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SYNTHESIS OF OPTICALLY ACTIVE 4-ALKOXYCARBONYL-β-LACTAMS FROM L-ASPARTIC ACID

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Abstract: Cyclization of L-aspartic acid to (*S*)-4-benzyloxycarbonyl-2-azetidinone followed by transesterification of this compound in the presence of titanium (IV) tetrabutoxide proved to be an exceedingly efficient method of general application for the preparation of (*S*)-4-alkoxycarbonyl-β-lactams.

Recently, we discovered that nylons bearing an alkoxycarbonyl group stereoregularly attached to the polymer backbone are unique amongst non-polypeptidic synthetic polyamides in taking up helical conformations similar to the α-helix characteristic of proteins[1-3]. As it is the case for polypeptides[4], the conformational properties of these modified nylons are expected to be decisively influenced by minor differences in the constitution of the alkyl side chain. It has also been shown that (*S*)-4-alkoxycarbonyl-2-azetidinones are highly convenient

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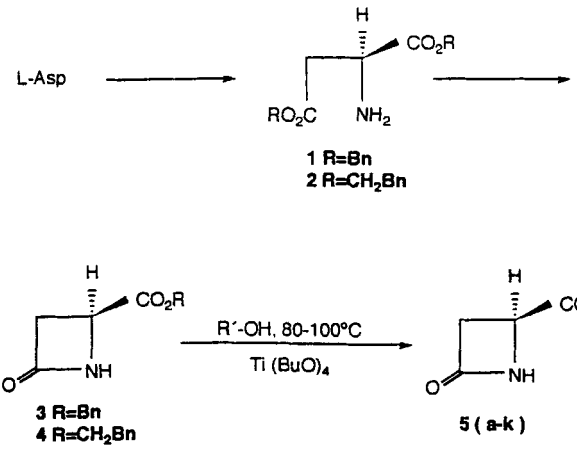
monomers to yield stereoregular 3-alkoxycarbonyl derivatives of nylon-3 by anionic ring-opening polymerization[5,6]. These findings have largely encouraged us to search for a general method of synthesis capable of furnishing such optically active β-lactams in multigram quantities. On the other hand, the lower members of the family are of potential interest as intermediates in β-lactam antibiotic chemistry since they could be converted into 4-acetoxy-2-azetidinone by oxidation with lead tetraacetate[7]. 4-Acetoxy-2-azetidinones are widely recognized as the most useful precursors for the synthesis of carbapenems involving the utilization of monocyclic β-lactams[8].

In spite of the copious literature produced along the last four decades on the synthesis of β-lactams, direct methods leading to the preparation of their monosubstituted alkoxycarbonyl derivatives are not available[9,10]. The Grignard-mediated cyclization of the *N*-silylated L-aspartate dibenzyl ester is the method described by Salzmann[11] for the synthesis of (*S*)-4-benzyloxycarbonyl-2-azetidinone. Our attempts to apply this procedure to the synthesis of alkyl β-lactam esters were unfruitful whereas we succeeded in obtaining (*S*)-4-(2-phenylethoxy)carbonyl-2-azetidinone in 22% yield. Therefore, feasibility of this method seems to be restricted to aspartate diesters of aromatic alcohols.

To circumvent the limitations found in the cyclization of alkyl diesters of aspartic acid, a strategy of synthesis based on the titanate-mediated transesterification method uncovered by Seebach[12] has been outlined. Such method is claimed to be appropriate for the transesterification of functionalized substrates, particularly when extremely mild conditions are required. Accordingly, (*S*)-4-

benzyloxycarbonyl-2-azetidinone **3** was prepared according to Salzmann[11] and then subjected to transesterification with a series of linear, branched and cyclic aliphatic alcohols in the presence of catalytic amounts of titanium(IV) tetrabutoxide.



