Tetrahedron: Asymmetry Vol. 4, No. 2, pp. 229-238, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00

Synthesis of *(R)*- 3-alkyl-3-benzyl-2-azetidinones in enantiomerically pure form

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(*Received in UK* 8 *December* 1992; *accepted* 19 *January* 1993)

Abstract: The diastereoselective alkylation of the enolate of 10-dicyclohexylsulfamoylisobornyl 3-phenyl-2-cyanopropanoate is reported. This alkylation took place with very 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 penicillins and cephalosporins constituted a breakthrough in the treatment of bacterial infections. The systematic chemical modification of natural lead structures has large 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 therapeutic 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.

Access to these compounds has been extensively studied under various conditions and 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 β-amino acids. Although several diastereoselective syntheses of β-amino acids and derivatives have been reported,[3] these compounds 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.

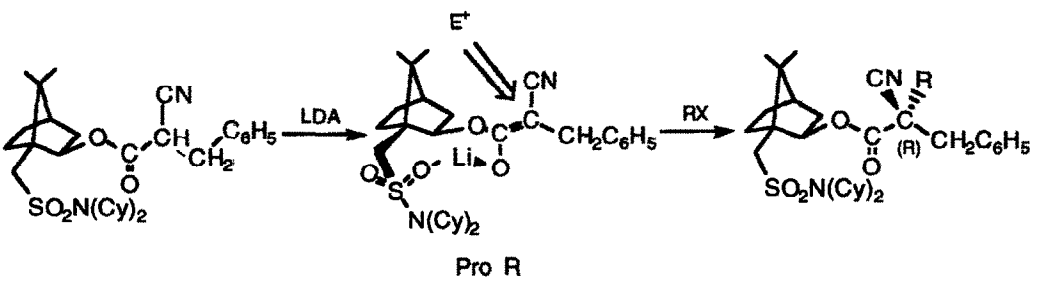
In the course of our research program on the asymmetric synthesis of amino acids we have developed a new approach to the synthesis of *(R)*- and *(S)*-3-benzyl-3-methyl-2-azetidinone in enantiomerically pure form[5] and now we have extended this approach to the synthesis of *(R)*-3-alkyl-3-benzyl-2-azetidinones.

Diastereoselective alkylation of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 3-phenyl-2-cyanopropanoate **1** was performed by generation of the enolate with lithium diisopropylamide for one hour in dry THF at low temperature followed by the addition of the corresponding alkyl halide in the presence of hexamethylphosphoramide (HMPA) (Scheme 1).

This protocol is effective for alkylation with activated halides, such as methyl iodide. With less activated halides, such as ethyl iodide, a substantial decrease in the yield was observed (only 50% conversion) although the diastereoselectivity in alkylation was still high (85/15), and with unactivated alkyl halides, such as n-propyl iodide, only decomposition of the starting material was observed.

Chemical yields can be slightly improved by reduction of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl (E)-2-cyanocinnamate with L-selectride followed by enolate trapping with the alkyl halide, as previously reported[7] but the diastereoselectivity was not so high.

A simple and reliable protocol that avoids these problems involves the use of the more reactive allyl halides which can be subsequently hydrogenated to the corresponding alkyl chain in the next step of the synthesis. In this way, high chemical yields of the alkylated compounds can be obtained with very high diastereoselectivities. The results of these alkylation reactions are collected in Table 1.



1 **2**

Scheme1

Table 1

Compound	R	Yield	Diastereomeric ratio	Diastereomeric ratio[a]
2a	CH_3I	96	80/20	>98/2
2b	$CH_2{=}CHCH_2Br$	96	91/9	-[b]
2c	$CH_2{=}C(CH_3)CH_2I$	94	90/10	>98/2
2d	$(CH_3)_2C{=}CHCH_2Br$	95	93/7	>98/2
2e	$C_6H_5CH{=}CHCH_2Br$	96	95/5	>98/2
2f	$HC{\equiv}CCH_2I$	97	97/3	-[b]

[a] after recrystallisation

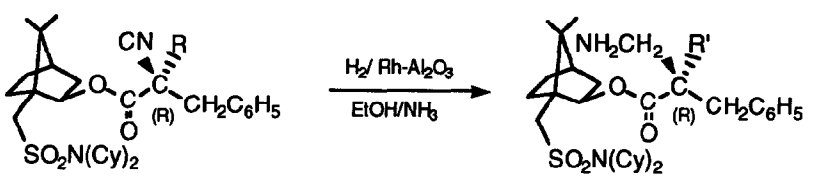
[b] oily compound that could not be recrystallized

