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Oxidation of N-(4-methoxybenzyl)-2-Pyrrolidinones to N-(4-methoxybenzoyl)-2-pyrrolidinones. Rapid entry to Optically Active Aniracetam Analogues.

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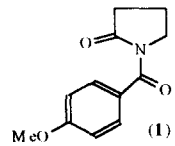
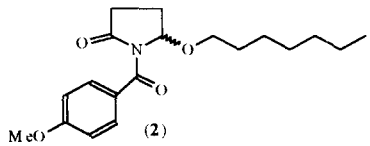
Abstract: Oxidation of readily available N-(4-methoxybenzyl)-5-alkylpyrrolidin-2-ones to the corresponding N-(4-methoxybenzoyl)-5-alkylpyrrolidin-2-ones gives direct access to enantiomerically pure 5-alkyl analogues of the cognition activating agent Aniracetam.

Increase in life expectancy has made the chemical prevention or treatment of age related disorders an important research area. Cognitive impairment, which can occur at any age, is most prevalent in the elderly. Consequently there has been growing interest in new drugs that may be useful in the prevention or treatment of cognitive problems in humans. Many of the drug candidates that have emerged in this area contain imide functionality based on a 2-pyrrolidinone with an imide linkage to an aromatic carboxylic acid. Hence Aniracetam (**1**) is of potential therapeutic value for the treatment of dementia[1] and of cognitive decline in elderly patients[2]. Recently, structural analogues with enhanced activity have emerged which contain an alkoxy side chain at the 5-position of the pyrrolidinone (**2**)[3]. Analogues with 5-alkyl substituents (**3**) have also shown promise as cognition activating agents[4].



(1)



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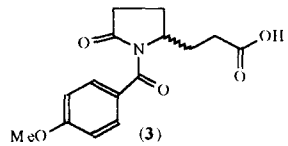
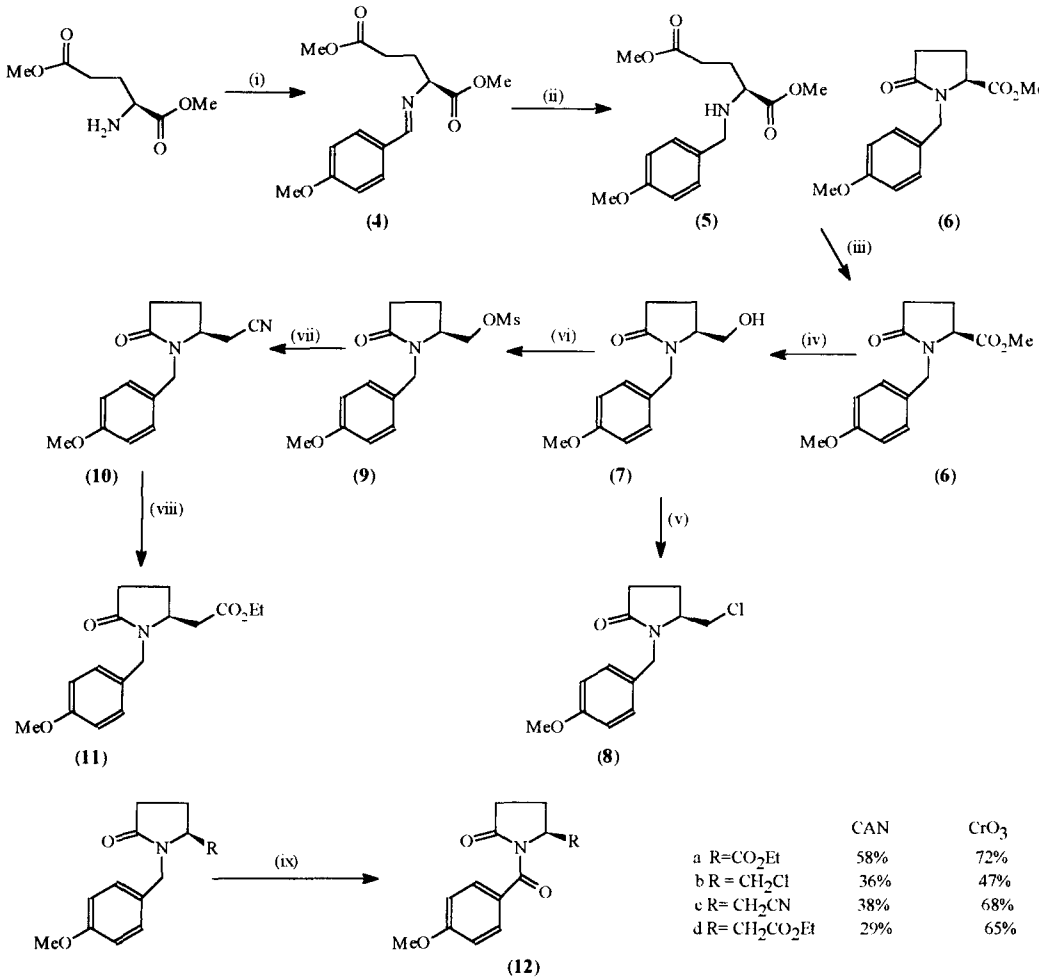