An almost complete replacement of the benzyl group was accomplished in all cases by a judicious combination of reaction temperature and time. The resulting (*S*)-4-alkoxycarbonyl-2-azetidinones **5** were isolated and purified by either vacuum distillation or crystallization. Confirmation of configurational retention was attained by hydrolysis of **5h** to L-aspartic acid with a specific optical rotation value similar to that of the starting material. The accompanying Table shows the yields achieved in each case as well as some properties of the resulting β-lactams. Characterization of compounds **5** was carried out by elemental analysis, infrared and $^{1}H/^{13}C$ NMR spectroscopies. IR characteristic

bands appeared at 3250 (NH), 1721 (N-CO) and 1750 cm^{-1} (O-CO). ^1H NMR signals arising from the β-lactam ring common to the whole series appeared at 6.30-6.40 (s, 1H, NH), 4.14-4.24 (2d, 1H, CH) and 3.15-3.20 ppm (m, 2H diastereotopic CH_2). Chemical shifts of ^{13}C NMR peaks due to ring carbons were 166.3-167.3 (N-CO), 47.1-47.9 (CH) and 43,0-44,0 ppm (CH_2). A detailed account of spectroscopical data including those arising from the alkoxycarbonyl group is given in the experimental part.

(*S*)-4-Alkoxycarbonyl-β-lactams

Compound	R'	Yield (%)	M.p. (°C)	$[\alpha]^{25}_D$ (in Cl_3CH)
	lineal			
5a	$-CH_3$	64	45-46	-41.4°
5b	$-C_4H_9$	69	43-44	-36.3°
5c	$-C_6H_{13}$	47	15-16	-33.6°
5d	$-C_8H_{17}$	58	42-43	-29.0°
5e	$-C_{12}H_{25}$	53	66-67	-22.4°
5f	$-C_{18}H_{37}$	51	89-90	-17.4°
	branched			
5g	*i*-C_3H_7	68	51-52	-40.4°
5h	*i*-C_4H_9	58	35-36	-37.7°
5i	*neo*-C_5H_{11}	75	43-44	-36.1°
	cyclic			
5j	$-C_5H_9$	56	43-44	-37.8°
5k	$-C_6H_{11}$	40	65-66	-30.8°

We conclude that the titanate-mediated transesterification of the easily accessible (*S*)-4-benzyloxycarbonyl-2-azetidinone is an expedient method to afford

(*S*)-4-alkoxycarbonyl-2-azetidinones in high optical purity and yields. The synthetic route here described combines cyclization with transesterification and offers new flexibility in generating this family of esters. Difficulty in separating the resulting β-lactam from its corresponding alcohol logically increases with the length of the alkyl side chain. This should be envisaged as a potential limitation to the scope of the method.

Experimental Part

Melting points are uncorrected. IR spectra were obtained with a Perkin-Elmer 783 grating spectrometer from samples in KBr pellets. NMR spectra were recorded on a Varian XL-GEM200(200MHz) in $CDCl_3$ solution using tetramethylsilane as internal standard. Optical rotations were measured in chloroform at concentrations of 1g/100mL in a polarimeter Perkin-Elmer 141 at 25°C. L-Aspartic acid ($[\alpha]^{25}_D$: +24.7±0.5, *c* 5 in 5N HCl) was supplied by Fluka. Aliphatic alcohols were supplied by Aldrich and used without further purification except *n*-butanol, *n*-hexanol and *n*-octanol which were dried on molecular sieves and distilled. All microanalysis were performed by the Servei de Microanàlisi, CSIC, Barcelona.

(*S*)-4-(2-phenylethoxy)carbonyl-2-azetidinone (**4**). In a similar way as reported by Salzmann for the synthesis of **3**, monosilylation of the di(2-phenylethyl)-L-aspartate **2** followed by treatment with *t*-butylmagnesium chloride led to the title compound which was isolated by precipitation with dibutyl ether. Crystallization from ethyl acetate-hexane afforded pure **4** in 22% yield. Mp 74°C, $[\alpha]^{25}_D$: -22.4°. ^{1}H NMR: δ 7.26 (m, 5H, ArH), 6.40(s, 1H, NH), 4.38 (t, 2H, CO_2CH_2), 4.13 (2d, 1H, CHNH), 3.10 (m, 2H, CH_2CO), 2.97 (t, 2H, CH_2Ar). ^{13}C NMR: δ 170.90, 166.49, 137.06, 128.82, 128.56, 126.78, 65.89, 47.20, 43.44, 34.87. Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.84; H, 6.00; N, 6.30.

