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The Development of a Manufacturing Route for the GPIIb/IIIa Receptor Antagonist SB-214857-A. Part 1: Synthesis of the Key Intermediate 2,3,4,5-Tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetic Acid Methyl Ester, SB-235349

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Abstract:

The development of an efficient manufacturing route to 2,3,4,5-tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetic acid methyl ester SB-235349, a key intermediate in the synthesis of lotrafiban is described. The synthesis starts with 2-nitrobenzyl alcohol which is mesylated, reacted with methylamine and then dimethylacetylene dicarboxylate followed by reduction of the nitro group. Treatment of the resultant aniline with acid gives an intermediate quinazoline which rearranges on treatment with base to give a 1,4-benzodiazapine. Reduction of the exocyclic double bond affords SB-235349. The process can be run without isolation of any of the intermediates and has been used to prepare several tons of SB-235349.

Introduction

Lotrafiban, SB-214857-A, **1**, acts as a potent nonpeptidic glycoprotein IIb/IIIa receptor antagonist to prevent platelet aggregation and thrombus formation.[1,2] The molecule has the (*S*)-stereochemistry, and only this enantiomer is active as a GPIIb/IIIa antagonist. To support the clinical development programme,[3] the Synthetic Chemistry group at Tonbridge had to prepare multi-ton quantities of homochiral SB-214857-A. A number of routes to SB-214857-A, **1**, were known starting from (*S*)-aspartic acid,[4−6] but for various reasons, none were suitable for scale-up into an efficient, safe, and economical manufacturing process.

All of the synthetic strategies adopted by Synthetic Chemistry during the lotrafiban **1** supply campaigns relied on a common intermediate having the basic racemic 1,4-benzodiazepine skeleton **2**, SB-235349 (Scheme 1). The 7-bipiperidyl amide was to be introduced via aminocarbonylation of a suitably 7-substituted 1,4-benzodiazepine with a mono-protected 4,4-bipiperidine.[7] The chirality could be introduced via a late-stage resolution or, more efficiently, by introducing the chirality directly after the synthesis of SB-235349, **2**. We report here how an efficient and economical synthesis of SB-235349, **2** was identified, developed, and refined to produce the target molecule using seven reactions in a "one pot" process (intermediates not isolated) with an overall yield of 70%.[8]

Results and Discussion

Initial Synthesis of SB-235349, 2. The initial synthesis of SB-235349, **2**, is outlined in Scheme 2. 2-*N*-Methylaminomethylnitrobenzene **5** was prepared from 2-nitrobenzyl alcohol **3** by bromination and reaction with aqueous methylamine. The latter stages were adapted from a sequence devised by GlaxoSmithKline Discovery chemists to prepare racemic 1,4-benzodiazepines of structure similar to that of **1**. This sequence was used to prepare multigram amounts of high quality **2** in the laboratory in about 40% overall yield from 2-nitrobenzylbromide **4**.[9] Whilst scaling up the synthesis, several deficiencies became apparent. The overall sequence was long with a modest yield of product. At each stage, the intermediates were isolated, and some were viscous oils. Bromide **4** was a very unpleasant material to handle (***Caution: lachrymatory!***), and we had concerns about its lack of thermal stability. Also, we wanted to avoid the use of BOC protection/deprotection if at all possible. The BOC deprotection stage required an excess of trifluoroacetic acid (TFA) in dichloromethane. The excess TFA had then to be removed. This left the bis-TFA salt of the acyclic **10** solvated with at least 2 equiv of TFA. In the final ring-closing reaction, up to 5 equiv of sodium methoxide had to be used to neutralise the TFA before the benzodiazepine ring would

