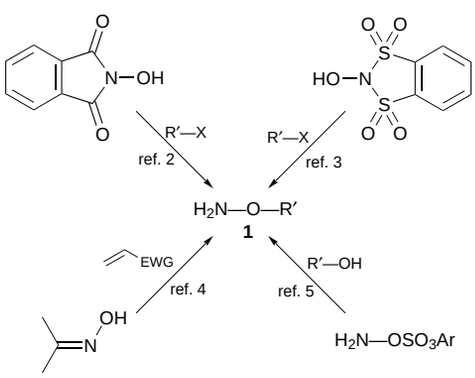
Synthesis and reactivity of a novel group of hydroxylamine-containing 2π- and 4π-components

Alan J. Pearce,[a] Daryl S. Walter,[b] Christopher S. Frampton[b] and Timothy Gallagher*,[a]

[a] *School of Chemistry, University of Bristol, Bristol, UK BS8 1TS*
[b] *Roche Discovery Welwyn, Welwyn Garden City, UK AL7 3AY*

The synthesis of hydroxylamine-based reagents, alkene 2, alkyne 3 and a butadienyl variant pyrone 4 are described. While the relative instability of alkyne 3 has limited further evaluation, alkene 2 and pyrone 4 successfully participate in 1,3-dipolar and Diels–Alder cycloaddition reactions respectively. Reaction of 4 with DMAD gives *O*-arylated hydroxylamine 13, the structure of which is confirmed by crystallographic analysis.

Hydroxylamines (RNHOR′) represent an important structural motif that is often associated with molecules exhibiting useful biological and medicinal profiles, including antiviral, antifungal and anxiolytic profiles.[1] The synthesis of variously *O*-substituted hydroxylamines **1** relies most usually on exploiting the nucleophilicity of either oxygen or nitrogen towards an appropriate electrophilic component and preparation may be carried our *via* either O–C or N–O bond formation, as illustrated in general terms in Scheme 1.[2–5]



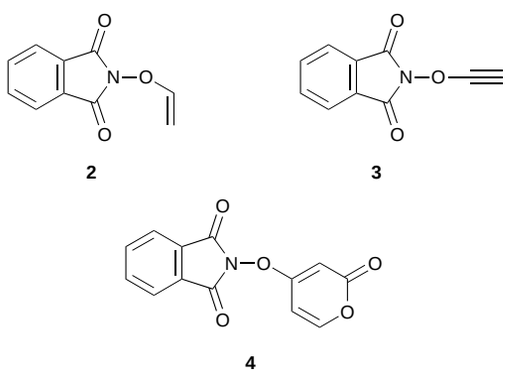
Scheme 1

We have sought to develop an alternative method for the synthesis of *O*-substituted hydroxylamines, substrates which can then be used to prepare *N*,*O*-disubstituted variants.[6] Our approach to the synthesis of *O*-substituted hydroxylamines is based on identifying synthetically flexible units that already contain a preformed N–O–C array, and in this paper we describe the preparation of a series of building blocks **2**, **3** and **4** based on this concept. A variety of routes have been evaluated for the synthesis of the 2π-containing components—the *O*-alkenyl and *O*-alkynyl derivatives **2** and **3** respectively—and a 4π dienyl variant, pyrone **4**, is also described. In addition, we present some preliminary studies relating to the reactivity of these molecules as participants in 1,3-dipolar and Diels–Alder cycloaddition processes.

Results and discussion

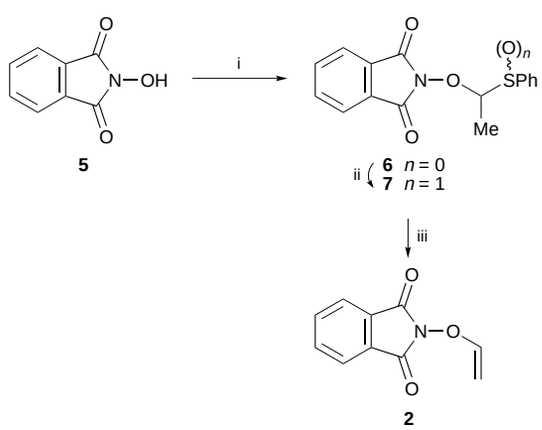
Synthesis of *N*-protected *O*-alkenyl hydroxylamines

The synthesis of *O*-alkenyl hydroxylamines has, to date, relied on the addition of a suitable *N*-substituted hydroxylamine to an electron-deficient alkyne.[7] Simple *O*-alkenyl derivatives, such as



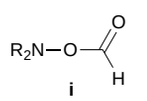
2, are attractive as a synthetically flexible class of electron-rich dieneophiles or dipolarophiles and two successful pathways to the *O*-ethenyl derivative **2** have been identified. Certain limitations also became apparent with the chemistry involved and these aspects of the study are also described.†

The first synthesis of **2** is illustrated in Scheme 2. *N*-Hydroxy-



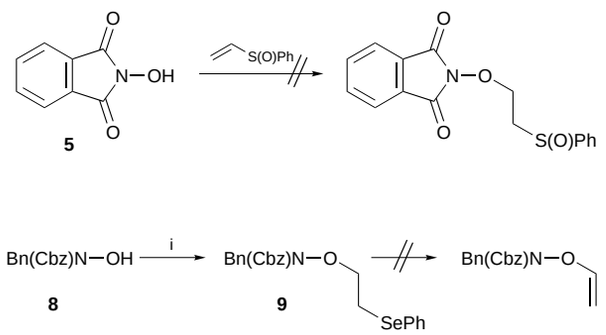
Scheme 2 *Reagents and conditions:* i, PhSCH(Me)Cl, Et_3N (66%); ii, MCPBA (84%); iii, xylene, $CaCO_3$, reflux (44%)

† Attempts to prepare *O*-alkenyl derivatives (*cf.* **2**) *via* methylenation of a range of *O*-formyl derivatives **i** using titanium-based reagents[16] was unsuccessful.



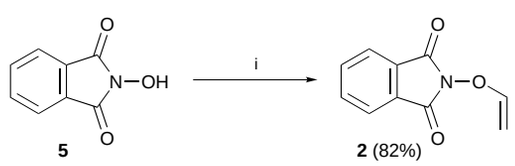
phthalimide (NHP) **5** underwent *O*-alkylation using 1-chloroethyl phenyl sulfide[8] to give adduct **6**. Oxidation of **6** gave a diastereomeric mixture of sulfoxides **7** (together with a small quantity of the corresponding sulfone), and thermolysis of sulfoxides **7** produced the crystalline *O*-ethenyl hydroxylamine **2** in 24% overall yield from **5**.

