Reinvestigation of the Base-Induced Ring Closure of Methylsulfonium Salts of *N*-Trityl-(*S*)-methioninehydroxamide and Derivatives

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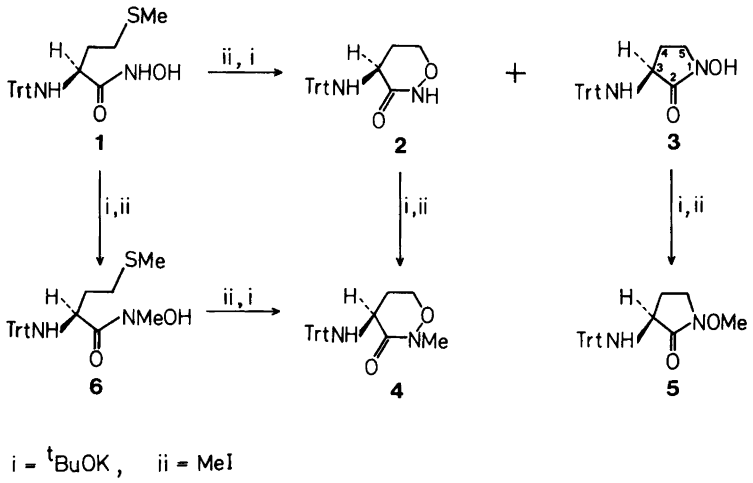
Base-induced ring closure of methylsulfonium salts of hydroxamate derivatives of *N*-trityl-(*S*)-methionine provides five-membered heterocycles resulting from nucleophilic displacement of Me_2S by either the O- or N-atom of the amide function. A three-step sequence starting from *N*-trityl-(*S*)-methionine 1-hydroxybenzotriazolyl ester has previously been used to provide a 3 % yield of a compound described as (*S*)-4-(*N*-tritylamino)-1,2-oxazinan-3-one. Using a new five-step sequence the same product was isolated in 34 % overall yield and is now shown to be (*S*)-2-hydroxyimino-3-(*N*-tritylamino)oxolane.

We have recently shown that the base-initiated ring closure of methylsulfonium salts of suitable derivatives of *N*-tritylmethionine provides a variety of heterocyclic compounds of synthetic and biological interest.[1] In particular, sequential treatment of *N*-trityl-(*S*)-methioninehydroxamide (**1**) with MeI and potassium *tert*-butoxide (^{t}BuOK) produced as the main product (51 % yield) (*S*)-1-hydroxy-3-(*N*-tritylamino)-2-pyrrolidone (**3**). The reactions are given in Scheme 1. The structure of **3** was unambigously determined by means of an X-ray structure analysis of the corresponding *O*-methylated derivative **5**. Based on microanalysis and spectroscopic data structure **2** was assigned to a minor (3 %) isomer (Scheme 1) which is related to the biologically active compound homocycloserine (cyclocanaline). Methylation of **1** in the presence of ^{t}BuOK produced a mixture of products from which the major component (**6**) was obtained by flash chromatography in 17 % yield. It was now evident that a high-yielding synthesis of **2**, using the present methodology would require protection of the amide function prior to ring closure. However, direct alkylation of **1** or



Scheme 1. Original proposal for the cyclisation of (*S*)-*N*-tritylmethioninehydroxamide (**1**).

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acylation of *N*-alkyl derivatives of hydroxylamine by (*S*)-*N*-tritylmethionine 1-hydroxybenzotriazolyl ester (Trt-Met-OBt) was unsuccessful in our hands. We thus decided to investigate the alkylation of **1** after prior selective silylation of the hydroxy function. In view of the very low hydrolytic stability of the Me_3Si group we preferred to utilise the $^tBuPh_2Si$ group. The latter group, besides being of low hydrolytic lability, can provide crystalline products and is compatible with the trityl group.[2]