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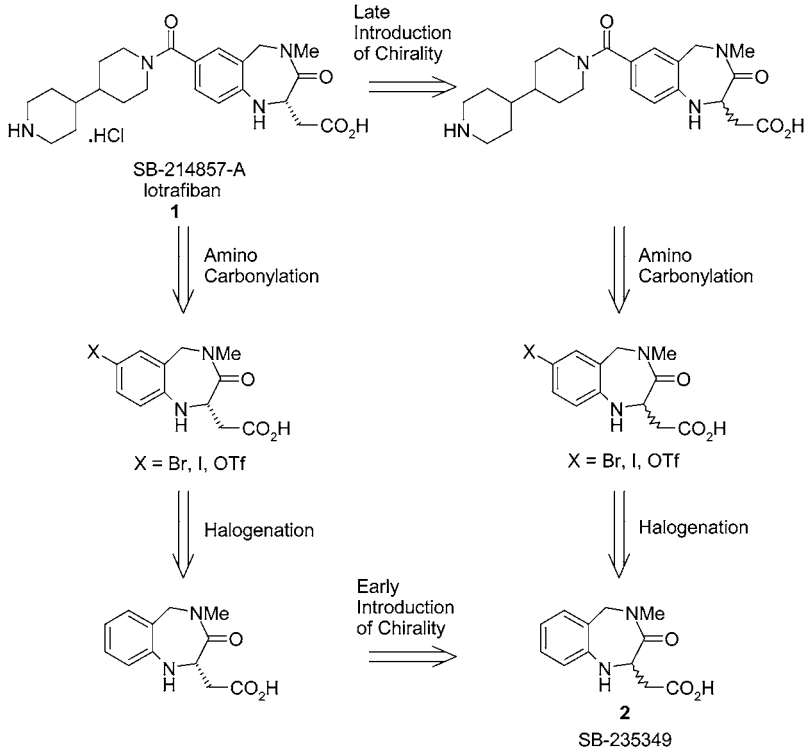
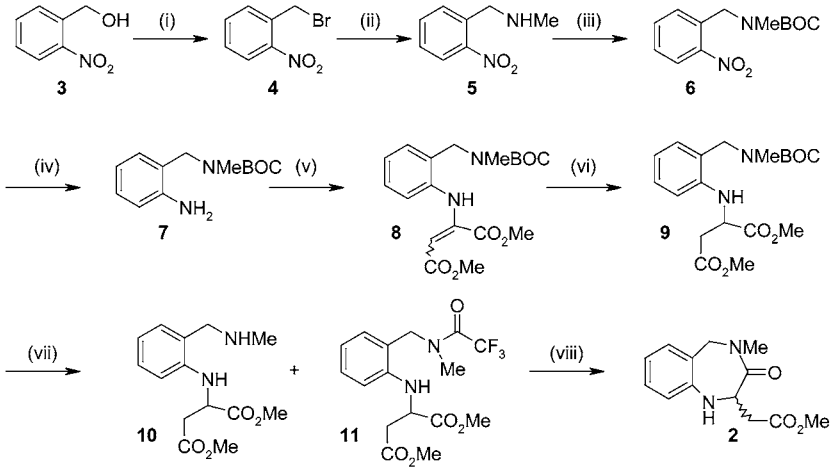
Scheme 1. **Synthetic Strategy**



Scheme 2. **Initial Synthesis of 2**[a]

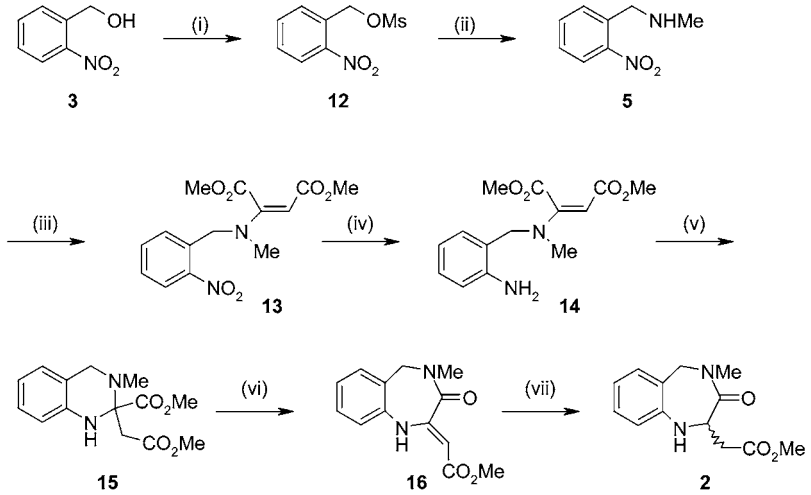


[a] Reagents: i) 48% aq HBr; ii) aq $MeNH_2$; iii) BOC_2O; iv) cyclohexene, Pd−C; v) DMAD; vi) $Et_2NH_2CO_2$, Pd−C; vii) TFA; viii) NaOMe.

form. During the scale-up of the BOC deprotection reaction it became evident that another product was being generated, and this was increasing with scale. This compound was the trifluoromethyl acetamide derivative of the secondary aliphatic amine **11** and was formed at 20−40% in larger-scale reactions. This compound **11** could be readily cleaved back to the secondary amine using potassium carbonate in methanol, but it meant adding another step to an already lengthy process.

Whilst this sequence was being scaled up and optimised, a chance observation lead to the identification of a much more direct and high-yielding process for the preparation of **2**. To explore new routes to lotrafiban **1** we needed some of the C-2 exocyclic double bond compound **16**, Scheme 3, to investigate chiral reduction as a potential way of introducing the chirality at C-2. A sample of the *N*-BOC acrylamide **8** was taken and deprotected before reduction of the double bond. It was thought that simple treatment with base would yield **16**. This did occur eventually, but it was observed that the unprotected acrylamide never directly cyclised to **16** but was converted to an intermediate that was then converted to **16** via a base-catalysed process. The intermediate compound was isolated and identified as the quinazoline **15**. Presumably, the ring expansion mechanism occurs via deprotonation at the carbon alpha to the methyl ester, followed by ring cleavage to produce an amine anion that then reacts with the ester group to produce the unsaturated diazepine. Interestingly, no eight-membered rings were seen and no products could be detected that would result from the initial anion fragmenting the other way to produce an anilino anion. Once formed, **16** would not revert back to **15** under basic conditions. This is contrary to literature precedent that shows

Scheme 3. **Final Synthesis of 2**[a]



[a] Reagents: i) $MeSO_2Cl$, Et_3N, THF; ii) aq $MeNH_2$ 92%; iii) DMAD, EtOAc, 100%; iv) cyclohexene, Pd−C, 92% or H_2, Raney Ni, 89%; v) AcOH, MeOH, 94%; vi) DBU or NaOMe, MeOH, 95%; vii) NH_4HCO_2 or $NaBH_4$, Pd−C, MeOH, H_2O, 93%.

