Organic Process Research & Development

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# Development of Synthetic Routes, via a Tropinone Intermediate, to a Long-Acting Muscarinic Antagonist for the Treatment of Respiratory Disease

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Supporting Information

**ABSTRACT:** This contribution describes the development of two synthetic routes to an investigational muscarinic antagonist for the treatment of chronic obstructive pulmonary disease. The first route used a starting material which was in plentiful supply within the GSK network and was used to make material for early clinical trials and safety assessment studies. Further investigations identified a second, potential long-term manufacturing route from commercially available building blocks, using substrate control to install the two stereocentres with excellent selectivity. A key step was a substrate-directed epoxide reduction which also gave rise to a minor byproduct through a skeletal rearrangement of the tropane ring. A deuterium-labeling experiment was carried out, which shed light on the origin of the byproduct, and also guided the improvement of reaction conditions.

Chronic obstructive pulmonary disease (COPD) is a fatal lung disease characterized by progressive and irreversible airflow limitation with systemic consequences.[1] It is the fifth leading cause of death worldwide, killing 250 people every hour, and is the only disease in the World Health Organization (WHO) top five with an increasing death rate.[2] While there is currently no cure, treatment focuses on bronchodilatation, targeting adrenergic and muscarinic receptors in the lung to cause smooth muscle relaxation.[3] Inhaled corticosteroidal anti-inflammatories are also used.[4] As part of GlaxoSmithKline's long-standing commitment to the development of novel medicines for the treatment of pulmonary disease, tropane (**1**) was designed as a long-acting, selective, and reversible muscarinic antagonist which might provide a once-daily inhaled treatment for COPD (Figure 1).

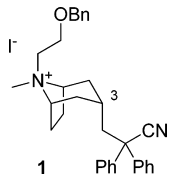


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**Figure 1.** Long-acting muscarinic antagonist for COPD.

Of key concern in designing the synthetic route was the diastereoselective alkylation of the tropane nitrogen to afford the requisite quaternary ammonium salt. Early studies revealed that alkylation to afford a quaternary ammonium salt occurred preferentially from the less hindered side of the nitrogen, adjacent to the methylene bridge. The initial synthetic route (route A) used tropane ester **2** as the starting material as it already had the correct stereochemistry at $C_3$ and was available in bulk quantities from other active research programmes within GlaxoSmithKline. Treatment with phenyllithium provided the tertiary alcohol **3** in good yield as a crystalline solid. Substitution of the hydroxyl group was accomplished by treatment with trimethylsilyl (TMS)-cyanide and a Lewis acid.[5] A screen of reaction conditions revealed tin tetrachloride in DCM as optimal, affording a 9:1 ratio of substitution to elimination products. The desired nitrile was purified as its HCl salt **4** by selective crystallization from the crude reaction mixture. On laboratory scale, this process reliably gave 70% yield. On the single batch carried out in pilot-plant equipment, poor mixing resulted in poor recovery and a lower 49% yield. Alkylation of the nitrile free-base with benzylbromoethyl ether afforded a 5:2 ratio of products, favoring undesired isomer **5**. Tropane **4** was therefore demethylated by treatment of its free base with 1-chloroethylchloroformate, and the resultant secondary amine **6** was realkylated with benzylbromoethyl ether to afford tertiary amine **7**.[6] Initially, demethylation was carried out using diisopropylamine as base. Under these conditions, some dealkylation of Hünig's base was observed, resulting in contamination of the isolated product with ethylisopropylamine and diisopropylamine hydrochloride. These impurities were readily purged during downstream steps. However, on scale up to 8.5 kg in pilot-plant equipment, these impurities sublimed during solvent distillations resulting in caking of the condenser system with white powder which was difficult to remove. Therefore, a second process, using $NaHCO_3$ as base in toluene was developed, affording reliably higher yields without amine impurities on laboratory scale. Alkylation with iodomethane afforded **1** as the major product in 7:1 solution ratio. The isolated ratio was improved to 99:1 by ripening the resultant slurry with added methanol before filtration. Subsequent recrystallization from aqueous methanol afforded product in greater than 99.5:0.5 dr (Scheme 1).

Route A provided material for early toxicological assessment and the first human clinical trials. However, the dealkylation/realkylation sequence adds two steps to the sequence, and tropane ester **2** is expensive. As a long-term manufacturing

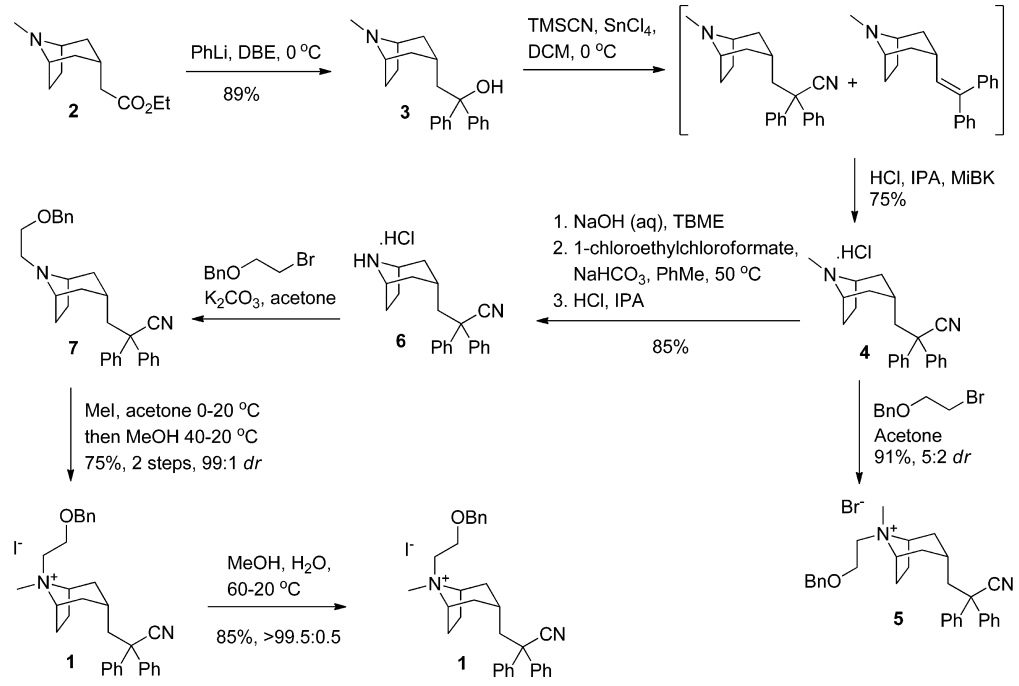
**Received:** October 19, 2012
**Published:** March 7, 2013



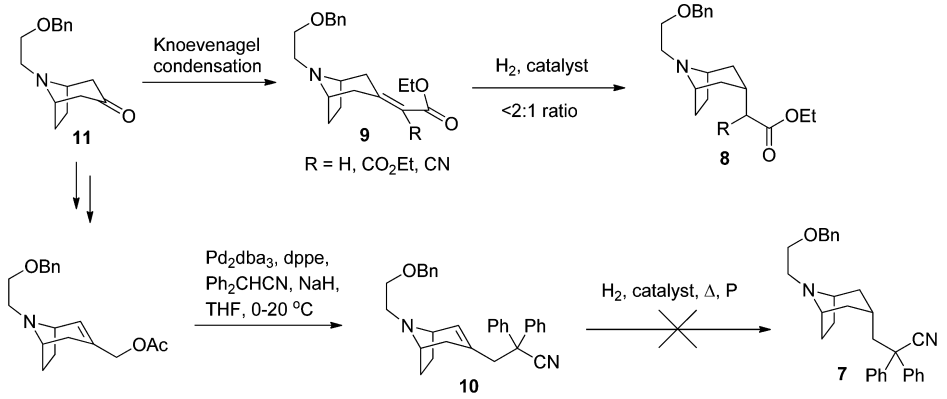


dx.doi.org/10.1021/op3002933 | *Org. Process Res. Dev.* 2013, 17, 641−650

**Scheme 1. Route A to troponium salt diastereomers**




**Scheme 2. Initial attempts to install $C_3$ stereochemistry with benzyloxyethyl group present**




strategy, more efficient access to **1** was sought from cheap and abundant starting materials. Given the required order of amine alkylation, we sought to install the benzyloxyethyl side chain at an early stage. The first strategy involved reduction of an olefin to generate the required stereocentre at $C_3$. Both *endo*- and *exo*-olefins, **9** and **10**, were synthesized in short order from tropinone **11**. However, reduction of olefins **9** by either hydrogenation or conjugate reduction[7] failed to give synthetically useful diastereoselectivity at the $C_3$. Diastereomeric ratios from 1:1 to 2:1 suggested that the olefin was too far from the steric bulk of the molecule for significant distinction between its two faces. Olefin **10** proved unreactive to a range of hydrogenation catalysts, even at elevated temperatures and pressures, likely due to the hindered steric environment provided by the tropane ring and the bulky diphenylacetonitrile group. (Scheme 2).

