Preparation of 2,3-dihydroselenolo[2,3-*b*]pyridines and related compounds by free-radical means†

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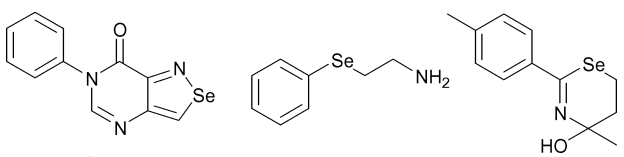
Received 21st October 2005, Accepted 28th November 2005
First published as an Advance Article on the web 21st December 2005
DOI: 10.1039/b515385a

Photolysis of the thiohydroximate ester derivative **21** of 2-carboethoxy-2-(2-(benzylseleno)pyridin-3-yl)tridecylcarboxylic acid (**20**) affords 2-dodecyl-2-carboethoxy-2,3-dihydroselenolo[2,3-*b*]pyridine (**22**) in 89% yield in a process presumably involving intramolecular homolytic substitution by a tertiary alkyl radical at selenium with loss of a benzyl radical. Alternatively, rearrangement of *O*-(ω-haloalkyl)esters **34** of 2-carboethoxy-*N*-hydroxypyridine-2-selone affords azonianaphthalenium halides **37** in 79% yield.

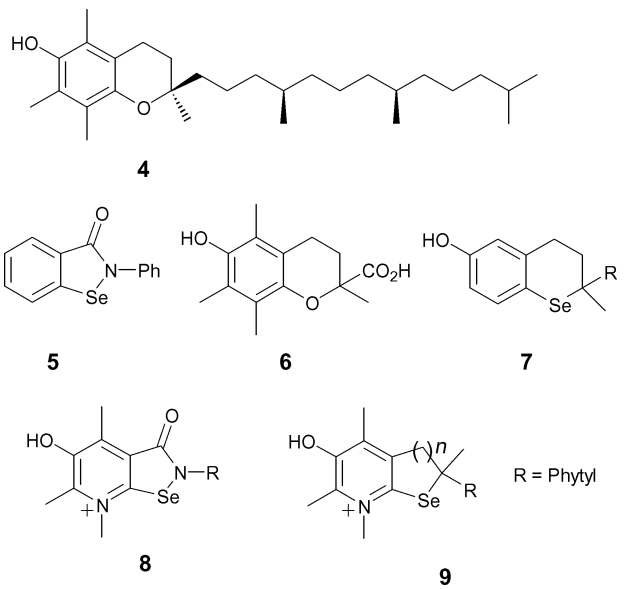
Introduction

Interest in selenium-containing therapeutics has grown over the last thirty years.[1] Simple organoselenium compounds have been prepared, such as selenazolopyrimidone (**1**), that show antitumor activity against mouse leukemia.[2] (Aminoethyl)phenylselenide (**2**) shows excellent antihypertensive activity and selenazine derivatives, such as **3**, show both antibacterial and antitumor activity.[3] Despite this, the major therapeutic benefit that selenium currently offers appears to be in the form of dietary supplements.[4] Selenium is an essential trace element and dietary deficiency can lead to ailments including gum disease, as well as debilitating conditions such as Keshan's disease.[4e] The biochemistry and pharmacology of selenium is of intense current interest. Selenium is now known to be intimately involved in the activity of enzymes such as glutathione peroxidase and thioredoxin reductase, that catalyse chemistry essential to the protection of biomolecules against oxidative stress and free radical damage.[5]



1 **2** **3**

Reactive oxygen species (ROS) are a byproduct of normal aerobic metabolism.[6] Superoxide is formed when electrons leak from the electron transport chain and react with molecular oxygen, and is also the product of some enzymatic processes.[6b,7] Superoxide dismutase converts superoxide to hydrogen peroxide, which can, in turn, lead to the formation of hydroxyl and lipid peroxyl radicals.[6b,7] Hydroxyl radicals are extremely reactive and can cause damage to important biomolecules that include DNA, while lipid peroxidation has been implicated in diseases such as atherosclerosis.[6a,8] Reactive oxygen species do have some positive roles in biology, such as providing defense against infection,[6a,9] however, excessive concentrations of ROS can lead to oxidative stress.[6a,9] Nature has evolved clever methods for controlling ROS. Preventative antioxidant enzymes such as glutathione peroxidase remove ROS through redox cycling,[5] while chain breaking antioxidants such as vitamin E, interrupt the chain reactions responsible for the formation of radical species.[10] It should be noted that vitamin E refers to a family of related compounds known as tocopherols of which α-tocopherol **4** is most potent.[10b]



4 **5** **6** **7** **8** **9**

In recent years there has been much interest in developing new, more potent antioxidants such as ebselen (**5**), that also acts as a glutathione peroxidase mimic and is due to be released for human use as a non-steroidal anti-inflammatory.[11] Water-soluble vitamin E analogues that have been prepared include Trolox (**6**),[12] while our group has used intramolecular homolytic substitution chemistry to prepare a selenium containing analogue **7** of vitamin E that possesses dual mode of action.[13]

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† Electronic supplementary information (ESI) available: B3LYP/6-311G** optimised geometries of **28a**, **28b**, **29a** and **29b** as Gaussian archive entries. See DOI: 10.1039/b515385a

‡ Parts of this work have been published in preliminary form: T. Fenner and C. H. Schiesser, *Molecules*, 2004, **9**, 472.

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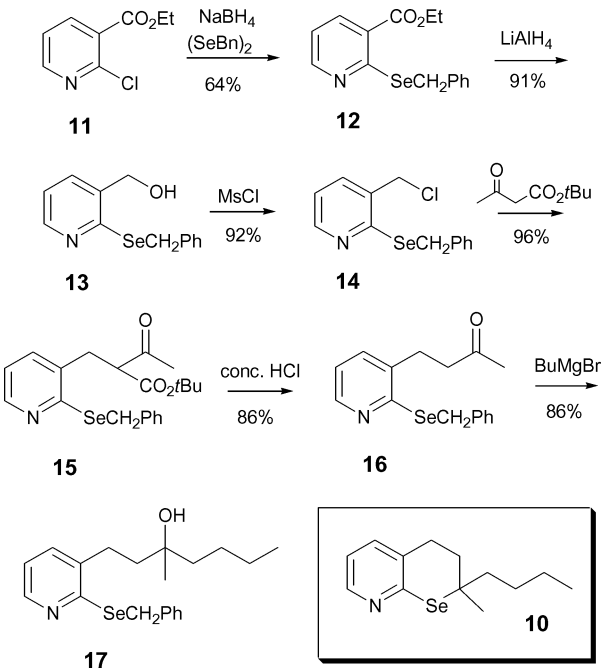
Work in our laboratories has also been directed at the development of water-soluble, dual acting, tocopherol/ebselen hybrids such as **8** and to pyridine-fused tocopherol systems such as **9**.

Results and discussion

Free radical ring closure approaches to the 2,3-dihydroselenolo[2,3-*b*]pyridine core structure

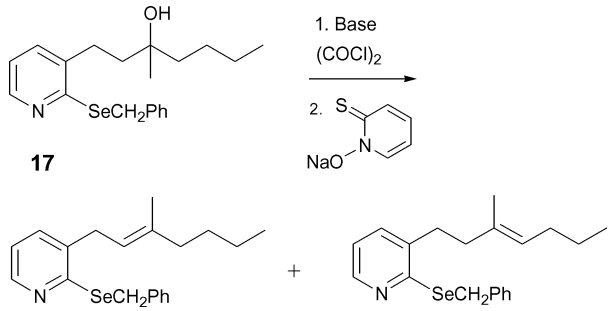
Preliminary investigations began with the attempted preparation of model compound **10** that contained many of the salient feature of structures **8** and **9**. To that end, ethyl 2-chloronicotinate (**11**) was reacted with sodium benzylselenoate, generated *in situ* by reduction of dibenzyl diselenide with sodium borohydride, to give ethyl 2-(benzylseleno)nicotinate (**12**) in 64% yield (Scheme 1).