that other 1,4-benzodiazepine-3-ones rearrange to quinazolines under base catalysis.[10]

First Pilot Synthesis of SB-235349, 2. Having identified this novel and irreversible ring expansion, we were able to devise a simplified process to prepare **2** on scale (Scheme 3). The process was designed to be a "one-pot" process, with no isolation of intermediates until crystallisation of **2**. 2-Nitrobenzyl bromide was replaced by the corresponding mesylate, **12**, derived from 2-nitrobenzyl alcohol, **3**. To minimise handling and exposure, the mesylate was prepared and added directly to a large excess of aqueous methylamine. The methylamine product, **5**, was extracted into dichloromethane after acid−base partitioning, and then the solvent was exchanged for ethyl acetate. The Michael reaction between **5** and dimethylacetylene dicarboxylate (DMAD) was straightforward. The selective reduction of the nitro group in **13** was more problematic. When the process was first piloted, the only clean reduction conditions found were a transfer hydrogenation with Pd/C and cyclohexene as the hydrogen donor. Other hydrogen donors gave complex mixtures or also reduced the acrylate double bond. The latter problem was also found with hydrogen and Pd/C catalysts without careful control of the reaction conditions. Prolonged heating cyclised the resulting aniline **14** to the quinazoline **15**. The ring expansion was performed with 2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reduction of **16** to **2** was readily accomplished using gas-phase hydrogenation. However, the large demands for supplies of **2** outstripped the R&D hydrogenation capacity available; therefore, a transfer hydrogenation was developed which utilised ammonium formate as the hydrogen donor.

Process Development. The route as shown in Scheme 3 worked well in the laboratory and scaled reasonably well in the plant, producing **2** in 50−55% overall yield from 2-nitrobenzyl alcohol, **3**. Some reactions were, however, a little capricious in the plant, and there were obvious areas where increases in throughput and efficiency could be achieved.

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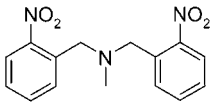

17

Figure 1.

The mesylation of **3** went cleanly in 7 volumes of THF and an excess of mesyl chloride (1.2 mol equiv) and triethylamine (1.1 mol equiv). The mesylate, **12** was formed in essentially quantitative yield from 2-nitrobenzyl alcohol, **3**. Water had to be rigourously excluded to avoid hydrolysis of the mesyl chloride. Prolonged contact of the product with the $Et_3N{\cdot}HCl$ formed led to slow conversion to 2-nitrobenzyl chloride, which reacted as the mesylate with aqueous methylamine in the subsequent step. To minimise handling the mesylate, the $Et_3N{\cdot}HCl$ byproduct was not removed. The resulting slurry from the mesylation reaction was transferred to an excess of aqueous methylamine. A large excess of methylamine is used to suppress the formation of the dialkylated product **17**, Figure 1. Apart from the loss in yield attributed to the formation of this byproduct, this compound could also act as a poison in the cyclohexene reduction; thus, it was deemed desirable to form as little of this material as possible. The dialkylated product **17** was usually formed at 3−5 mol % when 12 mol equiv of methylamine was used. The level of dialkylation was found to vary with the charge of methylamine and cosolvent. Optimisation eventually reduced the amount of methylamine added to 9 mol equiv. After the reaction the product, **5**, was originally extracted into dichloromethane. Initially, this presented no problem since the solutions were carried forward straight away. However, during one pilot-plant run, the dichloromethane solution of **5** had to be stored for a few days. The yields in subsequent steps were lower than expected. It was found that **5** had a lot of the HCl salt present as well as other decomposition products resulting from reaction with dichloromethane.[11] After this, the solvent was exchanged for ethyl acetate or toluene. Before further use, **5** was purified by

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extraction into aqueous sulphuric acid to remove traces of 2-nitrobenzyl alcohol, **3**, that could act as a catalyst poison in the cyclohexene reduction. After washing the aqueous acid, the product was extracted into ethyl acetate, and reaction with dimethylacetylene dicarboxylate, DMAD, could take place.

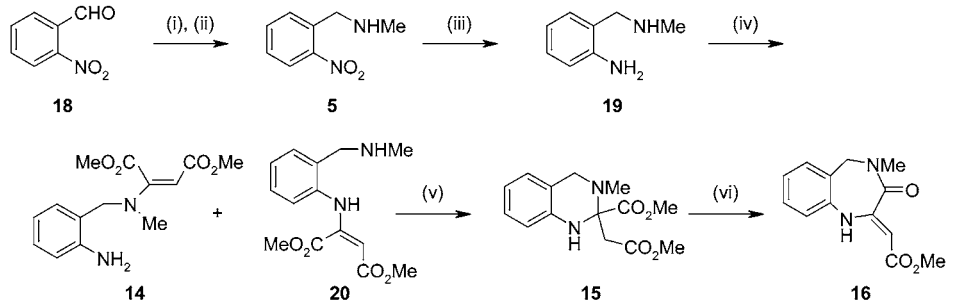
The reaction of **5** with DMAD was straightforward. The exothermic Michael reaction was readily controlled to below 30 °C by slowly adding the solution of DMAD to **5** with glycol cooling and control of addition rate. After the reaction, the methylamine can be replaced with the dialkylated material, **17**, and residual **5** could be removed by extraction into aqueous acid. This was done by washing with dilute sulphuric acid, aqueous sodium sulphate−sulphuric acid, dilute sodium carbonate, then water. Due to the instability of **13** to aqueous acids (fairly rapid hydrolysis occurs to give **5** and dimethyl 2-oxosuccinate), contact with the acid solutions had to be kept to a minimum and the solutions kept cold (5 °C). Whilst this removed all of the dimer, the process was very lengthy, and it was felt that the instability of **13** towards aqueous acids may prove problematic if control of the process was lost on scale-up. One of the long-term goals was to remove the acid−base manipulations of **13** and **5**, which would eliminate six extraction steps from the overall process.

