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"4,7-LACTAMS", INTERMEDIATES FOR PENEMS SYNTHESIS. I. 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

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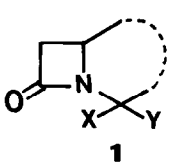
Summary. The synthesis of chiral "4,7-lactam" 5 has been accomplished starting from natural 6-aminopenicillanic acid.

Bicyclic lactams 1 are of demonstrated utility as key intermediates in the synthesis of "non classical" β-lactam antibiotics[1a-e]. Recently, Woodward and the Ciba-Geigy group introduced novel "4,7-lactams"[2] 2,2-dimethyl-9-oxo-3-oxa-6-thia-1-azabicyclo[5,2,0^{1,7}]nonane 2 and (+)-2,2,5-(5R)-trimethyl-(7R)-9-oxo-3-oxa-6-thia-1-azabicyclo[5,2,0^{1,7}]nonane 3 in their synthetic sequence leading to racemic[1e] trans-6-(α-hydroxyethyl)-2-penems 4a and, respectively, as a chiral synthon[2] for (5R)-penems 4b. The usefulness and versatility of these bicyclic precursors lay in their capability to be metallated at the position α to the carbonyl and quenched by different nucleophiles, thus allowing the early introduction of various side chains R at the prospective C-6 of the target product. Moreover, their protected functionalities unconceal smoothly to generate efficient moieties from which work for the building of the second ring can be undertaken.



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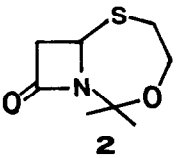

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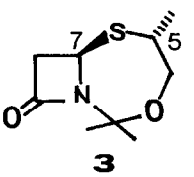

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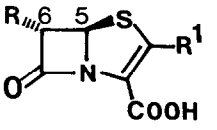
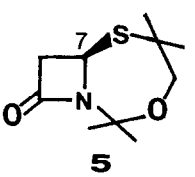


4a: (5R,S),(6R,S), R= 

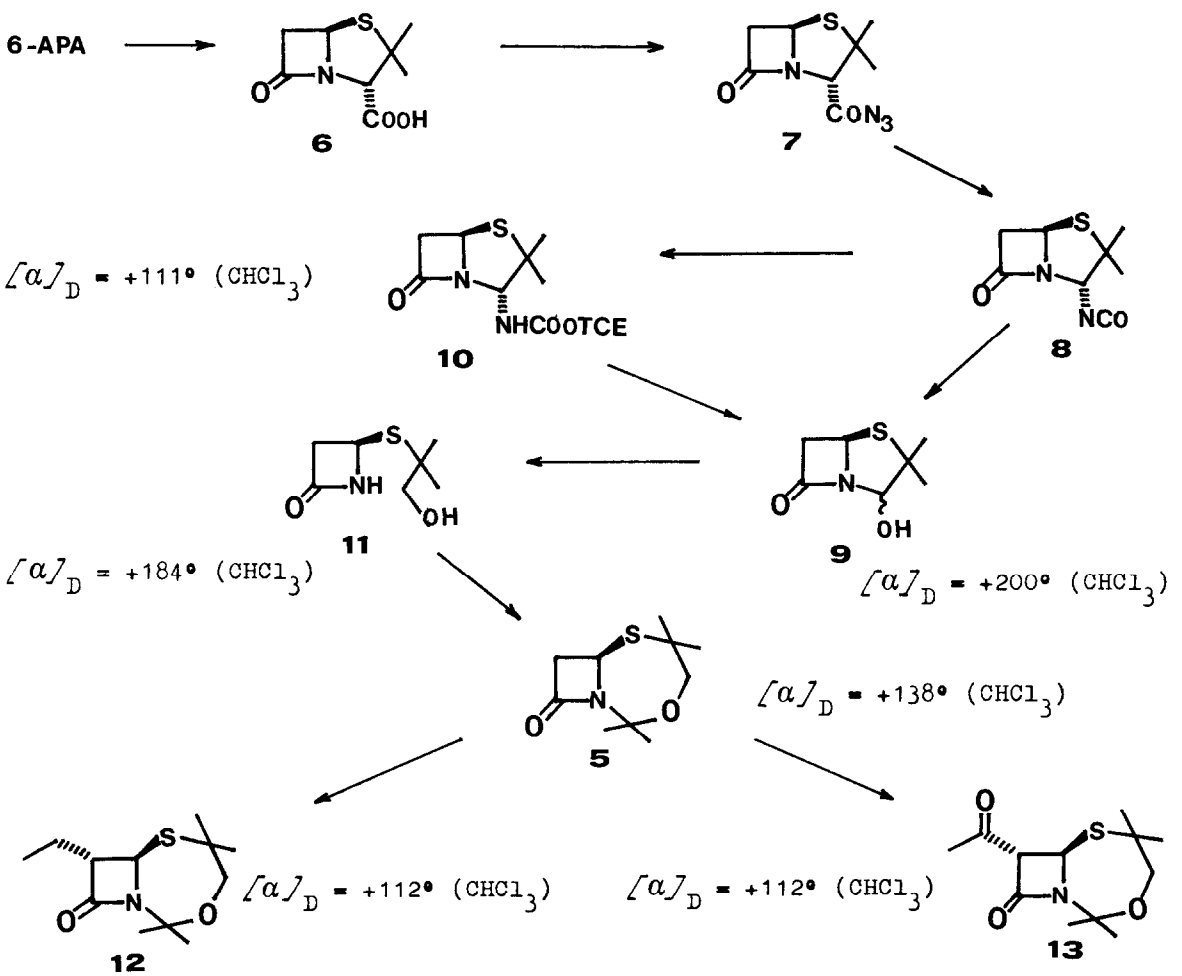
4b: (5R)



