THE SYNTHESIS OF OXA-ANALOGS OF THE KAINOID FAMILY

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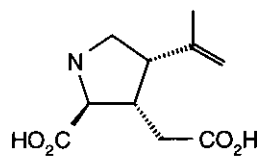
Abstract- In an effort to mimic the anthelmintic and insecticidal activities of kainic acid (**1**) and domoic acid (**2**) with compounds of simpler structure and much easier accessibility, the highly functionalised isoxazolidines (**4**) and (**20**) were prepared.

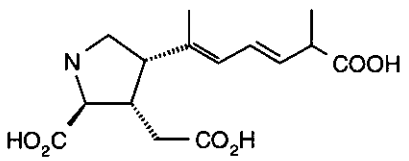
Introduction

The kainoids comprise a series of naturally occurring amino acid derivatives which have interesting anthelmintic and insecticidal activities arising from their interaction with glutamate receptors.[1] Indeed their structure incorporates a glutamate moiety bound in a pyrolidine ring. After kainic acid (**1**),[2] domoic acid (**2**),[3] and acromelic[4] acids were isolated, several syntheses of these compounds were developed,[1] and a number of derivatives were prepared.[1] As one of the results from this effort, the synthetic anisyl derivative (**3**) was found to be a more potent glutamate agonist than the naturally occurring domoic acid (**2**) or acromelic acid in certain nerve preparations.[5]

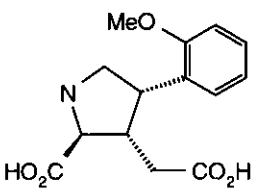
We wanted to examine new molecules which were simpler to prepare and would hopefully maintain the anthelmintic and insecticidal activities of the natural products.[6] The isoxazolidine (**4**) was considered to be a suitable target, as it is geometrically almost identical to **3** itself,[7] and also as a promising synthetic approach through the cycloaddition of the nitrone (**11**) with the alkene (**7**) (Scheme 2) was foreseen.[8-10] This paper describes the preparation of **4** as well as its simpler phenyl analog (**20**) by this route.



kainic acid **(1)**



domoic acid **(2)**



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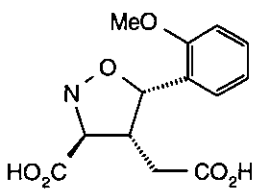
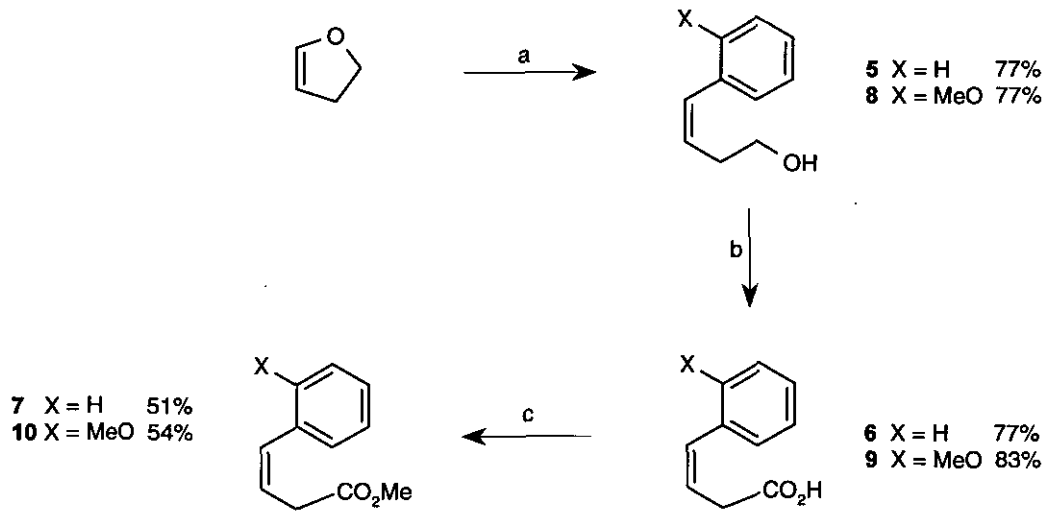


