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Synthesis of the Pleuromutilin Antibiotic SB-268091: A New Practical and Efficient Synthesis of Quinuclidine-4-thiol

Bernie Choudary,[†] Robert G. Giles,[†,∥] Florence Jovic,[†] Norman Lewis,[†] Steve Moore,[†] and Michael Urquhart*[,†,§]

[†]Formerly from GlaxoSmithKline, Old Powder Mills, Leigh, Tonbridge, Kent TN11 9AN, United Kingdom

Supporting Information

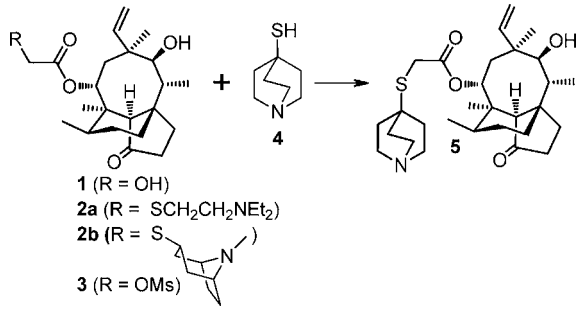
ABSTRACT: A synthesis of the pleuromutilin antibiotic SB-268091 is described which includes a new and improved route to the quinuclidine-4-thiol ligand. This chemistry has been run on multikilo scale and involved a reductive double debenzylation using sodium in liquid ammonia. Alternative conditions have been developed to prepare quinuclidine-4-thiol which avoid the use of sodium in liquid ammonia. The generality of this process to prepare differentially *S*-protected quinuclidine-4-thiols is also discussed and exemplified by the preparation of a range of analogues.

INTRODUCTION

Pleuromutilin **1** is a naturally occurring diterpenoid[1] antibiotic which can be obtained from various *Basidiomycetes* fungi.[2] Modification of the glycolic ester side chain in **1** has been shown to give derivatives with improved antimicrobial activity[3] particularly those containing an α-alkylthioester function. Tiamulin **2a** contains this type of subunit and was marketed by Sandoz for use as a veterinary antibiotic.[4] More recently GlaxoSmithKline marketed retapamulin **2b** for use as a topical antibiotic for the treatment of bacterial skin infections and this product also has efficacy against certain Gram-positive bacteria including MRSA.[5] The alkylthioester **5** (SB-268091) was in development for the treatment of sinusitis and otitis media.

The synthesis of **5** was semi-synthetic from the natural product and was prepared from reaction of the methanesulfonate **3** with quinuclidine-4-thiol **4** (Scheme 1). Extensive

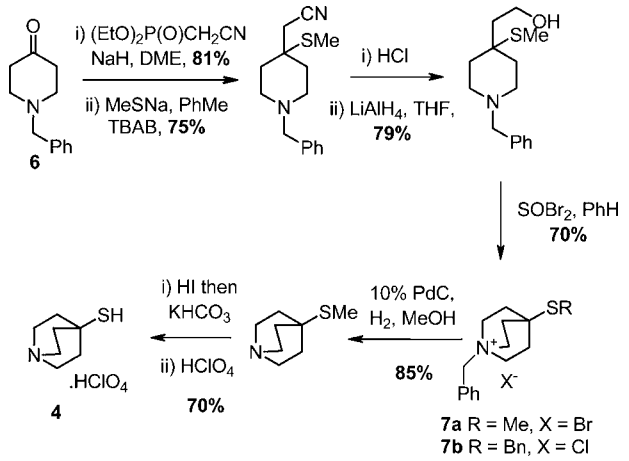
Scheme 1. Synthesis of pleuromutilin SB-268091



development studies were undertaken so that a robust fermentation and extraction procedure for pleuromutilin **1** was achieved which was capable of supplying sufficient material for preproject and phase I. The result of this work showed that pleuromutilin **1** could be fermented from the fungus *Octojuga pseudopinsitus* in 3000 L batches and titres of approximately 0.74 g L^{-1} were obtained. Later investigations identified the culture *Clitopilus passackerianus* which produced titres in excess of 1.5 g L^{-1} and this culture was likely to meet the requirements for phases II and III.

The quinuclidinethiol **4** is not commercially available although it is a literature compound[6] and the synthesis of **4**, as its perchlorate salt, is depicted in Scheme 2.

Scheme 2. Literature preparation of quinuclidine-4-thiol



The original medicinal chemistry route to the quinuclidine ligand **4** was based on the above route, but various problems were highlighted. The conjugate addition of methylmercaptan did not go to completion, it was difficult to remove HCl after the nitrile hydrolysis, and the presence of divalent sulfur leads to a very slow hydrogenation of intermediate **7a**. The hydrogen iodide mediated demethylation was particularly hazardous because pyrophoric phosphine gas was produced from degradation of the hypophosphoric acid stabilizer, and this had significant process safety implications.

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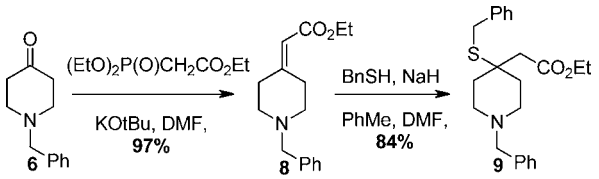
The above synthesis was long, required two chromatographic purifications, and was too hazardous for scale-up. A rapid development was required for **5**, so it was clear that any new route to **4** should follow a similar rationale to the above procedure. Incorporation of sulfur by conjugate addition worked well although methyl or *n*-alkyl groups are seldom used as protecting groups for thiols as they are notoriously difficult to cleave.[7] *N*-Benzylpiperidone **6** is cheap and readily available, and there would be potential for the removal of both benzyl protecting groups in the corresponding intermediate **7b** within a single step using a dissolved metal reduction i.e. sodium or lithium in liquid ammonia.[8] Conjugate addition to an acrylate rather than an acrylonitrile would remove the need for a hydrolysis step as well as the problems associated with it. The conjugate addition of benzylmercaptan to ethyl cyclohexylideneacetate has been reported;[9] hence, we decided to pursue this type of approach for the synthesis of quinuclidine-4-thiol **4**.

Reaction of piperidone **6** with triethyl phosphonoacetate gave the ester **8** in 97% yield, and reaction with benzylmercaptan following the conditions of Huffman and Yim[9] gave the conjugate adduct **9** in 84% yield (Scheme 3).

Scheme 3. Conjugate addition of benzyl mercaptan to ethyl 2-(1-benzylpiperidin-4-ylidene)acetate



Safety assessment of the conjugate addition chemistry showed that there was an uncontrollable gas evolution which was not seen as an issue on small scale but could cause problems on further scale-up. The published procedure describes the addition of benzylmercaptan to sodium hydride (0.1 equiv) in toluene followed by the addition of a solution of **8** in toluene and DMF. No effervescence was observed during the mercaptan addition, but vigorous effervescence ensued at the beginning of the addition of the solution of **8** after a short induction period. Simply adding the DMF solvent to the benzylmercaptan resulted in an addition rate-controlled gas evolution and a far safer process.[10]

Reduction of ester **9** using lithium aluminium hydride proceeded smoothly to give the alcohol **10** in 90% yield. Methanesulfonylation of **10** in THF gave a very good recovery of the salt **7b** after an extended reaction (6 days) at room temperature. A much more rapid conversion to **7b** was achieved if the intermediate solution of **11** was heated to reflux, and now a 2 h reaction time was achieved. A cleaner and more rapid reaction was achieved, however, by changing the reaction solvent to the less coordinating dichloromethane, and the salt **7b** was isolated in 91% yield[11] under these conditions.[12]

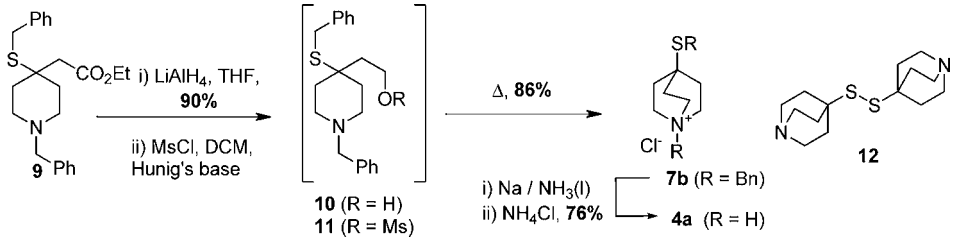
Reductive *bis*-debenzylation of **7b** was achieved using sodium (5 equiv) in liquid ammonia (30 vol) and gave quinuclidine-4-thiol **4** in 76% yield as its hydrochloride salt (**4a**) after an ammonium chloride workup. A direct crystallisation of **4a** from the quenched mixture was essential as earlier extraction procedures had demonstrated that the product had a propensity to dimerise to the disulfide **12** particularly when in solution (Scheme 4).[13,14]

The synthesis of **4a** to date involved the isolation of each intermediate from **6** to **4a** which enabled the potential for further purification by crystallization of the intermediates **9** (as it is HCl salt) and **10**.[15] Given the process from **6** to **7b** was inherently high yielding and the crystallization of **7b** gave highly pure product, it was decided to further streamline the process by combining the first four steps. This key modification would greatly improve processing times by removing the need for isolation of viscous oils and intermediate crystalline solids. The first isolated intermediate was now **7b**, and the overall yield from **6** was 57% as opposed to 63% where the intermediates had previously been isolated. This modification included using toluene for the extraction solvent for stages up to **10** so that efficient azeotropic drying of all product solutions would be achieved and simplified longer-term solvent recovery options. The reduction of **9** was also carried out in a toluene/THF mixture so that a commercial 3.5 M solution of $LiAlH_4$ in toluene could be used rather than the alternative 1 M solution in THF. This was particularly advantageous with respect to throughput. This process was subsequently transferred to small-scale pilot-plant equipment where a total of 4.3 kg of the quinuclidinium salt **7b** was obtained. This material was successfully converted to the target 4-mercaptoquinuclidin-1-ium chloride **4a** using sodium in liquid ammonia in two batches at −50 to −40 °C at a 45 L scale to give a total of 1.1 kg of product which averaged out at 53% for both batches.[16]

This new synthesis of **4** is shorter than the original Grob procedure[6] and offers significant advantages. All stages provide clean products, and thus, chromatographic isolation/purification of the intermediates is not required. The resulting purity of **4** derived from this route is typically high (96−99% based on GC assay) albeit as the hydrochloride salt (**4a**). This new route delivers **4a** in 48% overall yield from benzylpiperidone **6** which is significantly higher yielding than the original Grob procedure which delivered **4** as its perchlorate salt in 20% overall yield from **6**.

The next stages of the synthesis required the preparation of the methanesulfonate **3** from pleuromutilin **1** followed by formation of the thioether **5**.