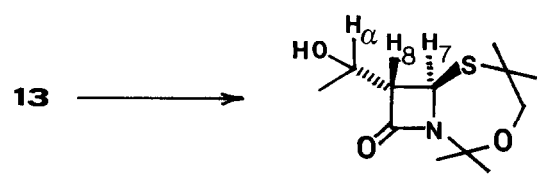
5

In connection with our recent studies[3] for improved syntheses of 2-penems 4b, we needed to prepare chiral "4,7-lactams" in order to test their potentiality as precursors. In the present communication we report the synthesis of novel (+)-2,2,5,5-tetramethyl-(7R)-9-oxo-3-oxa-6-thia-1-azabicyclo[5,2,$0^{1,7}$]nonane 5, starting from natural 6-aminopenicillanic acid, while in the following paper a total synthesis of chiral 2 is presented.

Curtius degradation, successfully employed by Sheehan[4] in the acylamino series, was here adjusted to penicillanic acid 6, which was transformed into the acylazide 7 (ν_{max}: 2150, 1780, 1710 cm^{-1}) by the mixed anhydride-NaN_3 method. Rearrangement of crude 7 afforded the isocyanate 8 (ν_{max}: 2245, 1785 cm^{-1}) which was hydrolised (dioxane, H_3O^+) to the carbinolamide 9 (m.p. 58-60°C, ν_{max}: 3350, 1768 cm^{-1})[5] in 23% yield, based on penicillanic acid. Alternatively, by



applying the Heusler by-pass[6], the isocyanate 8 was converted into the trichloroethyluretane 10 (m.p. 162-4°C, ν_{max}: 1780, 1743 cm^{-1})[5] which gave 9 in 38% yield based on 6, upon Zn-AcOH treatment. $NaBH_4$ reduction[7] of 9 delivered the alcohol 11 (ν_{max}: 3300, 1750 cm^{-1}, 96%)[5] which was cyclised (2,2-dimethoxypropane, $BF_3 . Et_2O$, CH_2Cl_2, 69 %)[1a] to the "4,7-lactam" 5 (m.p. 77-79°C, ν_{max}: 1740 cm^{-1})[5]. α-Metallation of 5 was performed with lithium di-iso-propylamide, according to T. Durst[8]: direct quenching with ethyl bromide furnished the trans derivative 12 (ν_{max}: 1745 cm^{-1}, 80 %)[5], whereas inverse quenching with ethyl acetate gave the important trans acetyl derivative 13 (m.p. 68-72°C, ν_{max}: 1750, 1720 cm^{-1}, 68 %)[5] which lends itself to be reduced to the α-hydroxyethyl side chain. Since recent reports[1e, 9] have indicated that the configuration at carbon bearing the hydroxyl remarkably affects the biological activity of the final penems, while investigating the stereoselective reduction of the keto group in 13, we have found that L- and K-Selectride, upon a judicious choice of solvent polarity, cation and temperature, can lead independently to either the carbinol 14 (m.p. 99-102°C, ν_{max}: 3600, 3460, 1740 cm^{-1}) or its epimer 15 (m.p. 126-130°C, ν_{max}: 3600, 3460, 1740 cm^{-1}). Our results, summarized in the table, are consistent with the picture below: assuming the bulky hydride will attack preferentially from the same side, the anti and, respectively, syn conformer will deliver different epimers.