(3)

One simple approach to single enantiomer 5-substituted Aniracetam analogues would involve functionalising the 5-carboxy group of pyroglutamic acid. In order to achieve this, or to avoid potential problems of water solubility of the products, it is generally desirable to protect the amide nitrogen. If the 4-methoxybenzoyl group could be incorporated into the product at an early stage it could also serve as protection for the nitrogen atom. Unfortunately carbonyl based protecting groups in pyroglutamates activate the carbonyl of the cyclic imide to nucleophilic attack[5] making selective functionalisation of the 5-carboethoxy group difficult. If a protecting group could be devised which could be directly converted to a 4-methoxybenzoyl group this would alleviate this problem.

We now report the use of 4-methoxybenzyl as an amide N-protecting group and its direct oxidation to 4-methoxybenzoyl using chromium trioxide or ceric ammonium nitrate (CAN) under mild conditions. This chemistry gives rapid access to a range of optically active Aniracetam analogues in modest to good yields, **Scheme1**.



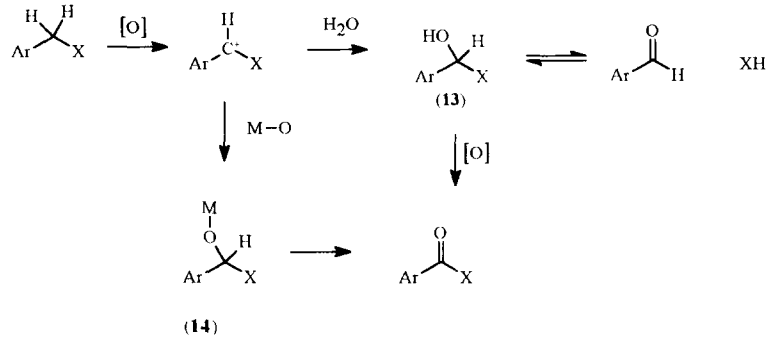
	CAN	CrO_3
a R=CO_2Et	58%	72%
b R = CH_2Cl	36%	47%
c R= CH_2CN	38%	68%
d R= CH_2CO_2Et	29%	65%

Reagents: (i) 4-Methoxybenzaldehyde/ methylene chloride, (ii) sodium borohydride/ methanol, (iii) xylene 140°C 8h, (iv) sodium borohydride/ ethanol 12h, (v) thionyl chloride, (vi) mesyl chloride/triethylamine, (vii) sodium cyanide/DMF, (viii) HCl/ethanol, (ix) CrO_3/acetic acid or CAN.

Scheme 1

Dimethyl glutamate condensed with 4-methoxybenzaldehyde to give imine (**4**) (not isolated) which was then reduced with sodium borohydride to give a mixture of (S)-N-4-methoxybenzyl dimethylglutamate (**5**) and (S)-(+)-1-(4-methoxybenzyl)-5-carbomethoxy-2-pyrrolidinone (**6**). Heating this mixture in xylene for eight hours effected complete cyclisation to give (**6**) in 69% overall yield from dimethyl glutamate hydrochloride. Sodium borohydride reduction of (**6**) in ethanol proceeded over 12hr to give primary alcohol (**7**, 74%). On analysis of (R) and (S) MTPA esters of (**7**), by ^1H nmr spectroscopy, only one diastereoisomer could be detected in each case showing the material to be of high optical purity. The alcohol was converted to the chloride (**8**, 74%) by reaction with thionyl chloride and to the mesylate with methanesulfonyl chloride. Mesylate (**9**) reacted with sodium cyanide in DMF to give nitrile (**10**) in 60% overall yield from alcohol (**6**). The nitrile (**10**) was converted to the ethyl ester (**11**) in 77% yield by treatment with hydrogen chloride in ethanol.

