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Development of a Bulk Enabling Route to Maraviroc (UK-427,857), a CCR-5 Receptor Antagonist

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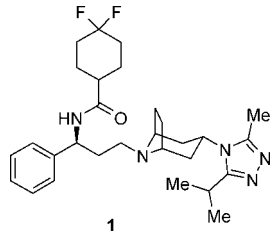
Abstract:

A bulk enabling synthesis of the CCR-5 receptor antagonist, Maraviroc (UK-427,857) (1), is presented. Synthesis of the three key fragments, β-amino ester 3, 4,4-difluorohexanecarboxylic acid (2), and 1,3,4-triazole-substituted tropane fragment 4 are described. Coupling strategies for these fragments are discussed and described, including synthetic challenges, protection strategies, impurity generation, and final scale-up of the developed route to 1.

1. Introduction

Worldwide, an estimated 39.4 million people are infected with human immunodeficiency virus (HIV), nearly half of them women, with approximately 5 million new cases diagnosed each year. In 2004, 3.1 million people died of acquired immune deficiency syndrome (AIDS), which equates to approximately 6 deaths per minute. Currently 2.2 million children are living with AIDS/HIV.[1] HIV is a retrovirus that attacks the immune system, leaving its victims susceptible to a wide variety of opportunistic and sometimes deadly infections. The virus targets white blood cells and incorporates itself into the cell's DNA, mutates easily, adapts rapidly, and develops drug resistance very effectively. The majority of currently available therapies for AIDS/HIV function by blocking viral enzymes, specifically proteases (protease inhibitors) or reverse transcriptases (nucleoside reverse transcriptases, NRTIs and non-nucleoside reverse transcriptase inhibitors, NNRTIs). Maraviroc (UK-427,857) (**1**) is a chemokine receptor 5 (CCR-5) receptor antagonist, that is currently under development for the treatment of HIV.

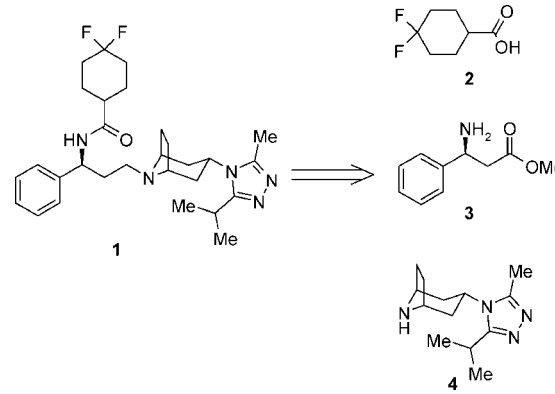


1

Maraviroc (UK-427,857)

Binding to the CCR-5 receptor has been identified as a necessary prerequisite for HIV to gain access to white blood cells. *In vivo* studies demonstrated that **1** is a highly selective CCR-5 antagonist, potentially capable of blocking viral entry into the human immune system cells, thus slowing progression of the disease. This represents a new mechanism of action compared to current available therapies.[2−5] A scaleable bulk enabling synthesis of **1** was urgently required to support toxicology and early clinical trials.

Scheme 1. **Retrosynthetic analysis of Maraviroc (UK-427,857)**



2. Results and Discussion

Retrosynthetic analysis of the target molecule **1**, leads to three key fragments, 4,4-difluorocyclohexanecarboxylic acid **2**, β-amino ester **3**, and a triazole-substituted tropane **4** (Scheme 1).

Initial efforts were focused on development of the synthesis of the tropane fragment **4**, the Medicinal Chemistry route to which is shown in Scheme 2.[6] This synthesis required work to make it a safe, robust and scaleable process due to the following challenges: (1) Safety concerns with the use of sodium metal in the reduction of oxime **6**. This process gave a 10:1 mixture *exo*-/*endo*-isomers, giving rise to concerns over removal of the undesired *endo*-isomer on scale, without the use of chromotography. (2) Acylation of **7** to **8** required long reaction times and proceeded in low yield. (3) Finally formation of triazole **9** gave low and variable yields, used chloroform as solvent, and required hydrolysis of unreacted amide **8** back to amine **7** to allow its removal by chromatography.

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(1) AIDS Epidemic update, December 2004, UNAIDS.

(2) Brelot, A.; Alizon, M. *AIDS* **2001**, *15* (Suppl. 5), S3−S11.

(3) Moore, J. P.; Trkola, A.; Dragic, T. *Curr Opin. Immunol.* **1997**, *9*, 551–562.

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(5) Stein, B. S.; Engelman, E. G. *Adv. Exp. Med. Biol.* **1991**, *300*, 71–86.

(6) Perros, M.; Price, D. A.; Stammen, B. L. C.; Wood, A. PCT Int. Appl. WO2001090106, 2001.

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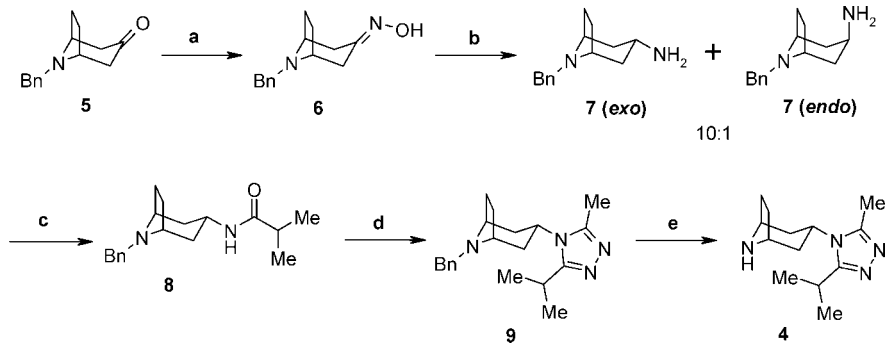
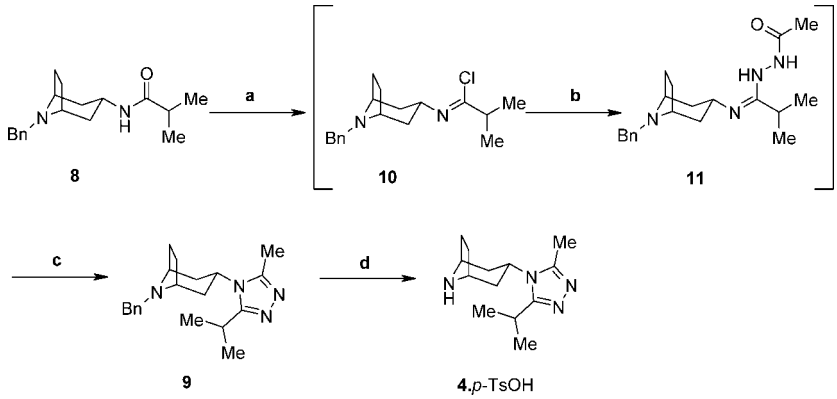
Scheme 2. **Medicinal Chemistry synthesis of 4[a,b]**



[a] Original Medicinal Chemistry conditions: (a) $NH_2OH \cdot HCl$, pyridine, EtOH, 96%; (b) Na, *n*-pentanol, reflux, 92%; (c) *i*-$PrCO_2H$, Et_3N, WSCDI, DCM, rt, 3 days, 53%; (d) (i) $POCl_3$, pyridine, $CHCl_3$, 18 h; (ii) $AcNHNH_2$, *p*-TsOH; (iii) 6 M HCl, reflux, 30−50%; (e) $Pd(OH)_2$, $NH_4^+HCO_2^-$, EtOH, 85%. [b] Conditions developed for scale-up: (a) $NH_2OH \cdot HCl$, EtOH, H_2O, $NaHCO_3$, 95%; (b) Na, toluene, reflux, 95%; (c) *i*-PrCOCl, EtOAc, Na_2CO_3, 72%; (d) (i) PCl_5, DCM, 0°C; (ii) $AcNHNH_2$; (iii) AcOH, 72%; (e) *p*-TsOH, H_2, 50 psi, 10% Pd/C, MeOH, rt, 92%.

Scheme 3. **Formation of the triazole 9[a]**



[a] Reagents and conditions: (a) PCl_5, DCM, 0°C; (b) $AcNHNH_2$, *tert*-amyl alcohol; (c) AcOH, *tert*-amyl alcohol, 72%; (d) *p*-TsOH, H_2, 10% Pd/C, 92%.

