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Preparation of novel selenapenams and selenacephems by nucleophilic and radical chemistry involving benzyl selenides

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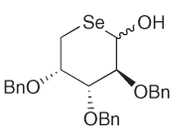
2,2a-Dihydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzoselenazin-1-one (**12**), 5-selena-1-azabicyclo[4.2.0]oct-3-en-8-one (**13**), ethyl 1-aza-7-oxo-4-selenabicyclo[3.2.0]heptane-2-carboxylate (**16**), and benzoselenopenem (**33**) can be prepared in 39–85% yield through the intramolecular homolytic substitution of aryl, vinyl or alkyl radicals at the selenium atom in suitably-substituted 4-benzylseleno-β-lactams, or through intramolecular nucleophilic substitution by the benzylseleno moiety in 4-halo-β-lactam precursors. Application of this chemistry to the preparation of optically active selenium-containing analogues of β-lactam antibiotics is also detailed.

Introduction

Free-radical homolytic substitution chemistry is rapidly gaining acceptance as a versatile synthetic method.[1] Over the past few years, we have demonstrated the effectiveness of this chemistry for the preparation of selenium and tellurium-containing higher heterocycles. Indeed, so versatile is the free-radical approach that many classes of compound including some of hitherto unknown structure have been successfully prepared. Among these are included 5-deoxy-5-selena pyranose sugars (*e.g.* **1**),[2] and novel selenium and tellurium analogues (*e.g.* **2**)[3] of the important antioxidant, α-tocopherol.



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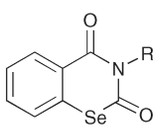

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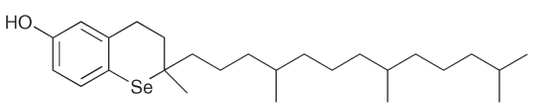

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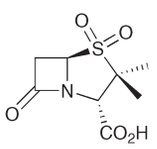
In parallel with this work, we have established that the benzyl selenide moiety acts as a "masked" selenoate ion in intramolecular nucleophilic chemistry and this observation has been used to good effect to provide further methods for the construction of selenium-containing rings that include the benzoselenazine-2,4-dione system (*e.g.* **3**).[4]

It is generally appreciated that β-lactam based antibiotics have a limited future given increased resistance demonstrated by many strains of bacteria.[5] There is an urgent need for the development of new classes of antibiotic and many laboratories have made significant progress in this area, especially with the introduction of peptide-based agents.[6]

A common mechanism of resistance in bacteria to the β-lactam class of antibiotics is through the β-lactamase enzymes.[7,8] These enzymes hydrolyse β-lactam antibiotics, rendering them impotent. Several β-lactamase inhibitors, such as sulbactam (**4**) and clavulanic acid (**5**) are known, and are able to be administered in conjunction with antibiotics susceptible to β-lactamase activity.[9]



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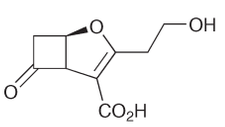

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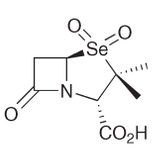

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In an attempt to extend the variety of available β-lactamase inhibitors, we considered that substitution of the sulfur atom in the bicyclic core with selenium may provide an analogue (**6**) of sulbactam that preserves its shape and electronic properties, but which may differ in reactivity, and thus potency.

Selenium analogues of β-lactam antibiotics have been reported on previous occasions together with limited biological testing data.[10–12] In each report the yields of the target molecules are either poor, or the compounds prepared bear functionality that compromises biological activity.[11,12] New methods for the preparation of these interesting systems are therefore important objectives.

As part of ongoing work, we have explored methods of incorporating selenium into penem and cephalosporin nuclei with the aim of providing some novel compounds of potential biological significance. We now report that selenium analogues of β-lactam antibiotic nuclei are conveniently prepared by extension of our previously established radical and nucleophilic methodologies.

Results and discussion

Free radical approaches to selenapenam and selenacephalosporin core structures

Our synthetic route began with commercially available 4-acetoxy-2-azetidinone which was reacted with sodium benzyl selenoate, prepared by treatment of dibenzyl diselenide with sodium borohydride, to give 4-(benzylseleno)-2-azetidinone (**7**) in quantitative yield. Subsequent treatment with either lithium hexamethyldisilazide (LiHMDS) in THF at −78° or sodium hydride in DMF at 0° followed by an activated electrophile afforded the *N*-alkylated products (**8**–**10**) in 36–92% yield.

The ester (**8**) was further treated with LiHMDS and *tert*-butyl bromoacetate followed by standard deprotection to afford the carboxylic acid (**11**, R = H) in good yield (Scheme 1). Acid **11** (R = H) was obtained as a 1 : 1 mixture of diastereoisomers as evidenced by ^{1}H NMR spectroscopy.

To our delight, treatment of iodides (**9**, **10**) with tributyltin hydride in benzene (0.03 M) under reflux afforded 2,2a-dihydro-

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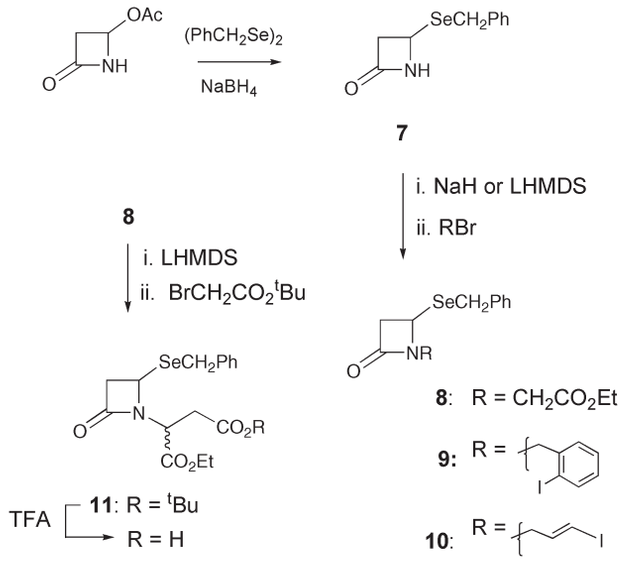
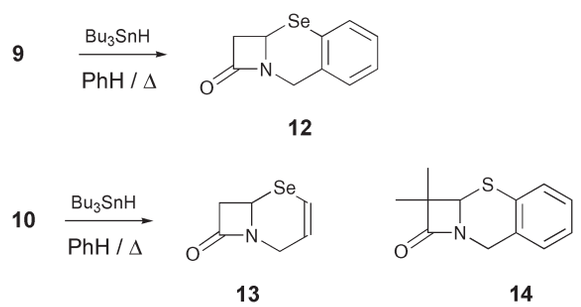


Scheme 1

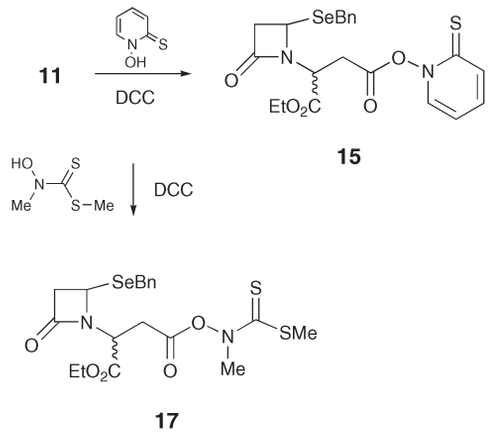
1*H*,8*H*-azeto[2,1-*b*][1,3]benzoselenazin-1-one (**12**) and 5-selena-1-azabicyclo[4.2.0]oct-3-en-8-one (**13**) in 85 and 84% yield respectively (Scheme 2). Presumably **12** and **13** are formed by homolytic attack of the first-formed aryl and vinyl radicals respectively at the selenium moiety, with expulsion of the benzyl leaving group; these compounds exhibited ^{77}Se NMR signals at δ 323 and 295 respectively, in the appropriate range for cyclic selenides.[13] In addition, **12** displayed signals at δ 4.15 (J = 18 Hz) and δ 4.79 (J = 18 Hz) in its ^{1}H NMR spectrum assigned to the non-equivalent benzylic protons, and at δ 5.10 for the C-4 proton. These values are in good agreement with those reported by Beckwith and Boate for the closely-related sulfur analogue (**14**).[14]



