CHAPTER FIVE

5. Conclusion

5.1 Conclusion

Alkyl *N*-acyloxybenzohydroxamates are relatively stable compounds which are readily synthesised from inexpensive starting materials and provide a convenient source of alkoxy stabilised nitrenium ions under acidic conditions.

In aqueous acetonitrile, butyl *N*-acetoxybenzohydroxamate **100a** decomposes *via* an $A_{Al}1$ mechanism to a nitrenium ion and follows pseudo-unimolecular kinetics. The progress of the reaction was monitored by ^1H NMR across the temperature range 298-338K. The solvolysis was repeated with a number of electron-donating and withdrawing *para* substituents and the Arrhenius data was obtained which determined that nitrenium ion formation proceeds with positive $\Delta S^{\ddagger}$ and modest activation energies. The Hammett correlation revealed an excellent σ^+ relationship at 308K indicating that the *para* substituents had some degree of interaction with a developing positive charge tempered by the intermediate carbonyl moiety. The moderate slope reflected this separation between the ring and nitrenium ion.

The extent to which electronic factors on the alkoxy side chain influence the formation of nitrenium ion during acid-catalysed solvolysis was measured by synthesis of a series of *para*-substituted benzyl *N*-acetoxybenzohydroxamates **151**. Hammett and Arrhenius relationships as well as isotope studies have been presented that indicate that nitrenium ion formation is modified by electronic effects exerted by the benzyloxy side chain and in cases where positive mesomerism is possible, elimination to give *para*-substituted benzyl cations is found.

The formation of the nitrenium ion was also investigated as a function of the differing electronic effects on the leaving group by synthesis of a series of benzyl *N*-(*para*-substituted benzoyloxy) benzohydroxamates **172**. Under acid-catalysis, increased electronegativity of the *para* substituent lowered the energy required for separation of the leaving group from the precursor and favoured nitrenium ion formation.

Analysis of the acid-catalysed solvolysis products revealed a number of complex solvolysis pathways. Across the three series, most products resulted from acid-catalysed decomposition of the transient intermediate *N*-alkoxybenzohydroxamic acids formed by water capture of *N*-acyl-*N*-alkoxynitrenium ions or through uncatalysed HERON reactions which afford esters.

Alkyl *N*-acetoxybenzohydroxamate **100** also react with hydroxide ion in a rare $B_{Al}2$ fashion. Attack at nitrogen was confirmed by measuring the rate of nitrenium ion formation by altering the electronic effects on the leaving group. The rate of reaction of benzyl *N*-(*para*-substituted benzoyloxy) benzohydroxamates **172** with hydroxide was determined at 275.4K by HPLC analysis. Hammett data are in accord with a $B_{Al}2$ reaction mechanism rather than the normal $B_{Ac}2$ solvolysis. Under basic conditions the products were esters formed by HERON rearrangement of *N*-alkoxy benzohydroxamate anion **177**.

The mutagenicity of alkyl *N*-acyloxybenzohydroxamates has been measured by the Ames test using TA100 *salmonella typhimurium* bacteria. While no conclusive relationship between electronic effects and mutagenicity levels was detected for the benzoyl series **100** and benzyloxy series **151**, in the benzoyloxy series **172**, a correlation with stability appears likely. In addition, an increase in the potency of the precursor was evident with an increase in the number of aromatic rings flanking the central nitrogen, or where biphenyl rather than phenyl groups were present. The significantly higher mutagenicity levels may be due to more efficient transportation across cellular membranes or, more likely, enhanced hydrophobic associations or intercalation with DNA.

These studies have indicated that while nitrenium ion formation is the likely course of reaction where acid-catalysis is possible, the mutagens can be expected to react readily with nucleophilic species. Recent evidence has indicated that they interact with N-7 of guanine, the most nucleophilic centre in DNA. Thus alkyl *N*-acyloxybenzohydroxamates are either source of the electrophilic nitrenium ions or may behave as electrophilic molecules. Interaction with DNA is mandatory for mutagenesis and results contained in this thesis indicate that activity may be enhanced where mutagens are least reactivate and can survive the environment long enough to allow them encounter nucleic acids. Furthermore hydrophobic substructure may in fact facilitate the association with DNA.

Studies in these laboratories now centre upon utilising the chemical and mutagenic results described herein to design anti-cancer agents based upon the alkyl *N*-acyloxybenzohydroxamate structure. To that end, substrates bearing DNA intercalators tethered to low reactivity mutagenic centres are being designed as part of a drug development program.

CHAPTER SIX

6. Experimental

6.1 General

Melting points were determined on a Reichert Microscopic Hot-Stage and are uncorrected. Infra red spectra were recorded on a Perkin Elmer 1725 x FT instrument. 300 MHz ^{1}H and 75 MHz ^{13}C NMR spectra were recorded on a Bruker AC-300P FT spectrometer. HPLC analyses were performed on a Waters 510 Analytical instrument using a model 481 UV absorbance detector linked to a Waters 740 data module. Mass spectral data was obtained on a Kratos MS902 Spectrometer through the Mass Spectroscopy Unit of Sydney University. Micro analytical data was obtained from The Research School of Chemistry at Canberra. Ames tests were carried out at the "Toxicology Unit of WorkSafe Australia" in Sydney. AM1 calculations were performed by the MOPAC (version 6) and MOPAC93 molecular orbital packages on the computer resources of the Department of Chemistry and Department of Computer Science at the University of New England. Stationary points were confirmed by force calculation which provided all force constants as positive numbers. Transition states were similarly confirmed by the presence of a single negative force constant. The keywords PRECISE, POINT, STEP, TS where used were appropriate. A recent development in molecular modelling has been the incorporation of algorithms that enable optimisation of geometric structures and energies in a solvent matrix. For the MOPAC package, the keyword COSMO was used when solvent shell optimisations were required with the dielectric value set at 32, to mimic MeOH as the solvent.

Acetonitrile used was HiPerSolv, 'Far UV' grade (BDH). Ether refers to anhydrous diethyl ether stored over sodium wire. Dichloromethane (DCM) and acetone were distilled and dried over 4Å molecular sieve. Ethyl acetate (EtOAc) and methanol (MeOH) were distilled before use. Hexane (Hex.) refers to hexane of the boiling range 60-70°C. Anhydrous sodium sulfate was used for drying all organic mixtures. Flash chromatography was executed on columns loaded with Kieselgel 60 (Merck). Thin Layer Chromatography was performed on aluminium sheets pre-coated with 0.2 mm of silica gel 60 F_{254} (Merck). 2,3-But-2-ene, 4-nitrobenzyl bromide, 4-phenoxyphenyl acetate and *para*-substituted benzoic acids were purchased from Aldrich, as was deuterio-acetonitrile (99.5%-*d*), deuterium oxide (99.8%-*d*), and H_2O (10% ^{18}O). ^{1}H and ^{13}C NMR designations are: s(singlet); st(singlet of triplets); d(doublet); dd(doublet of doublets); dt(doublet of triplets); t(triplet); q(quartet); qt(quintet); sxt(sextet) and m(multiplet).

6.2 Handling of suspect mutagenic compounds

Acyloxylation of the *N*-chloro intermediates were performed in a dedicated fumehood under anhydrous conditions. Careful filtration of the mixture, also in the fumehood, followed by removal of the solvent on a dedicated rotary evaporator and high vacuum pump, provided the alkyl *N*-acyloxybenzohydroxamates which were handled with extreme care. Generally, simple alkyl *N*-acyloxybenzohydroxamates were heavy, gummy oils that facilitated easy, safe manipulation of the compounds however occasionally light fine amorphous crystals were obtained which required particular care in handling to ensure that the mutagenic material was not dissipated in the fumehood.

All contaminated glassware was treated with a solution of sodium hydroxide dissolved in 50% aqueous ethanol to destroy the mutagenic compounds. Latex gloves were used at all times when handling contaminated glassware and during chromatographic purification.

Alkyl *N*-acyloxybenzohydroxamates were stored under refrigeration in designated areas enclosed in plastic containers.

6.3 Syntheses

6.3.1 General synthesis of alkyl *para*-substituted benzohydroxamates

Treatment of the appropriate *para*-substituted ethyl benzoate with hydroxylamine hydrochloride under basic conditions afforded a precipitate of potassium benzohydroxamate salt from MeOH after refrigeration.[251] (The esters were obtained by esterification of the appropriate *para*-substituted benzoic acid with an excess of ethanol under acidic conditions and were identified by NMR by comparison with authentic spectra). Condensation of the potassium salt with the appropriate alkyl bromide and a 10% excess of sodium carbonate in 50% aqueous MeOH provided the appropriate *para*-substituted benzohydroxamic ester in good yield.[251]

6.3.2 General synthesis of *para*-substituted benzyl benzohydroxamates

The general synthesis of hydroxamic ester from potassium benzohydroxamate and the appropriate benzyl bromide has been described.[168,251] Dideuteration of *para*-substituted benzyl alcohol and *para*-substituted benzyl bromides was confirmed by comparison with the ^{1}H and ^{13}C spectra of the protio species, as well as the presence of a pentet resonance

for the methylene carbon in the ^{13}C spectra where this was present. Deuterated hydroxamates were identified by comparison of their ^{1}H, ^{13}C and mass spectra with the protio species.[174] The condensation reaction involving 4-methoxybenzyl bromide and potassium benzohydroxamate did not provide the hydroxamic ester and hence an alternative method is described below.

butyl benzohydroxamate 98a

1-Bromobutane (13.93 g, 100 mmol), potassium benzohydroxamate (11.87 g, 67.0 mmol) and sodium carbonate (7.95 g, 75.0 mmol) was stirred overnight in 50% aq. methanol (300 ml) and refluxed for 2 hours. The crude product was obtained *via* the general procedure. Purification by flash column chromatography ($CHCl_3$) afforded pure butyl benzohydroxamate (6.68 g, 52%) as an orange oil, b.p. 190 ^{o}C @ 0.2 mm Hg (Found: C, 68.53; H, 8.06; N, 7.51. $C_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%); ν_{max} ($CHCl_3$)/cm^{-1} 3225 (NH), 1654 (CO); δ_H ($CDCl_3$) 0.87 (3H, t), 1.34 (2H, sxt), 1.60 (2H, qt), 3.95 (2H, t), 7.33 (2H, t, *m*-Ar), 7.44 (1H, t, *p*-Ar), 7.76 (2H, d, *o*-Ar), 11.17 (1H, br); δ_C ($CDCl_3$) 13.44 (q), 16.60 (t), 29.67 (t), 75.84 (t), 127.01 (d), 127.94 (d), 131.25 (d), 131.68 (s), 165.65 (s).

butyl 4-bromobenzohydroxamate 98g

Potassium 4-bromobenzohydroxamate was obtained as colourless prisms in the same manner as potassium benzohydroxamate (82%). 1-bromobutane (17.06 g, 124.5 mmol), potassium 4-bromobenzohydroxamate (19.09 g, 83 mmol) and sodium carbonate (10.8 g, 100 mmol) in 50% aq. MeOH (300 ml) were stirred at room temperature overnight and refluxed for two hours. Workup and recrystallisation ($CHCl_3$/Hex.) provided pure butyl 4-bromobenzohydroxamate (11.5 g, 67%), m.p. 109-110^{o}C (Found: C, 48.71; H, 5.31; N, 5.15, Br 29.46. $C_{14}NO_2Br$ requires C, 48.55; H, 5.19; N, 5.15; Br, 29.36%); ν_{max} ($CHCl_3$)/cm^{-1} 3250 (NH), 1696 (CO); δ_H ($CDCl_3$) 0.89 (3H, t), 1.34 (2H, sxt), 1.60 (2H, qt), 3.95 (2H, t), 7.47 (2H, d *J* 8.5, *m*-Ar), 7.63 (2H, d), 10.5 (1H, br, NH); δ_C ($CDCl_3$) 13.74 (q), 18.91 (t), 29.96 (t), 76.48 (t), 126.48 (s), 128.77 (d), 130.67 (s), 131.62 (d), 165.45 (s). $\frac{m}{z}$ 271 (M^+,45%), 262(35), 241(40), 228(40), 215(40), 199(80), 183(100).

butyl 4-chlorobenzohydroxamate 98f

Potassium 4-chlorobenzohydroxamate was obtained in the same manner as potassium benzohydroxamate (60%). 1-bromobutane (10 g, 73.0 mmol), potassium 4-chlorobenzohydroxamate (13.5 g, 73 mmol) and sodium carbonate (10.8 g, 100 mmol) in 50% aq. MeOH (200 ml) were stirred at room temperature overnight and refluxed for two hours. Workup and recrystallisation ($CHCl_3$/Hex.) provided pure butyl 4-chlorobenzohydroxamate (14.1 g, 85%), m.p. 95-96°C (Found: C, 58.09; H, 6.45; N, 6.22; Cl, 15.82. $C_{14}NO_2Cl$ requires C, 58.03; H, 6.20; N, 6.15; Cl, 15.57%): ν_{max} ($CHCl_3$)/cm^{-1} 3250 (NH), 1695 (CO); δ_H ($CDCl_3$) 0.88 (3H, t), 1.33 (2H, sxt), 1.57 (2H, qt), 3.95 (2H, t), 7.30 (2H, d), 7.70 (2H, d, *J* 8.3, *o*-Ar), 10.5 (1H, br); δ_C ($CDCl_3$) 13.66 (q), 18.86 (t), 29.90 (t), 76.37 (t), 128.55 (d), 128.66 (d), 130.21 (s), 137.93 (s, *p*-Ar), 165.29 (s). $\frac{m}{z}$ 227 (M^+,40%), 196(40), 182(45), 139(100), 111(65), 75(50), 28(70).