target **4**

Results and Discussion

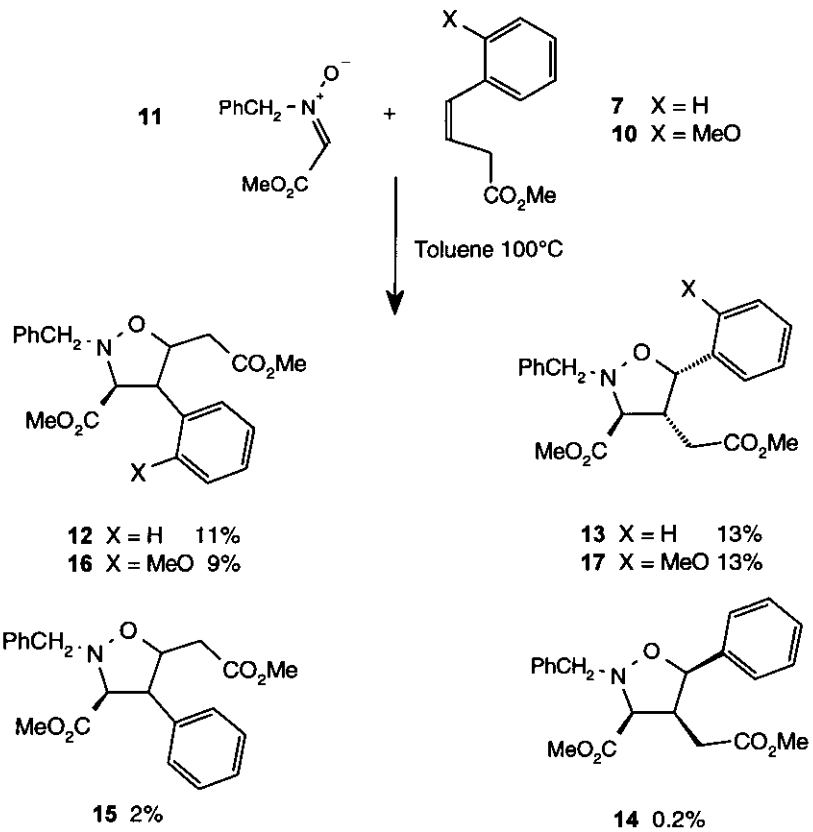
A simple synthesis of the $\Delta^{3,4}$-*Z*-alkene (**10**) was developed (Scheme 1). Two syntheses of **10** have been described previously. One involves a chain extension of a *Z*-cinnamate ester,[11] and the other reaction of a *Z*-styrylborane with diazoacetate.[12] The need to prepare **10** under non-basic conditions reduces the number of methods available for its synthesis. Its allylic hydrogens are easily removed to form a stable anion, which upon reprotonation yields an equilibrium mixture of $\Delta^{3,4}$-*E*- and $\Delta^{2,3}$-*E*- alkenes. This problem was avoided by preparing the *Z*-alkene (**8**) with the ester at the alcohol oxidation level, and oxidising and esterifying under acidic conditions. Addition of arylmagnesium bromide to dihydrofuran in a stereoselective nickel catalysed reaction described by Wenkert led to the *Z*-alkenols (**5**) and (**8**) in good yields.[13] The preactivation of the nickel complex with methyl magnesium bromide and the change of solvent from ether to benzene prior to the reaction were found to be unneccesary, making this method very practicable. Jones oxidation then yielded the carboxylic acids (**6**) and (**9**), which were isomerically pure but contaminated with the starting alcohols (**5**) and (**8**). Esterification under acidic conditions led to the desired esters (**7**) and (**10**). The moderate yields obtained in this step are due to the loss of the contaminants in the starting acids.



Scheme 1. a. ArMgBr, $(Ph_3P)_2NiCl_2$ (2%), Et_2O, 3 h rt. b. CrO_3, acetone, rt. c. H_2SO_4, MeOH, reflux, 3 h.

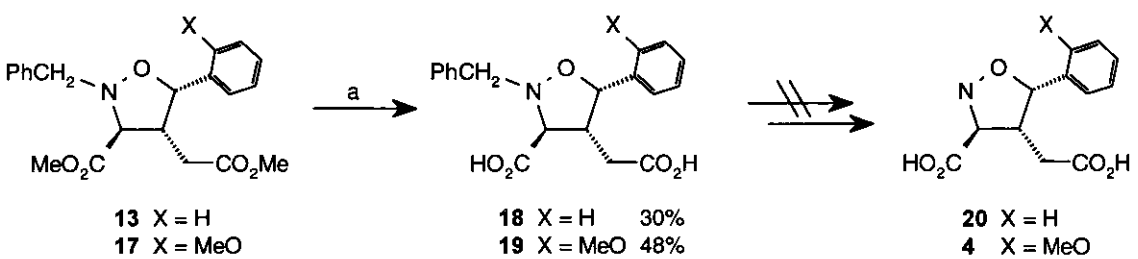
On heating in toluene the alkene (**7**) reacted with the nitrone (**11**), which is easily prepared from benzylhydroxylamine and methyl glyoxylate.[14] As already pointed out **7** is base sensitive and is unactivated for cycloaddition. Consequently the nitrone cycloaddition was slow and low yielding, and also poorly selective as is normal for such additions,[8-10] yielding all four possible regio/stereoisomers. The nitrone (**11**) exists as a mixture of *E* and *Z* isomers, but Inouye et al have shown that they interconvert readily.[14] Although the desired cycloadduct (**13**) resulting from exo cycloaddition was the major product, it was obtained after chromatography in only 13% yield. However, as both nitrone and alkene starting materials

were simple to prepare, substantial amounts of **13** were easily obtained. In a similar manner **17** was prepared from **11** and the alkene (**10**). The cycloaddition of the alkene (**7**) with azomethine ylids was attempted, but every attempt using various ylid precursors failed.[15]



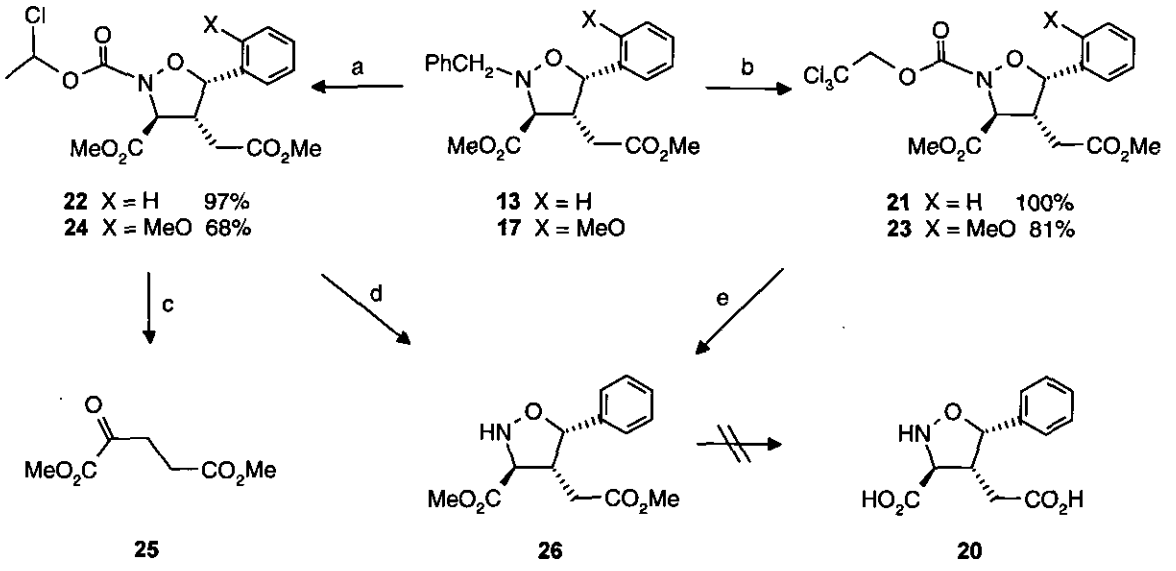
Scheme 2.