With a range of substituted pyroglutamates at hand we next turned our attention to oxidation of the N-4-methoxybenzyl to a 4-methoxybenzoyl group. Oxidation of tertiary amides to imides[6] and of benzylic methylene groups[7] is well documented. In the amide case, most studies involved the oxidation occurring in a ring, although some acyclic examples have also been reported[8]. Since the required position for oxidation in our case was both benzylic and amido, it was envisaged that the oxidation should be facile. However oxidative cleavage of 4-methoxybenzyl from a variety of heteroatoms X **Scheme** 2, is also well known, and forms the basis of a number of deprotection procedures for alcohol, X=O and amides X=NHCO[9]. We therefore had to find an oxidant which would give the required imide with no benzylic cleavage. In oxidation procedures there are two distinct scenarios, namely the metal can accept electrons and donate oxygen, or the metal can accept electrons with the oxygen supplied from elsewhere, usually water **Scheme 2**[10]. When water is supplied from the solvent then it is likely that intermediate hemiacetal (**13**) will break down to give aldehyde and XH before further oxidation to the imide. However, if the oxygen is supplied from a metal oxide then it is likely that species (**14**) will oxidise to imide faster than breakdown to aldehyde and amide. To test this theory an oxidant from each class, ceric ammonium nitrate (CAN) and chromium trioxide, was evaluated.



Scheme 2

Using CAN and Tereshima's conditions[11], with 5 molar equivalents of CAN, the major oxidation product of the 4-methoxybenzylpyrrolidinones was always 4-methoxybenzaldehyde with small amounts of imide (usually < 10%). The proportion of imide only marginally increased with time. By performing the reactions at 0°C and using acetonitrile/water 1:1, the proportion of imide increased up to 65% in the crude reaction mixtures but substantial amounts of 4-methoxybenzaldehyde were always present. In our hands, with pyrrolidinones as substrates, we have never been able to find oxidation conditions using CAN, where **no** imide is produced. When chromium trioxide in acetic acid was used as oxidant the imides (12a-d) were obtained in good yield **Scheme 1**, with no detectable benzylic cleavage. This chemistry gives access to a range of optically active Aniracetam analogues which would not be easily available by other routes.

Experimental.

General

Melting points were recorded using a Kofler hot stage apparatus and are uncorrected. I.R spectra were recorded on a Perkin-Elmer Model 983G instrument coupled to a Perkin-Elmer 3700 Data Station as potassium bromide (KBr) disks, or films (liquids). ^{1}H nuclear magnetic resonance (nmr) spectra were recorded

at 300MHz and 500MHz using General Electric QE and Omega nmr spectrometers. Chemical shifts are given in parts per million (δ) down field from tetramethylsilane as internal standard and coupling constants are given in Hertz. Unless otherwise stated, deuteriochloroform was used as solvent. The following abbreviations are used:- s = singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad. Mass spectra were recorded using Double Focusing Triple Sector VG Auto Spec and accurate molecular masses were determined by the peak matching method using perfluorokerosene as standard reference and were accurate to within +/-0.006 a.m.u. Microanalyses were obtained using a Perkin Elmer 2400 CHN elemental analyser. Optical rotations were determined on a Perkin-Elmer precision polarimeter Model 241, using specified solvent and concentration at the D-line 589 nm and at ambient temperature. Analytical tlc was carried out on Merck Kielselgel 60_{254} plates and the spots visualised using a Hanovia Chromatolite uv lamp. Flash chromatography was effected using Merck Kielselgel 60 (230-400 mesh).