Transesterification of (*S*)-4-Benzyloxycarbonyl-2-azetidinone (3) with aliphatic alcohols: General Procedure.

(*S*)-4-Benzyloxycarbonyl-2-azetidinone **3** was prepared according to Salzmann[11] by cyclization of dibenzyl L-aspartate **1**. Mp 139-140°C, $[\alpha]^{25}_D$: -38.7° (*c* 1.01 in Cl_3CH). (Lit[13]. mp 139-40°C, $[\alpha]^{25}_D$: -35.7° *c* 1.12 in MeOH).

A vigorous stirred solution of **3** (2.0g, 10 mmol) and titanium(IV) tetrabutoxide (0.1g, 0.3mmol) in the corresponding alcohol was heated at the selected temperature for a period of time ranging between two and four hours depending on the alcohol of choice. The course of the transesterification was followed by TLC, the reaction being assumed to be over when no trace of UV absortion indicative of **3** was detectable. The reaction mixture was then diluted with two volumes of chloroform, washed sucessivelly with 1N HCl, 2% hydrogen sodium carbonate and water in order to remove the catalyst and finally evaporated to an oily residue. Distillation under vacuum of this oil afforded compound **5** (**a-d** and **g-k**) as a white solid which was finally purified by crystallization. Non distillable compounds **5e** and **5f** were separated from the concentrated reaction mixture by precipitation and finally purified by repeated crystallization.

(*S*)-4-Methoxycarbonyl-2-azetidinone (**5a**). Transesterification of **3** with methanol (molar ratio 1:40) was performed in sealed ampoules at 86°C for a period of four hours. The title compound **5a** was purified by distillation at 140°/0.02 mm. Crystallization from ethyl acetate-hexane (1:1) gave pure **5a** in 64% yield. Mp 45.5-46.5°C, $[\alpha]^{25}_D$: -41.4°. ^{1}H NMR: δ 6.37 (s, 1H, NH), 4.20 (2d, 1H, CHNH), 3.79 (s, 3H, OCH_3), 3.20 (m, 2H, CH_2CO). ^{13}C NMR: δ 171.44, 166.41, 52.63, 47.15, 43.53. Anal. Calcd. for $C_5H_7O_3N$: C, 46.51; H, 5.47; N, 10.85. Found: C, 46.50; H, 5.47; N, 10.77.

(*S*)-4-Butoxycarbonyl-2-azetidinone (**5b**). Transesterification of **3** with *n*-butanol (molar ratio 1:20) was performed at 100°C for a period of two hours. Distillation at 140°C/0.02 mm gave **5b** which was crystallized from ethyl acetate-hexane. Yield 69%, mp 43-44°C, $[\alpha]^{25}_D$: -36.3°. ^{1}H NMR: δ 6.25 (s, 1H, NH), 4.20 (m, 3H, CHNH and CO_2CH_2), 3.20 (m, 2H, CH_2CO), 1.65 (m, 2H, $CO_2CH_2CH_2$), 1.40 (m, 2H, CH_2CH_3), 0.95 (t, 3H, CH_3). ^{13}C NMR: δ 171.07, 166.44, 65.64, 47.29, 43.52, 30.47, 19.00, 13.63. Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.69; N, 8.18. Found: C, 56.14; H, 7.69; N, 8.16.

