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AN AZIRIDINE ROUTE TO CHIRAL β-LACTAMS
A NOVEL ENTRY TO (+)-THIENAMYCIN

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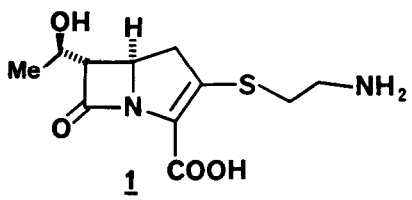
Abstract. Enantiomerically pure 2,3- epoxy alcohols are transformed readily and stereospecifically to the corresponding aziridines, regioselective ring-opening of which allows subsequent conversion to chiral β-lactams suitable for elaboration to the title antibiotic.

Thienamycin, 1, is an unusually potent antibiotic isolated[1] from Streptomyces cattleya. During the decade since its discovery this important carbapenem has stimulated the imagination of many organic chemists[2], partly due to the fact that large quantities of the antibiotic are not available from natural sources. We now wish to report a novel entry to the natural form of Thienamycin, our approach being based on chiral 2,3-aziridino alcohols such as 3 (see Schemes 1 and 2).



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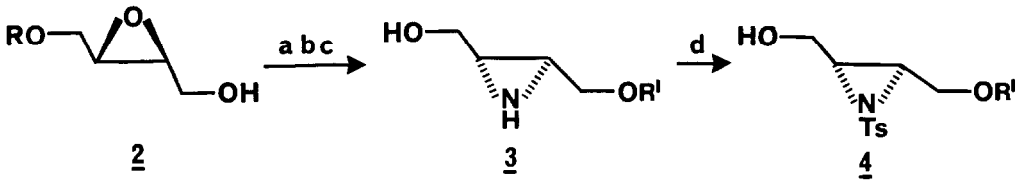
The known[3] chiral epoxide 2 (>98% e.e. by the Sharpless asymmetric epoxidation technique) was transformed on a multi-gram scale and in excellent overall yield to the key "inverted" aziridino alcohol 3 by a straightforward series of operations[4,5]. The amino function was then selectively protected as the p-toluenesulfonamide 4 ($[\alpha]_D$ +23°, CH_2Cl_2) and this material rapidly underwent clean ring-opening by Red-Al in THF to yield the 1,3-sulfonamido-alcohol 5 exclusively. After RuO_4 oxidation of the alcohol[6] and removal of the sulfonamide moiety by sodium naphthalide in DME[7] the resultant β-amino acid 6 was cyclised by the

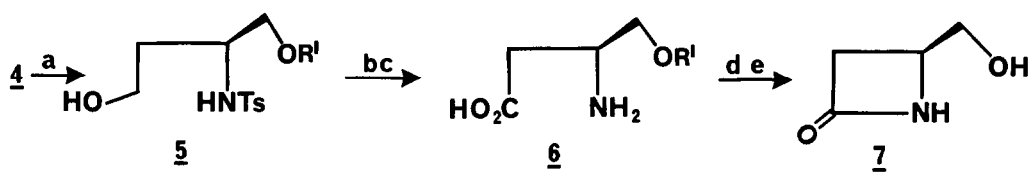
method of Ohno[8]. Desilylation then furnished the azetidinone 7 which is an early key intermediate in the Merck synthesis[9] of (+)-Thienamycin.



2 3 4

R = Bn, R' = Si^tBuMe_2

Scheme 1. (a) NaN_3,$MeO(CH_2)_2OH/H_2O$, 98% yield, then TBDMSCl,DMAP,NEt_3, CH_2Cl_2, 90% (b) $P(Ph)_3$,toluene,reflux, 86% (c) $Na/NH_3(l)$ 100% (d) TsCl,NEt_3,CH_2Cl_2, 88%.

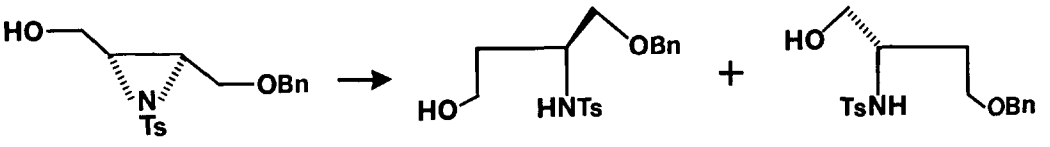


5 6 7

Scheme 2. (a) Red-Al, -78°C,THF, 92% (b) $RuCl_3/NaIO_4$,$CCl_4/H_2O/CH_3CN$, 90% (c) $C_{10}H_8/Na$, -60°C to RT (d)$PPh_3/(PyS)_2$, CH_3CN, 45%(two steps) (e) Bu_4NF,THF, HOAc, 92%.

The excellent regioselectivity (>100:1 according to 270 MHz ^1H NMR) observed in the ring-opening of aziridino alcohol 4 is in accord with the large body of results obtained for analogous epoxides by the Sharpless-Masamune constellation[10] and by Kishi[11]. With many epoxy alcohols, Red-Al consistently gave 1,3-diols (near) exclusively while ring-opening with DIBAL yielded, much less selectively[11], the regio-isomeric 1,2-diols. Lithium aluminium hydride was found to be either devoid of selectivity[11] or to favour slightly the 1,3 mode[10].

For the present study, the chiral aziridine 8 was prepared from 2 and subjected to the above-mentioned hydride reagents, the results being collected in the Table below. As shown, the same excellent regio-selectivity was observed in the ring-opening of 8 by both Red-Al and, perhaps surprisingly, LAH. The reactions with DIBAL usually gave much poorer chemical yields and were also markedly solvent-dependent (see Table).



8 9 10

Reagent and Reaction Conditions	% isolated yield	Product ratio[a] 9 : 10
Red-Al, THF, -78°C	86	>100 : 1
LAH, THF, -20°C	80	>100 : 1
DIBAL, THF, -78°C to RT	30[a,b]	>100 : 1
DIBAL, C_6H_6, 0°C to RT	20[b]	1 : 1
$NaBH_4/Ti(O^iPr)_4$, C_6H_6, RT[12]	No reaction	

Table. Reductive ring-opening of the aziridino alcohol 8
a) measured by 270 MHz ^{1}H NMR
b) reaction incomplete

Very recently[12], a combination of borohydride and titanium alkoxide was reported to be very effective for conversion of 2,3-epoxy alcohols to 1,2-diols, but this reagent was totally ineffective towards the aziridino alcohol 8, for which a "1,2-selective" reagent remains to be found.

Due to the obvious analogies with the well-explored chemistry of the corresponding epoxides, a more detailed and systematic study of the nucleophilic ring-opening of chiral 2,3-aziridino alcohols (e.g. use of cuprates and other organometallics) is now being undertaken in these laboratories. Substrates such as 2,3-aziridino acids (cf. Ref. 13) are also under consideration.

In conclusion, it has been demonstrated that chiral 2,3-aziridino alcohols provide a simple route to the important β-lactam ring system, this route being, potentially, a very flexible one. It is our belief that these aziridines hold much promise for the enantioselective synthesis of chiral ligands and a variety of natural products including, for example, congeners of 1 and also alkaloids. Results will be reported in due course.

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