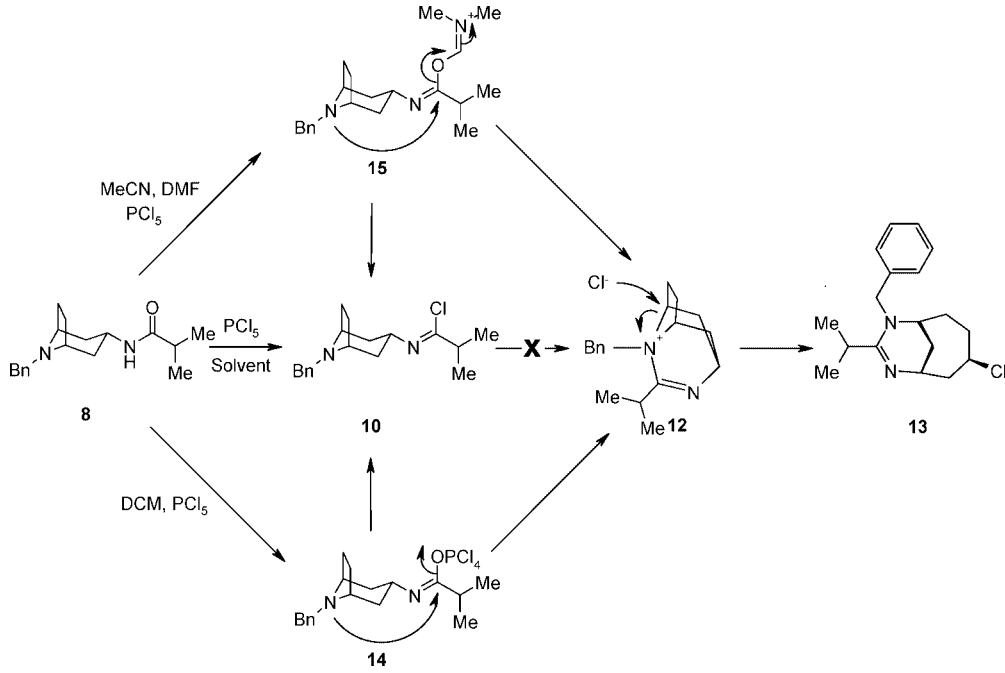
2.1. Synthesis of Triazole Fragment, 4. The tropinone **5** and oxime **6** were prepared following literature procedures, except that oxime formation was conducted in ethanol/water with sodium bicarbonate as the base, avoiding the original conditions which employed pyridine as base.[7,8] Alternatives to the sodium metal reduction of **6** to the corresponding *exo*-aminotropane **7** were considered due to safety concerns with handling of this reagent. Traditional hydride reduction of the oxime or corresponding imine are precedented to give predominantly the undesired *endo*-aminotropane **7** (***endo***) (Scheme 2).[8] Therefore, we decided to address the safety issues with using sodium metal, and the process was developed for potential scale-up.

Literature preparations of *exo*-amine **7** employ addition of a large excess of sodium to a solution of the oxime **6** in refluxing *n*-pentanol.[7] Inverse addition of a solution of **6** in *n*-pentanol to a mixture of molten sodium in refluxing toluene avoided the safety concerns and handling issues associated with the literature process. The *exo*-amine **7** isolated in 95% yield contained approximately 10% of the undesired *endo*-isomer. Preparation of *exo*-amine **7** was performed on 20 g scale in batch mode to support process research activities. Due to issues relating to the handling of molten sodium metal in our facilities (concerns of potential pooling of sodium metal due to vessel geometry and agitation efficiency beneath the baffle), an external supplier was found for bulk preparation of **7**. Synthesis of amide **8** was improved by switching to biphasic modified Schotten−Baumann conditions (EtOAc, $Na_2CO_{3\ aq}$, *i*-PrCOCl). The amide **8** was isolated by crystallisation from ethyl acetate in 72% yield, purging the undesired *endo*-amide isomer to <0.3%. The triazole **9** was synthesized in three steps, activation of **8** as its corresponding imidoyl chloride followed by trapping with acetic hydrazide and acid catalysed cyclisation to the triazole (Scheme 3).

As early investigations demonstrated that the imidoyl chloride **10** decomposed on heating, the original chlorination conditions of $POCl_3$ in refluxing chloroform were replaced by PCl_5 in DCM at 0 °C which resulted in the instantaneous and quantitative formation of **10** as determined by IR reaction monitoring. The chlorination with PCl_5 could also be performed in MeCN but was slower and required a catalytic amount of DMF to proceed. Conversion of **10** to the triazole proved to be more challenging. Addition of acetic hydrazide to a solution of **10** resulted in the deposition of a gum on the reaction vessel and was accompanied by 25−70% hydrolysis to the starting amide **8**. Hydrolysis could be suppressed to less than 10% by azeotropic drying of acetic hydrazide in acetonitrile prior to use, whilst addition of the acetic hydrazide (2 equiv) in *tert*-amyl alcohol circumvented the physical form issues (deposition of a

(7) Archer, S.; Lewis, T. R.; Unser, M. J. *J. Am. Chem. Soc.* **1957**, *79*, 4194–4198.
(8) Bagley, J. R.; Riley, T. N. *J. Heterocycl. Chem.* **1982**, *19*, 485–8.

Scheme 4. **Proposed mechanism for formation of 13**



gum) and gave clean conversion to intermediate **11**. Less hindered alcohols such as *i*-PrOH and EtOH gave significant amounts of the corresponding imidate, which did not react further. An aqueous workup was introduced following formation of **11** to remove HCl and phosphoric acid byproduct. N^1-Acylamidrazone **11** was isolated as a *tert*-amyl alcohol concentrate.

As initial investigations demonstrated that the thermal cyclisation of **11** to the triazole **9** was slow and low yielding, the effect of acid catalysis on the cyclisation was examined in hot *tert*-amyl alcohol. The addition of mineral acids (HCl, H_2SO_4, H_3PO_4) failed to promote cyclisation. Whilst slow cyclisation was observed with organic acids such as *p*-TSA and TFA, competing hydrolysis to **8** was also observed. Interestingly, addition of acetic acid to **11** in toluene gave a fast and clean cyclisation with <10% of reformed amide **8**. Cyclisation to the triazole was thus effected by addition of AcOH to the *tert*-amyl alcohol solution and heating to 60 °C to afford **9** in 72% yield after workup. Finally debenzylation of **9** was achieved by hydrogenolysis with *p*-TsOH, over 10% Pd/C, 50 psi H_2 in methanol at ambient temperature. Under these conditions, **4**, was isolated as the tosylate salt following workup and crystallisation from *i*-PrOH in 92% yield. The choice of acid utilised in the debenzylation reaction was very important. *p*-TsOH afforded the cleanest product with an acceptable physical form of the product **4** and purge of amide impurities; other acids (HCl, H_2SO_4, MsOH, AcOH) gave a much poorer impurity profile by HPLC.

An interesting impurity **13** was isolated and identified in the preparation of **9**. Proposed mechanisms are suggested (Scheme 4) for the formation of **13** under different chemical conditions. These are based on experimental observations, which demonstrated that formation of **13** is dependent on the temperature during addition of **8** to the PCl_5 slurry with either DCM or MeCN as the solvent. Interestingly with DCM as the solvent, higher temperatures suppressed the rearrangement compared to MeCN/cat. DMF where lower temperatures suppressed the formation of **13**. It is proposed that the conversion of **15** to **10** is faster in MeCN than the conversion of **14** to **10** in DCM, at low temperature, accounting for the temperature dependence. Conversion of **10** to **13** is not observed even on prolonged reaction or heating.

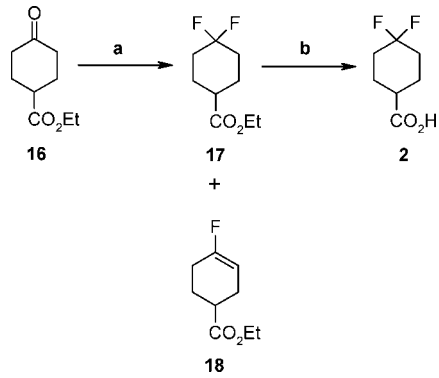
This process from **8** to **4** was successfully scaled to our Kilo Laboratory facility without any significant issues. In the preparation of amide **8**, the initial isolated yield was lower than anticipated (68%) although reaction completion was reached, but second cropping following concentration of the mother liquors increased the overall yield to 77%. Triazole **9** was isolated in 73% yield, and none of the cyclic impurity **13** was detected. The N-debenzylation of the triazole **9** was completed in several batches in the laboratory for convenience to furnish 3.5 kg of the triazole fragment **4**.