Alternative methods, using key tropinone **11** as the starting material, were therefore investigated. This was readily accessed by functionalization of amine **12** in a three-component Robinson tropinone reaction.[8,9] Optimization of reaction conditions using a DoE approach, setting the valuable amine as the limiting reagent, provided access to tropinone **11** in greater than 90% purity as a solution in 2-MeTHF (Scheme 3). A seven-factor, ten-experiment, DoE factor-screening study was used to explore the reaction.[10] Key findings were that 1.05 equiv of 2,5-dimethoxytetrahydrofuran proved insufficient for complete consumption of amine **12**, while high levels (1.55 equiv) resulted in the formation of increased levels of the main pyrrole impurity, formed by condensation of 2,5-dimethoxyfuran and amine **12**. A small reduction in the charge of sodium acetate (from 4 equiv to 3.5 equiv) was found to be beneficial to minimize formation of this impurity. The highest levels of the desired product were obtained in solution using the conditions reported in the Experimental Section.

Corey–Chaykovsky epoxidation provided **13** as a single diastereomer with the ylid attacking from the less hindered upper face.[11] It was found that using $^t$BuOH rather than DMSO as solvent increased the reaction rate 10-fold. While stereochemistry of **13** could not be assigned directly, the major byproduct **14**, made by addition of a second equivalent of ylid to the distal terminus of the epoxide, was isolated and characterized, and the configuration of **13** was assigned by


dx.doi.org/10.1021/op3002933 | Org. Process Res. Dev. 2013, 17, 641–650

**Scheme 3. Revised route to muscarinic antagonist 1**

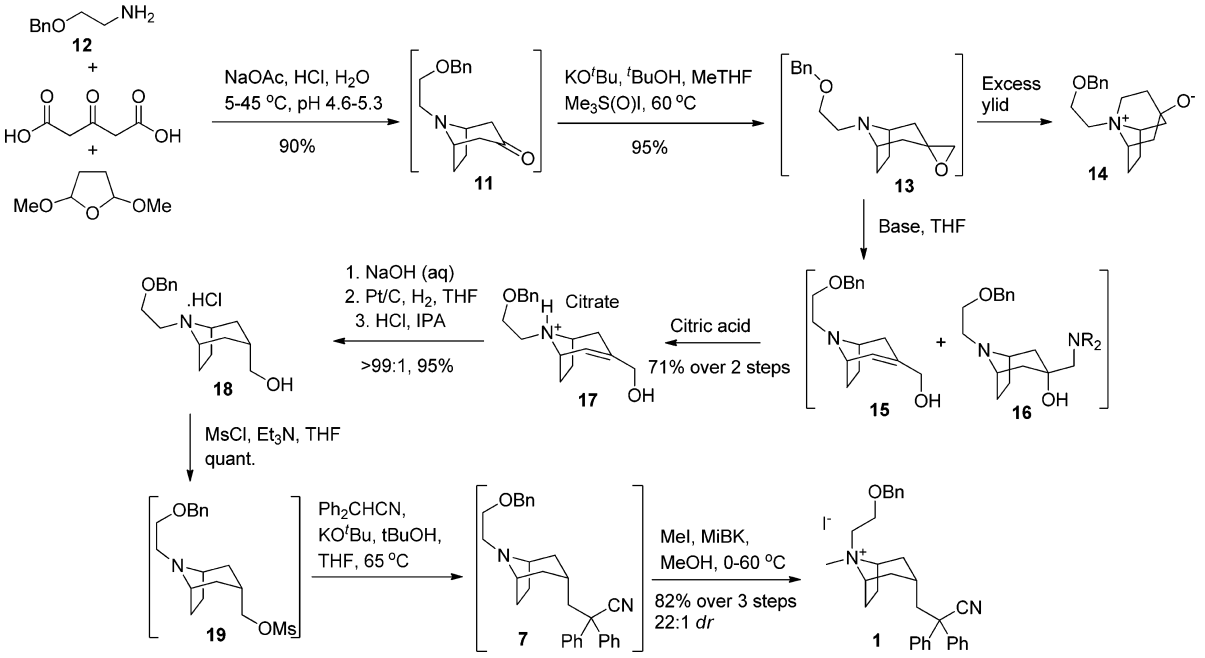
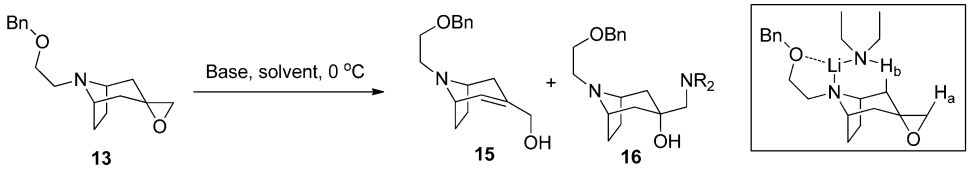



**Table 1. Optimization of reaction conditions for isomerization of epoxide 13**




| solvent | base | ratio 15:16 | time (min) |
|---|---|---|---|
| THF | $Et_2NLi$ | 14:1 | 15 |
| THF | $^iPr_2NLi$ | 1:1 | 45 |
| 2-MeTHF | $Et_2NLi$ | 6:1 | 15 |
| PhMe | $Et_2NLi$ | 1:7.5 | 5 |
| DME | $Et_2NLi$ | 1:1 | >500 |

analogy. Isomerization of the epoxide to allylic alcohol **15** was attempted under a range of Lewis acidic and basic conditions.[12] Rearrangement under acidic conditions gave only small amounts of the desired allylic alcohol, along with degradation products. Treatment with lithium amide bases gave the desired product along with amine addition products **16**.

A screen of solvents and bases (Table 1) revealed that less coordinating solvents such as PhMe gave a faster reaction but favored the amine addition product. DME gave a much slower and unselective reaction. Interestingly, using a more hindered base (LDA) also favored the addition product, which therefore seems unlikely to be formed by a simple $S_N2$ addition. One possibility is that the epoxide is deprotonated at the terminal carbon and then opens by rearrangement via a carbene, followed by protonation of the lithiated intermediate.[13] The combination of lithium diethylamide in THF was optimal, giving the desired allylic alcohol in 14:1 ratio which could be further purified by crystallization as its citric acid salt **17**. Simpler acid salts were not crystalline.

The selective reduction of allylic alcohol **15** was next investigated. It was hoped that the desired diastereomer **18** would be favored not only by sterics, but by delivery of the catalyst to the upper face of the olefin by the coordination with the tertiary amine. The minimization of byproducts due to alcohol debenzylation and reduction of potential $\pi$-allyl species was of key concern. After a series of screening experiments, looking at catalyst (metal and support), solvent, temperature and pressure, we settled on a 5 wt % platinum on graphite catalyst as optimum: a diastereomeric ratio in excess of 99:1 was achieved, and other byproducts were kept below 1%. Unfortunately, 30 wt % of metal catalyst was required to drive this reaction to completion, likely due to sequestering of the catalyst by impurities such as diamine **16**. Using allylic alcohol **15**, purified by silica gel chromatography, catalyst loading could be reduced to 5 wt %. However, chromatographic purification required a high loading of silica which would be impractical on manufacturing scale. Furthermore, the beneficial effect of purification could not be reproduced by multiple recrystallizations of the citrate salt **17**. Unbowed, we proceeded to investigate subsequent synthetic transformations. Alcohol **18** was converted to the mesylate **19** which, unpurified, reacted with the anion of diphenylacetonitrile, affording **7** and intercepting route A (cf. Scheme 1). At this point, alternative solvent mixtures for the methylation reaction were investigated with a view to finding a system which would be compatible with the aqueous workup required after diphenylacetonitrile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**Scheme 4. Directed epoxide reduction**

