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Synthesis of *(R)*- and *(S)*-3-benzyl-3-methyl-2-azetidinone in enantiomerically pure form

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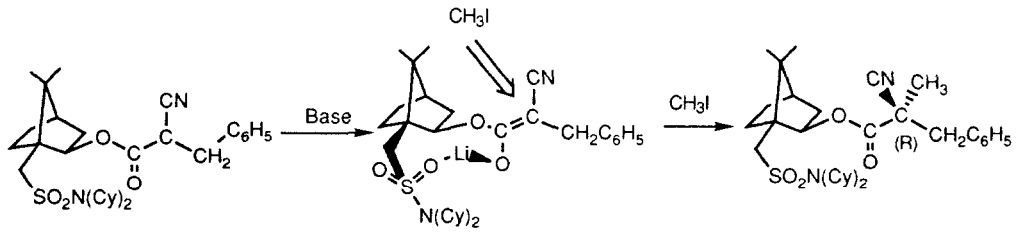
Abstract: The diastereoselective methylation of the enolate of 10-dicyclohexylsulfamoylisobornyl-3-phenyl-2-cyanopropanoate is reported. This methylation was carried out under a variety of conditions to achieve a good yield and selectivity and the reaction product was reduced and cyclised to the corresponding β-lactam in high yield.

The discovery of the antibiotic activity of the penicillins and cephalosporins constituted a breakthough in the treatment of bacterial infections. The systematic chemical modification of natural lead structures has no precedent and has provided a large number of clinically-valuable β-lactam antibiotics, which have facilitated the development of modern medicine. However, problems of resistance and new therapeutical approaches require a continual supply and development of enantiomerically pure new compounds. Comparatively little work has been done on β-lactams with two alkyl substituents at C(3) although it is known[1] that these substances can act on the central nervous system.

One of the synthetic approaches to the β-lactam ring is *via* the cyclisation of β-amino acids[2] so we have focused our attention on the diastereoselective synthesis of the corresponding β-amino acid. Although several diastereoselective synthesis of β-amino acids and derivatives have been reported,[3] they are often difficult to obtain in enantiomerically pure form.[4] As a consequence, the development of new methods providing a direct approach to β-amino acids constitutes an area of active research.

In the course of our research program on the asymmetric synthesis of amino acids we have studied the diastereoselective methylation of enolates derived from *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl-3-phenyl-2-cyanopropanoate **1** under a variety of conditions. The alkylation of **1** was performed by the treatment of the corresponding lithium or potassium enolate generated with lithium diisopropylamine (LDA) or potassium hexamethyldisilazide (KHMDS) in a dry solvent with methyl iodide and in the presence or absence of hexamethylphosphoramide (HMPA), as depicted in Scheme 1.



Pro R

1 **2**

SCHEME 1

The diastereomeric ratio of the products was determined in the crude reaction spectra by integration of the ^1H NMR (300 MHz) absortions of the methine proton of the ester as each diastereomer gave a doublet of doublets at about 5 ppm. The results are summarised in Table 1.

Table 1

Entry	Base	Solvent	Additive	Yield	Diastereomeric ratio
1	LDA	THF	-	90	75/25
2	LDA	THF	HMPA	100	80/20
3	LDA	Toluene	-	-	-
4	LDA	Toluene	HMPA	100	65/35
5	KHMDS	THF	-	70	80/20
6	KHMDS	THF	HMPA	100	65/35
7	LDA	THF	HMPA[a]	100	80/20

[a] added before deprotonation

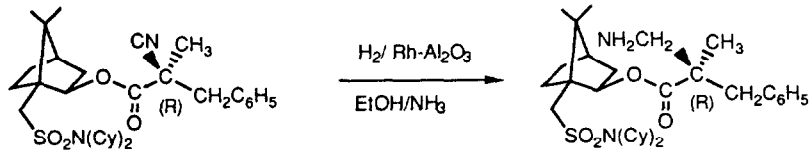
As shown in Table 1, the presence of HMPA increased the reaction yields and the diastereomeric ratio when the counterion was lithium. Nevertheless the diastereomeric ratio decreased in the presence of HMPA when the counter ion was potassium. The addition of HMPA before deprotonation[5] did not change the stereochemical course of the reaction, and we obtained the same major diastereomer in the same ratio.

The minor diastereomer could be eliminated by selective crystallization in hexane as it was the less soluble compound. After filtration of the solid which precipitates upon cooling, it was possible to obtain the major diastereomer in diastereomerically pure form by crystallization.

The absolute configuration of the newly-formed chiral centre *(R)* was assigned by hydrolysis of **2** in KOH/methanol which afforded *(R)* 2-methyl-3-phenyl-2-cyanopropanoic acid, whose $[\alpha]_D$ value ($[\alpha]_D$ = -27.1 c = 2.5 in $CDCl_3$)[6] confirmed both the chiral purity and absolute configuration of **2**.

