General Approach for the Stereocontrolled Construction of the β-Lactam Ring in Amino Acid-Derived 4-Alkyl-4-carboxy-2-azetidinones

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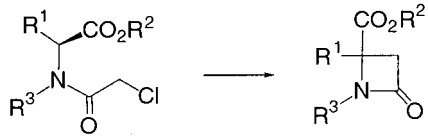
Abstract: The first general approach toward the asymmetric synthesis of 4-alkyl-4-carboxy-2-azetidinones derived from amino acids is described. The stereoselective construction of the β-lactam ring was achieved through base-mediated intramolecular cyclization of the corresponding N^{α}-chloroacetyl derivatives bearing (+)- or (−)-10-(*N*,*N*-dicyclohexylsulfamoyl)isoborneol as chiral auxiliary (ee up to 82%).

In connection with our current interest in conformationally constrained amino acid and peptide derivatives, we have recently reported the first concise and versatile route to the preparation of 3-unsubstituted 4-alkyl-4-carboxy-2-azetidinones II (Chart 1).[1,2] The synthetic strategy involves, as the key step, the formation of the C_3-C_4 bond of the β-lactam ring through base-promoted intramolecular alkylation of the corresponding easily available N^{α}-benzyl-N^{α}-chloroacetyl-substituted amino acid derivatives I.[2] While modest selectivity was found in the intramolecular cyclization of Trp, Phe, and Leu derivatives (ee up to 56%), no stereoselectivity at all was observed for Ala, Glu, and Orn analogues.[2] It was suggested that, in the particular cases of β-ramified amino acids, the cyclization reaction proceeded by way of planar enolate intermediates, which possess axial chirality, according to the recently proposed concept of the *memory of chirality*.[3]

Due to the moderate or null enantioselectivity of the intramolecular cyclization, the application of other asymmetric protocols to this convenient procedure needs to be addressed. It was expected that the chiral auxiliary-based methodologies commonly used for the asymmetric synthesis of α-alkyl α-amino acid derivatives[4] could result in a general strategy to facilitate the preparation of these β-lactams enantiomerically pure. In related amino acid templates the chiral auxiliary can be borne either at the amino or at the carboxylate functions.[5,6] In the case of structure I, the carboxylate moiety appears to be the most

Chart 1. 4-Alkyl-4-carboxy-2-azetidinones Derived from Amino Acids



I II

suitable position for the appendage of the asymmetric inductor. Among the carboxylate bearing auxiliaries, we selected the 10-(*N*,*N*-dicyclohexylsulfamoyl)isoborneol that was described to be a practical stereoface-directing moiety in Diels−Alder additions,[7] α-acetoxylation, and α-amination reactions,[8] 2 + 2 cycloadditions,[9] and C−C bond formation at both C^{α} or C^{β} positions of carboxylates.[10] In this respect, a few papers described its application to the diastereoselective alkylation of cyano esters that, after convenient elaboration, afforded both enantiomers of the same α,α-dialkylamino acid.[11] To the best of our knowledge, only one example describes the use of this auxiliary for the direct asymmetric alkylation of amino acid derivatives.[12]

In this paper, we wish to present our preliminary study on the asymmetric synthesis of 1,4,4-trisubstituted 2-azetidinones resulting from *N*-chloroacetyl Phe and Ala derivatives, bearing the chiral auxiliary 10-(*N*,*N*-dicyclohexylsulfamoyl)isoborneol at the carboxylic function.

To synthesize the required *N*-chloroacetyl derivatives **10**−**12**, we first investigate the incorporation of the alcoholic chiral auxiliary into Z-Phe-OH by DCC/DMAP-mediated esterification.[13] However, after several at-