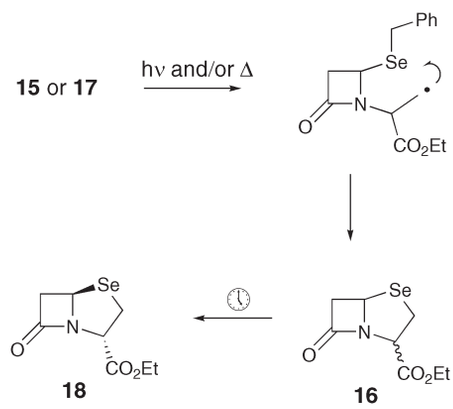
Scheme 2

Further reaction of (**11**, R = H) with *N*-hydroxypyridine-2-thione in the presence of dicyclohexylcarbodiimide (DCC) afforded the pyridinethioneoxycarbonyl (PTOC, Barton)[15] ester free radical precursor (**15**) (Scheme 3). The Barton ester proved to be quite labile and was not purified. Rather, a concentrated solution of (**15**) was transferred into benzene, after which irradiation with a tungsten lamp for about two hours resulted in a distinct colour change and the appearance of several components by TLC. The dominant TLC spot was isolated and characterized and proved to be the required ethyl 1-aza-7-oxo-4-selenabicyclo[3.2.0]heptane-2-carboxylate (**16**) which was isolated in 38% yield (based on **11**) as an inseparable mixture of diastereoisomers (Scheme 4). Attempts to improve the yield through irradiation at 0° or at reflux, or thermolysis in the dark did not result in any significant improvement. Presumably (**16**) arises through a mechanism involving intramolecular homolytic substitution at selenium (Scheme 4).

We were pleasantly surprised, however, to find significant improvements through the use of thiohydroximate ester derivative (**17**) of (**11**, R = H) as described recently by Kim.[16] The thiohydroximate ester (**17**) was prepared by the action of *N*-methylhydroxydithiocarbamate and dicyclohexylcarbodiimide (DCC) on the carboxylic acid (**11**), was stable to purification by



Scheme 3

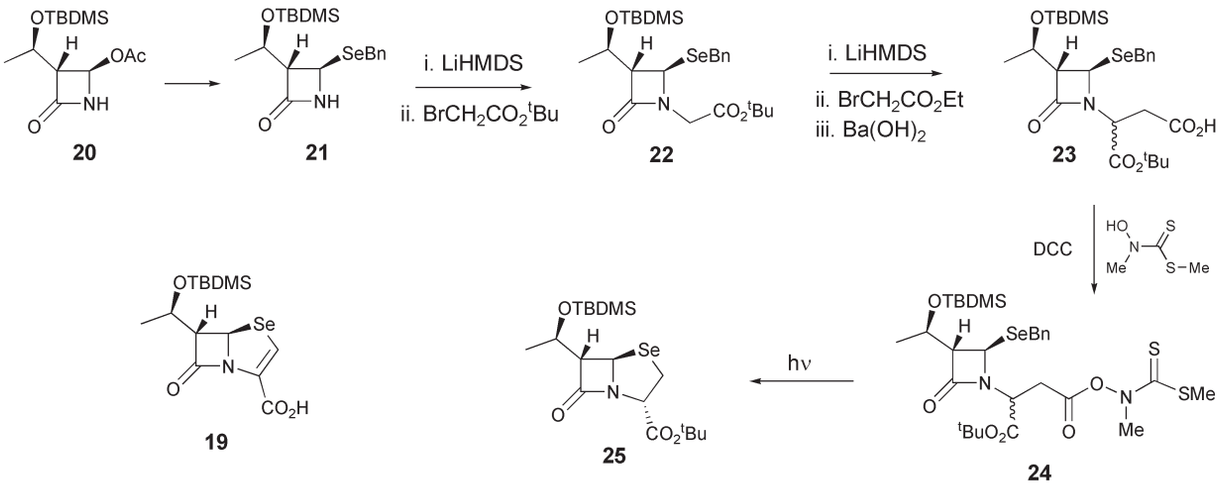


Scheme 4

flash chromatography, and was isolated as a thick yellow oil. When the radical precursor (**17**) was irradiated in benzene as described above for (**15**), the required selenapenam (**16**) was isolated in 71% yield. Interestingly, the diastereomeric ratio ranged from 1 : 1 to 8 : 1 depending upon conditions, however, upon standing, epimerization to a single diastereoisomer (**18**) was observed within 72 hours (Scheme 4). Selenapenam (**18**) displayed a signal at δ 301.0 in its ^{77}Se NMR spectrum, as well as a doublet of doublets at δ 3.74 for the proton at position-2 in (**18**) in the ^{1}H NMR spectrum. Coupling constants of 3.9 and 15.9 Hz for this proton are indicative of the relative stereochemistry depicted in (**18**).

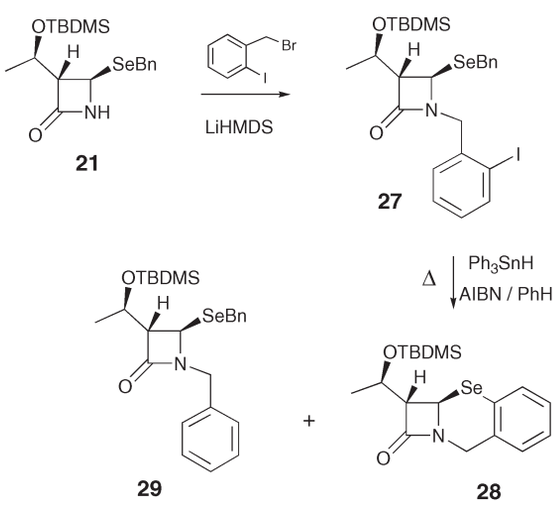
Radical routes to optically-active selenium analogues of β-lactam antiobiotics

While the synthesis described above affords the general core structure of a β-lactamase inhibitor, we were also interested in the preparation of selenium-containing analogues of penem and cephem β-lactam antibiotics (*e.g.* **19**). To that end, the commercially available, optically pure, (3*R*,4*R*)-4-acetoxy-3-[(*R*)-(*tert*-butyldimethylsilyloxyethyl]-2-azetidinone (**20**) was converted into the benzylseleno derivative (**21**) as described above for the preparation of (**7**), with complete retention of configuration (de > 98%). Because of the susceptibility of the protecting group in (**21**) to acidic workup, it was necessary to subtly change the order in which the subsequent steps were executed to that described in Scheme 1. The selenide (**21**) was reacted with *t*-butyl bromoacetate under alkaline conditions (LiHMDS) to afford the ester (**22**) in 94% yield. Subsequent reaction with ethyl bromoacetate and LiHMDS, followed by careful barium hydroxide hydrolysis provided the acid (**23**) as a 7 : 1 mixture of diastereoisomers. Further conversion of (**23**) into the thiohydroximate ester (**24**) and photolysis as described above afforded the required selenapenam (**25**) in 51% yield (based on **23**) (Scheme 5) and in 80% diastereomeric excess. Once again, NMR spectroscopy provided evidence for the formation of (**25**), in particular, the penam displayed a signal at δ 279.8 in its ^{77}Se NMR spectrum.



