Tetrahedron: Asymmetry Vol. 1, No. 12, pp. 881-884, 1990
Printed in Great Britain

0957-4166/90 $3.00+.00
Pergamon Press plc

Cyclic Sulphamidates: New Synthetic Precursors for β-functionalised α-Amino Acids.

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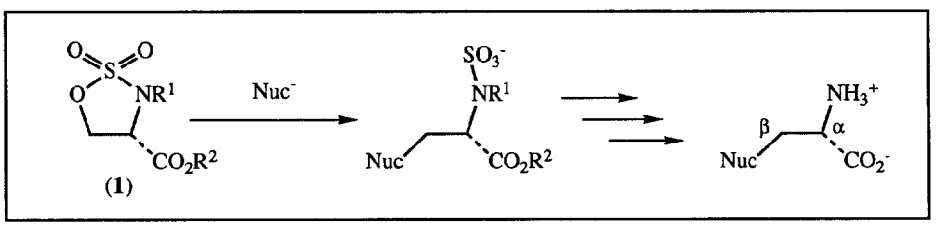
(*Received* 9 *November* 1990)

Abstract: The nucleophilic ring opening of cyclic sulphamidates derived from (S)-serine by a variety of nucleophiles, was utilised in a novel approach to the synthesis of β–substituted alanines.

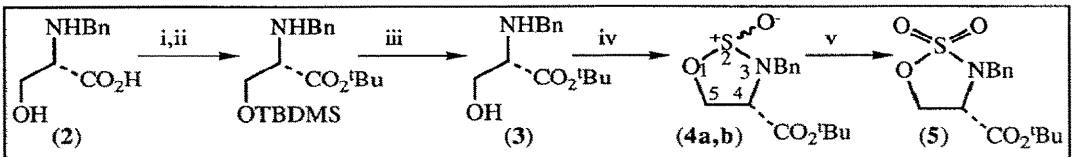
Due to the biological significance of many amino acids and their derivatives, the development of new methodology for the synthesis of amino acids continues to attract the attention of many synthetic organic chemists. Two main approaches have evolved: either the use of chiral templates (both in a stoichiometric and catalytic sense) or the modification of existing amino acids from the 'chiral pool'[1]. As an example of the latter we have developed the nucleophilic ring opening of aziridine-2-carboxylate esters with organocuprates[2] and other nucleophiles[3] to provide a useful route to α-amino acids and the literature contains many other complementary approaches[4].

The recent exploitation of vicinal diol cyclic sulphates as reactive epoxide equivalents by Sharpless and Gao[5, 6] suggested to us that a related methodology might be applicable to the synthesis of homochiral amino acids. We hypothesised that a cyclic sulphamidate (**1**)[7] derived from serine might simultaneously activate the β-position to nucleophilic attack and partially protect the amino group, and thus provide a useful 'β-alanyl cation' synthon for the synthesis of α-amino acids (Scheme 1).



Scheme 1

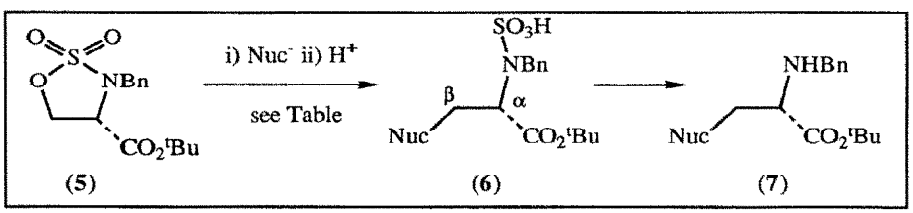
Synthesis of the desired cyclic sulphamidate was achieved from N-benzyl serine[8] (**2**) using essentially standard methodology (Scheme 2). The *tert*-butyl group was chosen for protection of the ester group to limit nucleophilic and or basic attack both on this functionality and at the α-position[9]. Formation of the cyclic suphamidate (**5**) was achieved from the 1,2-amino alcohol (**3**) by reaction with thionyl chloride to yield the cyclic sulphamidites (**4a** and **4b**), a 2:1 mixture of diastereomers. This mixture of diastereomers was oxidised directly to the cyclic sulphamidate (**5**) using sodium periodate with catalytic ruthenium (VIII)[10,12].