The conversion of **13** and **17** to the target compounds (**20**) and (**4**) involved merely the removal of the *N*-benzyl and ester protecting groups. However, it transpired that it was crucial to remove them in the correct order. Initial hydrolysis of the ester groups yielded the diacids (**18**) and (**19**), but attempted cleavage of the *N*-benzyl group of **18** failed. Treatment of **18** with chloroformates under conditions used successfully to debenzylate **13** (Scheme 4) led only to complex mixtures.

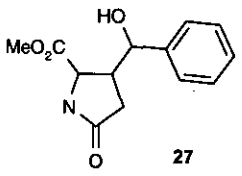


Scheme 3. a. 2M HCl, 60 °C, 24 h.

In their preparation of (±)-*allo*-kainic acid, DeShong and Kell debenzylated a pyrrolidine analog of **13** with chloroformate.[16] However **13** was unreactive to debenzylation with chloroformate under these standard conditions. Fortunately the desired carbamates (**21**) and (**22**) were formed in good yields when lithium iodide was used to catalyse this reaction.[17] Special attention had to be paid to the removal of these newly formed carbamate groups, which was unsuccessful under the standard conditions. Simply heating the chloroethyl carbamate (**22**) in methanol[18] led to a mixture of products, so attempts were made to improve the reaction by buffering with added acid or base. Heating a solution of **22** in methanol with a small amount of pyridine led to dimethyl 2-ketoglutarate (**25**) resulting from an elimination reaction, but heating **22** in dilute TFA led to the desired product (**26**) in moderate yield. The trichloroethyl carbonate group in **21** was cleaved reductively with zinc. Although on occasion good yields of **26** were obtained, the results were erratic and often **27**, which resulted from a reductive cleavage of the N-O bond, was formed as the major product. Finally **26** proved to be unsuitable as an intermediate, as attemped hydrolysis of its methyl esters led only to complex mixtures of products.



Scheme 4. a. ROCOCl (10 eq.), LiI (1 eq.), 16 h, rt. b. ROCOCl (10 eq.), LiI (1 eq.), 60 °C, 4 h. c. Pyr, THF, H_2O, 60 °C, 24 h, 22%. d. TFA, THF, 39%. e. Zn, THF, NaH_2PO_4, 16 h, rt, 20% (+ **27** (37%)).



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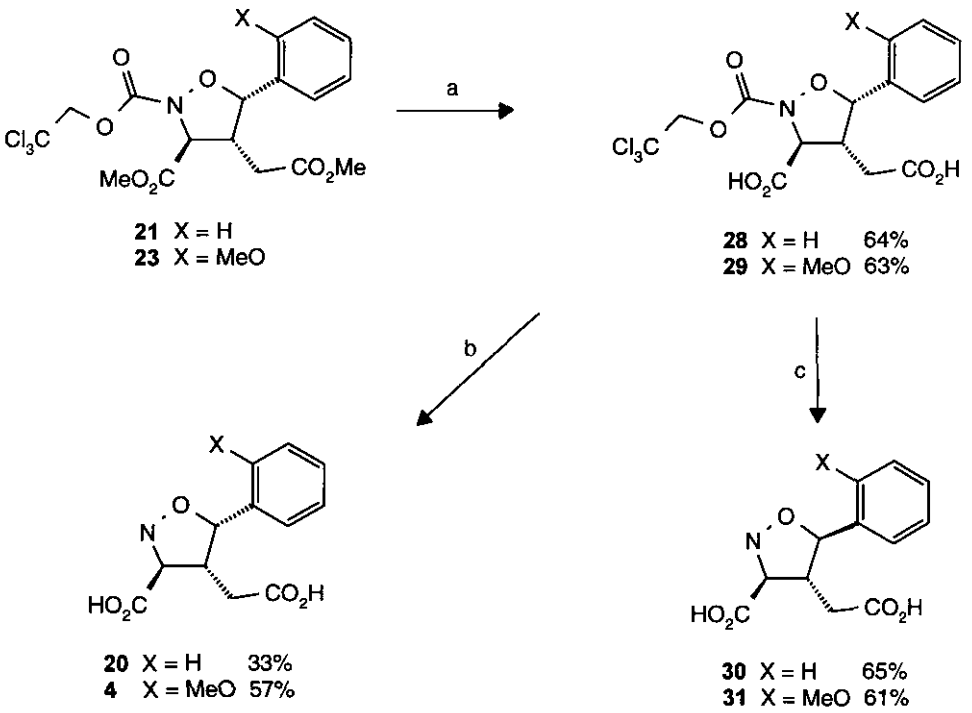
A successful deprotection route was found by first hydrolysing the ester groups of **21** and **23** in a simple manner to the diacids (**28**) and (**29**), and then cleaving the carbamate groups. The trichloroethoxycarbonyl groups of **28** and **29** were cleaved by reducing agents,[19] but this protecting group cleavage was

accompanied by an epimerisation reaction. Thus on treatment of **28** and **29** with zinc in formic acid, only the C(5)-epimers (**30**) and (**31**) of the desired compounds (**20**) and (**4**) were formed. It appears that the zinc salts formed from the spent zinc acted as Lewis acids, opening the oxazolidine ring to form a carbocation at C(5) which then reclosed to the C(5)-epimer, as has been described for a similar example.[20] Attempts were therefore made to cleave the trichloroethoxycarbamate with other reducing agents (LiSeH,[21] electrolysis[19]) which yield weaker Lewis acids after reaction, but again only epimerised products were formed. This problem was overcome in a simple manner by using basic hydrolysis to remove the carbamate, which led to the desired compounds (**20**) and (**4**) in good yield. The cyclic glutamate analogs (**20**) and (**4**) unfortunately showed no anthelmintic or insecticidal activity in our tests.