Scheme 4. Preparation of 4-mercaptoquinuclidin-1-ium chloride



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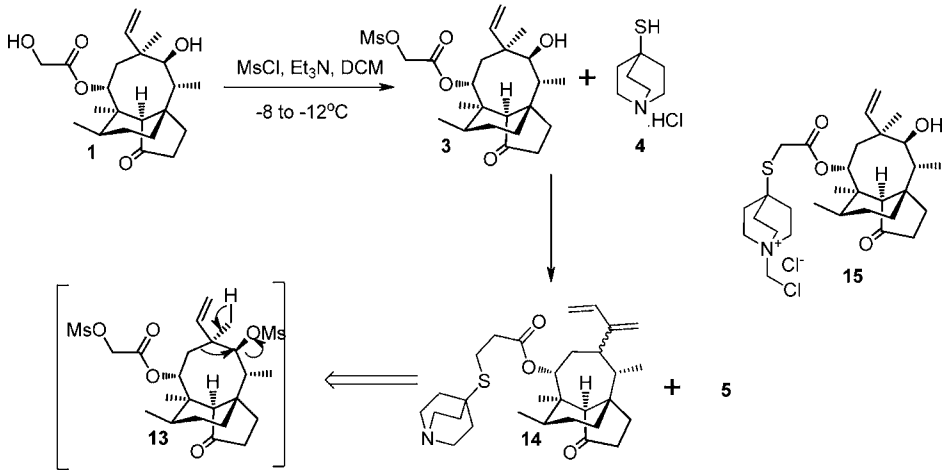
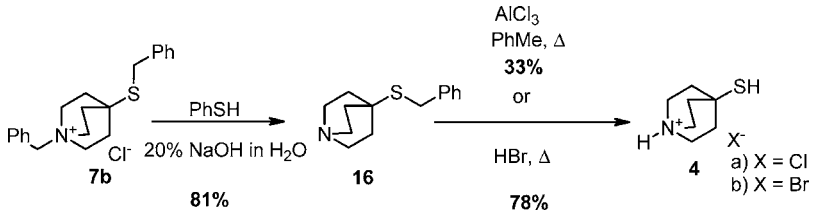
Scheme 5. Formation of ring-contracted by-product 14



Scheme 6. Alternative debenzylation conditions for the conversion of 11 to 4



The medicinal chemistry method for preparing SB-268091 was inefficient in two ways. It produced significant levels of by-products so that chromatography was required for product isolation. Also, crystallisation of the final product was inefficient, requiring 60 vol of solvent, seeding and 5 days to reach completion. This was attributed to the low purity of product derived from this processing.

The minimisation of impurities during these stages was considered vital to facilitate the final crystallisation of the drug substance.

Strict control on stoichiometry of methanesulfonyl chloride (MsCl) as well as addition temperature was required for the conversion of **1** to **3**. Exhaustive methanesulfonylation ultimately results in the formation of the ring-contracted product **14** possibly via the mechanism depicted in Scheme 5. This type of Wagner−Meerwein rearrangement/dehydration with pleuromutilins is known.[17] Simply conducting this reaction under cold conditions (<−15 °C) with 1.16 equiv of MsCl resulted in a much cleaner reaction[18] and **3** could be crystallised directly by concentration of the mixture followed by diluting with hexane.

The alkylthioester **5** is generated from the reaction between the sodium salt of **4** (generated from sodium methoxide in ethanol) and **3**. There was mass spectroscopic evidence that performing the coupling of **3** with a deficiency of **4a** led to the formation of by-products derived from the reaction of **5** with **3**. These impurities were completely removed when the reaction was conducted with a slight excess of **4a**.[19] Residual **4a** was readily removed during the aqueous workup of **5** as it is completely water-soluble. The initial workup method involved an aqueous quench and extraction into DCM, although the product solution had to be kept cold to limit the quaternisation of **5** to give **15**. Later studies demonstrated that ethyl acetate, toluene, or TBME could all be used as extraction solvents for **5**, thus avoiding the formation of **15**. Removal of solvent followed by IPA crystallisation of the residue gave **5** with an unacceptably high level of residual IPA (4−6% w/w). An aqueous acid/base rework was carried out which gave **5** with undetectable levels of IPA and a purity of >98%. This method was used to prepare 175 g of **5** which satisfied the first supplies requirement.

Further development showed that methanol and sodium hydroxide could be used as solvent and base, respectively, for the coupling of **3** with **4**, and as a result, dilution with water resulted in the direct crystallisation of **5** in 91% yield (96% purity). It was further demonstrated that an aqueous methanol recrystallisation of **5** increased the product purity to 98% with no residual solvent issues. These crystallization conditions removed the need for an acid/base rework, and this chemistry was run on the pilot plant where a total of 1.8 kg of **5** was prepared.[20]

The liquid ammonia was distilled off into sulfuric acid for this small-scale pilot-plant campaign to prepare 4-mercaptoquinuclidinium chloride **4a**, but the longer-term use of sodium in liquid ammonia for the conversion of **7b** to **4a** could have proved problematic. Clearly there is potential for recycling the ammonia used for this step, but this would be difficult to engineer, and because of the low site emission limits for ammonia (10 kg per annum), it was prudent to evaluate alternative methods to debenzylate **7b**.

Selective *N*-debenzylation was achieved in 78% yield using thiophenolate conditions[21] to give **16**. Apart from dissolved metal reductions (i.e. sodium in liquid ammonia or alcohols), there are relatively few methods available for the debenzylation of thioethers. Alternative methods include HF,[22] aluminium trichloride,[23] and HBr,[24] but HF was discounted because of potential handling issues with this reagent on larger scale. Removal of the *S*-benzyl function was achieved using

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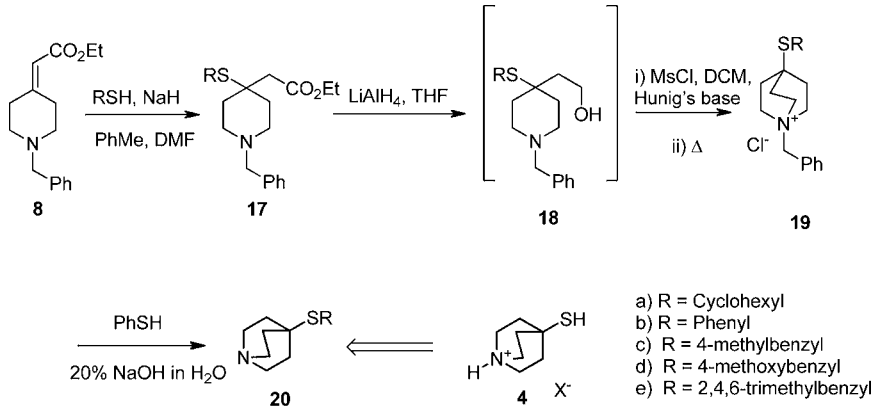

Compound	Yield	Compound	Yield	Compound	Yield	Compound	%Yield
17a	78	**18a**	86	**19a**	87	**20a**	55
17b	71	**18b**	92	**19b**	67	**20b**	64
17c	80	**18c**	92	**19c**	90	**20c**	74
17d	83	**18d**	79	**19d**	67	**20d**	68
17e	88	**18e**	98	**19e**	92	**20e**	54

Figure 1. Preparation of differentially protected quinuclidine-4-thiols.

aluminium trichloride, but the initial yield of **4a** was only 33%. Thus, this chemistry was not further optimised. A superior method involved heating **16** with hydrobromic acid under Dean and Stark conditions[25] such that the benzyl bromide that formed during the reaction was effectively removed.[26] In this way, the hydrobromide **4b** was formed in 78% yield and was of purity comparable to that of the corresponding hydrochloride salt **4a** produced from the dissolved metal conditions (Scheme 6).[27]

To gauge the generality of the above approach to quinuclidine-4-thiol, it was decided to explore a range of alternatively protected thiols within this chemistry. With this in mind, the unsaturated ester **8** was reacted with cyclohexanethiol, thiophenol,[28] 4-methylbenzylmercaptan, 4-methoxybenzylmercaptan, and 2,4,6-trimethylbenzylmercaptan; the corresponding conjugate adducts **17** were prepared in good to excellent yield. Reduction to the alcohol **18** also proceeded smoothly as did the two-step one-pot methanesulfonylation/cyclisation chemistry to give the quinuclidinium salts **19**. Finally, selective deprotection of the *N*-benzyl function using basic thiophenol conditions led to the corresponding protected quinuclidine-4-thioethers **20** (Figure 1). The above sequence of reactions certainly demonstrates the generality of this method to prepare differentially protected quinuclidine-4-thiols, and it is anticipated that subsequent deprotection to quinuclidine-4-thiol **4** would be readily achieved either using the methods already described above for **16** or using established literature methods for the corresponding thioethers.[7]

Conclusions. A synthesis of the pleuromutilin derived antibiotic **5** has been developed. This synthesis used quinuclidine-4-thiol **4** as a pharmaceutical ligand, and a new synthesis of this compound has been developed which is both efficient and safe. Sodium in ammonia was used to remove two benzyl protecting groups in a single step, and this was demonstrated on 45-L scale. An alternative two-step protocol was also developed using thiophenol for *N*-debenzylation and HBr for *S*-debenzylation which does not require a dissolved metal reduction. The generality of this approach was further demonstrated by preparing a range of differentially protected 4-quinuclidinethiols **20**. A useful synthesis of the pleuromutilin methanesulfonate **3** is discussed together with the development of its reaction with the quinuclidine-4-thiol **4** to deliver the antibiotic **5**. The control of pleuromutilin by-products is also described which obviated column chromatography, and the resulting chemistry was successfully run on the pilot plant and delivered 1.8 kg of **5**.

■ EXPERIMENTAL SECTION

General Procedures. Reactions requiring anhydrous conditions were performed using oven-dried glassware and conducted under nitrogen. Anhydrous solvents were purchased from Fisher Scientific and were used without further purification. Melting points were determined on a Buchi 510 apparatus and are uncorrected. IR spectra were recorded on a Nicolet 710 FT-IR spectrometer. NMR spectra were recorded on a JEOL GSX400 instrument operating at 400 MHz for proton NMR and 100 MHz for carbon NMR and were performed in DMSO-d_6 solutions using tetramethylsilane as the internal reference except where indicated otherwise. Mass spectra were recorded on a Micromess Platform II, Sciex API III and a VG Trio-2. High resolution mass spectra were recorded on a 70-VSEQ instrument. Flash chromatography was performed using Fisher Matrix silica gel (60, 40−63 μm)

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according to the published procedure.[29] TLC was performed on glass backed plates precoated with silica (0.2 mm, $60F_{254}$) and developed using standard visualising agents: UV fluorescence (254 and 366 nm), potassium permanganate and iodine.

Ethyl 1-Benzylpiperidin-4-ylideneacetate, ***8.*** Potassium *tert*-butoxide (124.5 g, 1.11 mol) was added portionwise to a solution of triethyl phosphonoacetate (248.9 g, 1.11 mol) in DMF (600 mL) at such a rate that the internal temperature did not exceed 50 °C. The mixture was stirred at 40−50 °C for 1 h and heated to 50 °C; a solution of *N*-benzylpiperidone (200 g, 1.06 mol) in DMF (400 mL) was added dropwise. The mixture was stirred for 10 min at 60 °C, cooled to 20 °C over 1 h, quenched by the dropwise addition of water (1.5 L), and extracted with ethyl acetate (2 × 700 mL). The combined extracts were washed with water (2 × 1 L) and dried (Na_2SO_4), and the solvent was removed under vacuum to afford the title compound as an orange oil (264.7 g, 97%). R_f 0.43 (1:1 EtOAc/lt. petrol 40:60); IR (Nujol) 3062, 3027, 2979, 2942, 2903, 2800, 1713, 1652, 1601, 1494, 1467, 1454, 1395, 1380, 1364, 1343, 1308, 1291, 1268, 1253, 1197, 1169, 1152, 1128, 1096, 1071, 1041, 991, 909, 865, 817, 783, 740, 699, 605, 540, 458; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (3H, t, J = 7.1), 2.32 (2H, t, J = 5.5), 2.52 (4H, t, J = 5.7), 2.99 (2H, t, J = 5.5), 3.52 (2H, s), 4.15 (2H, q, J = 7.1), 5.63 (1H, s), 7.25 (1H, m), 7.30 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.70, 29.83, 37.19, 54.49, 54.92, 59.99, 62.98, 114.44, 127.49, 128.64, 129.47, 138.68, 159.94, 166.98; MS (EI, 70 eV), m/z 260 (M + H), 232, 214, 168, 153, 125, 120, 91.

