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Synthesis of dehydrodipeptides as potential suicide substrates for D, D-peptidases

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Abstract
The synthesis of the dehydrodipeptide phenoxyacyl dehydroserine–D–alanine to act as a potential suicide substrate for D, D-peptidase is presented. Starting with the hydrochloride of serine methyl ester, this was chemically transformed to the key phenoxyacyl-β–chloro Ala Ala which was dehydrohalogenated to the desired dehydrodipeptide.

Keywords: Suicide substrate, Phenoxyacyldehydrodipeptide, D, D-Peptidases

Introduction

Penicillin exhibits its antibacterial properties by inhibiting β-lactamase, the enzyme responsible for the final step in bacterial cell wall biosynthesis. The bacterial cell wall is a macromolecular network that completely surrounds the cell and provides its structural integrity. In the presence of penicillins, the fine control of lytic and synthetic enzymes necessary for the proper development of the cell wall of the growing bacterium is perturbed and the cell wall so generated is defective and cannot support the fragile cytoplasmic membrane against the internal osmotic pressure. The cell fluid bursts through the cytoplasmic membrane and the organism is killed (Haslam 1979). The cross linking of the peptidolglycan chains is accompanied by the loss of the terminal D-alanine residue.

The enzyme responsible for catalyzing this step, a transpeptidase is inhibited by penicillin. (Frere *et al.*, 1980, Frere and Joris 1985) However evidence is accumulating that with some bacteria, inhibition of the tanspeptidase responsible for the final step of bacterial cell wall biosynthesis is not the site of action. The implication from the above is, some penicillins are not as effective in their antibacterial action. This therefore necessitates the generation of new compounds that hold the promise of enhancing antibacterial activity. Hence the synthesis of dipeptides as potential suicide substrates for D, D-peptidase. The compound whose synthesis is being reported is

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Phenoxyacyldehydroserine-D-alanine dipeptide 1.

Studies have been made (Hagen *et al.*, 1984) towards the synthesis of the chlorinated dipeptide 2 in the hope of converting it to the desired dehydrodipeptide 1 by coupling Boc. Ser with the tosyl salt of alanine benzylate to yield the protected dipeptide (Scheme 1) followed by treatment with the succinamide ester of phenoxyacetic acid to yield a mixture of three functionalized protected dipeptides among which was the desired intermediate 3, all in fairly low yield. The protected intermediate dipeptide 3 was converted to the desired 2 by sequentially treating it with PPh_3/ CCl_4 (or $SOCl_2$/pyridine CCl_4), then H_2, 10% Pd/C

Experimental

Melting points were determined on a Buchi Apparatus and are uncorrected. ^1H NMR spectra were determined on a JOEL PMX 60 SI or Varian XL 200 instruments. Optical rotations were obtained on a Perkin Elmer 241 MC Polarimeter with sodium light at 590 nm. NMR's were run using TMS as internal standard.

Boc Ser[8]: A mixture of L-serine (1.05g) in Dioxane/Water 2:1 (30 mL) and 1M NaOH (10 mL) was cooled in ice and Ditert-butyldicarbonate (2.4 g) was added to the mixture. This was stirred at room temperature for 30 min. after which most of the solvent was removed under reduced pressure. $KHSO_4$ (1M) was added to the solution until the pH was between 2 and 3 and the aqueous phase extracted with ethyl acetate (2 x 30 mL). The EtOAc layer was washed with water (25 ml) and dried ($MgSO_4$). Solvent was removed and a viscous product (0.855g, 52%) obtained which solidified on keeping in the cold room, mp 44-46, $[\alpha]^D_{20}$ − 7.76 (c = 3, H_20) ^1H NMR ($CDCl_3$) δ 4.3 (1H, m) (1H, m), 4.0 (2H, br s) 1.4(9H, s).

The reaction was run on a larger scale, the reaction time being increased to 4 hr.

Boc Ser. H_2O[10]: To a solution of L-Serine (10.51g) and sodium bicarbonate (22g) in H_2O(200 ml) and Dioxane (200mL) was added t-butylazidoformate (17.20g) drop by drop at a bath temperature of 45°. The mixture was stirred for 20 hours at this temperature after which it was ice cooled, neutralized by the addition of ice cold 4N HCl (57.5 mL) to pH 4.6 – 4.8 and concentrated to 80 mL at 40° *in vacuo*.

