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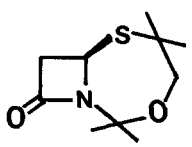
"4,7-LACTAMS", INTERMEDIATES FOR PENEMS SYNTHESIS. II. TOTAL SYNTHESIS OF (+)-2,2-DIMETHYL-9-OXO-3-OXA-6-THIA-1-AZABICYCLO [5.2.0^{1,7}]NONANE

Ferruccio Casabuona, Antonio Longo, Angelo Crugnola, and Paolo Lombardi*
Ricerca & Sviluppo Chimico, Farmitalia Carlo Erba SpA
Via Imbonati, 24 - Milano, Italy

Summary: The total synthesis of chiral "4,7-lactam" 4 has been accomplished starting from 4-acetoxyazetidinone. An independent route from methyl penicillanate has been used to test the efficiency of the foregoing synthesis.

We recently reported[1] the skeletal conversion of penicillanic acid to (+)-2,2,5,5-tetramethyl-9-oxo-3-oxa-6-thia-1-azabicyclo[5.2.0^{1,7}]nonane 1, akin to Ciba-Geigy's "4,7-lactams"[2a] 2[2b] and 3[2a]. We wish to present here the total synthesis of (+)-2,2-dimethyl-(7R)-9-oxo-3-oxa-6-thia-1-azabicyclo[5.2.0^{1,7}]nonane 4, thus completing the series of these useful precursors for the synthesis of 2-penems 5.



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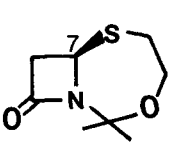
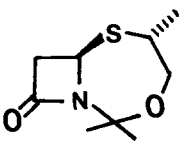


2:(7R,S)
4:(7R)



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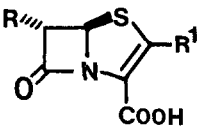