Two variants on this alkylation–elimination strategy have been examined, but without success. We were unable to alkylate NHP with phenyl vinyl sulfoxide under a variety of both base- and acid-mediated reaction conditions. Alternative *N*-protecting groups were also of interest and *N*-benzyl-*N*-benzyloxycarbonylhydroxylamine **8** did undergo alkylation with 2-bromoethyl phenyl selenide to give adduct **9** in 50% yield. Although use of a milder selenoxide fragmentation offered an opportunity to retain a more sensitive array of nitrogen protecting groups in the *O*-alkenyl product, we were not successful in oxidising adduct **9** (using either $NaIO_4$ or MCPBA) to promote a selenoxide-mediated elimination (Scheme 3).



Scheme 3 *Reagents and conditions:* i, $PhSeCH_2CH_2Br$, NaH (50%)

The second and more direct route to alkene **2**, which is shown in Scheme 4, was carried out using a transvinylation based on



Scheme 4 *Reagents and conditions:* i, $AcOCH{=}CH_2$, $Hg(OCOCF_3)_2$ (7 mol%) cat. H_2SO_4, reflux

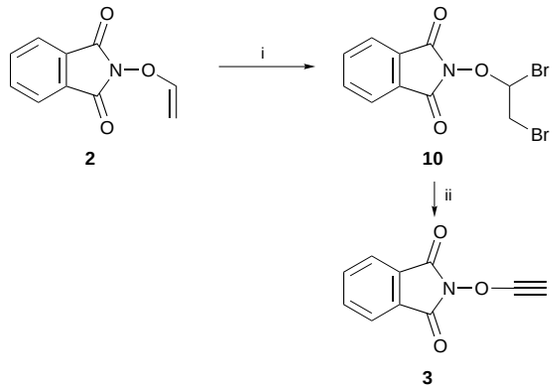
an exchange involving vinyl acetate.[9] This transformation was promoted by mercury(II) trifluoroacetate and **2** was isolated in 82% yield. This process involves a single step and isolation of the product from the reaction mixture is straightforward. It is, however, important to appreciate that this process did not accommodate other *N*-protected hydroxylamines, such as **8**, Bn_2NOH[10] and Boc_2NOH[11] and these substrates did not yield the corresponding *O*-ethenyl adducts under similar conditions.‡

Synthesis of *O*-alkynyl hydroxylamine 3

The synthesis of the corresponding *O*-ethynyl hydroxylamine **3**, also based on NHP, is shown in Scheme 5. Addition of bromine to alkene **2** provided the crystalline dibromide **10** which underwent a double elimination under basic conditions to give the *O*-ethynyl derivative **3** in 15% overall yield, a compound that proved difficult to fully characterise. Alkyne **3** proved to be relatively unstable—as with related alkoxyalkynes,[12] **3** was prone to polymerisation—and although accessible, the chemistry of this 2π-component has not been further explored.

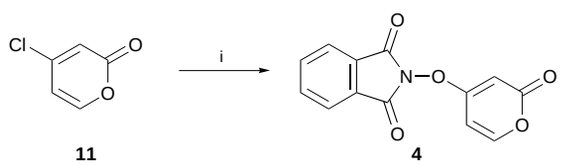
Synthesis of an *O*-butadienyl hydroxylamine 4

Electron-rich 4π components also offer significant synthetic potential, particularly in the construction of substituted *O*-aryl



Scheme 5 *Reagents and conditions:* i, Br_2, CH_2Cl_2 (91%); ii, LiHMDS, THF, −78 °C (17%)

hydroxylamine derivatives.§ With this objective in mind, the pyrone derivative **4** became an attractive target: pyrones are known to be highly effective dienes and, following initial cycloaddition, decarboxylation then restores a butadienyl or aryl moiety, depending on the nature of the dienophile used.[13] The synthesis of the pyrone derivative **4** is outlined in Scheme 6.



Scheme 6 *Reagents and conditions:* i, *N*-hydroxyphthalimide **5**, Et_3N, DMF (84%)

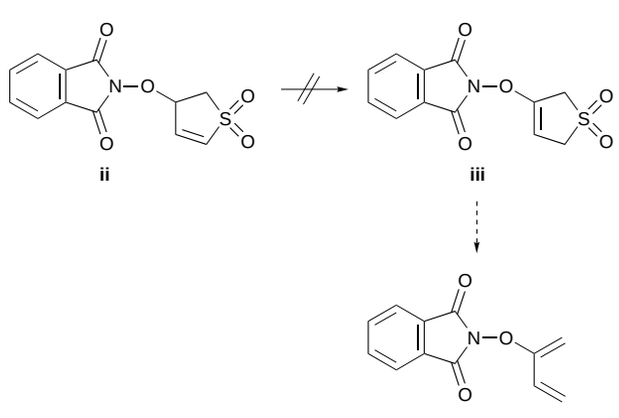
4-Chloro-2*H*-pyran-2-one **11**[14] underwent smooth (net) substitution using NHP **5** under mildly basic conditions to give **4** in 84% yield.

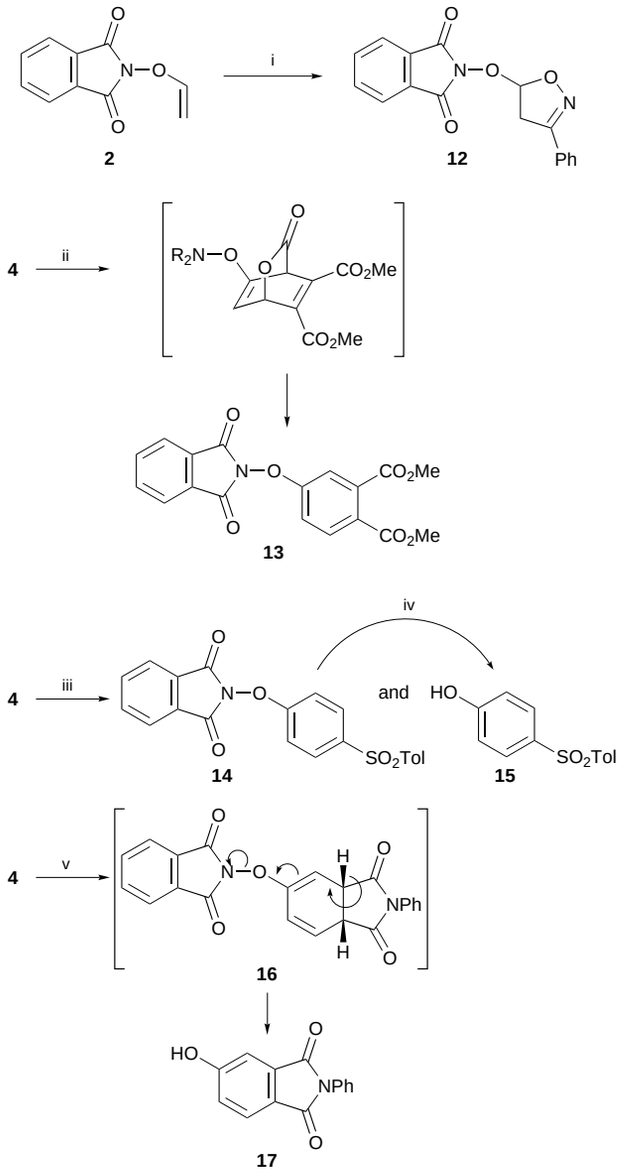
Preliminary cycloaddition studies

Both the *O*-alkenyl derivative **2** and butadien-2-yl variant **4** offer synthetic utility and, while this is not necessarily restricted