Scheme 1

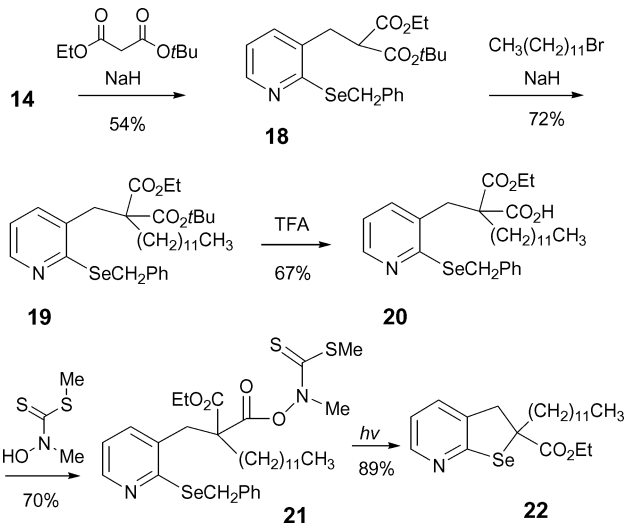
Further reduction with lithium aluminium hydride afforded alcohol **13** in 91% yield. It is interesting to note that the alternative sequence of reactions, namely reduction of the ester **11** followed by treatment with sodium benzylselenoate, proceeded only very poorly. We attribute this observation to the electrophilicity of the pyridine ring in the various substrates, specifically that the electron-withdrawing ester substituent is able to increase ring reactivity in a manner that the alcohol cannot. The alcohol **13** was further reacted with methanesulfonyl chloride to give the chloride **14** in 92% yield, which was subsequently reacted with *t*-butyl acetoacetate and base to give the ketoester **15** following the procedure developed by Engman and Malmström.[13] Treatment of **15** with concentrated hydrochloric acid afforded the required ketone **16** in excellent overall yield. Finally, reaction of **16** with *n*-butylmagnesium bromide gave the desired tertiary alcohol **17** in 86% yield (Scheme 1).

Following our previously published work, we expected that alcohol **17** could be converted into the PTOC oxalate ester, originally described by Barton and Crich as a suitable precursor for the generation of carbon-centered radicals from tertiary alcohols. To our surprise, reaction of **17** with oxalyl chloride, followed by sodium omadine®, afforded none of the desired cyclized product **10**, despite the reaction being carried out under a number of different conditions. ^{1}H NMR spectroscopy of the only identified product suggested strongly that elimination has occurred to afford a mixture of isomeric alkenes (Scheme 2).



Scheme 2

Given the problems associated with the methodology described above, it became apparent that an alternative method for the generation of the required radical was needed. Following a modification of the procedure described in Scheme 1, chloride **14** was reacted with *t*-butyl ethyl malonate to afford selenide **18** in moderate (54%) yield (Scheme 3). Further treatment with sodium hydride and 1-bromododecane provided diester **19** in 72% yield, which was selectively deprotected by the action of trifluoroacetic acid to afford 2-carboethoxy-2-(2-(benzylseleno)pyridin-3-yl)tridecylcarboxylic acid (**20**), suitable for conversion into a radical precursor.

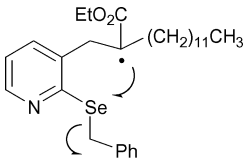


Scheme 3

Kim recently described a new method for generating carbon-centered radicals from thiohydroximate esters of carboxylic acids and we have generally found this precursor to be superior to those described by Barton and coworkers[14] for reasons including stability, especially in tertiary systems.[15] Therefore, **20** was converted into precursor **21** by the action of *N*-methylhydroxydithiocarbamate and dicyclohexylcarbodiimide (DCC); **21** was isolated

as a yellow oil after column chromatography. Photolysis of **21** in heptane afforded the target 2-dodecyl-2-carboethoxy-2,3-dihydroselenolo[2,3-*b*]pyridine (**22**) in 89% yield. The dihydroselenolo[2,3-*b*]pyridine **22** displayed a ^{77}Se NMR signal at δ 547.6 characteristic of structurally related selenium heterocycles.[16]

Having successfully demonstrated that tertiary carbon-centered radicals, such as **23** are capable of undergoing intramolecular homolytic substitution to afford dihydroselenolo[2,3-*b*]pyridines such as **22**, we next turned our attention to the preparation of a precursor for the synthesis of a six-membered ring such as that found in the initial target compound **10**.



23

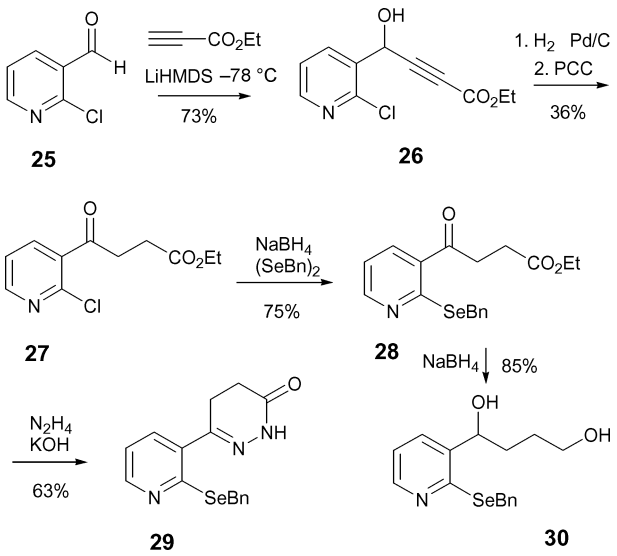
To that end, 2-chloronicotinaldehyde (**25**) was added to a solution of ethyl propiolate and lithium bis(trimethylsilyl)amide in THF at −78 °C. After stirring at −78 °C for 4 h, the reaction was quenched using saturated ammonium chloride solution to give the acetylinic alcohol **26** in 73% yield after purification. It is important that the reaction mixture is quenched at low temperature, as significantly lower yields were obtained when the mixture was allowed to warm before addition of the ammonium chloride solution.

Hydrogenolysis of alcohol **26** followed by PCC oxidation afforded ketone **27** in poor (36%) yield. Significant amounts of by-product appeared to accompany this transformation. Despite this, ketone **27** was further reacted with sodium benzylselenoate, generated as described above, to afford ethyl 3-oxo-3-(2-(benzylseleno)pyridin-3-yl)butyrate (**28**) in acceptable yield.

With **28** in hand, the next task was the removal of the ketone functional group. We envisaged that Wolff–Kischner or Clemenson techniques would result in the required compound. Unfortunately, the action of zinc-mercury amalgam (Clemensen reduction) returned only **28**, while reaction with alkaline hydrazine (Wolff–Kischner reduction) afforded a single product that was assigned to be pyradizinone **29** that was isolated in 63% yield. The formation of **29** can be rationalized by the nucleophilic capture of the initial ketone–hydrazine adduct by the proximate ester moiety, with subsequent dehydration (Scheme 4).

Ketone **28** proved to surprisingly difficult to reduce using standard techniques. Treatment with a large excess of sodium borohydride at room temperature resulted in no reduction, however in refluxing ethanol, clean conversion to the diol **30** was observed after several hours. Single crystal X-ray analysis of **28** provided interesting structural information that may help in our understanding of the relative inertness of the ketone moiety in **28** to reduction.