Ethyl 1-Benzyl-4-benzylthiopiperidin-4-ylacetate, ***9.*** A solution of benzyl mercaptan (138 mL, 1.173 mol) in toluene (500 mL) and DMF (60 mL) was slowly added to a suspension of sodium hydride (60% oil suspension, 8.16 g, 0.204 mol) in toluene (1 L), and the resulting mixture was stirred at ∼25 °C for 30 min. A solution of **8** (264.7, 1.02 mol) in toluene (1 L) was added, and the reaction mixture was stirred at 25−30 °C for 20 h. The reaction mixture was quenched with water (1 L), and the organic layer was separated. The aqueous layer was washed with toluene (500 mL). The combined toluene extracts were further washed with water (2 × 1 L) and dried via repeated azeotropic vacuum distillation, and the solvent was removed under vacuum to give the title compound as a yellow/orange oil (330 g, 84%). R_f 0.22 (1:1 EtOAc/lt. petrol 40:60); IR (Nujol) 3084, 3061, 3027, 2978, 2935, 2811, 2768, 1731, 1652, 1601, 1494, 1464, 1453, 1393, 1367, 1332, 1316, 1251, 1229, 1196, 1182, 1153, 1103, 1071, 1034, 976, 913, 865, 780, 738, 714, 698, 579, 463; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.28 (3H, t, J = 7.2), 1.89 (4H, m), 2.58 (4H, m), 2.65 (2H, s), 3.53 (2H, s), 3.71 (2H, s), 4.17 (2H, q, J = 7.1), 7.27 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.68, 32.30, 36.11, 47.23, 49.47, 49.69, 60.81, 63.36, 127.37, 128.59, 128.87, 129.51, 138.05, 138.86, 170.68; MS (EI, 70 eV), m/z 384 (M + H), 356, 338, 260, 232, 170, 168, 120, 91. HCl salt: white powder from EtOAc, mp 150−154 °C. Found: C, 65.74; H, 7.39; N, 3.32; S, 7.69; Cl, 8.30. $C_{23}H_{29}NO_2S$·HCl requires C, 65.77; H, 7.2; N, 3.33, S, 7.63, Cl, 8.44.

Alternative Synthesis of Ethyl 1-Benzyl-4-benzylthiopiperidin-4-ylacetate, ***9.*** Benzyl mercaptan (35 mL, 292.5 mmol) was added dropwise to a stirred suspension of powdered sodium hydroxide (2.0 g, 51 mmol) in DMF (14 mL) and toluene (270 mL). This mixture was stirred for 30 min then a solution of **8** (66.2 g, 255 mmol) in toluene (270 mL) was added dropwise. The resulting solution was stirred at 20 °C for 13.5 h and quenched by the dropwise addition of water (250 mL); the organic phase was separated and the aqueous extracted with toluene (2 × 250 mL). The organic phases were combined and dried via repeated azeotropic vacuum distillation, and the solvent was removed under vacuum to give **9** as a yellow/orange oil (97.7 g, 100%).

2-(1-Benzyl-4-benzylthiopiperidin-4-yl)ethanol, ***10.*** A solution of ester **9** (320.1 g, 0.835 mol) in THF (600 mL) was added dropwise to a stirred solution of lithium aluminium hydride (31.7 g, 0.835 mol) in THF (1.3 L) at 25 °C under nitrogen maintaining an addition temperature of below 35 °C. The mixture was stirred at 25 °C for 1 h then very carefully quenched by the dropwise addition of water (30 mL) over 1 h. The mixture was sequentially treated with 1 M NaOH (aq) (150 mL) and water (150 mL), stirred for 1.5 h then diluted with ethyl acetate (2L). The mixture was filtered through Celite, the residue was washed with ethyl acetate (500 mL), the filtrate and washings were combined, washed with brine (1 L) and dried (Na_2SO_4). The solvent was removed under vacuum to give the title compound **10** as a white solid which was dried (256.4 g, 90%). An analytical sample of **10** was prepared by dissolving **10** (6.0 g, 17.6 mmol) in methanol (30 mL), diluting with water (25 mL) dropwise and stirring for 1 h. Filtration gave **10** as white crystals (4.69 g, 78%), mp 85−86 °C. R_f 0.03 (1:1 EtOAc/lt. petrol 40:60); IR (Nujol) 3215, 3057, 3025, 2924, 2810, 2766, 1493, 1464, 1454, 1377, 1367, 1342, 1325, 1262, 1150, 1115, 1096, 1079, 1067, 1035, 1006, 782, 743, 715, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.72 (2H, m), 1.82 (2H, m), 1.90 (2H, t, J = 6.3), 2.57 (4H, m), 3.53 (2H, s), 3.71 (2H, s), 3.87 (2H, t, J = 6.3), 7.27 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 31.74, 35.94, 47.76, 63.13, 126.97, 127.07, 128.16, 128.19, 128.56, 129.02, 129.07, 137.59, 138.48; MS (EI, 70 eV), m/z 342 (M + H), 218, 91. Found: C, 73.88; H, 8.18; N, 4.06; S, 9.45%. $C_{21}H_{27}NOS$ requires C, 73.86; H, 7.97; N, 4.10, S, 9.39.

1-Benzyl-4-benzylthioquinuclidinium Chloride, {1-Azonia-1-(phenylmethyl)-bicyclo[2.2.2]octane chloride}, ***7b.*** A solution of methanesulfonyl chloride (61.4 mL, 0.792 mol) in DCM (400 mL) was added dropwise to a stirred solution of alcohol **10** (245.54 g, 0.720 mol) and *N*,*N*-diisopropyl-*N*-ethylamine (138 mL, 0.792 mol) in DCM (1.6 L) at 15 °C under nitrogen such that a steady reflux was achieved. The resulting solution was heated under reflux for 1.5 h, cooled to 35 °C and treated with brine (1 L) and water (500 mL). The biphasic mixture was stirred for 10 min, allowed to stand at 20 °C for 14 h; then the aqueous was removed and washed with DCM (500 mL). The combined organic phases were washed with brine (1 L) and dried (Na_2SO_4), and the solvent was removed under vacuum to give a cream-colored solid. The solid was diluted with THF (1 L), heated to reflux with stirring, stirred for 30 min, and then cooled to ambient. Filtration under vacuum gave **7b** as a cream-colored solid which was washed with THF (2 × 100 mL) and dried (248.45 g, 91%);[30] mp 136 to 137 °C. R_f 0.00 (EtOAc); IR (Nujol) 3405, 3028, 2928, 2854, 1601, 1496, 1461, 1378, 1343, 1254, 1216, 1076, 1045, 1029, 1007, 931, 843, 783, 775, 713, 697, 634, 486, 470; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.11 (6H, t, J = 7.7), 3.72 (2H, s), 3.89 (6H, t, J = 7.8), 5.05 (2H,s), 7.22 (2H, m), 7.28 (3H, m), 7.39 (3H, m), 7.65 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 30.74, 32.80, 38.50, 54.72, 67.02, 127.61, 127.71, 129.05, 129.18, 129.52, 130.87, 133.75, 137.48; MS (EI, 70 eV), m/z 323 (M +), 233, 91. Found: C, 66.65; H, 3.70; N, 7.65; S,

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8.62%. $C_{21}H_{26}NS.Cl.H_2O$ requires C, 66.57; H, 7.97; N, 3.69, S, 8.46%.

*Streamlined Preparation of 1-Benzyl-4-benzylthioquinuclidinium chloride, {1-Azonia-1-(phenylmethyl)-bicyclo[2.2.2]octane chloride}, **7b**.* Solid potassium *tert*-butoxide (Assay ~97%, 31.0 g, 0.285 mol) was added in portions to a solution of triethyl phosphonoacetate (63.0 g, 0.281 mol) in DMF (150 mL) so that the temperature did not exceed 50 °C. The reaction mixture was maintained at 50 °C for 30 min after the addition was complete. A solution of *N*-benzyl-4-piperidone **6** (50 g, 0.264 mol) in DMF (80 mL) was added at a rate so that the reaction temperature did not exceed 75 °C. When complete reaction was achieved, the reaction mixture was cooled to 25 °C, quenched with water (500 mL) and extracted into toluene (3 × 180 mL), and the combined organic extracts were washed with water (2 × 250 mL). The toluene solution was dried via repeated azeotropic vacuum distillation until a dry solution of **8** in toluene (approximately 250 mL) was obtained.

A solution of benzyl mercaptan (36.5 g, 0.293 mol) in toluene (125 mL) and DMF (1.5 L) was slowly added to a suspension of sodium hydride (60% oil suspension, 2.04 g, 51 mmol) in toluene (250 mL), and the resulting mixture was stirred at ~25 °C for 15 min. The previously prepared solution of **8** in toluene (approximately 250 mL) was added, and the reaction mixture was stirred at 25 to 30 °C for 20 h. The reaction mixture was quenched with water (250 mL), and the organic layer was separated. The aqueous layer was washed with toluene (125 mL). The combined toluene extracts were further washed with water (2 × 250 mL) before being dried via repeated azeotropic vacuum distillation, until a dry solution of **9** in toluene (approximately 250 mL) was obtained.

The toluene solution of **9** was added to a 3.5 M solution of lithium aluminium hydride in toluene/THF (75 mL, 264 mmol) in toluene (230 mL) over 1 h between 15 and 50 °C. The resulting reaction mixture was stirred at 40 °C for 1 h. A mixture of water (10 mL) and THF (90 mL) was carefully added to the reaction mixture at 0 °C, followed by 1 M aqueous sodium hydroxide (40 mL), and water (40 mL). The resulting precipitate of aluminium salts was removed via filtration, and the filtrate was extracted with toluene (250 + 125 mL). The combined organic extracts were washed with water (2 × 250 mL) and dried via repeated azeotropic vacuum distillation until a dry solution of **10** in toluene (approximately 90 mL) was obtained.

A solution of methanesulfonyl chloride (23 mL, 0.29 mol) in DCM (150 mL) was added to the previously prepared toluene solution of **10** admixed with DCM (600 mL) and Hunig's base [*N*,*N*-diisopropylethylamine] (51 mL, 0.29 mol). The addition rate was controlled by the rate of reflux. The resulting mixture was kept at reflux temperature for 2 h. Saturated brine solution (400 mL) was added to the cooled reaction mixture, and it was stirred for 20 h at 25 °C. The organic layer was removed, and the aqueous phase was extracted with DCM (180 mL). The combined organic extracts were washed with saturated brine (350 mL). The organic layer was concentrated via atmospheric distillation to a volume of 320 mL, and THF (750 mL) was added to the residue. Distillation was repeated until 500 mL of distillate had been removed and further THF (750 mL) was added. Distillation was repeated until 500 mL of distillate had been removed, and further THF (750 mL) was added. The resulting THF solution was cooled, and **7b** crystallised out of solution. The product was filtered, washed with THF (250 mL), and dried at 50 °C in vacuo (53.9 g, 57% from **6**).