The concentrated solution was then acidified to below pH 2 with ice cold 4N HCl in the presence of EtOAc (200 mL) at 0°.
The aqueous phase was extracted with cold EtOAc (3 x 100 mL), the combined organic layer dried (Na_2SO_4) and solvent removed at the rotor evaporator at 35-40° to give a syrup. This product, which was not weighed, was dissolved in ether (100 ml) to which was added 12.2g (13.40 mL) of dicyclohexylamine. Crystals formed at room temperature in a few minutes (30 min.). This was placed in a cold room for few hours after which it was filtered crystals washed with ether and dried at the aspirator. 17.041g (42%) of product was obtained. 17g of this sample was recrystallised from EtOAc to give product (12.562g), mp 139-140°, $[\alpha]^D_O$ 0.1 + 12.85° [Lit $^4[\alpha]^{25}_0$ + 13.3° ± 0.5] ^1H NMR (MeOH.d_4) δ 5.3, 4.2, 1.6 – 2.6.

The Boc-Serine dicyclohexylamine salt (12.1g) was dissolved in 50% EtOH (142 mL) and shaken in the presence of 32 mL (wet volume) of Dowex 50 W x 8 (H^+ form) at room temperature for 2.1 hr.
The resin was removed by filtration, the filtrate concentrated to a small volume at 40-45° *in vacuo* and cooled in an ice bath. 6.85g (96.5%) of the product was obtained $[\alpha]^D_{20}$ - 7.6° (c 3.05, H_2O)mp 46-48°. ^1H NMR (MeOH . d_4) δ 4.2 (br t, 1H), 4.0 (d, 2H) 1.5(s, 9H).

D-AlaOBzl tosylate[4]: D-Alanine (2.67g), $TsOH.H_2O$ (6.27) and benzyl alcohol (36 mL) in benzene (35 mL) was refluxed for 7 hours

after which benzene was removed at the rotor evaporator. Benzyl alcohol was removed under reduced (at the aspirator) pressure after which ethanol, then ether was added to the residue and left at room temperature. Some crystals were formed. More product was precipitated by adding ether. The reaction mixture was then filtered to obtain product (2.873g). 2.8g of this was recrystallised from EtOH – Et_2O to give pure product (1.4g) mp 105 – 107°.

^{1}H NMR ($CDCl_3$) δ 8.1 (br, s 3H), 6.9 – 7.8 (m; 9H, Aromatic protons) 4.9 (s, 2H, CH_2 pH), 4.0(br, s, 1H methine of Ala) 2.2(s, 3H), 1.4(d, 3H). This reaction was run on a larger scale, the reflux time being 21 hours. 39.9g (76%) of recrystallised product was obtained.

PhOCH$_2$COOSu[9]: $PhOCH_2COOH$ (1,52g), pyridine (0.81 ml), N, N-discuccinimidyl carbonate (2.562g) in dry CH_3CN(10 mL) was stirred at room temperature for 5 hours after which solvent was removed. The solid obtained was dissolved in EtOAc layer extracted successively with 5% HCl (4 x 50 mL), brine (4 x 25 mL) and dried (Na_2SO_4). Solvent was removed *in vacuo* to obtain product (1.98g) which was purified by flash chromatography (3% MeOH/$CHCl_3$) and recrystallisation (EtOAc-Hexane) 1.06g (80%) of pure product was obtained.

^{1}H NMR ($CDCl_3$) δ 7.0(m, 5H) 4.9(s, 2H), 2.8(s, 4H).

Boc Ser-AlaOBzl[5]: (a) DCC (103mg) was added to a chilled (-15°) mixture of Boc. Ser (50 mg), AlaOBzl tosylate (86 mg), HOBt (74 mg) and N-ethylmorpholine (30.7 mg) in CH_2Cl_2 (5 mL). After stirring for 1 hr. at -15° and 5 hr. at room temperature, DCU was removed by filtration and CH_2Cl_2 (10 mL) added. The solution was extracted successively with H_2O; 5% citric acid, 1M $NaHCO_3$ and H_2O (10 ml each), dried (Na_2SO_4), filtered and evaporated. The crude product (93 mg) was column chromatographed (SiO_2) with CH_2Cl_2 as eleuents. The product obtained was further purified by preparatory tlc (5% MeOH/$CHCl_3$) to yield product (53 mg).

