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Synthesis of dibenzylamino-1-methylcyclohexanol and dibenzylamino-1-trifluoromethylcyclohexanol isomers†

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The isomers of dibenzylamino-1-methylcyclohexan-1-ol and dibenzylamino-1-trifluoromethylcyclohexan-1-ol have been prepared. The stereochemistry of these compounds was unequivocally assigned through a combination of NMR spectroscopy and single crystal X-ray analysis. The *cis*-isomer of 3-*N*,*N*-dibenzylamino-1-trifluoromethylcyclohexanol and its derivatives display an unusual conformational behaviour in both solution-phase and the solid-state, where the amino group usually adopts an axial conformation.

Introduction

The introduction of three-dimensional shape through an increase in the proportion of sp^3 hybridised centres (Fsp^3) has been correlated to compound progress in a drug-discovery setting.[1–5] The reduction of aromatic ring count has also been shown to have beneficial effects on the development properties of oral drug candidates, including aqueous solubility, lipophilicity, serum albumin binding, CyP450 inhibition and hERG inhibition.[6] Based upon these important factors there has been significant interest in robust synthetic routes to building blocks and fragments which confer both shape and fixed conformation on a molecule through the introduction of saturation.[7–9]

Whilst there are advantages to the reduction in the number of aromatic rings within a compound,[6] the conformational constraints of a ring provide clear benefits in a medicinal chemistry setting, where functional groups can be held in positions to maximise ligand–receptor interaction.[10] For this reason the introduction of functional groups on an aromatic scaffold has provided significant benefits within drug-discovery. In addition, there are many simple and effective procedures for the formation of carbon–carbon and carbon–heteroatom bonds on aromatic and heteroaromatic rings allowing for the rapid introduction of diversity and complexity on these frameworks to establish and probe structure activity knowledge.[11]

A common motif found in many drug molecules is the aminophenol functionality. This can easily be introduced through a variety of bond construction procedures and both the amine and hydroxyl groups provide excellent synthetic handles through which to selectively introduce a variety of additional groups. Introduction of this functionality on a rigid aromatic scaffold can provide both hydrogen bond donor and hydrogen bond acceptor properties along with the provision of mildly basic and acidic functional groups. Therefore, this pharmacophore is prevalent in many bioactive molecules. A selection of marketed drugs which contain a 1,4-, 1,3- or 1,2-aminophenol functionality are collected in Fig. 1. Dofetilide **1** is a class III antiarrhythmic used for the maintenance of sinus rhythm.[12] Terconazole **2** is a broad spectrum antifungal agent which ultimately inhibits the ergosterol biosynthesis pathway.[13] Neostigmine **3** is a reversible acetylcholinesterase inhibitor which stimulates both nicotinic and muscarinic receptors.[14] Ivacaftor **4** is effective in the treatment of cystic fibrosis.[15] Suvorexant **5** is a orexin receptor antagonist,[16] approved for the treatment of insomnia and Eltombopag **6**, interacts with the thrombopoietin receptor and leads to an increased platelet count in patients.[17] These selected examples show the diversity in protein targets for this class of compound and highlight the importance and prevalence of the aminophenol functionality in compounds with profound biological activities.

From the examples outlined in Fig. 1 there are clear benefits to the use of aromatic rings to fix the aminophenol functionality in space. However, the correlation between

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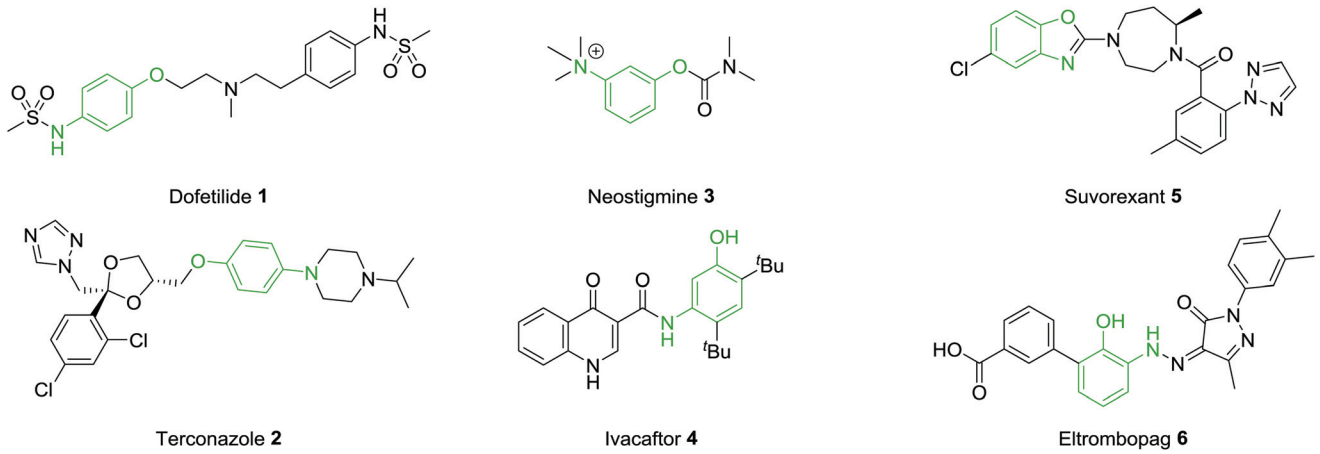


Fig. 1 Drug molecules containing the 1,4-, 1,3- and 1,2-aminophenol functionality.

developing an oral drug candidate and the number of aromatic rings in a compound provides a strong impetus to develop saturated analogues of common aromatic motifs found in drug molecules.[6] As part of an ongoing investigation we hypothesised that saturation of the aminophenol framework would provide a particularly useful series of aminocyclohexanol fragments for discovery research. Examination of the patent literature reveals a number of compounds which contain the aminocyclohexanol functionality suggesting that this grouping also has potential in the drug-discovery setting. Recent examples include the benzoxazole **7** which has been shown to be an *m*PGES-1 inhibitor and the 2-amidopyridine derivative **8**, synthesised as a potential 11β-HSD1 inhibitor (Fig. 2).[18,19]

A convenient synthetic precursor to the amino cyclohexanol framework would be a suitably N-protected derivative. A typical example that can readily be unmasked to reveal the desired functionality is dibenzylamino-1-methylcyclohexan-1-ol and dibenzylamino-1-trifluoromethylcyclohexan-1-ol, which each have six structural isomers **9–20** (Fig. 3).

Despite the prevalence of this framework in the patent literature relatively few syntheses of this scaffold have been reported in the primary literature. In an isolated report, Yamamoto described the ytterbium triflate-mediated ring opening

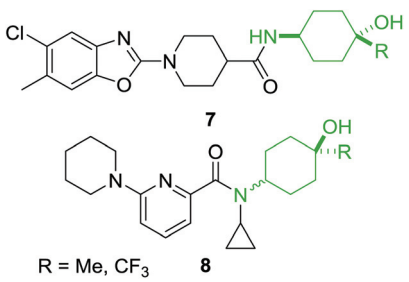


Fig. 2 Examples from recent patent literature containing the 4-amino-cyclohexanol functionality.