(S)-1-(4-Methoxybenzyl)-5-carboethoxy-2-pyrrolidinone (6). Triethylamine (18.0g, 178mmol) was added to a stirred solution of (S)-dimethylglutamate hydrochloride (35.2g, 198mmol) in dichloromethane (450ml). After five minutes 4-methoxybenzaldehyde (23.7g, 174mmol) was added followed by magnesium sulphate (12g). The resulting mixture was stirred at room temperature overnight whereupon the magnesium sulphate was removed by filtration and the methylene chloride removed under reduced pressure. Methanol (200ml) was added to the yellow oil, the solution cooled to 0°C and sodium borohydride (6.0g, 157.4mmol) added in small portions over five minutes, followed by stirring at 0°C for a further 60 minutes. The methanol was then removed under reduced pressure to give a mixture of N-(4-methoxybenzyl) dimethyglutamate (**5**) and (S)-(+)-1-(4-methoxybenzyl)-5-carbomethoxy-2-pyrrolidinone (**6**). It proved impossible to purify N-(4-methoxybenzyl) dimethylglutamate as it had a strong tendency to cyclise to the corresponding lactam. Heating the crude reaction mixture in boiling xylene (100ml) overnight gave after concentration a red oil. Purification by flash chromatography (100% ether) gave the titled compound (31.6 g, 69%) as a colourless oil[12], R_f=0.32 (ether); $[\alpha]_D$ = +33.9 (c =5.80, $CHCl_3$); Found: C, 63.5; H, 6.5; N, 5.0%. $C_{14}H_{17}NO_3$ requires: C, 63.8; H, 6.6; N, 5.3%; m/z(%) 263(M^+, 31.3), 204(13.6), 121(100.0); $\upsilon_{max.}$ (KBr) 3376, 3094, 2976, 1743, 1695, 1585, 1514, 1440, 1411, 1328 cm^{-1}; δ_H (300MHz) 1.25(3H, t, J=6.8, $\mathbf{CH_3}$), 2.08(1H, ddt, J=13.3, 9.6, 3.7, NCHC**H**H), 2.23(1H, m, NCHCH**H**), 2.45(1H, m, NCOC**H**H), 2.58(1H, dd, J=16.9, 9.6, NCOCH**H**), 3.79(3H, s, $\mathbf{OCH_3}$), 3.87(3H, s, $\mathbf{CO_2CH_3}$), 3.97(2x1H, m, C**H**HAr and NC**H**), 4.96 (1H, d, J=14.6, CH**H**Ar), 6.85(2H, d, J=8.2, Ar**H**), 7.15(2H, d, J=8.2, Ar**H**); $\delta_{C\text{-}13}$(75MHz) 23.43, 29.38, 45.43, 57.89, 59.73, 61.43, 113.97, 127.63, 129.32, 157.63, 172.49, 176.86.

(S)-(+)-1-(4-Methoxybenzyl)-5-(hydroxymethyl)-pyrrolidin-2-one (7). Sodium borohydride (2.58g, 68.46mmol) was added in small portions over 10 minutes to an ice cooled, magnetically stirred solution of (S)-(+)-1-(4-methoxybenzyl)-5-(carbomethoxy)-pyrrolidin-2-one (18.0g, 68.5mmol) in ethanol (300ml). The resulting solution was stirred overnight at room temperature whereupon the solvent was removed under reduced pressure. Hydrochloric acid (30ml, 2M) was added to the residue and this was extracted with dichloromethane (3x100ml). The combined dichloromethane extracts were dried over magnesium sulphate and concentrated under reduced pressure, to give an off white solid. This was recrystallised from methanol to give (S)-(+)-1-(4-methoxybenzyl)-5-(hydroxymethyl)-pyrrolidin-2-one (11.9g, 74%) as white prisms, m.p. 122.5-123.5°C. $[\alpha]_D$= +74.35 (c =4.7, $CHCl_3$); lit.[11] $[\alpha]_D$ = +73.2 (c =1.05, $CHCl_3$); m/z (%) 263(M^+, 18.7),

228(58.2), 135(93.4), 121(100.0), 107(14.9); $\upsilon_{max.}$ (KBr) 3286, 3043, 2917, 1648, 1608, 1446, 1247, 827cm^{-1}; δ_H(500MHz) 1.95-2.10(2 x 1H, 2 x m, $\mathbf{CH_2}CH_2CO$), 2.38(1H, ddd, J=17.1, 10.0, 5.9, $COCH\mathbf{H}CH_2$), 2.55(1H, ddd, J=17.1, 9.5, 7.1, $COCH\mathbf{H}CH_2$), 3.50(1H, dd, J=11.7, 3.2, $CH\mathbf{H}OH$), 3.52(1H, ddd, J=8.0, 3.6, 0.9, $CH\mathbf{H}N$), 3.74(1H, m, $CH\mathbf{H}OH$), 3.79(3H, s, OCH_3), 4.25 & 4.70(2 x 1H, 2 x d, J=14.9, $ArCH_2N$), 6.85(2H, d, J=8.6, Ar**H**), 7.21 (2H, d, J=8.6, Ar**H**); δ_{C-13} (125MHz) 20.48, 29.79, 39.14, 55.30, 59.00, 62.18, 115.19, 124.69, 135.53, 157.32, 175.97; (R) and (S)-MTPA esters of (S)-(+)-1-(4-methoxybenzyl)-5-(hydroxymethyl)-pyrrolidin-2-one were made by the standard procedure. One of the diastereotopic methylene $CH\mathbf{H}OCO$ protons from each diastereoisomer was used to determine the enantiomeric purity of the samples. (R,S) isomer δ_H(500MHz) 4.46(1H, dd, J=11.6, 3.9, $CH\mathbf{H}OCO$). (S,S) isomer δ_H(500MHz) 4.57(1H, dd, J=11.6, 4.5, $CH\mathbf{H}OCO$). In both samples none of the other diastereoisomer could be detected by ^{1}H nmr spectroscopy.