Treatment of crude **1**, as obtained by condensation of Trt-Met-OBt with *O*-trimethylsilylhydroxylamine,[1] with $^tBuPh_2SiCl$ and NaH in THF for 15 min at −10 °C, produced a ninhydrin-active compound as the main product. After purification by flash chromatography, this substance was obtained in 91 % yield as an oil containing (NMR) small amounts of residues from the slight excess of the silicon reagent actually employed. This intermediate was used as such in the next step. It was later shown that even purification by flash chromatography was unnecessary. The failure of attempts to obtain this product by an alternative route involving condensation of Trt-Met-OBt with $^tBuPh_2SiONH_2$ was presumably due to steric reasons. $^tBuPh_2SiONH_2$ was prepared from hydroxyammonium chloride and $^tBuPh_2SiCl$ using the procedure described for the preparation of Me_3SiONH_2.[3]

Since the position of Si could not otherwise be assigned with certainty, the product of the silylation of **1** was cyclised. Treatment of silylated **1** with MeI in ethyl acetate for 2 days at room temperature, produced a precipitate which was filtered off under nitrogen and used directly in the subsequent ring-closure step. Treatment of the precipitate with NaH in THF/DMF for 30 min at room temperature, produced a major product. Since attempts to purify this product by flash chromatography resulted in low mass recovery, it was further treated with tetrabutylammonium fluoride trihydrate in THF for 30 min at room temperature and the resulting reaction mixture, after work-up, was compared, by TLC, with the lactams **2** and **3**. The major product by far was the lactam **2** and no trace of **3** could be detected in the reaction product under these conditions. When, however, the silylation of **1** was conducted in THF/DMF (3:1) a small amount of **3** was indeed present in the final reaction mixture. It is of interest to note that lactam **2** can be readily obtained pure, in 34 % overall yield based on Trt-Met-OBt initially used, from the final reaction mixture simply by crystallisation from benzene/hexane (1:1).

The results thus far indicated that silylation of **1** must have taken place exclusively on the N-atom of the amide function. The heterocyclic ring proton region of the NMR spectrum of the intermediate, prior to F^- treatment, was identical with that for **2**. This rather unexpected finding, together with the results obtained when **2** was treated with HCl with a view to obtaining cyclocanaline hydrochloride, cast some doubt on the correctness of the structure initially proposed for **2**. Thus, treatment of **2** with HCl in THF/MeOH for a few minutes at room temperature, followed by trituration with diethyl ether produced crystalline material. Microscopic investigation of this product revealed that it consisted of two distinct kinds of crystal. X-ray analysis of the larger type of crystal showed that the compound was actually hydroxyammonium chloride. Meanwhile ^1H and ^{13}C NMR investigations of this optically active material revealed the presence of pure homoserine lactone as the other component; the absorption at 1775 cm^{-1} in the IR spectrum further supported this conclusion. Recrystallisation from MeOH/Et_2O provided a single crystalline compound which was unambiguously shown by X-ray analysis to be homoserine lactone (Hsl) hydrochloride (**12**); the corresponding racemic bromide has been examined previously.[4] The expected detritylation had thus been accompanied by hydrolysis of the oxime function, a fact explained by the small amounts of water expected to be present in the solvent system employed.

Additional evidence against structure **2** came from the ^1H NMR spectra, now recorded at 400 MHz, and the corresponding ^{13}C NMR spectra of the lactams **3** and **5** and the putative lactams **2** and **4** (Table 1). Thus, although the methylene protons next to the heteroatoms resonate at ca. 3.78–4.19 ppm for the pair **2/4** and at 3.00–3.35 ppm for the pair **3/5**, the OMe and presumed NMe protons appear at almost the same δ value in **4** and **5** (to within 0.12 ppm). This is underscored even more profoundly when the ^{13}C NMR spectra are compared. While the C-atoms next to the heteroatom of the ring resonate at ca. 42.70–43.30 ppm for the pair **3/5** and 69.46–69.56 ppm for the pair **2/4** as expected, the MeO and presumed NMe resonances are found at 62.543 and 62.027 ppm, respectively. Thus although the methylene carbons are indeed correctly attached to the corresponding heteroatoms, both methyl carbons must be attached to O-atoms.

