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THE FREE RADICAL CHEMISTRY OF CARBOXYLIC ESTERS OF 2-SELENOPYRIDINE-N-OXIDE; A CONVENIENT SYNTHESIS OF (L)-VINYLGLYCINE

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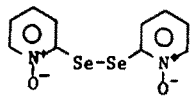
Abstract - Optically pure (L)-vinylglycine has been synthesised by two different methods. The first of these involves protected (L)-glutamate esters of N-hydroxy-2-seleno-pyridine. Such esters are shown to undergo the same decarboxylative rearrangement as their thio-analogues. Oxidative elimination of the selenopyridine residue with ozone, and with the aid of hex-1-ene as sacrificial olefin for the work-up, gave the desired (L)-vinylglycine derivatives. Similarly, the modified Hunsdiecker reaction on the terminal carboxyl of suitably protected (L)-glutamic derivatives gave the nor-bromide which readily afforded the corresponding phenylselenides on treatment with phenylselenide anion. The sequence was then as above. Using the methyl ester with carbobenzyloxy protection for the amino-function an overall yield of crystalline optically pure (L)-vinylglycine of about 45% was obtained by either route.

Vinylglycine, a natural β,γ-unsaturated α-amino acid found in mushrooms[1] and postulated as an intermediate in the enzymatic conversion of homoserine to threonine[2] and α-ketobutyrate[3], has been the target of several synthetic studies. Various modifications of a Strecker synthesis from acrolein have appeared. In two cases[4,5] the overall yields were less than 10%, but the variation of Baldwin et al.[6] gave 29%. An original route involving a 3,3 sigmatropic rearrangement and giving a 26% overall yield has recently appeared.[7] Hudrlik and Kulkarni adopted an approach[8] which consisted of the sequential treatment of protected glycine with butyllithium and then with an α-silylated acetaldehyde followed by elimination; the overall yield was 48%. Schöllkopf et al. used essentially the same approach[9], but employed valine as a chiral auxiliary and thus obtained (L)-vinylglycine of reasonable optical purity in 32% overall yield. With the exception of the latter, all the above syntheses necessarily give racemic vinylglycine.

Rapoport and Afzali-Ardakani[10] realised the first synthesis of optically pure (L)-vinylglycine (68% overall yield) by pyrolysis of a suitably protected methionine sulphoxide derivative. Previous attempts at the pyrolysis of free methionine sulphoxide and S-alkylated methionine led only to the formation of homoserine.[4]

We wish to report here a high yielding synthesis of optically pure (L)-vinylglycine from cheap and readily available (L)-glutamic acid. This synthesis is based upon our recent free radical method using O-esters of the thiohydroxamic acid 1 for the decarboxylative functionalisation of carboxylic acids[11], a method particularly well adapted to the modification of the side chain of aspartic and glutamic acids.[12] When our work was well underway a similar decarboxylative approach based on the treatment of protected (L)-glutamic acid with lead tetraacetate and cupric ion giving protected (L)-vinylglycine in 60% yield was reported[13] by Hanessian and Sahoo.

1 X = S
2 X = Se



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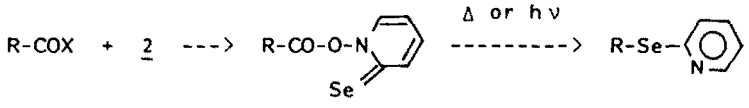
The pyrolysis of sulphoxides requires moderately high temperatures and can be difficult to carry out on a large scale. Selenoxides on the other hand frequently undergo syn elimination at, or around, room temperature. We reasoned that O-esters of selenohydroxamic acids would rearrange readily, via a free radical mechanism, to give nor-alkylselenides analogously to the decarboxylative rearrangement of O-esters of thiohydroxamic acids.[11] Furthermore the so obtained alkylselenides, on oxidation, would eliminate readily to the corresponding olefins. Thus we undertook to synthesise the selenohydroxamic acid 2 and to investigate the chemistry of its O-esters. By a slight modification of a literature procedure[14] we were able to obtain 2 in a pure state by treatment of 2-bromopyridine-N-oxide with sodium hydrogen selenide with yields around 50%. On standing in air 2 undergoes oxidation to the pale yellow diselenide 3 and thus it is preferable to use freshly or at least recently, prepared samples of 2. The treatment of 2 with either acid chlorides (Table 1, entries 1-5) or with mixed anhydrides (Table 1, entries 6, 7, and 8) gave the corresponding orange O-esters of 2 which were not isolated but which were subjected to thermolysis in benzene or photolysis with white light at room temperature to give the rearranged alkylpyridylselenides in moderate to good yields (Table 1). This rearrangement (Scheme 1) proceeds either by a free radical chain mechanism or via a cage mechanism.



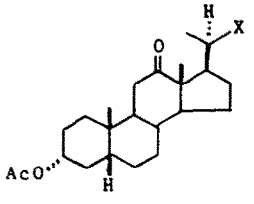
Scheme 1

$CH_3(CH_2)_{14}X$

4 X = COCl
5 X = 2-pyridylseleno

$(CH_3)_3CX$

8 X = COCl
9 X = 2-pyridylseleno



6 X = $(CH_2)_2COCl$
7 X = $(CH_2)_2$-2-pyridylseleno
18 X = $(CH_2)_2$-I
19 X = $(CH_2)_2$-Cl
22 X = $CH{=}CH_2$

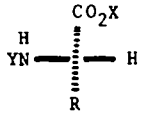
$(PhCH_2)_2CHX$

10 X = COCl
11 X = 2-pyridylseleno

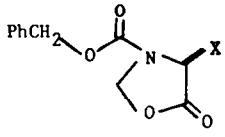
Table 1. Rearrangements to alkyl-2-pyridylselenides

Entry	Substrate	Method	Temp. (°C)	Time (mins)	Products (% Yields)
1	4	A	r.t.	5	5 (62)
2	6	B	80	30	7 (68)
3	6	A	r.t.	5	7 (55)
4	8	B	80	45	9 (51)
5	10	B	80	20	11 (76)
6	12	A	r.t.	35	13 (82)
7	14	C	66	60	15 (70)
8	16	A	r.t.	60	17 (58)

A: Room temperature (r.t.) photolysis with tungsten light.
B: Thermolysis in benzene at reflux.
C: in situ generation of Na^+ salt of 2 from 3 with Na amalgam; thermolysis in THF at reflux.