*Pilot-Scale Preparation of 1-Benzyl-4-benzylthioquinuclidinium Chloride, {1-Azonia-1-(phenylmethyl)-bicyclo[2.2.2]-octane chloride}, **7b**.* Potassium *tert*-butoxide (3.1 kg, 27.6 mol) was cautiously charged in two lots with intermediate cooling to a solution of triethyl phosphonoacetate (6.3 kg, 28.1 mol) in DMF (14.2 kg), keeping the temperature below 35 °C. The reaction mixture was warmed to 48 °C and stirred for 30 min. A solution of *N*-benzyl-4-piperidone **6** (5.0 kg, 26.4 mol) in DMF (7.6 kg) was charged to the reaction mixture over 25 min, keeping the temperature of the reaction mixture below 70 °C. The transfer line was rinsed by charging DMF (2.8 kg) to the reaction mixture. The reaction mixture was stirred at 70 °C for 1 h. TLC and HPLC indicated that the reaction was complete. The reaction mixture was cooled to 24 °C. Demineralised water (50.0 L) was added. The mixture was extracted with toluene (15.6 kg), and the aqueous layer was extracted twice with toluene (2 × 15.6 kg). The organic layers were combined and washed twice with demineralised water (2 × 25.0 L). The organic product solution was dried by distilling out 40 L of solvent, charging toluene (43.3 kg), and distilling out 40 L of solvent. Toluene (5.3 kg) was added to give a solution of **8** in toluene (22.6 kg).

A solution of benzyl mercaptan (3.65 kg, 29.4 mol) in DMF (1.4 kg) and toluene (4.4 kg) was added over 25 min to a suspension of sodium hydride (0.204 kg, 5.1 mol) in toluene (21.7 kg) at 21 to 25 °C. The transfer line was rinsed by charging toluene (8.1 kg) to the reaction mixture. The mixture was stirred at 20−25 °C for 15 min. The solution of **8** in toluene from above (22.6 kg) was charged to the reaction mixture over 25 min, maintaining the temperature below 25 °C. The transfer line was rinsed by charging toluene (4.4 kg) to the reaction mixture. The reaction mixture was stirred at 25−30 °C for 9.5 h. NMR indicated that the reaction had stopped at about 85% conversion. The reaction mixture was cautiously quenched with demineralised water (25.0 L), and the resulting phases were separated. The aqueous phase was extracted with toluene (10.8 kg). The organic layers were combined and washed twice with demineralised water (2 × 25.0 L). The solution of **9** was dried by distilling out 61 L of solvent, charging toluene (21.7 kg), distilling out 30 L of solvent, charging toluene (43.4 kg), and finally distilling out 45 L of solvent. The solution was cooled to 22 °C and discharged from the reactor to give 17.2 kg of a solution of **9** in toluene. The solution was not assayed, but used directly in the next stage of the process.

Toluene (19.9 kg) and a 3.5 M solution of lithium aluminum hydride in THF/toluene (6.7 kg, 26.3 mol) were charged into the reactor. The transfer line was rinsed by charging THF (4.5 kg) to the suspension. The suspension was cooled to 20 °C, and the solution of **9** in toluene (17.2 kg) was added in three lots with intermediate cooling over 45 min, maintaining the temperature below 30 °C. Toluene (4.5 kg) was added, and the reaction mixture was stirred at 40−45 °C for 1 h. TLC and MS indicated that the reaction was complete. The mixture was cooled to 12 °C. A mixture of THF (8.0 kg) and water (1.0 kg) was added to the reaction mixture over 16 min, followed by a slow addition of a solution of sodium hydroxide (0.16 kg) in demineralised water (4.0 L), and demineralised water (4.0 L). The temperature of the mixture was kept below 25 °C. The resulting suspension was warmed to 75 °C and stirred for 30 min. Finally, the suspension was cooled to 45 °C. The attempt to filter the suspension using a pressure plate filter was not

successful because blocking of the filter occurred. The contents of the filter were recharged into the reactor. Toluene (30 L) was used to wash the lines. The suspension was heated, and 25 L of solvent was distilled out. Toluene (10 L) was charged, and 20 L of solvent were distilled out. Toluene (8.7 kg) was charged, and the suspension was cooled to 50 °C. The suspension was filtered using the Ellerwerk centrifuge, which was precoated with Celite (1.0 kg). The solids in the centrifuge were washed with toluene (32.5 kg). Demineralised water (25.0 L) was added to the filtrate, and the mixture was stirred for 10 min. After settling for 2 h, only partial separation had occurred. The aqueous phase that had separated was drained off. The mixture was warmed to 25−30 °C and allowed to settle for 1.5 h. The lower aqueous phase was separated off. The organic mixture (49.4 kg) was drummed up and recharged into the reactor via an in-line filter. The drum and transfer line were rinsed by charging toluene (4.5 kg) to the mixture. The mixture was dried by distilling out 40.0 L of solvent, charging toluene (43.4 kg), distilling out 50 L of solvent, charging toluene (43.4 kg), and finally distilling out 50 L of solvent. The solution was cooled to 25 °C, and DCM (40 kg) was added. It was discharged from the reactor to give 49.6 kg of a solution of **10** in toluene/DCM. The solution was not assayed, but used directly in the next stage of the process.

DMF (3.78 kg, 29.3 mol), DCM (66.2 kg), and the solution of **10** in toluene/DCM (49.6 kg) were charged into a reactor. A solution of methanesulfonyl chloride (3.42 kg, 29.7 mol) in DCM (20.0 kg) was added in two lots over 30 min, maintaining the temperature below 25 °C. The transfer line was rinsed by transferring DCM (6.6 kg) to the reaction mixture. The mixture was stirred for 7 h at reflux. TLC and MS indicated that the reaction profile was satisfactory. The reaction mixture was cooled to 23 °C and transferred to another reactor. The transfer line was rinsed by charging DCM (6.6 kg) to the mixture. A solution of sodium chloride (23.6 kg) in demineralised water (70.8 kg) was added, and the mixture was stirred for 17.5 h at 20−30 °C. The mixture was allowed to settle for 30 min, and the lower organic layer was separated off. The aqueous layer was washed with DCM (23.9 kg). The organic phases were combined and extracted with a solution of sodium chloride (11.9 kg) in demineralised water (35.7 kg). The solvent of the organic phase, DCM, was replaced with THF in a "put-and-take" distillation step by distilling out 95.0 L of solvent, charging THF (66.7 kg), distilling out 50 L of solvent, charging THF (66.7 kg), distilling out 50 L of solvent, and finally charging THF (66.7 kg). The resulting suspension was cooled to 30 °C and stirred for 2 h at 25−30 °C. The product was isolated in a centrifuge and washed with THF (22.2 kg). The wet product (4.1 kg) was dried for 73.5 h under vacuum at 50 °C to give 2.7 kg of **7b** (28.4% yield from **6**).[31]

*4-Thioquinuclidinium Chloride, {1-Azoniabicyclo[2.2.2]-octane-4-thiol chloride}, **4a**.* Ammonia (220 mL, 12.94 mol) was condensed into a cooled (−40 °C) three-neck, 500-mL flask under nitrogen equipped with a coldfinger reflux head (cardice/propan-2-ol) and a glass-coated magnetic follower. The contents were kept cold by means of a cardice/propan-2-ol bath. Sodium metal (3.1g, 0.135g atoms) was added in portions to the stirred mixture over ∼30 min, and the resulting dark-blue (almost black) solution was stirred for 30 min. The salt **7b** (10.0g, 27.82 mmol) was added in portions over ∼30 min via a powder funnel to the stirred mixture. The dark mixture was stirred at −33 °C for 2.5 h and then very carefully quenched by the dropwise addition of methanol (200 mL).[32] Solid ammonium chloride (10.19 g, 0.19 mol) was added, the mixture was stirred for 20 min, and then the ammonia was allowed to distill out of the mixture.[33] Once the internal temperature had reached 25 °C, the stirred mixture was heated to reflux and sirred at reflux for 1 h. Filtration under vacuo removed inorganic insolubles, and the residue was washed with methanol (20 mL). The filtrate was evaporated in vacuo to give a white solid residue which was suspended in toluene (400 mL) and stirred at 25 °C for 30 min. Filtration under vacuum gave a cream-colored solid which was washed with toluene (100 mL) and pulled dry.

The solid (9.27 g) was suspended in propan-2-ol (120 mL), heated to reflux, and stirred for 30 min. Hot filtration under vacuum gave a white solid and a pale-yellow filtrate from which a colourless solid rapidly precipitated. The residue was washed with hot propan-2-ol (20 mL) and pulled dry. The combined filtrate and washings were cooled to −8 °C, allowed to stand for 16 h at this temperature, and filtered under vacuum. The residue was washed with cold propan-2-ol (20 mL) and pulled dry to give **4a** as colourless/grey crystals (wt = 3.77 g, 76%), mp >250 °C; IR (Nujol) 3392, 2924, 2779, 2727, 2552, 2470, 1644, 1463, 1438, 1377, 1333, 1281, 1224, 1171, 1038, 1005, 918, 839, 770, 722, 664, 555, 536, 526, 419; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.01 (6H, t, J = 7.9), 3.25 (6H, t, J = 7.9), 3.50 (1H, s), 11.15 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 32.50, 35.57, 46.41; MS (EI, 70 eV), m/z 144 (M + 1), 111, 83. Found: C, 46.83; H, 8.33; N, 7.79; S, 17.78. $C_7H_{13}NS{\cdot}HCl$ requires C, 46.78; H, 7.85; N, 7.79, S, 17.84.