21 X = H
23 X = MeO

28 X = H 64%
29 X = MeO 63%

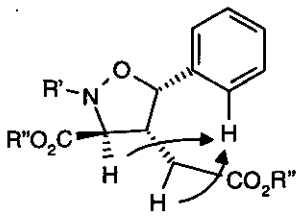
20 X = H 33%
4 X = MeO 57%

30 X = H 65%
31 X = MeO 61%

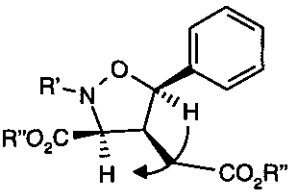
Scheme 5. a. 2M HCl, dioxane, 100°C, 16 h. b. NaOH. c. diverse. Zn, HCOOH.

Spectroscopy

The determination of the stereochemistry of the oxazolidines prepared in this work required careful consideration of the spectroscopic data. The coupling constants were not useful for this purpose because of the flexibility of the saturated isoxazolidine 5-membered rings, and the NOE measurements had to be examined thoroughly. One particular danger was that *trans*-vicinal protons often showed large enhancements, sometimes even larger than those from the *cis*-vicinal protons in the same molecule. Thus the NOE's had to be analysed *in toto*, with special attention paid to the longer range NOE's. In Figure 1 below some of the more decisive longer range enhancements are shown.



	R'	R"
13	Bn	Me
21	Troc	Me
28	Troc	H



	R'	R"
14	Bn	Me
30	H	H

Figure 1

EXPERIMENTAL

4-Phenylbut-3-en-1-ol (5)

Phenylmagnesium bromide was prepared from bromobenzene (214 g, 2 mol) and magnesium (48 g, 2 mol) in ether (1L). At 0 °C bis(triphenylphosphine)nickel dichloride (26 g, 40 mmol) was added slowly with stirring. The reaction was exothermic. At 0 °C dihydrofuran (150 mL, 140 g, 2 mol) was added at such a rate that the temperature stayed below 15 °C. The mixture was then stirred overnight at rt then poured onto NH_4Cl (aq. satd.) and extracted with ether. Drying ($MgSO_4$) and evaporation yielded the product, which was pure by NMR. (300 g, 100%). This material was used as such for the next step. A 1 mol batch was chromatographed on silica gel (20% EtOAc/hexane) to yield 114g (77%) of the product.[13]

4-(2-Methoxyphenyl)but-3-en-1-ol (8)

Compound (**8**) was prepared as above from 2-bromoanisole (158 g, 800 mmol) to yield 108 g (76%) after chromatography. ^{1}H-NMR (300 MHz, $CDCl_3$) 2.02 (s, OH); 2.48 (dq, J_d = 1, J_q = 7, 2H-C(2)); 3.67 (t, J = 7, 2H-C(1)); 5.73 (dt, J_d = 12, J_t = 7, H-C(3)); 6.66 (br d, J = 12, H-C(4)); 6.87 (d, J = 8, 1H); 6.93 (t, J = 7, 1H); 7.22 (m, 2H). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.90; H, 7.91

4-Phenylbut-3-enoic acid (6)

Jones reagent (240 mL), prepared from CrO_3 (60 g), H_2SO_4 (96%, 60 mL) and water (450 mL), was added dropwise with stirring to a solution of **5** (60 g, 400mmol) in acetone (1.2 L). (When ether was used as solvent benzoic acid was isolated.) TLC (50% EtOAc/hexane) after 10 min showed that the reaction was finished. The mixture was poured onto water, extracted with ether, dried ($MgSO_4$) and evaporated to yield 50 g (77%) crude **6**. According to NMR this material was impure, contaminated with the starting alcohol, but low yields were obtained when the material was chromatographed (silica gel, 50% EtOAc/hexane), so

it was used in crude form for the next step. ^{1}H-NMR (60 MHz, $CDCl_3$) 3.40 (d, J = 7, 2H-C(2)); 5.81 (dt, J_d = 11, J_t = 7, H-C(3)); 6.64 (d, J = 11, H-C(4)); 7.27 (m, Ph).

4-(2-Methoxyphenyl)but-3-enoic acid (9)

From **8** (80 g, 449 mmol) 72g (83%) of **9** was isolated. According to NMR it was impure and contaminated with starting alcohol. It was used directly for the esterification to **10**.

4-Phenylbut-3-enoic acid methyl ester (7)

A solution of crude **6** (50 g, 300 mmol) and H_2SO_4 (96%, 5 mL) in methanol (500 mL) was heated under reflux for 3 h. It was poured onto ice, extracted with ether, dried ($MgSO_4$), evaporated, and chromatographed (silica gel, 20% EtOAc/hexane) to yield 27 g (51%) of pure **7**. ^{1}H-NMR (300 MHz, $CDCl_3$) 3.3-3.4 (m, 2H-C(2)); 3.67 (s, MeO); 5.88 (dt, J_d = 11.5, J_t = 7.4, H-C(3)); 6.62 (d, J = 11.5, H-C(4)); 7.2-7.4 (m, Ph). ^{13}C-NMR ($CDCl_3$) 34.0 (C-2), 51.9 (MeO), 123.3 (C.3), 127.7 (C-4'), 128.5 (C-2', C-6'), 128.6 (C-3', C-5'), 131.6 (C-4), 136.6 (C-1'), 172.2 (C-1).

