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PALLADIUM-CATALYZED TRANSFORMATION OF A CHIRAL VINYLAZIRIDINE TO A β-LACTAM. AN ENANTIOSELECTIVE ROUTE TO THE CARBAPENEM (+)-PS-5

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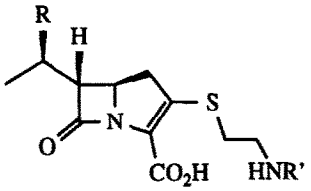
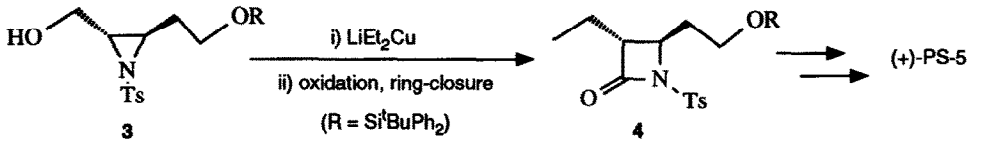
Abstract. The regio- and stereoselective carbonylation of optically pure *trans* vinylaziridine **5** to *trans* 3-vinylazetidinone **6** is catalyzed by Pd(0). Compound **6** is then transformed to a known key intermediate for the total synthesis of the carbapenem antibiotic (+)-PS-5.

The discovery of the carbapenems[1] was a major event in the field of β-lactam antibiotics and, of the members of this important family of compounds, the two which have attracted most interest from the synthetic point of view[2] are (+)-thienamycin (**1**) and (+)-PS-5 (**2**).



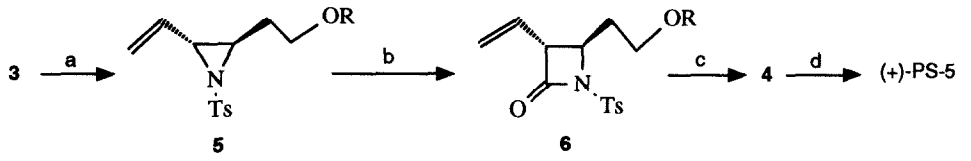
1 (+)-thienamycin, R = OH, R' = H
2 (+)-PS-5, R = H, R' = Ac

For the past few years, we have been developing an enantioselective approach to the carbapenems which relies on the use of optically pure 2,3-aziridino alcohols[3] as precursors of the monocyclic azetidinones required to build up the fused bicyclic system of the target antibiotics. The essentials of our approach, as applied[3d] to (+)-PS-5, are shown in Scheme 1.



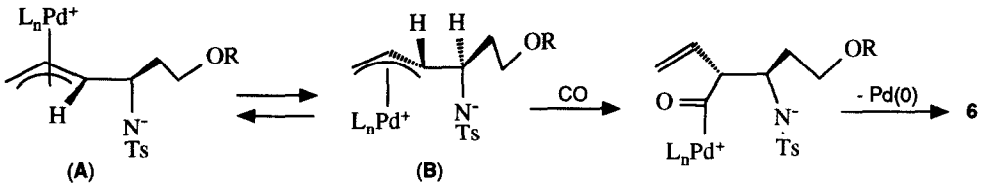
Scheme 1. Previous aziridine-based route to (+)-PS-5

In continuing to explore the synthesis of chiral β-lactams, we became attracted to an even more direct route which would involve the regioselective, transition-metal mediated, carbonylation[4] of a suitably substituted aziridine. The results of our initial efforts (again directed toward (+)-PS-5) are summarized in Scheme 2 and, to the best of our knowledge, provide the first example of the use of an optically pure vinyl aziridine in such a reaction.



Scheme 2. (a) TPAP, NMO, CH_2Cl_2, 90%, then CH_2=PPh_3, THF, -20°C, 86% (b) cat. $Pd_2(dba)_3.CHCl_3$, PPh_3, CO, benzene, 46% (c) H_2, Pd/C, EtOAc, 88% (d) see ref. 3d.

Mild oxidation of **3** (R = Si^tBuPh_2, see ref. 3d) to the corresponding aldehyde, by the method of Griffith and Ley[5], was followed by Wittig olefination using KHMDS as base. The resultant *trans* vinylaziridine **5** was then subjected to a carbonylation reaction catalyzed by the tris(dibenzylideneacetone)dipalladium(0)-chloroform complex (15 mol%) in the presence of excess triphenylphosphine (benzene, 50°C) to yield the desired *trans* 3-vinylazetidinone **6** (^{1}H NMR: $J_{3,4}$ = 2 Hz) in moderate yield. None of the corresponding *cis* isomer was observed (*cf.* ref. 4e) and this result can be explained on the basis of the mechanism depicted below.