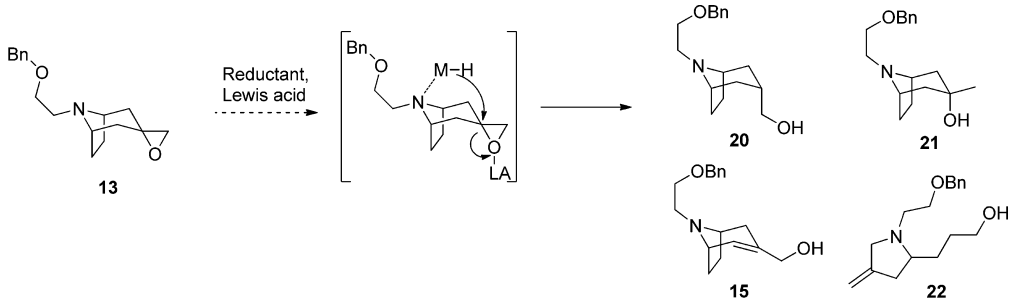
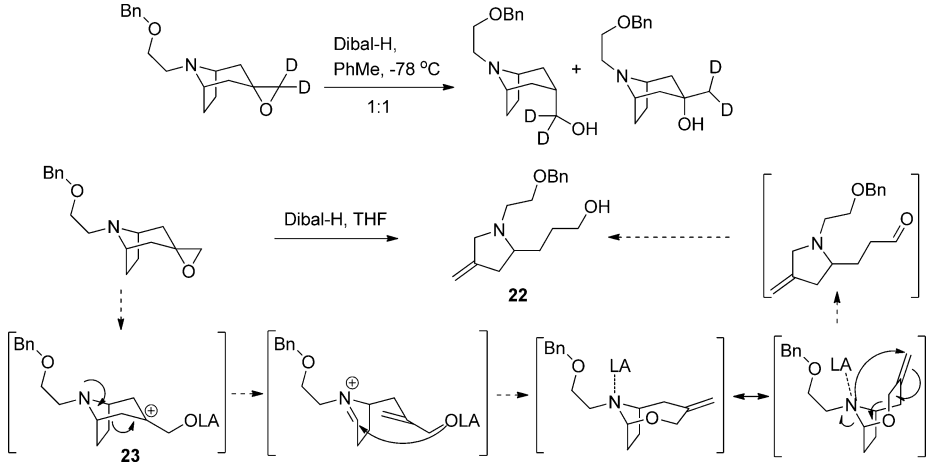



**Table 2. Optimization of reaction conditions for selective reduction of epoxide 13**[a]

| entry | reagent | solvent | temperature (°C) | **20** (%) | **21** (%) | **15** (%) | **22** (%) |
|---|---|---|---|---|---|---|---|
| 1 | $NaB(CN)H_3/BF_3{\cdot}OEt_2$ | THF | −78 to 20 | 12 | 54 | 11 | 23 |
| 2 | $Et_3SiH$ | PhMe | −20 to 20 | 0 | 0 | 0 | 0 |
| 3 | $BH_3{\cdot}Et_3N$ | PhMe | −20 to 20 | 0 | 0 | 0 | 0 |
| 4 | $BH_3$·pyridine | PhMe | −20 to 20 | 0 | 0 | 0 | 0 |
| 5 | Red-Al | PhMe | −20 | 0 | 100 | 0 | 0 |
| 6 | $LiAlH_4$ | PhMe | −20 | 0 | 100 | 0 | 0 |
| 7 | $LiBH_4$ | PhMe | −20 | 0 | 100 | 0 | 0 |
| 8 | $LiBH_4/BH_3{\cdot}THF$ | THF | −20 | 8 | 18 | 8 | 66 |
| 9 | Dibal-H | THF | −20 | 2 | 0 | 0 | 98 |
| 10 | Dibal-H | PhMe | −20 | 81 | 3 | 0 | 16 |
| 11 | Dibal-H | PhMe | −78 | 89 | 8 | 0 | 3 |
| 12 | Dibal-H | DCM | −20 | 79 | 7 | 0 | 14 |
| 13 | Dibal-H | TBME | −20 | 81 | 6 | 0 | 13 |

[a]Conditions: A 0.37 M solution of epoxide **13** in the given solvent was treated with reductant (and Lewis acid) at the given temperature and stirred until all epoxide was consumed. Ratio calculated by absolute HPLC area.

**Scheme 5. Mechanistic insight into the formation of pyrollidine 22**



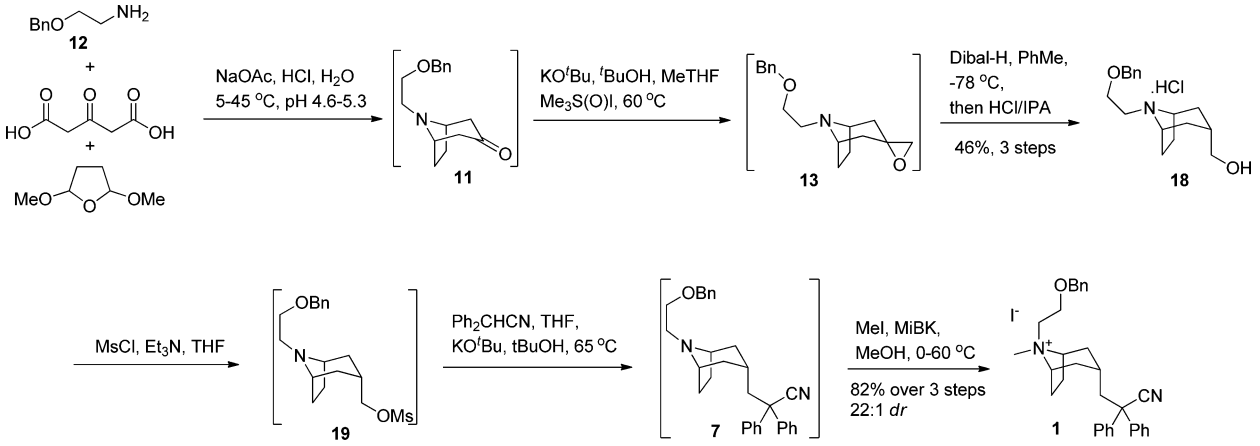

alkylation. The diastereomeric ratio (dr) is solvent-dependent, and the best selectivity was achieved using a 9:1 mixture of MiBK and MeOH, resulting in an absolute dr of 9:1 and, after ripening, an isolated dr of 22:1. Under these optimized conditions, and after a single recrystallization, the API produced was of comparable quality to that produced via route A.

The large platinum catalyst loading required for hydrogenation of the non-chromatographed allylic alcohol **15** made this route prohibitively expensive. To circumvent this problem, we speculated that a direct reduction of epoxide **13** might be possible by delivery of a reducing agent to the upper face of the oxirane ring (Scheme 4).[14] The effect of a range of reductants, with and without Lewis acids, on the epoxide was next investigated. A mixture of products was observed: the desired internal reduction product **20**, tertiary alcohol **21**, derived from reduction at the unsubstituted end of the epoxide, the allylic alcohol **15**, formed by Lewis acid-mediated isomerization, and the skeletal rearrangement product **22** (Scheme 4).

Strong reducing agents ($LiAlH_4$, $LiBH_4$, Red-Al, entries 5−7) attacked the epoxide from the least substituted end, affording mainly **21**. Milder reducing agents (borane, triethylsilane, entries 2−4) gave no reaction at all. Lewis acidic additives increased the amounts of products **15** and **22** (entries 1 and 8), presumably via a cationic intermediate. Dibal-H in non-coordinating solvent offered the best combination of Lewis acidity and reducing power, giving the desired product in 80%


dx.doi.org/10.1021/op3002933 | Org. Process Res. Dev. 2013, 17, 641−650

**Scheme 6. Route B to drug substance 1**




yield at −20 °C. Toluene was selected as solvent due to the ease of solvent swap from 2-MeTHF used in the previous telescoped step. The proportion of alcohol **20** could be further increased to 89% by performing the reaction at −78 °C. Interestingly, switching from toluene to THF completely changed the reaction course, affording **22** as the major product (Table 2).

To investigate the mechanism of formation of **22**, we made deuterium-labeled epoxide **13** using $CD_3I$ and $D_6$-DMSO as the ylid source.[15] On treatment with Dibal-H in toluene at −78 °C, only deuterium-labeled products analogous to **20** and **21** were formed, in a 1:1 ratio (Scheme 5). Neither of the products analogous to **15** or **22** was detected. The change in product ratio from that of the unlabeled experiment implies a secondary kinetic isotope effect. This provides indirect evidence that a cationic $sp^2$ intermediate, **23**, is involved in the generation of products **20**, **15**, and **22** since carbon−deuterium bonds offer inferior hyperconjugative stabilization.[16] Tertiary alcohol **21** is formed through an $S_N2$ mechanism, and no reduction in its rate of formation was observed: a secondary kinetic isotope effect would not be expected for this pathway as no cationic $sp^2$ intermediate is formed at the reacting carbon. A mechanism for the formation of **22** is proposed, invoking the Lewis acid-mediated formation of a tertiary carbocation and subsequent ring fragmentation, stabilized by the nitrogen lone pair. A similar fragmentation pathway was observed during synthetic work into epibatidine analogues.[17]

The epoxide reducation reaction has been incorporated into the new route, Route B, thereby eliminating a step. The new six-step route is shown in Scheme 6, split into two distinct stages with only two isolated intermediates. The process was demonstrated on 0.2 mol scale, and recrystallization was performed as described in the original process to deliver drug substance with the same crystalline form and purity as those of the substance generated via route A. Further development and scale up of this route to check performance in a pilot-plant setting were thwarted by unrelated project issues.