butyl 4-nitrobenzohydroxamate 98h

Potassium 4-nitrobenzohydroxamate was obtained in the same manner as potassium benzohydroxamate (90%). The title compound was generated *via* the general condensation and recrystallisation procedure as pale yellow crystals (52%), m.p. 99-101°C (Found: C, 54.99; H, 6.20; N, 11.66. $C_{11}H_{14}N_2O_4$ requires C, 55.46; H, 5.92; N, 11.76%); ν_{max} ($CHCl_3$)/cm^{-1} 1695 (CO); δ_H ($CDCl_3$) 0.90 (3H, t), 1.34 (2H, sxt), 1.66 (2H, qt), 4.03 (2H, t), 7.99 (2H, d), 8.22 (2H, d, *J* 8.8), 10.5 (1H, br); δ_C ($CDCl_3$) 13.66 (q), 18.88 (t), 29.93 (t), 76.75 (t), 123.57 (d, *m*-Ar), 128.47 (d), 137.47 (s), 149.63 (s, *p*-Ar), 164.14 (s). $\frac{m}{z}$ 238 (M^+, 25%), 206(30), 193(70), 167(40), 150(100), 57(55), 41(40), 29(95).

butyl biphenyl-4-carboxohydroxamate 98c

Potassium biphenyl-4-carboxohydroxamate was prepared *via* the general method (20%). The title compound was generated *via* the general condensation and recrystallisation procedure as colourless crystals (73%), m.p. 141-142°C (Found: C, 75.80; H, 7.32; N, 4.93. $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; N, 5.20%); ν_{max} ($CHCl_3$)/cm^{-1} 3406 (NH), 1684 (CO); δ_H ($CDCl_3$) 0.95 (3H, t), 1.44 (2H, sxt), 1.71 (2H, qt), 4.04 (2H, t), 7.4 (3H, m), 7.60 (4H, m), 7.81 (2H, d, *J* 8.5, *o*-Ar), 8.8 (1H, br); δ_C ($CDCl_3$) 13.85 (q), 19.06 (t), 30.08 (t), 76.62 (t), 127.14 (d), 127.26 (d), 127.60 (dd), 128.07 (dt),

128.91 (dd), 130.67 (st), 139.83 (s, *i'*-Ar), 144.77 (s, *p*-Ar), 166.38 (s). $\frac{m}{z}$ 269 (M^+, 71%), 197(43), 181(100), 153(77), 77(11), 76(15), 29(10).

butyl 4-tert-butylbenzohydroxamate 98e

Potassium 4-*tert*-butylbenzohydroxamate was obtained as colourless prisms in a yield of 20%. The title compound was generated *via* the general condensation and workup procedure. Purification by flash column chromatography (15% EtOAc, 85% Hex.) afforded pure butyl 4-*tert*-butylbenzohydroxamate (1.77 g, 71%) as a clear oil, b.p. 120°C @ 0.1 mm Hg (Found: C, 71.97; H, 9.50; N, 5.39. $C_{15}H_{23}NO_2$ requires C, 72.25; H, 9.30; N, 5.62%); ν_{max} ($CHCl_3$)/cm^{-1} 3259 (NH), 1679 (CO); δ_H ($CDCl_3$) 0.96 (3H, t), 1.33 (9H, s), 1.45 (2H, m), 1.70 (2H, qt), 4.03 (2H, t), 7.45 (2H, d), 7.75 (2H, d, *J* 6.8, *o*-Ar), 9.3 (1H, br); δ_C ($CDCl_3$) 13.81 (q), 19.01 (t), 30.03 (t), 31.06 (q), 34.89 (s), 76.64 (t), 125.49 (d), 126.92 (d), 129.12 (s), 155.41 (s), 166.42 (s). $\frac{m}{z}$ 249 (M^+, 51%), 234(33), 177(30), 161(74), 134(33), 77(19), 57(24), 44(41), 41(100), 29(57).

butyl 4-methylbenzohydroxamate 98d

Potassium 4-methylbenzohydroxamate was obtained as colourless prisms in the same manner as potassium benzohydroxamate (54%). Butyl 4-methylbenzohydroxamate was obtained under the general condensation reaction. Recrystallisation ($CHCl_3$/Hex.) provided pure butyl 4-methylbenzohydroxamate (70%), (Found: C, 69.95; H, 7.99; N, 6.79. $C_{12}H_{17}NO_2$ requires C, 69.54; H, 8.27; N, 6.76%); ν_{max}/cm^{-1} 1695 (CO), 3250 (NH); δ_H ($CDCl_3$) 0.92 (3H, t), 1.40 (2H, sxt), 1.67 (2H, qt), 2.37 (3H, s), 3.99 (2H, t), 7.18 (2H, d), 7.63 (2H, d, *J* 8, *o*-Ar), 9.1 (1H, br); δ_C ($CDCl_3$) 13.81 (q), 19.01 (t), 21.44 (q), 30.02 (t), 76.45 (t), 127.06 (d), 129.20 (d), 129.20 (s), 142.36 (s, *p*-Ar), 166.44 (s); $\frac{m}{z}$ **207** (M^+, 65%), 175(45), 151(30), 119(100), 91(25).

butyl 4-methoxybenzohydroxamate 98b

Potassium 4-methoxybenzohydroxamate was obtained in the same manner as potassium benzohydroxamate (62%). Butyl 4-methoxybenzohydroxamate was prepared *via* the general condensation reaction conditions. Recrystallisation ($CHCl_3$/Hex.) provided butyl 4-methoxybenzohydroxamate (40%), m.p. 43-44°C, b.p. 155°C @ 0.25 mmHg (Found: C, 63.58; H, 7.74; N, 6.16. $C_{17}NO_3$ requires C, 64.55; H, 7.87; N, 6.27%); ν_{max} ($CHCl_3$)/cm^{-1} 1692 (CO), 3250 (NH); δ_H ($CDCl_3$) 0.89 (3H, t), 1.38 (2H, sxt), 1.63

(2H, qt), 3.80 (3H, s), 3.96 (2H, t), 6.83 (2H, d), 7.75 (2H, d, *J* 8.9, *o*-Ar), 10.5 (1H, br); δ_C ($CDCl_3$) 13.72 (q), 18.92 (t), 29.96 (t), 55.21 (q), 76.39 (t), 113.59 (d, *m*-Ar), 124.18 (s), 128.97 (d), 162.28 (s, *p*-Ar), 166.12 (s). $\frac{m}{z}$ 223 (M^+,35%), 191(10), 167(10), 151(20), 135(100), 92(40), 77(45), 28(65).

6.3.3 General synthesis of *para*-substituted benzyl alcohols

The appropriate 4-substituted benzoic acid (or benzaldehyde) was reduced to the corresponding alcohol by treatment with $LiAlH_4$ in ether (or $NaBH_4$ in ethanol/water). The mixtures were first washed with dilute acid, 10% aq. sodium carbonate, and then extracted with DCM. The appropriate alcohols were obtained by this method in good yields and were of high purity. All alcohols were known compounds and exhibited the appropriate ^1H, ^{13}C NMR and IR spectra. Dideuteration of *para*-substituted benzyl alcohol was confirmed by comparison of the ^1H and ^{13}C spectra with those of the protio species, as well as the presence of a quintet resonance for the methylene carbon in the ^{13}C spectra.

4-nitro-α,α-dideuteriobenzyl alcohol

4-Nitrobenzoic acid was converted to 4-nitrobenzoyl chloride in 85% yield. Treatment with sodium borodeuteride in dioxane provided 4-nitro-α,α-dideuteriobenzyl alcohol in 80% yield.

6.3.4 General synthesis of *para*-substituted benzyl bromides

para-Substituted benzyl bromides (chloride) were prepared from the appropriate alcohols by refluxing with HBr/H_2SO_4 (HCl/H_2SO_4) in ether.[175] The mixture was washed with conc. HCl, H_2O, 10% aq Na_2CO_3, H_2O and extracted with DCM. Concentration *in vacuo* provided the 4-substituted benzyl bromides in good yield (>90%) and of sufficient purity (^1H and ^{13}C NMR, IR, m.p.) to be used directly in condensation reactions. While α,α-dideuterio-4-substituted benzyl alcohols displayed a weak but characteristic alpha ^{13}C quintet resonance, after conversion to α,α-dideuterio-*para*-substituted benzyl bromides and subsequently *para*-substituted-α,α-dideuteriobenzyl *N*-acetoxybenzohydroxamates, this resonance proved difficult to detect at 300MHz.

4-bromobenzyl bromide

m.p. 61-62°C (lit.,[252] 63°C) δ_H ($CDCl_3$) 4.44 (2H, s), 7.24 (2H, d), 7.46 (2H, d); δ_C ($CDCl_3$) 32.36 (tt), 122.38 (st), 130.60 (dq), 131.68 (dd), 136.70 (s).

4-chlorobenzyl bromide

m.p. 28-30°C (lit.,[252] 28-30°C) δ_H ($CDCl_3$) 4.45 (2H, s), 7.32 (4H, s); δ_C ($CDCl_3$) 32.34 (t), 128.91 (d), 130.30 (d), 134.20 (s), 136.22 (s).

4-methylbenzyl bromide

m.p. 32-34°C (lit.,[252] 32-35°C) δ_H ($CDCl_3$) 2.40 (3H, s), 4.52 (2H, s), 7.19 (2H, d), 7.32 (2H, d); δ_C ($CDCl_3$) 21.13 (q), 33.67 (t), 128.88 (d), 129.39 (d), 134.77 (s), 138.24 (s).

4-tert-butylbenzyl bromide

δ_H ($CDCl_3$) 1.3 (3H, s), 4.47 (2H, s), 7.29 (2H, d), 7.34 (2H, d); δ_C ($CDCl_3$) 31.22 (q), 33.55 (t), 34.57 (s), 125.69 (d), 128.71 (d), 134.71 (s), 151.46 (s).

4-phenylbenzyl bromide

m.p. 101-102.5°C (lit.,[252] 99-101°C) δ_H ($CDCl_3$) 4.72 (2H, s), 7.46 (5H, m), 7.64 (4H, m).

4-phenoxybenzyl bromide

δ_H ($CDCl_3$) 4.49 (2H, s), 6.93 (2H, d), 7.00 (2H, d), 7.12 (1H, t), 7.32 (4H, m); δ_C ($CDCl_3$) 33.3 (t), 118.6 (d), 119.2 (d), 123.6 (d), 129.8 (d), 130.5 (d), 132.3 (s), 156.5 (s), 157.5 (s).

4-methoxybenzyl chloride

n_D^{23}=1.5469 (lit.,[252] n_D=1.5482); ν_{max}/cm^{-1} 1612, 1515 1249; δ_H ($CDCl_3$) 3.77 (3H, s), 4.56 (2H, s), 6.86 (2H, d), 7.30 (2H, s); δ_C ($CDCl_3$) 46.27 (t), 55.28 (q), 114.11 (d), 129.88 (s), 130.03 (d), 159.66 (s).

α,α-dideuterio-4-methylbenzyl alcohol

p-Toluic acid (3.0 g, 22.1 mmol) was reduced by refluxing with $LiAlD_4$ (1.01 g, 15 mmol) in dry THF (20 ml) for 24 hours. Workup with D_2O provided pure α,α-dideuterio-4-methylbenzyl alcohol (99%). δ_H ($CDCl_3$) 2.27 (3H, s), 7.03 (2H, d), 7.10 (2H, d); δ_C ($CDCl_3$) 20.92 (q) **63.82** (qt), 126.94(d), 128.58 (d), 136.88 (s), 137.68 (s);

α,α-dideuterio-4-methylbenzyl bromide

α,α-Dideuterio-4-methylbenzyl alcohol (0.85 g, 14.6 mmol) was refluxed in hydrobromic acid (10 ml) and sulfuric acid (2 ml) for 1 hour. Workup provided pure α,α-dideuterio-4-methylbenzyl bromide (2.82 g, 75%) which was identical to the protio species by ^1H and ^{13}C NMR spectroscopy. δ_H ($CDCl_3$) 2.39 (3H, s), 7.17 (2H, d), 7.31 (2H, d); δ_C ($CDCl_3$) 21.13 (q), 33.61 (qt), 128.84 (d), 129.42 (d), 134.74 (s), 138.19 (s).

α,α-dideuterio-4-methoxybenzyl alcohol

4-Methoxybenzoic (6 g, 39.4 mmol) acid was reduced by refluxing with $LiAlD_4$ (0.63 g, 15 mmol) in dry ether (50 ml) for 24 hours. Workup with D_2O provided pure α,α-dideuterio-4-methoxybenzyl alcohol (76%). δ_H ($CDCl_3$) 3.77 (3H, s), 6.63 (2H, d), 7.22 (2H, d); δ_C ($CDCl_3$) 55.24 (q), **63.87** (qt), 113.73 (d), 128.74 (d), 133.04 (s), 158.94 (s).