A perspective diagram of **28** is presented in Fig. 1. There appears to be a remarkably short selenium–oxygen separation in **28**, which at 2.679(3) Å is well below the sum of the van der Waals radii of the two atoms involved (3.4 Å) and is suggestive of significant contribution of resonance structure **31** to the overall bonding in **28**. Indeed, the Se–O1 separation in **28** is, to the best of our knowledge, the shortest selenium–carbonyl oxygen interaction reported, being some 0.04 Å shorter than the previous "record" of 2.72 Å reported



Scheme 4

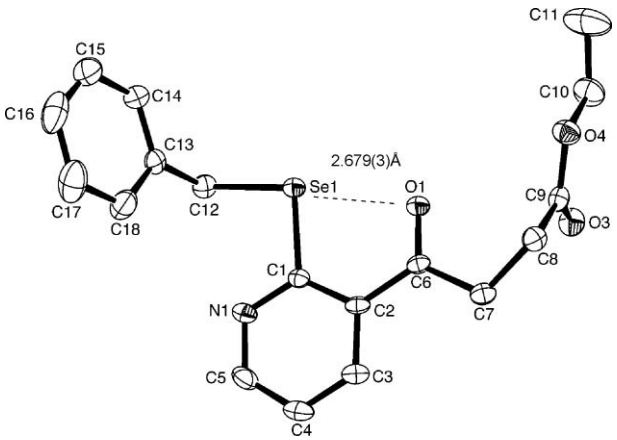


Fig. 1 Perspective diagram of **28**.

by us recently.[17] The Se–O1 interaction might possibly involve donation of electron density into the Se1–C12 σ* orbital, however the C1–C2 bond distance of 1.403(4) Å, the ketone carbonyl C6–O1 bond distance of 1.219(3) Å, the C2–C6 bond distance of 1.4629(4) Å and the C1–Se1 distance of 1.917(3) Å are all similar to bond distances for similar fragments which were extracted from the Cambridge Crystallographic Database[18] and thus do not provide any further structural evidence for contributions from resonance form **31**.

A second, weaker interaction exists between O1, and the ester carbonyl C9, this interaction is characterised by the O1 ··· C9 distance of 2.791(3) Å which is shorter than the sum of the van der Waals radii of oxygen and carbon (3.25 Å), furthermore the ester carbonyl carbon (C9) deviates by 0.019 Å from the plane defined by O4, O4 and C8 towards O1, this interaction may also stabilise the gauche conformation of the side chain substituent [C6–C7–C8–C9-65.9(4)] (Fig. 1).

The contribution of **31** to the overall structure of **28** is further supported by computational studies. B3LYP/6-311G** calculations[19] (Fig. 2) predict that in the closely-related methylselenides, conformation **28a** is preferred over **28b** by 17.6 kJ mol^{-1}. Conformer **28a** displays similar interations to those observed in the

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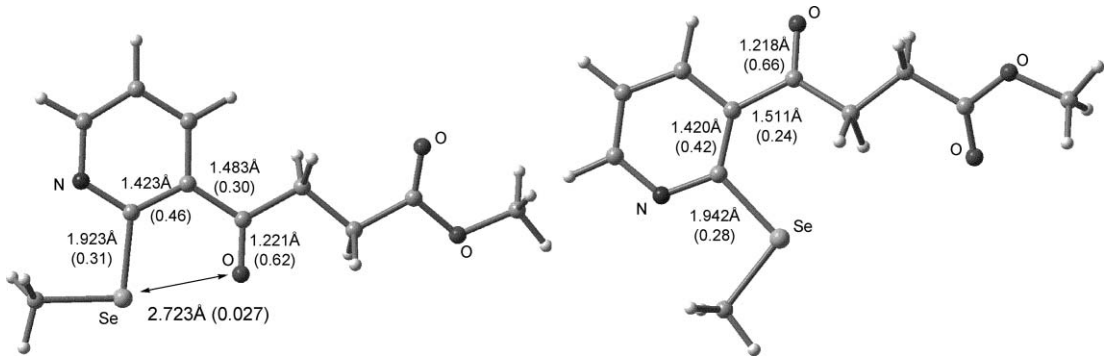


Fig. 2 B3LYP/6-311G** optimised structures for **28a** (left) and **28b** (right). Mulliken bond populations in parentheses.

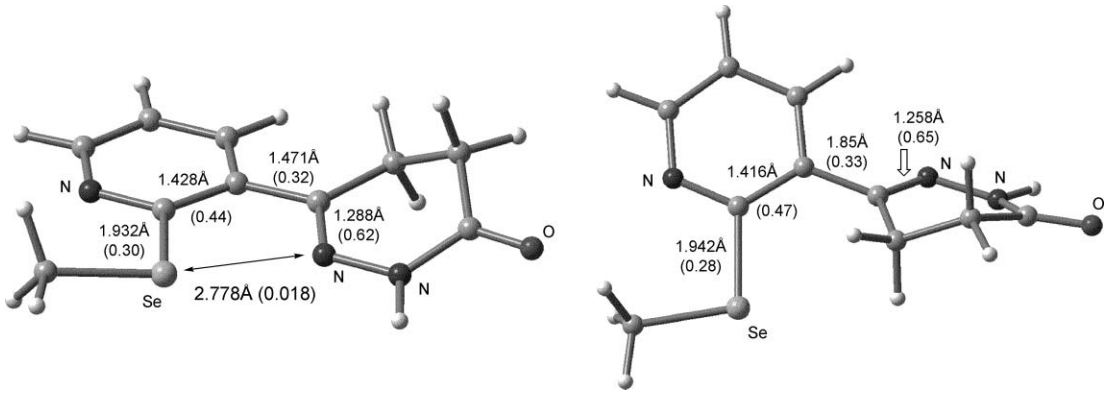
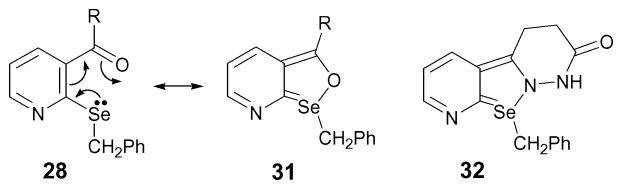


Fig. 3 B3LYP/6-311G** optimised structures for **29a** (left) and **29b** (right). Mulliken bond populations in parentheses.

X-ray structure of ketone **28** with a short (2.72 Å) N–Se separation. In addition, the N–Se Mulliken bond populations and remaining bond lengths in **28a** when compared with **28b** are supportive of the bonding interaction depicted in **31**, with the N–Se population of 0.027 corresponding to about a "10% bond".

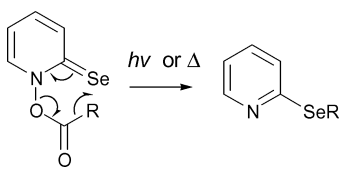
Similar reasoning can be used to explain the formation of **29** during the attempted Wolff–Kischner reduction; resonance structure **32** would be expected to contribute strongly to the stabilization of **29**. This hypothesis is once again supported by computational studies; B3LYP/6-311G** calculations (Fig. 3) predict that in the closely-related methylselenides, conformation **29a** is preferred over **29b** by 9.2 kJ mol^{-1}, with **29a** displaying similar interations to those observed in the X-ray structure of ketone **28** and the calculated structure **28a**, with a short (2.78 Å) N–Se separation. Once again, N–Se Mulliken bond populations and bond lengths are supportive of the bonding interaction depicted in **32**, with the N–Se population of 0.018 corresponding to about a "5% bond".



28 **31** **32**

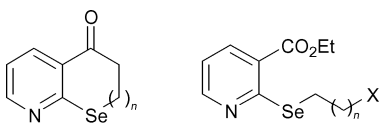
Free radical rearrangements of carboxylic esters of 2-selenopyridine-*N*-oxide

Some twenty years ago, Barton described the preparation of *O*-esters of 2-selenopyridine-*N*-oxide and their decarboxylative rearrangement to form 2-(alkylseleno)pyridines (Scheme 5) through a mechanism that is likely to involve a radical cage mechanism.[20]



Scheme 5

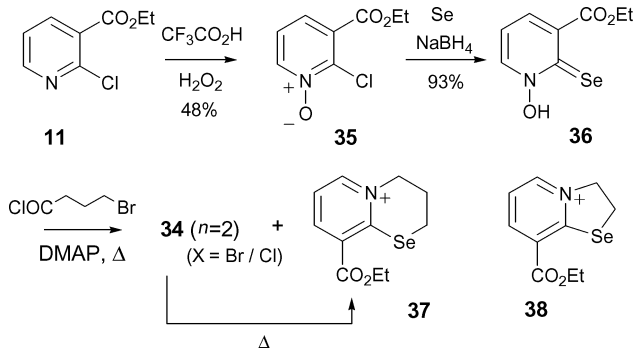
With the initial intention that cyclized structures such as **33** could be prepared from haloalkylselenides such as **34**, we chose to explore the use of the selone chemistry described above for the preparation of **34**.