2.2. Synthesis of Difluorocyclohexylcarboxylic Acid, 2. Ethyl-4-oxocyclohexanecarboxylate (**16**) was identified as a potential starting material to obtain the acid **2** (Scheme 5).[9] *gem*-Difluorination of **16** with diethylamino sulfur trifluoride (DAST) gave a 96% crude yield of the difluoro ester **17** which contained approximately 20% of the vinyl fluoride impurity **18**. Hydrolysis of crude **17** with aqueous sodium hydroxide gave **2** in 92% yield, with approximately 20% of the corresponding vinyl fluoride acid. Although this synthesis was demonstrated by Medicinal Chemistry on small scale, safety issues with the use of DAST (very strong exothermic activity observed from 131 °C to 163 °C,[10] −1215.52 J/g, very energetic decomposition at

(9) Mackenzie, A. R.; Marchington, A. P.; Middleton, D. S.; Meadows, S. D. PCT Int. Appl. WO97/27185, 1997.

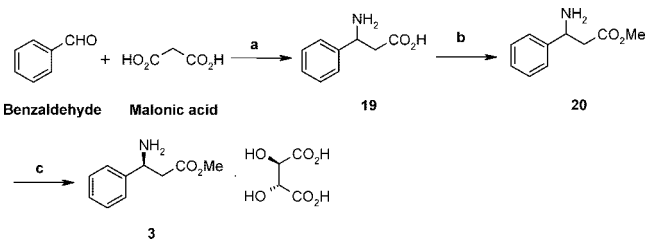
(10) DAST DSC Data for (diethylamino)sulfur trifluoride shows strong exothermic activity from 131 °C to 163 °C with a peak temperature at 162 °C, energy of −1215.52 J/g and heat flow of −32.33 W/g. Sample (11.4 mg) was heated from 25 °C to 350 °C at a rate of 5 K/min.

Scheme 5. **Synthesis of 2**[a]



[a] Reagents and conditions: (a) DAST, 96%; (b) NaOH, THF, 92%.

Scheme 6. **Synthesis of 3**[a]



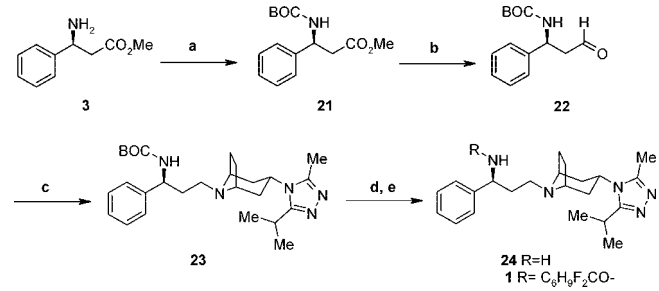
[a] Reagents and conditions: (a) $NH_4^+HCO_2^-$, EtOH, 55−80 °C, 44%; (b) H_2SO_4, MeOH, −5 °C−rt, 90%; (c) L-(+)-tartaric acid, MeOH, 21%.

50−60 °C)[11] and the need to control the vinyl fluoride impurities to low levels due to toxicity issues prevented further scale-up. Consequently, preparation of **2** was transferred to a specialist fluorination company and was developed to reduce the level of vinyl fluoride impurities to an acceptable limit.[12,13]

2.3. Synthesis of *β*-Amino Ester, 3. *β*-Amino ester **3** (Scheme 6) was synthesized according to literature procedures.[14] Benzaldehyde was condensed with ammonium acetate and malonic acid to yield the racemic *β*-amino acid **19**. During scale-up in the laboratory, a solid coating of ammonium acetate was observed on the condenser, which would have serious implications if this were transferred to our Kilo Laboratory facility. The amine source was consequently changed to ammonium formate, and no issues were observed with solid deposits during further laboratory and Kilo Laboratory scale-up. Esterification of **19** with methanol and 2 equiv of H_2SO_4 gave *β*-amino ester **20**. The racemic *β*-amino ester **20** was resolved using L-(+)-tartaric acid to provide the desired *β*-amino ester **3** as the L-(+)-tartaric acid salt in 10% overall yield from benzaldehyde (Scheme 6).[14] Resolution of **20** was only moderately efficient, with two recrystallisations required to achieve the desired enantiomeric excess of >95%.

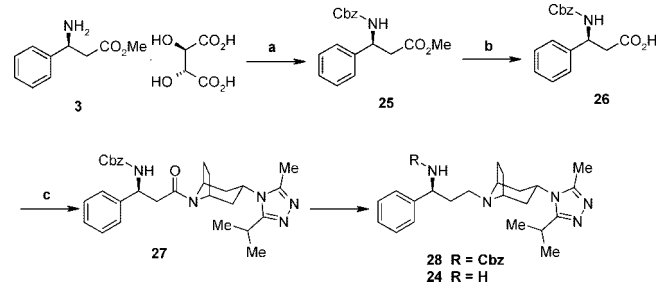
2.4. Coupling of the Fragments: Strategy 1. As the difluoro acid **2** was available in only limited quantities for initial route development work and scale-up, a strategy was sought which relied on late introduction of this fragment. This allowed completion of the majority of the synthesis to the advanced intermediate **24**, prior to delivery of the difluoro acid fragment **2**, thereby enabling delivery of initial bulk to very tight timelines.

Scheme 7. **Medicinal Chemistry route**[a]



[a] Reagents and conditions: (a) BOC_2O, THF, 2 M NaOH, quantitative; (b) DIBAL-H, DCM, −78 °C, 90%; (c) **4**, $NaBH(OAc)_3$, AcOH, DCM, rt, 66%; (d) 2.25 M HCl, MeOH, reflux, 91%; (e) 4-4-difluorocyclohexane carboxylic acid, *N*-benzyl-*N*′-cyclohexylcarbodiimide-polymer bound, DCM, rt, 48%.

Scheme 8. **Coupling of the fragments: strategy 1**[a]



[a] Reagents and conditions: (a) BnOC(O)Cl, $Na_2CO_{3\ aq}$, DCM, quantitative; (b) 1 M NaOH, 73%; (c) (i) $SOCl_2$, (ii) **4**.*p*-TsOH, 75%.

The Medicinal Chemistry route to Maraviroc was based on partial reduction of BOC protected ester **21** to its corresponding aldehyde **22** followed by reductive amination and deprotection to yield amine **24** (Scheme 7).[6] Initial studies by the Medicinal Chemistry group indicated that the use of DIBAL-H required cryogenic conditions in order to prevent over reduction to the primary alcohol. Our concerns over the potential robustness of this step led us to explore alternate routes avoiding the partial reduction of **21**.

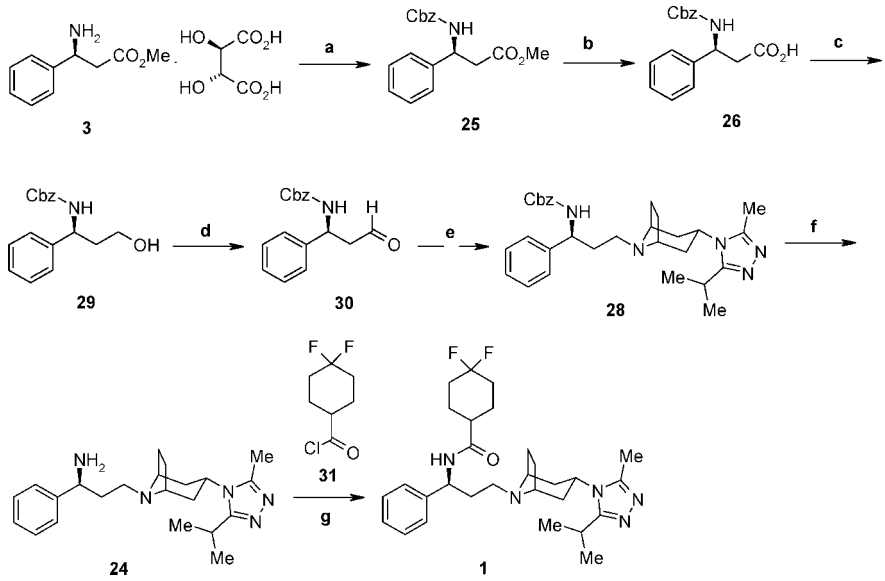
Our first route was based on the reduction of amide **27** to its corresponding amine **28**, with the same final bond-forming step to **1** as in the Medicinal Chemistry synthesis (Scheme 8). The Cbz group was selected for protection of the *β*-amino ester **3**, as it was hoped that this would provide solid intermediates and also potentially allow concomitant deprotection in the amide reduction step.[15]

Protection of **3** with benzyl chloroformate was carried out under modified Schotten−Baumann conditions and was followed by hydrolysis to the corresponding acid **26** in 73% overall yield. Activation of the acid **26** with thionyl chloride followed by reaction with triazole **4**·*p*-TsOH furnished amide **27** in 51% yield.