Scheme 5

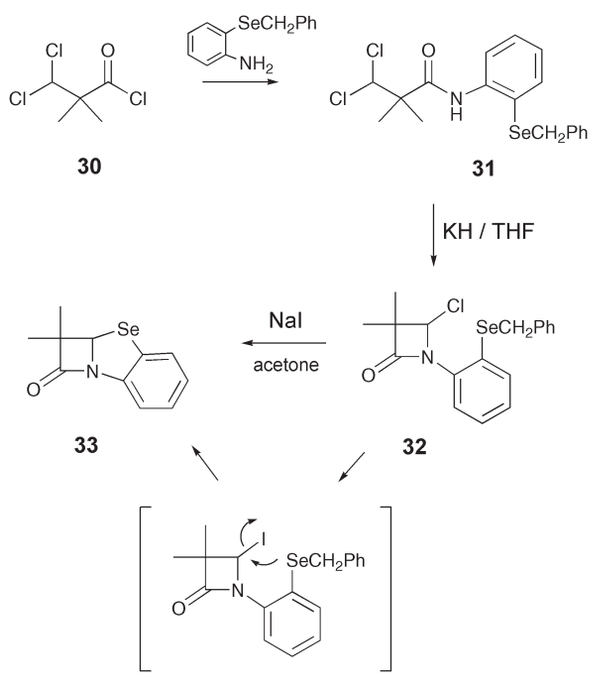
As a final example of the versatility of intramolecular homolytic substitution chemistry, and with the aim of further exploring biologically important selenium heterocycles, we considered the feasibility of preparing optically pure benzo-fused systems such as that found in the selenacephem (**12**). To that end, (**21**) was reacted with 2-(bromomethyl)iodobenzene under alkaline conditions to afford the aromatic iodide (**27**) in 96% yield. Reaction with triphenyltin hydride (>0.015 M) under standard radical conditions (AIBN, refluxing benzene) afforded the required product (**28**) together with the uncyclized (directly reduced) byproduct (**29**) (Scheme 6). When the concentration of stannane was kept below 0.015 M, selenapenam (**28**) was the sole product of the reaction and was isolated in 65% yield after chromatography. Selenide (**28**) exhibited a signal at δ 311.8 in its ^{77}Se NMR spectrum.



Scheme 6

Intramolecular nucleophilic chemistry: formation of benzo-fused selenapenems

Our alternative approach to these classes of compound began with the previously reported 3,3-dichloro-2,2-dimethylpropionyl chloride[17] (**30**) which was converted firstly into the corresponding benzylseleno amide (**31**) by reaction with 2-benzylselenoaniline and then into the chloroazetidinone (**32**) following the general procedure reported by Beckwith and Boate.[14] To our surprise, treatment of chloride (**32**) with one equivalent of sodium iodide in acetone did not provide the expected iodide, rather, the ring-closed selenapenem nucleus, 2,2a-dihydro-2,2-dimethyl-1*H*-azeto[2,1-*b*]benzoselenazol-1-one (**33**) was obtained in 46% isolated yield (Scheme 7).†



Scheme 7

Presumably the corresponding iodide is formed *in situ*, but undergoes rapid intramolecular attack by the nucleophilic benzylseleno moiety to provide **33**. Indeed, this transformation represents a further example of the synthetic utility of the intramolecular nucleophilic chemistry associated with benzyl selenides.[2,4,18]

Conclusion

We have demonstrated that the selenacephem and selenapenam nuclei are conveniently prepared by either intramolecular homolytic or nucleophilic substitution chemistry involving the benzyseleno moiety. The compounds prepared during this study are expected to exhibit interesting biological properties.

Experimental

4-Acetoxy-2-azetidinone and (3*R*,4*R*)-4-acetoxy-3-[(*R*)-(*tert*-butyldimethylsilyloxyethyl]-2-azetidinone were purchased from Aldrich and used without further purification. 3-Bromo-1-iodoprop-1-ene was prepared by the method of Brasseur *et. al.*[19] 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

† This transformation is catalytic in sodium iodide. While 5–10 %mol NaI will effect cyclization, the reaction proceeds at a more convenient rate with the addition of one equivalent of NaI. In our hands, addition of more than one equivalent proved detrimental with lower yields of product.

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.

4-[(Phenylmethyl)seleno]-2-azetidinone (7)

Sodium borohydride was added, in portions, to a stirred suspension of dibenzyl diselenide (1.33 g, 3.90 mmol), in absolute ethanol (20 mL), under nitrogen until the characteristic yellow color of the diselenide had disappeared. The mixture was cooled to 0 °C and 4-acetoxy-2-azetidinone (1.0 g, 7.74 mmol) in absolute ethanol (10 mL) was added over several minutes. After stirring for a further hour, 10% sodium bicarbonate (50 mL) was added. The mixture was extracted with ether (3 × 50 mL), the combined organic extracts were washed with brine (2 × 50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to flash chromatography (10% EtOAc/hexane) to afford the product as pale yellow crystals (1.75 g, 94%). mp 54–55 °C. ^{1}H NMR δ 2.90 (dt, 1H, J = 16 Hz), 3.34 (ddd, 1H, J = 1.5, 5.1, 15.6 Hz), 3.92 (s, 2H), 4.79 (dd, 1H, J = 2.1, 5.1 Hz), 6.26 (br s, 1H), 7.21–7.31 (m, 5H). ^{13}C NMR δ 27.26, 44.38, 46.47, 127.08, 128.73, 138.36, 166.10. ^{77}Se NMR (C_6D_6) δ 381.0. MS *m*/*z* (relative intensity); 240 (M^+, 1), 150 (44), 91 (90), 70 (65), 64 (35), 43 (41). (Found: C, 49.89; H, 4.62; N, 5.90. $C_{10}H_{11}NOSe$ requires C, 50.00; H, 4.63; N, 5.83%).

Ethyl 2-oxo-4-[(phenylmethyl)seleno]-1-azetidineacetate (8)

Lithium hexamethyldisilylazide (6 mL of a 1.0 M solution in THF) was added to a stirred solution of 4-[(phenylmethyl)seleno]-2-azetidinone (**7**) (1.3 g, 5.46 mmol) in THF (30 mL) at −78 °C and the resultant mixture stirred for 10 minutes at −78 °C. Ethyl bromoacetate (16.5 mmol, 1.83 mL) dissolved in THF (10 mL) was added dropwise over 5 minutes and the resulting mixture allowed to warm to ambient temperature overnight. The resulting reddish-brown mixture was quenched with 10% HCl (30 mL) and extracted with ether (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to afford a residue that was further subjected to flash chromatography (1 : 3 EtOAc/hexane) to afford the title ester as a colorless oil (1.93 g, 92%). ^{1}H NMR δ 1.26 (t, 3H, J = 7.2 Hz), 3.01 (dd, 1H J = 2.1, 15.6 Hz), 3.10 (d, 1H, J = 18 Hz), 3.44 (dd, 1H, J = 5.4, 15.6), 3.79 (s, 2H), 3.96 (d, 1H, J = 18.3 Hz), 4.10 (m, 2H), 5.03 (dd, 1H, J = 2.1, 5.4 Hz), 7.10 (m, 5H). ^{13}C NMR δ 13.94, 26.40, 40.96, 46.10, 51.10, 61.35, 126.94, 128.56, 138.71, 165.14, 167.73. ^{77}Se NMR 307. IR ν_{max} 2891, 1762, 1739. (Found: C, 51.60; H, 5.40; N, 4.20. $C_{14}H_{17}NO_3Se$ requires C, 51.54; H, 5.25; N, 4.29%).