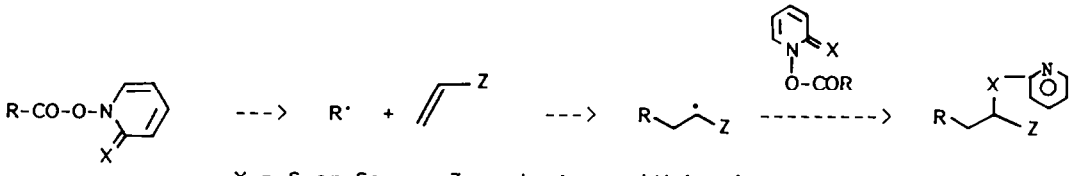


12 X = CH_2Ph, Y = BOC, R = $(CH_2)_2CO_2H$
13 X = CH_2Ph, Y = Boc R = $(CH_2)_2$-2-pyridylseleno
16 X = CH_3 Y = $PhCH_2OCO$ R = $(CH_2)_2CO_2H$
17 X = CH_3 Y = $PhCH_2OCO$ R = $(CH_2)_2$-2-pyridylseleno
24 X = CH_2Ph, Y = Boc R = $CH=CH_2$
26 X = CH_3 Y = $PhCH_2OCO$ R = $CH=CH_2$
27 X = CH_2Ph, Y = Boc R = $(CH_2)_2Br$
28 X = CH_2Ph, Y = Boc R = $(CH_2)_2SePh$
29 X = CH_3 Y = $PhCH_2OCO$ R = $(CH_2)_2Br$
30 X = CH_3 Y = $PhCH_2OCO$ R = $(CH_2)_2SePh$



14 X = $(CH_2)_2CO_2H$
15 X = $(CH_2)_2$-2-pyridylseleno
25 X = $CH=CH_2$

We also attempted to trap the carbon radicals formed in this rearrangement with activated double bonds and so establish a new carbon-carbon forming reaction (Scheme 2, X = Se) as we were able to do with radicals derived from esters of 1[15] (Scheme 2, X = S), but were unable to do so. O-Esters of 2 must consequently be considered either as better traps for carbon radicals than the corresponding esters of 1 or as undergoing rearrangement via a "tight" radical cage[16].

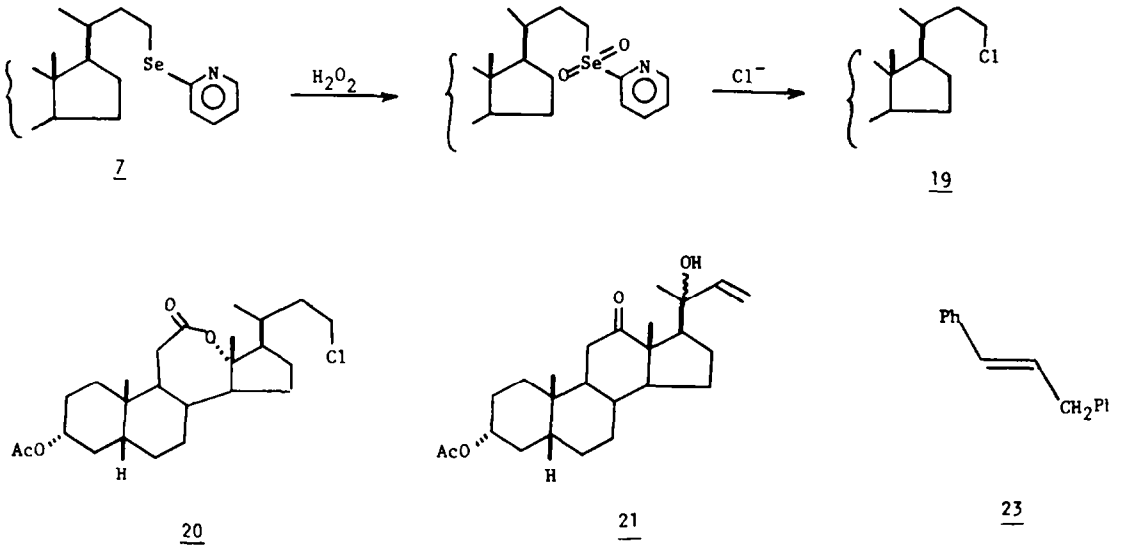


X = S or Se. Z = electron withdrawing group.

Scheme 2

Having established a high yielding process for the formation of nor-alkylpyridylselenides from the corresponding carboxylic acids we turned our attention to their oxidation and subsequent elimination. Treatment of the steroidal selenide 7 with excess hydrogen peroxide in THF at room temperature for several hours resulted in a complex mixture of products from which only two products 19 and 20 were identified (Table 2, entry 1). Use of metachloroperbenzoic acid gave equally

complex mixtures. In both 19 and 20 the 23-pyridylseleno group has been replaced by a 23-chloro substituent, this probably results from over oxidation of the selenide to the selenone and subsequent displacement by chloride ion during the work up which involved washing with brine (Scheme 3). Such reactions, although rare, are not unknown in the literature.[17] The 12-keto group present in 7 has also undergone Baeyer-Villiger oxidation in 20.



Scheme 3

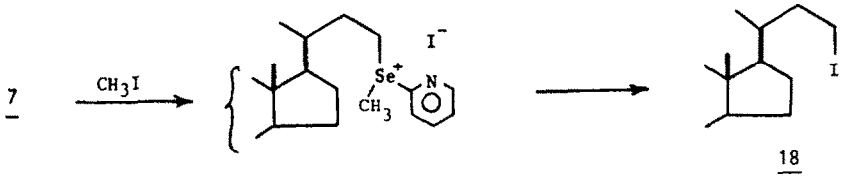
Table 2. Oxidation/Elimination of Alkylarylselenides.

Entry	Substrate	Oxidant	Temp. (°C)	Time (hrs)	Products (% Yields)
1	7	H_2O_2	r.t.	3.5	19 (16) + 20 (23)
2	7	$PhIO_2$	r.t.	5	----
3	7	$PhIO_2$	110	1	21 (40)
4	7	$PhIO_2$ [a]	80	17	21 (43) + 22 (51)
5	7	O_3 [b]	76	0.1	22 (45)
6	7	O_3	76	0.1	22 (98)
7	11	H_2O_2	r.t.	2	23 (65)
8	13	O_3	80	0.1	24 (81)
9	15	O_3	76	0.1	25 (82)
10	17	O_3	76	0.1	26 (78)
11	28	O_3	80	0.1	24 (95)
12	30	O_3	76	0.1	26 (80)
13	28	H_2O_2	r.t.	3	24 (56)

a): an excess of 1-hexene was used in this experiment.
b): 1-Hexene was not used in the work-up of this experiment.

