide formation, Raney nickel desulfurization of the terminal thiomethyl groups, and a one-pot exhaustive reduction of the oxalamide and the diester functionalities to afford the desired enantiopure (*S*,*S*)-ethambutol in good overall yield.

1. Introduction

(*S*,*S*)-Ethambutol (**1**), first reported in 1961 by Wilkinson and colleagues,[1] is among the frontline antimycobacterial agents, active against nearly all strains of *M. tuberculosis* and *M. kansasii* as well as a number of strains of *M. avium*.[2] Ethambutol has been used with notable success in the therapy of tuberculosis of various forms, especially when given concurrently with isoniazid. Importantly, it was also found to suppress the growth of most isoniazid- and streptomycin-resistant tubercle bacilli.

Mechanistically, the biological activity of ethambutol has been attributed to its inhibition of mycobacterial arabinosyl transferases involved in bacterial cell wall biosynthesis.[3] From a structure–activity relationship (SAR) viewpoint, the (*S*,*S*)-absolute configuration as present in ethambutol was found to be essential for optimum activity.[1a,4] For example, compared to the parent (*S*,*S*)-stereoisomer, the corresponding (*R*,*R*)-enantiomer and the optically inactive *meso*-isomer were found to exhibit only 0.2 and 8.3% antibacterial activity, respectively.

The literature methods for the synthesis of ethambutol involve direct alkylation (with 1,2-dibromoethane) or reductive alkylation (with glyoxal) of the amino group of (*S*)-2-amino-1-butanol, which in turn is obtained by resolution of the corresponding racemic material.[1,4a,5] More recently, a six step asymmetric synthesis of ethambutol has been reported by Trost and co-workers, wherein, a chiral palladium catalyst assisted regio- and stereoselective addition of phthalimide to butadiene monoepoxide constituted the key reaction step towards forming a masked 2-amino butanol precursor with appropriate stereochemistry.[6] In continuation of a research program aimed at stereoselective synthesis of natural and non-natural compounds of biomedical significance, utilizing amino acids as chiral pool starting materials,[7] we report herein an efficient, four step synthesis of (*S*,*S*)-ethambutol starting from L-methionine.

2. Results and discussion

The first two steps in our synthetic sequence involves esterification of L-methionine under standard reaction conditions, followed by treatment of the free amine with 0.5 equiv. of oxalyl chloride to form the desired oxalyl diamide derivative **2** (Scheme 1) in good yield. As evident, the key intermediate **2** already incorporates the required carbon framework and the absolute (*S*,*S*)-configuration as present in the target end product. Raney nickel desulfurization of the terminal thiomethyl groups provided the ethyl side-chain containing penultimate intermediate **3**. Finally, in a one-pot reaction, lithium aluminium hydride assisted exhaustive reduction of the diamide and the diester functional groups of **3** completed an efficient synthesis of (*S*,*S*)-ethambutol in good overall yield. The spectral and analytical data of **1** was in good agreement with the reported values, thereby confirming its structural and stereochemical integrity.

In conclusion, starting from a readily available enantiopure amino acid and following a short sequence of reactions, a novel, efficient and practical route to the tuberculostatic agent ethambutol has been developed. It is expected that the present method will provide an attractive alternative to the existing methods for the synthesis of this valuable therapeutic agent.

Keywords: ethambutol; tuberculostatic; L-methionine; dimerization; desulfurization.