*Pilot-Scale Preparation of 4-Thioquinuclidinium Chloride, {1-Azoniabicyclo[2.2.2]octane-4-thiol chloride}, **4a**.* THF (88.9 kg) was charged into the reactor and cooled to −50 °C using the liquid nitrogen heat exchanger. The cold contents of the reactor were discharged. Sodium sticks (0.62 kg, 27.0 mol) were charged into the reactor via the charge-hole. Liquid ammonia (35.2 kg) was added, which resulted in a total volume of the contents of the reactor of 45.0 L. The reactor was cooled to −44 °C, and **7b** (2.0 kg, 5.6 mol) was charged in five lots at −45 to −40 °C. The reaction mixture was stirred for 1 h between −45 and −40 °C. Methanol (4.0 kg) was cautiously charged over 20 min, allowing the temperature to rise to −32 °C. Methanol (27.7 kg) was added over 30 min. The temperature had risen to −18 °C. Ammonium chloride (2.04 kg, 38.1 mol) was added in four lots. The reaction mixture was warmed gradually from −18 to 55 °C over 3.5 h using consecutively cooling water, hot water, and steam. During the heat-up, 2.0 L of distillate was collected. The reaction mixture was stirred for 1 h at 55 to 60 °C and then cooled to 29 °C. The reaction mixture was filtered via a pressure plate filter, which was precoated with Celite (2.0 kg). The filter system was washed with methanol (5.4 kg). The filtrate (37.2 kg) was subjected to a "put-and-take" distillation by distilling out 32 L of solvent, charging 2-propanol (31.4 kg), distilling out 35 L of solvent, charging 2-propanol (31.4 kg) and finally distilling out 35 L of solvent. The hot product mixture was transferred to another reactor via a filter system, which was rinsed with hot 2-propanol (3.9 kg). The product solution was cooled to −3 °C and stirred for 2 h between −5 and 0 °C. The product was isolated using the Rosenmund pressure plate filter and washed with cold 2-propanol (3.9 kg). The wet product (1.2 kg) was dried under vacuum at 50 °C for 60 h to give 0.552 kg of **4a** (0.520 kg at 100%, 52.0% of theory from **7b**) (weight-based purity calculated as 94.1% pure).[16]

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4-Quinuclidinium Disulfide Dichloride, {4-(1-Azoniabicyclo[2.2.2]octane)disulfide chloride}, **12**. Sulfuryl chloride (0.45 mL, 5.56 mmol) was added dropwise to a stirred suspension of **4a** (2.0 g, 11.13 mmol) in pyridine (20 mL) at 25 °C such that the internal temperature did not exceed 53 °C. The suspension was stirred at room temperature for 24 h, and the solvent was removed under vacuum to afford a cream-colored solid. This solid was suspended in propan-2-ol (40 mL) and filtered under vacuum. The residue was washed with propan-2-ol (2 × 10 mL) to give the title compound **12** as a cream-colored solid (wt = 1.97 g, 99%). Recrystallisation from methanol and propan-2-ol gave **12** as cream-colored crystals; IR (thin film) 3390, 2924, 2853, 2780, 2727, 2698, 2624, 2573, 2471, 2351, 2089, 1643, 1492, 1465, 1436, 1417, 1377, 1334, 1305, 1281, 1253, 1169, 1162, 1046, 1027, 1008, 1004, 997, 917, 839, 791, 721, 659, 532, 471, 426, 419; ^{1}H NMR (400 MHz, CD_3OD) δ_H 2.18 (6H, t, J = 7.9), 3.50 (6H, t, J = 7.9); ^{13}C NMR (100 MHz, CD_3OD) δ_C 30.57, 42.80, 48.91; MS (FIA/ms/ms, 70 eV), m/z 285 (M + H), 176, 144, 110, 96, 82, 68.

Pleuromutilin Methanesulfonate, {(3aS,4R,5S,6S,8R,9-R,9aR,10R)-6-Ethenyldeca hydro-5-hydroxy-4,6,9,10-tetra-methyl-1-oxo-3a,9-propano-3aH-cyclopentacyclo-octen-8-yl Methanesulfonyloxyacetate}, **3**. Triethylamine (2.19 mL, 15.71 mmol) was added to a stirred solution of pleuromutilin 1 (5.31 g, 14.03 mmol) in DCM (54 mL) at 15 °C under nitrogen. The mixture was cooled to 15 °C and treated dropwise with a solution of methanesulfonyl chloride (1.27 mL, 16.40 mmol) in DCM (3 mL), maintaining an addition temperature of below −15 °C. The mixture was stirred below −15 °C for 1 h and warmed to 5 °C; water (50 mL) was added, and the mixture was stirred for 30 min. The organic phase was removed and the aqueous extracted with DCM (2 × 20 mL); the combined organic extracts were washed with brine (50 mL), and a quantity of DCM (60 mL) was removed by distillation. *n*-Hexane (66 mL) was added to the mixture slowly (over 30 min) whilst the distillation was continued, and a further 80 mL of distillate was collected. The white suspension was cooled to 5 °C and stirred for 1 h, and the solid was collected by filtration, washed with *n*-hexane (2 × 12 mL), and dried to give the title compound **3** as a white solid (wt = 5.10 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 0.73 (3H, d, J = 6.8), 0.90 (3H, d, J = 6.8), 1.23 (4H, m), 1.47 (7H, m), 1.72 (5H, m), 2.22 (5H, m), 3.19 (3H, s), 3.37 (1H, d, J = 6.4), 4.65 (2H, s), 5.22 (1H, d, J = 17.6), 5.35 (1H, d, J = 10.8), 5.84 (1H, d, J = 8.4), 6.45 (1H, dd, J = 17.6, 11.2); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 11.54, 14.74, 16.61, 24.83, 26.44, 26.80, 30.34, 34.40, 36.07, 36.53, 39.17, 41,84, 44.02, 44.62, 45.41, 58.02, 65.12, 70.54. 74.57, 77.23, 117.53, 138.65, 165.76, 216.74; MS (FIA-MS/MS, 70 eV), m/z 474 (M + NH_4), 303, 285, 245.

Pilot-Scale Preparation of Pleuromutilin Methanesulfonate, {(3aS,4R,5S,6S,8R,9R,9aR,10R)-6-Ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3aH-cyclopentacyclo-octen-8-yl methanesulfonyloxyacetate}, **3**. DCM (39.2 kg), pleuromutilin (**1**, 2.69 kg, 7.1 mol), and triethylamine (0.81 kg, 8.0 mol) were charged into the reactor, and the mixture was cooled to −17 °C. A solution of methanesulfonyl chloride (0.95 kg, 8.3 mol) in DCM (5.0 kg) was added over 1 h, maintaining the temperature below −15 °C. The transfer line was rinsed by charging DCM (3.0 kg) to the reaction mixture. The mixture was stirred for 25 min between −15 and −20 °C. The reaction mixture was heated to 13 °C, and demineralised water (24.0 L) was added. The contents of the reactor were stirred for 30 min and allowed to settle for 15 min. The lower organic layer was separated off, and DCM (8.1 kg) was added to the aqueous layer. After the mixture stirred for 5 min and settled for 15 min, the organic phase was separated. A large amount of interface was observed, which was drummed up and returned into the reactor via an in-line filter. DCM (8.1 kg) was charged via the in-line filter into the reactor, and the mixture was warmed to 23 °C. The mixture was stirred for 5 min and allowed to settle for 15 min. The organic layer was separated. The combined organic phases were heated, and 25 L of solvent was distilled off. Whilst continuing the distillation, *n*-hexane (22.1 kg) was slowly added over 1.5 h until the temperature of the mixture had risen to 46.3 °C and a further 10.7 L of distillate had been collected. Seed crystals of **3** (0.01 kg, 0.022 mol) were added during the hexane addition when the mixture appeared to have become cloudy. After the addition was complete, a sample was taken which indicated that the product had oiled out. The contents of the reactor were cooled to 34 °C, and seed crystals of **3** (0.01 kg, 0.022 mol) were added. The mixture was stirred for 40 min between 34 and 31 °C after which the product had crystallised. The mixture was cooled to 1 °C and stirred for 2 h between 0 and 5 °C. The product was isolated using the Rosenmund pressure plate filter and washed twice with *n*-hexane (8.0 and 3.2 kg). The wet product (2.6 kg) was dried under vacuum at room temperature for 13.5 h to give 2.1 kg of **3** (2.05 kg at 100%, 60% of theory from **1**) (weight-based purity calculated as 97.9% pure).

14-Deoxy-14-(quinuclidine-4-thioacetoxy)mutilin, {(3aS,4R,5S,6S,8R,9R,9aR,10R)-6-Ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3aH-cyclopentacycloocten-8-yl-[1-azoniabicyclo[2.2.2]octane-4-thio]-acetate}, **5**. Sodium hydroxide (1.54 g, 38.5 mmol) was added in portions to a stirred solution of **4a** (3.16 g, 17.59 mmol) in methanol (60 mL) at 15 °C under nitrogen, maintaining an internal temperature of below 20 °C. The mixture was stirred at 20 °C for 1 h, cooled to 15 °C, and **3** (6.99 g, 15.31 mmol) was added in portions so that the internal temperature did not exceed 20 °C. The mixture was stirred at 20 °C for 1.5 h and cooled to 2 °C; water (150 mL) was added, maintaining an internal temperature below 5 °C. After stirring at 5 °C for 1 h, the product was collected by filtration, washed with water (100 mL), and dried to give **5** as a white solid (wt = 7.21 g, 94%). An analytical sample of **5** was prepared by dissolving **5** (1.0 g, 1.99 mmol) in methanol (5 mL) at 60 °C and diluting with water (5 mL) dropwise such that the internal temperature was maintained above 60 °C. The mixture was cooled to 5 °C over 2 h and stirred at 5 °C for 1 h. The product **5** was collected by filtration, washed with water (5 mL) and dried (0.93 g, 93%). This material had spectroscopic properties identical to those reported.[34]

Pilot-Scale Preparation of 14-Deoxy-14-(quinuclidine-4-thioacetoxy)mutilin, {(3aS,4R,5S,6S,8R,9R,9aR,10R)-6-Ethenyldecahydro-5-hydroxy-4,6,9,10-tetramethyl-1-oxo-3a,9-propano-3aH-cyclopentacycloocten-8-yl [1-azoniabicyclo[2.2.2]octane-4-thio]acetate}, **5**. Methanol (6.79 kg) and **4a** (0.472 kg, 2.63 mol) were charged into the reactor, and the mixture was cooled to 13 °C. Sodium hydroxide (0.221 kg, 5.53 mol) was added over 5 min, maintaining the temperature below 20 °C. The mixture was stirred for 1 h between 18 and 22 °C and cooled to 14 °C. Methanesulfonate **3** (1.00 kg, 2.19 mol) was added over 10 min, and the reaction mixture was stirred for 2 h between 18 and 22 °C. HPLC indicated that the reaction had gone to

completion. The mixture was cooled to 3 °C, and demineralised water (21.5 L) was added in 1.0 L portions, maintaining the temperature below 5 °C. The suspension was stirred for 2 h between 4 and 6 °C. The product was isolated using the Rosenmund pressure plate filter and washed with demineralised water (15.0 L). The wet product (1.64 kg) was dried under vacuum at 50 °C for 22 h to give 1.03 kg of crude **5** (1.01 kg at 100%, 91.6% of theory from **3**).

Methanol (7.9 kg) and crude **5** (2.08 kg, 4.1 mol) were charged into the reactor. The solution was heated to 60 °C and stirred for 10 min between 60 to 65 °C. The solution was discharged into a preheated 20-L container, and the reactor was cleaned by boiling out with methanol (40.0 kg). The product solution was charged back into the reactor via an in-line filter. Methanol (3.4 kg) was heated to 50 °C and charged to the reaction mixture via the in-line filter. The reaction mixture was heated, and 3.0 L of solvent was distilled off. Demineralised water (10.5 L) was slowly added, maintaining the temperature of the reaction mixture at 60 to 65 °C. The suspension was gradually cooled over 2 h to 0−5 °C. The suspension was stirred for 2 h at 0 to 5 °C. The product was isolated using a Rosenmund pressure plate filter and washed with demineralised water (10.0 L). The wet product (2.4 kg) was dried under vacuum at 50 °C for 109 h to give 1.8 kg of **5** (1.76 kg at 100%, 84.8% of theory from crude **5**) (weight-based purity calculated as 98.0% pure).