4-(2-Methoxyphenyl)but-3-enoic acid methyl ester (10)

Using the procedure of **7**, crude **9** (52g, 270 mmol) was converted into pure **10** (30 g, 54%). ^{1}H-NMR (250 MHz, $CDCl_3$) 3.24 (dd, J = 1, 7, H-C(2)); 3.68 3.82 (2s, 2MeO); 5.91, (dt, J_d = 13, J_t = 7, H-C(3)); 6.71 (br d, J = 13, H-C(4)); 6.91 (m, 2H); 7.22 (m, 2H).

2-Benzyl-4-methoxycarbonylmethyl-5-phenylisoxazolidine-3-carboxylic acid methyl ester (13), 2-Benzyl-4-methoxycarbonylmethyl-5-phenylisoxazolidine-3-carboxylic acid methyl ester (14), and 2-Benzyl-5-methoxycarbonylmethyl-4-phenylisoxazolidine-3-carboxylic acid methyl ester (12)

A solution of **7** (15 g, 85 mmol) and **11** (16.4 g, 85 mmol) in toluene (200 mL) was heated at reflux for 24 h. The solvent was evaporated and the crude mixture chromatographed (silica gel, 30% Et_2O/hexane) to yield 5.1 g (16%) of **13**. The other fractions from the column were rechromatographed on silica gel (2x 30% Et_2O/hexane; 1x 1% MeOH / CH_2Cl_2) led to **14**, **12** and **15**. **15** was not isolated in pure form but was tentatively assigned as a diastereomer of **12**. The Rf values of **13**, **14**, **12**, and **15** in 7% Et_2O / CH_2Cl_2 were 0.30, 0.36, 0.27, and 0.48 respectively. **13** ^{1}H-NMR (300 MHz, $CDCl_3$) 1.96 (dd, J = 7, 16, HC-C(4)); 2.12 (dd, J = 8, 16, HC-C(4)); 3.35 (d, J = 7, H-C(3)); 3.44 3.68 (2s, 2 MeO); 3.51 (2t, J = 7 and 8, H-C(4)); 4.19 4.28 (2d, J = 14, CH_2Ph); 5.34 (d, J = 8, H-C(5)); 7.30 (m, Ph). ^{13}C-NMR ($CDCl_3$) 34.9 (CH_2C(4)); 47.1 (C(4)); 51.6 52.5 (2MeO); 61.6 (CH_2Ph); 72.9 (C(3)); 80.9 (C(5)); 127.2 127.7 128.1 128.3 128.6 129.0 129.9 135.6 135.9 (2Ph): 170.5 172.0 (2COO). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.50; H, 6.25; N, 3.71. **14** ^{1}H-NMR (250 MHz, $CDCl_3$) 2.08 (dd, J = 7, 16,

HC-C(4)); 2.28 (dd, J = 8, 16, HC-C(4)); 3.40 3.63 (2s, 2MeO); 3.71 (dq, J_d = 8, J_q = 7, H-C(4)); 4.08 (d, J = 7, H-C(3)); 4.10-4.30 (2d, J = 13, CH_2Ph); 5.47 d, J = 7, H-C(5)); 7.31 (m, Ph). ^{13}C-NMR ($CDCl_3$) 31.8 ($CH_2C(4)$); 45.4 (C(4)); 51.6 52.0 (2OMe); 61.4 (C(7)); 69.4 (C(3)); 81.0 (C(5)); 127.6 127.8 128.1 128.3 128.5 129.6 135.7 136.0 (2Ph); 170.1 172.3 (2COO). **12** ^{1}H-NMR (300 MHz, $CDCl_3$) 2.06 2.39 (2dd, J = 7, 16, $CH_2C(5)$); 3.50 3.61 (2s, 2MeO): 3.81 (d, J = 7, H-C(3)); 4.08 (t, J = 7, H-C(4)); 4.30 (s, CH_2Ph); 4.77 (q, J = 7, H-C(5)); 7.05-7.49 (m, Ph). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.18; H, 6.33; N, 3.80.

2-Benzyl-4-methoxycarbonylmethyl-5-(2-methoxyphenyl)isoxazolidine-3-carboxylic acid methyl ester (17) and **2-Benzyl-5-methoxycarbonylmethyl-4-(2-methoxyphenyl)isoxazolidine-3-carboxylic acid methyl ester (16)**

A solution of **10** (20.6 g, 100 mmol) and **11** (19.3g, 100 mmol) in toluene (300 mL) was heated under reflux for 24 h. The solvent was evaporated and the crude mixture chromatographed (silica gel, 30% Et_2O/hexane) to yield **17** (5.0 g, 13%) and **16** (3.4 g, 9%). **17** ^{1}H-NMR (300 MHz, $CDCl_3$) 1.96 (d, J = 8, $CH_2C(4)$); 3.38 (d, J = 5, H-C(3)); 3.50 3.70 3.80 (3s, 3MeO); 3.57 (m, H-C(4)); 4.18 4.27 (2d, J = 13, CH_2Ph); 5.50 (d, J = 7, H-C(5)); 6.80-7.49 (m, 2x aryl). Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.49; H, 6.37; N, 3.54. **16** ^{1}H-NMR (300 MHz, $CDCl_3$) 2.07 (dd, J = 5,15, HC-C(5)); 2.22 (dd, J = 8,15, HC-C(5)); 3.57 3.59 3.82 (3s, 3 MeO); 3.94 (d, J = 7, H-C(3)); 4.34 4.25 (2d, J = 12, H_2CPh); 4.58 (t, J = 7, H-C(4)); 4.90 (m, H-C(5)); 6.78-7.45 (m, Ph). Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.27; H, 6.33; N, 3.76.