The stereochemical results are consistent with the model proposed for the alkylation of the enolate generated by 1,4-adition of hydride to E *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl-2-cyanocinnamate.[7]

(2R)-(1S,2R,4R)-10-dicyclohexylsulfamoylisobornyl-2-methyl-3-phenyl-2-cyanopropanoate **2**[8] was converted into the corresponding β-amino ester **3**[9] in nearly quantitative yield by hydrogenation with rhodium on alumina of a solution of the precursor in 10 % ethanol- ammonia (Scheme 2).

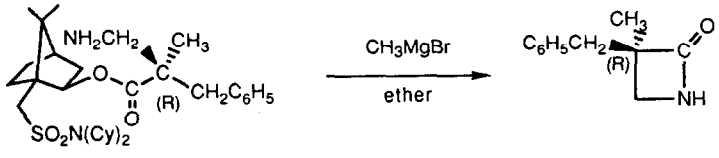


2 **3**

Scheme 2

At this stage it was also possible to separate the major diastereomer by medium pressure liquid chromatogarphy eluting with hexane-ethanol 8:2.

The cyclisation of chiral β-amino ester **3** (Scheme 3) with methylmagnesium bromide in ether afforded the enantiomerically pure β-lactam **4** of *R* configuration[10] in high yield in 3 hours and allowed the recovery of the chiral auxiliary by silica-gel chromatography. The enantiomerically pure β-lactam **4** of *S* configuration can simply be obtained by using the enantiomer of the chiral alcohol.



3 **4**

Scheme 3

The use of this methodology for the general synthesis of C(3) disubstituted β-lactams is now in progress.

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(8) *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl-2-methyl-3-phenyl-2-cyanopropanoate **2.** m.p. = 123°C. $[\alpha]_D$ = -62.8 (c = 1.56 in CHCl3) ^{1}H-NMR δ 0.89 (s, 3H), 1.08 (s, 3H), 1,43 (s, 3H), 1.00-2.20 (m, 27H), 2.66 (d, 1H, J = 13.5 Hz), 3.09 (d, 1H, J = 13.8 Hz), 3.22-3.36 (m, 2H), 3.37 (d, 1H, 13.8 Hz), 3.44 (d, 1H, J = 13.5 Hz), 5.06 (dd, 1H, J = 7.8 Hz, J = 3.3 Hz), 7.26-7.32 (m, 5H). ^{13}C NMR δ 20.0, 20.3, 21.9, 25.1, 26.2, 26.4, 26.9, 30.8, 32.1, 33.3, 39.3, 42.1, 44.0, 44.3, 49.3, 49.8, 53.9, 57.4, 80.5, 119.9, 127.6, 128.4, 130.3, 134.0, 167.9· IR (nujol) ν = 2243, 1748 cm $^{-1}$. HRMS (FAB): m/z = 568.3392 (M^+ calc for $C_{33}H_{48}N_2O_4S$ 568.3334)

(9) *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl-2-benzyl-2-methyl-3-aminopropanoate **3.** m.p. = 144°C. $[\alpha]_D$ = -30.6 (c = 0.87 in CHCl3). ^{1}H-NMR δ 0.62 (s, 3H), 0.77 (s, 3H), 1,10 (s, 3H), 1.00-2.20 (m, 27H), 2.35 (brs, 2H), 2.53 (d, 1H, J = 13.2 Hz), 2.63 (d, 1H, J = 12.9 Hz), 2.67 (d, 1H, J = 13.2 Hz), 2.99 (d, 1H, J = 13.2 Hz), 3.02 (d, 1H, J = 13.2 Hz), 3.13 (d, 1H, J = 12.9 Hz), 3.16-3.28 (m, 2H), 5.83 (dd, 1H, J = 7.8 Hz, J = 3.3 Hz), 7.08-7.26 (m, 5H). ^{13}C NMR δ 18.8, 19.6, 20.3, 25.1, 26.2, 26.3, 26.9, 30.7, 32.1, 33.4, 39.5, 42.9, 44.3, 49.0, 49.2, 49.4, 50.6, 54.0, 57.4, 78.7, 126.5, 127.9, 130.4, 136.9, 174.6. IR (nujol) ν = 3393, 3323, 1716 cm $^{-1}$· HRMS (FAB): m/z = 573.3733 (MH^+ calc for $C_{33}H_{53}N_2O_4S$ 573.3726)

(10) *(3R)*-3-benzyl-3-methyl-2-azetidinone **4.** m.p. = 98°C. $[\alpha]_D$ = -43.3 (c = 0.30 in CHCl3). ^{1}H-NMR δ 1,33 (s, 3H), 2.74 (d, 1H, J = 13.8 Hz), 2.96 (d, 1H, J = 5.4 Hz), 3.02 (d, 1H, J = 13.8 Hz), 3.20 (d, 1H, J = 5.4 Hz), 5.06 (brs, 1H), 7.16-7.32 (m, 5H). ^{13}C NMR δ 20.1, 40.5, 47.4, 57.2, 126.6, 128.3, 129.9, 137.0, 174.1· IR (nujol) ν = 3246, 1767 cm $^{-1}$. HRMS (EI): m/z = 176.1078 (MH^+ calc for $C_{11}H_{14}NO$ 176.1075)