A screen for the reduction of the amide **27** revealed that conversion to amine **28** was not trivial. Whilst no reaction was observed with sodium borohydride ($NaBH_4$/

(11) DAST decomposition data: *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Urben, P. G., Ed.; Butterworth-Heinemann: Oxford, Boston; 1999; Vol. 1, p 560.
(12) Lal, G. S.; Pez, G. P. Eur. Patent Appl. EP0905109, 1999.
(13) Lal, G. S.; Pez, G. P. U.S. Patent Appl. U.S. 6,222,064, 2001.
(14) Wasserman, H. H.; Berger, G. D. *Tetrahedron* **1983**, *39*, 2459–2464.
(15) Giannis, A.; Sandhoff, K. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 218–220.

Scheme 9. **Coupling of the fragments: strategy 2**[a]



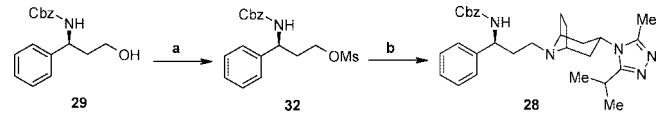
[a] Reagents and conditions: (a) BnOC(O)Cl, $NaHCO_{3\ aq}$, DCM, quantitative; (b) 1 M NaOH, 90%; (c) BH_3·THF, THF, 70%; (d) SO_3·py, Et_3N, DMSO, DCM, assumed quantitative; (e) **4**.*p*-TsOH, $NaBH(OAc)_3$, DCM, AcOH, 80%; (f) $Pd(OH)_2$, H_2, 50 psi, MeOH, 80%; (g) **31**, DCM, $Na_2CO_{3\ aq}$, 59%.

$TiCl_4$, $NaBH_4/Et_3O^+BF_4^-$),[16,17] other reducing agents (Red-Al, $LiBH_4$/DIPA, DEANB, and BH_3·DMS)[18−21] cleaved the Cbz group in preference to reduction of the amide. Limited success was achieved with BH_3·THF[22] and $LiBH_4/Me_3SiCl$;[15] some reduction to the desired amine **28** was observed but as a minor component of the reaction. Cbz deprotection was the major reaction product by HPLC. These results encouraged the search for a new approach for coupling of the fragments.

2.5. Coupling of the Fragments: Strategy 2. Another potential route to **1** involved coupling of the tropane fragment **4** and the chiral β-aminoaldehyde fragment **30** via reductive amination (Scheme 9). The aldehyde **30** was prepared in four steps from β-amino ester **3**. Protection and hydrolysis to **26** followed by borane-mediated reduction to **29** and oxidation under Parikh−Doering conditions (SO_3·py, DMSO, Et_3N) afforded the desired aldehyde **30**. Direct reduction of **25** to **29** proved difficult, unless the cryogenic conditions were employed. Fortunately, hydrolysis of the ester to the acid facilitated reduction with BH_3·THF to alcohol **29**. Purification of the intermediates (Scheme 9) was difficult because only **26** and **29** were crystalline. The aldehyde **30** was isolated as a toluene concentrate because stability was a potential concern. Consequently, all nonsolid intermediates were progressed without purification.

Reductive amination of amine **4** with aldehyde **30** was carried out using sodium triacetoxyborohydride in DCM. The amine **4** could be used directly as the tosylate salt, avoiding a low-yielding salt break, a consequence of the high water solubility of **4**. The coupled amine **28** was isolated in 80% yield as a crude oil after workup. Deprotection of **28** was accomplished by hydrogenolysis (10% $Pd(OH)_2$, H_2, 50 psi, MeOH) to form the desired amine **24** as an oil in 80% yield. Completion of the synthesis required coupling of the difluoro acid **2** with amine **24**. The acid **2** was converted to the acid chloride **31** by reaction with thionyl chloride and was isolated as a toluene concentrate in quantitative yield as judged by ^1H NMR. The conversion to **31** was highly dependent on the ratio of thionyl chloride to toluene. A molar ratio of ≥1.3:1 thionyl chloride/toluene was required for reaction completion. The excess thionyl chloride was removed during the distillation workup. Acylation of **24** with a toluene solution of the acid chloride **31** under modified Schotten−Baumann conditions (DCM, Na_2CO_3, water) afforded **1** in 59% yield following crystallisation from ethyl acetate.

Scheme 10. **Coupling of the fragments: strategy 3**[a]



[a] Reagents and conditions: (a) MsCl, Et_3N, DCM, 99%; (b) **4**·*p*-TsOH, solvent, base, 20%.

A third alternate examined involved activation of alcohol **29** to **32** with methanesulfonyl chloride followed by nucleophilic displacement with amine **4** (Scheme 10). Disappointingly, although the mesylate **32** was prepared in high yield (99%), attempted substitution with amine **4** and a range of bases and solvents resulted in mixtures of predominantly unreacted starting materials, desired product **28**, and an unknown impurity. On storage, degradation of the mesylate **32** was also observed, and this approach was terminated due to stability concerns of this intermediate.

(16) Kano, S.; Tanaka, Y.; Sugino, E.; Hibino, S. *Synthesis* **1980**, *9*, 695–697.
(17) Borch, R. F. *Tetrahedron Lett.* **1968**, *10*, 61–65.
(18) Tatee, T.; Kurashige, S.; Shiozawa, A.; Narita, K.; Takei, M.; Ito, S.; Miyazaki, H.; Yamanaka, H.; Mizugaki, M.; Sakamoto, T.; Fukuda, H. *Chem. Pharm. Bull.* **1986**, *34*, 1634–1642.
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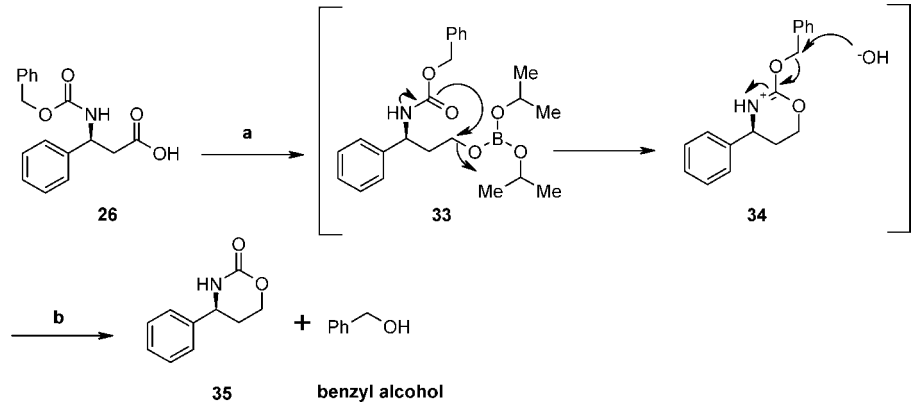
(21) Brown, H. C.; Narasimhan, S.; Choi, Y. M. *Synthesis* **1981**, *12*, 996–997.
(22) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912.

Scheme 11. **Proposed mechanism for formation of cyclic carbamate 35**[a]



[a] Reagents and conditions: (a) (i) BH_3·THF, (ii) acetone; (b) 1 M NaOH.

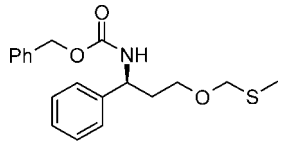


Figure 1. **Pummerer rearrangement impurity.**

2.6. Kilo Laboratory Campaign. The reductive amination route (Scheme 9) was scaled to our Kilo Laboratory facility to support toxicology demands for Maraviroc. The chemistry generally proved to be robust although some scale-up issues were encountered. To minimise hydrogen evolution during the quench of the borane reduction of **26**, the process was amended to include addition of acetone (5 equiv) on reaction completion, to quench unreacted excess hydrides. On scale-up in the laboratory, this process generated varying quantities of a cyclic carbamate impurity **35** during workup. The proposed mechanism for formation of **35** involves the isopropyl boronate ester acting as a leaving group (Scheme 11).

Fortunately only small amounts of the impurity **35** were formed during scale-up in the Kilo Laboratory, and the alcohol was obtained as a crude solid in 70% yield contaminated with approximately 5% benzyl alcohol. During scale-up of the oxidation of **29** an increase in the Pummerer rearrangement product, methyl thiomethyl ether (Figure 1), was observed, from the typical level of 10% in the laboratory to 18% on 2.6 kg scale.