2-Benzyl-4-carboxymethyl-5-phenylisoxazolidine-3-carboxylic acid (18)

13 (2.02 g, 5.4 mmol) was stirred in HCl (2M, 40 mL) and enough THF was added that it went into solution. The solution was heated at 60 °C overnight and the solvent evaporated. The reaction was followed by RP TLC (50% MeCN/water). The residue was dissolved in water and evaporated, and this procedure was repeated three times. The crude product (1.3 g) was purified on RP-HPLC (50% MeCN/water) to yield 500 mg (28%) **18**. ^{1}H-NMR (300 MHz, CD_3OD) 1.09 (dd, J = 8, 17, HC-C(4)); 2.22 (dd, J = 7, 17, HC-C(4)); 3.25 (m, H-C(3), H-C(4)); 4.11 4.36 2d, J = 15, CH_2Ph); 7.21-7.47 (m, 2Ph). MS (FD) 342 $[M+H]^+$.

2-Benzyl-4-carboxymethyl-5-(2-methoxyphenyl)isoxazolidine-3-carboxylic acid (19)

17 (1 g, 2.5 mmol) was treated as above but was crystallised from acetone to yield 442 mg (48%) of beige crystals. ^{1}H-NMR (300 MHz, CD_3OD) 2.15 (dd, J = 8, 17, HC-C(4)); 2.37 (dd, J = 7, 17, HC-C(4)); 3.67

(tt, J = 7, 8, H-C(4)); 3.87 (s, MeO); 4.76 4.96 (2d, J = 14, CH_2Ph); 4.78 (d, J = 8, H-C(3)); 5.74 (d, J = 7, H-C(5)); 6.96-7.61 (m, aryl). MS (FD) 372 $[M+H]^+$.

4-Methoxycarbonylmethyl-5-phenylisoxazolidine-2,3-dicarboxylic acid 2-(1-chloroethyl) ester 3-methyl ester (22)

Chloroethyl chloroformate (2.7 mL, 3.5 g, 25 mmol) was added dropwise with stirring to a solution of **13** (1 g, 2.7 mmol) and lithium iodide (347 mg, 2.5 mmol) in dichloroethane (20 mL) under argon. After 24 h at rt, TLC (1% MeOH/CH_2Cl_2) showed complete reaction, the suspension was diluted with dichloromethane, filtered, the filtrate evaporated, and the crude product chromatographed (silica gel, CH_2Cl_2) to yield 850 mg (85%) of the product as a mixture of two diastereomers as a yellow oil. ^{1}H-NMR (300 MHz, $CDCl_3$) 1.80 1.87 (2d, J = 7, Me-C); 2.18 2.19 (2dd, J = 7, 15, HC-C(4)); 2.39 (dd, J = 8, 17, HC-C(4)); 3.42 m, H-C(4)); 3.58 3.89 (2s, 2MeO); 4.65 4.66 (2d, J = 8, H-C(3)); 5.56 (m, H-C(5)); 6.60 6.63 (2q, J=7, HCCl); 7.34 (m, Ph). MS (FD) 420 422 $[M+Cl]^-$.

4 - Methoxycarbonylmethyl - 5 - (2 - methoxyphenyl) isoxazolidine - 2,3 - dicarboxylic acid 2 - (1 - chloroethyl) ester 3-methyl ester (24)

17 (3 g, 7.5 mmol) was treated as above to yield **24** (2.1 g, 68%) as a yellow oil. ^{1}H-NMR (250 MHz, $CDCl_3$) 1.82 (2d, J = 7, Me-C); 2.08 2.26 (2dd, J = 7, 16, H_2C-C(4)); 3.58 (m, H-C(4)); 3.58 3.82 3.90 (3s, 3MeO); 4.68 (2d, J = 8, H-C(3)); 5.80 (m, H-C(5)); 6.62 (m, HCCl); 6.86 (d, J = 10, 1H aryl); 7.00 7.31 7.44 (3t, J = 10, 3H aryl).

4-Methoxycarbonylmethyl-5-phenylisoxazolidine-2,3-dicarboxylic acid 3-methyl ester 2-(2,2,2-trichloroethyl) ester (21)

13 (3 g, 8.13 mmol) was heated with 2,2,2-trichloroethyl chloroformate (10.9 mL, 17.2 g, 81 mmol) in dichloroethane (40 mL) at 50 °C for 4 h. The solvent was evaporated and the residue chromatographed (silica gel, dichloromethane) to yield 3.5 g (95%) **21**. ^{1}H-NMR (250 MHz, $CDCl_3$) 2.18 (dd, J = 7, 16, H_2C-C(4)); 2.38 (dd, J = 8, 16, H_2C-C(4)); 3.45 (m, H-C(4)); 3.56 3.88 (2s, 2MeO); 4.72 (d, J = 4, H-C(3)); 4.80 4.92 (2d, J = 16, CH_2Cl_3); 5.62 (d, J = 5, H-C(5)); 7.32 (m, Ph). MS CI (+ve) 471 473 $[M+NH_4]^+$. ^{13}C-NMR ($CDCl_3$) 33.0 (CH_2C(4)); 46.6 (C(4)); 52.0 53.3 (2MeO); 64.9 (C(3)); 75.3 (CH_2CCl_3); 75.4 (CCl_3); 82.6 (C(5)); 126.4 128.7 128.8 133.6 (Ph); 169.6 171.3 (2COO).