(*S*)-4-Hexoxycarbonyl-2-azetidinone (**5c**). In substantially the same manner as given above for **5b** but using a temperature of 85°C for transesterification, the title compound **5c** was obtained in 47% yield. Mp 15-16°C, $[\alpha]^{25}_D$: -33.6°. ^{1}H NMR: δ 6.40 (s, 1H, NH), 4.18 (m, 3H, CHNH and CO_2CH_2), 3.20 (m, 2H, CH_2CO), 1.67 (m, 2H, $CO_2CH_2CH_2$), 1.31 (broad, 6H, $3CH_2$), 0.90 (t, 3H, CH_3). ^{13} NMR: δ 171.95, 166.45, 66.57, 47.91, 44.13, 31.94, 29.03, 26.05, 23.10, 14.58. Anal. Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.14; H, 8.65; N, 6.93.

(*S*)-4-Octoxycarbonyl-2-azetidinone (**5d**). Transesterification of **3** was carried out at 80°C for two hours with *n*-octanol in a molar ratio 1:11. Distillation at 210°C/ 0.02mm followed by crystallization from hexane afforded **5d** in a yield of 58%. Mp 42-43°C, $[\alpha]^{25}_D$: -29.0°. ^{1}H NMR: δ 6.25 (s, 1H, N*H*), 4.18 (t, 2H,

CO_2CH_2), 4.18 (2d, 1H, CHNH), 3.20 (m, 2H, CH_2CO), 1.66 (m, 2H, $CO_2CH_2CH_2$), 1.30 (broad, 10H, $5CH_2$), 0.89 (t, 3H, CH_3). ^{13}C NMR: δ 171.50, 65.98, 47.30, 43.53, 31.73, 29.12, 28.45, 25.77, 22.60, 14.07. Anal. Calcd. for $C_{12}H_{21}NO_3$: C, 63.44; H, 9.25; N, 6.17. Found: C, 63.58; H, 9.37; N, 6.02.

(*S*)-4-Dodecoxycarbonyl-2-azetidinone (**5e**). Transesterification at 105°C for four hours using a molar ratio of **3** to *n*-dodecyl alcohol of 10:1 led to compound **5e** which was recovered from the evaporated reaction mixture by adding hexane and then crystallized repeatedely from the same solvent. Yield 58%, mp 66-67°C, $[\alpha]^{25}_D$: -22.4°. ^1H NMR: δ 6.20 (s, 1H, NH), 4.18 (m, 3H, CHNH and CO_2CH_2), 3.20 (m, 2H, CH_2CO), 1.66 (m, 2H, $CO_2CH_2CH_2$), 1.26 (broad, 18H, $9CH_2$), 0.88 (s, 3H, CH_3). ^{13}C NMR: δ 171.01, 166.28, 65.97, 47.28, 43.56, 31.88, 29.58, 29.33, 29.18, 28.47, 25.77, 22.67, 14.11. Anal. Calcd. for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.69; H, 10.31; N, 4.93.

(*S*)-4-Octadecoxycarbonyl-2-azetidinone (**5f**). The title compound **5f** was obtained in substantially the same manner as described above for **5e** but at a reaction temperature of 91°C and using a molar ratio of **3** to alcohol of 4:1. Yield 51%, mp 89-90°C, $[\alpha]^{25}_D$: -17.4°. ^1H NMR: δ 6.20 (s, 1H, NH), 4.17 (t, 2H, CO_2CH_2), 4.18 (2d, 1H, CHNH), 3.20 (m, 2H, CH_2CO), 1.66 (m, 2H, $CO_2CH_2CH_2$), 1.25 (broad, 30H, $15CH_2$), 0.87 (t, 3H, CH_3). ^{13}NMR δ 171.62, 167.03 66.49, 47.30, 44.01, 32.41, 30.18, 30.07, 29.98, 29.80, 29.69, 29.45, 28.98, 26.77, 23.18, 14.61. Anal. Calcd. for $C_{22}H_{41}NO_3$: C, 71.89; H, 11.24; N, 3.81. Found: C, 71.12; H, 11.20; N, 3.68.