^{1}H NMR ($CDCl_3$) δ 7.3 (s, 5H), 5.6 (d, 1H), 5.1(d, 2H, 4.7(q, 1H), 4.1 (br, t, 2H), 1.5 (2 close singets 12H).

The above reaction was run on a larger scale, the stirring time being 21 hr. the product purified by flash chromatography and obtained in 74% yields (39.8g).

(b) Boc Ser-AlaOBzl: (a) DCC (206mg) was added to a chilled (-15°) mixture of Boc Ser. H_2O (50 mg), AlaOBzl tosylate (86 mg), HOBt (74 mg) and N-ethyl morpholine (30.7 mg) in CH_2Cl_2 (5 ml). After stirring for 1 hr. at -15° and 5 hr. at room temperature, the reaction was worked up as in (a). Analysis of the product indicate it was largely starting materials.

β -Chloroalanyl methyl ester HCl[7]: L-serine methyl ester. HCl (4.8g) was dissolved in freshly distilled CH_3COCl (48 ml) and ice cooled. PCl_5 (7.2g) was added over 10-15 min. after which the reaction mixture was stirred at room temperature for 3 hr. This was then filtered, the solid obtained washed with a little CH_3COCl and then petroleum ether to give after drying a nearly colourless product (2.71g) mp 136-138°, which was recrystallised from methanol containing HCl and hexane.

^{1}H NMR (MeOH . d_4) δ 4.9 (br.s, 4H), 4.2 (d, 2H), 3.9(s, 3H).

The above reaction was repeated on a larger (18g of ester) to give 16.4g (82%) of product mp 149°, the ^{1}H NMR being the same.

ß Cl-Alanyl. HCl[1]: ß – Cl Alanylmethylester. HCl (16g) was refluxed in 20% HCl (160 ml) for 1 hr. after which the solvent was removed under vacuum to give product (13.8g, 96%).

^{1}H NMR (MeOH . d_4) δ 5.4(br, s 3H), 4.5(t, 1H), 4.2(d, 2H).

Boc-ß (Cl)-Alanine[7]: Ditertbutyldicarbonate (2.177g) and Et_3N (2.765 ml) was added to a solution of ß (Cl) alanine 1.2g in DMF (27.2

ml) at room temperature. A precipitate formed. The mixture was stirred at room temperature for 12 hr. after which it was poured into EtOAc (50 ml).

The suspension was extracted with H_2O (2 x 30 ml), $NaHCO_3$ (2 x 30 ml), and the combined aqueous layers were acidified to between pH 2 and 3 with solid citric acid. This was extracted with EtOAc (3 x 30 ml), the combined layers washed with brine, dried ($MgSO_4$), filtered and solvent removed to give a semi-solid (1.509g) which was purified by flash chromatography (EtOAc) and recrystallised from EtOAc-Hexane.

^{1}H NMR ($CDCl_3$) δ 11.0(br s, 1H), 8.1 (br, s 1H), 5.9 (br, d 1H), 4.9 (m, 1H), 4.0 (br, s 2H), 1.5 (s, 9H).

The reaction was repeated on a larger scale (5.88g acid) to give 3,55g, (51%) of pure compound, the ^{1}H NMR being identical to that above.

Boc-ß (Cl)-Ala-AlaOBzl[5]: DCC (460 mg) was added to a chilled (-15°) mixture of Boc ß (Cl)-Alanine (224 mg) and AlaOBzl tosylate (383 mg), HOBt (332 mg) and N-ethylmorpholine (15 μL) in CH_2Cl_2 (3 ml). After stirring at -15° for 1 hr. and 4 hr. at room temperature, DCU was removed by filtration and CH_2Cl_2 (7.5ml) added. The solution was washed successively with H_2O 5% citric acid, 1M $NaHCO_3$ and H_2O (10ml each), dried (Na_2SO_4) filtered and evaporated to give product (460mg) which was purified by flash chromatography (5% MeOH/$CHCl_3$) and trituration with hexane to give product (285 mg, 74%).