In all cases the diastereomeric ratio of the products was determined in the crude reaction spectra by integration of the ^1H NMR (300 MHz) absorptions of the methine proton of esters, **2** as each diastereomer in the pair gave a doublet of doublets at about 5 ppm. Compounds **2**, which were obtained in nearly quantitative yields and with very high diastereoselectivity, can be purified to afford diastereomerically pure compounds in some cases (**2c**, **2d**, **2e**) as the minor diastereomer could be eliminated by selective crystallisation in hexane. When the minor diastereomer is the less soluble compound (R = CH_3), it was possible to obtain the major diastereomer in diastereomerically pure form by crystallisation after filtration of the solid which precipitates upon cooling.

The absolute configuration of the newly-formed stereogenic centre when R = CH_3 was assigned by hydrolysis of **2a** 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 enantiomeric purity and absolute configuration of **2a**.

As the stereochemical results are consistent with the model proposed for the alkylation of the enolate generated by 1,4-addition of hydride to *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl (E)-2-cyanocinnamate, [7] and in all cases the methine proton that appeared at a lower field was that of the major diastereomer, we assumed that in all cases the absolute configuration of the major diastereomer was *(R)*.

(2R)-(1S,2R,4R)-10-dicyclohexylsulfamoylisobornyl 2-alkyl-3-phenyl-2-cyanopropanoates **2** were converted into the corresponding β-amino esters **3** in nearly quantitative yields by hydrogenation with rhodium on alumina of a solution of the precursor in 10 % ethanol-ammonia (Scheme 2). Under these reaction conditions concomitant hydrogenation of the alkene moiety took place and we obtained the desired β-amino esters with a saturated substituent in C_2. The results are summarised in Table 2.



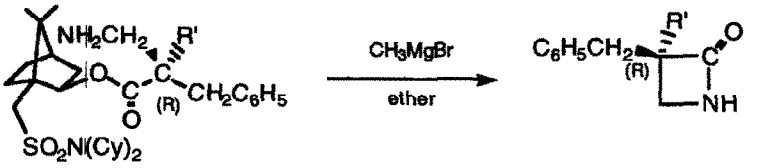
2 **3**

Scheme 2

At this stage compound **3b** can be obtained as a single diastereomer by flash chromatography, eluting with hexane/isopropanol 8:2.

The cyclisation of chiral β-amino esters **3** (Scheme 3) with methylmagnesium bromide in ether afforded the enantiomerically pure β-lactams **4** of *(R)* configuration in high yield in 3 hours and allowed the recovery of the chiral auxiliary by silica-gel chromatography. The results of these cyclizations are collected in Table 2. Confirmation of the absolute configuration of β-lactams **4b-e** (assumed to be *(R)*) was made by comparing its circular dichroism (CD) spectra with that of β-

lactam **4a** whose configuration is known. To obtain enantiomerically pure β-lactams **4** of *S* configuration, it would be enough to use the enantiomer of the chiral alcohol, as we have demostrated for compound **4a**[5].



3 **4**

Scheme 3

Table 2

Compound	R'	Yield 3	Yield 4
a	CH_3	93	89
b	$CH_3CH_2CH_2$	91	86
c	$CH_3CH(CH_3)CH_2$	91	92
d	$(CH_3)_2CHCH_2CH_2$	89	89
e	$C_6H_5CH_2CH_2CH_2Br$	90	91

Acknowledgement: This work was supported by the Dirección General de Investigación Científica y Técnica, project number PB91-0696.

EXPERIMENTAL

Apparatus: ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity 300 MHz spectrometer in deuteriochloroform using the solvent signal as internal standard, chemical shifts are expressed in ppm. IR spectra were recorded on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25°C. Circular dichroism spectra were measured on a Jasco-720 spectropolarimeter. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Mass spectra (MS) were determined on a high-resolution VG-Autospec spectrometer.