1-[(2-Iodophenyl)methyl]-4-[(phenylmethyl)seleno]-2-azetidinone (9)

4-[(Phenylmethyl)seleno]-2-azetidinone (**7**) (0.30 g, 1.25 mmol) in dry DMF (2 mL) was added to a stirred suspension of 2-iodobenzyl bromide (0.37 g, 1.25 mmol) and sodium hydride (0.03 g, 1.25 mmol) in dry DMF (3 mL) at 0 °C, under nitrogen. The resulting mixture was stirred for 2 hours at 0 °C, after which it was poured into water (5 mL), and extracted with dichloromethane (3 × 5 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude selenide. Flash chromatography (20% EtOAc/petroleum spirits) afforded the title selenide as a dark yellow gum (0.31 g, 53%). ^{1}H NMR δ 3.06 (d, 1H, J = 15.3 Hz), 3.44 (dd, 1H, J = 5.1, 15.5 Hz), 3.74 (dd, 2H J = 12.3, 24.1,), 4.03 (d, 1H, J = 15.9 Hz), 4.55 (d, 1H, J = 15.9 Hz), 4.67 (dd, 1H, J = 2.1, 5.1 Hz), 6.98–7.88 (m, 9H). ^{13}C NMR δ 26.40, 46.05, 49.54, 50.15, 98.58, 127.09, 128.54, 128.68, 128.81, 129.56, 129.73, 137.53, 138.19, 139.82, 165.33. ^{77}Se NMR (C_6D_6) δ 310. MS *m*/*z* (relative intensity) 456 (M^+, 1), 286 (47), 91 (48), 84 (98), 51 (100). (Found: C, 45.04; H, 3.31; N, 3.46. $C_{17}H_{16}NIOSe$ requires C, 44.75; H, 3.54; N, 3.07%).

1-(3-Iodo-2-propenyl)-4-[(phenylmethyl)seleno]-2-azetidinone (10)

4-[(Phenylmethyl)seleno]-2-azetidinone (**7**) (0.50 g, 2.09 mmol) in dry DMF (4 mL) was added to a stirred suspension of 3-bromo-1-iodoprop-1-ene (0.62 g, 2.51 mmol) and sodium hydride (0.07 g, 3.14 mmol) in dry DMF (4 mL) at 0 °C, under nitrogen. The resulting mixture was stirred for 2.5 hours at 0 °C, after which it was poured into water (10 mL) and extracted with dichloromethane (3 × 10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was separated by flash chromatography (30% EtOAc/petroleum spirits) to afforded the title selenide as a yellow gum (0.30 g, 36%). ^{1}H NMR δ 3.00 (d, 1H, J = 15 Hz), 3.37 (dd, 1H, J = 5, 15 Hz), 3.62 (dd, 1H, J = 7, 16 Hz), 3.87 (d, 2H, J = 3 Hz), 3.83–3.93 (m, 1H), 4.75 (dd, 1H, J = 2, 5 Hz), 6.28 (dt, 1H, J = 6.6, 7.5 Hz), 6.48 (dt, 1H, J = 1.5, 7.5 Hz), 7.23–7.32 (m, 5H). ^{13}C NMR δ 26.59, 45.33, 45.98, 50.18, 85.41, 127.08, 128.67, 128.81, 134.45, 138.14, 164.91. ^{77}Se-NMR (C_6D_6) δ 314. MS *m*/*z* (relative intensity) 407 (M^+, 5), 236 (91), 91 (100), 84 (81), 51 (82). (HRMS Found: 406.9288. $C_{13}H_{14}NOISe$ requires 406.9285).

4-*tert*-Butyl 1-ethyl-[2-oxo-4-[(phenylmethyl)seleno]-1-azetidinyl]butanedioate (11, R = ^{t}Bu)

Lithium hexamethyldisilylazide (7 mL of a 1.0 M solution in THF) was added dropwise to a solution of ethyl 2-oxo-4-[(phenylmethyl)seleno]-1-azetidineacetate (**8**) (2.0 g, 6.13 mmol) in THF (25 mL) at −78 °C under nitrogen. The resultant solution was stirred at −78° for 10 minutes, at which time *tert*-butyl bromoacetate (4.78 g, 24 mmol) dissolved in THF (5 mL), was added over several minutes. The mixture was stirred for 14 hours, during which time the mixture warmed to ambient temperature. Water (50 mL) was added and the mixture extracted with ether (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was subjected to flash chromatography (1 : 1 dichloromethane/hexane) to afford the title compound (2.16 g, 80%) as a mixture of diastereomers (2 : 1), and as a colorless oil. ^{1}H NMR (major isomer) δ 1.19 (t, 3H, J = 7.2 Hz), 1.37 (s, 9H), 2.7–3.0 (m, 3H), 3.25 (dd, 1H, J = 4.8, 15.2 Hz), 3.81 (s, 2H), 4.1 (m, 2H), 4.22 (dd, 1H, J = 6.0, 8.0 Hz), 4.82 (dd, 1H, J = 2.4, 5.2), 7.1–7.3 (m, 5H). ^{13}C NMR (major isomer) δ 13.84, 26.17, 27.77, 34.58, 45.97, 50.15, 51.97, 61.64, 81.14, 126.81, 128.44, 128.64, 138.13, 164.96, 168.78, 168.88; ^{77}Se NMR (major isomer) δ 302. IR ν_{max} 2977.9, 1766.7, 1737.7. MS *m*/*z* (relative intensity) 442 (M^+, 8), 298 (45), 276 (40), 202 (70). (Found: C, 54.75; H, 6.27; N, 3.13. $C_{20}H_{27}NO_5Se$ requires C, 54.55; H, 6.18; N, 3.18%).

3-Carboethoxy-3-[2-oxo-4-[(phenylmethyl)seleno]-1-azetidinyl]propanoic acid (11, R = H)

Trifluoroacetic acid (5 mL) was added dropwise to a cold (0 °C) stirred solution of 4-*tert*-butyl 1-ethyl [2-oxo-4-[(phenylmethyl)seleno]-1-azetidinyl]butanedioate (**11**, R = ^{t}Bu), (1.91 g, 4.33 mmol) prepared as described above, in dichloromethane (10 mL). The pale yellow solution was stirred at 0 °C for 2 hours, then allowed to stand in a refrigerator overnight. The solvent was removed under *in vacuo* and the residue subjected to flash chromatography (10% MeOH in EtOAc eluent) to provide the title ester as a yellow, viscous oil and as a mixture of diastereomers (3 : 2) (1.60 g, 96%). ^{1}H NMR δ 1.27 (t, 3H, J = 7.2 Hz), 2.9–3.2 (m, 3H), 3.38 (dd, 1H, J = 3.0, 15.6 Hz), 3.86 (s, 1H, isomer A), 3.91 (s, 1H, isomer B), 4.1–4.3 (m, 2.5H), 4.50, (t, 0.5H, J = 8.1 Hz, isomer B), 4.91 (d, 0.5H, J = 2.7H isomer A), 4.99 (d, 0.5H, J = 3 Hz, isomer B), 7.15–7.3 (m, 5H), 9.47 (br s, 1H); ^{13}C NMR isomer A δ: 13.65, 26.12, 33.05, 45.16, 50.41, 51.33, 61.82, 126.73, 128.54, 128.52, 137.86, 165.92, 168.11, 173.52; isomer B δ: 13.68, 26.20, 33.27, 45.41, 50.77, 51.72, 61.90, 126.77, 128.39, 128.56, 137.95, 166.31, 168.45, 173.65; ^{77}Se NMR δ 320; IR ν_{max} 3311, 2982.4, 1737.5; MS *m*/*z* (relative intensity) 386 (M^+, 70), 225 (100), 143 (75); (ESI HRMS: found: 408.0321. $C_{16}H_{19}NO_5SeNa$ requires 408.0326).