^{1}H NMR ($CDCl_3$) δ 7.3 (s, 5H), 7.0 (br, s 2H), 5.5(d, 1H), 5.2(s, 2H), 44.4 – 4.7(m, 2H), 3.8(m, 2H), 1.5(s, 12H).

$PhOCH_2CO$ ß (Cl)-Ala-AlaOBzl[5]: TFA (0.6 ml) was added to Boc-ß (Cl)-Ala-AlaOBzl and the reaction mixture stirred at room temperature for 30 minutes. The TFA was distilled under reduced pressure and the product dried *in vacuo* for 11 hr. at room temperature $PhOCH_2COOSu$ (168 mg) and Et_3N (82 μL) were added to a solution of the generated ß (Cl)-Ala-AlaOBzl in CH_2Cl_2 (0.84 ml) and the mixture stirred for 22 hr. CH_2Cl_2 (2.8 ml) was added and the solution washed successively with H_20, 5% critic acid, 1M $NaHCO_3$, 5% citric acid, H_2O (2.5 ml each), the CH_2Cl_2 layer dried (Na_2SO_4), filtered and the solvent removed on the rotary evaporator to give product (214 mg) which was further purified by flash chromatography (3% MeOH-$CHCl_3$) to give product (180 mg, 98%).

^{1}H NMR ($CDCl_3$) δ 7.4(m, 10H), 5.1(s, 2 H), 4.9(m, 1H0, 4.8 (m, 1H), 4.5(s, 2H), 4.0(d, 2H), 1.4(d, 3H).

$PhOCH_2CO$ – ß (Cl) Ala – Ala-OH

H_2 at 40 atm was passed through a solution of $PhOCH_2CO$–ß–Cl–Ala–AlaOBzl (154mg) in MeOH (12ml) in the presence of 10% Pd/C (111mg) for 6.5 hr. after which the mixture was filtered to give the product (106 mg), mp 130-132. This was recrystallised from MeOH-H_2O to give product (35mg) mp 146-146°. A second recrystallisation (MeOH-H_2O) gave a product (4mg) mp 145- 147°.

^{1}H NMR (CD_3 $COCD_3$) δ 7.9(br, s, 2H), 7.0(m, 5H), 5.5(s, which disappeared on a D_2O shake, COOH), 5.0(m,1H), 4.5(s, 2H), 4.0(d, 2H), 1.5(d, 3H).

Phenoxyacyldehydro Serine-Alanine

$PhOCH_2CO$ – ß – Cl – Ala – AlaOBzl (2 mg) was dissolved in EtoAc (0.7 mL), Dabco (2 mg) added and the reaction mixture stirred at room temperature for 6 hr. The EtOAc layer was extracted with 5% HCl, washed with H_2O (2.5 mL) dried (Mg SO_4) and solvent removed to give product (2 mg, 60%) ^{1}H NMR (acetone.d_6) … 7.9 (hr, s, 2H), 7.0 (m, 5H), 5.5 (S, 1H),5.32 (d, 1H), 5.18 (d, 1H)

Results

A synthetic strategy was devised to obtain the key intermediate 2 followed by

elimination of HCl to yield the desired dehydrodipeptide. (Scheme 2).

The desired molecule was divided into three segments to be synthesized independently. Condensation of these segments and further synthetic manipulation would lead to the desired compound.

Boc.Ser

This was prepared by two methods:

(i) Treatment of serine with ditertiarybutyl dicarbonate in dioxane/H_2O (2:1), (1M NaOH (Moroder *et al.*, 1976), to yield product in 52% yield ^{1}H NMR ($CDCl_3$) δ 4.3 (M, 1H), 4.0 (br s, 2H) 1.4 (s, 9H).