*4-Benzylthioquinuclidine, {1-Aza-4-(phenylmethylthio)-bicyclo[2.2.2]octane}, **16**.* Thiophenol (18.5 mL, 184.6 mmol) was added to a stirred suspension of **7b** (32.6 g, 91.2 mmol) in 20% sodium hydroxide solution (55 mL). The mixture was heated to 90 to 100 °C, stirred for 1 h and cooled to 20 °C. The mixture was quenched with water (200 mL), extracted with ethyl acetate (2 × 150 mL) and washed with water (100 mL). The combined organic extracts were washed with 1 M hydrochloric acid (2 × 100 mL), the acidic aqueous was washed with ethyl acetate (100 mL) then basified with 1 M sodium hydroxide solution (220 mL). The basic aqueous phase was extracted with ethyl acetate (2 × 150 mL), washed with water (100 mL) and dried (Na_2SO_4). The solvent was removed under vacuum to give crude **16** as a grey solid (16.59 g, 78%). An analytical sample of **16** (3.0 g, 12.88 mmol) was prepared by dissolving in methanol (20 mL), stirring and adding water (25 mL) dropwise. An oil was precipitated which solidified with continued stirring and after 30 min the solid was colected by filtration under vacuum. The residue was washed with water (2 × 10 mL) and dried to give **16** as a grey solid (2.35 g, 78%); mp = 94−95 °C. R_f 0.05 (1:9 MeOH: DCM); IR (thin film) 2925, 2858, 1600, 1582, 1495, 1452, 1377, 1348, 1314, 1264, 1240, 1200, 1168, 1149, 1065, 1052, 1028, 1013, 970, 917, 824, 807, 781, 715, 699, 651, 568, 486; ^{1}H NMR (400 MHz, DMSO) δ_H 1.64 (6H, t, J = 7.6), 2.79 (6H, t, J = 7.6), 3.76 (2H,s), 7.22 (2H, m), 7.31 (3H, m); ^{13}C NMR (100 MHz, DMSO) δ_C 31.20, 32.17, 40.71, 48.06, 126.51, 128.21, 128.85, 138.83; MS (EI, 70 eV), m/z 234 (M + H), 143, 115, 110, 91. Found: C, 72.03; H, 8.34; N, 5.95; S, 13.77. $C_{14}H_{19}NS$ requires C, 72.05; H, 8.21; N, 6.00, S, 13.74.

*Conversion of 4-Benzylthioquinuclidine, {1-Aza-4-(phenylmethylthio)bicyclo[2.2.2]octane}, **16**, to 4-Thioquinuclidinium Chloride, {1-Azoniabicyclo[2.2.2]octane-4-thiol chloride}, **4a**, Using $AlCl_3$.* A solution of **16** (2.0 g, 8.5 mmol) in toluene (50 mL) was added to a stirred suspension of $AlCl_3$ (2.28 g, 17 mmol) in toluene (50 mL) at 20 °C. The mixture was stirred at 20 °C for 2h then heated to 50 °C and stirred for 1h. The reaction mixture was cooled to 0 °C and quenched by the dropwise addition of methanol (50 mL) followed by water (100 mL). The mixture was washed with ethyl acetate (100 mL), and the organic phase was washed with water (100 mL). The combined aqueous phases were washed with ethyl acetate (25 mL), and the water was removed by evaporation to give a white solid. Recrystallisation from propan-2-ol (40 mL) with a hot filtration gave **4a** as white crystals (wt = 0.4 g, 33%). This material had physical and spectroscopic properties identical to those described above.

*Conversion of 4-Benzylthioquinuclidine, {1-Aza-4-benzylthiobicyclo[2.2.2]octane}, **16** to 4-Thioquinuclidinium Bromide, {1-Azoniabicyclo[2.2.2]octane-4-thiol bromide}, **4b** Using Aqueous HBr.* A suspension of **16** (2.0 g, 8.57 mmol) in 48% hydrobromic acid in water (30 mL) was heated under reflux under Dean and Stark conditions for 19 h such that the benzyl bromide formed was removed from the mixture. The mixture was allowed to cool to ambient and the hydrobromic acid removed by evaporation. The resulting gum was diluted with toluene (30 mL), this was removed under vacuum (repeat 3×), and the grey solid was suspended in toluene (30 mL) and propan-2-ol (30 mL). Filtration gave **4b** as a white solid which was washed with propan-2-ol (10 mL) and toluene (10 mL) and dried (wt = 1.50 g, 78%); IR (Nujol) 2921.5, 2853.8, 2769.8, 2719.8, 2631.9, 2578.4, 2466.9, 2341.1, 1958.2, 1491.3, 1459.6, 1423.9, 1377.3, 1343.4, 1327.1, 1306.2, 1283.2, 1253.2, 1175.1, 1164.2, 1048.0, 1032.6, 1010.2, 1004.9, 929.3, 918.7, 875.0, 855.8, 837.8, 722.0, 662.2, 531.7; ^{1}H NMR (400 MHz, CD_3OD) δ_H 2.22 (6H, t, J = 7.9), 3.48 (6H, t, J = 7.9); ^{13}C NMR (100 MHz, CD_3OD) δ_C 33.87, 35.98, 48.90.

General Method for the Preparation of Ethyl 1-Benzyl-4-alkylthiopiperidin-4-ylacetate, 17. The alkyl or phenyl mercaptan (46.0 mmol) was added dropwise to a stirred suspension of sodium hydride (60% oil suspension, 0.30 g, 15.4 mmol) in toluene (50 mL) and DMF (3 mL), and the resulting mixture was stirred at ambient for 30 min. A solution of **8** (10.0 g, 38.0 mmol) was added dropwise, and the reaction mixture was stirred at 25−30 °C for 20 h. The reaction mixture was quenched with 1 M hydrochloric acid (200 mL) and the suspension was stirred for 30 min. Filtration gave crude **17** which was washed with toluene or ethyl acetate (2 × 40 mL).

The following compounds were prepared according to this procedure.

*1-Benzyl-4-(cyclohexylthio)-4-(2-ethoxy-2-oxoethyl)-piperidin-1-ium Chloride, **17a**.* Reaction of **8** with cyclohexanethiol gave the title compound as a white solid (78%). Mp 187−189 °C; IR (Nujol) 2662, 2504, 2449, 1731, 1498, 1460, 1423, 1406, 1377, 1303, 1271, 1249, 1230, 1216, 1193, 1176, 1152, 1115, 1038, 1001, 984, 952, 940, 888, 751, 743, 698, 601; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.25 (4H, m), 1.40 (5H, m), 1.62, (4H, m), 1.83 (2H, m), 2.05 (2H, d, J = 15.4), 2.75 (5H, m), 3.19 (3H, m), 4.14 (4H, m), 7.44 (3H, m), 7.69 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.17, 25.25, 26.17, 33.14, 35.82, 41.20, 45.40, 47.06, 47.94, 60.93, 61.01, 128.08, 129.28, 130.06, 131.33, 169.14; MS (EI, 70 eV), m/z 376 (M + H), 260, 232, 188, 172, 141, 120, 113, 91.

17a was basified with 1 M sodium hydroxide, extracted into DCM, and dried ($MgSO_4$), and the solvent was removed under vacuum to give ethyl 2-(1-benzyl-4-(cyclohexylthio)piperidin-4-yl)acetate (83%) which was used directly in the next stage to prepare **18a**.

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1-Benzyl-4-(2-ethoxy-2-oxoethyl)-4-(phenylthio)piperidin-1-ium Chloride, ***17b.*** Reaction of **8** with thiophenol gave the title compound as a pale-yellow solid (71%).

This product was not further characterised, but rather basified with 1 M sodium hydroxide, extracted into DCM, and dried ($MgSO_4$). The solvent was removed under vacuum to give ethyl 2-(1-benzyl-4-(phenylthio)piperidin-4-yl)acetate as a pale-yellow oil (80%) which was used directly in the next stage to prepare **18b**.

1-Benzyl-4-(2-ethoxy-2-oxoethyl)-4-((4-methylbenzyl)-thio)piperidin-1-ium Chloride, ***17c.*** Reaction of **8** with 4-methylbenzylmercaptan gave the title compound as a white solid (80%). Mp 167−169 °C; IR (Nujol) 3337, 2921, 2854, 2663, 2497, 1727, 1514, 1499, 1462, 1409, 1377, 1343, 1299, 1255, 1218, 1196, 1189, 1180, 1148, 1121, 1071, 1038, 1013, 986, 953, 920, 838, 827, 784, 748, 742, 700, 664, 602, 566, 518, 495, 479; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.27 (3H, t, J = 7.1), 2.05 (2H, d, J = 15.2), 2.32 (3H, s), 2.58 (2H, t, J = 12.8), 2.70 (2H, s), 3.11 (4H, m), 3.67 (2H, s), 4.09 (2H, s), 4.17 (2H, q, J = 7.1), 7.12 (4H, m), 7.43 (3H, m), 7.63 (2H, m), 12.4 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.20, 21.05, 32.19, 32.58, 45.27, 46.44, 47.97, 60.78, 60.94, 128.07, 128.75, 129.26, 129.38, 130.08, 131.33, 133.59, 137.25, 169.14; MS (EI, 70 eV), m/z 398 (M + H), 260, 232, 168, 141, 120, 113, 105, 91.

17c was basified with 1 M sodium hydroxide, extracted into ethyl acetate, and dried ($MgSO_4$), and the solvent was removed under vacuum to give ethyl 2-(1-benzyl-4-((4-methylbenzyl)-thio)piperidin-4-yl)acetate (85%) which was used directly in the next stage to prepare **18c**.

1-Benzyl-4-(2-ethoxy-2-oxoethyl)-4-((4-methoxybenzyl)-thio)-1-methylpiperidin-1-ium Chloride, ***17d.*** Reaction of **8** with 4-methoxybenzylmercaptan gave the title compound as a white solid (83%). Mp 105−127 °C; IR (Nujol) 3328, 2924, 2853, 2549, 1726, 1631, 1609, 1584, 1511, 1496, 1462, 1376, 1341, 1318, 1301, 1243, 1218, 1195, 1184, 1176, 1145, 1112, 1095, 1032, 1006, 972, 944, 931, 866, 842, 780, 759, 742, 706, 699, 675, 603, 569, 529, 513; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (3H, t, J = 7.2), 2.03 (2H, d, J = 15.0), 2.59 (2H, m), 2.70 (2H, s), 3.13 (4H, m), 3.67 (2H, s), 3.78 (3H, s), 4.08 (2H, s), 4.17 (2H, q, J = 7.2), 6.82 (2H, m), 7.21 (2H, m), 7.43 (3H, m), 7.63 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.20, 31.37, 32.58, 45.23, 46.44, 47.96, 55.26, 60.79, 60.94, 114.1, 128.07, 128.47, 129.27, 129.97, 130.08, 131.32, 158.94, 169.16; MS (EI, 70 eV), m/z 414 (M + H), 260, 232, 211, 188, 168, 141, 121, 113, 91, 30. Found: C, 62.07; H, 7.29; N, 3.03. $C_{24}H_{32}NO_3SCl$ requires C, 62.02; H, 7.24; N, 3.01.