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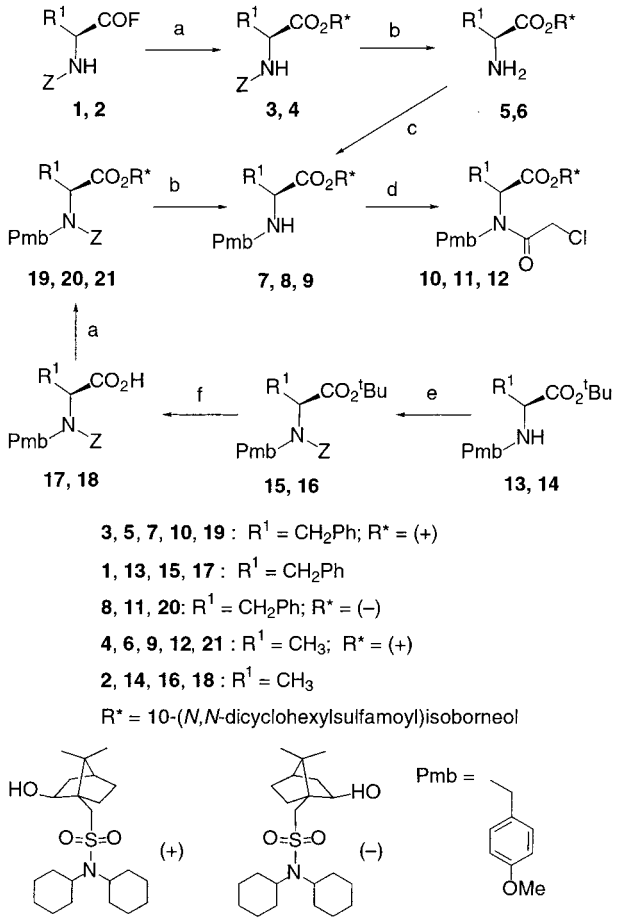
Scheme 1. Synthesis of *N*-*p*-Methoxybenzyl-*N*-chloroacetyl Derivatives[a]

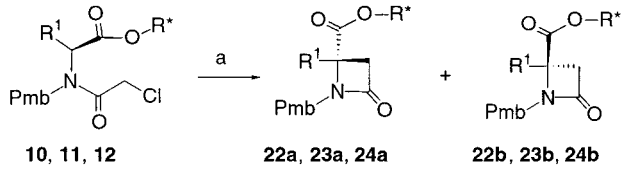


[a] Reagents and conditions: (a) R*OH/DMAP/CH_2Cl_2; (b) H_2/Pd–C/MeOH; (c) (1) (4-OMe)C_6H_5CHO/MeOH, (2) $NaBH_4$; (d) $ClCH_2COCl$/propylene oxide/THF; (e) $C_6H_5CH_2OCOCl$/propylene oxide/CH_2Cl_2; (f) 4 M HCl/EtOAc.

tempts, compound **3** was obtained in very low yield (10–20%), due to extensive Phe-derived *N*-acylurea formation.[13] This side reaction was avoided by using amino acid fluorides **1** and **2**, previously generated by "in situ" treatment of Z-Phe-OH and Z-Ala-OH, respectively, with cyanuric fluoride,[14] as the acylating agent for the preparation of compounds **3** and **4**. Removal of the Z group from **3** and **4** followed by treatment with anisaldehyde and reduction with $NaBH_4$ afforded the expected *p*-methoxybenzyl derivatives **7** and **9**. Alternatively, esterification of the fully *N*-protected Phe and Ala derivatives **17** and **18** resulted in satisfactory yields of compounds **19**–**21** (Scheme 1). Careful monitoring of the H_2/Pd–C-mediated Z removal, to avoid simultaneous hydrogenolysis of the *p*-methoxybenzyl group (Pmb), afforded compounds **7**–**9** in almost quantitative yield. Finally, *N*-chloroacetyl derivatives **10**–**12** were also quantitatively prepared by reaction of derivatives **7**–**9** with chloroacetyl chloride, using propylene oxide as HCl scavenger.

On the basis of our previous results,[2] Cs_2CO_3 was initially chosen as base to promote the cyclization of the N^{α}-chloroacetyl derivatives **10**–**12** to the corresponding β-lactams (Scheme 2). The reaction of compound **10**,

Scheme 2. Asymmetric Synthesis of 4-Alkyl-4-carboxy-2-azetidinones[a]



[a] Reagents and conditions: (a) base/solvent (see Table 1).