(ii) Reaction of serine with tertiary butyl azidoformate in dioxane/H_2O with heat for 20hr in the presence of dicyclohexylamine to yield the intermediate dicyclohexylamine salt which on treatment with Dowex 50W x 8 H^+ form (Otsuka *et al.*, 1966) yielded product in 42% overall yield. ^{1}H NMR (MeOH.d_4) δ 4.2 (br t, 1H) 4.0 (d, ZH), 1.5 (s, 9H)

D-Ala OBzl Tosylate

This was prepared by treating D-alanine and TsOH.H_2O with reflux in benzene (Gibian *et al.*, 1961) for 21 hr to yield the desired compound in 76% yield. ^{1}H NMR ($CDCl_3$) δ 8.1 (br s, 3H), 6.9 – 7.8 (m, 9H) 4.9 (s, 2H), 4.0 (br s, 1H), 2.2 (s, 3H) 1.4 (d, 3H).

Ph OCH_2 CO OSu

This was achieved by reacting phenoxyacetic acid with N, N, - disuccimidyl carbonate, pyridine in dry acetonitrite for 5 hr (Ogura *et al.*, 1979) to obtain product in 80% yield. ^{1}H NMR ($CDCl_3$) δ 7.0 (m, 5H), 4.9 (s, 2H), 2.8 (s, 4H).

Other methods employed to prepare this compound included

(i) Reacting phenoxyacetic acid with N – hydroxyl succinimide, DCC, in dry DMF yielded a product with ^{1}H NMR ($CDCl_3$) δ 6.7 – 7.3 (m), 5.0 (s), 4.7 (s) 2.8 (s), 1.0 – 2.1 (broad signal) and integrated spectrum somewhat inconclusive.

(ii) Phenoxycetic acid, N-hydroxy succinimide, diisopropyl carbodiimide and a catalytic amount of DMAP to yield a product that was polymeric with no suitable ^{1}H NMR spectral data.

Boc. Ser – D – AlaOBzl

Two methods were employed to synthesise this compound.

(i) Coupling Boc. Ser and TsO^- D-AlaOBzl using DCC, HOBt, N-ethylmorpholine in CH_2Cl_2 for 5 hr at room temperature (Hagen *et al.*, 1984) to yield product ^{1}H NMR ($CDCl_3$) δ 7.3 (s, 5H), 5.6 (d, 1H) 5.1 (d 2H), 4.7 (q, 1H), 4.1 (br t, 2H). 1.5 (two close signals, 2H) in 74% yield

(ii) Coupling Boc Ser. H_2O with TsO^- D-AlaOBzl in conditions identical to the first method. Analysis of product by ^{1}H NMR indicated starting materials.

Boc. B-Cl–Ala–Ala OBzl

Efforts aimed at converting Boc. Ser – D – AlaOBzl (Hagan *et al.*, 1984, Fischer *et al.*, 1970) to the above compound included.

(i) Treating Ser. AlaOBzl with PCl_5/CH_3COCl, RT. 2hr which yielded an isolated product with a proton NMR δ 7.2 (s), 3.5 (m), 1.2 (m).

(ii) Boc. Ser – D – AlaOBzl with $SOCl_2$/pyridine/CH_2Cl_2) 0°, then refluxing for 3hr, afforded a product with proton NMR δ 1.5 (s. 9H)

(iii) Boc. Ser – D – AlaOBzl with $SOCl_2$/pyridine (2 equivs), CH_2Cl_2 0°, then refluxing for 3hr generated a product with proton NMR δ 6.9 – 7.8 (m, 9H).

Two schemes were then devised to generate suitable intermediates that would eventually lead to the desired 1 (Schemes 3, and 4).

Starting with the hydrochloride salt of serine methyl ester, this was converted to the β – chloroalinine. HCl by treating it with

PCl_5/CH_3COCl, RT, 3 hr, then 20% HCl refluxing for 1 hr, in 80% overall yield. Conversion of this intermediate to phenoxyacetyl – β – chloroalanine by treating it with $PhOCH_2COCl$/DMF, Et_3N (3 equiv), RT, 14 hr yielded a product with proton NMR δ 7.9 (d,) 7.0 (m), (5.0 (q, 1H), 4.5 (d), 4.0 (d, 2H). There was difficulty with solubility of this product in acetone.d_6. A solid residue was obtained. Dissolution of this solid in methanol.d_4 gave NMR data as that for acetone.d_6.