In conclusion, we have developed two synthetic routes to an investigational muscarinic antagonist drug **1**. Route A took advantage of the ready availability of tropane ester **2** within our network and was used to make 5 kg of active substance in our pilot plant. The inefficient dealkylation/alkylation sequence led to the development of a second route, which employs readily available starting materials and provides access to **1** in 6 synthetic steps with just two isolated intermediates.

## EXPERIMENTAL SECTION

**General Methods.** All reactions were carried out in water, methanol, and acetone-washed glassware under a nitrogen atmosphere. Solvents and reagents were used without any purification or drying. $^1H$ and $^{13}C$ NMR spectra were acquired on a Bruker spectrometer at frequencies of 400 and 100 MHz, respectively. High-resolution mass spectra were recorded on a linear ion trap combined with a Fourier transform ion cyclotron resonance mass spectrometer using an electrospray ionization source operated in positive ion mode. IR spectra were recorded as solids or neat oils. HPLC chromatograms were recorded on a C18(2) column at 40 °C; eluent gradient: 100% 0.05% v/v TFA in water to 95% 0.05% v/v TFA in MeCN over 8 min. Melting points were recorded using an automated melting point apparatus.

*2-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-1,1-diphenylethanol* ***3***. Methyl 2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-acetate **2** (9.0 kg, 42.6 mol) was dissolved in dibutyl ether (DBE, 19.9 L) and added to a solution of phenyllithium (20 wt % in dibutyl ether, 40.7 kg, 96.2 mol), maintaining internal temperature below 5 °C. The solution was then warmed to 20 °C and stirred until all starting material and intermediates had been consumed as judged by HPLC. The reaction solution was chilled to 12 °C and quenched with water (45 L), maintaining the internal temperature below 30 °C. The resultant slurry was then aged at 12 °C for 1 h with stirring. The product was collected by vacuum filtration and washed with water/acetone (10 °C, 95:5 v/v, 2 × 45 L), followed by acetone (10 °C, 22.7 L) before drying in vacuo at 50 °C to afford 2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1,1-diphenylethanol **3**, 12.2 kg, 38.0 mol, 89%. $\delta_H$ ($(CD_3)_2SO$, 400 MHz) 1.16 (2H, d, $J$ = 12.9 Hz), 1.61−1.96 (7H, m), 2.03 (3H, s), 2.46 (2H, d, $J$ = 5.1 Hz), 2.88 (2H, s), 5.36 (1H, br s), 7.14 (2H, tt, $J$ = 7.6, 1.3 Hz), 7.26 (4H, t, $J$ = 7.6 Hz), 7.42 (4H, dd, $J$ = 7.6, 1.3 Hz); $\delta_C$ ($(CD_3)_2SO$, 100 MHz) 22.8, 26.2, 37.3, 39.6, 49.0, 59.7, 77.4, 125.9, 125.9, 127.6, 148.7; $\nu_{max}$ $cm^{-1}$ (solid) 3056.7, 2912.5, 1492.3, 1446.7, 1319.0, 1265.6, 1211.5, 1171.8, 1129.0, 1062.0, 1029.8, 1011.5, 976.1, 953.5, 935.9, 909.0, 895.7, 837.0, 818.2, 779.8, 753.3, 739.5, 696.7; HRMS $m/z$ calc'd for $C_{22}H_{28}NO$ 322.2165, found 322.2159; mp 145−148 °C.

**Laboratory-Scale Reaction.** *3-(8-Methyl-8-azabicyclo-[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile Hydrochloride* ***4***. Trimethylsilylcyanide (36.0 mL, 273 mmol) was added to a suspension of 2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1,1-diphenylethanol **3** (25.0 g, 77.8 mmol) in DCM (250 mL) at


dx.doi.org/10.1021/op3002933 | Org. Process Res. Dev. 2013, 17, 641−650

−5 °C. Tin tetrachloride (32.0 mL, 273 mmol) was added dropwise to the suspension at such a rate to maintain the internal temperature at −5 °C. The suspension was then warmed to 25 °C over 30 min and stirred for 2 h until the reactions was considered complete by HPLC. The slurry was added slowly to aqueous NaOH solution (5 M, 500 mL) at 0 °C over 5−10 min. The DCM layer was separated, and the aqueous layer washed with DCM (2 × 50 mL). The organic layers were combined and washed with water (2 × 50 mL), and the organic solvent was evaporated by vacuum distillation and MIBK (300 mL) added. The solution was then concentrated to 200 mL by vacuum distillation and passed through a Cuno Zetacarbon filter, eluting with an additional 200 mL of MIBK. The solution was then concentrated to 300 mL, and a solution of HCl in 2-propanol (5 M, 17.2 mL, 86 mmol) was added at 45 °C over 45 min. The resulting slurry was stirred for 2 h at 80 °C, then cooled to 20 °C over 1 h, and aged for 1 h. The product was collected by vacuum filtration and washed with MIBK (2 × 50 mL) before drying in vacuo at 50 °C to afford 3-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile hydrochloride **4** (20.0 g, 54.4 mmol, 70%) as a white solid. $\delta_H$ ($(CD_3)_2SO$, 400 MHz) 1.66 (2H, d, $J$ = 14.4 Hz), 1.72−1.83 (1H, m), 2.10−2.24 (4H, m), 2.30−2.43 (2H, m), 2.55 (3H, s), 2.93 (2H, d, $J$ = 5.3 Hz), 3.61−3.80 (2H, m), 7.33 (2H, tt, $J$ = 7.3, 1.5 Hz), 7.42 (4H, t, $J$ = 7.3 Hz), 7.48 (4H, dd, $J$ = 7.3, 1.5 Hz), 10.64 (1H, br s); $\delta_C$ ($(CD_3)_2SO$, 100 MHz) 22.9, 23.9, 34.1, 37.8, 44.8, 51.9, 61.8, 122.3, 126.8, 128.0, 129.0, 139.7; $\nu_{max}$ $cm^{-1}$ (solid) 2944.7, 2483.1, 1478.7, 1449.2, 1393.8, 1335.5, 1088.3, 1052.1, 968.6, 945.6, 881.7, 831.7, 760.6, 747.5, 694.5, 663.3; HRMS $m/z$ calc'd for $C_{23}H_{27}N_2$ 331.2169, found 331.2168; mp 245−247 °C.

**Single Pilot-Plant Scale Batch.** *3-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile Hydrochloride **4**.* Trimethylsilylcyanide (9.35 kg, 94.2 mol) was added to a suspension of 2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1,1-diphenylethanol **3** (8.65 kg, 26.9 mol) in DCM (86.5 L) at −5 °C over 7 min, followed by a line-wash of DCM (0.5 L). Tin tetrachloride (24.5 kg, 94.0 mol) was added over 75 min to the suspension at such a rate to maintain the internal temperature at −5 °C, followed by a line-wash of DCM (0.5 L). The suspension was then warmed to 25 °C over 30 min and stirred for 2 h until considered complete by HPLC. The slurry was added slowly to aqueous NaOH solution (5 M, 86.5 L) at 0 °C over 90 min, following by a line-wash of DCM (8.65 L). The DCM layer was separated, and the aqueous layer was washed with DCM (2 × 17.3 L). The organic layers were combined and washed with water (2 × 17.3 L), and the organic solvent was evaporated by vacuum distillation and MIBK (34.6 L) added. The solution was then concentrated to 34.6 L by vacuum distillation and passed through a Cuno Zetacarbon filter, eluting with an additional 17.3 L of MIBK. The solution was then concentrated to 51.9 L, and a solution of HCl in 2-propanol (5 M, 5.54 kg, 29.6 mol) was added at 45 °C over 45 min. The resulting slurry was stirred for 1 h at 80 °C, then cooled to 20 °C over 1 h, and aged for at least 1 h. The product was collected by vacuum filtration and washed with MIBK (52.0 L, 17.3 L) before drying in vacuo at 50 °C to afford 3-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile hydrochloride **4** (3.15 kg, 8.59 mol, 49.6%) as a white solid.