‡ The purity of the vinyl acetate used is important to the success of the transformation shown in Scheme 4 and must be *freshly* distilled otherwise *O*-acetylation of **5** predominates (A. J. Liepa, private communication). Using the other hydroxylamine derivatives mentioned, complex mixtures were obtained under the mercury-catalysed transvinylation conditions. With **8**, the major component has been tentatively assigned as the corresponding *O*-acylated adduct.[9b]

§ Attempts to prepare a simpler butadien-2-yl derivative **iv** failed. While adduct **ii** was obtained by alkylation of 4-bromo-4,5-dihydrothiophene dioxide,[17] we were unable to isomerise this product to give the desired 2,5-dihydrothiophene dioxide **iii**





Scheme 7 *Reagents and conditions:* i, $PhC{\equiv}N^{+}{-}O^{-}$ (25%); ii, $MeO_2CC{\equiv}CCO_2Me$, toluene, 150 °C (26%); iii, $TolO_2SC{\equiv}CH$, toluene, 190 °C (**14**: 7%; **15**: 43%); iv, toluene, 190 °C (quantitative by TLC); v, *N*-phenylmaleimide, toluene, 205 °C (84%)

to their use in Diels–Alder and related reactions, our initial studies have focused on these cycloaddition processes. Preliminary results pertaining to the reactivity associated with this aspect of the study are all shown in Scheme 7.

For a number of reasons, we were drawn towards verifying the use of the *O*-alkenyl derivative **2** as a 1,3-dipolarophile. Exposure of **2** to benzonitrile oxide gave the corresponding cycloadduct **12** (25%; 41% yield based on recovered **2**) with only one regioisomer being observed, which is consistent with the reactivity associated with simple vinyl ethers.[15]

As stated earlier, the instability of the *O*-alkynyl derivative **3** proved to be a problem, but the reactivity encountered with the pyrone-based 4π component **4** was more readily harnessed. Exposure of **4** to DMAD gave the expected *O*-arylated hydroxylamine **13** in 26% isolated yield, the structure of which was confirmed by single crystal X-ray analysis (Fig. 1). Pyrone **4** also underwent cycloaddition to *p*-tolylsulfonylacetylene, but in this case two products were obtained. The minor component was the desired *O*-arylated adduct **14** (isolated in 7% yield) and the major product was phenol **15** (43% yield). A simple control experiment showed that the adduct **14** fragmented, *via* N–O bond homolysis, to give phenol **15** (with phthalimide being

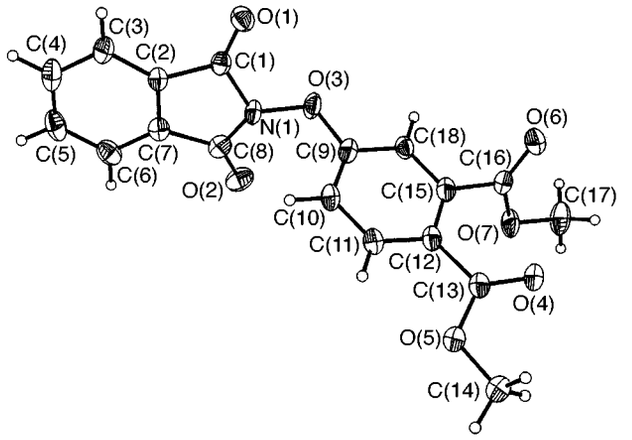


Fig. 1 ORTEP diagram of *O*-arylated hydroxylamine **13**. Thermal ellipsoids are at the 50% probability level.

detected) under the reaction conditions used to achieve cycloaddition (toluene, sealed-tube, 190 °C). The yield of the hydroxylamine derivative **14** has not been optimised, but quite clearly the limits on compatibility of the N–O bond to thermal reaction conditions must be recognised. A further aspect of the chemistry of pyrone **4** was uncovered following a reaction involving an alkene-based dienophile. Thermolysis of **4** in the presence of *N*-phenylmaleimide gave phenol **17** in 84% yield. This product is presumed to arise *via* aromatisation of adduct **16** in a process that again involves a facile N–O (likely heterolytic) cleavage.

In summary, *N*-hydroxyphthalimide is readily incorporated into the synthetically useful *O*-ethenyl and *O*-butadienyl derivatives **2** and **4** respectively. Problems were encountered with the stability of the simple *O*-alkynyl variant **3**, but this may not be an issue with more substituted analogues. Preliminary cycloaddition studies have already defined certain reactivity patterns, but further work will be undertaken to explore other, more general aspects of the chemistry of the hydroxylamine-based reagents that have been reported in this paper.

Experimental

General

All solvents and commercially available reagents were purified and dried as required, according to standard literature procedures. Light petroleum refers to the fraction boiling in the range 40–60 °C. Ether refers to diethyl ether. IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrophotometer. Mass spectra were obtained on a Fisons VG Analytical Autospec spectrometer using EI (70 eV), CI (CH_4 as reagent gas) or FAB modes. NMR spectra were recorded on a JEOL JNM-GX270, JEOL JNM-LA300 or JEOL JNM-GX400 spectrometer and *J* values are reported in Hz. Melting points were determined on a Kofler hot-stage and are uncorrected. Elemental analyses were determined on a Perkin-Elmer 240C elemental analyser. TLC was performed using aluminium plates coated with Merck silica gel $60F_{254}$ and flash chromatography was carried out using silica gel (Merck 60). Preparative reversed-phase (RP) HPLC was performed using a Dynamax column (20 mm ID × 5 cm L, 5 μm, C_{18}, 300 Å) and Gilson pump eluting at 20 cm^3 min^{-1} with detection (UV, 254 nm). Solvent A consisted of 0.1% TFA in water and solvent B of 0.1% TFA in acetonitrile. Reactions using a sealed-tube refer to a sealed reaction vessel with an internal volume of 7 cm^3.