Since **4** could be obtained from either **2** or **6** (Scheme 1), the ring-closure reaction of the sulfonium salt of **6** was investigated more carefully. Treatment of the latter using NaH as the base in THF/DMF (3:1) yielded the same two products as obtained when ^{t}BuOK was used as the base in THF, although the amount of the more polar component was considerably increased. In the present case the products were isolated in the ratio 3:1 by flash chromatography and shown by TLC and NMR to be identical with **4** (less polar product) and **5** (more polar product). It is apparent that the use of NaH as the base and DMF as the cosolvent leads to the increased formation of **5**.

While the formation of **4** from **6** might be readily understood, the production of **5** from the same starting material cannot be rationalised since the amide function is protected by the Me group. The initially proposed structure **6** could not thus correspond to the compound in question. At that time, careful recrystallisation of the compound provided us with crystals that, while not allowing accurate X-ray analysis, were adequate for the unambiguous determination of the position of the Me group (information related to the X-ray analysis may be obtained from the authors). Thus, as shown in Fig. 1, the Me group was actually attached to the hydroxy group rather than to the N-atom of the amide

Table 1. NMR data for the 5-membered ring heterocycles.[a]

^{1}H NMR[b]	^{13}C NMR
Lactam **3**	
7.549 (6 H, m, *o*-ArH)	170.388 (C-2)
7.267 (6 H, m, *m*-ArH)	145.749 (ArC-1)
7.194 (3 H, m, *p*-ArH)	128.915 (ArC-2/6)
3.415 (1 H, t, *J* 8.77 Hz, H-3)	128.013 (ArC-3/5)
3.346 (1 H, t, *J* 9.27 Hz, H-5)	126.672 (ArC-4)
3.204 (1 H, dt, *J* 9.27, 6.94 Hz, H-5')	71.072 (Ph_3C)
1.285 (1 H, m, *J* 12.99, 8.77, 6.94 Hz, H-4)	53.330 (C-3)
0.999 (1 H, m, H-4')	46.262 (C-5)
	27.666 (C-4)
Lactam **5**	
7.575–7.554 (6 H, m, *o*-ArH)	170.650 (C-2)
7.303–7.254 (6 H, m, *m*-ArH)	145.893 (ArC-1)
7.218–7.182 (3 H, m, *p*-ArH)	128.967 (ArC-2/6)
3.767 (3 H, s, OCH_3)	127.992 (ArC-3/5)
3.309 (1 H, dd, *J* 9.63, 8.21 Hz, H-3)	126.633 (ArC-4)
3.274 (1 H, dt, *J* 8.54, 0.88 Hz, H-5)	70.998 (Ph_3C)
3.027 (1 H, ddd, *J* 9.87, 8.54, 6.64 Hz, H-5')	62.027 (O–C)
1.255 (1 H, dddd, *J* 12.56, 9.87, 9.63, 8.54 Hz, H-4)	52.923 (C-3)
0.966 (1 H, dddd, *J* 12.56, 8.21, 6.64, 0.88 Hz, H-4')	42.699 (C-5)
	27.752 (C-4)
Imidate **7** (putative lactam **2**)[c]	
7.558–7.528 (6 H, m, *o*-ArH)	160.614 (C-2)
7.309–7.264 (6 H, m, *m*-ArH)	145.867 (ArC-1)
7.223–7.183 (3 H, m, *p*-ArH)	128.801 (ArC-2/6)
7.087 (1 H, br s, = NOH)	128.075 (ArC-3/5)
4.182 (1 H, dt, *J* 8.79, 1.91 Hz, H-5)	126.687 (ArC-4)
3.816 (1 H, ddd, *J* 10.91, 8.79, 5.71 Hz, H-5')	70.984 (Ph_3C)
3.759 (1 H, dd, *J* 10.07, 7.21 Hz, H-3)	69.461 (C-5)
2.642 (1 H, br, Trt–NH)	53.893 (C-3)
1.327 (1 H, dddd, *J* 12.50, 10.91, 10.07, 1.91 Hz, H-4)	33.541 (C-4)
0.967 (1 H, dddd, *J* 12.50, 8.79, 7.21, 5.71 Hz, H-4')	
Imidate **9** (putative lactam **4**)[c]	
7.558–7.537 (6 H, m, *o*-ArH)	158.950 (C-2)
7.306–7.266 (6 H, m, *m*-ArH)	145.850 (ArC-1)
7.242–7.173 (3 H, m, *p*-ArH)	128.887 (ArC-2/6)
4.152 (1 H, dt, *J* 8.58, 2.08 Hz, H-5)	127.964 (ArC-3/5)
3.885 (3 H, s, OCH_3)	126.644 (ArC-4)
3.788 (1 H, ddd, *J* 10.72, 8.96 5.74 Hz, H-5')	71.066 (Ph_3C)
3.648 (1 H, dd, *J* 10.00, 7.04 Hz, H-3)	69.558 (C-5)
2.916 (1 H, br s, Trt–NH)	62.543 (=NO–C)
1.402 (1 H, dddd, *J* 12.74, 10.72, 10.00, 2.08 Hz, H-4)	53.627 (C-3)
1.059 (1 H, dddd, *J* 12.74, 8.58, 7.04, 5.74 Hz, H-4')	33.646 (C-4)
Lactone **12**[d]	
4.616 (1 H, dt, *J* 9.30, 9.21, 1.24 Hz, H-5)	177.749 (C-2)
4.489 (1 H, ddd, *J* 10.98, 9.30, 6.14 Hz, H-5')	70.222 (C-5)
4.426 (1 H, dd, *J* 11.70, 9.00 Hz, H-3)	51.475 (C-3)
2.802 (1 H, dddd, *J* 12.74, 9.00, 6.14, 1.24 Hz, H-4)	29.791 (C-4)
2.432 (1 H, dddd, *J* 12.74, 11.70, 10.98, 9.21 Hz, H-4')	