2,2a-Dihydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzoselenazin-1-one (12)

A solution of 1-[(2-iodophenyl)methyl]-4-[(phenylmethyl)seleno]-2-azetidinone (**9**) (90 mg, 0.20 mmol), tributyltin hydride (0.06 mL, 0.23 mmol) and AIBN (2 crystals) in dry benzene (6.5 mL) was heated at 80 °C overnight under a nitrogen atmosphere. The resulting solution was cooled and concentrated *in vacuo*. The residue was dissolved in dichloromethane saturated with iodine and stirred with saturated aqueous potassium fluoride overnight at room temperature.[15] The precipitate was filtered through Celite and washed with dichloromethane, The aqueous layer was further extracted with dichloromethane. The combined organic phases were washed with saturated sodium thiosulfate, water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (20% EtOAc/petroleum spirits) to give the title selenacephem as an orange oil (40 mg, 85%). ^{1}H NMR δ 3.19 (d, 1H, J = 15 Hz), 3.66 (dd, 1H, J = 6, 15 Hz), 4.15 (d, 1H, J = 18 Hz), 4.79 (d, J = 18 Hz), 5.10 (d, 1H, J = 6 Hz). ^{13}C NMR δ 29.08, 44.10, 47.56, 126.53, 128.09, 128.64, 128.72, 130.53, 131.49. ^{77}Se NMR (C_6D_6) δ 323. MS *m*/*z* (relative intensity) 238 (M^+, 40), 210 (57), 87 (48), 85 (96), 83 (100). (HRMS Found: 238.9847. $C_{10}H_9NOSe$ requires 238.9849).

5-Selena-1-azabicyclo[4.2.0]oct-3-en-8-one (13)

A solution of 1-(3-iodo-2-propenyl)-4-[(phenylmethyl)seleno]-2-azetidinone (**10**) (60 mg, 0.15 mmol), tributyltin hydride (47 μL, 0.174 mmol) and AIBN (2 crystals) in dry benzene (5 mL) was flushed with nitrogen and heated at 80 °C for 18 hours. The solution was cooled and concentrated *in vacuo*. The residue was dissolved in dichloromethane saturated with iodine and stirred with saturated aqueous potassium fluoride overnight at room temperature.[15] The precipitate was filtered off (Celite) and washed with dichloromethane. The aqueous layer was extracted with dichloromethane and the combined organic phases were washed with saturated sodium thiosulfate, water, brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was separated by flash chromatography (30% EtOAC/petroleum spirits) to give the required selanacephem as an orange gum (20 mg, 84%). ^{1}H NMR δ 3.10 (d, 1H, J = 14 Hz), 3.57–3.68 (m, 2H), 4.30 (dt, 1H, J = 3, 13 Hz), 4.88 (d, 1H, J = 3 Hz), 5.99 (dt, 1H, J = 3, 4 Hz), 6.54 (dt, 1H, J = 2, 6). ^{13}C-NMR δ 39.09, 40.08, 47.86, 113.30, 117.91, 164.25. ^{77}Se-NMR (C_6D_6) 295. MS *m*/*z* (relative intensity) 188 (M^+, 83), 161 (99), 159 (73), 120 (100), 91 (60), 54 (61). (HRMS Found: 188.9689. C_6H_7NOSe requires 188.9693).

Ethyl *anti*-1-aza-7-oxo-4-selenabicyclo[3.2.0]heptane-2-carboxylate (18) *via* Barton ester

Dicylohexylcarbodiimide (DCC) (0.89 g, 4.5 mmol) was added to a stirred solution of 3-carboethoxy-3-[2-oxo-4-[(phenylmethyl)seleno]-1-azetidinyl]butanoic acid (**11**) (1.43 g, 3.92 mmol), *N*,*N*-dimethylaminopyridine (DMAP) (0.55 g, 4.5 mmol) and *N*-hydroxypyridine-2-thione (0.59 g, 4.6 mmol) in dichloromethane (15 mL) at 0 °C, with shielding from background light. The mixture was stirred for 2 hours, after which the precipitate was removed by filtration, with shielding from background light. The yellow filtrate was concentrated *in vacuo* to afford the crude Barton ester (**15**) which was immediately dissolved in benzene (30 mL) and subjected to photolysis with a 300 W tungsten lamp for 2 hours, during which time the mixture was heated to reflux. After cooling, the solvent was removed *in vacuo* and the residue subjected to flash chromatography (4 : 1 hexane/ethyl acetate) to afford the title ester (0.37 g, 38%) as a mixture of diastereoisomers. After standing in chloroform for several days complete conversion to only one isomer was observed, which was isolated as a clear viscous oil. ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.2 Hz), 3.15 (dd, 1H, J = 1.5, 15.9 Hz), 3.65 (m, 2H), 3.74 (dd, 1H, J = 3.9, 15.9 Hz), 4.24 (q, 2H, J = 7.2 Hz), 5.13, (dd, 1H, J = 3.6, 6.0 Hz), 5.36 (dd, 1H, J = 1.5, 3.9 Hz); ^{13}C NMR ($CDCl_3$) δ 13.95, 33.58, 48.21, 53.86, 60.90, 61.88, 168.59, 171.24; ^{77}Se NMR δ 301; IR ν_{max} 2956.0, 1778.4 MS *m*/*z* (relative intensity) 272 (MNa^+, 100), 250 (M^+, 30), 242 (40), 208 (30); (ESI HRMS: found: 271.9796. $C_8H_{11}NO_3SeNa$ requires 271.9802).

Ethyl *anti*-1-aza-7-oxo-4-selenabicyclo[3.2.0]heptane-2-carboxylate (18) *via* Kim ester

DCC (134 mg) was added to a stirred solution of 3-carboethoxy-3-[2-oxo-4-[(phenylmethyl)seleno]-1-azetidinyl]butanoic acid (**11**) (125 mg, 0.325 mmol) and *N*-methylhydroxydithiocarbamate (90 mg, 0.66 mmol) in dichloromethane (30 mL). After 3 hours stirring at ambient temperature, the mixture was filtered through a pad of med hyflo filter aid, followed by concentration of the solvent under reduced pressure. The residue was subjected to column chromatography (30% ethyl acetate in hexane eluent) to afford the Kim ester (**17**) (114 mg, 70%) as a thick yellow oil and as a mixture of diastereomers suitable for further use. ^{1}H NMR δ, 1.29 (t, 3H, J = 7.2 Hz), 2.58 (s, 3H), 3–3.2 (m, 3H), 3.4 (m, 1H), 3.81 (s, 3H), 3.89 (s, 1H, isomer A), 3.96, (s, 1H, isomer B), 4.1–4.3 (m, 2.5H), 4.55, (dd, 0.5H, J = 1.2, 4,5 Hz, isomer B), 5.01 (m, 1H), 7.2–7.4 (m, 5H). ^{13}C NMR ($CDCl_3$) (isomer A) δ 14.01, 18.59, 26.28, 31.19, 42.54, 45.73, 50.91, 51.07, 62.38, 127.17, 128.76, 128.12, 138.10, 165.29, 166.83, 167.69, 196.72; isomer B δ 14.01, 18.65, 26.78, 31.24, 42.59, 46.39, 51.01, 51.60, 62.54, 128.56, 128.76, 128.97, 138.32, 165.60, 167.24, 168.19, 196.03. IR 2932.4, 1746.1; MS *m*/*z* (relative intensity) 527 (M^+ + Na,100), 505, (M^+, 80), 312 (100), 187 (50). (ESI HRMS Found: 527.0177. $C_{19}H_{24}N_2O_5S_2SeNa$ requires 527.0188).