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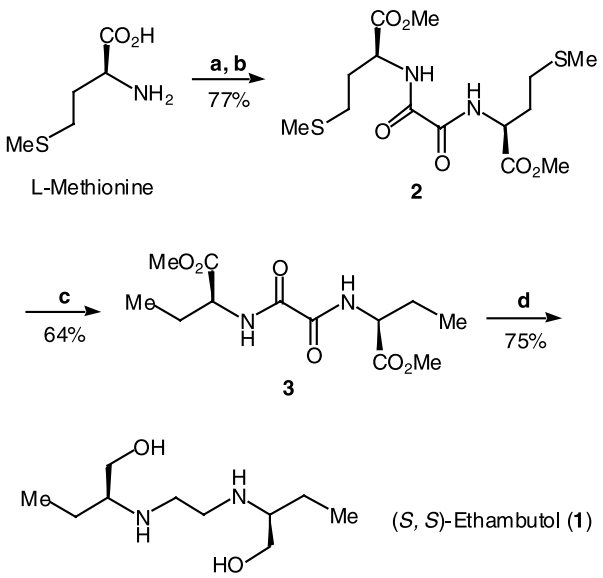
0040–4020/02/$ - see front matter
PII: S0040-4020(02)01308-X



Scheme 1. (a) MeOH, AcCl; (b) ClCOCOCl (0.5 equiv.), pyridine, CH_2Cl_2; (c) Raney Ni (W-4), MeOH–H_2O (9:1), Δ; (d) $LiAlH_4$, THF, Δ.

3. Experimental

3.1. General methods

All of the solvents and reagents used were obtained commercially and used as such unless noted otherwise. NMR spectra (^1H at 400 MHz and ^{13}C at 100 MHz) were recorded with a Bruker DRX-400 spectrometer with the chemical shifts (δ) reported in ppm relative to Me_4Si (for ^1H) and $CDCl_3$ (for ^{13}C) as internal standards, respectively. Mass spectroscopy was performed on a ZAB VG analytical spectrometer. IR spectra were recorded on a Nicolet FT-IR spectrophotometer. Optical rotations were measured on a Rudolph AUTOPOL IV automatic polarimeter. Melting points were obtained using a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were obtained from QTI, NJ.

3.1.1. (*S*,*S*)-2-[(Methoxycarbonyl-3-methylsulfanyl-propylaminooxalyl)-amino]-4-methylsulfanyl-butuyric acid methyl ester (2). To ice-cold methanol (100 mL) was added dropwise acetyl chloride (15 mL) with stirring. The resulting solution was stirred at the same temperature for another 10 min, followed by addition of L-methionine (8.5 g, 57 mmol) in one lot and stirring continued for another 10 min. The resulting solution was then refluxed for 4 h and stirred overnight at room temperature. Solvent was removed under vacuum, the resulting ester hydrochloride taken into chloroform (100 mL) and neutralized to pH 7–8 by careful addition of saturated aq. $NaHCO_3$ solution. The organic layer was separated and the aqueous layer extracted with chloroform (3×50 mL). The combined organic extract was dried (Na_2SO_4), concentrated, and the residue kept under high vacuum for 2 h to afford the amino ester derivative as a colourless oily liquid (crude yield 8.35 g, 90%; 51.2 mmol). To a well-stirred, ice-cold solution of the methionine methyl ester in anhydrous dichloromethane (100 mL) under argon atmosphere, anhydrous pyridine (9 mL, 113 mmol) was added, followed by dropwise addition of a solution of oxalylchloride (2.4 mL, 27 mmol) in dichloromethane (25 mL) with stirring. After completion of addition the mixture was allowed to attain room temperature and stirred overnight. The reaction was then quenched by addition of water (100 mL) and stirred for 15 min. The organic layer was separated, aqueous layer extracted with chloroform (3×75 mL) and the combined organic extract washed sequentially with 10% HCl, saturated $NaHCO_3$, and brine, dried (Na_2SO_4) and concentrated. Flash column chromatography (hexanes/ethyl acetate 1:1→1:3) of the residual liquid yielded **2** as a white solid (8.2 g, 85%): $[\alpha]_D^{22}=+34.0$ (c=0.51, $CHCl_3$); mp 109–110°C; IR (thin film, cm^{-1}) 3273, 1747, 1655, 1521; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (m, 1H), 2.11 (s, 3H), 2.21 (m, 1H), 2.53 (t, J=7.1 Hz, 2H), 3.79 (s, 3H), 4.73 (m, 1H), 7.81 (d, J=8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 29.8, 31.3, 51.7, 52.7, 158.9, 170.9; MS (FAB+) 381 (MH^+). Anal. calcd for $C_{14}H_{24}N_2O_6S_2$ (380.11): C, 44.19; H, 6.36; N, 7.36. Found: C, 44.21; H, 6.25; N, 7.23.