Subsequent investigations showed that changing the base from Et_3N to Hünig's base suppressed the formation of this byproduct to less than 5%.[23] The Cbz deprotection required several catalyst recharges to reach reaction completion, presumably due to catalyst poisoning from residual sulfur impurities entrained from the preceding oxidation. The final step acylation gave a disappointing 1.1 kg (37% yield) on scale-up compared to 59% laboratory yield although a further 507 g of **1** was isolated from the mother liquors via an acid/base cycle followed by crystallisation from ethyl acetate, increasing the yield to 54% for this step.

(23) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651–1660.
(24) (a) Mamaev, V. P. *Zh. Obshch. Khim.* **1957**, *27*, 1290. (b) Johnson, T. B.; Lival, J. E. *J. Am. Chem. Soc.* **1936**, *4A*, 134. (c) Cardillo, G.; Gentilucci, L.; Tolomelli, A.; Tomasini, C. *J. Org. Chem.* **1998**, *63*, 2351.

3. Conclusion

In summary a scaleable 12-step route to **1** was developed and used to produce within 4 months 1.6 kg of high chemically and chirally pure material suitable for clinical supply. The developed route has several advantages over the original Medicinal Chemistry synthesis. All chromatographic purifications were removed and noncryogenic conditions for the reduction of the acid **26** were developed suitable for scale-up. Biphasic Schotten−Baumann type coupling conditions for the acylation of **7** increased the yield to 75% accompanied by a purge of the unwanted *endo*-isomer in the workup. Triazole **9** was isolated as a solid following workup with an increased yield of 75% with unreacted amide **8** purged in the triazole crystallisation. The overall yield of the triazole was increased from 13.5% (using the original conditions) to 44%. Finally the overall yield for the sequence was increased to 31% compared to 27% originally. Further process research and development to support the ongoing progression of **1** through clinical trials will be reported in a separate article.

4. Experimental Section

4.1. General. All raw materials, reagents, and solvents were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing by TLC, HPLC, or ^{1}H NMR. TLC was performed using one of the following systems: 2:1 or 1:1 ethyl acetate/hexane visualised under UV or with Dragendorff reagent. HPLC analysis was performed using the following systems: Discovery C18 reverse phase column 4.6 mm × 50 mm, 5 μ; mobile phase consisting of solvent A 97.5% water, 2.45% MeCN, 0.05% TFA, solvent B 97.5% acetonitrile, 2.45% water, 0.05% TFA. Eluent gradients ranged from 0−100% mobile phase B; λ 210 nm.

4.2. 4,4-Difluoro-*N*-{(1*S*)-3-[*exo*-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide (1). Amine **24** (2.07 kg, 5.63 mol) was dissolved in dichloromethane (32.2 L) at ambient temperature, treated with a solution of saturated aqueous sodium carbonate (8.9 L) and water (33.1 L) and the mixture was cooled to 15 °C. A solution of **31** (1.54 kg, 8.45

mol) in toluene (5 L) was added to the reaction mixture (a 3 °C exotherm was observed), and the resultant mixture was stirred for 0.5 h at ambient temperature. The mixture was separated, and the aqueous phase was washed with dichloromethane (20.7 L). The combined organic phases were washed with 2 M sodium hydroxide (20.7 L) followed by water (20.7 L). The organic phase was concentrated and replaced with ethyl acetate (12.4 L) and concentrated to 8 L total volume. The mixture was cooled, granulated at 0 °C overnight, and filtered, and the solid was washed with ethyl acetate (4.0 L) and dried *in vacuo* (40 °C) for 12 h to give **1** as a white crystalline solid (1.08 kg, 37%). Mp 193.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.36 (m, 2), 7.23 (m, 3), 6.61−6.48 (m, br, 1), 5.15 (m, 1), 4.28 (m, 1), 3.36 (d, br, 2), 2.85 (m, 1), 2.48 (s, 3), 2.28 (m, 2), 2.18−1.61 (m, 19), 1.39 (d, 6). ^{1}H NMR (500 MHz, DMSO) δ [ppm] 8.22 (d, 1), 7.30(m, 4), 7.20 (m, 1), 4.96 (dt, 1), 4.21 (tt, 1), 3.28 (m, 1), 3.27 (m, 1), 3.13 (septet, 1), 2.38 (s, 3), 2.33 (t, 2), 2.32 (m, 1), 2.06−1.63 (m, 4), 2.03−1.82 (m, 2), 2.03−1.76 (m, 2),1.91−1.65 (m, 4), 1.82−1.6 (m, 2), 1.81 (m, 2), 1.74−1.56 (m, 2), 1.24 (d, 6). ^{13}C NMR (125 MHz, DMSO) δ [ppm] 12.2, 21.7, 24.7, 25.4 (J ^{13}C−^{19}F 9 Hz), 25.6 (J ^{13}C−^{19}F 9 Hz), 25.8, 25.9, 32.1 (J ^{13}C−^{19}F 24, 7 Hz), 32.3 (J ^{13}C−^{19}F 24, 7 Hz), 35.5, 35.8, 40.9, 46.7, 48.0, 50.3, 58.2, 58.4, 123.6, 126.2, 126.4, 128.1, 144.1, 149.6, 158.4, 172.9. FT-IR (cm^{-1}): 3264 (NH, 2° amide); 3062, 3022 (CH, aryl); 2955−2825 (CH, alkyl); 1662 (C═O, amide); 1531 (NH, amide); 1513, 1494 (C═C, aryl, *C*═N); 1453 (C−CH_3 asymmetric); 1432 (C−CH_2, scissor vibration); 1370 (C−CH_3, symmetric); 1290−1195 (CH in plane deformations, aryl); 1103 (CF); 962 (C−CH_3 rock), 754, 702 (CH out of plane deformations, monosubstituted aromatic). MS *m*/*z* 514.4 $[M + H]^+$. Anal. Calcd for $C_{29}H_{41}F_2N_5O$: C, 67.75; H, 8.06; N, 13.54. Found: C, 67.81; H, 8.04; N, 13.63.

4.3. 4,4-Difluorocyclohexanecarboxylic Acid (2). The ester **17** (44 g, 0.229 mol) was slurried in methanol (100 mL) and water (100 mL) at ambient temperature, sodium hydroxide (10.1 g, 0.252 mol) was added and the mixture stirred at ambient temperature for 15 h. Concentrated hydrochloric acid was added to adjust the mixture to pH 1, and stirring continued at ambient temperature for 15 h. The mixture was extracted with dichloromethane (3 × 300 mL). The organic extracts were combined and concentrated *in vacuo*, then purified by chromatography (90/10 v/v pentane/EtOAc) to yield crude **2** as a crystalline white solid (23 g). Further purification by two recrystallisations from hexane, furnished **2** as a crystalline white solid (19 g, 51%). Mp 105.9 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.54−1.65 (m, 2) 1.88 (s, 6) 2.40 (s, 1). ^{19}F NMR (500 MHz, $CDCl_3$) δ ppm −101−99 (d, 1) −96−94.2 (d, 1). MS *m*/*z* 163 $[M - H]^-$.

^{19}F NMR (300 MHz, $CDCl_3$) δ [ppm] (**vinyl fluoride acid**) −102.8 (s, 1).

4.4. Methyl (*S*)-3-Amino-3-phenylpropanoate (3·L-(+)-Tartaric Acid). L-(+)-Tartaric acid (5.61 kg, 37.39 mol) in methanol (43.6 L) was heated to 40 °C. A methanol solution of **20** (6.7 kg, 37.39 mol in ∼12 L methanol) was added, and the mixture was heated to reflux until complete solution was obtained. The resultant solution was cooled to 40 °C over 2 h. A seed from a laboratory batch was added (in the absence of seed the reaction can be cooled to 10 °C to initiate crystallisation), and the mixture was cooled to ambient temperature over 4 h and held for 15 h. The resultant solid was collected by filtration, washed with methanol (8.6 L), and dried *in vacuo* (40 °C) to give **3** as the L-(+)-tartrate salt (4.16 kg, 33%).

3·L-(+)-tartrate salt (11.1 kg, 33.71 mol) was slurried in methanol (98.1 L) at ambient temperature. The mixture was heated to reflux until a solution was obtained, and then it was cooled to 40 °C over 2 h. A seed was added, and the mixture cooled to ambient temperature over 4 h and stirred for 15 h. The reaction was filtered, washed with methanol (10 L), and dried in vacuo (40 °C) to yield **3**·L-(+)-tartrate salt as a white crystalline solid (6.9 kg, 63%, 95% ee by HPLC). Mp 179.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 7.40−7.25 (m, 5), 4.43 (t, 1), 3.68 (s, 3), 2.66 (d, 2), 1.70 (s, 2). MS *m*/*z* 180.3 $[M + H]^+$.