33 **34**

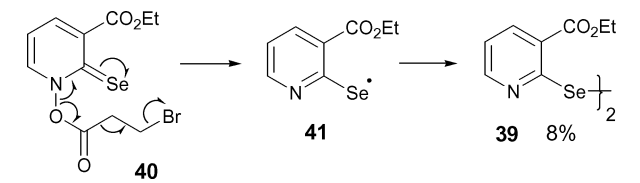
Ethyl 2-chloronicotinate **11** was oxidised using hydrogen peroxide in trifluoroacetic acid. The resultant *N*-oxide **35** was treated with selenium powder and sodium borohydride following Barton's protocol[20] to give 2-carboethoxy-*N*-hydroxypyridine-2-selone (**36**) as a yellow oil. As expected, selone **36** proved to be unstable and was immediately reacted with 4-bromobutanoyl chloride. After 30 min in benzene at reflux, the precipitate was collected and was shown to be the azonianaphthalenium halide **37** by HRMS. The filtrate was subjected to flash chromatography

affording the halopropylselenides **34** (X = Br/Cl) as an inseparable mixture. Clearly, the initially rearranged selenide **34** (X = Br) has undergone further nucleophilic attack by both chloride ion (intermolecularly), as well as the nucleophilic nitrogen in **34** to produce the observed products. When the reaction was repeated with overnight reflux, the azonianaphthalenium halide **37** was isolated in 79% yield, with no intermediate **34** present in the reaction mixture (Scheme 6).



Scheme 6

The preparation of the azonianaphthalenium halide **37** fits well with the original aim of preparing water-soluble selenium-containing antioxidants. With this in mind, we attempted to prepare the related compound **38**. Treatment of selone **36** with 3-bromopropanoyl chloride resulted in the rapid evolution of gas, presumably CO_2, and a complex mixture of products from which diselenide **39** was isolated as the only identifiable product. We speculate that the first-formed ester **40** decomposes through a β-cleavage machanism to afford radical **41** that dimerises to give the observed product (Scheme 7).



Scheme 7

Conclusion

We have presented work toward the preparation of novel pyridine-fused, selenium-containing antioxidants and have demonstrated that, intramolecular homolytic substitution as well as free-radical rearrangements of *O*-esters of 2-selenopyridine-*N*-oxide are effective methods for the preparation of model ring systems. The reactivity of ethyl 3-oxo-3-(2-(benzylseleno)pyridin-3-yl)butyrate (**28**) and 6-[2-(benzylseleno)pyridin-3-yl]-4,5-dihydro-2*H*-pyridazin-3-one (**29**) is attributed to strong non-bonded O–Se interactions that are supported by X-ray as well as computational analysis.

Experimental

Melting points are uncorrected. Unless otherwise stated, ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$ on a Varian unity 400 spectrometer. For proton spectra the residual peak of $CHCl_3$ was used as the internal reference (7.26 ppm) while the central peak of $CDCl_3$ (77.0 ppm) was used as the reference for carbon spectra. ^{77}Se NMR chemical shifts are given in ppm relative to externally referenced diphenyl diselenide (δ 464). EI mass spectra were recorded at 70 eV. M^+ ions are given for ^{80}Se. Tetrahydrofuran and diethyl ether were distilled under nitrogen from sodium–benzophenone. Benzene and pyridine were distilled under nitrogen from calcium hydride. Elemental analyses were performed by Chemical and Micro Analytical services Pty. Ltd, Geelong, Victoria, Australia.

Ethyl 2-(benzylseleno)nicotinate (12)

Sodium borohydride was added in portions to a suspension of dibenzyl diselenide (5.00 g, 14.7 mmol) in degassed ethanol (100 mL) under a flow of nitrogen until a colourless solution formed. Ethyl 2-chloronicotinate[21] (**11**) (5.47 g, 29.4 mmol) in ethanol (20 ml) was added and the reaction mixture refluxed for 3 h. Water (70 mL) was added and the volume of solvent reduced under vacuum. The residue was extracted with ether (3 × 70 mL) and the combined extracts dried ($MgSO_4$) and separated by flash chromatography (5% EtOAc–hexane followed by 20% EtOAc–hexane after residual dibenzyl diselenide had eluted). The title compound was obtained as pale yellow crystals (71%). Mp 52–53 °C. ^{1}H NMR δ 1.36 (t, 3H, J = 7.2), 4.35 (q, 2H, J = 7.2), 4.41 (s, 2H), 7.09–7.26 (m, 4H), 7.38 (d, 2H, J = 8.1), 8.20 (dd, 1H, J = 1.8, 7.8) 8.59 (dd, 1H, J = 1.8, 4.6). ^{13}C NMR δ 14.3, 29.2, 61.6, 119.0, 124.7, 126.5, 128.3, 129.3, 138.6, 139.2, 152.3, 160.7, 165.5. ^{77}Se NMR δ 469.8. IR 2918, 1701. MS m/z $(M + H)^+$ 322.3. (HRMS Found: 322.0346. $C_{15}H_{16}NO_2Se$ requires 322.0343). (Found: C, 56.14 H, 4.79 N, 4.36. $C_{15}H_{15}NO_2Se$ requires C, 56.26 H, 4.72 N, 4.37%).

[2-(Benzylseleno)pyridin-3-yl]methanol (13)

A solution of ethyl 2-(benzylseleno)nicotinate (**12**) (2.63 g, 8.23 mmol) in ether (50 mL) was added by a dropping funnel to an ice cooled suspension of lithium aluminiumhydride (0.34 g, 9.0 mmol) in ether (15 mL). After stirring at room temperature for 1.5 h under N_2, the reaction was quenched with water. After stirring for 30 min, the reaction mixture was washed with water (2 × 70 mL), sat. NaCl (40 mL) and the organic phase dried ($MgSO_4$). Flash chromatography (50% EtOAc–hexane) gave the title compound as a very pale oil (97%). ^{1}H NMR δ 4.52 (s, 2H, J_{77Se} = 10.2), 4.58 (s, 2H), 7.08 (dd, 1H, J = 4.9, 7.6), 7.18–7.27 (m, 3H), 7.35 (d, 2H, J = 8.3), 7.60 (dd, 1H, J = 1.2, 7.6), 8.43 (dd, 1H, J = 1.2, 4.9). ^{13}C NMR δ 29.2, 62.5, 120.5, 126.8, 128.4, 129.0, 134.3, 136.2, 139.1, 148.5, 154.2. ^{77}Se NMR δ 384.8; IR 3331 (br). MS m/z $(M + H)^+$ 280.2. (Found: C, 56.13 H, 4.71 N, 5.05. $C_{13}H_{13}NOSe$ requires C, 56.12 H, 4.71 N, 5.03%).