[a]All spectra were obtained in $CDCl_3$ with Me_4Si as an internal standard, except that of the lactone which was recorded in D_2O using $Me_3SiCD_2CD_2CO_2Na$ as an internal standard. [b]The proton resonances were assigned on the basis of chemical shifts, analysis of coupling patterns and selected proton decoupling. The spectral parameters for the lactone **12** were obtained by iterative computer analysis, whereas the coupling constants for the other compounds were obtained by first-order analysis of the splitting patterns. [c]The compounds originally thought to be the lactams **2** and **4** were shown to be the imidates **7** and **9**, respectively. [d]Assignment of the chemical shift values of L-homoserine lactone hydrochloride may be found in the literature.[6]

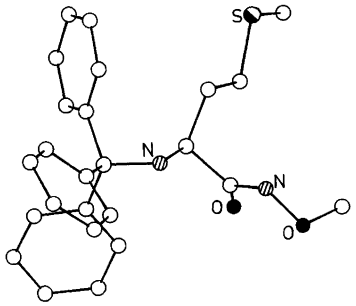
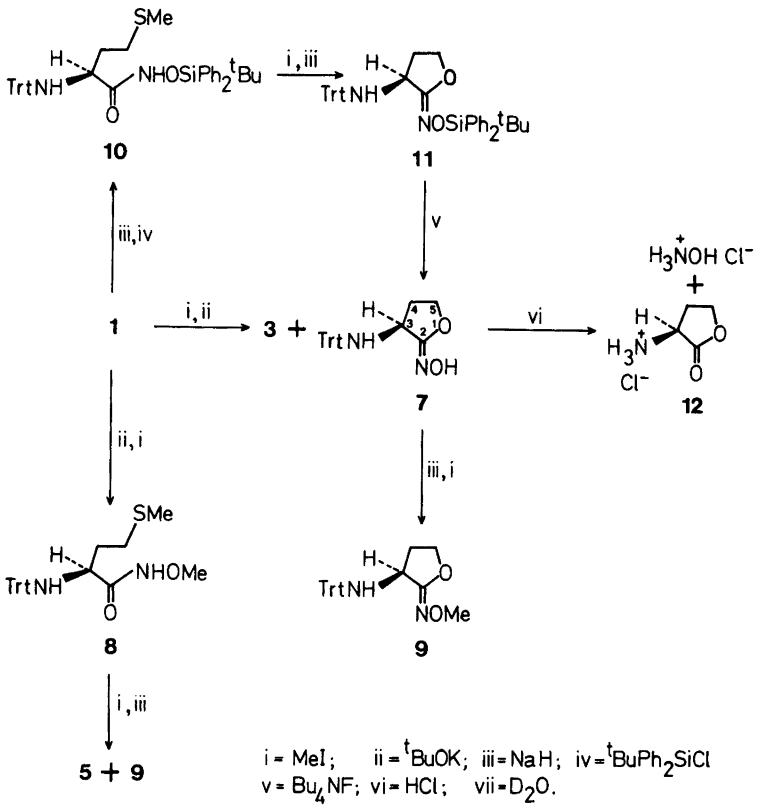


