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Stereoselective Amination of Chiral Enolates: Synthesis of Chiral Key Intermediates for β-Lactam Antibiotics.

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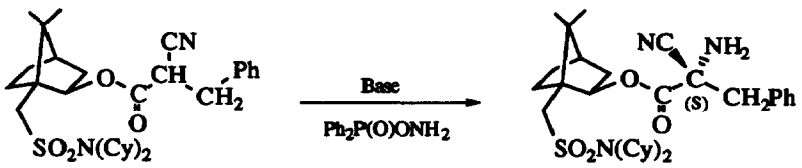
Abstract: Stereoselective enolate trapping of lithium *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl-2-cyano-3-phenylpropanoate with O-(diphenylphosphinyl) hydroxylamine followed by appropriate reduction, hydrolysis, and cyclisation processes allows the asymmetric synthesis of *(S)*-3-amino-3-benzyl-2-azetidinone.

The discovery of the antibiotic activity of penicillins and cephalosporins constituted a breakthrough in the treatment of bacterial infections. The systematic chemical modification of natural lead structures has set an important precedent and has provided a large number of clinically valuable β-lactam antibiotics,[1] which have facilitated the development of modern medicine. In the course of our synthetic studies on the synthesis of new enantiomerically pure β-lactams we have established a new and efficient asymmetric synthesis of 3,3-dialkyl-2-azetidinones based on the diastereoselective alkylation of chiral enolates with activated alkyl halides.[2]

Many β-lactam antibiotics which have a significant potency in terms of antibacterial activity[3] possess a 3-amino-2-azetidinone functionality characteristic. As an alternative to the existing synthetic approaches to 3-amino-2-azetidinones[4] we propose that the introduction of the required amino group at the C(3) position of the β-lactam ring can be carried out in a stereoselective manner by electrophilic amination[5] of chiral enolates derived from 2-cyanoesters. After functionalisation at C(2) reduction of the cyano group and subsequent cyclisation of the β-aminoacid would afford a key intermediate for the desired β-lactam antibiotics.

We have therefore investigated the electrophilic amination of the enolate generated from a chiral 2-cyanopropanoate with different amination reagents. In order to choose the most appropriate electrophilic amination reagent we tested the reaction of the enolate derived from **1** upon treatment with lithium diisopropylamide for 1 hour in THF at low temperature with mesitylsulfonylazide, diethylazadicarboxylate and O-(diphenylphosphinyl) hydroxylamine and the following features were observed: 1) with mesitylsulfonylazide we only detected decomposition of the starting material, 2) with diethylazadicarboxylate we obtained the desired *(1S,2R,4R)*-10-(dicyclohexylsulfamoyl)isobornyl 2-(N,N'-diethoxycarbonylhydrazino)-3-phenyl-2-cyanopropanoate in excellent yield (95%) but with very low diastereoselectivity (d.r = 57/43) and 3) O-(diphenylphosphinyl) hydroxylamine was the best amination reagent and we obtained the desired 2-amino-2-cyanopropanoate **2** directly in very good yield (92%) and with moderate diastereoselectivity (d.r. = 74/26).



1 (*S*)-2

Scheme 1

We then proceeded to investigate the influence of the base and additives on the formation of compound **2**. Lithium, sodium, potassium, boron and magnesium enolates were generated from **1** with lithium diisopropylamide or lithium hexamethyldisilazane, potassium hexamethyldisilazane, sodium hexamethyldisilazane, di(*n*-butyl) boryl trifluoromethanesulfonate and methylmagnesium bromide respectively and the enolates were quenched, sometimes in the presence of hexamethylphosphoramide, with O-(diphenylphosphinyl) hydroxylamine as the amination reagent (Scheme 1). Selected results of these reactions are summarised in Table 1.

Table 1. Diastereoselective Amination of **1** with O-(Diphenylphosphinyl)hydroxylamine

Base	HMPA	yield[%]	dr[a]	Configuration
LDA[b]	No	91	72/28	*S*
LDA[c]	No	92	74/26	*S*
LDA[b]	Yes	92	72/28	*S*
LiHMDS[c]	No	91	80/20	*S*
NaHMDS[c]	No	88	74/26	*S*
KHDMS[c]	No	81	78/22	*S*
(*n*-Bu)2BOTf/Et3N[c]	No	-		
MeMgBr[c]	No	-		

[a] Determined from the crude reaction spectra by integration of the ^{1}H NMR (300 MHz) absorptions of the methine protons of the diastereomeric esters. [b] Compound **1** dissolved in THF was added to a solution of freshly prepared base. [c] The appropriate amount of base was added to a solution of compound **1** in THF.

After the reaction the major diastereoisomer of compound **2** was easily isolated in diastereomerically pure form by flash chromatography (SiO_2; Et_2O/hexane = 1/3). The relative stereochemistry, determined by single crystal X-ray analysis,[6] showed *S* configuration at C(2) (Figure 1). This stereochemical configuration is consistent with the formation of a chelated *(Z)*-enolate and attack by the electrophile from the C_{α}-re face opposite to the 10-dicyclohexylsulfamoyl group. This parallels the results obtained in the enolate-trapping of enolates derived from **1** with activated halides.[2c]

