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AN EFFICIENT AND CONCISE ENTRY TO (-)-4,5-DIHYDROXY-D-threo-L-NORVALINE. FORMAL SYNTHESIS OF CLAVALANINE.

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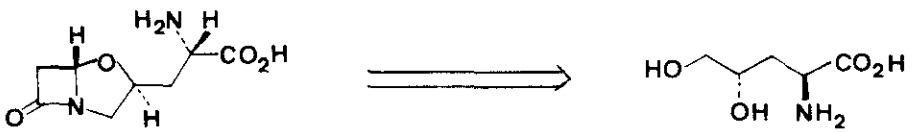
Summary: The title amino acid (2) has been synthesized for the first time in a seven-step sequence from D-ribonolactone, in 20% overall yield. Since the N-carbamoyl derivative of (2) in its γ-lactone form has been used to prepare clavalanine, a formal total synthesis of this antibiotic is derived.

Clavalanine (Ro 22-5417) (1) is a clavam antibiotic isolated from Streptomyces clavuligerus in 1983.[1] In contrast to the previously isolated β-lactams of this microorganism in all of which the carbon atom joining the bicyclic ring systems has the R configuration, the new congener possesses S stereochemistry at the ring juncture.[1c] Presumably as consequence of this stereochemical difference, clavalanine (1) does not exert its antimicrobial activity, like the other β-lactams, via inhibition of bacterial cell wall synthesis; it is also neither a substrate nor an inhibitor of β-lactamases. Moreover, (1) is unique in that it is an antimetabolite of O-succinylhomoserine and intervenes in methionine biosynthesis, whereas most β-lactam antibiotics inhibit peptidoglycan biosynthesis.[1a]

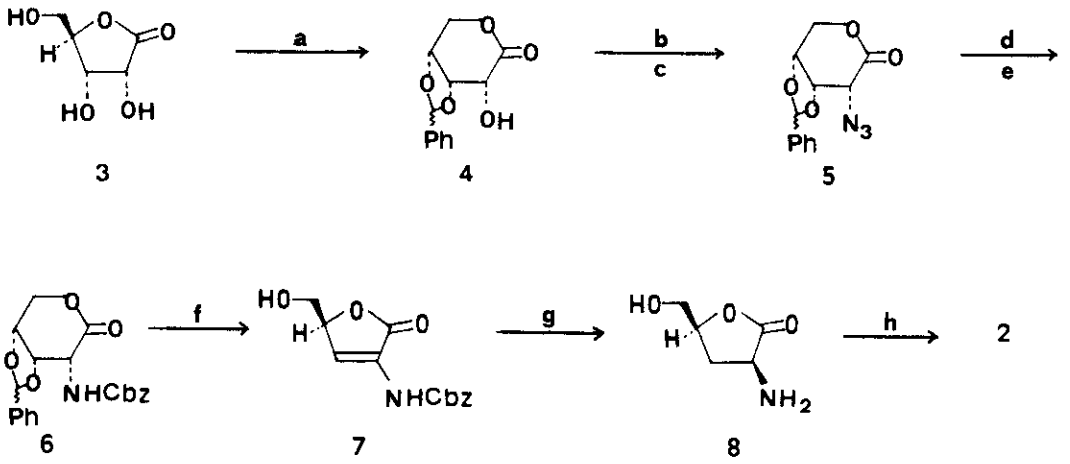
A total synthesis of (1) has been reported by a Hoffmann-La Roche group that involved the multistep preparation of the 4,5-dihydroxy-D-threo-L-norvaline derivative (10), as a key intermediate, from D-xylose.[2] Later, Williams et al.[3] have prepared (10) using an electrophilic glycine template obtained through resolution of a racemic suitable precursor.



1
clavalanine

2

We report herein the first enantioselective synthesis of the free amino acid (2), that has been also characterized in this work as the hydrochloride salt (9) and the N-carbamoyl derivative (10), using available D-ribonolactone as a chiral precursor in a short synthetic sequence. (Scheme 1).