3.1.2. (*S*,*S*)-2-[(1-Methyoxycarbonyl-propylamino-oxalyl)-amino]-butyric acid methyl ester (3). To a stirred solution of the oxamide **2** (1.0 g, 2.63 mmol) in 9:1 methanol–water (20 mL), freshly prepared W-4 Raney nickel[8] (~5 g) was added and the mixture refluxed for 6 h. The reaction mixture was cooled to room temperature, filtered, and the residual catalyst washed with methanol (3×20 mL). The combined filtrate was concentrated, the residual semi-solid redissolved in 9:1 methanol–water (20 mL), W-4 Raney nickel (~5 g) added to the resulting solution and the mixture refluxed overnight. After cooling to room temperature, the reaction mixture was filtered and the catalyst washed thoroughly with methanol (3×25 mL). The combined filtrate was concentrated and the crude product purified by flash column chromatography (hexanes/ethyl acetate 3:2) to yield the desulfurized product **3** as a white solid (0.48 g, 64%): $[\alpha]_D^{22}=+2.88$ (c=2.5, $CHCl_3$); mp 130–131°C; IR (thin film, cm^{-1}) 3283, 1746, 1649, 1526; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J=7.4 Hz, 3H), 1.81 (m, 1H), 1.94 (m, 1H), 3.76 (s, 3H), 4.53 (m, 1H), 7.80 (d, J=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.1, 25.6, 52.7, 54.1, 159.5, 171.7; MS (FAB+) 289 (MH^+). Anal. calcd for $C_{12}H_{20}N_2O_6$ (288.13): C, 49.99; H, 6.99; N, 9.72. Found: C, 49.81; H, 6.87; N, 9.47.

3.1.3. (*S*,*S*)-Ethambutol (1). To a stirred suspension of lithium aluminum hydride (0.46 g, 12.2 mmol) in anhydrous THF (10 mL) at room temperature and under argon atmosphere was added dropwise a solution of the diamide diester **3** (0.35 g, 1.2 mmol) in THF (10 mL). After completion of addition, the resulting solution was stirred at room temperature for another 30 min and then refluxed overnight. After cooling to room temperature, the reaction was quenched by careful addition of 10% aq. NaOH solution (1.0 mL) followed by addition of an equal amount of water. After stirring the mixture for 30 min, the precipitated solid was removed by filtration, washed with ethylacetate (3×25 mL), the combined filtrated dried (Na_2SO_4), concentrated and the residual product was crystallized (ethyl acetate/hexane) to yield pure ethambutol (**1**) as a white solid (0.19 g, 75%): $[\alpha]_D^{22}=+13.3$ (c=1.9, H_2O) {lit.[1c] $[\alpha]_D^{25}=+13.7$ (c=2, H_2O)}; mp 83–85°C {lit.[1c] mp 87.5–88.8°C}; IR (thin film, cm^{-1}) 3267, 3124, 1567,

1454; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, J=7.5 Hz, 3H), 1.41 (m, 2H), 2.54 (m, 1H), 2.67 (m, 1H), 2.84 (m, 1H), 3.03 (br s, 2H, exchangeable with D_2O), 3.36 (dd, J=7.4, 10.9 Hz, 1H), 3.62 (dd, J=3.4, 10.9 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 10.9, 24.6, 47.0, 60.8, 63.7; MS (FAB+) 205 (MH^+). Anal. calcd for $C_{10}H_{24}N_2O_2$ (204.18): C, 58.79; H, 11.84; N, 13.71. Found: C, 58.35; H, 11.45; N, 13.33.

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