However oxidation of the selenide 11 with hydrogen peroxide (Table 2, entry 7) gave the corresponding olefin 23 in moderate yield. The use of dianisyltelluroxide[18] and of p-nitropyridine-N-oxide as oxidants gave no reaction and starting materials were recovered unchanged. Iodoxybenzene is a mild oxidising agent which has been used for example in the oxidation of diphenyldiselenide to benzeneseleninic acid.[19] We decided therefore to attempt the oxidation of 7

with this readily available reagent. The treatment of 7 with excess iodoxybenzene in toluene at room temperature caused no reaction (Table 2, entry 2) but on heating to reflux in toluene for 1 hr 7 provided 21 in 40% yield (Table 2, entry 3). None of the desired olefin 22 was observed in this reaction. Seemingly 21 arises from the allylic oxidation of the olefin 22 by some oxidising agent present in the reaction mixture.[20] If this were the case then the addition of an excess of a sacrificial olefin to the reaction mixture ought to suppress the over-oxidation of 22 and allow its isolation in good yields. Thus oxidation of 7 with iodoxybenzene in benzene at reflux in the presence of 1-hexene gave 22 in 51% yield: the formation of 21 was however not completedly eliminated (Table 2, entry 4). A further possibility for the formation of olefins from alkylpyridylselenides was alkylation with a suitable alkylating agent and base treatment of the so formed salt. Unfortunately treatment of 7 with excess methyliodide in toluene at reflux afforded the iodide 18 in quantitative yield and we were unable to stop the reaction at the salt stage (Scheme 4).

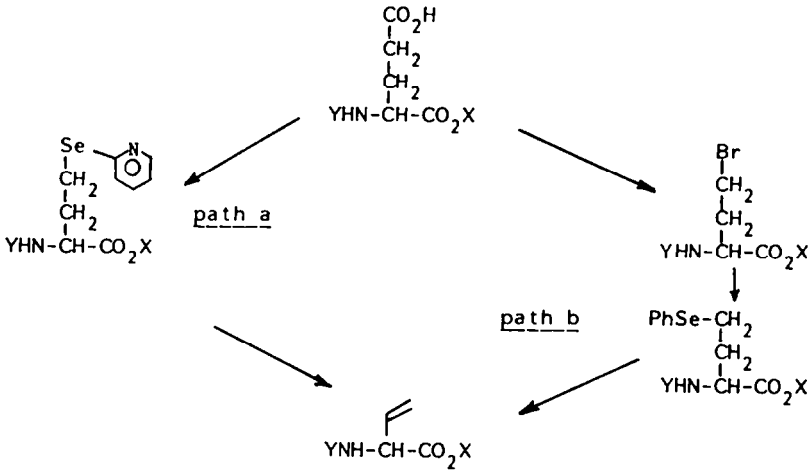


Scheme 4

Finally we turned our attention to the use of ozone as the oxidising agent. Thus low temperature (-78°C) ozonolysis of 7 followed by rapid addition of the cold blue solution to tetrachloromethane at reflux gave olefin 22 in 45% yield after chromatography (Table 2, entry 5). As in the case of the iodoxybenzene reactions we reasoned that the low yield of 22 was due to over oxidation of 22 either by the excess of ozone or by some other selenium based oxidising agent. Hence when a low temperature solution of 7 in dichloromethane was saturated with ozone and the cold blue solution treated with excess 1-hexene before being added to tetrachloromethane at reflux a 98% yield of 22 was obtained (Table 2, entry 6).

Having established optimum conditions for the oxidation and elimination of the pyridylselenyl group we were able to complete our synthesis of protected (L)-vinylglycine. Ozonolysis of the selenide 13 (Table 1), treatment with 1-hexene and then addition to benzene at reflux gave the protected vinyl glycine 24 in 81% isolated yield, the overall yield of 24 from 12 being a very respectable 66%. We then applied the same procedure to the readily available cyclic glutamic acid derivative 14.[21] Thus addition of the mixed anhydride from 14 and isobutylchloroformate to the sodium salt of 2, formed in situ by sodium amalgam reduction of 3, in THF at reflux gave the selenide 15 in 70% (Table 1, entry 7). Subsequent ozonolysis of 15 gave the protected crystalline vinylglycine 25 which was otherwise identical to the product described by Hanessian[13], in 82% yield. We were also able to prepare the vinylglycine derivative 25 in 71% overall yield from 14 without isolation and purification of the intermediate selenide. Thus we have been able to transform suitably protected glutamic acid derivatives to protected derivatives of (L)-vinylglycine in a two step procedure giving overall yields in excess of 66% (Scheme 5, path a). Nevertheless, and bearing in a mind the instability of the selenohydroxamic acid 2, we decided to make a comparative approach to the same target via a more classical route (Scheme 5, path b).

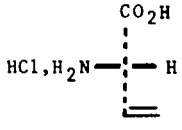
Thus application of our novel modification of the Hunsdiecker reaction to the acid 12 gave the bromide 27 in 82% yield. Treatment of 27 with phenylselenide anion in ethanol gave the selenide 28 quantitatively. This simple route to nor-alkylphenylselenides from carboxylic acids is complementary to our recently published decarboxylative chalcogenation procedure.[22]



Scheme 5

Ozonolysis of 28 afforded the protected vinylglycine 24 in 95% yield (Table 2, entry 11). The overall yield of 24 via this simple three step procedure from 12 is therefore 78% making this the most efficient synthesis to date. It is noteworthy that treatment of the selenide 28 with excess aqueous hydrogen peroxide gave 24 but only in 56% yield (Table 2, entry 13).

Thus having established two straightforward and high yielding routes to derivatives of (L)-vinylglycine we attempted their deprotection to optically pure (L)-vinylglycine hydrochloride 31. Treatment of (L)-benzyl N-t-butyloxycarbonyl-vinylglycine 24 with 6N hydrochloric acid at reflux for 1 hr yielded 70% of (L)-vinylglycine hydrochloride 31 of ee 93% after recrystallisation. The cyclic derivative 25 was deprotected in a similar manner giving 31 in 52% yield and with an ee of 72%. In the latter case the partial racemisation can be attributed to the facilitated enolisation of the ester into the five membered ring. In order to obtain an optically pure sample of 31, we determined to synthesise its N-benzyloxycarbonyl-methyl ester 26 which has previously been hydrolysed without racemisation.[10] Classically[23] the mono methyl ester 16 of glutamic acid was obtained by selective esterification and chromatography but we preferred the treatment of 14 with sodium methoxide in methanol as described by Hanessian.[13] The optically pure product, was isolated simply by extraction. Compound 16 was then transformed into the protected vinylglycine 26 by both routes outlined above (Scheme 5, paths a and b), the overall yields being 48 and 52% respectively. Deprotection of 26, as described by Rapoport[10], with 6N hydrochloric acid gave optically pure (L)-vinylglycine 31 in 91% yield after recrystallisation from acetone.