The selective reduction of the nitro group in **13** was initially achieved via a transfer hydrogenation using Pd−C catalyst and cyclohexene. When the process was first piloted, this was the only set of conditions found that gave excellent selectivity for the reduction of the nitro group and not the double bond in **13**. A large drawback was that 5 mol equiv of cyclohexene was required to achieve a reasonable reaction rate. Another undesirable feature was the production of benzene as a byproduct. The reaction was very sensitive to low levels of poisons such as 2-nitrobenzyl alcohol, **3**, or the dialkylated methylamine, **17**. Hence, the lengthy extraction processes to ensure that these were totally removed prior to the transfer hydrogenation. Despite its limitations, the transfer reduction was used in several campaigns and performed consistently well in the pilot plant, provided several precautions were observed. The **13** feedstock had to be free of the poisons as already mentioned.

Great care had to be taken to ensure that traces of acids were not introduced via the **13** solution or this could contaminate the hydrogenation vessel inadvertently. If the reduction medium became acidic, then considerable amounts of byproducts resulted from hydrogenolysis of the *N*-benzyl bond. One curious observation during the plant campaigns was the very variable length of the reaction (4−24 h). On occasion, the reaction would stop before complete consumption of **13** and would have to be restarted by the addition of a small amount of fresh catalyst or by filtering off the old catalyst and starting again with a fresh charge. Use-testing batches of Pd/C catalyst and solutions of **13** gave no indication of when this problem was likely to arise. Since the downstream reactions had to be anhydrous, the standard procedure was to charge the solution of **13**, add the catalyst, heat the reaction to reflux then add the cyclohexene and then run under Dean and Stark conditions to remove the water added via the **13** solution and the Pd/C catalyst. Investigations to find the cause of the variability revealed that dehydration of the catalyst was the cause of reactions stopping prematurely. This transfer reduction seems to be very sensitive to metal sintering on the catalyst surface (this probably occurs as a consequence of dehydration). The procedure for running the reaction in the plant was therefore modified. After the cyclohexene was added, the reaction was run under reflux until the reduction was about 80% complete. The reactor was then set to Dean and Stark to begin the drying process. This new procedure gave very reliable reaction times of about 4 h, and once the procedure was adopted, additional catalyst never had to be added. During the process-development phase, a major goal was to eliminate cyclohexene from the process and to identify conditions that could tolerate a feedstock solution of **13** that had not undergone extensive extractions to clean it up. Several grades of Pd/C catalyst were identified that gave good selectivity in the reduction using hydrogen gas; however, the best solution was to use washed Raney nickel as the catalyst with hydrogen gas. This gave excellent selectivity and could tolerate crude **13** solutions. The Raney nickel reduction was not scaled up onto the GlaxoSmithKline pilot plant but was later successfully scaled up at a contract facility.

During the course of the reduction, 20−60% of the aniline product **14** would cyclise to the quinazoline, **15**. When the reduction was complete and the Pd/C catalyst removed by filtration, the resulting mixture of **14** and **15** was refluxed to convert remaining aniline to **15**. The time for completion of this process was always very variable, on occasions up to 24 h. It was discovered that the cyclisation was much faster in protic solvents and could be catalysed by traces of weak anhydrous acids. It was found to be very important to prevent solutions of **15** from coming into contact with aqueous acid to prevent rapid hydrolysis of the aminal function. Since the solutions had to be azeotropically dried and the solvent replaced with methanol for the ring-expansion reaction, it was overall more efficient to run a solvent exchange immediately after the reduction of **13** had finished and the catalyst had been filtered off. Once the ethyl acetate had been removed and replaced with methanol, a small amount of acetic acid was added. This procedure ensured complete conversion of the aniline **14** to the quinazoline **15** in less than an hour. The ring-expansion reaction to give **16** was originally piloted using 2 mol equiv of DBU in ethyl acetate. This gave complete reaction in about 6 h at 80 °C. The DBU was then washed out into aqueous acetic acid. Whilst this gave a clean and high-yielding conversion, the relative high cost of DBU made this reagent unattractive for large-scale manufacture. A range of solvents and bases was screened. Overall, the best combination was found to be methanol with a few mol % of sodium methoxide as the basic catalyst. This fitted in well with the best conditions for the quinazoline-forming reaction. After the formation of the quinazoline, acetic acid was neutralised with sodium methoxide and a small excess added to act as a catalyst for the ring-expansion reaction. This typically took about 1 h at

Scheme 4. **Alternative Synthesis of 16**[a]



[a] Reagents: i) aq $MeNH_2$, MeOH; ii) $NaBH_4$, H_2O; iii) H_2, Pd−C, MeOH, iv) DMAD, MeOH; v) AcOH, MeOH; vi) NaOMe, MeOH.