Reagents and conditions: i) $^{t}BuMe_2SiCl$ (1.1 eq), imidazole (2.2 eq), DMF, 20°C, 4 days; ii) $\{CCl_3C(=NH)O^{t}Bu\}$[11](10.0 eq), $BF_3.Et_2O$ (cat.), CH_2Cl_2:cyclohexane (2:1), 20°C, 18 h, (**76%**); iii) $^{n}Bu_4N^{+}F^{-}$(1.0 M in THF, 1.5 eq), THF, 0°C, 1 h, (**82%**); iv) $SOCl_2$ (1.0 eq), Et_3N (2.0 eq), toluene, 0°C, (**92%**); v) $NaIO_4$ (1.0 eq), $RuCl_3.H_2O$ (cat.), MeCN:H_2O (1:1), 20°C, (**91%**).

Scheme 2

Initially we examined the nucleophilic ring opening of (**5**) with several heteroatomic nucleophiles (Table 1, entries 1 to 4). Substitution was found to occur best, under acidic (entry 1) or neutral conditions (entries 2-4).[13] It is of interest that the only isolated products apparently resulted from substitution at the β-position, since Sharpless has noted a bias to ring opening at the position α to the ester moiety in the nucleophilic ring opening of analogous cyclic sulphates[5]. The chiral integrity of product (**3**), resulting from ring opening by water under acidic conditions, neutralisation with sodium bicarbonate (sat.) and recrystallisation from ether-hexane, was judged by comparison of optical rotation values:{(**3**) $[\alpha]^{20}_{D}$= -35.5 (c.0.64, $CHCl_3$) prior to cyclisation, and (**3**) $[\alpha]^{20}_{D}$= -32.2 (c.0.65, $CHCl_3$) following ring opening}.

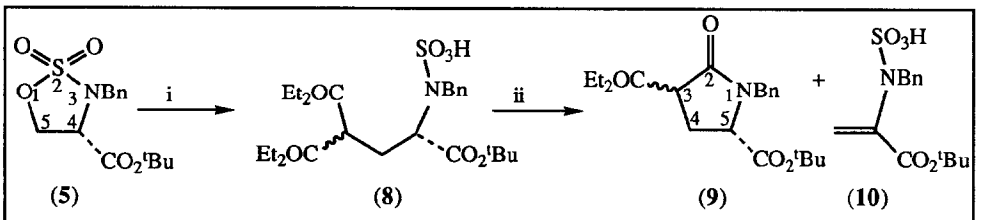


Entry	Product	Nucleophile	Reaction conditions[a]	Yield (%)[b]
1	3	H_2O	HCl (2.0 M aq.):dioxane (1:1), 14 h, 0-20°C	63
2	6b	N_3^-	NaN_3 (2 eq), acetone:water (1:1) 12 h, 20°C.	93
3	6c	SCN^-	NH_4SCN (2 eq), DMF, 12 h, 20°C	91
4	7d	pyrazole	pyrazole (5 eq), DMF, 11 h, 60°C	55
5	6e	CN^-	NaCN (2 eq), DMF, 12 h, 20°C.	82

[a]A typical experimental procedure is outlined (for entry 2) at the end of this paper. [b]Isolated yields.

Table 1

Sulphamidate (**5**) was also shown to react efficiently with sodium cyanide under neutral conditions to give the nitrile (**6e**). The discovery of the ideal conditions for reaction with organometallic reagents has proved more elusive, however (**5**) has been shown to undergo reaction with diethyl malonate to produce the desired product (**8**) which underwent cyclisation on work-up to produce the γ-lactam (**9**) (70% after chromatography) as a mixture of epimers at C-3, in addition to the dehydroalanyl derivative (**10**) (ca. 10%) (scheme 3).



Reagents and conditions: i) diethyl malonate (1.2 eq), Na (1.2 eq), THF:HMPA (4:1), 12 h, -78-20°C; ii) HCl (3.0 M aq), 30 min.

Scheme 3

The synthesis of a more efficacious version of (**5**) and investigation into the use of cyclic sulphamidates for the synthesis of more complex amino acids is currently in progress.