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Thus we have developped two new routes to protected optically pure (L)-vinylglycine from (L)-glutamic acid, one of which is based on new free radical chemistry of the selenohydroxamic acid 2, and the other on established methods.

General Experimental

NMR spectra were recorded at 60 MHz unless otherwise stated with either a Varian T60 or EM360L spectrometer for solutions in deuterochloroform. Chemical shifts are in ppm downfield from tetramethylsilane as internal standard. 200 MHz spectra were measured with a Brucker WM200 spectrometer. Infra red spectra were recorded with either a Perkin Elmer 297 or 257 Spectrophotometer. 70 eV E.I. mass spectra were recorded on either an AEI-MS9 or AEI MS50 apparatus. Optical rotations were measured with a Perkin Elmer 141 polarimeter. Melting points were taken on a Reichert hot stage apparatus and are uncorrected. All solvents were dried and distilled by standard procedures.

N-Hydroxypyridine-2-selenone (2) - Sodium borohydride (2 g) was added portionwise to a stirred suspension of selenium powder (2.76 g) in absolute ethanol (80 ml) at 0°C under nitrogen. The reaction mixture first turned dark red and then finally colourless. 2-Bromopyridine-N-oxide hydrochloride (5 g) and sodium hydrogen carbonate (1 g) were added and the mixture was brought to reflux for 1.5 hr. The reaction was then cooled to room temperature under N_2 and acidified with glacial acetic acid (20 ml) and concentrated almost to dryness. Benzene (20 ml) was added and the mixture was evaporated to dryness. The yellow-green solid residue was thoroughly extracted with chloroform (4 x 50 ml) and the extracts were concentrated to dryness and then further extracted with tetrahydrofuran (THF) (4 x 50 ml). Evaporation to dryness of the THF extracts gave pure selenohydroxamic acid 2 (typically 2.5-3 g) which could be recrystallised from absolute ethanol, m.p. 70-72° C (lit.[14] 72.5-73°C). On prolonged standing the selenohydroxamic acid 2 underwent oxidation to the pale yellow 2,2'-dipyridyldiselenide bis-N-oxide (3) which had m.p. 228-230°C (EtOH), δ 7.35 (2H, m); 8.0 (1H, m), 8.0 (1H, m); 312 + 314 + 316 ($M - 32^+$), 275, 277, 279 . (Found: C, 34.70; H, 2.29; N, 7.83. Calc. for $C_{10}H_8N_2O_2Se_2$: C, 34.70; H, 2.33; N, 8.09%)

n-Pentadecyl-2-pyridylselenide (5) - Palmitoyl choride (4) (274 mg, 1 mmol) in benzene (2 ml) was added at room temperature under nitrogen to a stirred solution of 2 (207 mg, 1.2 mmol), pyridine (0.25 ml) and DMAP (12 mg; 6.1 mmol) in benzene (10 ml). After stirring for 30 min the orange-yellow solution was filtered on celite and irradiated at room temperature with a 300W tungsten lamp. After 5 min irradiation the reaction was washed with dilute HCl (2 x 20 ml) and then water (2 x 20 ml), dried on Na_2SO_4, filtered and evaporated to dryness. Chromatography of the crude product on silica gel (eluant CH_2Cl_2) gave the selenide 5 as a white crystalline powder (227 mg, 62%) m.p. 34-35°C (pentane); b.p. 200°C/2 mm (Kugelrohr); δ 0.9 (3H, t), 1.40 (26H, m), 3.30 (2H, d, J = 7 Hz), 6.9 (1H, m), 7.2 (2H, m), 8.35 (1H, m); ν(CH_2Cl_2) 1570, 1560, 1100, 1080, 900 cm^{-1}; m/z 366 + 368 ($M^{+\cdot}$), 288 (M -Se$^+$). (Found: C, 64.96; H, 9.40; N, 3.83. Calc. for $C_{20}H_{35}NSe$: C, 65.19; H, 9.57; N, 3.80%)

3α-Acetoxy-12-keto-24-nor-23-(2'-pyridylseleno)-5βH-cholane (7) - The acid chloride (1 mmol) from acetyl 12-ketolithocholic acid (6) in benzene (5 ml) was added over 5 min to a stirred solution of 2 (207 mg, 1.2 mmol), DMAP (12 mg, 0.1 mmol) and pyridine (0.25 ml) in benzene (10 ml) at reflux under nitrogen. After 30 min at reflux the reaction was subject to aqueous work-up as above and the extracts were chromatographed (eluant CH_2Cl_2 + 2% EtOAc) on silica gel to provide the pure selenide 7 as a crystalline solid (369 mg, 68%), m.p. 118-119°C (Et_2O); $[\alpha]_D^{20}$ + 111° (c = 1.2 in $CHCl_3$); δ (200 MHz), 0.99 (3H, d, J = 7 Hz, 21 CH_3), 1.10 (6H, s, 18 + 19 CH_3); 2.00 (3H, s, CH_3CO_2); 2.50 (1H, m, 11βH), 3.10 (1H, m) + 3.30 (1H, m) [23 CH_2], 4.73 (1H, m, 3βH), 7.05 (1H, dd, $J_1 = J_2 = 5$ Hz), 7.45 (1H, dd, $J_2 = J_3 = 5$ Hz), 8.50 (1H, d, $J_3 = 5$ Hz); ν(CH_2Cl_2) 1720, 1700, 1565, 1555, 1360, 1025, 900 cm^{-1}; m/z 543 + 545 (M^+), 464 (M - SeH$^+$). (Found: C, 66.20; H, 8.10; N, 2.66. Calc. for $C_{30}H_{43}NO_3Se$: C, 66.16; H, 7.96; N, 2.57%)

A further sample of 7 was obtained by photolysis exactly according to the procedure described for 5 above.

t-Butyl-2'-pyridylselenide (9) - This colourless oil was prepared on a 1 mmol scale in benzene at reflux according to the procedure described for 7. It had b.p. 60°C/1.5 mm (Kugelrohr). δ 1.70 (9H, s), 7.10 (1H, m), 7.40 (2H, m), 8.40 (1H, d, J = 5 Hz); ν(film): 1570, 1560, 1445, 1410, 1155, 760, 700 cm^{-1}; m/z 213 + 215 ($M^{+\cdot}$) 157 + 159 (M - $C_4H_8^+$). (Found: C, 50.17; H, 5.95; N, 6.69. Calc. for $C_9H_{13}NSe$: C, 50.47; H, 6.12; N, 6.54%)