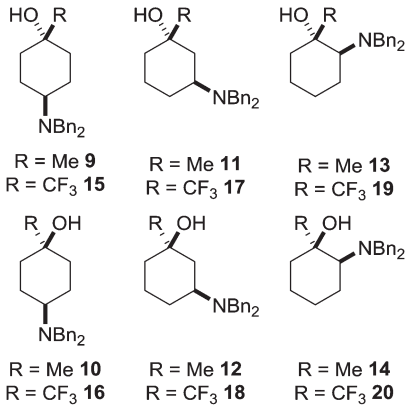
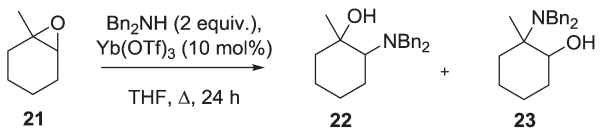


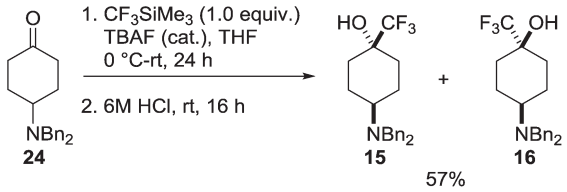
Fig. 3 Possible 1-methyl- and 1-trifluoromethyl dibenzylaminocyclohexanol isomers.

of epoxide **21** with dibenzylamine to give the amino alcohol **22** together with **23** as a 9 : 1 mixture of regioisomers (Scheme 1).[20] Although the stereochemistry of this product was not unequivocally assigned it is expected that this would be the *trans*-isomer **13**.

In the trifluoromethyl series (**15–20**) only the 4-amino-1-trifluoromethylcyclohexanol **15** has been reported, as a mixture along with minor isomer **16**.[19] This mixture was prepared through reaction of the dibenzylamino ketone **24** with Ruppert's reagent (CF_3SiMe_3) in the presence of tetra-*n*-butylammonium fluoride (TBAF) followed by acidic cleavage of the siloxy intermediate to give the products **15** and **16** as a



Scheme 1 Epoxide ring opening route to the 1,2-isomer.



Scheme 2 Preparation of the trifluoromethyl substituted 1,4-isomer **15**.

6 : 1 mixture of diastereoisomers (Scheme 2), the *trans*-isomer **15** predominating.

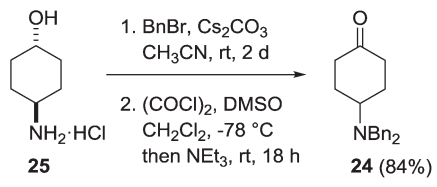
Whilst these isolated reports are of use to those wishing to exploit this functionality in their efforts, the synthesis and stereochemical assignment of all twelve isomers of this cyclohexyl motif would be of direct use in adding stereochemical complexity and 3-dimensional shape to discovery projects. Within this paper we describe the synthesis, isolation and purification of all 1-methyl- and 1-trifluoromethyl dibenzylaminocyclohexan-1-ol isomers **9–20** in three steps or fewer from readily available precursors, and unequivocally assign their stereochemistry based upon NMR spectroscopy and X-ray crystallographic experiments.

Results and discussion

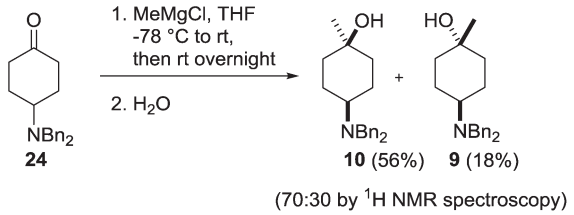
Our investigations began with the preparation of the 4-dibenzylamino derivatives **9**, **10**, **15** and **16** which were accessed from the common intermediate **24**. Dibenzylation of 4-aminocyclohexanol hydrochloride **25** followed by Swern oxidation provided the known ketone **24** in 84% yield (Scheme 3).[21]

Treatment of a THF solution of **24** with methylmagnesium chloride at −78 °C and allowing the reaction mixture to warm slowly to room temperature followed by an acidic workup provided access to the two diastereoisomers **10** and **9** in a 70 : 30 ratio, which were separated by column chromatography providing the products in 56% (**10**) and 18% (**9**) isolated yields (Scheme 4).

The stereochemistry of each isomer was confirmed by X-ray crystallographic analysis (Fig. 4). The *cis*-isomer **10** showed two crystallographically independent molecules within the unit cell characterised by slightly different conformations of the cyclohexane ring which formed a hydrogen-bonded closed tetramer of molecules.



Scheme 3 Preparation of 4-dibenzylaminocyclohexanone **24**.



Scheme 4 Synthesis of *cis*- and *trans*-4-dibenzylamino-1-methylcyclohexanol **10** and **9**.

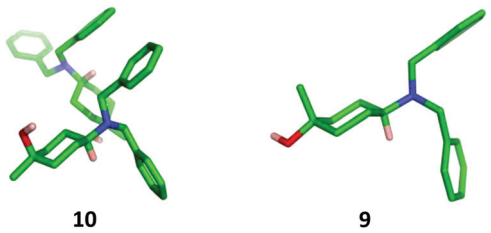
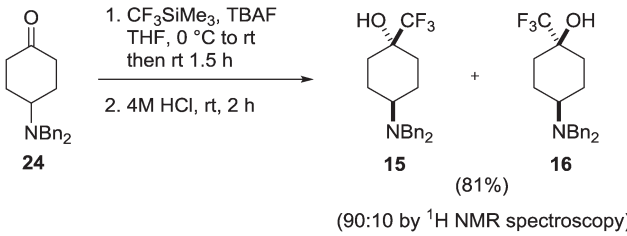


Fig. 4 X-Ray crystal structures of **10** and **9**.

Introduction of the trifluoromethyl group was achieved under standard conditions using Ruppert's reagent in the presence of TBAF, delivering the two diastereomeric products **15** and **16** in a 9 : 1 ratio as determined by ^{1}H NMR and ^{19}F NMR spectroscopy (Scheme 5). Although a small amount of the major diastereomer was purified by column chromatography, efficient separation of **15** and **16** could not be achieved due to their similar affinities to silica, and the mixture of diastereomers was isolated in 81% yield. X-Ray crystallography showed the major diastereoisomer from this transformation to be the *trans*-isomer **15** where the trifluoromethyl group had been introduced in an axial position.

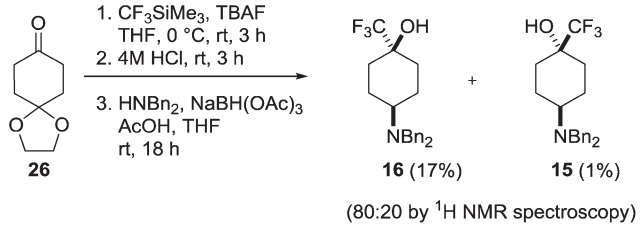
The complete reversal of *cis*/*trans* selectivity when compared to methyl analogues **9** and **10** is likely due to pre-complexation of the approaching nucleophile in the addition of the Grignard reagent, whereas the axial addition of the trifluoromethyl group relieves gauche interactions within the transition state.[22–24]

Although the *cis*-diastereoisomer **16** was present within the crude reaction mixture, its isolation proved challenging. We therefore examined alternative synthetic strategies to access this isomer. Initial attempts at using stoichiometric amounts



Scheme 5 Synthesis of 4-dibenzylamino-1-trifluoromethylcyclohexanols **15** and **16**.

of the bulky Lewis acid methylaluminium bis(2,6-di-*tert*-butyl-4-methyl)phenoxide to encourage the equatorial approach of the nucleophile were unsuccessful.[25] In addition, the more sterically demanding trifluoromethylating agent hexafluoroacetone hydrate-1,8-diaza-bicyclo[5.4.0]undec-7-ene salt only returned starting materials.[26] However, **16** was successfully prepared through the sequence outlined in Scheme 6. Trifluoromethylation of the mono-protected cyclohexanedione **26** followed by deprotection and subsequent reductive amination[27] gave the diastereomeric *cis*- and *trans*-isomers **16** and **15** in an 80 : 20 ratio, from which the required *cis*-isomer **16** could be isolated through purification by column chromatography in a poor but acceptable yield for the three steps (17%). The relative configuration of both the *trans*- and *cis*-diastereoisomers **15** and **16** was confirmed through X-ray crystallography (Fig. 5).