Fig. 1. ORTEP drawing of the intermediate **8**.

function. The correct structure for the major product of the methylation of **1** is actually **8** (Scheme 2) and not **6** as initially proposed. While this result allowed for the accommodation of **5** as a product of the above-mentioned ring-closure reaction, the formation of **4** now remained to be explained. Since the only other nucleophilic site in the sulfonium salt of **1** is the O-atom of the amide function, it is reasonable to propose that the correct structure for **4** is actually the *O*-methylated oxime (**9**) of *N*-tritylhomoserine lactone, which is formed as shown in eqn. (1) of Fig. 2. It follows that the compound for which the structure **2** was initially proposed is actually the oxime (**7**) of *N*-tritylhomoserine lactone. Structures **7** and **9** account not only for the available NMR data, but also explain the ready loss of an OH fragment ($M-17$) from both **3** and **7** and of a MeO fragment ($M-31$) from both **5** and **9** in their 70 eV mass spectra,[1] a fact not easily explained, were the structures **2** and **4** correct.

The sequence of reactions depicted in Scheme 2 are self-consistent. Thus, silylation of **1** takes place exclusively, in THF, on the hydroxy group as expected, whereas cyclisation takes place through the amide oxygen, which is the atom most remote from the bulky silyl group on the nucleophilic end of the amide function, and provides the intermediate **11** exclusively [Fig. 2, eqn. (1)]. However, when silylation takes place in THF/DMF, a small quantity of a product silylated on the amide function is formed and it is this which, on sulfonium ion formation and NaH treatment, leads ultimately on final desilylation with F^- to the production of **3**. This in turn indicates that the silyl group must migrate during cyclisation from the amide O-atom to the O-atom of the hydroxy group as depicted in eqn. (2) of Fig. 2.



Scheme 2. Reactions of (*S*)-*N*-tritylmethioninehydroxamide (**1**) as elucidated in the present report.

Treatment of intermediate **11** with Bu_4NF provides the final product **7**, which upon methylation provides **9**; **9** is also obtained from the hydroxamate **8** as described. Finally, reaction of **7** with methanolic HCl leads by fragmentation to hydroxyammonium chloride and Hsl hydrochloride (**12**). The latter compound was unambiguously determined by means of a crystal structure analysis, Fig. 3. The corresponding racemic bromide has been determined previously.[4] The present results (Table 2) are in general agreement with the bond lengths, bond angles and torsional angles then reported. Discrepancies in torsional angles are probably due to the different packing arrangements in the two space groups; the racemic bromide has space group *Pbca*, while the chiral chloride has space group $P2_12_12_1$. The absolute stereochemistry presented in Fig. 3 is based solely on LS refinement of the chirality parameter of Rogers.[5]

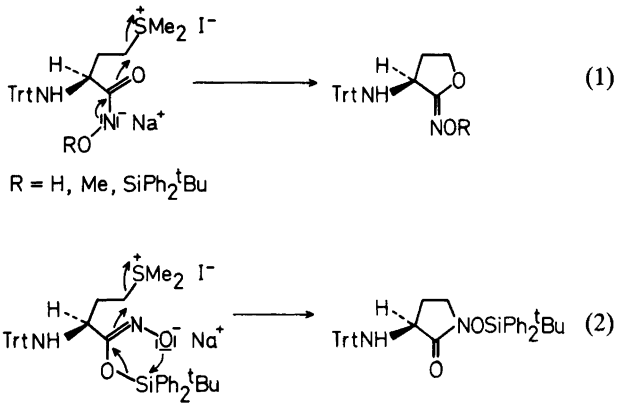


Fig. 2. Mechanisms for cyclisation of methioninesulfonium salts.