60 °C. The key to maintaining high yield and purity in this stage was to ensure the solution was dry before the sodium methoxide was added.

In the initial laboratory investigation into the synthesis of **2**, simple hydrogenation of **16** was shown to be feasible (Pd/C catalyst, 50 °C, 50 psi H_2). A transfer hydrogenation method was developed. The methanol solution of **16** was treated with a small amount of acetic acid to neutralise the sodium methoxide, Pd/C catalyst was added, and the mixture was heated to 65 °C. A solution of ammonium formate in water was added to act as the hydrogen source. This worked well in the laboratory, but scale-up was problematical. Often in the pilot plant, a very large excess of ammonium formate had to be added to drive the reaction to completion (up to 20 mol equiv). This was attributed to unproductive decomposition of the ammonium formate on the Pd catalyst. As a consequence of this, the process was very volume inefficient and could take up to 18 h to complete. To address this, a screen of other hydrogen donors was run. It was found that the best solution was to add aqueous sodium borohydride to a methanol solution of **16** and Pd/C catalyst at about 45 °C. This procedure gave a fast and clean reduction virtually as soon as the borohydride solution was added (reaction time was reduced from 18 to 1 h). When the reduction was complete, the mixture was neutralised with acetic acid. Attempts to process the basic reaction mixture lead to decomposition of **2**. The solution was then diluted with dichloromethane. During the reduction, the presence of water causes most of the **2** to crystallise out as it is formed. The dilution with dichloromethane was necessary to solubilise the product.

Thus, a chance observation in the laboratory led to a fast and efficient multistep process to produce **2**. At the end of the process-development phase, we could prepare **2** in 120-kg batches of starting from 100 kg of 2-nitrobenzyl alcohol, **3**. The process was suitable for multi-ton campaigns if required.

Later Process Refinements. While the route described above was successfully being run in a manufacturing plant, further laboratory investigations led to the evolution of a simplified version of the chemistry, and it is shown in Scheme 4. The commercially available 2-nitrobenzyl alcohol, **3**, used in the current process is, in fact, manufactured by reduction of 2-nitrobenzaldehyde, **18**. Accordingly, conversion of **18** to the current intermediate **5** via reductive amination with methylamine in the presence of sodium borohydride would appear to offer a significant advantage in terms of cost. The reaction was shown to proceed very efficiently with only 1.3 equiv of amine necessary for complete reaction and with no dialkylation being observed. Subsequent studies showed that **5** could readily be reduced via catalytic hydrogenation over Pd−C in methanol to furnish the diamine **19** in virtually quantitative yield over the two stages from **18**. Reaction of **19** with DMAD in methanol gave the conjugate adduct **14**, which upon standing partially isomerised to a mixture containing regioisomer **20** and quinazoline **15**. Treatment of this mixture with a catalytic quantity of acetic acid afforded the tetrahydoquinazoline **15**. Treatment of the solution of **15** with sodium methoxide in methanol as per the current synthesis furnished **16** which was isolated in an overall yield of 68% from **18**. This simplified procedure appears to circumvent the nitro group reduction of the current synthesis, and furthermore there is no solvent change when proceeding from **19** to **16** with all reactions being conducted in methanol.

During the course of these investigations work on the lotrafiban project was suspended, and so this simplified process just described was never subjected to scale-up.

Summary

An efficient synthesis of the key intermediate, 2,3,4,5-tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetic acid methyl ester **2**, for the synthesis of SB-214857-A is described. The starting material 2-nitrobenzyl alcohol, **3**, is converted into the required product **2** in seven chemical transformations. Since this process would be required to produce many hundreds of kilograms of ester **2** the process was adapted such that a "one-pot" procedure could be run, i.e., none of the six intermediates need be isolated en route to the product. Not isolating the intermediates leads to a high overall yield, since no loss upon crystallisation is encountered. Also, the process is more expedient to run on a pilot plant since isolations by filtration and subsequent drying tend to be time-consuming processes. This process was performed on a 100-kg scale in the GSK pilot plant where the molar isolated yield of ester **2** was 70%. Subsequently, larger quantities of ester **2** were produced by out-sourced contractors using this chemistry.

A modified route starting from 2-nitrobenzaldehyde, **18**, is also described. The modified procedure requires much less methylamine as reagent, and all reactions can be performed in a single solvent, methanol.

