PRELIMINARY COMMUNICATION

A New Stereocontrolled Approach to a Key Intermediate in the Synthesis of (2*S*,3*R*)-Capreomycidine

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A new synthetic approach to the key intermediate in the stereoselective synthesis of (2*S*,3*R*)-capreomycidine was developed. The synthesis is based on novel domino reaction combining (3,3)-sigmatropic rearrangement of chiral allylic thiocyanate derived from D-methionine and intramolecular amino addition to arising isothiocyanate to produce diastereomerically (4*R*,5*R*)-4-vinyltetrahydro-1*H*-imidazole-2-thione derivative.

Capreomycidine *I* is an unusual cyclic guanidine amino acid that is a component of the peptide antibiotics of the capreomycin and tuberactinomycin family [1, 2]. These groups of the cyclic peptides were shown to be the antituberculous agents [3, 4].

Several syntheses towards the capreomycidine and *epi*-capreomycidine in racemic and also optically pure form have been published [5—9]. The improved asymmetric synthesis of L-capreomycidine has been reported by *De Mong* and *Williams* [10] *via* a Mannich-type reaction between a chiral glycine aluminium enolate and the benzylimine derivative of 3-(*tert*-butyldimethylsilyloxy)propionaldehyde. Recently, the same authors [11] presented asymmetric synthesis of *I* and the total synthesis of capreomycin IB. By changing the imine nitrogen substituent in the key step of the synthesis of *I*, diastereoselectivity of the Mannich-type reaction was significantly improved. For the biosynthetic studies ^{13}C-labeled synthesis of *I* by *Zabriskie* and co-workers was completed [12].

Synthetic strategy is based on the novel domino reaction [13, 14] of the (3,3)-sigmatropic rearrangement of the chiral thiocyanates followed by stereoselective heterocyclization. The further step of this synthetic approach was to study whether the novel domino reaction is more general and can also be utilized for the stereocontrolled synthesis of the suitable synthon for the preparation of *I*.

As the starting material we have chosen D-methionine which was converted into (*R*)-α-ammonio-γ-butyrolactone chloride *II* [15]. Furthermore, from the lactone *II* suitable protected alcohol *III* was prepared by a series of functional group manipulations: *a*) *tert*-butoxycarbonylation with Boc_2O/Et_3N in CH_2Cl_2 (93 %), *b*) ring opening using $NaBH_4$ in THF (93 %), *c*) formation of the oxazolidine ring with DMP/acetone—$BF_3 \cdot OEt_2$ (86 %), *d*) *O*-benzylation of the resulting alcohol with BnBr/NaH in THF (87 %), *e*) hydrolysis of the acetonide moiety with Amberlyst 120H resin in MeOH : H_2O = 9 : 1 volume ratio (87 %) (Scheme 1).

In the subsequent three steps: *a*) oxidation with IBX in DMSO [16], *b*) Wittig olefination with $Ph_3PCHCOOMe$ in CH_2Cl_2 (80 %), *c*) DIBAH reduction in CH_2Cl_2 (77 %), the isolated allylic alcohol *IV* was converted into the chiral thiocyanate *V* by S_N2 displacement of *O*-mesyl group in the corresponding mesylate, derived from alcohol *IV* ($MsCl/Et_3N/CH_2Cl_2$) by thiocyanate group ($KSCN/CH_3CN$, 79 %). The thermal rearrangement of thiocyanate *V* was carried out at 80 °C in xylene under N_2 in the presence of catalytic amount of 2-hydroxypyridine for 5 h with high yield of (4*R*,5*R*)-4-vinyltetrahydro-1*H*-imidazole-2-thione *VII* [11], a single product in 78 % yield after silica gel chromatography. The observed stereochemistry of the cyclic thiourea *V* is in agreement with the previous works [15]. The single *trans* product *VII* is formed by intramolecular amino addition to isothiocyanate *syn*-*VIa* where the steric interactions between CH_2CH_2OBn moiety and vinyl group are significantly

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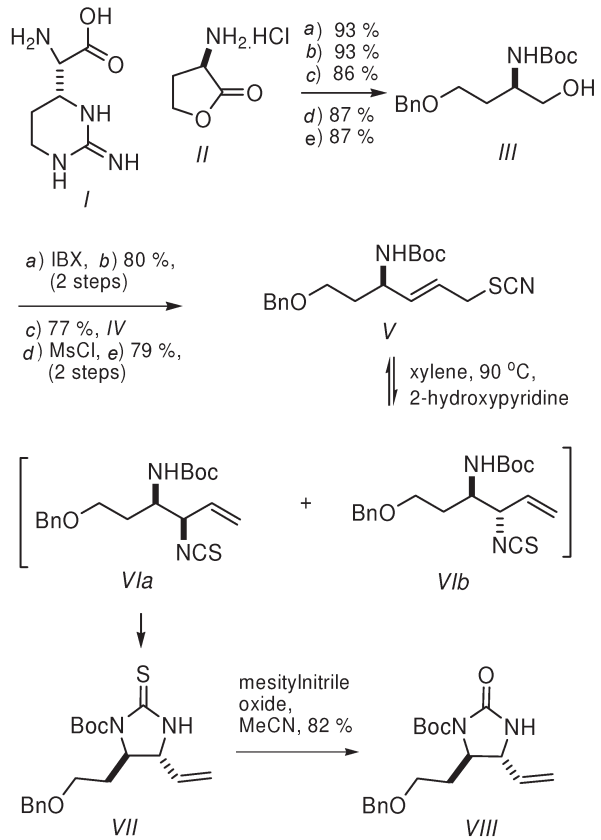

Scheme 1

reduced. The reversible rearrangement thiocyanate ↔ isothiocyanate is the reason for the complete conversion of isothiocyanate *anti-VIb* to *syn-VIa via* the corresponding thiocyanate *V*. The reaction of *VII* with mesitylnitrile oxide in CH_3CN (82 %) led to (4*R*,5*R*)-4-vinyltetrahydro-1*H*-imidazole-2-one derivative *VIII* as the key intermediate in the stereoselective synthesis of (2*S*,3*R*)-capreomycidine *I*.

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