Scheme 6 Alternative synthesis of *cis*-4-dibenzylamino-1-trifluoromethylcyclohexanol (**16**).

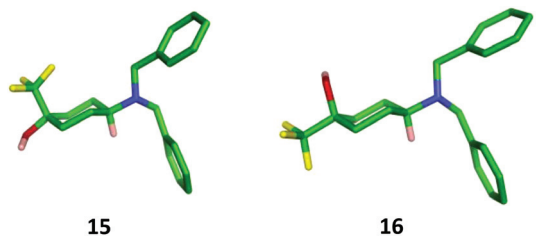


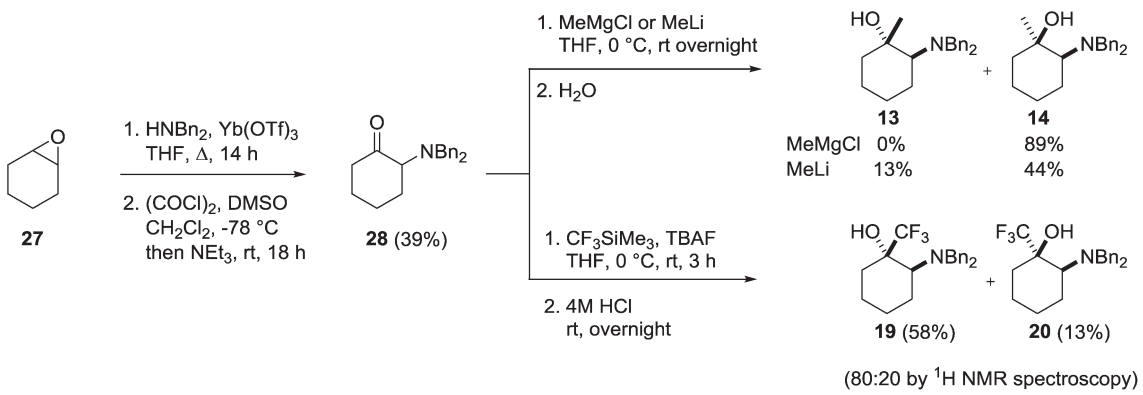
Fig. 5 X-Ray crystal structure of **15** and **16**.

Conveniently, the four possible 1,2-isomers **13**, **14**, **19** and **20** could be prepared and isolated from a common intermediate, greatly simplifying the synthesis of these compounds (Scheme 7). Intermediate **28** was prepared through a two-step literature procedure involving the ring opening of cyclohexene oxide **27** followed by Swern oxidation of the resulting amino-alcohol to give **28** in 39% isolated yield (Scheme 7).[20] Addition of methylmagnesium chloride to **28** at 0 °C gave the *cis*-amino-alcohol **14** in 89% isolated yield as a single isomer. Single crystal X-ray analysis of the hydrochloride salt of **14** confirmed the relative stereochemistry of this compound (Fig. 6) with the methyl group adopting an equatorial position. Chelation of the Grignard reagent to the carbonyl oxygen and the secondary amine would be expected to deliver the methyl group from an equatorial position, as was observed.

Changing the nucleophile to methyllithium resulted in the formation of both the *cis*- and *trans*-products **14** and **13** in a 80 : 20 ratio (^{1}H NMR analysis of the crude reaction mixture). The isomers were separated by column chromatography, and the ^{1}H NMR spectrum of the minor *trans*-isomer **13** agreed with the values reported for the product from ring-opening of 1-methylcyclohexene oxide by dibenzylamine.[20] Therefore, the diastereomers **13** and **14** can be accessed as single isomers in good yield *via* two complimentary routes.

Treatment of **28** with Ruppert's reagent and TBAF resulted in a 80 : 20 mixture of the expected products **19** and **20**, which were purified by column chromatography and isolated in 58% and 13% yields respectively (Scheme 7). The major diastereomer was shown to be the *trans*-isomer **19** by single crystal X-ray analysis (Fig. 7), and was supported by the observation of long range splitting of the axial NC-H proton by the *trans*-CF_3 group in the ^{1}H NMR spectrum. This coupling was not observed for the *cis*-isomer **20**.

Having successfully prepared each of the 1,4- and 1,2-isomers our attention moved to the synthesis of the 1,3-substituted amino alcohols **11**, **12**, **17** and **18**. Once again, these could be prepared from a common intermediate (**30**), which itself was prepared using a bismuth nitrate catalysed conjugate addition of dibenzylamine to cyclohexenone **29** (Scheme 8).[28] Isolation of the key intermediate **30** by chromatography proved



Scheme 7 Synthesis of 2-dibenzylamino-1-substituted cyclohexan-1-ols **13**, **14**, **19** and **20**.

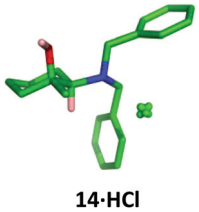


Fig. 6 X-Ray crystal structure of **14**·HCl.

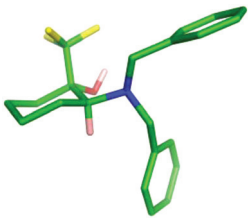


Fig. 7 X-Ray crystal structure of *trans*-isomer **19**.

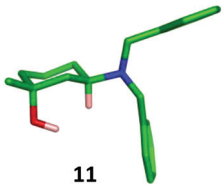


Fig. 8 X-Ray crystal structure of major *trans*-1,3-isomer **11**.

problematic due to decomposition of the adduct on silica, however, direct crystallisation from the crude reaction mixture using petroleum ether gave the amino ketone in 32% yield on scale without the need for chromatography.

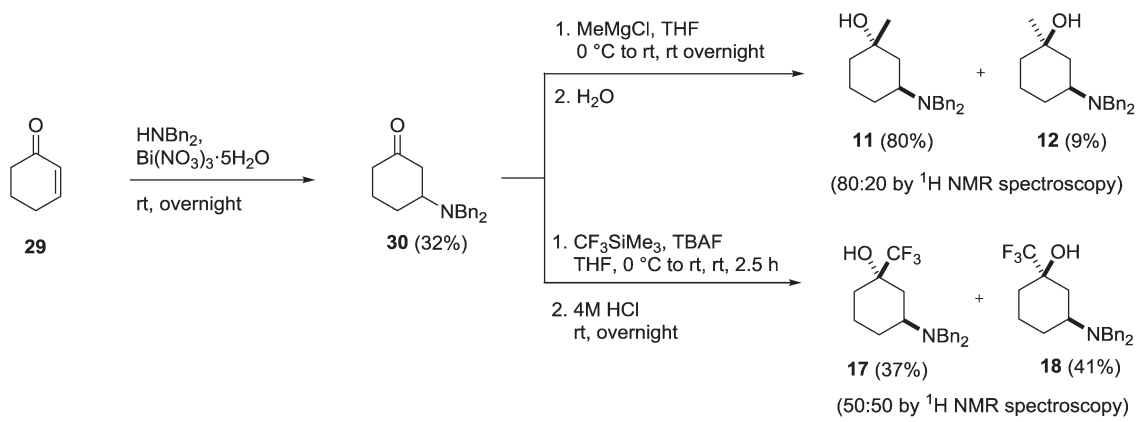
Addition of methylmagnesium chloride to **30** gave a 80 : 20 diastereomeric mixture of the expected *trans*-**11** and *cis*-**12** products, which were separated by column chromatography and isolated in 80% and 9% yields respectively. The identity of the major *trans*-isomer **11** was confirmed by single crystal X-ray analysis where the dibenzylamino group adopted an equatorial position (Fig. 8).