Table 1. Intramolecular Cyclization of 10-(*N*,*N*-Dicyclohexylsulfamoyl)isoborneol-Derived Amino Acids

starting compd	R^1	R*	base	solvent	time (d)	final compd	yield[a] (%)	ratio **a**/**b**[b]
10	CH_2Ph	(+)	Cs_2CO_3	MeCN	10	**22**	72	85:15
10	CH_2Ph	(+)	Cs_2CO_3	DMF	2	**22**	55	81:19
10	CH_2Ph	(+)	BTPP	MeCN	1	**22**	77	71:29
10	CH_2Ph	(+)	BTPP	CH_2Cl_2	1	**22**	60	73:27
11	CH_2Ph	(–)	Cs_2CO_3	MeCN	10	**23**	70	16:84
12	CH_3	(+)	Cs_2CO_3	MeCN	2	**24**	71	91:9

[a] Yield of isolated compounds. [b] Measured by HPLC of the crude reaction mixture.

bearing (+)-*N*,*N*-dicyclohexylisoborneol-10-sulfonamide as the chiral auxiliary, gave compound **22a** as the major isomer, in a 70% diastereoisomeric excess (Table 1). In this case, both the yield and the diastereoselectivity of the reaction was higher using MeCN as solvent than DMF. On the other hand, the use of the strong soluble base BTPP resulted in lower diastereomeric excesses than those obtained in the Cs_2CO_3-mediated cyclization. As expected, the use of the (–)-10-(*N*,*N*-dicyclohexylsulfamoyl)isoborneol derivative, as in compound **11**, allowed us the preparation of compound **23b** in 68% de. These results pointed out that the topicity of the intramolecular alkylation was exclusively governed by the chirality of the isoborneol derivative and not by the memory of chirality, as previously observed for the corresponding methyl and *tert*-butyl ester derivatives.[2] Still better diastereoselectivity was obtained in the alkylation of the Ala derivative **12**, which afforded a 91:9 mixture of azetidinones **24a** and **24b** (82% de). The observed difference in the diastereoisomeric ratio between the Phe and Ala derivatives was similar to those previously reported in the intermolecular α-alkylation of amino acids bearing the camphor sultam auxiliary,[15] and in the phase-transfer catalytic alkylation of aldimine Schiff bases derived from different amino acids.[16]

As shown in Scheme 3, the absolute configuration at C_4 in 2-azetidinones **22a** (**23a**) and **22b** (**23b**) was initially established by measuring the chemical shifts of the β-H protons of the Ala residue in the ^{1}H NMR spectra of the corresponding dipeptide derivatives **26a** and **26b**[17,18] and their respective retention times in the HPLC chromato-

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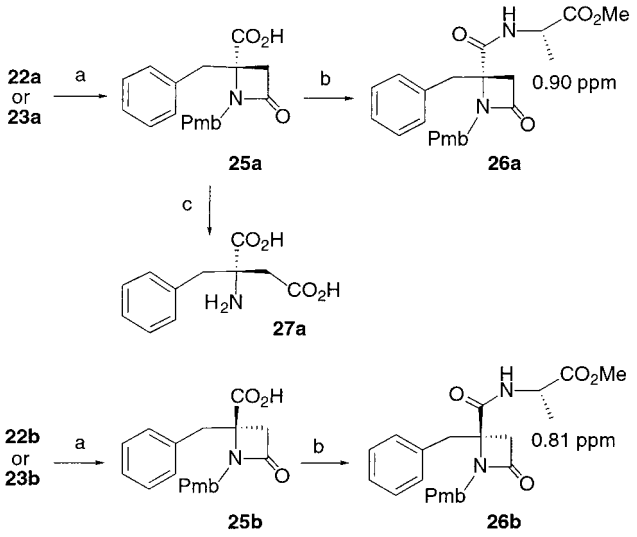
Scheme 3. Synthesis of Dipeptide Derivatives[a]



[a] Reagents and conditions: (a) (1) 2 N NaOH/MeOH/THF (2:1), (2) HCl (pH 3); (b) H−L-Ala-OMe/BOP/TEA; (c) 12 N HCl/85 °C.

grams.[19] Thus, the chemical shift of the *C*-terminal α-methyl hydrogens of isomer **26a** appeared at slightly lower field ($\Delta\delta \approx 0.1$ ppm) than that of the isomer **26b** (Scheme 3), while this latter compound is 0.7 min. more retained in the HPLC chromatogram with respect to isomer **26a**.[20] This assignment was then unambiguously confirmed by conversion of compound **25a** into the known (S)-α-benzyl aspartic acid **27a**.[21] The configuration of Ala derivatives **24a** and **24b** was assigned by comparison of the ^{1}H NMR data and the sign of the optical rotations with those of the corresponding Phe analogues **22a** and **22b**.[22]