(S)-(+)-1-(4-Methoxybenzyl)-5-chloromethyl-pyrrolidin-2-one (8). (S)-(+)-1-(4-Methoxybenzyl)-5-(hydroxymethyl)-pyrrolidin-2-one (1.50g, 5.7mmol) was dissolved in methylene chloride (25ml) and cooled to 0°C. Thionyl chloride (1.0g, 8.4mmol) was added over 3 minutes followed by triethylamine (1.0g, 9.9mmol) and the resulting solution was allowed to warm to room temperature and stirred for 48 hours. Saturated sodium bicarbonate solution (10ml) was added. The organic phase was separated and washed successively with dilute HCl (10ml), water (2x10ml), dried over magnesium sulfate and concentrated to yield a brown oil. Purification by flash chromatography (EtOAc, R_f =0.60) gave the titled compound as a pale brown oil (**8**, 1.20g, 74%). $[\alpha]_D$ = +61.6 (c= 7.8, $CHCl_3$). Found: M^+, 253.0875. $C_{13}H_{16}ClNO_2$ requires M^+, 253.0870; m/z(%) 253(M^+, 41), 255(^{37}Cl, 13), 121(100), δ_H(300MHz) 2.02 and 2.13(2x1H, 2xm, $CHNC\mathbf{H}_2$), 2.41 and 2.59(2x1H, 2xm, $COC\mathbf{H}_2$), 3.50(1H, dd, J=9.4, 1.6, $CH\mathbf{H}Cl$), 3.58(1H, dd, J=9.3, 4.5, $CH\mathbf{H}Cl$), 3.74(1H, m, $NC\mathbf{H}$), 3.80(3H, s, OMe), 3.94 and 4.97(2x1H, 2xd , J=15.0, Ar-$C\mathbf{H}_2$), 6.86(2H, d, J=8.3, Ar-**H**), 7.17(2H, d, J=8.4, Ar-**H**).

Methanesulfonic acid 1-(4-methoxybenzyl)-5-oxo-pyrrolidin-2-yl methyl ester (9). Methane sulfonyl chloride (7.32g, 63.82mmol) was added dropwise to a stirred solution of (S)-(+)-1-(4-methoxybenzyl)-5-(hydroxymethyl)-pyrrolidin-2-one (**7**, 10g, 42.55mmol) in anhydrous dichloromethane (200ml) at -40°C, followed by the dropwise addition of triethylamine (7.30g, 72.30mmol). The resulting mixture was stirred at this temperature for 6.5hrs, then allowed to warm to room temperature over 30 minutes and quenched with 5% aq. HCl (30ml). The aqueous layer was further extracted with dichloromethane solution (2x50ml) and the combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure to give methanesulfonic acid 1-(4-methoxybenzyl)-5-oxo-pyrrolidin-2-yl methyl ester (**9**, 12.96g, 97.3%) as a colourless liquid. Due to the instability of the mesylate, it was used in its crude form immediately for the next stage. δ_H (300MHz) 1.94 and 2.11(2x1H, 2xm, $COCH_2C\mathbf{H}_2$), 2.51(2x1H, 2xm, $COC\mathbf{H}_2$), 2.95(3H, s, $OSO_2C\mathbf{H}_3$), 3.74(1H, m, $CN\mathbf{H}$), 3.80(3H, s, $OC\mathbf{H}_3$), 4.07 and 4.91(2x1H, 2xd, J=14.4, $ArC\mathbf{H}_2$), 4.13(1H, m, $CH\mathbf{H}OS$), 4.25(1H, dd, J=8.8, 10.6, $CH\mathbf{H}OS$), 6.86(2H, d, J=8.6, Ar**H**), 7.32(2H, d, J=8.2, Ar**H**).