Reagents. (a): PhCHO, HCl. (b): $(CF_3SO_2)_2O$, pyr, 0 °C. (c): NaN_3, DMF, r.t. (d): H_2, 10% Pd/C, EtAcO. (e) $PhCH_2OCOCl$, $NaHCO_3$ 0 °C, 3:1 H_2O-THF. (f): NaH, THF, -20 °C; 1N HCl. (g): H_2, Ra-Ni, 2 atm, EtOH. (h): Dowex 50W-X2 (H^+).

Scheme 1

D-Ribonolactone (3) was easily converted into the known azido derivative (5) through the three-step sequence described by Fleet et al.[4] Thus, (3) reacted with benzaldehyde in concentrated hydrochloric acid to give the 3,4-O-benzylidene derivative (4).[5] Reaction of the alcohol (4) with trifluoromethane sulfonic anhydride in pyridine gave the corresponding triflate; subsequent treatment with sodium azide formed the azido lactone (5) (57% yield from (3)), with overall retention of configuration at C-2.[4]

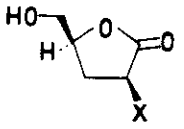
Hydrogenation of the azido group (10% palladium on charcoal) and reaction of the resultant amine with benzyloxycarbonyl chloride (benzyl chloroformate, CbzCl) and excess $NaHCO_3$ in 3:1 H_2O-THF, at 0 °C, gave the new carbamate (6), m.p. 129-131 °C, $[\alpha]_D$ -206° (c 3.8 in chloroform) (84% yield).[6] Butenolide (7), m.p. 141-143 °C, $[\alpha]_D$ -3.8° (c 2.66 in acetone), was obtained from (6) in 65% yield via a base (NaH) induced elimination of

benzaldehyde, followed by ring rearrangement to give the 1,4-lactone (7). This size ring contraction probably takes place during the acid hydrolysis of the reaction mixture.[7] The elimination reaction performed directly on the azide (5) was not satisfactory enough, obtaining the expected butenolide (11) in only 15% yield. This fact has been attributed to the lability of these azides in the reaction and work-up conditions.

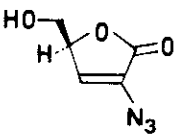
Hydrogenation of the C-C double bond in (7) (Ra-Ni, 2 atm. pressure) afforded diastereospecifically the amino lactone (8), immediate precursor of (2), as a single isomer (^{13}C NMR). This strategy to induce chirality at C-2 in D-ribonolactone derivatives, from C-4 as stereogenic center, has been previously used in our laboratory in the stereocontrolled syntheses of both (-)-erythro- and (-)-threo - γ - hydroxynorvalines.[8] Stereospecific hydrogenation of butenolides prior or later to the introduction of a nitrogen group provides an easy and useful method to control the relative and absolute configuration of homochiral 2,4-disubstituted amino 1,4-lactones.

Compound (8) was treated with Dowex 50W-X2 (H^+) resin to give the amino acid (2), m.p. 205-210 °C, $[\alpha]_D$ -19.5° (c 1.7 in water), in 20% overall yield from (3).

The derivatives (9) and (10) were also easily prepared from the amino lactone (8). Thus, treatment of (8) with hydrogen chloride gave the hydrochloride (9), m.p. 195-200 °C (dec.), $[\alpha]_D$ +18.0° (c 1.6 in water). On the other hand, reaction of (8) with CbzCl in the standard conditions described above yielded the carbamate (10), used as precursor of clavalanine,[2] whose physic constants compare well with those previously described for this compound: m.p. 114-115 °C, $[\alpha]_D$ +3.6° (c 1.6 in methanol) (Lit.[2] m.p. 112-115 °C, $[\alpha]_D$ +3.3 ° (c 1.1 in methanol)).



9 NH_2.HCl
10 NHCbz



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As conclusion, an efficient and concise method for the preparation of (-)-4,5-dihydroxy-D-threo-L-norvaline (2) and its derivatives (9) and (10) has been achieved, starting from D-ribonolactone. With these products in

our hand, a formal total synthesis of the antibiotic clavalanine (**1**) has been accomplished.

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6. All new compounds in this paper, (**2**), (**6**), (**7**), (**8**), (**9**), have satisfactory analytical data and spectra (IR, ^{1}H and ^{13}C NMR) consistent with the structures reported.
7. Details on this elimination-rearrangement process, its scope and limitations will be reported elsewhere.
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