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A FACILE SYNTHESIS OF TRANS (+)-4-CARBOXYMETHYL-3-ETHYLAZETIDIN-2-ONE AND ITS CONVERSION INTO NATURAL PS-5

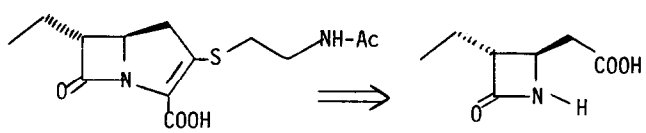
D.Favara *, A.Omodei-Salè, P.Consonni, and A.Depaoli
Gruppo Lepetit Research Laboratories, 20158 Milano, Italy

Summary : A novel simple synthesis of trans-4-carboxymethyl-3-ethylazetidin-2-one 2 is described together with its optical resolution. The (+) acid was converted in five steps into the natural carbapenem antibiotic (+) PS-5.

PS-5 1 is a carbapenem antibiotic active against Gram-positive and Gram-negative bacteria including β-lactamase producing organisms [1]. The low fermentation yields together with the chemical lability of the bicyclic ring system hampered the preparation of analogues and prompted us to look for a facile and efficient total synthesis.

In addition to the preparation of PS-5 from the related olivanic acids [2], two total syntheses of the racemic compound were recently described [3], but none of them seemed suitable to us for molar scale preparation of optically active material. Among the several methods developed for the construction of the carbapenem ring system, the one involving the N-C3 ring closure through a carbene insertion [4] is the most efficient and simple. Therefore we designed as key intermediate the β-lactam acetic acid 2 that fits with the above method and lends itself to optical resolution.

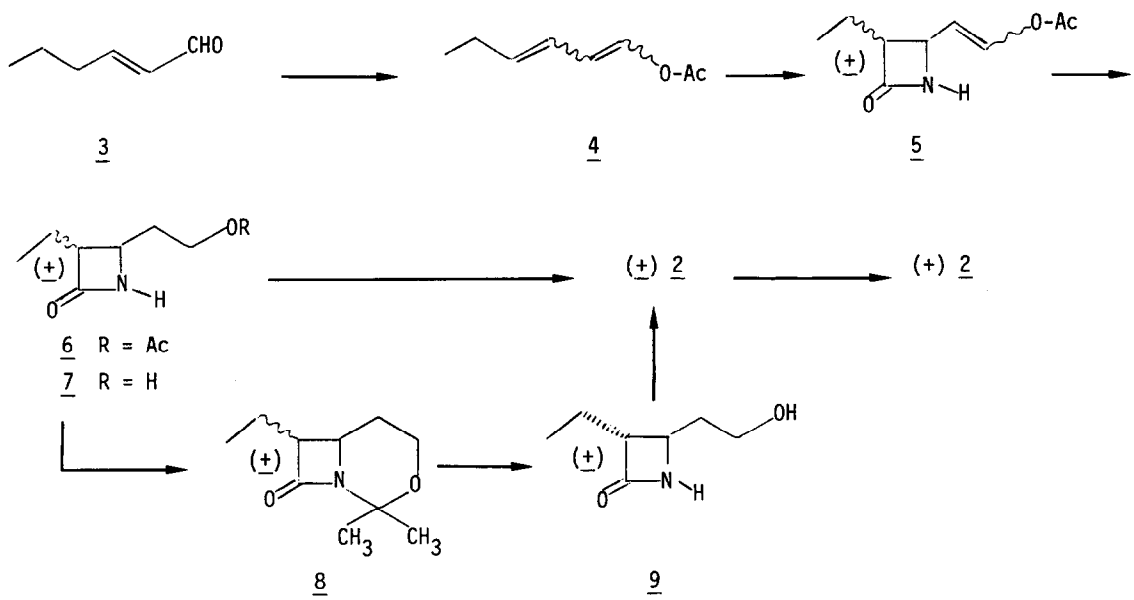
Here we would like to report a facile synthesis of the acid 2, its resolution and conversion into natural (+) PS-5 1.