**Laboratory Scale.** *3-(8-Azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile Hydrochloride **6**.* 3-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile hydrochloride **5** (15.0 g, 7.55 mol) was suspended in toluene (150 mL), and aqueous sodium hydroxide (1.33 M, 45 mL) was added before stirring for 30 min. The aqueous layer was removed, and the organics were distilled down to 75 mL under atmospheric pressure. The solution was cooled to 50 °C, and sodium bicarbonate (7.5 g, 88.2 mmol) was added followed by 1-chloroethyl chloroformate (11.1 mL, 102 mmol) at such a rate that the temperature remained below 55 °C. The reaction was stirred for 2 h until considered complete by HPLC, at which point, water (45 mL) was added and stirring continued for a further 1 h at 50 °C. A solution of aqueous potassium carbonate (18 g in 45 mL) was then added carefully to the reaction at 80 °C and stirred for 30 min, and the layers were allowed to settle, and the aqueous layer was removed. The organic layer was washed successively at 80 °C with water (45 mL) and brine (11.25 g NaCl in 30 mL water). A solution of HCl in 2-propanol (5 M, 9.0 mL, 45 mmol) was added slowly to the organic fraction at 80 °C and cooled to 60 °C. The mixture was stirred for 30 min at 60 °C and then cooled to 20 °C. The slurry was stirred for at least 60 min and product collected by filtration. The filter cake was washed with TBME (2 × 75 mL) and the product dried in vacuo at 50 °C to afford 3-(8-azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile hydrochloride **6** (12.3 g, 34.9 mmol, 85%) as a white solid. $\delta_H$ ($CDCl_3$, 400 MHz) 1.63 (2H, d, $J$ = 15.4 Hz), 2.00−2.09 (2H, m), 2.11−2.19 (1H, m), 2.27−2.38 (2H, m), 2.45 (2H, ddd, $J$ = 15.4, 7.6, 3.5 Hz), 2.71 (2H, d, $J$ = 5.8 Hz), 3.92−4.00 (2H, m), 7.28−7.41 (10H, m) 9.47 (2H, br s); $\delta_C$ ($CDCl_3$, 100 MHz) 24.6, 25.8, 33.8, 46.9, 51.4, 54.0, 122.1, 126.9, 128.2, 129.1, 139.3; $\nu_{max}$ $cm^{-1}$ (solid) 3365.1, 2883.1, 2787.9, 1636.4, 1490.2, 1447.3, 1410.5, 1382.4, 1207.7, 1035.4, 951.1, 770.9, 756.3, 747.4, 711.3, 693.4, 656.2; HRMS $m/z$ calc'd for $C_{22}H_{25}N_2$ 317.2012, found 317.2006; mp 221−223 °C.

**Pilot-Plant Scale Reaction.** *3-(8-Azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile Hydrochloride **6**.* 3-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile hydrochloride **5** (2.77 kg, 7.55 mol) was suspended in toluene (5.4 L) and acetone (8.1 L); diisopropylethylamine (2.38 kg, 18.4 mol) was added over 10 min and the resulting solution heated to 50 °C. 1-Chloroethyl chloroformate (2.65 kg, 18.5 mmol) was then added over 1 h at such a rate that the temperature remained below 55 °C. The solution was stirred for at least 2 h until the reaction was considered complete by HPLC. The reaction was then distilled under atmospheric conditions to ∼17.6 L, diluted with MIBK (32.4 L), and heated to 80 °C. A solution of potassium carbonate (3.24 kg, 23.4 mmol, in 8.1 L water) was then added to the reaction at 80 °C over 1 h, the biphasic mixture stirred for 30 min, the layers allowed to settle, and the aqueous layer removed. The organic layer was then washed with water at 80 °C (8.1 L) and brine (2.03 kg NaCl, in 5.4 L water). A solution of HCl in 2-propanol (5 M, 1.49 kg, 8.3 mol) was added over 30 min to the organic fraction at 80 °C and then the reaction cooled to 60 °C. The resulting slurry was stirred for 30 min at 60 °C and then cooled to 20 °C. The slurry was stirred for at least 60 min and product collected by filtration. The filter cake was washed with MIBK (2 × 13.5 L) and the product dried in vacuo at 50 °C to afford 3-(8-azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile hydrochloride **6** (2.54 kg, 7.36 mol, 89.2%) as a white solid. The isolated product was contaminated with ethylisopropylamine and diisopropylamine hydrochloride.

*8-(2-(Benzyloxy)ethyl)-3-(2-cyano-2,2-diphenylethyl)-8′-methyl-8-azabicyclo[3.2.1]octan-8-ium Iodide **1**.* To a stirred


dx.doi.org/10.1021/op3002933 | Org. Process Res. Dev. 2013, 17, 641−650

suspension of 3-(8-azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile hydrochloride **6** (2.54 kg, 7.20 mol) in acetone (15.1 L) were added potassium carbonate (2.99 kg, 21.6 mol) followed by benzylbromoethyl ether (1.86 kg, 8.67 mol) and the resultant suspension heated to 60 °C for at least 18 h. The suspension was cooled to 20 °C and filtered to remove inorganic material. The filter cake was washed with acetone (2 × 9.6 L), and the combined organics were distilled down to 17.9 L. The solution was cooled to 0 °C, and methyl iodide (1.23 kg, 8.67 mol) was added, maintaining temperature below 0 °C. The resulting slurry was allowed to warm to 20 °C and stirred for 18 h. MeOH (3.81 L) was added and the slurry heated at 55 °C for at least 18 h. After the slurry cooled to 20 °C and aged for 1 h, the precipitated product was collected by filtration. The filter cake was washed with acetone (3 × 10.2 L) and the product dried in vacuo at 50 °C to afford intermediate grade 8-(2-(benzyloxy)ethyl)-3-(2-cyano-2,2-diphenylethyl)-8-methyl-8-azabicyclo[3.2.1]octan-8-ium iodide **1** (3.06 kg, 5.16 mol, 72%) as a white solid. A portion of the resultant material (700 g, 1.18 mol) was recrystallized from 17.5 L of 5% aqueous MeOH to afford 8-(2-(benzyloxy)ethyl)-3-(2-cyano-2,2-diphenylethyl)-8′-methyl-8-azabicyclo[3.2.1]octan-8-ium iodide **1** (593 g, 1.00 mol, 85%) as a crystalline white solid. $\delta_H$ ($CD_3OD$, 400 MHz) 1.74 (2H, d, $J$ = 16.4 Hz), 2.10−2.21 (1H, ddd, $J$ = 14.9, 9.3, 5.9 Hz), 2.26−2.48 (4H, m), 2.56 (2H, ddd, $J$ = 16.4, 9.3, 3.8 Hz), 2.97 (2H, d, $J$ = 5.9 Hz), 3.02 (3H, s), 3.68 (2H, t, $J$ = 5.1 Hz), 3.85−3.92 (4H, m), 4.56 (2H, s), 7.27−7.37 (7H, m), 7.41 (4H, t, $J$ = 7.6 Hz), 7.47 (4H, dd, $J$ = 7.6, 1.7 Hz); $\delta_C$ ($CD_3OD$, 100 MHz) 22.6, 25.4, 33.5, 47.0, 50.3, 53.6, 56.3, 65.1, 70.3, 74.6, 123.7, 128.4, 129.1, 129.3, 129.4, 129.8, 130.4, 138.9, 141.4; $\nu_{max}$ $cm^{-1}$ (solid) 2973.3, 2946.7, 2872.8, 2231.5, 1600.6, 1582.9, 1495.9, 1457.5, 1448.3, 1412.1, 1356.0, 1124.1, 1048.4, 1025.8, 915.2, 900.6, 779.4, 755.0, 741.0, 714.3, 695.4; HRMS $m/z$ calc'd for $C_{32}H_{37}ON_2$ 465.2900, found 465.2887; ion chromatography: $I^-$, expected 21.4%, found 21.9%; mp 218−220 °C.

*8′-(2-(Benzyloxy)ethyl)-3-(2-cyano-2,2-diphenylethyl)-8-methyl-8-azabicyclo[3.2.1]octan-8-ium Iodide* ***5***. A sample of mother liquors after crystallization of 8-(2-(benzyloxy)ethyl)-3-(2-cyano-2,2-diphenylethyl)-8′-methyl-8-azabicyclo[3.2.1]-octan-8-ium iodide **1** was evaporated to dryness to afford a yellow oily solid, 19.4 g. This was triturated with acetone (40 mL) for 15 min and filtered, washing the cake with acetone (2 × 10 mL). The liquors were again evaporated to afford a yellow solid and further triturated with acetone (40 mL) for 15 min. The slurry was filtered, washing the cake with acetone (2 × 10 mL). Finally, the liquors were taken up in acetone (50 mL) at 55 °C. The mixture was allowed to cool to ambient temperature and aged overnight. The resultant slurry was filtered and washed with acetone (2 × 10 mL) and dried in vacuo to afford 8′-(2-(benzyloxy)ethyl)-3-(2-cyano-2,2-diphenylethyl)-8-methyl-8-azabicyclo[3.2.1]octan-8-ium iodide **5** (1.5 g) as a white solid. $\delta_H$ (MeOD, 400 MHz) 1.78 (2H, d, $J$ = 16.4 Hz), 2.15 (1H, ddd, $J$ = 14.7, 9.1, 5.6 Hz), 2.25−2.35 (2H, m), 2.40−2.53 (4H, m), 2.97 (2H, d, $J$ = 5.6 Hz), 3.09 (3H, s), 3.54 (2H, t, $J$ = 4.2 Hz), 3.89−3.98 (4H, m), 4.56 (2H, s), 7.26−7.37 (7H, m), 7.40 (4H, t, $J$ = 7.6 Hz), 7.47 (4H, d, $J$ = 8.3 Hz); $\delta_C$ (MeOD, 100 MHz) 23.1, 25.7, 33.6, 42.2, 50.1, 53.5, 61.9, 65.0, 69.2, 74.5, 123.7, 128.4, 129.2, 129.2, 129.4, 129.7, 130.3, 138.8, 141.4; $\nu_{max}$ $cm^{-1}$ (solid) 2943.9, 1492.8, 1449.3, 1358.4, 1219.0, 1105.6, 1084.4, 1019.9, 931.7, 899.5, 750.0, 696.7; HRMS $m/z$ calc'd for $C_{32}H_{37}N_2O$ 465.2900, found 465.2890; mp 161−165 °C.