Chemicals: All reactions were carried out under Ar with magnetic stirring. Solvents were dried prior to use. Lithium diisopropylamide (LDA) was generated in situ from diisopropylamine and butyl Lithium. Hexamethylphosphotriamide and methylmagnesium bromide 3.0 M solution in ether were purchased from Aldrich.Chemical Co. *(1S,2R,4R)*-10-Dicyclohexylsulfamoylisobornyl (E)-2-cyanocinnamate was prepared following the method described in the literature.[8] TLC was performed on Merk precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Flash column chromatography was performed using 230-400 mesh (Merk) silica-gel.

* *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 3-phenyl-2-cyanopropanoate 1

A solution of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl (E)-2-cyanocinnamate (3.52 g, 10 mmol) in methanol (50 ml) was hydrogenated with 10% palladium on charcoal (100 mg) at room temperature and atmospheric pressure and the reaction was monitored by TLC. When the reaction was finished, after 3 days, the catalyst was removed by filtration and the filtrate was evaporated to dryness to afford an oil, which quickly solidified, in nearly quantitative yield. Recrystallisation from hexane yielded analytically pure *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 3-phenyl-2-cyanopropanoate **1** as a mixture of diastereoisomers (de 50%), whose ^{1}H-NMR and ^{13}C NMR data are in agreement with those described in the literature.[7]

* *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-alkyl-3-phenyl-2-cyano propanoates 2

General procedure for enolate alkylation. To a dry THF solution (25 ml) of lithium diisopropylamine generated in situ from diisopropylamine (120 mg, 1.2 mmol) and buthyl lithium (1.1 mmol), under argon at -78° C was added a solution of *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 3-phenyl-2-cyanopropanoate (0.554 g, 1 mmol) in dry THF (5 ml). After 1 h a solution of the corresponding alkyl halide (10 mmol) and HMPA (270 mg, 1.5 mmol) in dry THF (5 ml) was added by syringe. The reaction mixture was allowed to warm to room temperature and stirring was continued for 1 day. The mixture was then quenched with saturated aqueous NH_4Cl solution (5 ml). An ether extraction, washing by water, drying on $MgSO_4$ and concentration in vacuo yielded a mixture of diastereoisomers of the corresponding *(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-alkyl-3-phenyl-2-cyanopropanoate **2** as a crude oil, which was chromatographed on a siliga-gel column (eluent ether/hexane 1/3). Recrystallization from hexane afforded enantiomerically pure samples of *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-alkyl-3-phenyl-2-cyanopropanoates **2** in most cases.

Products **2** have the following characteristics:

2a m.p. = 123°C. $[\alpha]_D$ = -62.8 (c = 1.56 in $CHCl_3$). ^{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, 20.8, 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)

2b m.p. = oil. ^{1}H-NMR δ 0.86 (s, 3H), 1.04 (s, 3H), 1.05-2.05 (m, 27H), 2.27 (dd, 1H, J = 13.8 Hz, J = 6.3 Hz), 2.52 (dd, 1H, J = 13.8 Hz, J = 8.4 Hz), 2.63 (d, 1H, J = 13.5 Hz), 3,13 (d, 1H, J = 13.8 Hz), 3.20-3.35 (m, 2H), 3.39 (d, 1H, J = 13.8 Hz), 3.47 (d, 1H, J = 13.5 Hz), 5.00 (dd, 1H, J = 8.4 Hz, J = 2.7 Hz), 5.10-5.20 (m, 2H), 5.66-5.82 (m, 1H), 7.31-7.33 (m, 5H). ^{13}C NMR δ 19.9, 20.3, 25.1, 26.1, 26.3, 27.0, 30.8, 32.1, 33.3, 39.3, 39.9, 41.3, 44.4, 49.0, 49.3, 49.7, 53.9, 57.4, 80.7, 118.7, 120.7, 127.5, 128.3, 130.4, 130.6, 133.8, 167.2. IR (nujol) ν = 2254, 1721 cm $^{-1}$. HRMS (FAB): m/z = 594.3494 (M^+ calc for $C_{35}H_{50}N_2O_4S$ 594.3491)