2-(Benzylseleno)-3-(chloromethyl)pyridine (14)

A solution of [2-(Benzylseleno)pyridin-3-yl]methanol (**13**) 4.40 g, 15.8 mmol) and triethylamine (4.4 mL, 32 mmol) in THF (30 mL) was cooled to 0°C and methanesulfonyl chloride (2.5 mL, 32 mmol) was slowly added under N_2. The mixture was allowed to warm to room temperature and then heated at reflux for 1 h. The reaction was quenched with water and extracted with ether

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(3 × 70 mL), the combined extracts dried ($MgSO_4$) and separated by flash chromatography (10% EtOAc–hexane) to afford the title compound as a colourless oil (96%). ^{1}H NMR δ 4.53 (s, 2H), 4.55 (s, 2H), 7.09 (dd, 1H, $J = 4.8, 7.8$), 7.18–7.28 (m, 3H), 7.38 (d, 2H, $J = 7.8$), 7.57 (1H, dd, $J = 1.5, 7.8$), 8.46 (1H, dd, $J = 1.5, 4.8$). ^{13}C NMR δ 29.6, 44.0, 120.4, 126.9, 128.4, 129.1, 132.8, 136.4, 138.9, 149.3, 156.2. ^{77}Se NMR δ 390.5. MS m/z $(M + H)^+$ 298.2. (HRMS found 319.9716. $C_{13}ClH_{12}NNaSe$ requires 319.9721).

tert-Butyl 2-[(2-(benzylseleno)pyridin-3-yl)methyl]-3-oxobutyrate (15)

tert-Butyl acetoacetate (0.95 mL, 5.67 mmol) was added to a suspension of sodium hydride (0.17 g of 60% in mineral oil, 5.66 mmol) in dry THF (2 mL) cooled to 0 °C under N_2. The mixture was stirred at room temperature for 45 min after which 2-(benzylseleno)-3-(chloromethyl)pyridine (**14**) (0.573 g, 1.93 mmol) was added and the reaction mixture refluxed for 18 h before quenching with water. The resultant mixture was extracted with diethyl ether (3 × 15 mL) washed with sat. NaCl (15 mL), dried ($MgSO_4$) and the solvent evaporated to afford the title ester as a colourless oil and of sufficient purity for further use (84%). ^{1}H NMR δ 1.39 (s, 9H), 2.18 (s, 3H), 3.05 (dd, 2H, $J = 1.8, 6.9$), 3.81 (t, 1H, $J = 6.9$) 4.53 (s, 2H, J_{77Se} 10.0), 6.99 (dd, 1H, $J = 4.5, 7.2$), 7.20–7.29 (m, 3H), 7.38 (d, 3H, $J = 7.8$), 8.38 (dd, 1H, $J = 1.9, 4.6$). ^{13}C NMR δ 27.9, 29.5, 29.6, 31.7, 59.0, 82.3, 120.2, 126.8, 128.5, 129.1, 133.8, 137.3, 139.2, 148.0, 167.8, 202.3. ^{77}Se NMR δ 385.5. IR 1715. MS m/z $(M + H)^+$ 420.4. (HRMS found 420.1066. $C_{21}H_{26}NO_3Se$ requires 420.1078).

4-[2-(Benzylseleno)pyridin-3-yl]butan-2-one (16)

A mixture of *tert*-butyl 2-[(2-(benzylseleno)pyridin-3-yl)methyl]-3-oxobutyrate (**15**) (4.96 g, 11.9 mmol) and conc. HCl (60 mL) was stirred at room temperature for 18 h. The reaction mixture was basified to pH 8.5 with 10% NaOH and extracted with ether (3 × 100 mL). The combined organics were dried ($MgSO_4$) and concentrated under vacuum. The residue was separated by flash chromatography (10% EtOAc–hexane) to give the title ketone as white crystals (86%). Mp 54–55 °C. ^{1}H NMR δ 2.11 (s, 3H), 2.72 (m, 2H), 2.83 (m, 2H) 4.51 (s, 2H, $J_{77Se} = 20.4$) 7.01 (dd, 1H, $J = 4.9, 7.6$) 7.20–7.29 (m, 3H) 7.35–7.39 (m, 3H), 8.36 (dd, 1H, $J = 1.7, 4.9$). ^{13}C NMR δ 27.5, 29.2, 29.9, 42.5, 120.7, 126.8, 128.4, 129.1, 136.1, 139.3, 147.6, 155.4, 207.2. ^{77}Se NMR δ 385.8. IR 1713. MS m/z $(M + H)^+$ 320.3. (Found: C, 60.47; H, 5.33; N, 4.41. $C_{16}H_{17}NOSe$ requires C, 60.38; H, 5.38; N, 4.40%).

1-[2-(Benzylseleno)pyridin-3-yl]-3-methylheptan-3-ol (17)

4-[2-(Benzylseleno)pyridin-3-yl]butan-2-one (**16**) (1.13 g, 3.57 mmol) in dry ether (15 mL) was added carefully, under N_2, to a cooled (0 °C) stirred solution of butylmagnesium bromide [prepared from 1-bromobutane (0.50 mL, 4.70 mmol) and magnesium (128 mg, 5.27 mmol) in dry ether (16 mL)]. The mixture was stirred for 1 h. Sat. NH_4Cl was added carefully and the reaction mixture was partioned between water and ether. The aqueous phase was extracted with ether (3 × 20 mL), the combined organics dried ($MgSO_4$), and the solvent removed *in vacuo*. The residue was separated by flash chromatography (20% EtOAc–petroleum spirit 60–80 °C) to give the title alcohol as a pale yellow oil (86%). ^{1}H NMR δ 0.91 (t, 3H, $J = 6.8$), 1.21 (s, 3H), 1.29–1.35 (m, 4H) 1.48 (m, 2H), 1.67 (m, 2H) 2.63 (m, 2H), 4.51 (s, 2H, $J_{77Se} = 10.2$) 7.01 (dd, 1H, $J = 4.6, 7.6$) 7.19–7.40 (m, 6H), 8.36 (dd, 1H, $J = 1.9, 4.6$). ^{13}C NMR δ 14.1, 23.2, 26.1, 26.7, 28.2, 29.1, 41.4, 41.7, 72.5, 121.0, 126.7, 128.4, 129.1, 135.4, 137.7, 139.4, 147.2, 155.4. ^{77}Se NMR δ 383.8. IR 3420 (br). MS m/z $(M + H)^+$ 378.4. (Found: C, 63.63; H, 7.20; N, 3.81. $C_{20}H_{27}NOSe$ requires C, 63.82; H, 7.23; N, 3.72%).

tert-Butyl ethyl 2-[2-(benzylseleno)pyridin-3-ylmethyl]malonate (18)

tert-Butyl ethyl malonate (0.92 mL, 4.87 mmol) was added to a suspension of sodium hydride (200 mg of a 60% suspension in oil, 4.87 mmol) in THF (5 mL) at 0 °C under N_2. After stirring at room temperature for 30 min, 2-(benzylseleno)-3-(chloromethyl)pyridine (**14**) (1.11 g, 3.75 mmol) was added and the reaction heated at reflux for 18 h, at which time water was added carefully to the cooled reaction mixture. After extraction with ether (3 × 30 mL), the combined extracts were dried ($MgSO_4$) and concentrated to dryness under vacuum. The residue was separated by flash chromatography (10% EtOAc–hexane) to give the title compound as a colourless oil (54%). ^{1}H NMR δ 1.21 (t, 3H, $J = 7.1$), 1.39 (s, 9H), 3.13 (d, 2H $J = 7.8$), 3.71 (t, 1H $J = 7.8$), 4.11–4.17 (m, 2H), 4.53 (s, 2H), 6.99 (dd, 1H, $J = 4.7, 7.2$), 7.19–7.21 (m, 1H), 7.25–7.29 (m, 2H), 7.38–7.40 (m, 3H), 8.38 (dd, 1H, $J = 1.5, 4.7$). ^{13}C NMR δ 14.0, 27.8, 29.3, 32.5, 51.6, 61.3, 82.1, 120.1, 126.8, 128.4, 129.1, 133.3, 136.9, 139.0, 148.0, 155.9, 167.5, 168.8; ^{77}Se NMR δ 385.1. IR 1730. (Found: C, 58.88; H, 5.93; N, 3.09. $C_{22}H_{27}NO_4Se$ requires C, 58.93; H, 6.07; N, 3.12%).

tert-Butyl ethyl 2-[2-(benzylseleno)pyridin-3-ylmethyl]-2-dodecylmalonate (19)