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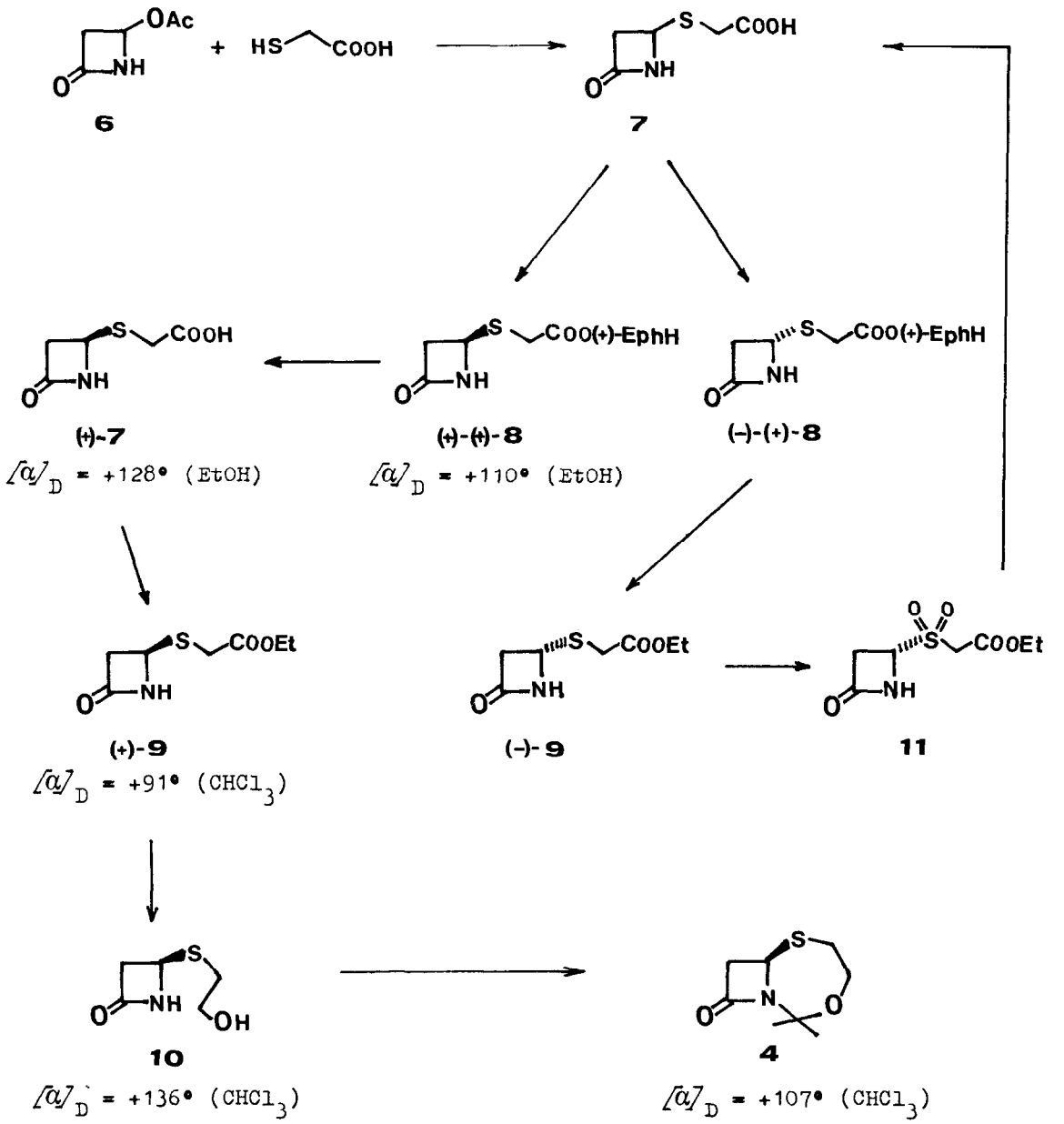
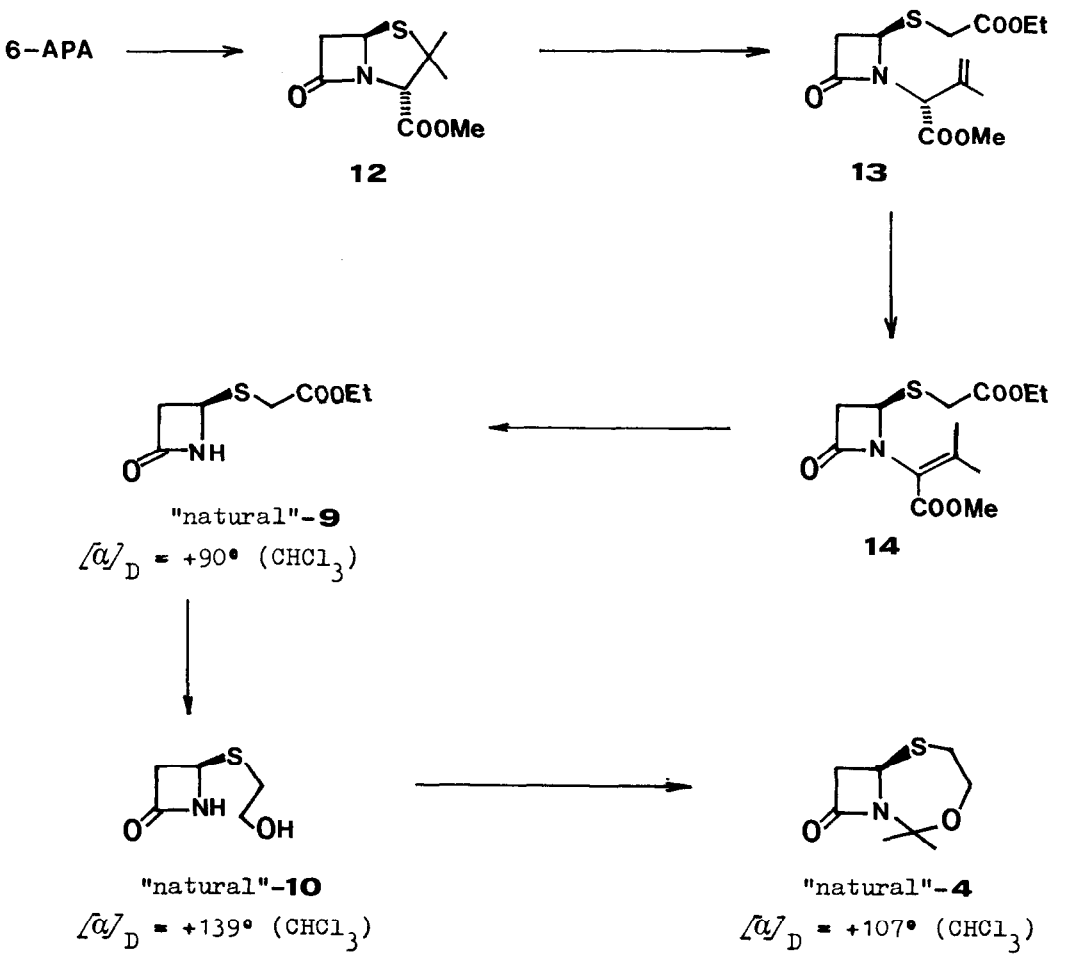
The reaction between 4-acetoxyazetidinone 6[3] and α-mercaptoacetic acid (2 eq. NaOH, EtOH, rt) gave the adduct 7, which crystallised from the reaction mixture upon acidification in the cold (m.p. 130°C dec, ν_{max}: 3450, 3300, 1745, 1710 cm^{-1}, 75%)[4]. Optical resolution was best achieved via the corresponding D-(+)-ephedrine salt, delivering the diastereoisomer (+)-(+)-8 as the less soluble material in absolute EtOH (70% after one crystallisation, m.p. 160-2°C). The free acid (+)-7 (m.p. 87-9°C) was liberated quantitatively by the action of an aqueous