2c m.p. = 120°C. $[\alpha]_D$ = -82.4 (c = 0.42 in $CHCl_3$). ^{1}H-NMR δ 0.87 (s, 3H), 1.06 (s, 3H), 1.05-2.05 (m, 27H), 1.75 (s, 3H), 2.19 (d, 1H, J = 13.8 Hz), 2.56 (d, 1H, J = 13.8 Hz), 2.63 (d, 1H, J = 13.5 Hz), 3,14 (d, 1H, J = 14.1 Hz), 3.20-3.35 (m, 2H), 3.42 (d, 1H, J = 14.1 Hz), 3.50 (d, 1H, J = 13.5 Hz), 4.82 (s, 1H), 4.87 (s, 1H), 4.99 (dd, 1H, J = 7.5 Hz, J = 2.7 Hz), 7.31-7.33 (m, 5H). ^{13}C NMR δ 19.9, 20.3, 23.3, 25.1, 26.2, 26.4, 27.0, 31.0, 32.1, 33.4, 39.1, 42.7, 43.1, 44.5, 48.3, 49.4, 49.9, 54.0, 57.5, 80.8, 116.2, 119.7, 127.6, 128.4, 130.6, 134.0, 139.4, 167.6. IR (nujol) ν = 2241, 1738 cm $^{-1}$. HRMS (FAB): m/z = 608.3625 (M^+ calc for $C_{36}H_{52}N_2O_4S$ 608.3647)

2d m.p. = 122°C. $[\alpha]_D$ = -65.6 (c = 0.43 in $CHCl_3$). ^{1}H-NMR δ 0.87 (s, 3H), 1.06 (s, 3H), 1.05-2.05 (m, 27H), 1.54 (s, 3H), 1.65 (s, 3H), 2.20 (dd, 1H, J = 13.8 Hz, J = 6.3 Hz), 2.57 (dd, 1H, J = 13.8 Hz, J = 9 Hz), 2.62 (d, 1H, J = 13.5 Hz), 3,13 (d, 1H, J = 14.1 Hz), 3.20-3.35 (m, 2H), 3.35 (d, 1H, J = 14.1 Hz), 3.46 (d, 1H, J = 13.5 Hz), 4.96 (dd, 1H, J = 7.8 Hz, J = 3 Hz), 5.10-5.18 (m, 1H), 7.28-7.33 (m, 5H). ^{13}C NMR δ 17.9, 19.7, 20.3, 25.1, 25 8, 26.2, 26.4, 27.0, 30.7, 32.1, 33.3, 35.0, 39.1, 41.3, 44.5, 49.3, 49.5, 49.7, 53.8, 57.4, 80.4, 116.9, 119.3, 127.5, 128.4, 130.4, 134.2, 137.4, 167.8. IR (nujol) ν = 2240, 1747 cm $^{-1}$. HRMS (FAB): m/z = 622.3810 (M^+ calc for $C_{37}H_{54}N_2O_4S$ 622.3804)

2e m.p. = 127°C. $[\alpha]_D$ = -78.6 (c = 0.41 in $CHCl_3$). ^{1}H-NMR δ 0.79 (s, 3H), 0.85 (s, 3H), 1.00-2.00 (m, 27H), 2.48 (dd, 1H, J = 13.2 Hz, J = 6.3 Hz), 2.62 (d, 1H, J = 13.2 Hz), 2.68 (dd, 1H, J = 13.2 Hz, J = 9,3 Hz), 3,21 (d, 1H, J = 13.8 Hz), 3.22-3.35 (m, 2H), 3.42 (d, 1H, J = 13.8 Hz), 3.45 (d, 1H, J = 13.2 Hz), 4.98 (dd, 1H, J = 7.8 Hz, J = 2.7 Hz), 6.13 (ddd, 1H, J = 6.3 Hz, J = 9.3 Hz, J = 15.9 Hz), 6.47 (d, 1H, J = 15.9 Hz), 7.20-7.38 (m, 10H). ^{13}C NMR δ 19.7, 20.2, 25.2, 26.2, 26.4, 26.9, 30.9, 32.2, 33.4, 39.2, 39.7, 41.4, 44.3, 49.2, 49.7, 49.8, 53.9, 57.5, 80.7, 119.0, 121.9, 126.3, 127.7, 127.8, 128.4, 128.5, 130.5, 134.0, 135.5, 136.2, 167.4. IR (nujol) ν = 2239, 1747 cm $^{-1}$. HRMS (FAB): m/z = 671.3905 (MH^+ calc for $C_{41}H_{55}N_2O_4S$ 671.3882).