α,α-dideuterio-4-methoxybenzyl bromide

α,α-Dideuterio-4-methoxybenzyl alcohol (2.0 g, 14.6 mmol) was stirred in hydrobromic acid (6 ml) and sulfuric acid (0.5 ml) for 1 hour. Workup provided pure α,α-dideuterio-4-methoxybenzyl bromide (2.82 g, 95%). δ_H ($CDCl_3$) 3.77 (3H, s), 6.91 (2H, d), 7.31 (2H, s); δ_C ($CDCl_3$) 55.28 (q), 114.11 (d), 129.88 (s), 130.03 (d), 159.66 (s).

α,α-dideuterio-4-phenylbenzyl alcohol

Biphenyl-4-carboxylic acid(21.6 g, 108 mmol) was reduced by refluxing with $LiAlD_4$ (10.0 g, 53.7 mmol) in dry ether (70 ml) for 30 hours. Workup with D_2O provided pure α,α-dideuterio-4-phenylbenzyl alcohol (53%). δ_H ($CDCl_3$) 7.41 (1H, t), 7.47 (4H, m),

7.64 (4H, d); δ_C ($CDCl_3$) **64.4** (qt), 127.05 (d), 127.28 (d), 127.45 (d), 128.75 (d), 139.73 (s), 140.59 (s), 140.78 (s).

α,α-dideuterio-4-phenylbenzyl bromide

α,α-Dideuterio-4-phenylbenzyl alcohol (3.4 g, 12.8 mmol) was refluxed in hydrobromic acid (10 ml) and sulfuric acid (1 ml) for 3 hours. Workup provided pure α,α-dideuterio-4-phenylbenzyl bromide (72%). δ_H ($CDCl_3$) 7.3 (1H, t), 7.4 (4H, m), 7.5 (4H, m); δ_C ($CDCl_3$) **32.89** (qt), 127.08 (d), 127.34 (d), 127.49 (d), 128.61 (d), 129.28 (d), 136.55 (s), 140.49 (s), 141.06 (s).

α,α-dideuterio-4-nitrobenzyl alcohol

4-Nitrobenzoic acid (15 g, 90 mmol) was treated with PCl_5 (18 g, 86 mmol) to give 4-nitrobenzoyl chloride in 85% yield. Reduction of the acyl chloride by $NaBD_4$ in dioxane gave, upon workup, α,α-dideuterio-4-nitrobenzyl alcohol (2.67 g, 80%). δ_H ($CDCl_3$) 7.30 (2H, d), 8.04 (2H, d); δ_C ($CDCl_3$) **63.27** (qt), 123.48 (d), 126.87 (d), 146.98 (s), 148.45 (s);

α,α-dideuterio-4-nitrobenzyl bromide

α,α-Dideuterio-4-nitrobenzyl alcohol (2.67 g, 17.3 mmol) was refluxed in hydrobromic acid (10 ml) and sulfuric acid (1 ml) for 12 hours. Workup provided pure α,α-dideuterio-4-nitrobenzyl bromide (0.4 g, 11%). δ_H ($CDCl_3$) 7.41 (2H, d), 8.06 (2H, d); δ_C ($CDCl_3$) 30.71 (qt), 123.85 (d), 129.80 (d), 144.59 (s), 147.47 (s).

6.3.5 General synthesis of *para*-substituted benzylbenzohydroxamates

The general synthesis of hydroxamic ester from potassium hydroxamate and the appropriate benzyl bromide has been described.

benzyl benzohydroxamate 149a

Potassium benzohydroxamate (10.2 g, 58.5 mmol), benzyl bromide (10.0 g, 58.5 mmol) and sodium carbonate (7.8 g, 73 mmol) were stirred overnight in 50% aq. MeOH (160 ml) and refluxed for 2 hours. Removal of MeOH *in vacuo* and acidification followed by extraction with DCM provided the crude hydroxamate. Pure benzyl benzohydroxamate (13.6 g, 93%) was obtained as colourless crystals upon recrystallisation ($CHCl_3$/Hex.),

m.p. 100-102°C (Found: C, 73.70; H, 5.98; N, 6.16. $C_{14}H_{13}NO_2$ requires C, 73.99; H, 5.77; N, 6.16%); ν_{max} ($CHCl_3$)/cm^{-1} 3250 (NH), 1678 (CO); δ_H ($CDCl_3$) 4.98 (2H, s), 7.31 (5H, m), 7.37 (2H, t), 7.43 (1H, t, *J* 7.4, *p*-Ar), 7.67 (2H, d, *J* 7.1, *o*-Ar), 9.55 (1H, br); δ_C ($CDCl_3$) 78.02 (t), 127.08 (dt, *p'* -Ar), 128.28 (d), 128.33 (d), 128.40 (d), 129.03 (d), 131.69 (dt), 131.70 (st, *i* -Ar), 135.13 (s, *i'* -Ar), 166.26 (s). $\frac{m}{z}$ **227** (M^+, 40%), 210(45), 105(45), 91(100), 77(30), 51(15), 28(20).

4-bromobenzyl benzohydroxamate 149g

Refluxing potassium benzohydroxamate (6.68 g, 38.2 mmol), 4-bromobenzyl bromide (9.68 g, 38.7 mmol) and sodium carbonate (4.9 g, 46 mmol) in 50% aq. MeOH (150 ml) gave the title compound (4.69 g, 40%) after workup and recrystallisation ($CHCl_3$/Hex.), m.p. 172-173°C (Found: C, 54.71; H, 3.87; N, 4.38; Br, 26.09. $C_{14}H_{12}NO_2Br$ requires C, 54.92; H, 3.95; N, 4.57; Br, 26.10%); ν_{max} ($CHCl_3$)/cm^{-1} 1680; δ_H ($CDCl_3$) 4.99 (2H, s), 7.32 (2H, d, *J* 8.4, *m'*-Ar), 7.41 (2H, t, *J* 6.8, *m*-Ar), 7.54 (3H, m), 7.66 (2H, d, *J* 7, *o*-Ar), 8.57 (1H, br); ^{13}C δ_C ($CDCl_3$) 77.46 (t), 122.83 (st, *i* -Ar), 126.67 (dt), 128.63 (dd), 130.78 (dq), 131.59 (st), 131.68 (dd), 132.09 (dt, *p*-Ar), 134.13 (s, *i'* -Ar), 166.50 (s). $\frac{m}{z}$ **307** (M^+,20%), 290(60), 169(60), 105(70), 90(50), 77(100), 51(80).

4-chlorobenzyl benzohydroxamate 149h

Refluxing potassium benzohydroxamate (7.66 g, 44 mmol), 4-chlorobenzyl bromide (8.98 g, 44 mmol) and sodium carbonate (5.8 g, 55 mmol) in aq. MeOH (150 ml) gave the title compound (10.92 g, 95%) upon workup and recrystallisation ($CHCl_3$/Hex.), m.p. 158-160°C (Found: C, 64.13; H, 4.69; N, 5.17; Cl,13.52. $C_{14}H_{12}NO_2Cl$ requires C, 64.25; H, 4.62; N, 5.35; Cl, 13.55%); ν_{max} ($CHCl_3$)/cm^{-1} 3406 (NH), 1687 (CO); δ_H ($CDCl_3$) 4.99 (2H, s), 7.36 (4H, s), 7.4 (2H, t, *J* 7, *m*-Ar), 7.5 (1H, t, *J* 7, *p*-Ar), 7.66 (2H, d, *J* 7, *o*-Ar), 8.62 (1H, br); δ_C ($CDCl_3$) 77.55 (t), 127.01 (dt, *m*-Ar), 128.75 (dd), 128.83 (dd), 130.63 (dq, *p'* -Ar), 131.74 (s), 131.21 (dt, *p*-Ar), 133.75 (s), 134.76 (s), 166.68 (s). $\frac{m}{z}$ **261** (M^+, 20%), 244(45), 139(20), 125(100), 105(60), 77(50), 51(25).

4-nitrobenzyl benzohydroxamate 149i

Potassium benzohydroxamate (4.05 g, 23.1 mmol), 4-nitrobenzyl bromide (5.0 g, 23.1 mmol) and sodium carbonate (3.0 g, 28 mmol) provided the crude hydroxamate *via* the general procedure. Pure 4-nitrobenzyl benzohydroxamate (5.92 g, 94%) was obtained as

pale yellow crystals upon recrystallisation ($CHCl_3$/Hex.), m.p. 159-161°C (Found: C, 61.38; H, 4.28; N, 10.04. $C_{14}H_{12}N_2O_4$ requires C, 61.76; H, 4.44; N, 10.29%); ν_{max} ($CHCl_3$)/cm^{-1} 3393 (NH), 1691 (CO); δ_H ($CDCl_3$) 5.14 (2H, s), 7.42 (2H, t, *J* 7, *m*-Ar), 7.51 (1H, t, *J* 7, *p*-Ar), 7.62 (2H, d, *J* 7, *o*-Ar), 7.65 (2H, d, *J* 8.4, *o'*-Ar), 8.22 (2H, d, *J* 6.9, *m'*-Ar), 8.79 (1H, br); δ_C (CD_3CN) 77.39 (t), 124.46 (dd), 128.04 (dt), 129.58 (d), 130.86 (d), 132.91 (dt), 133.18 (s), 144.62 (s), 148.99 (s), 166.59 (s); $\frac{m}{z}$ **272** (M^+, 5%), 136(12), 121(25), 105(100), 91(25), 77(45).

4-nitro-α,α-dideuteriobenzyl benzohydroxamate

Refluxing potassium benzohydroxamate (0.32 g, 1.8 mmol), 4-nitro-α,α-dideuteriobenzyl bromide (0.4 g, 1.84 mmol) and sodium carbonate (0.2 g) in MeOH/H_2O (20ml:20ml) for 2 hours provided pure 4-nitro-α,α-dideuteriobenzyl benzohydroxamate (0.342 g, 65%) after workup and recrystallisation ($CHCl_3$/Hex.). m.p. 159-161°C. δ_H ($CDCl_3$) 7.41 (2H, t), 7.54 (1H,t), 7.65 (2H, d), 7.68 (2H, d), 8.22 (2H, d), 8.78 (1H, br); δ_C ($CDCl_3$) 77.20 (qt), 123.79 (dd), 127.00 (d), 128.84 (d), 129.53 (d), 131.40 (st), 132.46 (dt), 142.45 (s), 148.08 (s), 167.02 (s); $\frac{m}{z}$ **274**(M^+, 6%), 138(15), 105(100), 77(38), 51(15).

*4-***tert***-butylbenzyl benzohydroxamate 149f*

Potassium benzohydroxamate (5.0 g, 28 mmol), 4-*tert*-butylbenzyl bromide (3.23 g, 14.2 mmol) and sodium carbonate (2.0 g, 19 mmol) provided pure 4-*tert*-butylbenzyl benzohydroxamate (2.9 g, 72%) *via* the general procedure after workup and recrystallisation (DCM/Hex.), m.p. 89-93°C (Found: C, 76.34; H, 7.69; N, 4.77. $C_{18}H_{21}NO_2$ requires C, 76.3; H, 7.47; N, 4.94 %); ν_{max} ($CHCl_3$)/cm^{-1} 3400 (NH), 1685 (CO); δ_H ($CDCl_3$) 1.32 (9H, s), 5.00 (2H, s), 7.38 (6H, m), 7.47 (1H, t, *p*-Ar), 7.66 (2H, d, *J* 7.1, *o*-Ar), 9.0 (1H, br); δ_C ($CDCl_3$) 31.27 (q), 34.63 (s), 78.09 (t), 125.57 (dd), 126.92 (s), 127.04 (d), 128.63 (d), 128.70 (s), 129.17 (d), 131.95 (s), 151.90 (s); $\frac{m}{z}$ **283**(M^+, 20%), 266(25), 147(100), 132(60), 117(45), 105(65), 91(50), 77(55).

4-phenylbenzyl benzohydroxamate 149d

Potassium benzohydroxamate (2.4 g, 13 mmol), 4-phenylbenzyl bromide (2.4 g, 13 mmol) and sodium carbonate (3.0 g, 28 mmol) provided pure 4-phenylbenzyl benzohydroxamate (0.62 g, 16%) after workup and recrystallisation ($CHCl_3$/Hex.), m.p.

177-179°C, (Found: C, 79.07; H, 5.85; N, 4.35. $C_{20}H_{17}NO_2$ requires C, 79.19; H, 5.65; N, 4.62%); ν_{max} ($CHCl_3$)/cm^{-1} 3320 (NH), 1674 (CO); δ_H (CD_3COCD_3) 5.03 (2H, s), 7.22 (1H,t), 7.39 (4H, m), 7.42 (1H,t), 7.49 (2H, d), 7.58 (4H, d), 7.63 (2H, d), 9.62 (1H, br); δ_C (50% $CDCl_3$/CD_3CN) 126.05 (d), 126.20 (s), 126.66 (s), 127.68 (dd), 128.03 (d), 128.94 (s), 130.62 (s), 130.92 (dt), 164.91 (s); $\frac{m}{z}$ **303**(M^+, 4%), 288(55), 286(50), 181(85), 167(100), 152(50), 121(40), 105(60), 77(60).