suspension of activated Amberlite IR-120 and its corresponding ethyl ester (+)-9 (ν_{max}: 3350, 1770, 1725 cm^{-1})[4] was obtained in 90% yield by exposure to the same resin in absolute EtOH. Reduction of the ester moiety ($LiAlH_4$, THF, -40°C, 60%) yielded the carbinol 10 (m.p. 47-9°C, ν_{max}: 3330, 1760 cm^{-1})[4] which was cyclised[5] to chiral "4,7-lactam" 4 (m.p. 92-3°C, ν_{max}: 1750 cm^{-1}, 70%)[4].



Evaporation of the mother liquor from the optical resolution afforded impure (-)-(+)-8 which was transformed into its corresponding ester (-)-9, oxidized ($KMnO_4$-AcOH)[6] to sulphone 11 (ν_{max}: 3400, 1790, 1740 cm^{-1}) and recycled to racemic[7] starting material 7 by exposure of 11 to the disalt of α-mercaptoacetic acid. The optical efficiency of the foregoing synthetic route was tested by an independent preparation of bicyclic lactam 4 from natural 6-aminopenicillanic acid. Heating methyl penicillanate 12 and ethyl diazoacetate (C_6H_6, $Cu(acac)_2$, 80°C) yielded 1,2-secopenam 13[4], as in the penicillins series[8]. Isomerisation of the olefinic bond (CH_2Cl_2, Et_3N) to 14[4], followed by alkaline $KMnO_4$ oxidative removal[9] of the nitrogen appendage furnished "natural"-9, from which "natural"-10 and "natural"-4 (m.p. 93-4°C) were obtained.



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4. NMR data (90 MHz, $CDCl_3$, δ). 7: 2.89 (1H, dd, J = 2.5, 16 Hz); 3.38 (2H, s + 1H, m); 4.92 (1H, dd, J = 2.5, 5 Hz); 7.88 (1H, br); 9.66 (1H, br). (+)-9: 1.33 (3H, t, J = 7 Hz); 2.96 (1H, ddd, J = 15.5, 2.5, 1.3 Hz); 3.40 (2H, s); 3.45 (1H, ddd, J = 15.5, 5, 1.7 Hz); 4.93 (1H, dd, J = 2.5, 5 Hz); 7.05 (1H, br). 10: 2.60 (1H, s); 2.70-3.30 (2H, m); 3.25-3.50 (2H, m); 3.7-3.9 (2H, m); 4.81 (1H, dd, J = 2.5, 5 Hz); 7.32 (1H, s). 4: 1.50 (3H, s); 1.73 (3H, s); 2.70 (1H, dd, J = 2, 15 Hz); 2.71 (1H, dt, J = 3, 14 Hz); 3.05 (1H, dt, J = 3, 14 Hz); 3.20 (1H, dd, J = 5, 15 Hz); 4.16 (2H, dd, J = 3, 5.5 Hz); 5.03 (1H, dd, J = 2.0, 5 Hz); 13: 1.29 (3H, t, J = 7 Hz); 1.92 (3H, brs); 3.07 (1H, dd, J = 2.5, 16 Hz); 3.39 (2H, s); 3.49 (1H, dd, J = 5, 16 Hz); 3.80 (3H, s); 4.21 (2H, q, J = 7 Hz); 4.80 (1H, s); 5.02 (1H, brs); 5.15 (1H, brs); 5.91 (1H, dd, J = 2.5, 5 Hz). 14: 1.28 (3H, t, J = 7 Hz); 2.03 (3H, s); 2.27 (3H, s); 3.02 (1H, dd, J = 2.5, 16 Hz); 3.30 (2H, s); 3.44 (1H, dd, J = 5, 16 Hz); 3.81 (3H, s); 4.20 (2H, q, J = 7 Hz); 5.29 (1H, dd, J = 2.5, 5 Hz).

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