1,3-Diphenyl-2-(2'-pyridylseleno)propane (10) - This compound was prepared according to the procedure described for 7. It was a colourless oil, b.p. 175°C/2 mm (Kugelrohr), δ 3.20 (4H, d, J = 7 Hz), 4.60 (1H, quintet, J = 7 Hz), 7.30 (13H, M), 8.40 (1H, d, J = 5 Hz); ν(film) 1570, 1450, 1410, 1100 cm^{-1}; m/z 351 + 353 (M^+), 260 + 262 (M - $PhCH_2^+$). (Found: C, 68.20; H, 5.25; N, 3.70. Calc. for $C_{20}H_{19}NSe$: C, 68.18; H, 5.44; N, 3.96%)

(L)-Benzyl 2-(t-butyloxycarbonylamino)-4-(2'-pyridylseleno)butanoate (13):N-Methylmorpholine (0.11 ml, 1.1 mmol) and isobutylchloroformate (0.14 ml, 1 mmol) were added to a stirred solution of 12 (337 mg, 1 mmol) at -15°C under nitrogen in THF (5 ml). After 5 min at -15°C a solution of 2 (346 mg, 2 mmol) and triethylamine (0.28 ml) in THF (10 ml) was added and the reaction mixture was stirred at -15°C for 1hr after which it was irradiated at room temperature for 35 min with two 100W tungsten lamps. The reaction was then diluted with ether and washed with saturated K_2CO_3, water, dilute HCl and finally with saturated aqueous sodium chloride. After drying on Na_2SO_4 the solution was filtered, evaporated to dryness and the crude product was purified by chromatography on silica gel (eluant: CH_2Cl_2 - 0.5% MeOH) to give the pyridyl selenide 13 (368 mg, 82%) as an oil, $[\alpha]_D$ -34° (c = 1, MeOH), δ 1.38 (9H, s), 2.18 (2H, m), 3.04 (2H, t, J = 7 Hz, CH_2-Se), 4.2 (1H, m), 4.95 (2H, s), 5.54 (1H, m, NH), 6.43 (1H, m), 7.2 (7H, m), 8.2 (1H, m); ν(film): 3430, 1730, 1700 cm. (Found: C, 55.84; H, 5.85; N, 6.23; O, 14.26. Calc. for $C_{21}H_{26}N_2O_4Se$: C, 56.12; H, 5.83; N, 6.23; O, 14.24%)

Pyridylselenide 15 - 3% sodium amalgam (2.40 g) was added under an argon atmosphere to a stirred suspension of the diselenide 3 (520 mg, 1.4 mmol) in THF (20 ml) at room temperature and the mixture was stirred for 15 hr and then brought to reflux. A solution of the mixed anhydride of acid 14 was prepared by adding N-methylmorpholine (220 mg, 2.1 mmol) and isobutylchloroformate (300 mg, 2.2 mmol) to 14 (586 mg, 2 mmol) at -15°C and then stirring for 5 min at -15°C. This cold solution was added rapidly to the solution of the reagent at reflux and the reaction maintained at reflux for 1 hr, after which the organic phase was decanted from the insoluble residues and poured into water (50 ml). The aqueous phase was extracted with ethylacetate (3 x 25 ml) and the extracts were thoroughly washed with water (3 x 50 ml) and then with saturated aqueous NaCl, dried on Na_2SO_4, filtered and evaporated to dryness. Chromatography on silica gel (eluant: EtOAc-hexane 3:7) gave the pure selenide 15 (567 mg, 70%) as a colourless oil with $[\alpha]_D^{20}$ +63° (c = 1 in $CHCl_3$); δ (200 MHz), 2.3 (2H, m), 3.13 (2H, t, J = 7 Hz, CH_2Se), 4.33 (1H, dd, $J_1 = J_2 = 6.5$ Hz, NCH-CO), 5.10 (2H, s), 5.17 (1H, d, J = 2.5 Hz) + 5.22 (1H, d, J = 2.5 Hz), 5.50 (1H, m, NH), 6.90 (1H, dd, $J_3 = J_4 = 6.5$ Hz), 7.2 (7H, m), 8.30 (1H, d, J = 2.5 Hz); ν(nujol) 1800, 1720, 1575, 1420 cm^{-1}; m/z 403, 405, 407 (M^+), 312, 314, 316 ($M - PhCH_2^+$), 249 ($M - C_5H_4NSe^+$). (Found: C, 52.97; H, 4.39; N, 6.98. Calc. for $C_{18}H_{18}N_2O_4Se$: C, 53.34; H, 4.48; N, 6.91%)

(L)-Methyl 2-benzyloxycarbonylamino-4-(2-'pyridylseleno)butanoate (7): N-Methylmorpholine (161 mg, 1.6 mmol) in THF (1 ml) and isobutylchloroformate (217 mg, 1.6 mmol) in THF (1 ml) were added to a stirred solution of the protected amino acid 16 (442 mg, 1.5 mmol) in THF (5 ml) under nitrogen at -15°. After 15 min a solution of the selenohydroxamic acid 2 (0.5 g, 2.8 mmol) and N-methylmorpholine (280 mg, 2.8 mmol) in THF (5 ml) was added and the solution was stirred at -15°C for 1 hr and then irradiated with two 100W tungsten lamps at room temperature for 1hr. The reaction mixture was filtered on celite and evaporated to dryness. The crude mixture was chromatographed on silica gel (eluant: hexane-EtOAc 3:1) to give the pyridylselenide 17 (357 mg, 58%) as a white crystalline solid with m.p. 67-67.5°C (EtOAc-hexane); $[\alpha]_D^{20}$ -27° (c = 0.5 in MeOH); δ 2.30(2H, m), 3.15 (2H, t, J = 8 Hz, CH_2-SeC_5H_4N), 3.7 (3H, s, CH_3O), 4.40 (1H, m, NHCHCO), 5.15 (2H, s,), 6.20 (1H, m, NH), 7.0 (1H, m), 7.3 (7H, m), 8.50 (1H, d, J = 6 Hz); ν(nujol) 3320, 1750, 1690, 1575, 1520 cm^{-1}; m/z 406 + 408 (M^+), 184 + 186 ($C_5H_4NSeCH_2CH_2^+$), 91 ($PhCH_2^+$). (Found: C, 53.12; H, 4.99; N, 6.89. Calc. for $C_{18}H_{20}N_2O_4Se$: C, 53.08; H, 4.95; N, 6.88%)