In the present study, the observed asymmetric induction could be explained by preferential formation of a chelated *E* enolate, as the reactive intermediate, and approach of the electrophile ($COCH_2Cl$) by the opposite face of the $SO_2N(Chx)_2$ moiety (Figure 1). A similar asymmetric induction was observed in the intermolecular alkylation of related camphorsultam-derived amino acids, different from Gly.[15] In our case, all attempts to stereoselectively prepare the corresponding 2-azetidinones derived from the *N*-chloroacetyl Phe derivative bearing (+)-2,10-camphorsultam as the chiral auxiliary failed.[23]

In conclusion, we have shown that the 10-(*N*,*N*-dicyclohexylsulfamoyl)isoborneol can be utilized as a

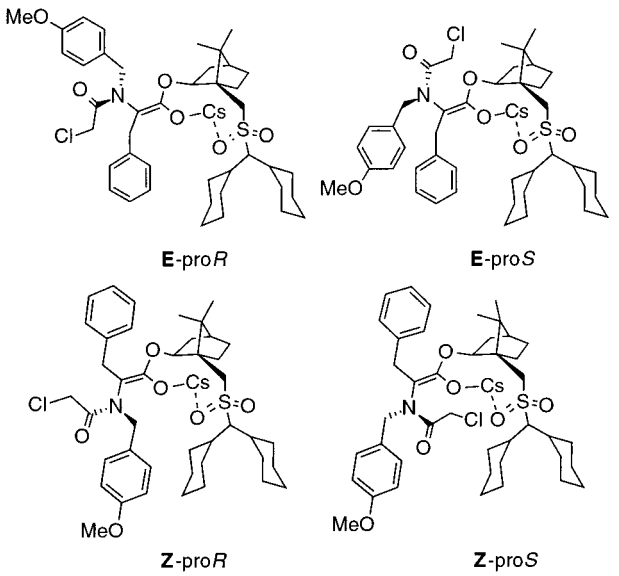


Figure 1. Possible transition states for the intramolecular alkylation using (+)-10-(*N*,*N*-dicyclohexylsulfamoyl)isoborneol as the chiral auxiliary.

highly effective chiral auxiliary in the intramolecular $N^{\alpha}-C^{\alpha}$-cyclization of *N*-(*p*-methoxy)benzyl-*N*-chloroacetyl Phe and Ala derivatives, making this an attractive procedure for the stereocontrolled preparation of amino acid-derived 2-azetidinones. The diastereoselectivity seems to be governed by the *E* geometry of the enolate and by the intramolecular alkylation opposite to the SO_2 function. The broader conceptualization of this asymmetric alkylation process, both by further optimization of the procedure described here or by a search for other appropriate chiral auxiliaries, and its application to the construction of new optically active β-lactams may be anticipated.

Experimental Section

For general experimental procedures regarding the preparation of *N*-(*p*-methoxy)benzyl- and *N*-(*p*-methoxy)benzyl-*N*-chloroacetyl derivatives see ref 2. Z-Phe-F and Z-Ala-F derivatives **1** and **2** were synthesized by reaction of the corresponding Z amino acid with cyanuric fluoride in pyridine.[24]

General Procedures for the Synthesis of the 10-(*N*,*N*-Dicyclohexylsulfamoyl)isoborneol-Derived 2-Azetidinones. A solution of the corresponding *N*-chloroacetyl-*N*-*p*-methoxybenzyl derivative **10**−**12** (2.02 mmol) in dry CH_3CN or

(18) In our previous publication (ref 2) the assignment of homochiral and heterochiral 2-azetidinone-containing dipeptide derivatives **26** was erroneously made. In that case, the 4*R*,1′*S* isomer was mistakenly correlated to an L−L homochiral dipeptide derivative, by considering that the benzyl group at C_4 position in the 4*R* isomer showed the same spatial disposition that the amino acid side chain in the L-Phe, instead of just considering the absolute configuration at this position, indicating that the 4*R*,1′*S* isomer is the heterochiral one.

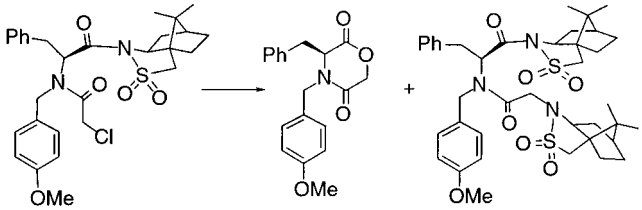
(19) In dipeptides and retrodipeptides, it was shown that heterochiral derivatives are more retained than homochiral analogues: Fournié-Zaluski, M. C.; Lucas-Soroca, E.; Devin, J.; Roques, B. P. *J. Med. Chem.* **1986**, *29*, 751−757.