Treatment of **30** with Ruppert's reagent in the presence of TBAF gave a 50 : 50 mixture of the diastereomeric products **17** and **18**, which were separated by column chromatography and isolated in 37% and 41% yields respectively (Scheme 8). The stereochemistry of *cis*-isomer **18** was deduced by ^{1}H NMR spectroscopy due to its intriguing behaviour in solution. In $CDCl_3$, **18** adopted a conformation (**A**) where the large dibenzylamino group resided in an axial position due to an intramolecular hydrogen bond, whereas in the H-bonding deuterated solvent CD_3OD the amino group adopted the more common equatorial conformation (**B**) (Fig. 9).

This solvent-dependant conformational change has been observed previously for *cis*-1,5,5-trimethylcyclohexane-1,3-diol and *cis*-1,5,5-trimethyl-3-aminocyclohexanol in $CDCl_3/D_2O$,[29] but it is impressive that such a bulky dibenzylamino group displays this strong conformational fluxionality. The effect can in part be attributed to the size of the trifluoromethyl group, although the fact that the effect is reversed in CD_3OD suggests there is a hydrogen-bonding interaction involved (Fig. 9). Interestingly, this is not seen in the methyl analogue **12** which suggests that the trifluoromethyl group plays a pivotal role in the conformation adopted by **18** in solution, presumably by tuning the acidity of the alcohol.[30] ^{1}H NMR analysis of **18**·HCl (in $CDCl_3$) showed the dibenzylamino group in an equatorial position, supporting the proposal that an intramolecular hydrogen bond alters the conformational preference of **18** in non-polar solvents.

This behaviour was further investigated through the preparation of a series of analogues of **18** (Scheme 9). Deprotection of the amine through hydrogenolysis gave the amine **31** (94%) which was acylated under standard conditions to give the amide **32** (69%). Reduction of the amide with borane gave the secondary amine **33** (76%).

The relative stereochemistry of amine **31** was confirmed by single crystal X-ray where the amine substituent adopts an



Scheme 8 Synthesis of 3-dibenzylamino-1-substituted cyclohexanol derivatives.

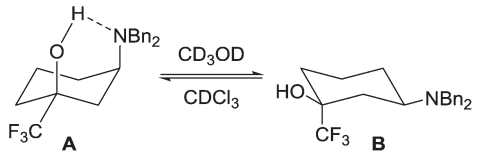
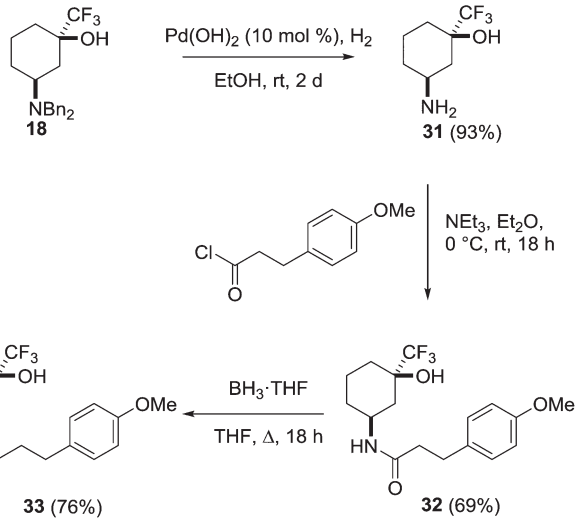


Fig. 9 Solvent-dependant conformational change of **18** in solution.



Scheme 9 Derivatisation of the amine **18**.

axial conformation (Fig. 10). ^{1}H NMR analysis of **31** showed the NH_2 group adopts an axial conformation in solution in both $CDCl_3$ and CD_3OD showing the subtle interplay of sterics and electronics in the benzylated analogue **18**. Amide **32** and secondary amine **33** displayed the same conformational behaviour, suggesting that all *cis*-3-amino-1-trifluoromethylcyclohexanols possessing groups bonded to nitrogen that are less bulky than two benzyl groups are likely to always adopt a conformation with the amino functionality axial. This has interesting implications for adopting these monomers in a drug-discovery setting, where functional group disposition is critical to ligand–receptor interaction. It is entirely feasible that for compounds containing the *cis*-3-amino-cyclohexan-1-ol motif as exemplified by **12** and **18**, axial/equatorial conformation could be controlled through incorporation of either a methyl or a trifluoromethyl group.

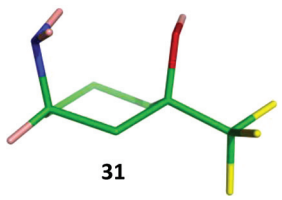


Fig. 10 X-Ray crystal structure of **31**.

Conclusion

The twelve isomers of amino-1-methylcyclohexan-1-ol and amino-1-trifluoromethylcyclohexan-1-ol were successfully prepared in three-steps or fewer from commercially available starting materials. The stereochemistry of each isomer was assigned *via* a combination of ^{1}H NMR spectroscopy and single crystal X-ray analysis. An interesting conformational behaviour was observed and investigated for *cis*-3-amino-1-trifluoromethylcyclohexan-1-ol derivatives, which could have structural implications for molecules containing this motif. This work provides robust routes to the isomers of amino-1-methylcyclohexan-1-ol and amino-1-trifluoromethylcyclohexan-1-ol, which will be of use for introducing 3D shape to drug-like molecules.

Experimental

Materials and methods

All commercial materials were used as received without further purification. THF was dried using a solvent purification system. Flash chromatography was carried out using Merck Kieselgel 60 H silica. Analytical thin layer chromatography was carried out using aluminum-backed plates coated with Merck Kieselgel 60 GF254 that were visualized under UV light (at 254 nm) or stained using $KMnO_4$. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III or a Bruker Avance spectrometer, operating at 400 MHz (^{1}H), 376 MHz (^{19}F) and 101 MHz (^{13}C). Chemical shifts were reported in parts per million (ppm) in the scale relative to residual solvent signals. Multiplicities are abbreviated as: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; tt, triplet of triplets; pent; pentet; hept, heptet; m, multiplet; br, broad. Coupling constants are measured in Hertz (Hz). High-resolution mass spectra (HRMS) were obtained courtesy of the EPSRC National Mass Spectrometry Facility at Swansea University, U.K.

trans-4-(Dibenzylamino)cyclohexan-1-ol

Cesium carbonate (51.4 g, 158 mmol) was added to a solution of *trans*-4-aminocyclohexanol (7.9 g, 52.3 mmol) in acetonitrile (150 mL). Benzyl bromide (12.7 mL, 106 mmol) was added and the mixture left to stir at room temperature for 2 days. The crude reaction mixture was filtered, and the solid washed with additional acetonitrile (100 mL). The filtrate was concentrated under reduced pressure, dissolved in dichloromethane (100 mL) and washed with water (3 × 50 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give *trans*-4-(dibenzylamino)cyclohexan-1-ol as a colourless solid (15.1 g, 98%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (4H, d, J = 7.2 Hz), 7.29 (4H, ddd, J = 7.1, 6.1 Hz), 7.19–7.24 (2H, m), 3.62 (4H, s), 3.54 (1H, tt, J = 10.9, 4.3 Hz), 2.53 (1H, tt, J = 11.8, 3.5 Hz), 1.95–2.04 (2H, m), 1.87–1.94 (2H, m), 1.36–1.61 (1H, br s), 1.36–1.49 (2H, m), 1.12–1.30 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0 (quat C), 128.5 (CH),

128.3 (CH), 126.8 (CH), 71.0 (CH), 56.9 (CH), 54.1 (CH_2), 35.0 (CH_2), 26.0 (CH_2); HRMS calc. for $C_{20}H_{26}ON$ 296.2009 ($M^+ + 1$), found 296.2011.