Experimental Section

2,3,4,5-Tetrahydro-4-methyl-3-oxo-1*H*-1,4-benzodiazepine-2-acetic Acid Methyl Ester (2) from Nitrobenzyl Alcohol (3). A solution of methanesulphonyl chloride (87 kg, 795 mol) in tetrahydrofuran (THF) (35 kg) was added to a solution of 2-nitrobenzyl alcohol **3** (100 kg, 653 mol) and triethylamine (71.5 kg, 706 mol) in THF (620 kg) over 2 h, allowing the temperature to rise from 17 °C to a maximum of 34 °C. The headtank and transfer lines were washed through with THF (10 kg). The reaction mixture was stirred at 32 °C for 1 h. The mixture was added to 40% w/w methylamine in water (620 kg, 7985 mol) over 45 min, allowing the temperature to rise from 20 to a maximum of 33 °C. The transfer line was washed through with THF (89 kg), and stirring continued at 32 °C for 1.5 h. The phases were allowed to separate for 15 min. The phases were separated, and the aqueous phase was extracted with toluene (256 kg) and then discarded. The organic phases were combined, and solvent (900 L) was distilled off under vacuum, maximum base temperature 22 °C. The resulting concentrate was cooled to 8 °C (pH 10.3) and the pH adjusted to 4.3 by the addition of 12% v/v aqueous sulphuric acid solution (177 L), taken from a bulk solution of concentrated sulphuric acid (340 kg) and demineralised water (1500 L). The temperature was allowed to rise to a maximum of 17 °C. The mixture was stirred for 5 min, and the phases were allowed to separate for 15 min. The phases were separated, and the organic phase was discarded. The aqueous phase was diluted with demineralised water (150 L) and then basified to pH 11.7 with 50% w/w sodium hydroxide solution (110 kg). Compound **5** was extracted into ethyl acetate (270 kg), and the mixture was warmed to 27 °C. The aqueous phase was separated off and extracted with further ethyl acetate (135 kg), maintaining the temperature at 25−30 °C, and then discarded. The organic phases were combined.

A solution of dimethylacetylene dicarboxylate (86 kg, 605 mol) in ethyl acetate (90 kg) was added over 1 h with cooling applied, allowing the temperature to rise to a maximum of 29 °C. The headtank and transfer lines were washed through with ethyl acetate (9.0 kg). The reaction mixture was stirred at 23−24 °C for 40 min. The mixture was cooled to 4 °C, and demineralised water (50 L) was charged, followed by ethyl acetate (180 kg). The pH was adjusted from 10.9 to 2.6 by the careful addition of 12% v/v aqueous sulphuric acid (45 L), maintaining the temperature between 0 and 5 °C. The mixture was stirred for 5 min, and the phases were allowed to separate for 15 min. The aqueous phase was separated off and discarded, and the organic phase washed with an aqueous solution of sulphuric acid and sodium sulphate (135 kg), taken from a bulk solution of sodium sulphate (50 kg), concentrated sulphuric acid (9.0 kg), and demineralised water (650 L), maintaining the temperature between 0 and 5 °C. The headtank and transfer lines were washed through with demineralised water (10 L). The mixture was stirred for 5 min, and the phases were allowed to separate for 15 min. The aqueous phase was separated off and discarded and the organic phase washed twice with 10% w/w sodium bicarbonate solution (2 × 125 kg), allowing the temperature to rise to 7 °C. After addition of the second bicarbonate wash, the headtank and transfer lines were washed through with demineralised water (10 L).

Ten percent palladium on charcoal (Pd−C), 59% water wet (30 kg, source Johnson Matthey, 87L) was charged and the mixture heated to 66 °C. Cyclohexene (240 kg, 2921 mol) was added over 35 min, maintaining reflux. The headtank and transfer lines were washed through with ethyl acetate (9 kg). The reaction mixture was stirred at reflux (68 °C) for 4.5 h, and then the water was separated off by Dean−Stark distillation over a further 4 h 20 min. The total volume of water collected was 54 L.

The mixture was cooled to 25 °C and filtered, washing the filters and lines through with ethyl acetate (89 kg). A mixture of ethyl acetate and unreacted cyclohexene was distilled off at atmospheric pressure (950 L), the temperature rising to a maximum of 82 °C. The remaining contents of the vessel were cooled to 62 °C, and methanol (550 kg) was added. The distillation was continued at atmospheric pressure until a further 200 L of solvent had been distilled out (maximum temperature 65 °C). Glacial acetic acid (2.1 kg, 35 mol) was charged, washing through with methanol (8 kg), and the mixture stirred at reflux for 1.5 h.

A 30% solution of sodium methoxide in methanol (19.7 kg, 109 mol) was added, maintaining reflux, and the headtank and lines were washed through with methanol (8 kg). The mixture was stirred at reflux for 2 h. The mixture was cooled to 33 °C and the pH (10.0) adjusted to 7.7 by the addition of glacial acetic acid (5.1 kg, 85 mol). The mixture was stirred at 30−35 °C for 33 min (final pH 7.5). Ten percent Pd−C, 59% water wet (15 kg, source Johnson Matthey 87L) was charged, and a solution of sodium borohydride in demineralised water containing sodium hydroxide [sodium borohydride (20.0 kg, 528.7 mol) in demineralised water (265 L) containing sodium hydroxide (0.12 kg)] was added over 2 h 45 min, allowing the temperature to rise from 33 °C and maintaining at 40−45 °C. The headtank and transfer lines were washed through with demineralised water (5 L). The mixture was stirred at 40−42 °C for 55 min.