(20) Isomer (*R*,*S*)-**26a**: HPLC: $t_R = 9.58$ min (A:B = 35:65). Isomer (*S*,*S*)-**26b**: HPLC: $t_R = 10.28$ min (A/B = 35:65). A: MeCN. B: H_2O (0.05% TFA).

(21) **27a** $[\alpha]_D = +48.60$ (described $[\alpha]_D = +50.00$): Juaristi, E.; López-Ruiz, H.; Madrigal, D.; Ramírez-Quirós, Y.; Escalante, J. *J. Org. Chem.* **1998**, *63*, 4706−4710.

(22) The signal corresponding to the low field 1-CH_2 proton of 4*S* isomers (**22b** and **24b**) is shielded (0.3−0.4 ppm) with respect to the same proton in the 4*R*-configured analogues (**22a** and **24a**). **22a** $[\alpha]_D = +66.86$; **24a** $[\alpha]_D = +21.79$.

(23) Reaction of compound **28** with Cs_2CO_3 or BTPP resulted in partial *O*-alkylation to morpholine derivative **29**,[2] with the concomitant release of camphorsultam. The nucleophilic attack of the free sultam to compound **28** furnished the bis-sultam derivative **30** as the major product in these reactions. Compound **30**: HPLC: $t_R = 20.51$ min (A/B = 55:45). ES MS: 738.5 $(M + 1)^+$, 760.5 $(M + Na)^+$. ^{1}H NMR (300 MHz, DMSO-d_6, 80 °C): δ 1.08, 0.96, 0.92, 0.87 (4s, 3H, Me camphorsultam).



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DMF (50 mL) was treated with Cs_2CO_3 or BTPP (4.04 mmol) and stirred at room temperature until disappearance of the starting material. After evaporation of the solvent, the residue was partitioned between EtOAc and H_2O, and the phases were separated. The organic layer was dried over Na_2SO_4 and evaporated, leaving a residue that was purified on a silica gel column, using the solvent system specified in each case.

(4*S*)-Pmb-α-Bzl-Azn-OR*(+) (22a). Yield: 61% (from **10**, Cs_2CO_3/CH_3CN), 44% (from **10**, Cs_2CO_3/DMF), 55% (from **10**, BTPP/CH_2Cl_2), 43% (from **10**, BTPP/CH_3CN). Eluent: EtOAc/hexane (1:15). Foam. HPLC: t_R = 12.76 min (A/B = 75:25). $[\alpha]_D$ = +66.86 (c = 1.24, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, 2H, J = 8.7), 7.18 (m, 3H), 6.96 (m, 2H), 6.86 (d, 2H, J = 8.7), 5.03 (m, 1H), 4.73 (d, 1H, J = 15.3), 4.26 (d, 1H, J = 15.3), 3.79 (s, 3H), 3.23 (d, 1H, J = 14.4), 3.21 (m, 2H), 3.20 (d, 1H, J = 13.9), 3.11 (d, 1H, J = 13.3), 2.92 (d, 1H, J = 14.4), 2.73 (d, 1H, J = 13.9), 2.63 (d, 1H, J = 13.3), 1.85 (m, 2H), 1.71 (m, 16H), 1.60 (m, 2H), 1.34 (m, 5H), 1.11 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (75 MHZ, $CDCl_3$): δ 169.46, 165.67, 158.97, 134.72, 130.06, 129.82, 128.99, 128.42, 127.14, 113.88, 79.40, 63.31, 57.49, 55.22, 54.46, 49.54, 47.18, 45.01, 44.36, 44.26, 40.59, 39.10, 33.25, 32.26, 31.25, 26.94, 26.25, 26.15, 25.09, 20.27, 19.78. MS (ES, positive mode): 705.4 (M + 1)$^+$. Anal. Calcd for $C_{41}H_{56}N_2O_6S$: C, 69.85; H, 8.01; N, 3.97; S, 4.55. Found: C, 69.79; H, 7.99; N, 4.03; S, 4.62.