General Procedure 1. Swern oxidation

A solution of DMSO (11.6 mL, 163 mmol) in anhydrous dichloromethane (20 mL) was added drop-wise *via* a dropping funnel to a cooled solution of oxalyl chloride (6.8 mL, 80.8 mmol) in anhydrous dichloromethane (100 mL) at −78 °C. The reaction mixture was left to stir for an additional 15 minutes following completion of addition, and a solution of *trans*-4-(dibenzylamino)cyclohexan-1-ol (14.0 g, 47.5 mmol) in anhydrous dichloromethane (50 mL) was added drop-wise *via* a dropping funnel. Following completion of addition, the reaction mixture was stirred for 30 minutes before triethylamine (46 mL, 328 mmol) was added slowly drop-wise *via* syringe, and the cooling bath removed to allow the reaction mixture to warm to room temperature. The rubber septa were removed to allow the evaporation of SMe_2, and the mixture left to stir overnight at room temperature. The crude reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate (150 mL) and washed with water (3 × 100 mL). The organic extract was dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (8 : 1 petroleum ether : ethyl acetate) to give **24** as peach coloured solid (13.9 g, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (4H, d, J = 7.2 Hz), 7.29–7.34 (4H, m), 7.21–7.26 (2H, m), 3.66 (4H, s), 3.02 (1H, tt, J = 11.5, 3.4 Hz), 2.37–2.45 (2H, m), 2.12–2.33 (4H, m), 1.76–1.89 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1 (quat C), 140.4 (quat C), 128.5 (CH), 128.4 (CH), 127.0 (CH), 55.9 (CH), 54.2 (CH_2), 40.3 (CH_2), 27.5 (CH_2); HRMS calc. for $C_{20}H_{24}ON$ 294.1852 ($M^+ + 1$), found 294.1854.

General Procedure 2. Addition of methylmagnesium chloride

To a solution of **24** (4.41 g, 15.05 mmol) in anhydrous THF (45 mL) cooled to −78 °C under a N_2 atmosphere, was added 3.0 M MeMgCl in THF (8.02 mL, 24.06 mmol) drop-wise. Following completion of addition, the cooling bath was removed and the reaction mixture left to warm to room temperature and stirred overnight. Water (10 mL) was added drop-wise, and the aqueous layer extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude products, which were purified by column chromatography on silica (5 : 1 petroleum ether : ethyl acetate followed by 4 : 1 and finally 3 : 1) to give **10** as a colourless solid (2.62 g, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (4H, d, J = 7.2 Hz), 7.29 (4H, *app* t, J = 7.6 Hz), 7.21 (2H, t, J = 7.3 Hz), 3.67 (4H, s), 2.43–2.53 (1H, m), 1.62–1.83 (6H, m), 1.25–1.38 (2H, m), 1.17 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2 (quat C), 128.5 (CH), 128.2 (CH), 126.7 (CH), 69.2 (quat C), 57.2 (CH), 54.1 (CH_2), 38.5 (CH_2), 31.4 (CH_3), 23.5 (CH_2); HRMS calc. for $C_{21}H_{28}ON$ 310.2165 ($M^+ + 1$), found 310.2157. A sample was crystallised by slow evaporation of a solution in cyclohexane. Followed by **9** as a colourless solid (0.85 g, 18%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (4H, d, J = 7.1 Hz), 7.26–7.31 (4H, m), 7.21 (2H, dt, J = 7.2, 1.3 Hz), 3.63 (4H, s), 2.56 (1H, tt, J = 11.6, 3.7 Hz), 1.78–1.88 (2H, m), 1.67–1.77 (2H, m), 1.32–1.55 (4H, m), 1.25 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.0 (quat C), 128.5 (CH), 128.3 (CH), 126.8 (CH), 71.0 (quat C), 57.5 (CH), 54.3 (CH_2), 39.8 (CH_2), 25.6 (CH_2), 25.5 (CH_3); HRMS calc. for $C_{21}H_{28}ON$ 310.2165 ($M^+ + 1$), found 310.2168. Crystals were grown by slow evaporation of a solution in cyclohexane.

General Procedure 3. Reaction with Ruppert's reagent

To a solution of **24** (2.0 g, 6.83 mmol) in anhydrous THF (15 mL) cooled to 0 °C, was added trifluoromethyltrimethylsilane (1.2 mL, 8.20 mmol) under a N_2 atmosphere. The mixture was stirred rapidly, and a solution of TBAF (5 mg, cat) in anhydrous THF (1 mL) was added slowly drop-wise. Following completion of addition, the cooling bath was removed and the reaction mixture left to warm to room temperature and stirred until consumption of starting material was apparent by TLC (1.5 h). The reaction mixture was exposed to air, 4 M HCl (aq) solution (10 mL) was added and the reaction mixture left to stir at room temperature until consumption of the siloxy intermediate was apparent by TLC (2 h). The pH was adjusted to 7 by the drop-wise addition of a saturated solution of K_2CO_3, and dichloromethane (30 mL) was added. The mixture was washed with water (3 × 15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (10 : 1 petroleum ether : ethyl acetate) to give **15** and **16** as a colourless solid as a 9 : 1 *trans* : *cis* mixture of diastereomers (2.0 g, 81%). A small amount of pure *trans*-**15** was obtained and used for characterisation purposes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.36 (8H, m), 7.19–7.24 (2H, m), 3.65 (4H, s), 2.73 (1H, pent, J = 6.3 Hz), 2.18 (2H, *app* dt, J = 10.7, 4.5 Hz), 1.83 (4H, *app* q, J = 6.7 Hz), 1.52–1.57 (1H, br s), 1.47 (2H, *app* dt, J = 14.0, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3 (quat C), 128.6 (CH), 128.3 (CH), 126.9 (CH), 126.8 (quat C, q, J = 283 Hz), 72.4 (quat C, q, J = 30.3 Hz), 55.3 (CH), 53.9 (CH_2), 29.9 (CH_2), 23.5 (CH_2); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −80.1; HRMS calc. for $C_{21}H_{25}ONF_3$ 364.1883 ($M^+ + 1$), found 364.1882; Crystals obtained from cold toluene.

4-Oxo-1-(trifluoromethyl)cyclohexan-1-ol

4-Oxo-1-(trifluoromethyl)cyclohexan-1-ol was prepared using General Procedure 3 (reaction mixture was stirred overnight at rt following addition of 4 M HCl (aq) solution) from 1,4-dioxaspiro[4.5]decan-8-one (2.00 g, 12.8 mmol), trifluoromethyltrimethylsilane (2.08 mL, 14.1 mmol), anhydrous THF (30 mL) and a solution of TBAF (5 mg) in THF (1.0 mL) to give the crude product, which was purified by column chromatography on silica (3 : 1 petroleum ether : ethyl acetate) to give 4-oxo-1-trifluoromethylcyclohexan-1-ol as a colourless solid (1.28 g, 55%); ^{1}H NMR (400 MHz, d_6-Acetone) δ 5.30 (1H, s), 2.69 (2H, ddd, J = 14.4, 6.4, 6.4 Hz), 2.06–2.27 (6H, m); ^{13}C NMR (100 MHz, d_6-Acetone) δ 208.3 (quat C), 127.7 (quat C, q, J = 308 Hz), 71.8 (quat C, q, J = 22 Hz), 35.8 (CH_2), 30.4 (CH_2);

$^{19}F\{^1H\}$ NMR (376 MHz, d_6-Acetone) δ −93.4; HRMS calc. for $C_7H_8O_2F_3$ 181.0482 ($M^+ - 1$), found 181.0485.