4-Methoxycarbonylmethyl-5-(2-methoxyphenyl)phenylisoxazolidine-2,3-dicarboxylic acid 3-methyl ester 2-(2,2,2-trichloroethyl) ester (23)

17 (3 g, 7.5 mmol) was treated as above to yield 2.9 g (81%) of **23**. ^{1}H-NMR (250 MHz, $CDCl_3$) 2.08 (dd, J = 6, 16, H_2C-C(4)); 2.24 (dd, J = 8, 16, H_2C-C(4)); 3.62 (m, H-C(4)); 3.56 3.82 3.98 (3s, 3MeO); 4.75 (d, J = 5, H-C(3)); 4.78 4.98 (2d, J = 13, CH_2Cl_3); 5.74 (d, J = 6, H-C(5)); 6.87 7.48 (2d, J = 8, 2H aryl); 6.98 7.31 (2t, J = 8, 2H aryl).

4-Methoxycarbonylmethyl-5-phenylisoxazolidine-3-carboxylic acid methyl ester (26) and 3-(Hydroxyphenylmethyl)-5-oxopyrrolidine-2-carboxylic acid methyl ester (27)

a. From 21.

A solution of **21** (50 mg, 113 µmol) in THF (1 mL) was stirred with NaH_2PO_4 (140 mg in 1 mL of water) and zinc dust (200 mg, 3.06 mmol) overnight at rt. The solid was filtered off and the mixture shaken between EtOAc and $NaHCO_3$ (sat.), dried ($MgSO_4$), the solvent evaporated and the crude product chromatographed (silica gel, 20% EtOAc/hexane) to yield 6 mg (20%) of **26.** On repeating the reaction under identical conditions but on a larger scale 1.2 g (37%) of **27** was isolated.

b. From 22.

A solution of **22** (700 mg, 1.82 mmol) and pyridine (7 mg, 90 µmol) in THF (16 mL) and water (4 mL) was heated for 3 h at 50 °C. The solvent was evaporated and the crude material chromatographed (silica gel, 50% EtOAc/hexane) to yield 360 mg of recovered **22** and 100 mg (13%) of **26.** When the reaction was repeated but left overnight at 60 °C, dimethyl 2-ketoglutarate (**25**) (22%) was isolated. Dimethyl 2-ketoglutarate (28%) was also isolated from the attempted deprotection of **24.**

26 ^{1}H-NMR (250 MHz, $CDCl_3$) 2.12 2.32 (2dd, J = 6, 16, H_2C-C(4)); 3.32 (dq, J = 7, 7, H-C(4)); 3.48 3.84 (2s, 2MeO); 3.88 (m, H-C(3)); 5.11 (d, J = 7, H-C(5)); 6.10 (br d, J = 10, NH); 7.34 (m, Ph). MS (CI -ve) 277 278 279 $[M]^-$, 245 246 247 248 249 $[M\text{-}MeOH]^-$. (CI +ve) 280 281 $[M]^+$, 297 $[M+NH_4]^+$.

27 ^{1}H-NMR (250 MHz, $CDCl_3$) 2.71 (dd, J = 4, 8, 2H-C(4)); 2.90 (m, H-C(3)); 3.51 (s, MeO); 3.58 (d, J = 5, H-C(2)); 5.42 (d, J = 5, HCPh); 7.35 (m, Ph). MS (CI +ve) 250 $[M+H]^+$, 267 $[M+NH_4]^+$. (-ve) 284 286 287 $[M+Cl]^-$. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.41; H, 5.96; N, 5.40.

Carboxymethyl-5-phenylisoxazolidine-2,3-dicarboxylic acid 2-(2,2,2-trichloroethyl) ester (28)

A solution of **21** (4.6 g, 10.1 mmol) in dioxane (50 mL) and HCl (2M, 50 mL) was heated at 100 °C overnight. The solvent was then evaporated and the residue crystallised from CH_2Cl_2 / hexane to yield

3.2g, (76%) **28**. mp 177-80 °C. ^{1}H-NMR (250 MHz, D_6-DMSO) 1.98 (dd, J = 7, 16, HC-C(4)); 2.29 (dd, J = 8, 16, HC-C(4)); 3.39 (m, H-C(4)); 4.62 (d, J = 4, H-C(3)); 4.90 (s, CH_2Cl_3); 5.52 (d, J = 6, H-C(5)); 7.32 (m, Ph). MS (EI +ve) 443 $[M+NH_4]^+$ (-ve) 425 $[M]^-$ 389 $[M-Cl]^-$. ^{13}C-NMR (CD_3OD) 33.9 ($CH_2C(4)$); 48.2 (C(4)); 66.0 (C(3)); 76.2 (CH_2CCl_3); 83.9 (C(5)); 127.6 129.6 129.7 135.7 (Ph); 154 (NCO); 172 174.2 (2COOH).

4-Carboxymethyl-5-(2-methoxyphenyl)isoxazolidine-2,3-dicarboxylic acid 2-(2,2,2-trichloroethyl) ester (29)

A solution of **23** (2.8 g, 5.7 mmol) in dioxane (50 mL) and HCl (2M, 50 mL) was heated at 100 °C overnight. The solvent was then evaporated and the residue crystallised from CH_2Cl_2 / hexane to yield 1.82 g (82%) of **29**. ^{1}H-NMR (250 MHz, $CDCl_3$) 2.17 (dd, J = 4, 16, HC-C(4)); 2.32 (dd, J = 10, 16, HC-C(4)); 3.68 (m, H-C(4)); 3.31 (s, MeO); 4.76 (d, J = 2, H-C(3)); 4.80 4.96 (2d, J = 13, CH_2Cl_3); 5.73 (d, J = 6, H-C(5)); 6.89 (d, J = 8, 1H); 7.00 (t, J = 8, 1H); 7.32 (t, J = 8, 1H); 7.46 (d, J = 8, 1H, aryl). MS (EI +ve) 458 $[M+H]^+$.