A solution of *tert*-butyl ethyl 2-[2-(benzylseleno)pyridin-3-ylmethyl]malonate (**18**) (920 mg, 2.02 mmol) and sodium hydride (100 mg of a 60% suspension in mineral oil) in THF (5 mL) was stirred at 0 °C for 30 min under N_2. 1-Bromododecane (1. 5 mL, 6.25 mmol) was added and the mixture heated under reflux for 5 h and partitioned between water and ether. The aqueous phase was further extracted with ether (2 × 20 mL) and the combined ether extracts dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue separated by flash chromatography (5% EtOAc–hexane) to give the title compound as a viscous oil (74%). ^{1}H NMR δ 0.87 ((t, 3H, $J = 6.9$), 1.16 (t, 3H, $J = 7.1$), 1.22–1.25 (m, 20H), 1.37 (s, 9H), 1.80 (m, 2H), 3.18 (s, 2H), 4.05–4.16 (m, 2H), 4.46 (s, 2H), 6.93–6.96 (dd, 1H, $J = 4.9, 7.5$), 7.16 (d, 1H, $J = 7.2$), 7.20–7.25 (m, 2H), 7.33–7.40 (m, 3H), 8.34 (dd, 1H, $J = 1.3, 4.6$). ^{13}C NMR δ 13.9, 14.0, 22.6, 24.2, 27.7, 27.6, 29.2, 29.3, 29.4, 29.5, 29.6, 29.7, 29.9, 31.8, 33.4, 35.6, 58.7, 61.0, 81.7, 119.8, 126.6, 128.6, 129.0, 133.1, 136.5, 139.2, 147.6, 157.0, 170.0, 171.4. ^{77}Se NMR δ 392.1. IR 1732. (Found: C, 66.30; H, 8.28; N, 2.25. $C_{34}H_{51}NO_4Se$ requires C, 66.21; H, 8.34; N, 2.27%).

2-(Ethoxycarbonyl)-2-[2-(benzylseleno)pyridin-3-ylmethyl]tetradecanoic acid (20)

tert-Butyl ethyl 2-(2-benzylselenopyridin-3-ylmethyl)-2-dodecyl malonate (**20**) (90.1 mg, 1.45 mmol) and trifluoroacetic acid (4 mL) were stirred at 0 °C in dichloromethane (4 mL). After

1 h, sat. $NaHCO_3$ was added carefully and the resultant mixture extracted with dichloromethane (3 × 20 mL). The combined extracts were dried ($MgSO_4$) and the solvent removed *in vacuo.* Flash chromatography (20% EtOAc–hexane) afforded the title compound as a colorless oil (67%). ^{1}H NMR δ 0.87 (t, 3H, J = 6.3), 1.14 (t, 3H, J = 6.1), 1.22–1.29 (m, 20H), 1.94 (m, 2H), 3.21 (d, 1H, J = 14.8), 3.32 (d, 1H, J = 14.9), 4.06–4.20 (m, 2H), 4.40 (d, 1H, J = 11.7), 4.46 (d, 1H, J = 11.6), 7.00 (dd, 1H, J = 4.9, 7.5), 7.17–7.39 (m, 6H), 8.40 (d, 1H, J = 4.5). ^{13}C NMR δ 13.7, 14.1, 22.6, 24.7, 24.8, 29.2, 29.3, 29.4, 29.5, 29.5, 29.7, 30.3, 31.9, 35.8, 38.2, 58.1, 62.0, 120.4, 126.8, 128.4, 129.0, 132.8, 136.5, 138.9, 148.0, 156.5, 173.6, 174.2; ^{77}Se NMR δ 391.8. IR 1740, 1713. (HRMS found 562.2448. $C_{30}H_{44}NO_4Se$ requires: 562.2448).

N-[2-(Ethoxycarbonyl)-2-[2-(benzylseleno)pyridin-3-ylmethyl]tetradecanoyloxy]-*N*,*S*-dimethyldithiocarbamate (21)

N,*S*-dimethyl-*N*-hydroxydithiocarbamate[22] (70 mg, 0.56 mmol) was added to a solution of 2-(ethoxycarbonyl)-2-[2-(benzylseleno)pyridin-3-ylmethyl]tetradecanoic acid (**20**) (244 mg, 0.435 mmol), dicyclocarbodiimide (90 mg, 0.44 mmol) and DMAP (catalytic) in dichloromethane (4 mL). The reaction mixture was stirred for 18 h before being filtered through a plug of celite. The fitrate was washed with sat. $NaHCO_3$ and the dried ($MgSO_4$). Separation of the residue by flash chromatography (gradient: 5–50% EtOAc–hexane) afforded the title compound as a yellow oil (70%). ^{1}H NMR δ 0.87 (t, 3H, J = 6.9), 1.15 (m, 3H), 1.20–1.29 (m, 20H), 2.03 (t, 2H, J = 8.4), 2.52 (s, 3H), 3.28 (d, 1H, J = 15.3), 3.42 (d, 1H, J = 15.3), 3.66 (s, 3H), 4.08–4.17 (m, 2H), 4.48 (s, 2H), 6.98–7.02 (m, 1H), 7.18–7.26 (m, 3H), 7.35 (d, 1H, J = 8.1), 7.44 (d, 1H, J = 7.6), 8.39 (m, 1H). ^{13}C NMR δ 13.8, 14.1, 18.6, 22.6, 24.3, 29.22, 29.3, 29.4, 29.5, 29.6, 30.1, 31.9, 33.6, 35.9, 42.3, 42.3, 57.7, 61.7, 62.2, 119.9, 126.8, 128.4, 129.0, 131.7, 136.9, 139.0, 148.2, 157.2, 167.9, 169.3, 197.6. ^{77}Se NMR δ 394.8. (HRMS found 681.2291 $C_{33}H_{49}N_2O_4S_2Se$ requires: 681.2298).

2-Dodecyl-2-ethoxycarbonyl-2,3-dihydroselenolo[2,3-*b*]pyridine (22)

N-[2-(Ethoxycarbonyl)-2-[2-(benzylseleno)pyridin-3-ylmethyl]-tetradecanoyloxy]-*N*,*S*-dimethyldithiocarbamate (**21**) (0.100 g, 0.157 mmol) and AIBN (approx. 4 mg) in heptane (20 mL) was irradiated with a low-pressure mercury lamp for 4 h. The solvent was removed *in vacuo* and the residue was separated by flash chromatography (gradient: 10% EtOAc–hexane to 20% EtOAc–hexane) to give the title compound as a colourless oil (89%) ^{1}H NMR δ 0.86 (t, 3H, J = 6.5), 1.12–1.38 (m, 23H), 2.05–2.24 (m, 2H), 3.18 (d, 1H, J = 16.2), 3.79 (d, 1H, J = 16.2), 4.20 (m, 2H), 6.96 (dd, 1H, J = 4.8, J = 7.2), 7.34 (d, 1H, J = 7.2), 8.22 (d, 1H, J = 0.6). ^{13}C NMR δ 14.0, 14.1, 22.6, 26.2, 29.3, 29.3, 29.4, 29.5, 29.5, 29.6, 29.6, 31.9, 39.7, 42.5, 59.0, 61.7, 120.0, 128.3, 129.0, 131.7, 148.4, 173.7. ^{77}Se NMR δ 547.6. IR 1732. (Found: C, 62.16; H, 8.35; N, 3.28. $C_{22}H_{35}NO_2Se$ requires C, 62.25; H, 8.31; N, 3.30%.)

Ethyl 4-(2-chloropyridin-3-yl)-4-hydroxybut-2-ynoate (26)

Lithium bis(trimethylsilyl)amide (40 mL of a 1 M in THF, 40.0 mmol) was added to a solution of ethyl propiolate (4.1 mL, 40.4 mmol) in THF (80 mL) at −78 °C under N_2. The reaction mixture was stirred for 15 min after which 2-chloronicotinaldehyde[21] (**25**) (5.1 g, 36.2 mmol) in THF (5 mL) was added slowly. The reaction was monitored by TLC and after stirring for 5 h at −78 °C, sat. NH_4Cl was added dropwise and the reaction allowed to warm to room temperature. The reaction mixture was partitioned between water and ether and the aqueous phase extracted with ether (3 × 50 mL). The combined ethereal layers were dried ($MgSO_4$) and the solvent removed *in vacuo.* The residue was separated by flash chromatography (10% to 50% EtOAc–hexane) to give the title compound as a pale yellow crystalline solid (92%). Mp 68–69.5 °C. ^{1}H NMR δ 1.32 (t, 3H, J = 7.2), 2.70 (bs, 1H), 4.26 (q, 2H, J = 7.2), 5.90 (s, 1H), 7.35 (dd, 1H, J = 4.8, 7.6), 8.08 (dd, 1H, J = 2.0, 7.6), 8.42 (dd, 1H, J = 2.0, 4.8). ^{13}C NMR δ 13.9, 60.7, 62.4, 74.4, 84.0, 123.0, 133.3, 137.2, 149.3, 149.5, 153.0. IR 3155 (br), 2230, 1719. MS m/z 240.1 $(M + H)^+$. (Found: C, 55.18; H, 4.21; N, 5.90. $C_{11}H_{10}ClNO_3$ requires: C, 55.13; H, 4.21; N, 5.84%).