4.5. 3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-*exo*-8-azabicyclo[3.2.1]octane *p*-Toluenesulfonic Acid Salt (4·*p*-TsOH). Triazole **9** (600 g, 1.85 mol) and *p*-toluenesulfonic acid monohydrate (351 g, 1.85 mol) were dissolved in methanol (3 L), and 10% palladium on carbon (60 g, 10 wt %) was added. The mixture was stirred under an atmosphere of hydrogen at 50 psi at ambient temperature for 12 h. The reaction mixture was filtered through Arbocel (filtration aid), and the filter pad was washed with methanol (500 mL). The methanol was evaporated under reduced pressure, and the resultant brown oil was dissolved in hot *i*-propanol (1.8 L). The solution was allowed to granulate at room temperature for 12 h and then at 0 °C for 2 h. The white solid was filtered off and dried *in vacuo* (50 °C) for 12 h to give **4** as the tosylate salt (623 g, 83%). Mp 117.0 °C. ^{1}H NMR (300 MHz, CD_3OD) δ [ppm] 7.71 (d, 2), 7.23 (d, 2), 4.54 (m, 1), 4.23 (s, br, 2), 3.30−3.25 (m, 1), 2.52 (s, 3), 2.47−2.43 (m, 2), 2.36 (s, 3), 2.22−2.10 (m, 6), 1.34 (d, 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.23 (d, J = 6.84 Hz, 18 H) 2.01 (s, 18 H) 2.28 (s, 15 H) 3.15−3.38 (m, 13 H) 4.23−4.38 (m, 3 H) 7.12 (d, J = 7.82 Hz, 6 H) 7.50 (d, J = 8.06 Hz, 5 H). ^{13}C NMR (75 MHz, CD_3OD) δ [ppm] 11.30, 20.20, 21.07, 25.38, 25.46, 33.25, 46.25, 55.34, 125.74, 128.79, 140.74, 142.33, 151.43, 160.36.

4.6. *exo*-8-Benzyl-8-azabicyclo[3.2.1]oct-3-ylamine (7). Sodium metal (24.3 g, 1.06 mol) was added in pieces to toluene (300 mL) at ambient temperature, and the mixture was heated to reflux. A solution of **6** (20.0 g, 87 mmol) in toluene (200 mL) and *n*-pentanol (120 mL) was added slowly over 15 min to the refluxing reaction when gas evolution was observed. The resultant mixture was heated at reflux for 2 h to ensure complete consumption of sodium when a thick white slurry formed. The reaction was cooled to 80 °C, *i*-propanol (200 mL) was added, and the reaction was allowed to cool to ambient temperature before water (700 mL) was added. Concentrated hydrochloric acid (140 mL) [exothermic] was added to adjust the aqueous layer to pH 1. The mixture was stirred for 15 min, and the layers were separated. Ethyl acetate (700 mL) was added to the aqueous layer, which was adjusted to pH 12 by the addition of 10 M aqueous sodium hydroxide (40 mL). The layers were separated, and the organic layer was concentrated under reduced pressure to yield a pale-yellow oil. *n*-Pentanol contained in the oil was removed by azeotropic distillation with water (200 mL)

followed by azeotropic distillation with toluene (200 mL) to give **7** (18.0 g, 95%) as a pale-yellow oil containing traces of toluene. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] (***exo*-isomer**) 7.37 (d, 2), 7.30 (m, 2), 7.26−7.18 (m,1), 3.57 (s, 2), 3.19 (s, br, 2), 2.95 (m, 1), 2.00 (m, br, 2), 1.76−1.64 (m, br, 2), 1.58 (d, 2), 1.48 (m, 2), 1.40−1.20 (m, br, 2). MS *m*/*z* 217.3 $[M + H]^+$.

^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] (***endo*-isomer**) 7.37 (d, 2), 7.32−7.27 (m, 2), 7.25−7.19 (m,1), 3.52 (s, 2), 3.25 (t, 1), 3.14 (s, br, 2), 2.19−2.09 (m, 2), 2.03 (s, br, 4), 1.39 (d, 2), 1.31 (s, br, 2).

4.7. *exo*-*N*-(8-Benzyl-8-azabicyclo[3.2.1]oct-3-yl)-2-methylpropanamide (8). A mixture of **7** (5.0 kg, 23.15 mol), dichloromethane (25 L), sodium carbonate (6.9 kg), water (50 L) was cooled to 0 °C, and isobutyryl chloride (2.9 L, 27.57 mol) was added over 30 min whilst maintaining the temperature below 10 °C. The resultant mixture was warmed to ambient temperature and was stirred for 0.5 h. Dichloromethane (5 L) was added, the aqueous phase adjusted to pH 9 with sodium carbonate, and the phases were separated. The organic layer was washed with 1 M NaOH (5 L) and then concentrated under reduced pressure, then distilled and replaced with ethyl acetate (20 L) to a final volume of 15 L. The solution was cooled to 0 °C over 4 h and held at that temperature for 2 h. The white solid formed was collected by filtration and dried *in vacuo* (40 °C) to afford **8** (4.48 kg, 68%). The liquors were evaporated under reduced pressure to a total volume of 8 L, and the solution was cooled to 0 °C over 6 h and held at 0 °C for 2 h. The white crystalline solid was filtered, washed with ethyl acetate (1 L), and dried *in vacuo* (40 °C) to give a second crop of **8** (580 g, 9%; overall yield: 5.06 kg, 77%). Mp 138−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.40−7.20 (m, 5), 5.15 (m, 1), 4.10 (m, 1), 3.20 (s, 2), 2.27 (m, 1), 2.02 (m, 2), 1.80 (m, 2), 1.70 (m, 2), 1.60 (s, 2), 1.47 (t, 2), 1.10 (d, 6). ^{13}C NMR (75 MHz, CD_3OD) δ [ppm] 19.59, 26.35, 35.67, 38.38, 41.00, 56.24, 58.94, 126.95, 128.24, 128.66, 139.35, 176.25. MS *m*/*z*: 287.4 $[M + H]^+$.

4.8. *exo*-8-Benzyl-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane (9). A mixture of dichloromethane (34.3 L) and PCl_5 (4.05 kg, 19.45 mol) was cooled to −5 °C. A solution of **8** (4.28 kg, 14.94 mol) in dichloromethane (11.5 L) was added over 1.5 h keeping the temperature below 10 °C. The solution warmed to ambient temperature over 0.5 h and held at this temperature for 2 h, then cooled back to −5 °C. A solution of acetic hydrazide (1.76 kg, 23.79 mol) in 2-methyl-2-butanol was prepared by dissolving the acetic hydrazide in acetonitrile (6.63 L) and 2-methyl-2-butanol (12.5 L), and then concentration to approximately 7.0 L by distillation under reduced pressure. The acetic hydrazide solution was added to the reaction mixture over 0.5 h keeping the temperature below 10 °C. The resultant solution was warmed to ambient temperature and stirred for 15 h. The reaction was complete by HPLC analysis after 0.5 h, but was held here for convenience. The mixture was cooled to −5 °C, and 2 M NaOH (45.7 L) was added, keeping the temperature below 10 °C. The aqueous layer was adjusted from pH 6 to pH 9 with 10 M NaOH (∼0.5 L), and the layers were separated. The organic layer was concentrated under reduced pressure, distilling and replacing with 2-methyl-2-butanol (10 L) to a total volume of 11 L. Acetic acid (1.4 L) was added and the solution heated to 80 °C for 2 h. The solution was cooled to 0 °C and treated with 2 M sodium hydroxide (12 L), followed by 10 M sodium hydroxide to adjust the aqueous phase to pH 12. The layers were separated, and the aqueous layer was washed with ethyl acetate (3 L). The combined organic layers were concentrated to low volume, and heptane (20 L) was added. The mixture was further concentrated to 15 L under reduced pressure. Ethyl acetate (1.6 L) was added, and the mixture was heated to 75 °C for 2 h, then cooled to 0 °C over 2.5 h and held for 2 h. The resultant solid formed was collected by filtration, washed with heptane (3 L), and dried *in vacuo* (40 °C) overnight to give **9** as a white crystalline solid (3.54 kg, 73%). Mp 148.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 7.40−7.25 (m, 5), 4.30 (m, 1), 3.60 (s, 2), 3.37 (s, 2), 3.07 (m, 1), 2.60 (s, 3), 2.40−2.15 (m, 4), 1.70 (m, 4), 1.40 (d, 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.25 (d, J = 6.84 Hz, 18 H) 1.63−1.76 (m, 12 H) 2.03−2.16 (m, 12 H) 3.11−3.20 (m, 3 H) 3.27 (s, 6 H) 4.21−4.31 (m, 3 H) 7.23 (t, J = 7.21 Hz, 3 H) 7.33 (t, J = 7.57 Hz, 6 H) 7.36−7.40 (m, 6 H). ^{13}C NMR (75 MHz, CD_3OD) δ [ppm] 13.20, 21.67, 25.82, 26.41, 37.04, 47.31, 56.58, 58.89, 127.17, 128.37, 150.75, 159.10. MS *m*/*z* 325.3 $[M + H]^+$.