(4*R*)-Pmb-α-Bzl-Azn-OR*(+) (22b). Yield: 11% (from **10**), 11% (from **10**, Cs_2CO_3/DMF), 22% (from **10**, BTPP/CH_2Cl_2), 19% (from **10**, BTPP/CH_3CN). Eluent: EtOAc/CH_2Cl_2 (1:15). Foam. HPLC: t_R = 10.73 min (A/B = 75:25). $[\alpha]_D$ = −15.04 (c = 1.04, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, 2H, J = 8.7), 7.15 (m, 3H), 6.88 (m, 2H), 6.81 (d, 2H, J = 8.7), 4.97 (m, 1H), 4.44 (d, 1H, J = 15.1), 4.17 (d, 1H, J = 15.1), 3.77 (s, 3H), 3.32 (d, 1H, J = 14.5), 3.17 (d, 1H, J = 14.5), 3.13 (m, 2H), 3.11 (d, 1H, J = 13.4), 3.02 (d, 1H, J = 14.5), 2.76 (d, 1H, J = 14.5), 2.60 (d, 1H, J = 13.4), 1.84 (m, 2H), 1.69 (m, 16H), 1.50 (m, 2H), 1.17 (m, 5H), 0.98 (m, 2H), 0.88 (s, 3H), 0.82 (s, 3H). ^{13}C NMR (75 MHZ, $CDCl_3$): δ 169.82, 166.45, 159.17, 134.76, 130.42, 129.96, 128.68, 128.43, 126.98, 113.96, 79.94, 62.70, 57.49, 55.28, 54.17, 49.56, 49.21, 44.78, 44.46, 44.26, 39.27, 38.15, 33.21, 32.24, 30.98, 26.95, 26.29, 25.03, 20.31, 20.07. MS (ES, positive mode): 705.4 (M + 1)$^+$. Anal. Calcd for $C_{41}H_{56}N_2O_6S$: C, 69.85; H, 8.01; N, 3.97; S, 4.55. Found: C, 69.81; H, 8.10; N, 3.90; S, 4.58.

(4*S*)-Pmb-α-Bzl-Azn-OR*(−) (23a). Enantiomer of **22b**. Yield: 60% (from **11**). Eluent: EtOAc/hexane (1:15). $[\alpha]_D$ = +14.78 (c = 0.76, $CHCl_3$). MS (ES, positive mode): 705.6 (M + 1)$^+$. Anal. Calcd for $C_{41}H_{56}N_2O_6S$: C, 69.85; H, 8.01; N, 3.97; S, 4.55. Found: C, 69.73; H, 7.82; N, 4.09; S, 4.66.

(4*R*)-Pmb-α-Bzl-Azn-OR*(−) (23b). Enantiomer of **22a**. Yield: 12% (from **11**). Eluent: EtOAc/hexane (1:15). $[\alpha]_D$ = −68.30 (c = 1.07, $CHCl_3$). MS (ES, positive mode): 705.5 (M + 1)$^+$. Anal. Calcd for $C_{41}H_{56}N_2O_6S$: C, 69.85; H, 8.01; N, 3.97; S, 4.55. Found: C, 69.70; H, 7.85; N, 4.12; S, 4.70.

(4*S*)-Pmb-α-Bzl-Azn-OR*(+) (24a). Yield: 67.3% (from **12**). Eluent: gradient from 5 to 15% of AcOEt in CH_2Cl_2. Mp = 173−174 °C (CH_2Cl_2). HPLC: t_R = 13.80 min (A:B = 65:35). $[\alpha]_D$ = +21.79 (c = 1.32, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, 2H, J = 8.5), 6.81 (d, 2H, J = 8.5), 4.93 (m, 1H), 4.65 (d, 1H, J = 14.9), 4.17 (d, 1H, J = 14.9), 3.76 (s, 3H), 3.34 (d, 1H, J = 14.2), 3.16 (m, 2H), 3.09 (d, 1H, J = 13.3), 2.74 (d, 1H, J = 14.2), 2.61 (d, 1H, J = 13.3), 1.98 (dd, 1H, J = 6.7, 14.6), 1.89 (m, 1H), 1.73 (m, 15H), 1.57 (m, 3H), 1.25 (s, 3H), 1.13 (m, 7H), 0.90 (s, 3H), 0.84 (s, 3H). ^{13}C NMR (75 MHZ, $CDCl_3$): δ 170.51, 165.48, 159.03, 129.94, 127.66, 113.81, 79.47, 58.60, 57.39, 55.09, 54.08, 49.37, 49.21, 49.08, 44.16, 44.10, 39.48, 32.89, 32.77, 30.78, 26.82, 26.25, 24.94, 20.81, 20.17, 19.87. MS (ES, positive mode): 629.3 (M + 1)$^+$. Anal. Calcd for $C_{35}H_{52}N_2O_6S$: C, 66.85; H, 8.33; N, 4.45; S, 5.10. Found: C, 66.62; H, 8.20; N, 4.54; S, 5.07.