The Kim ester (**17**) (33 mg, 0.067 mmol) was dissolved in benzene (10 mL) and subjected to photolysis from a 300 W tungsten lamp under reflux for 2 hours, after which, the product was isolated as described above to afford the title heterocycle (10 mg, 71%).

(3*S*,4*R*)-3-[(*R*)-*tert*-Butyldimethylsilyloxyethyl]-4-[(phenylmethyl)seleno]-2-azetidinone (21)

The title compound was prepared as described for 4-[(phenylmethyl)seleno]-2-azetidinone (**7**) (above) using (3*R*,4*R*)-4-acetoxy-3-[(*R*)-(*tert*-butyldimethylsilyloxyethyl]-2-azetidinone and was isolated as a colorless solid (86%). mp 59–61 °C. $[\alpha]_D^{25}$ = +44.2° (c = 1.00, $CHCl_3$). ^{1}H NMR δ 0.023 (s, 3H), 0.046 (s, 3H), 0.856 (s, 9H), 1.17 (d, 3H, J = 6.0 Hz), 3.12 (t, 1H, J = 2.7 Hz), 3.93 (d, 1H, J = 12 Hz), 3.94 (d, 1H, J = 12 Hz), 4.18 (dq, 1H, J = 3.6, 6.3 Hz), 4.90 (d, 1H, J = 2.4 Hz), 5.78 (br s, 1H), 7.2–7.35 (m, 5H). ^{13}C NMR δ −5.23, −4.39, 17.84, 22.09, 25.62, 27.30, 46.81, 64.56, 66.45, 127.08, 128.76, 138.59, 167.09. ^{77}Se NMR δ 374. IR ν_{max} 3193.2, 2853.8, 1767.6. (Found: C, 54.31; H, 7.16; N, 3.41. $C_{18}H_{28}NO_2SiSe$ requires C, 54.39; H, 7.12; N, 3.52%).

***tert*-Butyl 3-[(3*S*,4*R*)-(*R*)-*tert*-butyldimethylsilyloxyethyl]-2-oxo-4-[(phenylmethyl)seleno]-1-azetidineacetate (22)**

The title compound was prepared from (3*S*,4*R*)-3-[(*R*)-*tert*-butyldimethylsilyloxyethyl]-4-[(phenylmethyl)seleno]-2-azetidinone (**21**) and *tert*-butyl bromoacetate as that described for ethyl 2-oxo-4-[(phenylmethyl)seleno]-1-azetidineacetate (**8**) and isolated as a viscous oil in 94% yield. $[\alpha]_D^{25}$ = +41.07° (c = 1.00, $CHCl_3$). ^{1}H NMR δ 0.03 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 1.12 (d, 2H, J = 6.3 Hz), 1.48 (s, 9H), 3.20 (dd, 1H, J = 2.1, 4.8 Hz), 3.37 (d, 1H, J = 18.0 Hz), 3.83 (s, 2H), 3.84 (d, 1H, J = 18 Hz), 4.19 (dq, 1H, J = 4.8, 6.3 Hz), 5.14 (d, 1H, J = 2.1 Hz), 7.18–7.30 (m, 5H). ^{13}C NMR δ −5.06, −4.41, 17.86, 22.00, 25.67, 26.60, 27.98, 41.59, 54.04, 65.24, 65.97, 82.06, 126.92, 128.61, 128.83, 138.77, 166.14, 166.71. ^{77}Se NMR δ 292; IR ν_{max} 1767.3, 1250, 1156. MS *m*/*z* (relative intensity) 514 (M^+, 12), 382 (30), 360 (100), 304 (45), 248 (41). (ESI HRMS: found: 536.1716. $C_{24}H_{39}NO_4SeSiNa$ requires 536.1706).

1-*tert*-Butyl 4-ethyl [(3*S*,4*R*)-3-[(*R*)-*tert*-butyldimethylsilyloxyethyl]-2-oxo-4-[(phenylmethyl)seleno]-1-azetidinyl]butanedioate

The title compound was prepared from *tert*-butyl 3-[(3*S*,4*R*)-(*R*)-*tert*-butyldimethylsilyloxyethyl]-2-oxo-4-[(phenylmethyl)seleno]-1-azetidineacetate (**22**) and ethyl bromoacetate in the manner

described for the preparation of 4-*tert*-butyl 1-ethyl [2-oxo-4-[(phenylmethyl)seleno]-1-azetidinyl]butanedioate (above) and isolated as a yellow oil in 76% yield as a 7 : 1 mixture of diastereomers of which the major isomer was fully characterized. ^{1}H NMR δ 0.01 (m, 6H), 0.83 (s, 9H), 1.03 (d, 3H, J = 6.3 Hz), 1.25 (q, 3H, J = 6.9 Hz), 1.45, (s, 9H), 2.79 (dd, 1H, J = 7.8, 16.8 Hz), 3.00 (dd, 1H, J = 6.0, 16.8 Hz), 3.18 (dd, 1H, J = 2.1, 3.9 Hz), 3.89 (d, 1H, J = 11.7 Hz), 4.01 (d, 1H, J = 11.7 Hz), 4.3 (m, 3H), 4.39 (dd, 1H, J = 6.3, 7.8 Hz), 5.06 (d, 1H, J = 2.1 Hz), 7.1–7.4 (m, 5H). ^{13}C NMR δ −4.99, −4.74, 14.01, 17.76, 25.60, 25.83, 51.76, 53.66, 60.77, 62.12, 64.91, 65.54, 82.62, 126.77, 128.46, 128.51, 128.87, 128.95,138.31, 165.98, 167.28, 170.26. ^{77}Se NMR δ 299.76. IR ν_{max} 1766, 1738, 1255, 1153. MS m/z (relative intensity) 600 (M^+, 100), 544 (15), 500 (12), 446 (68), 442 (55). (ESI HRMS: found: 622.2082. $C_{28}H_{45}NO_6SeSiNa$ requires 622.2079).