N-(1-Phenylsulfonylethoxy)phthalimide and *N*-(1-Phenylsulfinylethoxy)phthalimide 7

N-(1-Phenylthioethoxy)phthalimide[8] **6** (4.46 g, 14.9 mmol) was dissolved in dichloromethane (10 cm^3), cooled to 0 °C and vigorously stirred. *m*-Chloroperbenzoic acid (86% pure, 3.64 g,

21.1 mmol) was added portionwise over 20 min after which time TLC (ether) indicated no starting material. The reaction mixture was immediately poured into a separating funnel containing ether (50 cm^3) and washed with aq. sodium sulfite (50 cm^3, 1 mol dm^{-3}) and then saturated aq. sodium hydrogen carbonate (2 × 50 cm^3), The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash chromatography (ether–pentane, 2:3) afforded N-(1-*phenylsulfonylethoxy*)*phthalimide* (0.21 g, 4%), as a colourless crystalline solid, mp 158–160 °C (ethyl acetate–light petroleum) (Found: C, 58.1; H, 3.9; N, 4.1. $C_{16}H_{13}NO_5S$ requires C, 58.0; H, 3.95; N, 4.2%); ν_{max}(KBr)/cm^{-1} 1789 (C=O), 1737 (C=O), 1310 (SO_2), 1135 (SO_2); δ_H(270 MHz, $CDCl_3$) 8.29 (2 H, m, Ph), 7.89–7.60 (7 H, m, Ar), 5.32 (1 H, q, *J* 6.4, C*H*), 1.64 (3 H, d, *J* 6.4, CH_3); *m*/*z* (FAB+) 332 (M + H^+, 46%), 190 [(M + H − $PhSO_2H)^+$, 100].

Further elution (ether) yielded N-(1-*phenylsulfinylethoxy*)-*phthalimide* **7** (3.95 g, 84%), as a *ca*. 1:1 mixture of diastereomers, as a colourless solid, mp 102 °C (decomp.) (ethyl acetate–light petroleum) (Found: C, 60.7; H, 4.5; N, 4.3. $C_{16}H_{13}NO_4S$ requires C, 60.95; H, 4.2; N, 4.5%); ν_{max}(KBr)/cm^{-1} 1792 (C=O), 1737 (C=O), 1045 (S=O); δ_H(270 MHz, $CDCl_3$) 8.03–7.49 (9 H, m, Ar), 5.21/5.01 (1 H, q, *J* 6.2, C*H*), 1.54/1.29 (3 H, d, *J* 6.2, CH_3); *m*/*z* (FAB+) 316 (M + H^+, 71%), 190 {[M + H − $PhS(O)H]^+$, 100}.

N-Ethenyloxyphthalimide 2

(*i*) *Via* thermolysis of the sulfoxide 7. Calcium carbonate (3.70 g, 37.0 mmol) was added to a solution of *N*-(1-phenylsulfinylethoxy)phthalimide **7** (3.89 g, 0.63 mmol) in xylene (20 cm^3) and the mixture was heated to reflux. After 15.5 h, reaction was complete, as judged by TLC (ether), and the reaction mixture was cooled to room temperature, filtered through Celite and the solvent removed *in vacuo*. Flash chromatography (ether–light petroleum, 2:5) afforded N-*ethenyloxyphthalimide* **2** (1.04 g, 44%), as a colourless crystalline solid. For characterisation see route (*ii*).

(*ii*) *Via* transetherification. Mercury(II) trifluoroacetate (425 mg, 1.0 mmol) was dissolved in *freshly* distilled‡ vinyl acetate (42.0 g, 0.49 mol) and the solution was stirred at room temperature under nitrogen in the dark. After 15 min, *N*-hydroxyphthalimide **5** (15.2 g, 93.2 mmol) and then concentrated sulfuric acid (0.02 cm^3 in 1.0 cm^3 EtOAc) were added and the mixture was heated to reflux. Further mercury(II) trifluoroacetate (2.40 g, 5.63 mmol) was added portionwise over 24 h and after a further 24 h at reflux, TLC (ethyl acetate–light petroleum, 1:2) indicated consumption of **5**. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was initially purified by filtration through a silica plug (ethyl acetate–light petroleum, 6:1). The crude solid was then dissolved in ethyl acetate (100 cm^3) and washed with saturated aq. sodium hydrogen carbonate (50 cm^3). The aqueous layer was extracted with ethyl acetate (2 × 100 cm^3) and the combined organic extracts were washed with brine (25 cm^3), dried (Na_2SO_4), filtered and the solvent was removed *in vacuo*. Recrystallisation gave N-*ethenyloxyphthalimide* **2** (12.2 g, 70%) and purification of the mother liquors by flash chromatography (ethyl acetate–light petroleum, 1:3) gave an additional quantity of **2** (2.12 g, total yield of 82%), as a colourless crystalline solid, mp 105–107 °C (decomp.) (ethyl acetate–light petroleum) (Found: C, 63.4; H, 3.6; N, 7.3. $C_{10}H_7NO_3$ requires C, 63.5; H, 3.7; N, 7.4%); ν_{max}(KBr)/cm^{-1} 1728 (C=O), 1641 (C=C); δ_H(270 MHz, $CDCl_3$) 7.85 (4 H, m, Ar), 6.71 (1 H, dd, *J* 13.6, *J* 6.2, OC*H*), 4.67 (1 H, dd, *J* 13.6, *J* 4.0, H_{trans}), 4.47 (1 H, dd, *J* 6.2, *J* 4.0, H_{cis}); δ_C(67.8 MHz, $CDCl_3$) 162.4 (*C*=O), 151.1 (O*C*H), 134.8, 123.9 (2 × *C*H, Ar), 128.9 (C_{ipso}), 90.7 (CH_2); *m*/*z* (FAB+) 190 (M + H^+, 100%); *m*/*z* (CI) 190 (M + H^+, 5%), 148 [(M + H − $C_2H_2O)^+$, 100] (Found: M + H^+, 190.0504. $C_{10}H_7NO_3$ requires *M* + H^+, 190.0497).

N-Benzyl-*N*-benzyloxycarbonylhydroxylamine 8

N-Benzylhydroxylamine hydrochloride (752 mg, 4.7 mmol) was added to a solution of sodium hydrogen carbonate (792 mg, 9.4 mmol) in water (15.0 cm^3) and stirred at 0 °C for 0.5 h. Dichloromethane (10 cm^3) and benzyl chloroformate (0.67 cm^3, 4.7 mmol) were added dropwise, and the reaction mixture stirred for 0.5 h at 0 °C. After a further 0.5 h at room temperature, the organic layer was separated and the aqueous layer was extracted with dichloromethane (5 cm^3). The combined extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford N-*benzyl*-N-*benzyloxycarbonylhydroxylamine* **8** (957 mg, 79%), as a colourless crystalline solid, mp 93–95 °C (dichloromethane–light petroleum) (Found: C, 69.8; H, 5.9; N, 5.2. $C_{15}H_{15}NO_3$ requires C, 70.0; H, 5.9; N, 5.45%); ν_{max}(KBr)/cm^{-1} 1697 (C=O); δ_H(270 MHz, $CDCl_3$) 7.38–7.28 (10 H, m, Ph), 6.02 (1 H, br s, N-O*H*), 5.22 (2 H, s, PhCH_2), 4.71 (2 H, s, PhCH_2); *m*/*z* (EI) 239 (M^+ − H_2O, 1%), 213 (M^+ − CO_2, 2), 91 ($C_7H_7^+$, 100), 65 ($C_5H_5^+$, 7); *m*/*z* (FAB+) 258 (M + H^+, 100).