2f m.p. = oil. ^{1}H-NMR δ 0.87 (s, 3H), 1.09 (s, 3H), 1.05-2.05 (m, 27H), 2.15 (dd, 1H, J = 2.4 Hz, 2.7 Hz), 2.44 (dd, 1H, J = 16.8 Hz, J = 2.7 Hz), 2.65 (d, 1H, J = 13.5 Hz), 2.66 (dd, 1H, J = 16.8 Hz, J = 2.4 Hz), 3,19 (d, 1H, J = 14.1 Hz), 3.22-3.38 (m, 2H), 3.40 (d, 1H, J = 14.1 Hz), 3.45 (d, 1H, J = 13.5 Hz), 5.01 (dd, 1H, J = 7.8 Hz, J = 3.6 Hz), 7.25-7.35 (m, 5H). ^{13}C NMR δ 20.0, 20.4, 25.2, 25.6, 26.3, 26.4, 27.0, 30.9, 32.3, 33.3, 39.3, 40.7, 44.5, 48.6, 49.4, 49.8, 49.8, 53.9, 57.6, 73.2, 77.3, 81.3, 118.3, 127.9, 128.6, 130.4, 133.1, 166.4. IR (nujol) ν = 2251, 1738 cm $^{-1}$. HRMS (FAB): m/z = 593.3423 (MH$^+$ calc for $C_{35}H_{49}N_2O_4S$ 593.3413).

* *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl-2-alkyl-2-benzyl-3-amino propanoates 3

General method for nitrile hydrogenation. A solution of compound **2a-f** (1 mmol) in 10 % ethanol-ammonia (25 ml) was hydrogenated with 5% rhodium on alumina (100 mg) at room temperature and atmospheric pressure. The reaction was followed by TLC (kiesegel Merck 60 F_{254}) and when the reaction was finished (24 h), the catalyst was removed by filtration and the filtrate was evaporated to dryness to afford the corresponding *(2R)-(1S,2R,4R)*-10-dicyclohexylsulfamoylisobornyl 2-alkyl-2-benzyl-3-aminopropanoate **3** as a single diastereoisomer (**3a, 3c, 3d, 3e**) or as a mixture of diastereoisomers (**3b**) in nearly quantitative yield. Purification of the residue by flash chromatography (silicagel 60, eluent: hexane/isopropanol 8:2) afforded diastereomerically pure samples of compounds **3a-e**.

Products **3** have the following characteristics:

3a m.p. = 144°C. $[\alpha]_D$ = -30.6 (c = 0.87 in $CHCl_3$). ^{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)

3b m.p. =oil. $[\alpha]_D$ = -23.6 (c = 0.94 in $CHCl_3$). ^{1}H-NMR δ 0.80 (s, 3H), 0.81 (s, 3H), 0.89 (t, 3H, J = 6.6 Hz), 1.00-2.00 (m, 31H), 2.59 (d, 1H, J = 13.5 Hz), 2.63 (d, 1H, J = 13.5 Hz), 2.89 (d, 1H, J = 13.5 Hz), 2.92 (d, 1H, J = 13.8 Hz), 3.04 (d, 1H, J = 13.8 Hz), 3.20 (d, 1H, J = 13.5 Hz), 3.15-3.25 (m, 2H), 3.85 (brs, 2H), 4.89 (dd, 1H, J = 7.5 Hz, J = 3.0 Hz), 7.10-7.28 (m, 5H). ^{13}C NMR δ 14.3, 17.3, 19.7, 20.3, 25.1, 26.3, 26.9, 30.9, 32.1, 33.4, 33.9, 37.0, 39.8, 44.3, 46.7, 49.1, 49.5, 52.3, 54.0, 57.4, 79.1, 126.4, 128.1, 130.4, 137.1, 174.4. IR (nujol) ν = 3400, 3334, 1736 cm $^{-1}$. HRMS (FAB): m/z = 601.404 (MH$^+$ calc for $C_{35}H_{57}N_2O_4S$ 601.4038)

3c m.p. = oil. $[\alpha]_D$ = -29.8 (c = 1.14 in $CHCl_3$). ^{1}H-NMR δ 0.85 (s, 3H), 0.89 (d, 3H, J = 7.8 Hz), 0.91 (d, 3H, J = 6.3 Hz), 0.94 (s, 3H), 1.42 (d, 2H, J = 6.3 Hz), 1.00-2.20 (m, 28H), 2.02 (brs, 2H), 2.64 (d, 1H, J = 13.8 Hz), 2.71 (d, 1H, J = 13,5 Hz), 2.87 (d, 1H, J = 13.5 Hz), 2.91 (d, 1H, J = 13.5 Hz), 3.14 (d, 1H, J = 13.8 Hz), 3.24 (d, 1H, J = 13.5 Hz), 3.18-3.28 (m, 2H), 4.85 (dd, 1H, J = 6.3 Hz, J = 2.7