The π-allyl complex (**A**) is assumed to be formed initially by attack, with inversion[6], of Pd(0) on the vinylaziridine. Isomerization[7] can then occur to (**B**) which may be stabilized by internal coordination between nitrogen and palladium. Insertion of carbon monoxide, with retention[8], is followed by ring-closure and regeneration of the catalytic species, the entire sequence thus being regio- and stereoselective. Finally, catalytic hydrogenation of **6** yielded **4**, identical with that prepared previously[3d].

Experimental

Vinylaziridine **5**. A solution of aziridino alcohol **3** (0.250 g, 0.49 mmol) in dry CH_2Cl_2 (1 mL) was added to a slurry of powdered activated 4 Å molecular sieves (0.250 g) in dry CH_2Cl_2 (2 mL) under nitrogen. To the stirred mixture was added *N*-methylmorpholine-*N*-oxide (0.088 g, 0.75 mmol) followed by tetra-*n*-propylammonium peruthenate (TPAP) (0.009 g, 0.75 mmol). The resultant mixture was stirred for 15 min at room temperature (reaction complete according to TLC) then filtered through a pad of silica gel, eluting with fresh CH_2Cl_2. The solvent was removed to give the aziridino aldehyde (IR: 1720 cm^{-1}) as a clear oil (0.223 g, 90%). This material was homogeneous according to TLC and was used directly in the next step.

Methyltriphenylphosphonium bromide (0.386 g, 1.08 mmol) was stirred under nitrogen in dry THF (10 mL) and cooled to -20°C. A solution of potassium bis(trimethylsilyl)amide (0.5M in toluene, 2.14 mL, 1.07 mmol) was added dropwise and the resultant orange-yellow mixture was stirred for 20 min before addition of a solution of the aziridino aldehyde from above (0.220 g, 0.43 mmol) in THF (1 mL). After 20 min at -20°C, TLC analysis indicated complete consumption of the aldehyde. The mixture was

partitioned between water and ether, the ethereal layer was dried over $MgSO_4$, and the solvents were removed to yield a residue which was purified by flash chromatography over silica gel (5% to 20% gradient of ether/pentane). There was obtained 0.187 g (86%) of the vinylaziridine as a colorless oil. $[\alpha]_D$ 36.2° (*c* 1.22, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$/TMS): δ 7.80 and 7.24 (4H, *AA'BB'*, J_{AB} = 8Hz); 7.61 (4H, m); 7.39 (6H, m); 6.05 (1H, ddd, J = 17, 11, 9); 5.47 (1H, d with fine splitting, J_{trans} = 17); 5.35 (1H, d with fine splitting, J_{cis} = 11); 3.59 (2H, app. t, J = 6.5); 3.18 (1H, dd, J = 9, 3.8) overlapping 3.15 (1H, m); 2.38 (3H, s); 1.84 (2H, m); 1.00 (9H, s).

β-*Lactam* **6**. Tris(dibenzylideneacetone)dipalladium(0)-chloroform complex ($Pd_2(dba)_3.CHCl_3$, 0.030 g, 0.029 mmol) was dissolved with stirring in dry benzene (8 mL) and stirred under argon during the addition of triphenylphosphine (0.063 g, 0.24 mmol). This caused the original purple solution to turn yellow. The resultant mixture was stirred for 1 h, the argon source was replaced by a thick-walled balloon filled with carbon monoxide, and a solution of vinylaziridine **5** (0.100 g, 0.19 mmol) in dry benzene (2 mL) was added dropwise. The resultant mixture was heated to 50°C, kept at that temperature for 48 h, cooled, and concentrated to give a residue which was purified by flash chromatography (silica gel, 30% ether/pentane). There was obtained 0.046 g (46%) of the β-lactam as a colorless oil. $[\alpha]_D$ -12.4° (*c* 0.90, CH_2Cl_2). ^1H NMR: 7.83 and 7.32 (4H, *AA'BB'*, J_{AB}= 8); 7.62 (4H, m); 7.41 (6H, m); 5.91 (1H, ddd, J = 17, 11, 7); 5.36 (1H, d with fine splitting, J_{trans} = 17); 5.28 (1H, d with fine splitting, J_{cis} = 11); 3.88 (1H, m, $J_{3,4}$ = 2); 3.75 (3H, m); 2.44 (3H, s); 2.37 (1H, m); 1.79 (1H, m); 1.05 (9H, s). IR: 1790 cm^{-1}.

β-*Lactam* **4**. Compound **6** (0.030 g, 0.056 mmol) was dissolved with stirring in ethyl acetate (2 mL), Pd/C (Aldrich, 5 mg) was added, and the flask was alternately evacuated and filled with argon. After five cycles, the flask was placed under balloon pressure of hydrogen and the reaction mixture was stirred overnight at room temperature. The flask was evacuated, flushed with argon, and the spent catalyst was removed by filtration through a pad of celite. The filter-cake was washed with fresh ethyl acetate (2 mL) and the combined filtrate and washings were stripped down to yield a residue which was purified by flash chromatography (silica gel, 25% ether/pentane). There was obtained 0.0265 g (88%) of **4**, identical with material prepared previously by a different route[3d].

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