Experimental Procedures

N-Benzyl-(2R)-oxo-1,2,3-oxathiazolidine-(4S)-carboxylic acid *tert*-butyl ester and **N-Benzyl-(2S)-oxo-1,2,3-oxathiazolidine-(4S)-carboxylic acid *tert*-butyl ester (4a,b)**: To a solution of (**3**) (1.52 g, 6 mM) in dry toluene was added dropwise, successively, triethylamine (1.85 ml, 13 mM, 2.2 eq), followed by freshly distiled thionyl chloride (486 µl, 6.6 mM, 1.1 eq) over a period of 15 min. The temperature was allowed to rise to room temperature and after a further 1 h, ether (100 ml) was added and the combined organic phases extracted with water (2x20 ml), dried ($MgSO_4$), filtered, and evaporated to dryness to yield a pale yellow oil (**4a**:**4b**, ratio 2:1, by ^1H NMR, inseparable by flash chromatography) (1.65 g, 92%): R_f (50% ethyl acetate:hexane) 0.5; υ_{max} (neat) 3384(w) 2980(s) 2935(m) 1718(s) 1500(s) 1394(s) 1157(s) 1058(m) cm^{-1}; (**4a**) δ_H (500MHz, $CDCl_3$) 1.47 (9H, s, $C(CH_3)_3$), 4.04 (1H, dd, *J*=4.5, 7.5 Hz, H-4), 4.28, 4.46 (2H, AB_q, *J*=14.0 Hz, CH_2Ph), 4.61 (1H, dd, *J* =4.5, 9.0 Hz, H-5), 4.95 (1H, dd, *J*=7.5, 9.0 Hz, H-5), 7.31-7.49 (5H, m, aromatic CH); (**4b**) δ_H (500MHz, $CDCl_3$) 1.48 (1H, s, $C(CH_3)_3$), 3.88 (1H, dd, *J*=6.5, 7.5 Hz, H-4), 4.49, 4.53 (2H, AB_q, *J*=14.0 Hz, CH_2Ph), 4.56 (1H, dd, *J*=7.5, 8.5 Hz, H-5), 5.05 (1H, dd, *J*=8.5, 6.5 Hz, H-5), 7.32-7.46 (5H, m, aromatic CH); (**4a**) δ_C (125 MHz, $CDCl_3$) 27.9 ($C(CH_3)_3$),49.1 (CH_2Ph), 60.8 (C-4), 72.2 (C-5), 83.2 ($C(CH_3)_3$), 128.2, 128.7 129.1 (aromatic CH), 135.7 (aromatic ipso-C), 168.4 ($CO_2{}^tBu$); (**4b**) δ_C (125 MHz, $CDCl_3$) 28.1 ($C(CH_3)_3$), 49.2 (CH_2Ph), 61.3 (C-4), 72.8 (C-5), 83.3 ($C(CH_3)_3$), 128.3, 128.9, 129.3 (aromatic CH), 135.9 (aromatic ipso-C), 168.1 ($CO_2{}^tBu$); (m/e (NH_3 CI$^+$) 315 (MNH_4^+, 3%), 298 (MH^+, 100%), 242 (90%), 196 (65%), 108 (20%), 91 (Bn^+, 81%).

N-Benzyl-2,2-dioxo-1,2,3-oxathiazolidine-(4S)-carboxylic acid *tert*-butyl ester (5): The mixture of diastereomers (**4a** and **4b**) (1.65 g, 6 mM) was dissolved in 40 ml of dry acetonitrile and cooled to 0°C over ice. Ruthenium (III) chloride monohydrate (<1 mg) was added followed by sodium periodate (1.39 g, 6.5 mM, 1.1 eq). Water (25 ml) was added and a thick white precipitate appeared. The solution was stirred vigorously for a further 2 h and then diluted with ether (150 ml). The phases were separated, the aqueous phase re-extracted with ether (3x30 ml), and the combined organic fractions washed with saturated aqueous sodium bicarbonate (50 ml) and brine (50 ml), dried ($MgSO_4$) filtered through a plug of celite under suction, and rotary evaporated to yield a pale yellow viscous oil, which crystallised as (5) (1.57 g, 85%): R_f (50% ethyl acetate:hexane) 0.8; mp=41-43°C; $[\alpha]^{20}_D$ -48.4 (c.0.75, $CHCl_3$); Found C 53.7, H 6.2, N 4.7%,