Hz), 7.14-7.27 (m, 5H). ^{13}C NMR δ 20.0, 20.5, 24.1, 24.2, 24.5, 25.1, 26.3, 27.0, 30.7, 32.2, 33.3, 38.2, 39.7, 41.2, 44.3, 47.0, 49.0, 49.6, 52.1, 53.9, 57.4, 79.7, 126.3, 128.0, 130.5, 137.3, 174.8. IR (nujol) ν = 3405, 3330, 1721 cm $^{-1}$. HRMS (FAB): m/z = 615.4181 (MH^+ calc for $C_{36}H_{59}N_2O_4S$ 615.4195)

3d m.p. = oil. $[\alpha]_D$ = -32 (c = 1.45 in $CHCl_3$). ^1H-NMR δ 0.77 (s, 3H), 0.78 (s, 3H), 0.85 (d, 3H, J = 6.3 Hz), 0.87 (d, 3H, J = 6.3 Hz), 1.00-2.19 (m, 32H), 2.62 (d, 1H, J = 13.8 Hz), 3.02-3.06 (m, 4H), 3.20 (d, 1H, J = 13.8 Hz), 3.12-3.24 (m, 2H), 4.95 (dd, 1H, J = 7.8 Hz, J = 3.0 Hz), 5.84 (brs, 2H), 7.14-7.24 (m, 5H). ^{13}C NMR δ 19.8, 20.2, 22.3, 22.6, 25.1, 26.4, 26.9, 28.7, 30.3, 31.3, 32.3, 33.2, 38.1, 39.4, 44.3, 44.8, 49.1, 49.9, 54.9, 57.7, 79.2, 126.8, 128.2, 130.4, 136.0, 174.0. IR (nujol) ν = 3394, 3325, 1715 cm $^{-1}$. HRMS (FAB): m/z = 629.4328 (MH^+ calc for $C_{37}H_{61}N_2O_4S$ 629.4352)

3e m.p. = 144°C. $[\alpha]_D$ = -27.9 (c = 1.93 in $CHCl_3$). ^1H-NMR δ 0.79 (s, 3H), 0.83 (s, 3H), 0.94-2.04 (m, 31H), 2.38 (brs, 2H), 2.52-2.60 (m, 2H), 2.62 (d, 1H, J = 13.5 Hz), 2.76-2.78 (m, 2H), 2.83 (d, 1H, J = 13.8 Hz), 2.97 (d, 1H, J = 13.8 Hz), 3.14-3.32 (m, 2H), 3.21 (d, 1H, J = 13.5 Hz), 4.87 (dd, 1H, J = 7.5 Hz, J = 3.0 Hz), 6.97-7.30 (m, 10H). ^{13}C NMR δ 19.7, 20.3, 25.1, 26.0, 26.5, 26.9, 30.8, 30.9, 32.3, 33.4, 36.1, 37.0, 39.8, 44.2, 47.0, 49.0, 49.4, 52.3, 54.0, 57.5, 79.0, 125.8, 126.3, 128.0, 128.3, 128.4, 130.2, 137.0, 141.8, 174.3. IR (nujol) ν = 3400, 3333, 1714 cm $^{-1}$. HRMS (FAB): m/z = 677.4289 (MH^+ calc for $C_{41}H_{61}N_2O_4S$ 677.4352)

* *(3R)*-3-phenyl-3-alkyl-2-azetidone 4

General procedure for β-amino acid cyclization. To a stirred solution of methylmagnesium bromide (0.5 mL of 3.0 M solution in ether, 0.5 mmol) in ether (25 mL) was added dropwise compound **3a-e** (0.5 mmol) in ether (5 ml) and the mixture was stirred for 3 h at room temperature. When the reaction was finished aqueous 10% ammonium chloride (25 mL) was added and the mixture was stirred until the two layers became clear. The aqueous layer was separated and extracted with ether The combined ether solutions were dried over $MgSO_4$, filtered and concentrated in vacuo to yield the corresponding *(3R)* -3-phenyl-3-alkyl-2-azetidone **4** as a crude oil, which was chromatographed on a siliga-gel column (eluent ether/hexane 2/1) to afford enantiomerically pure samples of *(3R)*-3-phenyl-3-alkyl-2-azetidone **4**