4.9. (1*R*,4*R*,6*R*)-9-Benzyl-4-chloro-8-isopropyl-7,9-diazabicyclo[4.3.1]dec-7-ene (13): ^{1}H NMR (500 MHz, $CDCl_3$) δ [ppm] 11.56 (br s, 1), 7.44 (br s, 3), 7.14 (br s, 2), 4.97 (d, J = 16.8 Hz, 1), 4.57 (d, J = 16.8 Hz, 1), 4.38 (br s, 2), 3.80 (br s, 1), 3.21 (m, 1), 3.12 (br s, 1), 1.70−2.51 (m, 7 H) 1.51 (br s, 6 H). MS *m*/*z* 305.2 $[M + H]^+$. FT-IR (cm^{-1}): 3061−3031 (CH, aryl); 2937−2821 (CH, alkyl); 1625−1497 (C═C); 1454 (C−CH_3 asymmetric); 1372 (C−CH_3 symmetric); 1327 (CH bend, alkyl); 1284−1031 (CH in plane deformations, aryl); 740, 717 (CH out of plane deformation vibrations, monosubstituted aromatic); 702 (C−Cl).

4.10. 4,4-Difluorocyclohexanecarboxylic Acid Ethyl Ester (17). DAST (200 mL, 2.0 mol) was dissolved in dichloromethane (1.5 L) at 0 °C, to which was added a solution of the ester **16** (130 g, 0.764 mol) in dichloromethane (500 mL) over 20 min. The mixture was allowed to warm to ambient temperature overnight. Water (250 mL) was added carefully (CAUTION: strong exotherm). A 10% aqueous solution of sodium bicarbonate (2.9 L) was slowly added over 2 h and stirred for a further 18 h. The mixture was separated, and the aqueous phase was extracted with dichloromethane (1.0 L). The combined organic phase was concentrated to an orange oil and purified by distillation under reduced pressure to yield crude **17** as a yellow oil (110.7 g).

^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.26−1.31 (t, 3) 1.97−2.04 (m, 4) 1.97−2.04 (m, 2) 2.06−2.16 (m, 2) 2.25−2.36 (m, 1) 4.14−4.2 (q, 2). ^{19}F NMR (500 MHz, $CDCl_3$) δ ppm −100.5−99.3 (d, 1) −95.3−94.2 (d, 1).

4.11. 3-Amino-3-phenylpropanoic Acid (19). Malonic acid (2.45 kg, 23.6 mol) and ammonium formate (2.96 kg, 47.2 mol) were slurried in ethanol (8.25 L) at ambient temperature and heated to 60 °C; benzaldehyde (2.39 L, 23.6 mol) was added, maintaining the temperature below 65 °C. The reaction was heated to reflux for 4 h then cooled to ambient temperature

over 6 h. The mixture was stirred at ambient temperature for 12 h, filtered, washed with ethanol (2 × 1.5 L), and dried *in vacuo* (40 °C) to give acid **19** as a white crystalline solid (1.7 kg, 44%). Mp 224.0 °C (lit. 220−227 °C,[24a] 216 °C,[24b] 216−218 °C,[24c]). ^{1}H NMR (300 MHz, D_2O) δ [ppm] 7.55−7.16 (m, 5), 4.60−4.50 (t, 1), 2.97−2.51 (m, 2).

4.12. Methyl 3-Amino-3-phenylpropanoate (20). 19 (4.02 kg, 24.33 mol) was slurried in methanol (24 L) and cooled to −10 °C; concentrated sulfuric acid (2.58 L) was added to the mixture over 1 h, maintaining the temperature below 5 °C. On completion of the addition, the reaction was warmed to ambient temperature and stirred for 5 h. The reaction mixture was reduced in volume to 12 L by atmospheric distillation and was then cooled to ambient temperature. Dichloromethane (48 L) was added, the biphasic solution was cooled to 5 °C, and 2 M sodium hydroxide (20 L) was added to adjust the pH of the aqueous layer to ∼12. The phases were separated, and the aqueous phase was extracted further with dichloromethane (16 L). The organic extracts were combined and washed with water (8 L) and concentrated at atmospheric pressure, replacing the solvent with methanol (16 L) to a total volume of 16 L. The solution was cooled to ambient temperature giving **20** as a methanol concentrate. A small amount of sample was concentrated to dryness to obtain spectral data. The yield was estimated to be 90%, determined from ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 7.35−7.26 (m, 5), 4.41 (t, 1), 3.68 (s, 3), 2.67 (d, 2), 1.76 (s, 2).

4.13. (1*S*)-3-[*exo*-3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylamine (24). A solution of amine **28** (309 g, 0.62 mol) in methanol (3.1 L) was treated with palladium(II) hydroxide (31 g, 10 wt %, and the resultant slurry was stirred under an atmosphere of hydrogen at 50 psi for 12 h at ambient temperature. The reaction mixture was filtered through Arbocel (filtration aid), and the filter pad was washed with methanol (500 mL). The methanol solution was concentrated to afford **24** as a white foam (176 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.30 (m, 5), 4.30 (m, 1), 4.10 (m, 1), 3.37 (m, 2), 3.00 (m, 1), 2.42 (m, 5), 2.20 (m, 2), 2.05 (m, 2), 1.85 (m, 2), 1.42 (m, 4), 1.37 (m, 6).

4.14. Methyl (*S*)-3-[(Benzyloxycarbonyl)amino]-3-phenylpropanoate (25). 3. L-(+)-Tartrate salt (4.9 kg, 14.9 mol) was slurried in dichloromethane (24.5 L) and treated with a solution of sodium carbonate (5.3 kg) in water (19.2 L); the reaction mixture was cooled to 0 °C. Benzyl chloroformate (2.55 L, 17.9 mol) was added while maintaining the temperature below 10 °C, and upon completion of the addition the reaction was warmed to 20 °C. Dichloromethane (10 L) and water (20 L) were added, the phases were separated, and the aqueous phase was extracted with dichloromethane (6.13 L). The organic extracts were combined and washed with sodium carbonate solution (2.65 kg in 9.6 L water) followed by water (12.25 L). The organic layer was concentrated under reduced pressure, distilling and replacing with *i*-propanol (6.37 L) to a total volume of ∼6.62 L. The mixture was cooled to 20 °C and diluted with methanol (3.43 L) giving **25** as an *i*-propanol/methanol solution. Yield assumed quantitative. A small amount of sample was concentrated to dryness to obtain spectral data. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 7.32 (m, 10), 5.72 (d, br, 1), 5.17 (m, 1), 5.10 (s, 2), 3.61 (s, 3), 2.88 (m, 2).

4.15. (*S*)-3-[(Benzyloxycarbonyl)amino]-3-phenylpropanoic Acid (26). An *i*-propanol/methanol solution of **25** (4.66 kg, 14.86 mol in ∼1 L *i*-propanol, 3.43 L methanol) was stirred with 1 M sodium hydroxide (37.15 L, 37.15 mol) at ambient temperature for 2 h. Dichloromethane (23.35 L) was added and the biphasic solution separated. The organic phase was stirred with 6 M hydrochloric acid, and the phases were separated. The aqueous phase was washed with dichloromethane (23.35 L). The organic extracts were combined and washed with water (14.0 L) and concentrated under reduced pressure, distilling and replacing with ethyl acetate (9.34 L) to a total volume of 12 L. The mixture was cooled to 20 °C to allow precipitation of the product. The slurry was diluted with heptane (28.0 L) and was granulated overnight at ambient temperature. The resultant solid was collected by filtration and dried *in vacuo* (40 °C) to give **26** as a white crystalline solid (4.02 kg, 90.3%). Mp 225.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 7.38−7.25 (m, 10), 5.69 (s, br, 1), 5.18 (s, br, 1), 5.10 (s, 2), 3.04−2.81 (m, br, 2).