(L)-Benzyl 2-t-butyloxycarbonylamino-4-bromobutanoate (27) - N-Methylmorpholine (0.11 ml) and isobutylchloroformate (0.14 ml) were added to a stirred solution of the acid 12 (337 mg, 1 mmol) in THF (5 ml) at -15°C under nitrogen. After 5 min a solution of thiohydroxamic acid 1 (152 mg, 1.2 mol) and triethylamine (0.17 ml, 1.2 m,mol) in THF (4 ml) was added and the reaction mixture was stirred at -15°C for 15 min. The solution was then filtered and concentrated to dryness in vacuo at room temperature. The residue was taken up in bromotrichloromethane (10 ml) and irradiated at room temperature under nitrogen for 45 min with two 100W tungsten lamps. After removal of the solvent the crude product was purified by chromatography on silica gel (eluant: CH_2Cl_2-cyclohexane) giving the crystalline bromide 27 (305 mg, 82%), m.p. 53°C (pentane); $[\alpha]_D^{20}$ -34° (c = 1, MeOH); δ 1.45 (9H, s), 2.32 (2H, m), 3.4 (2H, t, J = 7 Hz, CH_2Br), 4.47 (1H, m, NHCHCO), 5.1 (1H, m, NH), 5.22 (2H, s), 7.42 (5H, s); ν(nujol) 3370, 1770, 1685 cm^{-1}. (Found: C, 51.53; H, 5.96; Br, 21.61; N, 3.85; O, 16.94. Calc. for $C_{16}H_{22}BrNO_4$: C, 51.62; H, 5.96; Br, 21.47; N, 3.76; O, 17.19%)

(L)-Benzyl 2-t-butyloxycarbonylamino-4-phenylselenobutanoate (28) - Diphenyldiselenide (343 mg, 1.1 mmol) was dissolved in absolute ethanol (15 ml) at room temperature under nitrogen. Sodium borohydride (95 mg) was then added portionwise until complete decolourisation of the yellow solution was observed. A solution of the bromide 27 (372 mg, 1 mmol) in absolute ethanol (6 ml) was then added and the reaction was stirred under nitrogen at room temperature for 20 min. The reaction was then diluted with ether (40 ml) and washed with dilute sodium hydrogen carbonate (2 x 15 ml), water (2 x 15 ml) and saturated aqueous NaCl (30 ml). After drying over Na_2SO_4, filtration and evaporation, chromatography of the crude reaction mixture on silica gel (EtOAc-cyclohexane 1:3) gave the pure selenide 28 (437 mg, 100%) as a colourless oil, with $[\alpha]_D^{20}$ -39.7° (c = 1.2 in MeOH), δ: 1.42 (9H, s), 2.12 (2H, m), 2.85 (2H, t, J = 6.4 Hz, CH_2SePh), 4.47 (1H,m), 5.05 (1H, m, NH), 5.15 (2H, s), 7.1-8.0 (10H, m); ν(film) 3360, 1745, 1700 cm^{-1}. (Found: C, 58.77; H, 5.95; N, 2.93; O, 14.43. Calc. for $C_{22}H_{27}NO_4Se$: C, 58.92; H, 6.07; N, 3.12; O, 14.27%)

(L)-Methyl 2-benzyloxycarbonylamino-4-bromobutanoate (29) - N-Methylmorpholine (505 mg, 5 mmol) in THF (1 ml) and isobutylchloroformate (816 mg, 6 mmol) in THF (1 ml) were added to a stirred solution of the acid 16 (1.48 g, 5 mmol) in THF (15 ml) under nitrogen at -15°C. After 15 min at -15°C the thiohydroxamic acid 2 (762 mg, 6.5 mmol) and N-methylmorpholine (650 mg, 6.5 mmol) in THF (10 ml) were added and the reaction was stirred at -15°C for 45 min. After filtration on celite the solvent was removed under vacuum at room temperature. The residue, taken up in bromotrichloromethane (30 ml), was irradiated with two 100W tungsten lamps at room temperature for 3 hr. After removal of the solvent the crude reaction mixture was

chromatographed on silica gel (eluant: Et_2O-pentane 2:1) to give first trichloromethyl-2-pyridylsulphide (870 mg, 77%) which was identical to an authentic sample, and then the nor-bromide 29 (1.29g, 78%) as a colourless oil with $[\alpha]_D^{20}$ -6° (c = 0.8 in $CHCl_3$); δ 2.1 (2H, m), 3.3 (2H, t, J = 4 Hz, CH_2Br), 3.70 (3H, s), 4.40 (1H, m, NHCHCO), 5.1 (2H, s), 6.2 (1H, m, NH), 7.3 (5H, m); ν(film) 3320, 1730(broad), 1450, 1420 cm^{-1}; m/z 329 + 331 (M^+), 270 + 272 ($M - CO_2CH_3^+$), 226 + 228. (Found: C, 47.49; H, 4.44. Calc. for $C_{13}H_{16}BrNO_4$: C, 47.43; H, 4.90%)

(L)-Methyl 2-benzyloxycarbonylamino-4-phenylselenobutanoate (30) - Sodium borohydride (110 mg) was added portionwise to a stirred solution of diphenyldiselenide (753 mg) in absolute ethanol (30 ml) at 0°C under nitrogen. The bromide 29 (800 mg) in absolute ethanol (5 ml) was added to the almost colourless solution and stirring was maintained at 0°C for 20 min before the reaction mixture was poured into dilute hydrochloric acid (150 ml) and thoroughly extracted with ethylacetate. After drying on $MgSO_4$, filtration and evaporation of the solvent the crude reaction mixture was chromatographed on silica gel (eluant: hexane-EtOAc 4:1) to give the selenide 30 as a slightly yellow oil (825 mg, 84%) which had $[\alpha]_D^{20}$ -28° (c = 0.6 in MeOH); δ 2.2 (2H, m), 2.8 (2H, t, J = Hz, CH_2Se), 3.7 (3H, s), 4.50 (1H, m), 5.1 (2H, s), 5.3 (1H, m, NH), 7.3 (10H, m); ν(CH_2Cl_2) 1745, 1730, 1510, 1210 cm^{-1}; m/z 404 + 406 (M^+), 249 ($M^+ - PhSe^+$). (Found: C, 55.89; H, 5.21; N, 3.61. Calc. for $C_{19}H_{21}NO_4Se$: C, 56.16; H, 5.21; N, 3.45%)

Reaction of 7 with Methyl iodide : 3α-Acetoxy-23-iodo-24-nor-5βH-cholan-12-one (18) - Methyl iodide (30 mg, 0.2 mmol) was added to a stirred solution of the pyridylselenide 7 (100 mg, 0.18 mmol) at room temperature in toluene (1 ml). After 1 hr the solution was brought to reflux (using an efficient condenser) and maintained at reflux for 24 hr with portionwise addition of methyl iodide (total 1 ml). The reaction was then evaporated to dryness and the product was purified by filtration on silica gel to give the pure iodide 18 (92 mg, 100%), m.p. 228-230°C (benzene-hexane), lit.[11], m.p. 228-230°C.