Products **4** have the following characteristics:

4a m.p. = 98°C. $[\alpha]_D$ = -43.3 (c = 0.30 in $CHCl_3$). ^1H-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)

4b m.p. = oil. $[\alpha]_D$ = -63.7 (c = 0.60 in $CHCl_3$). ^1H-NMR δ 0.92 (t, 3H, J = 7.2 Hz), 1.40-1.72 (m, 4H), 2.77 (d, 1H, J = 13.8 Hz), 3.03 (d, 1H, J = 5.7 Hz), 3.04 (d, 1H, J = 13.8 Hz), 3.09 (d, 1H, J = 5.7 Hz), 5.47 (brs, 1H), 7.18-7.32 (m, 5H). ^{13}C NMR δ 14.3, 17.8, 35.8, 39.2, 44.7, 61.4, 126.6,

128.3, 130.0, 137.0, 173.3. IR (nujol) ν = 3252, 1747 cm $^{-1}$. HRMS (EI): m/z = 204.1385 (MH^+ calc for $C_{13}H_{18}NO$ 204.1388)

4c m.p. = 98°C. $[\alpha]_D$ = -39.4 (c = 0.32 in $CHCl_3$). ^{1}H-NMR δ 0.93 (d, 3H, J = 6.6 Hz), 0.97 (d, 3H, J = 6.3 Hz), 1.53 (dd, 1H, J = 14.4 Hz, J = 9 Hz), 1.77 (dd, 1H, J = 9 Hz, J = 4.8 Hz), 1.82-1.94 (m, 1H), 2.77 (d, 1H, J = 13.8 Hz), 2.97 (d, 1H, J = 13.8 Hz), 3.07 (d, 1H, J = 5.7 Hz), 3.10 (d, 1H, J = 5.7 Hz), 5.44 (brs, 1H), 7.18-7.32 (m, 5H). ^{13}C NMR δ 22.8, 24.3, 24.7, 38.5, 42.5, 45.5, 60.8, 126.5, 128.2, 130.1, 136.8, 173.6. IR (nujol) ν = 3196, 1712 cm $^{-1}$. HRMS (EI): m/z = 218.1559 (MH^+ calc for $C_{14}H_{20}NO$ 218.1544)

4d m.p. = 79°C. $[\alpha]_D$ = -36.9 (c = 0.64 in $CHCl_3$). ^{1}H-NMR δ 0.87 (d, 3H, J = 6.6 Hz), 0.88 (d, 3H, J = 6.6 Hz), 1.16-1.44 (m, 5H), 2.77 (d, 1H, J = 13.8 Hz), 3.00 (d, 1H, J = 5.7 Hz), 3.02 (d, 1H, J = 13.8 Hz) , 3.07 (d, 1H, J = 5.7 Hz), 5.61 (brs, 1H), 7.18-7.32 (m, 5H). ^{13}C NMR δ 22.4, 22.5, 28.4, 31.4, 33.2, 39.1, 44.6, 61.2, 126.5, 128.2, 130.0, 136.9, 173.4. IR (nujol) ν = 3238, 1713 cm $^{-1}$. HRMS (EI): m/z = 232.1713 (MH^+ calc for $C_{15}H_{22}NO$ 232.1701)

4e m.p. = 120°C. $[\alpha]_D$ = -30.0 (c = 0.50 in $CHCl_3$). ^{1}H-NMR δ 1.60-1.44 (m, 4H), 2.57-2.64 (m, 2H), 2.76 (d, 1H, J = 13.8 Hz), 2.98 (d, 1H, J ∓ 5.7 Hz), 3.02 (d, 1H, J = 13.8 Hz) , 3.05 (d, 1H, J = 5.7 Hz), 5.63 (brs, 1H), 7.12-7.29 (m, 10H). ^{13}C NMR δ 26.4, 33.1, 36.0, 39.0, 44.6, 61.0, 125.8, 126.5, 128.2, 128.3, 128.3, 129.9, 136.8, 141.8, 173.2. IR (nujol) ν = 3205, 1713 cm $^{-1}$. HRMS (EI): m/z = 279.1617 (M^+ calc for $C_{19}H_{21}NO$ 279.1623)

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