4.16. Benzyl {(1*S*)-3-[*exo*-3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-3-oxo-1-phenylpropyl}carbamate (27). Acid **26** (5.00 g, 0.017 mol) was slurried in dichloromethane (60 mL) at ambient temperature under an atmosphere of nitrogen. Thionyl chloride (1.25 mL, 0.17 mol) was added (off gassing observed) and the reaction stirred at ambient temperature for 1 h. The resultant slurry was added to a biphasic mixture of amine tosylate salt **4** (6.00 g, 0.014 mol) in dichloromethane (60 mL), saturated sodium carbonate (30 mL) and water (30 mL) (off gassing observed), and the mixture was stirred at ambient temperature for 12 h. The phases were separated and the aqueous phase was re-extracted with dichloromethane (60 mL). The organic extracts were combined, washed with 2 M KOH (60 mL) followed by water (60 mL). The extract was concentrated to dryness under reduced pressure to give **27** (3.69 g, 51%) as a crystalline white solid. ^{1}H NMR (300 MHz, CD_3OD) δ [ppm] 7.51−7.09 (m, 10), 5.32−5.13 (m, 1), 5.13−4.95 (m, 2), 4.76−4.67 (m, br, 1), 4.67−4.56 (m, br, 1), 4.55−4.44 (m, br, 1), 3.16−2.99 (m, 2), 2.93 (d, 1), 2.31 (s, 3), 2.24−2.00 (m, 2), 2.00−1.74 (m, 6), 1.34 (d, 6). MS *m*/*z* 516 $[M + H]^+$.

4.17. Benzyl (1*S*)-3-[3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-*exo*-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropylcarbamate (28). The tosylate salt of amine **4** (3.26 kg, 8.54 mol) was slurried in dichloromethane (32.6 L) and treated with a solution of **30** (2.66 kg, 9.39 mol) as a toluene concentrate, followed by addition of acetic acid (0.724 L). To the resultant solution was added sodium triacetoxyborohydride (2.17 kg, 10.24 mol) portionwise, maintaining the temperature below 30 °C. The resultant slurry was stirred at ambient temperature for 1.5 h the treated with water (7.24 L) followed by 2 M sodium hydroxide solution (7.24 L). The aqueous layer was adjusted to pH 11−12 by addition of 10 M sodium hydroxide solution, the layers were separated, and the aqueous phase was re-extracted with dichloromethane (7.24 L). The organic extracts were combined, washed with 1 M sodium hydroxide solution (7.24 L) and brine (7.24 L), and then concentrated under reduced pressure to yield **28** as a toluene concentrate (∼7.24 L). A small

amount of sample was concentrated to dryness under reduced pressure to obtain spectral data. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 7.40−7.10 (m, 10), 5.10 (m, 2), 4.93 (s, br, 1), 4.25 (m, 1), 3.45 (s, br, 1), 3.36 (s, br, 1), 2.97 (m, 1), 2.45−2.15 (m, 6), 2.05 (m, 2), 1.84 (m, 2), 1.75−1.55 (m, 4), 1.39 (d, 6). MS *m*/*z* 502 $[M + H]^+$.

4.18. Benzyl (*S*)-3-Hydroxy-1-phenylpropylcarbamate (29). A solution of **26** (4.02 kg, 13.42 mol) was slurried in THF (20.1 L) under an atmosphere of nitrogen and cooled to 0 °C. BH_3•THF (2 M solution in THF, 26.86 L) was added to the reaction over 3 h, maintaining the temperature below 10 °C, and the reaction was stirred for a further 0.5 h. The excess BH_3•THF was quenched by the addition of acetone (4.02 L) over 0.5 h, maintaining the temperature below 10 °C. The reaction was quenched by the addition of water (40.2 L) added over 1 h, maintaining the temperature below 10 °C, and then warmed to ambient temperature. The THF was removed by concentration under reduced pressure, and dichloromethane (40.2 L) was added to give a biphasic solution. The layers were separated, and the aqueous phase was extracted further with dichloromethane (40.2 L). The combined organic extracts were washed with 1 M sodium hydroxide solution (40.2 L), followed by water (10 L), and concentrated under reduced pressure, distilling and replacing with ethyl acetate (4.02 L) to a total volume of ∼6.3 L. Heptane (4.02 L) was added, and the mixture was cooled to ambient temperature to granulate. Further heptane (36.18 L) was added, and the resultant slurry was cooled to 0 °C and granulated overnight. The resultant solid was collected by filtration and dried *in vacuo* (40 °C) to give **29** as a white crystalline solid (2.68 kg, 70%), containing 5% benzyl alcohol by HPLC. Mp 86 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 7.38−7.25 (m, 10), 5.44 (d, br, 1), 5.16−5.05 (q, 2), 4.96 (m, br, 1), 3.70−3.66 (m, br, 2), 2.70(s, br, 1), 2.15−2.00 (m, 1), 1.95−1.84 (m, 1).

4.19. Benzyl (*S*)-3-Oxo-1-phenylpropylcarbamate (30). Sulfur trioxide pyridine complex (4.48 kg, 28.91 mol) was slurried in dichloromethane (9.38 L) and DMSO (9.38 L) under an atmosphere of nitrogen and was cooled to 0 °C. A solution of **29** (2.68 kg, 9.39 mol) and triethylamine (3.93 L, 28.19 mol) in dimethylsulfoxide (4.69 L) and dichloromethane (4.69 L) was added slowly to the reaction mixture over 1.5 h, keeping the temperature below 10 °C. The resultant yellow solution was stirred at 0 °C for 1.25 h. Water (40.2 L) was added to the reaction mixture over 1 h maintaining the temperature below 20 °C. The mixture was diluted with toluene (40.2 L), and the layers were separated. The organic layer was washed with 0.5 M hydrochloric acid (40.2 L), followed by saturated brine solution (40.2 L), and then concentrated under reduced pressure to yield **30** as a toluene concentrate (final total volume ∼6.4 L), which was progressed without further purification. The yield was assumed to be quantitative. A small amount of sample was concentrated to dryness and purified by chromatography to obtain spectral data. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 9.74 (s, 1), 7.33 (m, 10), 5.38 (d, br, 1), 5.27 (m, 1), 5.10 (m, 2), 3.01 (m, 2). MS *m*/*z* 283 [M].

4.20. Pummerer rearrangement impurity (36: ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 7.32 (m, 10), 5.62 (d, br, 1), 5.06 (q, 2), 4.92 (m, br, 1), 4.59 (s, 2), 3.51 (m, 2), 2.12 (s, 3), 2.06 (m, 2). MS *m*/*z* 346.1 $[M + H]^+$.

4.21. 4,4-Difluorocyclohexanecarbonyl Chloride (31). 4,4-Difluorocyclohexanecarboxylic acid (**2**) (1.5 kg, 9.14 mol) was dissolved in toluene (3.75 L), treated with thionyl chloride (3.32 L, 45.69 mol), and the mixture was heated at reflux (∼92 °C) for 2.5 h. The reaction was cooled to ambient temperature, and the thionyl chloride was removed under reduced pressure and replaced with toluene (5 L) to give the **31** as a toluene concentrate (total volume 9 L) in quantitative yield. A small amount of sample was concentrated to dryness to obtain spectral data. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 2.85 (m,1), 2.18−1.73 (m, 8).

4.22. (*S*)-3-(Benzyloxycarbonylamino)-3-phenylpropyl Methanesulfonate (32). (**8**) (1.5 g, 0.0053 mol) and triethylamine (0.81 mL, 0.0058 mol) were dissolved in dichloromethane (21 mL) and cooled to 5 °C. A solution of methanesulfonyl chloride (0.42 mL, 0.0055 mol) in dichloromethane (5.2 mL) was added over 20 min, keeping temperature below 10 °C. The resultant solution was stirred at 5 °C for 60 min. The dichloromethane was removed under reduced pressure, distilling and replacing with ethyl acetate (40 mL). Water (40 mL) was added to give a biphasic solution, which was separated. The organic phase was washed sequentially with 5 wt % $NaHCO_3$ solution (20 mL) and 20 wt % brine solution (20 mL), dried over magnesium sulfate and filtered. The ethyl acetate was removed under reduced pressure, distilling and replacing with *i*-propanol (80 mL) and concentrated to dryness to give **32** (1.90 g, 94%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ [ppm] 7.34 (m, 10), 5.08 (q, br, 3), 4.89 (m, 1), 4.23 (m, 1), 4.02 (m, 1), 2.94 (s, br, 3), 2.25 (m, 2).

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