N-Benzyl-*N*-benzyloxycarbonyl-*O*-[2-(phenylseleno)ethyl]-hydroxylamine 9

Sodium hydride (4.4 mg, 0.11 mmol, 60% in mineral oil) was added to a solution of *N*-benzyl-*N*-benzyloxycarbonylhydroxylamine **8** (28 mg, 0.11 mmol) in tetrahydrofuran (0.5 cm^3) and the mixture was stirred under nitrogen at room temperature. After 15 min, a solution of 2-bromoethyl phenyl selenide[18] (31.9 mg, 0.12 mmol) in tetrahydrofuran (0.1 cm^3) was added and the mixture was stirred at room temperature for 20.5 h. After heating at reflux for a further 4 h, the mixture was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified by flash chromatography (ethyl acetate–light petroleum, 5:95) to afford N-*benzyl*-N-*benzyloxycarbonyl*-O-[2-(*phenylseleno*)*ethyl*]*hydroxylamine* **9** (24 mg, 50%), as a colourless oil (Found: C, 63.0; H, 4.9; N, 3.2. $C_{23}H_{23}NO_3Se$ requires C, 62.7; H, 5.3; N, 3.2%); ν_{max}(film)/cm^{-1} 1711 (C=O), 1221 (C–O), 1081 (C–O); δ_H(270 MHz, $CDCl_3$) 7.43–7.19 (15 H, m, Ar), 5.19 (2 H, s, PhCH_2), 4.64 (2 H, s, PhCH_2), 3.97 (2 H, t, *J* 7.3, OCH_2), 2.93 (2 H, t, *J* 7.3, SeCH_2); *m*/*z* (CI) 442 (M + H^+, 22%), 185 ($Ph^{80}SeCH_2CH_2^+$, 82), 91 ($C_7H_7^+$, 100) (Found: M + H^+, 442.0925. $C_{23}H_{23}NO_3{}^{80}Se$ requires *M* + H^+, 442.0921).

1,2-Dibromo-1-(phthalimidooxy)ethane 10

Bromine (366 mg, 2.3 mmol) was added dropwise over 5 min to a suspension of *N*-ethenyloxyphthalimide **2** (332 mg, 1.76 mmol) in dichloromethane (5 cm^3) at 0 °C. After stirring for 10 min at 0 °C and 1.5 h at room temperature, the reaction mixture was washed with 10% aq. sodium thiosulfate (10 cm^3). The aqueous layer was then extracted with dichloromethane (2 × 10 cm^3) and combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford 1,2-*dibromo*-1-(*phthalimidooxy*)*ethane* **10** (558 mg, 91%), as a colourless crystalline solid, mp 120–122 °C (ether–light petroleum) (Found: C, 34.4; H, 1.9; N, 4.0. $C_{10}H_7Br_2NO_3$ requires C, 34.4; H, 2.0; N, 4.0%); ν_{max}(KBr)/cm^{-1} 1790 (C=O), 1734 (C=O); δ_H(400 MHz, $CDCl_3$) 7.92–7.76 (4 H, m, Ar), 6.55 (1 H, dd, *J* 8.4, *J* 3.3, OC*H*Br), 4.12 (1 H, dd, $J_{2,2'}$ 11.8, *J* 8.4, 2-H), 3.99 (1 H, dd, $J_{2,2'}$ 11.8, *J* 3.3, 2′-H); δ_C(75.45 MHz, $CDCl_3$) 162.4 (*C*=O), 135.0 (*C*H, Ar), 128.6 (C_{ipso}), 124.1 (*C*H, Ar), 88.0 (*C*H, 1-C), 31.2 (CH_2, 2-C); *m*/*z* (CI) 352 {[M($^{81}Br^{81}Br$) + H]$^+$, 0.3%}, 350 {[M($^{81}Br^{79}Br$) + H]$^+$, 0.6}, 348 {[M($^{79}Br^{79}Br$) + H]$^+$, 0.3}.

N-Ethynyloxyphthalimide 3

A solution of lithium hexamethyldisilazide (1.10 cm^3, 1.10 mmol, 1 mol dm^{-3} in THF) was added dropwise to a solution of 1,2-dibromo-1-(phthalimidooxy)ethane **10** (151 mg, 0.43 mmol) in THF (2 cm^3) at −78 °C under nitrogen. After stirring at −78 °C for 1 h and then room temperature for 1 h, the reaction mixture was washed with saturated aq. NH_4Cl (3 cm^3) and

the aqueous layer was extracted with ethyl acetate (2 × 3 cm^3). The combined organic extracts were washed with HCl (1 cm^3, 2 mol dm^{-3}), water (1 cm^3), saturated aq. sodium hydrogen carbonate (1 cm^3), dried (Na_2SO_4), filtered and the solvent removed *in vacuo*. The residue was purified by flash chromatography (ethyl acetate–light petroleum, 2:5) to afford N-*ethynyloxyphthalimide* **3** (14 mg, 17%), as a colourless solid; ν_{max}(KBr)/cm^{-1} 3203 (C–H alkyne), 2949, 1775 (C=O), 1732 (C=O); δ_H(270 MHz, C_6D_6) 7.39 (2 H, m, Ar), 6.85 (2 H, m, Ar), 0.34 (1 H, s, C≡C–*H*); *m*/*z* (EI) 187 (M^+, 7%), 162 [$(M - C_2H)^+$, 4], 147 ($Phth^+$, 100). Attempts to recrystallise **3** without extensive decomposition failed, and we were unable to obtain satisfactory microanalytical data or high resolution mass data for this compound.