The pH was adjusted from 9.6 to 7.0 by the addition of glacial acetic acid (25 kg, 416 mol). The headtank and transfer lines were washed through with demineralised water (10 L). Dichloromethane (930 kg) was added and the slurry (35 °C) filtered to a clean vessel. The filters and lines were washed through with dichloromethane (266 kg) at 30 °C. A mixture of dichloromethane and methanol was distilled off at atmospheric pressure to a base temperature of 50 °C (volume of distillate 800 L). The distillation was continued under vacuum to a base temperature of 53 °C (volume of distillate 511 L). Demineralised water (500 L) was added to the concentrate and the mixture cooled to 20 °C to crystallise the product. After stirring the slurry for 1 h at 17−20 °C, the product was filtered off in a filter drier, washed with demineralised water (200 L), and dried at 35−40 °C under vacuum for 14 h to give **2** as a white solid, 117 kg 70% from 2-nitrobenzyl alcohol, **3**: mp 174−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (td, 1 H, J = 7.7, 1.4 Hz), 6.93

(dd, 1 H, $J = 7.5, 1.1$ Hz), 6.67 (td, 1 H, $J = 7.4, 1.0$ Hz), 6.57 (dd, 1 H, $J = 8.1, 0.9$ Hz), 5.42 (d, 1 H, $J = 16.3$ Hz), 5.00 (q, 1 H, $J = 6.1$ Hz), 4.09 (d, 1 H, $J = 5.4$ Hz), 3.73 (s, 3 H), 3.72 (d, 1 H, $J = 16.4$ Hz), 3.07 (s, 3 H), 2.98 (dd, 1 H, $J = 16.0, 6.8$ Hz), 2.65 (dd, 1 H, $J = 16.0, 6.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 169.6, 145.1, 129.5, 129.0, 119.8, 118.2, 117.5, 53.3, 51.9, 51.8, 35.9, 34.6; IR (neat, cm^{-1}) 1728, 1650; LRMS (CI +ve) *m*/*z* 249 ($M^+ + H$).

HPLC in process-control method; Luna or Prodigy ODS column 75 mm × 4.6 mm, 3 μm. Eluent A: 0.05 M NaH_2PO_4 adjusted to pH 7.0 with aq NaOH. Eluent B: acetonitrile. Isocratic with 35% B, run time 10 min, Flow rate 1.5 mL/min. Detector at 254 nm. Injection volume 10 μL. Sample preparation 0.1 mg/mL. Typical retention times; 2-nitrobenzyl alcohol **3** 1.6 min, mesylate **12** 3.8 min, amine **5** 0.7 min, nitro **13** 7.0 min, aniline **14** 3.6 min, quinazoline **15** 2.9 min, unsaturated ester **16** 3.3 min, ester **2** 1.9 min.

A sample of intermediate **(2-nitrophenyl)methyl methanesulfonate 12** was isolated in the laboratory and characterised as a light tan solid: mp 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, 1 H, $J = 8.0, 0.8$ Hz), 7.76−7.73 (m, 2 H), 7.58 (td, 1 H, $J = 8.0, 0.5$ Hz), 5.67 (s, 2 H), 3.13 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 134.3, 130.1, 129.7, 129.4, 125.3, 68.0, 37.8; IR (neat, cm^{-1}) 1521, 1340, 1171.

A sample of intermediate ***N*-methyl-1-(2-nitrophenyl)-methanamine 5** was isolated in the laboratory and characterised as the hydrochloride salt. The data obtained was in accordance with the published data.[9]

A sample of intermediate **dimethyl (2*E*)-2-[methyl(2-nitrobenzyl)amino]but-2-enedioate 13** was isolated in the laboratory and characterised as a yellow solid: mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (dd, 1 H, $J = 8.2, 1.2$ Hz), 7.67 (td, 1 H, $J = 7.6, 1.3$ Hz), 7.48 (td, 1 H, $J = 7.8, 1.9$ Hz), 7.38 (dd, 1 H, $J = 7.8, 0.9$ Hz), 4.75 (s, 2 H), 4.68 (s, 1 H), 3.91 (s, 3 H), 3.64 (s, 3 H), 2.92 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 165.6, 154.8, 147.8, 134.2, 131.8, 128.5, 128.0, 125.4, 86.0, 53.8, 53.0, 50.8, 38.4; IR (neat, cm^{-1}) 1732, 1694; LRMS (CI +ve) *m*/*z* 309 ($M^+ + H$).

A sample of intermediate **dimethyl (2*E*)-2-[(2-aminobenzyl)(methyl)amino]but-2-enedioate 14** was isolated in the laboratory and characterised as a viscous yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (td, 1 H, $J = 7.7, 1.4$ Hz), 7.00 (dd, 1 H, $J = 7.5, 1.2$ Hz), 6.72 (td, 1 H, $J = 7.4, 1.1$ Hz), 6.66 (dd, 1 H, $J = 8.0, 0.9$ Hz), 4.77 (s, 1 H), 4.19 (s, 2 H), 3.96 (s, 3 H), 3.65 (s, 3 H), 2.66 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 166.7, 154.9, 145.6, 130.6, 129.6, 118.3, 118.1, 116.1, 86.0, 53.7, 53.1, 50.9, 35.2; IR (neat, cm^{-1}) 1734, 1685; LRMS (CI +ve) *m*/*z* 279 ($M^+ + H$).