cis-4-(Dibenzylamino)-1-(trifluoromethyl)cyclohexan-1-ol 16

Following the procedure reported by Abdel-Magid,[27] 4-oxo-1-trifluoromethylcyclohexan-1-ol (0.20 g, 1.1 mmol), dibenzylamine (0.21 mL, 1.1 mmol), $NaBH(OAc)_3$ (0.33 g, 1.5 mmol) and acetic acid (0.13 mL, 2.2 mmol) were mixed in anhydrous THF (5 mL). The resulting mixture was stirred under an Ar atmosphere for 16 h, before further portions of $NaBH(OAc)_3$ (0.33 g, 1.5 mmol) and acetic acid (0.13 mL, 2.2 mmol) were added and the mixture stirred for a further 6 h. The reaction mixture was quenched with 1 M NaOH (aq) solution (20 mL), poured into a separating funnel and extracted with dichloromethane (3 × 15 mL). The combined organic extract was washed with water (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (6 : 1 petroleum ether : ethyl acetate) to give *cis* **16** (0.12 g, 31%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 (4H, d, J = 7.2 Hz), 7.31 (4H, *app* t, J = 7.2 Hz), 7.23 (2H, t, J = 7.2 Hz), 3.68 (4H, s), 2.46–2.62 (1H, m), 1.72–1.90 (6H, m), 1.67 (1H, br s), 1.55 (1H, *app* td, J = 12.5, 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8 (quat C), 128.5 (CH), 128.4 (CH), 126.9 (CH), 126.4 (quat C, q, J = 280 Hz), 72.5 (quat C, q, J = 30 Hz), 56.6 (CH), 54.0 (CH_2), 29.7 (CH_2), 22.0 (CH_2); $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ −84.5; HRMS calc. for $C_{21}H_{25}ONF_3$ 364.1883 ($M^+ + 1$), found 364.1880. Crystals were grown by slow evaporation of a saturated solution in $CHCl_3$.

trans-2-(Dibenzylamino)cyclohexan-1-ol

Following the procedure reported by Yamamoto,[20] dibenzylamine (3.9 mL, 20.0 mmol) was added to a mixture of cyclohexene oxide (1.0 mL, 10.0 mmol), ytterbium triflate (0.62 g, 1.0 mmol) and anhydrous THF (10 mL). The mixture was refluxed under an Ar atmosphere for 14 h. Ethyl acetate (30 mL) was added, and the solution was washed with a saturated solution of K_2CO_3 (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (9 : 1 petroleum ether : ethyl acetate) to give *trans*-2-(dibenzylamino)cyclohexan-1-ol as a colourless solid (1.5 g, 50%); ^1H NMR (500 MHz, $CDCl_3$) δ 7.22–7.36 (10H, m), 3.87 (2H, d, J = 13.3 Hz), 3.73–3.77 (1H, br s), 3.52 (1H, *app* td, J = 10.1, 4.5 Hz), 3.40 (2H, d, J = 13.3 Hz), 2.37 (1H, ddd, J = 10.9, 10.6, 3.5 Hz), 2.04–2.12 (1H, m), 1.96–2.02 (1H, m), 1.75–1.85 (1H, m), 1.61–1.72 (1H, m), 1.05–1.33 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (quat C), 129.1 (CH), 128.6 (CH), 127.3 (CH), 69.2 (CH), 64.3 (CH), 53.7 (CH_2), 33.3 (CH_2), 25.6 (CH_2), 24.2 (CH_2), 22.2 (CH_2); HRMS calc. for $C_{20}H_{26}ON$ 296.2009 ($M^+ + 1$), found 296.2010.

2-(Dibenzylamino)cyclohexan-1-one 28

Compound **28** was prepared using General Procedure 1 from *trans*-2-(dibenzylamino)cyclohexan-1-ol (1.20 g, 4.1 mmol), oxalyl chloride (0.48 mL, 5.6 mmol), DMSO (1.00 mL, 14.1 mmol), triethylamine (3.92 mL, 28.1 mmol) and anhydrous dichloromethane (30 mL in total) to give the crude product, which was purified by column chromatography on silica (8 : 1 petroleum ether : ethyl acetate) to give **28** as a light yellow solid (0.93 g, 78%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (4H, d, J = 7.2 Hz), 7.26–7.32 (4H, m), 7.18–7.24 (2H, m), 4.00 (2H, d, J = 14.3 Hz), 3.76 (2H, d, J = 14.3 Hz), 3.31 (1H, dd, J = 12.4, 5.7), 2.34–2.44 (1H, m), 2.10–2.25 (2H, m), 1.76–2.02 (3H, m), 1.44–1.66 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.2 (quat C), 140.8 (quat C), 128.5 (CH), 128.3 (CH), 126.9 (CH), 66.6 (CH), 54.9 (CH_2), 42.6 (CH_2), 31.7 (CH_2), 27.2 (CH_2), 25.1 (CH_2); HRMS calc. for $C_{20}H_{24}ON$ 294.1852 ($M^+ + 1$), found 294.1852.

cis-2-(Dibenzylamino)-1-methylcyclohexan-1-ol 14

Compound **14** was prepared following General Procedure 2 at a reduced temperature of 0 °C, from **28** (0.25 g, 0.85 mmol), anhydrous THF (10 mL) and 3.0 M MeMgCl in THF (0.45 mL, 1.35 mmol), and was isolated as a yellow oil (0.23 g, 89%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (4H, d, J = 7.3 Hz), 7.30 (4H, *app* t, J = 7.3 Hz), 7.22 (2H, t, J = 7.3 Hz), 4.14 (2H, d, J = 13.8 Hz), 3.39 (2H, d, J = 13.8 Hz), 2.29 (1H, dd, J = 12.2, 3.4 Hz), 1.80–1.90 (2H, m), 1.65–1.79 (1H, m), 1.48–1.57 (2H, m), 1.38–1.48 (1H, m), 1.08–1.27 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2 (quat C), 129.0 (CH), 128.2 (CH), 126.7 (CH), 74.3 (quat C), 63.1 (CH), 55.9 (CH_2), 41.4 (CH_2), 29.2 (CH_3), 26.4 (CH_2), 21.8 (CH_2), 20.1 (CH_2); HRMS calc. for $C_{21}H_{28}ON$ 310.2165 ($M^+ + 1$), found 310.2166. The HCl salt of **14** was prepared by forming a saturated HCl solution in diethyl ether. Crystals were grown by the slow evaporation of a concentrated solution of the salt **14**·HCl in methanol.

trans-2-(Dibenzylamino)-1-methylcyclohexan-1-ol 13 and *cis*-2-(dibenzylamino)-1-methylcyclohexan-1-ol 14

Compounds **13** and **14** were prepared following General Procedure 2 at a reduced temperature of 0 °C, using **28** (0.050 g, 0.17 mmol), dry THF (10 mL) and a 1.6 M solution of MeLi in diethyl ether (0.16 mL, 0.26 mmol) to give the crude products, which were purified by column chromatography on silica (10 : 1 petroleum ether : ethyl acetate) to give **14** (0.023 g, 44%) which was identical to an authentic sample, followed by **13** as a colourless residue (0.007 g, 13%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.17–7.46 (10H, m), 3.85 (2H, d, J = 13.7 Hz), 3.42 (2H, d, J = 13.7 Hz), 2.61 (1H, *app* d, J = 10.6 Hz, CH), 1.84, (2H, *app* d, J = 8.8 Hz), 1.50–1.72 (4H, m), 1.36–1.47 (2H, m), 1.27 (3H, s); HRMS calc. for $C_{21}H_{28}ON$ 310.2165 ($M^+ + 1$), found 310.2166.