*O-Benzylethanolamine* ***12***:[9] Ethanolamine (40.5 g, 0.663 mol) was added dropwise to a suspension of sodium hydride (60% dispersion in mineral oil, 26.5 g, 0.663 mol) in THF (640 mL) at 0 °C. The temperature was then raised to reflux and the solution aged for 30 min, at which point, benzyl chloride (75.5 g, 0.596 mol) was added dropwise. The solution was aged at reflux for 2 h, then cooled to 20 °C and quenched with water (100 mL). The THF was removed by distillation and the pH adjusted with 1 M aqueous HCl (200 mL). The aqueous layer was extracted with DCM (3 × 150 mL) and the remaining aqueous fraction basified with 5% aqueous NaOH (70 mL). This was extracted with DCM (3 × 150 mL), and the combined organic fractions were dried over $Na_2SO_4$, filtered, and condensed in vacuo. The resultant oil was distilled (1.5 mbar, 100−102 °C) to afford *O*-benzylethanolamine **12** (69.0 g, 0.456 mol, 77%) as a colourless oil. $\delta_H$ ($CDCl_3$, 400 MHz) 1.28 (2H, br s), 2.91 (2H, t, $J$ = 5.1 Hz), 3.53 (2H, t, $J$ = 5.1 Hz), 4.55 (2H, s), 7.28−7.39 (5H, m).

*(8-(2-(Benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-yl)-methanol Hydrochloride* ***18***. 2,5-Dimethoxyfuran (35.2 g, 0.266 mol) was heated to 80 °C for 30 min in water (100 mL) with concentrated HCl (37%, 2.80 mL, 0.034 mol). The solution was then cooled to 0 °C. In a separate vessel, acetone-1,3-dicarboxylic acid (43.6 g, 0.298 mol) was added to a solution of NaOAc (61.2 g, 0.746 mol), *O*-benzylethanolamine **12** (32.2 g, 0.213 mol), and concentrated HCl (37%, 2.98 mL, 0.036 mol) in water (200 mL) at 5 °C. The furan (dialdehyde) solution was then added and washed in with an additional 100 mL water. The solution was aged at 5 °C for 10 min, heated to 45 °C over 2 h, and aged at 45 °C until considered complete by HPLC. NaCl (150 g) was added followed by a solution of NaOH (25 g) in water (30 mL). The biphasic solution was then extracted with 2-MeTHF (3 × 200 mL). The combined organics were then distilled down to a volume of 100 mL at atmospheric pressure to afford a solution of 8-(2-(benzyloxy)-ethyl)-8-azabicyclo[3.2.1]octan-3-one **11**. In a separate vessel, a solution of KO$^t$Bu in $^t$BuOH (1 M, 266 mL, 0.266 mol) was added to a stirred suspension of trimethylsulfoxonium iodide (58.7 g, 0.266 mol) in 2-MeTHF (200 mL) at 20 °C and the mixture aged for 1 h. The solution of 8-(2-(benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-one **11** was then added over 20 min and washed in with a further 50 mL 2-MeTHF. The solution was then heated to 75 °C for at least 16 h until considered complete by HPLC. Toluene (200 mL) was added and the reaction quenched at 50 °C by addition of water (300 mL). The aqueous fraction was decanted and the organics washed with water (200 mL) and distilled down to 200 mL. Toluene (200 mL) was added and the solution again distilled down to 200 mL to afford a solution of 8-(2-(benzyloxy)ethyl)-8-azaspiro[bicyclo[3.2.1]octane-3,2′-oxirane] **13** which was cooled to −25 °C. A solution of Dibal-H in toluene (1.5 M, 213 mL, 0.320 mol) was charged to a clean dry vessel and cooled to −78 °C. The solution of 8-(2-(benzyloxy)ethyl)-8-azaspiro[bicyclo[3.2.1]octane-3,2′-oxirane] **13** was added over at least 1.5 h, maintaining temperature below −60 °C, and washed in with a further 2 × 50 mL toluene. The solution was aged at −60 °C for 30 min, until complete epoxide consumption as judged by HPLC, and quenched by slow addition of ethyl acetate (100 mL). The solution was then added slowly to a saturated solution of Rochelle's salt (500 mL) at 0 °C and aged with vigorous stirring for 4 h. The aqueous layer was decanted, and the organics were washed with water (200 mL). The solution was concentrated to 300 mL, and


dx.doi.org/10.1021/op3002933 | Org. Process Res. Dev. 2013, 17, 641−650

toluene (300 mL) was added. The solution was again distilled down to 300 mL and cooled to 65 °C, where 2-propanol (11.4 mL) was added. A solution of HCl in 2-propanol (5 M, 42.6 mL, 0.213 mol) was added dropwise, and the mixture was seeded with 100 mg of (8-(2-(benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-yl)methanol hydrochloride **18** at 60 °C and aged for 30 min. The suspension was cooled to 10 °C over 2 h, aged for 2 h, filtered, washed with toluene (3 × 100 mL) and dried in vacuo to afford (8-(2-(benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-yl)methanol hydrochloride **18** (30.3 g, 97.2 mmol, 46%) as an off-white solid: $\delta_H$ ($CDCl_3$, 400 MHz) 1.83−2.06 (5H, m), 2.20−2.36 (4H, m), 3.19−3.36 (2H, m), 3.59 (2H, d, $J$ = 8.6 Hz), 3.83 (2H, t, $J$ = 5.0 Hz), 3.92−4.04 (2H, m), 7.28−7.41 (5H, m); $\delta_C$ ($CDCl_3$, 100 MHz) 25.6, 31.2, 31.4, 52.7, 63.7, 65.9, 66.6, 74.5, 129.2, 129.3, 129.7, 139.0; $\nu_{max}$ $cm^{-1}$ (solid) 3280.7, 2984.7, 2862.8, 2648.4, 2591.2, 2549.7, 1477.3, 1451.7, 1369.6, 1324.1, 1253.4, 1114.8, 1085.8, 1057.8, 1031.3, 980.9, 940.2, 917.8, 829.0, 735.1, 695.1, 655.0; HRMS $m/z$ calc'd for $C_{17}H_{26}NO_2$ 276.1958, found 276.1956; mp 144−146 °C.

Intermediates **11** and **13** were isolated and subsequently characterized by evaporation of in process solutions and purification.

8-(2-(Benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-one **11**, purified by silica gel chromatography, eluting with 20−80% EtOAc in heptane: $\delta_H$ ($CDCl_3$, 400 MHz) 1.55−1.65 (2H, m), 1.99−2.10 (2H, m), 2.18 (2H, dd, $J$ = 16.1, 1.5 Hz), 2.69 (2H, dd, $J$ = 16.1, 4.4 Hz), 2.86 (2H, t, $J$ = 5.8 Hz), 3.57−3.64 (2H, m), 3.69 (2H, t, $J$ = 5.8 Hz), 4.58 (2H, s), 7.28−7.40 (5H, m); $\delta_C$ ($CDCl_3$, 100 MHz) 27.9, 47.2, 49.9, 59.3, 69.8, 73.2, 127.5, 127.6, 128.4, 138.2, 210.0; $\nu_{max}$ $cm^{-1}$ (oil) 2951.3, 1710.1, 1496.3, 1453.5, 1411.0, 1347.7, 1318.5, 1277.8, 1196.4, 1098.3, 1071.7, 1027.9, 1007.8, 941.7, 907.4, 840.4, 735.5, 697.2; HRMS $m/z$ calc'd for $C_{16}H_{22}NO_2$ 260.1645, found 260.1643.