Experimental

IR spectra were recorded as 5 % $CHCl_3$ solutions or as Nujol mulls on a Perkin–Elmer model 399B spectrometer. The ^1H and ^{13}C NMR spectra were obtained at 400.13 and 100.63 MHz, respectively, on a Bruker AM400 spectrometer. Homonuclear proton decoupling was used when necessary for chemical shift assignments. The broad-band decoupled ^{13}C-spectra were obtained using standard one-pulse and spin-echo experiments. The latter technique was used in order to distinguish methyl and methine carbons from methylene and quaternary carbons.[7] Chemical shifts

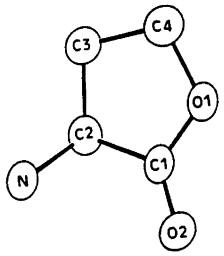


Fig. 3. ORTEP drawing of (*S*)-homoserine lactone hydrochloride (**12**). All three hydrogen atoms on nitrogen were involved in intermolecular H–Cl–H interactions. The chlorine atoms are omitted for clarity.

Table 2. Table of bond distances (Å) bond angles (°) and torsional angles (°) in (*S*)-homoserine lactone hydrochloride (**12**). Numbers in parentheses are estimated standard deviations in the least significant digits.

Atoms	Distance	Atoms	Angle	Atoms	Torsional angle
O1–C1	1.328(4)	C1–O1–C4	111.8(2)	C4–O1–C1–O2	−176.5(4)
O1–C4	1.446(4)	O1–C1–O2	123.4(3)	C4–O1–C1–C2	4.6(4)
O2–C1	1.178(4)	O1–C1–C2	109.6(3)	C1–O1–C4–C3	6.8(4)
N–C2	1.479(4)	O2–C1–C2	127.0(3)	O1–C1–C2–N	−137.1(3)
C1–C2	1.520(5)	N–C2–C1	110.2(3)	O1–C1–C2–C3	−14.0(4)
C2–C3	1.517(4)	N–C2–C3	114.1(2)	O2–C1–C2–N	44.1(5)
C3–C4	1.511(5)	C1–C2–C3	104.6(3)	O2–C1–C2–C3	167.2(4)
		C2–C3–C4	103.6(3)	N–C2–C3–C4	137.5(3)
		O1–C4–C3	107.3(3)	C1–C2–C3–C4	16.9(4)
				C2–C3–C4–O1	−14.9(4)

are reported in δ units, parts per million (ppm) downfield from the internal standard. Mass spectra were recorded using the direct insertion probe on a JEOL JMS D-100 instrument operating at 70 eV with a source temperature of 180 °C and the minimum sample temperature required to ensure volatilisation. Optical rotations were recorded using a Carl–Zeiss precision polarimeter.

Flash chromatography was performed on silica gel 60 (230–400 mesh, Merck) and TLC was carried out on Polygram precoated plastic sheets (0.20 mm, silica gel N-HR/UV_{254}, Macherey–Nagel) and the spots were visualised with a UV lamp at 254 nm and by spraying with ninhydrin. TLC solvents were as follows: (A) toluene/hexane/ethyl acetate (7:3:2) and (B) toluene/ethyl acetate (6:4). Tetrahydrofuran (THF) was distilled from sodium/benzophenone under an atmosphere of dry nitrogen, and *N,N*-dimethylformamide (DMF) from calcium hydride under reduced pressure and kept over molecular sieves (3 Å).