(S)-(+)-[1-(4-Methoxybenzyl)-5-oxo-pyrrolidin-2-yl]-acetonitrile (10). Potassium cyanide (4.16g, 65.83mmol) and sodium iodide (0.64g, 4.26mmol) were added to a solution of methanesulfonic acid 1-(4-methoxybenzyl)-5-oxo-pyrrolidin-2-yl methyl ester (**9**, 12.96g, 41.41mmol) in DMSO (300ml) and the resulting mixture was heated at 60°C for 3 days. The solvent was removed by vacuum distillation and the residue was dissolved in dichloromethane (200ml), washed with saturated brine (3 x 100ml), followed by water

(3 x 50ml). The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a dark brown oil. Purification by flash chromatography (98% ethyl acetate/ 2% pet.ether R_f=0.33,) gave the titled compound as a white crystalline solid. Recrystallisation from ether gave (S)-(+)-[1-(-methoxybenzyl)-5-oxo-pyrrolidin-2-yl]-acetonitrile (**10**, 6.24g, 60.1%, based on alcohol), as colourless prisms m.p. 38-40°C. $[\alpha]_D$= +24.52 (c =4.2, $CHCl_3$); Found: C, 69.1; H, 6.5; N, 11.2%. $C_{14}H_{16}N_2O_2$ requires: C, 68.8; H, 6.6; N, 11.5%; $\upsilon_{max.}$ (KBr) 2963, 2931, 2839, 2246, 1672cm^{-1}; δ_H(300MHz) 1.93 and 2.30(2x1H, 2xm, $COCH_2CH_2$), 2.39-2.51(3x1H, 3xm, $COCH_2$ and CHHCN) 2.58(1H, m, CHHCN), 3.70(1H, m, CNH), 3.79(3H, s, OCH_3), 4.09 and 4.85(2x1H, 2xd, J=15.1, $ArCH_2$), 6.86(2H, d, J=8.6, ArH), 7.16(2H, d, J=8.6, ArH).

(S)-(+)-[1-(4-Methoxybenzyl)-5-oxo-pyrrolidin-2-yl]-acetic acid ethyl ester (11). Hydrogen chloride was bubbled through a solution of (S)-(+)-[1-(4-methoxybenzyl)-5-oxo-pyrrolidin-2-yl]-acetonitrile (**10**, 4g, 16.4mmol) in ethanol (100ml) at 65°C for 30 minutes. The resulting solution was kept at that temperature for a further 45 minutes, followed by a further addition of hydrogen chloride for another 30 minutes. The mixture was concentrated under reduced pressure and the resulting residue was extracted with methylene chloride (100ml). The methylene chloride extract was washed with sodium bicarbonate (2x30ml), dried over magnesium sulfate and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (ethyl acetate, R_f =0.32) gave (S)-(+)-[1-(4-methoxybenzyl)-5-oxo-pyrrolidin-2-yl]-acetic acid ethyl ester (**11**, 3.67g, 76.9%) as a colourless oil $[\alpha]_D$= +29.13 (c=7.6, $CHCl_3$); Found: M^+, 291.1478. $C_{16}H_{21}NO_4$ requires: M^+, 291.1471. m/z(%) 291(M^+, 5.6), 279(4.0), 231(6.0), 194(8.2), 121(100.0); δ_H(300MHz) 1.17(3H, t, J=6.9, $CO_2CH_2CH_3$), 1.80 and 2.17(2x1H, 2xm, $COCH_2CH_2$), 2.29-2.48(3x1H, 3xm, $NCOCH_2$ & $CHHCO_2$), 2.64 (1H, dd, J=15.5, 4.1 $CHHCO_2$), 3.82(3H s, OCH_3), 3.83(1H, m, CHN), 4.10 and 4.84(2x1H, 2xd, J=14.9, $ArCH_2$), 4.12(3H, q, J=6.9, CO_2CH_2), 6.87(2H, d, J=8.6, ArH), 7.20(2H, d, J=8.6, ArH).

General preparation for imides

Method A Ceric Ammonium Nitrate.

Ceric ammonium nitrate (2.5mmol) was dissolved in 50% water/acetonitrile (2ml) and this was cooled to 0°C. 4-Methoxybenzyl amide (0.5mmol) in 50% water/acetonitrile (1ml) was added all at once and the resulting solution was stirred at 0°C until the dark red colour discharged (typically 15 minutes). Acetonitrile was removed under reduced pressure, water (5ml) was added and this was extracted with methylene chloride (2x10ml). The combined methylene chloride extracts were dried over magnesium sulfate and concentrated. Flash chromatography gave the required imides.