trans-2-(Dibenzylamino)-1-(trifluoromethyl)cyclohexan-1-ol 19 and *cis*-2-(dibenzylamino)-1-(trifluoromethyl)cyclohexan-1-ol 20

Compounds **19** and **20** were prepared using General Procedure 2 in which 4 M HCl was added after 3 h, using **28** (0.234 g, 0.80 mmol), trifluoromethyltrimethylsilane (0.14 mL, 0.95 mmol), anhydrous THF (10 mL) and a solution of TBAF (5 mg) in THF (1.0 mL) to give the crude products, which were purified by column chromatography on silica (5 : 1, followed by 5 : 2 petroleum ether : ethyl acetate) to give **19** as a colourless solid (0.167 g, 58%); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.44

(10H, m), 3.69–4.15 (2H, br s), 3.63 (1H, s), 3.36 (2H, d, J = 13.3 Hz), 2.78–2.89 (1H, m), 2.21–2.31 (1H, m), 1.91–2.01 (2H, m), 1.75–1.91 (1H, m), 1.28–1.69 (3H, m), 1.19 (1H, dddd, J = 16.4, 9.4, 4.6, 2.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4 (quat C), 129.2 (CH), 128.7 (CH), 127.6 (CH), 127.2 (quat C, q, J = 293.0 Hz), 72.3 (quat C, q, J = 20.1 Hz), 66.3 (CH), 55.9 (CH_2, br), 34.1 (CH_2), 26.0 (CH_2), 21.5 (CH_2), 21.4 (CH_2); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −69.4; HRMS calc. for $C_{21}H_{25}ONF_3$ 364.1883 (M^+ + 1), found 364.1878; crystallised from cold MeOH. Followed by **20** as a colourless solid (0.037 g, 13%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.46 (4H, m), 7.35 (4H, *app* t, J = 7.2 Hz), 7.28 (2H, t, J = 7.2 Hz), 3.66–4.38 (2H, br s), 3.52 (2H, d, J = 13.8 Hz), 3.00 (1H, dd, J = 10.1, 4.4 Hz), 2.31–2.58 (1H, m), 1.72–1.94 (4H, m), 1.47–1.64 (3H, m), 1.16–1.40 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.7 (quat C), 129.2 (CH), 128.4 (CH), 127.1 (CH), 126.4 (quat C, q, J = 293.0 Hz), 76.3 (quat C, q, J = 20.2 Hz), 58.6 (CH), 55.5 (CH_2, br), 32.8 (CH_2), 25.2 (CH_2), 20.8 (CH_2), 20.5 (CH_2); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −78.2; HRMS calc. for $C_{21}H_{25}ONF_3$ 364.1883 (M^+ + 1), found 364.1883.

3-(Dibenzylamino)cyclohexan-1-one 30

Following the procedure reported by Banik and Srivastava,[28] bismuth(III) nitrate pentahydrate (10.0 g, 21 mmol) was added to a solution of cyclohexen-1-one (10 mL, 103 mmol) and dibenzylamine (20 mL, 104 mmol) in dichloromethane (80 mL). Most of the dichloromethane was removed under reduced pressure, and the resulting slurry stirred at room temperature overnight. Dichloromethane (100 mL) was added and the resulting suspension filtered by gravity filtration through filter paper. The filtrate was washed with sat. $NaHCO_3$ (2 × 30 mL) and brine (2 × 30 mL), dried over $MgSO_4$, filtered once again and the dichloromethane removed under reduced pressure (taking care not to heat above 40 °C) to give the crude product. Purification was achieved by twice recrystallising from warm petroleum ether to give **30** as colourless crystals (9.7 g, 32%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (4H, d, J = 7.0 Hz), 7.27–7.33 (4H, m), 7.20–7.25 (2H, m), 3.72 (2H, d, J = 14.0 Hz), 3.62 (2H, d, J = 14.0 Hz), 2.95 (1H, *app* tt, J = 12.2, 3.7 Hz), 2.61–2.69 (1H, m), 2.39–2.49 (1H, m), 2.27–2.36 (1H, m), 2.15–2.27 (1H, m), 1.95–2.13 (2H, m), 1.65–1.78 (1H, m), 1.61–1.69 (1H, br s), 1.33–1.48 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8 (quat C), 140.0 (quat C), 128.5 (CH), 128.4 (CH), 127.1 (CH), 58.2 (CH), 53.8 (CH_2), 44.3 (CH_2), 41.3 (CH_2), 27.9 (CH_2), 22.6 (CH_2); HRMS calc. for $C_{20}H_{24}ON$ 294.1852 (M^+ + 1), found 294.1855.

trans-3-(Dibenzylamino)-1-methylcyclohexan-1-ol 11 and *cis*-3-(dibenzylamino)-1-methylcyclohexan-1-ol 12

Compounds **11** and **12** were prepared following General Procedure 2 at a reduced temperature of 0 °C, using **30** (0.40 g, 1.36 mmol), anhydrous THF (15 mL) and 3.0 M MeMgCl in THF (0.73 mL, 2.18 mmol), and the products purified by column chromatography on silica (6 : 1 petroleum ether : ethyl acetate) to give **11** as a colourless solid (0.34 g, 80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (4H, d, J = 7.4 Hz), 7.28 (4H, *app* t, J = 7.4 Hz), 7.19 (2H, t, J = 7.4 Hz), 3.63 (3H, s), 2.92 (1H, *app* tt, J = 12.2, 3.4 Hz), 1.80–1.95 (2H, m), 1.36–1.67 (4H, m), 1.15–1.30 (5H, m), 0.98 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.1 (quat C), 128.6 (CH), 128.3 (CH), 126.7 (CH), 71.0 (quat C), 54.0 (CH_2), 53.7 (CH), 41.1 (CH_2), 38.7 (CH_2), 32.1 (CH_3), 27.7 (CH_2), 20.7 (CH_2); HRMS calc. for $C_{21}H_{28}ON$ 310.2165 (M^+ + 1), found 310.2164; crystallised from cold MeOH. Followed by **12** as a colourless oil that solidified on standing (0.04 g, 9%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.39 (8H, m), 7.22 (2H, t, J = 7.0 Hz), 3.71 (2H, d, J = 14.0 Hz), 3.65 (2H, d, J = 14.0 Hz), 2.74 (1H, *app* tt, J = 9.4, 3.4 Hz), 1.64–1.85 (4H, m), 1.39–1.62 (3H, m), 1.17–1.30 (1H, m), 1.12 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.0 (quat C), 128.9 (CH), 128.3 (CH), 126.9 (CH), 71.6 (quat C), 55.3 (CH), 53.6 (CH_2), 41.1 (CH_2), 40.4 (CH_2), 28.6 (CH_2), 27.4 (CH_3), 21.0 (CH_2); HRMS calc. for $C_{21}H_{28}ON$ 310.2165 (M^+ + 1), found 310.2160.

trans-3-(Dibenzylamino)-1-(trifluoromethyl)cyclohexan-1-ol 17 and *cis*-3-(dibenzylamino)-1-(trifluoromethyl)cyclohexan-1-ol 18