4-phenyl-α,α-dideuteriobenzyl benzohydroxamate

Potassium benzohydroxamate (1.0 g, 5.7 mmol), 4-phenyl-α,α-dideuteriobenzyl bromide (1.4 g, 5.6 mmol) and sodium carbonate (1.4 g) in refluxing dry THF provided pure 4-phenyl-α,α-dideuteriobenzyl benzohydroxamate (1.01 g, 59%) after workup and recrystallisation ($CHCl_3$/Hex.). m.p. 177-179°C. δ_H ($CDCl_3$) 7.38-7.53 (8H, m), 7.58 (4H, m), 7.67 (2H, d); δ_C ($CDCl_3$) 126.12 (d), 126.34 (s), 126.67 (s), 127.68 (dd), 128.11 (d), 128.98 (s), 130.45 (s), 130.98 (dt), 164.91 (s); $\frac{m}{z}$ **305**(M^+, 5), 288 (40), 183(20), 169(60), 152(32), 105(100), 77(60).

4-methylbenzyl benzohydroxamate 149e

Potassium benzohydroxamate (7.33 g, 42 mmol), 4-methylbenzyl bromide (7.74 g, 41.9 mmol) and sodium carbonate (5.55 g, 51.9 mmol) provided pure 4-methylbenzyl benzohydroxamate (5.92 g, 59%) *via* the general procedure after workup and recrystallisation ($CHCl_3$/Hex.), m.p. 106-107°C (Found: C, 74.35; H, 6.27; N, 5.57. $C_{15}H_{15}NO_2$ requires C, 74.67; H, 6.27; N, 5.80%); ν_{max} ($CHCl_3$)/cm^{-1} 3200 (NH), 1681 (CO); δ_H ($CDCl_3$) 2.33 (3H, s), 4.93 (2H, s), 7.11 (2H, d, *J* 7.8), 7.29 (2H, d, *J* 7.8), 7.34 (2H, t, *J* 7.6, *m*-Ar), 7.45 (1H, t, *J* 7.6, *p*-Ar), 7.68 (2H, d, *J* 7, *o*-Ar), 9.62 (1H, br); δ_C ($CDCl_3$) 21.09 (q), 77.96 (t), 127.07 (dt), 128.40 (dd), 129.06 (d), 129.24 (d), 131.74 (dt, *p*-Ar), 131.85 (s), 132.14 (st), 138.33 (s, *p'*-Ar), 166.24 (s); $\frac{m}{z}$ **241**(M^+, 5), 226 (80), 136(13), 121(25), 105(100), 77(70), 51(40).

4-methyl-α,α-dideuteriobenzyl benzohydroxamate

Potassium benzohydroxamate (0.60 g, 3.43 mmol), 4-methyl-α,α-dideuteriobenzyl bromide (0.64 g, 3.42 mmol) and sodium carbonate (1.1 g, 10.3 mmol) provided pure 4-methyl-α,α-dideuteriobenzyl benzohydroxamate (0.62 g, 75%) *via* the general procedure after workup and recrystallisation ($CHCl_3$/Hex.). δ_H ($CDCl_3$) 2.33 (3H, s), 7.11 (2H, d,

J 7.4), 7.27 (2H, d, *J* 7.4), 7.34 (2H, t, *J* 7.3, *m*-Ar), 7.45 (1H, t, *J* 7.3, *p*-Ar), 7.69 (2H, d, *J* 7.3, *o*-Ar); δ_C ($CDCl_3$) 21.11 (q), 127.07 (d), 128.42 (d), 129.08 (d), 129.30 (d), 131.65 (dt), 131.77 (s), 131.99 (s), 138.39 (s), 166 (s); $\frac{m}{z}$ 227(M^+-16, 18), 205(35), 121(15), 107(100), 105(38), 91(30), 77(42), 51(41).

4-phenoxybenzyl benzohydroxamate 149b

Potassium benzohydroxamate (5.0 g, 28 mmol), 4-phenoxybenzyl bromide (3.1 g, 12 mmol) and sodium carbonate (7.0 g, 65 mmol) provided pure 4-phenoxybenzyl benzohydroxamate (2.42 g, 65%) after workup and recrystallisation ($CHCl_3$/Hex.). m.p. 186-189°C, (Found: C, 74.94; H, 5.44; N, 4.68. $C_{20}H_{17}NO_3$ requires C, 75.22; H, 5.37; N, 4.39%) ν_{max} ($CHCl_3$)/cm^{-1} 3390 (NH), 1690 (CO); δ_H ($CDCl_3$) 5.00 (2H, s), 7.00 (4H, m), 7.13 (1H, t, *J* 6.8, *p'''*-Ar), 7.43 (6H, m), 7.43 (1H, t, *J* 7, *p*-Ar), 7.67 (2H, d, *J* 7, *o*-Ar), 8.7 (1H, br); δ_C ($CDCl_3$) 77.01 (t), 116.59 (dd), 119.21 (d), 123.63 (dt, *p''* -Ar), 126.66 (s), 126.98 (d), 128.69 (dd), 128.78 (s), 129.81 (dd), 131.07 (d), 131.74 (d), 132.04 (d), 156.68 (s), 157.95 (s); $\frac{m}{z}$ 302(5), 197(40%), 183(100), 105(25), 77(40), 51(25).

4-methoxybenzyl benzohydroxamate 149c

Benzohydroxamic acid (1.4 g,10 mmol), 4-methoxybenzyl chloride (1.6 g, 10 mmol) and triethylamine (3.0 g, 30 mmol) were refluxed in $CHCl_3$ (30 ml) for 2 hours. After washing with 10% aq. sodium carbonate and dilute HCl, the organic layer was dried and the solvent removed *in vacuo* affording the crude hydroxamate. Recrystallisation (EtOH/H_2O) provided pure 4-methoxybenzyl benzohydroxamate (0.48 g, 19%), m.p. 119-121°C, (Found: C, 70.22; H, 6.04; N, 5.40. $C_{15}H_{15}NO_3$ requires C, 70.02; H, 5.88; N, 5.44%); ν_{max} ($CHCl_3$)/cm^{-1} 3407 (NH), 1684 (CO); δ_H ($CDCl_3$) 3.75 (3H, s), 4.92 (2H, s), 6.62 (2H, d, *J* 9, *m'*-Ar), 7.31 (2H, d, *J* 9, *o'*-Ar), 7.34 (2H, t, *J* 7, *m*-Ar), 7.43 (1H, t, *J* 7, *p*-Ar), 7.68 (2H, d, *J* 7, *o*-Ar); δ_C ($CDCl_3$) 55.15 (q), 77.78 (t), 113.80 (d, *m'*-Ar), 127.05 (d, *o*-Ar), 127.33 (s), 128.48 (d, *m*-Ar), 130.94 (d, *o'*-Ar), 131.79 (d, *p*-Ar), 159.83 (s); $\frac{m}{z}$ **257** (M^+, 55%), 135(40), 121(100), 105(50), 77(60), 51(50).

4-methoxy-α,α-dideuteriobenzyl benzohydroxamate

Benzohydroxamic acid (2.4 g, 14.7 mmol), 4-methoxy-α,α-dideuteriobenzyl chloride (2.03 g, 14.7 mmol) and triethylamine (3 g) were stirred at room temperature in ether (30 ml) for 20 hours. Workup and recrystallisation ($EtOH/H_2O$) provided pure 4-methoxy-α,α-dideuteriobenzyl benzohydroxamate (0.50 g, 13%). m.p. 115-118°C δ_H ($CDCl_3$) 3.79 (3H, s), 6.86 (2H, d), 7.33 (2H, d), 7.38 (2H, t), 7.54 (1H, t), 7.66 (2H, d); δ_C ($CDCl_3$) 55.11 (q), 113.76 (d), 127.04 (d), 127.16 (s), 128.46 (d, *m*-Ar), 130.92 (d, *o*'-Ar), 131.19 (d), 131.86 (s, *p*-Ar), 159.81 (s, *p*'-Ar), 166.23 (s); $\frac{m}{z}$ **259** (M^+, 1%), 242(60), 123(100), 105(40), 77(53), 51(20).

6.3.6 *N*-Chlorination of alkyl benzohydroxamates

N-Chlorination of alkyl benzohydroxamates was achieved in quantitative yields by stirring with a 3*M* excess of *tert*-butyl hypochlorite in DCM or $CHCl_3$ at room temperature for 2-12 hours. The progress of *N*-chlorination was followed by ^1H NMR through monitoring the formation of a slightly downfield resonance (≈ δ5.1) due of the methylene protons of the *N*-chloro species and slightly downfield of the corresponding protons in the parent hydroxamic ester. In the dideuterio compounds this probe was not available and *N*-chlorination of the hydroxamate was assumed to proceed in quantitative yields after 24 hours. ^{13}C shifts in the *N*-chlorinated species were generally not significant enough to be used to monitor the progress of chlorination. *N*-chloro compounds were used directly in acetoxylation reactions without the need for further purification.

butyl* N-*chlorobenzohydroxamate 99a

δ_H ($CDCl_3$) 0.87 (3H, t), 1.33 (2H, m), 1.56 (2H, m), 4.12 (2H, t), 7.44 (2H, t, *m*-Ar), 7.54 (1H, t, *p*-Ar), 7.77 (2H, d, *o*-Ar).

butyl* N-*chloro-4-bromobenzohydroxamate 99g

δ_H ($CDCl_3$) 0.88 (3H, t), 1.31 (2H, sxt), 1.59 (2H, qt), 4.11 (2H, t), 7.57 (2H, d), 7.64 (2H, d).

butyl* N-*chloro-4-chlorobenzohydroxamate 99f

δ_H ($CDCl_3$) 0.87 (3H, t), 1.31 (2H, sxt), 1.55 (2H, qt), 4.11 (2H, t), 7.39 (2H, d), 7.71 (2H, d).

butyl* N-*chloro-4-methylbenzohydroxamate 99d

δ_H ($CDCl_3$) 0.88 (3H, t), 1.34 (2H, sxt), 1.58 (2H, qt), 2.39 (3H, s), 4.12 (2H, t), 7.21 (2H, d), 7.67 (2H, d).

butyl* N-*chloro-4-nitrobenzohydroxamate 99h

δ_H ($CDCl_3$) 0.88 (3H, t), 1.31 (2H, sxt), 1.57 (2H, qt), 4.15 (2H, t), 7.92 (2H, d), 8.30 (2H, d).

butyl* N-*chloro-4-methoxybenzohydroxamate 99b

δ_H ($CDCl_3$) 0.89 (3H, t), 1.31 (2H, sxt), 1.58 (2H, qt), 3.84 (3H, s), 4.12 (2H, t), 6.92 (2H, d), 7.78 (2H, d).

butyl* N-*chloro-4-*tert-*butylbenzohydroxamate 99e

δ_H ($CDCl_3$) 0.87 (3H, t), 1.33 (9H, s), 1.34 (2H, sxt), 1.60 (2H, qt), 4.13 (2H, t), 7.44 (2H, d), 7.72 (2H, d).

butyl* N-*chloro-4-phenylbenzohydroxamate 99c

δ_H ($CDCl_3$) 0.89 (3H, t), 1.34 (2H, sxt), 1.63 (2H, qt), 4.16 (2H, t), 7.40-7.47 (4H, m), 7.61-7.68 (3H, m), 7.87 (2H, d).

benzyl* N-*chlorobenzohydroxamate 149a

Benzyl benzohydroxamate (3.41 g, 15 mmol) and *tert*-butyl hypochlorite (4.87 g, 45 mmol) in DCM was stirred for 5 hours in the dark. Removal of solvent *in vacuo* provided the title compound which was used immediately without further purification. δ_H ($CDCl_3$) 5.09 (2H, s), 7.26 (2H, m), 7.30 (3H, m), 7.40 (2H, t), 7.54 (1H, t), 7.68 (2H, d).

4-bromobenzyl* N-*chlorobenzohydroxamate* *149g

δ_H ($CDCl_3$) 5.03 (2H, s), 7.11 (2H, d), 7.41 (4H, m), 7.52 (1H, t), 7.68 (2H, d).

4-chlorobenzyl* N-*chlorobenzohydroxamate* *149h

The title compound was obtained by the general chlorination procedure in $CHCl_3$. δ_H ($CDCl_3$) 5.04 (2H, s), 7.17 (2H, d), 7.26 (2H, d), 7.40 (2H, t), 7.54 (1H, t), 7.66 (2H, d).

4-nitrobenzyl* N-*chlorobenzohydroxamate* *149i

δ_H ($CDCl_3$) 5.21 (2H, s), 7.44 (4H, m), 7.54 (1H, t), 7.70 (2H, d), 8.18 (2H, d).

4-methylbenzyl* N-*chlorobenzohydroxamate* *149e

δ_H ($CDCl_3$) 2.35 (3H, s), 5.06 (2H, s), 7.15 (4H, s), 7.41 (2H, t), 7.54 (2H, t), 7.72 (2H, d).