14: $[\alpha]_D$ = +111° ($CHCl_3$)

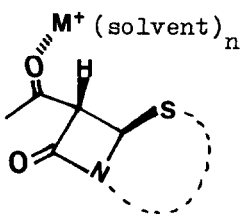
δ_{H_7} 5.02, δ_{H_8} 2.88, δ_{H_α} 4.17

$J_{7,8}$ = 2 Hz, $J_{8,\alpha}$ = 5.25 Hz

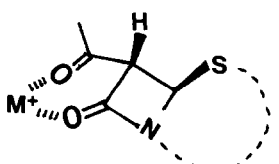
15: $[\alpha]_D$ = +80° ($CHCl_3$)

δ_{H_7} 5.17, δ_{H_8} 2.85, δ_{H_α} 4.22

$J_{7,8}$ = 2.2 Hz, $J_{8,\alpha}$ = 4.0 Hz



anti
highly solvating media
higher polarizing cation



syn
weakly solvating media
weaker polarizing cation

Cation	Conditions	% 14*	% 15*
Li^+	THF, -78°C	95	5
Li^+	THF, 20°C	75	25
Li^+	THF-Et_2O, -78°C	80	20
Li^+	THF-Et_2O, 20°C	40	60
K^+	THF, -78°C	50	50
K^+	THF, 20°C	40	60
K^+	THF-Et_2O, -78°C	20	80
K^+	THF-Et_2O, 20°C	10	90

* Relative percentage determined by NMR.

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5. NMR data (90 MHz, $CDCl_3$, δ): 9: 1.49 (3H, s); 1.53 (3H, s); 3.02 (1H, dd, J = 2, 18 Hz); 3.47 (1H, dd, J = 5, 18 Hz); 4.00 (1H, br); 5.16 (1H, dd, J = 2, 5 Hz); 5.29 (1H, br). 10: 1.51 (3H, s); 1.57 (3H, s); 3.14 (1H, dd, J = 2, 18 Hz); 3.58 (1H, dd, J = 5, 18 Hz); 4.75 (2H, m); 5.12 (1H, dd, J = 2, 5 Hz); 5.45 (1H, brm); 5.64 (1H, J = 9 Hz). 11: 1.26 (3H, s); 1.38 (3H, s); 2.81 (1H, ddd, J = 1.5, 2.5, 18 Hz); 3.42 (1H, ddd, J = 1.5, 5, 18 Hz); 3.56 (2H, s); 3.90 (1H, br); 5.00 (1H, dd, J = 2.5, 5 Hz); 7.58 (1H, br). 5: 1.20 (3H, s); 1.46 (3H, s); 1.55 (3H, s); 1.71 (3H, s); 2.65 (1H, dd, J = 2.5, 15 Hz); 3.18 (1H, dd, J = 5, 15 Hz); 3.60 (1H, d, J = 12 Hz); 4.14 (1H, d, J = 12 Hz); 5.06 (1H, dd, J = 2.5, 5 Hz). 12: 1.04 (3H, t, J = 8 Hz); 1.18 (3H, s); 1.47 (3H, s); 1.55 (3H, s); 1.71 (3H, s + 2H, q, J = 8 Hz); 2.80 (1H, m); 3.60 (1H, d, J = 13 Hz); 4.14 (1H, d, J = 13 Hz); 4.77 (1H, d, J = 2 Hz). 13: 1.22 (3H, s); 1.47 (3H, s); 1.57 (3H, s); 1.71 (3H, s); 2.33 (3H, s); 3.65 (1H, d, J = 13 Hz); 3.91 (1H, d, J = 2.5 Hz); 4.11 (1H, d, J = 13 Hz); 5.70 (1H, d, J = 2.5 Hz).

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