Treatment of 7 with excess 30% Hydrogen peroxide - A solution of the selenide 7 (162 mg, 0.3 mmol) in THF (2 ml) was treated with 30% hydrogen peroxide solution (4 ml) with stirring at room temperature for 3.5 hr. The reaction was then diluted with water (20 ml) and extracted with dichloromethane (3 x 10 ml). The extracts were washed with water (10 ml) and then with saturated aqueous sodium chloride (10 ml), dried on Na_2SO_4, filtered and evaporated to dryness. Chromatography on silica gel (eluant: CH_2Cl_2) gave first 3α-acetoxy-23-chloro-24-nor-5βH-cholan-12-one (19) (20 mg, 16%) m.p. 209-211°C (MeOH-Et_2O); $[\alpha]_D^{20}$ +113° (c = 0.8 in $CHCl_3$); δ 1.00 (6H, s, 18 + 19 CH_3), 2.00 (3H, s, CH_3CO_2), 3.70 (2H, m, 23CH_2), 4.70 (1H, m, 3βH); ν(CH_2Cl_2) 1720, 1710, 1025 cm^{-1}; m/z 422 + 424 (M^+), 362 + 364 ($M - HOAc^+$). (Found: C, 71.05; H, 9.34. Calc. for $C_{25}H_{39}ClO_3$: C, 70.98; H, 9.29%)

Further elution with the same solvent gave the C-homosteroid 20 (31 mg, 23%) as a noncrystalline resin with δ (400 MHz): 0.89 (3H, s, 19CH_3), 1.08 (3H, d, J = 7 Hz, 21CH_3), 1.38 (3H, s, 18CH_3), 2.02 (3H, s, CH_3CO_2), 2.45 (1H, dd, J_1 = J_2 13 Hz, 11βH), 2.63 (1H, d, J = 13 Hz, 1αH), 3.56 + 3.63 (2 x 1H, m, 23CH_2), 4.73 (1H, m, 3βH); ν(CH_2Cl_2) 1710, 1700, 1025 cm^{-1}; m/z 438 + 440 (M^+). (Found: M^+ 438.2518. Calc. for $C_{25}H_{39}ClO_4$: 438.2534)

Treatment of 7 with Iodoxybenzene - The steroid 7 (100 mg, 0.18 mmol) and iodoxybenzene (see Table 2) was brought to reflux in the appropriate solvent (see Table 2) under a nitrogen atmosphere. When all the substrate had been consumed (t.l.c. see Table 2) the reaction was cooled, filtered and evaporated to dryness. Chromatography on silica gel gave 3α-acetoxy-24-nor-5βH-chol-22-en-12-on-20-ol (21) as a mixture of stereoisomers at position 20. The mixture had δ (400 MHz): 1.00 + 1.01 (2 x 1.5H, s, 19 CH_3), 1.04 + 1.19 (2 x 1.5 H, s, 18CH_3), 1.23 + 1.24 (2 x 1.5 H, s, 21CH_3), 2.01 (3H, s, CH_3CO_2), 4.71 (1H, m, 3βH), 4.92 + 5.01 (2 x 0.5H, dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz), 5.22 + 5.31 (2 x 0.5 H, dd, J_3 = 17 Hz, J_2 = 1.5 Hz), 6.05 (1H, m, 22H); ν(CH_2Cl_2) 3400, 2900, 2850, 1720, 1710, 1030, 920 cm^{-1}; m/z 402 (M^+), 387 (M - 15); 327 (387 - AcOH). (Found: C, 74.34; H, 9.32. Calc. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51%)

Treatment of 7 with Iodoxybenzene in presence of 1-Hexene - The above experiment was repeated exactly with the exception that 1-hexene (= 1 ml) was added to the reaction mixture. Chromatography on silica gel gave first the olefinic steroid 22 and then 21 which was identical to the above described sample. Steroid 2 had m.p. 138-140°C (Et_2O); $[\alpha]_D^{20}$ + 93° (c = 0.6 in $CHCl_3$); δ (200 MHz) 0.73 (3H, d, J = 6 Hz, 21 CH_3), 1.05 (6H, s, 18 + 19 CH_3), 2.00 (3H, s, CH_3CO_2), 2.46 (1H, dd, J_1 = J_2 = 12 Hz, 11βH), 4.70 (1H, m, 3βH), 4.83 (1H, dd, J_1 = 10 Hz, J_2 = 2 Hz), 4.93 (1H, dd, J_2 = 2 Hz, J_3 = 17.5 Hz), 5.70 (1H, m, 22H); ν(CH_2Cl_2) 1720, 1710, 920 cm^{-1}; m/z 386 (M^+), 326 (M^+ - AcOH). (Found: C, 77.72; H, 9.94. Calc. for $C_{25}H_{38}O_3$: C, 77.68; H, 9.91%)

E-1,3-Diphenylpropene (23) - 30% Aqueous hydrogen peroxide (1 ml) was added to a stirred solution of selenide 11 (31 mg) in THF (1 ml) at room temperature and under nitrogen. After 2 hr at room temperature the reaction was diluted with ether (10 ml), washed with dilute hydrochloric acid (10 ml), water (10 ml) dried on Na_2SO_4, filtered and evaporated to dryness. Kugelrohr distillation (110°C/1 mm) of the crude extracts yielded E-1,3-diphenylpropene 23 (11 mg, 65%) as a viscous oil.