In general all reactions were carried out under an atmosphere of dry nitrogen. (*S*)-*N*-Tritylmethioninehydroxamide (**1**) was prepared from Trt-Met-OBt purchased from Biohellas S.A., and $H_2NOSiMe_3$ as described.[1] *O*-(*tert*-Butyl)diphenylsilylhydroxylamine was prepared according to the procedure described for the preparation of the corresponding *O*-trimethylsilyl derivative[3] in 88 % yield after recrystallisation from pentane. It had m.p. 88–90 °C. Anal. $C_{16}H_{21}NOSi$: C,H,N. MS [IP 70 eV; *m/z* (% rel. int.)]: *M* = 271 (absent), 214 (96), 199 (100), 197 (78), 181 (23), 152 (24), 138 (46), 136 (30), 121 (20), 105 (21), 77 (38). ^{1}H NMR ($CDCl_3$): δ 7.744–7.715 (4 H, m, *o*-ArH), 7.441–7.361 (6 H, m, *m*- and *p*-ArH), 1.085 (9 H, s, CH_3). ^{13}C NMR ($CDCl_3$): δ 135.505 (*o*-ArC), 133.458 (*ipso*-ArC), 129.652 (*p*-ArC), 127.755 (*m*-ArC), 27.071 (CH_3), 19.177 (C-Me). IR: 3310, 3100–2770, 1585, 1570, 1475, 1425, 1190, 1115, 1040, 905, 850, 710, 690, 670 cm^{-1}.

(S)-*2-Hydroxyimino-3-(N-tritylamino)oxolane* (**7**). A solution of the crude hydroxamic acid **1** (obtained[1] from 20 mmol of Trt-Met-OBt) was added dropwise at −10 °C to a suspension of NaH (0.96 g; 40 mmol) in THF (40 ml). The resulting mixture was stirred at this temperature for a further 5 min and treated with ^{t}BuPh$_2$SiCl (5.2 ml; 20 mmol). After being stirred for an additional 15 min, the mixture was cautiously neutralised with glacial acetic and the reaction mixture was allowed to attain room temperature. It was subsequently diluted with a 5 % aqueous citric acid solution and extracted with diethyl ether. The organic phase was washed with water and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure left the crude intermediate **10** [R_F(A) = 0.77] as an oil. When silylation was carried out in THF/DMF (3:1) a less polar ninhydrin-active product, presumably arising by silylation of the amide function, was formed in small quantities and had R_F(A) = 0.82. A small portion of crude **10** was chromatographed (flash chromatography), with TLC system A as the eluant, and the NMR of almost pure oily **10** recorded. ^{1}H NMR ($CDCl_3$): δ 7.763 (1 H, s, CONH), 7.701–7.657 (4 H, m, ArH), 7.451–7.319 (12 H, m, ArH), 7.200–7.119 (9 H, m, ArH), 4.073–4.018 (1 H, m, CH), 2.500 (1 H, br, NH), 2.018–1.927 (1 H, m, SCH_2), 1.800–1.673 (1 H, m, SCH_2), 1.665 (SMe), 1.670–1.564 (1 H, m, CH_2) 1.245–1.136 (1 H, m, CH_2), 1.041 (9 H, s, C–CH_3). ^{13}C NMR ($CDCl_3$): δ 171.547 (CONH), 145.510, 135.616, 131.004, 129.588, 128.554, 128.034, 127.671, 126.787 (ArC), 71.615 (Ph_3C), 56.113 (CH), 32.949 (SCH_2), 29.318 (CH_2), 26.612 (CH_3–C), 18.871 (CH_3–*C*), 15.087 (SCH_3).

Crude **10**, obtained above, was dissolved in ethyl acetate (120 ml), MeI (12 ml, 0.19 mmol) added and the resulting solution was stirred in the dark, at room temperature, for 2 days. The resulting suspension was diluted with diethyl ether (240 ml) and filtered under nitrogen. The collected precipitate was washed with diethyl ether and dissolved in DMF (60 ml). This solution was then added dropwise to a cooled (0 °C) suspension of NaH (0.48 g; 20 mmol) in THF (90 ml). The resulting mixture was then stirred at 0 °C for 10 min and at room temperature for a further 30 min before being worked-up, as described for the intermediate **10**, to give the crude cyclised derivative **11**. Flash chromatography of a small quantity of crude **11** led to isolation of almost pure **11** [R_F(A) = 0.80] as an oil but resulted in considerable mass loss. The NMR spectra of purified **11** were as follows: ^{1}H NMR ($CDCl_3$): δ 7.847–7.773 (4 H, m,