4-(Phthalimidooxy)-2*H*-pyran-2-one 4

Triethylamine (1.28 cm^3, 9.19 mmol) was added dropwise over 5 min to a solution of *N*-hydroxyphthalimide **5** (1.50 g, 9.20 mmol) and 4-chloro-2*H*-pyran-2-one[14] **11** (1.09 g, 8.35 mmol) in dry DMF (10 cm^3) at room temperature under nitrogen. After stirring for 2 h, ice–water (20 cm^3) was added and the precipitate was filtered and washed with water (10 cm^3), saturated aq. sodium hydrogen carbonate (10 cm^3), water (10 cm^3) and ice-cold ether–pentane (1:1, 15 cm^3). Drying *in vacuo* afforded 4-(*phthalimidooxy*)-2H-*pyran*-2-*one* **4** (1.81 g, 84%), as a cream solid, mp >230 °C (decomp., ethyl acetate–light petroleum) (Found: C, 60.9; H, 2.6; N, 5.6. $C_{13}H_7NO_5$ requires C, 60.7; H, 2.7; N, 5.45%); ν_{max}(KBr)/cm^{-1} 1798 ($C{=}O_{imide}$), 1735 ($C{=}O_{imide}$), 1717 ($C{=}O_{pyrone}$), 1644 (C=C), 1574 (C=C), 1192 (C–O); δ_H(300 MHz, $CDCl_3$) 7.98–7.87 (4 H, m, Ar), 7.53 (1 H, dd, $J_{5,6}$ 6.0, $J_{3,6}$ 0.6, 6-H), 6.34 (1 H, dd, $J_{5,6}$ 6.0, $J_{3,5}$ 3.0, 5-H), 5.77 (1 H, dd, $J_{3,5}$ 3.0, $J_{3.6}$ 0.6, 3-H); δ_C(100.61 MHz, [$^2H_6$]DMSO) 169.3, 162.5, 162.1 (3 × *C*, 2-C, 4-C, C=O), 154.5 (*C*H, 6-C), 135.2 (*C*H, Ar), 129.1 (C_{ipso}), 123.8 (*C*H, Ar), 99.2, 92.0 (2 × *C*H, 3-C, 5-C); *m*/*z* (CI) 258 ($M + H^+$, 55%).

5-(Phthalimidooxy)-3-phenyl-4,5-dihydroisoxazole 12

Benzohydroxamoyl chloride[19] (107 mg, 0.69 mmol) in ether (0.5 cm^3) was added to a stirred solution of *N*-ethenyloxyphthalimide **2** (100 mg, 0.53 mmol) in ether (3 cm^3) at room temperature under nitrogen. Triethylamine (70 mg, 0.69 mmol) was added dropwise over 20 min. Three further equivalents each of benzohydroxamoyl chloride and triethylamine were added over 24 h, after which TLC (ether–pentane, 2:3) indicated the presence of starting material (R_f 0.6) and a major product (R_f 0.3), together with some baseline material. Saturated aq. NH_4Cl (5 cm^3) was added and the mixture was extracted with ether, dried ($MgSO_4$) and filtered. Solvent was removed *in vacuo* and flash chromatography (ether–pentane, 2:3) afforded 5-(*phthalimidooxy*)-3-*phenyl*-4,5-*dihydroisoxazole* **12** (40 mg, 25%, 41% based on recovered **2**), as a colourless crystalline solid, mp 151–152 °C (ethyl acetate–light petroleum) (Found: C, 66.6; H, 3.7; N, 9.0. $C_{17}H_{12}N_2O_4$ requires C, 66.2; H, 3.9; N, 9.1%); ν_{max}(KBr)/cm^{-1} 1787, 1732; δ_H(270 MHz, $CDCl_3$) 7.89–7.42 (9 H, m, Ar), 6.31 (1 H, dd, $J_{4',5}$ 5.5, $J_{4,5}$ 1.8, 5-H), 3.74 (1 H, dd, $J_{4,4'}$ 18.0, $J_{4,5}$ 1.8, 4-H), 3.64 (1 H, dd, $J_{4,4'}$ 18.0, $J_{4',5}$ 5.5, 4′-H); *m*/*z* (FAB+) 309 ($M + H^+$, 40%), 146 (100).

Dimethyl 4-(phthalimidooxy)phthalate 13

A mixture of pyrone **4** (44 mg, 0.17 mmol) and freshly distilled dimethyl acetylenedicarboxylate (0.5 cm^3) was stirred in a sealed-tube and heated at 150 °C for 20 h. The solvent was then removed *in vacuo* and flash chromatography (ether–light petroleum, 3:2) afforded a mixture of *trimethyl* 5-*methoxyfuran*-2,3,4-*tricarboxylate* (a by-product derived from DMAD) and *dimethyl* 4-(*phthalimidooxy*)*phthalate* **13**.

Preparative RPHPLC (0–20 min, linear gradient of 5 to 95% solvent B in solvent A) afforded *trimethyl* 5-*methoxyfuran*-2,3,4-*tricarboxylate* (16 mg; t_r 6.3 min), as a colourless solid, mp 118 °C (lit.,[20] mp 117–118 °C).

Continued elution gave *dimethyl* 4-(*phthalimidooxy*)*phthalate* **13** (16 mg, 26%; t_r 10.6 min) as a colourless crystalline solid, mp 58–60 °C (ether–light petroleum) (Found: $M + H^+$, 356.0766. $C_{18}H_{13}NO_7$ requires $M + H^+$, 356.0770); ν_{max}(KBr)/cm^{-1} 1741 (C=O), 1288; δ_H(400 MHz, $CDCl_3$) 7.89–7.78 (4 H, m), 7.75 (1 H, d, $J_{5,6}$ 8.6, 6-H), 7.31 (1 H, d, $J_{3,5}$ 2.6, 3-H), 7.23 (1 H, dd, $J_{5,6}$ 8.6, $J_{3,5}$ 2.6, 5-H), 3.82 (6 H, br s, OCH_3); *m*/*z* (FAB+) 356 ($M + H^+$, 40%), 324 ($M + H^+ - CH_3OH$, 100).

***N*-[4-(*p*-Tolylsulfonyl)phenoxy]phthalimide 14 and 4-(*p*-tolylsulfonyl)phenol 15**

A mixture of pyrone **4** (40 mg, 0.16 mmol) and *p*-tolylsulfonylacetylene (34 mg, 0.19 mmol) in toluene (1 cm^3) was heated in a sealed-tube at 150 °C for 24 h and then 35 h at 190 °C. The solvent was removed *in vacuo* and flash chromatography (ether–light petroleum, 3:1) afforded a mixture of N-[4-(p-*tolylsulfonyl*)*phenoxy*]*phthalimide* **14** and 4-(p-*tolylsulfonyl*)*phenol* **15**.

Preparative RPHPLC (0–20 min, linear gradient of 5 to 95% of solvent B in solvent A) afforded 4-(p-*tolylsulfonyl*)*phenol* **15** (17 mg, 43%, t_r 8.4 min), as a colourless solid, mp 140–142 °C (lit.,[21] mp 143–144 °C); ν_{max}(KBr)/cm^{-1} 3361, 1587, 1286; δ_H(400 MHz, $CDCl_3$) 7.74 (4 H, m), 7.21 (2 H, d, *J* 8.1), 6.82 (2 H, d, *J* 8.8), 5.61 (1 H, br s, O*H*), 2.32 (3 H, s, CH_3); *m*/*z* (FAB+) 249 ($M + H^+$, 100%).