1 2

Enolacetylation of the commercially available trans-2-hexenal 3 in the presence of a catalytic amount of 4-dimethylaminopyridine [5] (DMAP), led to a mixture of isomeric 1-acetoxy-1,3-hexadienes 4 [6,7] containing about 70% of the desired 3E isomers (Ac_2O, Et_3N, 0.04 eq DMAP, 50°, 85%). When the reaction was performed without the catalyst, or with other

well established methods (e.g. isopropenyl acetate, TsOH, $Cu(OAc)_2$[8]), a 1:1 E/Z ratio was uniformly obtained. The stereospecific [2+2] cycloaddition[9] of excess chlorosulphonyl-isocyanate (CSI) to the conjugated dienes 4 (toluene, -5°, 3 h) followed by reductive hydrolysis[10] (aq Na_2SO_3, pH 7-8, 0°) yielded a four isomers mixture of β-lactams 5 in 50% yield. Each of the four isomers were separated by preparative HPLC (hexane/CH_2Cl_2/i-PrOH 70:25:5, silica gel), but this separation proved to be unnecessary. Catalytic hydrogenation of 5 (10% Pd/C, AcOEt, rt, 100%) followed by deacetylation (K_2CO_3, MeOH, rt, 85%) afforded the alcohol 7 (7:3 trans/cis). Simultaneous blocking[11] of the alcohol and lactam (2,2-dimethoxypropane, toluene, TsOH, rt, 18 h) yielded the bicyclic acetonide 8 that was epimerized in situ with 1N potassium ter-amylate, providing the trans isomer. Removal of the protecting group (10% AcOH, 70°, 3 h) gave the trans alcohol 9 in 65% total yield from 7.

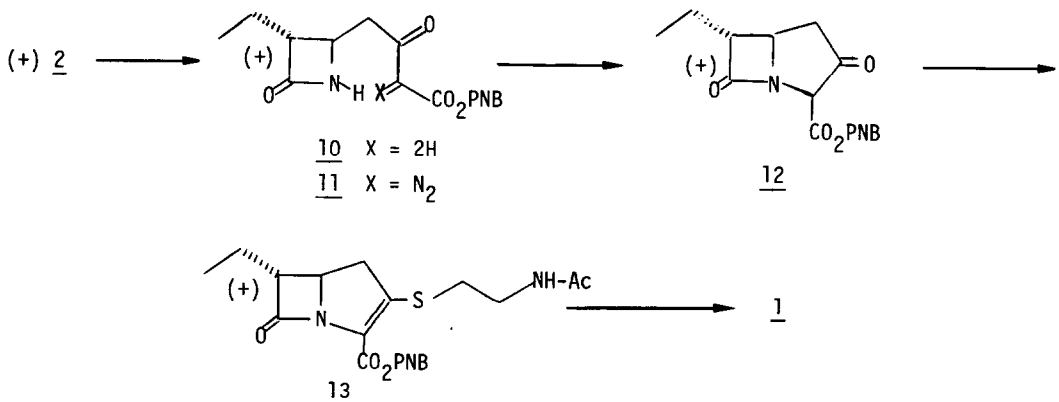


The success of our synthetic pathway was based on an efficient and simple oxidation of the alcohol 9 into the corresponding carboxylic acid 2. Previously, this type of alcohol was oxidized to aldehyde with Collins reagent[4], whereas Kametani has reported the oxidation of a related aldehyde to the corresponding acid with Jones reagent[12]; but, as far as we know, the direct transformation to the acid has not yet been reported. Our initial attempts with oxygen and PtO_2 or Jones reagent gave poor results, therefore the use of $KMnO_4$ in aqueous solution was investigated. We found that, by running the oxidation with the stoichiometric amount of permanganate in the pH range 6.5-8.5 at room temperature overnight, the desired

trans acid was obtained in 60% yield. Moreover, when the cis-trans mixture of β-lactam alcohol 7 was submitted to the same procedure, the pure trans acid 2 was selectively obtained (43%) after crystallization from ethyl acetate, thus avoiding the epimerization procedure. Additional process improvements, including running the cycloaddition in a continuous reactor at room temperature, allowed the preparation of molar amounts of 2.

With this material at hand, we proceeded to its optical resolution. Among the several bases tested, α-ℓ-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol [13], a by-product of the synthesis of propoxyphene, allowed the separation of the desired (+) acid in good yield, after two crystallizations of the salt from acetone [14].