4-Carboxymethyl-5-phenylisoxazolidine-3-carboxylic acid (30)

a. Electrolysis

Electricity was passed through a solution of **28** (86 mg, 208 µmol) in $LiClO_4$ / MeOH (0.1 M, 25 mL) with a platinum anode and a mercury cathode maintaining the voltage at -1.5V. After 3.5 h. 78 amperes of current had passed. The solvent was then evaporated, the residue stirred with ether, and the ether phase decanted off to yield 54 mg (100%) of **30**, which was nearly pure according to NMR. ^{1}H-NMR (400 MHz, D_2O + TFA) 2.81 (dd, J = 10, 17, HC-C(4)); 3.05 (dd, J = 8, 17, HC-C(4)); 3.24 (m, H-C(4)); 4.25 (d, J = 4, H-C(3)); 5.74 (d, J = 9, H-C(5)); 7.50 (m, Ph). ^{13}C-NMR (DMSO-d_6) 31.3 ($CH_2C(4)$); 46.1 (C(4)); 53.3 (C(3)); 82.6 (C(5)); 126.5 128.6 128.7 138.9 (Ph); 172.5 175.5 (2COO).

b. With lithium selenide

A solution of **28** (150 mg, 350 µmol) in DMF (2.5 mL) was added to a mixture of $NaBH_4$ (130 mg, 3.5 mmol) and selenium (55 mg, 700 µmol). The solution foamed and turned dark and the temperature rose to 27 °C. After 1 h the solution had turned clear green. Water was added and the solvent then evaporated. The residue was dissolved in methanol and after standing for *ca* 10 min the red precipitate was filtered off, and the solvent evaporated. This procedure of dissolving in methanol, filtering, and evaporating was repeated 4 times. Then the material was no longer soluble in methanol and after stirring with methanol (4 mL) the product (88 mg) was filtered off. The NMR in D_2O + TFA was identical to that described above.

c. With zinc / formic acid.

A suspension of zinc powder (200 mg, 3 mmol) in a solution of **28** (728 mg, 1.7 mmol) in formic acid (20 mL) was stirred overnight at rt. The solids were then filtered off and the solvent evaporated. The product was crystallised from water (*ca.* 4 mL) to yield 277 mg (65%) of **30.** The compound was hygroscopic and did not give an accurate microanalysis but the value of 11.0% for zinc indicates that the product was isolated as a zinc salt. mp 172-175 °C. The NMR spectrum on acidification with TFA was identical to that described above.

4-Carboxymethyl-5-(2-methoxyphenyl)isoxazolidine-3-carboxylic acid (31)

A suspension of zinc powder (200 mg, 3 mmol) in a solution of **29** (730 mg, 1.6 mmol) in formic acid (20 mL) was stirred overnight at rt. The solids were then filtered off and the solvent evaporated. The product was crystallised from water (ca. 4mL) to yield 273 mg (61%) of 31. Anal. Calcd for C: 55.51 H:5.38 N: 4.98. Found C: 55.21 H: 5.66 N: 5.01. ^{1}H-NMR (400 MHz, D_2O + TFA) 2.76 (dd, J = 47, 17, HC-C(4)); 3.08 (dd, J = 10, 17, HC-C(4)); 3.28 (m, H-C(4)); 3.84 (s, MeO); 4.38 (d, J = 4, H-C(3)); 5.87 (d, J = 6, H-C(5)); 7.02 (t, J = 8) 7.09 (d, J = 8) 7.32 (d, J = 8) 7.43 (t, J = 8) (4 aryl).

4-Carboxymethyl-5-phenylisoxazolidine-3-carboxylic acid (20)

Compound **28** (700 mg, 1.64 mmol) was stirred in NaOH (2M, 20 mL). After 20 min a trace of phenolphthalein was added and the solution neutralised with HCl (2M). The solvent was evaporated and the residue dried with high vacuum. The crude product was stirred with methanol (15 mL) and the NaCl filtered off. The methanol was evaporated and the material stirred with ether. The solid product was filtered off and dried with high vacuum yielding 384 mg of **20** (36% pure, 33% yield). In the NMR only signals for **20** were seen, but inorganic impurities were present as shown by microanalysis. We assume the impurity is NaCl. ^{1}H-NMR (250 MHz, D_2O + TFA) 2.18 (dd, J = 8, 16, HC-C(4)); 2.50 (dd, J = 7, 16, HC-C(4)); 3.63 (m, H-C(4)); 4.77 (d, J = 6, H-C(3)); 5.62 (d, J = 7, H-C(5)); 7.20 7.32 (2 br s, Ph). Anal. Calcd for $C_{12}H_{13}NO_5$ (36% pure): C, 20.65; H, 1.88; N, 2.01. Found: C, 20.70; H, 1.94; N, 1.84.

4-Carboxymethyl-5-(2-methoxyphenyl)isoxazolidine-3-carboxylic acid (4)

From **29** (400 mg) treated according to the above procedure 240 mg of **4** (61% pure, 57% yield) was isolated. In the NMR only signals for **20** were seen. Microanalysis showed it to be 61% pure. The other 39% of the material is presumably NaCl.

^{1}H-NMR (400 MHz, D_2O + TFA) 1.99 (dd, J = 10, 16, HC-C(4)); 2.50 (dd, J = 6, 16, HC-C(4)); 3.48 (m, H-C(4)); 4.36 (d, J = 7, H-C(3)); 5.78 (d, J = 7, H-C(5)); 7.01 (t, J = 8, 1H aryl); 7.06 (d, J = 10, 1H aryl);

7.27 (d, J = 8, 1H aryl); 7.41 (t, J = 8, 1H aryl). Anal. Calcd for $C_{13}H_{15}NO_6$ (61% pure): C, 33.86; H, 3.28; N, 3.04. Found: C, 33.8; H, 3.6; N, 2.9.

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