Ethyl 4-(2-chloropyridin-3-yl)-4-hydroxybutyrate

Ethyl 4-(2-chloropyridin-3-yl)-4-hydroxybut-2-ynoate (1.57 g, 6.56 mmol) and 10% Pd/C (catalytic) in methanol (30 mL) was reacted with hydrogen gas at atmospheric pressure for 5 h, at which time approximately 430 mL of H_2 had been consumed. The reaction mixture was passed through a plug of Celite and the solvent removed under vacuum. The residue was separated by flash chromatography (20 to 50% EtOAc–hexane) to give the title compound as a pale yellow oil (48% yield) together with ethyl 4-(pyridin-3-yl)butyrate (15%).

Ethyl 4-(2-chloropyridin-3-yl)-4-hydroxybutyrate. ^{1}H NMR δ 1.17 (t, 3H, J = 7.2), 1.88 (ddt, 1H, J = 7.2, 8.1, 14.5), 2.06 (ddt, 1H, J = 3.5, 7.2, 14.5), 2.42 (t, 2H, J = 7.2), 3.67 (bs, 1H), 4.04 (q, 2H, J = 7.2), 5.01 (dd, 1H, J = 3.5, 8.1), 7.19 (dd, 1H, J = 4.7, 7.6), 7.90 (dd, 1H, J = 1.8, 7.6), 8.15 (dd, 1H, J = 1.8, 4.7). ^{13}C NMR δ 14.0, 30.6, 31.8, 60.7, 69.0, 122.8, 136.4, 138.6, 147.9, 148.4, 174.0. IR 3363 (br) 1788, 1715. MS m/z 244.1 $(M + H)^+$. (Found C, 54.24; H, 5.70; N, 5.76. $C_{11}H_{15}ClNO_3$ requires: C, 54.22; H, 5.79; N, 5.75%).

Ethyl 4-(pyridin-3-yl)butyrate. ^{1}H NMR δ 1.25 (t, 3H, J = 9.2), 1.95 (m, 2H), 2.33 (m, 2H), 2.66 (m, 2H), 4.11 (q, 2H, J = 9.2), 7.21 (m, 1H), 7.49 (m, 1H), 8.4.2 (m, 2H). ^{13}C NMR δ 14.1, 26.1, 32.1, 33.3, 60.3, 123.3, 136.0, 136.7, 147.3, 149.6, 173.0. IR 1732. MS m/z 194.1 $(M + H)^+$ (Found: C, 68.41; H, 7.80; N, 7.19. $C_{11}H_{15}NO_2$ requires: C, 68.37; H, 7.82; N, 7.25%).

Ethyl 4-(2-chloropyridin-3-yl)-4-oxobutyrate (27)

Ethyl 4-(2-chloropyridin-3-yl)-4-hydroxybutyrate (0.753 g, 3.08 mmol) and pyridinium chlorochromate (1.6 g) were stirred in dichloromethane (10 mL) at room temperature for 6 h. The solid was washed with ether (4 × 15 mL) and the combined washings reduced *in vacuo*. Purification was effected by flash chromatography (50% EtOAc–hexane) to give the title compound as a colourless oil (67%). ^{1}H NMR δ 1.27 (t, 3H, J = 7.2), 2.80 (t, 2H, J = 6.4), 3.29 (t, 2H, J = 6.4), 4.14 (q, 2H, J = 7.2), 7.33 (dd, 1H, J = 4.6, 7.6), 7.90 (d, 1H, J = 7.6), 8.47 (d, 1H, J = 4.6). ^{13}C NMR δ 14.2, 28.6, 37.5, 60.9, 122.5, 135.3, 138.4, 147.3,

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151.3, 172.4, 200.0. IR 1724, 1676. (HRMS found: 242.0585. $C_{11}H_{13}ClNO_3$ requires 242.0584).

Ethyl 4-[2-(benzylseleno)pyridin-3-yl]-4-oxobutyrate (28)

Sodium borohydride was added in portions to a suspension of dibenzyl diselenide (2.00 g, 5.87 mmol) in degassed ethanol (30 mL) under a flow of N_2 until a colourless solution formed. Benzophenone (2 g) was added to quench excess sodium borohydride and the reaction mixture stirred for 20 min after which time ethyl 4-(2-chloropyridin-3-yl)-4-oxobutyrate (**27**) (1.52 g, 6.30 mmol) was added. The reaction mixture was refluxed under nitrogen for 12 h before being worked up as described for **12**. Purification was effected by flash chromatography (10% EtOAc–hexane) and the product recrystallised (chloroform) to give the title compound as a crystalline solid (75%). Mp 70–71.5 °C. ^{1}H NMR δ 1.25 (t, 3H, $J = 7.2$), 2.76 (t, 2H, $J = 6.8$), 3.25 (t, 2H, $J = 6.8$), 4.14 (q, 2H, $J = 7.2$), 4.41 (s, 2H), 7.16–7.19 (m, 2H), 7.23–7.26 (m, 2H, 7.39 (d, 2H, $J = 7.6$), 8.18 (dd, 1H, $J = 1.6, 7.6$), 8.64 (dd, 1H, $J = 1.6, 4.8$). ^{13}C NMR δ 14.1, 28.0, 29.1. 33.5, 60.7, 118.8, 126.4, 128.3, 129.3, 129.8, 137.7, 139.2, 152.2, 161.1, 172.6, 197.5. ^{77}Se NMR δ 492.6. IR 1728, 1661. MS m/z 378.1 $(M + H)^+$. (Found: C, 57.53; H, 5.10; N, 3.61. $C_{18}H_{19}NO_3Se$ requires: C, 57.45; H, 5.09; N, 3.72%).

6-[2-(Benzylseleno)pyridin-3-yl]-4,5-dihydro-2*H*-pyridazin-3-one (29)

Ethyl 4-(2-benzylseleno-pyridin-3-yl)-4-oxobutyrate (**28**) (207 mg, 0.549 mmol), potassium hydroxide (0.2 g, 3.56 mmol) and hydrazine monohydrate (2 mL, 41.2 mmol) were heated at reflux for 5 h in digol (2 mL). The reaction mixture was diluted with water (20 mL) and acidified to pH 8–9 with 10% hydrochloric acid. The aqueous solution was extracted with toluene (3 × 20 mL) and the combined organics dried ($MgSO_4$). Flash chromatography (50% EtOAc–hexane) gave the title compound as colourless crystals (61%) mp 151–152 °C (toluene). ^{1}H NMR δ 2.62 (t, 2H, $J = 7.8$), 2.93 (t, 2H, $J = 7.8$), 4.41 (s, 2H), 7.14–7.19 (m, 2H), 7.27 (m, 2H), 7.37 (m, 2H), 7.61 (dd, 1H, $J = 1.8, 7.8$), 8.52 (dd, 1H, $J = 1.8, 4.7$), 8.61 (bs, 1H). ^{13}C NMR δ 23.5, 26.3, 30.6, 119.3, 126.5, 128.4, 129.2, 131.2, 134.6, 139.2, 149.2 (2C), 156.5, 166.6; ^{77}Se NMR δ 456.7; IR 3198, 1678. MS m/z 346.1 $(M + H)^+$ (40%), 336.1 (100%). HRMS found: 346.0457. $C_{16}H_{16}N_3OSe$ requires: 346.0459).