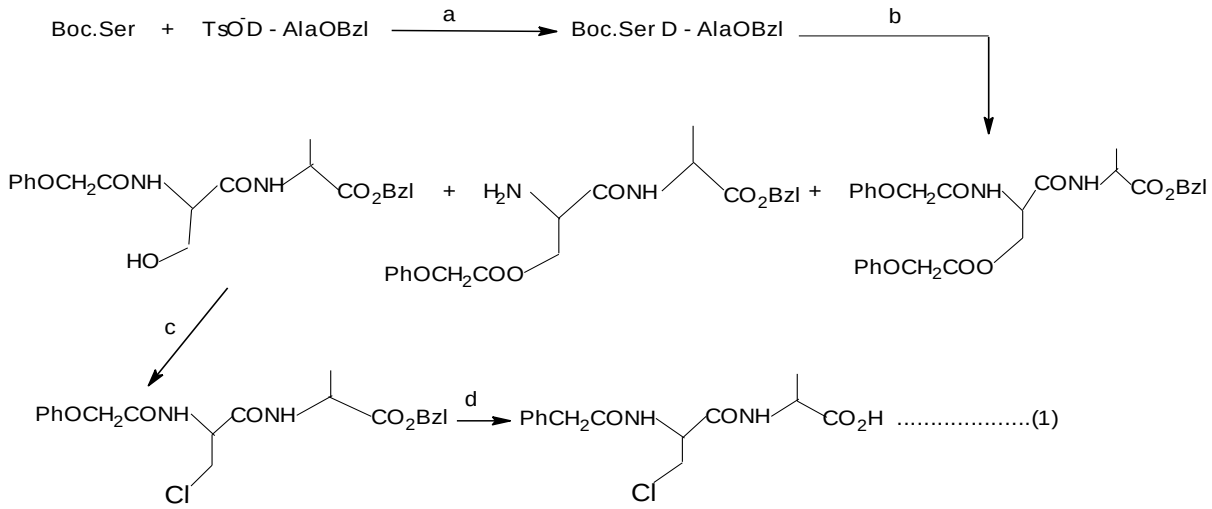
Another route to this compound was therefore adopted (Scheme 4). Starting with the hydrochloride of serine methyl ester, this was converted to β-chloroadanyl hydrochloride. This intermediate was transformed sequentially to Boc. β - chloroalanine (Ditertiarybutyl dicarbonate/DMF, Et_3N (2 equivs), RT, 12 hr. 51% yield).

Boc. β – Cl – Ala – AlaOBzl, (TsOAlaOBzl, N – ethylmorpholine, HOBt in CH_2Cl_2, DCC, RT, 4 hr, 74%) to the phenoxyacetylated compound (TFA, RT, 0.5 hr; $PhOCH_2$ $COOSu$/ CH_2Cl_2 Et_3N, 22 hr, 98% yield) to generate a product with proton NMR δ 7.9 (br, s, 2H), 7.0 (m, 5H), 5.5 (s, which disappeared on shaking with D_2O) 5.0 (m, 1H), 4.5 (s, 2H), 4.0 (d, 2H) 1.5 (d, 3H).

This intermediate product obtained was treated with Dabco/EtOAc, RT, 6 hr to generate what was considered the desired compound (60% yield) with proton NMR. δ 7.9 (br, s, 2H) 7.0 (m, 5H) 5.5 (s, 1H) 5.32 (d, 1H) 5.18 (d, 1H)