Continued elution gave N-[4-(p-*tolylsulfonyl*)*phenoxy*]-*phthalimide* **14** (4 mg, 7%, t_r 12.6 min), as a colourless solid, mp 185 °C (decomp.) (Found: $M + H^+$, 394.0745. $C_{21}H_{15}NO_5S$ requires $M + H^+$, 394.0749); ν_{max}(KBr)/cm^{-1} 1795 ($C{=}O_{imide}$), 1742 ($C{=}O_{imide}$), 1586, 1151, 1106; δ_H(400 MHz, $CDCl_3$) 7.88–7.85 (4 H, m), 7.78 (2 H, m), 7.72 (2 H, d, *J* 8.3), 7.23 (2 H, d, *J* 8.1), 7.15 (2 H, m, *J* 8.9), 2.32 (3 H, s, CH_3); *m*/*z* (FAB+) 394 ($M + H^+$, 15%), 149 (100).

Thermolysis of a solution of **14** in toluene (sealed-tube, 190 °C, 20 h) showed complete conversion to **15**, as judged by TLC.

5-Hydroxy-2-phenylisoindole-1,3(2*H*)-dione 17

A mixture of pyrone **4** (27 mg, 0.11 mmol) and *N*-phenylmaleimide (55 mg, 0.32 mmol) in toluene (1 cm^3) was heated in a sealed-tube at 205 °C for 24 h. The solvent was then removed *in vacuo* and flash chromatography (ether–light petroleum, 3:1) afforded 5-*hydroxy*-2-*phenylisoindole*-1,3(2H)-*dione* **17** (21 mg, 84%), as a pale yellow crystalline solid, mp 250–252 °C (CH_2Cl_2–light petroleum) (lit.,[22] mp 251 °C) (Found: M^+, 239.0578. $C_{14}H_9NO_3$ requires M^+, 239.0582); ν_{max}(KBr)/cm^{-1} 3216br, 1776 (C=O), 1710 (C=O); δ_H(400 MHz, $CDCl_3$) 7.83 (1 H, d, $J_{6,7}$ 8.2, 7-H), 7.51–7.37 (5 H, m, Ph), 7.35 (1 H, d, $J_{4,6}$ 2.2, 4-H), 7.17 (1 H, dd, $J_{6,7}$ 8.2, $J_{4,6}$ 2.2, 6-H), 5.95 (1 H, br s, O*H*); *m*/*z* (EI) 239 (M^+, 75%), 149 (100).

Crystallographic data for 13

$C_{18}H_{13}N_1O_7$, $M = 355.29$, monoclinic, space group $P2_1/a$, $a = 9.471(4)$, $b = 9.776(8)$, $c = 17.477(3)$ Å, $\beta = 91.93(3)°$, $U = 1617.2(15)$ $Å^3$ [from 2θ values of 25 reflections measured at $\pm\omega$ ($89.10 \leqslant 2\theta \leqslant 102.10°$ Cu-Kα, $\lambda = 1.541\,78$ Å)], $Z = 4$, $D_c = 1.459$ g cm^{-1}, $\mu = 0.971$ mm^{-1}, $F(000) = 736$, $T = 123(1)$ K.

Data collection and processing.[23] A colourless plate crystal, 0.26 × 0.20 × 0.10 mm was mounted on a Rigaku AFC7R four-circle diffractometer equipped with an Oxford Cryosystems Cryostream Cooler.[24] 3115 reflections were collected at 123(1) K with ω–2θ scans using graphite-monochromated Cu-Kα radiation, ($\lambda = 1.541\,78$ Å), scan-width = (1.31 + 0.14 tan θ)°, scan speed 32° min^{-1} to a θ_{max} of 70.01°, (h 0 to 11, k 0 to 11, l −21 to 21). 2912 reflections unique ($R_{int} = 0.0130$) and 2523 observed with $I < 2\sigma(I)$. Analysis of the intensities of three standard reflections recorded every 150 reflections showed an overall decrease in the intensity of 3.17% and the data were scaled accordingly. The data were corrected for Lorentz and polarisation effects. No absorption correction was applied

since preliminary ψ-scans revealed no significant absorption effects.

Structure solution and refinement.[25] The structure was solved by direct methods. Full-matrix least-squares refinement on F^2 with weighting scheme $w^{-1} = \sigma^2(F_o^2) + (0.1000P)^2 + 1.5000P$, where $P = (F_o^2 + 2F_c^2)/3$, anisotropic displacement parameters, riding hydrogen atoms and a secondary extinction correction $x = 0.0043(6)$, where $F_c^* = kF_c[1 + 0.001xF_c^2\lambda^3/\sin(2\theta)]^{-\frac{1}{4}}$, converged with a Δ/σ_{max} of 0.001. Final $R_w = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]^{\frac{1}{2}}\} = 0.1610$ for all data, conventional $R = 0.0503$ on F values of 2523 reflections with $I > 2\sigma(I)$, $S = 1.007$ for all data and 236 parameters. Final difference map between +0.26 and −0.25 e Å^{-3}. Full crystallographic details, excluding structure factor tables, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc.*, *Perkin Trans. 1*, available *via* the RSC Web pages (http://www.rsc.org/authors). Any request to the CCDC for this material should quote the full literature citation and the reference number 207/189.

Acknowledgements

We thank EPSRC and Roche Discovery Welwyn for a CASE studentship (to A. J. P.), and Dr A. J. Liepa (CSIRO, Melbourne) for observations relating to the transvinylation route to **2**.

References

1 (*a*) J. B. Hester, A. D. Rudzik and P. F. VonVoigtlander, *J. Med. Chem.*, 1980, **23**, 392; (*b*) K. R. Scott, C. J. Alt, M. Kemp, E. Hayes and V. G. Telang, *J. Pharm. Sci.*, 1984, **73**, 1531; (*c*) G. Johnson, P. A. Boxer, J. T. Drummond, D. K. Boyd and R. J. Anderson, *Arzneim.-Forsch.*, 1989, **39**, 432; (*d*) J. M. J. Tronchet, G. Zosimo-Landolfo, G. Galland-Barrera and N. Dolatshahi, *Carbohydr. Res.*, 1990, **204**, 145; (*e*) A. Ejima, H. Teresawa, M. Sugimori, S. Ohsuki, K. Matsumoto, Y. Kawato, M. Yasuoka and H. Tagawa, *Chem. Pharm. Bull.*, 1992, **40**, 683; (*f*) J. Stanek, J. Frei, H. Mett, P. Schneider and U. Regenass, *J. Med. Chem.*, 1992, **35**, 1339; (*g*) L. Maier and H. Sporri, *Phosphorus Sulfur*, 1992, **70**, 49; (*h*) J. Guo, Y. Q. Wu, D. Rattendi, C. J. Bacchi and P. M. Woster, *J. Med. Chem.*, 1995, **38**, 1770.