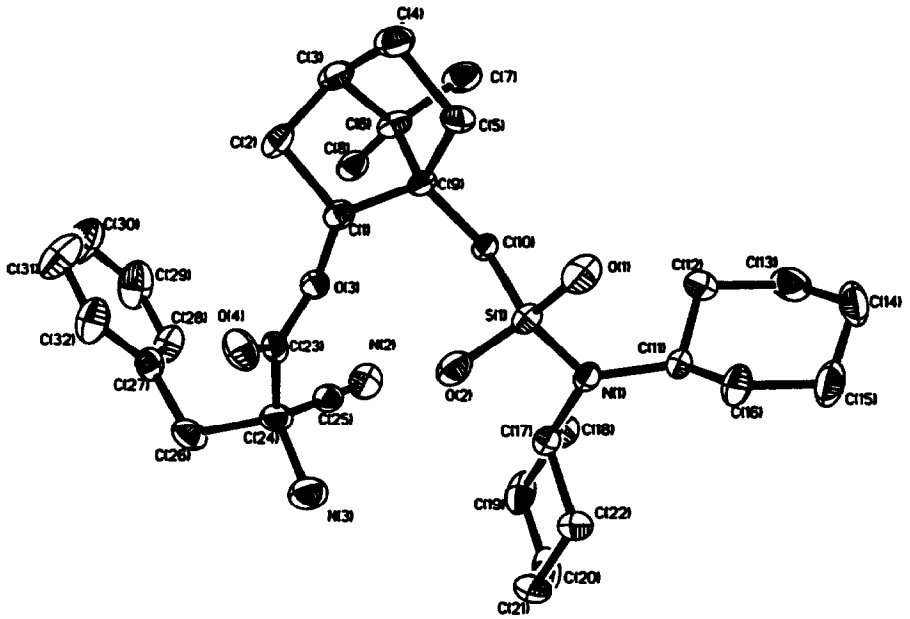
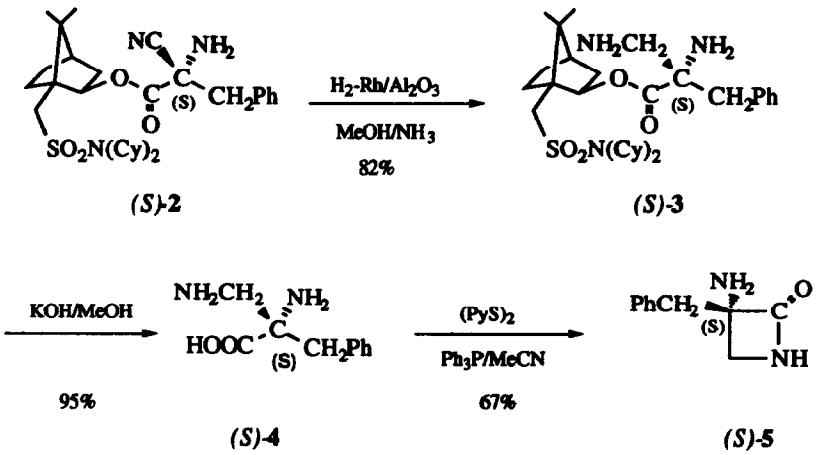


Figure 1

From this chiral intermediate, enantiomerically pure *(S)*-3-amino-3-benzyl-2-azetidinone *(S)*-**5** was easily synthesised in a multi step reaction (Scheme 2). Hydrogenation of the cyano group of the parent aminoester *(S)*-**2** dissolved in a 1% solution of ammonia in ethanol with rhodium on alumina as catalyst furnished the α,β-diaminoester *(S)*-**3** which was subsequently hydrolysed to the corresponding α,β-diaminoacid (S)-4 with KOH/methanol. Compound *(S)*-**4** was then cyclised to azetidinone *(S)*-**5**[7] with triphenylphosphine and 2,2'-dipyridyldisulfide in acetonitrile as the condensing system.



Scheme 2

To sum up, electrophilic amination of a chiral enolate allowed us to obtain a chiral 2-amino-2-cyanoester in diastereomerically pure form. This compound happens to be a valuable key intermediate to the asymmetric synthesis of enantiomerically pure *(S)*-3-amino-3-benzyl-2-azetidinone. The use of this methodology for the general asymmetric synthesis of 3-amino-3-alkyl-2-azetidinones is now in progress and will be published in due course.

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6. $C_{32}H_{47}N_3O_4S$. M_t = 569.8, orthorhombic, space group $P2_12_12$, a = 12.541(3), b = 21.943(4), c = 11.396(2)Å, V = 3136.03(1) $Å^3$, Z = 4, ρ_{calc} = 1.207 g cm^{-3}, $F(000)$ = 1232, $Mo_{K\alpha}$-radiation, λ = 0.71069 Å, μ = 1.352 cm^{-1}. The structure was determined by direct methods and refined by full-matrix least-squares analysis (SHELXTL PLUS) using all 3115 independent reflections measured at 298 K with a 4-Circle Siemens AED diffractometer($2\phi_{max}$ = 50°), with anisotropic atomic displacement parameters, and with isotropic H in calculated positions. Final $R(F)$ = 0.0516, $\omega R(F)$ = 0.0530 for 362 variables and 2281 observed reflections.
7. The spectral and physical properties of *(S)*-**5** are as follows: m.p. 101 °C; $[\alpha]_D$ = - 142 (c = 0.5 in chloroform); ^1H NMR (300 MHz, $CDCl_3$): δ = 2.78(brs, 2H), 3.00(d, J = 13.8 Hz, 1H), 3.08(d, J = 13.8 Hz, 1H), 3.17(d, J = 5.4 Hz, 1H), 3.36(d, J = 5.4 Hz, 1H), 6.04(brs, 1H), 7.20-7.25 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.8, 49.6, 70.8, 127.0, 128.5, 130.0, 135.3, 172.7; IR(Nujol): ν = 3500-3000, 1740 cm^{-1} ; HRMS (EI): m/z = 177.1037 (MH^+ calc for $C_{10}H_{13}N_2O$ 177.1027).

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