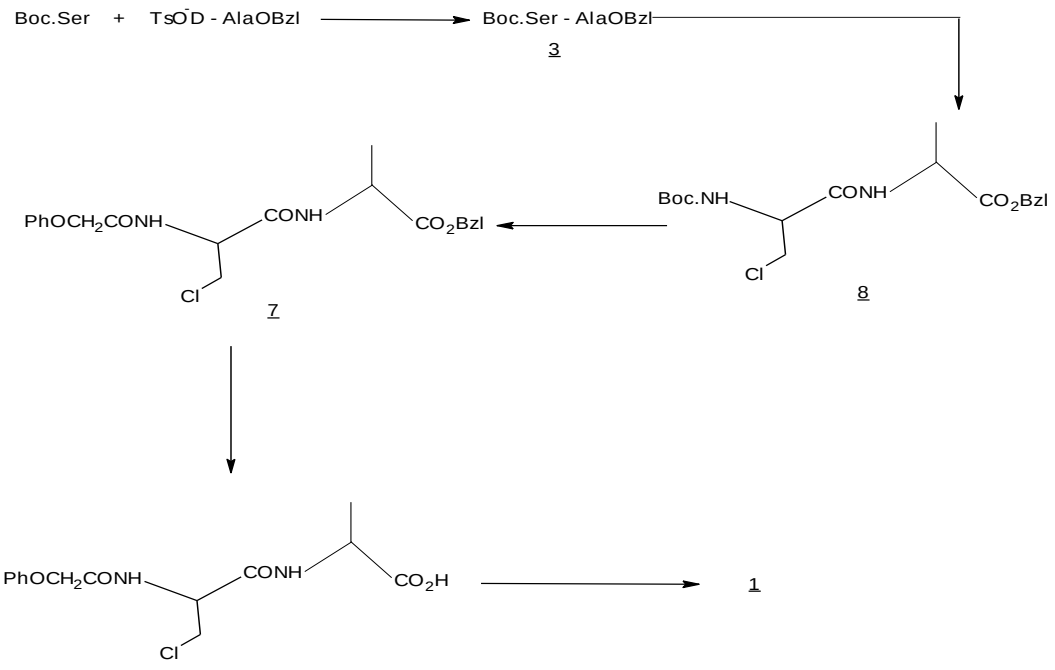
The compound generated was submitted for biological evaluation. At this stage funding, support for this investigation ran out.

SCHEMES AND FIGURES

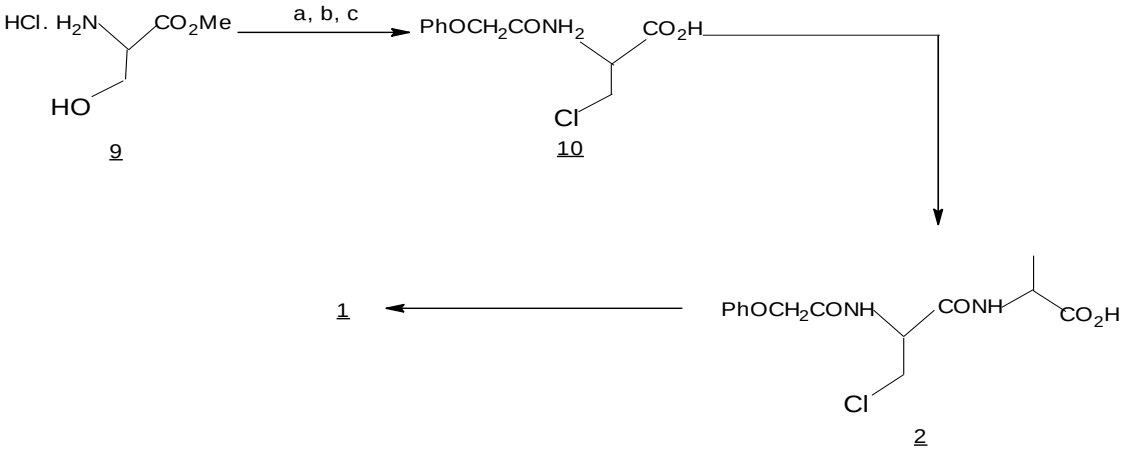


[A]Key (a) DCC (b) $PhOCH_2COOSu$ (c) PPh_3/CCl_4 or $SOCl_2/pyr/CCl_4$ (d) H_2, 10% Pd/C