1-Benzyl-4-(2-ethoxy-2-oxoethyl)-4-((2,4,6-trimethylbenzyl)thio)piperidin-1-ium Chloride, ***17e.*** Reaction of **8** with 2,4,6-trimethylbenzylmercaptan[36] gave the title compound as a white solid (88%). Mp 186−188 °C; IR (Nujol) 3450, 2919, 2853, 2644, 2315, 1727, 1610, 1584, 1511, 1457, 1377, 1346, 1305, 1279, 1238, 1223, 1174, 1154, 1117, 1088, 1066, 1031, 1006, 959, 948, 932, 873, 850, 772, 759, 711, 570, 458; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.28 (3H, t, J = 7.2), 2.24 (12H, m), 2.75 (4H, m), 3.24 (4H, m), 3.66 (2H, s), 4.24 (4H, m), 6.83 (2H, s), 7.44 (3H, m), 7.61 (2H, m) 12.4 (1H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 14.21, 19.38, 20.91, 26.69, 32.51, 34.78, 44.61, 46.47, 47.90, 60.97, 127.88, 128.36, 129.25, 129.38, 130.23, 131.44, 136.98, 137.30, 169.27; MS (EI, 70 eV), m/z 426 (M + H), 294, 260, 202, 188, 168, 141, 133, 120, 91.

17e was basified with 1 M sodium hydroxide, extracted into ethyl acetate, and dried ($MgSO_4$). The solvent was removed under vacuum to give ethyl 2-(1-benzyl-4-((2,4,6-trimethylbenzyl)thio)piperidin-4-yl)acetate (80%) which was used directly in the next stage to prepare **18e**.

General Method for the Preparation of 2-(1-Benzyl-4-alkylthiopiperidin-4-yl)ethanols, 18. A solution of the ester **17** (73.3 mmol) in THF (100 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (4.50 g, 0.1 mmol) in THF (60 mL) under nitrogen at ambient. The reaction mixture was quenched by the dropwise addition of 1 M sodium hydroxide (200 mL) after which ethyl acetate (120 mL) was added, and the reaction mixture was stirred at 25−30 °C for 1 h. The reaction mixture was filtered through Celite, and the residue was washed with ethyl acetate (2 × 80 mL). The organic phase was separated, washed with brine (100 mL), and dried (Na_2SO_4), and the solvent was removed under vacuum to give the title compound.

The following compounds were prepared according to this procedure.

2-(1-Benzyl-4-(cyclohexylthio)piperidin-4-yl)ethanol, ***18a.*** Reduction of **17a** (free base) gave the title compound as a white solid (86%). Mp 84 °C; IR (Nujol) 3195, 3028, 2926, 2854, 1497, 1463, 1377, 1366, 1350, 1334, 1307, 1252, 1223, 1196, 1140, 1117, 1100, 1088, 1078, 1063, 1023, 991.2, 969, 940, 909, 885, 810, 775, 741, 693, 617, 571, 536, 501; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.23 to 1.43 (5H, m), 1.55 (1H, m), 1.74 (6H, m), 1.91 (4H, m), 2.59 (6H, m), 3.52 (2H, s), 3.86 (2H, t, J = 6.2), 7.21 to 7.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 25.47, 26.38, 36.03, 36.42, 40.36, 47.72, 49.14, 59.30, 63.16, 126.97, 128.18, 129.08, 138.45; MS (EI, 70 eV), m/z 334 (M + H), 252, 218, 188, 175, 128, 120, 110, 98, 91, 56, 42.

2-(1-Benzyl-4-(phenylthio)piperidin-4-yl)ethanol, ***18b.*** Reduction of **17b** (free base) gave the title compound as a white solid (92%). IR (Nujol) 3353, 2853, 2781, 1465, 1377, 1350, 1306, 1133, 1085, 1077, 1066, 1024, 978, 922, 775, 751, 741, 700, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.70 to 1.78 (6H, m), 2.56 (2H, m), 2.70 (2H, m), 3.57 (2H, s), 3.98 (2H, t, J = 6.6), 7.24 to 7.34 (8H, m), 7.53 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 35.45, 49.2, 50.59, 59.27, 59.58, 63.12, 127.1, 128.23, 128.79, 128.98, 129.19, 130.66, 137.50; MS (EI, 70 eV), m/z 328 (M + H), 218, 188, 175, 160, 142, 132, 128, 120, 110, 106, 98, 91, 82, 56, 42.

2-(1-Benzyl-4-((4-methylbenzyl)thio)piperidin-4-yl)-ethanol, ***18c.*** Reduction of **17c** (free base) gave the title compound as a cream-colored solid (92%). Mp 84−86 °C; IR (Nujol) 3190, 3064, 3020, 2855, 2827, 2780, 2724, 1914, 1513, 1498, 1474, 1454, 1431, 1399, 1377, 1364, 1344, 1307, 1285, 1260, 1225, 1214, 1189, 1164, 1141, 1110, 1100, 1082, 1057, 1023, 1002, 990, 949, 925, 916, 900, 886, 816, 797, 744, 698, 662, 608, 584, 524, 513, 481, 464; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.71 (2H, m), 1.81 (2H, m), 1.88 (2H, t, J = 6.3), 2.31 (3H, s), 2.55 (4H, m), 3.52 (2H, s), 3.63 (2H, s), 3.86 (2H, t, J = 6.3), 7.09 (2H, d, J = 7.8), 7.20 (2H, d, J = 8.0), 7.24 to 7.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 21.06, 31.39, 35.86, 47.66, 48.93, 59.24, 63.12, 126.97, 128.16, 129.09, 129.11, 129.30, 134.34, 136.72, 138.46; MS (EI, 70 eV), m/z 356 (M + H), 218, 188, 174, 160, 128, 120, 110, 105, 98, 91, 56, 30.

2-(1-Benzyl-4-((4-methoxybenzyl)thio)piperidin-4-yl)-ethanol, ***18d.*** Reduction of **17d**[37] gave the title compound as a white solid (79%). Mp 83−85 °C; IR (Nujol) 3193, 3021, 2922, 2853, 2781, 1880, 1608, 1581, 1511, 1497, 1467, 1457, 1440, 1401, 1377, 1366, 1348, 1330, 1299, 1247, 1184, 1174,

1140, 1127, 1119, 1100, 1088, 1077, 1065, 1029, 991, 970, 940, 911, 831, 814, 777, 745, 693, 618, 546, 514, 501, 441, 421, 405; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.72 (2H, m), 1.81 (2H, m), 1.90 (2H, t, J = 6.3), 2.56 (4H, m), 3.54 (2H, s), 3.63 (2H, s), 3.79 (3H, s), 3.86 (2H, t, J = 6.3), 6.84 (2H, m), 7.25 (3H, m), 7.29 to 7.32 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 31.05, 35.79, 55.24, 59.14, 63.08, 114.00, 127.00, 128.23, 129.13, 129.32, 130.06, 138.29, 158.67; MS (EI, 70 eV), m/z 372 (M + H), 218, 211, 207, 188, 174, 160, 128, 121, 110, 98, 91, 56.

2-(1-Benzyl-4-((2,4,6-trimethylbenzyl)thio)piperidin-4-yl)-ethanol, ***18e.*** Reduction of **17e** (free base) gave the title compound as a cream-colored solid (98%). Mp 115−116 °C; IR (Nujol) 3131, 2930, 1611, 1455, 1377, 1334, 1312, 1266, 1235, 1200, 1150, 1118, 1105, 1090, 1055, 1002, 977, 964, 921, 853, 826, 777, 746, 709, 619, 576, 470; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.78 (2H, m), 1.88 (2H, m), 1.96 (2H, t, J = 6.4), 2.24 (3H, s), 2.37 (6H, s), 2.59 (4H, m), 3.54 (2H, s), 3.63 (2H, s), 3.95 (2H, t, J = 6.4), 6.83 (2H, s), 7.25 to 7.32 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.47, 20.87, 25.89, 35.73, 47.05, 49.08, 59.35, 63.16, 127.01, 128.20, 129.09, 129.63, 136.69, 136.99, 138.30; MS (EI, 70 eV), m/z 384 (M + H), 252, 218, 207, 188, 174, 160, 133, 128, 116, 110, 91, 56.

General Method for the Preparation of 1-Benzyl-4-(alkylthio)quinuclidin-1-ium Chlorides, 19. Methanesulfonyl chloride (6.0 mL, 79 mmol) was added dropwise to a stirred solution of the alcohol **18** (70.4 mmol) and DIPEA (15.4 mL, 88 mmol) in DCM (200 mL) under nitrogen at ambient. The reaction mixture was heated to reflux and stirred for 5 h. The reaction mixture was cooled to room temperature, and brine (200 mL) was added. The organic phase was separated, and the aqueous was washed with DCM (100 mL). The combined organic phases were washed with brine (100 mL) and dried (Na_2SO_4), and the solvent was removed under vacuum to give the crude title compound.

The following compounds were prepared according to this procedure.

1-Benzyl-4-(cyclohexylthio)quinuclidin-1-ium Chloride, ***19a.*** Reaction of **18a** gave the title compound as a white solid (87%) after column chromatography (40% MeOH in DCM). Mp 78−81 °C; IR (Nujol) 2926, 2850, 1494, 1457, 1376, 1345, 1263, 1215, 1073, 1039, 1000, 928, 884, 842, 817, 771, 709, 631, 475; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.17 (1H, m), 1.27 (4H, m), 1.51 (1H, m), 1.66 (2H, m), 1.83 (2H, m), 2.10 (6H, m), 2.65 (1H, m), 3.83 (6H, m), 4.98 (2H, s), 7.33−7.41 (3H, m), 7.61 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 25.21, 26.01, 30.90, 35.88, 37.99, 40.69, 54.37, 66.73, 127.19, 129.25, 130.76. 133.31; MS (EI, 70 eV), m/z 316 (M^+), 234, 200, 110, 91.

1-Benzyl-4-(phenylthio)quinuclidin-1-ium Chloride, ***19b.*** Reaction of **18b** gave the title compound as a white solid (67%) after triturating with THF. IR (Nujol) 3384, 3324, 3229, 2924, 2856, 1619, 1584, 1571, 1499, 1464, 1410, 1376, 1343, 1306, 1066, 1053, 1032, 1004, 974, 919, 842, 774, 758, 710, 704, 696, 651, 632, 582, 546, 507, 466, 424, 412; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.05 (6H, m), 3.83 (6H, m), 5.06 (2H, s), 7.31−7.42 (8H, m), 7.60 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 30.40, 40.22, 54.54, 66.74, 127.13, 128.20, 129.15, 129.28, 130.05, 130.51, 133.36, 137.58; MS (EI, 70 eV), m/z 310 (M^+), 110, 91, 56.

1-Benzyl-4-((4-methylbenzyl)thio)quinuclidin-1-ium Chloride, ***19c.*** Reaction of **18c** gave the title compound as a pale brown solid (90%) after trituration with toluene. Mp 213−218 °C; IR (Nujol) 3472, 3387, 2928, 2855, 1614, 1515, 1496, 1458, 1417, 1377, 1348, 1307, 1252, 1213, 1153, 1074, 1038, 1003, 940, 930, 891, 844, 825, 816, 771, 752, 743, 711, 635, 583, 520, 482, 467; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.09 (6H, m), 2.28 (3H, s), 3.67 (2H, s), 3.83 (6H, m), 5.00 (2H, s), 7.05 (2H, d, J = 7.9), 7.14 (2H, d, J = 8.0), 7.33 to 7.41 (3H, m), 7.61 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 21.00, 30.30, 31.55, 37.97, 54.36, 66.71, 127.16, 128.63, 129.10, 129.31, 130.43, 133.32, 133.90, 136.98; MS (EI, 70 eV), m/z 338 (M^+), 233, 205, 172, 110, 105, 91.