4-*tert*-butylbenzyl* N-*chlorobenzohydroxamate* *149f

The title compound was obtained by the general chlorination procedure in 50% DCM/$CHCl_3$. δ_H ($CDCl_3$) 1.30 (3H, s), 5.05 (2H, s), 7.16 (2H, d), 7.32 (2H, d), 7.40 (2H, t), 7.53 (1H, t), 7.66 (2H, d).

4-phenylbenzyl* N-*chlorobenzohydroxamate* *149d

The title compound was obtained by chlorination in 50% CH_3CN/CH_2Cl. δ_H ($CDCl_3$) 2.35 (3H, s), 5.06 (2H, s), 7.15 (4H, s), 7.41 (2H, t), 7.54 (2H, t), 7.72 (2H, d).

4-phenoxybenzyl* N-*chlorobenzohydroxamate* *149b

δ_H ($CDCl_3$) 5.05 (2H, s), 6.92 (2H, d), 7.2-7.6, 7.69 (2H, d).

4-methoxybenzyl* N-*chlorobenzohydroxamate* *149c

δ_H ($CDCl_3$) 3.78 (3H, s), 5.01 (2H, s), 6.82 (2H, s), 7.17 (2H, t), 7.38 (2H, t), 7.53 (1H, d), 7.67 (1H, d).

6.3.7 General synthesis of alkyl *N*-acetoxy benzohydroxamates

6.3.7.1 Method 1

Acetoxylation of the *N*-chlorohydroxamic ester derivatives was achieved in ether by stirring with a 0.5 molar excess of silver acetate at room temperature in the dark. The progress of the reaction was monitored by HPLC. Reaction times varied from 3-36 hours. Where applicable, fair to excellent yields were obtained by this method. It was not successful with benzyl *N*-chlorohydroxamates bearing significantly electron-donating and electron-withdrawing *para* substituents. An alternative, more general method was developed in these cases.

6.3.7.2 Method 2

Para-substituted benzyl *N*-chlorobenzohydroxamates were stirred with 1.4 molar equivalents of anhydrous sodium acetate in dry acetone, at room temperature, for 12-72 hours in the dark. The reaction was monitored by ^{1}H NMR. Filtration and concentration provided the *N*-acetoxy derivatives, frequently with quantitative conversion. Yields were obtained with sufficient purity or isolated by flash chromatography. In all cases, mutagens were characterised spectroscopically.

6.3.8 Butyl *N*-acetoxybenzohydroxamates

butyl N-*acetoxybenzohydroxamate 100a*

The title compound was prepared according method 1 in a yield of 82%. Purification was achieved by flash chromatography (75% DCM:25% Hex.). ν_{max} ($CHCl_3$)/cm^{-1} 1732 (CO), 1795 (CO) δ_H ($CDCl_3$) 0.89 (3H, t), 1.37 (2H, sxt), 1.62 (2H, qt), 2.09 (3H, s), 4.17 (2H, t), 7.41 (2H, t), 7.47 (1H, d, *p*-Ar), 7.75 (2H, t). δ_C ($CDCl_3$) 13.45 (q), 18.42 (q), 18.72 (t), 29.79 (t), 75.06 (t), 128.03 (d), 128.73 (d), 131.57 (s), 132.49 (d), 167.84 (s), 173.91 (s).

butyl N-*acetoxy-4-bromobenzohydroxamate 100g*

The title compound was prepared according to method 1. Butyl *N*-chloro-4-bromobenzohydroxamate (2.1 g, 6.86 mmol) in dry ether was stirred in the dark at room temperature with silver acetate (1.11 g, 10.30 mmol) for 24 hours. Filtration and removal

of solvent *in vacuo* provided the crude mutagen. Flash column chromatography (75% DCM: 25% Hex.) provided the title compound in a yield of 48%. ν_{max} ($CHCl_3$)/cm^{-1} 1791 (CH_3CO), 1731 (Ar-CO); δ_H ($CDCl_3$) 0.90 (3H, t), 1.35 (2H, sxt), 1.63 (2H, qt), 2.12 (3H, s, OAc), 4.17 (2H, t), 7.58 (2H, d, *J* 8.7, *m*-Ar), 7.64 (2H, d); δ_C ($CDCl_3$) 13.58 (q), 18.59 (q), 18.63 (t), 29.86 (t), 75.31 (t), 127.54 (s), 130.43 (d), 131.47 (d), 167.94 (s), 173.12 (s).

butyl* N-*acetoxy-4-chlorobenzohydroxamate* *100f

The title compound was prepared according to method 2. Butyl *N*-chloro-4-chlorobenzohydroxamate (1.15 g, 5.06 mmol) in dry acetone was stirred at room temperature with sodium acetate (0.50 g, 7.08 mmol) for 30 hours in the dark. Filtration and removal of solvent *in vacuo* provided the crude product. Purification by flash chromatography (85% Hex.: 15% EtOAc) provided the title compound (69%) as a viscous oil that solidified upon standing. ν_{max} ($CHCl_3$)/cm^{-1} 1792 (CH_3CO), 1728 (Ar-CO); δ_H ($CDCl_3$) 0.89 (3H, t), 1.35 (2H, sxt), 1.63 (2H, qt), 2.12 (3H, s), 4.17 (2H, t), 7.39 (2H, d), 7.75 (2H, d, *J* 8.6, *o*-Ar); δ_C ($CDCl_3$) 13.47 (q), 18.46 (q), 18.75 (t), 29.78 (t), 75.17 (t), 128.40 (d), 129.80 (s), 130.27 (d, *o*-Ar), 138.84 (s, *p*-Ar), 167.82 (s), 172.85 (s).

butyl* N-*acetoxy-4-methylbenzohydroxamate* *100d

Butyl *N*-chloro-4-methylbenzohydroxamate (1.17 g, 4.28 mmol) in dry acetone (50 ml) was stirred at room temperature with sodium acetate (0.49 g, 6.00 mmol) in the dark for 42 hours. Filtration and removal of solvent *in vacuo* provided the crude product. Purification by flash chromatography (85% Hex.: 15% EtOAc) provided the title compound (76%) as a yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 1790 (CH_3CO), 1730 (Ar-CO); δ_H ($CDCl_3$) 0.90 (3H, t), 1.35 (2H, sxt), 1.63 (2H, qt), 2.10 (3H, s), 2.39 (3H, s), 4.18 (2H, t), 7.21 (2H, d), 7.67 (2H, d, *J* 8.2, *o*-Ar); δ_C ($CDCl_3$) 13.53 (q), 18.61 (q), 18.81 (t), 21.42 (q), 29.67 (t), 53.32 (t), 75.03 (t), 128.57 (s), 128.78 (d), 129.02 (d), 143.45 (s, *p*-Ar), 168.01 (s), 173.93 (s).

butyl* N-*acetoxy-4-nitrobenzohydroxamate* *100h

Butyl *N*-chloro-4-nitrobenzohydroxamate (2.32 g, 7.56 mmol) was stirred with sodium acetate (1.26 g, 7.57 mmol) in dry acetone at room temperature for 40 hours. Filtration

and removal of solvent *in vacuo* provided the crude product. Flash chromatography (75% DCM: 25% Hex.) provided the title compound (89%).ν_{max} ($CHCl_3$)/cm^{-1} 1794 (CH_3CO), 1729 (Ar-CO); δ_H ($CDCl_3$) 0.90 (3H, t), 1.32 (2H, sxt), 1.62 (3H, qt), 2.13 (3H, s), 4.16 (2H, t), 7.91 (2H, d), 8.28 (2H, d); δ_C ($CDCl_3$) 13.57 (q), 18.47 (q), 18.82 (t), 29.62 (t), 75.72 (t), 123.32 (d, *m*-Ar), 129.82 (d), 137.58 (s), 149.83 (s, *p*-Ar), 167.83 (s), 172.15 (s).

butyl N-acetoxy-4-methoxybenzohydroxamate 100b

The title compound was prepared according to method 1 in a yield of 68%. Butyl *N*-chloro-4-methoxybenzohydroxamate (1.61 g, 6.28 mmol) was stirred with silver acetate (1.57 g, 9.42 mmol) in the dark in dry ether at room temperature for 40 hours. Filtration and removal of solvent *in vacuo* provided the crude product. Purification was achieved by flash chromatography (75% DCM: 25% Hex.). ν_{max} ($CHCl_3$)/cm^{-1} 1790 (CH_3CO), 1728 (Ar-CO); δ_H ($CDCl_3$) 0.90 (3H, t), 1.36 (2H, sxt), 1.64 (2H, qt), 2.12 (3H, s), 3.84 (3H, s), 4.18 (2H, t), 6.90 (2H, d), 7.78 (2H, d, *J* 8.9, *o*-Ar); δ_C ($CDCl_3$) 13.47 (q), 18.59 (q), 18.76 (t), 29.82 (t), 55.18 (q), 74.78 (t), 113.39 (d, *m*-Ar), 123.22 (s), 131.28 (d), 163.18 (s, *p*-Ar), 168.02 (s), 173.18 (s).

butyl* N-*acetoxy-4-*tert-*butylbenzohydroxamate 100e

The title compound was prepared according to method 2 in a yield of 58%. Butyl *N*-chloro-4-tert-benzohydroxamate (0.87 g, 3.05 mmol) was stirred with sodium acetate (0.35 g, 4.21 mmol) in the dark in dry acetone at room temperature for 25 hours. Filtration and removal of solvent *in vacuo* provided the crude product (58%). Purification was achieved by flash chromatography (15% EtOAc: 85% Hex.). ν_{max} ($CHCl_3$)/cm^{-1} 1787 (CH_3CO), 1721 (CO); δ_H ($CDCl_3$) 0.90 (3H, t), 1.32 (9H, s), 1.33 (2H, sxt), 1.64 (2H, qt), 2.12 (3H, s), 4.19 (2H, t), 7.43 (2H, d), 7.73 (2H, d, *J* 8.9, *o*-Ar); δ_C ($CDCl_3$) 13.57 (q), 18.72 (q), 18.85 (t), 29.93 (t), 30.92 (q), 34.96 (s), 75.11 (t), 116.03 (s), 125.12 (d), 128.54 (s), 128.97 (d), 156.45 (s, *p*-Ar), 168.08 (s), 173.70 (s).

butyl* N-*acetoxy-4-phenylbenzohydroxamate 100c

The title compound was prepared according to method 2 in a yield of 82%. Butyl *N*-chloro-4-phenylbenzohydroxamate (1.16 g, 3.83 mmol) was stirred with sodium acetate (0.44 g, 5.36 mmol) in the dark in dry acetone at room temperature for 35 hours.

Filtration and removal of solvent *in vacuo* provided the crude product (82%). Purification was achieved by flash chromatography (5% EtOAc: 95% Hex.). ν_{max} ($CHCl_3$)/cm^{-1} 1794 (CH_3CO), 1721 (CO); δ_H ($CDCl_3$) 0.91 (3H, t), 1.33 (2H, sxt), 1.64 (2H, qt), 2.14 (3H, s), 4.21 (2H, t), 7.39-7.47 (3H, m), 7.66 (4H, t), 7.86 (2H, d, *J* 8.9, *o*-Ar); δ_C ($CDCl_3$) 13.71 (q), 18.83 (q), 18.97 (t), 30.03 (t), 30.89 (q), 75.36 (t), 126.66 (d), 127.21 (d), 128.25 (d), 128.94 (d), 129.67 (d), 130.24 (s), 139.71 (s), 145.53 (s), 166.24 (s), 173 (s).

6.3.9 Benzyl *N*-acetoxybenzohydroxamates

benzyl N-*acetoxybenzohydroxamate 151a*

The title compound was prepared according to method 2. Purification by flash chromatography (90% Hex.: 10% EtOAc) provided (87%) as a viscous oil. ν_{max} ($CHCl_3$)/cm^{-1} 1798 (CH_3CO), 1728 (CO); δ_H ($CDCl_3$) 2.11 (3H, s), 5.19 (2H, s), 7.28-7.48 (7H, m), 7.54 (1H, t), 7.75 (2H, d); δ_C ($CDCl_3$) 18.62 (q), 77.5 (t), 128.34 (d), 128.52 (d), 128.75 (d), 129.08(d), 129.22 (d), 131.65 (s), 132.84 (d), 134.75 (s), 168.08 (s), 174.12 (s).

4-*bromobenzyl* N-*acetoxybenzohydroxamate 151g*

The title compound was prepared according to method 2. 4-bromobenzyl *N*-chloro-benzohydroxamate (1.87 g, 5.49 mmol) was stirred with sodium acetate (0.63 g, 7.68 mmol) in the dark in dry acetone at room temperature for 22 hours. Filtration and removal of solvent *in vacuo* provided the crude product. Purification by flash chromatography (90% Hex.: 10% EtOAc) provided the title compound (94%) as a yellow oil. (Yield *via* Method 1, 25%). ν_{max} ($CHCl_3$)/cm^{-1} 1791 (CH_3CO), 1731 (CO); δ_H ($CDCl_3$) 2.05 (3H, s), 5.12 (2H, s), 7.23 (2H, d, *J* 8.3, *m'*-Ar), 7.40 (2H, t, *J* 7.1, *m*-Ar), 7.45 (2H, d, *J* 8.3, *o'*-Ar), 7.55 (1H, t, *J* 7.1, *p*-Ar), 7.69 (2H, d, *J* 7.1, *o*-Ar); δ_C ($CDCl_3$) 18.56 (q), 76.54 (t), 122.66 (st, *p'* -Ar), 128.21 (dd, *o*-Ar), 128.82 (dt, *m*-Ar), 130.64 (dq, *o'*-Ar), 131.40 (st, *i* -Ar), 131.49 (dd, *m'*-Ar), 132.74 (d, *p*-Ar), 133.73 (s, *i'* -Ar), 168.02 (sq, Ac), 174.04 (s).