Scheme 1

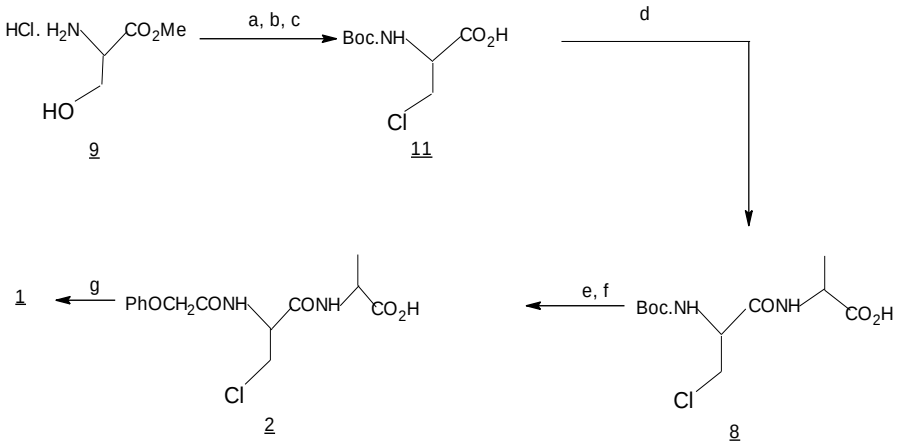


Scheme 2



[A]Key (a) PCl_5/CH_3COCl, 3hr RT, 82% (b) 20% HCl, Heat 1 hr, 96% (c) $PhOCH_2COCl$/DMF, Et_3N, 3eq, 14 hr, RT

Scheme 3



[A]Key

(a) PCl_5/CH_3COCl, 3hr RT, 82% (b) 20%HCl, Heat 1hr, 96%

(c) Ditert-butyl dicarbonate/DMF, Et_3N 2 equiv, 12hr, RT, 51%

(d) TsOAlaOBzl, N-ethyl morpholine, $HOBt/CH_2Cl_2$, DCC, 4hr, RT 74%

(e) TFA,0.5hr, RT, $PhOCH_2COOSu/CH_2Cl_2$, Et_3N, 98%

(f) H_2 , 10% Pd/C, 6.5hr 90% (g) Dabco/EtOAc, 6hr, RT, 60%

Scheme 4

Discussion

Previous work (Hagen *et al.,* 1984) in the synthesis of the intermediate 3 was rather inefficient as it was one obtained from a mixture of three compounds and in low yield. The desired molecule was divided into three segments to be synthesized. Condensation of these segments with further synthetic manipulation would lead to the product.

Boc. Ser was prepared by two independent routes in good yield as well as D – AlaOBzl tosylate. The same was for the succinimide of pheonxyacetic acid which was achieved by treating phenoxyacetic acid with N_1 N – discuccimidyl carbonate, pyridine in dry acetonitrile. Preparation of this latter compound by reacting phenoxyacetic acid with N- hydroxyl succinimide DCC, in dry DMF, or phenoxyacetic acid, N-hydroxysuccinimide, diisopropyl carbodiimide and a catalytic amount of DMAP were unsuccessful. The first method yielded a product whose proton NMR was inconclusive, the second yielded a polymeric product whose proton NMR was difficult to obtain.

Boc. Ser –D- AlaOBzl: This compound was obtained in good yield by coupling Boc. Ser. and Tsõ D - AlaOBzl using DCC, HOBt, N-ethylmorpholine, CH_2Cl_2. Coupling utilising Boc. Ser.H_2O in conditions identical to the one just described did not take place; only starting materials were obtained as evidenced from the proton NMR analysis of the reaction.

Boc. ß – Cl – Ala – Ala OBzl: Methods employed to convert 3 to the above compound involved:

a) Interacting it with PCl_5/CH_3 COCl, RT, 2 hr.

b) $SOCl_2$/pyridine, CH_2Cl_2, O°, then refluxing for 3 hr.

c) $SOCl_2$/pyridine, (2 equiv.)/ CH_2Cl_2, O°, refluxing for 3 hr.

For a) the isolated product gave a proton NMR with weak multiplets; for b) and c) the

major isolated products gave a proton NMR with peaks due to Boc. and benzyl groups.

Because of the failure to convert the hydroxyl group in serine to the chloro group in the dipeptide alternative synthetic schemes were made (Schemes 3 and 4) in order to generate suitable intermediates. In one strategy, Scheme 3, the hydrochloride salt of serine methylester was converted to ß – choloroalanine. HCl salt which was to be phenoxyacetylated ß-choloroalanine. The proton NMR obtained indicated peaks characteristic of the desired compound but there were more protons than could be accounted for and there were problems with solubility of the material in deuterated acetone and methanol. It probably is a dimer or a polymeric form of the desired product. This scheme was therefore not pursued any further.

Scheme 4 involved starting with the same starting material as in Scheme 3 and was sequentially converted to various intermediates in good yield to eventually generate the desired compound.

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