2 (*a*) J. N. Kim, K. M. Kim and E. K. Ryu, *Synth. Commun.*, 1992, **22**, 1427; (*b*) T. Fuji, C. C. Wu and S. Yamada, *Chem. Pharm. Bull.*, 1967, **15**, 345; (*c*) T. Henmi, T. Sakamoto and Y. Kikugawa, *Org. Prep. Proced. Int.*, 1994, **26**, 111; (*d*) A. T. Fuller and H. King, *J. Chem. Soc.*, 1947, 963; (*e*) S.-H. Kim, D. Augeri, D. Yang and D. Kahne, *J. Am. Chem. Soc.*, 1994, **116**, 1766; (*f*) A. Fruchier, V. Moragues, C. Pétrus and F. Pétrus, *Bull. Soc. Chim. Fr.*, 1984, II, 173; (*g*) I. A. Motorina, F. Parly and D. Grierson, *Synlett*, 1996, 389.

3 J. B. Hendrickson, S. Okano and R. K. Bloom, *J. Org. Chem.*, 1969, **34**, 3434.

4 (*a*) E. L. Schumann, L. A. Paquette, R. V. Heinzelman, D. P. Wallach, J. P. DaVanzo and M. E. Grieg, *J. Med. Pharm. Chem.*, 1962, **5**, 464; (*b*) A. D. Zorina, V. F. Martynov, L. G. Matyukhina and I. A. Saltykova, *J. Gen. Chem. USSR* (*Engl. Transl.*), 1982, **52**, 204; (*c*) A. Balsamo, G. Broccali, A. Lapucci, B. Macchia, F. Macchia, E. Orlandini and A. Rossello, *J. Med. Chem.*, 1989, **32**, 1398.

5 Y. Endo, K. Shudo and T. Okamoto, *Synthesis*, 1980, 461.

6 For recent and representative examples, see: (alkylation) S. D. Young and P. P. Tamburini, *J. Am. Chem. Soc.*, 1989, **111**, 1933; V. Dupont, A. Lecoq, J.-P. Mangeot, A. Aubry, G. Boussard and M. Marraud, *J. Am. Chem. Soc.*, 1993, **115**, 8898; D. V. Patel, M. G. Young, S. P. Robinson, L. Hunihan, B. J. Dean and E. M. Gordon, *J. Med. Chem.*, 1996, **39**, 4197; (reductive amination) F.-C. Huang, T. S. Shoupe, C. J. Lin, T. D. Y. Lee, W.-K. Chan, J. Tan, M. Schnapper, J. T. Suh, R. J. Gordon, P. A. Sonnino, C. A. Sutherland, R. G. Vaninwegen and S. M. Coutts, *J. Med. Chem.*, 1989, **32**, 1836; S. Venkatraman, R. J. Roon, M. K. Schulte, J. F. Koerner and R. L. Johnson, *J. Med. Chem.*, 1994, **37**, 3939; (acylation) R. A. Farr, P. Bey, P. S. Sunkara and B. J. Lippert, *J. Med. Chem.*, 1989, **32**, 1879. See also reference 1.

7 (*a*) E. J. Breaux, *J. Heterocycl. Chem.*, 1986, **23**, 463; (*b*) S. Bottle, W. K. Busfield, I. D. Jenkins, B. W. Skelton, A. H. White, E. Rizzardo and D. H. Solomon, *J. Chem. Soc.*, *Perkin Trans. 2*, 1991, 1001; (*c*) S. D. Pastor and E. T. Hessell, *J. Org. Chem.*, 1988, **53**, 5776; (*d*) E. Winterfeldt and W. Krohn, *Chem. Ber.*, 1969, **102**, 2336.

8 I. Vlattas, L. Della Vecchia and J. J. Fitt, *J. Org. Chem.*, 1973, **38**, 3749.

9 (*a*) W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, 1957, **79**, 2828; (*b*) H.-J. Gi, Y. Xiang, R. F. Schinazi and K. Zhao, *J. Org. Chem.*, 1997, **62**, 88; (*c*) E. Bayer and K. Geckeler, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 533.

10 L. W. Jones and M. C. Sneed, *J. Am. Chem. Soc.*, 1917, **39**, 674.

11 L. C. Chan, PhD Thesis, University of Bath, 1992.

12 (*a*) J. F. Arens, *Adv. Org. Chem.*, 1960, **2**, 117; (*b*) T. L. Jacobs and W. P. Tuttle, *J. Am. Chem. Soc.*, 1949, **71**, 1313; (*c*) T. L. Jacobs and W. R. Scott, *J. Am. Chem. Soc.*, 1953, **75**, 5497.

13 K. Afarinkia, V. Vinader, T. D. Nelson and G. H. Posner, *Tetrahedron*, 1992, **48**, 9111.

14 V. Kvita and H. Sauter, *Helv. Chim. Acta*, 1990, **73**, 883.

15 (*a*) A. N. Boa, S. E. Booth, D. A. Dawkins, P. R. Jenkins, J. Fawcett and D. R. Russell, *J. Chem. Soc.*, *Perkin Trans. 1*, 1993, 1277; (*b*) O. Moriya, Y. Urata and T. Endo, *J. Chem. Soc.*, *Chem. Commun.*, 1991, 17.

16 N. A. Petasis, S.-P. Lu, E. I. Bzowej, D.-K. Fu, J. P. Staszewski, I. Akritopoulou-Zane, M. A. Patane and Y.-H. Hu, *Pure Appl. Chem.*, 1996, **68**, 667.

17 W. J. Bailey and E. W. Cummins, *J. Am. Chem. Soc.*, 1954, **76**, 1932.

18 (*a*) E. G. Kataev, T. G. Mannafov, E. G. Berdnikov and O. A. Komarovskaya, *Zh. Org. Khim.*, 1973, **9**, 1983; (*b*) B. Lindgren, *Acta Chem. Scand.*, *Ser. B*, 1977, **31**, 1.

19 P. Rajagopalan, B. G. Advani and C. N. Talaty, *Org. Synth.*, 1973, **Coll. Vol. V**, 504.

20 C. F. Huebner, E. Donoghue, L. Dorfman, F. A. Stuber, N. Danieli and E. Wenkert, *Tetrahedron Lett.*, 1966, 1185.

21 S. H. Reich, M. A. M. Fuhry, D. Nguyen, M. J. Pino, K. M. Welsh, S. Webber, C. A. Janson, S. R. Jordan, D. A. Matthews, W. W. Smith, C. A. Bartlett, C. L. J. Booth, S. M. Hermann, E. F. Howland, C. A. Morse, R. W. Ward and J. White, *J. Med. Chem.*, 1992, **35**, 847.

22 C. Graebe and J. Buenzod, *Ber.*, 1899, **32**, 1993.

23 TEXSAN Single Crystal Structure Analysis Software, Version 1.6, Molecular Structure Corporation, The Woodlands, TX 77381, USA, 1993.

24 J. Cosier and A. M. Glazer, *J. Appl. Crystallogr.*, 1986, **19**, 105.

25 G. M. Sheldrick, SHELXTL, Program for Crystal Structure Solution and Refinement, University of Göttingen, Germany, 1993.

Paper 7/08380G
Received 20*th November* 1997
Accepted 12*th January* 1998