3-Carbo-(*tert*-butoxy)-3-[(3*S*,4*R*)-3-[(*R*)-*tert*-butyldim ethylsilyloxyethyl]-2-oxo-4-[(phenylmethyl)seleno]-1-azetidinyl]propanoic acid (23)

Barium hydroxide octahydrate (291 mg, 0.9 mmol) was added to a stirred mixture of 1-*tert*-butyl 4-ethyl (3*S*,4*R*)-[3-[(*R*)-*tert*-butyldimethylsilyloxyethyl]-2-oxo-4-[(phenylmethyl)seleno]-1-azetidinyl]butanedioate (460 mg, 0.77 mmol) in 1 : 1 ethanol/water (20 mL) at 0 °C and the mixture stirred for 24 hours, at which time TLC indicated the absence of starting material. The mixture was acidified to pH 5 (10% HCl), and saturated by the addition of solid sodium chloride. The solution was extracted with ether (5 × 40 mL), the combined organic extracts dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to double flash chromatography (1 : 1 ethyl acetate/dichloromethane followed by 1 : 1 ethyl acetate/methanol) to afford the title compound as a yellow semi-solid that proved to be a 3 : 1 mixture of diastereomers (422 mg, 89%) of which the major isomer was fully characterized. ^{1}H NMR (d_6-DMSO) δ 0.03 (s, 3H), 0.09, (s, 3H), 0.87 (s, 9H), 1.15 (d, 3H, J = 6.3 Hz), 1.45 (s, 9H), 2.88 (dd, 1H, J = 11.0, 6.3 Hz), 3.05 (dd, 1H, J = 11.0, 7.5 Hz), 3.24 (m, 1H), 3.9 (m, 2H), 4.29 (t, 1H, J = 6.6 Hz), 4.38 (m, 1H), 4.97 (d, 1H, J = 2.1 Hz), 7.15–7.30 (m, 5H), 10.2 (br s, 1H). ^{13}C NMR (d_6-DMSO) δ −4.891, −4.604, 17.86, 21.95, 25.65, 26.72, 52.08, 53.38, 65.24, 65.51, 83.04, 126.94, 128.65, 128.93, 138.24, 166.48, 167.18, 175.28; IR 3322.1, 1737.7, 1251.7, 1153.4, 837.0. MS m/z (relative intensity) 572.2 (80, M^+) 514..2 (70), 414.1 (75), 300.0, (100). (ESI HRMS: found: 594.1773. $C_{26}H_{41}NO_6SeSiNa$ requies 594.1766).

***tert*-Butyl (2*S*,5*R*,6*S*)-1-aza-6-[(*R*)-*tert*-butyldimethylsilyloxy-ethyl]-7-oxo-4-selenabicyclo[3.2.0]heptane-2-carboxylate (25)**

3-Carbo-(*tert*-butoxy)-3-[(3*S*,4*R*)-3-[(*R*)-*tert*-butyldimethyl-silyloxyethyl]-2-oxo-4-[(phenylmethyl)seleno]-1-azetidinyl]-propanoic acid (**23**) was converted into the dithiocarbamate (Kim ester) derivative in the manner described during the preparation of ethyl *anti*-1-aza-7-oxo-4-selenabicyclo[3.2.0]heptane-2-carboxylate (**18**). The crude Kim ester was dissolved in benzene and photolysed under reflux for 2 hours. The solvent was removed *in vacuo* and the residue subjected to flash chromatography (3 : 1 hexane/ethyl acetate) to afford the title selenapenam as a pale solid (51%). mp 62–64 °C. ^{1}H NMR δ 0.05 (s, 6H), 0.86 (s, 9H), 1.21 (d, 3H, J = 6.4 Hz), 1.44 (s, 9H), 3.28 (d, 1H, J = 4.8 Hz), 3.51 (m, 2H), 4.20 (m, 1H), 4.98 (t, 1H, J = 4.8 Hz), 5.30 (s, 1H). ^{13}C NMR δ −5.06, −4.38, 17.88, 22.32, 25.66, 27.77, 56.31, 60.94, 65.48, 70.22, 82.51, 167.37, 171.77. ^{77}Se NMR δ 280. IR ν_{max}1755.1, 1732.0, 1367.4, 1141.8, 1062.7. MS m/z (relative intensity) 458 (15, M^+), 392 (57), 336 (81), 278 (100). (ESI HRMS: found: 458.1248. $C_{18}H_{33}NO_4SeSiNa$ requires 458.1242).

(3*S*,4*R*)-3-[(*R*)-*tert*-Butyldimethylsilyloxyethyl]-1-[(2-iodo-phenyl)methyl]-4-[(phenylmethyl)seleno]-2-azetidinone (27)

Lithium hexamethyldisilazide (1.4 mL of a 1.0 M soln in THF) was added to a stirred solution of (3*S*,4*R*)-3-[(*R*)-*tert*-butyldimethyl-silyloxyethyl]-4-[(phenylmethyl)seleno]-2-azetidinone (**21**) (0.50 g, 1.25 mmol) in THF (30 mL) at −78 °C and under nitrogen. After 15 minutes, 2-iodobenzyl bromide (1.0 g, 3.36 mmol) in THF (5 mL) was added and the mixture stirred for 4 hours, at which time TLC analysis revealed an absence of starting material. Water (50 mL) was added and the mixture extracted with ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was subjected to flash chromatography (9 : 1 hexane/ethyl acetate) to afford the title compound (0.84 g, 96%) as a colourless viscous oil. $[\alpha]_D^{25}$ = +84.52° (c = 1.00, $CHCl_3$). ^{1}H NMR δ 0.03 (s, 3H), 0.10 (s, 3H), 0.86 (s, 9H), 1.13 (d, 3H, J = 6.3 Hz), 3.28 (dd, 1H, J = 2.1, 4.5 Hz), 3.64 (d, 1H, J = 17.7 Hz), 3.76 (d, 1H, J = 17.7 Hz), 4.09 (d, 1H, J = 18 Hz), 4.26 (dq, 1H, J = 2.1, 6.3 Hz), 4.53 (d, 1H, J = 17.7 Hz), 4.84 (d, 1H, J = 2.1 Hz), 6.9–7.4 (m, 9H). ^{13}C NMR δ −4.90, −4.58, 17.97, 21.99, 25.72, 49.05, 52.50, 64.72, 65.85, 98.38, 126.93, 128.36, 128.51, 128.82, 128.93, 129.17, 137.64, 138.01, 139.49, 166.48. ^{77}Se NMR δ 295. IR 1760, 1251, 1064, 432. (ESI HRMS: found: 638.0469. $C_{25}H_{34}NO_2SiSeINa$ requires 638.0465).

(2*S*,2a*R*)-2-[(*R*)-*tert*-Butyldimethylsilyloxyethyl]-2,2a-dihydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzoselenazin-1-one (28)

A solution containing (3*S*,4*R*)-3-[(*R*)-*tert*-butyldimethylsilyloxy-ethyl]-1-[(2-iodophenyl)methyl]-4-[(phenylmethyl)seleno]-2-azetidinone (**27**) (0.750 g, 1.22 mmol), triphenyltin hydride (0.514 g, 1.4 mmol) and AIBN (10 mg) in benzene (80 mL) was stirred at reflux for thirty hours. The solvent was removed under reduced pressure and the residue subject to flash chromatography (9 : 1 hexane/ethyl acetate) to afford the cyclised product (**28**) as a pale semi-solid (0.29 g, 65%). $[\alpha]_D^{25}$ = +194.9° (c = 1.00, $CHCl_3$). ^{1}H NMR δ 0.05 (s, 6H), 0.85 (s, 9H), 1.22 (d, 3H, J = 6.0 Hz), 3.32 (m, 1H), 4.80 (d, 1H, J = 16.8 Hz), 4.23 (m, 1H), 4.74 (d, 1H, J = 16.8 Hz), 5.06 (s, 1H), 7.0–7.3 (m, 4H). ^{13}C NMR δ −5.18, −4.29, 17.81, 22.53, 25.58, 43.20, 46.23, 64.99, 69.27, 126.14, 126.30, 127.91, 128.63, 130.39, 131.40, 166.49. ^{77}Se NMR δ 312; IR ν_{max}1766.7, 837.0. (ESI HRMS: found: 420.0873. $C_{18}H_{27}NO_2SiSeNa$ requires 420.0874).