(*S*)-4-Isopropoxycarbonyl-2-azetidinone (**5g**). Transesterification of **3** with isopropyl alcohol (molar ratio 1:15) was performed at 105°C for a period of two hours. Distillation at 120°C/0.02 mm gave **5g** which was then crystallized from hexane. Yield 68%, mp 51-52°C. $[\alpha]^{25}_D$: -40.4°. ^1H NMR: δ 6.41 (s, 1H, NH), 5.09 (h, 1H, CO_2CH), 4.14 (2d, 1H, CHNH), 3.18 (m, 2H, CH_2CO), 1.30 (d, 6H, $2CH_3$). ^{13}C NMR: δ 171.12, 167.27, 70.07, 47.94, 43.90, 22.15. Anal. Calcd. for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.46; H, 7.08; N, 8.85.

(*S*)-4-Isobutoxycarbonyl-2-azetidinone (**5h**). As above for **5g** but at a reaction temperature of 85°C, compound **5h** was obtained in 58% yield. Mp 35-36°C, $[\alpha]^{25}_D$: -37.7°. ^1H NMR: δ 6.45 (s, 1H, NH), 4.18 (2d, 1H, CHNH), 3.95 (d, 2H, CO_2CH_2) 3.20 (m, 2H, CH_2CO), 1.95 (m, 1H, $CH(CH_3)_2$), 0.95 (d, 6H, $2CH_3$). ^{13}C NMR: δ 171.12, 166.69, 71.60, 47.24, 43.40, 27.57, 18.86. Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.11; H, 7.69; N, 8.12.

(*S*)-4-(2,2'-dimethyl)propoxycarbonyl-2-azetidinone (**5i**). As above for **5g** but at a reaction temperature of 100°C and distillation at 135°C/0.02mm, compound **5i**

was obtained in 75% yield. Mp 43-44°C, $[\alpha]^{25}_D$: -36.1°. ^{1}H NMR: δ 6.16 (s, 1H, NH), 4.24 (2d, 1H, CHNH), 3.81 (s, 2H, CO_2CH_2) 3.26 (m, 2H, CH_2CO), 0.89 (s, 9H, $3CH_3$). ^{13}C NMR: δ 171.86, 167.15, 75.34, 47.84, 44.00, 31.91, 26.89, Anal. Calcd. for $C_9H_{13}NO_3$: C, 58.37; H, 8.16; N, 7.56. Found: C, 58.48; H, 8.13; N, 7.53.

(*S*)-4-cyclopentoxycarbonyl-2-azetidinone (**5j**). Transesterification of **3** with cyclopentanol at a molar ratio of 15:1 for two hours and half at 85°C and distillation at 150°C/0.02 mm afforded compound **5j** in 56% yield. Mp 43-44°C, $[\alpha]^{25}_D$: -36.1°. ^{1}H NMR: δ 6.35 (s, 1H, NH), 5.23 (m, 1H, CO_2CH), 4.14 (2d, 1H, CHNH), 3.17 (m, 2H, CH_2CO), 1.70 (m, 8H, $4CH_2$). ^{13}C NMR: δ 171.37, 167.25, 79.26, 47.93, 43.89, 33.06, 24.14, Anal. Calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.64. Found: C, 59.05; H, 7.15; N, 7.67.

(*S*)-4-cyclohexoxycarbonyl-2-azetidinone (**5k**). Reaction of **3** with cyclohexanol for three hours at 105°C and distillation at 155°C/0.02mm afforded compound **5k** in 56% yield. Mp 65-66°C, $[\alpha]^{25}_D$: -30.8°. ^{1}H NMR: δ 6.11 (s, 1H, NH), 4.85 (m, 1H, CO_2CH), 4.16 (2d, 1H, CHNH), 3.15 (m, 2H, CH_2CO), 1.47 (m, 10H, $5CH_2$). ^{13}C NMR: δ 170.47, 167.00, 74.33, 47.68, 43.73, 31.36, 25.13, 23.56. Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.10; N, 7.67. Found: C, 60.82; H, 7.06; N, 7.56.

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