Compounds **17** and **18** were prepared following General Procedure 3 quenching with 4 M HCl after 2.5 h, from **30** (1.40 g, 4.75 mmol), trifluoromethyltrimethylsilane (0.77 mL, 5.21 mmol), anhydrous THF (20 mL) and a solution of TBAF (5 mg) in THF (1.0 mL) to give the crude products, which were purified by column chromatography on silica (3 : 1 petroleum ether : ethyl acetate) to give **17** as a colourless solid (0.64 g, 37%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (4H, d, J = 7.3 Hz), 7.30 (4H, *app* t, J = 7.4 Hz), 7.22 (2H, t, J = 7.4 Hz), 3.62 (4H, br s), 1.89–2.03 (1H, m), 1.89–2.02 (2H, m), 1.42–1.79 (6H, m), 1.27–1.41 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5 (quat C), 128.6 (CH), 128.4 (CH), 126.9 (CH), 126.1 (quat C, q, J = 283 Hz), 74.5 (quat C, q, J = 30.3 Hz), 53.9 (CH_2), 52.3 (CH), 32.1 (CH_2), 29.7 (CH_2), 27.4 (CH_2), 19.7 (CH_2); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −84.8; HRMS calc. for $C_{21}H_{25}ONF_3$ 364.1883 (M^+ + 1), found 364.1885. Followed by **18** as a colourless solid (0.70 g, 41%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.48 (1H, br s), 7.29–7.36 (4H, m), 7.22–7.29 (6H, m), 3.81 (2H, d, J = 14.3 Hz), 3.76 (2H, d, J = 14.3 Hz), 3.19 (1H, *app* pent, J = 3.2 Hz), 2.48 (1H, *app* d, J = 14.1 Hz), 2.03–2.17 (1H, *app* d, J = 14.3 Hz), 1.83–1.95 (1H, *app* d, J = 11.6 Hz), 1.44–1.82 (5H, m); ^{1}H NMR (400 MHz, CD_3OD) δ 7.25–7.34 (8H, m), 7.17–7.23 (2H, m), 3.68 (2H, d, J = 13.8 Hz), 3.61 (2H, d, J = 13.8 Hz), 2.91 (1H, *app* tt, J = 10.8, 3.6 Hz), 2.18–2.28 (1H, m), 1.95–2.05 (1H, m), 1.75–1.84 (1H, m), 1.62–1.74 (2H, m), 1.26–1.60 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3 (quat C), 129.5 (CH), 128.7 (CH), 127.6 (CH), 126.0 (quat C, q, J = 284 Hz), 73.8 (quat C, q, J = 28.7 Hz), 54.9 (CH), 53.2 (CH_2), 31.2 (CH_2), 30.2 (CH_2), 28.3 (CH_2), 16.4 (CH_2); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −84.4; HRMS calc. for $C_{21}H_{25}ONF_3$ 364.1883 (M^+ + 1), found 364.1885.

cis-3-Amino-1-(trifluoromethyl)cyclohexan-1-ol 31

Pearlman's catalyst (10% palladium hydroxide on carbon, 0.49 g, 5.38 mmol) and **18** (1.96 g, 0.538 mmol) were added to a Schlenk flask which was evacuated and back-filled with N_2. Ethanol (20 mL) was added and the flask evacuated using a diaphragm pump and back-filled with H_2 from a balloon three times. The reaction mixture was left to stir vigorously until

consumption of starting material was apparent by TLC analysis (2 days at room temperature). Ethyl acetate (20 mL) was added, and the mixture passed through a short Celite plug using additional ethyl acetate. The filtrate was concentrated under reduced pressure to give **31** as a light yellow oil, which crystallised upon standing (0.93 g, 93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35–3.30 (1H, *m*), 1.86–1.96 (2H, m), 1.79–1.82 (2H, m,), 1.74–1.78 (1H, m), 1.64–1.74 (2H, m), 1.54–1.63 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.5 (quat C, q, J = 283.0 Hz), 74.0 (quat C, q, J = 30.3 Hz), 46.8 (CH), 35.3 (CH_2), 32.9 (CH_2), 31.2 (CH_2), 16.5 (CH_2); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −85.2; HRMS calc. for $C_7H_{13}ONF_3$ 184.0944 (M^+ + 1), found 184.0941.

N-cis-3-Hydroxy-3-(trifluoromethyl)cyclohexyl)-3-(4-methoxyphenyl)propanamide 32

3-(4-Methoxyphenyl)propionic acid (0.79 g, 4.38 mmol) was refluxed in thionyl chloride (0.58 mL, 8.0 mmol) under an atmosphere of N_2 for 2 h. Excess thionyl chloride was removed under reduced pressure to give the crude acid chloride, which was used without further purification. In a separate flask, a solution of **31** (0.73 g, 3.99 mmol) and triethylamine (0.61 mL, 4.38 mmol) in anhydrous diethyl ether (20 mL) under a N_2 atmosphere was cooled to 0 °C. A solution of the freshly prepared acid chloride in anhydrous ether (2 mL) was added drop-wise with vigorous stirring of the reaction mixture. Upon completion of addition, the cooling bath was removed and the mixture left to stir overnight at room temperature. The reaction mixture was poured into a separating funnel containing water (20 mL), and was extracted with ethyl acetate (3 × 15 mL). The combined organic extract was washed with 1 M HCl (2 × 20 mL), water (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (1 : 9 methanol : ethyl acetate) to give **32** as a yellow oil (0.96 g, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (2H, d, J = 8.6 Hz), 6.81 (2H, d, J = 8.6 Hz), 6.77 (1H, br d, J = 8.2 Hz), 4.28–4.36 (1H, m), 3.76 (3H, s), 2.88 (2H, t, J = 7.4 Hz), 2.40 (2H, t, J = 7.4 Hz), 1.67–1.83 (4H, m), 1.48–1.64 (3H, m), 1.32–1.42 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (quat C), 158.3 (quat C), 132.9 (quat C), 129.5 (CH), 125.8 (quat C, q, J = 289 Hz), 114.1 (CH), 73.6 (quat C, q, J = 28 Hz), 55.4 (CH_3), 42.9 (CH), 39.3 (CH_2), 32.3 (CH_2), 31.2 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 15.1 (CH_2); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −85.1; HRMS calc. for $C_{17}H_{23}O_3NF_3$ 346.1625 (M^+ + 1), found 346.1626.

cis-3-((3-(4-Methoxyphenyl)propyl)amino)-1-(trifluoromethyl)-cyclohexan-1-ol 33

To a solution of **32** (0.93 g, 2.69 mmol) in anhydrous THF (25 mL) under a N_2 atmosphere, was added drop-wise a 1 M solution of BH_3·THF (27.0 mL, 27.0 mmol). Upon completion of addition, the mixture was heated at reflux overnight. The reaction mixture was cooled to 0 °C and methanol (5 mL) was added carefully drop-wise and the mixture stirred at room temperature for 1 hour. 2 M HCl (aq) (5 mL) was added, and the mixture was stirred for an additional 30 minutes at room temperature, after which the volatiles were removed under reduced pressure to give the aqueous residue. The aqueous residue was adjusted to pH 10 using 2 M NaOH (aq), and extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica (3 : 1 dichloromethane : methanol) to give **33** as a light yellow oil (0.68 g, 76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (2H, d, J = 8.8 Hz), 6.83 (2H, d, J = 8.8 Hz), 3.78 (3H, s), 3.65 (1H, *app* t, J = 6.4 Hz), 3.14 (1H, *app* pent, J = 3.0 Hz), 2.46–2.77 (4H, m), 1.67–2.03 (7H, m), 1.43–1.65 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0 (quat C), 133.7 (quat C), 129.4 (CH), 125.8 (quat C, q, J = 281 Hz), 114.0 (CH), 73.4 (quat C, q, J = 30 Hz), 55.4 (CH_3), 53.0 (CH), 47.0 (CH_2), 34.5 (CH_2), 32.6 (CH_2), 31.8 (CH_2), 31.3 (CH_2), 30.6 (CH_2), 15.3 (CH_2); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ −85.2; HRMS calc. for $C_{17}H_{25}O_2NF_3$ 332.1832 (M^+ + 1), found 332.1836.

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