8-(2-(Benzyloxy)ethyl)-8-azaspiro[bicyclo[3.2.1]octane-3,2′-oxirane] **13** purified by silica gel chromatography, eluting with 30−80% EtOAc in heptane: $\delta_H$ ($CDCl_3$, 400 MHz) 1.12 (2H, d, $J$ = 14.2 Hz), 1.92−2.06 (4H, m), 2.38 (2H, dd, $J$ = 14.2, 3.2 Hz), 2.39 (2H, s), 2.69 (2H,, $J$ = 6.3 Hz), 3.31−3.39 (2H, m), 3.62 (2H, t, $J$ = 6.3 Hz), 4.56 (2H, s), 7.25−7.39 (5H, m); $\delta_C$ ($CDCl_3$, 100 MHz) 26.1, 38.7, 48.4, 51.5, 54.7, 59.5, 69.9, 73.1, 127.5, 127.6, 128.3, 138.5; $\nu_{max}$ $cm^{-1}$ (oil) 3030.4, 2942.2, 1496.1, 1453.8, 1346.9, 1325.4, 1218.4, 1101.5, 1072.1, 1055.0, 1028.3, 1010.8, 940.2, 903.8, 843.5, 785.6, 734.1, 696.8; HRMS $m/z$ calc'd for $C_{17}H_{23}NO_2$ 274.1802, found 274.1798.

8-(2-(Benzyloxy)ethyl)-3-(2-cyano-2,2-diphenylethyl)-8′-methyl-8-azabicyclo[3.2.1]octan-8-ium iodide **1**. Triethylamine (16.0 mL, 115 mmol) and methanesulfonyl chloride (5.33 g, 68.9 mmol) were added sequentially to a stirred suspension of (8-(2-(benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-yl)-methanol hydrochloride **18** (17.9 g, 57.4 mmol) in THF (150 mL) at 0 °C. After 1 h the resultant slurry was filtered and the cake washed with a further 100 mL THF. The combined organics were distilled down to 100 mL to afford a solution of (8-(2-(benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-yl)methyl methanesulfonate **19**. In a separate vessel, a solution of KO$^t$Bu in $^t$BuOH (1 M, 115 mL, 115 mmol) was added to a solution of diphenylacetonitrile (22.2 g, 115 mmol) in THF (80 mL) at 20 °C. After 1 h the solution of (8-(2-(benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-yl)methyl methanesulfonate **19** was added and washed in with a further 20 mL THF; the solution was heated to reflux for at least 1 h until complete consumption of mesylate as indicated by HPLC. The reaction was quenched with water (100 mL) and most of the THF removed by distillation. The bi-phasic mixture was then extracted with MiBK (3 × 100 mL) and distilled down to 120 mL to afford a solution of 3-(8-(2-(benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile **7**. MeOH (11 mL) was added and the solution cooled to 0 °C. Iodomethane (4.65 mL, 74.6 mmol) was added and after aging for 1 h the mixture allowed to warm to 20 °C and aged for a further 16 h. The slurry was heated to 60 °C for 6 h, then cooled to 20 °C over 1 h and aged for a further 1 h. The slurry was filtered and the resulting solid washed with MiBK (2 × 100 mL) and dried in vacuo to afford 8-(2-(benzyloxy)ethyl)-3-(2-cyano-2,2-diphenylethyl)-8′-methyl-8-azabicyclo[3.2.1]octan-8-ium iodide **1** (28.0 g, 47.3 mmol, 82%) as an off-white solid. The resultant material (10.0 g, 16.9 mmol) was recrystallized from 250 mL 5% aqueous MeOH to afford 8-(2-(benzyloxy)ethyl)-3-(2-cyano-2,2-diphenylethyl)-8′-methyl-8-azabicyclo[3.2.1]octan-8-ium iodide **1** (8.2 g, 13.8 mmol, 82%) as a crystalline white solid. Analytical data match those previously reported.

Intermediates **19** and **7** were isolated and subsequently characterized by evaporation of in-process solutions and purification.

(8-(2-(Benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-yl)-methyl methanesulfonate **19** was purified by silica gel chromatography, eluting with 0−10% MeOH in TBME: $\delta_H$ ($CDCl_3$, 400 MHz) 1.41 (2H, d, $J$ = 13.9 Hz), 1.49−1.57 (2H, m), 1.97−2.08 (2H, m), 2.09−2.22 (3H, m), 2.62 (2H, t, $J$ = 6.1 Hz), 3.00 (3H, s), 3.24−3.33 (2H, m), 3.60 (2H, t, $J$ = 6.1 Hz), 4.18 (2H, d, $J$ = 7.3 Hz), 4.54 (2H, s), 7.25−7.38 (5H, m); $\delta_C$ ($CDCl_3$, 100 MHz) 26.9, 27.9, 31.1, 37.4, 51.6, 58.6, 69.7, 73.1, 74.0, 127.5, 127.5, 128.3, 138.3; $\nu_{max}$ $cm^{-1}$ (oil) 2922.3, 2851.3, 1454.1, 1352.9, 1264.6, 1172.4, 1086.2, 1027.9, 948.4, 887.9, 846.5, 811.9, 731.5, 698.1; HRMS $m/z$ calc'd for $C_{18}H_{28}NO_4S$ 354.1734, found 354.1734.

3-(8-(2-(Benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-yl)-2,2-diphenylpropanenitrile **7** was purified by silica gel chromatography, eluting with 0−5% MeOH in TBME: $\delta_H$ ($CDCl_3$, 400 MHz) 1.25 (d, $J$ = 13.9 Hz), 1.63−1.71 (2H, m), 1.89−2.02 (3H, m), 2.08 (2H, ddd, $J$ = 13.4, 8.3, 5.2 Hz), 2.54 (2H, t, $J$ = 6.3 Hz), 2.62 (2H, d, $J$ = 5.8 Hz), 3.13−3.21 (2H, m), 3.53 (2H, t, $J$ = 6.3 Hz), 4.50 (2H, s), 7.23−7.41 (15H, m); $\delta_C$ ($CDCl_3$, 100 MHz) 25.2, 26.8, 36.5, 48.4, 51.4, 51.6, 58.7, 69.9, 73.1, 122.7, 127.0, 127.5, 127.5, 127.8, 128.3, 128.8, 138.5, 140.4; $\nu_{max}$ $cm^{-1}$ (oil) 2928.4, 2236.0, 1598.8, 1494.0, 1449.3, 1320.2, 1205.6, 1073.1, 1029.3, 1001.9, 909.3, 818.6, 731.1, 694.8; HRMS $m/z$ calc'd for $C_{31}H_{35}N_2O$ 451.2744, found 451.2738.

*(8-(2-(Benzyloxy)ethyl)-8-azabicyclo[3.2.1]oct-3-en-3-yl)-methanol Citrate* ***17***. Diethylamine (48.0 mL, 0.464 mol) was added dropwise to a solution of $^n$BuLi in THF (2.5 M, 185 mL, 0.464 mol) maintaining temperature below 0 °C. After aging for 30 min, the solution was cooled to −20 °C and a solution of 8-(2-(benzyloxy)ethyl)-8-azaspiro[bicyclo[3.2.1]octane-3,2′-oxirane] **13** (50.7 g, 0.185 mol) in THF (70 mL) added over 30 min, maintaining temperature below −10 °C, and washed in with an additional 30 mL THF. After 1 h water (500 mL) was added maintaining temperature below 20 °C, and the THF removed by distillation. The residue was extracted with 2-MeTHF (300 mL) and the solution dried over $Na_2SO_4$ and filtered. The resultant solution was passed through a Cuno Zetacarbon filter, eluting with 2-MeTHF (200 mL) and evaporated to dryness. The resultant oil was taken up in IPA (500 mL) and 2-MeTHF (200 mL) and heated to 75 °C. A


dx.doi.org/10.1021/op3002933 | Org. Process Res. Dev. 2013, 17, 641−650

solution of citric acid (39.2 g, 0.204 mol) in IPA (300 mL) at 75 °C was added and the mixture cooled to 65 °C. The solution was seeded with 100 mg (8-(2-(benzyloxy)ethyl)-8-azabicyclo[3.2.1]oct-3-en-3-yl)methanol citrate **17** and aged at 65 °C for 1 h. The slurry was then cooled to 20 °C over 3 h and aged at 20 °C for 3 h. The resultant slurry was filtered, and the cake was washed with 2-MeTHF (2 × 200 mL) and dried in vacuo to afford (8-(2-(benzyloxy)ethyl)-8-azabicyclo[3.2.1]oct-3-en-3-yl)methanol citrate **17** (56.9 g, 0.122 mol, 66%) as a white solid: $\delta_H$ ($(CD_3)_2SO$, 400 MHz) 1.62−1.74 (1H, m), 1.95 (2H, m), 2.04−2.26 (2H, m), 2.48 (2H, d, $J$ = 15.2 Hz), 2.55 (2H, d, $J$ = 15.2 Hz), 2.55−2.64 (1H, m), 3.15 (2H, t, $J$ = 5.1 Hz), 3.69 (1H, dd, $J$ = 11.2, 5.1 Hz), 3.73 (1H, dd, $J$ = 11.2, 5.1 Hz), 3.79 (2H, s), 3.94 (1H, dd, $J$ = 6.1, 5.1 Hz), 4.03 (1H, t, $J$ = 5.4 Hz), 4.49 (2H, s), 5.74 (1H, d, $J$ = 5.4 Hz), 7.23−7.38 (5H, m); $\delta_C$ ($(CD_3)_2SO$, 100 MHz) 27.1, 31.8, 31.9, 58.5, 58.6, 62.8, 65.7, 71.5, 72.2, 119.4, 127.6, 127.6, 128.4, 136.8, 137.9, 171.5, 176.9; $\nu_{max}$ $cm^{-1}$ (solid) 3378.6, 2860.9, 1726.1, 1575.8, 1433.0, 1399.5 1349.4, 1316.8, 1251.1, 1206.4, 1171.4, 1108.3, 1075.0, 1038.9, 1012.7, 979.6, 913.0, 892.8, 846.8, 791.9, 748.5, 699.1, 664.9; HRMS $m/z$ calc'd for $C_{17}H_{23}NO_2$ 274.1802, found 274.1805; mp 120−122 °C.