(4*R*)-Pmb-α-Bzl-Azn-OR*(+) (24b). Yield: 6.6% (from **12**). Eluent: CH_2Cl_2/MeOH (99:1). Foam. HPLC: t_R = 15.55 min (A/B = 65:35). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, 2H, J = 8.6), 6.89 (d, 2H, J = 8.6), 4.96 (m, 1H), 4.16 (d, 1H, J = 12.7), 4.02 (d, 1H, J = 12.7), 3.80 (s, 3H), 3.33 (d, 1H, J = 14.2), 3.18 (d, 1H, J = 13.4), 3.17 (m, 2H), 2.78 (d, 1H, J = 14.2), 2.67 (d, 1H, J = 13.4), 1.94 (m, 2H), 1.60 (m, 18H), 1.37 (s, 3H), 1.27 (m, 7H), 1.03 (s, 3H), 0.87 (s, 3H). ^{13}C NMR (75 MHZ, $CDCl_3$): δ 168.93, 166.70, 159.37, 130.02, 127.55, 114.30, 79.68, 59.19, 57.46, 55.28, 54.12, 49.58, 49.48, 48.50, 44.35, 44.67, 39.11, 33.21, 32.69, 30.18, 27.06, 26.39, 25.15, 21.19, 20.41, 20.10. MS (ES, positive mode): 629.3 (M + 1)$^+$. Anal. Calcd for $C_{35}H_{52}N_2O_6S$: C, 66.85; H, 8.33; N, 4.45; S, 5.10. Found: C, 66.66; H, 8.27; N, 4.61; S, 5.15.

Removal of the Chiral Auxiliary from the Isoborneol-Derived 2-Azetidinones. A solution of the corresponding 10-(*N*,*N*-dicyclohexylsulfamoyl)isoborneol-derived 2-azetidinone (0.43 mmol) in MeOH (6 mL) was treated with 2 N NaOH (0.32 mL, 0.64 mmol), and the mixture was stirred overnight at room temperature. After evaporation of the MeOH, the remaining aqueous mixture was diluted with H_2O (5 mL) and extracted with EtOAc to recover up to 90% of the corresponding isoborneol chiral auxiliary. The remaining aqueous layer was acidified with 1 N HCl to pH 3 and extracted again with EtOAc. The extract was dried (Na_2SO_4) and evaporated. The resulting residue was purified on a silica gel column as specified.

(4*S*)-Pmb-α-Bzl-Azn-OH (25a). Yield: 89% (from **22a**). Eluent: CH_2Cl_2/MeOH (98:2). Foam. HPLC: t_R = 6.03 min (A/B = 65:35). $[\alpha]_D$ = +41.38 (c = 1.13, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.28 (d, 2H, J = 8.4), 7.23 (m, 3H), 7.02 (m, 2H), 6.86 (d, 2H, J = 8.4), 4.56 (d, 1H, J = 15.3), 4.30 (d, 1H, J = 15.3), 3.78 (s, 3H), 3.24 (d, 1H, J = 14.8), 3.22 (d, 1H, J = 14.1), 2.95 (d, 1H, J = 14.8), 2.92 (d, 1H, J = 14.1). ^{13}C NMR (50 MHZ, $CDCl_3$): δ 175.18, 166.79, 159.31, 134.52, 130.28, 129.80, 128.75, 128.18, 127.47, 114.07, 63.29, 55.35, 54.46, 45.44, 44.91, 39.58. MS (ES, positive mode): 326.4 (M + 1)$^+$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.03; H, 5.85; N, 4.22.

(4*R*)-Pmb-α-Bzl-Azn-OH (25b). Enantiomer of **25a** Yield: 80% (from **23b**). Eluent: CH_2Cl_2/MeOH (98:2). $[\alpha]_D$ = −43.76 (c = 0.52, $CHCl_3$). MS (ES, positive mode): 326.4 (M + 1)$^+$. Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 69.97; H, 5.93; N, 4.04.

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Supporting Information Available: Experimental procedures and analytical and spectroscopic data of compounds **3**, **4**, **7**−**12**, **19**−**21**, **28**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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