δ(200 MHz) 3.56 (2H, d, J_1 = 6.7 Hz), 6.33 (1H, dd, J_1 = 6.7 Hz, J_2 = 16.7 Hz), 6.47 (1H, dd, J_2 = 16.7 Hz), lit.[24], E-olefin δ 3.48 (2H, d, J = 5 Hz), 6.25 (1H, dd, J_1 = 16 Hz, J_2 = 5 Hz), 6.40 (1H, d, J = 16 Hz). Lit.[24], Z-olefin δ 3.62 (2H, dd, J_1 = J_2 = 7.5 Hz), 5.82 (1H, dd, J_1 = 7.5 Hz, J_3 = 11.5 Hz), 6.52 (1H, d, J_3 = 11.5 Hz)

Oxidation of 28 with Hydrogen peroxide: Benzyl 2-t-butyloxycarbonylaminobut-3-enoate (24) - The phenylselenide 28 (179 mg, 0.4 mmol) in ethanol (10 ml) was treated with 30% aqueous hydrogen peroxide (4 ml) at 0°C and stirred at room temperature for 3 hr after which the reaction was poured into water and ether extracted. Preparative t.l.c. (EtOAc-cyclohexane 1:3) of the crude extracts gave the protected vinylglycine 24 (65 mg, 56%) as a colourless oil with $[\alpha]_D$ -12.8° (c = 1 in $CHCl_3$) and -22° (c = 1 in MeOH); δ 1.45 (9H, s), 4.91 (1H, m, NHCH-CO_2), 5.2 (2H, s), 5.3 (3H, m, olefinic H), 5.9 (1H m, NH), 7.3 (5H, s); ν(film) 3420, 1760, 1700, 1600 cm^{-1}. (Found: C, 66.21; H, 7.37; N, 4.56; O, 21.95. Calc. for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81; O, 21.97%)

General Procedure for Ozonolysis of Alkylarylselenides

The selenide (see Table 2) was dissolved in dichloromethane and saturated with ozone at -78°C. 1-Hexene (2 ml per mmol selenide) was then added cautiously to the so obtained blue solution at -78°C and the resulting colourless solution was added to either benzene or tetrachloromethane (10 ml per mmol selenide) at reflux. Reflux was maintained for 10-15 min before the solvent was removed under vacuum and the products isolated by chromatography on silica gel.

Ozonolysis of 7 gave 98% of 22 which was identical in all respects to the above described sample.

(L)-Benzyl 2-t-Butyloxycarbonylaminobut-3-enoate (24), prepared by standard ozonolysis of the pyridyl selenide 13 and the phenylselenide 28, was identical to the above isolated sample.

Ozonolysis of 15 - According to the standard procedure and subsequent chromatography (eluant: hexane-EtoAc 4:1) on silica gel this gave pure 25 in 82% yield. This compound was an oil which solidified on standing m.p. 42-44°C; $[\alpha]_D^{20}$ +86.2° (c = 1.1 in $CHCl_3$), lit.[13]; $[\alpha]_D^{20}$ = +89° ($CHCl_3$); δ (200 MHz), 4.93 (1H, d, J = 5 Hz, ring CH), 5.26 (2H, s), 5.53 (2H, 2 x d, J = 5Hz, ring CH_2), 5.50 (2H, m), 5.93 (1H, ddd, J_{trans} = 16 Hz, J_{cis} = 10 Hz, J (ring methine) = 5 Hz). ν(CH_2Cl_2) 1800, 1720, 1500, 1350 cm^{-1}; m/z 247 (M^+), 202, 174, 116, 91.

(L)-Methyl 2-benzyloxycarbonylaminobut-3-enoate (26) - This compound, prepared by ozonolysis of both 17 and 30, was a colourless oil that was further purified by Kugelrohr distillation (150°C/2 mm). It had $[\alpha]_D^{20}$ -11.3° (c = 0.5 in MeOH), lit.[13] $[\alpha]_D^{21}$ -12.4° (c = 0.5 in MeOH), $[\alpha]_D^{20}$ -11.8° (c = 1.8 in MeOH); δ (200 MHz), 3.76 (3H, s), 4.95 (1H, m), 5.12 (2H, s), 5.31 (1H, d, J_1 = 10 MHz), 5.36 (1H, d, J_2 = 17 Hz), 5.5 (1H, m), 5.9 (1H, ddd, J_1 = J_3 = 10 Hz, J_2 = 17 Hz).

Preparation of 25 from 14 without Isolation of Intermediates - N-Methylmorpholine (220 mg) and isobutylchloroformate (326 mg) were added to 14 (586 mg) in THF (5 ml) at -15°C under nitrogen. After stirring for 10 min at -15°C the selenohydroxamic acid 2 (436 mg) and N-methylmorpholine (220 mg) in THF (2 ml) were added and stirring maintained 30 min during which time the reaction was allowed to warm to room temperature. The reaction mixture was then irradiated (two 100W tungsten lamps) at room temperature for 1 hr before being poured into dilute hydrochloric acid (75 ml) and washed with ether (2 x 50 ml). The aqueous phase was neutralised at 0°C with saturated aqueous sodium hydrogen carbonate and then ether-extracted (4 x 50 ml). The combined extracts were washed with water (3 x 50 ml) and saturated aqueous sodium chloride (50 ml), dried on Na_2SO_4, filtered and evaporated to dryness. The crude selenide so obtained was subject to the standard ozonolysis procedure yielding the protected vinylglycine derivative 25 (350 mg) in 71% overall yield.

Standard Procedure for Deprotection of Derivatised Vinylglycine

The protected amino acid was heated to reflux in 6N HCl (5 ml per mmol) with stirring for 1 hr. The cooled solution was then washed with chloroform and evaporated to dryness to give crude vinylglycine hydrochloride.

Deprotection of 24 by the standard procedure on a 1 mmol scale yielded, after recrystallisation from ethanol-ether, (L)-vinylglycine hydrochloride 31 (96 mg, 70%) with m.p. 169°C; $[\alpha]_D^{20}$ +73° (c = 1 in H_2O), +70° (c = 1 in 2N HCl), lit.[10], m.p. 175-177°C, $[\alpha]_D^{20}$ +78.5° (c = 1.9, H_2O), +96° (c = 1 in 2N HCl); lit.[13], m.p. 171-173°C; $[\alpha]_D$ +77.5° (c = 0.5 in H_2O).

Deprotection of 25 (150 mg, 0.6 mmol) according to the standard procedure gave 31 (43 mg, 52%) on refluxing of the crude product in acetone, m.p. 172-176°C, $[\alpha]_D^{20}$ +57° (c = 1 in H_2O).

Deprotection of 26 (200 mg, 0.8 mmol) by the standard procedure gave a white crystalline residue after evaporation of the solvent. This residue was then dried under vacuum (0.1 mm, 20°C) for 3 hr and then heated to reflux in dry acetone (5 ml) for 10 min. The acetone was decanted off and the residual white crystals were washed with cold acetone (5 ml) to give 31 as a white, odourless, crystalline sold (48 mg), m.p. 172-174°C; $[\alpha]_D^{20}$+77.5° (c = 0.5 in H_2O). The mother liquors and washings were combined and concentrated to yield a second crop of 31 (52 mg) with m.p. 173-175°C. Total yield of pure crystalline 31 91%.

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