$C_{14}H_{19}NO_5S$ requires C 53.7, H 6.1, N 4.5%; υ_{max} (neat) 2981(m) 1740(s) 1370(s) 1353(s) 1192(s) 1154(s) cm^{-1}; δ_H (500MHz, $CDCl_3$) 1.46 (9H, s, $C(C\underline{H}_3)_3$), 3.94 (1H, dd, *J*=4.5, 7.5 Hz, <u>H</u>-4), 4.49, 4.54 (2H, AB_q, *J*=14.5 Hz, $C\underline{H}_2Ph$), 4.59 (1H, dd, *J*=9.0, 7.5 Hz, <u>H</u>-5), 4.64 (1H, dd, *J*=9.0, 4.5 Hz, <u>H</u>-5), 7.35-7.43 (5H, m, aromatic C<u>H</u>); δ_C (125 MHz, $CDCl_3$) 27.9 ($C(\underline{C}H_3)_3$), 50.2 ($\underline{C}H_2Ph$), 58.7 (<u>C</u>-4), 67.6 (<u>C</u>-5), 84.1 ($\underline{C}(CH_3)_3$), 128.6, 128.8, 129.1 (aromatic <u>C</u>H), 133.9 (aromatic ipso-<u>C</u>), 166.8 ($\underline{C}O_2{}^tBu$); m/e (NH_3 CI^+) 331 (MNH_4^+, 70%), 314 (MH^+, 5%), 275 (100%), 134 (30%), 108 (73%), 91 (Bn^+, 65%).

N-Benzyl-N-sulpho-3-azido-(2<u>S</u>)-alanine *tert*-butyl ester (6b): To a solution of (**5**) (271 mg, 0.86 mM) in acetone (5 ml) was added NaN_3 (112 mg, 1.72 mM, 2 eq) as a solution in water (5 ml) and the mixture allowed to stir for 12 h. The resulting pale yellow, clear solution was then concentrated and re-dissolved in dry acetonitrile (10 ml) before filtering through a short plug of celite and concentrating again to yield a white powder which was then recrystallised (ethyl acetate-hexane) to give a white powder (**6b**) (288 mg, 93%): R_f(80% CH_3CN:H_2O) 0.8; mp=154-156°C (decomp.); $[\alpha]^{20}{}_D$ -24.3 (c.1.05, CH_3CN); υ_{max} ($CHCl_3$) 2982(w) 2107(s) 1723(s) 1371(m) 1256(s) 1057(s) cm^{-1}; δ_H (500MHz, CD_3CN) 1.43 (9H, s, $C(C\underline{H}_3)_3$), 3.57 (1H, dd, *J*=6.0, 12.5 Hz, βC<u>H</u>H), 3.67 (1H, dd, *J*=8.0, 12.5 Hz, βCH<u>H</u>), 3.99 (1H, dd, *J*=8.0, 6.0 Hz, αC<u>H</u>), 4.28, 4.44 (2H, AB_q, *J*=16.0 Hz, $C\underline{H}_2Ph$), 7.22-7.26 (1H, m, aromatic C<u>H</u>), 7.3-7.33 (2H, m, aromatic C<u>H</u>), 7.44-7.46 (2H, m, aromatic C<u>H</u>); δ_C (125 MHz, CD_3CN) 28.2 ($C(\underline{C}H_3)_3$), 51.6 ($\underline{C}H_2Ph$), 51.7 (β$\underline{C}H_2$), 61.7 (α<u>C</u>H), 83.0 ($\underline{C}(CH_3)_3$), 127.7, 129.0, 129.2 (aromatic <u>C</u>H), 140.9 (aromatic ipso-<u>C</u>), 171.4 ($\underline{C}O_2{}^tBu$); m/e (NH_3 CI^+) 277 (MH^+-SO_3, 100%), 221 (24%), 175 (10%), 164 (10%), 91 (Bn^+, 30%).

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13. Cyclic sulphamidates derived from (*S*)-prolinol have also been shown to undergo ring opening under acidic conditions, D. Alker, K. J. Doyle, L. M. Harwood, and A. McGregor, *Tetrahedron Asymmetry*, in press.