4-chlorobenzyl N-*acetoxybenzohydroxamate 151h*

The title compound was prepared according to method 2. 4-chlorobenzyl *N*-chloro-benzohydroxamate (2.89 g, 9.75 mmol) was stirred with sodium acetate (1.12 g, 13.65 mmol) in the dark in dry acetone at room temperature for 28 hours. Filtration and removal of solvent *in vacuo* provided the crude product. Purification by flash chromatography (90% Hex.: 10% EtOAc) provided the title compound as a pale yellow oil (96%) which solidified upon standing. (Yield *via* Method 1, 45%). ν_{max} ($CHCl_3$)/cm^{-1} 1793 (CH_3CO), 1731 (CO); δ_H ($CDCl_3$) 2.04 (3H, s), 5.14 (2H, s), 7.30 (4H, s), 7.39 (2H, t, *J* 7.6, *m*-Ar), 7.53 (1H, t, *J* 7.6, *p*-Ar), 7.69 (2H, d, *J* 7.6, *o*-Ar); δ_C ($CDCl_3$) 18.58 (q), 76.54 (t), 128.22 (dd), 128.54 (dd), 128.85 (dt), 130.41 (d), 132.76 (dt), 133.25 (s), 134.48 (s), 168.02 (s), 174.08 (s).

4-nitrobenzyl N-acetoxybenzohydroxamate 151i

The title compound was prepared according to method 2. 4-nitrobenzyl *N*-chloro-benzohydroxamate (2.30 g, 7.57 mmol) was stirred with sodium acetate (0.87 g, 10.61 mmol) in the dark in dry acetone at room temperature for 19 hours. Filtration and removal of solvent *in vacuo* provided the crude product. Purification by flash chromatography (90% Hex.: 10% EtOAc) provided the crude product (93%) as a yellow oil. (Yield *via* Method 1, 0%). ν_{max} ($CHCl_3$)/cm^{-1} 1793 (CH_3CO), 1740 (CO); δ_H ($CDCl_3$) 2.04 (3H, s, OAc), 5.29 (2H, s), 7.40 (2H, t, *J* 8, *m*-Ar), 7.55 (3H, m), 7.69 (2H, d, *J* 6.8, *m'*-Ar), 8.18 (2H, d); δ_C ($CDCl_3$) 18.66 (q), 75.98 (t), 123.60 (dd), 128.42 (d), 128.87 (d), 129.24 (d), 131.29 (st, *i*-Ar), 133.04 (dt, *p*-Ar), 142.29 (s, *i'*-Ar), 147.90 (s, *p'*-Ar), 168.18 (s), 174.20 (s).

4-nitro-α,α-dideuteriobenzyl N-acetoxybenzohydroxamate 151m

Anhydrous sodium acetate (0.12 g, 1.4 mmol) was added in one portion to a stirred solution of 4-nitro-α,α-dideuteriobenzyl *N*-chlorobenzohydroxamate (0.306 g, 1 mmol) in dry acetone (20 ml). After stirring at room temperature for 24 hours, the mixture was filtered. Removal of solvent *in vacuo* and flash chromatography (90% Hex.: 10% EtOAc) provided the title compound as a yellow solid in 87% yield. ν_{max} ($CHCl_3$)/cm^{-1} 1793 (CH_3CO), 1732 (CO); δ_H ($CDCl_3$) 2.04 (3H, s), 7.40 (2H, t), 7.54 (1H, t), 7.57 (2H, d),

7.69 (2H, d), 8.16 (2H, d); δ_C ($CDCl_3$) 18.41 (q), **75.40** (qt), 123.35 (dd), 128.22 (d), 128.65 (d), 129.15 (d), 131.08 (st), 132.85 (dt), 142.04 (s), 147.66 (s), 168.01 (s), 173.98 (s).

4-methylbenzyl N-acetoxybenzohydroxamate 151e

The title compound was prepared according to method 2. 4-methylbenzyl *N*-chloro-benzohydroxamate (1.82 g, 6.61 mmol) was stirred with sodium acetate (0.76 g, 9.25 mmol) in the dark in dry acetone (35 ml) at room temperature for 19 hours. Filtration and removal of solvent *in vacuo* provided the crude product. Purification by flash chromatography (90% Hex.: 10% EtOAc) provided the pure compound (60%) as a yellow oil. (Yield *via* Method 1, <5%). ν_{max} ($CHCl_3$)/cm^{-1} 1791 (CH_3CO), 1729 (CO); δ_H ($CDCl_3$) 2.05 (3H, s, OAc), 2.33 (3H, s), 5.13 (2H, s), 7.13 (2H, d, *J* 7.8, *m'*-Ar), 7.25 (2H, d), 7.40 (2H, t), 7.51 (1H, t), 7.74 (2H, d, *J* 8, *o*-Ar); δ_C ($CDCl_3$) 18.70 (q), 21.20 (q), 77.42 (t), 128.21 (dd), 129.05 (d), 129.12 (d), 129.25 (d), 131.59 (s), 131.65 (s), 132.68 (dt, *p*-Ar), 138.56 (s, *p* '-Ar), 168.10 (s), 174.14 (s).

4-methyl-α,α-dideuteriobenzyl N-*acetoxybenzohydroxamate 151k*

Anhydrous sodium acetate (0.17 g, 2.1 mmol) was added to 4-methyl-α,α-benzyl *N* -chlorobenzohydroxamate (0.41 g, 1.49 mmol) in dry acetone. Stirring at room temperature for 36 hours followed by filtration and removal of solvent *in vacuo* provided the crude mixture. Purification by flash chromatography (90% Hex.: 10% EtOAc) provided the pure compound (48%) as a pale yellow oil. δ_H ($CDCl_3$) 2.04 (3H, s), 2.34 (3H, s), 7.13 (2H, d), 7.3 (2H, d), 7.41 (2H, t), 7.52 (1H, t), 7.76 (2H, d); δ_C ($CDCl_3$) 18.68 (q), 21.21 (q), 128.23 (d), 129.05 (d), 129.12 (d), 129.25 (d), 131.57 (s), 131.65 (s), 132.68 (d), 138.50 (s), 168.14 (s), 174.09 (s).

4-tert-*butylbenzyl* N-*acetoxybenzohydroxamate 151f*

The title compound was prepared according to method 2. Anhydrous sodium acetate (0.30 g, 3.7 mmol) was added to 4-*tert*-butylbenzyl *N*-chlorobenzohydroxamate (0.84 g, 2.64 mmol) in dry acetone. Stirring in the dark at room temperature for 48 hours followed by filtration and removal of solvents *in vacuo* provided the crude mixture. Purification by flash chromatography (90% Hex.: 10% EtOAc) provided 4-*tert*-butylbenzyl *N*-acetoxybenzohydroxamate (26%) as a yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 1790 (CH_3CO),

1725 (CO); δ_H ($CDCl_3$) 1.29 (9H, s), 2.02 (3H, s), 5.14 (2H, t), 7.26-7.40 (6H, m), 7.49 (1H, t, *J* 7, *p*-Ar), 7.73 (2H, d, *J* 7, *o*-Ar); δ_C ($CDCl_3$) 18.49 (q), 31.11 (q), 34.44 (s), 77.17 (t), 125.25 (dd, *m'*-Ar), 128.09 (dd), 128.92 (d), 128.96 (d), 131.46 (s), 131.53 (s), 132.57 (dt, *p*-Ar), 151.62 (s, *p'* -Ar), 167.89 (s), 173.94 (s).

4-phenylbenzyl* N-*acetoxybenzohydroxamate 151d

The title compound was prepared according to method 2 as a yellow oil. Anhydrous sodium acetate (0.12 g, 0.94 mmol) was added to 4-phenylbenzyl *N*-chlorobenzohydroxamate (0.28 g, 0.82 mmol) in dry acetone. Stirring in the dark at room temperature for 42 hours followed by filtration and removal of solvents *in vacuo* provided the crude mixture. Purification by flash chromatography (90% Hex.: 10% EtOAc) provided (48%) as a viscous yellow oil. ν_{max} ($CHCl_3$)/cm^{-1} 1791(CH_3CO), 1729(CO); δ_H ($CDCl_3$) 2.03 (3H, s), 5.20 (2H, s), 7.4 (7H, m), 7.51 (5H, m), 7.76 (2H, d); δ_C ($CDCl_3$) 18.55 (q), 77.11 (t), 126.93 (dd), 127.04 (dd), 127.37 (dt), 128.16 (d), 128.67 (d), 128.91 (d), 129.54 (d), 131.49 (s), 132.66 (dq), 133.53 (s), 140.39 (s), 141.43 (s), 168.10 (s), 174.14 (s).

4-phenyl-α,α-dideuteriobenzyl* N-*acetoxybenzohydroxamate 151l

The title compound was prepared according to method 2 in acetonitrile (50 ml) and DCM (50 ml). Anhydrous sodium acetate (0.21 g, 2.59 mmol) was added to 4-phenyl-α,α-dideuteriobenzyl *N*-chlorobenzohydroxamate (0.63 g, 1.85 mmol) in dry acetone. Stirring in the dark at room temperature for 24 hours followed by filtration and removal of solvents *in vacuo* provided the crude mixture. Purification by flash chromatography (92% Hex.: 8% EtOAc) provided the title compound (60%) as a viscous oil. δ_H ($CDCl_3$) 2.10 (3H, s), 7.39-7.6 (10H, m), 7.62 (2H, d), 7.81 (2H, d); δ_C ($CDCl_3$) 18.43 (q), 126.84 (dd), 126.94 (dd), 127.29 (dt), 128.08 (d), 128.60 (d), 128.82 (d), 129.51 (d), 131.43 (s), 132.57 (dt), 133.37 (s), 140.28 (s), 141.34 (s), 167.91 (s), 173.96 (s).

4-phenoxybenzyl* N-*acetoxybenzohydroxamate 151b

The title compound was prepared according to method 2. 4-phenoxybenzyl *N*-chloro-benzohydroxamate (1.22 g, 3.45 mmol) was stirred with sodium acetate (0.40 g, 4.81 mmol) in the dark in dry acetone at room temperature for 19 hours. Filtration and removal of solvent *in vacuo* provided the crude product. Purification by flash

chromatography (85% Hex.: 15% EtOAc) provided (78%) as a very viscous oil. ν_{max} ($CHCl_3$)/cm^{-1} 1795 (CH_3CO), 1725 (CO); δ_H ($CDCl_3$) 2.09 (3H, s), 5.14 (2H, s), 6.9 (4H, m), 7.1 (1H, t, *J* 7, *p''*-Ar), 7.2-7.4 (6H, m), 7.53 (1H, t, *J* 7, *p*-Ar), 7.71 (2H, d, *J* 7, *o*-Ar); δ_C ($CDCl_3$) 18.75 (q), 54.94 (q), 76.95 (t), 118.61 (d, *o''* -Ar), 120.27 (dd, *m'*-Ar), 128.28 (dd), 129.00 (d), 129.76 (dd), 131.09 (dq), 132.80 (d), 155.46 (st), 157.40 (s), 168.15 (s, Ac), 174.17 (s).

4-methoxybenzyl N-*acetoxybenzohydroxamate 151c*

The title compound was prepared according to method 2. 4-methoxybenzyl *N*-chloro-benzohydroxamate (1.90 g, 6.50 mmol) was stirred with sodium acetate (0.67 g, 9.1 mmol) in the dark in dry acetone at room temperature for 18 hours. Filtration and removal of solvent *in vacuo* provided the crude product. Purification by flash chromatography (85% Hex.: 15% EtOAc) provided the title compound (57%). ν_{max} ($CHCl_3$)/cm^{-1} 1795 (CH_3CO), 1725 (CO); δ_H ($CDCl_3$) 2.03 (3H, s), 3.73 (3H, s), 5.09 (2H, s), 6.82 (2H, d, *J* 7, *m'*-Ar), 7.26 (2H, d, *J* 7, *o'*-Ar), 7.36 (2H, t, *J* 7, *m*-Ar), 7.48 (1H, t), 7.69 (2H, d); δ_C ($CDCl_3$) 18.45 (q), 55.94 (q), 76.95 (t), 113.60 (d, *m'*-Ar), 126.47 (s, *i'* -Ar), 128.01 (dd, *o*-Ar), 128.78 (dt, *m*-Ar), 130.77 (dq, *o'*-Ar), 131.44 (st, *p*-Ar), 132.49 (dt), 159.77 (s, *p'* -Ar), 168.15 (s), 174.17 (s).