2-[(Phenylmethyl)seleno]nitrobenzene

Sodium borohydride was added, in portions, to a stirred suspension of dibenzyl diselenide (2.63 g, 7.73 mmol), in absolute ethanol (150 mL), under nitrogen until the characteristic yellow color of the diselenide had disappeared. 2-Fluoronitrobenzene (1.63 mL, 15.5 mmol) was added and the resulting solution was stirred for 1.5 hours at ambient temperature. The solvent was removed *in vacuo*, water (100 mL) added and the mixture extracted with ether (3 × 70 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude product which was recrystallized from ethanol to give the title selenide as bright yellow needles (3.37 g, 75%). mp 98–99 °C. ^{1}H NMR δ 4.14 (s, 2H), 7.21–7.57 (m, 8H), 8.23 (d, 1H, J = 8 Hz); ^{13}C NMR δ 31.11, 125.56, 126.39, 127.46, 128.85, 129.14, 129.30, 133.78, 135.49. ^{77}Se NMR δ 399. MS m/z (relative intensity) 292 (M^+, 33), 186 (43), 93 (45), 91(100), 65 (51). (Found: C, 53.68; H, 3.94; N, 4.77. $C_{13}H_{11}NO_2Se$ requires C, 53.44; H, 3.79; N, 4.79%).

2-[(Phenylmethyl)seleno]aniline

Concentrated HCl (30 mL) was slowly added to a mixture of 2-[(phenylmethyl)seleno]nitrobenzene (2.83 g, 9.70 mmol) and finely-divided tin (5.76 g, 48.5 mmol). The suspension was heated at 50 °C for 2 days. After cooling, the mixture was washed with ether (3 × 30 mL), basified with 10% NaOH and the product extracted with ether (4 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (20% EtOAc/petroleum spirits) to give the title compound as pale plates (1.92 g, 75%). mp 50–51.5 °C. ^{1}H NMR δ 3.93 (s, 2H), 4.23 (s (br), 2H), 6.58 (t, 1H, J = 7.1 Hz), 6.72 (d, 1H, J = 8.1 Hz), 7.08–7.23 (m, 6H,), 7.34 (dd, 1H, J = 7.7, 1.8 Hz). ^{13}C NMR δ 31.50, 114.53, 118.60, 126.65, 128.27, 128.65, 130.27, 138.19, 139.16. ^{77}Se NMR

(C_6D_6) δ 282. MS *m*/*z* (relative intensity) 263 (M^+, 100), 261 (70), 183 (57), 92 (86), 65 (38). (Found: C, 59.50; H, 5.02: N, 5.40. $C_{13}H_{13}Nse$ requires C, 59.54; H, 5.01; N, 5.34%).

3,3-Dichloro-2,2-dimethyl-*N*-[2-[(phenylmethyl)seleno]phenyl]-propanamide (31)

A mixture of 3,3-dichloropivalic acid (0.21 g, 1.21 mmol) and thionyl chloride (5 mL) was heated at 80 °C for 4 hours. Excess thionyl chloride was removed under reduced pressure and the resulting crude 3,3-dichloro-2,2-dimethylpropionyl chloride (**30**) was dissolved in carbon tetrachloride (5 mL) and added to a suspension of 2-[(phenylmethyl)seleno]aniline (0.32 g, 3.11 mmol) and triethylamine (0.51 mL, 3.63 mmol) in carbon tetrachloride (15 mL). The resulting solution was heated at reflux under nitrogen for 18 hours, cooled to room temperature, the solids filtered off and the filtrate concentrated *in vacuo* to give the crude amide. Flash chromatography (5% EtOAc/petroleum spirits) provided the title amide as an orange gum (0.34 g, 68%). ^{1}H NMR δ 1.39 (s, 6H), 3.92 (s, 2H), 6.17 (s, 1H), 6.94–6.97 (m, 2H), 7.08 (dt, 1H, J = 1.2, 9 Hz,), 7.16–7.19 (m, 3H), 7.36 (t, 1H, J = 7.8 Hz), 7.55 (d, 1H, J = 7.6 Hz), 8.37 (d, 1H, J = 8.1 Hz), 8.77 (s (br), 1H). ^{13}C NMR δ 21.05, 33.73, 52.69, 79.53, 119.39, 119.95, 124.77, 127.20, 128.31, 128.55, 130.52, 138.06, 138.41, 139.66, 171.24. ^{77}Se NMR (C_6D_6) δ 286. MS *m*/*z* (relative intensity) 415 (M^+, 19), 414 (30), 92 (47), 91 (100), 65 (42). (Found: C, 52.20; H, 4.72; N, 3.15. $C_{18}H_{19}Cl_2NOSe$ requires C, 52.06; H, 4.62; N, 3.37%).

4-Chloro-3,3-dimethyl-1-[2-[(phenylmethyl)seleno]phenyl]-2-azetidinone (32)

3,3-Dichloro-2,2-dimethyl-*N*-[2-[(phenylmethyl)seleno]phenyl] propanamide (**31**) (0.10 g, 0.25 mmol) in THF (2 mL) was added to a stirred suspension of potassium hydride (0.03 g, 0.25 mmol) in THF (3 mL). The resulting mixture was stirred for 18 hours at room temperature under nitrogen, after which it was poured into water (10 mL), extracted with ether (3 × 15 mL), the combined extracts washed with brine, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was purified by flash chromatography (10% EtOAc/petroleum spirits) to give the title azetidinone as an orange gum (0.05 g, 59%). ^{1}H NMR δ 1.42 (d, 6H, J = 6.9 Hz), 4.04 (s, 2H), 5.71 (s, 1H), 7.07–7.54 (m, 9H). ^{13}C NMR δ 18.37, 20.82, 32.88, 57.53, 78.98, 126.93, 127.22, 127.46, 128.38, 128.58, 128.60, 128.71, 135.10, 136.36, 137.98, 169.95. ^{77}Se NMR (C_6D_6) δ 338. MS *m*/*z* (relative intensity) 379 (M^+, 2), 91, (32), 85 (100), 83 (33), 50 (5). (HRMS: found: 379.0236. $C_{18}H_{18}CINOSe$ requires 379.0237).

2,2a-Dihydro-2,2-dimethyl-1*H*-azeto[2,1-*b*]benzoselenazol-1-one (33)

Sodium iodide (0.02 g, 0.14 mmol) was added to a stirred solution of 4-chloro-3,3-dimethyl-1-[2-[(phenylmethyl)seleno]phenyl]-2-azetidinone (**32**) (0.05 g, 0.14 mmol) in acetone (5 mL) and the resultant mixture stirred for a further 18 hours at ambient temperature. The solvent was removed under reduced pressure, water (10 mL) added and the product extracted with ethyl acetate (3 × 15 mL), the combined extracts dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product which was purified by flash chromatography (10% EtOAc/petroleum spirits) to give the required benzoselanapenem (**33**) as thick gum (0.02 g, 46%). ^{1}H NMR δ 1.52 (s, 3H), 1.60 (s, 3H), 5.84 (s, 1H), 7.01–7.29 (m, 4H). ^{13}C NMR δ 21.78, 22.92, 58.11, 70.30, 118.20, 125.91, 126.20, 126.49, 133.62, 137.76, 126.43. ^{77}Se NMR (C_6D_6) δ 347. MS *mz* (relative intensity) 252 (M^+, 37), 184 (68), 91 (31), 84 (56), 70 (100), 51 (36). (HRMS: found: 252.9999. $C_{11}H_{11}NOSe$ requires 253.0003).

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