1-Benzyl-4-((4-methoxybenzyl)thio)quinuclidin-1-ium Chloride, ***19d.*** Reaction of **18d** gave the title compound as a white solid (67%) after trituration with THF. Mp 121−123 °C; IR (Nujol) 3575, 3339, 3266, 3033, 2924, 2853, 2099, 1902, 1655, 1608, 1582, 1513, 1491, 1461, 1446, 1424, 1380, 1344, 1305, 1253, 1242, 1218, 1181, 1136, 1101, 1070, 1036, 1014, 929, 839, 821, 777, 755, 736, 714, 700, 632, 600, 483, 523, 473, 429; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.09 (6H, m), 3.70 (2H, s), 3.75 (3H, s), 3.86 (6H, m), 5.01 (2H, s), 6.78 (2H, m), 7.21 (2H, m), 7.37 (3H, m), 7.61 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 30.29, 31.78, 37.93, 54.36, 55.22, 66.71, 114.05, 127.14, 128.82, 129.11, 129.87, 130.44, 133.31, 158.77; MS (EI, 70 eV), m/z 354 (M^+), 233, 205, 172, 121, 110, 91.

1-Benzyl-4-((2,4,6-trimethylbenzyl)thio)quinuclidin-1-ium Chloride, ***19e.*** Reaction of **18e** gave the title compound as a white solid (92%) after trituration with THF. Mp 239−242 °C; IR (Nujol) 3380, 2925, 2725, 1612, 1582, 1461, 1377, 1342, 1213, 1158, 1076, 1038, 932, 851, 765, 709, 633, 561, 495; ^{1}H NMR (400 MHz, DMSO) δ_H 2.18 (9H, m), 2.29 (6H, s), 3.70 (2H, s), 3.55 (6H, m), 3.75 (2H, s), 4.52 (2H, s), 6.80 (2H, s), 7.54 (5H, bs); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 18.86, 25.71, 29.28, 37.76, 54.12, 65.97, 127.63, 128.67, 128.92, 129.25, 130.17, 133.00, 135.98, 136.52; MS (EI, 70 eV), m/z 366 (M^+), 233, 205, 172, 148, 133, 110, 91.

General Method for the Preparation of 1-Benzyl-4-(alkylthio)quinuclidines, 20. A suspension of the quinuclidinium salt **19** (56.8 mmol) in 20% sodium hydroxide (50 mL) and thiophenol (11.5 mL, 115 mmol) was heated to 90−100 °C and stirred until reaction was complete (6 h). The reaction mixture was cooled to ambient, diluted with water (200 mL), and extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were washed with water (150 mL) followed by 1 M hydrochloric acid (2 × 120 mL). The organic phase was discarded, the acidic aqueous phase was basified with 1 M sodium hydroxide (300 mL) and extracted with ethyl acetate (2 × 200 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was removed under vacuum to afford the crude product **20**.

The following compounds were prepared according to this procedure.

4-(Cyclohexylthio)quinuclidine, ***20a.*** Reaction of **19a** gave the title compound as a pale-green oil (55%) which crystallised on standing. Mp 49−52 °C; IR (Nujol) 2901, 1451, 1377, 1350, 1312, 1259, 1198, 1171, 1118, 1052, 1009, 997, 971, 924, 883, 855, 825, 818, 763, 743, 698, 647, 517; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.22 (1H, m), 1.33 (4H, m), 1.54 (1H, m), 1.71 (8H, m), 1.89 (2H, m), 2.76 (1H, m), 2.91 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 25.46, 26.28, 33.36, 36.28, 39.08, 40.51, 48.66; MS (EI, 70 eV), m/z 226 (M + 1), 144, 115, 87.

4-(Phenylthio)quinuclidine, ***20b.*** Reaction of **19b** gave the title compound as a white solid (64%). Mp 75−76 °C, IR (Nujol) 3073, 3057, 2938, 2866, 1581, 1571, 1472, 1452, 1436, 1377, 1353, 1313, 1259, 1168, 1150, 1064, 1053, 1024, 1007, 998, 970, 922, 826, 784, 758, 705, 696, 648, 513, 435; ^{1}H NMR

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(400 MHz, $CDCl_3$) δ_H 1.69 (6H, m), 2.89 (6H, m), 7.35 (3H, m), 7.48 (2H, m);[38] MS (EI, 70 eV), m/z 220 (M + 1), 163, 123, 111, 96, 83, 68, 56, 42.

4-((4-Methylbenzyl)thio)quinuclidine, ***20c.*** Reaction of **19c** gave the title compound as a pale-brown solid (74%). Mp 97−99 °C; IR (Nujol) 2857, 1512, 1454, 1377, 1315, 1255, 1237, 1210, 1172, 1111, 1053, 1012, 973, 821, 784, 739, 693, 649, 523, 477; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.73 (6H, m), 2.31 (3H, s), 2.93 (6H, m), 3.71 (2H, s), 7.09 (2H, d, J = 7.8), 7.27 (2H, d, J = 7.6); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 21.02, 30.89, 32.56, 40.42, 48.63, 128.69, 129.10, 135.31, 136.40; MS (EI, 70 eV), m/z 248 (M + H), 143, 128, 115, 110, 82.

4-((4-Methoxybenzyl)thio)quinuclidine, ***20d.*** Reaction of **19d** gave the title compound as a white solid (68%). Mp 97−98 °C; IR (Nujol) 2936, 1608, 1583, 1508, 1462, 1417, 1377, 1351, 1312, 1303, 1247, 1229, 1183, 1170, 1096, 1053, 1024, 1009, 968, 875, 837, 831, 782, 745, 695, 647, 553, 513; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.71 (6H, m), 2.94 (6H, m), 3.73 (2H, s), 3.80 (3H, s), 6.83 (2H, m), 7.25 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 30.58, 32.52, 38.61, 48.64, 55.25, 113.90, 129.95, 130.31, 158.51; MS (EI, 70 eV), m/z 264 (M + H), 143, 128, 121, 115, 110, 100, 86, 82.

4-((4-Trimethylbenzyl)thio)quinuclidine, ***20e.*** Reaction of **19e** gave the title compound as a white solid (54%). Mp 106−107 °C; IR (Nujol) 2725, 1612, 1578, 1458, 1378, 1352, 1312, 1262, 1203, 1172, 1053, 1032, 1018, 972, 853, 828, 784, 723, 695, 650, 560; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.81 (6H, m), 2.34 (3H, s), 2.38 (6H, s), 2.98 (6H, m), 3.71 (2H, s), 7.01 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.22, 19.43, 25.13, 32.18, 39.88, 48.69, 128.96, 130.17, 136.42, 136.83; MS (EI, 70 eV), m/z 276 (M + H), 143, 115, 100, 86, 82, 71, 58.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H, ^{13}C NMR, and MS spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Michael.W.Urquhart@gsk.com

Present Address

[§]Glaxo Group Limited, Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, SG1 2NY, United Kingdom.

Notes

The authors declare no competing financial interest.

[‖]Deceased.

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■ DEDICATION

This manuscript is dedicated to the memory of both Robert (Rob) Giles and Duncan Bryant both of whom died in 2005.

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(10) Later work demonstrated that sodium hydride could be replaced for sodium hydroxide which represents a far safer and cheaper alternative.

(11) Product was isolated as a hydrate, and corrected yield for **7b** is 86%.

(12) Additional studies showed that triethylamine can be used in place of Hunigs base (*N*,*N*-diisopropyl-*N*-ethylamine) which represents a significant cost saving.

(13) Compound **4a** can be recrystallised from IPA (22 vol) in excellent yield.

(14) An authentic sample of disulfide **12** was prepared in excellent yield by reacting **4a** with sulfuryl chloride in pyridine using reported conditions for disulfide formation: Derbesy, G.; Harpp, D. N. *Tetrahedron Lett.* **1994**, *35*, 5381−5384.

(15) The HCl salt of **9** can be purified by slurrying within a 3:1 heptane/toluene mixture which removes unreacted ester **8** as well as benzyl mercaptan. Compound **10** can be purified by crystallisation from aqueous denatured alcohol (1:1).

(16) This yield was significantly lower than expected following on from the small-scale investigational work, and this was attributed to physical losses of the substrate **7b** up the reactor riser during the addition process and was caused by localized boiling. Future work would have evaluated adding the substrate as a slurry within a suitable solvent to minimize such losses.

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(18) Purity of methansulfonate **3** derived under these conditions was approximately 98%.

(19) Purity of product **5** from using equimolar equivalents of **3** with **4a** was 87%, whereas using 1.2 equiv of **4a** resulted in an increase in product purity to 98%. Quinuclidine-4-thiol **4a** was charged on the basis of its assay.

(20) To generate a longer term specification for the 4-mercaptoquinuclidinium salt (**4a** or **4b**) that is appropriate for its reaction with methanesulfonate **3**, it would be necessary to understand acceptable levels of disulfide **12**, as well as any by-products derived from incomplete debenzylation of **7b**, that could be contained within **4**. This understanding would be gained through appropriate doping work of such impurities within the coupling reaction of **3** with **4** to prepare **5**.

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(27) It was observed through informal stability evaluations that both crystalline products **4a** and **4b** showed no appreciable degradation (oxidation to **12**) within a reasonable time frame under standard storage conditions.
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(30) Karl Fischer inspection showed this material contained 5% water, and is thus a *mono*-hydrate (MW = 378.03).
(31) The very poor yield observed on scale-up compared to those from laboratory runs (averaging at 73% of **10** from **6**) was attributed to the formation of gelling of the reaction mixture during the quench of the lithium aluminium hydride reduction. Subsequent removal of the inorganic residues from the product solution became very difficult as the filters became clogged, and therefore yield was lost in order to deliver inorganic free product for use in the next stage. Future modifications would be needed to address this gelling issue by using an agitated filtration kit, by using Rochelle's salt (aqueous sodium potassium tartrate) to break up the emulsion, or by developing conditions to avoid the gelling in the first place.
(32) Vigorous reaction ensues during this quench so that greater care is required at the beginning of the quench.
(33) The exit port for the ammonia gas was situated such that the gas passed through a dilute hydrochloric acid reservoir (2.5 L conc HCl in 9.5 L water; conc ≈ 2.3 M).
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(35) This material can be effectively recrystallised from toluene (15 vol) to provide an analytically pure sample.
(36) Further development had shown that powdered sodium hydroxide could be used as a replacement for sodium hydride at this stage, and this reaction used sodium hydroxide rather than sodium hydride. This modification has significant processing and safety advantages.
(37) The HCl salt of **17d** was used for this reaction, and reaction with 3 mol equiv of lithium aluminium hydride proved very slow in 15 vol of THF. This was a consequence of the poor solubility of **17d**; therefore, triethylamine (1 mol equiv) was added which led to solvation of the substrate and complete reaction after stirring overnight at ambient.
(38) ^{13}C NMR data were not collected for this compound.