4-methoxy-α,α-dideuteriobenzyl N-*acetoxybenzohydroxamate 151j*

The title compound was prepared according to method 2. 4-methoxy-α-α-dideuteriobenzyl *N*-chloro-benzohydroxamate (0.38 g, 1.29 mmol) was stirred with sodium acetate (0.15 g, 1.82 mmol) in the dark in dry acetone at room temperature for 14 hours. Filtration and removal of solvent *in vacuo* provided the crude product. Purification by flash chromatography (85% Hex.: 15% EtOAc) provided the title compound (44%) as a pale yellow oil. δ_H ($CDCl_3$) 2.06 (3H, s), 3.77 (3H, s), 6.83 (2H, d), 7.27 (2H, d), 7.38 (2H, t), 7.51 (1H, t), 7.69 (2H, d); δ_C ($CDCl_3$) 18.64 (q), 55.13 (q), 77.2 (qt), 113.75 (d), 126.50 (s), 128.15 (dd), 128.94 (dt), 130.91 (dq), 131.58 (st), 132.62 (dt), 159.92 (s), 168.06 (s), 174.07 (s).

6.3.10 Benzyl *N*-benzoyloxybenzohydroxamates

Sodium *para*-substituted benzoate compounds were prepared by treatment of the appropriate acid with aq. Na_2CO_3. Filtration from the solid and drying provided the sodium salt which was used without further purification.

benzyl N-*benzoyloxybenzohydroxamate 172a*

Sodium benzoate (0.91 g, 6.3 mmol) was stirred at room temperature with benzyl *N*-chlorobenzohydroxamate (1.18 g, 4.5 mmol) in acetone for 48 hours. Purification by flash chromatography (88% Hex.: 12% EtOAc) provided the title compound (60%). ν_{max} ($CDCl_3$)/cm^{-1} 1758, 1731 (CO); δ_H ($CDCl_3$) 5.26 (2H, s), 7.26-7.40 (9H, m), 7.46 (1H,t, *J* 8, *p*-Ar), 7.54 (1H, t, *p''*-Ar), 7.77 (2H, d, *J* 8, *o*-Ar), 7.91 (2H, d, *J* 8, *o''*-Ar); δ_C ($CDCl_3$) 77.44 (t), 127.07 (s), 128.18 (d), 128.35 (d), 128.49 (d), 128.54 (d), 128.97 (d), 129.11 (d), 129.85 (dt), 131.51 (s), 132.67 (dt), 133.92 (dt), 134.64 (s), 164.13 (s), 174.28 (s).

benzyl N-*(4-chlorobenzoyloxy)benzohydroxamate 172d*

The title compound was prepared according to method 2. Purification by flash chromatography (88% Hex.: 12% EtOAc) provided the title compound (83%). ν_{max} ($CDCl_3$)/cm^{-1} 1759, 1734 (CO); δ_H ($CDCl_3$) 5.26 (2H, s), 7.26 - 7.40 (9H, m), 7.47 (1H,t, *J* 8), 7.77 (2H, d, *J* 8), 7.82 (2H, d, *J* 8); δ_C ($CDCl_3$) 77.62 (t), 125.51 (st), 128.16 (d), 128.32 (d), 128.54 (d), 128.80 (d), 128.94 (d), 129.08 (d), 131.15 (dd), 131.32 (s), 132.73 (dt), 134.52 (s), 140.32 (s), 163.25 (s), 174.2 (s).

benzyl N-*(4-formylbenzoyloxy)benzohydroxamate 172e*

The title compound was prepared according to method 2. Purification by flash chromatography (85% Hex.: 15% EtOAc) provided the title compound (50%). ν_{max} ($CDCl_3$)/cm^{-1} 1761 (ester CO), 1735 (amide CO), 1707 (CHO); δ_H ($CDCl_3$) 5.27 (2H, s), 7.26 (3H, m), 7.39 (4H, m), 7.49 (1H,t), 7.78 (2H, d, *J* 8), 7.89 (2H, d, *J* 8), 8.06 (2H, d, *J* 8), 10.06 (H, s); δ_C ($CDCl_3$) 21.61 (q), 77.87 (t), 128.31 (d), 128.45 (d), 128.70 (d), 129.09 (d), 129.19 (d), 129.45 (d), 130.45 (dd), 131.26 (st), 132.10 (st), 132.97 (dt), 134.48 (s), 139.63 (s), 163.21 (s), 174.07 (s), 191.28 (d).

benzyl* N-*(4-trifluoromethylbenzoyloxy)benzohydroxamate 172f

The title compound was prepared according to method 2. Purification by flash chromatography (85% Hex.: 15% EtOAc) provided the title compound (78%). ν_{max} ($CDCl_3$)/cm^{-1} 1765, 1734 (CO); δ_H ($CDCl_3$) 5.27 (2H, s), 7.26 (3H, m), 7.39 (4H, m), 7.52 (1H, t), 7.66 (2H, d, *J* 8), 7.78 (2H, d, *J* 8), 8.02 (2H, d, *J* 8); δ_C ($CDCl_3$) 77.91 (t), 125.52 (dq), 128.35 (d), 128.49 (d), 128.74 (d), 129.12 (d), 129.23 (d), 129.63 (d), 130.33 (dd), 130.59 (s), 131.32 (s), 133.0 (dt), 134.54 (s), 135.03 (s), 163.07 (s), 174.12 (s).

benzyl* N-*(4-methylbenzoyloxy)benzohydroxamate 172c

The title compound was prepared according to method 2. Purification by flash chromatography (88% Hex.: 12% EtOAc) provided the title compound (47%). ν_{max} ($CDCl_3$)/cm^{-1} 1756, 1733 (CO); δ_H ($CDCl_3$) 2.38 (3H, s), 5.26 (2H, s), 7.19 (2H, d), 7.2-7.4 (7H, m), 7.47 (1H, t, *J* 8), 7.77 (2H, d, *J* 8), 7.81 (2H, d, *J* 8); δ_C ($CDCl_3$) 21.61 (q), 77.58 (t), 124.27 (st), 128.15 (d), 128.34 (d), 128.50 (d), 128.99 (d), 129.11 (d), 129.23 (d), 129.94 (d), 131.64 (dt), 132.59 (s), 134.75 (s), 144.94 (s), 164.21 (s), 174.36 (s).

benzyl* N-*(4-methoxybenzoyloxy)benzohydroxamate 172b

The title compound was prepared according to method 2. Purification by flash chromatography (84% Hex.: 16% EtOAc) provided the title compound (39%). ν_{max} ($CDCl_3$)/cm^{-1} 1750 (ester CO), 1718 (amide CO); δ_H ($CDCl_3$) 3.73 (3H, s), 5.26 (2H, s), 6.81 (2H, d), 7.25 - 7.47 (8H, m), 7.75 (2H, d, *J* 8), 7.86 (2H, d, *J* 8); δ_C ($CDCl_3$) 55.18 (q), 77.31 (t), 113.73 (d), 118.92 (s), 128.01 (d), 128.20 (d), 128.36 (d), 128.80 (d), 128.98 (d), 131.55 (s), 131.94 (d), 132.43 (d), 134.69 (s), 163.70 (s), 164.04 (s), 174.25 (s).

benzyl* N-*(4-cyanobenzoyloxy)benzohydroxamate 172g

The title compound was prepared according to method 2. Purification by flash chromatography (86% Hex.: 14% EtOAc) provided the title compound (34%). ν_{max} ($CDCl_3$)/cm^{-1} 2235, 2236 (CN), 1763 (ester CO), 1732 (amide CO); δ_H ($CDCl_3$) 5.26 (2H, s), 7.25 - 7.44 (7H, m), 7.55 (1H,t, *J* 8), 7.73 (2H, d, *J* 8), 7.78 (2H, d, *J* 8), 8.00 (2H, d, *J* 8); δ_C ($CDCl_3$) 78.05 (t), 117.29 (st), 117.62 (s), 128.42 (d), 128.54 (d),

128.92 (d), 129.18 (d), 129.26 (d), 129.56 (d), 130.39 (d), 131.21 (s), 132.30 (d), 133.15 (d), 134.46 (s), 162.70 (s), 174.04 (s).

benzyl* N-*(4-nitrobenzoyloxy)benzohydroxamate 172h

The title compound was prepared according to method 2. Purification by flash chromatography (88% Hex.: 12% EtOAc) provided the title compound (55%). ν_{max} ($CDCl_3$)/cm^{-1} 1764, 1733 (CO); δ_H ($CDCl_3$) 5.27 (2H, s), 7.27 - 7.43 (6H, m), 7.54 (1H,t, *J* 8), 7.79 (2H, d, *J* 8), 8.05 (2H, d, *J* 8), 8.21 (2H, d); δ_C ($CDCl_3$) 78.02 (t), 123.55 (d), 128.32 (d), 128.43 (d), 128.71 (d), 129.08 (d), 129.18 (d), 130.98 (d), 131.07 (dd), 132.67 (s), 133.12 (dt), 134.39 (s), 150.84 (s), 162.37 (s), 173.93 (s).

6.4 Miscellaneous syntheses

Oxidation of benzohydroxamic acid in the presence of cyclopentadiene

Benzohydroxamic acid was generated by acidification and crystallisation of potassium benzohydroxamate (20 g) in glacial acetic acid.[253] Recrystallisation from EtOAc provided the pure compound, m.p. 126-128°C. Cyclopentadiene was prepared by distillation according to a standard literature procedure.[175]

3-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene 123

N-Bromosuccinimide (1.78 g, 10 mmol) was added over 10 minutes to a stirred solution of Benzohydroxamic acid (1.37 g, 10 mmol), pyridine (0.79 g, 10 mmol) and cyclopentadiene (3.5 ml) in DCM (50 ml). After the solution cleared, the organic layer was washed with water, sat. Na_2CO_3, water, dried ($CaCl_2$) and then reduced *in vacuo*. Flash chromatography ($CHCl_3$) and normal-phase preparatory chromatography ($CHCl_3$), provided pure 3-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene (1.55 g, 77%) as a gummy oil. The structure was characterised by ^1H, ^{13}C, gated decoupled, ^1J and cosy experiments at 323K. δ_H (DMSO-d_6) 1.8 (1H, d), 2.05 (1H, dd), 5.32 (1H, s), 5.42 (1H, s), 6.42 (1H, d) 6.5 (1H, s) 7.39 (2H, t), 7.54 (1H, t), 7.72 (2H, d); δ_C (DMSO-d_6) 47.75 (t), 63.99 (s), 83.91 (s), 127.83 (d, *m*), 128.09 (d, *o*), 131.03 (d, *p*), 132.94 (d), 134.15 (s), 135.01 (s), 171.02 (s). $\frac{m}{z}$ **201** (M^+, 4.2%), 122(58), 105(100), 77(90), 51(41).

Bicycloadduct adduct 123 from the acid-catalysed decomposition of butyl* N-*acetoxybenzohydroxamate 100a in H_2O-CH_3CN.

Butyl *N*-acetoxybenzohydroxamate (125 mg, 0.49 mmol) was stirred for 6 hours at 308K in an acidified solution (H_2SO_4; 170 μL; 0.5 mol/L) of freshly prepared cyclopentadiene (198 mg, 3 mmol) in acetonitrile (4.0 ml) and water (1.0 ml). The solvent was removed under reduced pressure and washed with Na_2CO_3 (10%) and water and extracted with DCM. 3-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene was separated by normal-phase preparative HPLC (1.4 mg, 1.4%). $\frac{m}{z}$ **203** (M^++2, *ca.* 0.0%), 201(M^+, 4.5), 105(100), 77(45), 51(20).

Bicycloadduct adduct 123 from the acid-catalysed decomposition of butyl* N-*acetoxybenzohydroxamate 100a in $H_2{}^{18}O$-CH_3CN.

Butyl *N*-acetoxybenzohydroxamate (324.2 mg, 1.084 mmol) was stirred for 4 hours at 308K in an acidified solution (H_2SO_4; 70 μL; 0.4 mol/L) of freshly prepared cyclopentadiene (0.143 g, 2.17 mmol) in acetonitrile (3.5 ml) and water (0.92 ml; 10% ^{18}O labelled). The solvent was removed under reduced pressure and washed with Na_2CO_3 (10%), water and extracted with DCM. The components were separated by normal-phase preparative HPLC to give 3-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene, incorporating ^{18}O at the 2-position. $\frac{m}{z}$ **203** (M^+, 0.4%), 201 (2.7), 105(100), 77(75), 51(25).

Bicycloadduct adduct 123 from the acid-catalysed decomposition of 4-methoxybenzyl* N-*acetoxybenzohydroxamate 151c

4-Methoxybenzyl *N*-acetoxybenzohydroxamate **151c** (210 mg, 0.817 mmol) was stirred for 6 hours at 308K in an acidified solution (H_2SO_4; 50 μL; 0.25 mol/L) of freshly prepared cyclopentadiene (0.054 g, 0.628 mmol) in acetonitrile (4 ml) and water (10% ^{18}O labelled, 1 ml). Removal of solvent *in vacuo*, washing with Na_2CO_3 (10%), water and extraction with DCM, provided the crude reaction mixture that was separated by normal-phase preparative HPLC to give 3-benzoyl-2,3-oxazabicyclo[2.2.1]hept-5-ene. $\frac{m}{z}$ **203** (M^++2, *ca.* 0.0%), 201(M^+, 5.2), 105(100), 77(30), 51(8); A second fraction was ^{18}O enriched 4-methoxybenzyl alcohol. $\frac{m}{z}$ **140** (M^++2, 10.3%), 138 (M^+, 100%), 137(71.8), 121(58), 109(64), 77(35), 51(10).