Method B Chromium trioxide.

Chromium trioxide (1.05g, 6.5mmol) was dissolved in acetic acid/water 20:1 (10ml) and the resulting solution was stirred for 15 minutes at room temperature. The resulting solution was added dropwise over 5 minutes to a solution of the amide (2mmol) in acetic acid (10ml) and this was stirred for three hours. Water (20ml) was added and this was extracted with methylene chloride (2x20ml). The combined methylene chloride extracts were washed with sodium bicarbonate solution, dried over magnesium sulfate and concentrated. Flash chromatography gave the required imides.

(S)-1-(4-Methoxybenzoyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (12a). (S)-(+)-1-(4-Methoxybenzyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (130mg, 0.47mmol) and CAN (1.28g,

2.35mmol) reacted according to the general procedure to give (S)-(+)-1-(4-methoxybenzoyl)-5-oxo-pyrrolidine-2-carboxylic acid ethyl ester (**12a**, 79mg, 58%) as a light yellow solid m.p. 149-150^{0}C R_f=0.41 (EtOAc/hexane, 1:1); $[\alpha]_D$ = +17.70°, (c=4.80, $CHCl_3$). Found: M^+ 291.1104. $C_{14}H_{17}NO_5$ requires M^+ 291.1107. m/z(%), 291(M^+, 11), 206(8), 149(7), 135(100). ν_{max} (KBr); 2940, 2963, 1744, 1675, 1605, 1515, 1322, 1232, 1197cm^{-1} δ_H (300MHz) 1.25(3H, t, J=7.2 $CO_2CH_2CH_3$), 2.13 and 2.45(2x1H, 2xm, $COCH_2CH_2$), 2.57 and 2.72(2x1H, 2xm, $COCH_2$), 3.85(3H, s, OCH_3), 4.25(2H, m, CO_2CH_2), 4.86(1H, dd, J =4.2, 4.4, CHN), 6.91(2H, d, J=8.4, Ar-H), 7.71(2H , d, J=8.4 Ar-H). δ_{C-13}(125MHz) 14.07, 21.8, 31.84, 55.38, 59.08, 61.74, 113.17, 113.24, 113.70, 131.97, 132.27, 163.18, 171.16, 173.56.

Procedure B yield 72%. Spectroscopic Data identical.

(S)-(-)-1-(4-Methoxybenzoyl)-5-chloromethylpyrrolidin-2-one (12b). (S)-(+)-1-(4-Methoxybenzyl)-5-chloromethyl-pyrrolidin-2-one (100mg, 0.4mmol) and CAN (650mg, 1.2mmol) reacted according to the general procedure to give to give the titled compound as a pale yellow oil (38mg, 36%) R_f=0.58. (50% EtOAc/Hexane), $[\alpha]_D$ = -191.2 (c=10.1, $CHCl_3$). Found: M^+, 267.0674. $C_{13}H_{14}ClNO_3$ requires M^+, 267.0662. m/z (%) 267 (M^+, 4), 269(^{37}Cl, 1), 135(100); δ_H(300MHz) 2.28(2x1H, 2xm, CH_2CH_2CO), 2.57 and 2.79(2x1H, 2xm, CH_2CO), 3.74(1H, dd, J =11.7, 2.2, CHHCl), 3.86(3H, s, OCH_3), 4.05(1H, dd, J=11.6, 4.5, CHHCl), 4.79(1H, m, CHN), 6.91(2H, d, J =6.8, Ar-H), 7.68(2H, d, J =6.8, Ar-H,) ; δ_{C-13}(125MHz) 20.83, 31.97, 45.95, 55.40, 57.03, 113.30, 126.20, 131.88, 163.22, 170.08, 174.72.

Procedure B yield 47%. Spectroscopic data identical.