ArH), 7.391–7.358 (12 H, m, ArH), 7.134–7.104 (9 H, m, ArH), 4.171 (1 H, dt, *J* 8.72 and 1.68 Hz, H-5), 3.799 (1 H, ddd, *J* 11.19, 9.01 and 5.65 Hz, H-5′), 3.717 (1 H, dd, *J* 10.05 and 7.33 Hz, H-3), 1.318–1.182 (1 H, m, H-4), 1.208 (9 H, s, C–CH_3), 0.873–0.782 (1 H, m, H-4′). ^{13}C NMR ($CDCl_3$): δ 162.451 (C-2), 145.818, 133.952, 129.428, 128.716, 127.901, 127.652, 126.467 (ArC), 70.826 (Ph_3C), 69.728 (C-5), 53.929 (C-3), 33.692 (C-4), 27.421 (CH_3–C), 19.424 (CH_3–C).

Crude **11**, as obtained from the ring-closure step, was dissolved in THF (50 ml) and treated with $Bu_4NF{\cdot}3H_2O$ (6.9 g; 22 mmol) at room temperature for 30 min. The resulting solution was then worked up as for **10** to give the crude product **7** as an oil. Dissolution of crude **7** in benzene (30 ml), trituration with hexane (30 ml) and seeding the resulting clear solution led to crystallisation of **7**. After being allowed to stand at room temperature for 24 h a pure crystalline product was obtained (2.44 g; 34 % overall yield based on Trt-Met-OBt). This product had physical and spectral data identical with those previously reported for compound **2**. Product **7** had R_F(A) = 0.25 and R_F(B) = 0.52 as compared with 0.09 and 0.22, respectively, for the isomer **3**. The latter was also present, albeit in small amounts, in the final reaction mixture provided that silylation had taken place in THF/DMF.

Formation of the sulfonium salt of hydroxamate **8** *followed by cyclisation with NaH in THF/DMF. Isolation of lactams* **5** *and* **9**. Crystalline **8** (0.39 g; 1 mol) was dissolved by being heated in ethyl acetate (6 ml) and treated with MeI (0.6 ml; 10 mmol) at room temperature for 24 h. The precipitated sulfonium salt was washed with ethyl acetate, dried at room temperature for 2 h under vacuum, and added to a cooled (0 °C) suspension of NaH (0.04 g; 1.5 mmol) in THF/DMF (15 ml, 3:1). The resulting mixture was stirred at that temperature for 10 min and at room temperature for 30 min prior to work-up as described for **10**. The mixture of the lactam **5** [R_F(A) = 0.14] and imidate **9** [R_F(A) = 0.42] thus obtained was separated by flash chromatography by eluting first **9** (210 mg) with system A and then **5** (70 mg) with system B. Compound **9** had physical constants identical with those previously reported[1] for compound **4**. Lactam **5** had physical constants identical with those previously reported[1] for this compound.

Deprotection of **7** *with methanolic HCl.* Compound **7** (0.72 g; 2 mmol) was dissolved in THF (5 ml) and treated with a 4 % methanolic solution (4 ml) of HCl for 15 min at room temperature. The resulting solution was triturated with diethyl ether (10 ml) and refrigerated overnight to give 0.3 g of a crystalline material which gave a diffuse spot on TLC [R_F = 0.38, acetonitrile/water (85:15) and R_F = 0.03, $CHCl_3$/MeOH (9:1)]. The product was a mixture of two compounds which were shown by X-ray determination of the separated components to be hydroxyammonium chloride and homoserine lactone hydrochloride (**12**). The latter had physical constants and spectroscopic data identical with those of an authentic sample.

Crystal structure analysis of (S)*-homoserine lactone hydrochloride* (**12**). $C_4H_8NO_2^+{\cdot}Cl^-$, M = 137.54, orthorhombic, $P2_12_12_1$, a = 5.247(1), b = 8.285(1), c = 14.699(1) Å, Z = 4, D_x = 1.430 g cm^{-3}, V = 638.9 Å, λ(Mo-K^α) = 0.71073 Å, μ = 5.085 cm^{-1}. The structure was solved by direct methods and refined by full-matrix LS to R = 0.041, R_w = 0.033, S = 1.45 for 939 unique reflections of which 657 had $I > 2\sigma(I)$. An ORTEP diagram of the structure is shown in Fig. 3, while bond distances, bond angles and torsional angles may be found in Table 2.

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