The conversion of the (+) acid 2 into PS-5 was achieved by employing the Merck method [15] as follows : treatment of 2 with N,N'-carbonyldiimidazole (THF, rt, 2 h) followed by the in situ addition of the magnesium salt of mono p-nitrobenzylester of malonic acid (THF, rt, 19 h) provided the keto-ester 10 (70%). The carbene precursor 11 was prepared from 10 in 90% yield by diazo-exchange with p-carboxybenzenesulphonylazide (Et_3N, MeCN, rt). Thermolysis of the diazoketoester 11 in refluxing 1,2-dichloroethane containing a catalytic amount of rhodium acetate, smoothly led to the bicyclic ketoester 12 (91%) that was activated by conversion to the enolphosphate ($ClP(O)(OC_6H_5)_2$, $i\text{-}Pr_2NEt$, MeCN, 0°) and treated in situ with N-acetylcysteamine ($i\text{-}Pr_2NEt$, MeCN, 0°) to provide the protected PS-5 derivative 13 (76.5%). Catalytic hydrogenation of 13 (H_2, 10% Pd/C, THF, 0.075 M phosphate buffer pH 8, rt, 1 atm) followed by chromatography on a XAD-2 column gave (+) PS-5 identical in all respects, including microbiological activity, with a natural sample. The above route is currently being used for the preparation of PS-5 analogues.



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6) Satisfactory IR, MS, and NMR spectra were obtained on each intermediate.

7) Selected data. 4: bp 58°C/0,5 mm; δ($CDCl_3$, 270 MHz) 6.97 (d, J = 6.5, H_1 of 1Z, 3Z, 6%), 7.08 (d, J = 6.5, H_1 of 1Z, 3E, 15%), 3.71 (d, J = 11.5, H_1 of 1E, 3Z, 23%), 7.37 (d, J = 12, H_1 of 1E, 3E, 56%). 5: δ($CDCl_3$), (3,4-trans, E) 1.05 (t, 3, J = 6.5, CH_3), 1.73 (dq, 2, J = 6.5, CH_2CH_3), 2.17 (s, 3, $COCH_3$), 2.93 (dt, 1, J = 2.5, H_3), 3.87 (dd, 1, J = 8, H_4), 5.57 (dd, 1, J = 12, CH=CHO), 6.25 (b, 1, NH), 7.42 (d, 1, CH=CHO); (3,4-trans, Z) 4.33 (dd, 1, J = 2.5 and 8, H_4), 5.12 (dd, 1, J = 7, CH=CHO), 7.23 (d, 1, CH=CHO); (3,4-cis, E) 3.27 (m, 1, H_3), 4.30 (dd, 1, J = 5.5 and 8.5, H_4), 5.54 (dd, 1, J = 12, CH=CHO), 7.38 (d, 1, CH=CHO); (3,4-cis, Z) 4.71 (dd, 1, J = 5.5 and 8.5, H_4), 4.98 (dd, 1, J = 6.5, CH=CHO), 7.24 (d, 1, CH=CHO). 8 (trans): δ($CDCl_3$) 1.00 (t,3,J = 6.5,CH_2CH_3), 1.41 and 1.74 (2 s, 6, gem-diCH_3), 1.75 (m, 4, CH_2CH_3 and CH_2CH_2O), 2.74 (dt, 1, J = 2 and 6.5, H_3), 3.30 (ddd, 1, J = 6 and 9, H_4), 3.83 (dd, 2, J = 3 and 8, CH_2O). 9: δ($CDCl_3$) 1.03 (t, 3, J = 6.5, CH_3), 1.75 (m, 4, CH_2CH_3 and CH_2CH_2O), 2.78 (dt, 1, J = 2 and 6.5, H_3), 3.48 (ddd, 1, J = 5 and 8, H_4), 3.75 (m, 3, CH_2OH), 6.98 (b, 1, NH). 2: mp 104-6°C; (+) 2: mp 113-5°C, $[\alpha]_D^{24}$ = + 16° (c = 1, EtOH). 10: mp 85-6°C, $[\alpha]_D^{24}$ = + 40.7° (c = 1, $CHCl_3$). 11: mp 111-2°C, $[\alpha]_D^{24}$ = + 64.7° (c = 1, $CHCl_3$). 12: mp 79-80°C, $[\alpha]_D^{24}$ = + 224.1° (c = 1, $CHCl_3$). 13: mp 172-4°C, $[\alpha]_D^{24}$ = + 71.5° (c = 1, $CHCl_3$), 1: $[\alpha]_D^{24}$ = + 74.9° (c = 1, H_2O), (lett.[1] $[\alpha]_D^{22}$ = + 77.3°).

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