^{18}O-labelled 4-methoxybenzyl alcohol via an alternative method.

4-methoxybenzyl bromide (0.5 g, 3.6 mmol) was stirred in approximately 25% aqueous acetonitrile (10% ^{18}O water) for 64 hours. The solution was reduced *in vacuo* and re-diluted with DCM. Washing with 5% w/v sodium carbonate, water and removal of solvent *in vacuo* provided pure 4-methoxybenzyl alcohol. The ^{1}H and ^{13}C spectra were identical to authentic 4-methoxybenzyl alcohol. $\frac{m}{z}$ **140** (M^{+}+2, 10.3%), 138 (M^{+}, 85%), 137(84.3), 121(100), 109(58), 77(44), 51(15).

4-methoxybenzyl alcohol without ^{18}O.

Reduction of 4-methoxybenzaldehyde with sodium borohydride in ethanol/water provided the title compound as a clear oil. $\frac{m}{z}$ **140** (M^{+}+2, 0.7%), 138 (M^{+}, 100%), 137(74.5), 121(93), 109(63), 77(40), 51(15).

6.5 Acid-catalysed solvolysis procedure

The acid-catalysed solvolysis of the alkyl *N*-acyloxybenzohydroxamates were monitored in the variable temperature probe of the Bruker AC-300P NMR spectrometer (298-338K). 10-40 mg of substrate in CD_3CN (400 µL) was diluted with D_2O such that after addition of an appropriate volume (2-15 µL) of a solution of sulfuric acid in D_2O (typically 0.5-1.5 mol/L), the ratio of CD_3CN:D_2O was constant at 3.81:1. The acid solution was agitated into the mixture to initiate reaction immediately prior to insertion in the probe.

^{1}H NMR spectra were acquired automatically at pre-programmed intervals and the peak areas for the acetoxy methyl singlet were obtained by integration. Automatically acquired spectra files could not be automatically processed due to software limitations in normalising integration signals between spectra, subsequently all spectra were manually integrated to ensure normalisation of the integrals with reference to the first spectrum.

Arrhenius studies were carried out at appropriate acid concentrations to enable data collection at each temperature. A minimum of five temperatures between 298K and 338K were used for each substrate.

6.6 Base hydrolysis procedure

An aliquot of sodium hydroxide solution (200 µL; 0.9M) was added to a 25% aq. acetonitrile solution (50 ml) of alkyl *N*-acyloxybenzohydroxamate (typically 0.00400

mmol), stirred at 275.4K. The progress of the reaction was monitored by reverse-phase analytical HPLC analysis, with the major product being the alkyl benzoate ester. Where appropriate, naphthalene was used as the internal reference.

6.7 Ester crossover experiments

Acid-catalysed solvolysis of 100f and 151a

A solution of butyl *N*-acetoxy-4-chlorobenzohydroxamate **100f** (0.01282 mmol) and benzyl *N*-acetoxybenzohydroxamate **151a** (0.01172 mmol) in 25% aq. acetonitrile (50.00 ml) was equilibrated for 1 hour at 298K. Dilute aq. H_2SO_4 (1.31 ml; 2.55 mol/L) was added and the reaction was stirred for 15 hours. Analytical HPLC analysis of the complex reaction mixture revealed the presence of benzyl benzoate (54%), butyl 4-chlorobenzoate (33%) and the complete lack of the crossover esters, benzyl 4-chlorobenzoate and butyl benzoate.

Base hydrolysis of 100f and 151a

A solution of butyl *N*-acetoxy-4-chlorobenzohydroxamate (0.013 mmol) and benzyl *N*-acetoxybenzohydroxamate (0.01174 mmol) in 25% aq. acetonitrile (50.00 ml) was equilibrated for 1 hour at 298K. Dilute aq. NaOH (170 µL; 0.90 M) was added and the reaction was complete within 60 seconds. Analytical HPLC analysis of the reaction mixture revealed the presence of benzyl benzoate (43.3%), butyl 4-chlorobenzoate (46.3%) and the complete lack of the crossover esters, benzyl 4-chlorobenzoate and butyl benzoate.

6.7.1 Synthesis and decomposition studies of *N*-4-chlorobenzoyl-*N*-butoxy-*N'*-benzoyl-*N'*-benzyloxyhydrazine

Lead tetraacetate (LTA)

The compound was synthesised by a standard procedure from red lead and acetic acid.[175] Lead oxide red (60 g) was added in 10 g portions, over 1 hour, to a vigorously stirred solution of glacial acetic acid (100 ml) and acetic anhydride (40 ml) at 55-60° C. The solution was cooled and filtered. Recrystallisation of the crude crystals from a solution of glacial acetic acid (95%), acetic anhydride (5%) and charcoal provided pure LTA as colourless crystals which were stored in the dark under acetic acid.

N-*4-chlorobenzoyl*-N-*butoxy*-N'-*benzoyl*-N'-*benzyloxyhydrazine* **143**

The title compound was generated *via* a standard method.[207]

LTA (5.3 g, 12.0 mmol) in DCM (20 ml) was added in portions over 1 hour to a DCM solution of butyl 4-chlorobenzohydroxamate (1.7 g, 7.49 mmol) and benzyl benzohydroxamate (1.7 g, 7.49 mmol). Each aliquot added only after the preceding portion of lead acetate had been completely consumed. The solution was stirred at room temperature for a further 1.5 hours. Removal of solvent *in vacuo* (less then 30 ^{o}C) and TLC analysis revealed 3 major components. Separation by flash chromatography (8% EtOAc:92 Hex) provided the three possible dimers, *N,N'*-butoxy-*N,N'*-4-chlorobenzoyl hydrazine, *N,N'*-benzyl-*N,N'*-benzoyl hydrazine, and *N*-4-chlorobenzoyl-*N*-butoxy-*N'*-benzoyl-*N'*-benzyloxyhydrazine **143** (as the most polar component). All were unstable compounds but were satisfactorily characterised by ^{1}H, ^{13}C and gated-decoupled NMR spectra.

N-4-chlorobenzoyl-*N*-butoxy-*N'*-benzoyl-*N'*-benzyloxyhydrazine: δ_H ($CDCl_3$) 0.83 (3H, t), 1.24 (2H, p), 1.51 (2H, p), 4.03 (1H, t), 4.11 (1H, t), 5.05 (1H, d), 5.11 (1H, d), 7.20 (2H, m), 7.25 (3H, m), 7.36 (4H, m) 7.46 (1H, t) 7.6 (4H, dd); δ_C ($CDCl_3$) 13.62 (q), 18.89 (t), 29.99 (t), 76.01 (t), 78.38 (t), 128.04 (d), 128.31 (d), 128.34 (d), 128.43 (d), 128.66 (d), 129.41 (d), 129.99 (d), 130.63 (s), 131.88 (d), 132.23 (s), 134.30 (s), 138.17 (s), 168.74 (s), 169.68 (s).

N,N'-butoxy-*N,N'*-4-chlorobenzoyl hydrazine: δ_H ($CDCl_3$) 0.85 (6H, t), 1.28 (4H, p), 1.51 (4H, p), 4.04 (2H, t) 4.11 (2H, t), 7.34 (4H, d), 7.60 (4H, d). δ_C ($CDCl_3$) 13.64 (q), 18.93 (t), 30.02 (t), 76.05 (t), 128.40 (d), 129.96 (d), 130.62 (s), 138.25 (s), 168.67 (s).

Thermal decomposition of N-*4-chlorobenzoyl*-N-*butoxy*-N'-*benzoyl* N'-*benzyloxyhydrazine* **143**

N-4-Chlorobenzoyl-*N*-butoxy-*N'*-benzoyl-*N'*-benzyloxyhydrazine (36.7 mg, 0.0811 mmol) was refluxed for 4 hours in dry $CHCl_3$. HPLC analysis of the reaction mixed revealed 2 major components, butyl 4-chlorobenzoate (41%) and benzyl benzoate (57%) and the two crossover esters, benzyl 4-chlorobenzoate (9%) and butyl benzoate (6%) as minor components. The Arrhenius parameters were obtained by solvolysis of *N*-4-

chlorobenzoyl-*N*-butoxy-*N'*-benzoyl-*N'*-benzyloxyhydrazine in $CDCl_3$ over the temperature range 298-332K with the rate being monitored by HPLC or ^1H NMR through integration of the resonance of the benzyloxy methylene singlet of the starting material.

6.8 Nitrene trapping Experiments

butoxyamine

Butyl benzohydroxamate (6 g, 31 mmol) was refluxed in ethanol (50 ml) and concentrated HCl (5 ml) for 3 hours. Benzoic acid was removed by extraction with chloroform (twice) and the aqueous layer was washed with 10% aq. Na_2CO_3 solution and the crude product was extracted with chloroform. Purification of the low boiling clear liquid was achieved by removal of solvent under rotary evaporator pressures only, followed by flash chromatography (4% EtOAc:96% hexane then DCM). Yield 40%. δ_H ($CDCl_3$) 0.92 (3H, t), 1.37 (2H, sxt), 1.54 (2H, qt), 3.65 (2H, t). δ_C ($CDCl_3$) 13.65 (q), 18.95 (t), 30.26 (t), 75.56 (t).

N-*butoxy-2,2,3,3-tetramethyl aziridine.*

The compound was synthesised by a known procedure.[229]

LTA (5 g, 13.5 mmol) and excess 2,3-but-2-ene (2.5 g, 30 mmol) where stirred vigorously in DCM at -45° C for 1 hour. Butoxyamine (0.40 g, 4.5 mmol) was added in small portions over 30 minutes and the solution was stirred for a further one hour at -45°C and then one hour at room temperature. The solution was filtered, washed with 10% aq. Na_2CO_3, filtered and washed with water and dried. DCM was removed *in vacuo* under water pump pressures only. Flash chromatography (10% Ether:90% Hexane) provided the title compound that was identical by NMR spectroscopy to the literature data (34%). δ_H ($CDCl_3$) 0.911 (3H, t), 1.15 (6H, s), 1.19 (6H, s), 1.33 (2H, sxt), 1.54 (2H, qt), 3.67 (2H, t).

7. Appendix

7.1 Acid-catalysed solvolysis results

Table 7-1 Natural logarithms of rate constants (ln k_H) for solvolysis of butyl *N*-acetoxy (*para*-substituted) benzohydroxamates **100**, (298-338K).

K	NO_2	Cl	Br	H	Me	Bu^t	Ph	MeO
298	-7.171	-5.863	-5.721	-5.215	-4.404	-4.527	-4.905	-2.493
303				-4.489				
308			-4.280	-3.661		-3.036		-1.094
308	-6.097	-3.892						
318	-4.769	-2.964	-2.752	-1.964	-1.383	-1.293	-1.669	0.247
328	-3.710	-1.694	-1.534	-0.922	0.0490	0.0287	-0.229	1.470
328				-0.819				
333	-3.265							
338	-2.615	-0.355	-0.345	0.507	1.312	1.191	0.940	2.980
338				0.129				
338				0.466				

Table 7-2 Natural logarithms of rate constants (ln k_H) for solvolysis of *para*-substituted benzyl *N*-acetoxy benzohydroxamates **151**, (239-388K).

K	NO_2	Cl	Br	H	Me	Bu^t	Ph	MeO	PhO
298	-8.730	-7.420	-7.569	-6.978	-5.518	-5.570	-6.386	-3.343	-4.939
308	-7.530	-6.103	-6.042	-5.407	-3.965	-4.123	-4.719	-2.042	-3.597
308	-7.503								
313								-0.972	
318	-6.188	-4.454		-3.614	-2.318	-2.438	-3.14	-0.572	-1.831
328	-5.106	-2.954	-3.278	-2.135	-0.754	-1.025	-1.901	0.593	-0.745
338	-3.617	-1.680	-1.913	-0.981	0.666	0.188	-0.506	2.493	-0.022
338	-3.672								

Table 7-3 Natural logarithms of rate constants (ln k_H) for solvolysis of benzyl *N*-(*para*-substituted benzoyloxy) benzohydroxamates **172**, (298-338K).

Temp	NO_2	CN	CF_3	CHO	Cl	H	Me	MeO
298	-6.210	-6.368	-6.423	-6.600	-6.909	-6.947	-7.031	-7.076
308	-4.571	-5.231	-4.971	-5.305	-5.566	-5.507	-5.716	-5.665
318	-3.535	-3.671	-3.747	-3.663	-3.981	-4.192	-4.210	-3.893
328	-2.363	-2.607	-2.173	-2.360	-2.793	-2.738	-2.820	-2.756
338	-0.932	-1.377	-0.924	-1.321	-1.527	-1.508	-1.417	-1.393
338						-1.456		

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