A sample of intermediate **methyl 2-(2-methoxy-2-oxoethyl)-3-methyl-1,2,3,4-tetrahydroquinazoline-2-carboxylate 15** was isolated in the laboratory and characterised as viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (td, 1 H, $J = 8.0, 0.8$ Hz), 6.91 (dd, 1 H, $J = 7.5, 0.7$ Hz), 6.72 (td, 1 H, $J = 7.4, 1.1$ Hz), 6.64 (dd, 1 H, $J = 8.0, 0.8$ Hz), 5.13 (s, 1 H), 4.07 (d, 1 H, $J = 16.8$ Hz), 3.81 (s, 3 H), 3.73 (d, 1 H, $J = 16.7$ Hz), 3.68, (s, 3 H), 3.15, (d, 1 H, $J = 15.8$ Hz), 2.93 (d, 1 H, $J = 15.8$ Hz), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.9, 140.3, 127.6, 127.0, 118.4, 117.0, 115.1, 74.5, 52.9, 52.0, 51.8, 42.1, 38.3; IR (neat, cm^{-1}) 1732; LRMS (CI +ve) *m*/*z* 279 ($M^+ + H$).

A sample of intermediate **(1,3,4,5-tetrahydro-4-methyl-3-oxo-2*H*-1,4-benzodiazepin-2-ylidene)acetic acid methyl ester 16** was isolated in the laboratory and characterised as a white solid: mp 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1 H), 7.30 (td, 1 H, $J = 7.7, 1.5$ Hz), 7.17 (d, 1 H, $J = 7.5$ Hz), 7.06−7.02 (m, 2 H), 5.43, (s, 1 H), 4.27, (s, 2 H), 3.74 (s, 3 H), 3.10 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 162.5, 153.6, 139.2, 129.5, 128.3, 127.5, 123.6, 120.5, 89.4, 50.8, 50.8, 34.5; IR (neat, cm^{-1}) 1650, 1613, 1582; LRMS (CI +ve) *m*/*z* 247 ($M^+ + H$).

Procedure for the Reduction of 13 to 14 Using Raney Nickel. Nitro-aromatic **13** (5.00 g, 16.2 mmol) was dissolved in a mixture of toluene (30 mL) and methanol (20 mL) and then added to Raney nickel (0.6 g dry weight, source W. R. Grace and Co., previously washed with water until pH 7) in a suitable pressure vessel. The system was purged with hydrogen, pressurised to 40 psi with hydrogen, and then heated to 45 °C. After 8 h the reaction was complete, and the reaction mixture was cooled, purged with nitrogen, and then filtered through Celite. The filtercake was washed with toluene (30 mL) and water (50 mL). The layers were separated, and the organic layer was dried over $MgSO_4$ and then concentrated by vacuum distillation to leave aniline **14** as a viscous yellow oil (4.00 g, 89%).

(1,3,4,5-Tetrahydro-4-methyl-3-oxo-2*H*-1,4-benzodiazepin-2-ylidene)acetic Acid Methyl Ester (16) from Nitrobenzaldehyde (18). A solution of 2-nitrobenzaldehyde **18** (15.1 g, 100 mmol) in methanol (90 mL) was treated with aqueous methylamine (40%, 10 mL, 130 mmol) and the solution stirred at 25 °C for 15 min. A solution of sodium borohydride (2.86 g) in water (15 mL) was added dropwise at 25−30 °C over 10 min and the resulting mixture stirred at 25 °C for a further 1 h. The solution was hydrogenated over 10% Pd−C (0.6 g, 59% wet, 0.28 mmol, Johnson Matthey 87L) at 60 psi and 25 °C for 1.5 h. The mixture was filtered through Celite and the bed rinsed with methanol (30 mL). The combined filtrate and rinse were partitioned into ethyl acetate and water. The aqueous phase was re-extracted with ethyl acetate, and the combined organic phases were dried over magnesium sulphate and evaporated to give the diamine **19** as a pale brown oil (13.24 g, 97.4%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (td, 1 H, $J = 7.6, 1.6$ Hz), 7.01 (dd, 1 H, $J = 7.2, 1.2$ Hz), 6.68−6.62 (m, 2 H), 3.73 (s, 2 H), 2.41 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 129.8, 128.3, 124.1, 117.6, 115.6, 55.1, 36.0; IR (neat, cm^{-1}) 1614, 1493. A further sample was isolated as the mixed oxalate/hydrochloride salt. The data obtained was in accordance with the published data.[9]

A solution of the diamine **19** (13.2 g, 97 mmol) in methanol (70 mL) at 0−5 °C was treated with a solution of DMAD (13.8 g, 11.9 mL, 97 mmol) in methanol (30 mL), added dropwise over 30 min. After stirring for a further 1 h,

glacial acetic acid (0.79 g, 0.75 mL, 13 mmol) was added and the solution heated under reflux for 1 h. After cooling to 50 °C, a solution of sodium methoxide in methanol (30%, 6.25 mL, 34.7 mmol) was added and the resulting solution heated under reflux for 2 h. The solution was cooled to 50 °C, and glacial acetic acid (2.1 g, 2 mL, 35 mmol) was added followed by water (120 mL) at 50 °C. The solution was cooled to 0−5 °C over 1 h and stirred at this temperature for 5 h. The resulting solid was collected via suction filtration, washed with 3:2 water:methanol (75 mL), and dried in air to give the benzodiazepine **16** as a white crystalline solid (16.3 g, 68.3% from **18**), identical to an authentic sample described above.

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