1-[2-(Benzylseleno)pyridin-3-yl]-butane-1,4-diol (30)

A large excess of sodium borohydride and ethyl 4-(2-benzylselenopyridin-3-yl)-4-oxobutyrate (**28**) (150 mg, 0.399 mmol) in methanol (6 mL) were heated at reflux for 4 h, at which time TLC analysis showed the absence of starting material. The reaction mixture was partitioned between water and dichloromethane and the aqueous phase extracted with dichloromethane (4 × 15 mL). After evaporation of the solvent, the residue was separated by flash chromatography (50% EtOAc–hexane) to give the title compound as a colourless oil (95%). ^{1}H NMR δ 1.60–1.66 (m, 3H), 1.76 (m, 1H), 3.54 (dt, 1H, $J = 5.8, 10.1$), 3.60 (dt, 1H, $J = 5.8, 10.1$), 4.45 (d, 1H, $J = 12$), 4.49 (d, 1H, $J = 12$), 4.75 (dd, 1H, $J = 3.6, 8.0$), 7.04 (dd, 1H, $J = 4.7, 7.6$), 7.16–7.23 (m, 3H), 7.32 (m, 2H), 7.65 (dd, 1H, $J = 1.8, 7.6$), 8.36 (dd, 1H, $J = 1.8, 4.7$). ^{13}C NMR δ 29.0, 29.6, 34.9, 62.5, 70.8, 120.7, 126.8, 128.4, 129.0, 133.1, 139.1, 140.5, 148.3, 153.0. ^{77}Se NMR δ 380.8; IR 3265 (br). MS m/z 338.1 $(M + H)^+$. (Found: C, 56.33; H, 5.39; N, 3.71. $C_{16}H_{19}NO_2Se + 33\%$ methanol requires: C, 56.54; H, 5.91; N, 4.04%).

Ethyl 2-chloronicotinate-*N*-oxide[23] (35)

Ethyl 2-chloronicotinate (**11**) (4.102 g, 22.0 mmol) and 30% aqueous hydrogen peroxide (4 mL) were heated to 60 °C for 36 h in trifluoroacetic acid (40 mL). The solution was concentrated *in vacuo* and the residue neutralised with sat. $NaHCO_3$. The mixture was extracted with dichloromethane (3 × 45 mL), the combined organics dried ($MgSO_4$) and the solvent removed. The residue was purified by flash chromatography (100% EtOAc) to give the title compound as a pale solid (48%). Mp 39–40 °C. ^{1}H NMR δ 1.43 (t, 3H, $J = 7.2$), 4.45 (q, 2H, $J = 7.2$), 7.33 (dd, 1H, $J = 6.4, 7.8$), 7.69 (dd, 1H, $J = 1.2, 7.8$), 8.49 (dd, 1H, $J = 1.2, 6.4$). ^{13}C NMR δ 13.9, 62.6, 122.7, 126.7, 130.6, 142.0, 162.6; MS m/z $(M + H)^+$ 201.8.

3-Carboethoxy-*N*-hydroxypyridine-2-selone (36)

Sodium borohydride (0.57 g, 15 mmol) was added to a suspension of selenium powder (0.57 g, 7.2 mmol) in ethanol (6 mL) under a flow of nitrogen. After 45 min, ethyl 2-chloronicotinate-*N*-oxide (**33**) (0.997 g, 4.94 mmol) in ethanol (2 mL) and $NaHCO_3$ (140 mg) were added to the colourless solution. A bright yellow precipitate formed immediately. The mixture was heated at reflux for 1 h under nitrogen at which time glacial acetic acid was added and the solvent removed *in vacuo*. The residue was mixed with benzene (15 mL) and the solvent removed. The residue was extracted with chloroform (4 × 30 mL) and THF (4 × 30 mL). The combined extracts were dried ($MgSO_4$) and the solvent removed to give the title compound as an unstable yellow oil (93%) that was used immediately and without further purification. ^{1}H NMR δ 1.42 (t, 3H, $J = 7.2$), 4.44 (q, 2H, $J = 7.2$), 7.03 (m, 1H), 7.75 (d, 1H, $J = 7.2$) 8.39 (d, 1H, $J = 6.8$). ^{77}Se NMR δ 380.3.

2-Carboethoxy-3,4,-dihydro-2*H*-1-seleno-4*a*-azonianaphthalenium halide (37)

A solution of 4-bromobutanoyl chloride (0.19 mL, 1.95 mmol) in benzene (15 mL) was added slowly to a refluxing solution of freshly prepared 3-carboethoxy-*N*-hydroxypyridine-2-selone (**36**) (0.48 g, 1.95 mmol), DMAP (spatula tip) and pyridine (0.2 mL) in benzene (20 mL) and under nitrogen. The bright orange solution was heated at reflux overnight and the yellow precipitate collected by filtration and identified as the title compound (79%). Mp 175–177.5 °C ^{1}H NMR (d_6-DMSO) δ 1.37 (m, 3H), 2.38 (m, 2H), 3.26 (t, 2H, $J = 6.3$), 4.41 (m, 2H), 4.62 (m, 2H), 7.85 (m, 1H), 8.74 (d, 1H, $J = 6.1$), 9.07 (d, 1H, $J = 7.6$). ^{13}C NMR (d_6-DMSO) δ 14.0, 22.2, 24.1, 60.4, 63.0, 122.0, 130.6, 144.2, 151.0, 158.4, 163.1. MS m/z $(M)^+$ 271.9 (100%);. (HRMS found: 272.0177. $C_{11}H_{14}NO_2Se$ requires 272.0190).

Bis(2-carboethoxypyridine-2-selenide) (39)

3-Bromopropionic acid (0.340 g, 2.22 mmol) and DMF (3 drops) was heated at reflux in thionyl chloride (5 mL) for 2 h. The excess thionyl chloride was removed *in vacuo* and the residue

dissolved in benzene (3 mL) and reacted with freshly prepared 3-carboethoxy-*N*-hydroxypyridine-2-selone (**36**) (0.46 g, 1.87 mmol) in accordance with the procedure described above. After the vigorous evolution of gas had ceased, the reaction mixture was worked-up as described above and the residue separated by flash chromatography (hexane) to afford the title compound (8%) as the only isolable compound. Mp 204–206 °C. ^{1}H NMR δ 1.45 (t, 3H, J = 7.2), 4.46 (q, 2H, J = 7.2), 7.15 (dd, 1H, J = 4.7, 7.8), 8.23 (dd, 1H, J = 1.7, 7.6), 8.50 (dd, 1H, J = 1.8, 4.8). MS m/z $(M + H)^+$ 461.0; (HRMS found: 460.9513. $C_{16}H_{17}N_2O_4Se_2$ requires 460.9519).

Crystallography

Intensity data were collected with a Bruker SMART Apex CCD detector using Mo Kα radiation (graphite crystal monochromator λ = 0.71073). Data were reduced using the program SAINT.[24] The structure was solved by direct methods and difference Fourier synthesis using the SHELX suite of programs[25] as implemented with the WINGX software.[26]

Crystal data for 28§. $C_{18}H_{19}NO_3Se$, M = 376.30, T = 295(2) K, λ = 0.71069, orthorhombic, space group $P2_12_12_1$, a = 4.8305(8), b = 13.532(2), c = 26.210(4), Å, V = 1713.3(5) Å^3, Z = 4, D_c = 1.459 mg M^{-3} μ(Mo Kα) 2.205 mm^{-1}, F(000) = 768, crystal size 0.35 × 0.15 × 0.10 mm. 10646 reflections measured, 3892 independent reflections (R_{int} = 0.10) the final R was 0.0408 [I > 2σ(I)] and $wR(F^2)$ was 0.0791 (all data).

Computational chemistry

Ab initio molecular orbital calculations were carried out using the Gaussian 03 program.[19] Geometry optimisations were performed using standard gradient techniques at the B3LYP/6-311G** level of theory.

Acknowledgements

Financial support from the Australian Research Council is gratefully acknowledged.

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§ CCDC reference number 288081. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b515385a

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