Various impurities were isolated from reaction mixtures during route investigation work; their isolation is documented below:

4-(2-(Benzyloxy)ethyl)octahydro-1*H*-3,7-methanoindolizin-4-ium-7-olate **14** was isolated as a hygroscopic solid by filtration of the white precipitate formed when excess sulfoxonium ylid is added to 8-(2-(benzyloxy)ethyl)-8-azabicyclo[3.2.1]octan-3-one **13** during the epoxidation reaction: $\delta_H$ (MeOD, 400 MHz) 1.74 (2H, d, $J$ = 12.5 Hz), 1.90−1.97 (2H, m), 2.00−2.08 (2H, m), 2.38 (2H, t, $J$ = 10.8 Hz), 2.47−2.55 (2H, m), 3.40−3.45 (2H, m), 3.86−3.93 (2H, m), 3.94−4.00 (2H, m), 4.17−4.25 (2H, m), 4.60 (2H, s), 7.28−7.41 (5H, m); $\delta_C$ (MeOD, 100 MHz) 31.1, 34.5, 43.1, 53.4, 60.4, 63.3, 64.9, 68.3, 74.5, 129.2, 129.3, 129.7, 138.9; $\nu_{max}$ $cm^{-1}$ (solid) 3292.0, 2960.8, 2881.8, 1591.0, 1453.0, 1435.9, 1363.9, 1352.7, 1327.6, 1263.7, 1225.5, 1207.2, 1152.6, 1139.7, 1111.0, 1074.1, 1032.9, 1020.4, 990.5, 956.4, 929.1, 886.0, 835.1, 818.0, 759.5, 707.8; HRMS $m/z$ calc'd for $C_{18}H_{26}O_2N$ 288.1958, found 288.1955.

8-(2-(Benzyloxy)ethyl)-3-((diethylamino)methyl)-8-azabicyclo[3.2.1]octan-3-ol **16** was isolated by purification of the free-based liquors from isolation of (8-(2-(benzyloxy)-ethyl)-8-azabicyclo[3.2.1]oct-3-en-3-yl)methanol citrate **17** by silica gel chromatography on a SNAP KP-NH Biotage cartridge, eluting with 0−25% TBME in cyclohexane: $\delta_H$ ($CDCl_3$, 400 MHz) 0.99 (6H, t, $J$ = 7.1 Hz), 1.54 (2H, d, $J$ = 13.4 Hz), 1.76 (2H, dd, $J$ = 13.6, 3.0 Hz), 1.83−1.92 (2H, m), 2.17 (2H, dd, $J$ = 13.6, 6.1 Hz), 2.23 (2H, s), 2.57 (4H, q, $J$ = 7.1 Hz), 2.62 (2H, t, $J$ = 6.3 Hz), 3.20−3.29 (2H, m), 3.60 (2H, t, $J$ = 6.3 Hz), 4.54 (2H, s), 7.24−7.42 (5H, m); $\delta_C$ ($CDCl_3$, 100 MHz) 12.2, 25.7, 43.1, 48.8, 51.6, 59.3, 66.5, 67.9, 69.9, 73.1, 127.5, 127.6, 128.3, 138.5; $\nu_{max}$ $cm^{-1}$ (oil) 3400.7, 2925.3, 2852.9, 1496.4, 1454.4, 1384.5, 1373.0, 1349.01294.5, 1258.1, 1227.8, 1202.5, 1079.4, 1059.8, 1028.6, 976.0, 953.5, 930.2, 887.7, 875.3, 832.2, 787.1, 732.3, 696.4, 661.6; HRMS $m/z$ calc'd for $C_{21}H_{35}N_2O_2$ 347.2693, found 347.2693.

*3-(1-(2-(Benzyloxy)ethyl)-4-methylenepyrrolidin-2-yl)-propan-1-ol* ***22***. A solution of Dibal-H in THF (1 M, 0.549 mL, 0.549 mmol) was added dropwise to a solution of 8-(2-(benzyloxy)ethyl)-8-azaspiro[bicyclo[3.2.1]octane-3,2′-oxirane] **13** (100 mg, 0.366 mmol) in THF (1 mL) at −30 °C. After 30 min, the reaction was quenched with EtOAc (1 mL) and stirred with saturated aqueous Rochelle's salt (20 mL) for 2 h. The biphasic solution was extracted with EtOAc (2 × 20 mL), dried over $Na_2SO_4$, filtered, and condensed in vacuo. The resultant oil was purified by silica gel chromatography, eluting with 0−10% 2 M $NH_3$/MeOH in DCM to afford 3-(1-(2-(benzyloxy)ethyl)-4-methylenepyrrolidin-2-yl)propan-1-ol **22** (77.6 mg, 0.282 mmol, 77%) as an orange oil: $\delta_H$ ($CDCl_3$, 400 MHz) 1.66−1.83 (4H, m), 2.26−2.37 (2H, m), 2.41−2.53 (2H, m), 2.61−2.70 (1H, m), 3.08−3.23 (2H, m), 3.60−3.70 (2H, m), 3.94 (1H, d, $J$ = 12.0 Hz), 3.98 (1H, d, $J$ = 12.0 Hz), 4.53 (2H, s), 4.87 (1H, s), 5.10 (1H, s), 7.25−7.38 (5H, m); $\delta_C$ ($CDCl_3$, 100 MHz) 22.7, 27.6, 38.3, 54.1, 54.5, 63.8, 66.8, 68.9, 73.2, 116.5, 127.6, 127.7, 128.3, 138.2, 145.7; $\nu_{max}$ $cm^{-1}$ (oil) 3371.8, 3066.5, 2860.2, 1647.3, 1496.3, 1453.9, 1359.4, 1305.8, 1250.1, 1205.5, 1094.1, 1028.5, 960.9, 900.8, 848.6, 734.9, 969.8; HRMS $m/z$ calc'd for $C_{17}H_{26}O_2N$ 276.1958, found 276.1960.

*8-(2-(Benzyloxy)ethyl)-3-methyl-8-azabicyclo[3.2.1]octan-3-ol* ***21***. A solution of RedAl in PhMe (3.5 M, 0.157 mL, 0.549 mmol) was added dropwise to a solution of 8-(2-(benzyloxy)-ethyl)-8-azaspiro[bicyclo[3.2.1]octane-3,2′-oxirane] **13** (100 mg, 0.366 mmol) in toluene (1 mL) at −30 °C. After 30 min, the reaction was quenched with EtOAc (1 mL) and stirred with saturated, aqueous Rochelle's salt (20 mL) for 2 h. The reaction was extracted with EtOAc (2 × 20 mL), dried over $Na_2SO_4$, filtered, and condensed in vacuo. The resultant oil was purified by silica gel chromatography, eluting with 0−5% 2 M $NH_3$/MeOH in DCM to afford 8-(2-(benzyloxy)ethyl)-3-methyl-8-azabicyclo[3.2.1]octan-3-ol **21** (82.6 mg, 0.300 mmol, 82%) as colourless oil: $\delta_H$ ($CDCl_3$, 400 MHz) 1.12 (1H, br s), 1.16 (3H, s), 1.57 (2H, d, $J$ = 14.2 Hz), 1.83−1.97 (4H, m), 2.02−2.10 (2H, m), 2.62 (2H, t, $J$ = 6.4 Hz), 3.18−3.26 (2H, m), 3.59 (2H, t, $J$ = 6.4 Hz), 4.54 (2H, s), 7.23−7.38 (5H, m); $\delta_C$ ($CDCl_3$, 100 MHz) 25.8, 34.1, 44.1, 51.4, 58.9, 69.0, 69.9, 73.0, 127.4, 127.5, 128.3, 138.4.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

NMR data for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We acknowledge Michael R. Webb for valuable advice in preparing this manuscript and for supervision of A.J.W. We thank Andrew Richards for help with the DoE to investigate factors for the tropinone synthesis.

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