(S)-(-)-[1-(4-Methoxybenzoyl)-5-oxopyrrolidin-2-yl]-acetonitrile (12c). (S)-(+)-[1-(4-Methoxybenzyl)-5-oxopyrrolidin-2-yl]-acetonitrile (100mg, 0.4mmol) and CAN (1.28g, 2.35mmol) reacted according to the general procedure to give the titled compound (40mg, 38%) as a white solid m.p. 89-92°C; $[\alpha]_D$= -116.74, (c=1.9, $CHCl_3$); Found: 258.0990. $C_{14}H_{16}N_2O_2$ requires M^+ 258.1004. m/z(%) 259(M^+, 18.5), 135(100.0); $\upsilon_{max.}$ (KBr) 2964, 1738, 1677, 1605cm^{-1}; δ_H(300MHz) 2.11 and 2.41(2x1H, 2xm, $COCH_2CH_2$), 2.58 and 2.80(3x1H, 3xm, CHHCN and $COCH_2$), 3.08(1H, m, CHHCN), 3.86(3H, s, OCH_3), 4.64(1H, m, NCH), 6.92(1H, d, J =8.9, ArH), 7.70(1H, d, J=8.9, ArH).

Procedure B yield 68%. Spectroscopic data identical.

(S)-(-)-[1-(4-Methoxybenzoyl)-5-oxopyrrolidin-2-yl]-acetic acid ethyl ester (12d).

(S)-(+)-[1-(4-Methoxybenzyl)-5-oxopyrrolidin-2-yl]-acetic acid ethyl ester (110mg, .38mmol) and CAN (1.28g, 2.35mmol) reacted according to the general procedure to give the titled compound (30mg, 29%), $[\alpha]_D$ = -142.76, (c=2.9, $CHCl_3$). as a clear oil R_f =0.55 (ether). Found M^+ 305.1257, $C_{15}H_{19}NO_5$ requires M^+ 305.1263; m/z(%) 305 (M^+, 9.0), 276(2.5), 260(2.8), 135(100.0); $\upsilon_{max.}$ (KBr) 1981, 2937, 1733, 1669, 1604 cm^{-1}; δ_H(300MHz) 1.24(3H, t, J=6.9, OCH_2CH_3), 2.01(1H, m, $COCH_2CHH$), 2.34-2.76(4H, 4xm, $COCH_2CHH$ & $CHHCO_2$), 2.98(1H, dd, J=15.7, 3.6, $CHHCO_2$), 3.56(3H, s, OCH_3), 4.09-4.20(2H, m, OCH_2CH_3), 4.73-4.81(1H, m, CNH), 6.90(2H, d, J=9.0, ArH), 7.66(2H, d, J=9.0, ArH).

Procedure B yield 65%. Spectroscopic data identical.

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Notes and References.

1. Martin, J.R.; Haefely, W.E. *Drug Investigation* 1993, **5**, 4-49.
2. Senin, U.; Parnetti, L.; Cucinotta, D.; Criscuola, D.; Longo, A.; Marini, G. *Drug Investigation* 1993, **5**, 96-105.
3. Toja, E.; Gorina, C.; Zirotti. C.; Barzaghi, F.; Galliani, G. *Eur. J. Med. Chem.* 1991, **26**, 414-422.
4. Huang, C.C. *J. Labelled Comp. Radiopharm.*1987, **24**, 675-681.
5. Flynn, D.L.; Zelle, R.E. Grieco, P.A. *J. Org. Chem.* 1983, **43**, 2424-2426. Molina, M.T.; del Valle, C. Escribano, A.M.; Ezquerra, J.; Pedregal, C. *Tetrahedron* 1993, **49**, 3801-3808. Ohta, T.; Kimura, T.; Sato, N.; Nozoe, S. *Tetrahedron Lett.* 1988, **29**, 4303-4304. Langlois, N; Rousseau, A.R.; Decavallas, O. *Tetrahedron Asymmetry* 1996, **7**, 1095-1100.
6. Tanagari, N.; Tortorella, V. *J. Chem. Soc. Chem. Comm.* 1975, 75- Lin, G.; Micha, K.K.; Hawes, E.M. *J. Heterocyclic Chem.* 1991, **28**, 215-219.
7. Burnam, J.W.; Duncan, P.D.; Eisenbraun, E.J. *J. Org. Chem.* 1974, **39**, 1416-1419.
8. Torii, S.; Inokuchio, T.; Yukawa, T. *Chem. Lett.* 1984, 1063-1066.
9. Kocienski, P.J. *Protecting Groups.* Thieme 1994.
10. Editors Mijs, W.J.; de Jonge, C.R.H.I. *Organic Synthesis by Oxidation with Metal Compounds.* Plenum Press New York 1986.
11. Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Tereshima, S. *Tetrahedron*, 1994, **50**, 6221-6238.
12. The ethyl ester has previously being reported, reference 11, but the current route is more efficient and convenient.

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